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(54)发明名称

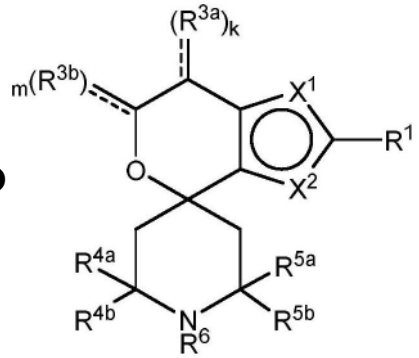
作为APOL1抑制剂的2-甲基-4',5'-二氢螺[哌啶-4,7'-噻吩并[2,3-c]吡喃]衍生物和其使用方法

(57)摘要

本公开提供了至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐,其选自式I化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐;包括其的组合物;以及使用其的方法,包含治疗APOL1介导的疾病的用途,所述APOL1介导的疾病包含胰腺癌、局灶性节段性肾小球硬化(FSGS)和/或非糖尿病性肾病(NDKD)。

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1.一种由以下结构式表示的化合物：

● 

其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中：

X^1和X^2选自-S-、-S(=O)$_2$-、-S(=O)-和-CR^2,其中：

X^1和X^2之一选自-S-、-S(=O)$_2$-和-S(=O)-；

当X^1是-S-、-S(=O)$_2$-或-S(=O)-时,则X^2是-CR^2;并且

当X^2是-S-、-S(=O)$_2$-或-S(=O)-时,则X^1是-CR^2;

R^1选自氰基、卤素、C_1-C_4烷基、C_1-C_4卤代烷基和C_3-C_6环烷基,其中：

R^1的所述C_1-C_4烷基任选地被1至3个独立地选自以下的基团取代：-OH和C_1-C_4烷氧基；

R^2选自氢、C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)、-C(=O)N$R^n$$R^o$以及卤素基团,其中：

R^2的所述C_1-C_6烷基任选地被1至3个独立地选自以下的基团取代：-OH、卤素和C_1-C_4烷氧基;并且

R^n和R^o独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_6环烷基和-(C_1-C_4亚烷基)R^p基团,其中R^p选自C_3-C_6环烷基;或者

R^1和R^2与其所连接的碳原子一起形成C_6芳基；

k选自0、1和2；

m选自0、1和2；

每个R^{3a}独立地选自-OH、-CN、-N$R^{a1}$$R^{a2}$、$C_1$-$C_6$烷基、$C_1$-$C_6$卤代烷基、$C_1$-$C_6$烷氧基、-OC(=O)($C_1$-$C_4$烷基)、6至8元芳基、6至8元杂芳基和卤素基团,其中：

每个R^{a1}和R^{a2}独立地选自氢、C_1-C_4烷基和-C(=O)(C_1-C_4烷基)基团;或者

两个R^{3a}一起形成氧代基团;或者

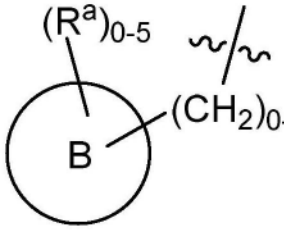
两个R^{3a}与其所连接的碳原子一起形成C_3-C_6环烷基；

每个R^{3b}独立地选自C_1-C_4烷基,其中：

R^{3b}的所述C_1-C_4烷基任选地被1至3个独立地选自以下的基团取代：-OH、卤素和C_1-C_4烷氧基;或者

一个R^{3a}和一个R^{3b}与其所连接的碳原子一起形成C_3-C_6环烷基；

R^{4a}、R^{4b}、R^{5a}和R^{5b}各自独立地选自氢和C_1-C_4烷基；

R^6选自C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)和

基团,其中:

R^6的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-OH、-NH_2、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环基、C_6芳基、-O-(C_6芳基)、5至10元杂环基和5至10元杂芳基,其中:

所述C_6芳基和-O-(C_6芳基)基团各自任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基;

环B选自C_3-C_{12}碳环基、3至12元杂环基、C_6和C_{10}芳基以及5至10元杂芳基,其中环B任选地被1个、2个、3个、4个或5个R^a基团取代;其中:

R^a在每次出现时独立地选自

卤素、

氰基、

C_1-C_8烷基、

C_1-C_6卤代烷基、

C_2-C_8烯基、

C_1-C_6卤代烯基、

C_1-C_6烷氧基、

C_1-C_6卤代烷氧基、

C_3-C_{12}碳环基、

C_6和C_{10}芳基、

3至12元杂环基、

5至10元杂芳基、

-C(=O)NR^hR^i、

-C(=O)OR^k、

-C(=O)(C_1-C_4亚烷基)OR^k、

-C(=O)R^k、

-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、

-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、

-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、

-C(=O)(C_1-C_4亚烷基)NR^hC(=O)R^k、

-C(=O)C(=O)R^k、

-NR^hR^i、

-NH(CH_2)$_qCHR^hR^i$、

-NH(CH_2)$_qNR^hR^i$、

-NR^hC(=O)R^k、

-$NR^hC(=O)OR^k$、

-$NR^hC(=O)(C_1$-C_4亚烷基)OR^k、

-$NR^hC(=O)O(C_1$-C_4亚烷基)R^k、

-$NR^hC(=O)NR^iR^j$、

-$NR^hC(=O)(C_1$-C_4亚烷基)$NR^iS(=O)_pR^k$、

-$NR^hS(=O)_pR^k$、

-$NR^hC(=O)(C_1$-C_4亚烷基)$S(=O)_pR^k$、

-$NR^hS(=O)_p(C_1$-C_4亚烷基)$C(=O)OR^k$、

-$NR^hC(=O)[O(CH_2)_q]_rOC(=O)NR^hR^i(CH_2)_q[O(CH_2)_q]_r(C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、

-$NR^hC(=O)(C_1$-C_6亚烷基)$[O(CH_2)_q]_rOC(=O)NR^hR^i(CH_2)_q[O(CH_2)_q]_r(C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、

-OR^k、

-$OC(=O)R^k$、

-$OC(=O)OR^k$、

-$OC(=O)NR^hR^i$、-$[O(CH_2)_q]_rO(C_1$-C_6烷基)、

-$S(=O)_pR^k$和

-$S(=O)_pNR^hR^i$基团,

其中:

以下中的每一者中的所述C_1-C_4亚烷基任选地被1至3个独立地选自-OH的基团取代:-$C(=O)(C_1$-C_4亚烷基)$S(=O)_pR^k$、-$C(=O)(C_1$-C_4亚烷基)OR^k、-$C(=O)(C_1$-C_4亚烷基)$S(=O)_pNR^hR^i$、-$C(=O)(C_1$-C_4亚烷基)$NR^iS(=O)_pR^k$、-$C(=O)(C_1$-C_4亚烷基)$NR^hC(=O)R^k$、-$NR^hC(=O)O(C_1$-C_4亚烷基)R^k、-$NR^hC(=O)(C_1$-C_4亚烷基)OR^k、-$NR^hS(=O)_p(C_1$-C_4亚烷基)$C(=O)OR^k$和-$NR^hC(=O)(C_1$-C_4亚烷基)$NR^iS(=O)_pR^k$,

R^a的所述C_1-C_8烷基、所述C_1-C_6卤代烷基、所述C_1-C_6烷氧基和所述C_2-C_8烯基各自任选地被1至3个独立地选自以下的基团取代:氰基、-$C(=O)R^k$、-$C(=O)OR^k$、-$C(=O)NR^hR^i$、-NR^hR^i、-$NR^hC(=O)R^k$、-$NR^hC(=O)OR^k$、-$NR^hC(=O)NR^iR^j$、-$NR^hS(=O)_pR^k$、-OR^k、-$[O(CH_2)_q]_rOH$、-$OC(=O)R^k$、-$OC(=O)OR^k$、-$OC(=O)NR^hR^i$、-SR^k、-$S(=O)_pR^k$、-$S(=O)_pNR^hR^i$、-$[O(CH_2)_q]_rO(C_1$-C_4烷基)、-O-(C_6芳基或5至8元杂芳基)(任选地被1至3个R^m基团取代)、C_3-C_6碳环基(任选地被1至3个R^m基团取代)、C_6至C_{10}芳基(任选地被1至3个R^m基团取代)、4至10元杂环基(任选地被1至3个R^m基团取代)和5至10元杂芳基(任选地被1至3个R^m基团取代);

R^a的所述C_3-C_{12}碳环基、所述3至12元杂环基、所述C_6和C_{10}芳基和所述5至10元杂芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、C_1-C_6烷基(任选地被1至3个R^m基团取代)、-$C(=O)R^k$、$C(=O)OR^k$、-NR^hR^i、-OR^k、-$S(=O)_pR^k$、-$S(=O)_pNR^hR^i$和5至10元杂环基,其中:

R^h、R^i和R^j在每次出现时各自独立地选自氢、C_1-C_6烷基(任选地被1至4个R^m基团取代)、C_6-C_{10}芳基、C_3-C_8碳环基(任选地被1至3个R^m基团取代)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代),其中:

R^h、R^i和R^j中的任一者的所述C_1-C_6烷基任选地被1至3个独立地选自以下的基团取代:卤

素、氰基、-OH、C_1-C_4烷氧基、-C(=O)NH(C_1-C_4烷基)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代);

R^k在每次出现时独立地选自氢、NH_2(任选地被1个或2个选自C_1-C_3烷基的基团取代)、C_1-C_6烷基、苄基、C_6芳基、C_3-C_6碳环基、5至10元杂环基和5至10元杂芳基,其中:

R^k中的任一者的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-NH_2、-OH、C_1-C_4烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、4至10元杂环基(任选地被1至3个-OH基团取代)、5至10元芳基(任选地被1至3个选自以下的基团取代:C_1-C_4烷基和卤素)和5至10元杂芳基(任选地被1至3个-OH基团取代);并且

R^k中的任一者的所述C_3-C_6碳环基、所述苄基和所述C_6芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、氧代、-OH、-C(=O)NH_2、-C(=O)N(CH_3)$_2$、C_1-C_6烷基(任选地被1至3个-OH基团取代)、C_1-C_6卤代烷基、C_1-C_6烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、C_6芳基(任选地被1至3个卤素基团取代)和5至10元杂芳基(任选地被1至3个卤素基团取代);并且

R^k中的任一者的所述5至10元杂芳基和所述5至10元杂环基各自任选地被1至3个独立地选自以下的基团取代:卤素、氧代、氰基、-C(=O)CH_3、-NH_2、-OH、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_4卤代烷基、5至10元杂环基和C_1-C_4烷氧基;

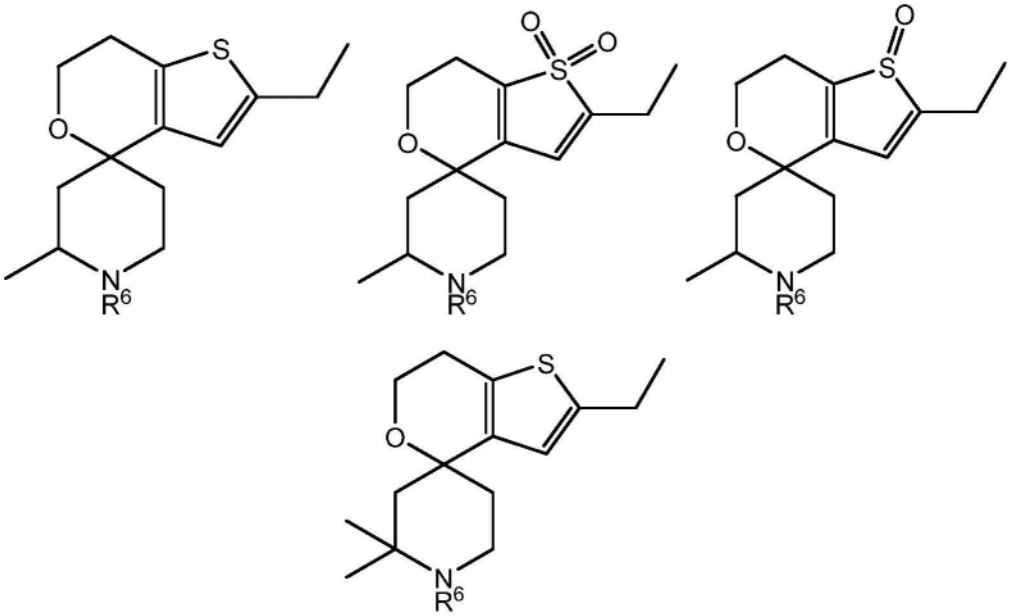
R^m在每次出现时独立地选自卤素、氰基、氧代、-NH_2、C_1-C_6烷基、C_1-C_6烷氧基、-C(=O)R^k、-S(=O)$_p$$R^k$、-O$R^k$和5至10元杂环基,其中:

R^m中的任一者的所述C_1-C_6烷基、所述C_1-C_6烷氧基和所述5至10元杂环基任选地被1至3个独立地选自以下的基团取代:卤素、氰基、-OH和C_1-C_4烷氧基;

p在每次出现时是独立地选自1和2的整数;并且

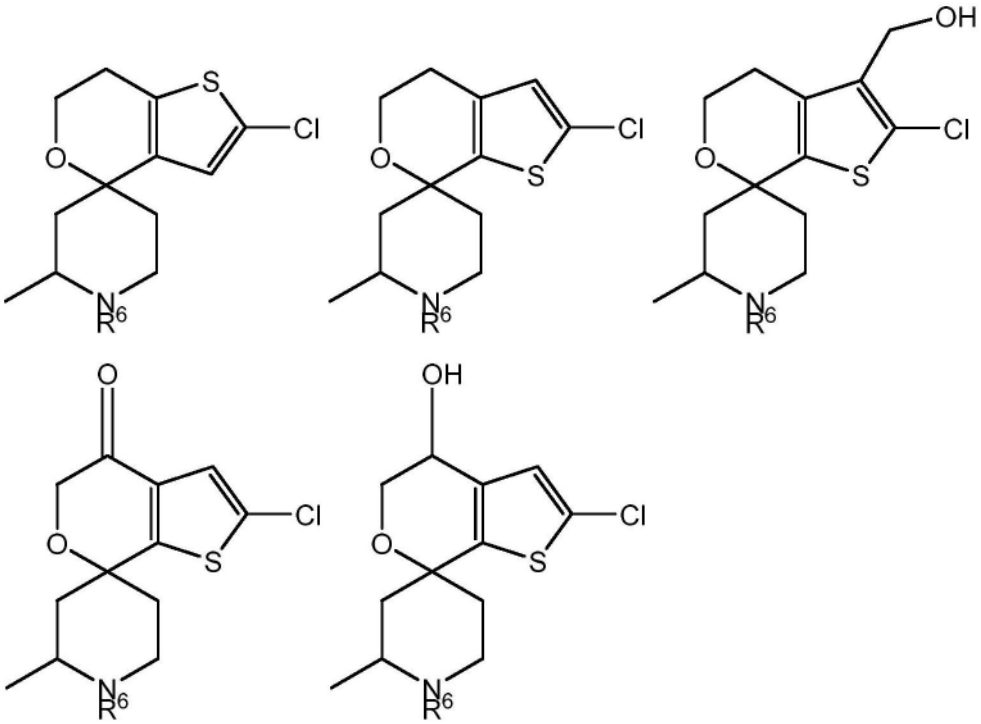
q和r在每次出现时是独立地选自0、1、2和3的整数。

2.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述化合物由以下结构式之一表示:



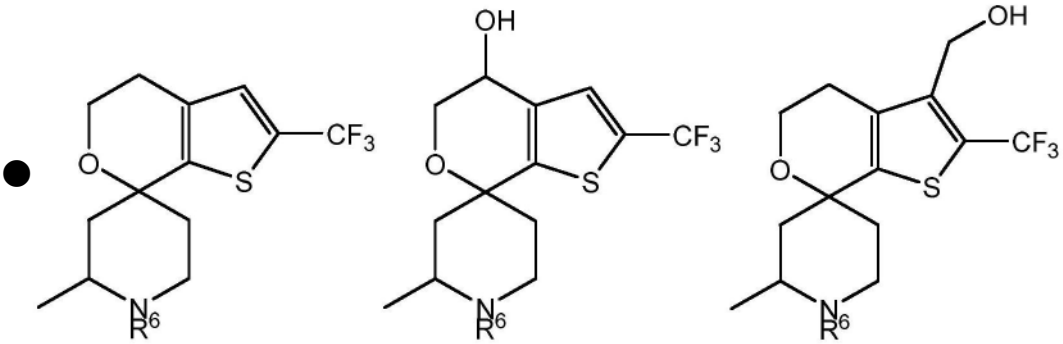
其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中R^6如权利要求1所定义。

3.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述化合物由以下结构式之一表示:



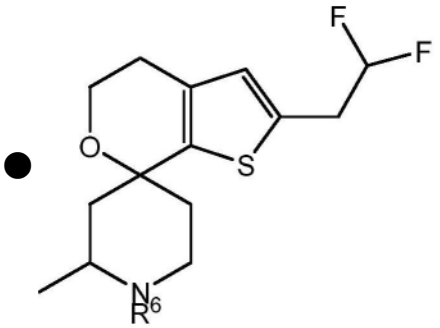
其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中R^6如权利要求1所定义。

4.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述化合物由以下结构式之一表示:



其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中R^6如权利要求1所定义。

5.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述化合物由以下结构式之一表示:



其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中R^6如权利要求1所定义。

6.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量X^1选自S、S(=O)和$S(=O)_2$,并且所述变量X^2是$-CR^2$。

7.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量X^2选自S、S(=O)和$S(=O)_2$,并且所述变量X^1是$-CR^2$。

8.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^2是氢。

9.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量X^1是S,所述变量X^2是$-CR^2$,并且所述变量R^2是氢。

9.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量X^1是$-CR^2$,所述变量X^2是S,并且所述变量R^2是氢。

10.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2选自氢、卤素、$-CH_3$、$-CH_2OH$、$-CH_2(OH)CH_3$和$-C(=O)NR^nR^o$,其中

R^n和R^o独立地选自氢、$-C_1$-C_4烷基、$-C_1$-C_4卤代烷基、$-C_3$-C_6环烷基和$-(C_1$-C_4亚烷基)R^p基团,并且其中

R^p选自$-C_3$-C_6环烷基。

11.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2选自卤素。

12.根据权利要求11所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2选自Br和Cl。

13.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^2选自$-CH_3$、$-CH_2OH$和$CH(OH)CH_3$。

14.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2是$-C(=O)NR^nR^o$,并且其中R^n是氢并且R^o是CH_3。

15.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2是$-C(=O)NR^nR^o$,并且其中R^n是氢并且R^o是被环丙基取代的CH_3。

16.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2是$-C(=O)NR^nR^o$,并且其中R^n是氢并且R^o是$-CH_2CH_2CH_3$。

17.根据权利要求10所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^2是$-C(=O)NR^nR^o$,并且其中R^n是氢并且R^o是$-CH_2CF_2$。

18.根据权利要求1和6至17中任一项所述的化合物、互变异构体、氘化衍生物或药学上

可接受的盐,其中R^1选自氰基、卤素、C_1-C_4烷基(任选地被1至3个独立地选自以下的基团取代:-OH和C_1-C_4烷氧基)、C_1-C_4卤代烷基和C_3-C_6环烷基。

19.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1选自-CN、-Br、-Cl、CH3、CH_2OH、$-CH_2CH_3$、$-CH_2CH_2CH3$、叔丁基、$-CH_2CF_2$、$-CF_2$、$-CF_3$、$-CF_2CF_2$、$-CH_2OCH_3$、$-CH_2OCH_2CH_3$、环丙基和环丁基。

20.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是CF_3。

21.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是Cl。

22.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CH_2OH$。

23.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CH_2CF_3$。

24.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_2CF_3$。

25.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CH_2(OH)CH_3$。

26.根据权利要求18所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1包括氘。

27.根据权利要求26所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$CD-OCH_2CH_3$。

28.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1和R^2与其所连接的碳原子一起形成C_6芳基。

29.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是-Cl,并且所述变量R^2是$-CH_2OH$。

30.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是Cl,并且所述变量R^2是$-CH_3$。

31.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是Cl,并且所述变量R^2是氢。

32.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是-Cl,并且所述变量R^2是-Cl。

33.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_3$,并且所述变量R^2是氢。

34.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中

35.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中$-CF_2CF_3$和所述变量R^2是氢。

36.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中$-CH_2CF_3$和所述变量R^2是氢。

37.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_2$,并且所述变量R^2是$-CH_2OH$。

38.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_3$,并且所述变量R^2是$-CH_2OH$。

39.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_3$,并且所述变量R^2是$-CH_2(OH)CH_3$。

40.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是$-CF_3$,并且所述变量R^2是-Cl。

41.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是CH_3,并且所述变量R^2是氢。

42.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是CH_2CH_3,并且所述变量R^2是氢。

43.根据权利要求1、6和7中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量R^1是CH_2OH,并且所述变量R^2是氢。

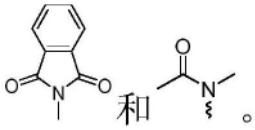
44.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m和k是零。

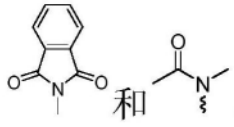
45.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量变量m是零,并且所述变量k是一。

46.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是零,并且所述变量k是二。

47.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量变量m是一,并且所述变量k是零。

48.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是二,并且所述变量k是零。

49.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是零,所述变量k是一或二,并且每个R^{3a}变量独立地选自-OH、F、F_2、CF_2、$-OCH_3$、$-OCH_2CH_3$、$-OCH_2(CH_3)_2$、$-OC(=O)CH_3$、NH_2、$NHC(=O)CH_3$、CN、和。

50.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是零,所述变量k是一,并且所述变量R^{3a}独立地选自-OH、F、F_2、CF_2、$-OCH_3$、$-OCH_2CH_3$、$-OCH_2(CH_3)_2$、$-OC(=O)CH_3$、NH_2、$NHC(=O)CH_3$、CN、和。

50.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是零,所述变量k是一,并且所述变量R^{3a}是-OH。

51.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中所述变量m是零,所述变量k是一,并且所述变量R^{3a}选自$-OCH_3$和$-OCH_2CH_3$。

52.根据权利要求1和6至43中任一项所述的化合物、互变异构体、氘化衍生物或药学上

可接受的盐,其中所述变量m是零,所述变量k是二,并且两个R^{3a}变量一起形成=O。

53.根据权利要求1所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中两个R^{3a}变量存在并选自以下:

$-CF_2$和-OH;

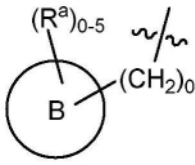
$-CF_2$和$-CH_3$;

-OH和$-CH_3$;以及

-OH和苯基。

54.根据权利要求1和6至53中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中变量R^{4a}、R^{4b}、R^{5a}和R^{5b}中的三个变量是氢并且剩余变量选自C1-C4烷基。

55.根据权利要求1和6至53中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中变量R^{4a}、R^{4b}、R^{5a}和R^{5b}中的三个变量是氢并且剩余变量是CH_3。

56.根据权利要求6至55中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^6选自C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)和

基团,其中:

R^6的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-OH、$-NH_2$、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环基、C_6芳基、-O-(C_6芳基)、5至10元杂环基和5至10元杂芳基,其中:

所述C_6芳基和-O-(C_6芳基)基团各自任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基;

环B选自C_3-C_{12}碳环基、3至12元杂环基、C_6和C_{10}芳基以及5至10元杂芳基,其中环B任选地被1个、2个、3个、4个或5个R^a基团取代;其中:

R^a在每次出现时独立地选自

卤素、

氰基、

C_1-C_8烷基、

C_1-C_6卤代烷基、

C_2-C_8烯基、

C_1-C_6卤代烯基、

C_1-C_6烷氧基、

C_1-C_6卤代烷氧基、

C_3-C_{12}碳环基、

C_6和C_{10}芳基、

3至12元杂环基、

5至10元杂芳基、

-C(=O)NR^hR^i、

-C(=O)OR^k、

-C(=O)(C_1-C_4亚烷基)OR^k、

-C(=O)R^k、

-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、

-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、

-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、

-C(=O)(C_1-C_4亚烷基)NR^hC(=O)R^k、

-C(=O)C(=O)R^k、

-NR^hR^i、

-NH$(CH_2)_qCHR^hR^i$、

-NH$(CH_2)_qNR^hR^i$、

-NR^hC(=O)R^k、

-NR^hC(=O)OR^k、

-NR^hC(=O)(C_1-C_4亚烷基)OR^k、

-NR^hC(=O)O(C_1-C_4亚烷基)R^k、

-NR^hC(=O)NR^iR^j、

-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、

-NR^hS(=O)$_pR^k$、

-NR^hC(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、

-NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k、

-NR^hC(=O)[O$(CH_2)_q$]$_r$OC(=O)$NR^hR^i(CH_2)_q$[O$(CH_2)_q$]$_r$(C_1-C_6烷基)(任选地被1至3个R^m基团取代)、

-NR^hC(=O)(C_1-C_6亚烷基)[O$(CH_2)_q$]$_r$OC(=O)$NR^hR^i(CH_2)_q$[O$(CH_2)_q$]$_r$(C_1-C_6烷基)(任选地被1至3个R^m基团取代)、

-OR^k、

-OC(=O)R^k、

-OC(=O)OR^k、

-OC(=O)NR^hR^i、-[O$(CH_2)_q$]$_r$O(C_1-C_6烷基)、

-S(=O)$_pR^k$和

-S(=O)$_pNR^hR^i$基团,

其中:

以下中的每一者中的所述C_1-C_4亚烷基任选地被1至3个独立地选自-OH的基团取代:-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)OR^k、-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)NR^hC(=O)R^k、-NR^hC(=O)O(C_1-C_4亚烷基)R^k、-NR^hC(=O)(C_1-C_4亚烷基)OR^k、-NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k和-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$,

R^a的所述C_1-C_8烷基、所述C_1-C_6卤代烷基、所述C_1-C_6烷氧基和所述C_2-C_8烯基各自任选地被1至3个独立地选自以下的基团取代:氰基、-C(=O)R^k、-C(=O)OR^k、-C(=O)NR^hR^i、-NR^hR^i、-NR^hC(=O)R^k、-NR^hC(=O)OR^k、-NR^hC(=O)NR^iR^j、-NR^hS(=O)$_pR^k$、-OR^k、-[O$(CH_2)_q$]$_r$OH、-OC(=O)R^k、-OC(=O)OR^k、-OC(=O)NR^hR^i、-SR^k、-S(=O)$_pR^k$、-S(=O)$_pNR^hR^i$、-[O$(CH_2)_q$]$_r$O(C_1-

C_4烷基)、-O-(C_6芳基或5至8元杂芳基)(任选地被1至3个R^m基团取代)、C_3-C_6碳环基(任选地被1至3个R^m基团取代)、C_6至C_{10}芳基(任选地被1至3个R^m基团取代)、4至10元杂环基(任选地被1至3个R^m基团取代)和5至10元杂芳基(任选地被1至3个R^m基团取代);

R^a的所述C_3-C_{12}碳环基、所述3至12元杂环基、所述C_6和C_{10}芳基和所述5至10元杂芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、C_1-C_6烷基(任选地被1至3个R^m基团取代)、-C(=O)R^k、C(=O)OR^k、-N$R^h$$R^i$、-O$R^k$、-S(=O)$_p$$R^k$、-S(=O)$_pNR^h$$R^i$和5至10元杂环基,其中:

R^h、R^i和R^j在每次出现时各自独立地选自氢、C_1-C_6烷基(任选地被1至4个R^m基团取代)、C_6-C_{10}芳基、C_3-C_8碳环基(任选地被1至3个R^m基团取代)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代),其中:

R^h、R^i和R^j中的任一者的所述C_1-C_6烷基任选地被1至3个独立地选自以下的基团取代:卤素、氰基、-OH、C_1-C_4烷氧基、-C(=O)NH(C_1-C_4烷基)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代);

R^k在每次出现时独立地选自氢、NH_2(任选地被1个或2个选自C_1-C_3烷基的基团取代)、C_1-C_6烷基、苄基、C_6芳基、C_3-C_6碳环基、5至10元杂环基和5至10元杂芳基,其中:

R^k中的任一者的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-NH_2、-OH、C_1-C_4烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、5至10元杂环基(任选地被1至3个-OH基团取代)、5至10元芳基(任选地被1至3个选自以下的基团取代:C_1-C_4烷基和卤素)和5至10元杂芳基(任选地被1至3个-OH基团取代);并且

R^k中的任一者的所述C_3-C_6碳环基、所述苄基和所述C_6芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、氧代、-OH、-C(=O)NH_2、-C(=O)N(CH_3)$_2$、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_6卤代烷基、C_1-C_6烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、C_6芳基(任选地被1至3个卤素基团取代)和5至10元杂芳基(任选地被1至3个卤素基团取代);并且

R^k中的任一者的所述5至10元杂芳基和所述5至10元杂环基各自任选地被1至3个独立地选自以下的基团取代:卤素、氧代、氰基、-C(=O)CH_3、-NH_2、-OH、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_4卤代烷基、5至10元杂环基和C_1-C_4烷氧基;

R^m在每次出现时独立地选自卤素、氰基、氧代、-NH_2、C_1-C_6烷基、C_1-C_6烷氧基、-C(=O)R^k、-S(=O)$_p$$R^k$、-O$R^k$和5至10元杂环基,其中:

R^m中的任一者的所述C_1-C_6烷基、所述C_1-C_6烷氧基和所述5至10元杂环基任选地被1至3个独立地选自以下的基团取代:卤素、氰基、-OH和C_1-C_4烷氧基;

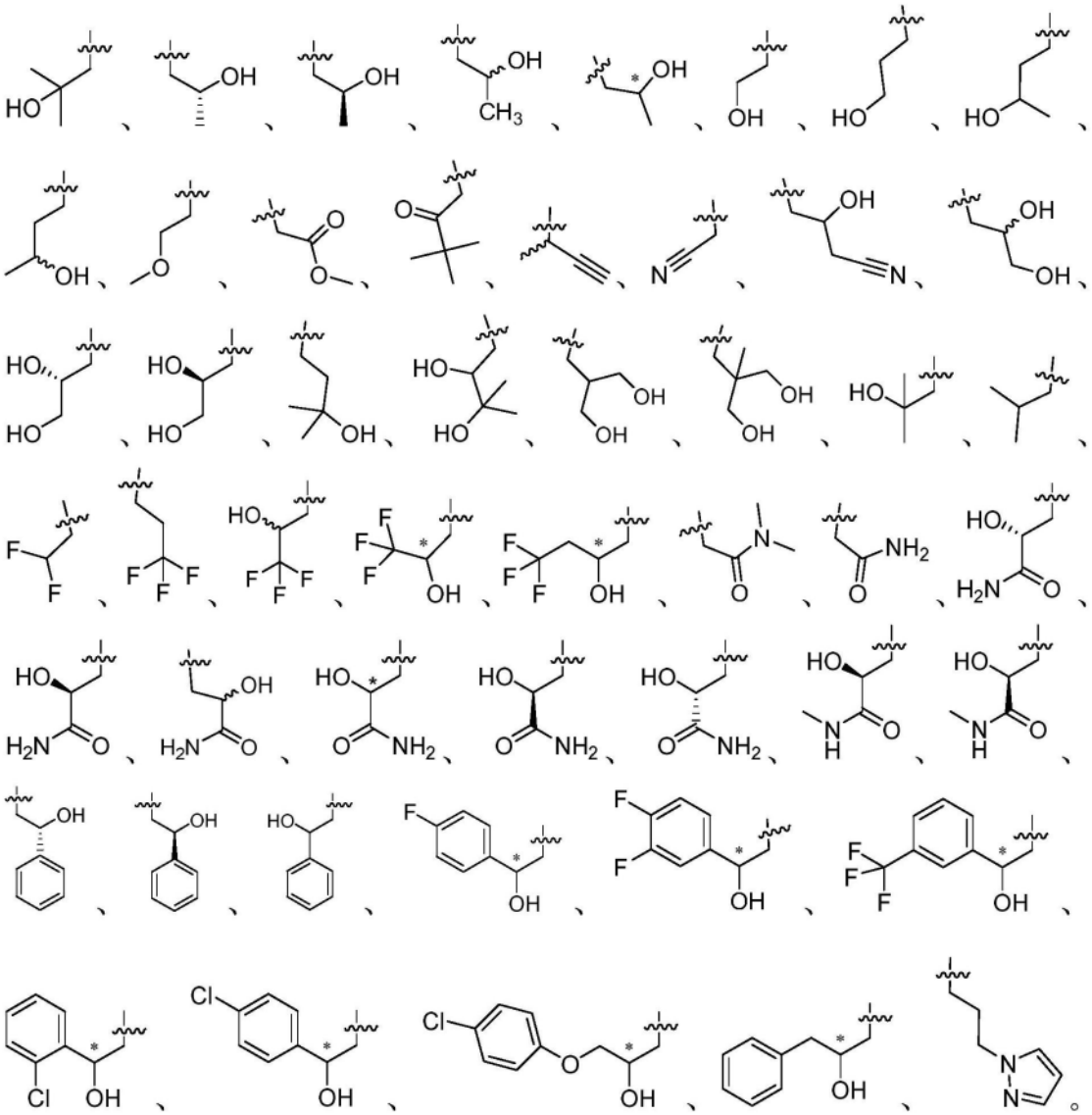
p在每次出现时是独立地选自1和2的整数;并且

q和r在每次出现时是独立地选自0、1、2和3的整数。

57.根据权利要求1至56中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^6选自任选地被1至5个独立地选自以下的基团取代的C_1-C_6烷基:卤素、氰基、-OH、-NH_2、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环基、C_6芳基(其任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、-O-(C_6芳基)(其任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、

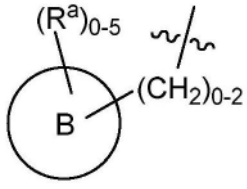
5至10元杂环基和5至10元杂芳基。

58.根据权利要求1至57中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^6是选自以下的经取代的C_1-C_6烷基:



58.根据权利要求1至56中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^6选自-C(=O)O(C_1-C_4烷基)。

59.根据权利要求1至56中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中R^6选自R^6选自如权利要求56所定义的



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60.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中环B选自C_3-C_{12}碳环基,所述C3-C12碳环基任选地被如权利要求56所定义的1个、2个、3个、4个或5个R^a基团取代。

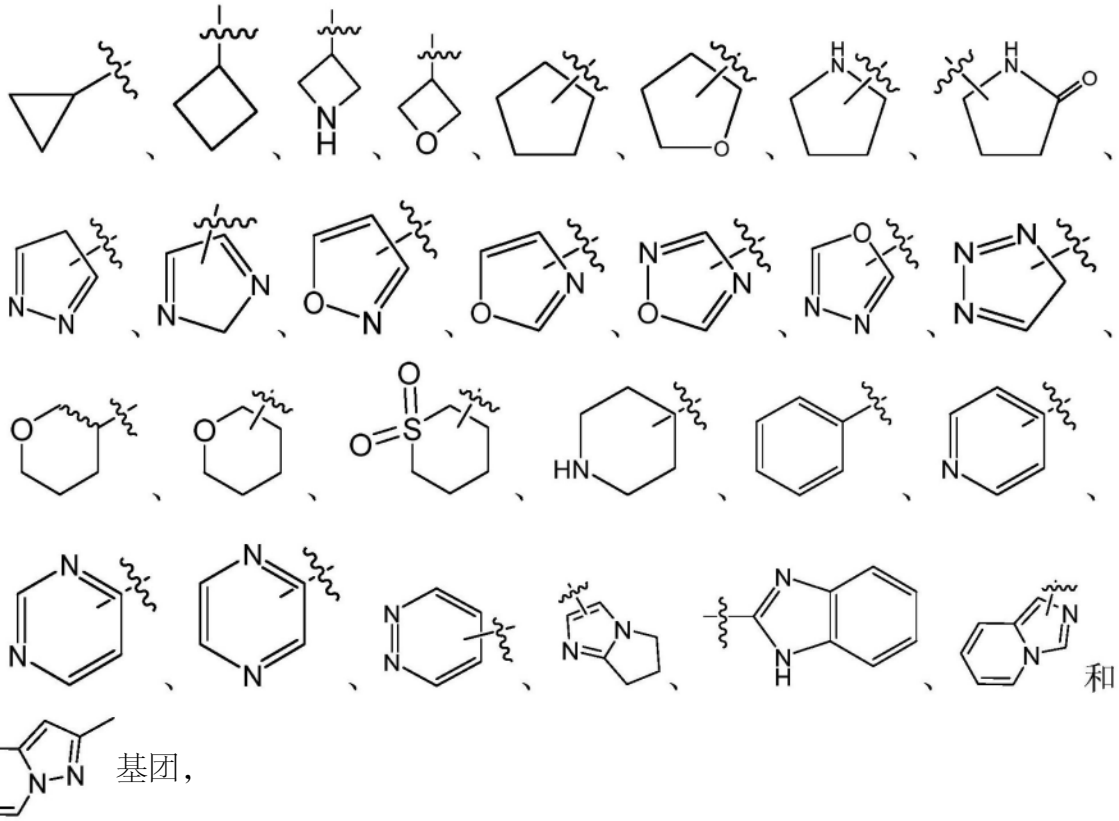
61.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其

中环B选自3至12元杂环基,所述3至12元杂环基任选地被如权利要求56所定义的1个、2个、3个、4个或5个R^a基团取代。

62.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中环B选自C_6和C_{10}芳基,所述C6和C10芳基任选地被如权利要求56所定义的1个、2个、3个、4个或5个R^a基团取代。

63.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中环B选自5至10元杂芳基,所述5至10元杂芳基任选地被如权利要求56所定义的1个、2个、3个、4个或5个R^a基团取代。

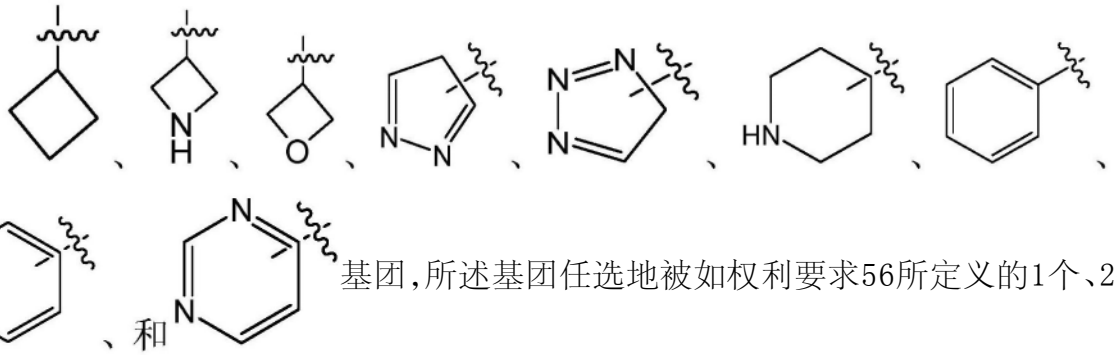
64.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中环B选自以下:



基团,

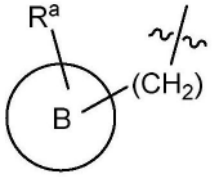
所述基团任选地被如权利要求56所定义的1个、2个、3个、4个或5个R^a基团取代。

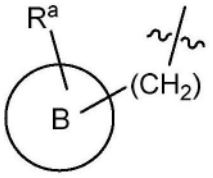
65.根据权利要求64所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐,其中环B选自以下:



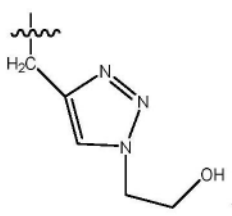
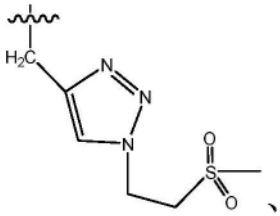
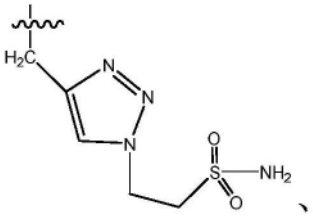
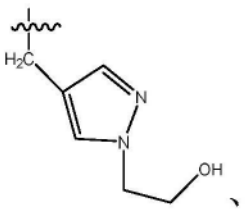
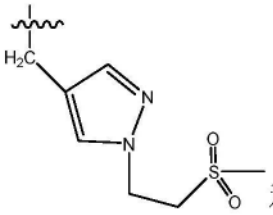
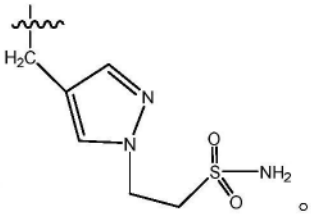
基团,所述基团任选地被如权利要求56所定义的1个、2个、3

个、4个或5个R^a基团取代。

66.根据权利要求56所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^6选自：其中环B是5元杂芳基，并且R^a如针对式I所定义。

67.根据权利要求56所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^6选自：其中环B是5元杂芳基，并且R^a是氧代或选自C_1-C_8烷基、C_3-C_{12}碳环基以及C_6和C_{10}芳基，其中的每一者可以任选地被1至3个选自以下的基团取代：卤素和C_1-C_8烷基(其中所述C_1-C_8烷基可以任选地被1至3个选自以下的基团取代：卤素、-OH、SO_2CH_3和SO_2NH_2)。

68.根据权利要求56所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^6选自：

、、、、和。

69.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^a选自C_1-C_4烷基、卤素、-OH和C_1-C_4烷氧基，其中R^a的所述C_1-C_4烷基任选地被1至3个极性基团，例如砜、磺胺和醇取代。

70.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^a是如针对式I所定义的任选取代的C_1-C_6烷基；在一些实施例中，R^a的所述C_1-C_6烷基任选地被1至3个选自以下的基团取代：-OH、-SO_2CH_3、C_1-C_3烷氧基、C(=O)$NHCH_3$、-$SO_2NHCH_2CH_2OH$、-SCF_3、-$SCH_2C(CH_2)_2OH$、-SO_2苯基、4至6元杂环(任选地被1至3个R^m基团取代)、4至6元杂芳基(任选地被1至3个R^m基团取代)、氰基、NHC(=O)-4至6元杂芳基。

71.根据权利要求59所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐，其中R^a选自任选取代的4至6元碳环、4至6元杂环和4至6元杂芳基。

72.一种选自以下的化合物：化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐，其中所述化合物不是化合物285、化合物489、化合物539、化合物691、化合物692、化合物741、化合物747、化合物749、化合物751、

化合物752、化合物753、化合物795、化合物814或化合物868。

73.一种药物组合物,其包括根据权利要求1至72中任一项所述的化合物。

74.一种治疗ApoL1介导的疾病的方法,所述方法包括施用根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物。

75.一种治疗局灶性节段性肾小球硬化(FSGS)的方法,所述方法包括施用根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物。

76.一种治疗非糖尿病性肾病(NDKD)的方法,所述方法包括施用根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物。

77.一种治疗ApoL1介导的癌症的方法,所述方法包括施用根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物。

78.根据权利要求77所述的治疗癌症的方法,其中所述癌症是胰腺癌。

79.根据权利要求74至78中任一项所述的治疗方法,其中待治疗的患者具有APOL1遗传变体。

80.根据权利要求79所述的治疗方法,其中所述遗传变体选自G1:S342G:I384M和G2:N388del:Y389del。

81.一种抑制APOL1活性的方法,所述方法包括使所述APOL1与至少一种根据权利要求1至72中任一项所述的化合物、互变异构体、氘化衍生物或药学上可接受的盐或根据权利要求73所述的药物组合物接触。

82.一种根据权利要求1至72中任一项所述的化合物在制造用于治疗ApoL1介导的疾病的药物中的用途。

83.一种根据权利要求1至72中任一项所述的化合物在制造用于治疗FSGS的药物中的用途。

84.一种根据权利要求1至72中任一项所述的化合物在制造用于治疗NDKD的药物中的用途。

85.一种根据权利要求1至72中任一项所述的化合物在制造用于治疗ApoL1介导的癌症的药物中的用途。

86.一种根据权利要求1至72中任一项所述的化合物在制造用于治疗ApoL1介导的胰腺癌的药物中的用途。

87.一种根据权利要求1至72中任一项所述的化合物在制造用于抑制有需要的患者的ApoL1活性的药物中的用途。

88.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物,其用于抑制有需要的患者的ApoL1活性。

89.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物,其用于治疗ApoL1介导的病症。

90.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物,其用于治疗FSGS。

91.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物,其用于治疗NDKD。

92.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物,

其用于治疗ApoL1介导的癌症。

93.根据权利要求1至72中任一项所述的化合物或根据权利要求73所述的药物组合物，其用于治疗ApoL1介导的胰腺癌。

作为APOL1抑制剂的2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]衍生物和其使用方法

[0001] 本申请要求于2022年2月8日提交的美国临时申请第63/307,875号的权益,所述美国临时申请的内容通过引用以其整体并入。

[0002] 本公开提供了可以抑制载脂蛋白L1(APOL1)的化合物和使用这些化合物治疗APOL1介导的疾病的方法,例如,胰腺癌、局灶性节段性肾小球硬化(FSGS)和/或非糖尿病性肾病(NDKD)。在一些实施例中,FSGS和/或NDKD与2种常见APOL1遗传变体(G1:S342G:I384M和G2:N388del:Y389del)中的至少一种相关。在一些实施例中,胰腺癌与APOL1的水平升高(例如,胰腺癌组织中APOL1的水平升高)相关。

[0003] FSGS是一种罕见的肾病,据估计全球发病率为0.2至1.1/100,000/年。FSGS是造成蛋白尿和肾脏功能进行性下降的足细胞(肾小球内脏上皮细胞)疾病。NDKD是涉及并非由糖尿病引起的足细胞或肾小球血管床的损害的肾病。NDKD是特征在于高血压和肾脏功能进行性下降的疾病。人类遗传学支持G1和G2 APOL1变体在诱导肾病中的因果作用。具有2个APOL1风险等位基因的个体患有终末期肾病(ESKD)的风险增加,包含原发性(特发性)FSGS、人免疫缺陷病毒(HIV)相关FSGS、NDKD、动脉肾硬化、狼疮性肾炎、微量白蛋白尿和慢性肾病。参见P.Dummer等人,《肾脏病研讨会(Semin Nephrol.)》35(3):222-236(2015)。

[0004] FSGS和NDKD可以根据潜在的病因学分为不同的亚组。FSGS的一个同质亚组的特征在于载脂蛋白L1(APOL1)基因中称为G1和G2的独立常见序列变体的存在,其被称为“APOL1风险等位基因”。G1编码一对相关的非同义氨基酸变化(S342G和I384M),G2编码蛋白质的C末端附近的2个氨基酸缺失(N388del:Y389del),而G0为祖先(低风险)等位基因。在具有APOL1遗传风险变体的患者中也发现了NDKD的独特表型。在APOL1介导的FSGS和NDKD中,与没有或仅有1个APOL1遗传风险变体的患者相比,具有两个风险等位基因的患者出现更高水平的蛋白尿和更快的肾脏功能丧失。或者,在AMKD中,具有一个风险等位基因的患者也可能出现较高水平的蛋白尿和加速的肾功能丧失。参见,G.Vajgel等人,《风湿病学杂志(J.Rheumatol.)》,2019年11月,jrheum.190684。

[0005] APOL1是仅在人、大猩猩和狒狒中表达的44kDa蛋白质。APOL1基因在人类的多个器官中表达,包括肝脏和肾脏。APOL1主要由肝脏产生,并且含有允许分泌到血流中的信号肽,在血流中其与高密度脂蛋白亚群结合循环。APOL1负责保护免受侵袭性寄生虫,布氏锥虫指名亚种(Trypanosoma brucei brucei/(T.b.brucei))的侵害。APOL1被布氏锥虫内吞并转运到溶酶体,在溶酶体中它插入溶酶体膜并形成导致寄生虫肿胀和死亡的孔。

[0006] 虽然所有3种APOL1变体(G0、G1和G2)都具有裂解布氏锥虫的能力,但APOL1 G1和G2变体提供了针对已进化出抑制APOL1 G0的血清抗性相关蛋白(SRA)的寄生虫物种的额外保护;APOL1 G1和G2变体提供了针对引起昏睡病的锥虫的另外的保护。G1和G2变体逃避SRA的抑制;G1提供了针对冈比亚锥虫(T.b.gambiense)的另外的保护,而G2提供了对罗得西亚锥虫(T.b.rhodesiense)的另外的保护。

[0007] 在肾脏中,APOL1在足细胞、内皮细胞(包含肾小球内皮细胞)和一些肾小管细胞中表达。APOL1 G1或G2(但非G0)在转基因小鼠中的足细胞特异性表达诱导结构和功能变化,

包含蛋白尿、肾脏功能降低、足细胞异常和肾小球硬化。与这些数据一致,APOL1的G1和G2变体在诱导FSGS和加速其在人中的进展中起因果作用。具有APOL1风险等位基因(即,对APOL1 G1或APOL1 G2等位基因是纯合的或化合物杂合的)的个体发生FSGS的风险增加,并且如果其发生FSGS,则其将面临肾脏功能迅速下降的风险。因此,抑制APOL1可能对携带APOL1风险等位基因的个体产生积极影响。

[0008] 尽管APOL1的正常血浆浓度相对较高并且在人中可能变化至少20倍,但循环的APOL1与肾病没有因果关系。然而,肾脏中的APOL1被认为是肾病发展的原因,包含FSGS和NDKD。在某些情况下,促炎细胞因子如干扰素或肿瘤坏死因子-α可使APOL1蛋白合成增加大约200倍。另外,若干研究已表明,APOL1蛋白可以在细胞膜中形成pH门控Na^+/K^+孔,导致细胞内K^+的净流出,最终导致局部和全身炎性应答的激活、细胞肿胀和死亡。

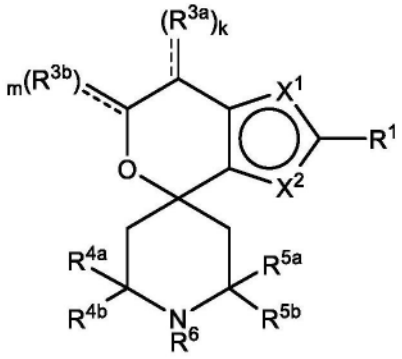
[0009] 与欧洲血统的人相比,近期撒哈拉以南非洲血统的人患ESKD的风险明显更高。在美国,ESKD导致女性寿命损失的年数几乎与乳腺癌一样多,并且男性寿命损失的年数比结肠直肠癌更多。

[0010] FSGS和NDKD是由足细胞损伤引起的,所述足细胞是肾小球滤过屏障的一部分,因此导致蛋白尿。蛋白尿患者发生终末期肾病(ESKD)和发生蛋白尿相关并发症如感染或血栓栓塞事件的风险更高。对于FSGS或NDKD,没有标准化治疗方案,也没有批准的药物。目前,FSGS和NDKD采用对症治疗(包含使用肾素血管紧张素系统阻断剂控制血压)进行管理,并且患有FSGS和重度蛋白尿的患者可能会接受大剂量的类固醇。目前对NDKD的治疗选项是基于血压控制和肾素血管紧张素系统的阻断。

[0011] 皮质类固醇单独使用或与其它免疫抑制剂组合使用可诱导少数患者病情缓解(例如,少数患者出现蛋白尿缓解),并伴有多种副作用。然而,即使在最初对皮质类固醇和/或免疫抑制剂治疗有应答的患者中,缓解也常常是不可逆转的。因此,患者,特别是具有2个APOL1风险等位基因的近代撒哈拉以南非洲血统的个体,经历了导致终末期肾病(ESRD)的快速疾病进展。因此,对于用于FSGS和NDKD的治疗的医疗需求没有得到满足。说明性地,鉴于APOL1在诱导和加速肾病的进展中起因果作用的证据,APOL1的抑制应当对患有APOL1介导的肾病的患者,特别是那些携带两个APOL1风险等位基因(即,对G1或G2等位基因是纯合的或化合物杂合的)的患者具有积极影响。

[0012] 另外地,APOL1是在多种癌症中异常表达的基因(Lin等人,《细胞死亡和疾病(Cell Death and Disease)》(2021),12:760)。最近,发现与邻近组织相比,APOL1在人胰腺癌组织中异常升高,并且与胰腺癌患者的不良预后相关。在体内和体外实验中,APOL1的敲低显著抑制癌细胞增殖并促进胰腺癌细胞的凋亡。

[0013] 本公开的一个方面提供了至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I化合物、式I的互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐,其可以用于治疗APOL1介导的疾病,如FSGS和NDKD。例如,在一些实施例中,所述至少一种化合物是由式I表示的化合物:

[0014] 

(I),

[0015] 其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐,其中:

[0016] X^1和X^2选自-S-、-S(=O)$_2$-、-S(=O)-和-CR^2,其中:

[0017] X^1和X^2之一选自-S-、-S(=O)$_2$-和-S(=O)-;

[0018] 当X^1是-S-、-S(=O)$_2$-或-S(=O)-时,则X^2是-CR^2;并且

[0019] 当X^2是-S-、-S(=O)$_2$-或-S(=O)-时,则X^1是-CR^2;

[0020] R^1选自氰基、卤素、C_1-C_4烷基、C_1-C_4卤代烷基和C_3-C_6环烷基,其中:

[0021] R^1的所述C_1-C_4烷基任选地被1至3个独立地选自以下的基团取代:-OH和C_1-C_4烷氧基;

[0022] R^2选自氢、C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)、-C(=O)NR^nR^o以及卤素基团,其中:

[0023] R^2的所述C_1-C_6烷基任选地被1至3个独立地选自以下的基团取代:-OH、卤素和C_1-C_4烷氧基;并且

[0024] R^n和R^o独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_6环烷基和-(C_1-C_4亚烷基)R^p基团,其中R^p选自C_3-C_6环烷基;或者

[0025] R^1和R^2与其所连接的碳原子一起形成C_6芳基;

[0026] 每个R^{3a}独立地选自-OH、-CN、-$NR^{a1}R^{a2}$、C_1-C_6烷基、C_1-C_6卤代烷基、C_1-C_6烷氧基、-OC(=O)(C_1-C_4烷基)、6至8元芳基、6至8元杂芳基和卤素基团,其中:

[0027] 每个R^{a1}和R^{a2}独立地选自氢、C_1-C_4烷基和-C(=O)(C_1-C_4烷基)基团;或者

[0028] 两个R^{3a}一起形成氧代基团;或者

[0029] 两个R^{3a}与其所连接的碳原子一起形成C_3-C_6环烷基;

[0030] 每个R^{3b}独立地选自C_1-C_4烷基,其中:

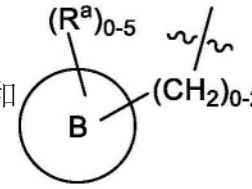
[0031] R^{3b}的所述C_1-C_4烷基任选地被1至3个独立地选自以下的基团取代:-OH、卤素和C_1-C_4烷氧基;或者

[0032] 一个R^{3a}和一个R^{3b}与其所连接的碳原子一起形成C_3-C_6环烷基;

[0033] k选自0、1和2;

[0034] m选自0、1和2;

[0035] R^{4a}、R^{4b}、R^{5a}和R^{5b}各自独立地选自氢和C_1-C_4烷基;

[0036] R^6选自C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)和 

基团,其中:

[0037] R^6的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-OH、-NH_2、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环基、C_6芳基、-O-(C_6芳基)、5至10元杂环基和5至10元杂芳基,其中:

[0038] 所述C_6芳基和-O-(C_6芳基)基团各自任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基;

[0039] 环B选自C_3-C_{12}碳环基、3至12元杂环基、C_6和C_{10}芳基以及5至10元杂芳基,其中环B任选地被1个、2个、3个、4个或5个R^a基团取代;其中:

[0040] R^a在每次出现时独立地选自卤素、氰基、C_1-C_8烷基、C_1-C_6卤代烷基、C_2-C_8烯基、C_1-C_6卤代烯基、C_1-C_6烷氧基、C_1-C_6卤代烷氧基、C_3-C_{12}碳环基、C_6和C_{10}芳基、3至12元杂环基、5至10元杂芳基、-C(=O)NR^hR^i、-C(=O)OR^k、-C(=O)(C_1-C_4亚烷基)OR^k、-C(=O)R^k、-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)NR^hC(=O)R^k、-C(=O)C(=O)R^k、-NR^hR^i、-NH$(CH_2)_qCHR^hR^i$、-NH$(CH_2)_qNR^hR^i$、-NR^hC(=O)R^k、-NR^hC(=O)OR^k、-NR^hC(=O)(C_1-C_4亚烷基)OR^k、-NR^hC(=O)O(C_1-C_4亚烷基)R^k、-NR^hC(=O)NR^iR^j、-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-NR^hS(=O)$_pR^k$、-NR^hC(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k、-NR^hC(=O)$[O(CH_2)_q]_rOC$(=O)$NR^hR^i(CH_2)_q[O(CH_2)_q]_r$($C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、-$NR^hC$(=O)($C_1$-$C_6$亚烷基)$[O(CH_2)_q]_rOC$(=O)-$NR^hR^i(CH_2)_q[O(CH_2)_q]_r$($C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、-$OR^k$、-OC(=O)$R^k$、-OC(=O)$OR^k$、-OC(=O)$NR^hR^i$、-$[O(CH_2)_q]_rO$($C_1$-$C_6$烷基)、-S(=O)$_pR^k$和-S(=O)$_pNR^hR^i$基团,其中:

[0041] 以下中的每一个中的所述C_1-C_4亚烷基任选地被1至3个-OH基团取代:-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)OR^k、-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)-NR^hC(=O)R^k、-NR^hC(=O)O(C_1-C_4亚烷基)R^k、-NR^hC(=O)(C_1-C_4亚烷基)-OR^k、NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k和-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$,

[0042] R^a的所述C_1-C_8烷基、所述C_1-C_6卤代烷基、所述C_1-C_6烷氧基和所述C_2-C_8烯基各自任选地被1至3个独立地选自以下的基团取代:氰基、-C(=O)R^k、-C(=O)OR^k、-C(=O)NR^hR^i、-NR^hR^i、-NR^hC(=O)R^k、-NR^hC(=O)OR^k、-NR^hC(=O)NR^iR^j、-NR^hS(=O)$_pR^k$、-OR^k、-$[O(CH_2)_q]_rOH$、-OC(=O)R^k、-OC(=O)OR^k、-OC(=O)NR^hR^i、-SR^k、-S(=O)$_pR^k$、-S(=O)$_pNR^hR^i$、-$[O(CH_2)_q]_rO$(C_1-C_4烷基)、-O-(C_6芳基或5至8元杂芳基)(任选地被1至3个R^m基团取代)、C_3-C_6碳环基(任选地被1至3个R^m基团取代)、C_6至C_{10}芳基(任选地被1至3个R^m基团取代)、4至10元杂环基(任选地被1至3个R^m基团取代)和5至10元杂芳基(任选地被1至3个R^m基团取代);并且

[0043] R^a的所述C_3-C_{12}碳环基、所述3至12元杂环基、所述C_6和C_{10}芳基和所述5至10元杂芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、C_1-C_6烷基(任选地被1至3个R^m基团取代)、-C(=O)R^k、C(=O)OR^k、-NR^hR^i、-OR^k、-S(=O)$_pR^k$、-S(=O)$_pNR^hR^i$和5至10元杂环基,其中:

[0044] R^h、R^i和R^j在每次出现时各自独立地选自氢、C_1-C_6烷基、C_6-C_{10}芳基、C_3-C_8碳环基(任选地被1至3个R^m基团取代)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代),其中:

[0045] R^h、R^i和R^j中的任一者的所述C_1-C_6烷基任选地被1至4个独立地选自以下的基团取代:卤素、氰基、-OH、C_1-C_4烷氧基、-C(=O)NH(C_1-C_4烷基)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代);

[0046] R^k在每次出现时独立地选自氢、NH_2(任选地被1个或2个选自C_1-C_3烷基的基团取代)、C_1-C_6烷基、苄基、C_6芳基、C_3-C_6碳环基、5至10元杂环基和5至10元杂芳基,其中:

[0047] R^k中的任一者的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-NH_2、-OH、C_1-C_4烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、4至10元杂环基(任选地被1至3个-OH基团取代)、5至10元芳基(任选地被1至3个选自以下的基团取代:C_1-C_4烷基和卤素)和5至10元杂芳基(任选地被1至3个-OH基团取代);并且

[0048] R^k中的任一者的所述C_3-C_6碳环基、所述苄基和所述C_6芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、氧代、-OH、-C(=O)NH_2、-C(=O)N(CH_3)$_2$、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_6卤代烷基、C_1-C_6烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、C_6芳基(任选地被1至3个卤素基团取代)和5至10元杂芳基(任选地被1至3个卤素基团取代);

[0049] R^k中的任一者的所述5至10元杂芳基和所述5至10元杂环基各自任选地被1至3个独立地选自以下的基团取代:卤素、氧代、氰基、-C(=O)CH_3、-NH_2、-OH、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_4卤代烷基、5至10元杂环基和C_1-C_4烷氧基;

[0050] R^m在每次出现时独立地选自卤素、氰基、氧代、-NH_2、C_1-C_6烷基、C_1-C_6烷氧基、-C(=O)R^k、-S(=O)$_p$$R^k$、-O$R^k$和5至10元杂环基,其中:

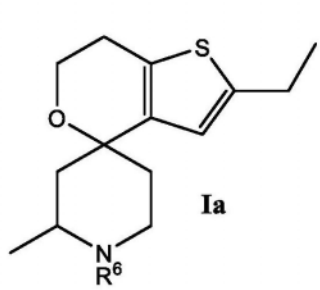
[0051] R^m中的任一者的所述C_1-C_6烷基、所述C_1-C_6烷氧基和所述5至10元杂环基任选地被1至3个独立地选自以下的基团取代:卤素、氰基、-OH和C_1-C_4烷氧基;

[0052] p在每次出现时是独立地选自1和2的整数;并且

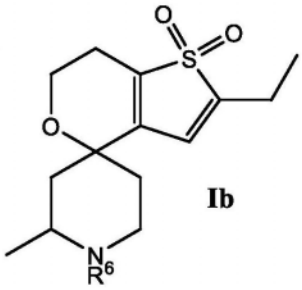
[0053] q和r在每次出现时是独立地选自0、1、2和3的整数。

[0054] 在一些实施例中,本公开的至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐是由以下结构式表示的化合物:Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im,如下:

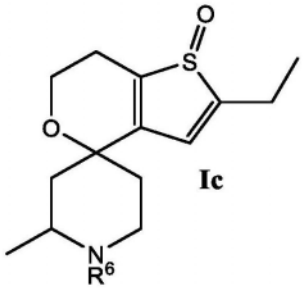
[0055]



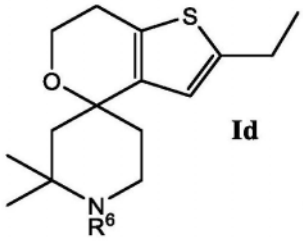
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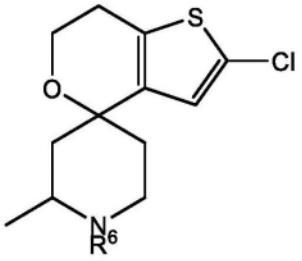
Ib

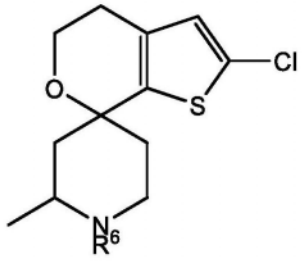


Ic

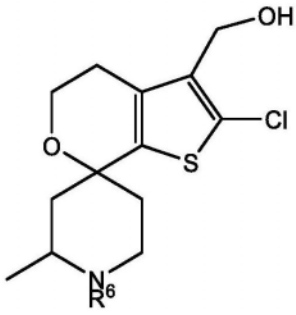


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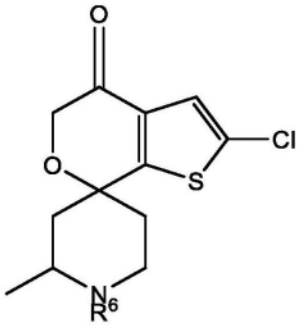




(Ie)、

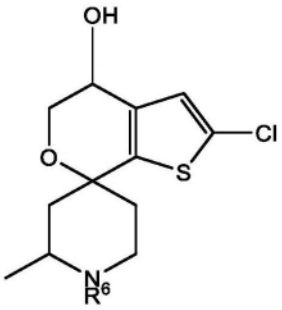


(If)、

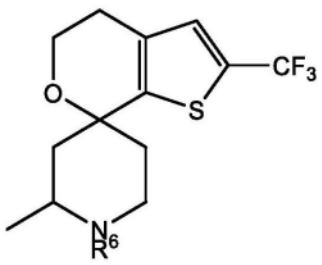


(Ig)、

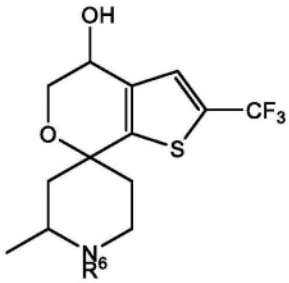
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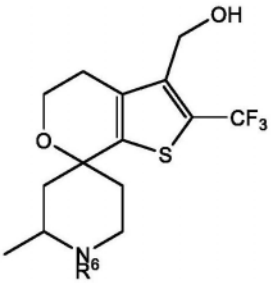
(Ii)、



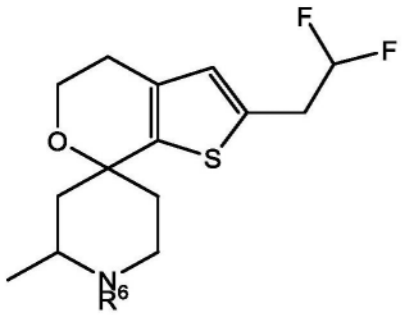
(Ij)、



(Ik)、

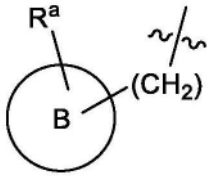


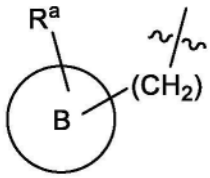
(II)、

[0056] 

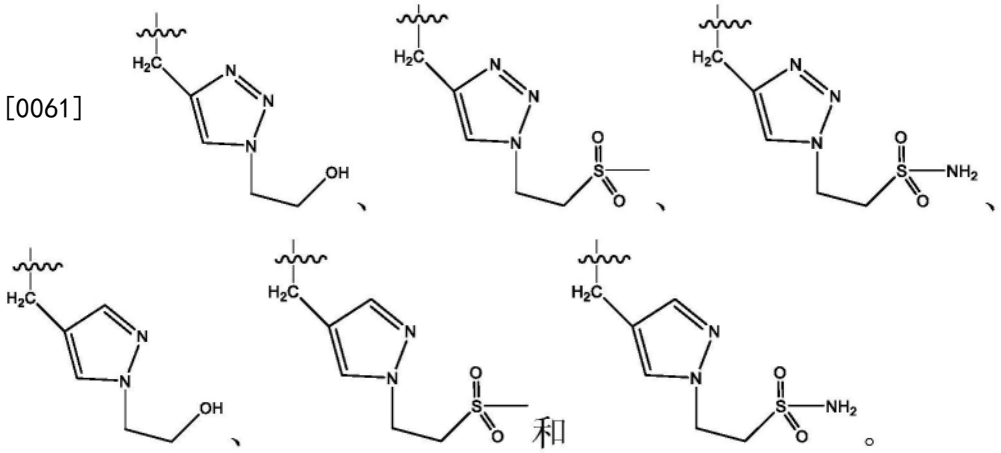
(Im)，

[0057] 其中R^6如上文针对式I所定义。

[0058] 在一些实施例中，在式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im中的化合物、互变异构体、氘化衍生物或药学上可接受的盐中，R^6选自以下： 其中环B是5元杂芳基，并且R^a如针对式I所定义。

[0059] 在一些实施例中，在式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im中的化合物、互变异构体、氘化衍生物或药学上可接受的盐中，R^6选自以下： 其中环B是5元杂芳基，并且R^a是氧代或选自C_1-C_8烷基、C_3-C_{12}碳环基以及C_6和C_{10}芳基，其中的每一个可以任选地被1至3个选自以下的基团取代：卤素和C_1-C_8烷基(其中所述C_1-C_8烷基可以任选地被1至3个选自以下的基团取代：卤素、-OH、SO_2CH_3和SO_2NH_2)。

[0060] 在一些实施例中，在式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im中的化合物、互变异构体、氘化衍生物或药学上可接受的盐中，R^6选自以下：

[0061] 

[0062] 在本公开的一个方面，式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物选自化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中，本公开提供了一种药物组合物，所述药物组合物

包括至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,所述药物组合物可以包括至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。这些组合物可以进一步包含至少一种另外的活性药物成分和/或至少一种载体。

[0063] 本公开的另一个方面提供了治疗APOL1介导的疾病的方法,所述方法包括向有需要的受试者施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il、和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或包括所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物。在一些实施例中,所述方法包括施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0064] 本公开的另一个方面提供了治疗APOL1介导的癌症(例如,胰腺癌)的方法,所述方法包括向有需要的受试者施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或包括所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物。在一些实施例中,所述方法包括施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0065] 本公开的另一个方面提供了治疗APOL1介导的肾病(例如,ESKD、FSGS和/或NDKD)的方法,所述方法包括向有需要的受试者施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il、和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或包括所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物。在一些实施例中,所述方法包括施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0066] 在一些实施例中,所述治疗方法包含向有需要的受试者施用至少一种另外的活性剂,或以与至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐相同的药物组合物的形式:式I、Ia、Ib、Ic、Id、Id、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或以单独的组合物的形式。在一些实施例中,所述方法包括在相同的药物组合物中或在单独的组合物中用至少一种另外的活性剂施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0067] 还提供了抑制APOL1的方法,介导的癌症(例如,胰腺癌)的方法,所述方法包括向

有需要的受试者施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或包括所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物。在一些实施例中,抑制APOL1的方法包括施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐或包括所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物。

[0068] 本文公开的所有化合物1至1183在一个或多个测定中都证明了抑制ApoL1的能力。在一些实施例中,化合物、互变异构体、氘化衍生物或药学上可接受的盐选自式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐,不包含化合物285、化合物489、化合物539、化合物691、化合物692、化合物741、化合物747、化合物749、化合物751、化合物752、化合物753、化合物795、化合物814和化合物868。

具体实施方式

[0069] 定义

[0070] 如本文所使用的,术语“APOL1”意指载脂蛋白L1蛋白,并且术语“APOL1”意指载脂蛋白L1基因。

[0071] 术语“APOL1介导的疾病”是指与异常APOL1(例如,某些APOL1遗传变体;APOL1的水平升高)相关的疾病或病状。在一些实施例中,APOL1介导的疾病是APOL1介导的肾病。在一些实施例中,APOL1介导的疾病与具有两个APOL1风险等位基因的患者(例如,对G1或G2等位基因是纯合的或化合物杂合的患者)相关。在一些实施例中,APOL1介导的疾病与具有一个APOL1风险等位基因的患者相关。

[0072] 术语“APOL1介导的肾病”是指损害肾脏功能并可归因于APOL1的疾病或病状。在一些实施例中,APOL1介导的肾病与具有两个APOL1风险等位基因的患者(例如,对G1或G2等位基因是纯合的或化合物杂合的患者)相关。在一些实施例中,APOL1介导的肾病选自ESKD、NDKD、FSGS、HIV相关肾病、动脉肾硬化(arterionephrosclerosis)、狼疮性肾炎、微量白蛋白尿和慢性肾病。在一些实施例中,APOL1介导的肾病是慢性肾病或蛋白尿。

[0073] 如本文所使用的,术语“FSGS”意指局灶性节段性肾小球硬化,其是造成蛋白尿和肾脏功能进行性下降的足细胞(肾小球内脏上皮细胞)的疾病并且与2种常见APOL1遗传变体(G1:S342G:I384M和G2:N388del:Y389del)相关。

[0074] 如本文所使用的,术语“NDKD”意指非糖尿病性肾病,其特征在于严重的高血压和肾脏功能进行性下降,并且与2种常见APOL1遗传变体(G1:S342G:I384M和G2:N388del:Y389del)相关。

[0075] 术语“ESKD”和“ESRD”在本文中可互换使用,指终末期肾病(end stage kidney disease)或终末期肾病(end stage renal disease)。ESKD/ESRD是肾病的最后阶段,即肾脏衰竭,并且意指肾脏已经停止足够好地工作,使得患者在不进行透析或肾脏移植的情况下无法存活。在一些实施例中,ESKD/ESRD与两个APOL1风险等位基因相关。

[0076] 在提及本公开的化合物时,术语“化合物”是指除了分子的组成原子之间可能存在同位素变化之外具有相同化学结构的分子的集合,除非另有说明为立体异构体的集合(例如,外消旋体的集合、顺式/反式立体异构体的集合、或(E)和(Z)立体异构体的集合)。因此,本领域技术人员应清楚,由含有指示的氘原子的特定化学结构表示的化合物还将含有较少量的在该结构中的一个或多个指定氘位置处具有氢原子的同位素体。本公开的化合物中此类同位素体的相对量将取决于许多因素,包含用于制备化合物的试剂的同位素纯度和用于制备化合物的各种合成步骤中同位素的并入效率。然而,如上文所阐述,全部此类同位素体的相对量将小于化合物的49.9%。在其它实施例中,此类同位素体的总体相对量将小于化合物的47.5%、小于40%、小于32.5%、小于25%、小于17.5%、小于10%、小于5%、小于3%、小于1%或小于0.5%。

[0077] 如本文所用,“任选地被取代的”与表述“取代或未取代的”可互换使用。通常,术语“取代的”,无论前面是否有术语“任选地”,都是指用特定取代基的基团置换给定结构中的氢基团。除非另外指示,否则“任选地被取代”的基团可在该基团的每个可取代位置处具有取代基,并且当任何给定结构中的多于一个位置可以被选自指定基团的多于一个取代基取代时,在每个位置处的取代基可以相同或不同。本公开所设想的取代基的组合为导致形成稳定或化学上可行的化合物的取代基的组合。

[0078] 术语“同位素体”是指其中化学结构与参考化合物仅在其同位素组成方面不同的物种。另外,除非另有说明,否则本文描述的结构还意在包括仅在一个或多个同位素富集原子的存在方面不同的化合物。例如,除了用氘或氚替代氢或用^{13}C或^{14}C替代碳之外,具有本发明结构的化合物都在本公开的范围内。

[0079] 除非另有说明,否则本文所描绘的结构还意指包含结构的所有异构体形式,例如,外消旋混合物、顺式/反式异构体、几何(或构象)异构体,如(Z)和(E)双键异构体,以及(Z)和(E)构象异构体。因此,本发明化合物的几何和构象混合物在本公开的范围内。除非另有说明,否则本公开的化合物的所有互变异构形式均在本公开的范围内。

[0080] 如本文所使用的术语“互变异构体”是指化合物的两种或多种异构体中的一种,其在平衡状态下共存,并容易通过原子(例如,氢原子)或分子内基团的迁移而互换。

[0081] 如本文所使用的“立体异构体”是指对映异构体和非对映异构体。

[0082] 如本文所使用的,“一或多种氘化衍生物”是指具有与参考化合物相同的化学结构但一个或多个氢原子被氘原子(“D”或“^{2}H”)置换的化合物。应认识到,取决于合成中使用的化学材料的来源,合成的化合物中会出现天然同位素丰度的一些变化。尽管存在这种变化,但与本文描述的氘化衍生物的稳定同位素取代程度相比,天然丰富的稳定氢同位素的浓度小而无关紧要。因此,除非另有说明,否则当提及本公开的化合物的“氘化衍生物”时,至少一个氢被远高于其天然同位素丰度(通常为约0.015%)的氘替代。在一些实施例中,本公开的氘化衍生物对于每个氘原子具有至少3500(在每个指定氘处52.5%氘掺入)、至少4500(67.5%氘掺入)、至少5000(75%氘掺入)、至少5500(82.5%氘掺入)、至少6000(90%氘掺入)、至少6333.3(95%氘掺入)、至少6466.7(97%氘掺入)或至少6600(99%氘掺入)的同位素富集因子。

[0083] 如本文所使用的,术语“同位素富集因子”意指指定同位素的同位素丰度与天然丰度之间的比率。

[0084] 如本文所使用的“烷基”或“脂肪族”意指完全饱和的直链(即,线性或非支链)或支链、经取代或未经取代的烃链。除非另有规定,否则烷基含有1至20个烷基碳原子。在一些实施例中,烷基含有1个至10个脂肪族碳原子。在一些实施例中,烷基含有1个至8个脂肪族碳原子。在一些实施例中,烷基含有1个至6个烷基碳原子。在一些实施例中,烷基含有1至4个烷基碳原子,在其它实施例中,烷基含有1至3个烷基碳原子,并且在又其它实施例中,烷基含有1或2个烷基碳原子。在一些实施例中,烷基是线性的或直链的或非支链的。在一些实施例中,烷基是支链的。

[0085] 如本文所使用的术语“碳环基”、“环烷基”和“环状烷基”是指完全饱和的单环C_{3-8}烃或螺环、稠合或桥接的双环或三环C_{8-14}烃,其中所述双环系统中的任何单独的环具有3至7个成员。在一些实施例中,环烷基是C_3至C_{12}环烷基。在一些实施例中,环烷基是C_3至C_8环烷基。在一些实施例中,环烷基是C_3至C_6环烷基。单环环烷基的非限制性实例包含环丙基、环丁基、环戊烷基和环已基。

[0086] 如本文所使用的术语“碳环基”或“脂环族”涵盖术语“环烷基”或“环状烷基”,并指完全饱和或部分饱和的单环C_{3-8}烃或螺环、稠合或桥接的双环或三环C_{8-14}烃,因为其含有一个或多个不饱和单元但不是芳香族的,其中所述双环系统中的任何单独的环具有3至7个成员。双环碳环基包含与苯基稠合的单环碳环的组合。在一些实施例中,碳环基是C_3至C_{12}碳环基。在一些实施例中,碳环基是C_3至C_{10}碳环基。在一些实施例中,碳环基是C_3至C_8碳环基。

[0087] 如本文所使用的术语“杂烷基”或“杂脂肪族”意指如上定义的烷基或脂肪族基团,其中一个或两个碳原子独立地被氧、硫、氮、磷或硅中的一个或多个置换。

[0088] 如本文所使用的术语“烯基”意指含有一个或多个双键的直链(即,线性或非支链)或支链烃链。在一些实施例中,烯基是直链的。在一些实施例中,烯基是支链的。

[0089] 如本文所使用的“杂环(heterocycle)”、“杂环基”和“杂环(heterocyclic)”是指非芳香族(即,完全饱和或部分饱和,因为其含有一个或多个不饱和单元但不是芳香族的)、单环或螺环、稠合的或桥接的双环或三环系统,其中一个或多个环成员是独立地选择的杂原子。双环杂环基包含以下单环的组合:与单环杂环基稠合的单环杂芳基;与另一个单环杂环基稠合的单环杂环基;与苯基稠合的单环杂环基;与单环碳环基/环烷基稠合的单环杂环基;以及与单环碳环基/环烷基稠合的单环杂芳基。

[0090] 在一些实施例中,杂环包括被一个或多个氧代基团(例如,C=0基团、S=0基团或SO_2基团)取代的环原子。

[0091] 在一些实施例中,“杂环”、“杂环基”、“杂环脂族”或“杂环的”基团具有3至14个环成员,其中一个或多个环成员是独立地选自氧、硫、氮、硅和磷的杂原子。在一些实施例中,双环或三环系统中的每个环含有3至7个环成员。在一些实施例中,杂环具有至少一个不饱和碳-碳键。在一些实施例中,杂环具有至少一个不饱和碳-氮键。在一些实施例中,杂环具有一个独立地选自以下的杂原子:氧、硫、氮、硅和磷,任何碱性氮的季铵化形式;或杂环的可取代氮,例如N(如在3,4-二氢-2H-吡咯基中)、NH(如在吡咯烷基中)或NR^+(如在N取代的吡咯烷基中)。在一些实施例中,杂环具有一个为氮原子的杂原子。在一些实施例中,杂环具有一个为氧原子的杂原子。在一些实施例中,杂环具有两个各自独立地选自氮和氧的杂原子。在一些实施例中,杂环具有三个各自独立地选自氮和氧的杂原子。在一些实施例中,杂环基是3至12元杂环基。在一些实施例中,杂环基是3至10元杂环基。在一些实施例中,杂环

基是3至8元杂环基。在一些实施例中,杂环基是5至10元杂环基。在一些实施例中,杂环基是5至8元杂环基。在一些实施例中,杂环基是5或6元杂环基。单环杂环基的非限制性实例包含哌啶基、哌嗪基、四氢吡喃基、氮杂环丁烷基、四氢噻吩基1,1-二氧化物等。

[0092] 如本文所使用的术语“不饱和”意指部分具有一个或多个不饱和单元或不饱和程度。不饱和是其中化合物中并非所有可用的价键都被取代基占完并因此化合物含有双键或三键的状态。

[0093] 如本文所使用的术语“烷氧基”或“硫代烷基”是指如前所定义的烷基,其中烷基的一个碳分别被氧(“烷氧基”)或硫(“硫代烷基”)原子替代,前提条件是氧和硫原子连接在两个碳原子之间。“环状烷氧基”是指含有至少一个烷氧基但不为芳香族的单环、螺环、双环、桥接双环、三环或桥接三环烃。环状烷氧基的非限制性实例包含四氢吡喃基、四氢呋喃基、氧杂环丁烷基、8-氧杂双环[3.2.1]辛基和氧杂环庚烷基。

[0094] 如本文所使用的术语“卤代烷基”、“卤代烯基”和“卤代烷氧基”分别意指被一个或多个卤素原子取代的直链或支链烷基、烯基或烷氧基。卤代烷基的非限制性实例包含-CHF_2、-CH_2F、-CF_3、-CF_2-和全卤代烷基,如-CF_2CF_3。卤代烷氧基的非限制性实例包含-$OCHF_2$、-OCH_2F、-OCF_3和-OCF_2。

[0095] 术语“卤素”包含F、Cl、Br和I,即,分别为氟、氯、溴和碘。

[0096] 术语“氨基烷基”意指被氨基基团所取代或含有氨基基团的烷基基团。

[0097] 如本文所使用的,“氨基”是指为伯胺、仲胺或叔胺的基团。

[0098] 如本文所使用的,“羰”基是指C=O。

[0099] 如本文所使用的,“氰基”或“腈”基是指-C≡N。

[0100] 如本文所使用的,“羟”基是指-OH。

[0101] 如本文所使用的,“硫醇”基是指-SH。

[0102] 如本文所使用的,“tert”和“t-”各自是指叔。

[0103] 如本文所使用的,“芳香族基团”或“芳香族环”是指含有共轭平面环系统的化学基团,该环系统具有由[4n+2]p轨道电子组成的离域的π电子轨道,其中n为范围为0至6的整数。芳香族基团的非限制性实例包含芳基和杂芳基。

[0104] 单独使用或作为较大部分(如在“芳基烷基”、“芳基烷氧基”或“芳氧基烷基”中)的一部分使用的术语“芳基”是指具有总共五至十四个环成员的单环或螺环、稠合或桥接双环或三环系统,其中所述系统中的每个环是仅含碳原子的芳香族环,并且其中双环或三环系统中的每个环含有3至7个环成员。芳基的非限制性实例包含苯基(C_6)和萘基(C_{10})环。

[0105] 单独使用或作为较大部分(如在“杂芳基烷基”或“杂芳基烷氧基”中)的一部分使用的术语“杂芳基”是指具有总共五至十四个环成员的单环或螺环、稠合或桥接双环和三环系统,其中所述系统中的至少一个环是芳香族的,其中所述系统中的至少一个环含有一个或多个杂原子,并且其中双环或三环系统中的每个环含有3至7个环成员。双环杂芳基包含下列单环的组合:与另一个单环杂芳基稠合的单环杂芳基;和与苯基稠合的单环杂芳基。在一些实施例中,杂芳基具有选自氮、氧和硫的一个或多个杂原子。在一些实施例中,杂芳基具有一个杂原子。在一些实施例中,杂芳基具有两个杂原子。在一些实施例中,杂芳基为具有五个环成员的单环系统。在一些实施例中,杂芳基为具有六个环成员的单环系统。在一些实施例中,杂芳基是3至12元杂芳基。在一些实施例中,杂芳基是3至10元杂芳基。在一些实

施例中,杂芳基是3至8元杂芳基。在一些实施例中,杂芳基是5至10元杂芳基。在一些实施例中,杂芳基是5至8元杂芳基。在一些实施例中,杂芳基是5或6元杂芳基。单环杂芳基的非限制性实例是吡啶基、嘧啶基、噻吩基、噻唑基、异噁唑基等。

[0106] 在一些实施例中,杂芳基包括被一个或多个氧代基团(例如,C=O基团、S=O基团或SO_2基团)取代的环原子。示意性地,杂芳基的非限制性实例为苯并[d]噁唑-2(3H)-酮基团。

[0107] 含氮基团如胺基团的有用保护基团的非限制性实例包含例如氨基甲酸叔丁酯(Boc)、苄基(Bn)、四氢吡喃基(THP)、9-芴基甲基氨基甲酸酯(Fmoc)、氨基甲酸苄酯(Cbz)、乙酰胺、三氟乙酰胺、三苯甲胺、亚苄基胺和对甲苯磺酰胺。添加(通常称为"保护"的方法)和去除(通常称为"脱保护"的方法)此类胺保护基团的方法在本领域是众所周知的并且在例如P.J.Kocienski,《保护基团(Protecting Groups)》,泰米出版社(Thieme),1994中可得到,所述文献通过引用以其整体并入本文,并且在Greene and Wuts,《有机合成中的保护性基团(Protective Groups in Organic Synthesis)》,第3版(纽约州的约翰威利父子出版社(John Wiley&Sons,New York),1999)和第4版(新泽西州的约翰威利父子出版社(John Wiley&Sons,New Jersey),2014)。

[0108] 可以用于本公开的合适的溶剂的非限制性实例包含但不限于:水、甲醇(MeOH)、乙醇(EtOH)、二氯甲烷或"亚甲基氯"(CH_2Cl_2)、甲苯、乙腈(MeCN)、二甲基甲酰胺(DMF)、二甲基亚砜(DMSO)、乙酸甲酯(MeOAc)、乙酸乙酯(EtOAc)、庚烷、乙酸异丙酯(IPAc)、乙酸叔丁酯(t-BuOAc)、异丙醇(IPA)、四氢呋喃(THF)、2-甲基四氢呋喃(2-Me THF)、甲基乙基酮(MEK)、叔丁醇、二乙醚(Et_2O)、甲基叔丁基醚(MTBE)、1,4-二噁烷和N-甲基吡咯烷酮(NMP)。

[0109] 可以用于本公开的合适的碱的非限制性实例包含但不限于:1,8-二氮杂二环[5.4.0]十一碳-7-烯(DBU)、叔丁醇钾(KOtBu)、碳酸钾(K_2CO_3)、N-甲基吗啉(NMM)、三乙胺(Et_3N;TEA)、二异丙基乙胺(i-Pr_2EtN;DIPEA)、吡啶、氢氧化钾(KOH)、氢氧化钠(NaOH)、氢氧化锂(LiOH)和甲醇钠(NaOMe;$NaOCH_3$)。

[0110] 本公开包含所公开的化合物的药学上可接受的盐。化合物的盐在酸与化合物的碱性基团如氨基官能团或者碱与化合物的酸性基团如羧基官能团之间形成。

[0111] 如本文所使用的,术语"药学上可接受的"是指在合理的医学判断范围内适合与人类和其他哺乳动物的组织接触而没有过度的毒性、刺激、过敏反应等并且与合理的收益/风险比相称的组分。"药学上可接受的盐"意指在施用于接受者时能够直接或间接提供本公开的化合物的任何无毒盐。合适的药学上可接受的盐是例如S.M.Berge等人《药物科学杂志(J.Pharmaceutical Sciences)》,1977,66,1至19中所公开的那些盐。

[0112] 通常用于形成药学上可接受的盐的酸包含无机酸,如二硫化氢、盐酸、氢溴酸、氢碘酸、硫酸和磷酸,以及有机酸,如对甲苯磺酸、水杨酸、酒石酸、二酒石酸、抗坏血酸、马来酸、苯磺酸(besylic acid)、富马酸、葡糖酸、葡糖醛酸、甲酸、谷氨酸、甲磺酸、乙磺酸、苯磺酸、乳酸、草酸、对溴苯磺酸、碳酸、琥珀酸、柠檬酸、苯甲酸和乙酸,以及相关的无机酸和有机酸。因此,此类药学上可接受的盐包含硫酸盐、焦磷酸盐、硫酸氢盐、亚硫酸盐、亚硫酸氢盐、磷酸盐、磷酸单氢、磷酸二氢、偏磷酸盐、焦磷酸盐、氯化物、溴化物、碘化物、乙酸盐、丙酸盐、癸酸盐(decanoate)、辛酸盐、丙烯酸盐、甲酸盐、异丁酸盐、癸酸盐(caprate)、庚酸盐、丙酸盐、草酸盐、丙二酸、琥珀酸盐、辛二酸盐、癸二酸盐、富马酸盐、马来酸盐、丁-1,4-

二酸盐、己-1,6-二酸盐、苯甲酸盐、氯苯甲酸盐、苯甲酸盐、二硝基苯甲酸盐、羟基苯甲酸盐、甲氧基苯甲酸盐、邻苯二甲酸盐、对苯二甲酸盐、磺酸盐、二甲苯磺酸盐、苯乙酸盐、苯丙酸盐、苯丁酸盐、柠檬酸盐、乳酸盐、β-羟基丁酸盐、乙醇酸盐、马来酸盐、酒石酸盐、甲磺酸盐、丙烷磺酸盐、萘-1-磺酸盐、萘-2-磺酸盐、扁桃酸盐和其它盐。在一些实施例中,药学上可接受的酸加成盐包含用如盐酸和氢溴酸等矿物酸形成的酸加成盐,以及用如马来酸等有机酸形成的酸加成盐。

[0113] 衍生自适当碱的药学上可接受的盐包含碱金属、碱土金属、铵和$N^+(C_{1-4}$烷基$)_4$盐。本公开还设想本文公开的化合物的任何碱性含氮基团的季铵化。碱金属和碱土金属盐的合适的非限制性实例包含钠、锂、钾、钙和镁。药学上可接受的盐的另外的非限制性实例包含铵、季铵以及使用抗衡离子,如卤化物、氢氧化物、羧酸盐、硫酸盐、磷酸盐、硝酸盐、较低烷基磺酸盐和芳基磺酸盐形成的胺阳离子。药学上可接受的盐的其它合适的非限制性实例包含苯磺酸盐和葡糖胺盐。

[0114] 术语“患者”和“受试者”在本文可互换使用并且指包含人的动物。

[0115] 术语“有效剂量”和“有效量”在本文中可互换使用并且是指产生其施用的所期望效果(例如,改善FSGS和/或NDKD的症状、减轻FSGS和/NDKD的严重程度或FSGS和/或NDKD的症状和/或减少FSGS和/或NDKD的进展或FSGS和/或NDKD的症状)的化合物的量。有效剂量的确切量将取决于治疗目的,并且将由本领域技术人员使用已知技术确定(参见例如,Lloyd(1999)《药物复合的艺术、科学和技术(The Art,Science and Technology of Pharmaceutical Compounding)》)。

[0116] 如本文所使用的,术语“治疗”和其同源词是指减缓或停止疾病进展。如本文所使用的,“治疗”和其同源词包含但不限于以下:完全或部分缓解、降低肾脏衰竭(例如,ESRD)以及疾病相关并发症(例如,水肿、易感染或血栓栓塞事件)的风险。可以根据本领域已知或随后开发的方法和技术容易地评估这些症状中任一者的改善或其严重程度的减轻。

[0117] 当与组合物或剂型的成分的剂量、量或重量百分比结合使用时,术语“约”和“大约”包含本领域的普通技术人员认为提供与从指定剂量、量或重量百分比获得的药理学作用等效的药理学作用的指定剂量、量或重量百分比的值、或所述剂量、量或重量百分比的范围。

[0118] 可以每天施用一次、每天使用两次或每天施用三次至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐例如用于治疗AMKD(包含FSGS和/或NDKD):式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,可以每天施用一次、每天使用两次或每天施用三次至少一种选自以下的化合物例如用于治疗AMKD(包含FSGS和/或NDKD):化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用一次至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用一次至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用两次至少一种选自以下的化合物、互

变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用两次至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用三次至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用三次至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0119] 在一些实施例中,每天施用一次、每天施用两次或每天施用三次2mg至1500mg或5mg至1000mg的至少一种选自以下的化合物:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,每天施用一次、每天施用两次或每天施用三次2mg至1500mg或5mg至1000mg的至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

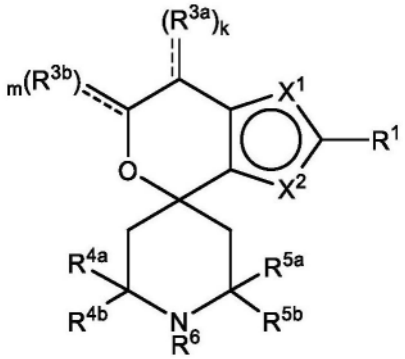
[0120] 本领域的普通技术人员将认识到,当公开化合物的量时,化合物的药学上可接受的盐形式的相关量是等效于化合物的游离碱的浓度的量。本文公开的化合物、药学上可接受的盐、溶剂化物和氘化衍生物的量基于参考化合物的游离碱形式。例如,“1000mg的选自式I化合物和其药学上可接受的盐的至少一种化合物或药学上可接受的盐”包含1000mg的式I化合物和浓度相当于1000mg式I化合物的式I化合物的药学上可接受的盐。

[0121] 如本文所使用的,术语“环境条件”意指室温、露天条件和不受控制的湿度条件。

[0122] 化合物和组合物

[0123] 在一些实施例中,至少一种选自以下的化合物可以用于治疗AMKD(包含FSGS和NDKD):式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物可以选自化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,包括至少一种选自以下的化合物的药物组合物可以用于治疗AMKD(包含FSGS和NDKD):式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,所述药物组合物包括至少一种选自以下的化合物:化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0124] 在式I的一些实施例中:

[0125] 

[0126] 变量X^1选自S、S(=O)和S(=O)$_2$,并且变量X^2是-CR^2。在式I的一些实施例中,变量X^1是S,并且变量X^2是-CR^2。在式I的一些实施例中,变量X^2选自S、S(=O)和S(=O)$_2$,并且变量X^1是-CR^2。在式I的一些实施例中,变量X^2是S,并且变量X^1是-CR^2。

[0127] 在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2选自氢、C_1-C_6烷基(任选地被1至3个独立地选自以下的基团取代:-OH、卤素和C_1-C_4烷氧基)、-C(=O)O(C_1-C_4烷基)、-C(=O)NR^nR^o和卤素基团,其中R^n和R^o独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_6环烷基和-(C_1-C_4亚烷基)R^p基团,并且其中R^p选自C_3-C_6环烷基。

[0128] 在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2选自氢、卤素、-CH_2OH、-CH_2(OH)CH_3和-C(=O)NR^nR^o。在一些实施例中,R^2是氢。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是卤素。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是Br。在一些实施例中,R^2是Cl。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是CH_3。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-CH_2OH。在一些实施例中,R^2是CH_2(OH)CH_3。在一些实施例中,R^2是-C(=O)OCH_3。

[0129] 在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-C(=O)NR^nR^o和卤素基团,其中R^n和R^o独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_6环烷基和-(C_1-C_4亚烷基)R^p基团,并且其中R^p选自C_3-C_6环烷基。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-C(=O)NR^nR^o(其中R^n是氢并且R^o是CH_3)。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-C(=O)NR^nR^o(其中R^n是氢并且R^o是环丙基取代的CH_3)。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-C(=O)NH $CH_2CH_2CH_3$(即,其中R^n是氢并且R^o是-$CH_2CH_2CH_3$)。在一些实施例中(包含上述定义变量X^1和X^2的实施例),R^2是-C(=O)NH CH_2CF_2(即,其中R^n是氢并且R^o是-CH_2CF_2)。

[0130] 在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1选自氰基、卤素、-C_1-C_4烷基、-C_1-C_4卤代烷基和-C_3-C_6环烷基,其中:R^1的所述-C_1-C_4烷基任选地被1至3个独立地选自以下的基团取代:-OH和-C_1-C_4烷氧基。

[0131] 在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1选自-CN、-Br、-Cl、-C_1-C_4烷基、-CH_2OH、-CH_2CF_2、-CF_2CF_2、-CF_2、-CF_3、-CH_2OCH_3、-$CH_2OCH_2CH_3$、环丙基和环丁基。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1选自-CH_3、-CH_2OH、-CH_2CH_3、-$CH_2CH_2CH_3$、叔丁基、-Cl、-CH_2-CF_2、-CF_2CF_3和-CF_3。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是氘化的,例如-$CDOCH_2CH_3$。

[0132] 在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是CF_3。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是Cl。在式I(包含上述定

义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是-CH_2OH。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是-CH_2CF_3。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是-CF_2CF_3。在式I(包含上述定义变量X^1、X^2和R^2的实施例)的一些实施例中,变量R^1是-$CH_2(OH)CH_3$。

[0133] 在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1和R^2与其所连接的碳原子一起形成C_6芳基。

[0134] 在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-Cl并且变量R^2是-CH_2OH。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是Cl并且变量R^2是-CH_3。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是Cl并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-Cl并且变量R^2是-Cl。

[0135] 在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_3并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_2CF_3并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CH_2CF_3并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_2并且变量R^2是-CH_2OH。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_3并且变量R^2是-CH_2OH。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_3并且变量R^2是-$CH_2(OH)CH_3$。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是-CF_3并且变量R^2是-Cl。

[0136] 在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是CH_3并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是CH_2CH_3并且变量R^2是氢。在式I(包含上述定义变量X^1和X^2的实施例)的一些实施例中,变量R^1是CH_2OH并且变量R^2是氢。

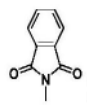
[0137] 在式I的一些实施例中,变量m和k两者都是零,导致变量R^{3a}和R^{3b}不存在。在式I的一些实施例中,变量m是零,导致变量R^{3b}不存在,并且变量k是一,导致存在一个R^{3a}变量。在式I的一些实施例中,变量m是零,导致变量R^{3b}不存在,并且变量k是二,导致两个R^{3a}变量存在于式I中。

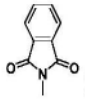
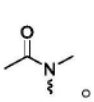
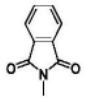
[0138] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,每个R^{3a}独立地选自-OH、-CN、-$NR^{a1}R^{a2}$、C_1-C_6烷基、C_1-C_6卤代烷基、C_1-C_6烷氧基、-OC(=O)(C_1-C_4烷基)、6至8元芳基、6至8元杂芳基和卤素基团,其中:

[0139] 每个R^{a1}和R^{a2}独立地选自氢、C_1-C_4烷基和-C(=O)(C_1-C_4烷基)基团;或者

[0140] 两个R^{3a}一起形成氧代基团;或者

[0141] 两个R^{3a}与其所连接的碳原子一起形成C_3-C_6环烷基。

[0142] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,每个R^{3a}选自-OH、F、F_2、CF_2、-OCH_3、-OCH_2CH_3、-$OCH_2(CH_3)_2$、-OC(=O)CH_3、NH_2、NHC(=O)CH_3、CN、和。在式I的一些实施例中,变量k是一,并且变量R^{3a}选自-OH、F、F_2、CF_2、-OCH_3、-

OCH_2CH_3、-O-$CH_2(CH_3)_2$、-O-C(=O)CH_3、NH_2、NH-C(=O)CH_3、CN、和。在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量m是零,变量k是一,并且变量R^{3a}选自-OH、F、F_2、CF_2、-OCH_3、-OCH_2CH_3、-O-$CH_2(CH_3)_2$、-O-C(=O)CH_3、NH_2、NH-C(=O)CH_3、CN、和。在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量m是零,变量k是一,并且变量R^{3a}是-OH。在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量m是零,变量k是一,并且变量R^{3a}选自-OCH_3和-OCH_2CH_3。

[0143] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量k是二,并且两个R^{3a}变量选自(a)-CF_2和-OH;(b)-CH_3和-OH;以及(c)-OH和苯基。在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量m是零,变量k是二,并且两个R^{3a}变量选自(a)-CF_2和-OH;(b)-CH_3和-OH;以及(c)-OH和苯基。

[0144] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,变量R^{3a}是氘化的。在一些实施例中,氘化的R^{3a}是-O-CD_3。

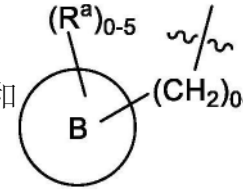
[0145] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,两个R^{3a}一起形成氧代基团。

[0146] 在式I(包含上述定义变量X^1和X^2、R^1、R^2的实施例)的一些实施例中,两个R^{3a}一起形成C_3-C_6环烷基。

[0147] 在式I(包含上述定义变量X^1和X^2、R^1、R^2和R^{3a}的实施例)的一些实施例中,变量R^{3b}选自任选地被-OH或卤素取代的C_1-C_3烷基。在式I(包含上述定义变量X^1和X^2、R^1、R^2和R^{3a}的实施例)的一些实施例中,R^{3b}是CH_3。在式I(包含上述定义变量X^1和X^2、R^1、R^2和R^{3a}的实施例)的一些实施例中,R^{3b}选自CF_2和CF_3。

[0148] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}和R^{3b}的实施例)的一些实施例中,变量R^{4a}、R^{4b}、R^{5a}和R^{5b}中的三个变量是氢并且剩余变量选自C_1-C_4烷基。在式I的一些实施例中,变量R^{4a}、R^{4b}、R^{5a}和R^{5b}中的三个变量是氢并且剩余变量选自甲基、乙基、环丙基、稠合环丙基和稠合环丁基。在式I的一些实施例中,变量R^{4a}、R^{4b}和R^{5b}是氢并且变量R^{5a}选自甲基、乙基、环丙基、稠合环丙基和稠合环丁基。在式I的一些实施例中,变量R^{4b}、R^{5a}和R^{5b}是氢并且变量R^{4a}选自甲基、乙基、环丙基、稠合环丙基和稠合环丁基。在式I的一些实施例中,变量R^{4a}、R^{4b}、R^{5a}和R^{5b}中的三个变量是氢并且剩余变量是CH_3。

[0149] 在上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的一些实施例中,以及式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il、和Im的实施例中,

[0150] R^6选自C_1-C_6烷基、-C(=O)O(C_1-C_4烷基)和

基团,其中:

[0151] R^6的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-OH、-NH_2、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环

基、C_6芳基(任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、-O-(C_6芳基)(任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、5至10元杂环基和5至10元杂芳基;

[0152] 环B选自C_3-C_{12}碳环基、3至12元杂环基、C_6和C_{10}芳基以及5至10元杂芳基,其中环B任选地被1个、2个、3个、4个或5个R^a基团取代;其中:

[0153] R^a在每次出现时独立地选自卤素、氰基、C_1-C_8烷基、C_1-C_6卤代烷基、C_2-C_8烯基、C_1-C_6卤代烯基、C_1-C_6烷氧基、C_1-C_6卤代烷氧基、C_3-C_{12}碳环基、C_6和C_{10}芳基、3至12元杂环基、5至10元杂芳基、-C(=O)NR^hR^i、-C(=O)OR^k、-C(=O)(C_1-C_4亚烷基)OR^k、-C(=O)R^k、-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)NR^hC(=O)R^k、-C(=O)C(=O)R^k、-NR^hR^i、-NH$(CH_2)_qCHR^hR^i$、-NH$(CH_2)_qNR^hR^i$、-NR^hC(=O)R^k、-NR^hC(=O)OR^k、-NR^hC(=O)(C_1-C_4亚烷基)OR^k、-NR^hC(=O)O(C_1-C_4亚烷基)R^k、-NR^hC(=O)NR^iR^j、-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-NR^hS(=O)$_pR^k$、-NR^hC(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k、-NR^hC(=O)[O$(CH_2)_q$]$_r$OC(=O)$NR^hR^i$$(CH_2)_q$[O$(CH_2)_q$]$_r$($C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、-$NR^hC$(=O)($C_1$-$C_6$亚烷基)[O$(CH_2)_q$]$_r$OC(=O)-$NR^hR^i$$(CH_2)_q$[O$(CH_2)_q$]$_r$($C_1$-$C_6$烷基)(任选地被1至3个$R^m$基团取代)、-$OR^k$、-OC(=O)$R^k$、-OC(=O)$OR^k$、-OC(=O)$NR^hR^i$、-[O$(CH_2)_q$]$_r$O($C_1$-$C_6$烷基)、-S(=O)$_pR^k$和-S(=O)$_pNR^hR^i$基团,其中:

[0154] 以下中的每一个中的所述C_1-C_4亚烷基任选地被1至3个-OH基团取代:-C(=O)(C_1-C_4亚烷基)S(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)OR^k、-C(=O)(C_1-C_4亚烷基)S(=O)$_pNR^hR^i$、-C(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$、-C(=O)(C_1-C_4亚烷基)-NR^hC(=O)R^k、-NR^hC(=O)O(C_1-C_4亚烷基)R^k、-NR^hC(=O)(C_1-C_4亚烷基)-OR^k、NR^hS(=O)$_p$(C_1-C_4亚烷基)C(=O)OR^k和-NR^hC(=O)(C_1-C_4亚烷基)NR^iS(=O)$_pR^k$,

[0155] R^a的所述C_1-C_8烷基、所述C_1-C_6卤代烷基、所述C_1-C_6烷氧基和所述C_2-C_8烯基各自任选地被1至3个独立地选自以下的基团取代:氰基、-C(=O)R^k、-C(=O)OR^k、-C(=O)NR^hR^i、-NR^hR^i、-NR^hC(=O)R^k、-NR^hC(=O)OR^k、-NR^hC(=O)NR^iR^j、-NR^hS(=O)$_pR^k$、-OR^k、-[O$(CH_2)_q$]$_r$OH、-OC(=O)R^k、-OC(=O)OR^k、-OC(=O)NR^hR^i、-SR^k、-S(=O)$_pR^k$、-S(=O)$_pNR^hR^i$、-[O$(CH_2)_q$]$_r$O(C_1-C_4烷基)、-O-(C_6芳基或5至8元杂芳基)(任选地被1至3个R^m基团取代)、C_3-C_6碳环基(任选地被1至3个R^m基团取代)、-C_6至C_{10}芳基(任选地被1至3个R^m基团取代)、4至10元杂环基(任选地被1至3个R^m基团取代)和5至10元杂芳基(任选地被1至3个R^m基团取代);并且

[0156] R^a的所述C_3-C_{12}碳环基、所述3至12元杂环基、所述C_6和C_{10}芳基和所述5至10元杂芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、C_1-C_6烷基(任选地被1至3个R^m基团取代)、-C(=O)R^k、C(=O)OR^k、-NR^hR^i、-OR^k、-S(=O)$_pR^k$、-S(=O)$_pNR^hR^i$和5至10元杂环基,其中:

[0157] R^h、R^i和R^j在每次出现时各自独立地选自氢、C_1-C_6烷基(任选地被1至4个R^m基团取代)、C_6-C_{10}芳基、C_3-C_8碳环基(任选地被1至3个R^m基团取代)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代),其中:

[0158] R^h、R^i和R^j中的任一者的所述C_1-C_6烷基任选地被1至4个独立地选自以下的基团取代:卤素、氰基、-OH、C_1-C_4烷氧基、-C(=O)NH(C_1-C_4烷基)、5至10元杂芳基(任选地被1至3个R^m基团取代)和5至10元杂环基(任选地被1至3个R^m基团取代);

[0159] R^k在每次出现时独立地选自氢、NH_2(任选地被1个或2个选自C_1-C_3烷基的基团取代)、C_1-C_6烷基、苄基、C_6芳基、C_3-C_6碳环基、5至10元杂环基和5至10元杂芳基,其中:

[0160] R^k中的任一者的所述C_1-C_6烷基任选地被1至5个独立地选自以下的基团取代:卤素、氰基、-NH_2、-OH、C_1-C_6烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、4至10元杂环基(任选地被1至3个-OH基团取代)、5至10元芳基(任选地被1至3个选自以下的基团取代:C_1-C_4烷基和卤素)和5至10元杂芳基(任选地被1至3个-OH基团取代);并且

[0161] R^k中的任一者的所述C_3-C_6碳环基、所述苄基和所述C_6芳基各自任选地被1至3个独立地选自以下的基团取代:卤素、氰基、氧代、-OH、-C(=O)NH_2、-C(=O)N$(CH_3)_2$、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_6卤代烷基、C_1-C_6烷氧基、C_3-C_6环烷基(任选地被1至3个卤素基团取代)、C_6芳基(任选地被1至3个卤素基团取代)和5至10元杂芳基(任选地被1至3个卤素基团取代);

[0162] R^k中的任一者的所述5至10元杂芳基和所述5至10元杂环基各自任选地被1至3个独立地选自以下的基团取代:卤素、氧代、氰基、-C(=O)CH_3、-NH_2、-OH、C_1-C_4烷基(任选地被1至3个-OH基团取代)、C_1-C_4卤代烷基、5至10元杂环基和C_1-C_4烷氧基;

[0163] R^m在每次出现时独立地选自卤素、氰基、氧代、-NH_2、C_1-C_6烷基、C_1-C_6烷氧基、-C(=O)R^k、-S(=O)$_pR^k$、-OR^k和5至10元杂环基,其中:

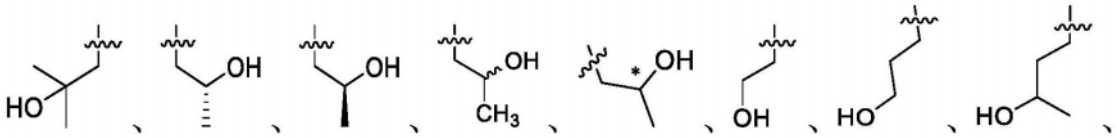
[0164] R^m中的任一者的所述C_1-C_6烷基、所述C_1-C_6烷氧基和所述5至10元杂环基任选地被1至3个独立地选自以下的基团取代:卤素、氰基、-OH和C_1-C_4烷氧基;

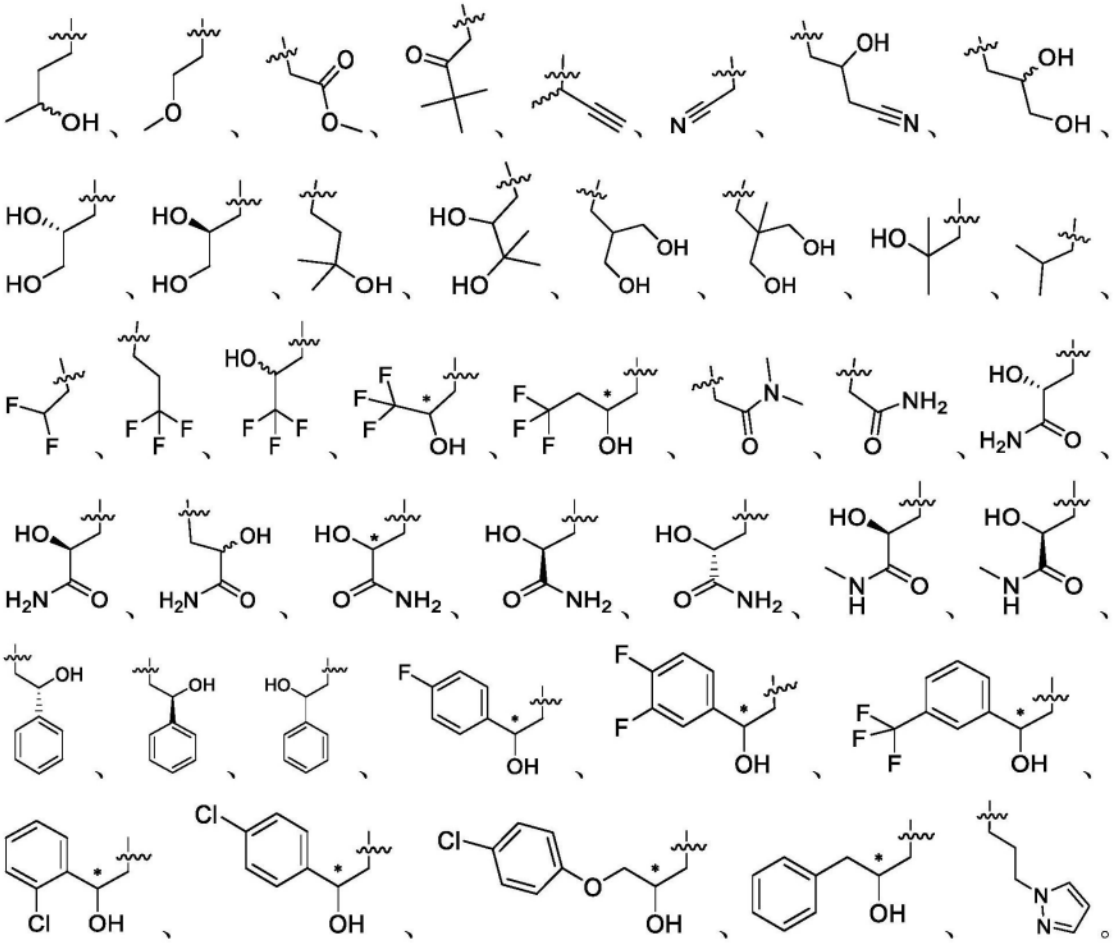
[0165] p在每次出现时是独立地选自1和2的整数;并且

[0166] q和r在每次出现时是独立地选自0、1、2和3的整数。

[0167] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,-R^6选自任选地被1至5个独立地选自以下的基团取代的C_1-C_6烷基:卤素、氰基、-OH、-NH_2、-NH(C_1-C_4烷基)、-N(C_1-C_4烷基)$_2$、-C(=O)NH_2、-C(=O)(C_1-C_4烷基)、-C(=O)OH、-C(=O)O(C_1-C_4烷基)、-C(=O)NH(C_1-C_4烷基)、-C(=O)N(C_1-C_4烷基)$_2$、C_1-C_4烷氧基、C_3-C_6碳环基、C_6芳基(其任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、-O-(C_6芳基)(其任选地被1至3个独立地选自以下的基团取代:卤素和C_1-C_4卤代烷基)、5至10元杂环基和5至10元杂芳基。

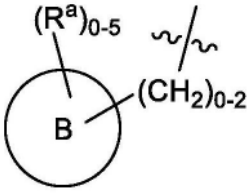
[0168] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6是选自以下的任选取代的C_1-C_6烷基:





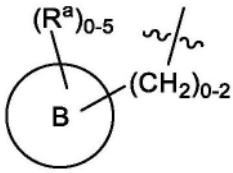
[0169] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自-C(=O)O(C_1-C_4烷基)。

[0170] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自



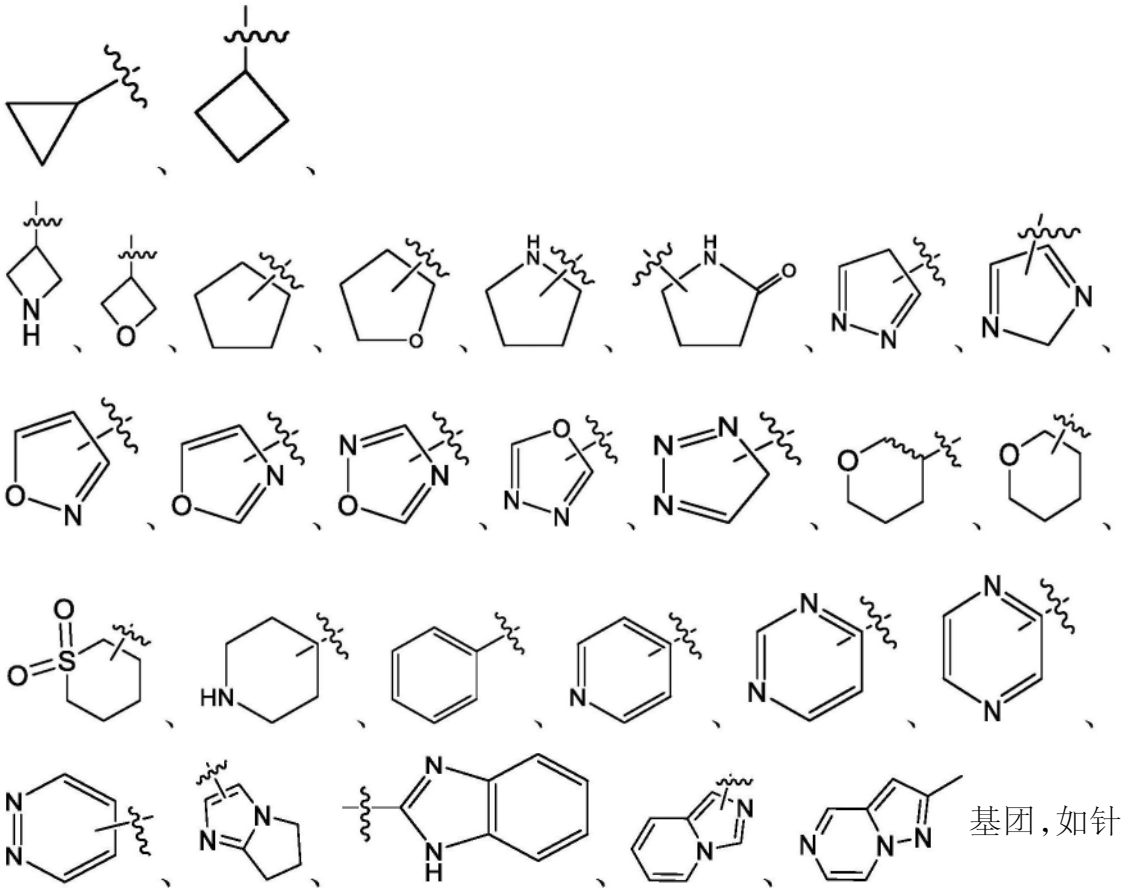
如上文针对式I所定义。在这些实施例中的一些实施例中,环B选自任选地被1个、2个、3个、4个或5个R^a基团取代的C_3-C_{12}碳环基,如针对式I所定义。在这些实施例中的一些实施例中,环B选自3至12元杂环基。在这些实施例中的一些实施例中,环B选自任选地被1个、2个、3个、4个或5个R^a基团取代的C_6和C_{10}芳基,如针对式I所定义。在这些实施例中的一些实施例中,环B选自任选地被1个、2个、3个、4个或5个R^a基团取代的5至10元杂芳基,如针对式I所定义。

[0171] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自

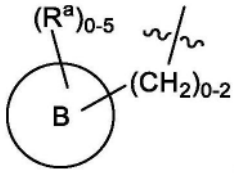


并且环B选自任选地被1个、2个、3个、4个或5个R^a基团取代的

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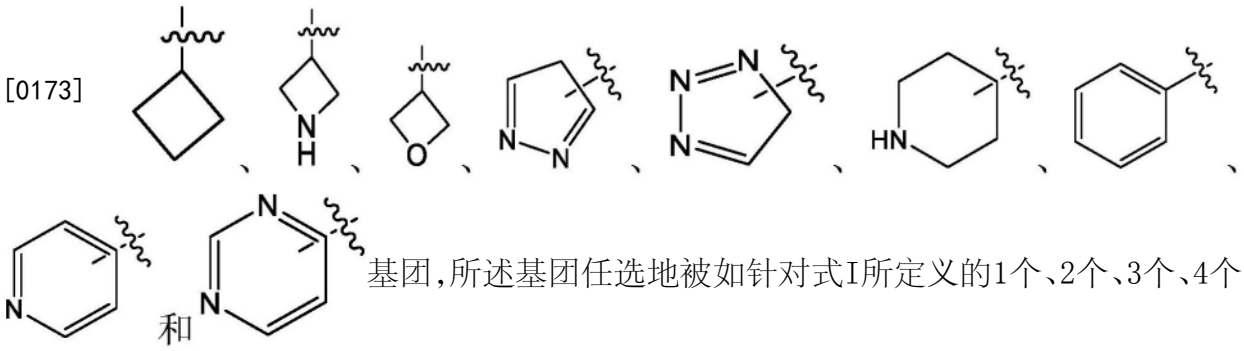

基团，如针对式I所定义。

[0172] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中，R^6选自

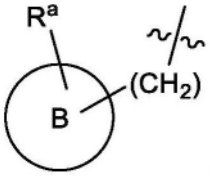


并且环B选自以下：

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[0173] 
基团，所述基团任选地被如针对式I所定义的1个、2个、3个、4个或5个R^a基团取代。

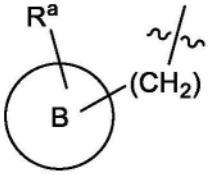
[0174] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自以下:



其中环B是5元杂芳基,并且R^a如针对式I所定义。

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[0175] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b},、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自:

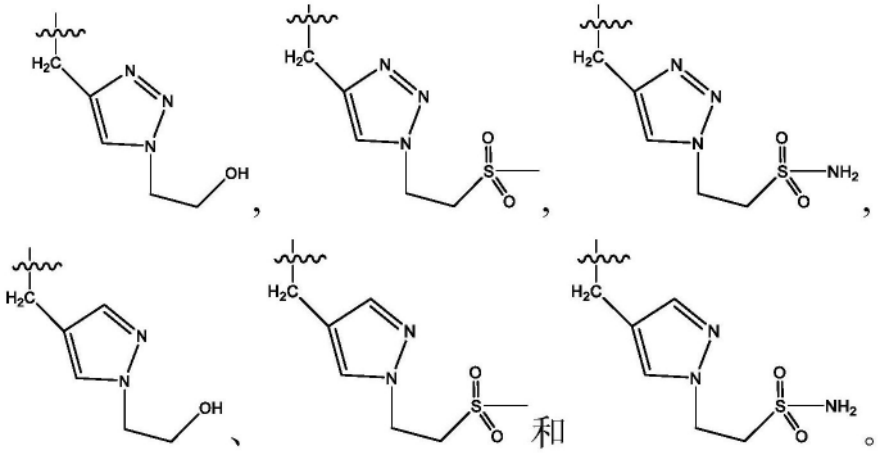


其中环B是5元杂芳基,并且R^a是氧代或选自C_1-C_8烷基、C_3-C_{12}碳环基以及C_6和C_{10}芳基,其中的每一个可以任选地被1至3个选自以下的基团取代:卤素和C_1-C_8烷基(其中所述C_1-C_8烷基可以任选地被1至3个选自以下的基团取代:卤素、-OH、SO_2CH_3和SO_2NH_2)。

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[0176] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}和R^{5b}的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^6选自以下:

[0177]



,和。

[0178] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}、R^{5b}和R^6的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^a选自C_1-C_4烷基、卤素、-OH和C_1-C_4烷氧基,其中R^a的所述C_1-C_4烷基任选地被1至3个极性基团,例如,砜、磺胺和醇取代。

[0179] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}、R^{5b}和R^6的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^a是C_1-C_6烷基,任选地如针对式I所定义被取代。在一些实施例中,R^a的所述C_1-C_6烷基任选地被1至3个选自以下的基团取代:-OH、-SO_2CH_3、C_1-C_3烷氧基、C(=O)$NHCH_3$、-$SO_2NHCH_2CH_2OH$、-SCF_3、-$SCH_2C(CH_2)_2OH$、-SO_2苯基、4至6元杂环(任选地被1至3个R^m基团取代)、4至6元杂芳基(任选地被1至3个R^m基团取代)、氰基、NHC(=O)-4至6元杂芳基。

[0180] 在式I(包含上述定义变量X^1和X^2、R^1、R^2、k、m、R^{3a}、R^{3b}、R^{4a}、R^{4b}、R^{5a}、R^{5b}和R^6的实施例)的一些实施例中和式Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im的实施例中,R^a选自4至6元碳环、4至6元杂环和4至6元杂芳基,其中的任一者是任选取代的,如上文针对式I所定

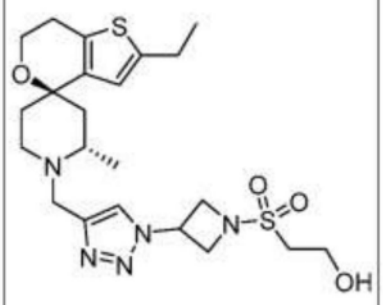
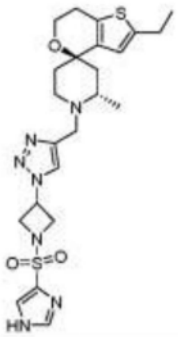
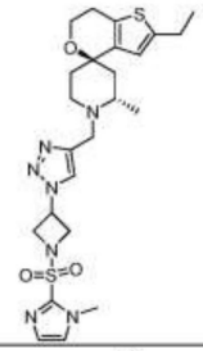
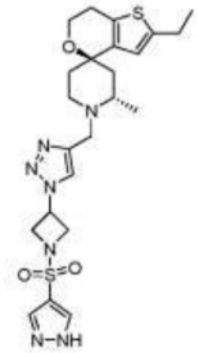
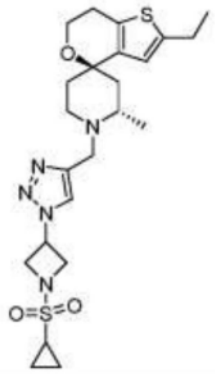
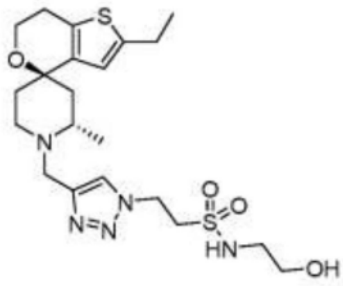
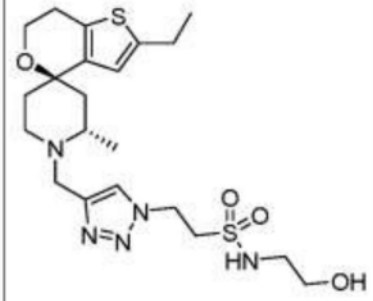
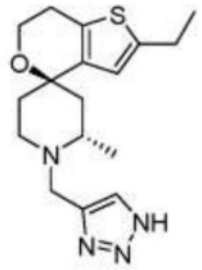
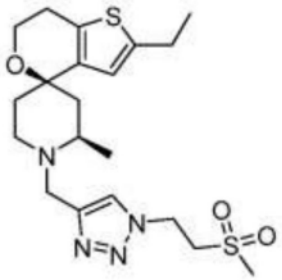
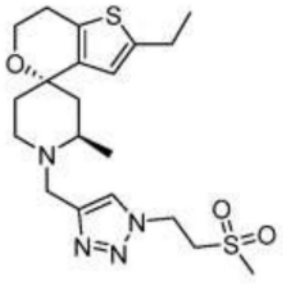
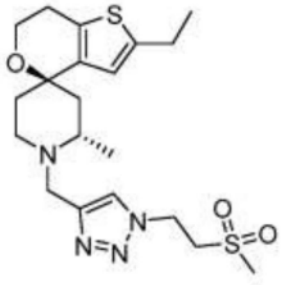
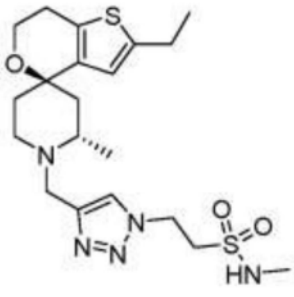
义。

[0181] 在一些实施例中,本公开的所述至少一种化合物、互变异构体、氘化衍生物或药学上可接受的盐选自表1中描绘的化合物1至1183、其互变异构体、所述化合物或所述互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐。表1中的化合物中的波浪线(即,)描绘两个原子之间的键,并指示分子的集合的混合立体化学的位置,如外消旋混合物、顺式/反式异构体或(E)/(Z)异构体。表1中化合物中的原子附近的星号(例如,)指示分子中的手性位置。

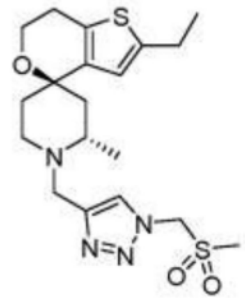
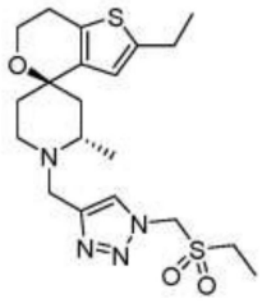
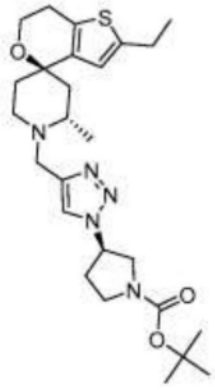
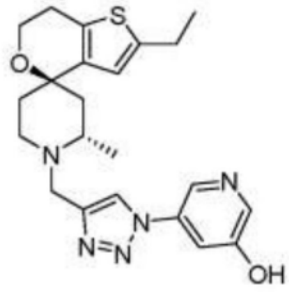
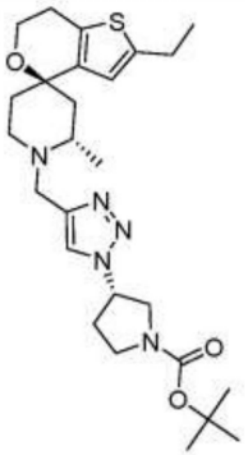
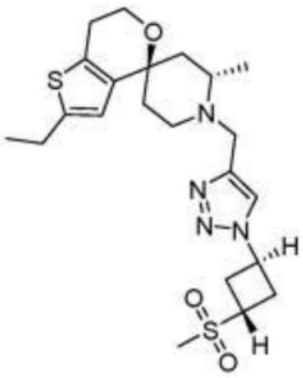
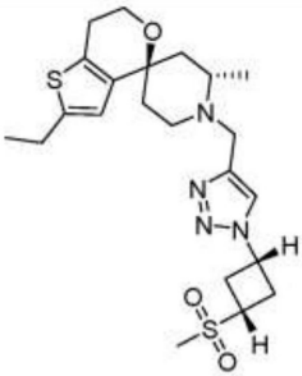
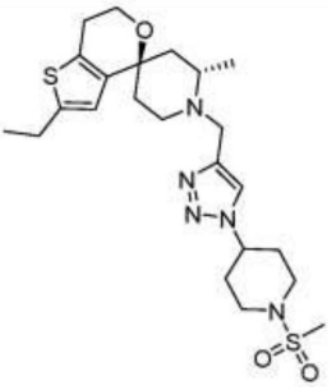
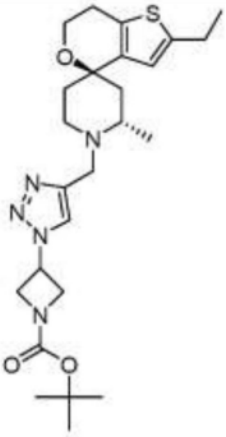
[0182] 在一些实施例中,所述式(I)化合物选自下表1呈现的化合物、这些化合物的互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0183] 表1:化合物1至1183

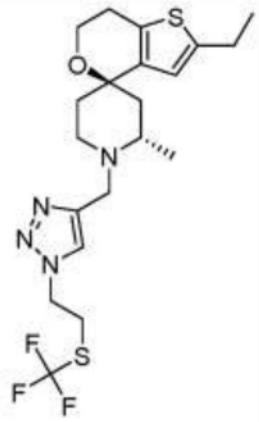
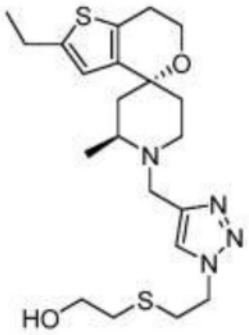
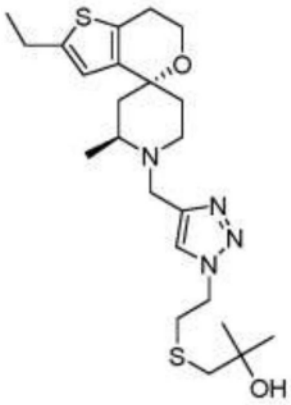
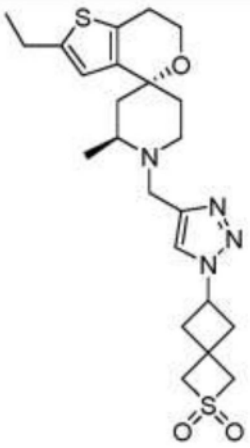
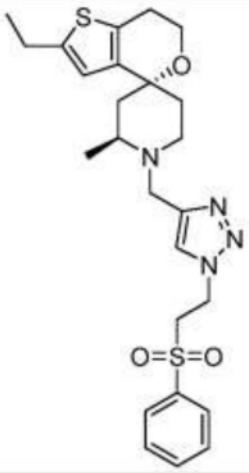
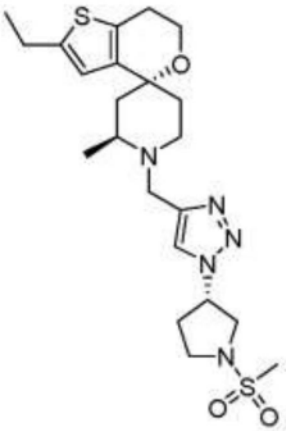
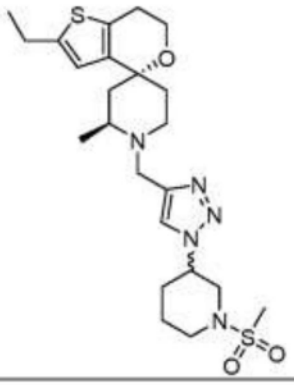
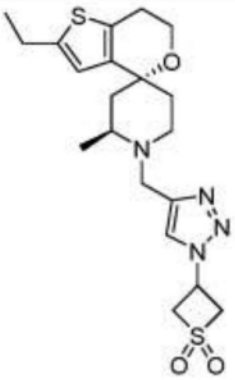
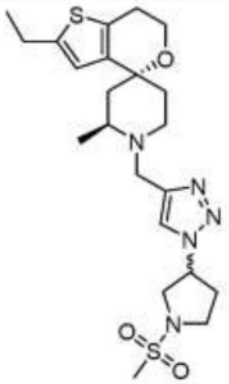
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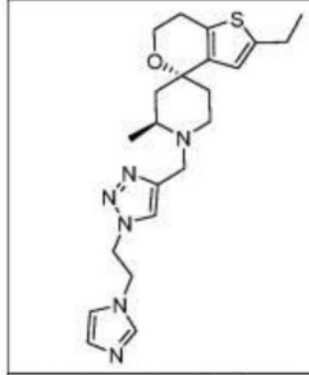
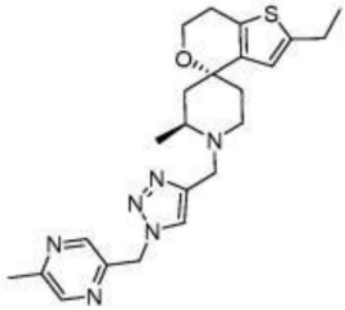
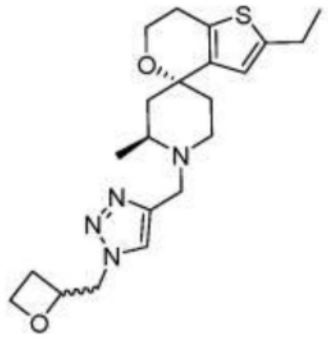
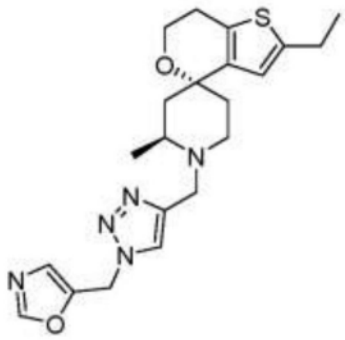
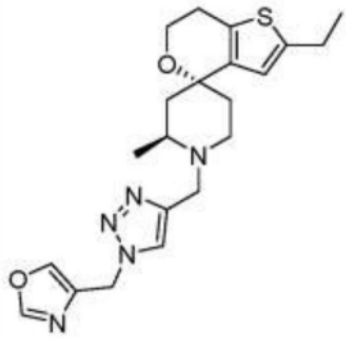
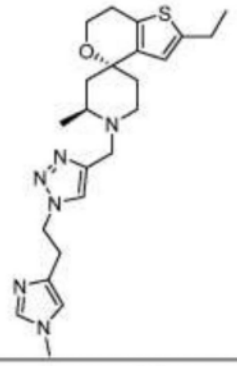
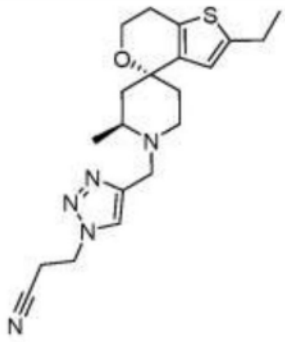
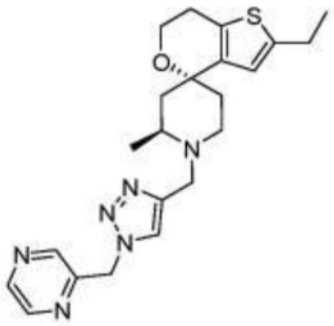
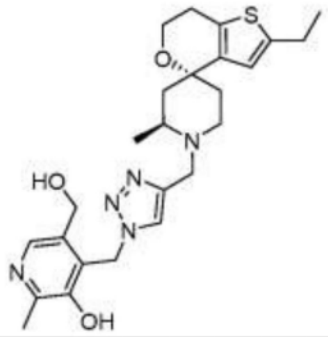
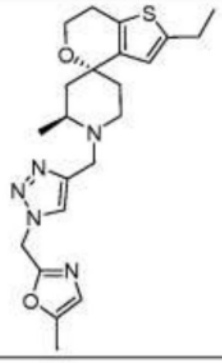
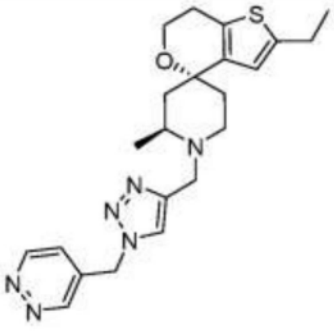
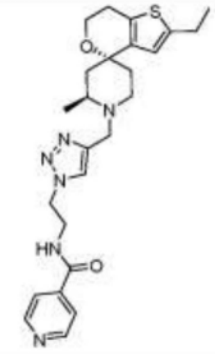
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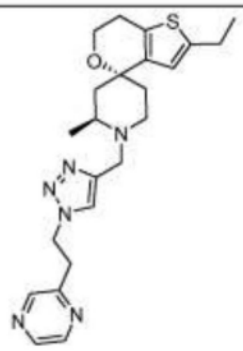
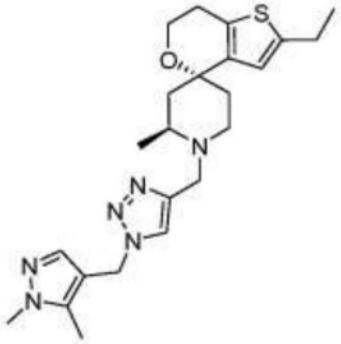
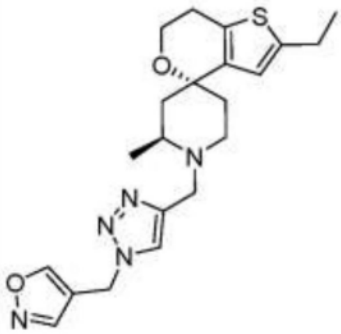
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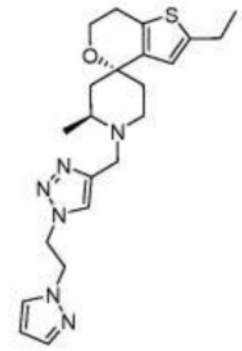
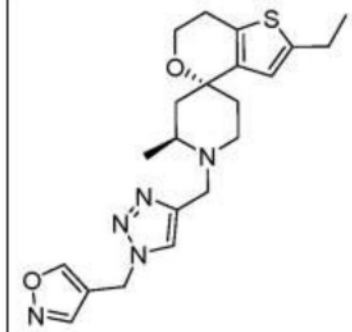
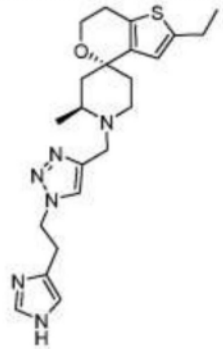
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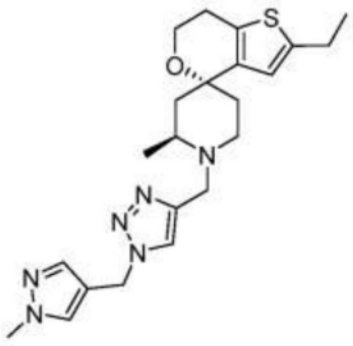
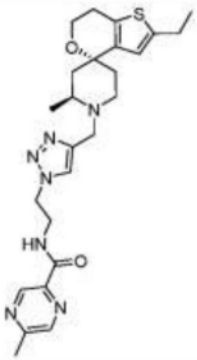
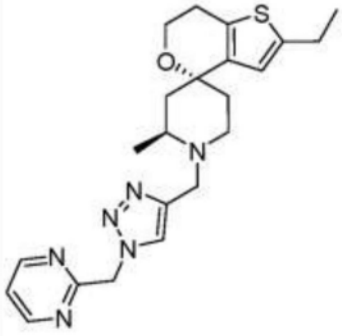
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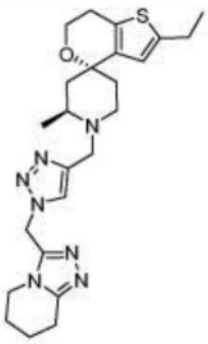
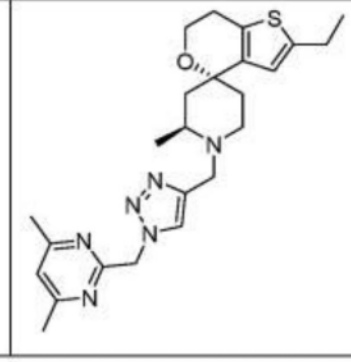
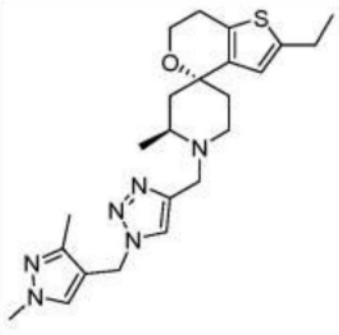
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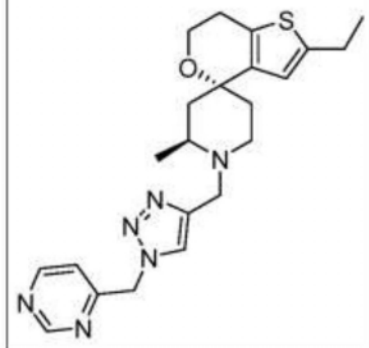
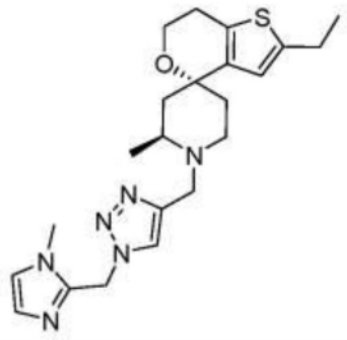
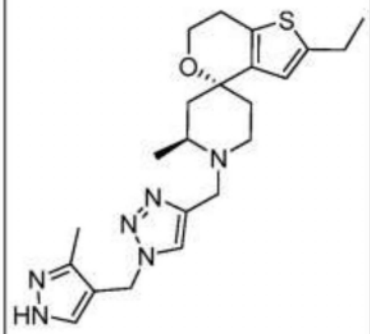
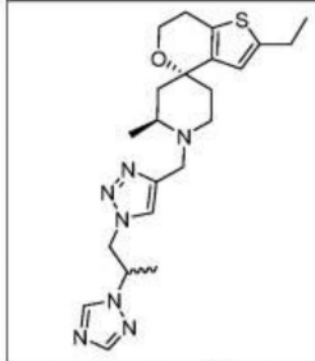
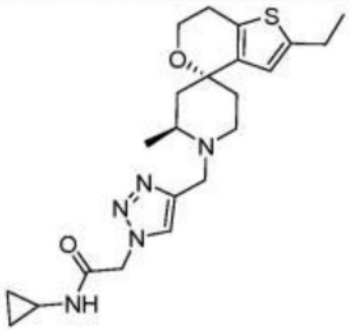
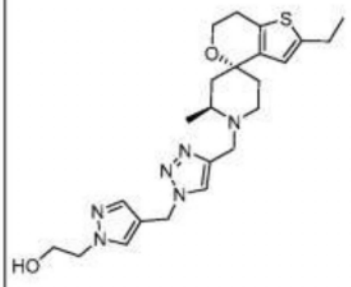
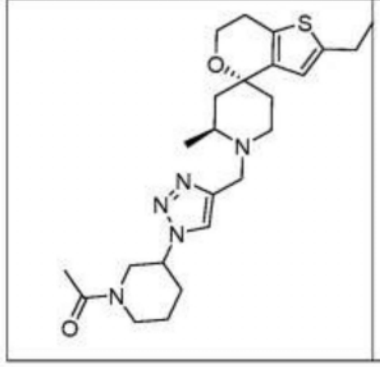
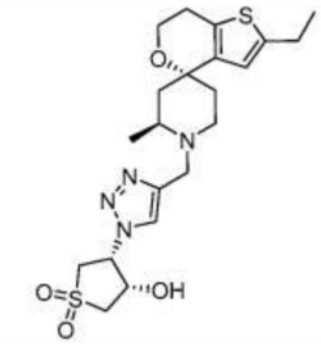
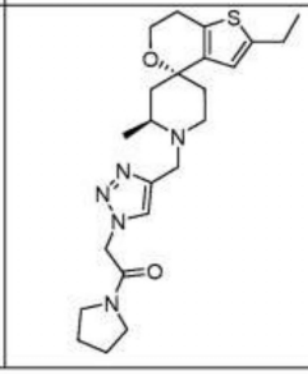
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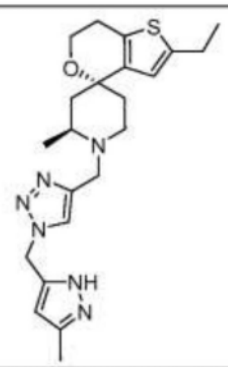
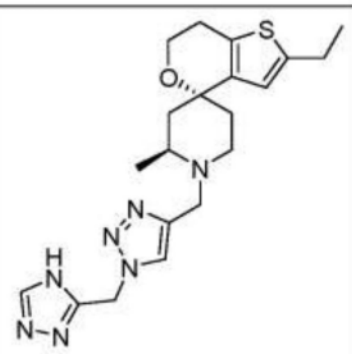
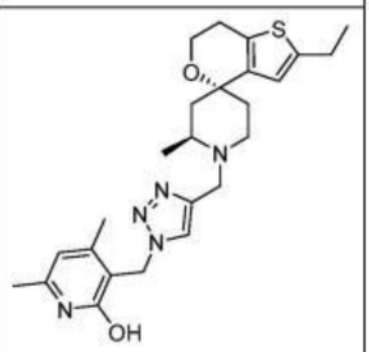
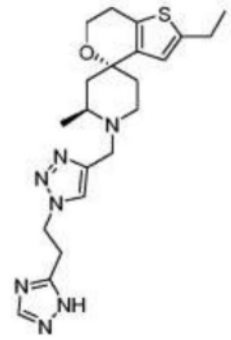
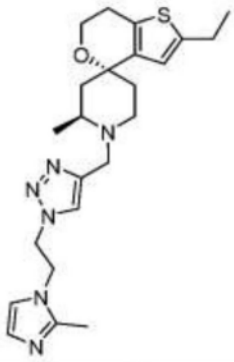
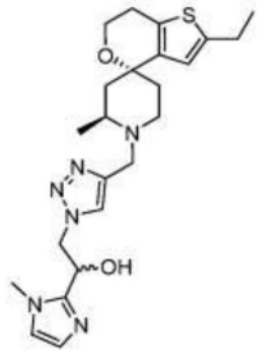
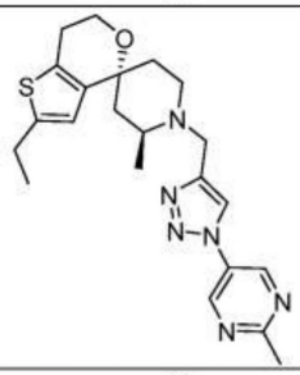
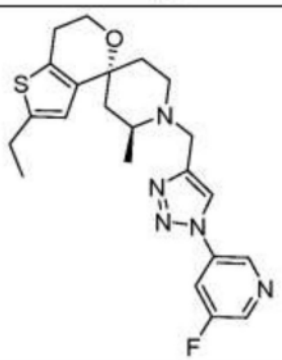
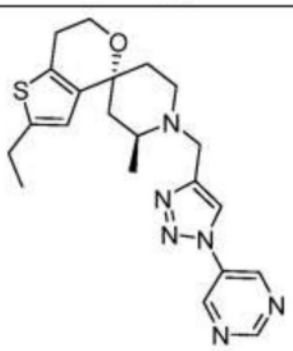
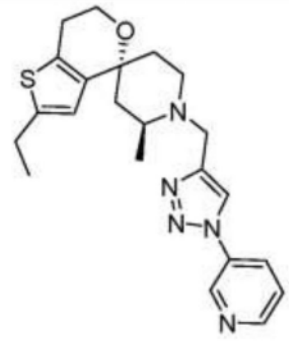
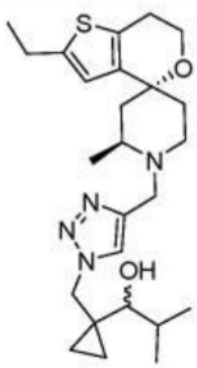
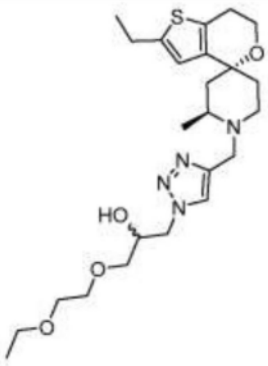
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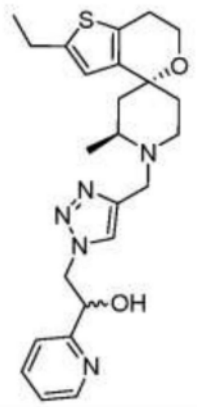
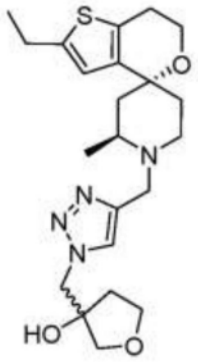
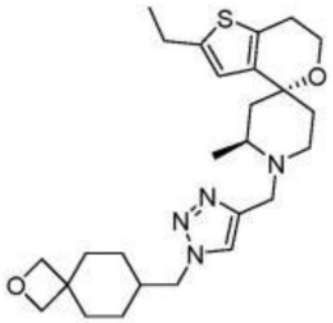
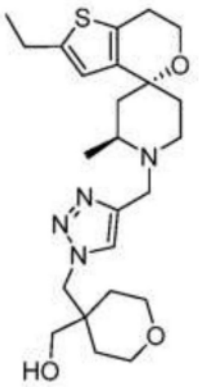
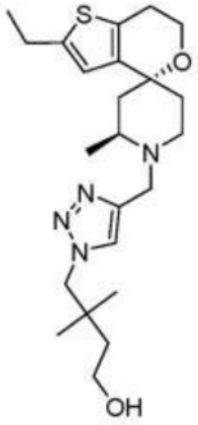
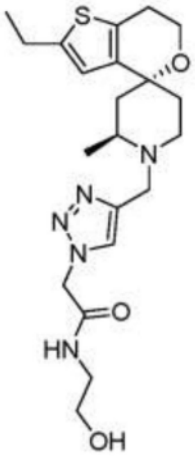
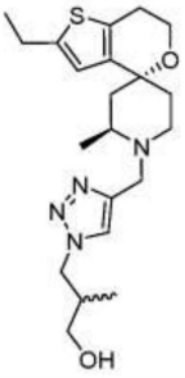
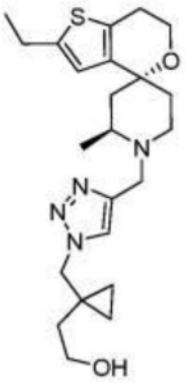
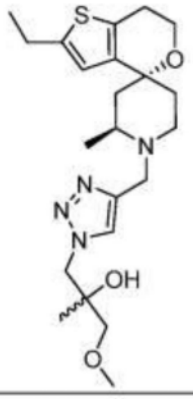
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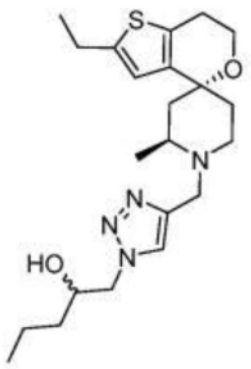
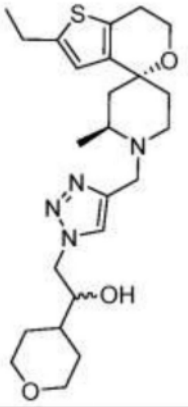
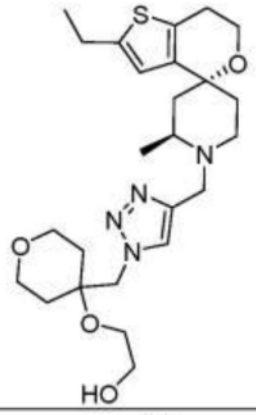
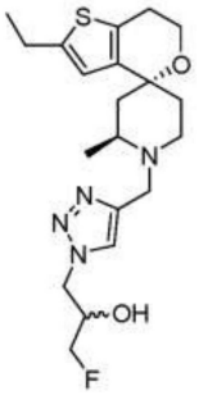
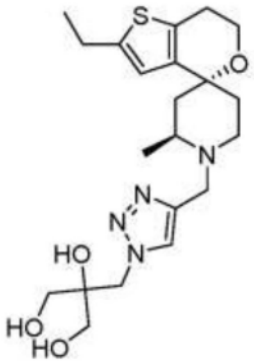
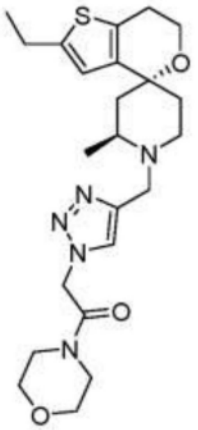
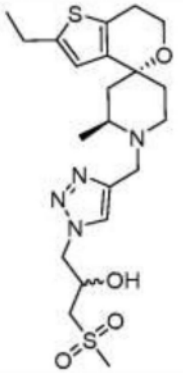
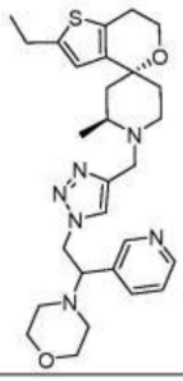
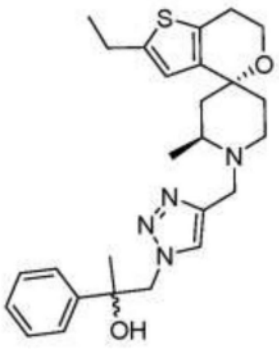
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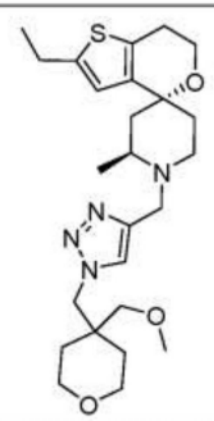
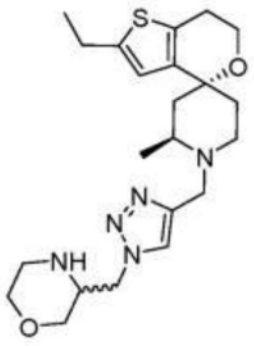
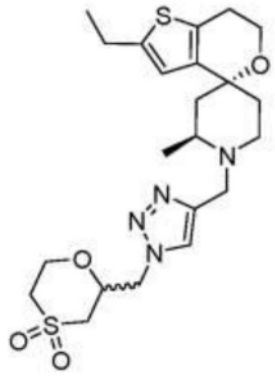
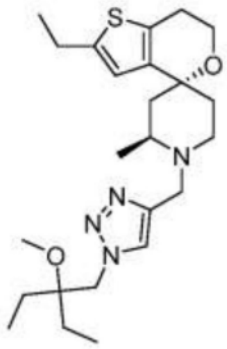
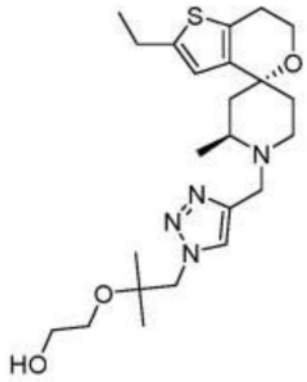
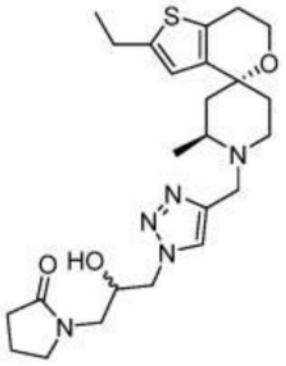
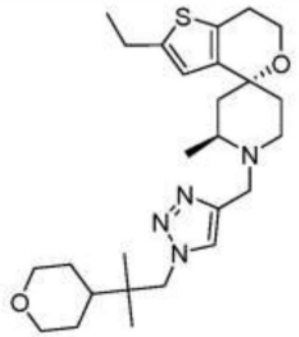
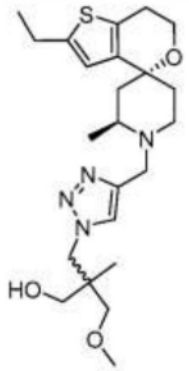
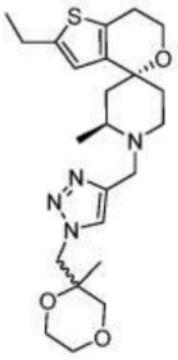
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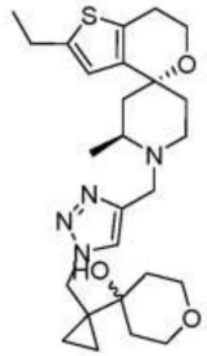
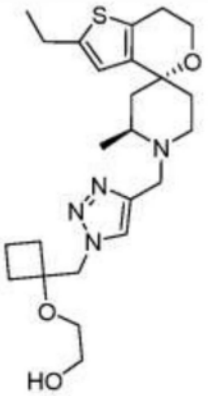
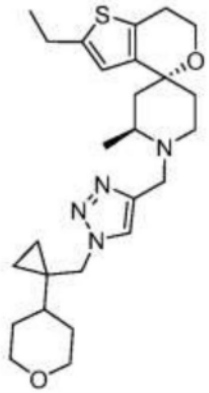
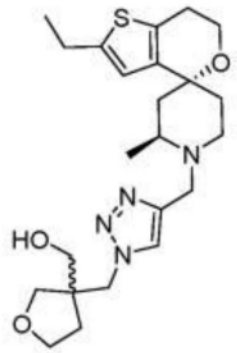
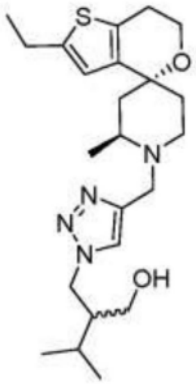
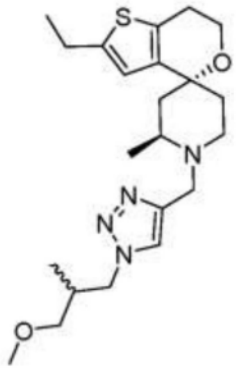
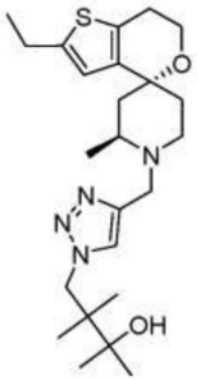
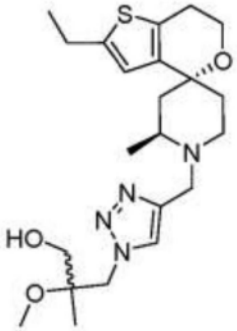
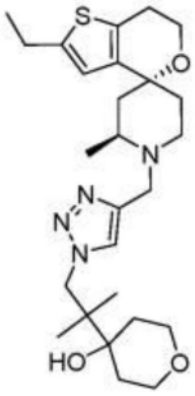
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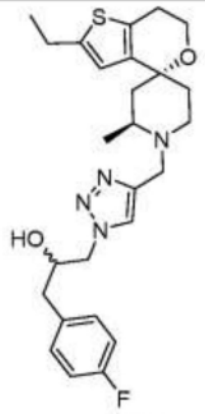
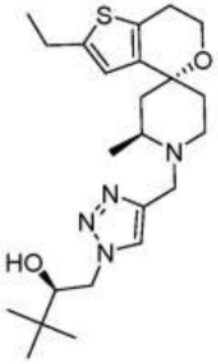
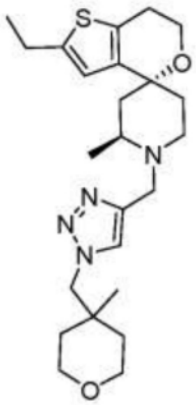
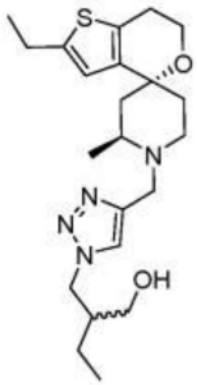
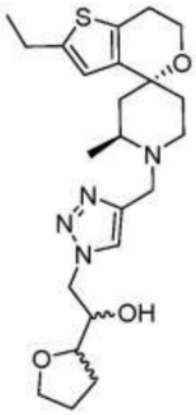
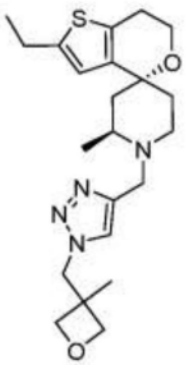
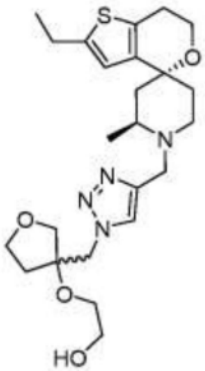
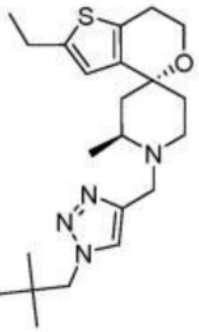
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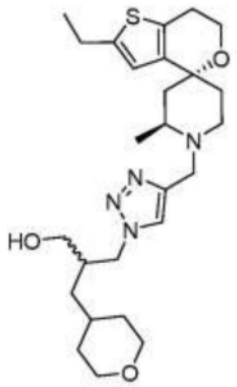
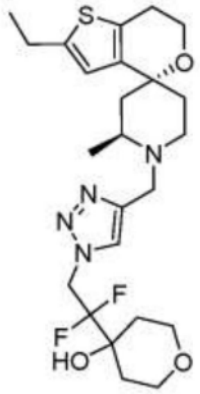
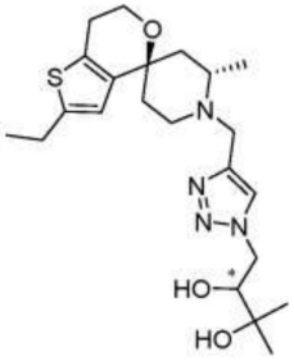
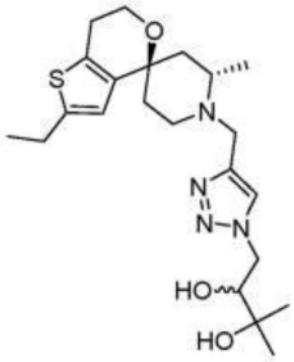
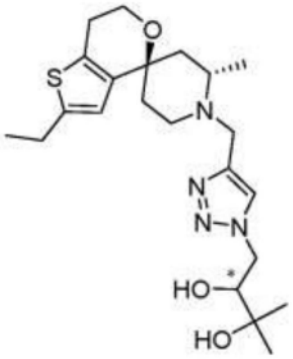
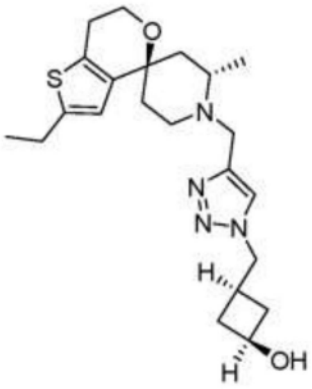
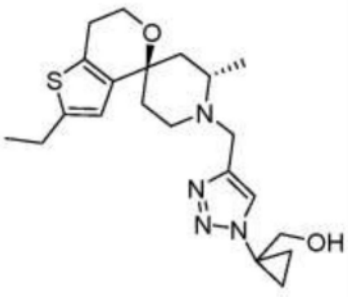
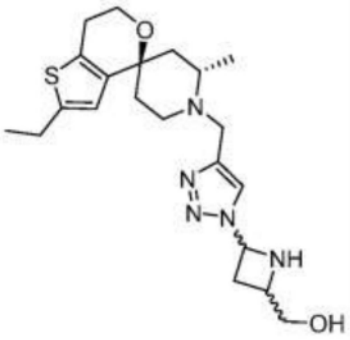
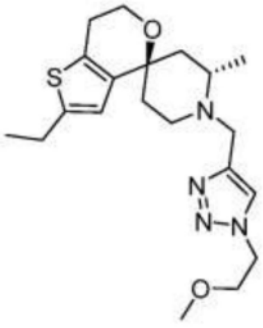
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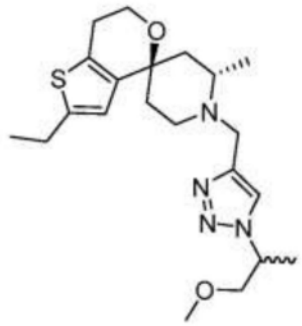
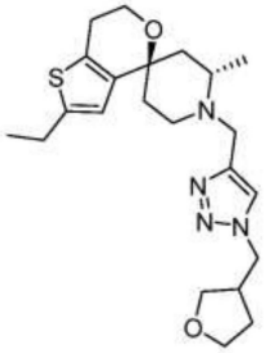
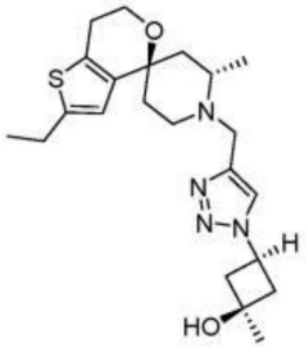
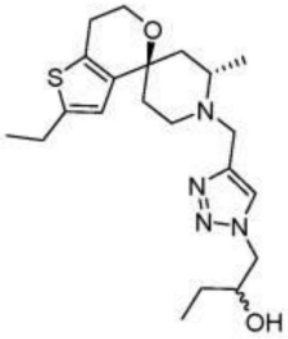
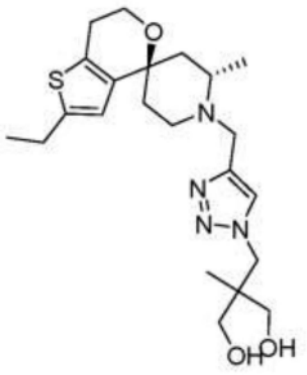
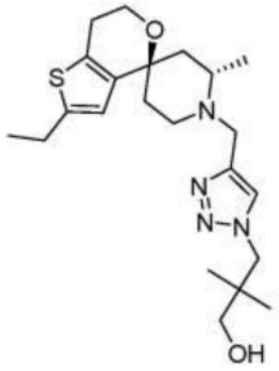
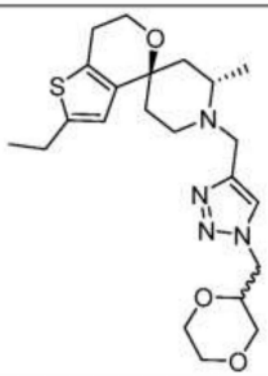
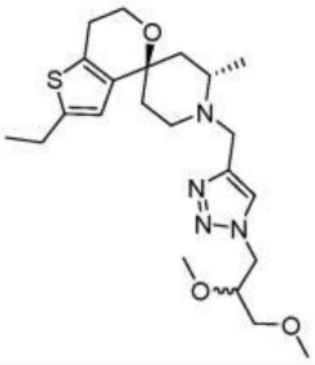
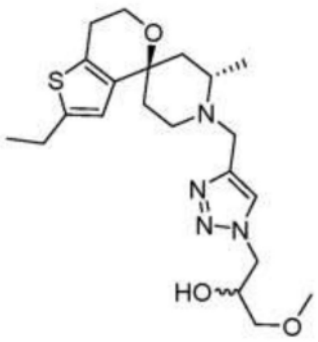
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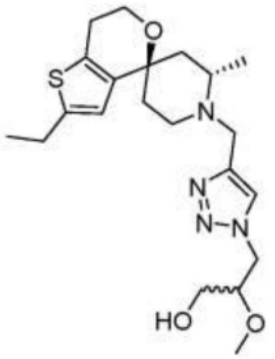
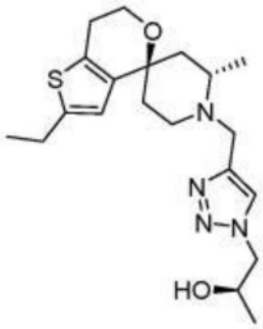
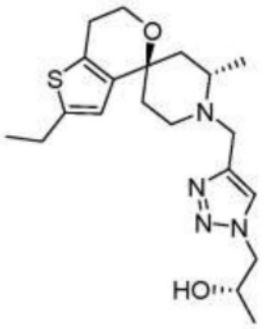
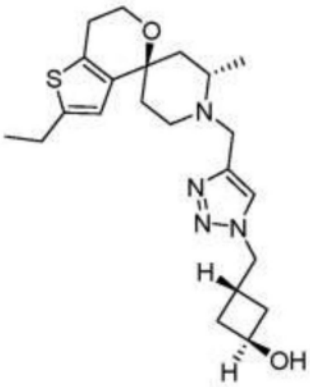
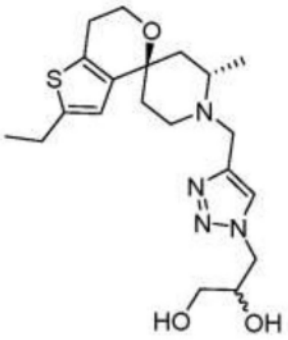
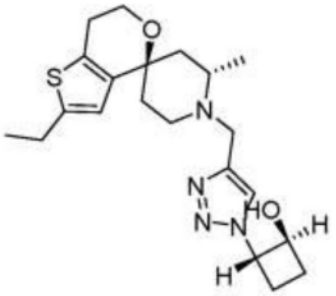
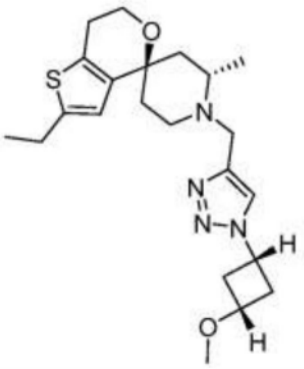
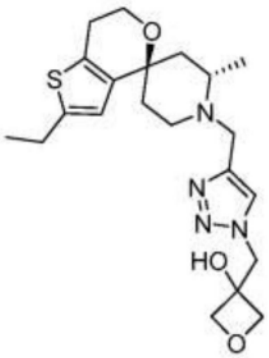
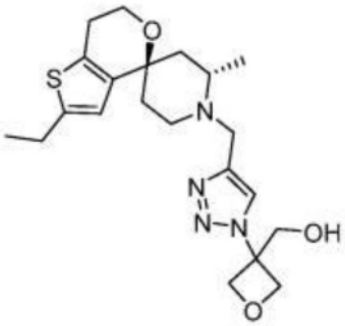
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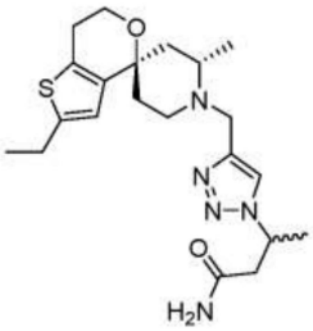
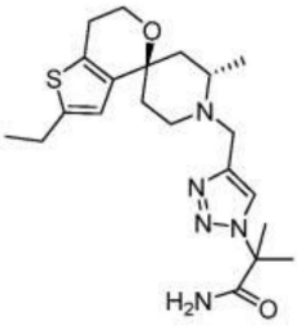
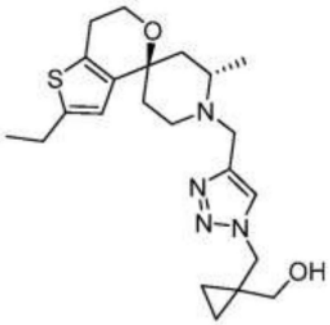
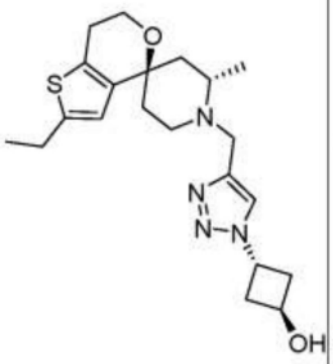
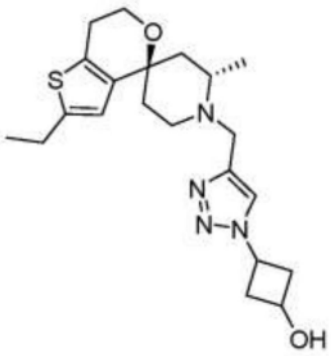
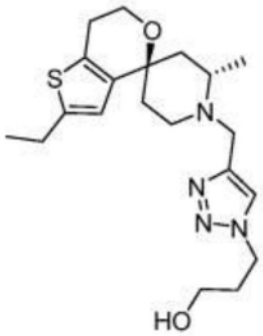
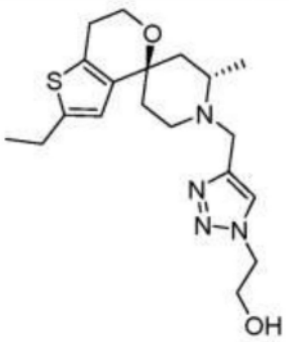
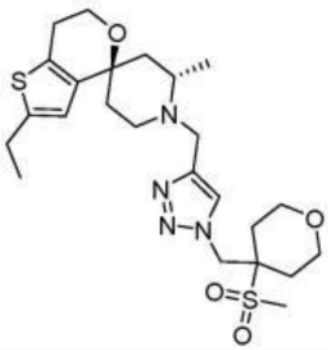
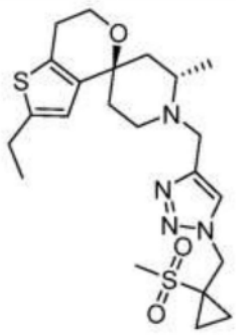
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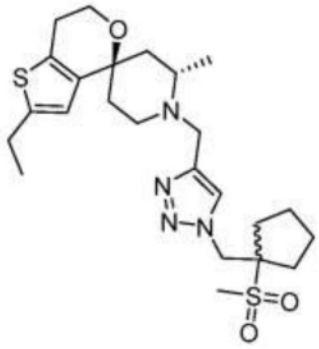
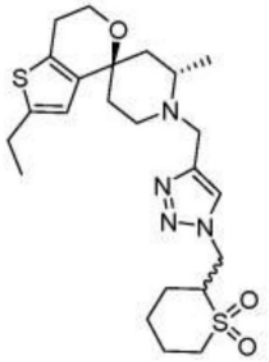
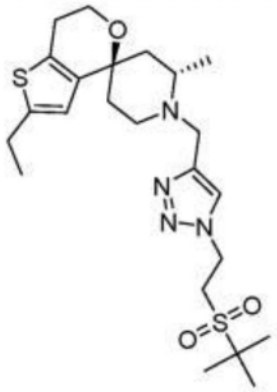
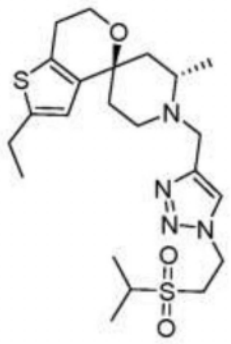
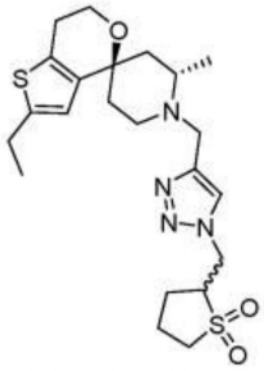
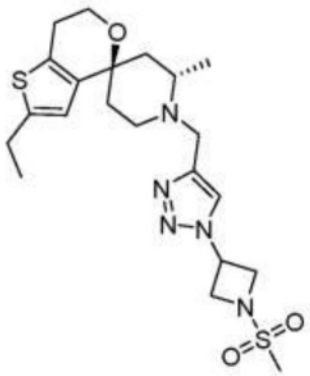
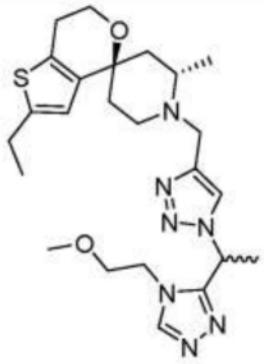
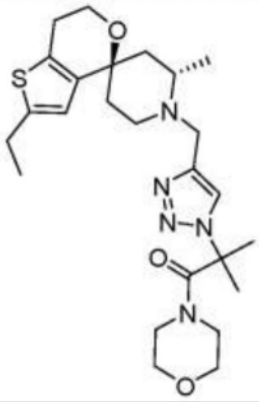
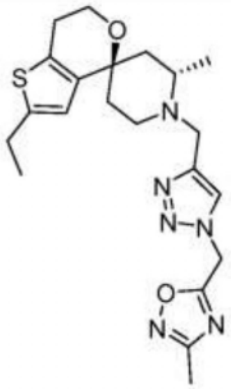
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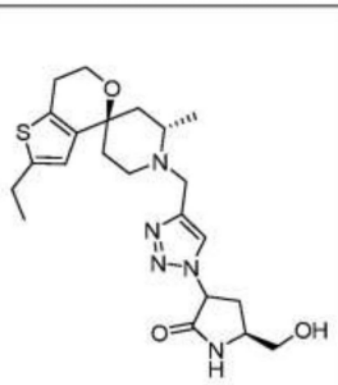
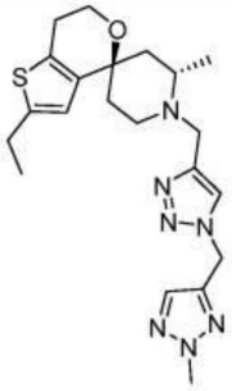
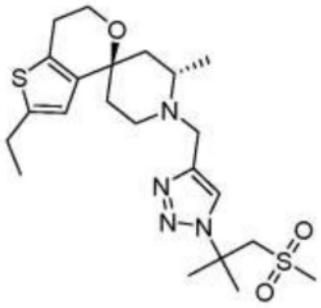
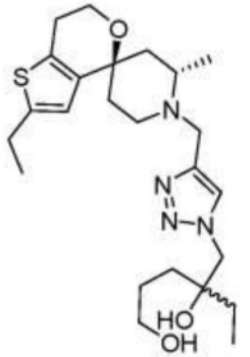
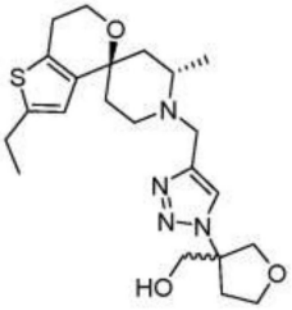
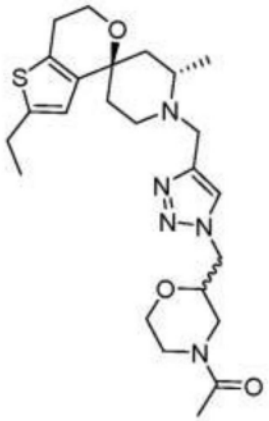
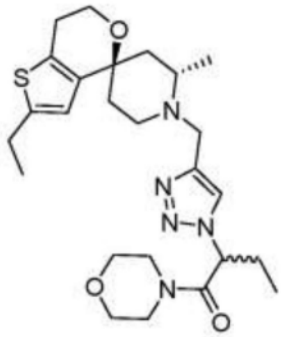
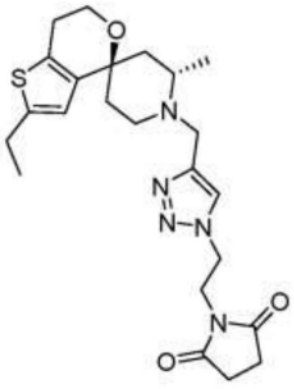
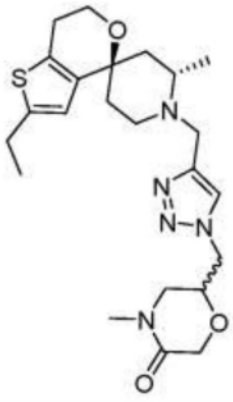
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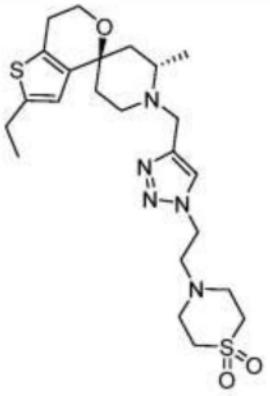
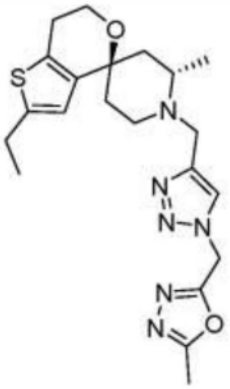
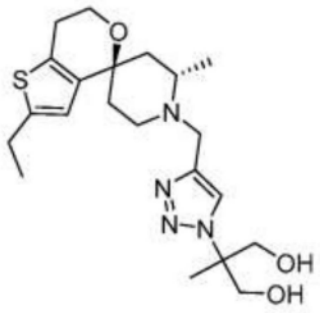
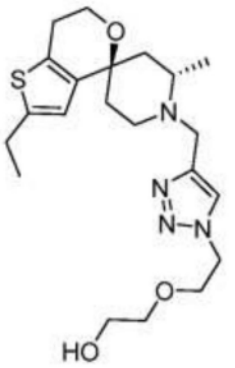
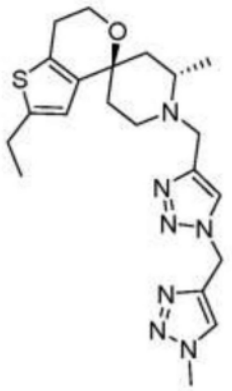
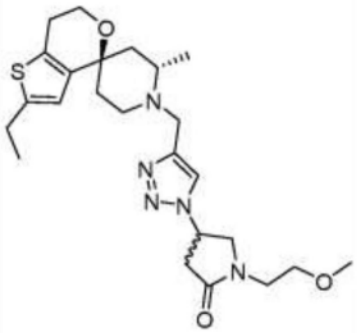
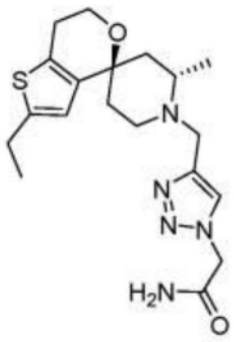
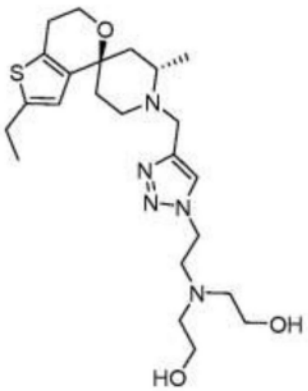
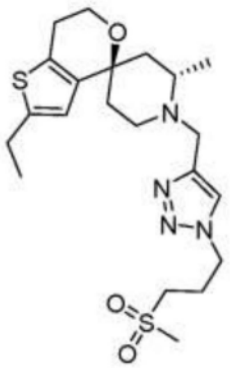
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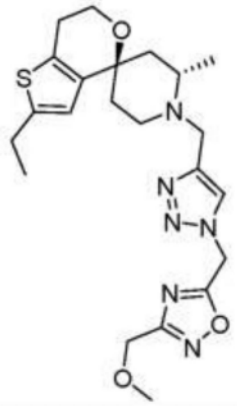
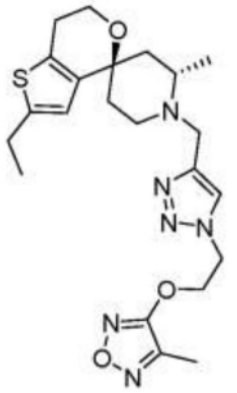
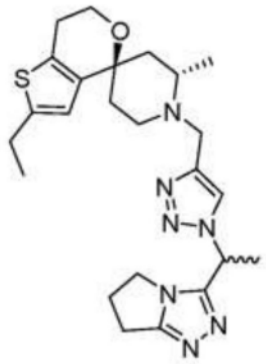
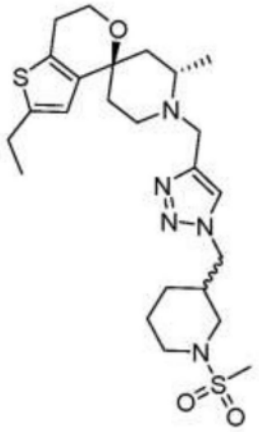
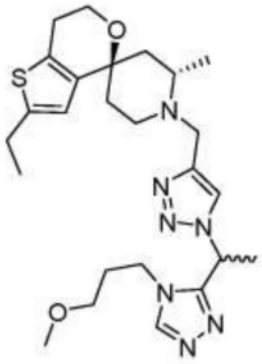
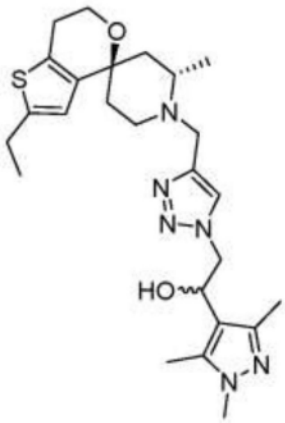
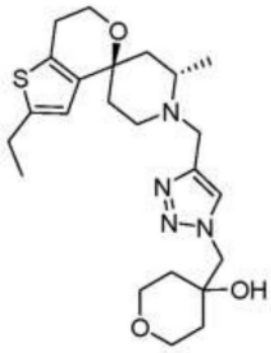
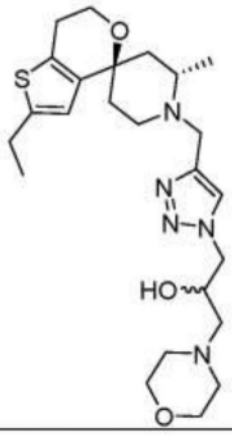
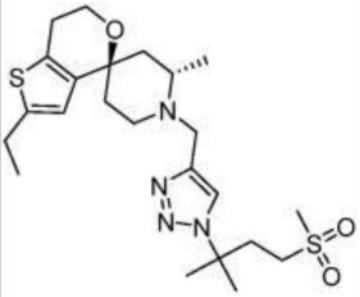
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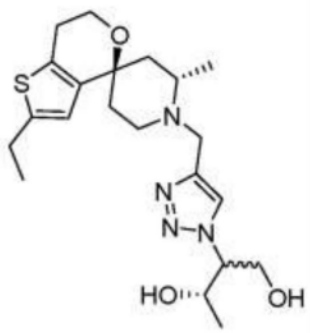
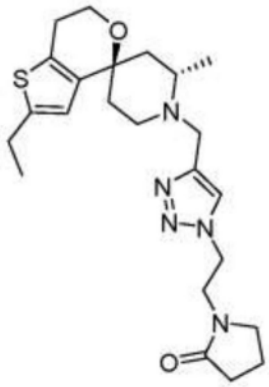
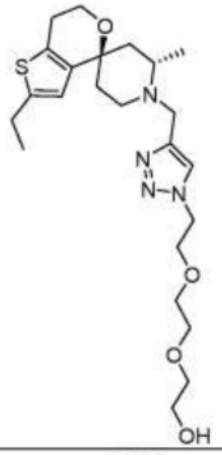
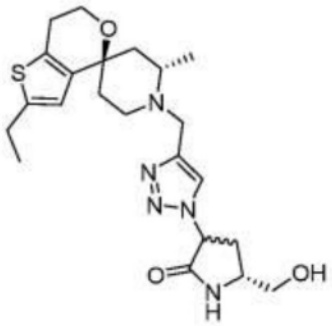
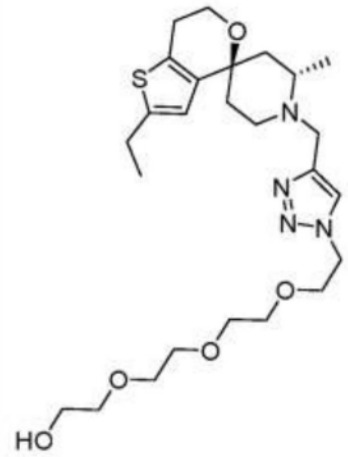
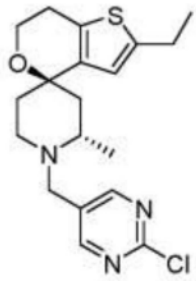
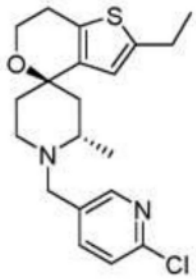
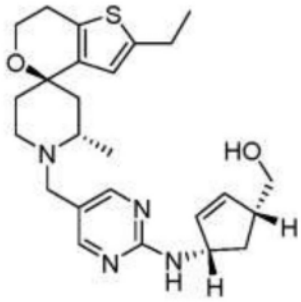
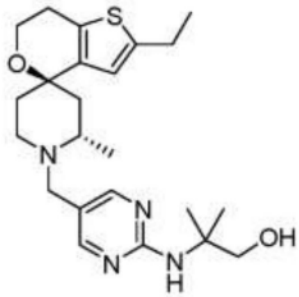
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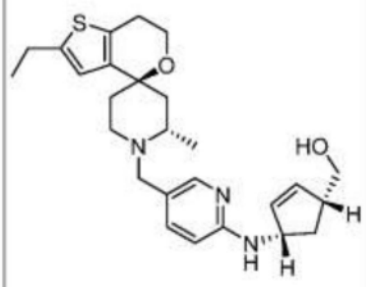
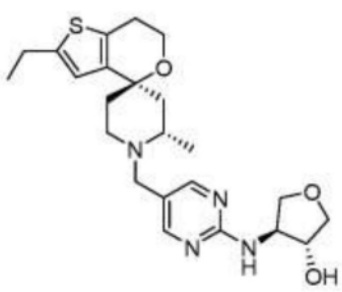
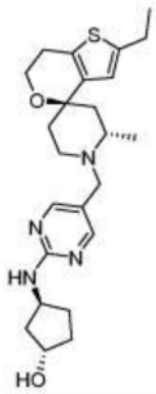
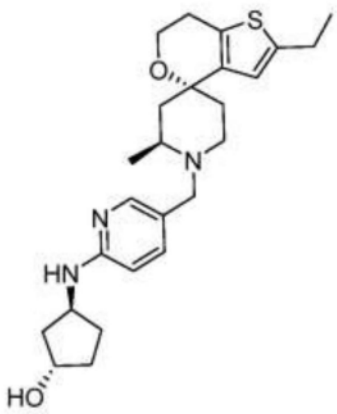
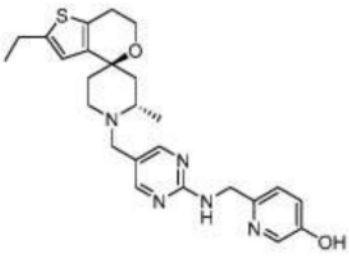
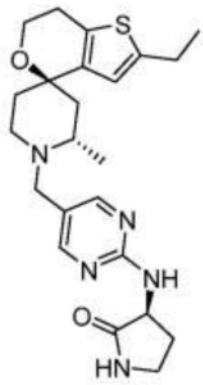
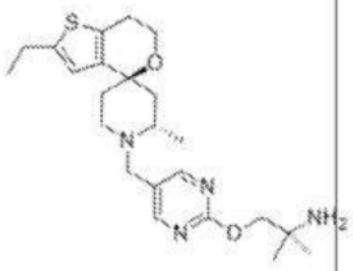
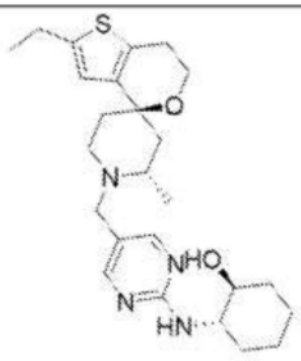
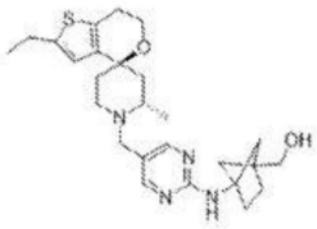
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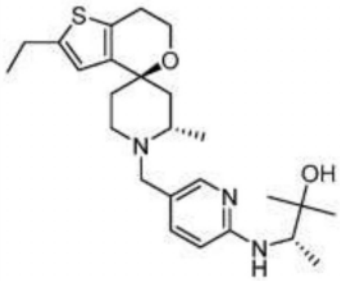
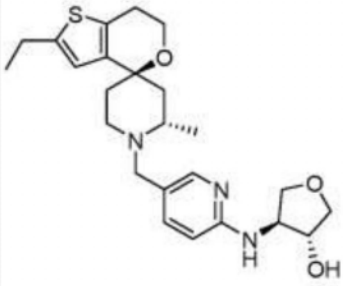
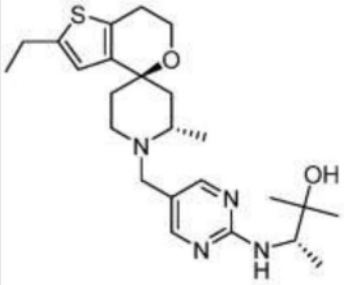
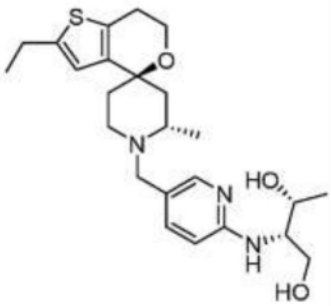
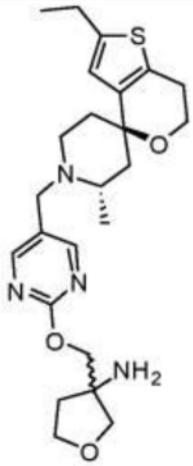
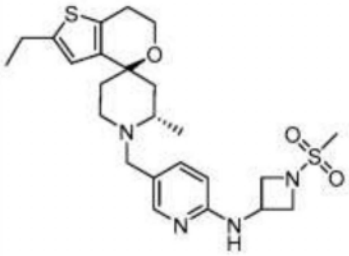
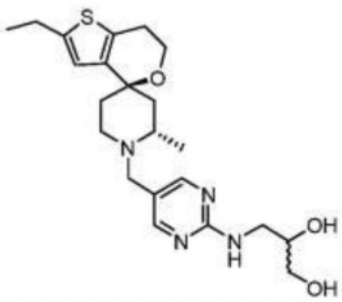
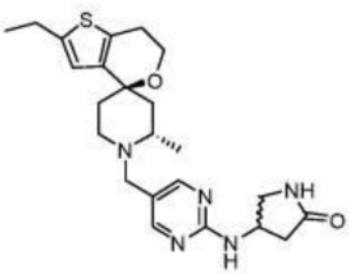
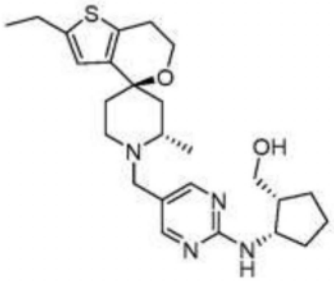
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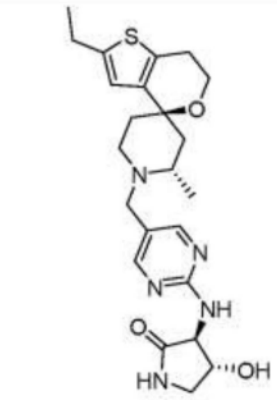
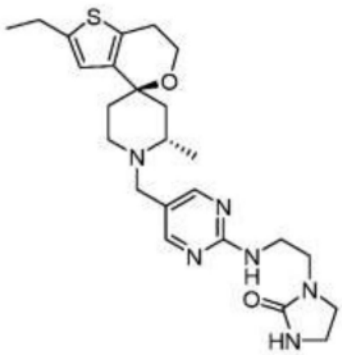
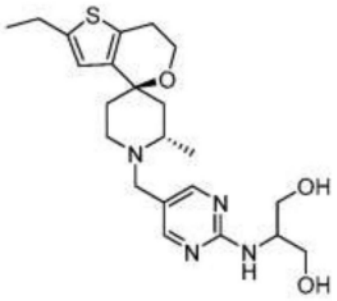
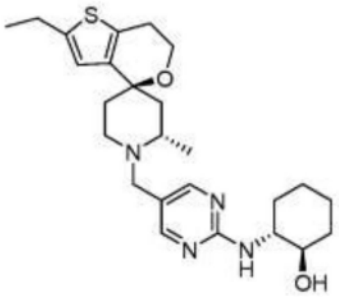
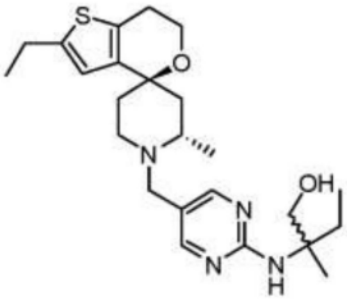
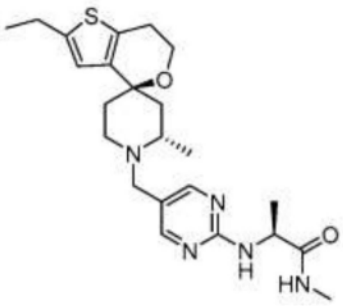
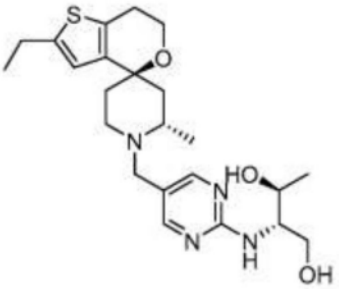
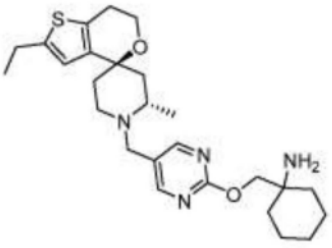
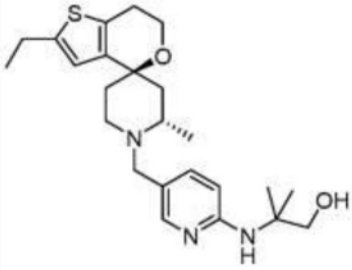
[0206]

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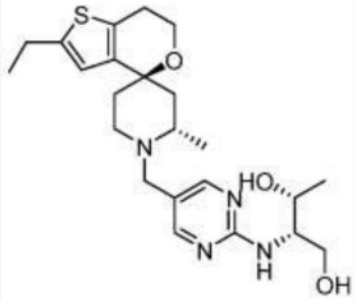
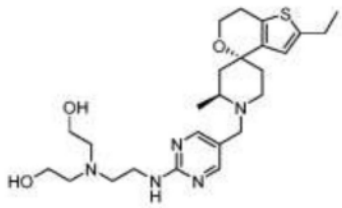
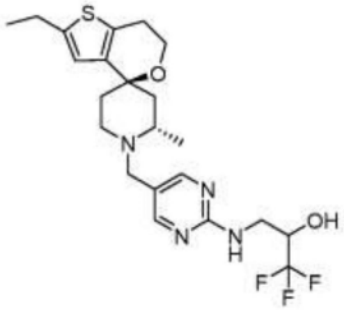
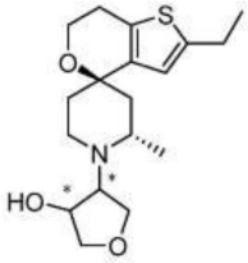
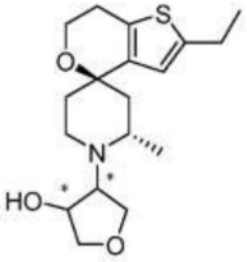
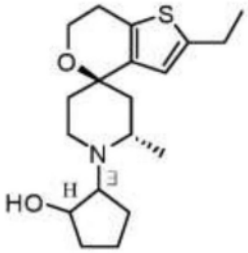
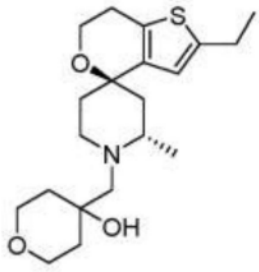
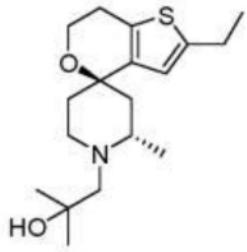
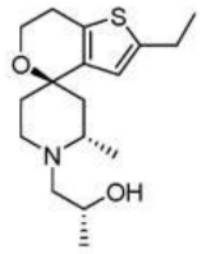
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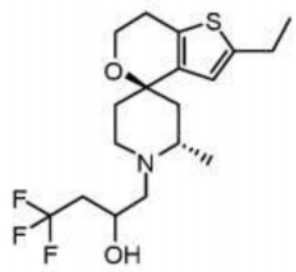
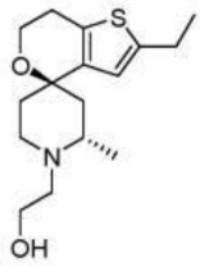
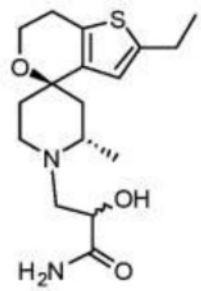
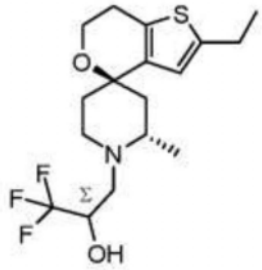
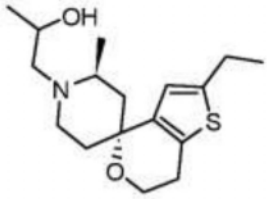
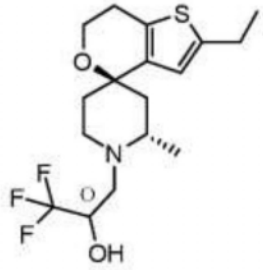
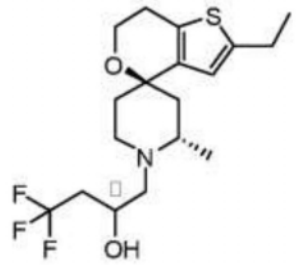
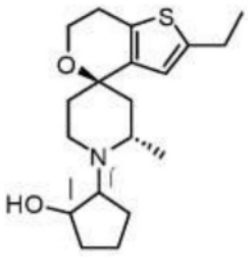
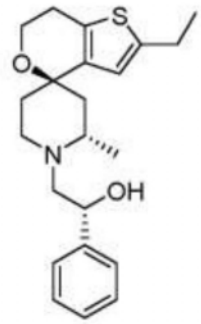
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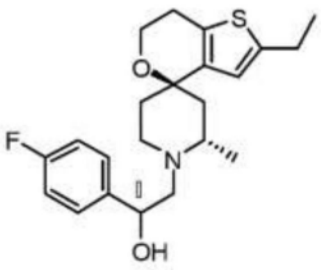
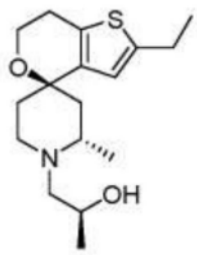
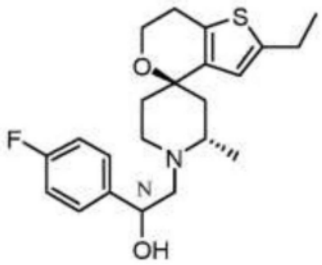
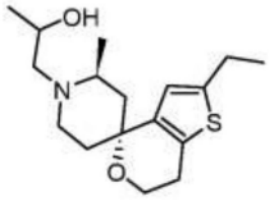
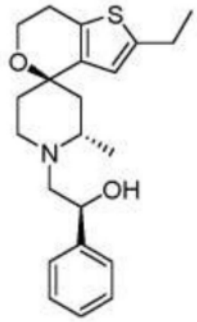
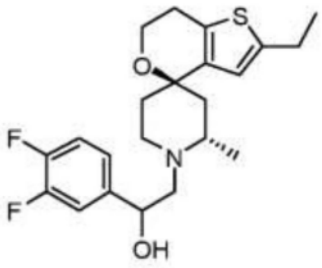
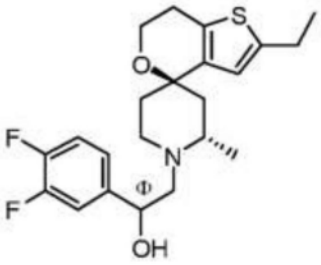
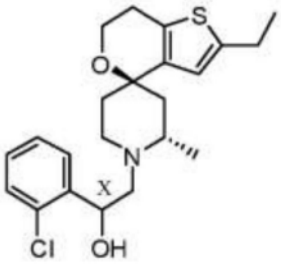
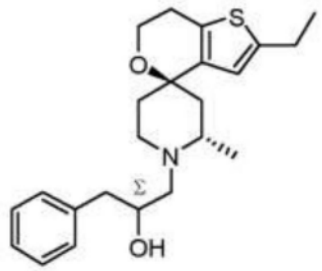
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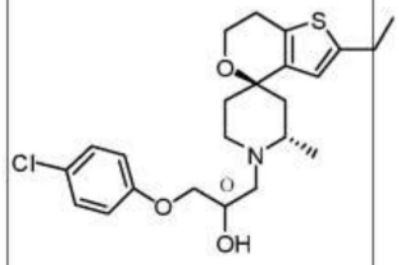
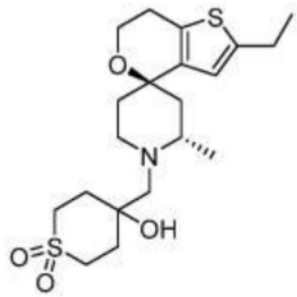
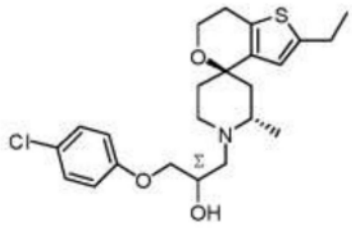
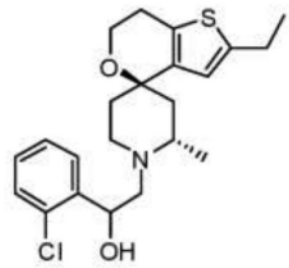
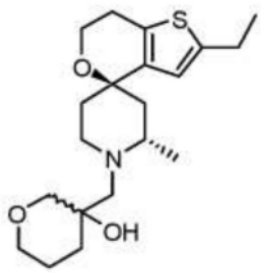
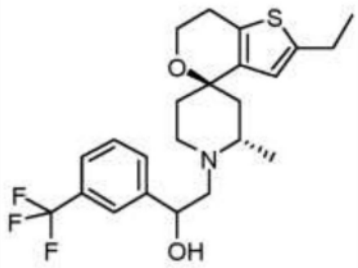
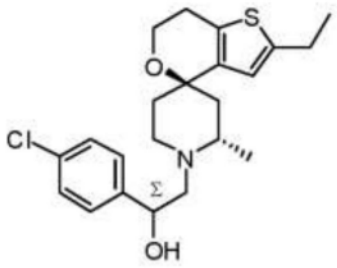
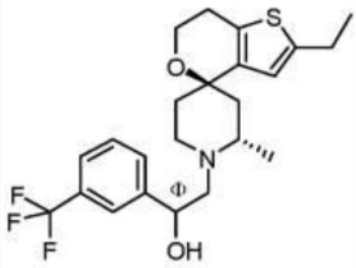
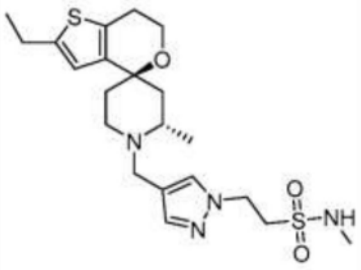
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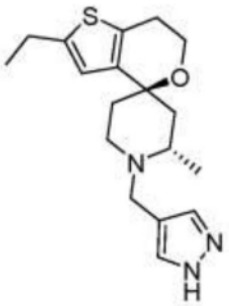
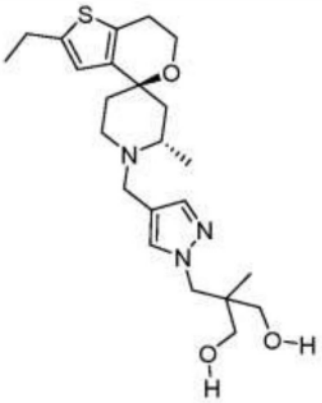
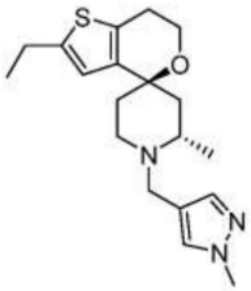
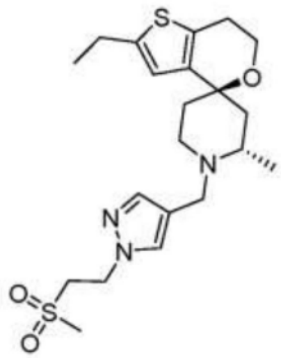
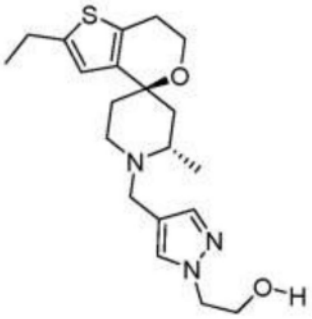
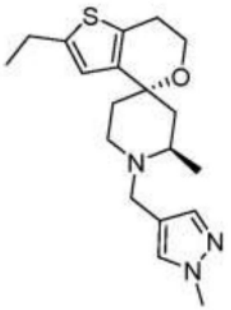
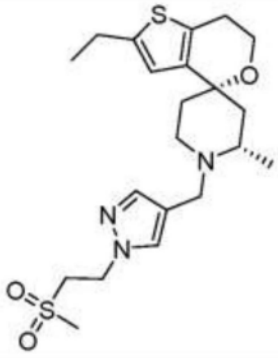
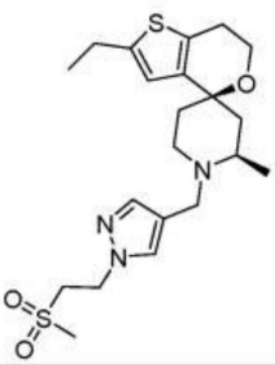
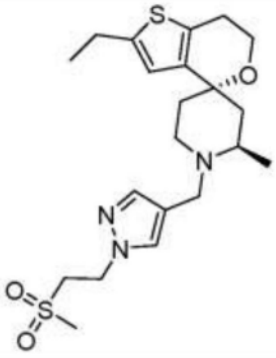
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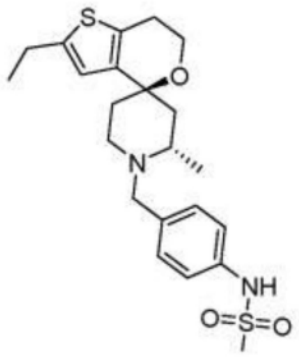
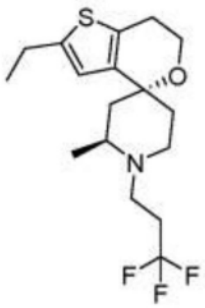
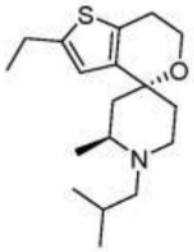
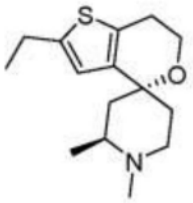
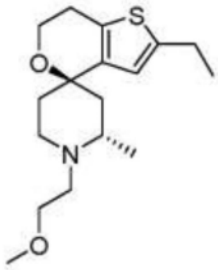
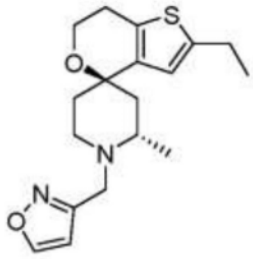
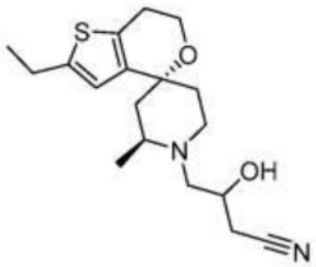
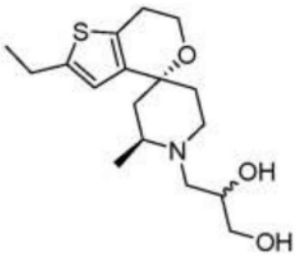
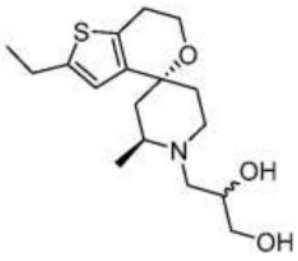
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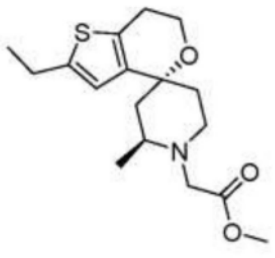
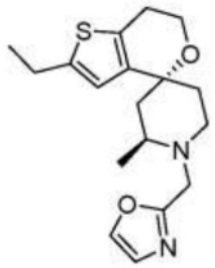
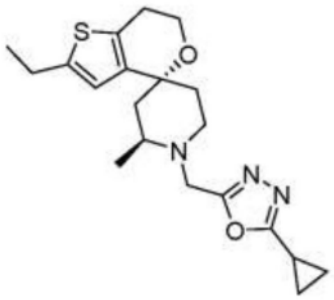
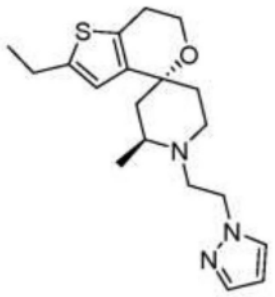
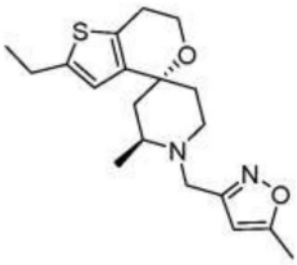
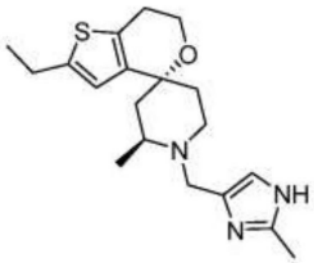
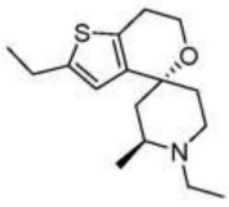
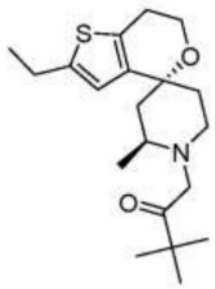
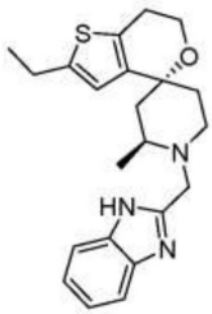
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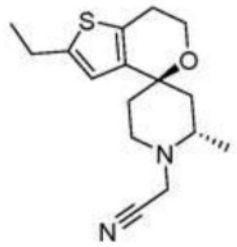
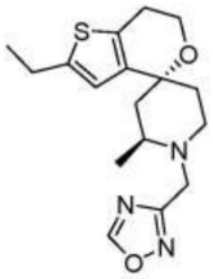
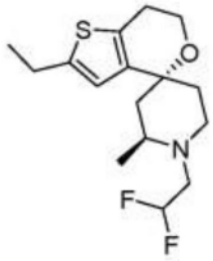
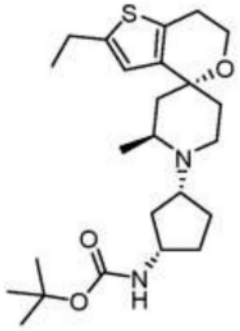
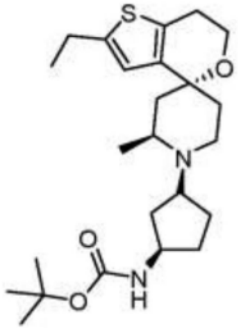
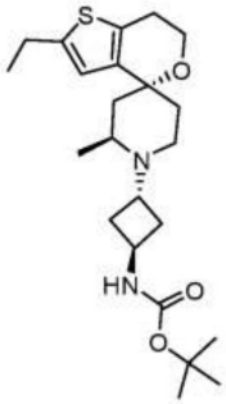
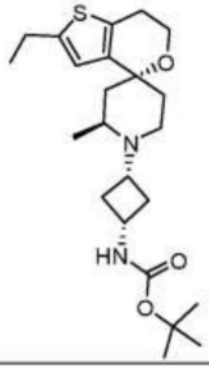
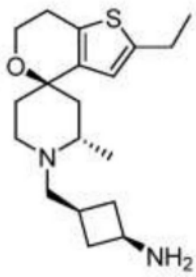
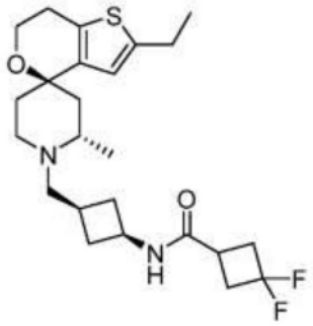
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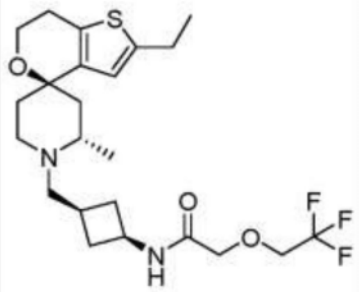
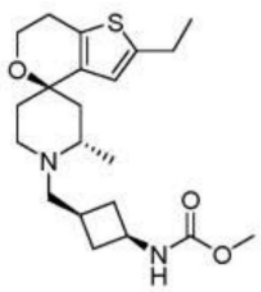
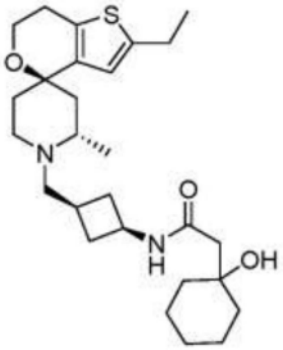
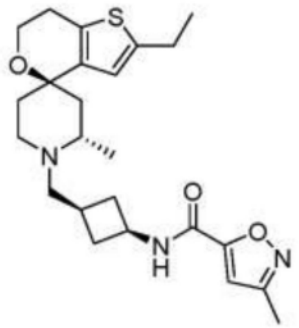
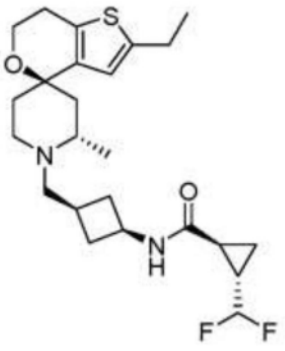
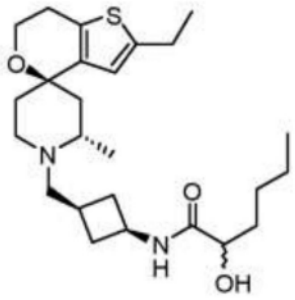
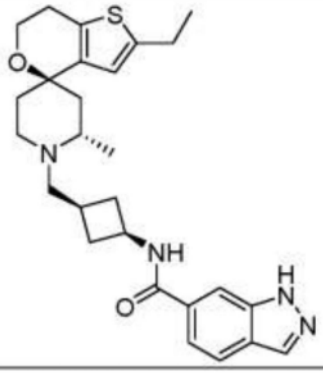
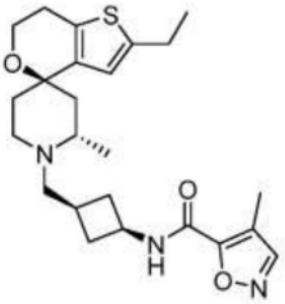
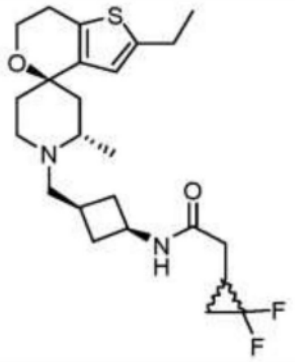
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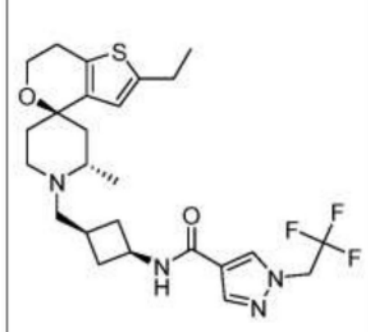
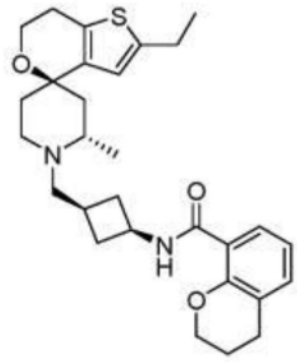
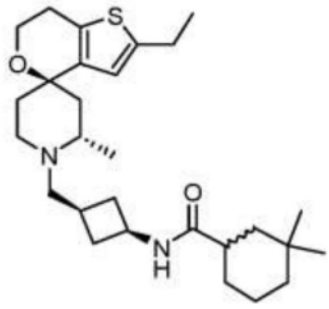
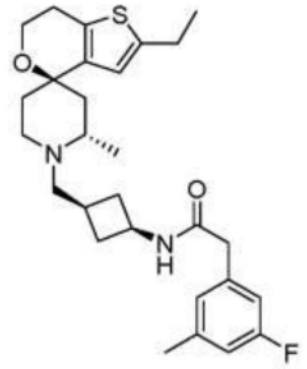
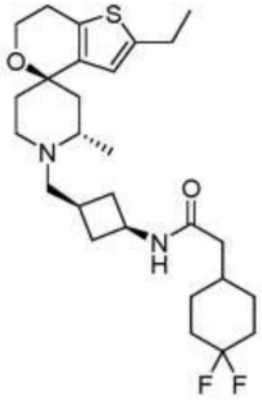
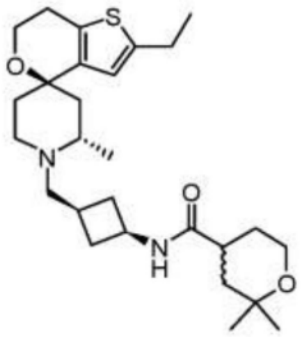
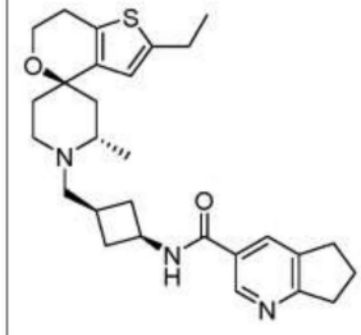
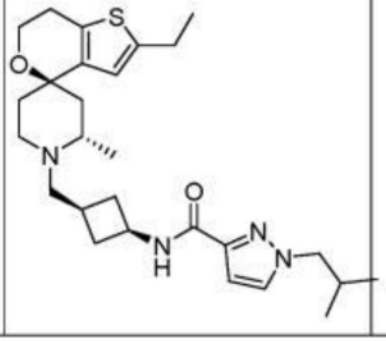
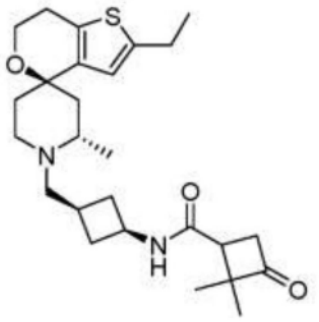
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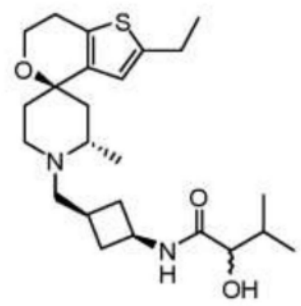
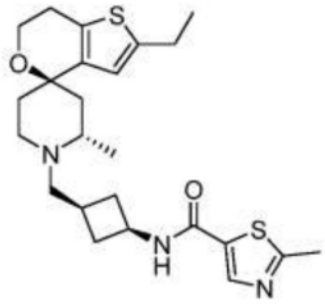
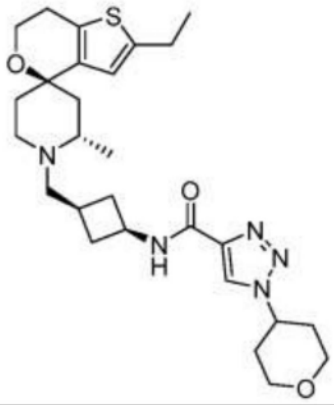
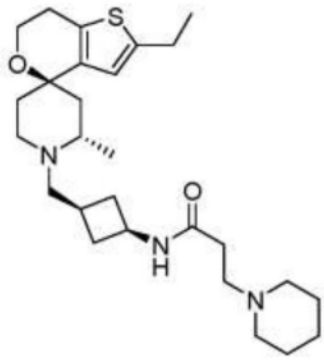
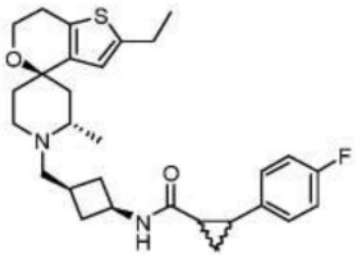
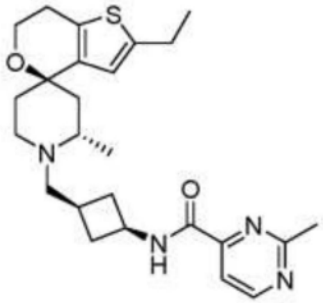
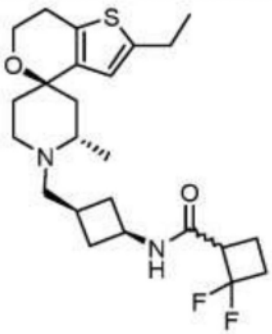
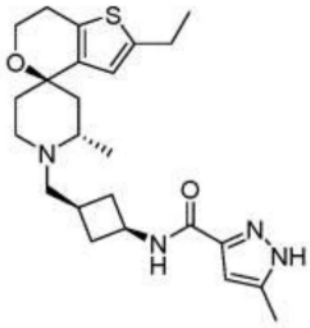
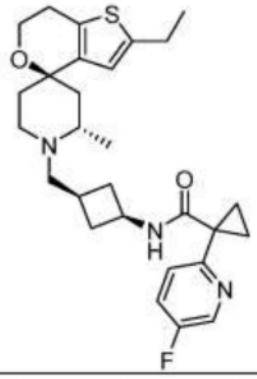
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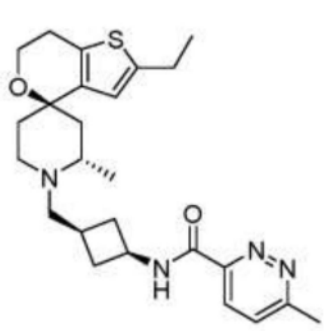
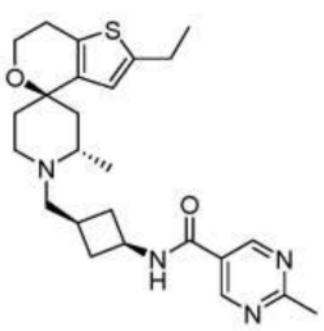
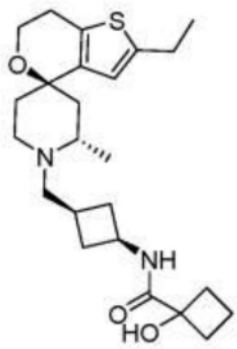
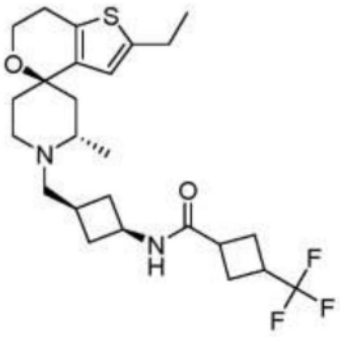
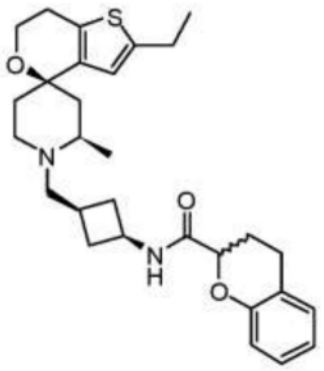
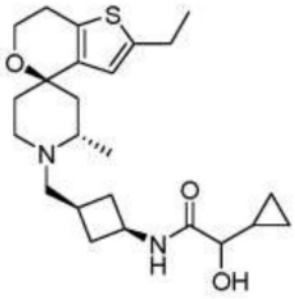
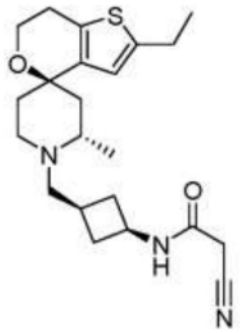
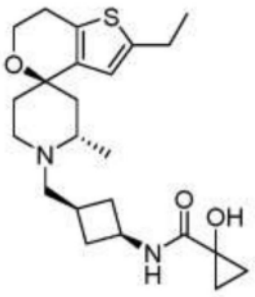
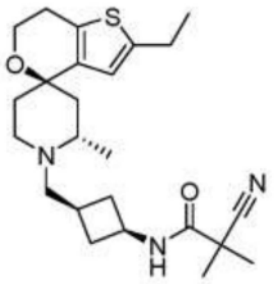
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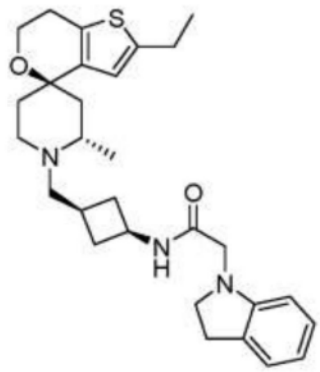
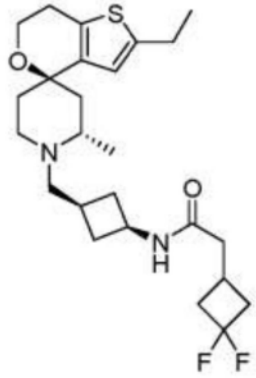
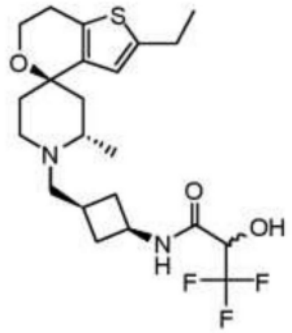
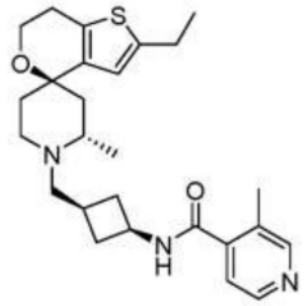
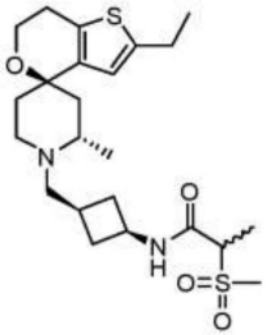
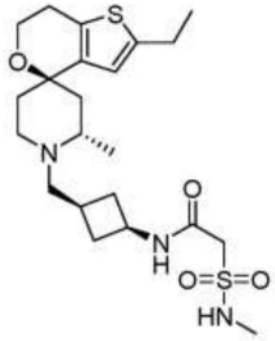
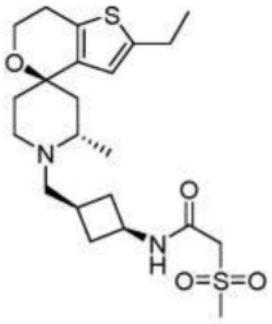
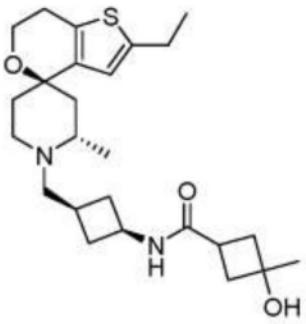
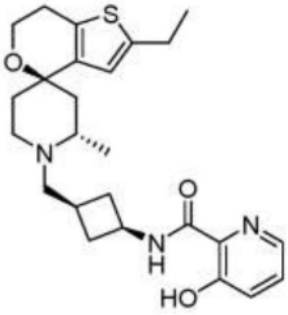
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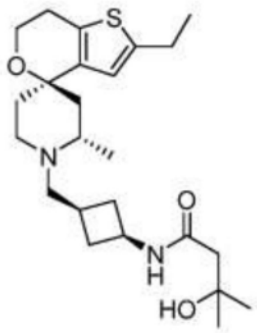
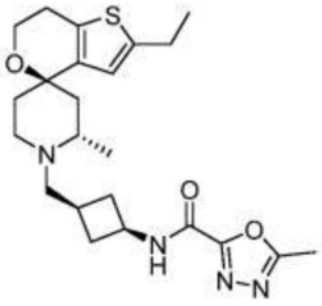
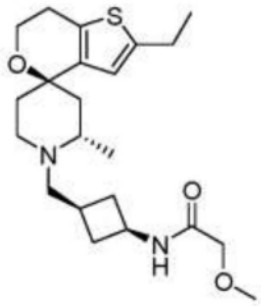
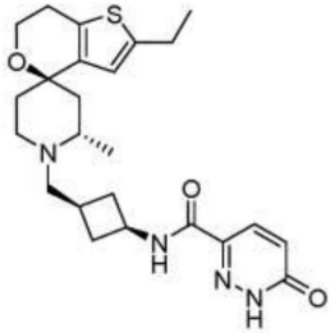
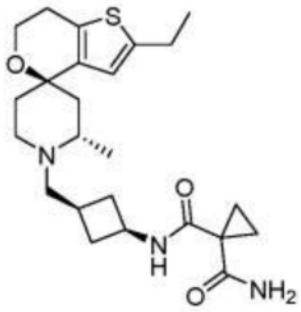
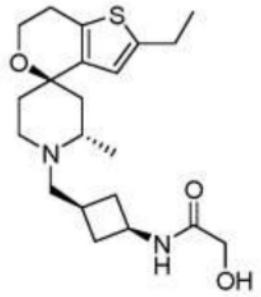
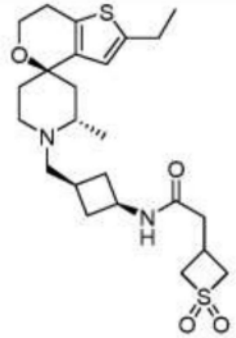
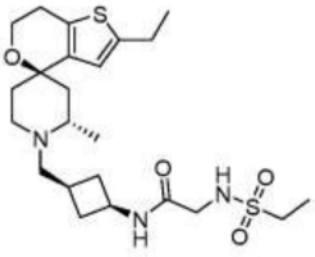
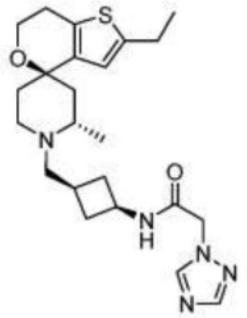
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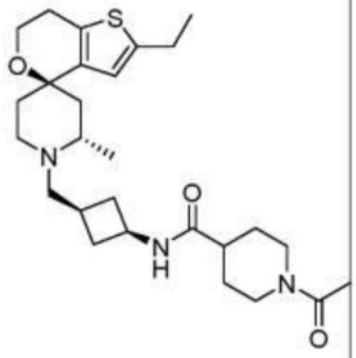
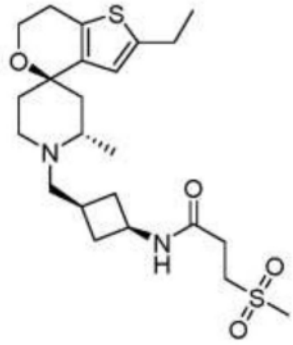
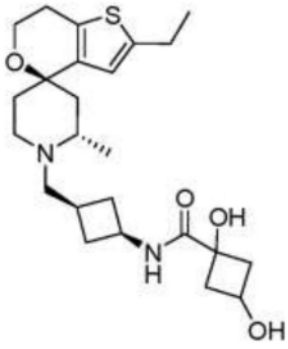
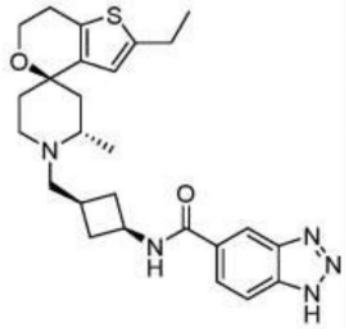
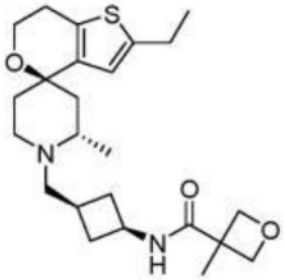
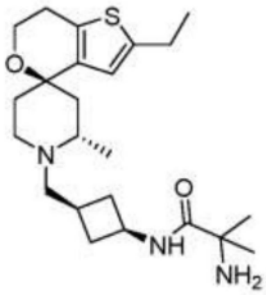
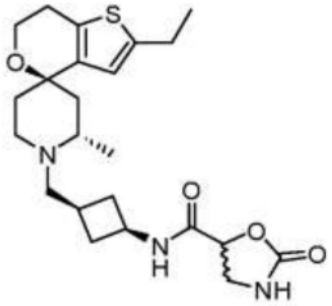
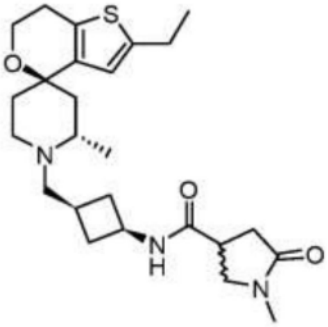
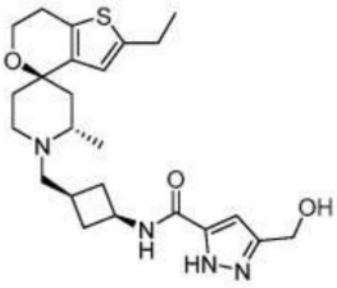
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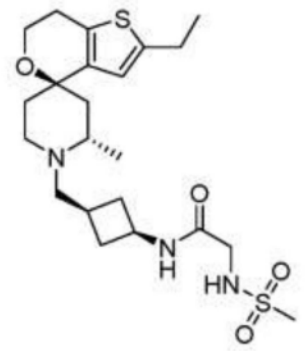
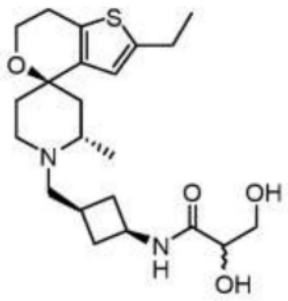
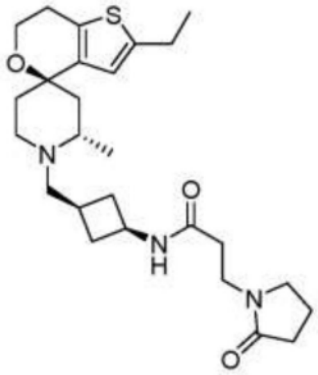
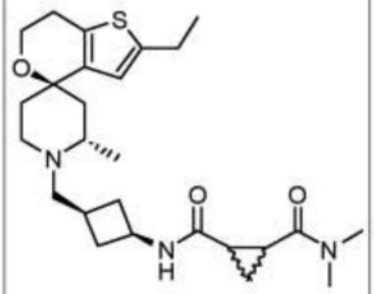
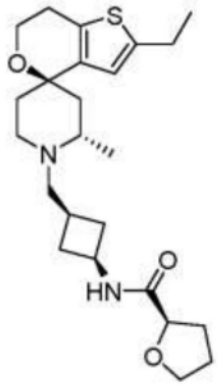
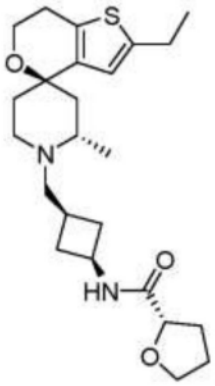
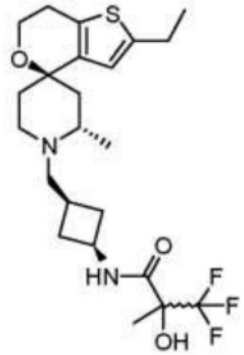
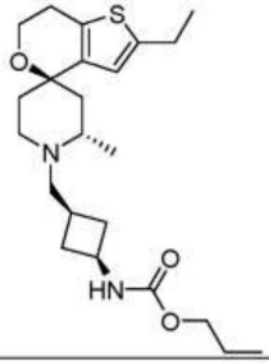
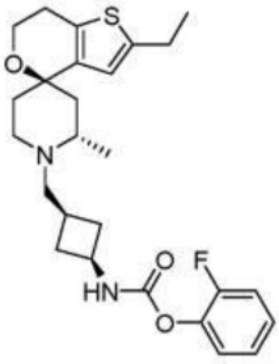
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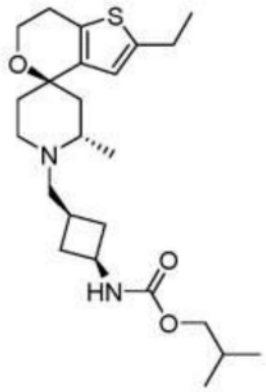
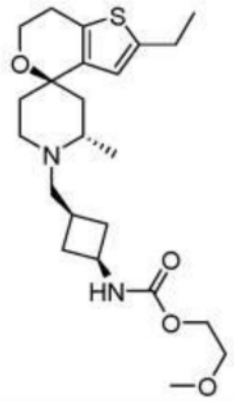
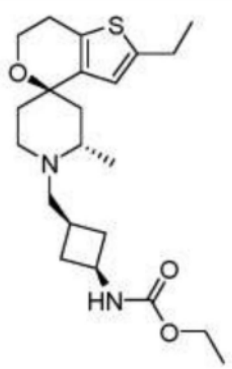
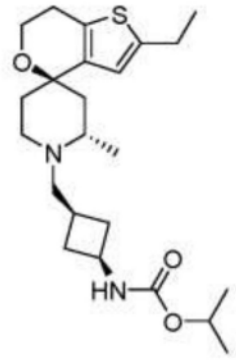
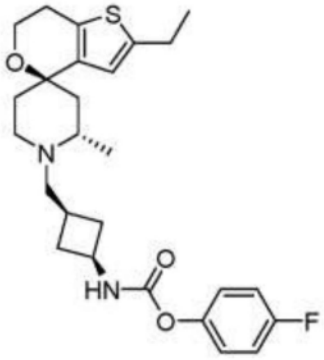
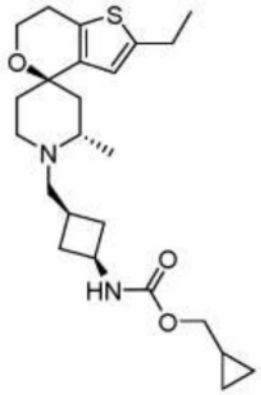
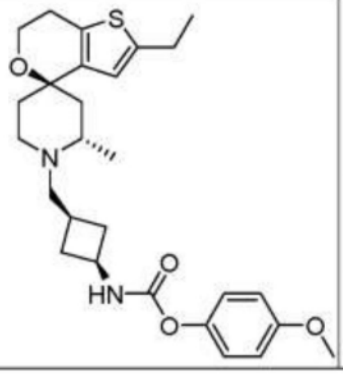
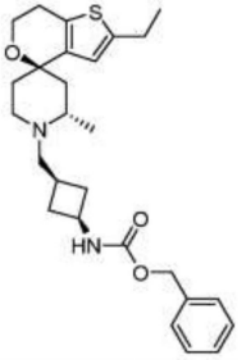
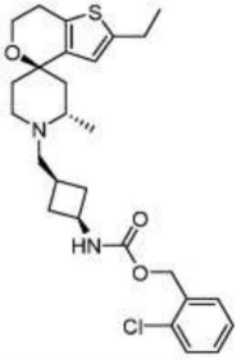
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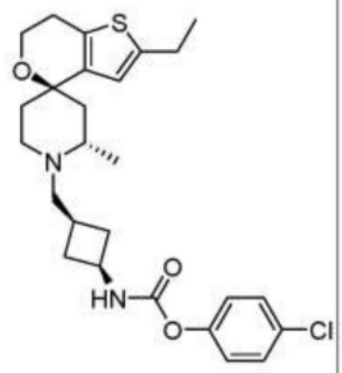
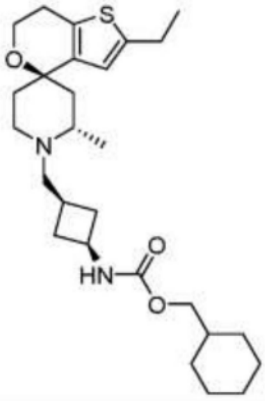
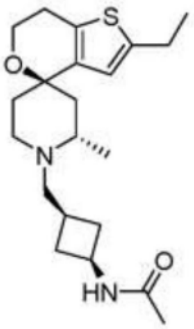
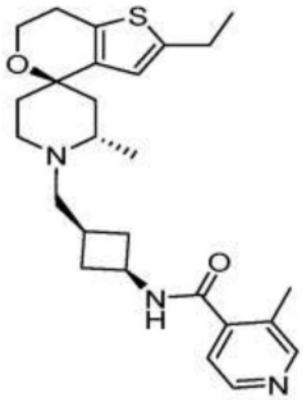
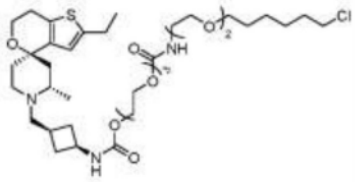
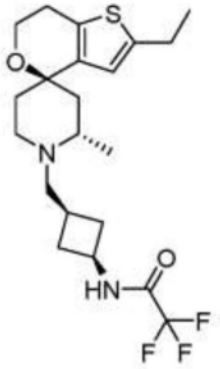
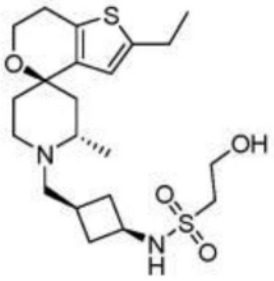
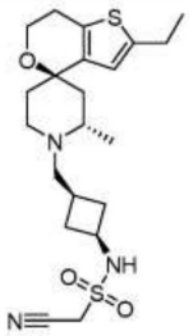
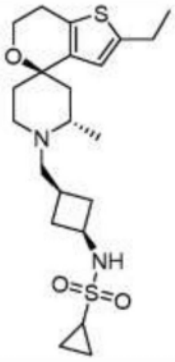
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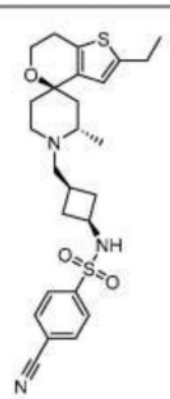
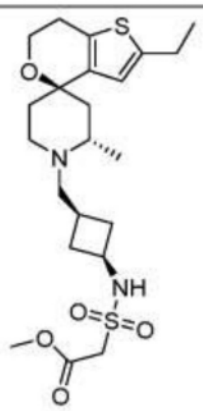
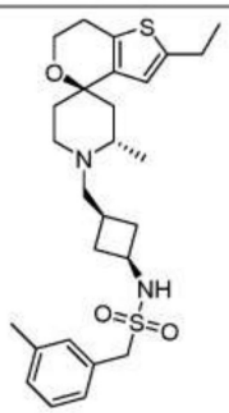
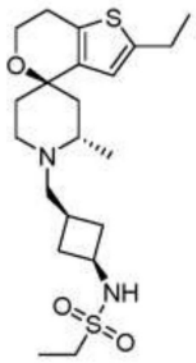
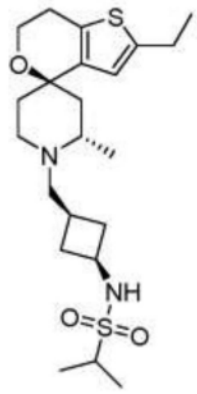
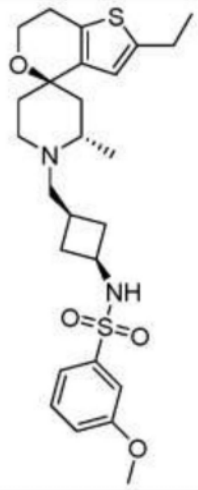
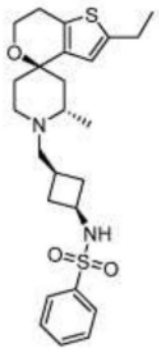
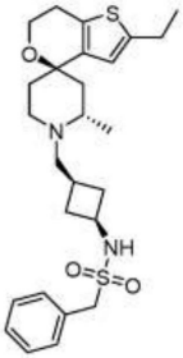
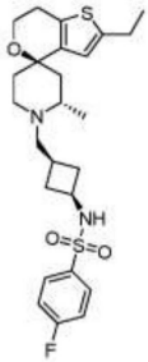
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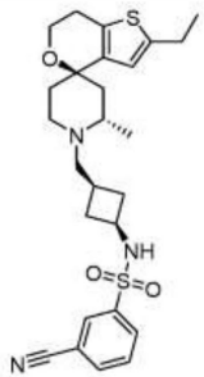
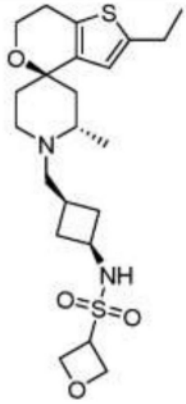
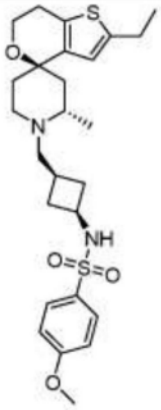
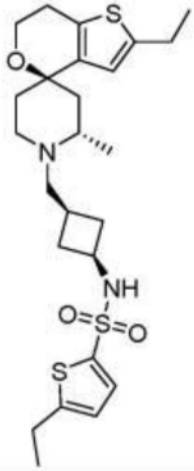
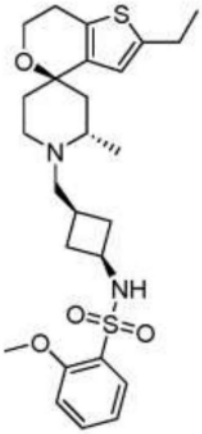
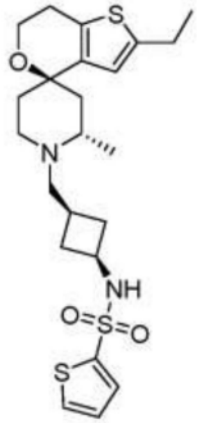
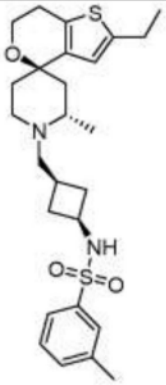
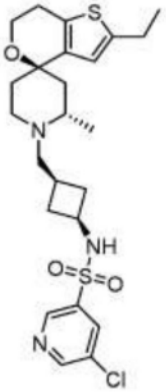
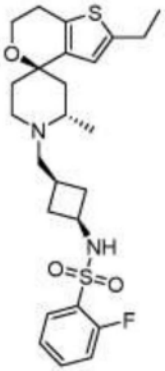
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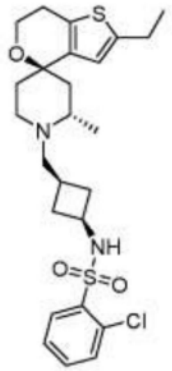
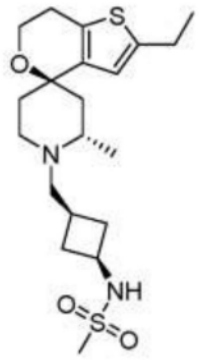
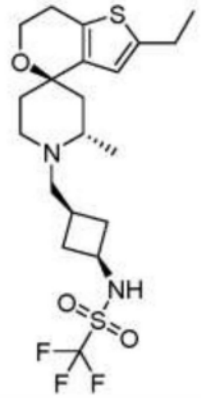
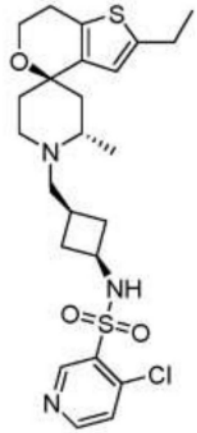
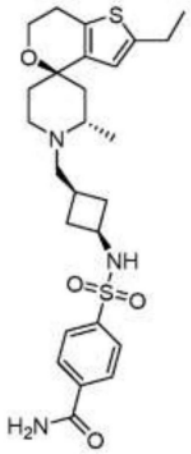
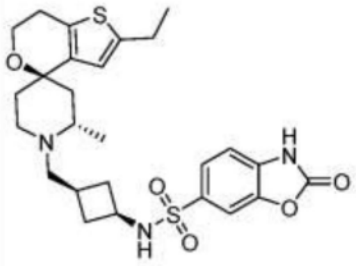
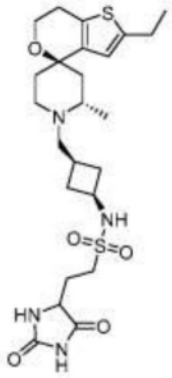
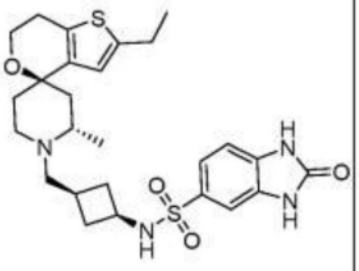
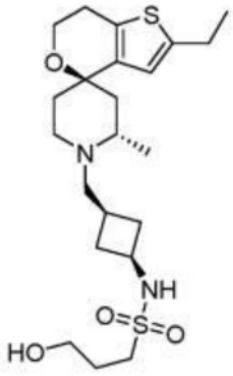
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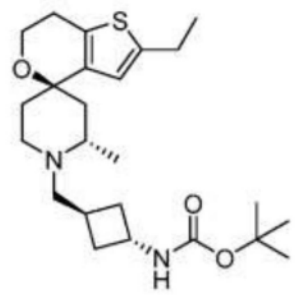
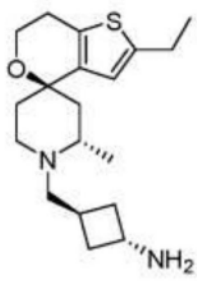
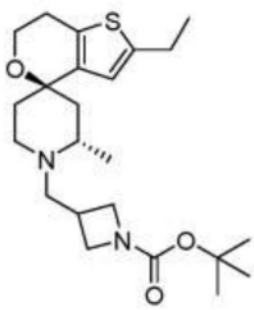
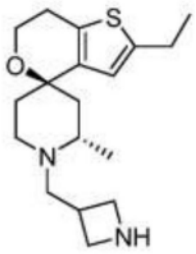
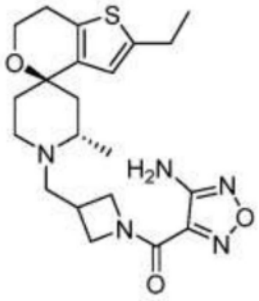
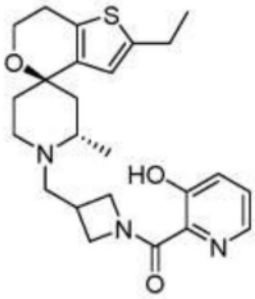
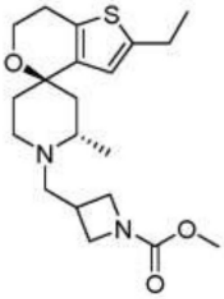
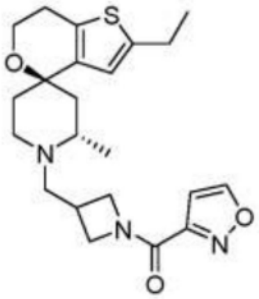
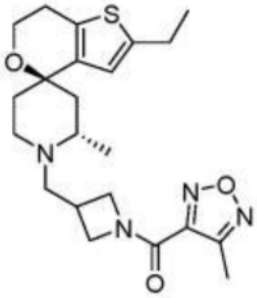
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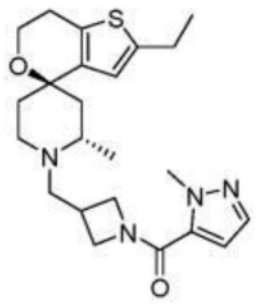
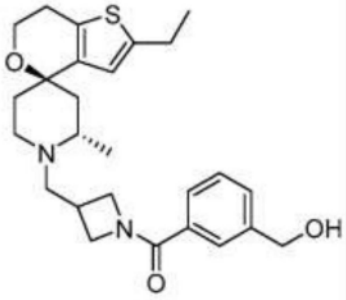
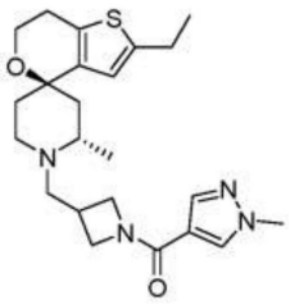
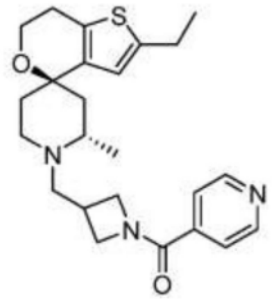
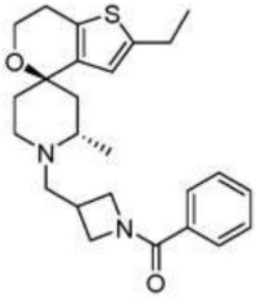
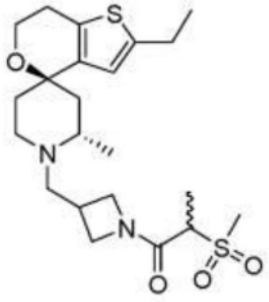
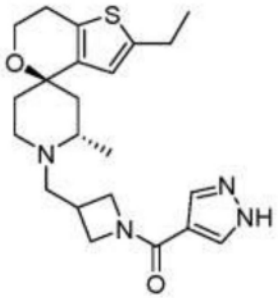
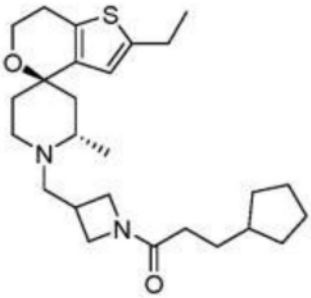
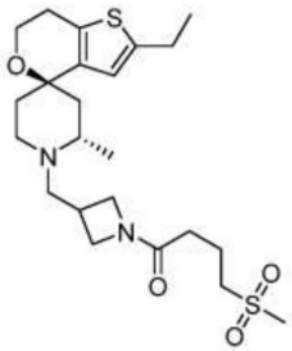
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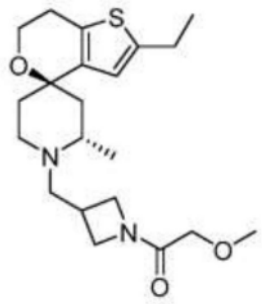
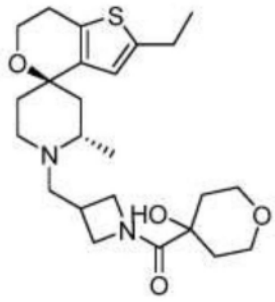
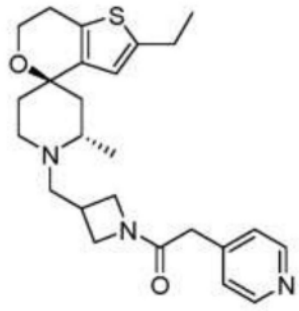
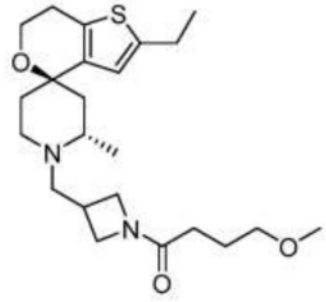
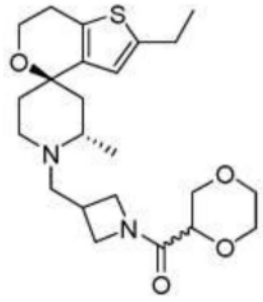
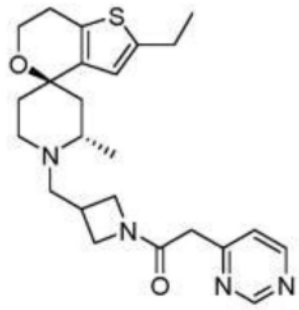
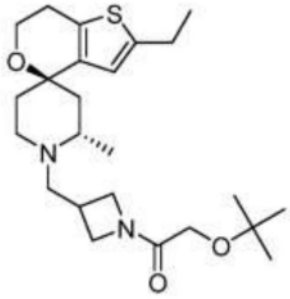
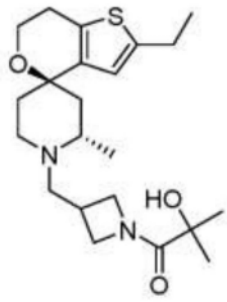
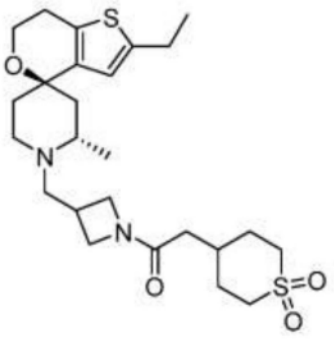
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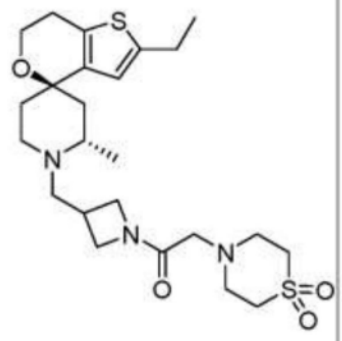
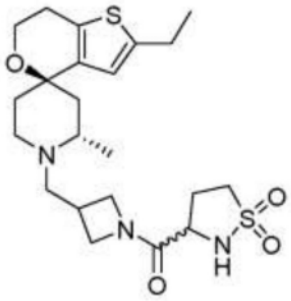
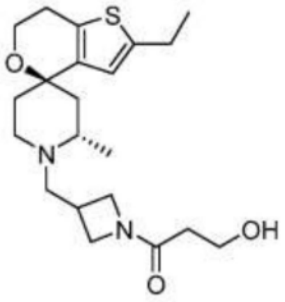
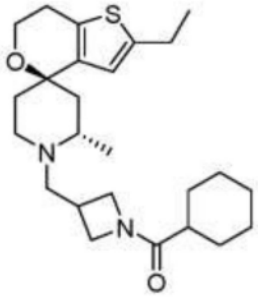
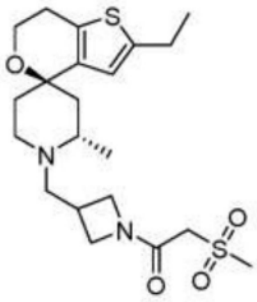
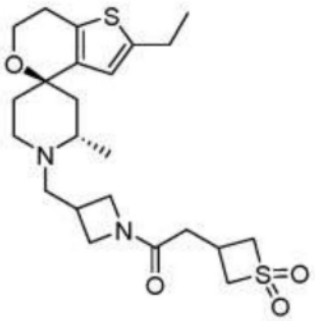
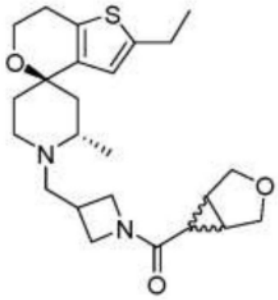
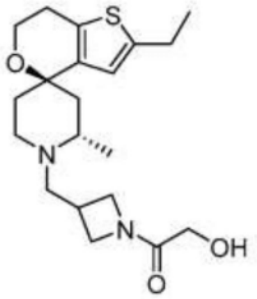
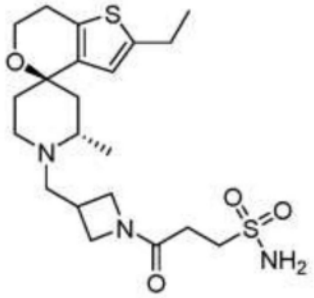
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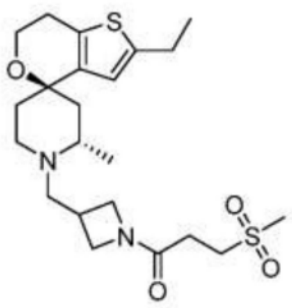
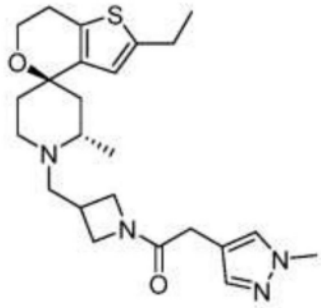
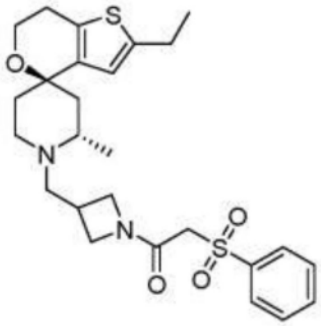
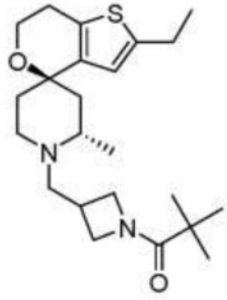
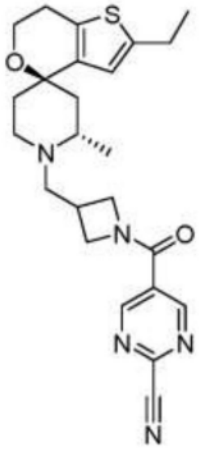
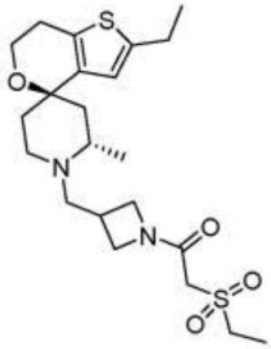
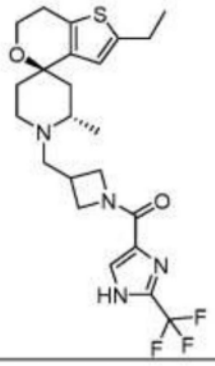
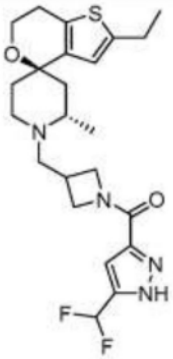
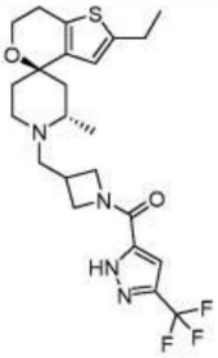
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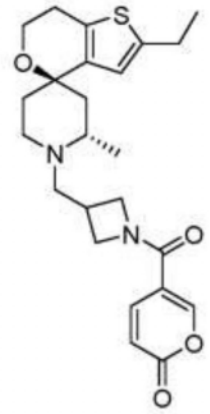
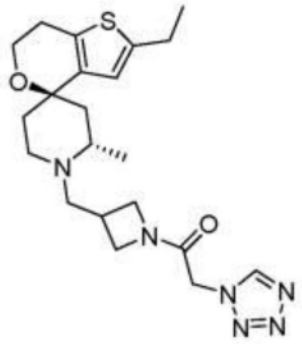
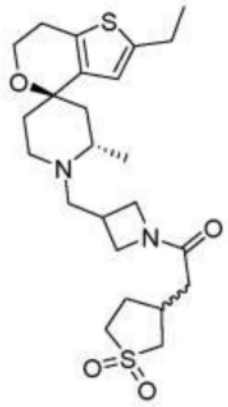
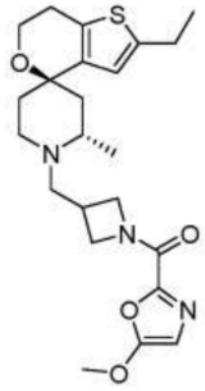
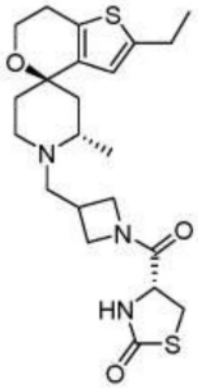
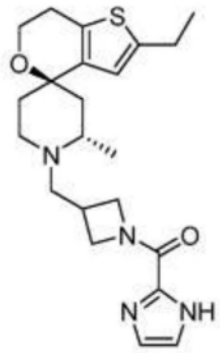
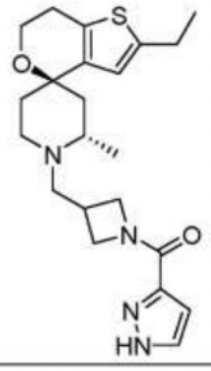
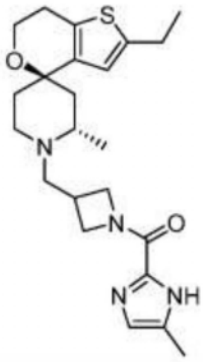
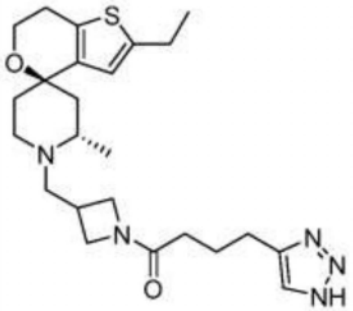
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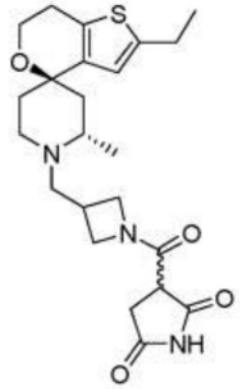
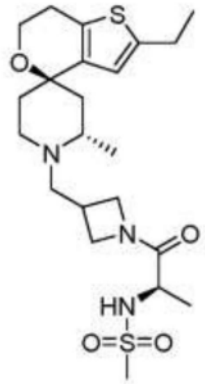
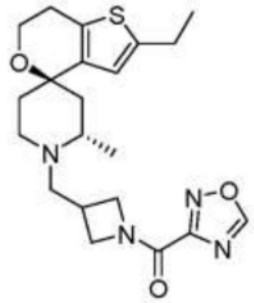
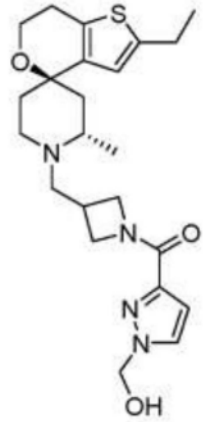
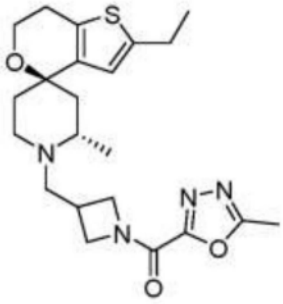
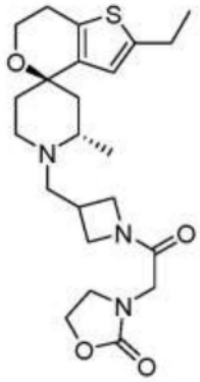
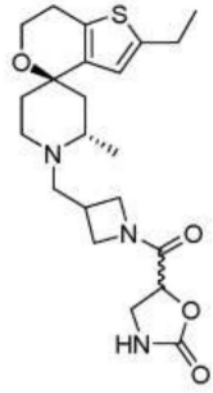
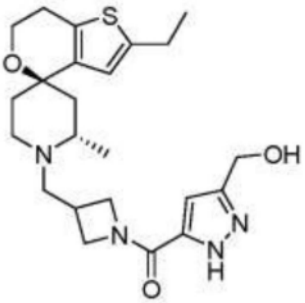
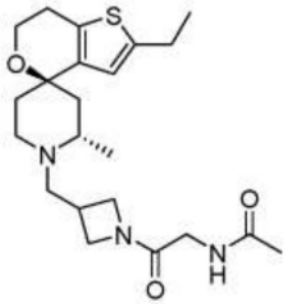
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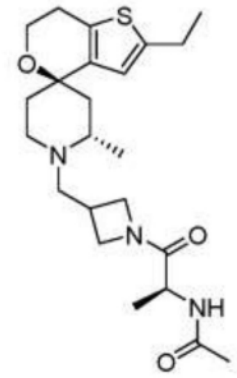
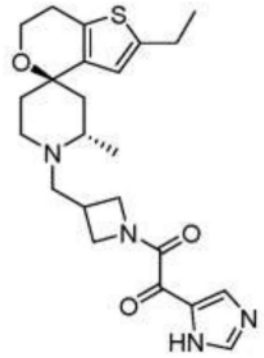
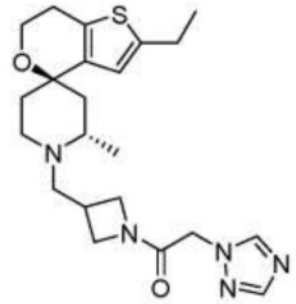
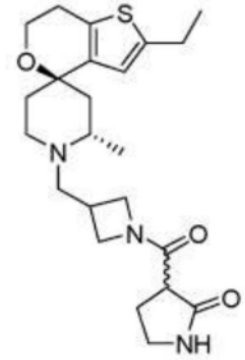
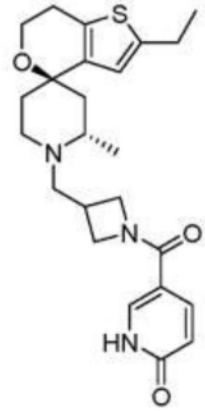
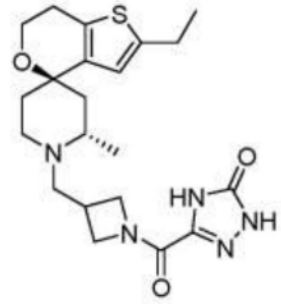
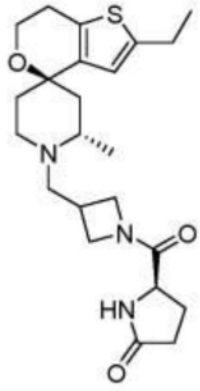
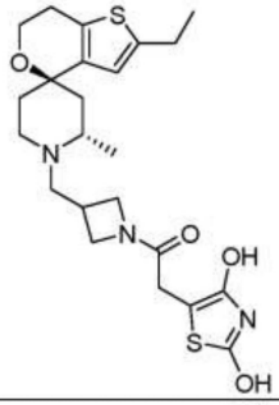
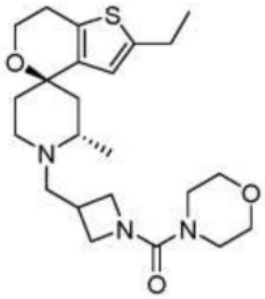
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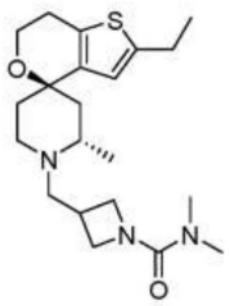
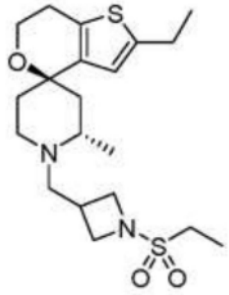
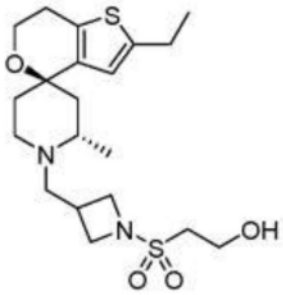
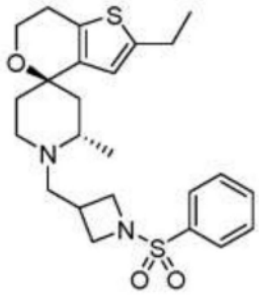
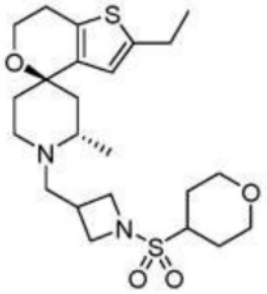
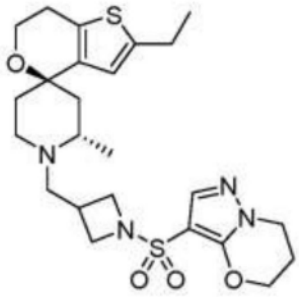
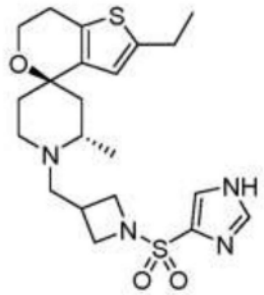
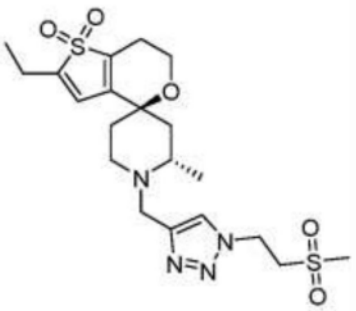
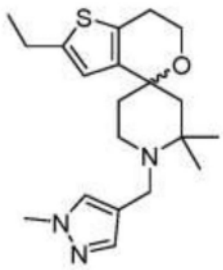
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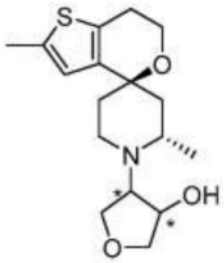
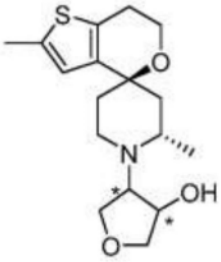
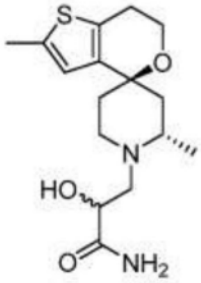
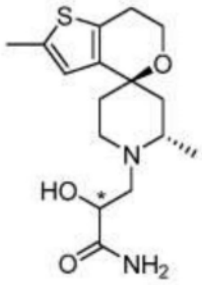
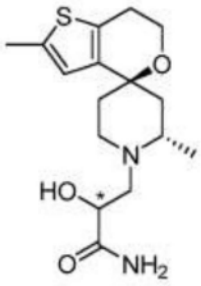
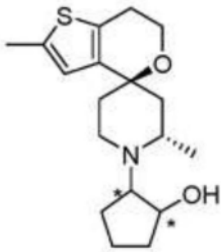
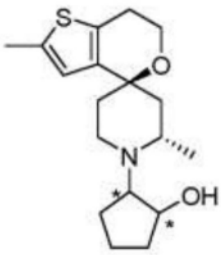
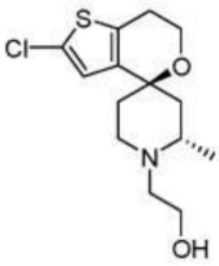
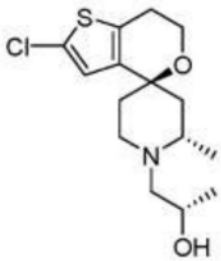
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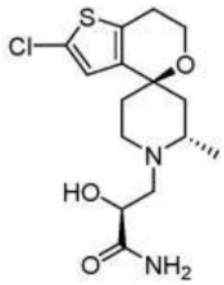
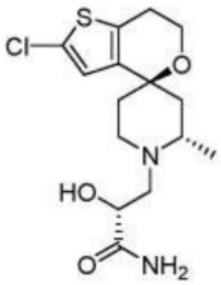
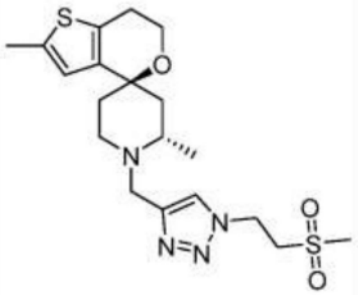
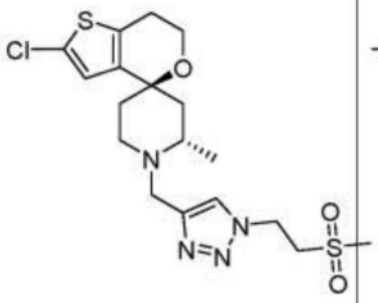
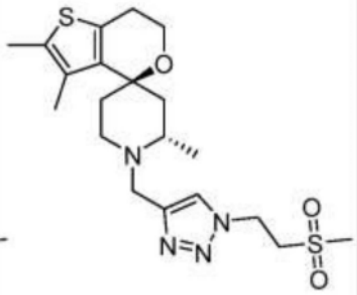
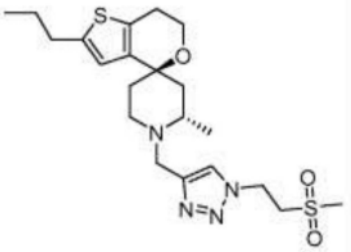
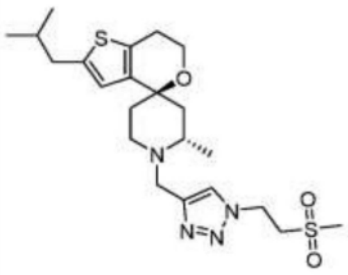
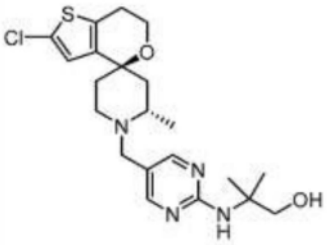
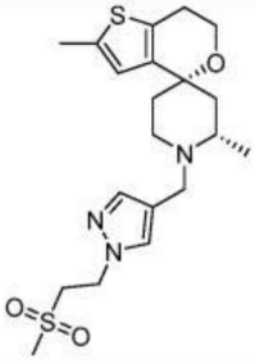
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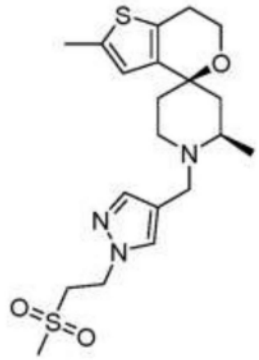
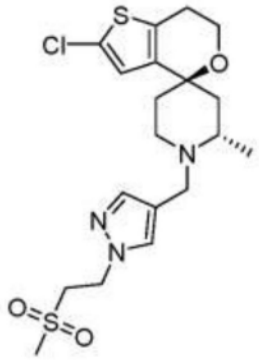
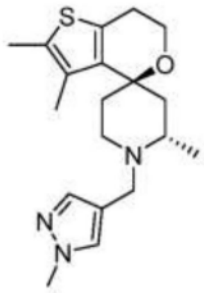
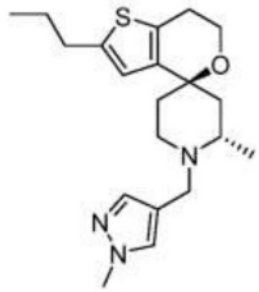
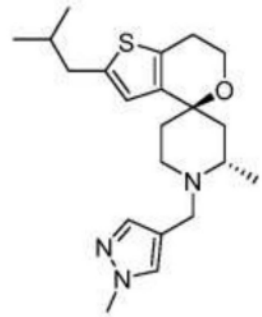
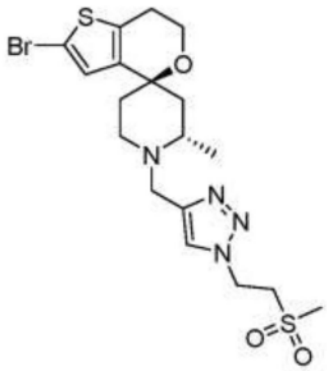
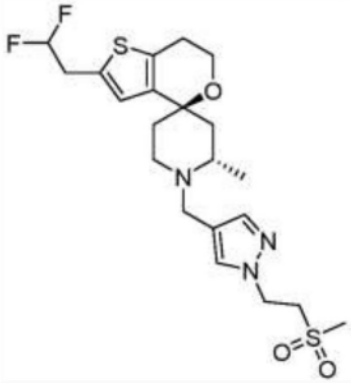
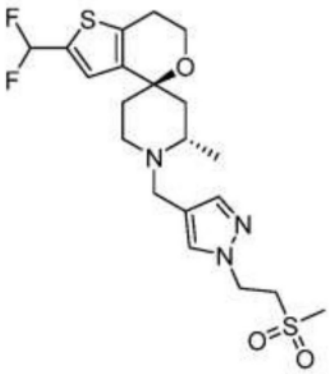
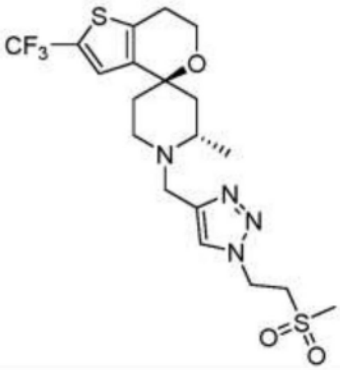
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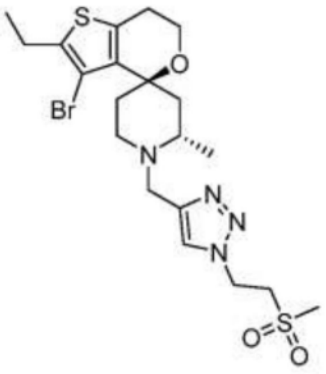
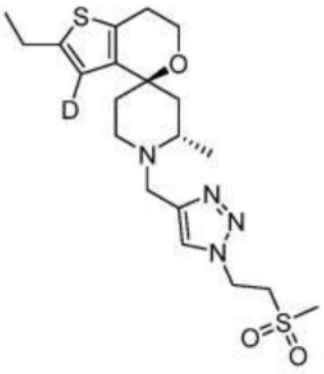
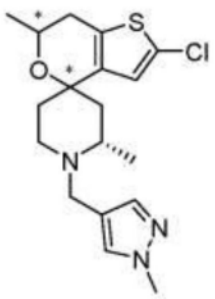
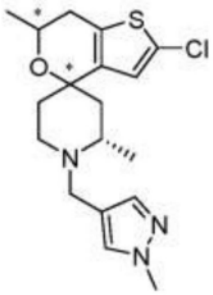
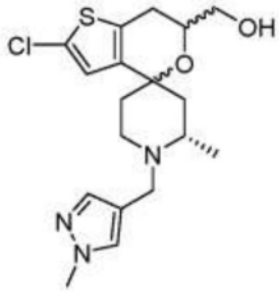
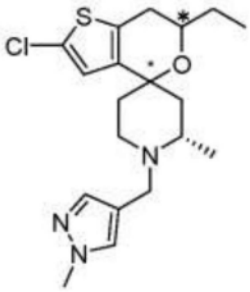
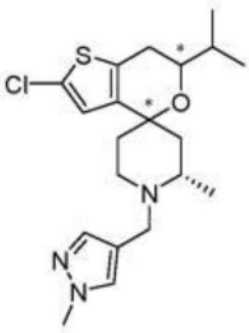
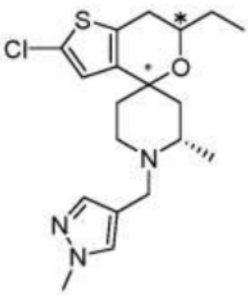
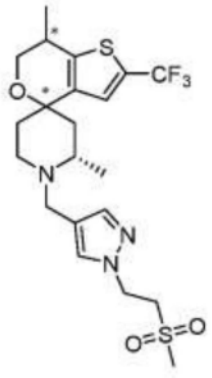
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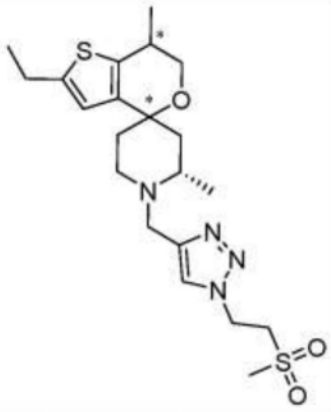
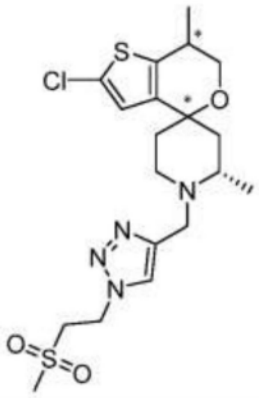
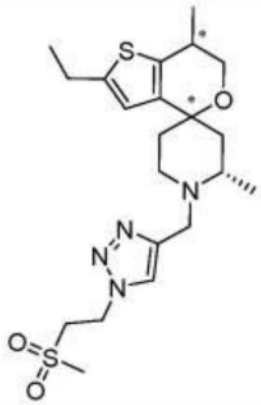
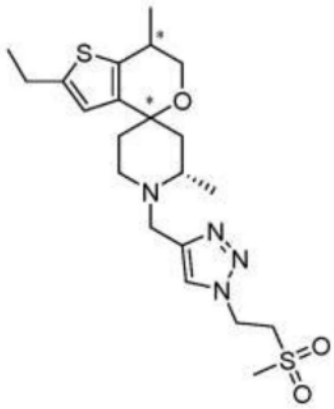
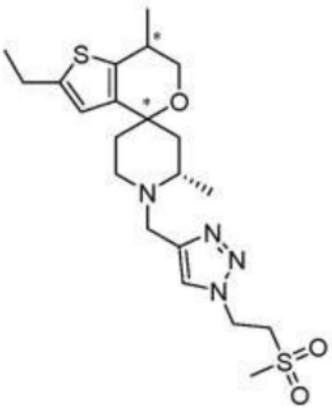
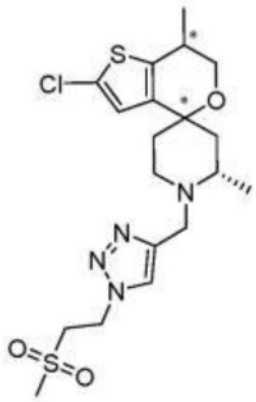
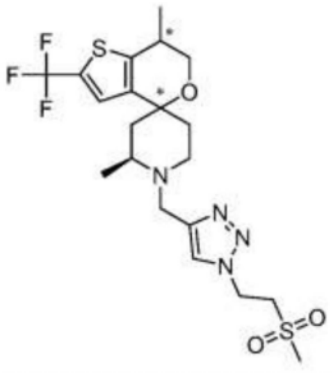
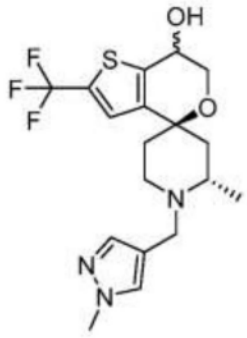
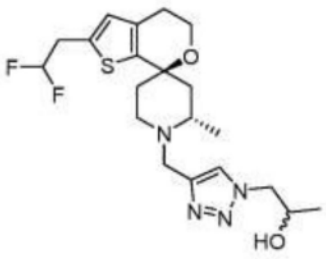
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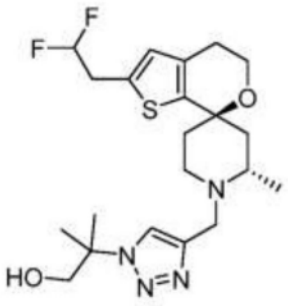
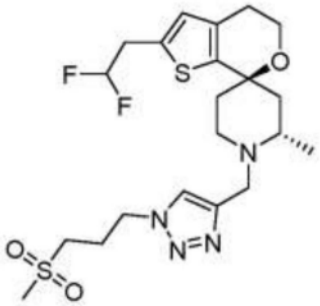
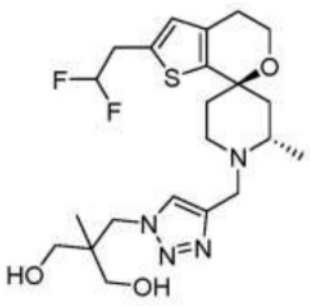
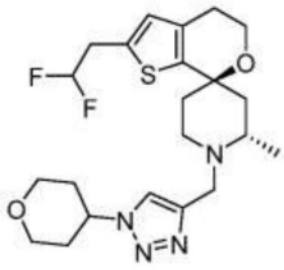
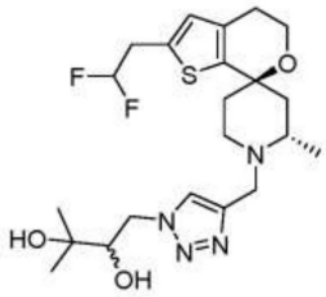
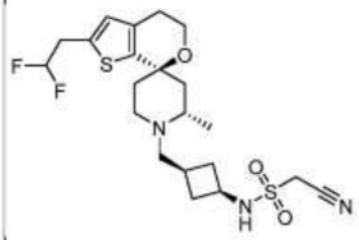
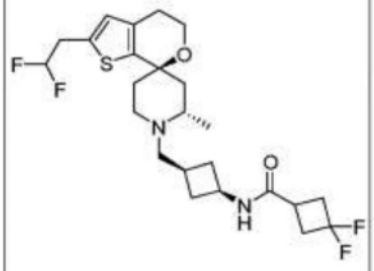
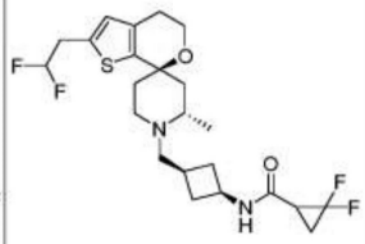
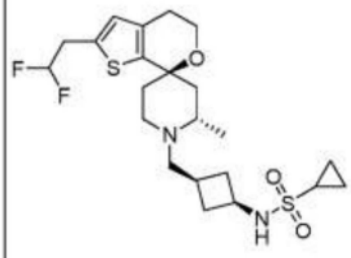
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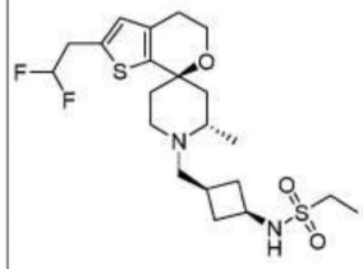
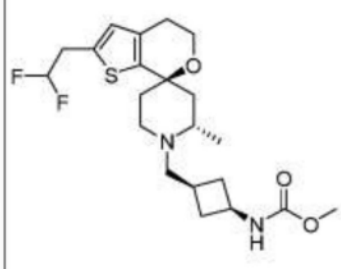
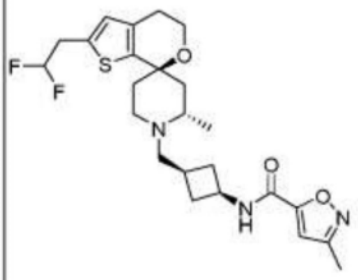
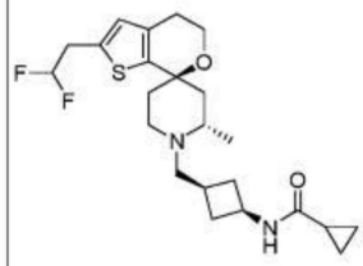
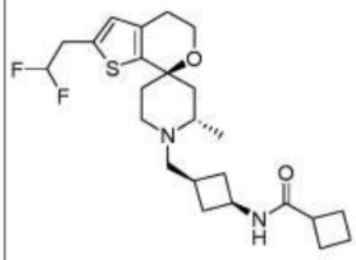
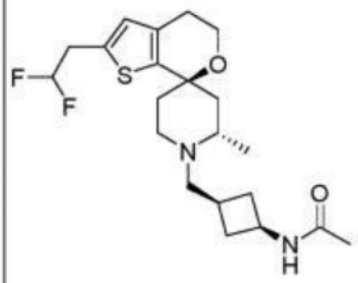
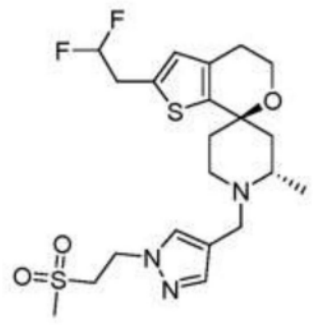
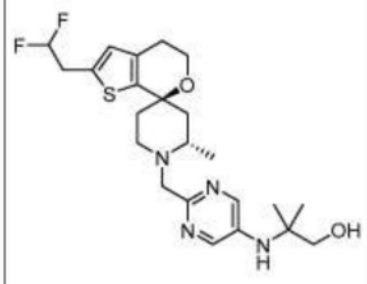
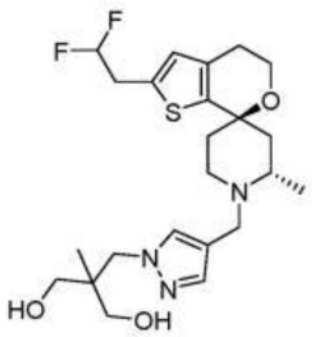
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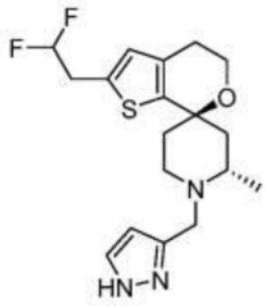
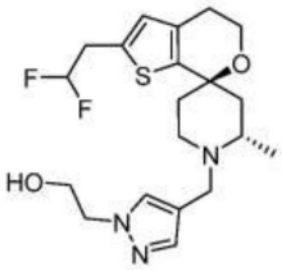
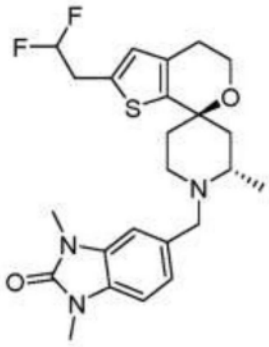
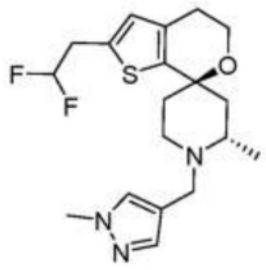
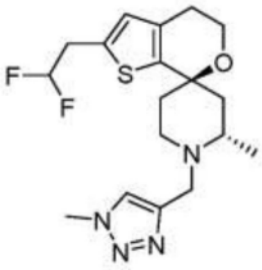
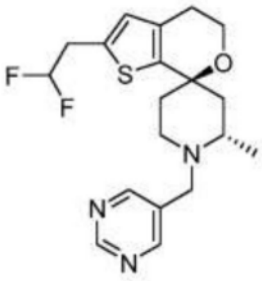
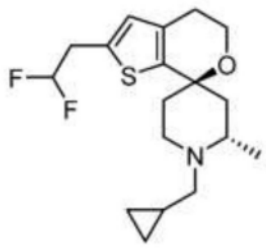
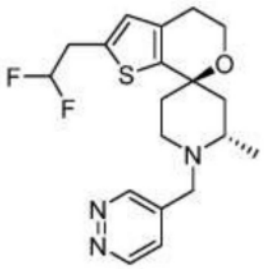
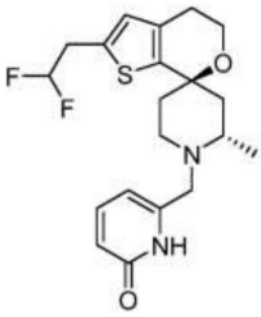
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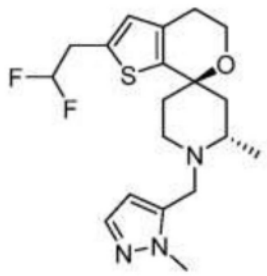
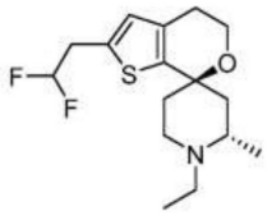
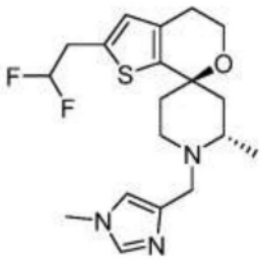
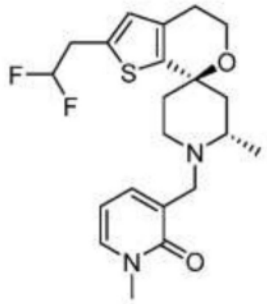
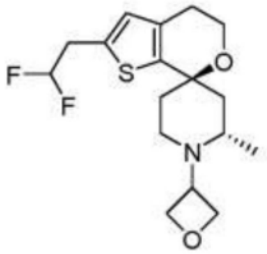
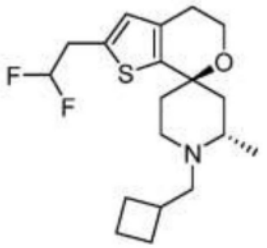
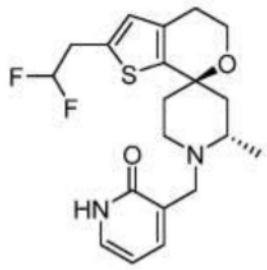
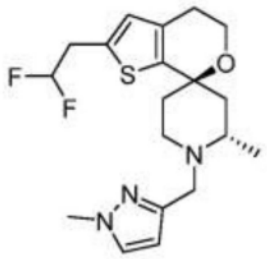
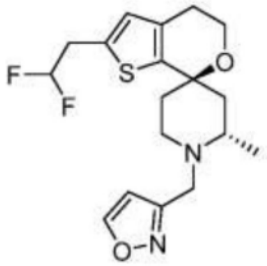
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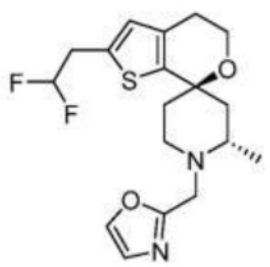
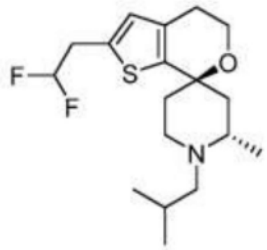
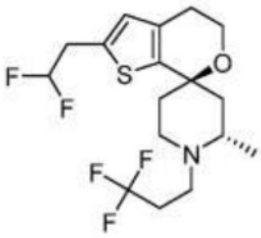
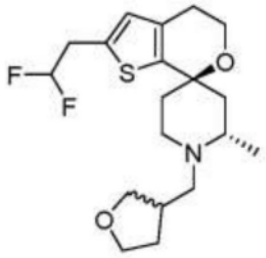
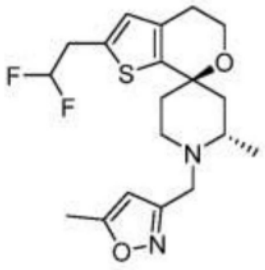
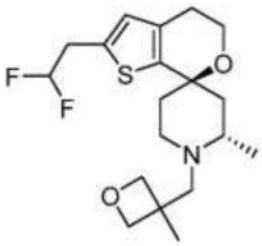
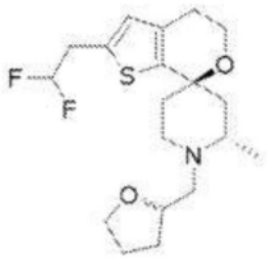
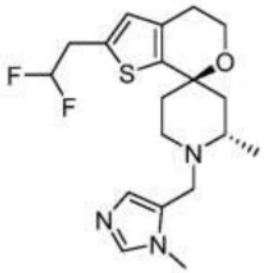
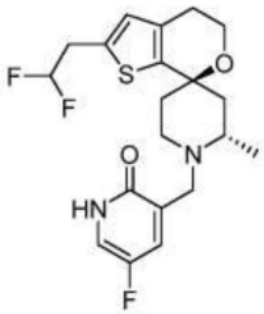
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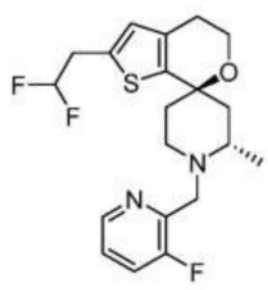
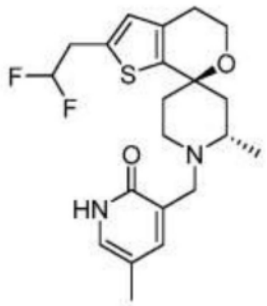
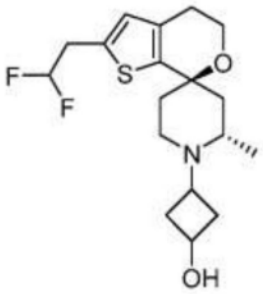
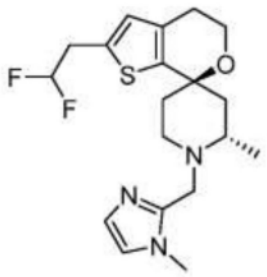
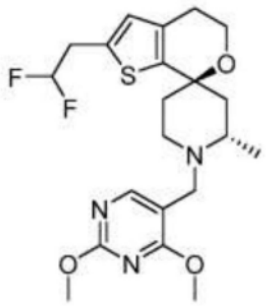
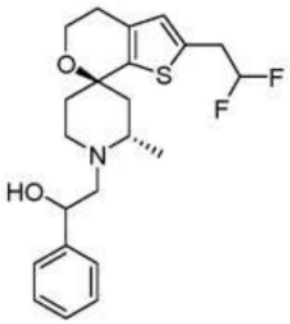
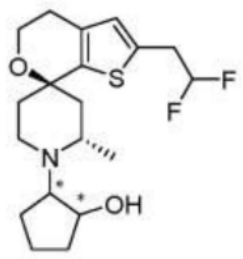
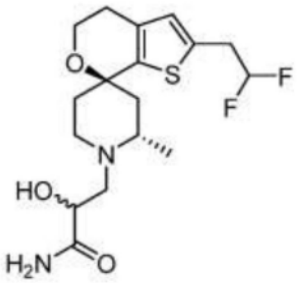
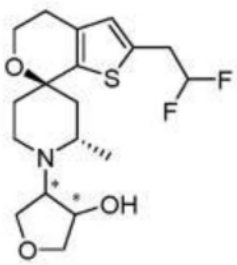
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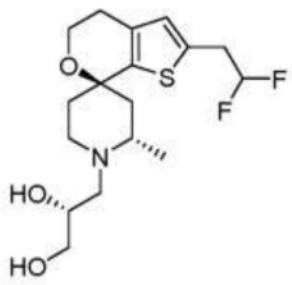
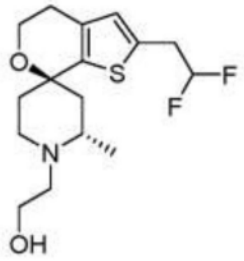
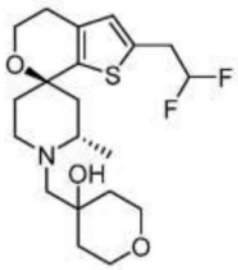
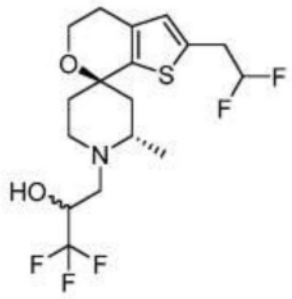
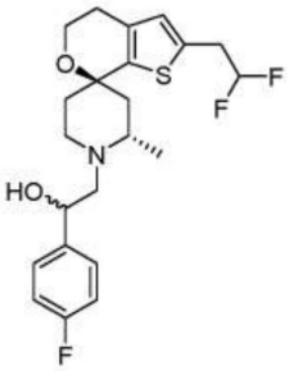
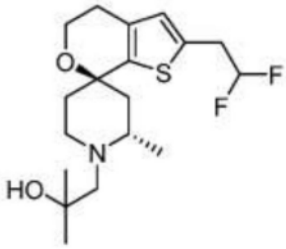
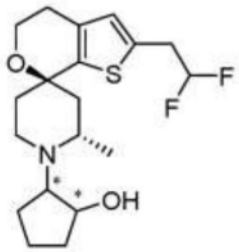
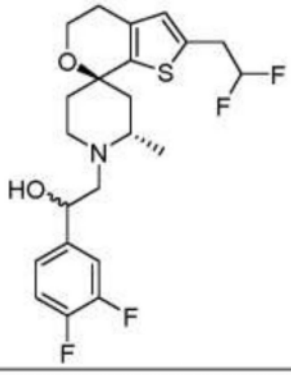
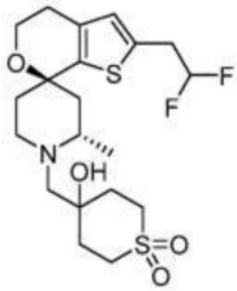
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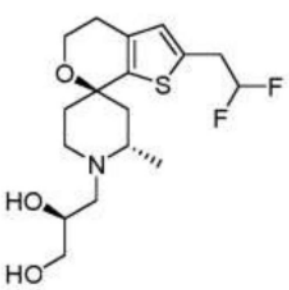
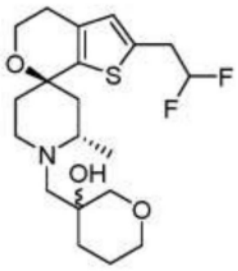
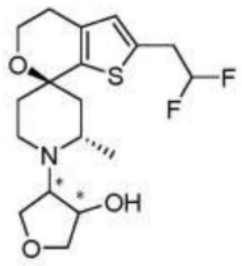
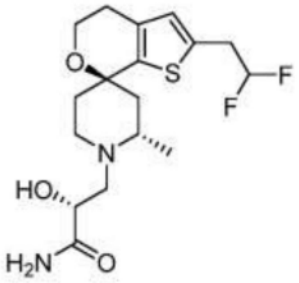
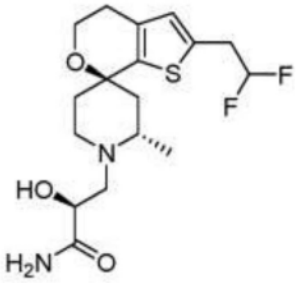
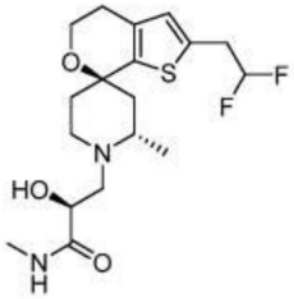
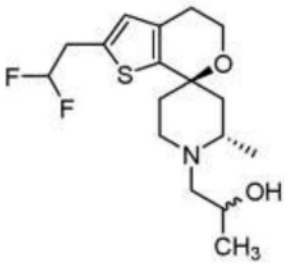
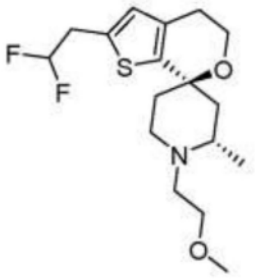
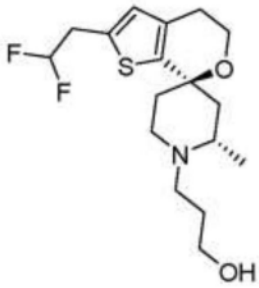
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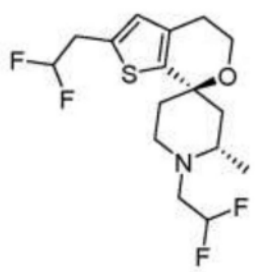
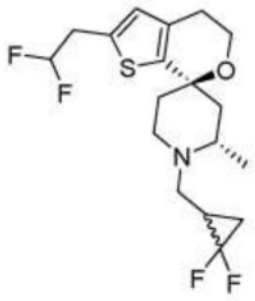
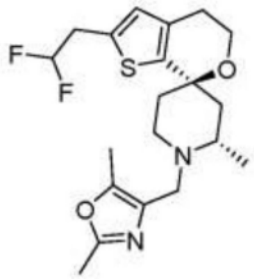
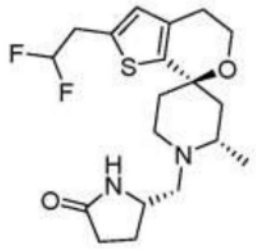
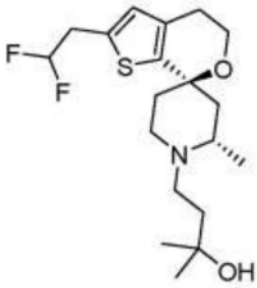
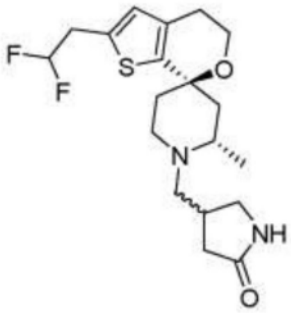
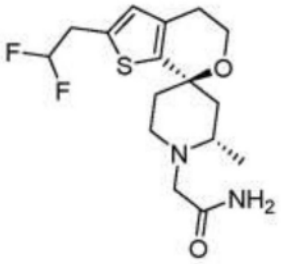
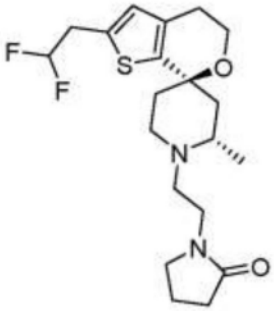
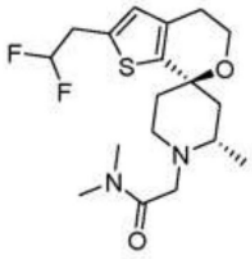
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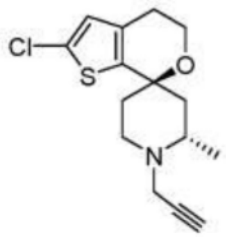
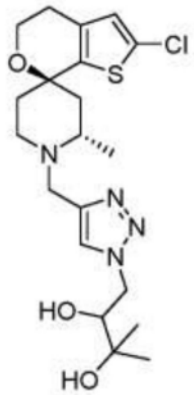
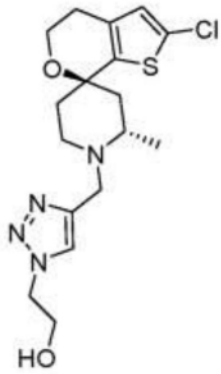
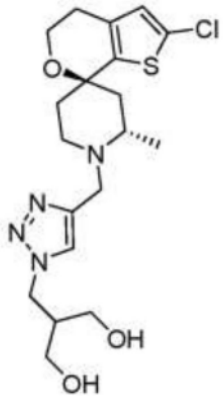
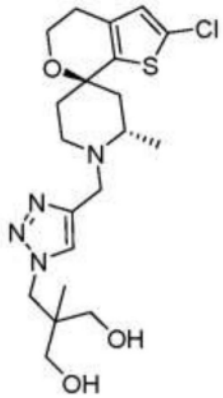
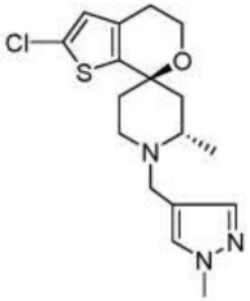
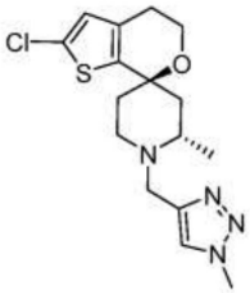
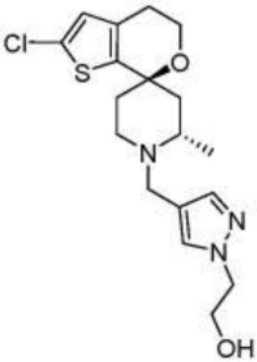
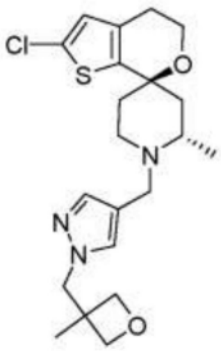
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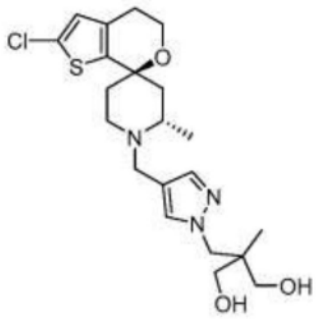
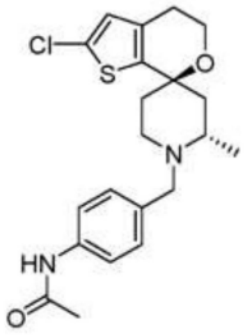
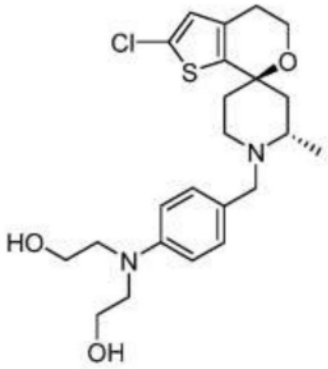
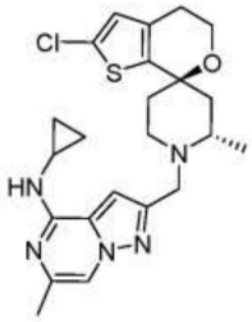
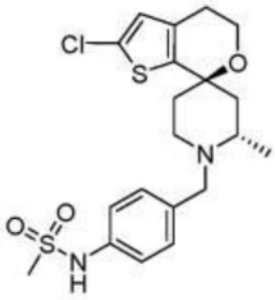
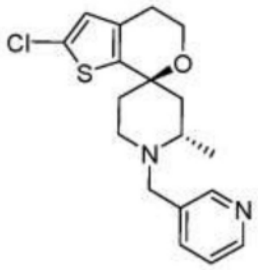
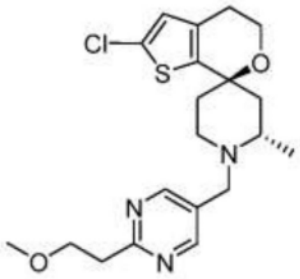
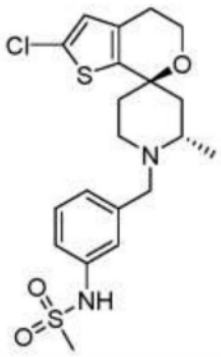
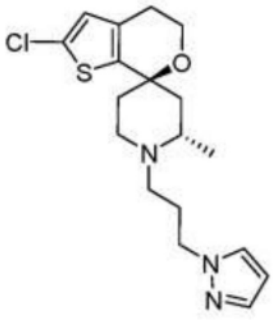
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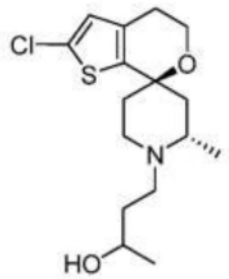
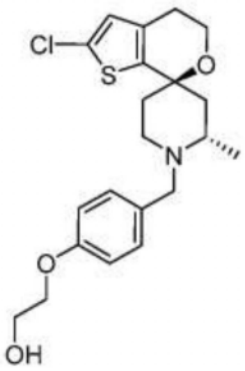
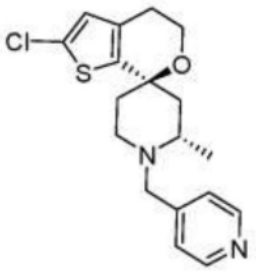
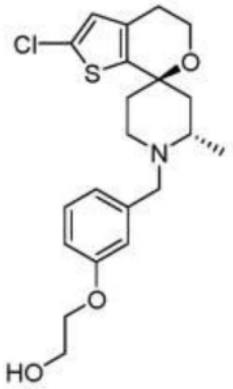
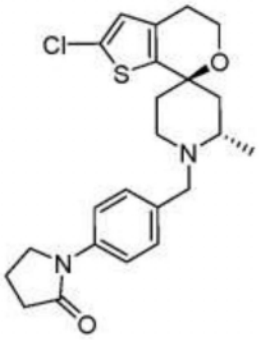
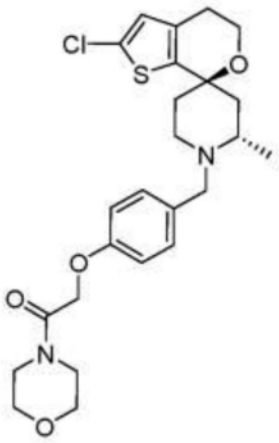
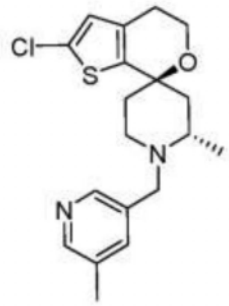
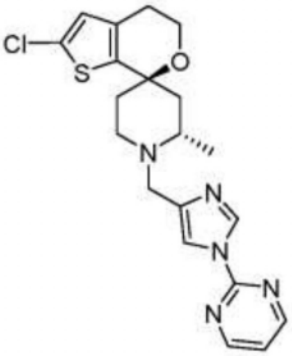
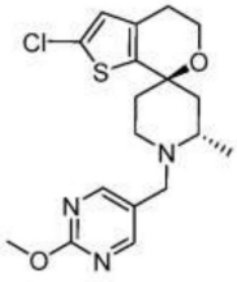
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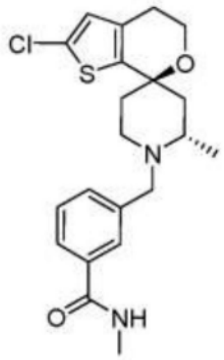
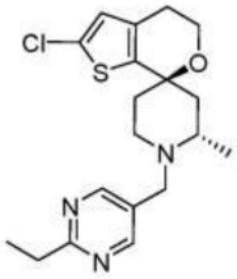
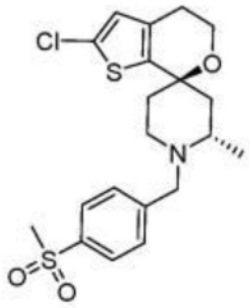
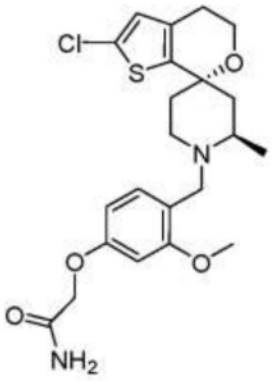
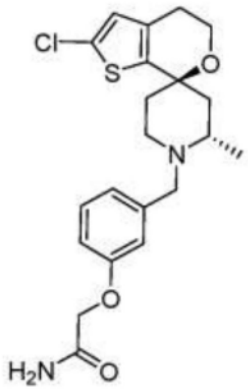
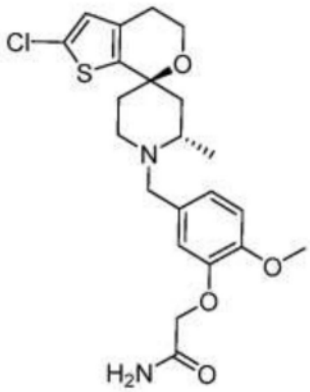
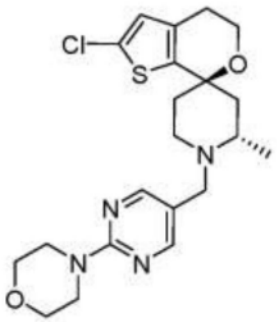
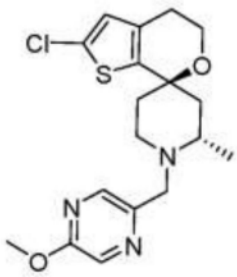
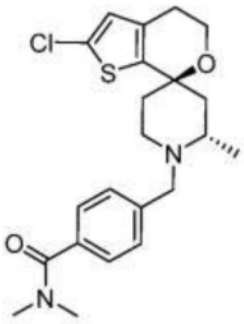
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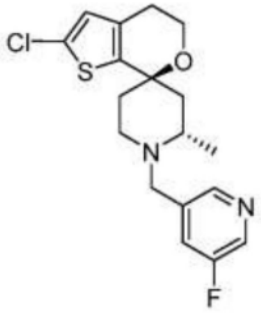
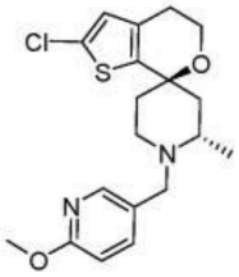
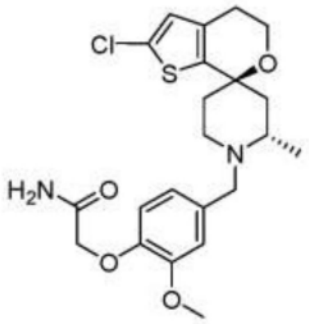
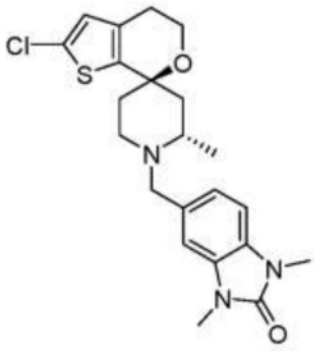
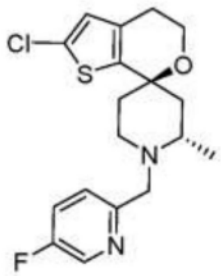
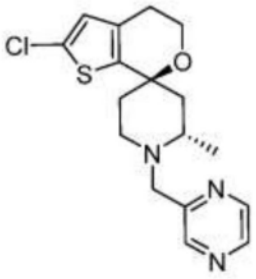
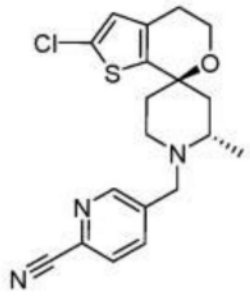
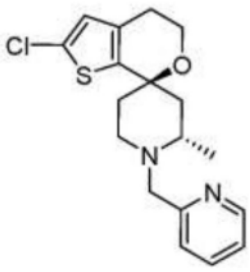
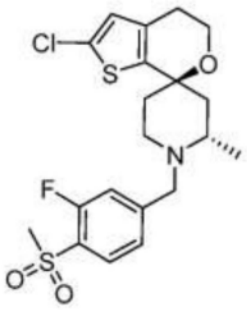
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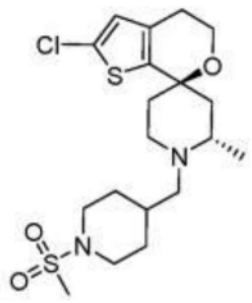
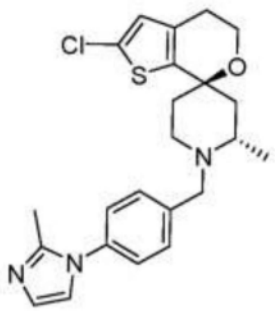
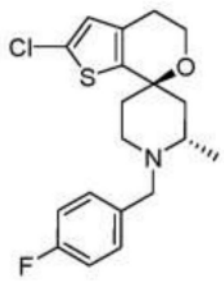
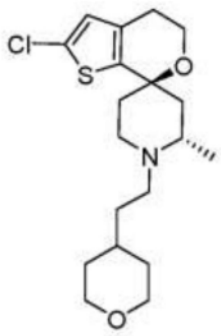
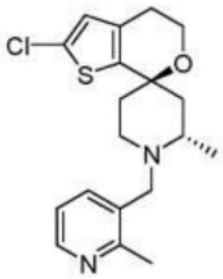
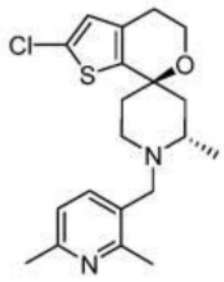
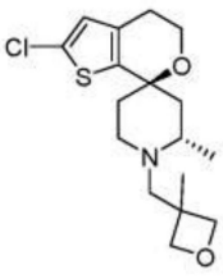
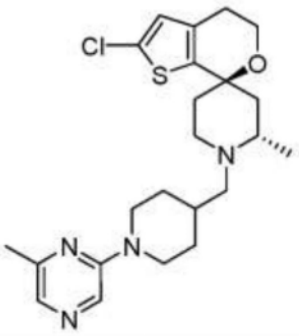
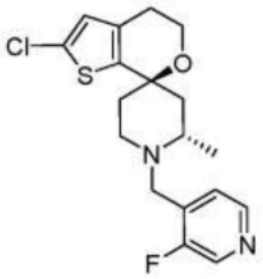
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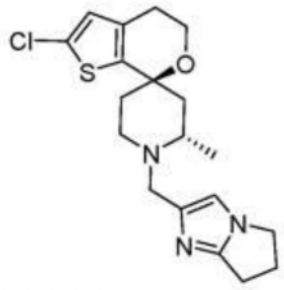
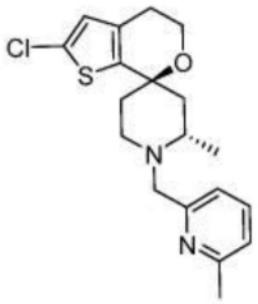
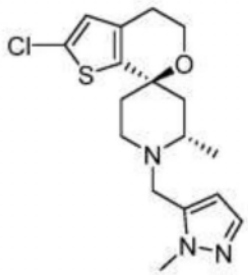
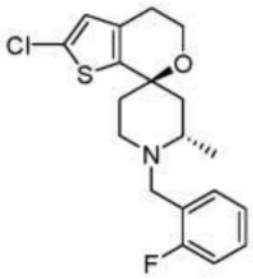
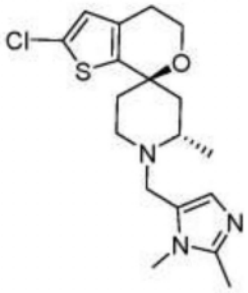
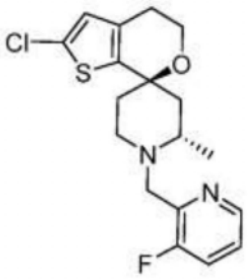
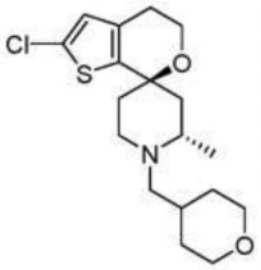
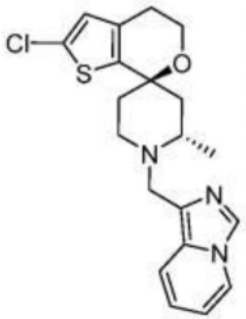
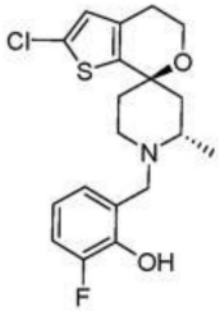
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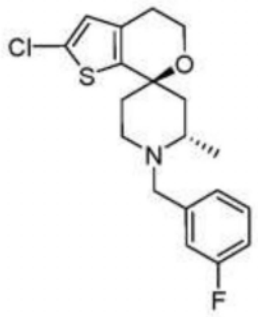
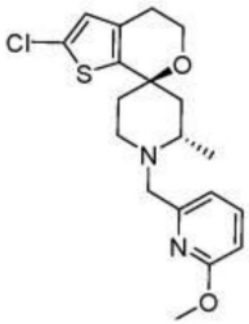
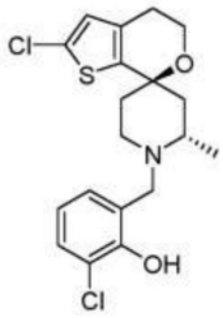
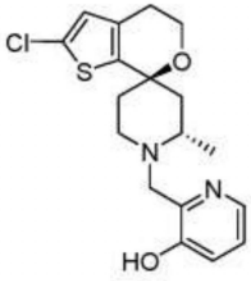
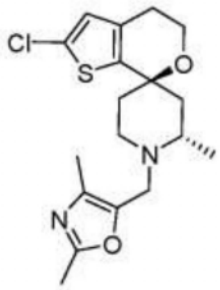
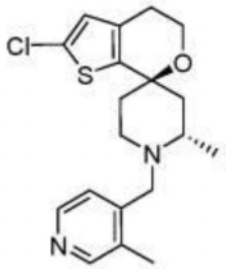
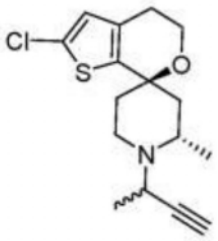
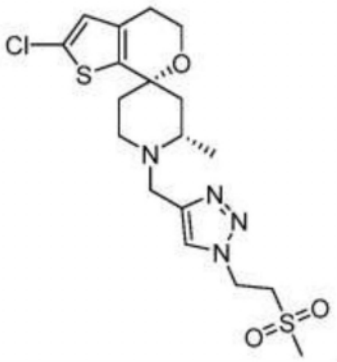
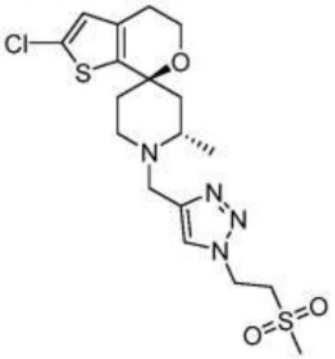
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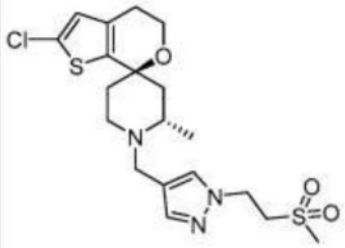
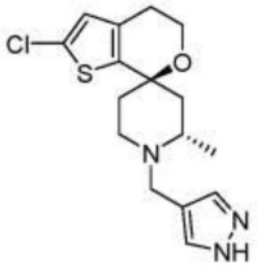
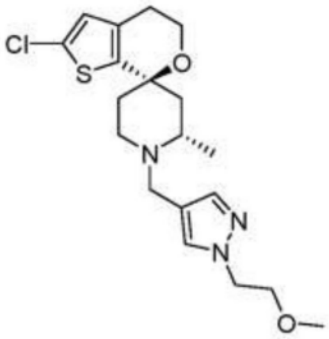
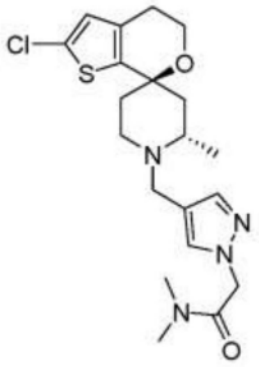
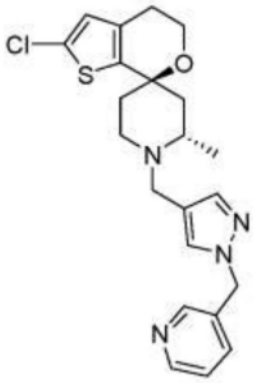
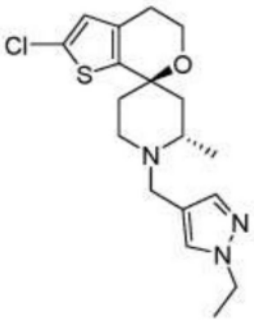
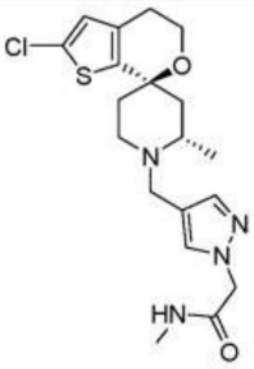
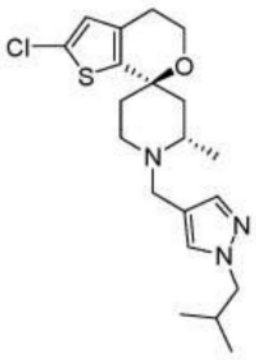
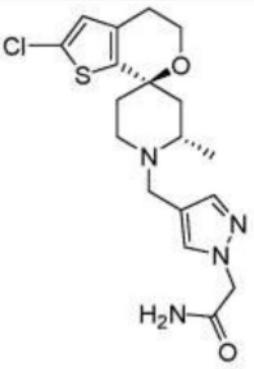
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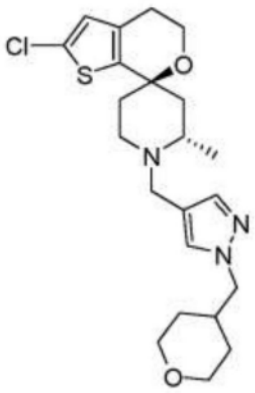
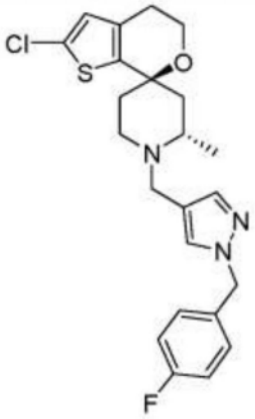
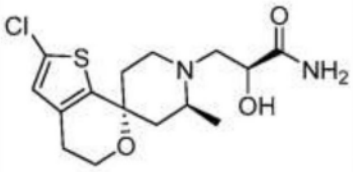
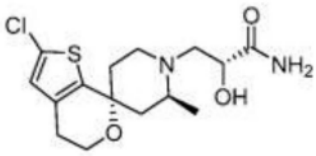
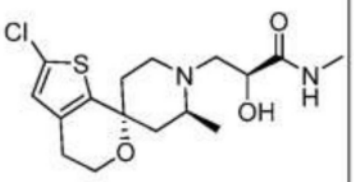
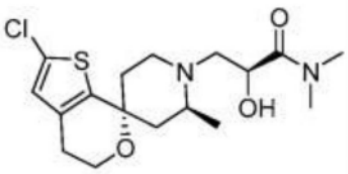
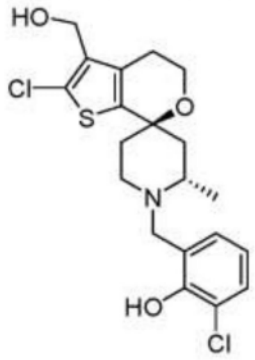
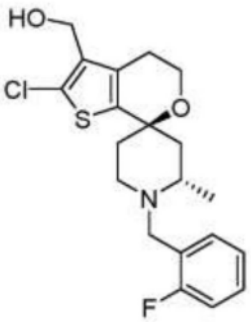
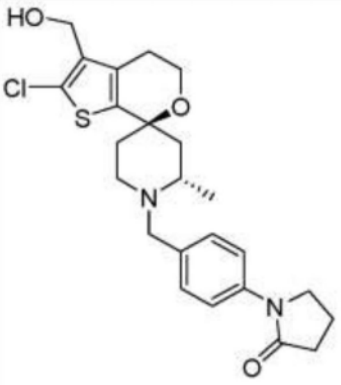
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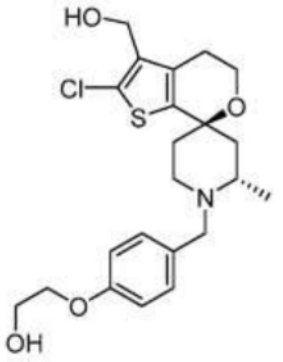
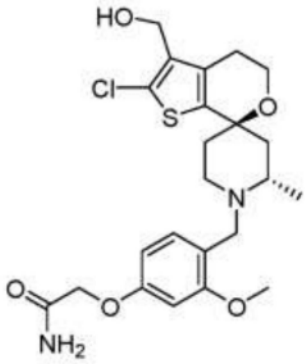
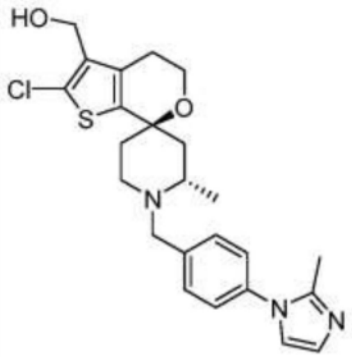
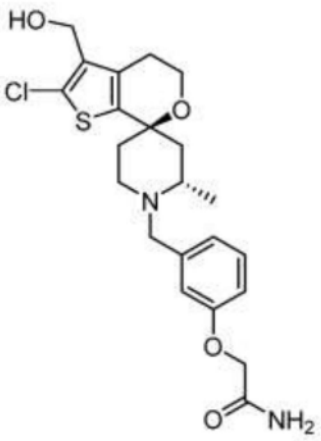
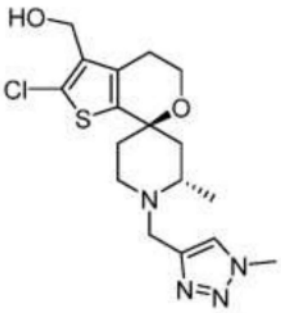
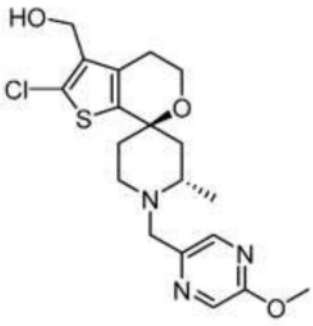
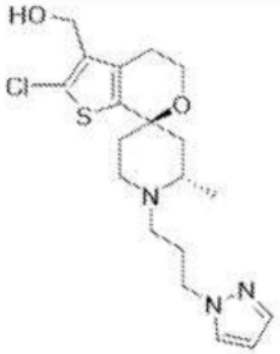
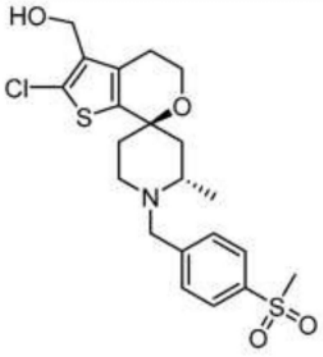
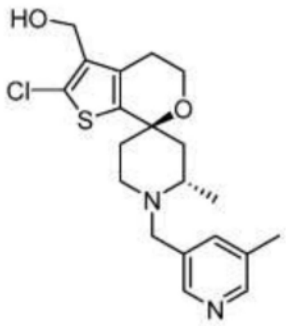
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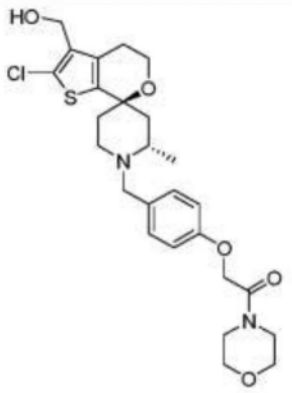
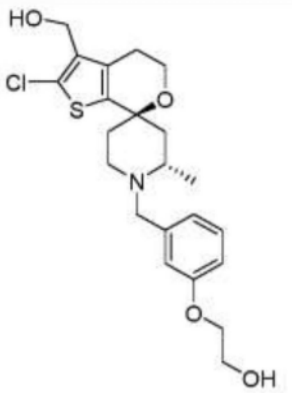
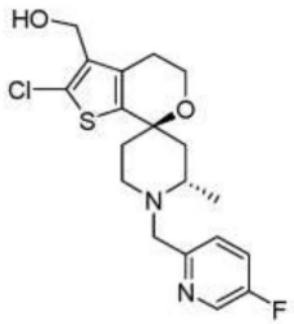
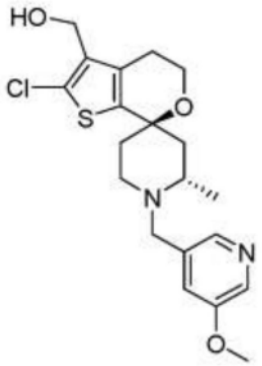
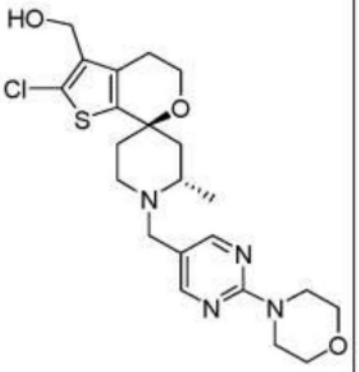
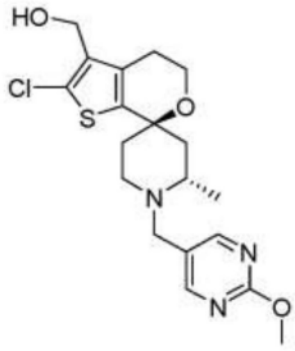
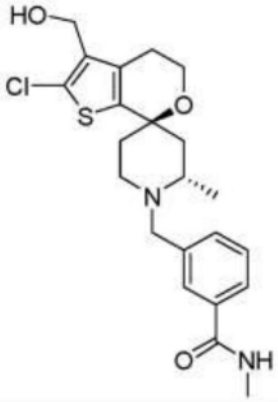
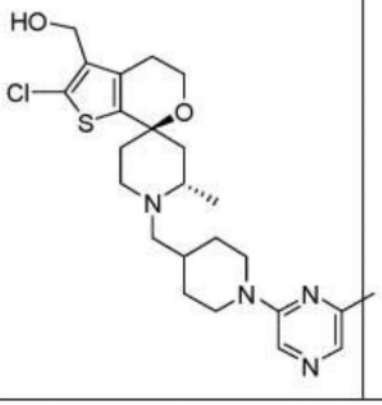
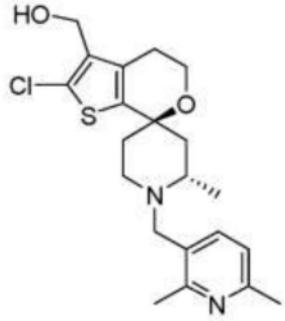
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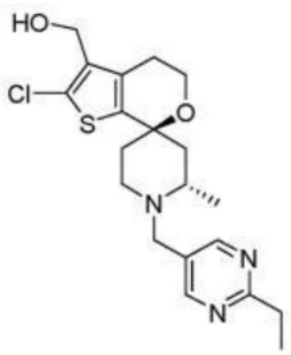
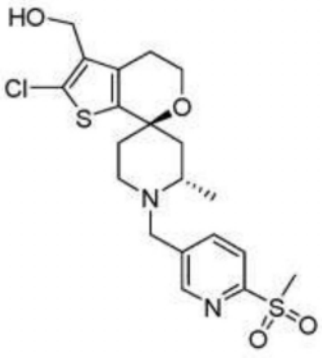
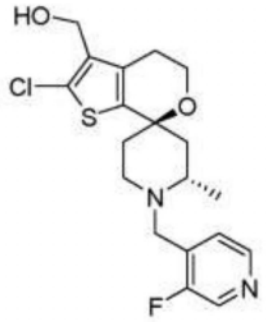
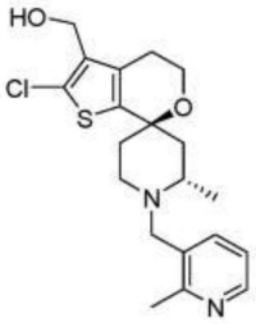
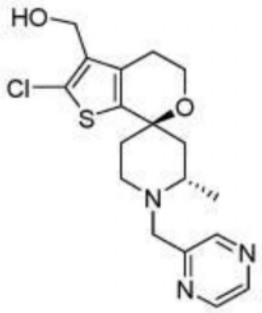
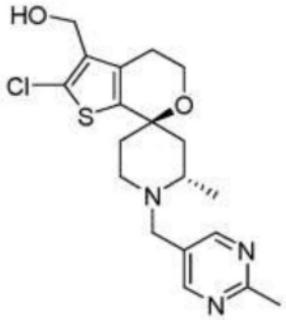
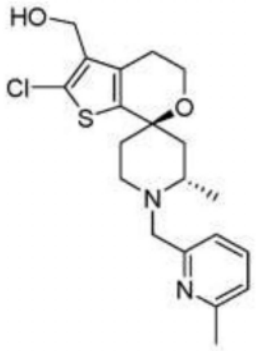
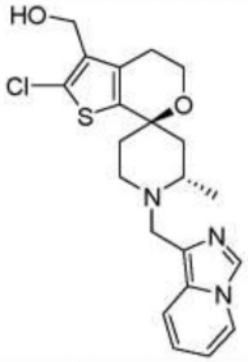
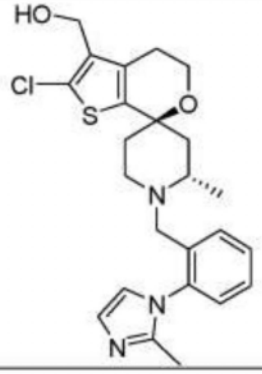
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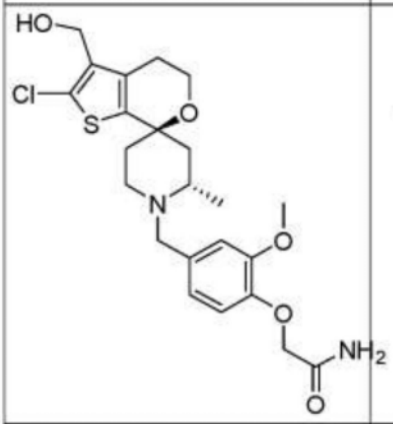
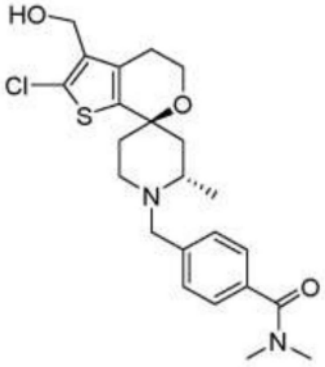
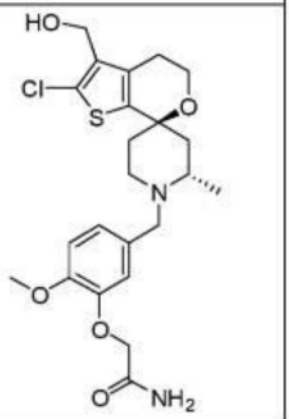
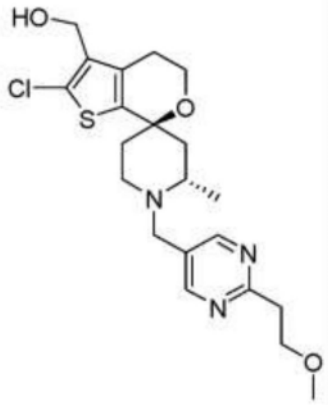
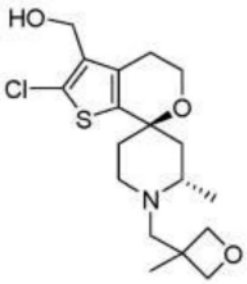
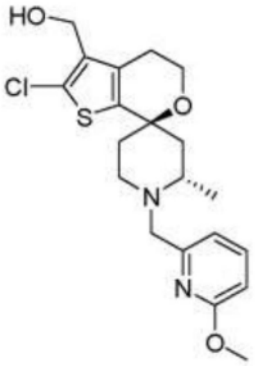
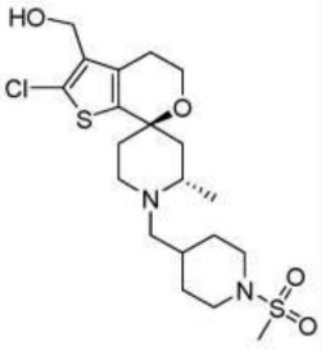
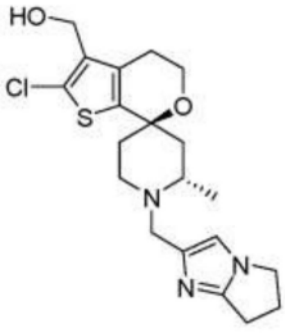
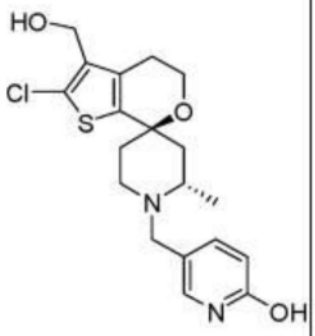
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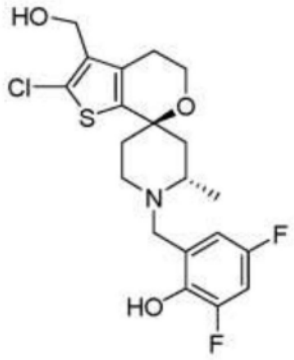
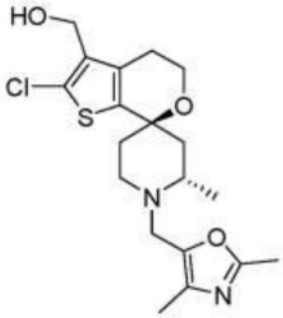
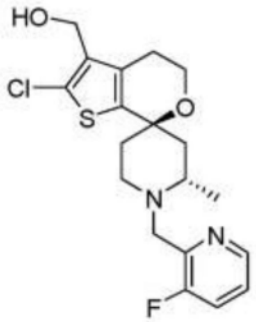
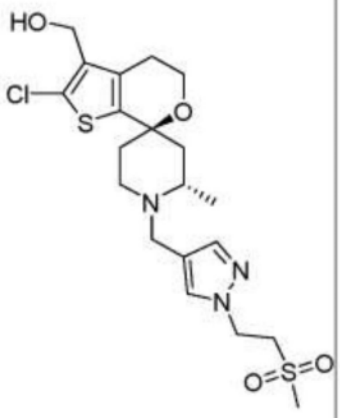
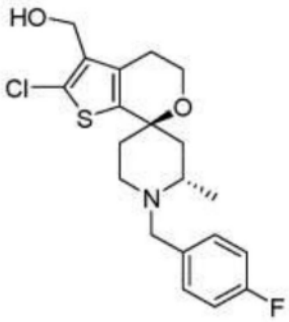
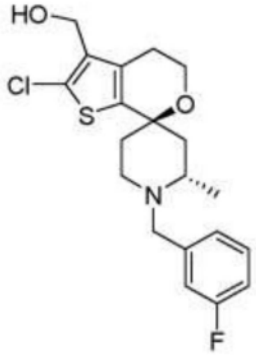
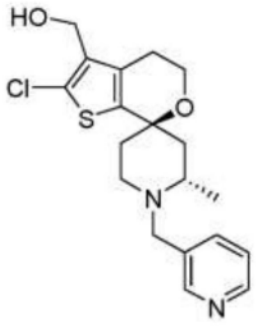
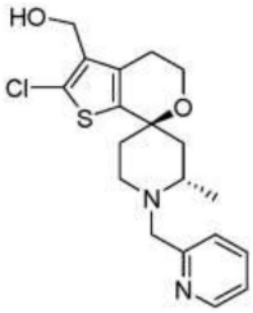
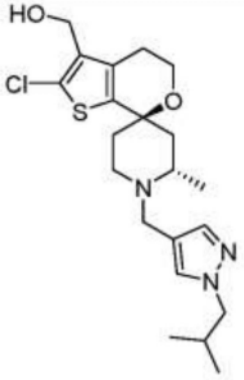
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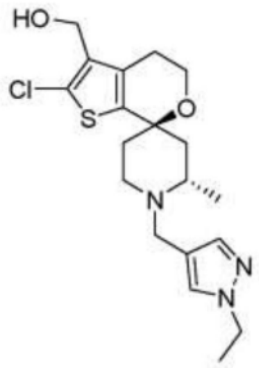
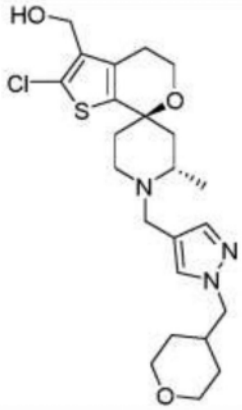
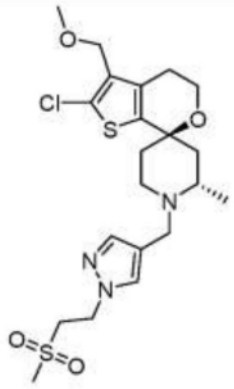
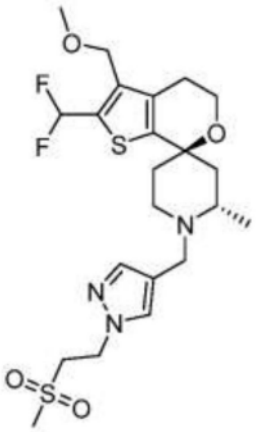
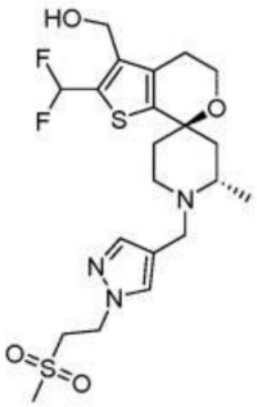
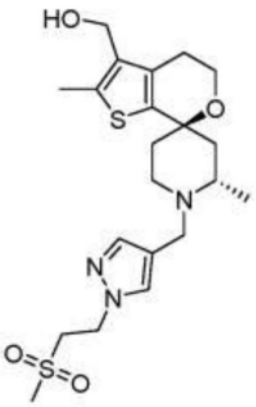
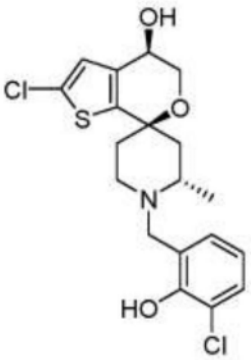
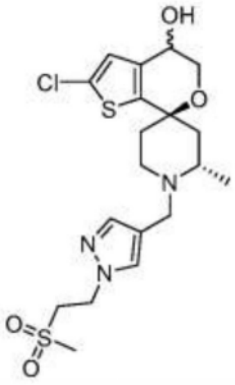
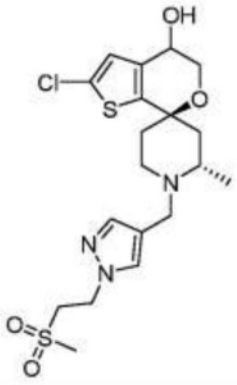
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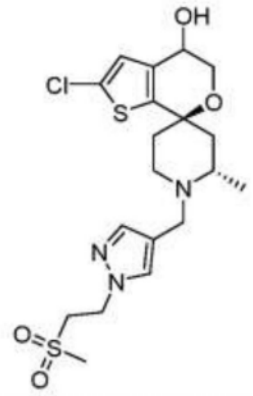
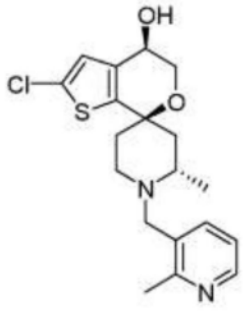
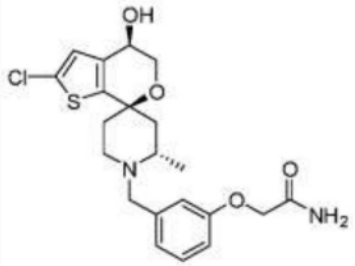
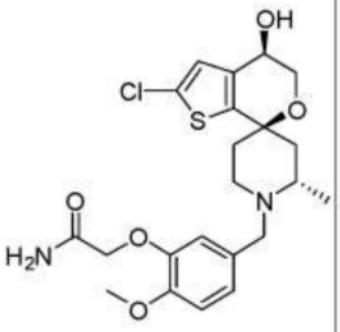
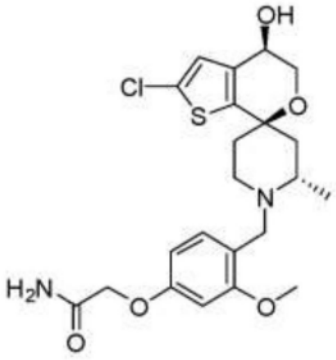
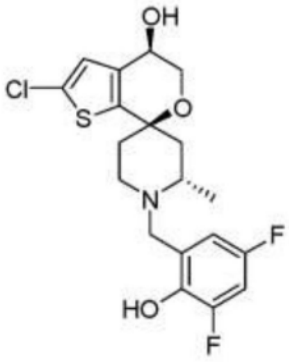
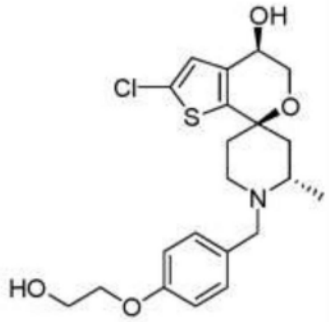
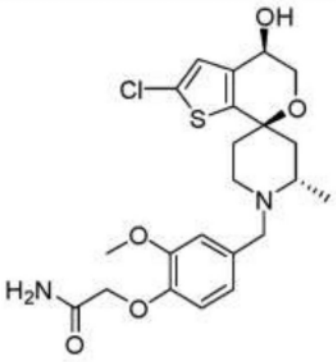
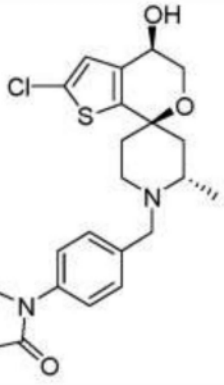
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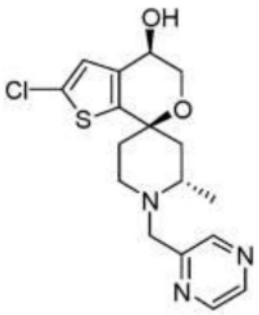
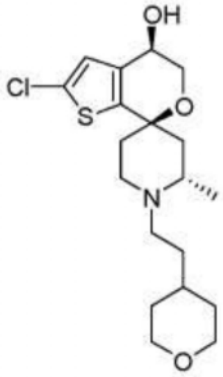
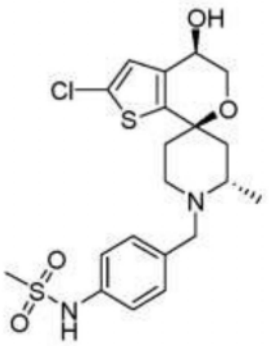
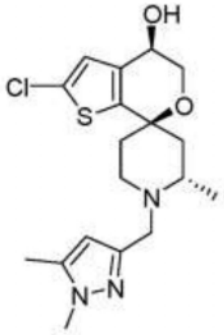
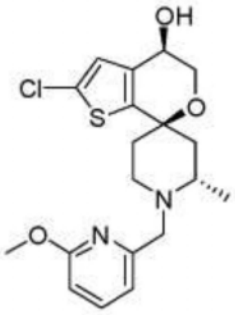
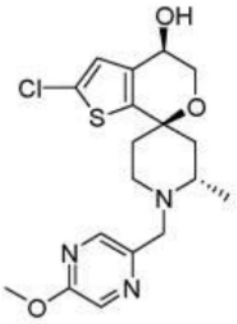
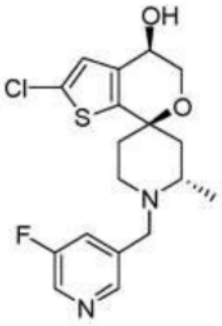
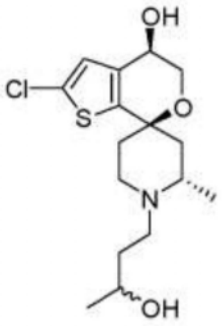
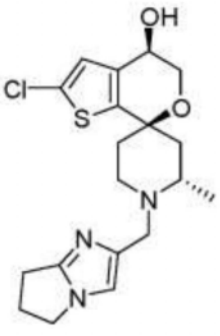
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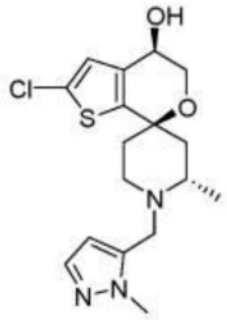
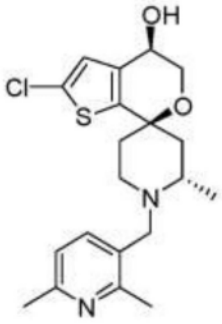
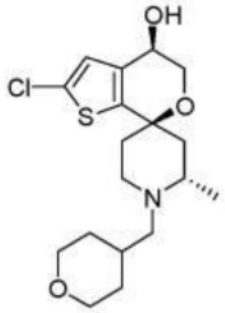
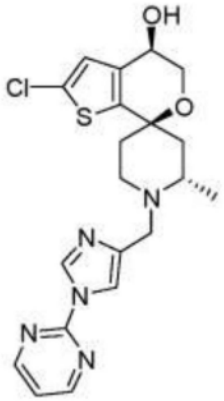
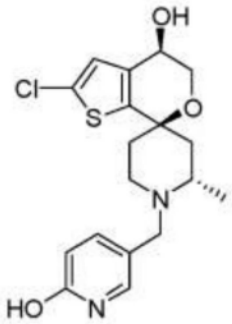
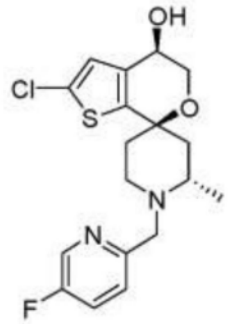
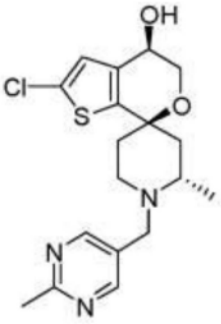
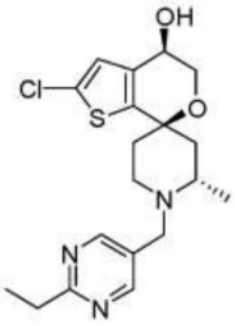
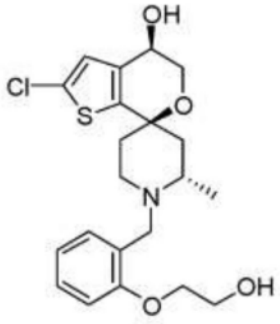
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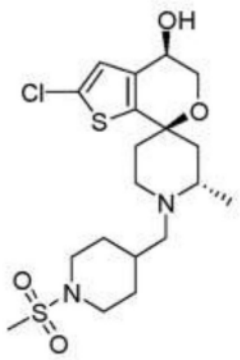
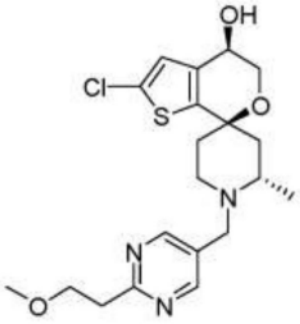
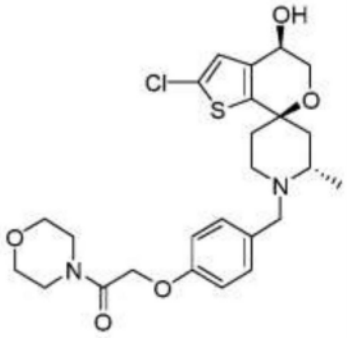
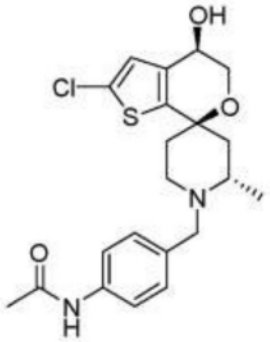
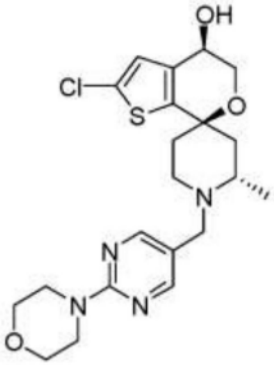
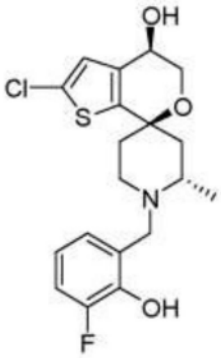
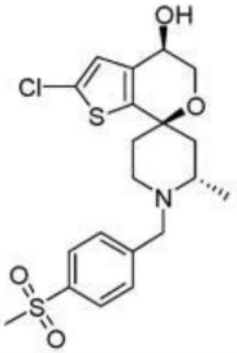
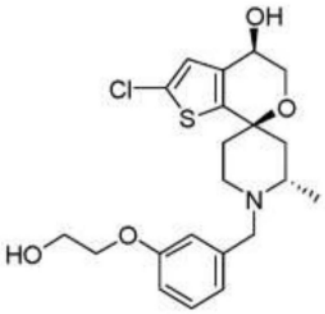
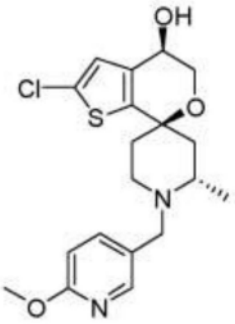
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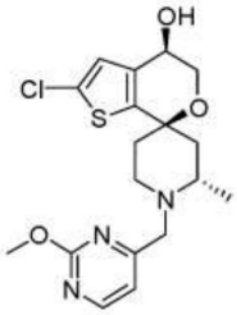
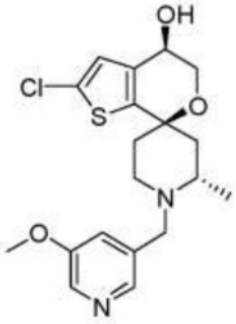
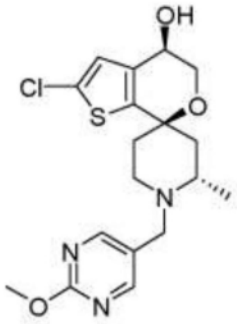
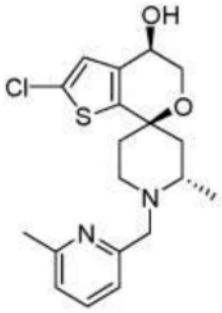
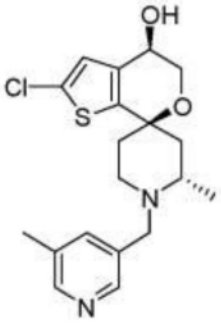
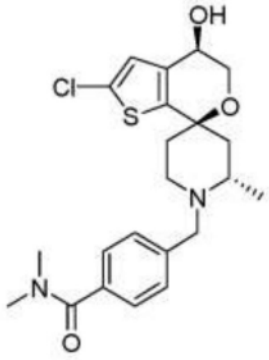
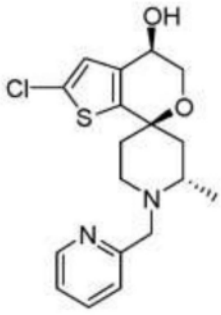
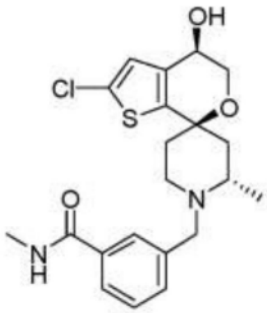
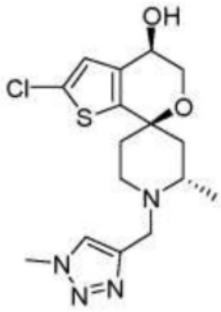
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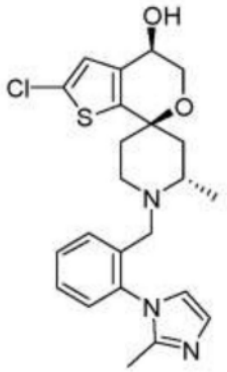
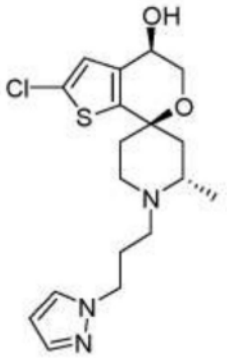
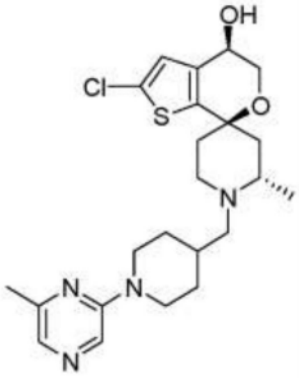
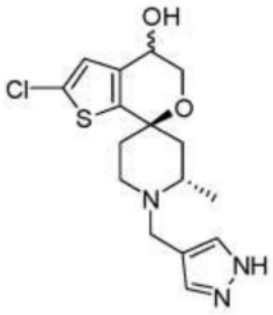
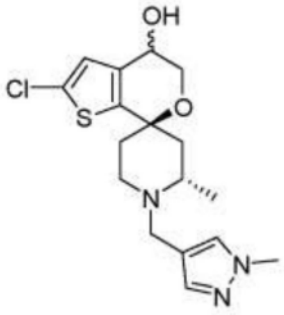
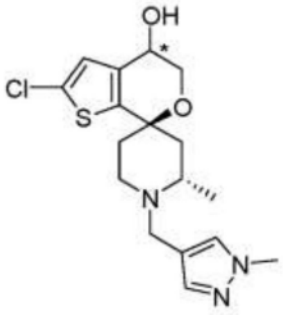
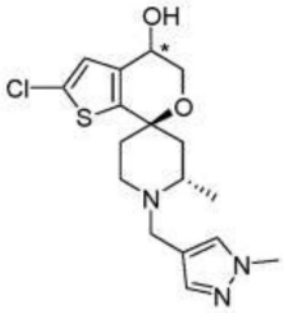
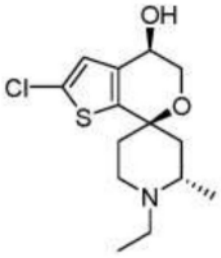
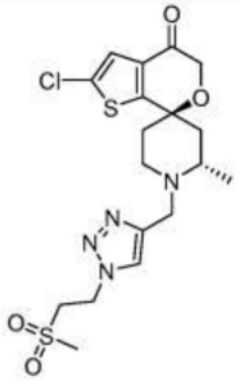
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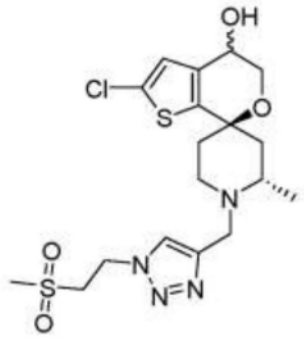
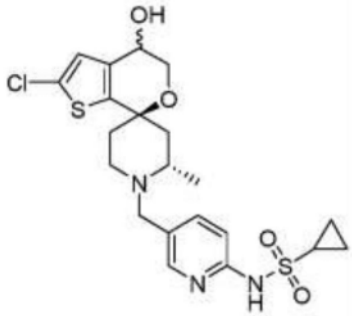
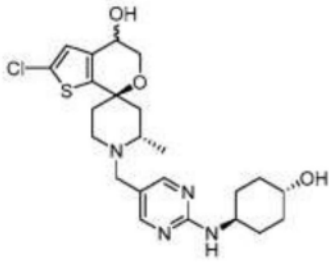
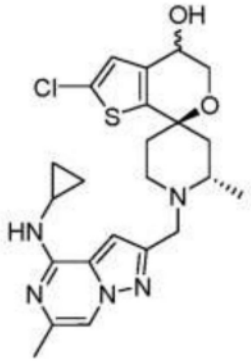
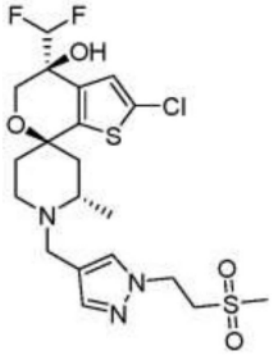
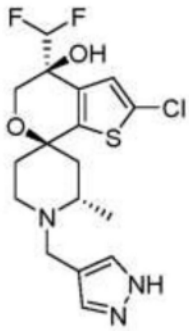
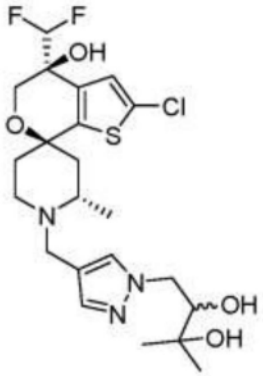
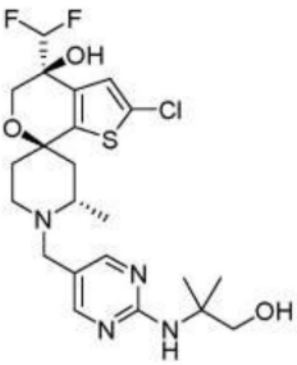
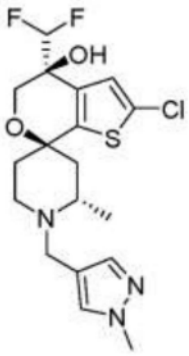
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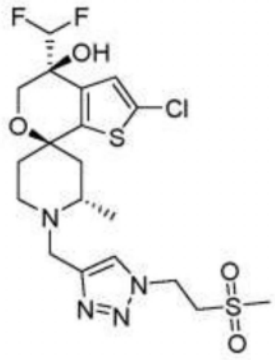
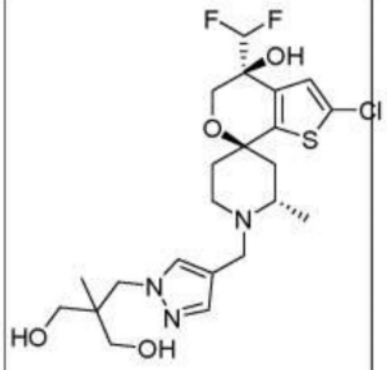
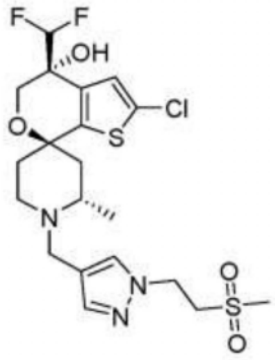
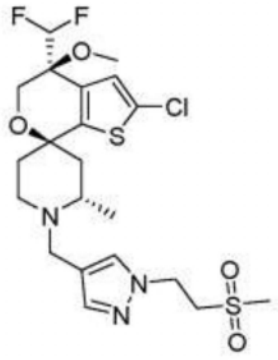
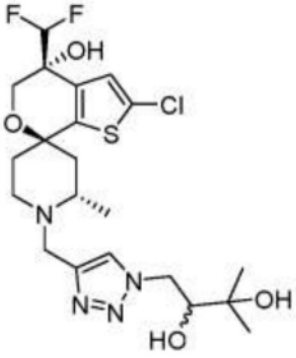
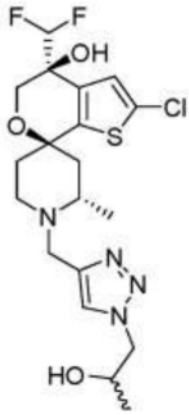
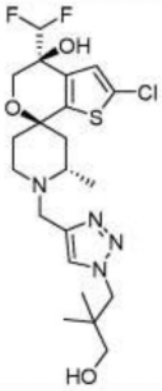
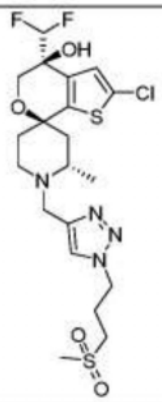
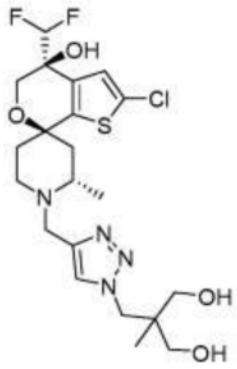
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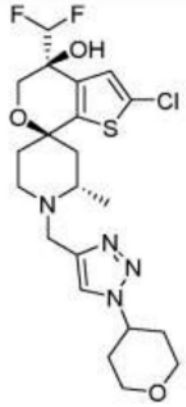
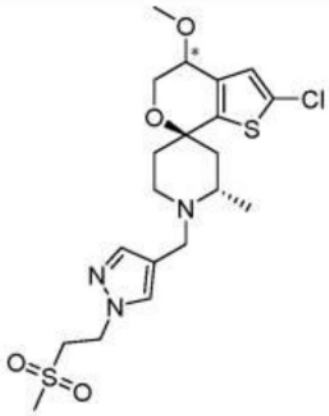
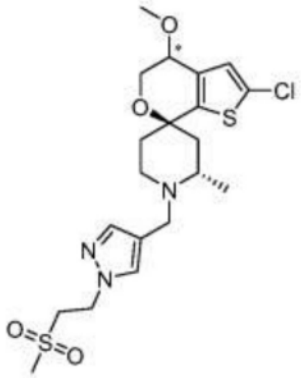
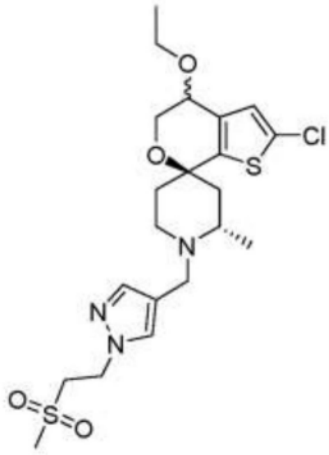
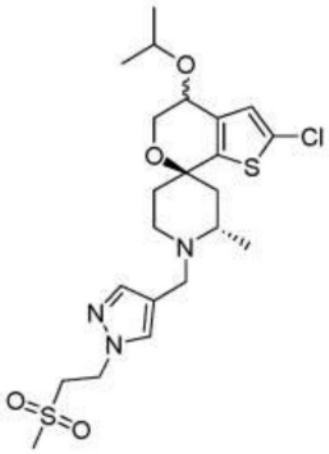
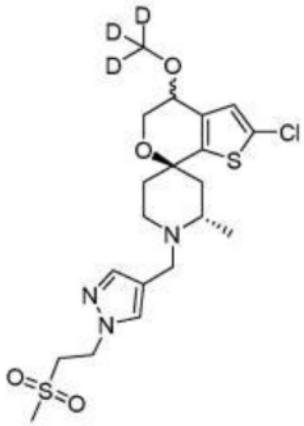
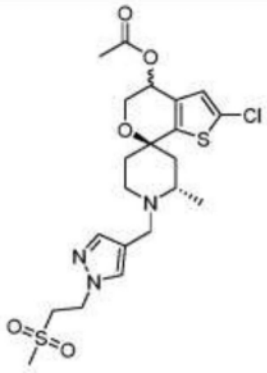
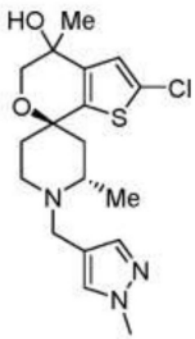
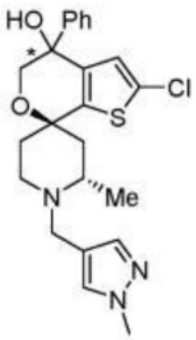
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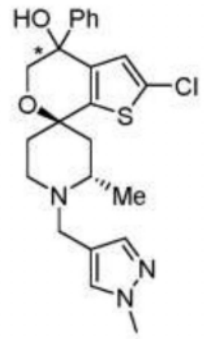
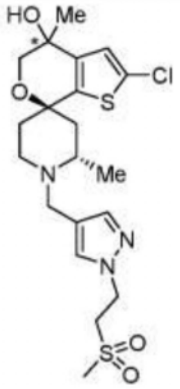
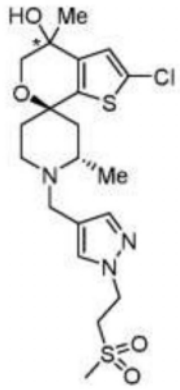
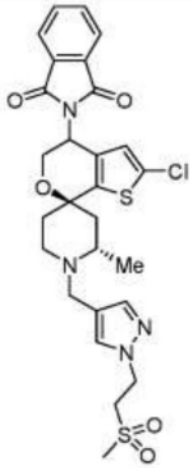
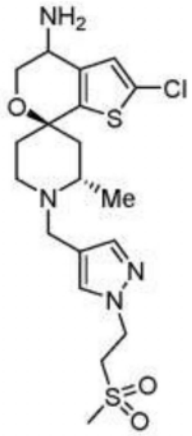
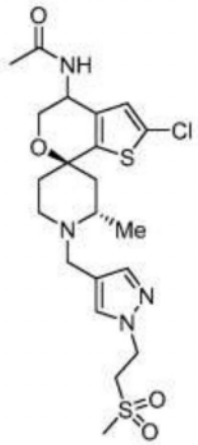
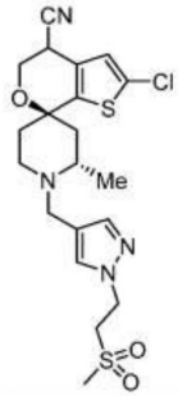
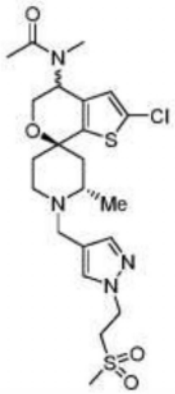
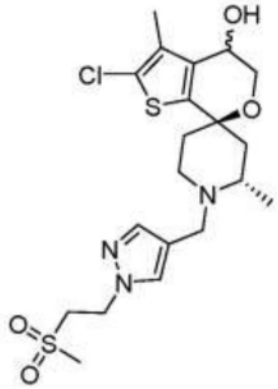
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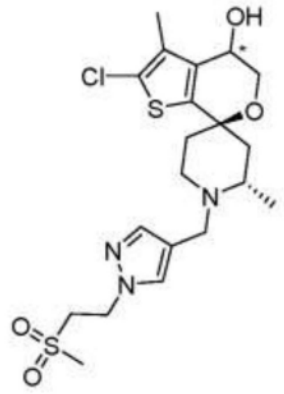
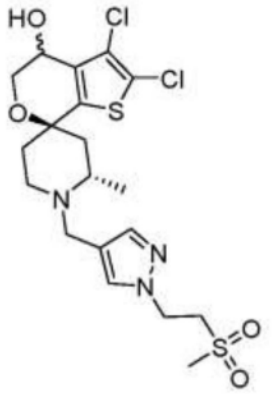
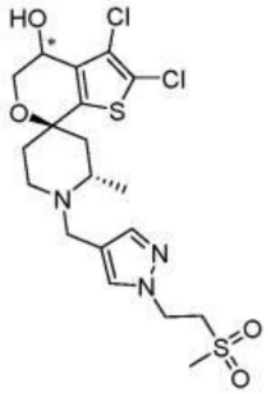
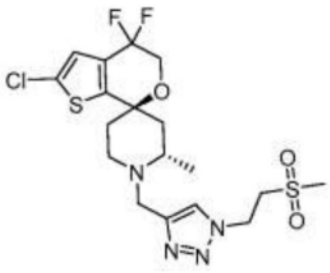
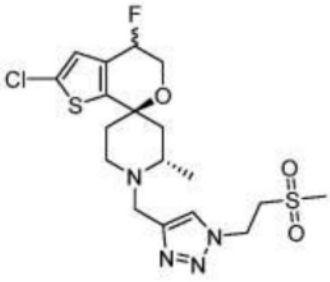
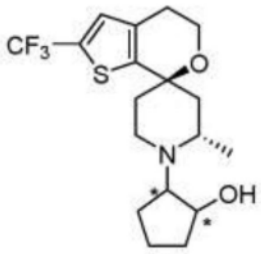
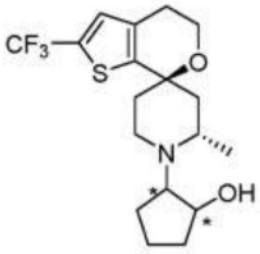
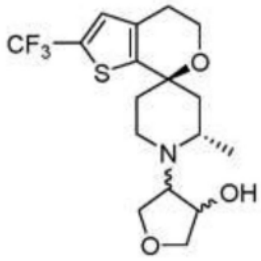
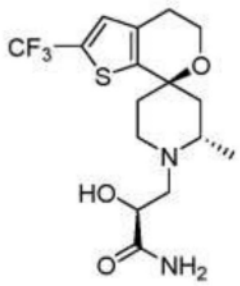
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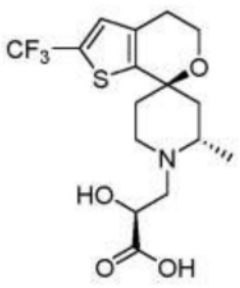
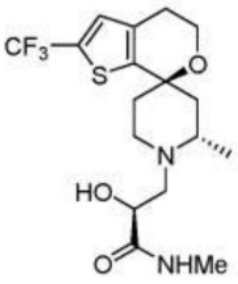
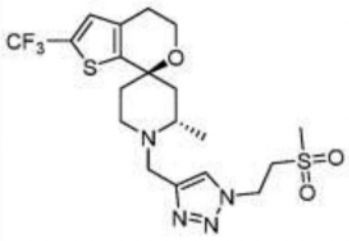
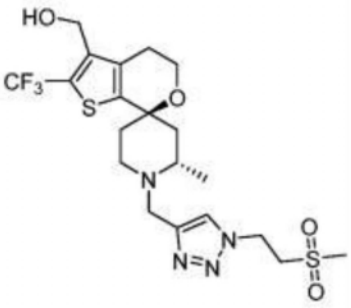
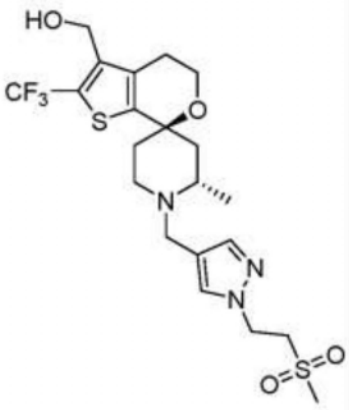
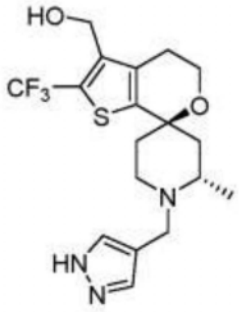
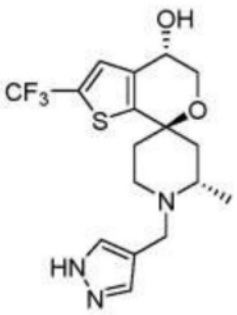
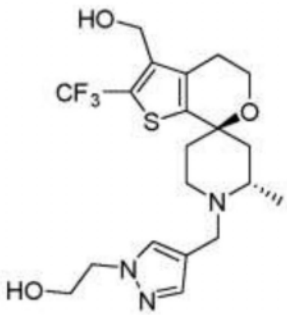
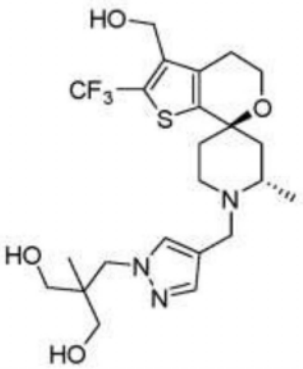
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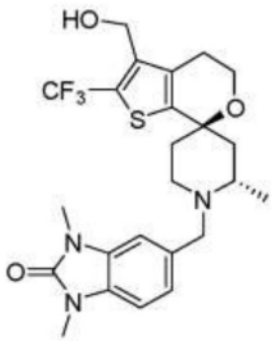
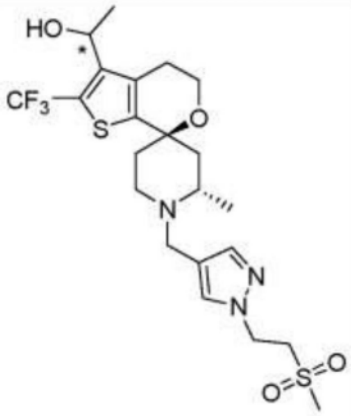
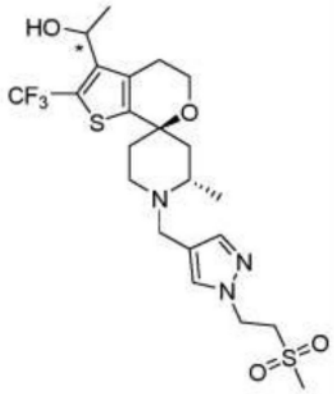
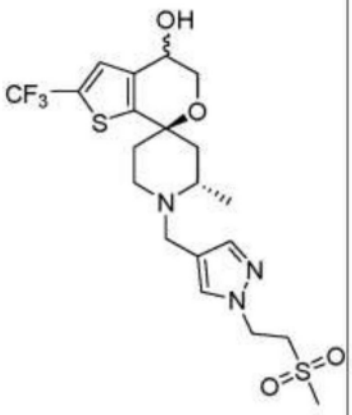
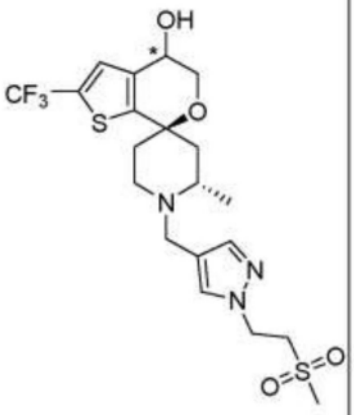
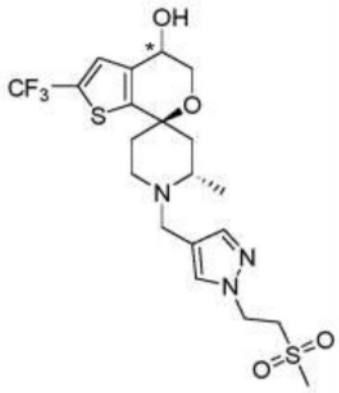
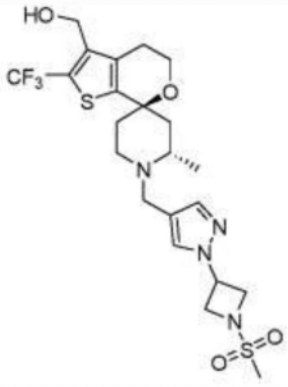
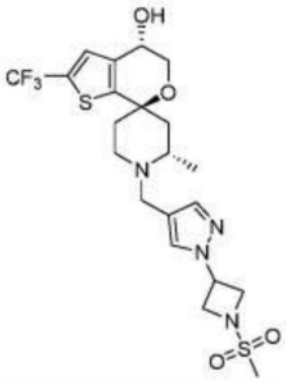
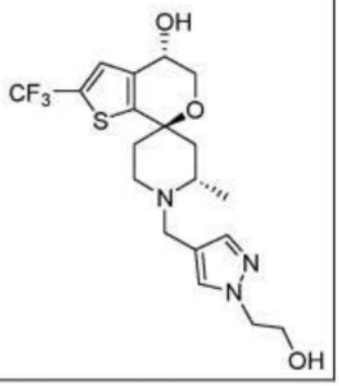
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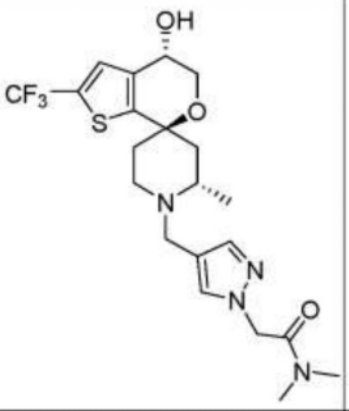
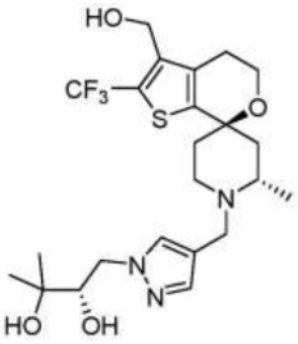
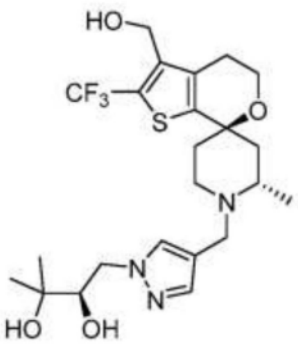
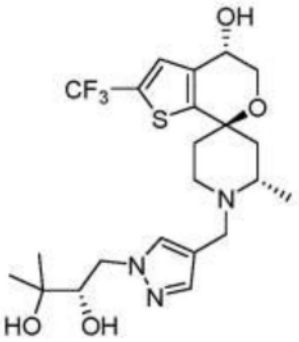
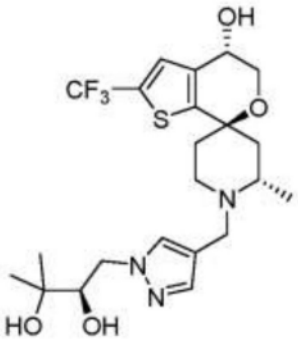
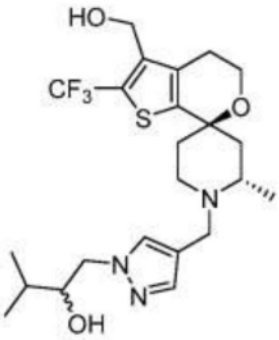
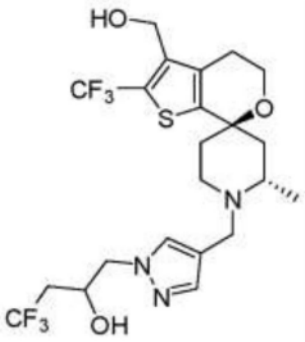
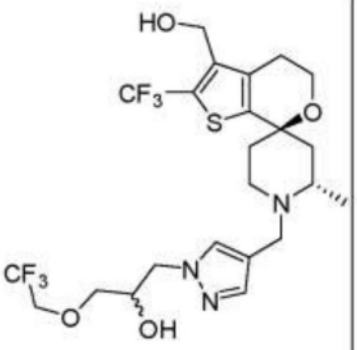
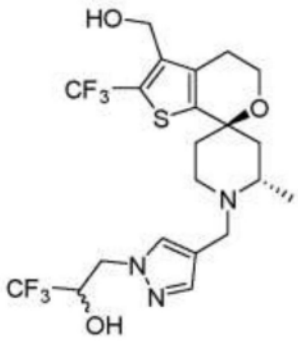
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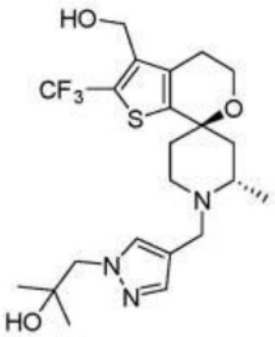
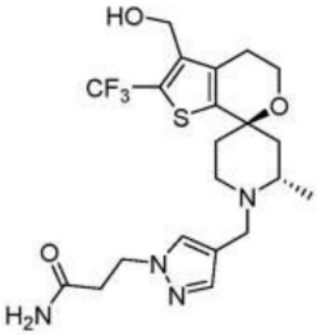
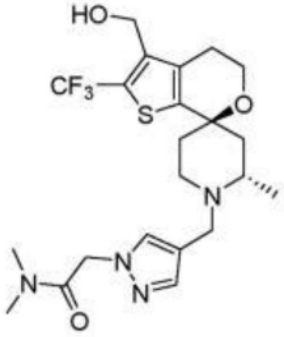
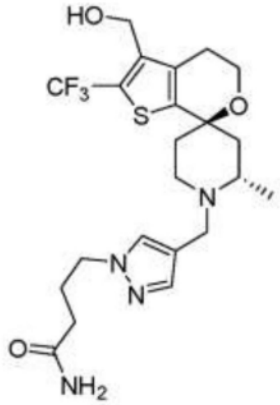
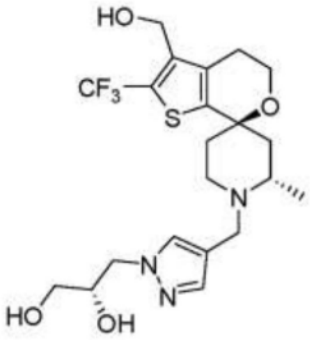
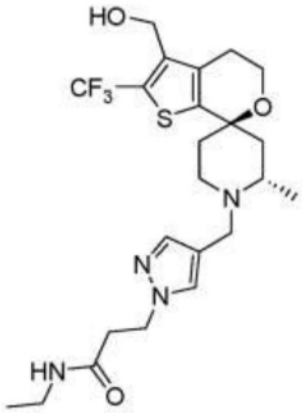
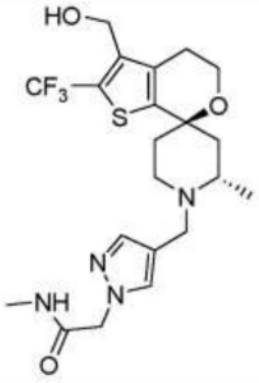
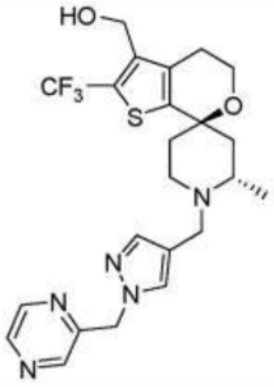
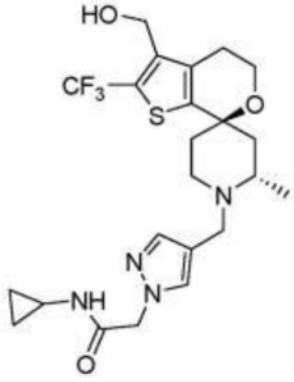
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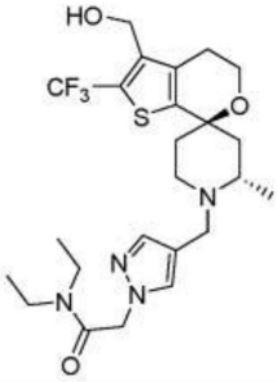
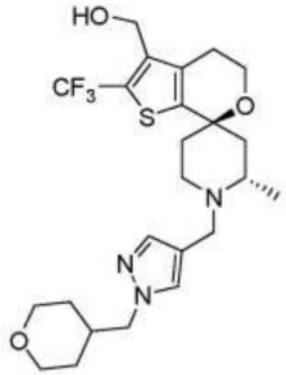
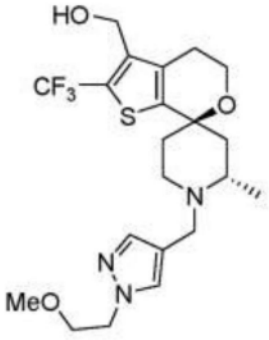
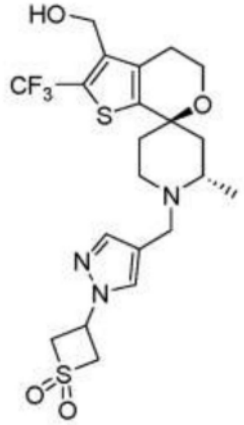
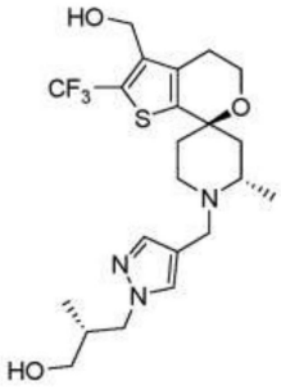
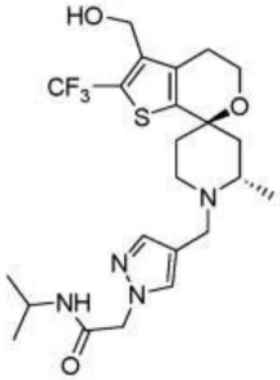
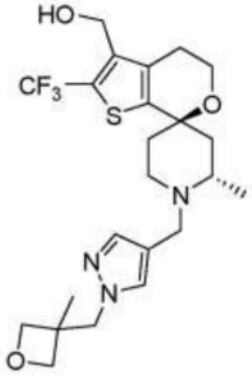
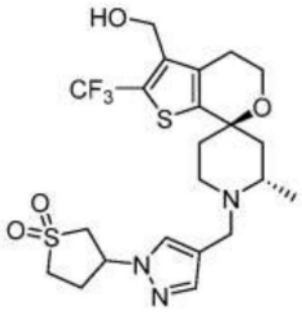
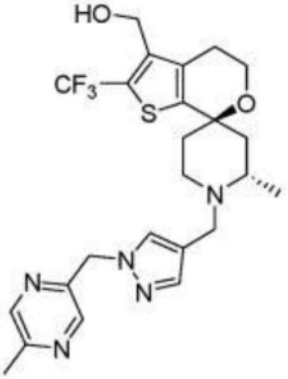
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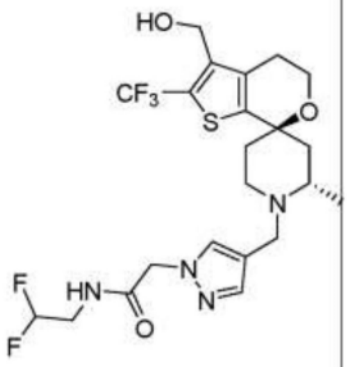
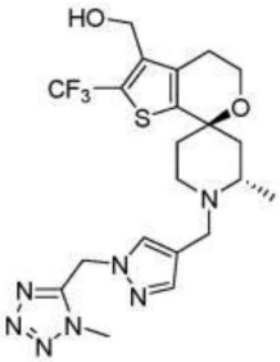
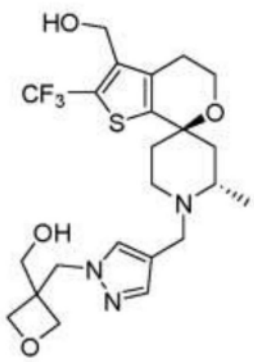
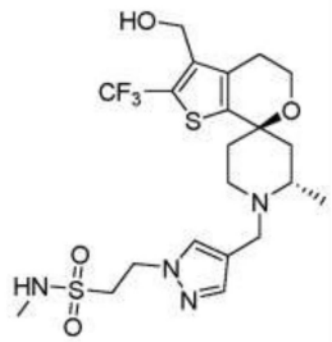
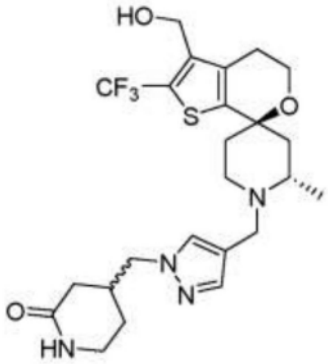
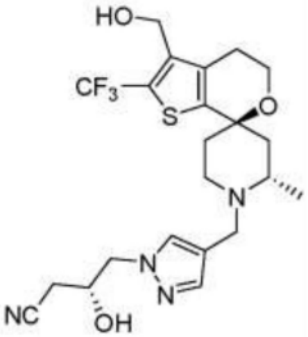
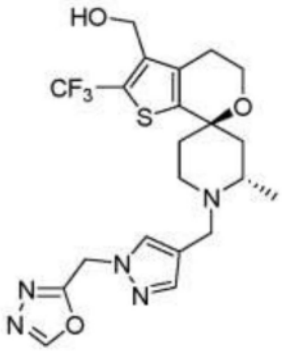
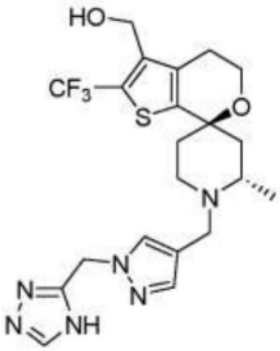
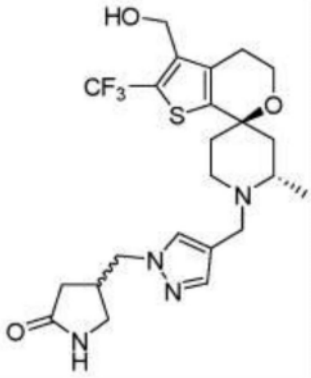
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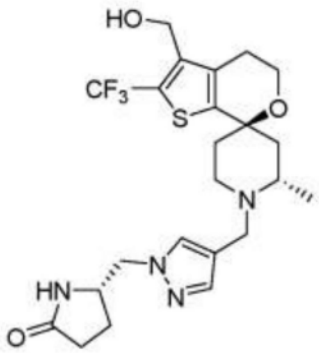
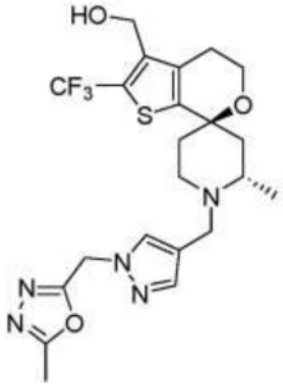
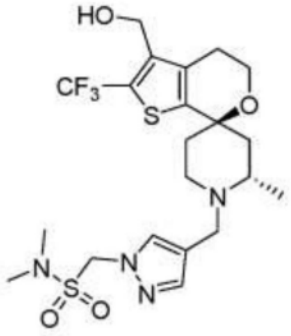
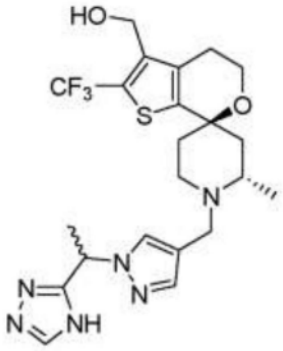
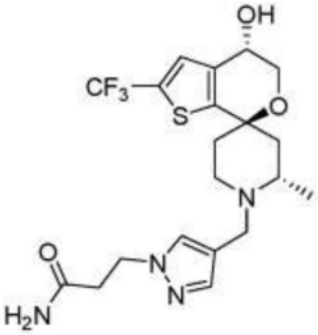
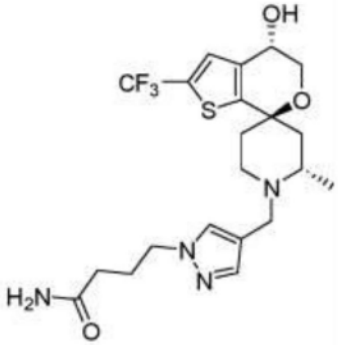
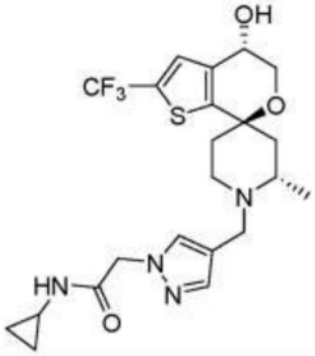
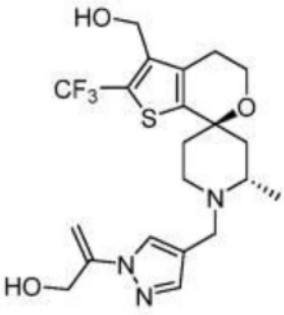
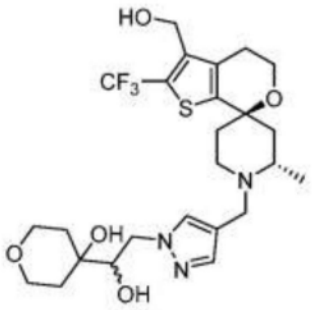
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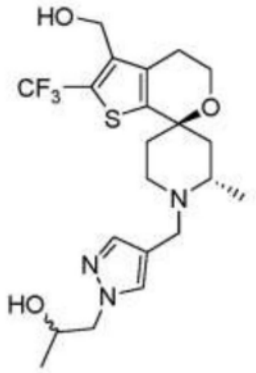
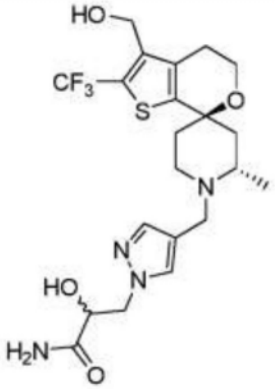
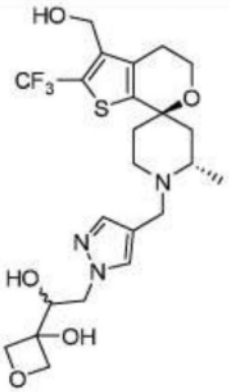
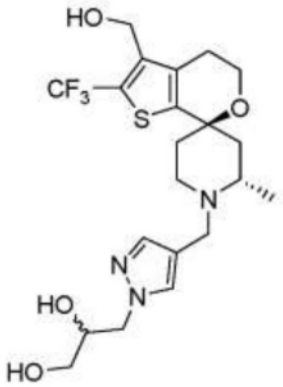
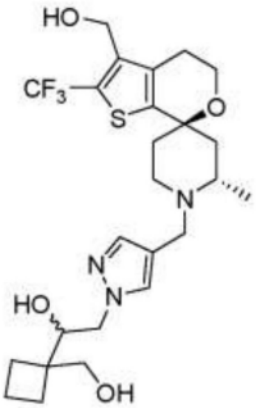
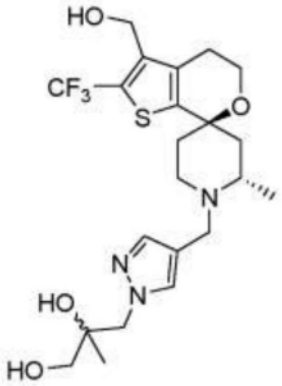
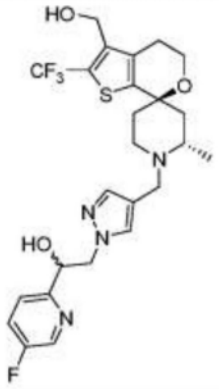
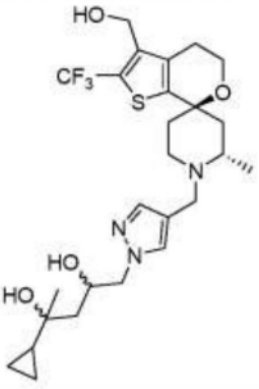
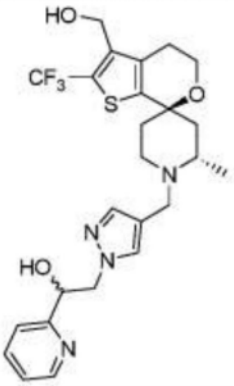
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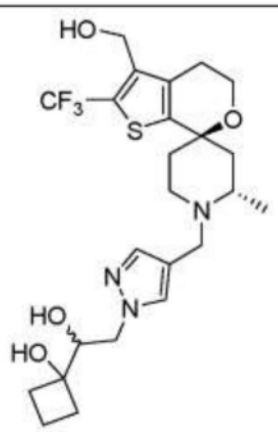
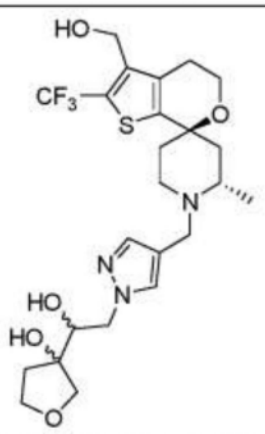
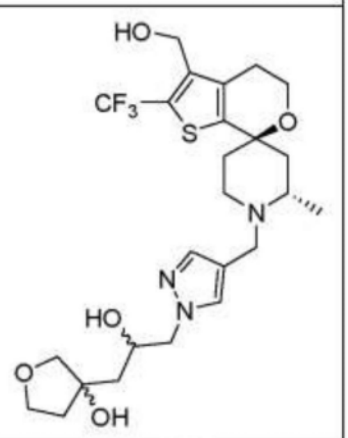
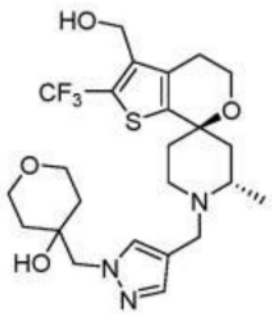
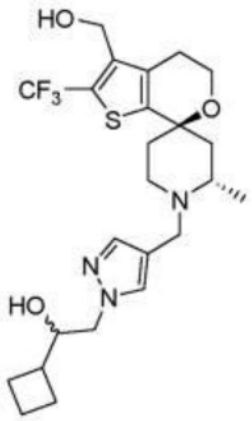
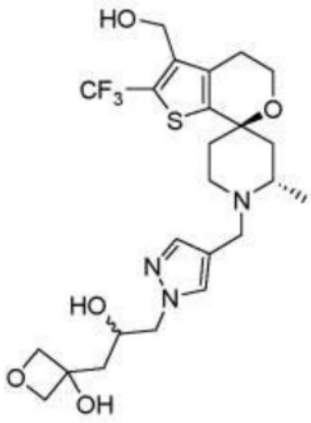
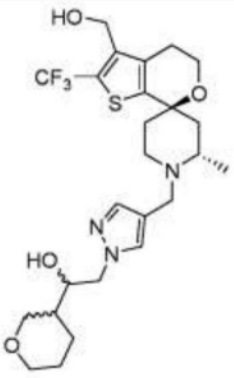
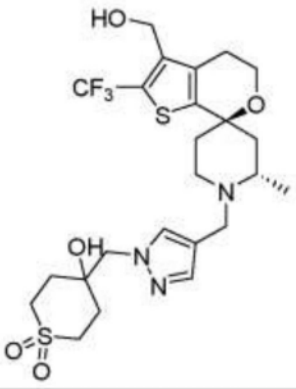
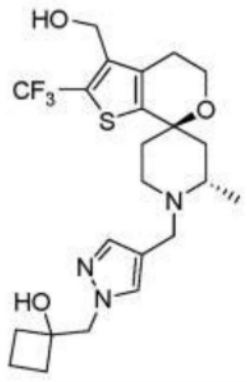
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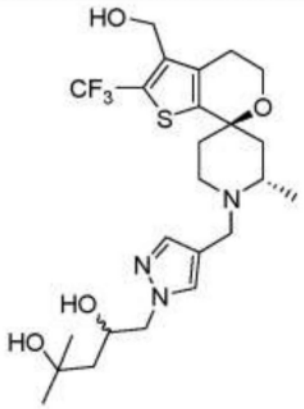
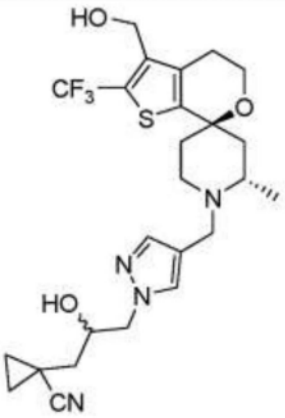
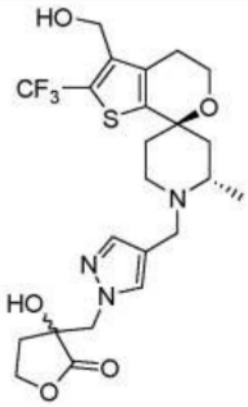
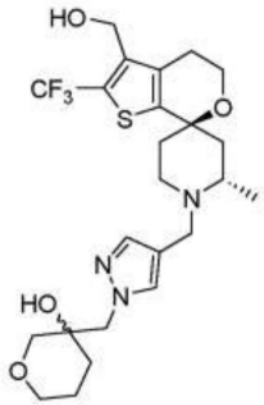
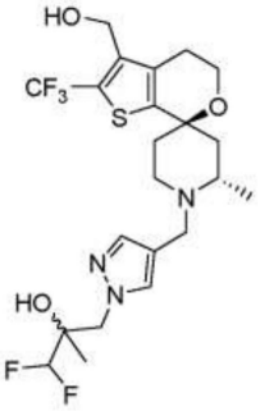
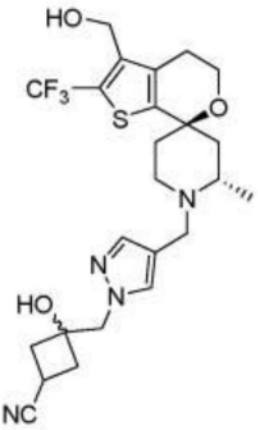
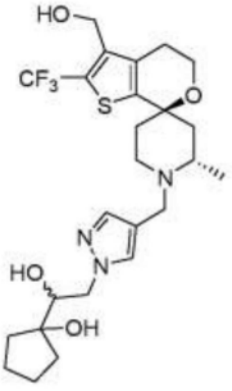
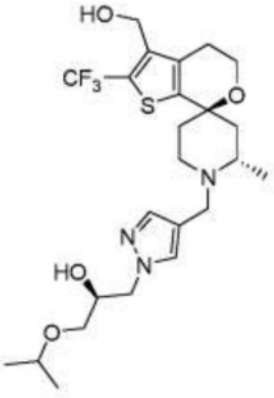
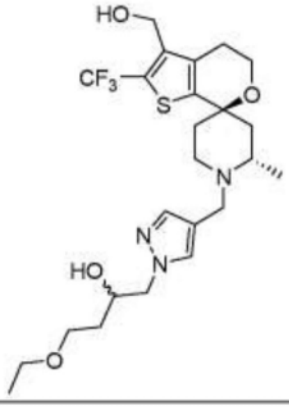
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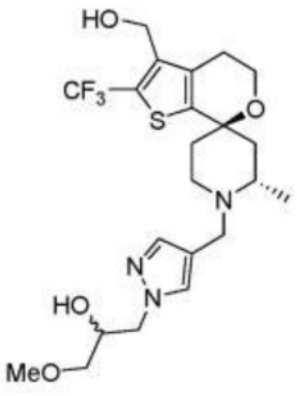
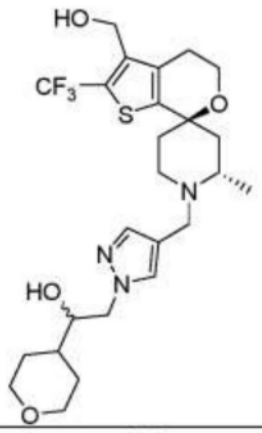
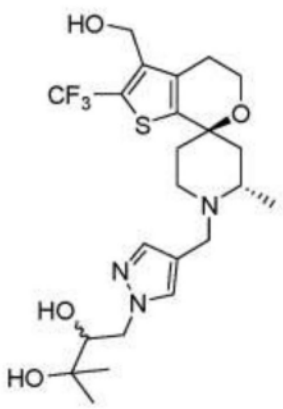
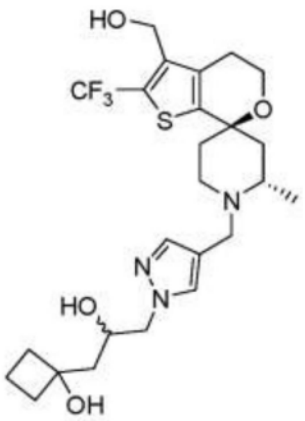
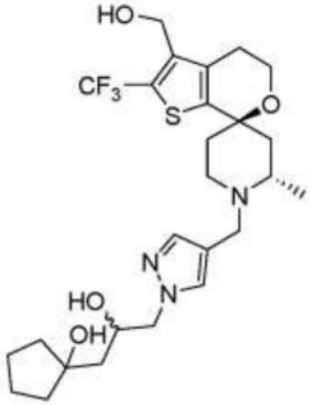
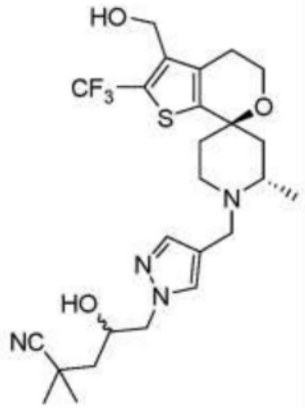
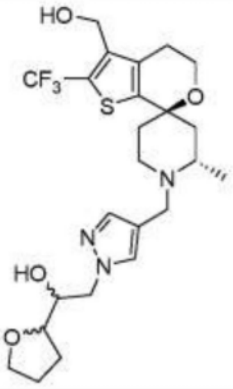
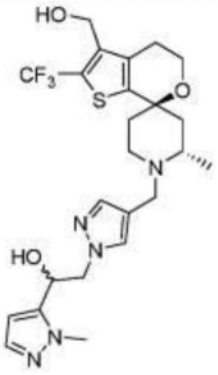
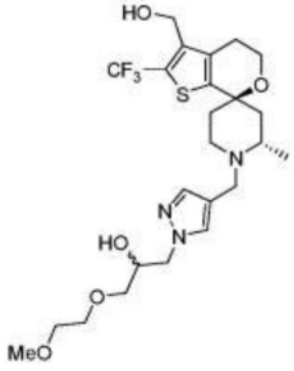
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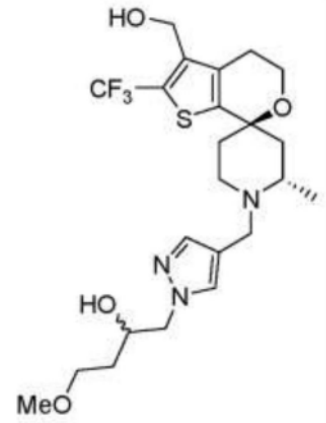
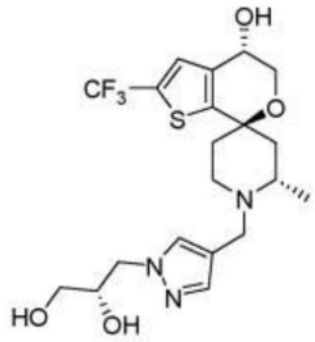
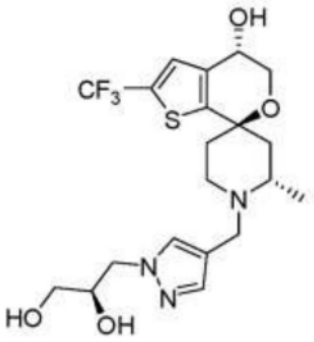
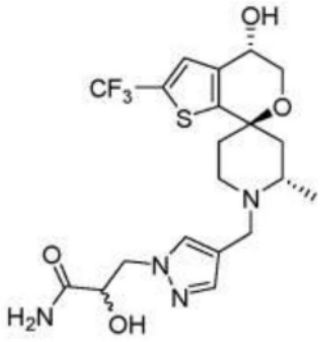
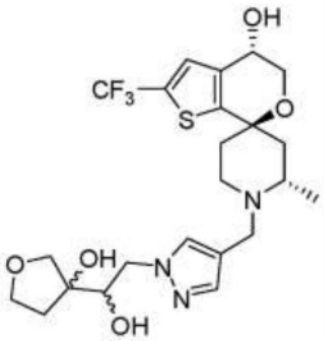
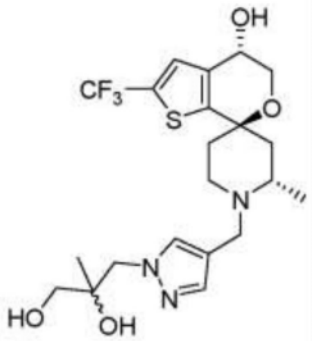
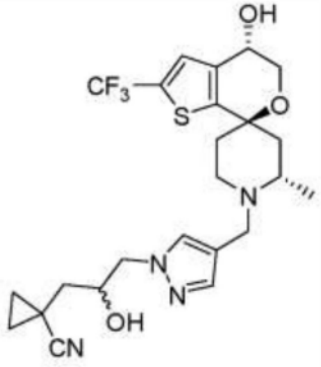
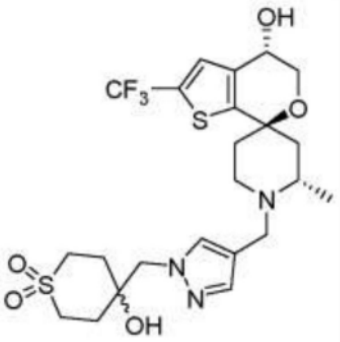
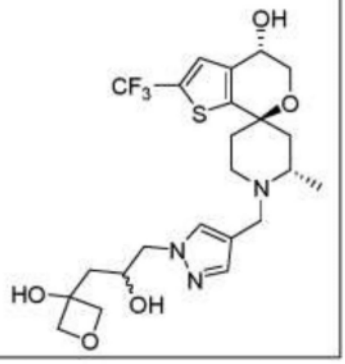
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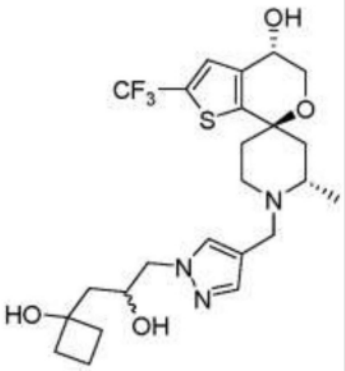
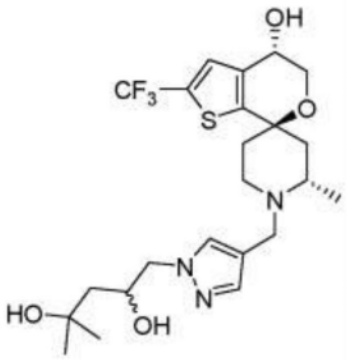
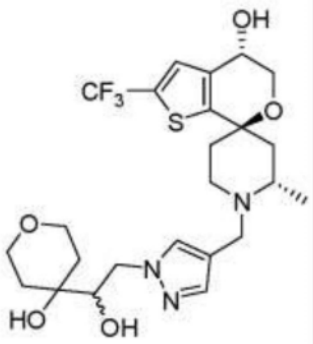
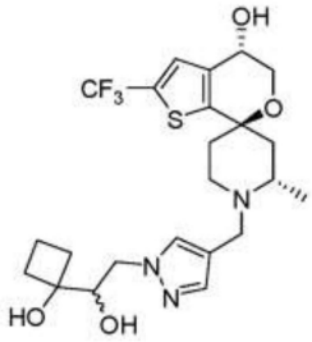
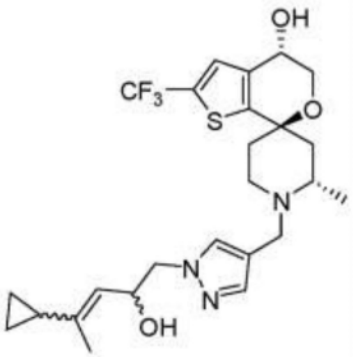
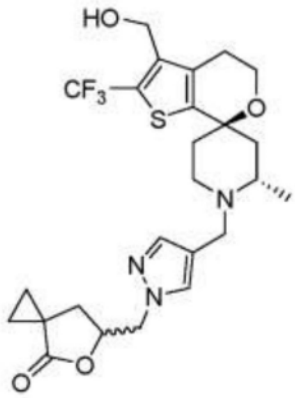
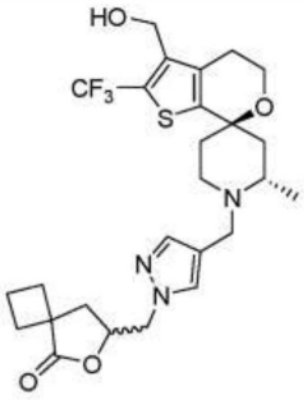
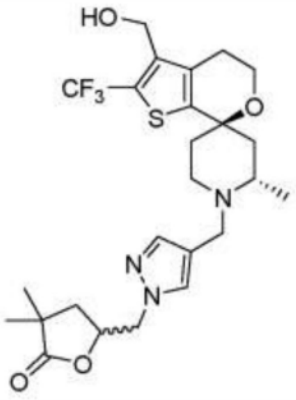
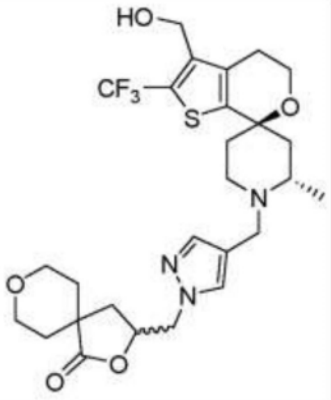
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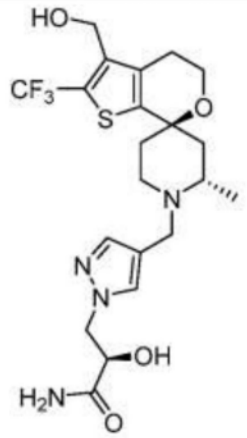
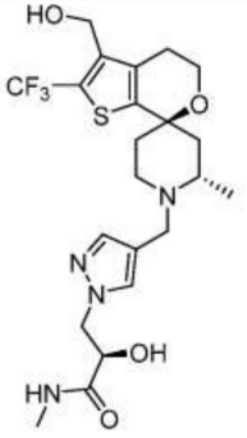
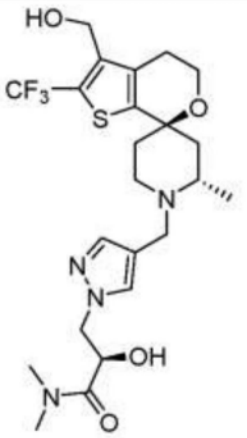
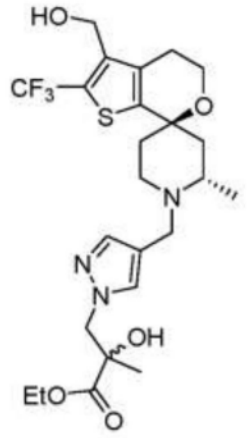
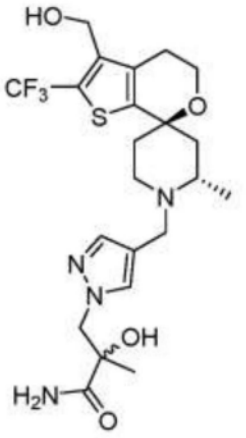
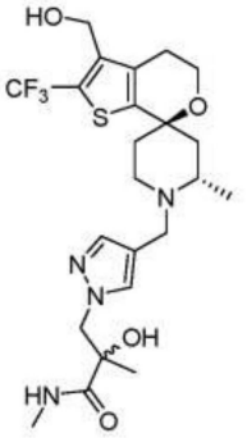
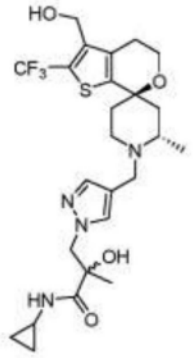
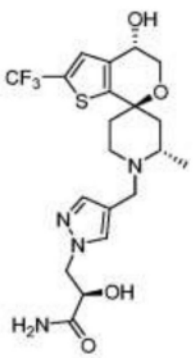
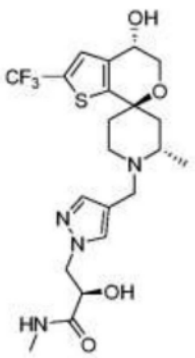
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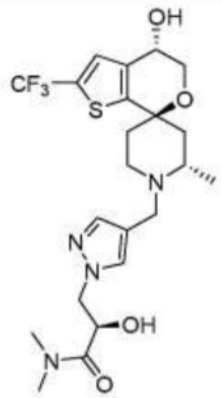
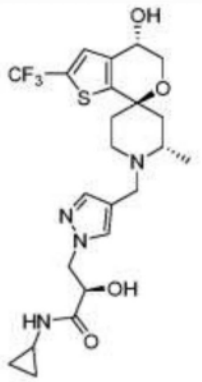
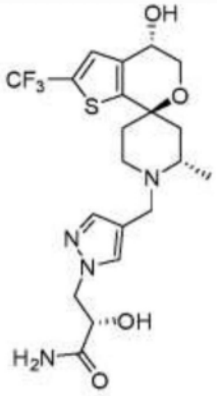
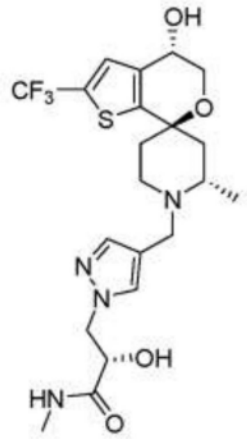
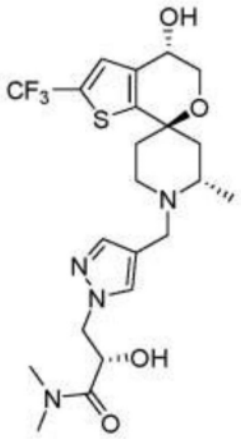
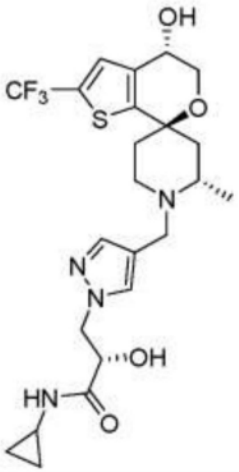
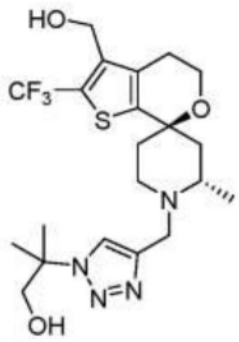
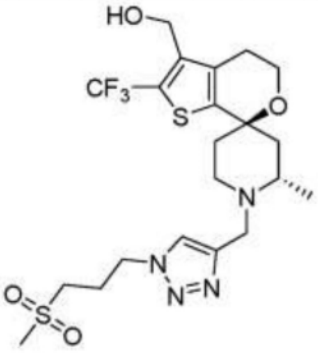
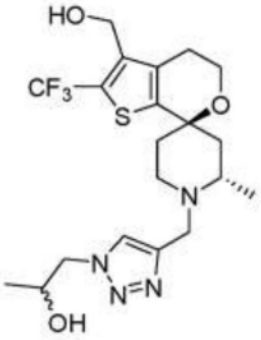
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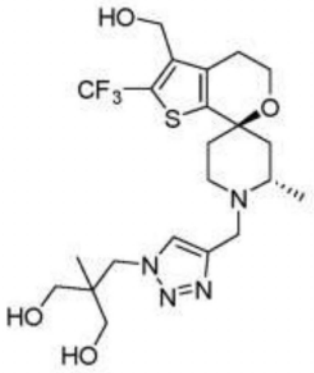
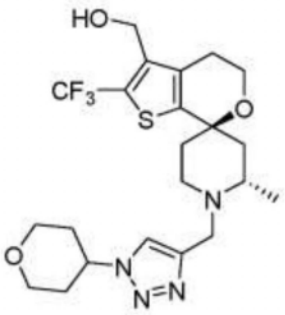
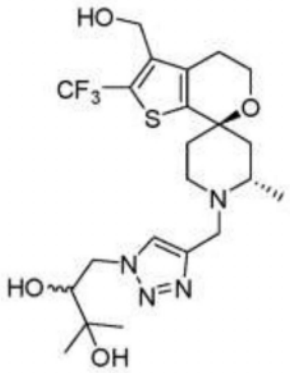
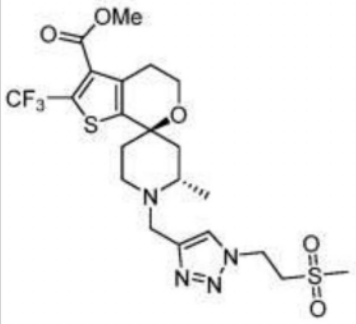
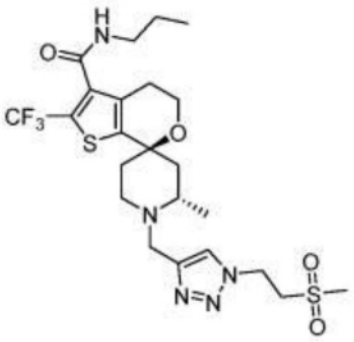
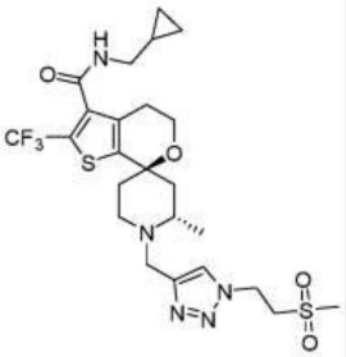
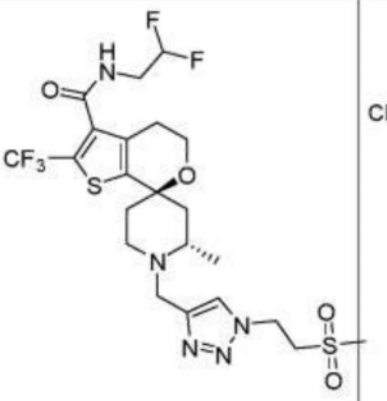
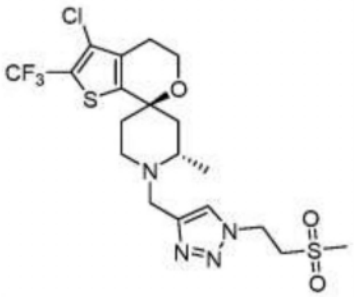
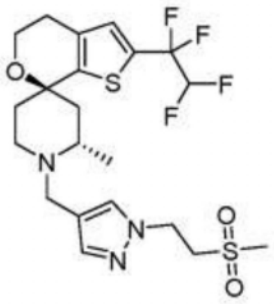
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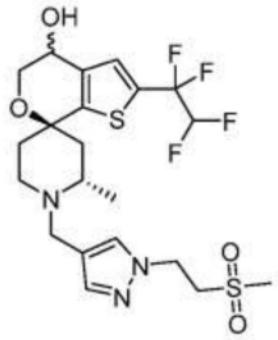
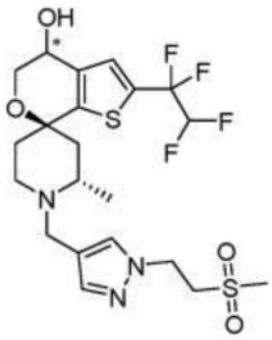
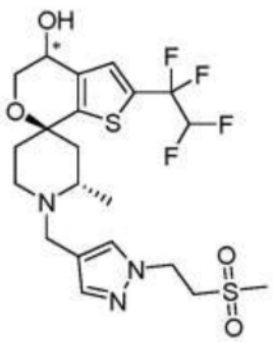
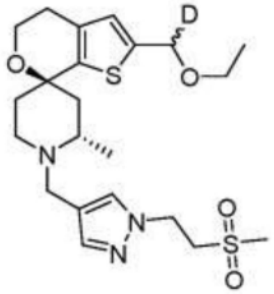
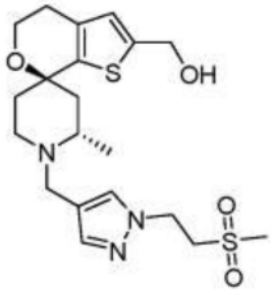
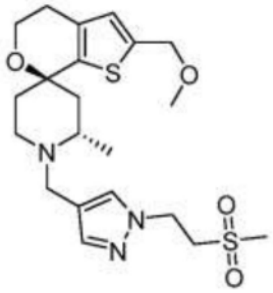
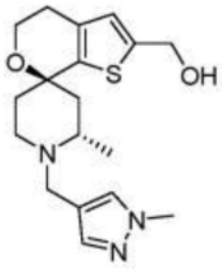
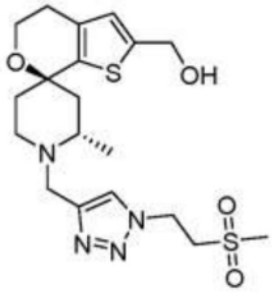
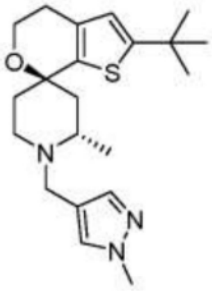
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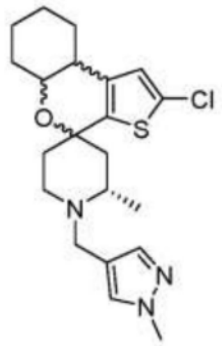
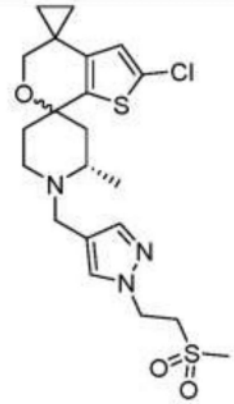
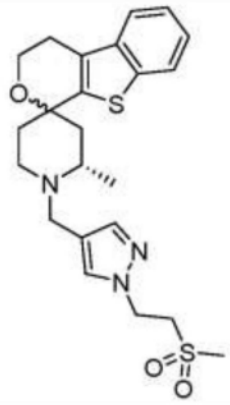
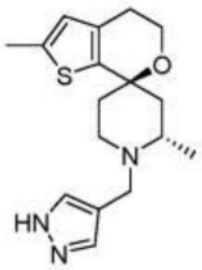
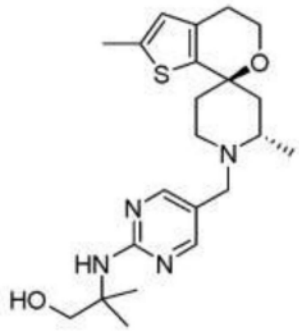
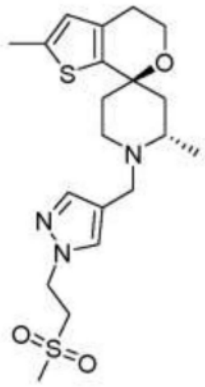
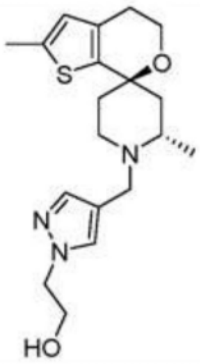
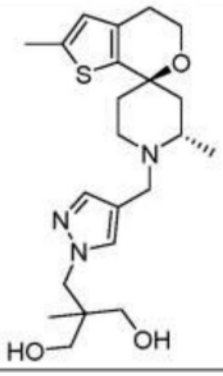
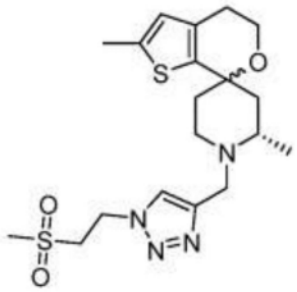
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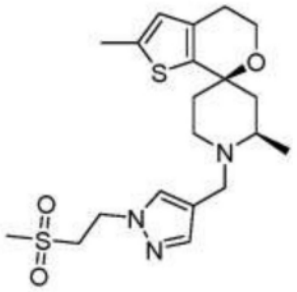
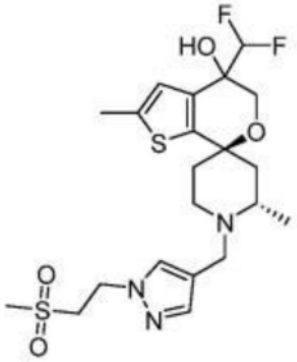
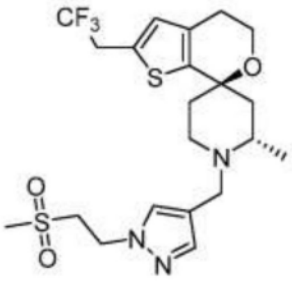
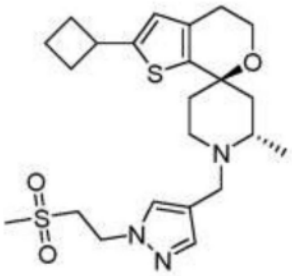
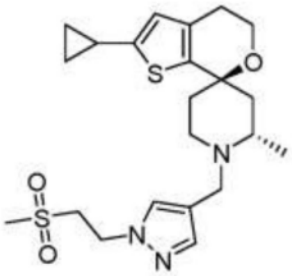
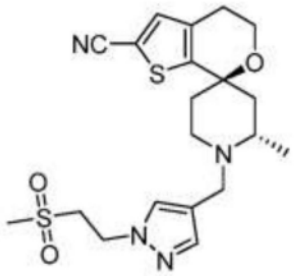
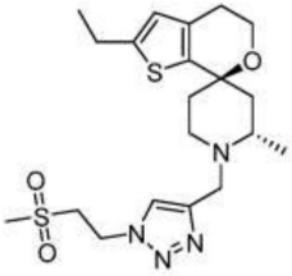
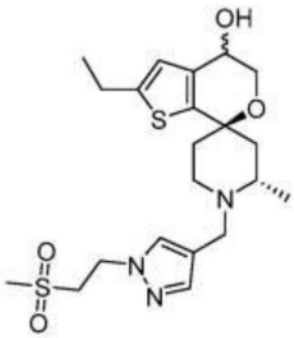
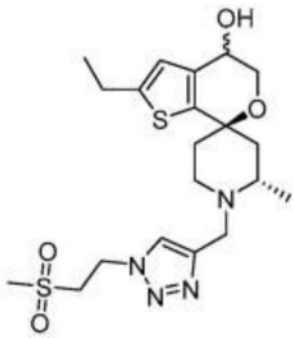
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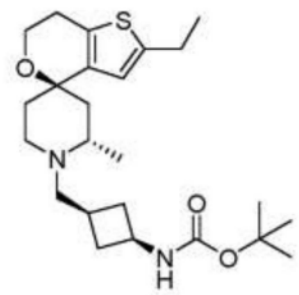
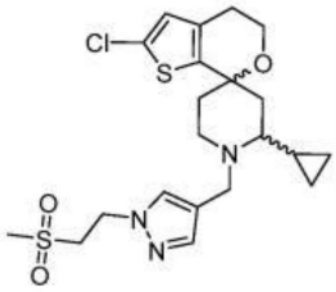
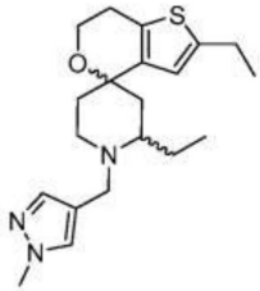
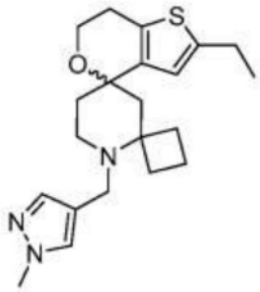
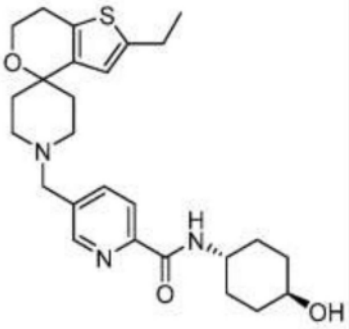
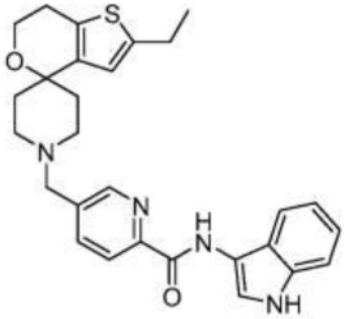
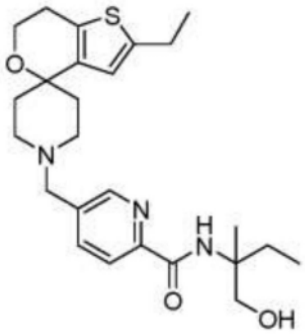
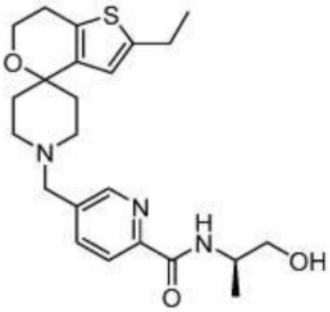
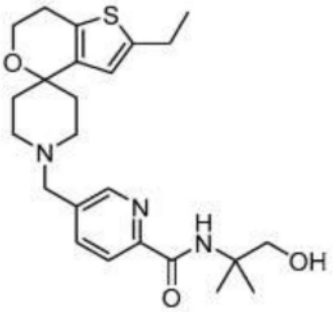
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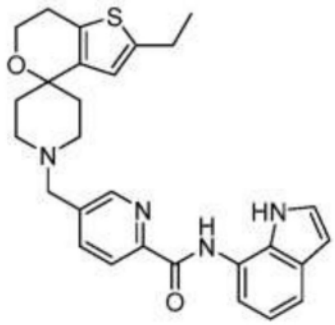
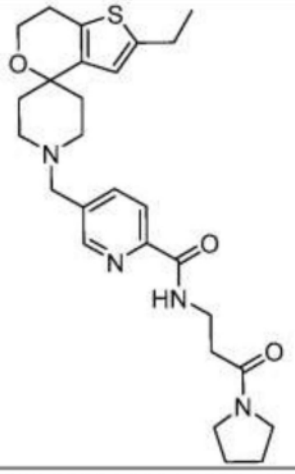
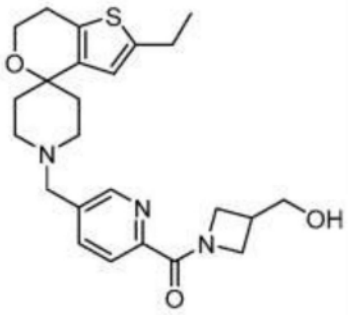
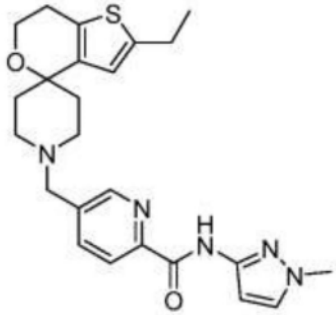
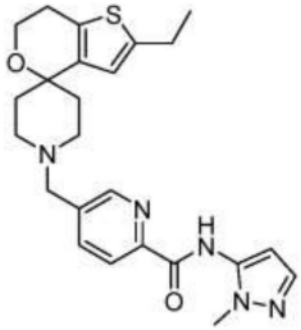
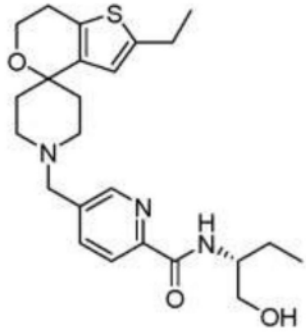
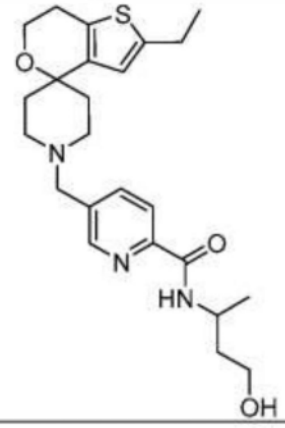
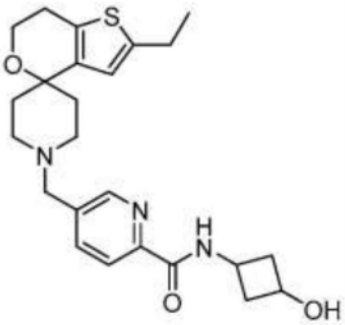
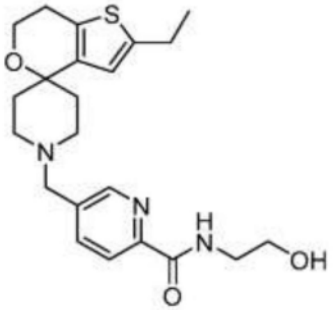
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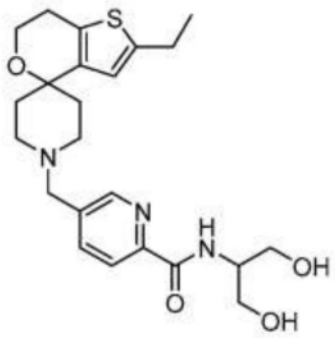
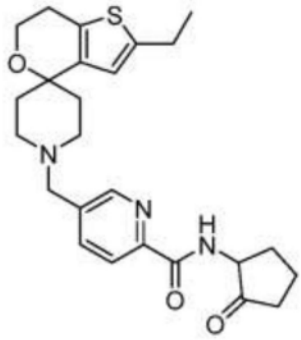
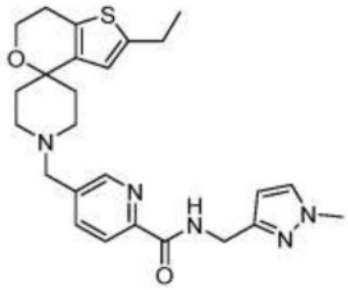
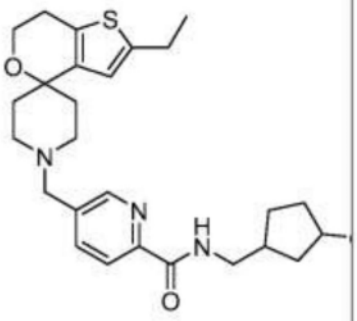
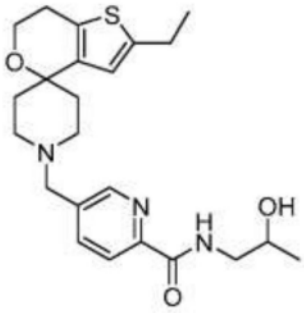
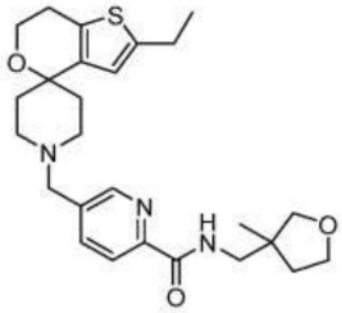
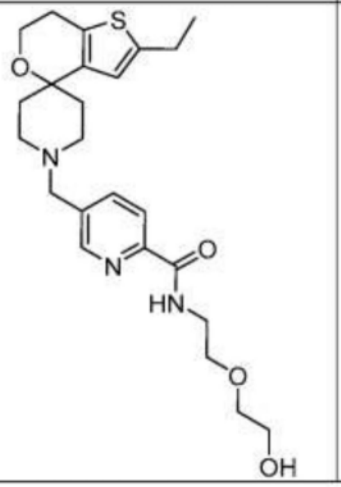
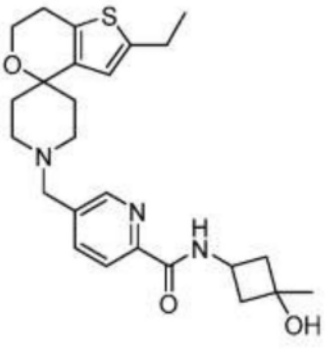
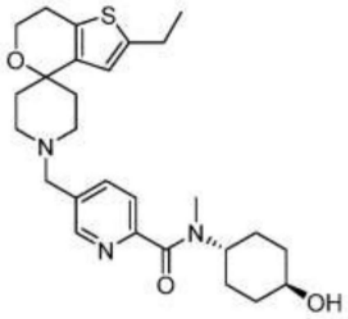
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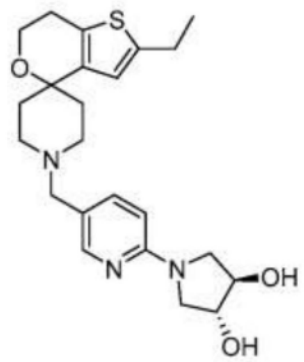
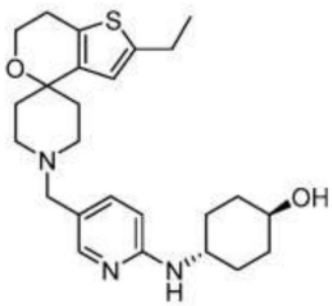
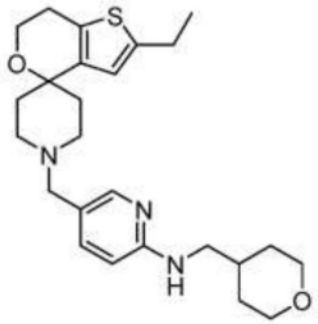
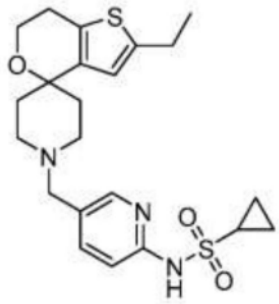
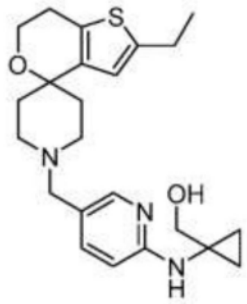
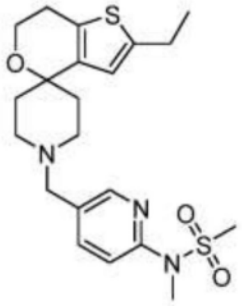
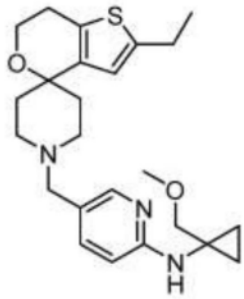
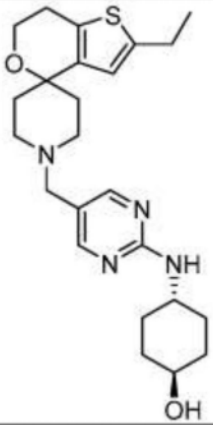
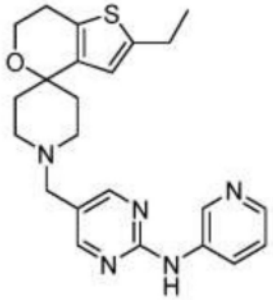
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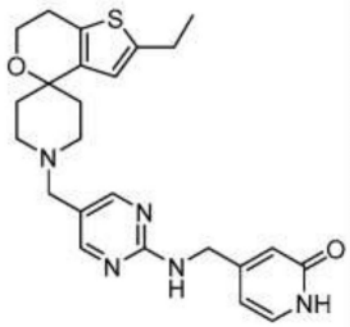
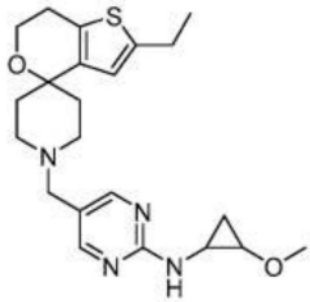
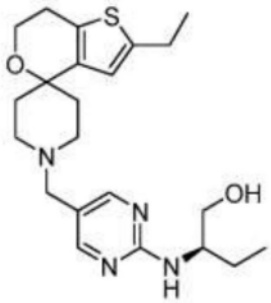
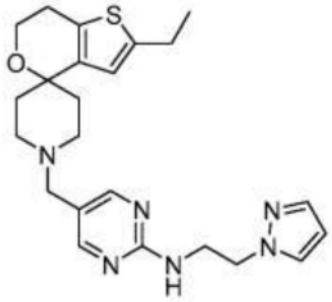
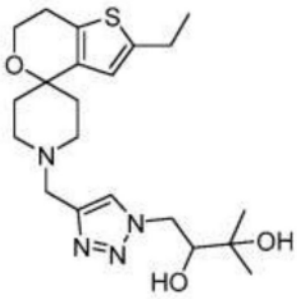
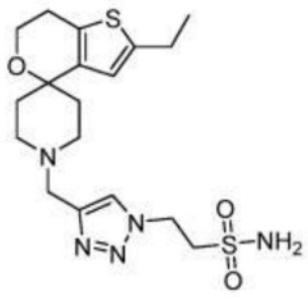
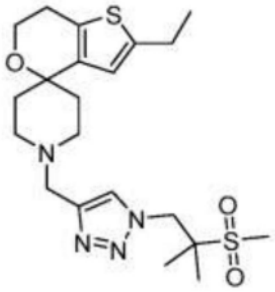
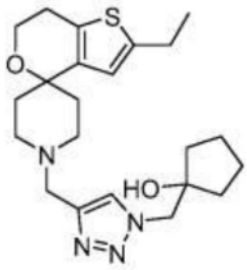
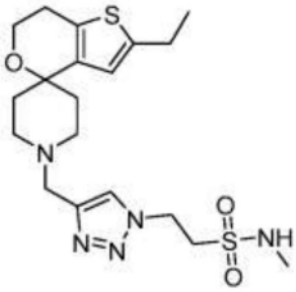
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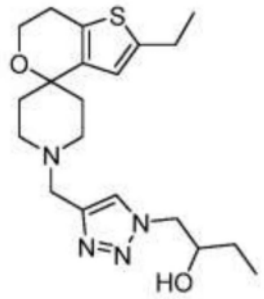
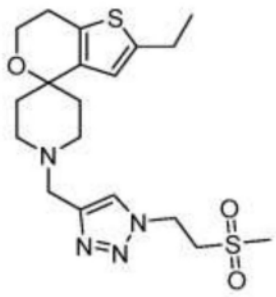
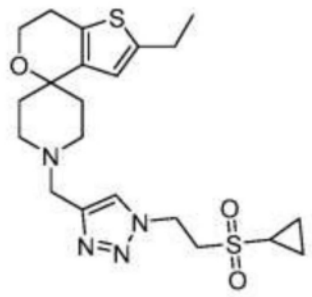
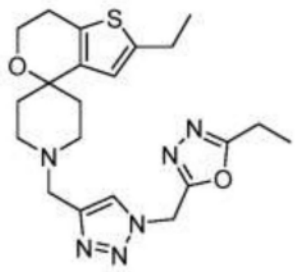
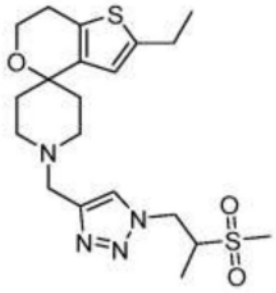
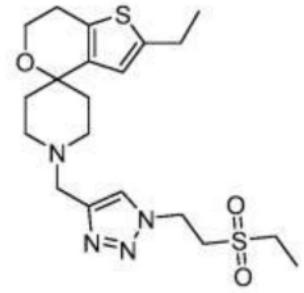
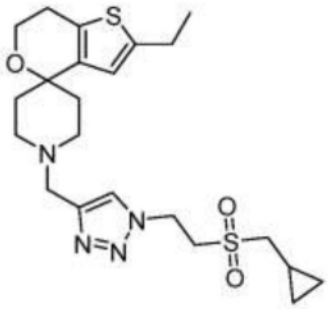
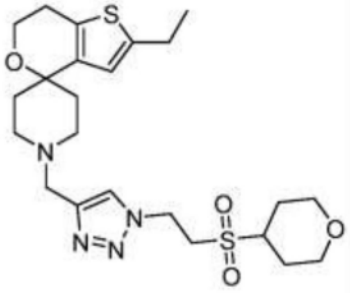
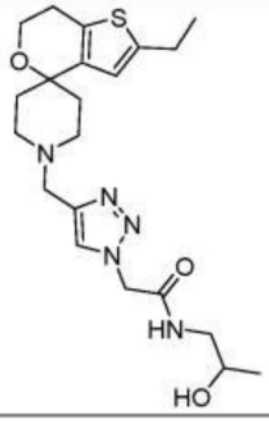
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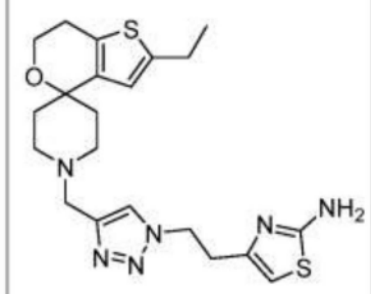
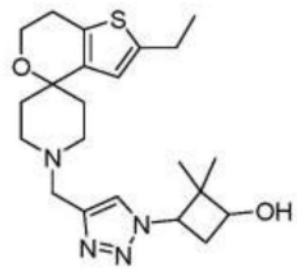
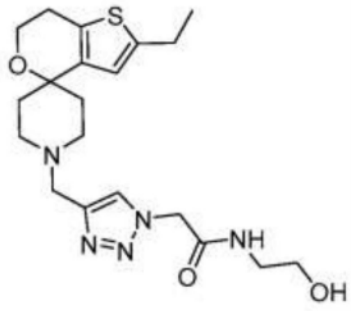
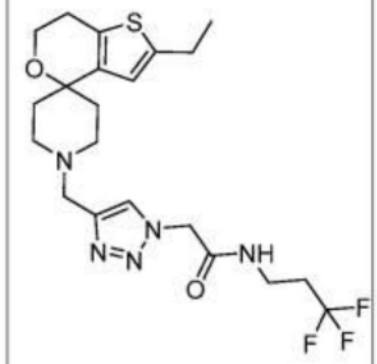
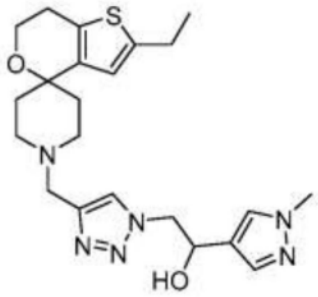
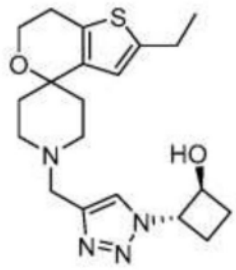
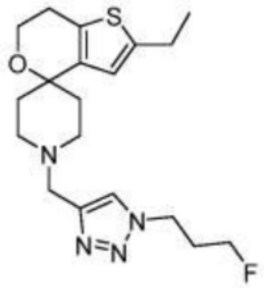
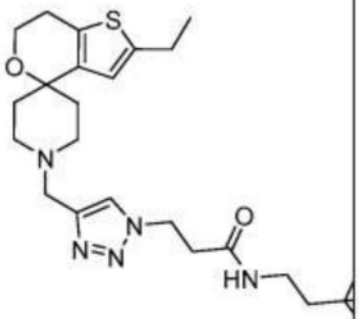
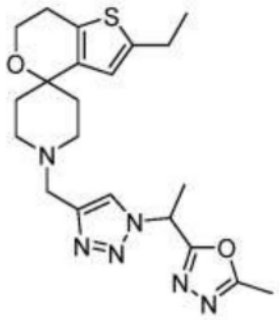
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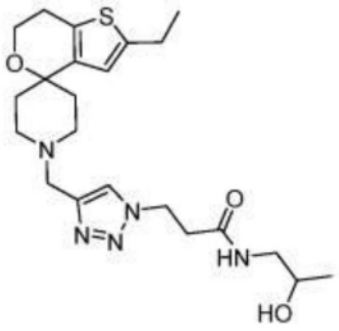
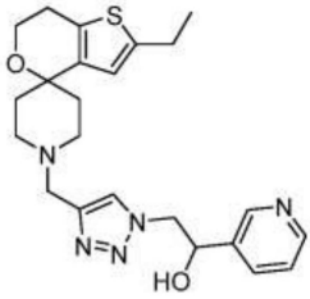
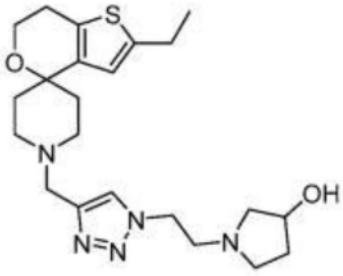
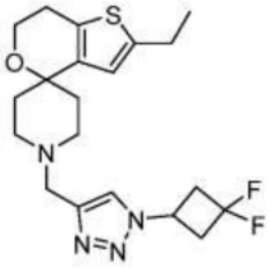
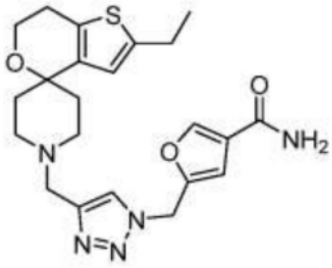
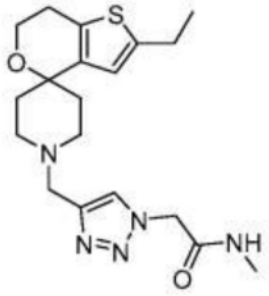
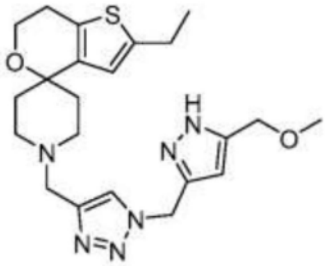
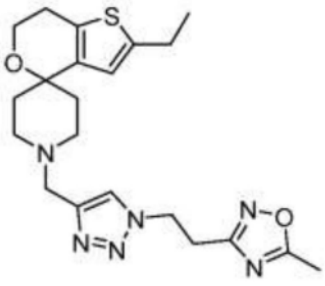
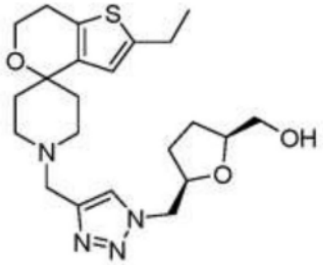
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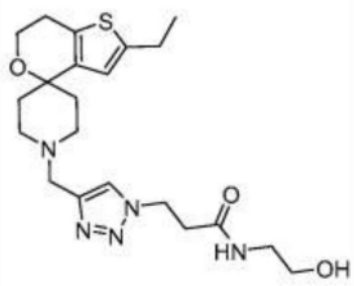
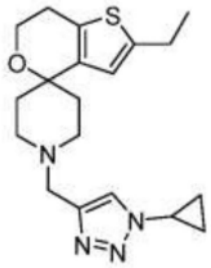
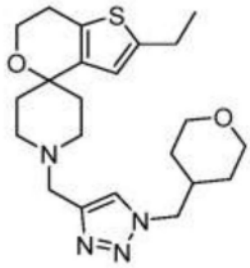
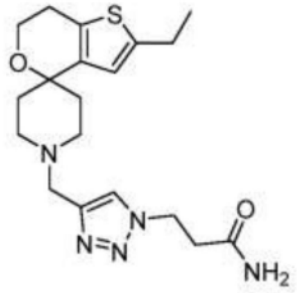
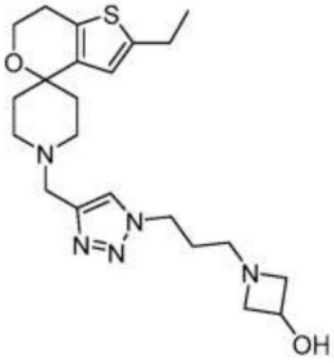
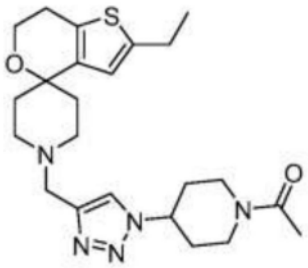
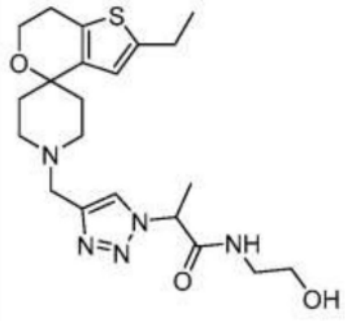
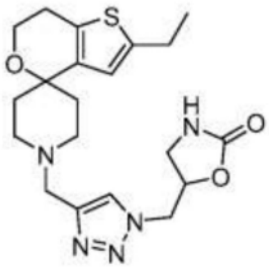
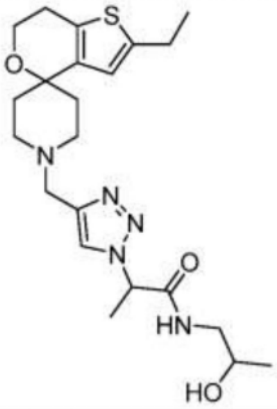
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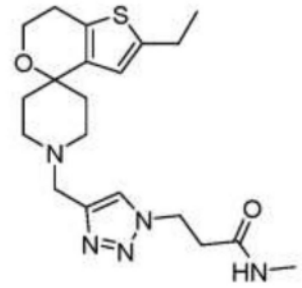
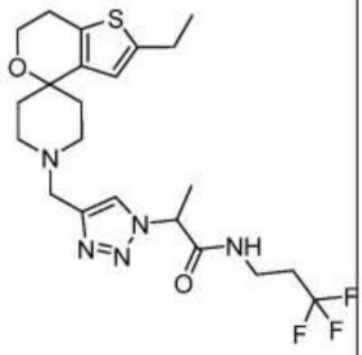
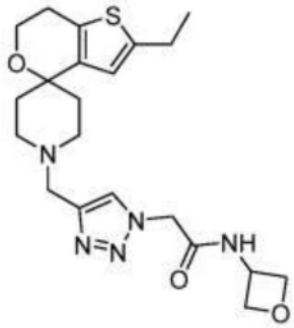
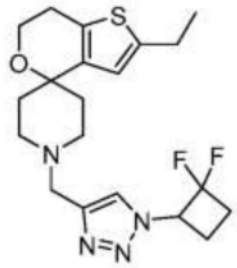
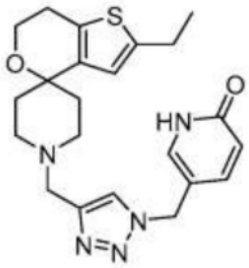
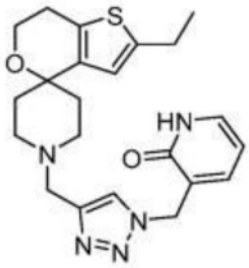
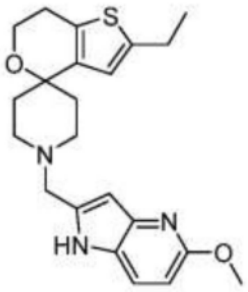
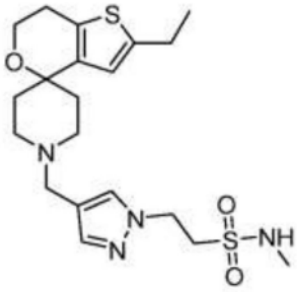
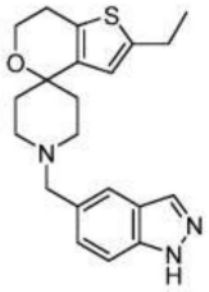
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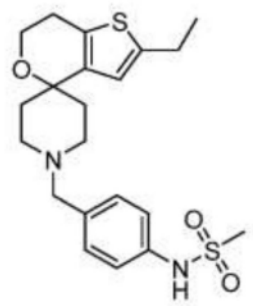
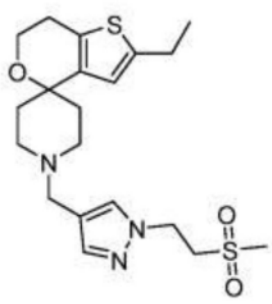
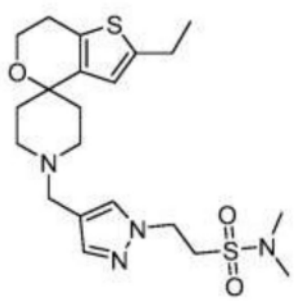
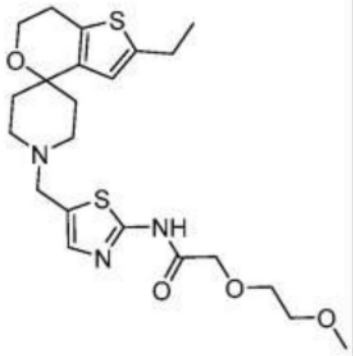
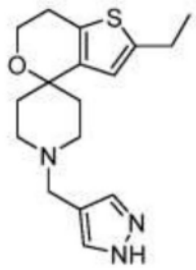
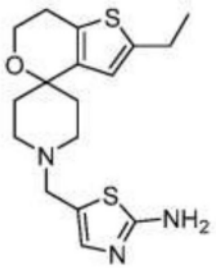
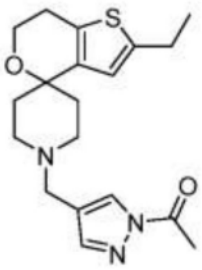
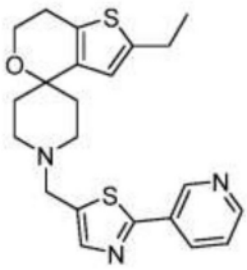
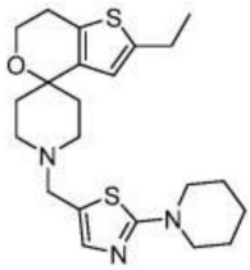
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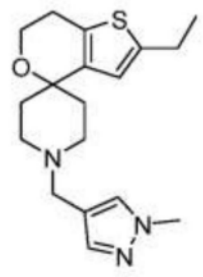
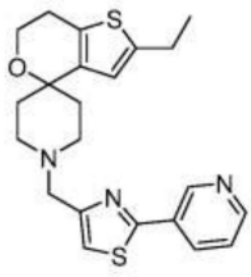
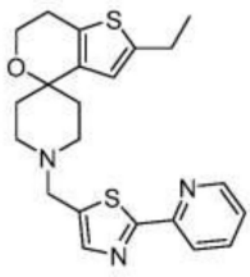
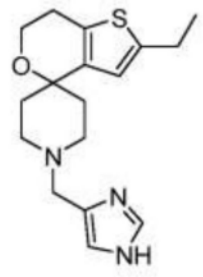
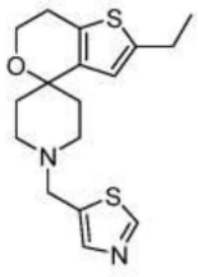
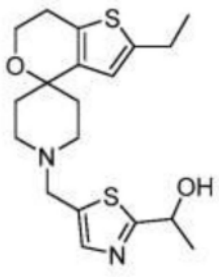
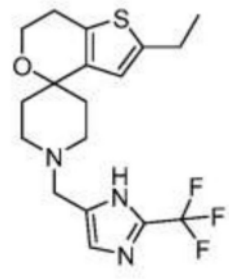
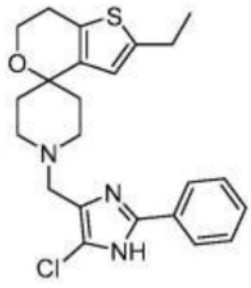
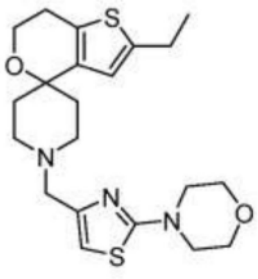
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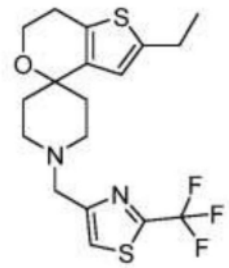
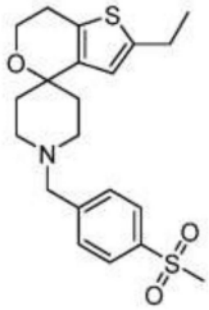
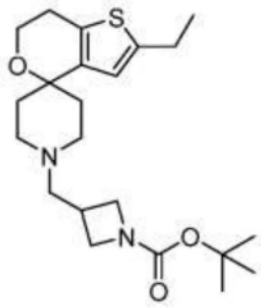
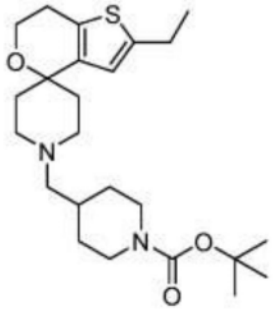
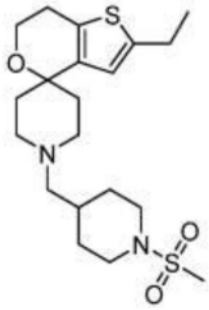
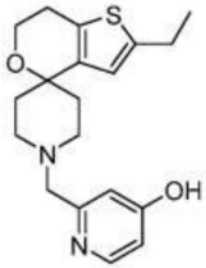
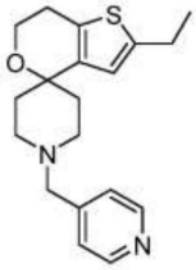
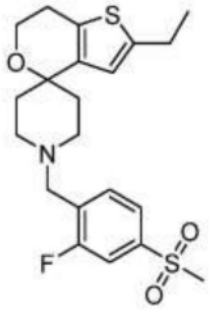
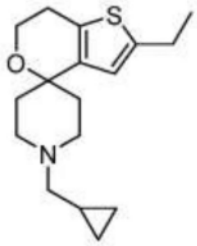
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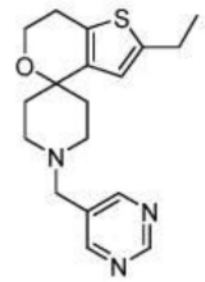
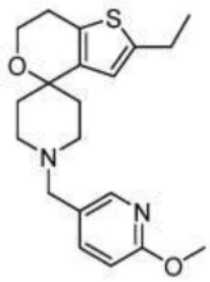
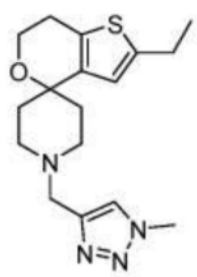
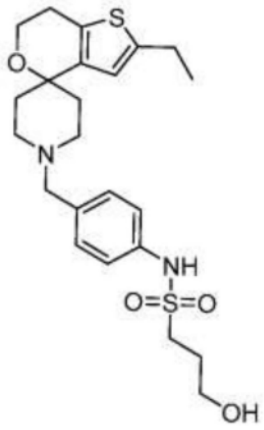
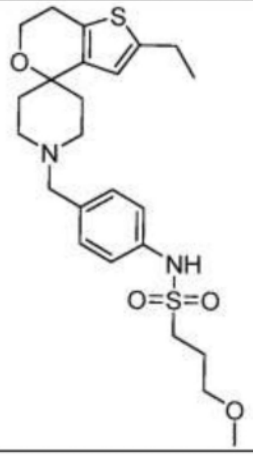
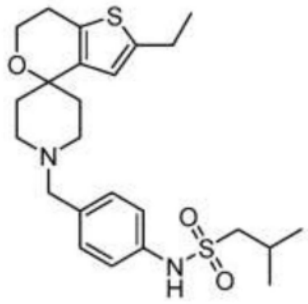
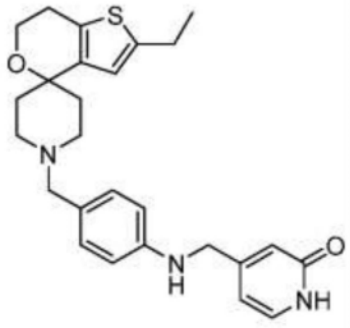
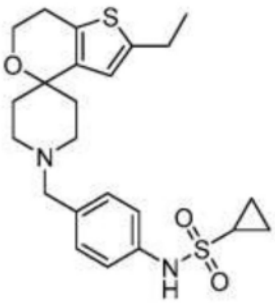
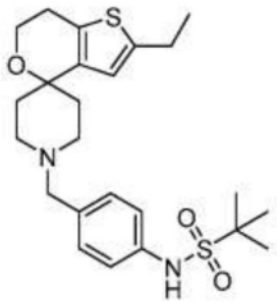
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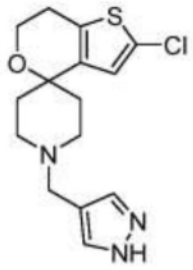
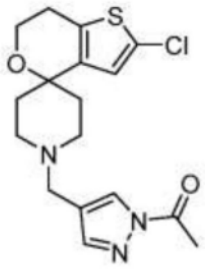
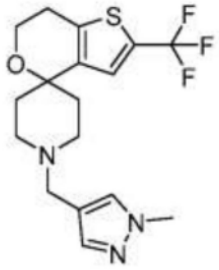
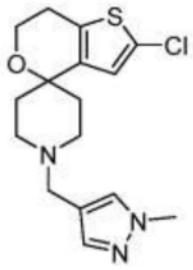
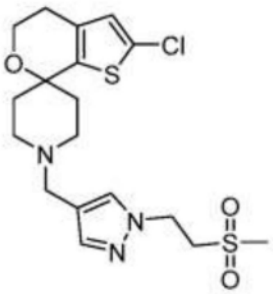
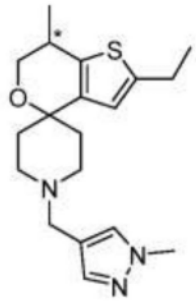
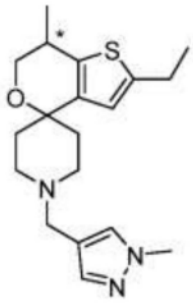
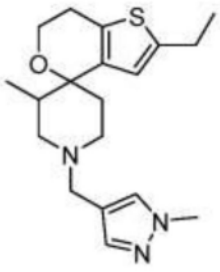
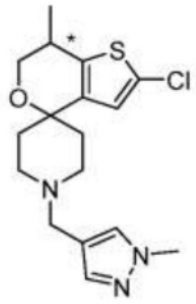
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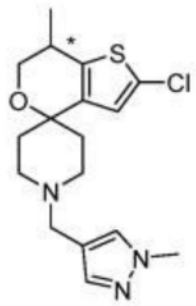
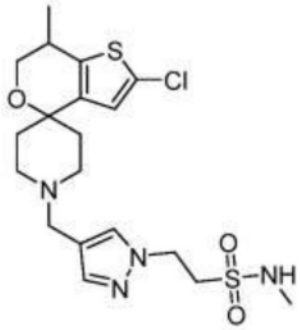
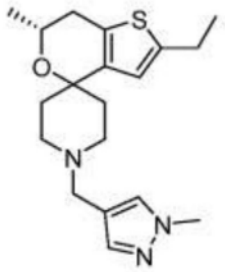
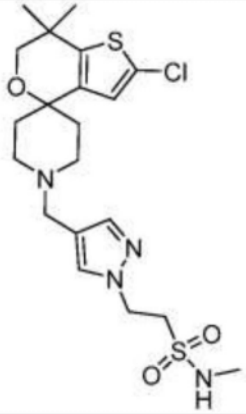
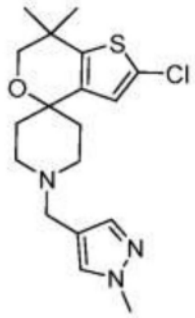
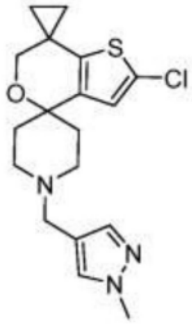
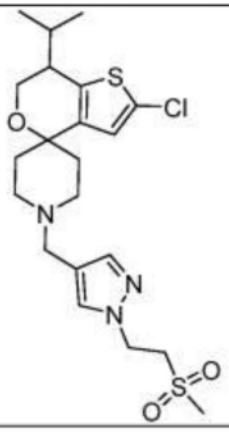
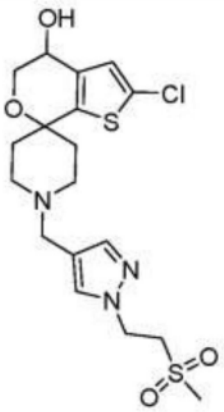
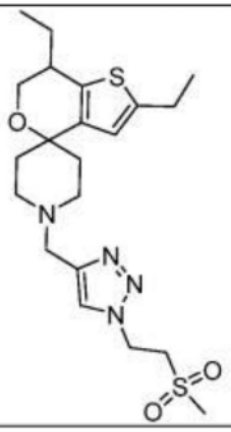
[0312]

1156	1157	1158
		
1159	1160	1161
		
1162	1163	1164
		

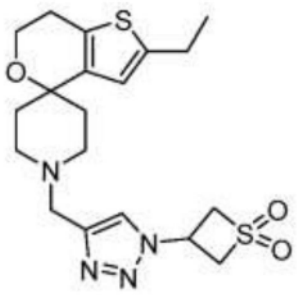
[0313]

1165	1166	1167
		
1168	1169	1170
		
1171	1172	1173
		

[0314]

1174	1175	1176
		
1177	1178	1179
		
1180	1181	1182
		

[0315]

1183


[0316] 本公开的一些实施例包含以下的衍生物:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐。在一些实施例中,所述衍生物是硅衍生物,其中化合物、互变异构体、氘化衍生物或药学上可接受的盐中的至少一个选自以下的碳原子已被硅替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,所述衍生物是硼衍生物,其中化合物、互变异构体、氘化衍生物或药学上可接受的盐中的至少一个选自以下的碳原子已被硼替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在其它实施例中,所述衍生物是磷衍生物,其中化合物、互变异构体、氘化衍生物或药学上可接受的盐中的至少一个选自以下的碳原子已被磷替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0317] 在一些实施例中,所述衍生物是硅衍生物,其中选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐中的一个碳原子被硅或硅衍生物(例如,-Si$(CH_3)_2$-或-Si$(OH)_2$-)替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。被硅替代的碳可以是非芳香族碳。在其它实施例中,氟被硅衍生物(例如,-Si$(CH_3)_3$)替代。在一些实施例中,本公开的硅衍生物可以包含一个或多个被氘替代的氢原子。在一些实施例中,选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐的硅衍生物可以将硅结合到杂环中:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、所述化合物或互变异构体的氘化衍生物或前述中任一者的药学上可接受的盐。

[0318] 在一些实施例中,所述衍生物是硼衍生物,其中化合物、互变异构体、氘化衍生物或药学上可接受的盐中的一个选自以下的碳原子已被硼或硼衍生物替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或

互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0319] 在一些实施例中,所述衍生物是磷衍生物,其中化合物、互变异构体、氘化衍生物或药学上可接受的盐中的一个选自以下的碳原子已被磷或磷衍生物替代:化合物1至1183或式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0320] 本公开的另一方面提供了药物组合物,所述药物组合物包括至少一种根据选自以下式的任一者的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物和化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,向有需要的患者施用药物组合物,所述药物组合物包括至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物和化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0321] 药物组合物可以进一步包括至少一种药学上可接受的载体。在一些实施例中,至少一种药学上可接受的载体选自药学上可接受的媒介物和药学上可接受的佐剂。在一些实施例中,至少一种药学上可接受的选自药学上可接受的填充剂、崩解剂、表面活性剂、粘合剂和润滑剂。

[0322] 还应理解,本公开的药物组合物可以用于组合疗法中;即,本文所描述的药物组合物可以进一步包含至少一种另外的活性治疗剂。可替代地,包括至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物可以作为单独的组合物与包括至少一种其它活性治疗剂的组合物同时、之前或之后施用:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,包括至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐的药物组合物可以作为单独的组合物与包括至少一种其它活性治疗剂的组合物同时、之前或之后施用:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0323] 如上所述,本文公开的药物组合物可以任选地进一步包括至少一种药学上可接受的载体。至少一种药学上可接受的载体可选自佐剂和媒剂。如本文所使用的,至少一种药学上可接受的载体包含适合于所需的特定剂型的任何和所有溶剂、稀释剂、其它液体媒剂、分散助剂、悬浮液助剂、表面活性剂、等渗剂、增稠剂、乳化剂、防腐剂、固体粘合剂和润滑剂。《雷明顿:药学的科学与实践(Remington:The Science and Practice of Pharmacy)》,第21版,2005,D.B.Troy编辑,费城的利平科特·威廉斯·威尔金斯出版公司(Troy,Lippincott Williams&Wilkins,Philadelphia)以及《药剂百科全书(Encyclopedia of Pharmaceutical Technology)》,J.Swarbrick和J.C.Boylan编辑,1988至1999,Marcel Dekker,New York公开了用于配制药物组合物的各种载体和用于制备其的已知技术。除非任何常规载体与本公开的化合物不兼容,如通过产生任何不期望的生物效应或另外以有害方式与药物组合物的任何其它组分相互作用,否则其用途被预期在本公开的范围内。合适的药学上可接受的载体的非限制性实例包含但不限于离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白(例如,人血清白蛋白)、缓冲物质(例如,磷酸盐、甘氨酸、山梨酸和山梨酸钾)、

饱和植物脂肪酸、水、盐和电解质的偏甘油酯混合物(例如,硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠和锌盐)、胶体二氧化硅、三硅酸镁、聚乙烯吡咯烷酮、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯嵌段聚合物、羊毛脂、糖(例如,乳糖、葡萄糖和蔗糖)、淀粉(例如,玉米淀粉和马铃薯淀粉)、纤维素和其衍生物(例如,羧甲基纤维素钠、乙基纤维素和乙酸纤维素)、粉状黄蓍胶、麦芽、明胶、滑石、赋形剂(例如,可可脂和栓剂蜡)、油(例如,花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油)、二醇(例如,丙二醇和聚乙二醇)、酯(例如,油酸乙酯和月桂酸乙酯)、琼脂、缓冲剂(例如,氢氧化镁和氢氧化铝)、海藻酸、无热原水、等渗盐水、林格氏溶液(Ringer's solution)、乙醇、磷酸盐缓冲溶液、无毒相容性润滑剂(例如,月桂基硫酸钠和硬脂酸镁)、着色剂、脱模剂、包衣剂、甜味剂、调味剂、芳香剂、防腐剂和抗氧化剂。

[0324] 用于治疗的化合物和组合物

[0325] 在本公开的一些实施例中,本文所述的化合物和药物组合物用于治疗FSGS和/或NDKD。在一些实施例中,FSGS由APOL1介导。在一些实施例中,NDKD由APOL1介导。

[0326] 在本公开的一些实施例中,本文所述的化合物和药物组合物用于治疗癌症。在一些实施例中,癌症由APOL1介导。

[0327] 在本公开的一些实施例中,本文所述的化合物和药物组合物用于治疗胰腺癌。在一些实施例中,胰腺癌由APOL1介导。

[0328] 在一些实施例中,本公开的方法包括向有需要的患者施用至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,化合物、互变异构体、氘化衍生物或药学上可接受的盐选自化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,所述有需要的患者具有APOL1遗传变体,即,G1:S342G:I384M和G2:N388del:Y389del。

[0329] 本公开的另一个方面提供了抑制APOL1活性的方法,所述方法包括使所述APOL1与至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐接触:式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。在一些实施例中,抑制APOL1活性的方法包括使所述APOL1与至少一种选自以下的化合物、互变异构体、氘化衍生物或药学上可接受的盐接触:化合物1至1183、其互变异构体、这些化合物或互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐。

[0330] 实例

[0331] 为了可以更充分地理解本文描述的公开内容,阐述了以下实例。应理解,这些实施例仅用于说明性目的,并且不应解释为以任何方式限制本公开。

[0332] 本公开的化合物可以根据标准化学实践或如本文所述来制备。在以下合成方案中以及在制备式I、Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il和Im化合物选自化合物1至1183、其互变异构体、这些化合物和互变异构体的氘化衍生物和前述中任一者的药学上可接受的盐的描述中,使用以下缩写:

[0333] 缩写

[0334] AcOH＝乙酸

[0335] ARP＝即用型测定板(assay ready plate)

[0336] Boc_2O＝脱碳酸二叔丁酯

[0337] n-BuLi＝正丁基锂

[0338] CFL＝紧凑型荧光灯

[0339] 18-冠-6＝1,4,7,10,13,16-六氧杂环十八烷

[0340] DAST＝二乙氨基三氟化硫

[0341] DBDMH＝1,3-二溴-5,5-二甲基乙内酰脲

[0342] DBU＝1,8-二氮杂二环[5.4.0]十一碳-7-烯

[0343] DCE＝1,2-二氯乙烷

[0344] DCM＝二氯甲烷

[0345] Deoxo-fluor＝双(2-甲氧基乙基)氨基三氟化硫

[0346] DIBAL-H＝氢化二异丁基铝

[0347] DIPEA或DIEA＝N,N-二异丙基乙胺或N-乙基-N-异丙基-丙烷-2-胺

[0348] DMAP＝二甲基氨基吡啶

[0349] DMA＝二甲基乙酰胺

[0350] DME＝二甲氧基乙烷

[0351] DMEM＝杜氏改良伊格尔氏培养基(Dulbecco's modified Eagle's medium)

[0352] DMF＝二甲基甲酰胺

[0353] DMPU＝N,N′-二甲基丙烯脲

[0354] DMSO＝二甲基亚砜

[0355] dppf＝1,1′-双(二苯基膦基)二茂铁

[0356] ESI＝电喷射离子化

[0357] EtOAc＝乙酸乙酯

[0358] EtOH＝乙醇

[0359] Et_2O＝乙醚

[0360] Et_2NH＝二乙胺

[0361] Et_3N＝三乙胺

[0362] FA＝甲酰胺

[0363] FBS＝胎牛血清

[0364] GF-AFC＝甘氨酰基-苯丙氨酰基氨基氟香豆素

[0365] HATU＝[二甲基氨基(三唑并[4,5-b]吡啶-3-基氧基)亚甲基]-二甲基-铵(六氟化磷离子)

[0366] HDMC＝N-[(5-氯-3-氧代-1H-苯并三唑-1-基)-4-吗啉亚甲基]-N-甲基甲铵六氟磷酸盐

[0367] HPLC＝高效液相色谱法

[0368] IPA＝异丙醇

[0369] $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$＝[4,4′-双(1,1-二甲基乙基)-2,2′-联吡啶-N1,N1′]双[3,5-二氟-2-[5-(三氟甲基)-2-吡啶基-N]苯基-C]铱(III)六氟磷酸盐

[0370] [Ir{dFCF3ppy}2(bpy)]PF6＝(2,2′-联吡啶)双[3,5-二氟-2-[5-(三氟甲基)-2-吡啶基-kN][苯基-kC]铱(III)六氟磷酸盐

[0371] LDA＝二异丙基酰胺锂

[0372] LED＝发光二极管

[0373] MeCN或ACN＝乙腈

[0374] MeI＝甲基碘

[0375] MeMgCl＝甲基氯化镁

[0376] MeOH＝甲醇

[0377] MsOH＝甲磺酸

[0378] MTBE或TBME＝甲基叔丁基醚

[0379] n-BuLi＝正丁基锂

[0380] n-BuOH＝1-丁醇

[0381] NaOtBu＝叔丁醇钠

[0382] NBS＝N-溴代琥珀酰亚胺

[0383] NCS＝N-氯代琥珀酰亚胺

[0384] NHPI＝N-羟基邻苯二甲酰亚胺

[0385] NIS＝N-碘代琥珀酰亚胺

[0386] NMM＝N-甲基吗啉

[0387] NMP＝N-甲基吡咯烷

[0388] PBS＝磷酸盐缓冲盐水

[0389] $Pd(dppf)_2Cl_2$＝[1,1′-双(二苯基膦基)二茂铁]二氯化钯(II)

[0390] $PdCl_2(PPh_3)_2$＝双(三苯基膦)二氯化钯(II)

[0391] pet＝石油

[0392] PP＝聚丙烯

[0393] PPh_3＝三苯基膦

[0394] PhMgCl＝苯基氯化镁

[0395] PSCBH＝聚合物负载的氰基硼氢化物

[0396] PTSA＝对甲苯磺酸一水合物

[0397] RBF＝圆底烧瓶

[0398] SFC＝超临界流体色谱法

[0399] SPE＝固相萃取

[0400] STAB＝三乙酰氧基硼氢化钠

[0401] T3P＝2,4,6-三丙基-1,3,5,2,4,6-三氧杂三磷杂环已烷-2,4,6-三氧化物

[0402] TBAF＝四正丁基氟化铵

[0403] TBS＝叔丁基二甲基甲硅烷基

[0404] TBSCl＝叔丁基二甲基氯硅烷

[0405] TBTA＝三((1-苄基-4-三唑基)甲基)胺

[0406] TBuONO＝亚硝酸叔丁酯

[0407] tBuXPhos Pd G1＝[2-(二叔丁基膦)-2′,4′,6′-三异丙基-1,1′-联苯][2-(2-氨

基乙基)苯基)]氯化钯(II)

[0408] tBuOH＝叔丁醇

[0409] TEA＝三乙胺

[0410] tet＝四环素

[0411] TFA或TFAA＝三氟乙酸

[0412] TfOH＝三氟甲磺酸

[0413] THF＝四氢呋喃

[0414] T3P＝2,4,6-三丙基-1,3,5,2,4,6-三氧杂三磷杂环己烷-2,4,6-三氧化物

[0415] 2-Me-THF＝2＝甲基四氢呋喃

[0416] THP＝四氢吡喃

[0417] TLC＝薄层色谱法

[0418] TMS-OTf＝三氟甲磺酸三甲基甲硅烷基酯

[0419] TMSCl＝三甲基甲硅烷基氯

[0420] $TMSCF_3$＝三氟甲基三甲基硅烷

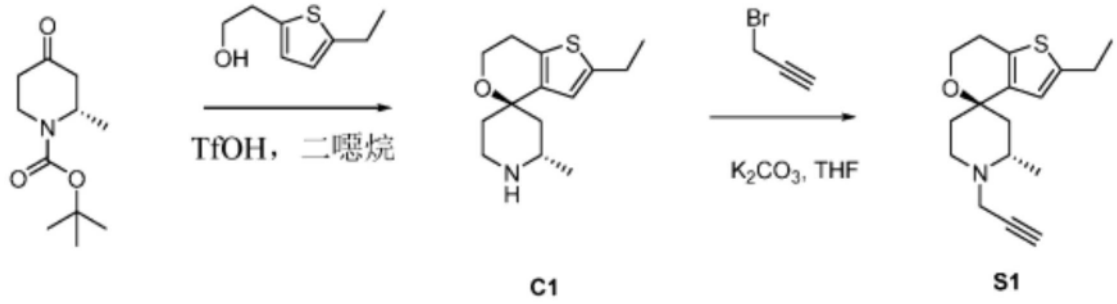
[0421] XPhos Pd G3＝(2-二环己基膦-2′4′6′-三异丙基-1,1′-联苯)-[2-(2′-氨基-1,1′-联苯)]甲磺酸钯(II)

[0422] 实例1:化合物的合成

[0423] 所有具体和一般的化合物和公开用于制备那些化合物的中间体都被认为是本文公开的公开内容的一部分。

[0424] 制备S1

[0425] (2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S1)

[0426] 

C1 S1

[0427] 步骤1:(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶(C1)的合成

[0428] 在0℃下在15分钟内向(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(10g,46.89mmol)和2-(5-乙基-2-噻吩基)乙醇(7g,42.56mmol)于二噁烷(80mL)中的溶液中添加三氟甲磺酸(12.4mL,140.1mmol)于二噁烷(20mL)中的溶液。将反应物在相同温度下搅拌1小时,并且然后温热至环境温度并搅拌3.5小时。将混合物用水(300mL)和乙酸乙酯(200mL)稀释。将有机层分离,并且将水层用EtOAc(100mL×2)萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物溶解在DCM中并通过硅胶塞(250g)过滤,用DCM洗脱,随后用25% MeOH/DCM洗脱,得到期望产物。将产物溶解在Et_2O(500mL)中,并在回流下加热15分钟。冷却至环境温度后,添加庚烷(500mL),并过滤固体,用庚烷洗涤并干燥以提供呈灰色

固体的标题化合物(三氟甲磺酸盐)(11.36g,67%)。^{1}H NMR(400MHz,DMSO-d6)δ6.46(d,J=1.1Hz,1H),3.96-3.79(m,2H),3.42-3.34(m,1H),3.27-3.00(m,2H),2.80-2.63(m,4H),2.01-1.87(m,3H),1.79(dd,J=14.5,12.2Hz,1H),1.24-1.16(m,6H)。LCMS m/z 252.01[M+H]$^+$。

[0429] 步骤2:(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S1)的合成

[0430] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C1(三氟甲磺酸盐)(76.7g,187.7mmol)和K_2CO_3(46g,332.8mmol)于THF(900mL)中的混合物中添加炔丙基溴(21mL,188.5mmol,含80%w/w溶液的甲苯)。将所得混合物在45℃下加热5小时,并且然后冷却至室温并搅拌过夜。将反应物用EtOAc(350mL)、盐水(150mL)和2M $Na_2S_2O_3$水溶液(25mL)稀释。将有机层分离,并且将水层用EtOAc(100mL)萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物用Et_2O研磨。将所得无色固体过滤并干燥,得到S1(55.7g,92%)。^{1}H NMR(300MHz,氯仿-d)δ6.47(d,J=1.1Hz,1H),4.05-3.85(m,2H),3.67(dd,J=17.3,2.4Hz,1H),3.44(dd,J=17.3,2.4Hz,1H),3.00-2.64(m,7H),2.25(t,J=2.4Hz,1H),2.03-1.81(m,3H),1.68(dd,J=13.8,11.5Hz,1H),1.28(t,J=7.5Hz,3H),1.10(d,J=6.3Hz,3H)。LCMS m/z 290.11[M+H]$^+$。

[0431] 制备S2

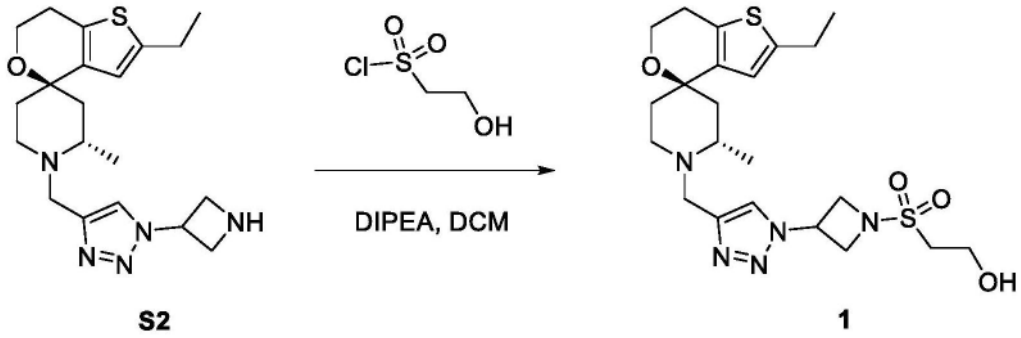
[0432] (2′S,4R)-1′-[[1-(氮杂环丁烷-3-基)三唑-4-基]甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S2)

[0433] 

[0434] 采用与化合物1所述相同的方法,由S1和3-叠氮基氮杂环丁烷制备化合物S2。

[0435] 化合物1

[0436] 2-[3-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]氮杂环丁烷-1-基]磺酰基乙醇(1)

[0437] 

[0438] 2-[3-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-

哌啶]-1′-基]甲基]三唑-1-基]氮杂环丁烷-1-基]磺酰基乙醇(1)的制备

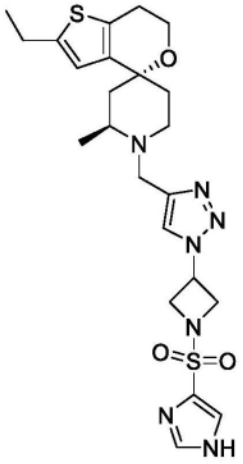
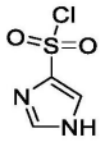
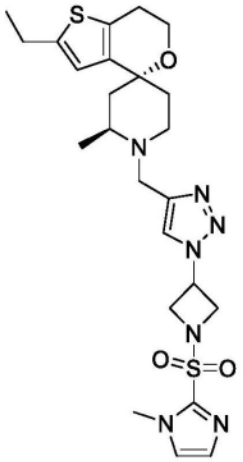
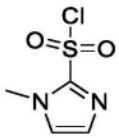
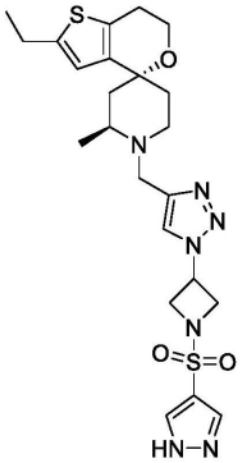
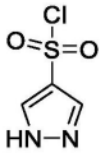
[0439] 向(2′S,4R)-1′-[[1-(氮杂环丁烷-3-基)三唑-4-基]甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S2(10mg,0.026mmol)于DCM(0.65mL)中的溶液中添加2-羟基乙烷-1-磺酰氯(4.1mg,0.028mmol)和DIPEA(9.0μL,0.052mmol)。将反应物在室温下搅拌2小时。然后去除挥发物并将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1%TFA),得到1(3.1mg,24%)。^{1}H NMR(300MHz,甲醇-d4)δ8.44(s,1H),6.51(s,1H),5.57(ddd,J=13.5,7.8,5.7Hz,1H),4.80-4.37(m,6H),3.97(t,J=5.9Hz,2H),3.88(p,J=6.0,5.5Hz,2H),3.57(d,J=7.9Hz,1H),3.40(q,J=6.4,5.9Hz,4H),2.88-2.56(m,4H),2.28-1.85(m,4H),1.58(d,J=6.4Hz,3H),1.25(t,J=7.5Hz,3H)。LCMS m/z 496.14$[M+H]^+$。

[0440] 化合物2-5

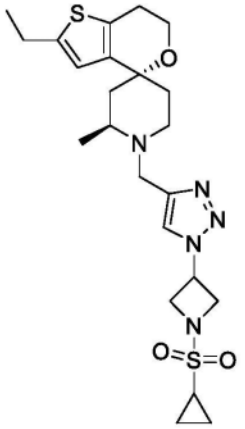
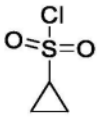
[0441] 采用与化合物1所述相同的方法,使用适当的磺酰氯由S2制备化合物2-5(参见表2)。除非另有说明,否则所有磺酰氯均从商业来源获得。表2和随附脚注中注明了对方法的任何修改。

[0442] 表2:化合物2-5的结构和物理化学数据

[0443]

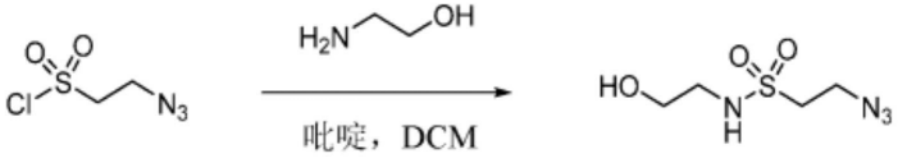
化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
2			化合物 1	LCMS *m/z* [M+H]$^+$ 518.06
3			化合物 1	LCMS *m/z* [M+H]$^+$ 532.23
4			化合物 1	LCMS *m/z* [M+H]$^+$ 518.22

[0444]

化合物	结构	胺	方法	^{1}H NMR；LCMS m/z[M+H]$^+$。
5			化合物 1	LCMS m/z [M+H]$^+$ 492.2

[0445] 制备S3

[0446] 2-叠氮基-N-(2-羟乙基)乙烷-1-磺酰胺(S3)

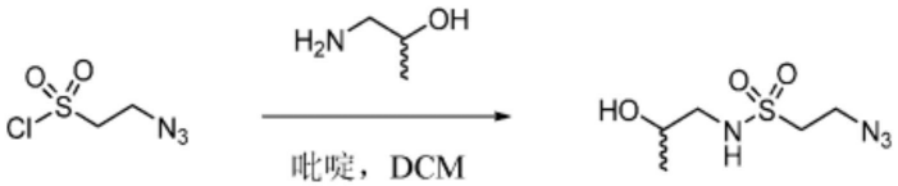
[0447] 

S3

[0448] 向2-叠氮乙磺酰氯(60mg,0.35mmol)于DCM(2mL)中的溶液中添加吡啶(60μL,0.7418mmol)和2-氨基乙醇(30μL,0.50mmol)。将混合物在室温(“rt”)下搅拌2小时(“h”)。去除挥发物,以得到标题化合物。粗产物无需进一步纯化即可直接使用。

[0449] 制备S4

[0450] 2-叠氮基-N-(2-羟丙基)乙烷-1-磺酰胺(S4)

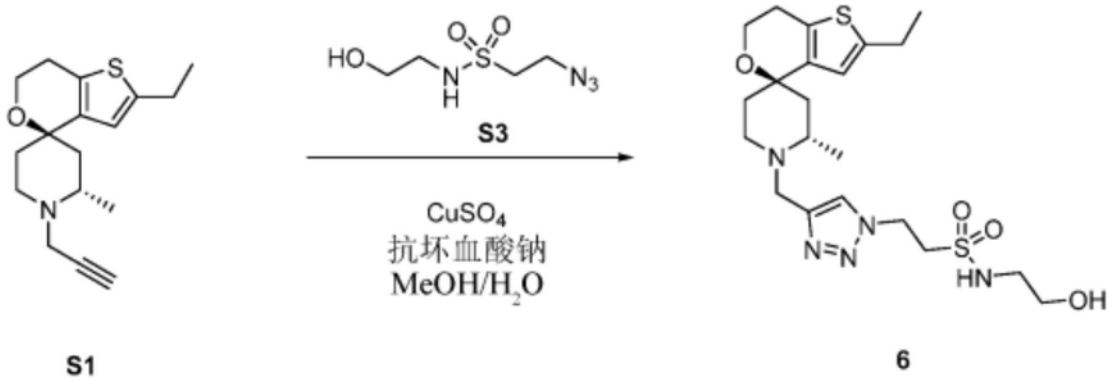
[0451] 

S4

[0452] 使用与S3所述相同的方法,由2-叠氮乙磺酰氯和1-氨基丙-2-醇制备化合物S4。粗标题化合物无需进一步纯化即可直接使用。

[0453] 化合物6

[0454] 2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]-N-(2-羟乙基)乙磺酰胺(6)

[0455] 

S1 6

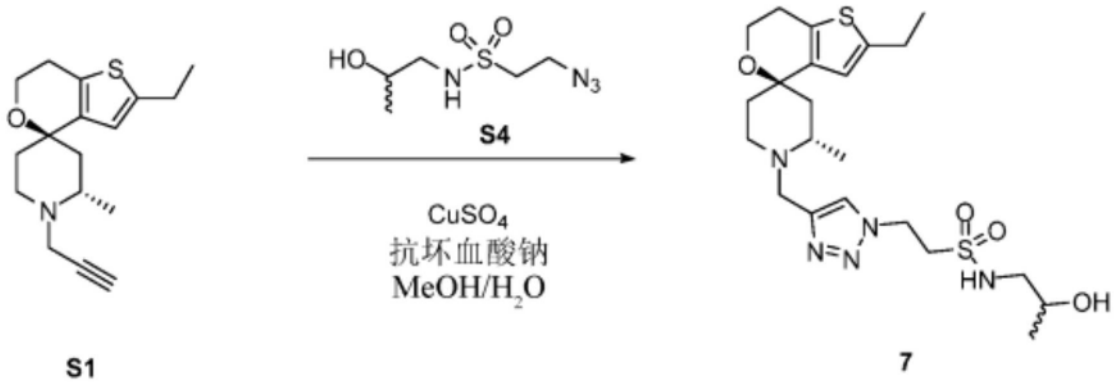
[0456] 2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]-N-(2-羟乙基)乙磺酰胺(6)的制备

[0457] 向2-叠氮基-N-(2-羟乙基)乙烷-1-磺酰胺(67.9mg,0.35mmol)于MeOH(2mL)和H_2O(0.2mL)中的溶液中添加(2′S)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S1(50mg,0.17mmol)、抗坏血酸钠(37mg,0.21mmol)和$CuSO_4$(1mg,0.006mmol)。将混合物在50℃下加热1小时。在冷却至室温后,将混合物用DCM和H_2O稀释。将水层的pH调节至pH 10。将有机层分离并且将水层用DCM萃取。将合并的有机萃取物在真空中浓缩。将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% HCl),得到标题化合物(13.9mg,17%)。^1H NMR(400MHz,DMSO-d6)δ8.54(s,1H),7.53(s,2H),7.05(s,1H),5.29(t,J=7.3Hz,2H),4.45-4.08(m,5H),3.73(s,6H),3.26-3.04(m,5H),2.36-1.96(m,4H),1.73-1.61(m,6H)。LCMS m/z 484.12$[M+H]^+$。

[0458] 化合物7

[0459] 2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-

[0460] 基]甲基]三唑-1-基]-N-(2-羟丙基)乙磺酰胺(7)

[0461] 

S1 7

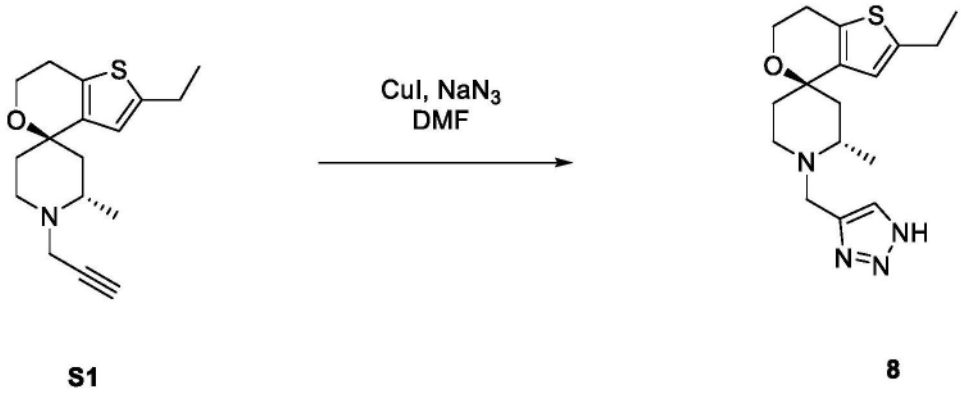
[0462] 2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]-N-(2-羟丙基)乙磺酰胺(7)的制备

[0463] 使用与化合物6所述相同的方法,由(2′S)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]和2-叠氮基-N-(2-羟丙基)乙烷-1-磺酰胺制备化合物7。将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% HCl),得到标题化合物(7.1mg,8%)。^1H NMR(400MHz,DMSO-d6)δ8.53(d,J=3.5Hz,1H),7.71(t,J=6.1Hz,1H),7.05(s,1H),5.26(q,J=6.9Hz,2H),4.40-4.06(m,6H),3.45-3.25(m,2H),

3.46-2.92(m,7H),2.35-1.93(m,5H),1.75-1.53(m,9H)。LCMS m/z 498.19[M+H]$^+$。

[0464] 化合物8

[0465] (2′S,4R)-2-乙基-2′-甲基-1′-(1H-三唑-4-基甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](8)

[0466] 

S1 8

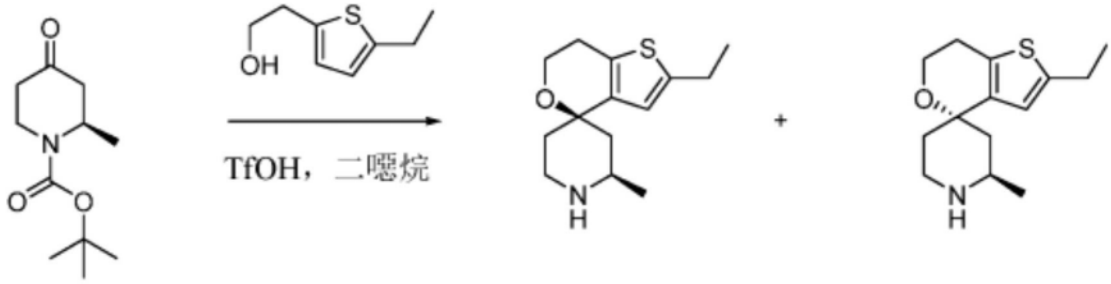
[0467] (2′S,4R)-2-乙基-2′-甲基-1′-(1H-三唑-4-基甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](8)的制备

[0468] 向(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](40mg,0.14mmol)于DMF(2mL)中的溶液中添加叠氮化钠(30mg,0.46mmol)和CuI(30mg,0.16mmol)。将混合物在rt下搅拌过夜。将混合物过滤,并将滤液浓缩。将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% HCl),得到标题化合物(4.6mg,9%)。^{1}H NMR(400MHz,DMSO-d6)δ8.53(d,J=3.5Hz,1H),7.71(t,J=6.1Hz,1H),7.05(s,1H),5.26(q,J=6.9Hz,2H),4.40-4.06(m,6H),3.45-3.25(m,2H),3.46-2.92(m,7H),2.35-1.93(m,5H),1.75-1.53(m,9H)。LCMS m/z333.16[M+H]$^+$。

[0469] 制备S5和S6

[0470] (2′R,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S5)

[0471] (2′R,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S6)

[0472] 

S5 S6

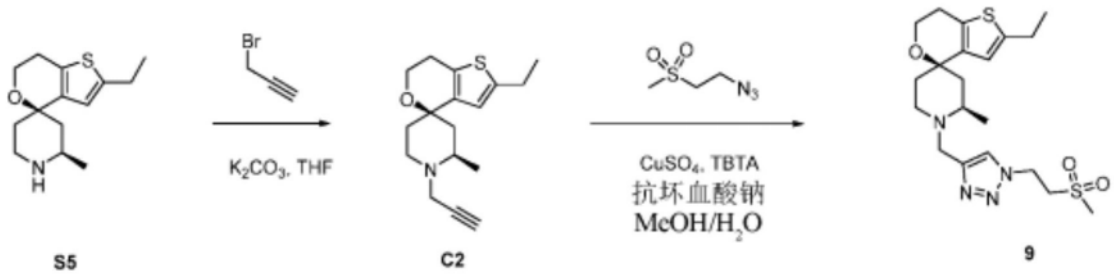
[0473] (2′R,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S5)和(2′R,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S6)的制备

[0474] 向2-(5-乙基-2-噻吩基)乙醇(1.0g,6.4mmol)和(2R)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(1.5g,7.03mmol)于二噁烷(15mL)中的溶液中缓慢添加三氟甲磺酸(1.8mL,20.34mmol)于二噁烷(5mL)中的溶液。将混合物在rt下搅拌过夜。将混合物用H_2O和EtOAc稀释。将有机层分离并将水层用EtOAc(x2)萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物纯化以得到呈三氟甲磺酸盐的标题化合物S5(2.0g,纯度:23%,

18%)和S6(2.0g,纯度:77%,60%)。LCMS m/z 252.11[M+H]$^+$。

[0475] 化合物9

[0476] (2′R,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](9)

[0477] 

[0478] 步骤1:(2R,4R)-2′-乙基-2-甲基-1-(丙-2-炔-1-基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃](C2)的合成

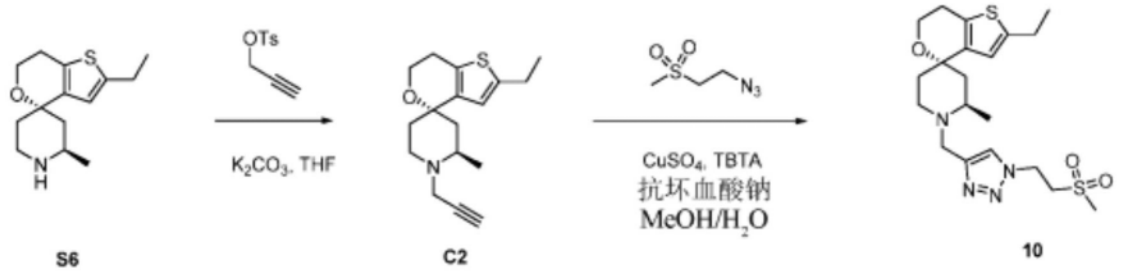
[0479] 向(2′R,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S5(三氟甲磺酸盐)(3.0g,7.473mmol)于THF(35mL)中的溶液中添加K_2CO_3(2.0g,14.47mmol)和炔丙基溴(930μL,80%w/w溶液于甲苯中,8.35mmol)。将混合物在45℃下加热8小时,并且然后冷却至室温并搅拌过夜。将反应物用EtOAc(350mL)、盐水(150mL)和2M的硫代硫酸钠水溶液(25mL)稀释。将有机层分离,并且将水层用EtOAc(100mL)萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩。将残余物用Et_2O研磨。过滤出所得无色固体,并将滤液在真空中浓缩以得到呈浅棕色油的标题化合物(2.1g,74%)。产物无需进一步纯化即可直接使用。LCMS m/z 290.11[M+H]$^+$。

[0480] 步骤2:(2′R,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](9)的合成

[0481] 向(2′R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C2(1.0g,3.46mmol,纯度:23%)于MeOH(12.75mL)和H_2O(4.25mL)中的溶液中添加$CuSO_4$(30mg,0.19mmol)、TBTA(110mg,0.21mmol)和抗坏血酸钠(619mg,3.52mmol)。将混合物在室温下搅拌,并且然后逐滴添加1-叠氮基-2-甲基磺酰基-乙烷(600mg,4.02mmol)于MeOH(2mL)中的溶液。添加后,将混合物搅拌90分钟。将混合物在真空中浓缩。将残余物悬浮在EtOAc中并过滤。将滤液用饱和$NaHCO_3$溶液和H_2O(1:1,50mL)的混合物洗涤。将水洗液用EtOAc(25mL)反萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物通过MPLC在硅胶上纯化(含0-10% MeOH的DCM)以得到呈无色玻璃的标题化合物(40mg,48%)。^{1}H NMR(300MHz,氯仿-d)δ8.18(s,1H),6.51(s,1H),4.92(t,J=6.6Hz,2H),4.13(s,2H),3.91(td,J=6.6,5.9,3.3Hz,2H),3.77(t,J=6.6Hz,2H),3.57-3.37(m,1H),3.35-3.17(m,1H),2.99(d,J=12.0Hz,1H),2.87(s,3H),2.82-2.64(m,4H),2.26(td,J=15.7,15.3,4.8Hz,2H),2.07-1.80(m,2H),1.49(d,J=6.8Hz,3H),1.26(t,J=7.5Hz,3H)。LCMS m/z 440.27[M+H]$^+$。

[0482] 化合物10

[0483] (2′R,4S)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](10)

[0484] 

[0485] 步骤1:(2′S,4S)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](C2)的合成

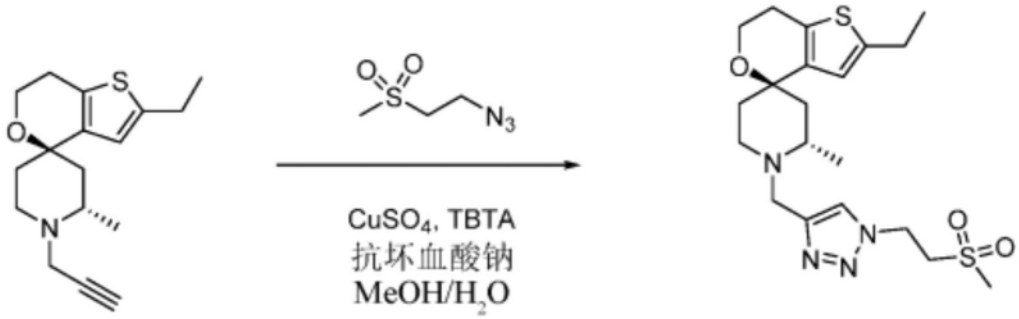
[0486] 向(2′R,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸盐)S6(1.14g,2.460mmol)于DMF(2mL)和THF(8mL)中的溶液中添加碳酸钾(1g,7.24mmol)和4-甲基苯磺酸丙-2-炔酯(500μL,2.90mmol)。将混合物在30℃下搅拌过夜。将反应物用EtOAc(30mL)、H_2O(20mL)和盐水(10mL)稀释。将有机层分离,并且将水层用EtOAc(50mL)萃取。将合并的有机萃取物用盐水洗涤,经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物使用硅胶色谱法纯化(含10-35% EtOAc的己烷)以得到C2(350mg,44%)。^{1}H NMR(300MHz,氯仿-d)δ6.41(d,J=1.1Hz,1H),3.96-3.74(m,2H),3.47(ddd,J=71.3,17.3,2.4Hz,2H),2.98-2.48(m,7H),1.92-1.72(m,3H),1.60(dd,J=13.8,11.5Hz,1H),1.21(t,J=7.5Hz,4H),1.03(d,J=6.3Hz,3H)。LCMS m/z 290.11$[M+H]^+$。

[0487] 步骤2:(2′R,4S)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](10)的合成

[0488] 向(2′R,4S)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[3a,6,7,7a-四氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C2(350mg,1.20mmol)于MeOH(8mL)和H_2O(2mL)中的溶液中添加$CuSO_4$(5mg,0.031mmol)、TBTA(25mg,0.047mmol)和抗坏血酸钠(300mg,1.70mmol)。将混合物在rt下搅拌,并且然后通过加料漏斗逐滴添加1-叠氮基-2-甲基磺酰基-乙烷(200mg,1.34mmol)于MeOH(2mL)中的溶液。将混合物在室温下搅拌2小时。将反应物过滤,并将滤液在真空中浓缩。将残余物溶解在EtOAc(150mL)和H_2O(100mL)中。将有机层分离,并将水层用EtOAc(150mL×2)萃取。将合并的有机萃取物经Na_2SO_4干燥,过滤并在真空中浓缩,以产生棕褐色固体。通过硅胶色谱法纯化(含0-40% EtOAc的己烷),得到10(448mg,81%)。^{1}H NMR(300MHz,氯仿-d)δ7.66(s,1H),6.40(d,J=1.2Hz,1H),4.81(t,J=6.4Hz,2H),3.98(d,J=14.6Hz,1H),3.89-3.65(m,5H),2.72-2.46(m,10H),1.85-1.57(m,4H),1.26-1.11(m,6H)。LCMS m/z 439.17$[M+H]^+$。

[0489] 化合物11

[0490] (2′S,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](11)

[0491] 

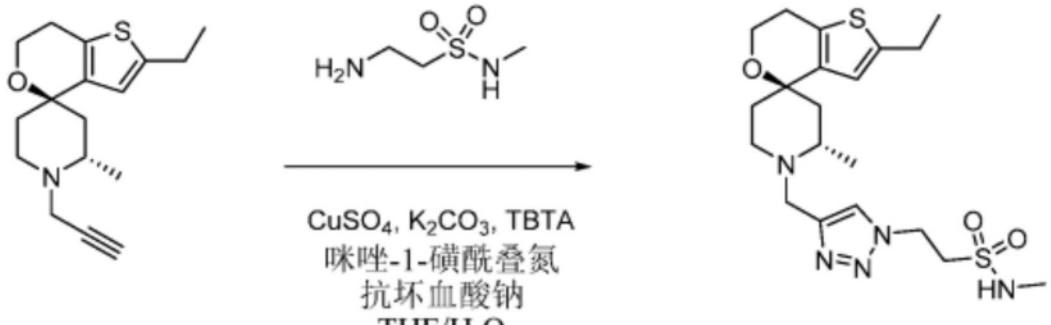
S1 11

[0492] (2′S,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](11)的制备

[0493] 使用与10所述相同的方法,由(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]和1-叠氮基-2-甲基磺酰基-乙烷制备化合物11。将粗产物悬浮在EtOAc中,并在50℃下加热10分钟。将混合物用Et_2O稀释,并冷却至0℃,并搅拌10分钟。将混合物过滤,并将滤饼用Et_2O洗涤,并干燥以得到标题化合物(595mg,70%)。^1H NMR(400MHz,DMSO-d6)δ8.08(s,1H),6.58(d,J=1.1Hz,1H),4.80(t,J=6.9Hz,2H),3.91-3.65(m,6H),2.92(s,3H),2.70(qd,J=7.5,0.9Hz,2H),2.65-2.53(m,3H),2.48-2.36(m,2H),1.82-1.62(m,3H),1.54(dd,J=13.6,11.2Hz,1H),1.19(t,J=7.5Hz,3H),1.13(d,J=6.1Hz,3H)。LCMS m/z 439.56$[M+H]^+$。

[0494] 化合物12

[0495] 2-[4-[[(2′S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]-N-甲基-乙磺酰胺(12)

[0496] 

S1 12

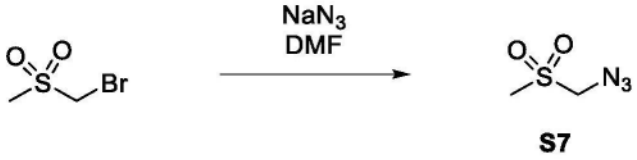
[0497] 2-[4-[[(2′S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]-N-甲基-乙磺酰胺(12)的制备

[0498] 向2-氨基-N-甲基-乙磺酰胺(HCl盐)(55mg,0.31mmol)于THF(2.5mL)和H_2O(1mL)中的溶液中添加$CuSO_4$(1mg,0.0063mmol)和K_2CO_3(30mg,0.2171mmol),随后添加N-二叠氮乙烷-1-磺酰胺(四氟硼酸盐)(120mg,0.46mmol)。将反应物在室温下搅拌过夜。随后将TBTA(10mg,0.019mmol)、抗坏血酸钠(40mg,0.23mmol)和(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S1(HCl盐)(56mg,0.17mmol)添加到反应物中。将所得混合物在55℃搅拌30分钟。将反应物冷却至室温,并去除挥发物。将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA)以产生呈TFA盐的期望产物。将产物溶解在DCM中,并用饱和$NaHCO_3$溶液处理。将有机层分离并在真空中浓缩以得到

呈游离碱的12(53.5mg,70%)。^{1}H NMR(400MHz,氯仿-d)δ7.54(s,1H),6.38(s,1H),4.74(t,J=6.3Hz,2H),4.63(s,1H),3.93(s,2H),3.86-3.69(m,2H),3.60(q,J=6.4Hz,2H),2.76-2.58(m,5H),2.56(s,3H),2.52-2.37(m,2H),1.89-1.71(m,3H),1.61(dd,J=13.8,11.3Hz,1H),1.24-1.10(m,6H)。LCMS m/z 454.45[M+H]$^+$。

[0499] 制备S7

[0500] 叠氮基(甲基磺酰基)甲烷(S7)

[0501] 

S7

[0502] 叠氮基(甲基磺酰基)甲烷(S7)的制备

[0503] 向溴(甲基磺酰基)甲烷(100mg,0.58mmol)于DMF(3mL)中的溶液中添加叠氮化钠(150mg,2.31mmol)。将所得混合物在80℃下加热过夜。在冷却至室温后,将混合物用EtOAc稀释并过滤。将滤液在真空中浓缩。将粗产物溶解在DCM(5mL)中,并再次过滤。将滤液在真空中浓缩以得到呈红色油的标题化合物(75mg,82%)。粗产物无需进一步纯化即可直接使用。^{1}H NMR(400MHz,氯仿-d)δ4.20(s,2H),2.98(t,J=0.9Hz,3H)。

[0504] 制备S8

[0505] 1-(叠氮基甲基磺酰基)乙烷(S8)

[0506] 

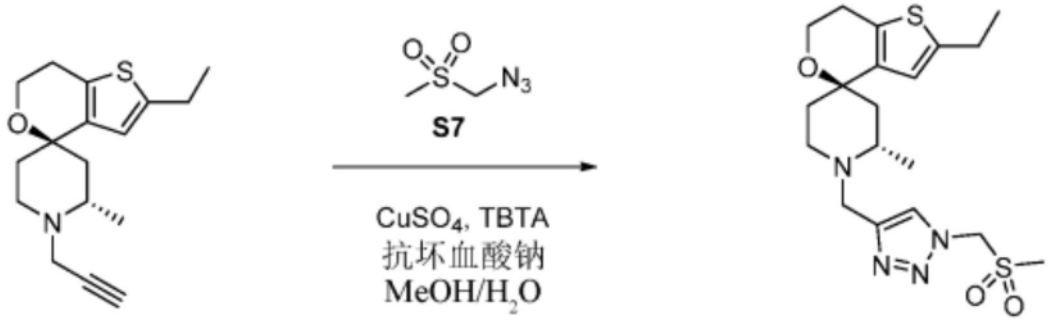
S8

[0507] 1-(叠氮基甲基磺酰基)乙烷(S8)的制备

[0508] 使用与S7所述相同的方法,由1-(溴甲基磺酰基)乙烷制备化合物S8。将粗标题化合物分离为红色油(300mg,88%),并且无需进一步纯化即可直接使用。

[0509] 化合物13

[0510] (2′S)-2-乙基-2′-甲基-1′-[[1-(甲基磺酰基甲基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](13)

[0511] 

S1 13

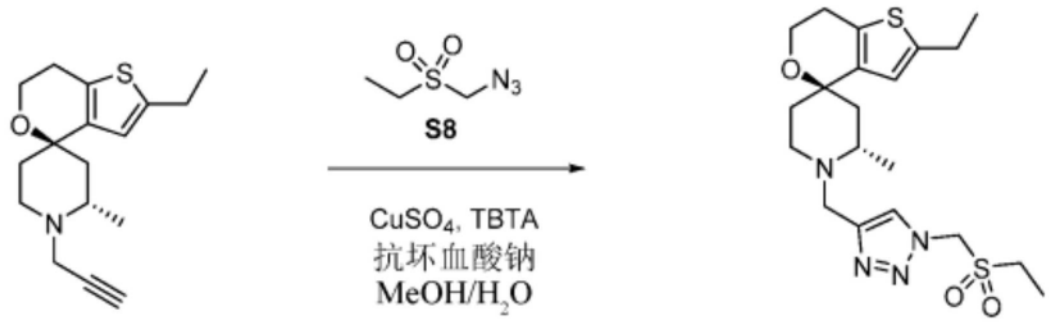
[0512] (2′S)-2-乙基-2′-甲基-1′-[[1-(甲基磺酰基甲基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](13)的制备

[0513] 向叠氮基(甲基磺酰基)甲烷(75mg,0.47mmol)、(2′S,4R)-2-乙基-2′-甲基-1′-

丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](50mg,0.16mmol)于MeOH(3mL)和H_2O(2mL)中的混合物中添加$CuSO_4$(0.6mg,0.004mmol)、TBTA(4mg,0.008mmol)和抗坏血酸钠(28mg,0.16mmol)。将所得混合物在50℃下加热10分钟。冷却至rt后,将混合物浓缩。将粗产物使用硅胶色谱法纯化(含0-10% MeOH的DCM)以得到标题化合物(59mg,85%)。^{1}H NMR(400MHz,氯仿-d)δ7.81(s,1H),6.45(d,J=1.1Hz,1H),5.61-5.47(m,2H),4.08(d,J=14.7Hz,1H),3.92-3.76(m,3H),2.89(d,J=0.9Hz,3H),2.79-2.51(m,7H),1.94-1.76(m,3H),1.68(dd,J=14.0,11.3Hz,1H),1.25(t,J=7.5Hz,3H),1.21(d,J=6.2Hz,3H)。LCMS m/z 425.52$[M+H]^+$。

[0514] 化合物14

[0515] (2′S)-2-乙基-1′-[[1-(乙基磺酰基甲基)三唑-4-基]甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](14)

[0516] 

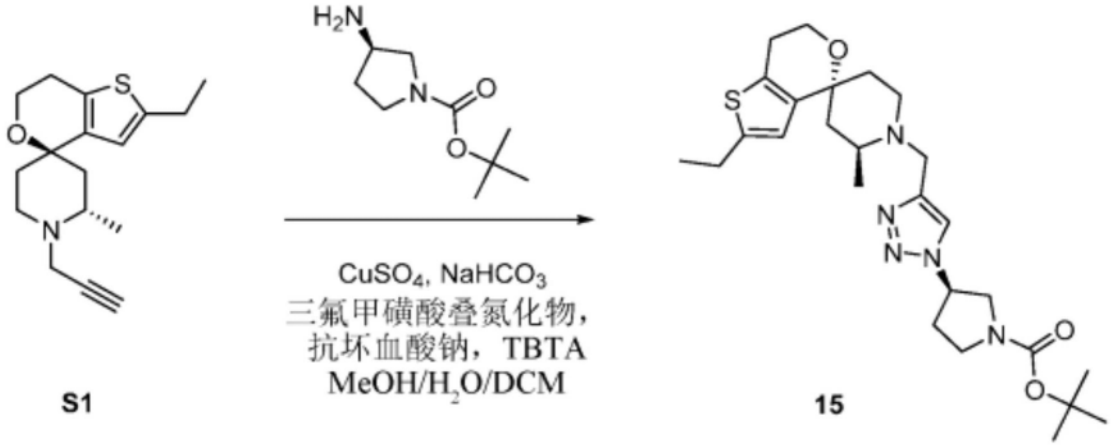
S1 14

[0517] (2′S)-2-乙基-1′-[[1-(乙基磺酰基甲基)三唑-4-基]甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](14)的制备

[0518] 使用与13所述相同的方法,由(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]和1-(叠氮基甲基磺酰基)乙烷制备14。将粗产物使用硅胶色谱法纯化(含0-100% EtOAc的庚烷)以得到呈澄清油的14(46mg,67%)。^{1}H NMR(400MHz,氯仿-d)δ7.81(s,1H),6.50-6.41(m,1H),5.63-5.44(m,2H),4.06(d,J=14.7Hz,1H),3.94-3.74(m,3H),2.96(q,J=7.5Hz,2H),2.78-2.52(m,7H),1.93-1.77(m,3H),1.68(dd,J=14.0,11.3Hz,1H),1.37(t,J=7.5Hz,3H),1.25(t,J=7.5Hz,3H),1.21(d,J=6.2Hz,3H)。LCMS m/z 439.56$[M+H]^+$。

[0519] 化合物15

[0520] (3R)-3-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]吡咯烷-1-甲酸叔丁酯(15)

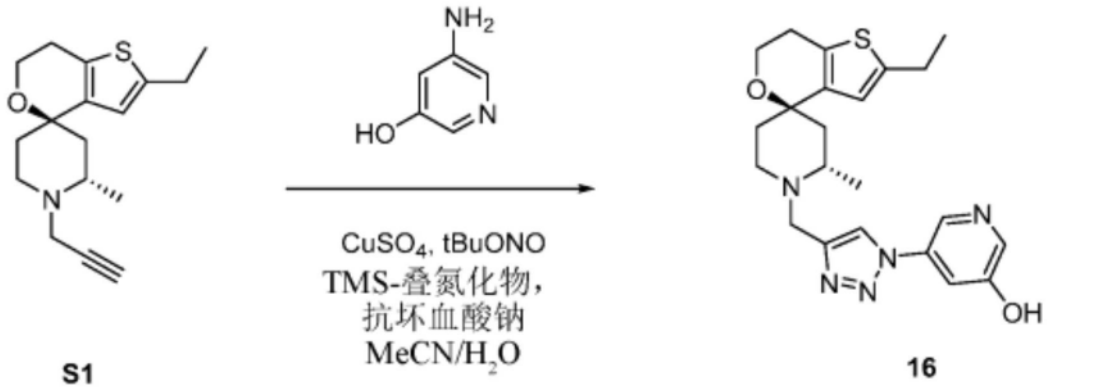
[0521] 

[0522] (3R)-3-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]吡咯烷-1-甲酸叔丁酯(15)的制备

[0523] 向(R)-3-氨基吡咯烷-1-甲酸叔丁酯(9.1μL,0.054mmol)于MeOH(600μL)中的溶液中添加$CuSO_4$(0.15mg,0.026mmol)于H_2O(75μL)中的溶液和$NaHCO_3$于H_2O(75μL)中的溶液。然后添加三氟甲磺酸叠氮化物(0.15mL,0.45mmol)于DCM中的溶液。将混合物在rt下搅拌1小时后,添加(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](10mg,0.036mmol)于MeOH(100μL)中的溶液,随后添加抗坏血酸钠(7mg,0.040mmol)于H_2O(50μL)中的溶液和TBTA(2mg,0.004mmol)于MeOH(100μL)中的溶液。将所得混合物在50℃下加热过夜。冷却至室温后,去除挥发物,并将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA),得到15(5.3mg,30%)。^1H NMR(300MHz,甲醇-d4)δ8.01(s,1H),6.49(d,J=1.1Hz,1H),5.26(tt,J=6.1,4.2Hz,1H),4.04(d,J=14.5Hz,1H),3.96-3.70(m,5H),3.57(d,J=7.9Hz,2H),2.83-2.36(m,9H),2.01-1.57(m,4H),1.47(s,8H),1.38-1.10(m,7H)。LCMS m/z 502.38$[M+H]^+$。

[0524] 化合物16

[0525] 5-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]吡啶-3-醇(16)

[0526] 

[0527] 5-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]三唑-1-基]吡啶-3-醇(16)的制备

[0528] 向5-氨基吡啶-3-醇(18mg,0.16mmol)于MeCN(2mL)中的溶液中逐滴添加tBuONO(0.28mL,0.24mmol)和TMS叠氮化物(0.025mL,0.19mmol)。在rt下搅拌2小时后,添加(2′S,4R)-2-乙基-2′-甲基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](35mg,

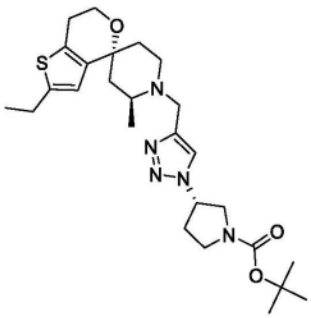
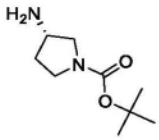
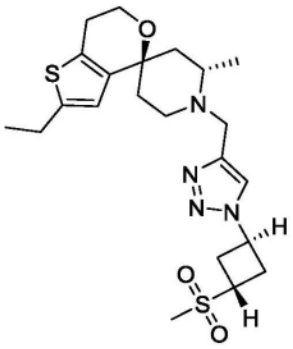
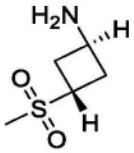
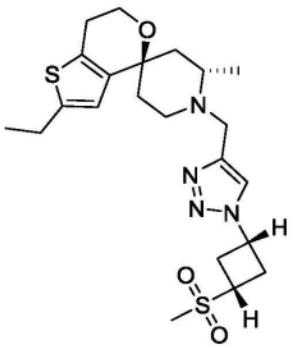
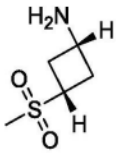
0.11mmol),随后添加$CuSO_4$(1.2mg,0.008mmol)和抗坏血酸钠(30mg,0.17mmol)于H_2O(0.2mL)中的水溶液。将所得混合物在65℃下搅拌过夜。冷却至rt后,将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA)以产生呈TFA盐的期望产物。将产物溶解在DCM(2mL)中,并用饱和$NaHCO_3$水溶液(2mL)处理。将有机层分离并在真空中浓缩以得到呈游离碱的标题化合物(15.4mg,33%)。^1H NMR(400MHz,氯仿-d)δ8.44(s,1H),8.36(dd,J=10.0,2.2Hz,2H),8.10(s,1H),6.40(d,J=1.1Hz,1H),4.22(d,J=14.5Hz,1H),3.97-3.71(m,3H),2.94-2.53(m,8H),1.98-1.62(m,4H),1.27(d,J=6.2Hz,3H),1.19(t,J=7.5Hz,3H)。LCMS m/z 426.17$[M+H]^+$。

[0529] 化合物17-197

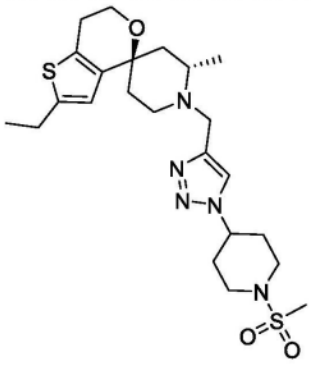
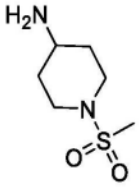
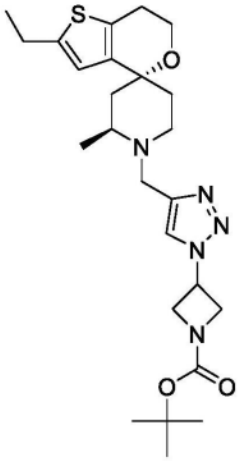
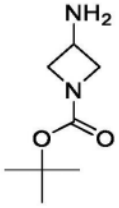
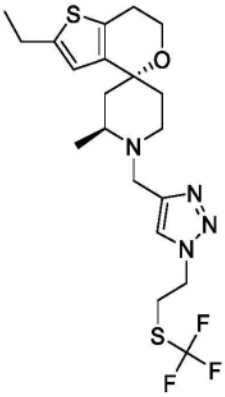
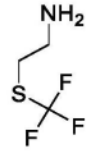
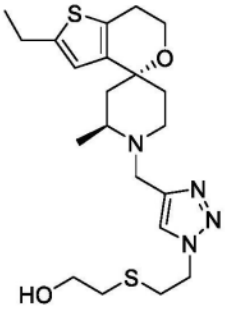
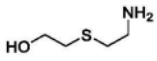
[0530] 化合物17-197(参见表3)由S1使用适当的胺采用一般方法B或C制备。除非另有说明,否则所有胺均从商业来源获得。表2和随附脚注中注明了对方法的任何修改。

[0531] 表3:化合物17-197的结构和物理化学数据

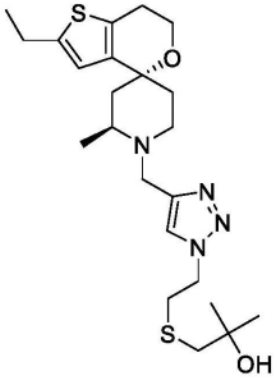
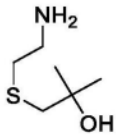
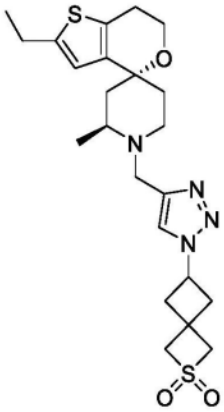
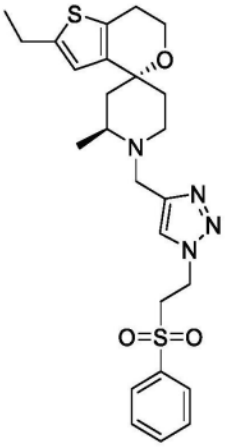
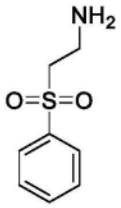
[0532]

化合物	结构	胺	方法	^1H NMR; LCMS *m/z*$[M+H]^+$。
17			化合物 15	LCMS *m/z* $[M+H]^+$ 502.38
18			化合物 15	LCMS *m/z* $[M+H]^+$ 465.19
19			化合物 15	LCMS *m/z* $[M+H]^+$ 465.2

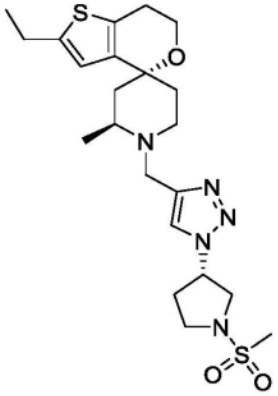
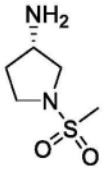
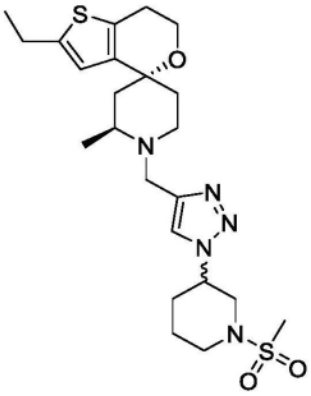
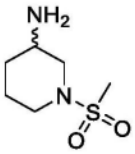
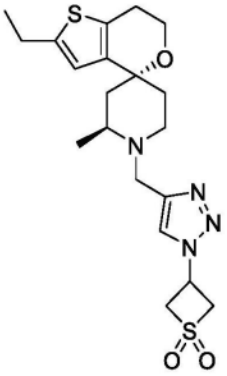
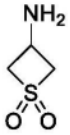
[0533]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
20			化合物 15	LCMS *m/z* [M+H]$^+$ 494.05
21			化合物 15	LCMS *m/z* [M+H]$^+$ 488.07
22			化合物 15	LCMS *m/z* [M+H]$^+$ 461.19
23			化合物 15	LCMS *m/z* [M+H]$^+$ 437.21

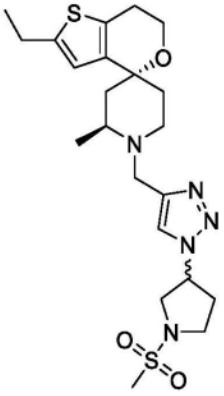
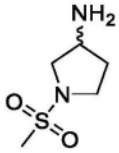
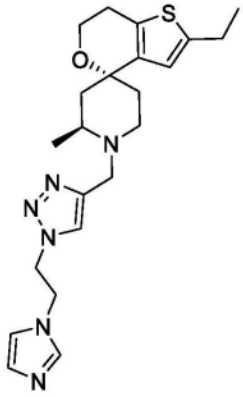
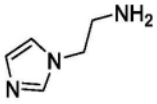
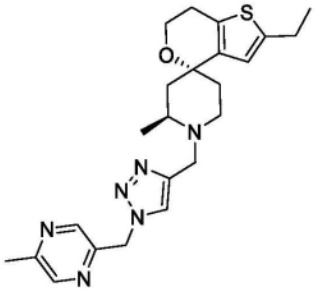
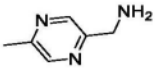
[0534]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
24			化合物 15	LCMS *m/z* [M+H]$^+$ 465.26
25			化合物 15	LCMS *m/z* [M+H]$^+$ 477.35
26			化合物 15	LCMS *m/z* [M+H]+ 501.22

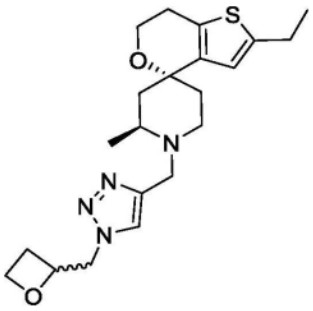
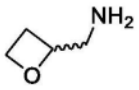
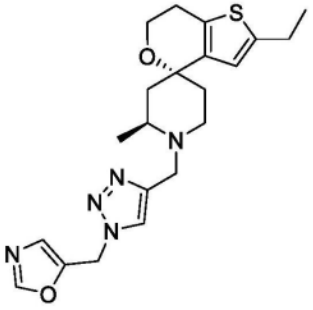
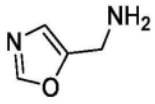
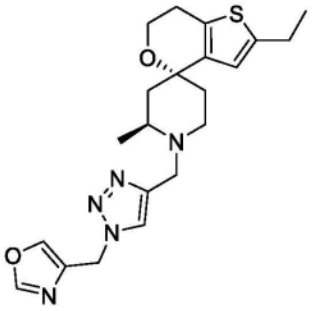
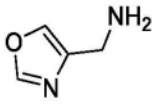
[0535]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
27			化合物 15	LCMS *m/z* [M+H]$^+$ 480.23
28			化合物 15	LCMS *m/z* [M+H]$^+$ 494.28
29			化合物 15	LCMS *m/z* [M+H]$^+$ 437.2

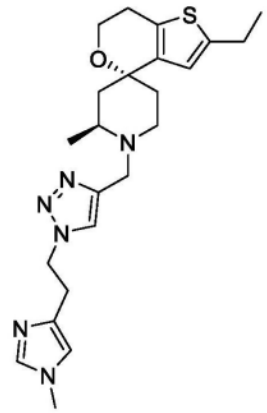
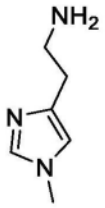
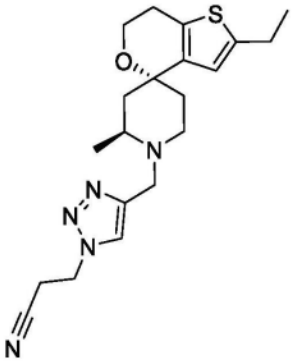
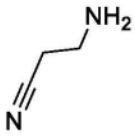
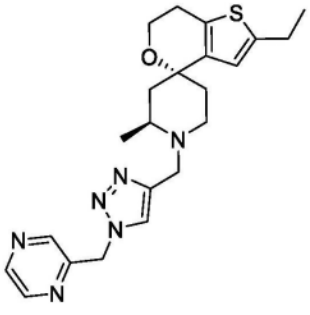
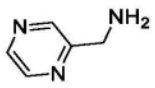
[0536]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
30			化合物 15	LCMS *m/z* [M+H]$^+$ 480.19
31			化合物 15	LCMS *m/z* [M+H]$^+$ 427.01
32			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.47 (s, 1H), 6.46 (s, 1H), 5.85 (s, 2H), 4.64 (d, J = 14.2 Hz, 1H), 4.53 (d, J = 14.5 Hz, 1H), 3.82 (q, J = 6.2 Hz, 3H), 3.32 (d, J = 11.9 Hz, 2H), 3.15 (s, 2H), 2.68 (s, 2H), 2.54 (s, 3H), 2.04 (t, J = 10.1 Hz, 4H), 1.44 (d, J = 6.4 Hz, 3H), 1.23 - 1.16 (m, 3H)。 LCMS *m/z* [M+H]$^+$ 439.2

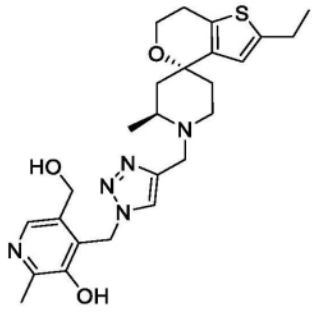
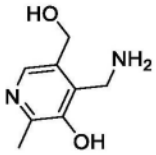
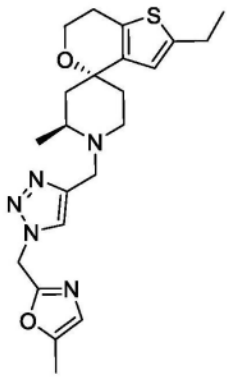
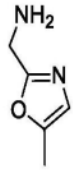
[0537]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
33			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 8.29 (s, 1H), 6.47 (d, J = 5.7 Hz, 1H), 4.76 - 4.30 (m, 4H), 4.00 (s, 1H), 3.82 (s, 3H), 3.33 (s, 2H), 3.15 (s, 2H), 2.67 (s, 3H), 2.02 (d, J = 18.5 Hz, 4H), 1.75 - 1.50 (m, 2H), 1.45 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.5 Hz, 3H)。更新的 1.75-1.50 峰。LCMS *m/z* [M+H]$^+$ 403.23
34			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.08 (s, 1H), 8.46 - 8.34 (m, 1H), 8.38 (s, 1H), 7.35 (d, J = 3.5 Hz, 1H), 6.46 (s, 1H), 5.88 (d, J = 3.4 Hz, 2H), 4.63 (d, J = 13.9 Hz, 1H), 4.51 (d, J = 14.9 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 1H), 3.32 (s, 1H), 3.15 (s, 2H), 2.68 (s, 2H), 2.03 (s, 4H), 1.44 (d, J = 7.0 Hz, 3H), 1.20 (q, J = 7.8, 6.9 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 414.21
35			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.44 (d, J = 3.7 Hz, 1H), 8.38 (d, J = 3.5 Hz, 1H), 8.26 (d, J = 3.6 Hz, 1H), 6.46 (s, 1H), 5.64 (d, J = 3.5 Hz, 2H), 4.63 (d, J = 14.2 Hz, 1H), 4.51 (d, J = 14.8 Hz, 1H), 3.82 (s, 2H), 3.62 (s, 1H), 3.32 (s, 2H), 3.15 (s, 2H), 2.68 (s, 2H), 2.02 (d, J = 13.2 Hz, 4H), 1.44

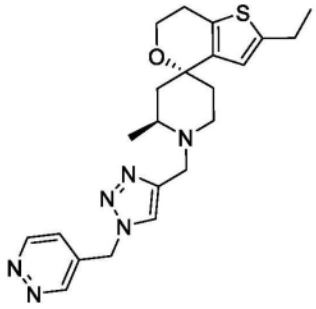
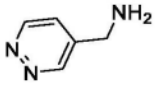
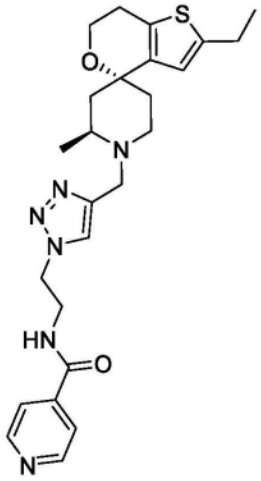
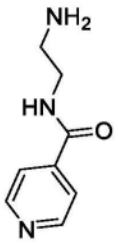
[0538]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				(d, J = 6.1 Hz, 3H), 1.23 - 1.12 (m, 3H)。LCMS *m/z* [M+H]$^+$ 414.21
36			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.33 (d, J = 3.3 Hz, 1H), 7.30 (d, J = 12.3 Hz, 1H), 6.49 (s, 1H), 4.75 (s, 2H), 4.58 (s, 1H), 4.51 (d, J = 13.8 Hz, 1H), 3.83 (s, 2H), 3.77 (d, J = 3.3 Hz, 3H), 3.63 (s, 1H), 3.27 (s, 4H), 3.13 (s, 2H), 2.69 (s, 2H), 2.05 (s, 4H), 1.43 (s, 3H), 1.21 (d, J = 10.1 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 441.22
37			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.45 (d, J = 3.1 Hz, 1H), 6.47 (s, 1H), 4.81 - 4.70 (m, 2H), 4.67 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 14.6 Hz, 1H), 3.81 (s, 2H), 3.34 - 3.03 (m, 7H), 2.68 (s, 2H), 2.03 (s, 4H), 1.45 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 9.4 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 386.2
38			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.08 (s, 1H), 8.73 (s, 1H), 8.69 - 8.59 (m, 2H), 8.50 (s, 1H), 6.47 (s, 1H), 5.92 (s, 2H), 4.65 (d, J = 14.3 Hz, 1H), 4.55 (d, J = 14.3 Hz, 1H), 3.81 (dd, J = 12.6, 6.5 Hz, 2H), 3.63 (s, 1H), 3.33 (d, J = 12.6 Hz, 2H), 3.24 - 3.07 (m, 2H),

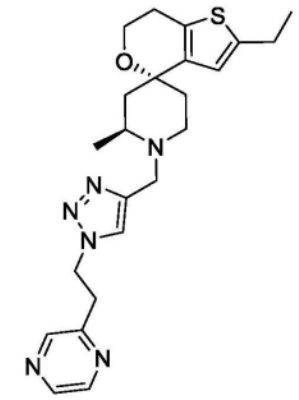
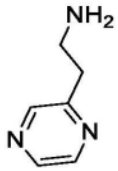
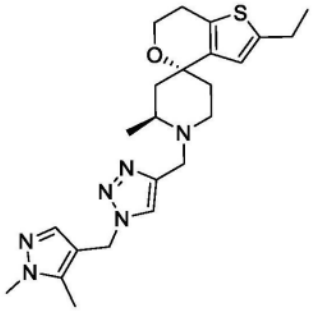
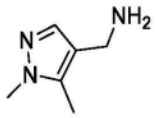
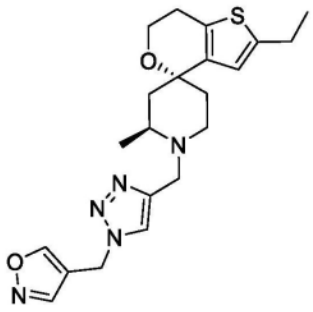
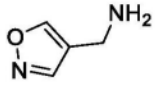
[0539]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				2.68 (s, 2H), 2.03 (q, J = 17.4, 14.4 Hz, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 425.06
39			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.09 (s, 1H), 8.97 (s, 2H), 8.28 (s, 1H), 8.14 (s, 1H), 6.46 (s, 1H), 5.77 (s, 2H), 4.67 (s, 2H), 4.60 (d, J = 14.3 Hz, 1H), 4.47 (d, J = 14.3 Hz, 1H), 3.84 - 3.80 (m, 4H), 3.62 (d, J = 3.9 Hz, 2H), 3.30 (s, 2H), 3.14 (dd, J = 7.3, 4.1 Hz, 2H), 2.67 (s, 2H), 1.99 (dd, J = 21.8, 10.8 Hz, 4H), 1.42 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 484.35
40			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.48 (s, 1H), 6.88 (s, 1H), 6.46 (s, 1H), 5.88 (s, 2H), 4.66 (d, J = 14.3 Hz, 1H), 4.54 (d, J = 14.3 Hz, 1H), 3.82 (td, J = 12.1, 5.9 Hz, 2H), 3.72 - 3.49 (m, 1H), 3.30 (s, 1H), 3.22 - 3.04 (m, 2H), 2.68 (d, J = 5.8 Hz, 2H), 2.28 (s, 3H), 2.03 (d, J = 10.6 Hz, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.6 Hz, 4H)。LCMS *m/z* [M+H]$^+$ 428.22

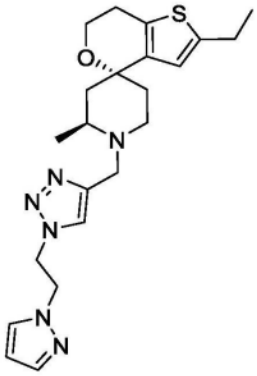
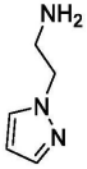
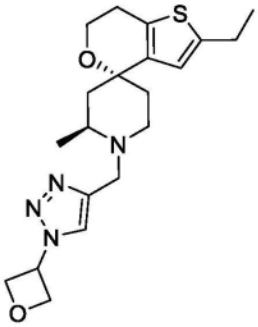
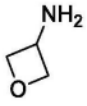
[0540]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
41			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.10 (s, 1H), 9.26 (d, J = 5.3 Hz, 1H), 9.16 (d, J = 2.1 Hz, 1H), 8.54 (s, 1H), 7.58 - 7.44 (m, 1H), 6.47 (s, 1H), 5.86 (s, 2H), 4.66 (d, J = 14.2 Hz, 1H), 4.56 (d, J = 14.3 Hz, 1H), 3.83 (tt, J = 11.6, 5.8 Hz, 3H), 3.34 (d, J = 12.2 Hz, 2H), 3.25 - 3.03 (m, 2H), 2.68 (s, 2H), 2.14 - 1.82 (m, 4H), 1.45 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 7.7 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 425.22
42			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.98 (s, 1H), 8.97 (s, 1H), 8.72 (d, J = 5.2 Hz, 2H), 8.36 (s, 1H), 7.67 (d, J = 5.4 Hz, 2H), 6.45 (s, 1H), 4.75 - 4.39 (m, 4H), 3.77 (d, J = 5.7 Hz, 5H), 3.37 - 3.19 (m, 2H), 3.18 - 3.03 (m, 2H), 2.66 (s, 2H), 1.95 (dd, J = 39.0, 11.3 Hz, 4H), 1.40 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 481.19

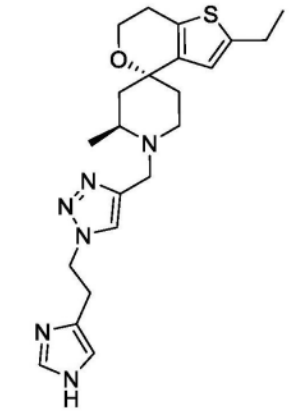
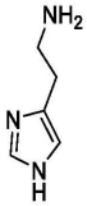
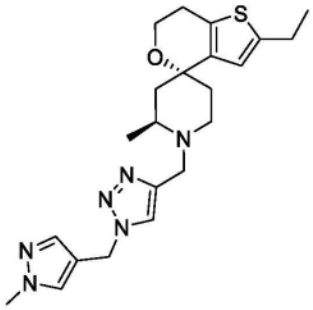
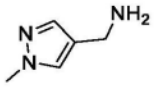
[0541]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
43			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.02 (s, 1H), 8.55 (t, J = 2.0 Hz, 1H), 8.51 (d, J = 2.0 Hz, 2H), 8.31 (s, 1H), 6.46 (s, 1H), 4.88 (t, J = 6.8 Hz, 2H), 4.57 (d, J = 14.1 Hz, 1H), 4.48 (d, J = 13.8 Hz, 1H), 3.83 (h, J = 6.2 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 3.29 - 3.02 (m, 4H), 2.68 (s, 2H), 2.21 - 1.83 (m, 4H), 1.41 (d, J = 6.4 Hz, 3H), 1.23 - 1.12 (m, 3H)。LCMS *m/z* [M+H]$^+$ 439.07
44			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.28 (d, J = 3.4 Hz, 1H), 7.46 - 7.36 (m, 1H), 6.46 (s, 1H), 5.48 (d, J = 3.5 Hz, 2H), 4.59 (d, J = 14.2 Hz, 1H), 4.47 (d, J = 14.7 Hz, 1H), 3.82 (s, 2H), 3.71 (d, J = 3.6 Hz, 3H), 3.62 (s, 1H), 3.30 (d, J = 11.9 Hz, 2H), 3.14 (s, 2H), 2.68 (s, 2H), 2.26 (d, J = 3.5 Hz, 3H), 2.02 (d, J = 10.2 Hz, 4H), 1.43 (d, J = 6.3 Hz, 3H), 1.20 (q, J = 7.3 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 441.22
45			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.05 (s, 1H), 9.10 (s, 1H), 8.72 (s, 1H), 8.42 (s, 1H), 6.46 (s, 1H), 5.64 (s, 2H), 4.62 (d, J = 14.2 Hz, 1H), 4.50 (d, J = 14.4 Hz, 1H), 3.98 - 3.71 (m, 2H), 3.62 (d, J

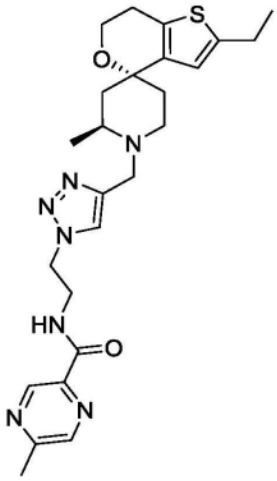
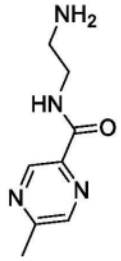
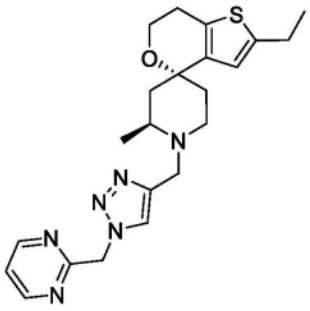
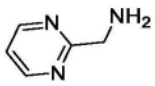
[0542]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				= 5.4 Hz, 1H), 3.29 (s, 2H), 3.14 (dd, J = 7.4, 4.1 Hz, 2H), 2.67 (t, J = 5.5 Hz, 2H), 2.02 (d, J = 10.1 Hz, 4H), 1.43 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 414.18
46			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.05 (s, 1H), 7.96 (s, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 6.47 (s, 1H), 6.17 (t, J = 2.1 Hz, 1H), 4.88 (t, J = 5.7 Hz, 2H), 4.64 (t, J = 5.9 Hz, 2H), 4.61 - 4.45 (m, 2H), 3.95 - 3.74 (m, 2H), 3.62 (s, 1H), 3.13 (dd, J = 41.5, 11.9 Hz, 4H), 2.69 (d, J = 5.6 Hz, 2H), 2.03 (p, J = 14.8, 14.3 Hz, 4H), 1.40 (d, J = 6.4 Hz, 3H), 1.23 - 1.15 (m, 3H)。LCMS *m/z* [M+H]$^+$ 427.24
47			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.98 (s, 1H), 8.35 (s, 1H), 6.46 (s, 1H), 5.05 (t, J = 7.3 Hz, 1H), 4.92 (q, J = 6.0 Hz, 1H), 4.71 - 4.42 (m, 3H), 3.82 (d, J = 6.0 Hz, 3H), 3.62 (s, 1H), 3.33 - 3.02 (m, 4H), 2.68 (s, 2H), 2.04 (d, J = 7.8 Hz, 4H), 1.45 (dd, J = 6.5, 2.5 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 389.19

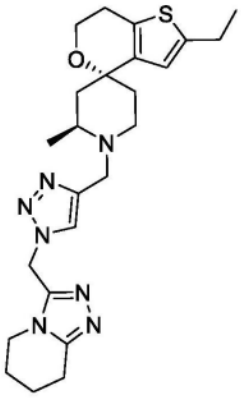
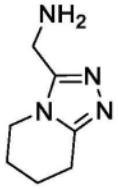
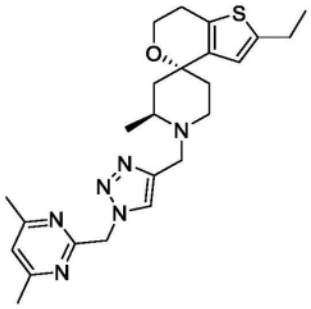
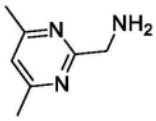
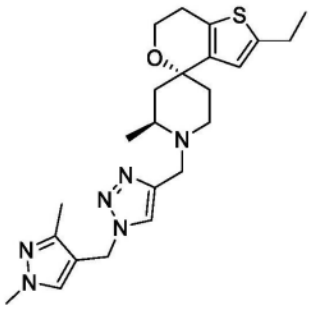
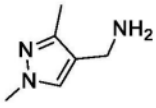
[0543]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
48			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 2H), 8.31 (s, 1H), 7.31 (s, 1H), 6.48 (s, 1H), 4.78 (t, J = 6.8 Hz, 2H), 4.59 (d, J = 14.6 Hz, 1H), 4.49 (d, J = 14.4 Hz, 1H), 3.82 (q, J = 6.3 Hz, 2H), 3.62 (s, 1H), 3.29 (t, J = 6.8 Hz, 4H), 3.18 - 3.05 (m, 2H), 2.70 (d, J = 11.0 Hz, 2H), 2.01 (q, J = 19.1, 14.3 Hz, 4H), 1.42 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 427.34
49			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.32 (s, 1H), 7.81 (s, 1H), 7.48 (s, 1H), 6.46 (s, 1H), 5.52 (s, 2H), 4.59 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 14.6 Hz, 1H), 3.81 (s, 5H), 3.63 (s, 1H), 3.30 (d, J = 11.9 Hz, 2H), 3.21 - 3.04 (m, 2H), 2.67 (s, 2H), 2.02 (d, J = 9.8 Hz, 4H), 1.43 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 427.21

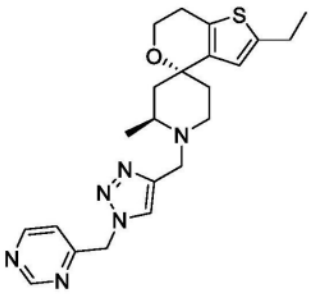
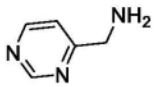
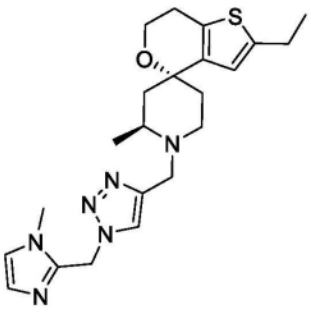
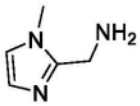
[0544]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
50			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 9.07 (t, J = 6.2 Hz, 1H), 8.96 (s, 1H), 8.62 (s, 1H), 8.32 (s, 1H), 6.45 (s, 1H), 4.65 (t, J = 5.8 Hz, 2H), 4.58 (d, J = 14.3 Hz, 1H), 4.47 (d, J = 14.2 Hz, 1H), 3.78 (d, J = 6.5 Hz, 4H), 3.62 (s, 1H), 3.21 (s, 2H), 3.13 (d, J = 14.4 Hz, 2H), 2.67 (s, 2H), 2.57 (s, 3H), 1.96 (dd, J = 29.3, 11.3 Hz, 4H), 1.39 (d, J = 6.3 Hz, 3H), 1.22 - 1.17 (m, 3H)。LCMS *m/z* [M+H]$^+$ 496.17
51			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.09 (s, 1H), 8.81 (s, 1H), 8.80 (s, 1H), 8.49 (s, 1H), 7.50 (t, J = 4.9 Hz, 1H), 6.47 (s, 1H), 5.96 (s, 2H), 4.68 (d, J = 14.2 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 3.83 (q, J = 6.0 Hz, 2H), 3.63 (d, J = 6.6 Hz, 1H), 3.34 (d, J = 11.8 Hz, 2H), 3.19 (d, J = 12.3 Hz, 2H), 2.67 (d, J = 5.6 Hz, 2H), 2.06 (t, J = 11.3 Hz, 4H), 1.46 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 425.22

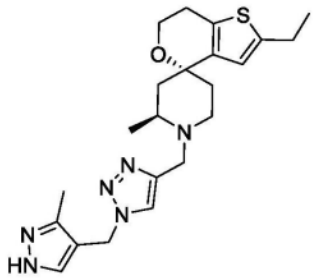
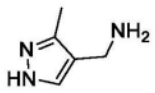
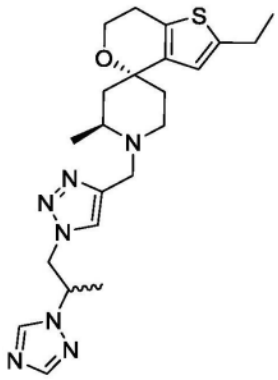
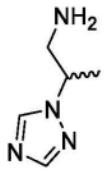
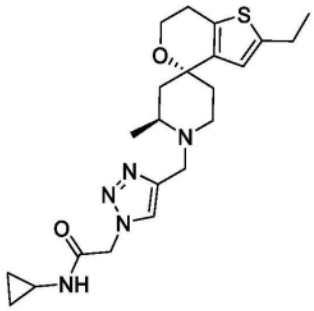
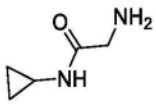
[0545]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
52			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 8.46 (s, 1H), 6.46 (s, 1H), 5.94 (s, 2H), 4.64 (d, J = 14.3 Hz, 1H), 4.53 (d, J = 14.2 Hz, 1H), 3.95 (d, J = 6.2 Hz, 2H), 3.81 (p, J = 5.6 Hz, 3H), 3.32 (d, J = 11.9 Hz, 2H), 3.00 (s, 2H), 2.86 (t, J = 6.4 Hz, 2H), 2.67 (s, 2H), 2.06 (q, J = 16.0, 14.8 Hz, 4H), 1.91 (d, J = 5.9 Hz, 2H), 1.81 (d, J = 6.5 Hz, 2H), 1.44 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 468.25
53			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.08 (s, 1H), 8.45 (s, 1H), 7.25 (d, J = 14.4 Hz, 1H), 6.47 (s, 1H), 5.84 (s, 2H), 4.68 (d, J = 14.3 Hz, 1H), 4.59 (d, J = 14.4 Hz, 1H), 3.81 (q, J = 5.9 Hz, 3H), 3.32 (d, J = 11.7 Hz, 2H), 3.24 - 3.04 (m, 2H), 2.67 (s, 2H), 2.37 (s, 6H), 2.06 (t, J = 12.0 Hz, 4H), 1.46 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 453.2
54			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.25 (s, 1H), 7.72 (s, 1H), 6.46 (s, 1H), 5.47 (s, 2H), 4.58 (d, J = 14.3 Hz, 1H), 4.48 (d, J = 12.3 Hz, 1H), 3.81 (h, J = 5.8 Hz, 3H), 3.73 (s, 3H), 3.30

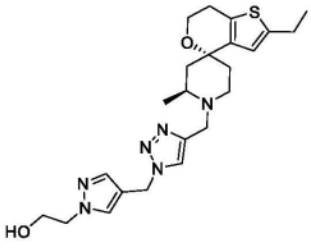
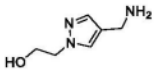
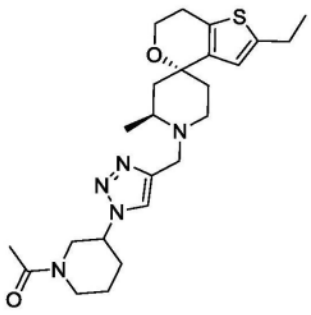
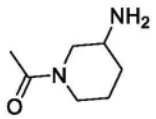
[0546]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				(d, J = 11.9 Hz, 2H), 3.13 (s, 2H), 2.66 (d, J = 5.7 Hz, 2H), 2.09 (s, 3H), 2.01 (q, J = 16.9, 13.8 Hz, 4H), 1.43 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 441.25
55			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.09 (s, 1H), 9.14 (d, J = 1.4 Hz, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.50 (s, 1H), 7.41 (d, J = 5.2 Hz, 1H), 6.47 (s, 1H), 5.91 (s, 2H), 4.68 (d, J = 14.3 Hz, 1H), 4.58 (d, J = 14.4 Hz, 1H), 3.83 (q, J = 6.1 Hz, 2H), 3.62 (s, 1H), 3.34 (d, J = 12.0 Hz, 2H), 3.26 - 3.07 (m, 2H), 2.67 (d, J = 5.5 Hz, 2H), 2.05 (t, J = 10.5 Hz, 4H), 1.46 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 7.3 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 425.22
56			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.97 (s, 1H), 8.47 (s, 1H), 7.53 (s, 1H), 7.37 (s, 1H), 6.47 (s, 1H), 6.01 (s, 2H), 4.64 (d, J = 14.4 Hz, 1H), 4.54 (d, J = 14.4 Hz, 1H), 3.80 (s, 4H), 3.65 - 3.60 (m, 1H), 3.32 (d, J = 11.5 Hz, 2H), 3.15 (d, J = 7.5 Hz, 2H), 2.68 (s, 2H), 2.01 (dd, J = 24.3, 11.1 Hz, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.19 (q, J = 7.6 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 427.21

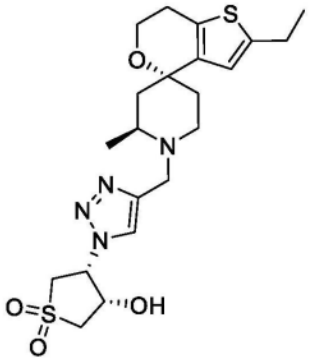
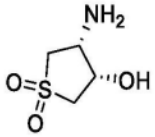
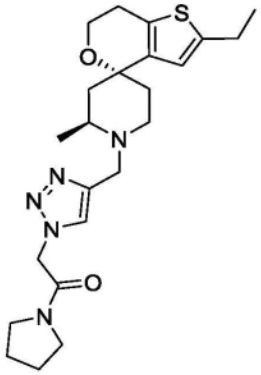
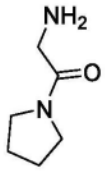
[0547]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
57			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.26 (s, 1H), 7.60 (s, 1H), 6.46 (s, 1H), 5.49 (s, 2H), 4.59 (d, J = 14.3 Hz, 1H), 4.48 (d, J = 14.3 Hz, 1H), 3.83 - 3.79 (m, 2H), 3.65 - 3.60 (m, 1H), 3.28 (s, 2H), 3.21 - 3.07 (m, 2H), 2.67 (s, 2H), 2.18 (s, 3H), 2.01 (q, J = 17.1, 14.2 Hz, 4H), 1.43 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 427.24
58			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.32 (d, J = 12.2 Hz, 1H), 8.03 (d, J = 11.6 Hz, 1H), 7.96 (d, J = 3.8 Hz, 1H), 6.46 (s, 1H), 5.09 (s, 1H), 4.91 (dt, J = 13.8, 4.5 Hz, 1H), 4.82 (td, J = 8.9, 4.5 Hz, 1H), 4.54 (d, J = 18.5 Hz, 2H), 3.86 (q, J = 9.1, 6.8 Hz, 3H), 3.12 (d, J = 98.3 Hz, 4H), 2.68 (s, 2H), 2.13 - 1.90 (m, 4H), 1.55 (dd, J = 6.9, 2.4 Hz, 3H), 1.40 (dd, J = 11.8, 6.3 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 442.19
59			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.54 (d, J = 4.1 Hz, 1H), 8.33 (s, 1H), 6.47 (s, 1H), 5.13 (s, 2H), 4.65 (d, J = 14.3 Hz, 1H), 4.55 (d, J = 14.5 Hz, 1H), 3.82 (q, J = 6.2 Hz, 2H), 3.22 -

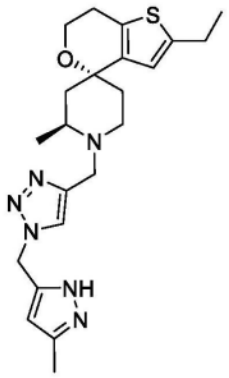
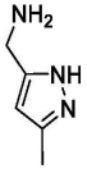
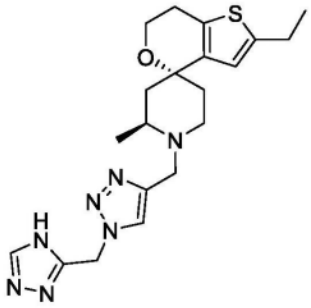
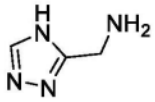
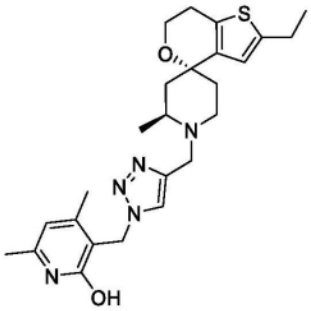
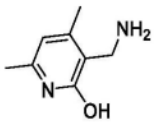
[0548]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				3.06 (m, 2H), 2.66 (d, J = 7.2 Hz, 3H), 2.05 (t, J = 10.5 Hz, 4H), 1.45 (d, J = 6.3 Hz, 3H), 1.32 (d, J = 40.1 Hz, 2H), 1.19 (d, J = 7.4 Hz, 3H), 0.66 (td, J = 6.9, 4.7 Hz, 2H), 0.53 - 0.40 (m, 2H)。LCMS *m/z* [M+H]$^+$ 430.24
60			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.34 (s, 1H), 7.83 (s, 1H), 7.50 (s, 1H), 6.46 (s, 1H), 5.53 (s, 2H), 4.60 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 14.9 Hz, 1H), 4.11 (t, J = 5.5 Hz, 2H), 3.81 (d, J = 7.2 Hz, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.63 (s, 2H), 3.30 (d, J = 11.8 Hz, 2H), 3.22 - 3.02 (m, 2H), 2.66 (d, J = 5.8 Hz, 2H), 2.01 (d, J = 14.7 Hz, 4H), 1.43 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 457.21
61			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.97 (s, 1H), 8.45 (d, J = 18.5 Hz, 1H), 6.46 (s, 1H), 4.79 - 4.36 (m, 4H), 4.04 (d, J = 16.7 Hz, 1H), 3.83 (t, J = 6.7 Hz, 2H), 3.76 - 3.57 (m, 2H), 3.33 - 3.07 (m, 5H), 2.68 (s, 2H), 2.18 (dd, J = 41.3, 10.7 Hz, 4H), 1.99 (d, J = 2.6 Hz, 3H), 1.79 (s, 1H), 1.70 - 1.49 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H), 1.20 (t, J = 7.6

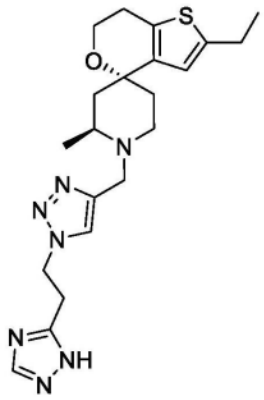
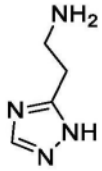
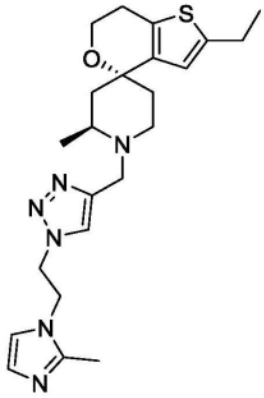
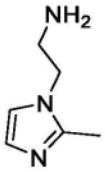
[0549]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				Hz, 3H)。LCMS *m/z* [M+H]$^+$ 458.25
62			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.52 (s, 1H), 6.47 (s, 1H), 6.25 (d, J = 4.5 Hz, 1H), 5.72 - 5.49 (m, 1H), 4.78 (s, 1H), 4.63 (d, J = 13.1 Hz, 1H), 4.55 (s, 1H), 4.05 - 3.86 (m, 2H), 3.82 (q, J = 6.3 Hz, 2H), 3.63 (dd, J = 13.7, 4.6 Hz, 1H), 3.41 (d, J = 13.2 Hz, 3H), 3.31 (s, 1H), 3.20 (s, 1H), 2.67 (d, J = 5.6 Hz, 2H), 2.17 - 1.92 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS LCMS *m/z* [M+H]$^+$ 467.15
63			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 5.45 (s, 2H), 4.66 (d, J = 14.1 Hz, 1H), 4.56 (d, J = 13.8 Hz, 1H), 3.82 (q, J = 6.1 Hz, 2H), 3.56 (s, 4H), 3.33 (t, J = 6.9 Hz, 4H), 3.19 (s, 1H), 2.68 (d, J = 6.1 Hz, 2H), 2.04 (d, J = 9.6 Hz, 4H), 1.94 (p, J = 7.0 Hz, 2H), 1.81 (p, J = 6.8 Hz, 2H), 1.46 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS LCMS *m/z* [M+H]$^+$ 444.21

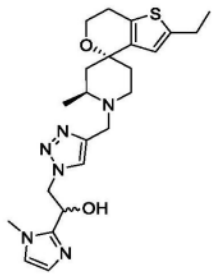
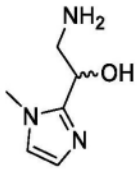
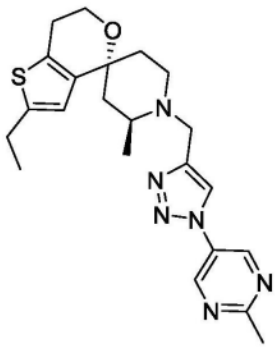
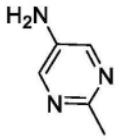
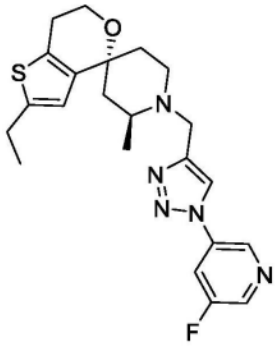
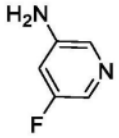
[0550]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
64			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 8.32 (s, 1H), 6.46 (s, 1H), 5.99 (s, 1H), 5.56 (s, 2H), 4.61 (d, J = 14.2 Hz, 1H), 4.49 (d, J = 15.4 Hz, 1H), 3.81 (q, J = 6.0 Hz, 3H), 3.31 (d, J = 12.0 Hz, 2H), 3.21 - 3.06 (m, 2H), 2.67 (s, 2H), 2.20 (s, 3H), 2.03 (t, J = 9.5 Hz, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.25 (q, J = 7.3, 6.8 Hz, 3H)。LCMS LCMS *m/z* [M+H]$^+$ 427.24
65			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 14.19 (s, 1H), 10.03 (s, 1H), 8.57 (s, 1H), 8.41 (s, 1H), 6.46 (s, 1H), 5.78 (s, 2H), 4.64 (d, J = 14.1 Hz, 1H), 4.52 (d, J = 14.7 Hz, 1H), 3.83 (tt, J = 12.1, 5.9 Hz, 2H), 3.62 (d, J = 5.5 Hz, 2H), 3.32 (d, J = 12.2 Hz, 2H), 3.24 - 3.04 (m, 2H), 2.69 (d, J = 15.0 Hz, 2H), 2.02 (d, J = 11.2 Hz, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.26 (t, J = 6.2 Hz, 3H)。LCMS LCMS *m/z* [M+H]$^+$ 414.21
66			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.00 (s, 1H), 8.25 (s, 1H), 6.46 (s, 1H), 5.96 (s, 1H), 5.42 (s, 2H), 4.60 (d, J = 14.2 Hz, 1H), 4.45 (d, J = 14.9 Hz, 1H), 3.82 (dq, J = 12.5, 6.0 Hz, 2H), 3.70 - 3.55 (m,

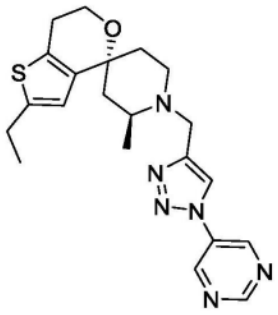
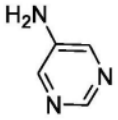
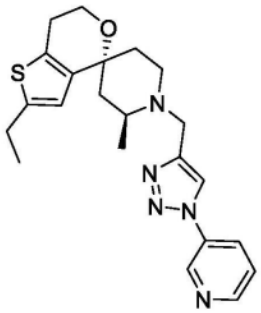
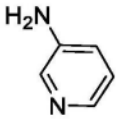
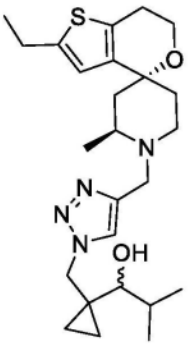
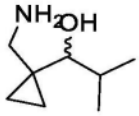
[0551]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				1H), 3.36 - 3.06 (m, 4H), 2.67 (s, 2H), 2.25 (s, 3H), 2.14 (s, 3H), 2.01 (d, J = 12.0 Hz, 4H), 1.42 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]+ 468.19
67			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.28 (s, 2H), 6.46 (s, 1H), 4.81 (t, J = 6.9 Hz, 2H), 4.59 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 14.3 Hz, 1H), 3.68 - 3.56 (m, 2H), 3.36 - 3.17 (m, 5H), 3.10 (s, 2H), 2.68 (s, 2H), 2.16 - 1.94 (m, 4H), 1.42 (d, J = 6.3 Hz, 3H), 1.26 (t, J = 6.2 Hz, 3H)。LCMS *m/z* [M+H]+ 428.22
68			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.98 (s, 1H), 8.34 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 6.49 (s, 1H), 4.94 (t, J = 5.7 Hz, 2H), 4.67 (d, J = 5.8 Hz, 2H), 4.57 (s, 2H), 3.89 - 3.73 (m, 2H), 3.62 (s, 1H), 3.25 (d, J = 13.2 Hz, 2H), 3.16 - 3.04 (m, 2H), 2.68 (s, 2H), 2.35 (s, 3H), 2.02 (dd, J = 24.4, 11.1 Hz, 4H), 1.43 (d, J = 6.3 Hz, 3H), 1.20 (t, J = 7.7 Hz, 3H)。LCMS *m/z* [M+H]+ 441.22

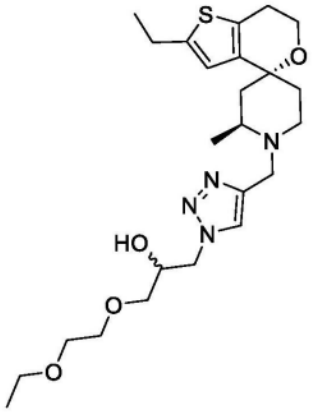
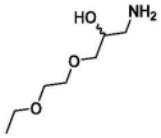
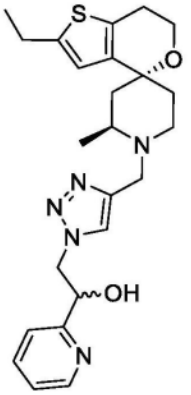
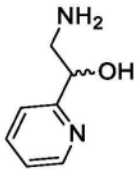
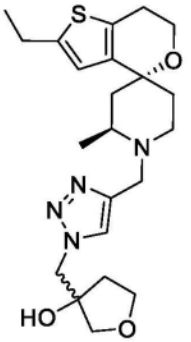
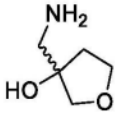
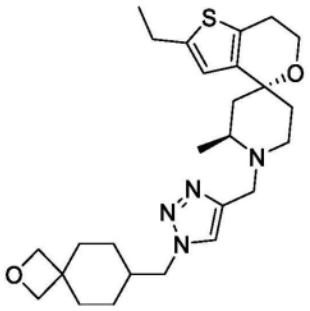
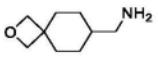
[0552]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
69			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.36 (d, J = 4.5 Hz, 1H), 7.63 (s, 1H), 7.49 (s, 1H), 6.48 (s, 1H), 5.54 (s, 1H), 4.92 (d, J = 5.3 Hz, 2H), 4.68 - 4.50 (m, 2H), 3.82 (s, 5H), 3.62 (s, 2H), 3.28 (s, 2H), 3.14 (dd, J = 7.5, 4.2 Hz, 2H), 2.68 (s, 2H), 2.07 (d, J = 27.6 Hz, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.25 (q, J = 7.1, 6.7 Hz, 3H)。LCMS *m/z* [M+H]+ 457.21
70			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 9.09 (s, 2H), 7.98 (s, 1H), 6.48 (d, J = 1.1 Hz, 1H), 4.17 (d, J = 14.8 Hz, 1H), 4.01 - 3.78 (m, 3H), 2.86 (s, 3H), 2.84 - 2.60 (m, 7H), 1.99 - 1.84 (m, 3H), 1.73 (dd, J = 13.9, 11.4 Hz, 1H), 1.33 - 1.23 (m, 6H)。LCMS *m/z* [M+H]+ 425.18
71			化合物 16	1H NMR (400 MHz, 氯仿-d) δ 8.78 (dt, J = 2.1, 0.7 Hz, 1H), 8.51 (dd, J = 2.6, 0.5 Hz, 1H), 7.98 - 7.89 (m, 2H), 6.40 (d, J = 1.1 Hz, 1H), 4.12 - 4.04 (m, 1H), 3.88 (d, J = 14.7 Hz, 1H), 3.85 - 3.72 (m, 2H), 2.75 - 2.52 (m, 7H), 1.90 - 1.73 (m, 3H), 1.65 (dd, J = 13.9, 11.4 Hz, 1H), 1.24 - 1.16 (m, 6H)。LCMS *m/z* [M+H]+ 428.1

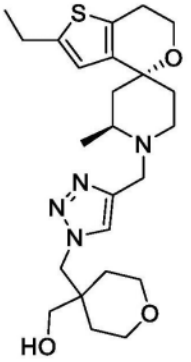
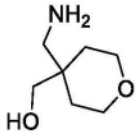
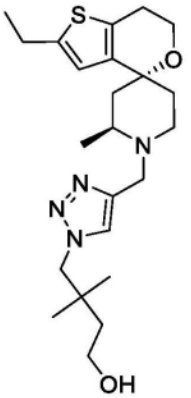
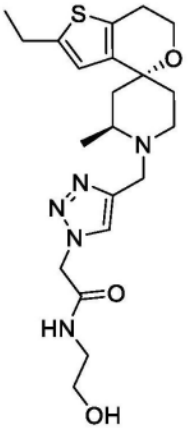
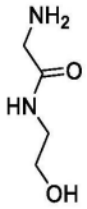
[0553]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
72			化合物 16	1H NMR (400 MHz, 氯仿-d) δ 9.24 (s, 1H), 9.15 (s, 2H), 7.94 (s, 1H), 6.40 (d, J = 1.1 Hz, 1H), 4.10 (d, J = 14.8 Hz, 1H), 3.89 (d, J = 14.7 Hz, 1H), 3.87 - 3.73 (m, 2H), 2.77 - 2.53 (m, 7H), 1.90 - 1.71 (m, 3H), 1.68 (s, 1H), 1.24 - 1.15 (m, 6H)。LCMS *m/z* [M+H]+ 411.13
73			化合物 16	1H NMR (400 MHz, 氯仿-d) δ 8.95 (dd, J = 2.7, 0.7 Hz, 1H), 8.63 (dd, J = 4.8, 1.5 Hz, 1H), 8.10 (ddd, J = 8.3, 2.6, 1.5 Hz, 1H), 7.92 (s, 1H), 7.43 (ddd, J = 8.3, 4.8, 0.8 Hz, 1H), 6.40 (t, J = 1.1 Hz, 1H), 4.08 (d, J = 14.7 Hz, 1H), 3.88 (d, J = 14.7 Hz, 1H), 3.85 - 3.72 (m, 2H), 2.78 - 2.52 (m, 7H), 1.90 - 1.74 (m, 3H), 1.65 (dd, J = 14.0, 11.3 Hz, 1H), 1.24 - 1.15 (m, 6H)。LCMS *m/z* [M+H]+ 410.19
74			化合物 15	LCMS *m/z* [M+H]+ 459.3

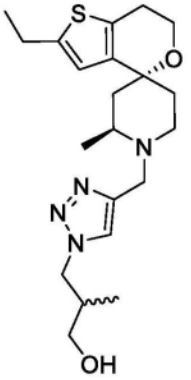
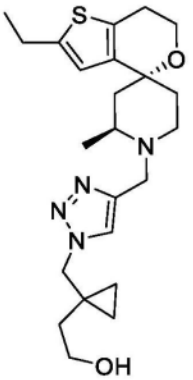
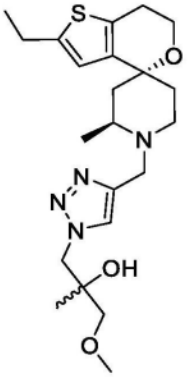
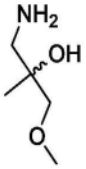
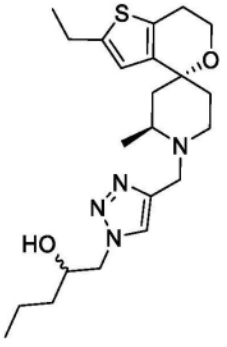
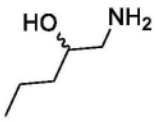
[0554]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
75			化合物 15	LCMS *m/z* [M+H]+ 479.3
76			化合物 15	LCMS *m/z* [M+H]+ 454.21
77			化合物 15	LCMS *m/z* [M+H]+ 433.24
78			化合物 15	LCMS *m/z* [M+H]+ 471.28

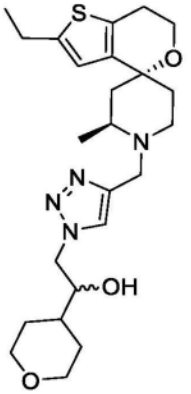
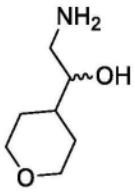
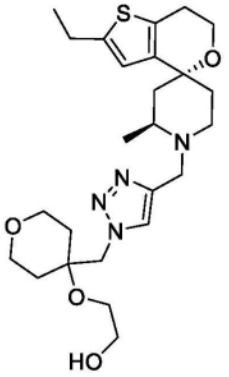
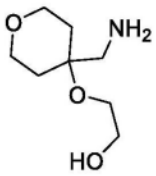
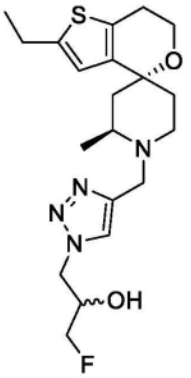
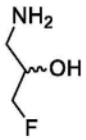
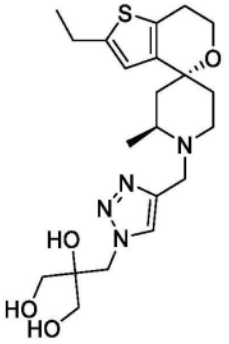
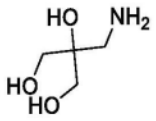
[0555]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
79			化合物 15	LCMS *m/z* [M+H]+ 461.28
80			化合物 15	LCMS *m/z* [M+H]+ 433.3
81			化合物 15	LCMS *m/z* [M+H]+ 434.21

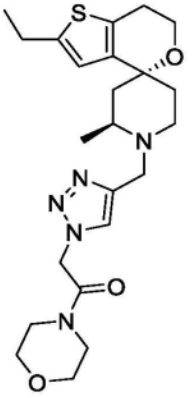
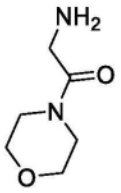
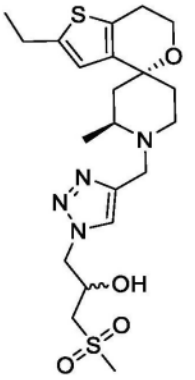
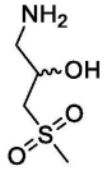
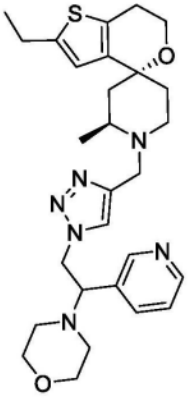
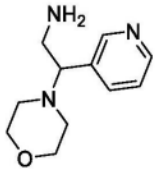
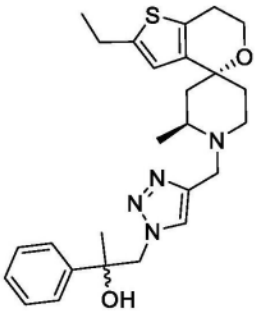
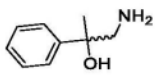
[0556]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
82			化合物 15	LCMS *m/z* [M+H]+ 405.22
83			化合物 15	LCMS *m/z* [M+H]+ 431.28
84			化合物 15	LCMS *m/z* [M+H]+ 435.29
85			化合物 15	LCMS *m/z* [M+H]+ 419.26

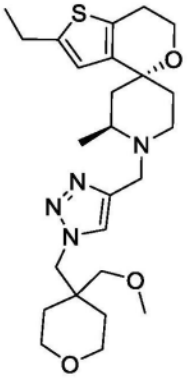
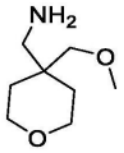
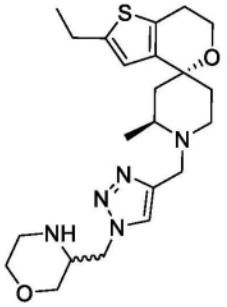
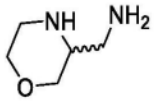
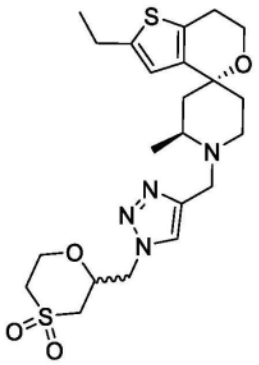
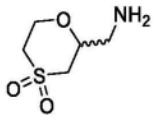
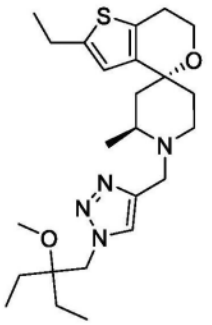
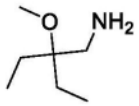
[0557]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
86			化合物 15	LCMS *m/z* [M+H]+ 461.28
87			化合物 15	LCMS *m/z* [M+H]+ 491.28
88			化合物 15	LCMS *m/z* [M+H]+ 409.23
89			化合物 15	LCMS *m/z* [M+H]+ 437.24

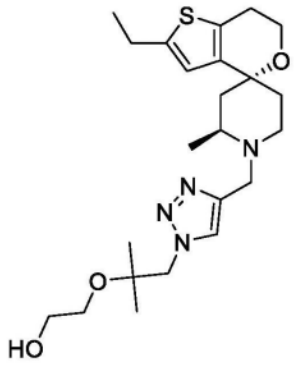
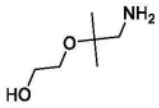
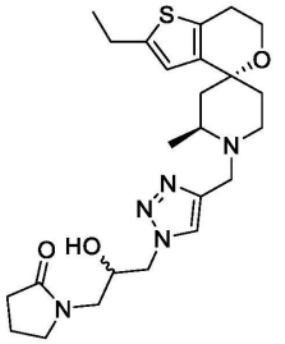
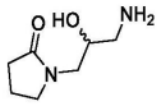
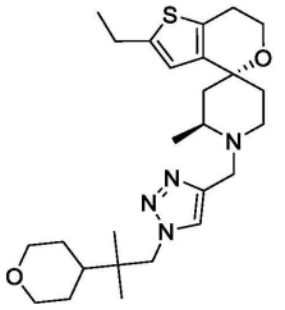
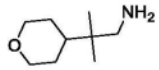
[0558]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
90			化合物 15	LCMS *m/z* [M+H]+ 460.24
91			化合物 15	LCMS *m/z* [M+H]+ 469.2
92			化合物 15	LCMS *m/z* [M+H]+ 523.3
93			化合物 15	LCMS *m/z* [M+H]+ 467.28

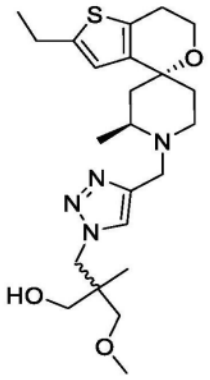
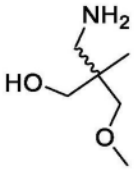
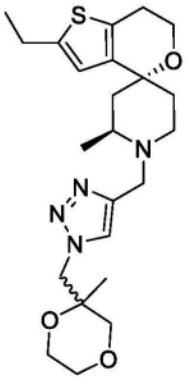
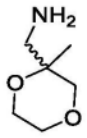
[0559]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
94			化合物 15	LCMS *m/z* [M+H]+ 475.32
95			化合物 15	LCMS *m/z* [M+H]+ 432.23
96			化合物 15	LCMS *m/z* [M+H]+ 481.19
97			化合物 15	LCMS *m/z* [M+H]+ 447.28

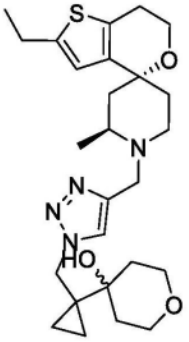
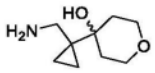
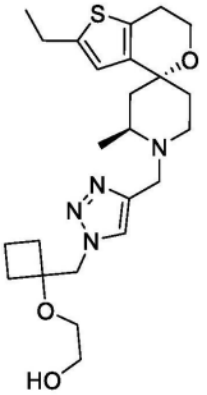
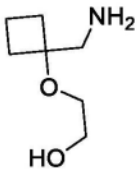
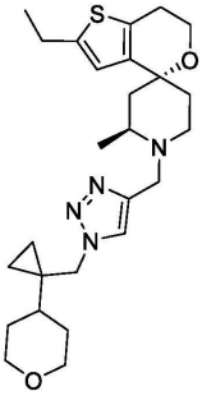
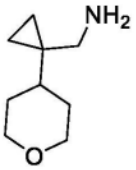
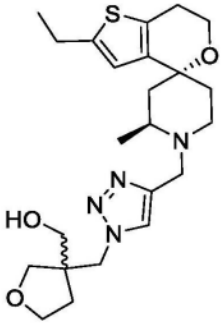
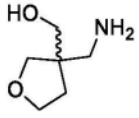
[0560]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
98			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.86 (s, 1H), 6.47 (t, J = 1.1 Hz, 1H), 4.38 (s, 2H), 4.12 (d, J = 14.4 Hz, 1H), 3.94 - 3.78 (m, 3H), 3.78 - 3.71 (m, 2H), 3.53 (ddt, J = 4.2, 3.3, 2.1 Hz, 2H), 2.80 - 2.60 (m, 8H), 1.94 (td, J = 13.3, 12.5, 4.7 Hz, 1H), 1.88 - 1.71 (m, 3H), 1.25 (td, J = 6.8, 6.1, 4.8 Hz, 6H), 1.20 (s, 3H), 1.17 (s, 3H)。LCMS *m/z* [M+H]+ 449.23
99			化合物 15	LCMS *m/z* [M+H]+ 474.28
100			化合物 15	LCMS *m/z* [M+H]+ 473.21

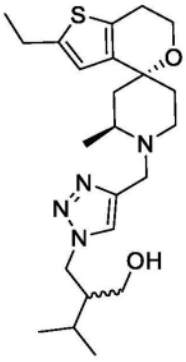
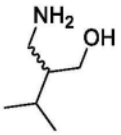
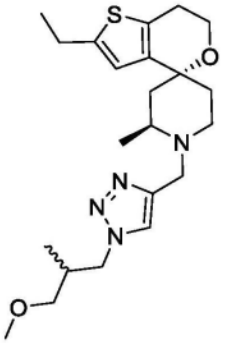
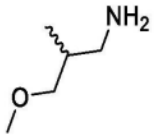
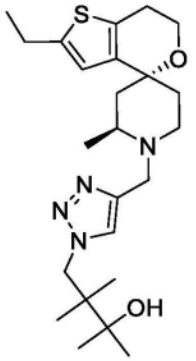
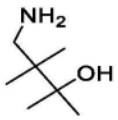
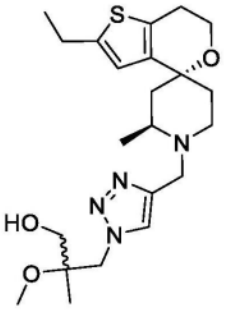
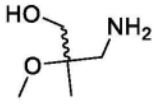
[0561]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
101			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.58 (d, J = 2.7 Hz, 1H), 6.47 (d, J = 1.1 Hz, 1H), 4.53 - 4.39 (m, 2H), 4.07 (dd, J = 14.5, 2.4 Hz, 1H), 3.94 - 3.79 (m, 3H), 3.52 (d, J = 11.6 Hz, 1H), 3.49 (s, 1H), 3.39 (s, 3H), 3.35 - 3.28 (m, 2H), 3.22 (d, J = 9.4 Hz, 1H), 2.80 - 2.57 (m, 6H), 1.98 - 1.78 (m, 3H), 1.72 (ddd, J = 13.9, 11.4, 2.5 Hz, 1H), 1.33 - 1.21 (m, 6H), 0.88 (d, J = 0.6 Hz, 3H)。LCMS *m/z* [M+H]+ 449.64
102			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.58 (d, J = 2.7 Hz, 1H), 6.47 (d, J = 1.1 Hz, 1H), 4.53 - 4.39 (m, 2H), 4.07 (dd, J = 14.5, 2.4 Hz, 1H), 3.94 - 3.79 (m, 3H), 3.52 (d, J = 11.6 Hz, 1H), 3.49 (s, 1H), 3.39 (s, 3H), 3.35 - 3.28 (m, 2H), 3.22 (d, J = 9.4 Hz, 1H), 2.80 - 2.57 (m, 8H), 1.98 - 1.78 (m, 3H), 1.72 (ddd, J = 13.9, 11.4, 2.5 Hz, 1H), 1.33 - 1.21 (m, 6H), 0.88 (d, J = 0.6 Hz, 3H)。LCMS *m/z* [M+H]+ 447.61

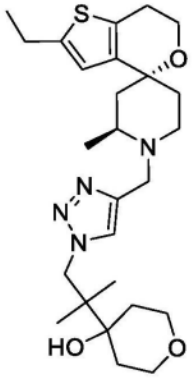
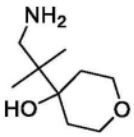
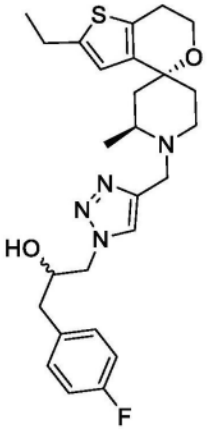
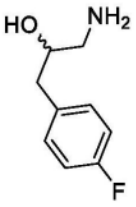
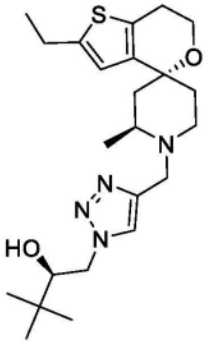
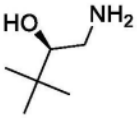
[0562]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
103			化合物 15	LCMS *m/z* [M+H]+ 487.24
104			化合物 15	LCMS *m/z* [M+H]+ 461.28
105			化合物 15	LCMS *m/z* [M+H]+ 471.28
106			化合物 15	LCMS *m/z* [M+H]+ 447.24

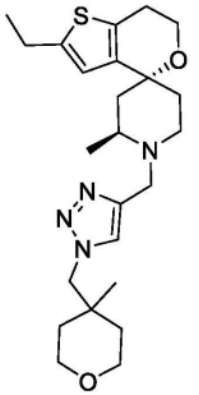
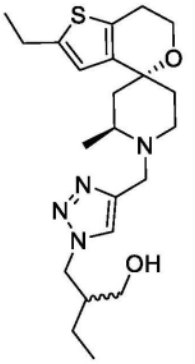
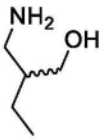
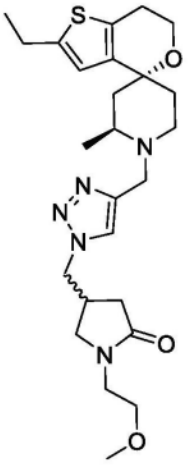
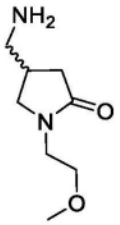
[0563]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
107			化合物 15	LCMS *m/z* [M+H]+ 433.3
108			化合物 15	LCMS *m/z* [M+H]+ 419.29
109			化合物 15	LCMS *m/z* [M+H]+ 447.28
110			化合物 15	LCMS *m/z* [M+H]+ 435.29

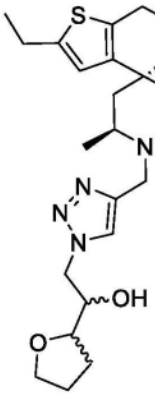
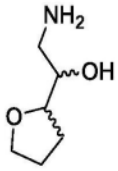
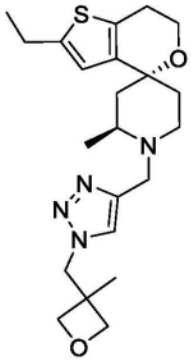
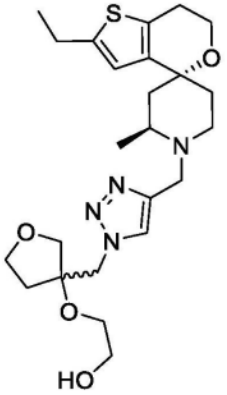
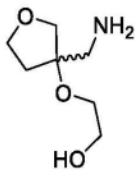
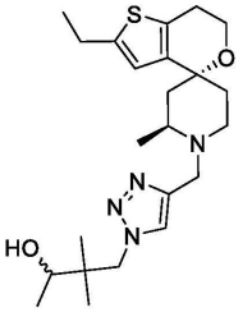
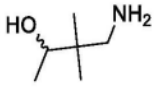
[0564]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
111			化合物 15	LCMS *m/z* [M+H]+ 489.3
112			化合物 15	LCMS *m/z* [M+H]+ 485.26
113			化合物 15	LCMS *m/z* [M+H]+ 433.3

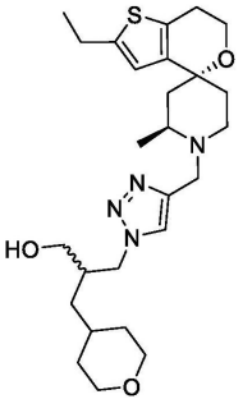
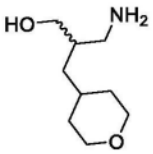
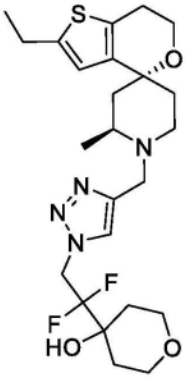
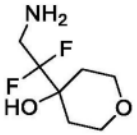
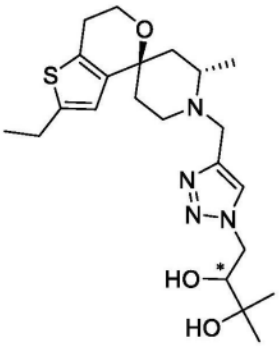
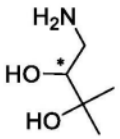
[0565]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
114			化合物 15	LCMS *m/z* [M+H]+ 445.29
115			化合物 15	LCMS *m/z* [M+H]+ 419.26
116			化合物 15	LCMS *m/z* [M+H]+ 488.29

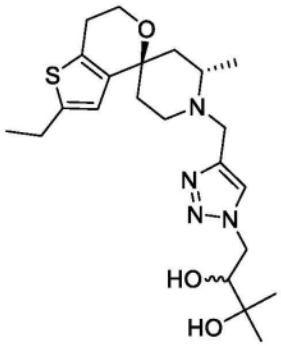
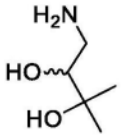
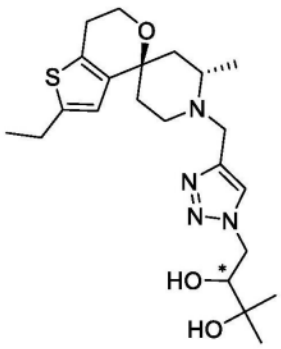
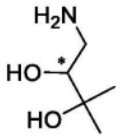
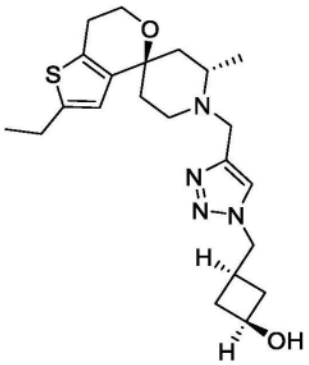
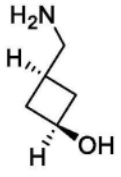
[0566]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
117			化合物 15	LCMS *m/z* [M+H]+ 447.28
118			化合物 15	LCMS *m/z* [M+H]+ 417.24
119			化合物 15	LCMS *m/z* [M+H]+ 477.28
120			化合物 15	LCMS *m/z* [M+H]+ 433.27

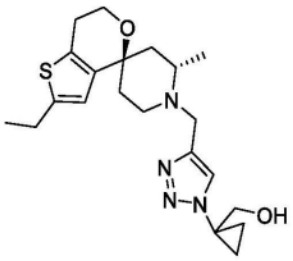
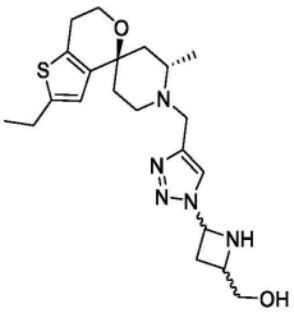
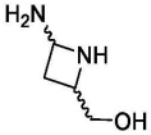
[0567]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
121			化合物 15	LCMS *m/z* [M+H]+ 489.3
122			化合物 15	LCMS *m/z* [M+H]+ 497.21
123			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.65 (s, 1H), 6.48 (d, J = 1.1 Hz, 1H), 4.64 (dd, J = 13.9, 2.3 Hz, 1H), 4.31 (dd, J = 13.9, 9.4 Hz, 1H), 4.08 (d, J = 14.5 Hz, 1H), 3.95 - 3.78 (m, 4H), 3.49 (d, J = 17.0 Hz, 1H), 2.86 - 2.57 (m, 7H), 2.20 (s, 1H), 1.97 - 1.81 (m, 3H), 1.75 (d, J = 12.1 Hz, 1H), 1.41 - 1.19 (m, 12H)。[2] LCMS *m/z* [M+H]+ 435.55

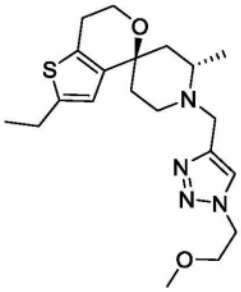
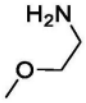
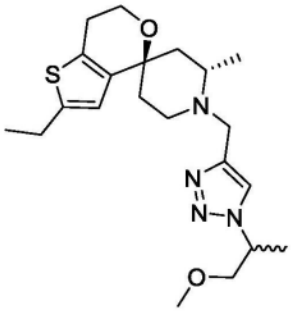
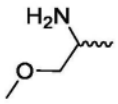
[0568]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
124			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.64 (s, 1H), 6.48 (s, 1H), 4.64 (dt, J = 13.9, 2.5 Hz, 1H), 4.32 (ddd, J = 13.9, 9.3, 2.2 Hz, 1H), 4.08 (d, J = 15.2 Hz, 1H), 3.98 - 3.73 (m, 4H), 3.34 (s, 1H), 2.87 - 2.53 (m, 6H), 2.00 - 1.80 (m, 3H), 1.80 - 1.49 (m, 5H), 1.41 - 1.32 (m, 5H), 1.28 (dd, J = 9.0, 6.0 Hz, 5H)。[3] LCMS *m/z* [M+H]+ 435.6
125			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.64 (s, 1H), 6.48 (d, J = 1.1 Hz, 1H), 4.65 (dd, J = 13.9, 2.3 Hz, 1H), 4.31 (dd, J = 13.9, 9.4 Hz, 1H), 4.06 (d, J = 14.5 Hz, 1H), 3.91 - 3.81 (m, 3H), 3.48 (d, J = 11.3 Hz, 1H), 2.88 - 2.49 (m, 7H), 2.21 (d, J = 8.0 Hz, 1H), 1.98 - 1.81 (m, 3H), 1.80 - 1.72 (m, 2H), 1.41 - 1.12 (m, 12H)。[2] LCMS *m/z* [M+H]+ 435.6
126			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.93 (s, 1H), 6.58 (s, 1H), 5.05 (d, J = 6.3 Hz, 1H), 4.34 (d, J = 6.5 Hz, 2H), 3.92 (q, J = 6.9 Hz, 1H), 3.84 (d, J = 14.4 Hz, 1H), 3.80 - 3.66 (m, 3H), 2.70 (q, J = 7.5 Hz, 2H), 2.62 (d, J = 6.1 Hz, 2H), 2.57 (s, 1H), 2.42 (t, J = 11.3 Hz, 2H), 2.18 (tt, J

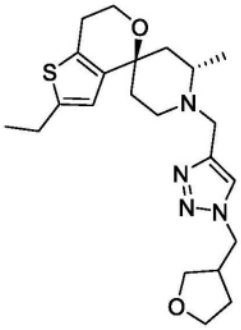
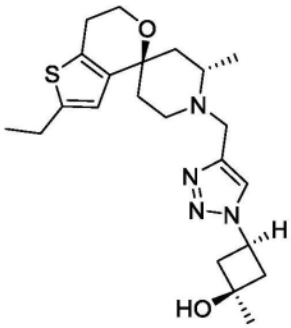
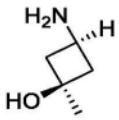
[0569]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				= 15.1, 7.4 Hz, 3H), 1.76 (dt, J = 12.5, 6.7 Hz, 1H), 1.68 (d, J = 12.9 Hz, 2H), 1.63 - 1.48 (m, 3H), 1.19 (t, J = 7.5 Hz, 3H), 1.12 (d, J = 6.1 Hz, 3H)。LCMS *m/z* [M+H]+ 417.6
127			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.98 (s, 1H), 6.59 (s, 1H), 5.12 (t, J = 5.7 Hz, 1H), 3.87 (d, J = 14.3 Hz, 1H), 3.77 (h, J = 6.0 Hz, 2H), 3.68 (d, J = 5.6 Hz, 2H), 3.59 (d, J = 14.3 Hz, 1H), 2.70 (q, J = 7.6 Hz, 2H), 2.61 (d, J = 5.6 Hz, 3H), 2.41 (dd, J = 22.7, 11.0 Hz, 2H), 1.77 (td, J = 12.8, 12.1, 4.2 Hz, 1H), 1.69 (d, J = 9.1 Hz, 2H), 1.55 (t, J = 12.5 Hz, 1H), 1.23 (t, J = 3.5 Hz, 2H), 1.19 (dd, J = 8.1, 6.9 Hz, 3H), 1.12 (d, J = 5.4 Hz, 5H)。LCMS *m/z* [M+H]+ 403.56
128			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.80 (s, 1H), 8.97 (s, 1H), 8.46 (d, J = 20.5 Hz, 1H), 6.45 (s, 1H), 5.34 - 5.01 (m, 1H), 4.70 (s, 1H), 4.63 (d, J = 14.2 Hz, 1H), 4.47 (d, J = 14.3 Hz, 1H), 3.93 - 3.68 (m, 2H), 3.59 - 3.42 (m, 3H), 3.20 (d, J = 16.0 Hz, 1H), 2.83 - 2.64 (m, 4H), 2.39 (d, J = 9.3 Hz, 1H), 2.30 (d, J = 6.4 Hz, 2H), 2.00 (t, J = 14.0 Hz, 4H), 1.44

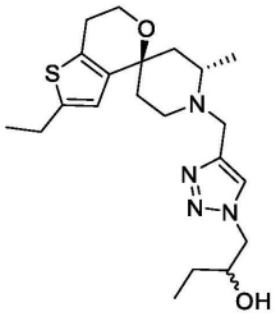
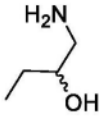
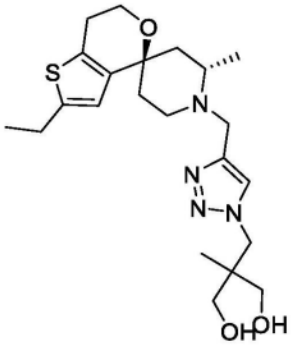
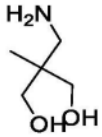
[0570]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				(d, J = 6.3 Hz, 3H), 1.36 (d, J = 11.6 Hz, 1H), 1.21 (q, J = 7.5 Hz, 4H)。LCMS *m/z* [M+H]+ 417.27
129			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.96 (s, 1H), 6.58 (s, 1H), 4.52 (t, J = 5.3 Hz, 2H), 3.88 (s, 1H), 3.75 (dt, J = 14.7, 5.4 Hz, 5H), 3.23 (d, J = 1.4 Hz, 3H), 2.70 (q, J = 7.6 Hz, 2H), 2.61 (d, J = 6.0 Hz, 3H), 2.47 (d, J = 18.3 Hz, 2H), 1.78 (s, 1H), 1.73 - 1.62 (m, 2H), 1.56 (t, J = 12.4 Hz, 1H), 1.22 - 1.16 (m, 3H), 1.14 (d, J = 6.2 Hz, 3H)。LCMS *m/z* [M+H]+ 391.54
130			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.98 (s, 1H), 8.40 (d, J = 2.3 Hz, 1H), 6.46 (s, 1H), 4.97 (q, J = 6.6 Hz, 1H), 4.63 (d, J = 14.3 Hz, 1H), 4.50 (d, J = 15.7 Hz, 1H), 3.82 (h, J = 6.0 Hz, 2H), 3.74 - 3.63 (m, 2H), 3.32 (d, J = 11.9 Hz, 2H), 3.22 (s, 3H), 3.15 (s, 1H), 2.74 (q, J = 7.5 Hz, 2H), 2.68 (d, J = 5.9 Hz, 2H), 2.04 (dd, J = 12.6, 7.8 Hz, 4H), 1.50 (d, J = 6.9 Hz, 3H), 1.45 (d, J = 6.3 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 405.25

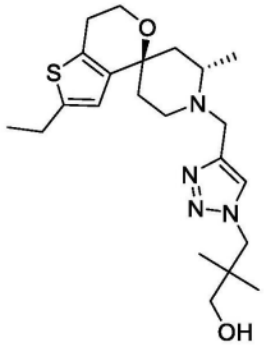
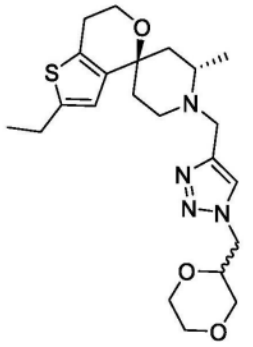
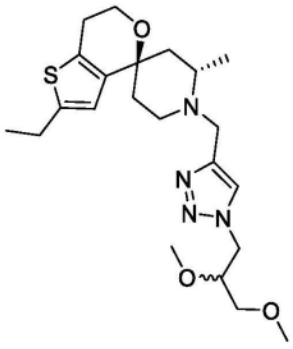
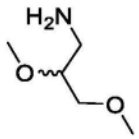
[0571]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
131			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.83 (s, 1H), 8.42 (s, 1H), 6.45 (s, 1H), 4.64 (d, J = 14.3 Hz, 1H), 4.52 (d, J = 14.4 Hz, 1H), 4.46 (d, J = 7.5 Hz, 2H), 3.87 - 3.70 (m, 3H), 3.65 (p, J = 7.7 Hz, 2H), 3.49 (d, J = 6.7 Hz, 1H), 3.14 (s, 1H), 2.75 (p, J = 7.5 Hz, 4H), 2.67 (s, 2H), 2.10 - 1.87 (m, 5H), 1.62 (dd, J = 12.8, 6.5 Hz, 1H), 1.44 (d, J = 6.4 Hz, 3H), 1.24 (s, 1H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 417.24
132			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.86 - 9.76 (m, 1H), 8.42 (s, 1H), 6.45 (s, 1H), 5.39 (s, 1H), 5.01 - 4.71 (m, 1H), 4.64 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 14.2 Hz, 1H), 3.94 - 3.65 (m, 2H), 3.29 - 3.12 (m, 2H), 2.85 - 2.65 (m, 4H), 2.65 - 2.57 (m, 3H), 2.02 (d, J = 12.4 Hz, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.35 (s, 4H), 1.24 (s, 1H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 417.27

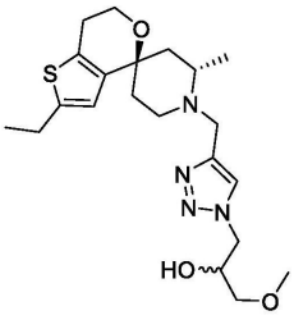
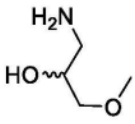
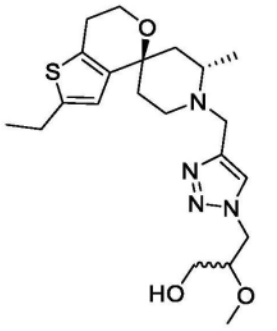
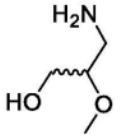
[0572]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
133			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 8.29 (d, J = 2.1 Hz, 1H), 6.46 (s, 1H), 5.11 (s, 1H), 4.63 (d, J = 14.3 Hz, 1H), 4.57 - 4.39 (m, 2H), 4.31 (dd, J = 14.0, 7.3 Hz, 1H), 3.82 (td, J = 17.0, 14.4, 8.1 Hz, 3H), 3.29 (d, J = 1.8 Hz, 1H), 3.17 (d, J = 11.1 Hz, 1H), 2.88 - 2.58 (m, 4H), 2.02 (d, J = 11.4 Hz, 4H), 1.45 (d, J = 6.3 Hz, 3H), 1.34 (tdd, J = 21.3, 13.1, 7.4 Hz, 3H), 1.21 (q, J = 7.9, 7.5 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H)。LCMS *m/z* [M+H]+ 405.25
134			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.85 (s, 1H), 6.59 (s, 1H), 4.83 - 4.62 (m, 2H), 4.26 (s, 2H), 3.85 (d, J = 14.5 Hz, 1H), 3.80 - 3.61 (m, 3H), 3.21 (t, J = 5.0 Hz, 4H), 2.70 (q, J = 7.5 Hz, 2H), 2.61 (s, 2H), 2.57 (s, 1H), 2.43 (t, J = 11.5 Hz, 2H), 1.77 (t, J = 12.5 Hz, 1H), 1.68 (d, J = 13.6 Hz, 2H), 1.54 (t, J = 12.3 Hz, 1H), 1.19 (td, J = 7.4, 1.8 Hz, 3H), 1.12 (d, J = 6.1 Hz, 3H), 0.66 (d, J = 1.8 Hz, 3H)。LCMS *m/z* [M+H]+ 435.55

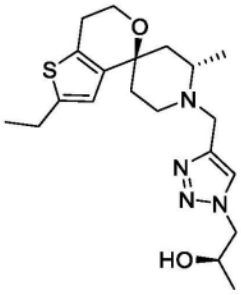
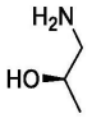
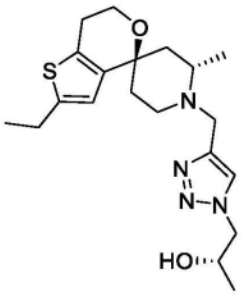
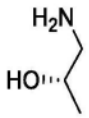
[0573]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
135			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.29 (s, 1H), 6.46 (s, 1H), 4.91 (d, J = 37.5 Hz, 1H), 4.75 - 4.48 (m, 2H), 4.30 (s, 2H), 3.80 (h, J = 6.1 Hz, 2H), 3.29 (s, 3H), 3.14 (s, 3H), 2.82 - 2.63 (m, 3H), 2.02 (q, J = 14.8, 12.5 Hz, 3H), 1.46 (t, J = 7.3 Hz, 3H), 1.37 - 1.15 (m, 3H), 0.81 (s, 6H)。LCMS *m/z* [M+H]+ 419.29
136			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.94 (s, 1H), 6.59 (s, 1H), 4.43 (d, J = 4.2 Hz, 2H), 3.96 - 3.82 (m, 2H), 3.75 (d, J = 11.1 Hz, 5H), 3.64 (d, J = 11.5 Hz, 1H), 3.55 (t, J = 11.3 Hz, 1H), 3.44 (d, J = 11.3 Hz, 2H), 3.20 (t, J = 10.8 Hz, 1H), 2.76 - 2.65 (m, 2H), 2.62 (s, 2H), 2.43 (s, 2H), 1.76 (d, J = 12.9 Hz, 1H), 1.69 (d, J = 13.0 Hz, 2H), 1.55 (t, J = 12.4 Hz, 1H), 1.19 (dt, J = 9.9, 5.1 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H)。LCMS *m/z* [M+H]+ 433.53
137			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.32 (d, J = 1.7 Hz, 1H), 6.47 (s, 1H), 4.69 - 4.44 (m, 4H), 3.78 (dp, J = 12.7, 5.1, 4.3 Hz, 3H), 3.38 - 3.36 (m, 1H), 3.35 - 3.30 (m, 1H), 3.29 (s, 4H), 3.23 (d, J = 1.5

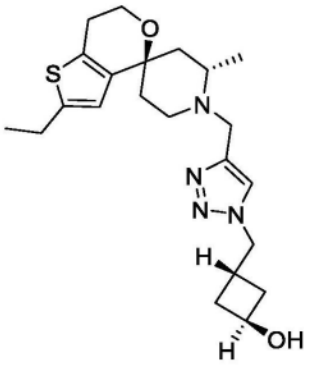
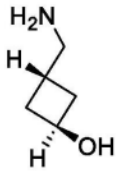
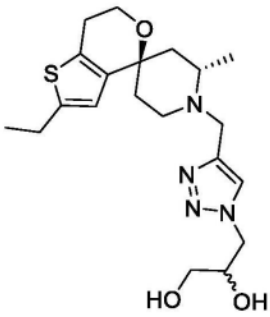
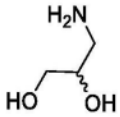
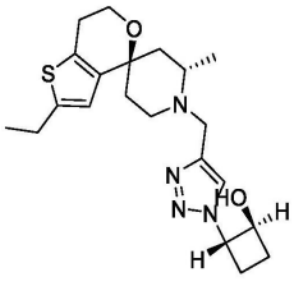
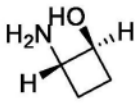
[0574]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				Hz, 3H), 3.15 (s, 1H), 2.79 - 2.63 (m, 4H), 2.04 (t, J = 11.2 Hz, 4H), 1.45 (d, J = 6.3 Hz, 3H), 1.25 (t, J = 5.5 Hz, 1H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 435.29
138			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.97 (s, 1H), 8.29 (d, J = 1.6 Hz, 1H), 6.46 (s, 1H), 5.40 (s, 1H), 4.63 (d, J = 14.2 Hz, 1H), 4.52 (dd, J = 13.8, 3.7 Hz, 2H), 4.37 (dd, J = 13.8, 7.7 Hz, 1H), 4.00 (s, 1H), 3.82 (h, J = 6.2, 5.8 Hz, 2H), 3.29 (s, 6H), 3.17 (s, 1H), 2.79 - 2.61 (m, 4H), 2.02 (d, J = 11.4 Hz, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 421.25
139			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 7.92 (s, 1H), 6.59 (s, 1H), 4.91 (t, J = 5.6 Hz, 1H), 4.54 (dd, J = 14.2, 3.8 Hz, 1H), 4.36 (dd, J = 14.1, 7.5 Hz, 1H), 3.87 (d, J = 14.7 Hz, 1H), 3.74 (h, J = 5.9 Hz, 3H), 3.57 (dd, J = 8.0, 4.2 Hz, 1H), 3.43 (td, J = 5.3, 1.8 Hz, 2H), 3.20 (s, 3H), 2.70 (q, J = 7.5 Hz, 2H), 2.66 - 2.58 (m, 2H), 2.57 (s, 1H), 2.44 (s, 2H), 1.78 (t, J = 11.3 Hz, 1H), 1.68 (d, J = 13.3 Hz, 2H), 1.55 (t, J = 12.4 Hz, 1H), 1.19 (t, J = 7.5 Hz,

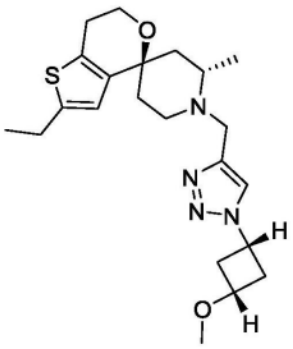
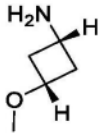
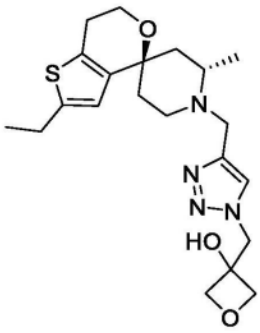
[0575]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				3H), 1.14 (d, J = 6.1 Hz, 3H)。LCMS *m/z* [M+H]+ 421.56
140			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.29 (s, 1H), 6.46 (s, 1H), 5.13 (s, 1H), 4.64 (d, J = 13.8 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.42 (dd, J = 13.5, 4.0 Hz, 1H), 4.36 - 4.26 (m, 1H), 4.02 (d, J = 7.0 Hz, 1H), 3.96 - 3.73 (m, 2H), 3.30 (s, 1H), 3.17 (s, 2H), 2.80 - 2.61 (m, 3H), 2.28 - 1.83 (m, 4H), 1.52 - 1.34 (m, 4H), 1.30 - 1.16 (m, 3H), 1.07 (d, J = 6.2 Hz, 3H)。LCMS *m/z* [M+H]+ 391.25
141			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.30 (s, 1H), 6.46 (d, J = 7.2 Hz, 1H), 5.13 (s, 1H), 4.64 (d, J = 13.8 Hz, 1H), 4.51 (d, J = 15.2 Hz, 1H), 4.46 - 4.34 (m, 2H), 4.30 (dd, J = 13.8, 7.1 Hz, 1H), 4.03 (s, 1H), 3.97 - 3.73 (m, 2H), 3.24 - 3.15 (m, 2H), 2.79 - 2.61 (m, 3H), 2.36 - 1.85 (m, 5H), 1.45 (d, J = 6.5 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H)。LCMS *m/z* [M+H]+ 391.25

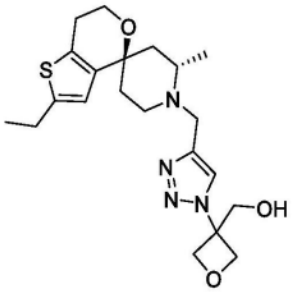
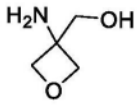
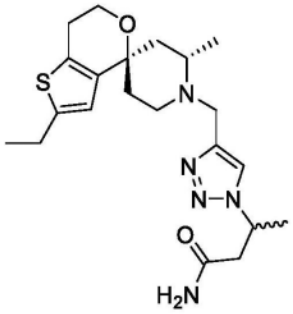
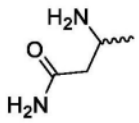
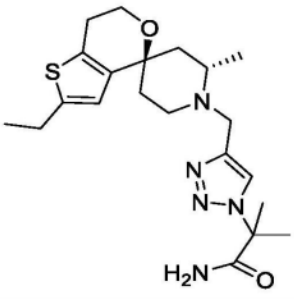
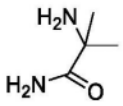
[0576]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
142			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.38 (s, 1H), 6.46 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 13.9 Hz, 1H), 4.57 - 4.45 (m, 3H), 4.27 - 4.12 (m, 1H), 3.83 (dq, J = 19.1, 7.3, 6.4 Hz, 2H), 3.31 (d, J = 13.2 Hz, 3H), 3.15 (s, 1H), 2.81 - 2.57 (m, 5H), 2.03 (s, 5H), 1.98 - 1.87 (m, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.20 (td, J = 7.5, 3.7 Hz, 3H)。LCMS *m/z* [M+H]+ 417.27
143			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 2H), 8.29 (s, 1H), 6.46 (s, 1H), 5.23 (s, 1H), 4.91 (s, 1H), 4.57 (td, J = 23.8, 23.0, 14.1 Hz, 5H), 4.40 - 4.26 (m, 2H), 3.84 (s, 4H), 2.80 - 2.62 (m, 4H), 2.02 (d, J = 10.7 Hz, 4H), 1.45 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 407.24
144			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.88 (s, 1H), 8.49 (s, 1H), 6.45 (s, 1H), 5.86 (s, 1H), 4.82 (q, J = 8.6 Hz, 1H), 4.63 (d, J = 14.0 Hz, 1H), 4.51 (s, 1H), 4.37 (d, J = 8.9 Hz, 1H), 3.94 - 3.66 (m, 3H), 3.19 (d, J = 14.7 Hz, 1H), 2.80 - 2.64 (m, 4H), 2.21 (dp, J = 27.0, 9.0 Hz, 3H), 2.02 (d, J = 12.1 Hz, 3H),

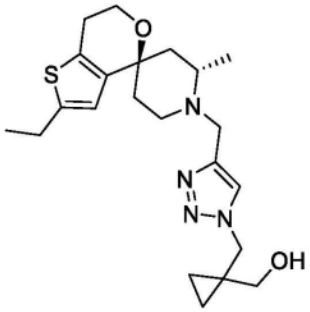
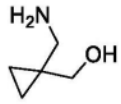
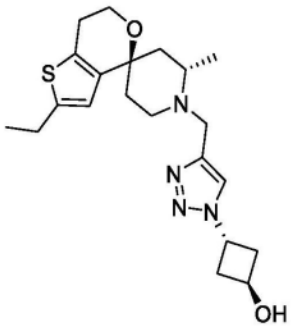
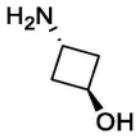
[0577]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				1.92 (p, J = 10.0, 9.5 Hz, 2H), 1.68 (q, J = 9.6 Hz, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 403.23
145			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.98 (s, 1H), 8.49 (s, 1H), 6.50 (d, J = 33.9 Hz, 1H), 4.87 (p, J = 8.3 Hz, 1H), 4.62 (d, J = 14.1 Hz, 1H), 4.48 (d, J = 15.4 Hz, 1H), 3.91 - 3.76 (m, 3H), 3.21 (s, 5H), 2.97 - 2.88 (m, 2H), 2.86 - 2.58 (m, 4H), 2.44 - 2.34 (m, 2H), 2.18 - 1.90 (m, 4H), 1.44 (d, J = 6.4 Hz, 3H), 1.37 (d, J = 6.4 Hz, 1H), 1.31 - 1.11 (m, 3H)。LCMS *m/z* [M+H]+ 417.27
146			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.97 (s, 1H), 8.31 (d, J = 2.8 Hz, 1H), 6.42 (d, J = 31.7 Hz, 1H), 4.77 (s, 3H), 4.64 (d, J = 13.7 Hz, 1H), 4.60 - 4.37 (m, 6H), 3.83 (dt, J = 13.6, 7.1 Hz, 2H), 3.27 - 3.10 (m, 2H), 2.78 - 2.59 (m, 4H), 2.26 - 1.83 (m, 4H), 1.45 (t, J = 7.0 Hz, 3H), 1.25 - 1.14 (m, 3H)。LCMS *m/z* [M+H]+ 419.23

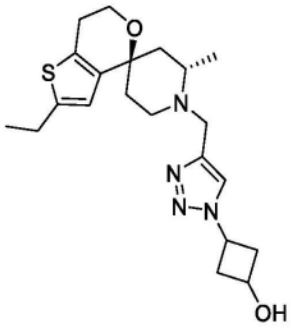
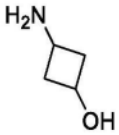
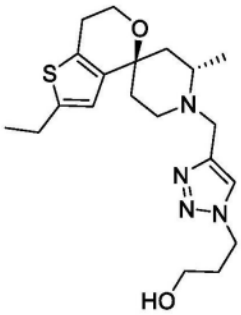
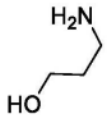
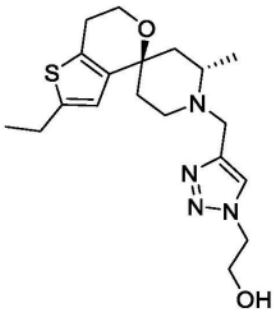
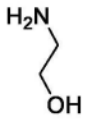
[0578]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
147			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.02 (s, 1H), 8.49 (d, J = 3.0 Hz, 1H), 6.47 (s, 1H), 5.80 - 5.56 (m, 1H), 5.00 (dd, J = 6.9, 4.3 Hz, 2H), 4.83 (d, J = 7.0 Hz, 2H), 4.67 (d, J = 14.1 Hz, 1H), 4.51 (d, J = 13.5 Hz, 1H), 4.06 (s, 2H), 3.97 - 3.78 (m, 2H), 3.35 - 3.06 (m, 2H), 2.92 - 2.59 (m, 4H), 2.24 - 1.89 (m, 4H), 1.46 (t, J = 7.0 Hz, 3H), 1.31 - 1.15 (m, 3H)。LCMS *m/z* [M+H]+ 419.23
148			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.46 (s, 1H), 6.92 (s, 1H), 6.46 (s, 1H), 5.10 (q, J = 7.1 Hz, 1H), 4.62 (d, J = 14.2 Hz, 1H), 4.48 (d, J = 15.1 Hz, 1H), 3.82 (dq, J = 11.9, 5.6 Hz, 2H), 2.75 (tdd, J = 22.0, 12.7, 6.0 Hz, 7H), 2.08 (dd, J = 49.0, 13.0 Hz, 4H), 1.53 (d, J = 6.8 Hz, 4H), 1.44 (d, J = 6.5 Hz, 3H), 1.38 (d, J = 7.4 Hz, 1H), 1.21 (q, J = 7.7 Hz, 3H)。LCMS *m/z* [M+H]+ 418.28
149			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.44 (d, J = 3.3 Hz, 1H), 7.45 (d, J = 6.6 Hz, 2H), 6.47 (d, J = 7.1 Hz, 1H), 4.71 - 4.39 (m, 2H), 3.84 (dt, J = 14.1, 6.4 Hz, 2H),

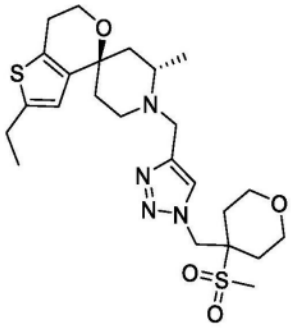
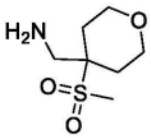
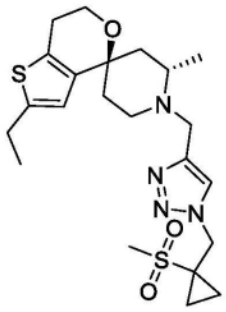
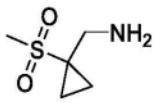
[0579]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				3.21 (s, 2H), 2.87 - 2.65 (m, 4H), 2.27 - 1.90 (m, 4H), 1.85 (s, 6H), 1.46 (t, J = 6.7 Hz, 3H), 1.41 - 1.25 (m, 1H), 1.20 (td, J = 7.5, 3.0 Hz, 3H)。LCMS *m/z* [M+H]+ 418.25
150			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.06 (d, J = 39.7 Hz, 1H), 8.36 (s, 1H), 6.46 (s, 1H), 4.98 - 4.25 (m, 6H), 3.81 (d, J = 6.5 Hz, 2H), 3.31 (d, J = 12.3 Hz, 3H), 3.13 (s, 3H), 2.79 - 2.61 (m, 2H), 2.06 (dq, J = 27.6, 17.4, 15.5 Hz, 4H), 1.49 - 1.34 (m, 3H), 1.32 - 1.09 (m, 3H), 0.66 (d, J = 4.4 Hz, 2H), 0.52 (s, 2H)。LCMS *m/z* [M+H]+ 417.24
151			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.04 (d, J = 46.6 Hz, 1H), 8.46 (d, J = 2.7 Hz, 1H), 6.47 (d, J = 7.7 Hz, 1H), 5.42 (s, 1H), 5.25 (dq, J = 8.6, 4.8, 4.1 Hz, 1H), 4.62 (d, J = 14.1 Hz, 1H), 4.57 - 4.47 (m, 2H), 3.84 (dd, J = 15.5, 9.5 Hz, 2H), 3.18 (s, 2H), 2.88 (dd, J = 31.0, 6.4 Hz, 1H), 2.79 - 2.64 (m, 5H), 2.15 (d, J = 14.4 Hz, 1H), 2.02 (d, J = 17.3 Hz, 3H), 1.45 (t, J = 6.8 Hz, 3H), 1.40 - 1.23 (m, 2H), 1.32 - 1.15 (m, 3H)。LCMS *m/z* [M+H]+ 403.27

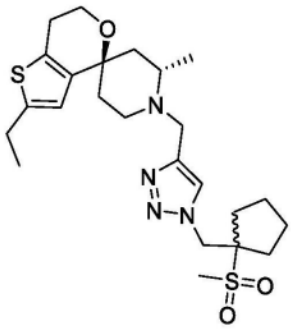
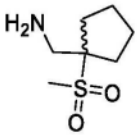
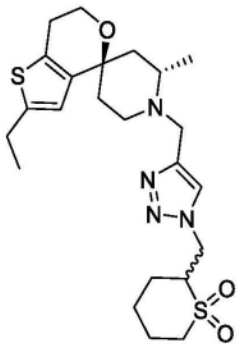
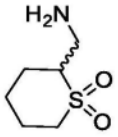
[0580]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
152			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 9.99 (s, 1H), 8.45 (s, 1H), 6.47 (d, J = 7.1 Hz, 1H), 5.44 (s, 1H), 4.73 (q, J = 8.4 Hz, 1H), 4.62 (d, J = 14.0 Hz, 1H), 4.44 (d, J = 49.1 Hz, 2H), 4.05 (p, J = 7.1 Hz, 1H), 3.83 (tt, J = 12.4, 5.7 Hz, 2H), 3.18 (s, 2H), 2.94 - 2.80 (m, 2H), 2.72 (dt, J = 21.9, 6.9 Hz, 4H), 2.42 - 2.32 (m, 2H), 2.02 (d, J = 15.9 Hz, 4H), 1.45 (d, J = 6.5 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 403.23
153			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.37 (d, J = 2.2 Hz, 1H), 6.46 (s, 1H), 4.62 (d, J = 13.9 Hz, 1H), 4.49 (t, J = 7.1 Hz, 4H), 3.82 (d, J = 6.7 Hz, 3H), 3.17 (s, 2H), 2.80 - 2.62 (m, 4H), 2.09 - 1.91 (m, 7H), 1.45 (t, J = 7.0 Hz, 4H), 1.20 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 391.25
154			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.02 (d, J = 39.0 Hz, 1H), 8.33 (s, 1H), 6.46 (s, 1H), 5.11 (s, 1H), 4.63 (d, J = 14.0 Hz, 1H), 4.58 - 4.42 (m, 4H), 3.90 - 3.74 (m, 5H), 3.18 (d, J = 12.0 Hz, 1H), 2.78 - 2.62 (m, 4H), 2.04 (s, 4H), 1.41 (d, J = 25.5 Hz, 3H), 1.27 - 1.17

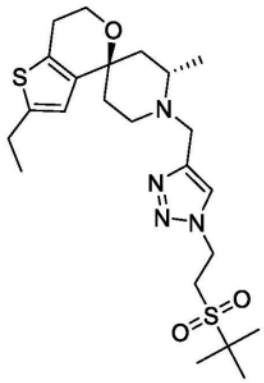
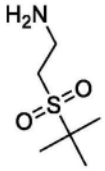
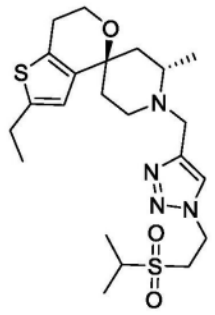
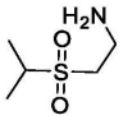
[0581]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				(m, 3H)。LCMS *m/z* [M+H]+ 377.04
155			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.31 (s, 1H), 6.45 (d, J = 1.1 Hz, 1H), 5.08 (s, 2H), 4.77 (d, J = 14.2 Hz, 1H), 4.38 (d, J = 14.2 Hz, 1H), 4.17 - 4.08 (m, 2H), 3.93 - 3.79 (m, 4H), 3.55 (s, 1H), 3.29 (d, J = 13.4 Hz, 2H), 2.83 (s, 3H), 2.81 - 2.71 (m, 4H), 2.33 - 2.18 (m, 4H), 2.07 - 1.99 (m, 2H), 1.87 - 1.77 (m, 2H), 1.61 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 509.295
156			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.39 (s, 1H), 6.45 (d, J = 1.1 Hz, 1H), 4.83 (d, J = 15.0 Hz, 3H), 4.32 (d, J = 14.0 Hz, 1H), 3.93 - 3.81 (m, 2H), 3.60 (s, 1H), 3.30 (q, J = 13.3, 10.3 Hz, 2H), 2.79 (s, 3H), 2.76 (t, J = 7.4 Hz, 4H), 2.35 - 2.19 (m, 2H), 2.09 - 1.98 (m, 2H), 1.72 - 1.66 (m, 2H), 1.60 (s, 3H), 1.41 - 1.36 (m, 2H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 465.32

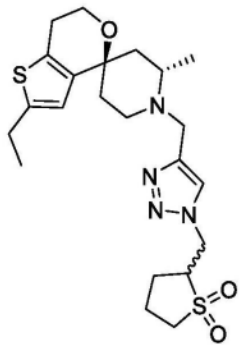
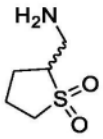
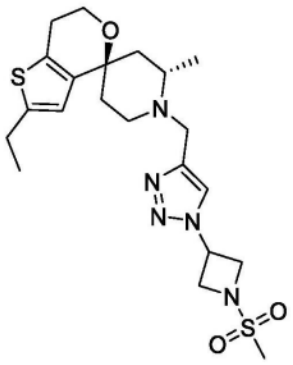
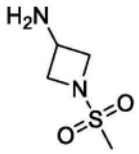
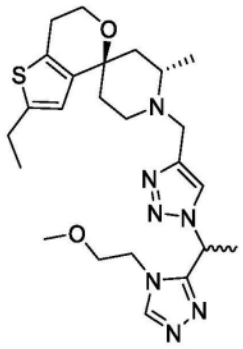
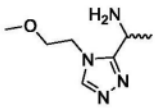
[0582]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
157			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.32 (s, 1H), 6.47 (d, J = 1.2 Hz, 1H), 4.78 (d, J = 14.3 Hz, 3H), 4.33 (d, J = 14.1 Hz, 2H), 3.93 - 3.80 (m, 2H), 3.55 (s, 1H), 3.27 (d, J = 15.4 Hz, 2H), 2.80 (s, 3H), 2.75 (dd, J = 10.0, 5.6 Hz, 4H), 2.40 - 2.24 (m, 4H), 2.05 (ddt, J = 18.9, 12.9, 6.4 Hz, 4H), 1.85 (d, J = 6.9 Hz, 2H), 1.74 - 1.61 (m, 2H), 1.61 (d, J = 6.5 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 493.21
158			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.24 (d, J = 10.1 Hz, 1H), 6.46 (d, J = 1.2 Hz, 1H), 5.04 (ddd, J = 14.6, 8.6, 7.1 Hz, 1H), 4.64 (ddd, J = 14.4, 8.0, 6.1 Hz, 2H), 4.34 (dd, J = 14.1, 7.8 Hz, 1H), 3.86 (ddd, J = 15.4, 6.6, 4.5 Hz, 2H), 3.57 (d, J = 6.0 Hz, 2H), 3.32 (s, 2H), 3.16 (dd, J = 14.5, 4.2 Hz, 1H), 3.06 - 2.93 (m, 1H), 2.77 (q, J = 7.1 Hz, 4H), 2.35 - 2.19 (m, 2H), 2.15 - 1.98 (m, 5H), 1.95 - 1.81 (m, 2H), 1.60 (dd, J = 6.5, 5.0 Hz, 3H), 1.52 (d, J = 10.6 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 479.04

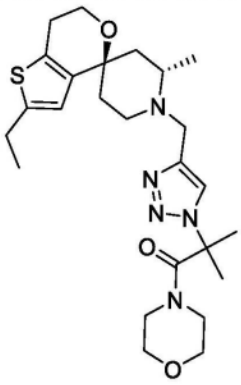
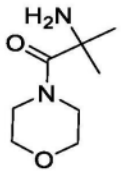
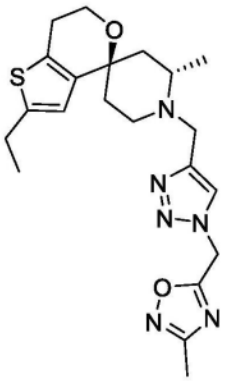
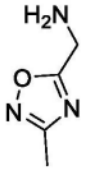
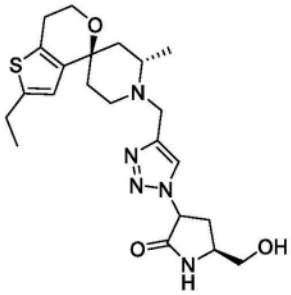
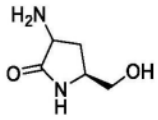
[0583]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
159			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.25 (s, 1H), 6.45 (d, J = 1.3 Hz, 1H), 5.01 (td, J = 6.8, 2.9 Hz, 2H), 4.77 (d, J = 14.1 Hz, 1H), 4.34 (d, J = 14.1 Hz, 1H), 3.95 - 3.78 (m, 2H), 3.60 (t, J = 6.8 Hz, 3H), 3.31 (d, J = 14.9 Hz, 2H), 2.85 - 2.69 (m, 4H), 2.34 - 2.19 (m, 2H), 2.03 (ddd, J = 12.6, 6.3, 3.2 Hz, 2H), 1.60 (d, J = 6.5 Hz, 3H), 1.44 (s, 9H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 481.22
160			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.27 (s, 1H), 6.46 (d, J = 1.1 Hz, 1H), 4.99 (td, J = 6.7, 2.7 Hz, 2H), 4.78 (d, J = 14.1 Hz, 1H), 4.31 (d, J = 14.0 Hz, 1H), 3.96 - 3.80 (m, 2H), 3.65 - 3.54 (m, 3H), 3.29 (dd, J = 20.1, 7.8 Hz, 2H), 3.13 (p, J = 6.9 Hz, 1H), 2.84 - 2.71 (m, 4H), 2.35 - 2.19 (m, 2H), 2.09 - 1.97 (m, 2H), 1.60 (d, J = 6.5 Hz, 3H), 1.41 (dd, J = 6.9, 1.4 Hz, 6H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 467.18

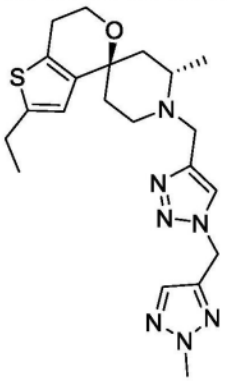
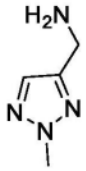
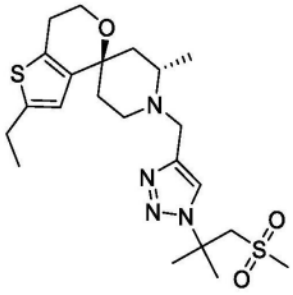
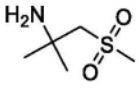
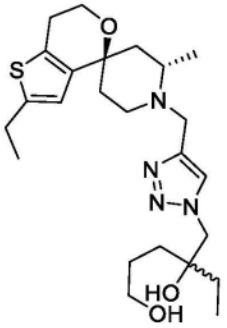
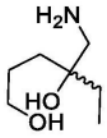
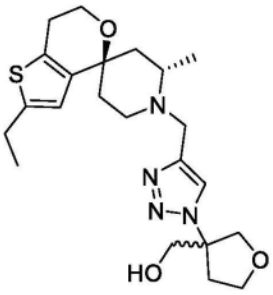
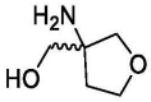
[0584]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
161			化合物 15	1H NMR (300 MHz, 氯仿-d) δ 8.25 (s, 1H), 6.46 (d, J = 1.8 Hz, 1H), 4.89 (ddd, J = 14.6, 8.3, 2.4 Hz, 1H), 4.80 - 4.70 (m, 2H), 4.41 - 4.29 (m, 1H), 3.95 - 3.79 (m, 2H), 3.63 (p, J = 7.5 Hz, 2H), 3.37 - 3.19 (m, 3H), 3.10 (tdd, J = 10.8, 7.7, 3.9 Hz, 1H), 2.77 (td, J = 7.7, 5.9 Hz, 4H), 2.51 - 2.40 (m, 1H), 2.35 - 2.15 (m, 4H), 2.08 - 1.92 (m, 3H), 1.60 (t, J = 6.3 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]+ 465.16
162			化合物 15	1H NMR (400 MHz, 氯仿-d) δ 7.71 (s, 1H), 6.49 (d, J = 1.1 Hz, 1H), 5.40 (tt, J = 7.8, 6.1 Hz, 1H), 4.58 - 4.38 (m, 4H), 4.12 - 4.06 (m, 1H), 3.96 - 3.81 (m, 3H), 3.06 (s, 3H), 2.84 - 2.55 (m, 7H), 1.97 - 1.82 (m, 3H), 1.77 - 1.68 (m, 1H), 1.29 (t, J = 7.5 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H)。[2] LCMS *m/z* [M+H]+ 466.315
163			化合物 15	LCMS *m/z* [M+H]+ 486.27

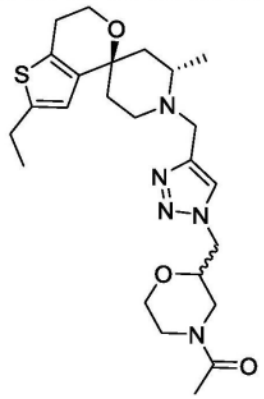
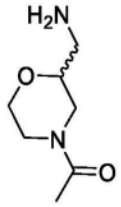
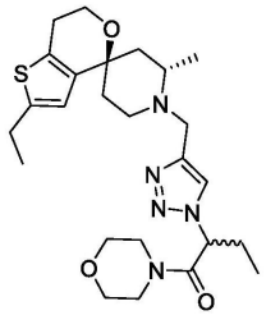
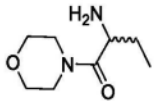
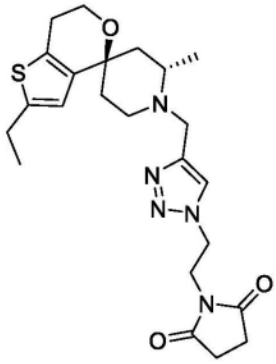
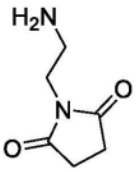
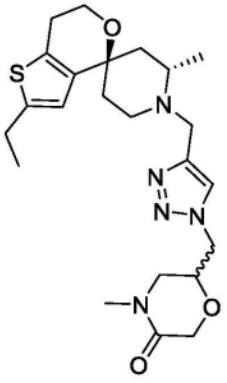
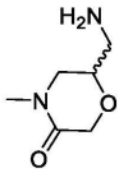
[0585]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
164			化合物 15	LCMS *m/z* [M+H]+ 488.29
165			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.56 (s, 1H), 6.47 (s, 1H), 6.21 (s, 2H), 4.69 (d, J = 14.3 Hz, 1H), 4.59 (d, J = 14.5 Hz, 1H), 3.89 - 3.76 (m, 2H), 3.62 (d, J = 3.8 Hz, 1H), 3.32 (s, 2H), 3.23 - 3.06 (m, 2H), 2.68 (s, 2H), 2.34 (s, 3H), 2.06 (t, J = 11.1 Hz, 4H), 1.46 (d, J = 6.3 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H)。[2] LCMS *m/z* [M+H]+ 429.215
166			化合物 15	LCMS *m/z* [M+H]+ 446.2

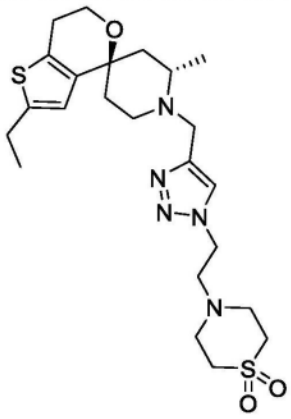
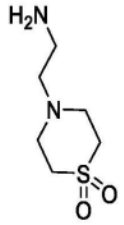
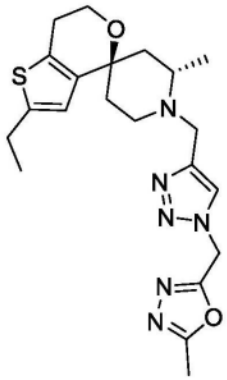
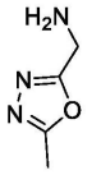
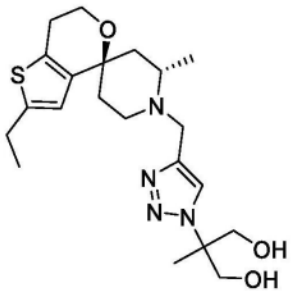
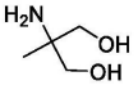
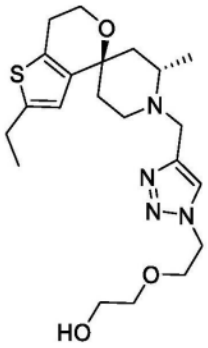
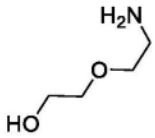
[0586]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
167			化合物 15	LCMS *m/z* [M+H]+ 428.38
168			化合物 15	LCMS *m/z* [M+H]+ 467.21
169			化合物 15	LCMS *m/z* [M+H]+ 463.27
170			化合物 15	LCMS *m/z* [M+H]+ 433.24

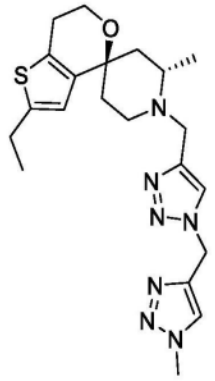
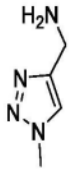
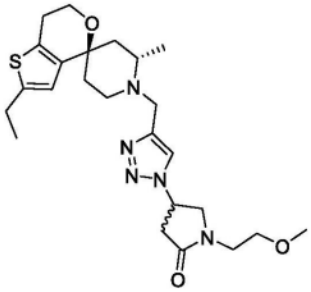
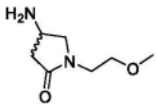
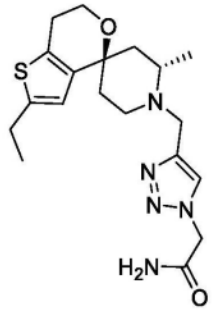
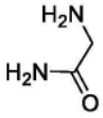
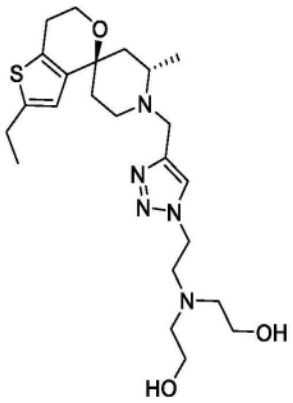
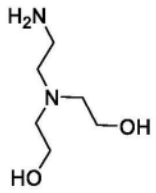
[0587]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
171			化合物 15	LCMS *m/z* [M+H]+ 474.25
172			化合物 15	LCMS *m/z* [M+H]+ 488.25
173			化合物 15	LCMS *m/z* [M+H]+ 458.22
174			化合物 15	LCMS *m/z* [M+H]+ 460.21

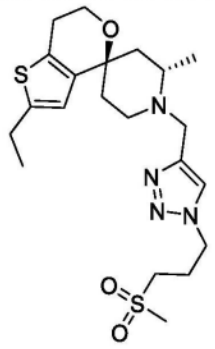
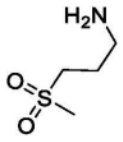
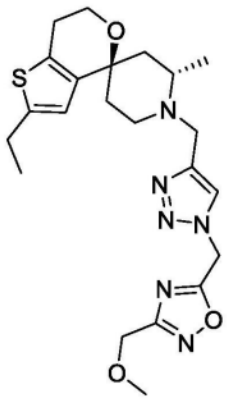
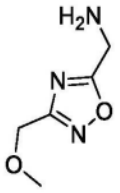
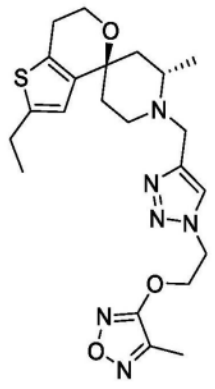
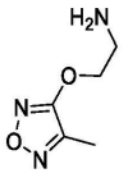
[0588]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
175			化合物 15	LCMS *m/z* [M+H]+ 494.05
176			化合物 15	LCMS *m/z* [M+H]+ 429.2
177			化合物 15	LCMS *m/z* [M+H]+ 421.21
178			化合物 15	LCMS *m/z* [M+H]+ 421.08

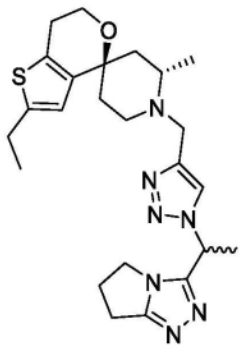
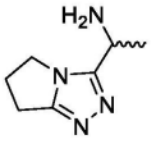
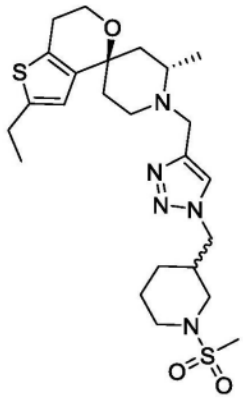
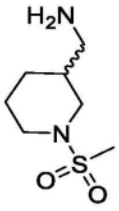
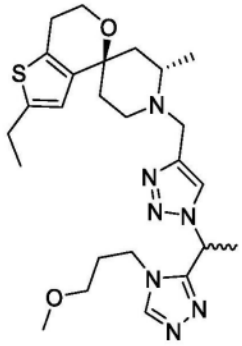
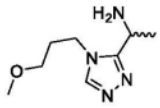
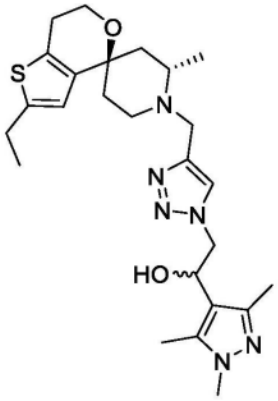
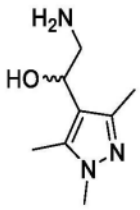
[0589]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
179			化合物 15	LCMS *m/z* [M+H]+ 428.25
180			化合物 15	LCMS *m/z* [M+H]+ 474.28
181			化合物 15	LCMS *m/z* [M+H]+ 390.04
182			化合物 15	LCMS *m/z* [M+H]+ 464.25

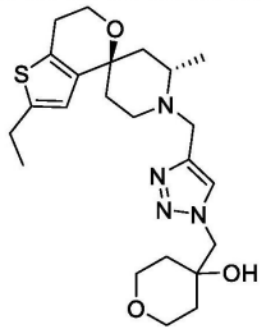
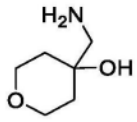
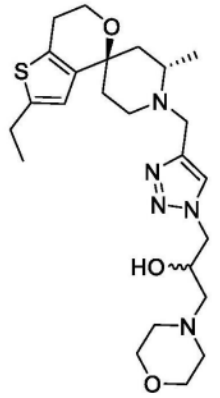
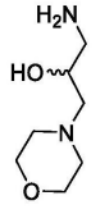
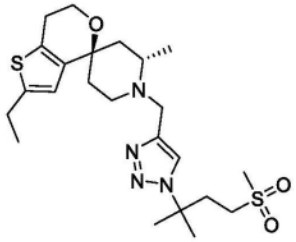
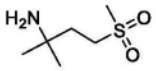
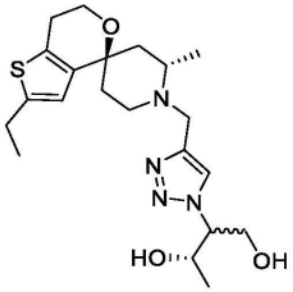
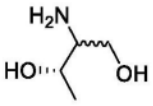
[0590]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
183			化合物 15	LCMS *m/z* [M+H]+ 453.2
184			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.19 (s, 1H), 8.57 (s, 1H), 6.47 (s, 1H), 6.27 (s, 2H), 5.52 (s, 1H), 4.74 - 4.55 (m, 3H), 4.54 (s, 3H), 3.95 - 3.75 (m, 3H), 3.73 (s, 1H), 3.61 (d, J = 5.9 Hz, 1H), 3.16 (s, 2H), 2.68 (s, 2H), 2.06 (t, J = 11.1 Hz, 4H), 1.45 (d, J = 6.5 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H)。[2] LCMS *m/z* [M+H]+ 459.17
185			化合物 15	1H NMR (400 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.46 (s, 1H), 6.47 (s, 1H), 4.93 (t, J = 4.7 Hz, 2H), 4.77 (t, J = 4.8 Hz, 2H), 4.63 (d, J = 14.1 Hz, 1H), 4.54 (d, J = 14.7 Hz, 1H), 3.78 (h, J = 6.1 Hz, 2H), 3.62 (d, J = 3.9 Hz, 1H), 3.27 (d, J = 12.3 Hz, 2H), 3.22 - 3.02 (m, 1H), 2.79 - 2.62 (m, 3H), 2.18 (s, 3H), 2.13 - 1.93 (m, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.25 (q, J = 7.3, 6.7 Hz, 2H), 1.20 (t, J = 7.5 Hz, 2H)。[2] LCMS *m/z* [M+H]+

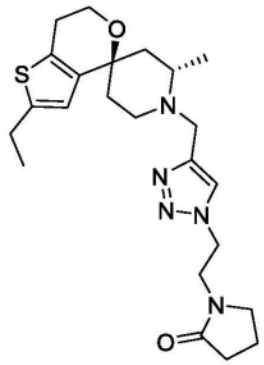
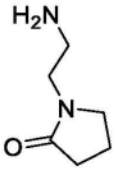
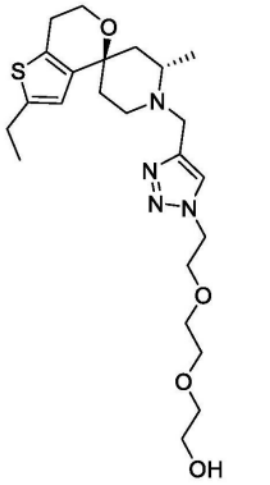
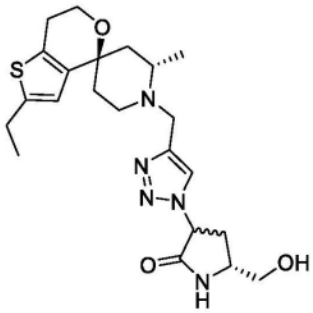
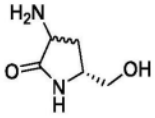
[0591]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				459.165
186			化合物 15	LCMS *m/z* [M+H]+ 468.25
187			化合物 15	LCMS *m/z* [M+H]+ 508.22
188			化合物 15	LCMS *m/z* [M+H]+ 500.31
189			化合物 15	LCMS *m/z* [M+H]+ 485.29

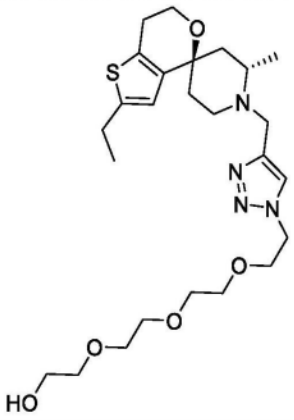
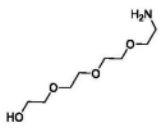
[0592]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
190			化合物 15	LCMS *m/z* [M+H]+ 447.24
191			化合物 15	LCMS *m/z* [M+H]+ 476.3
192			化合物 15	LCMS *m/z* [M+H]+ 481.22
193			化合物 15	LCMS *m/z* [M+H]+ 421.25

[0593]

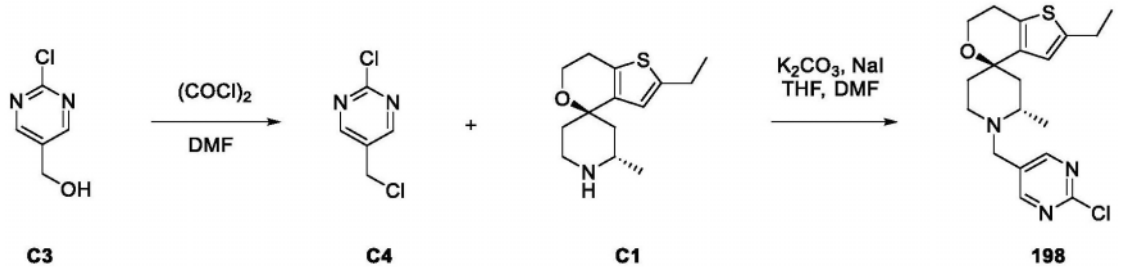
化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
194			化合物 15	LCMS *m/z* [M+H]+ 444.25
195			化合物 15	LCMS *m/z* [M+H]+ 465.26
196			化合物 15	LCMS *m/z* [M+H]+ 446.2

[0594]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
197			化合物 15	LCMS *m/z* [M+H]+ 509.27

[0595] 化合物198

[0596] (2′S,4R)-1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](198)

[0597] 

C3 C4 C1 198

[0598] 步骤1:2-氯-5-(氯甲基)嘧啶(C4)

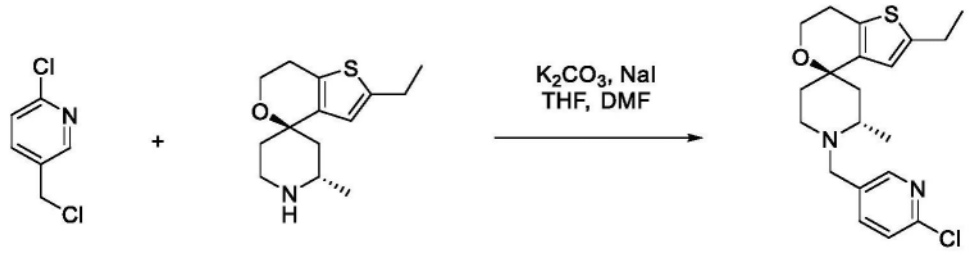
[0599] 在底烧瓶中装入(2-氯吡啶-5-基)甲醇(1g,6.92mmol)和亚硫酰氯(12.5mL,171mmol)。向悬浮液中添加DMF(32.5μL,0.42mmol),并将所得混合物在回流下加热5小时。加热后,混合物溶解形成澄清的黄色均匀溶液。完全转化后,将反应物冷却至环境温度,并且然后在真空中浓缩。将粗产物与二氯乙烷(x2)共沸,并在高真空下干燥至恒定质量,以得到C4(1.08g,92%)。^{1}H NMR(300MHz,氯仿-d)δ8.67(s,2H),4.57(d,J=0.6Hz,2H)。LCMS m/z 331.25$[M+H]^+$。

[0600] 步骤2:(2′S,4R)-1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](198)

[0601] 在40℃下将(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸盐)(2g,4.99mmol)、2-氯-5-(氯甲基)嘧啶(3g,6.07mmol)、K_2CO_3(2.2g,15.92mmol)和NaI(750mg,5.00mmol)于THF(18mL)和DMF(2mL)中的溶液加热过夜。将混合物用H_2O(30mL)稀释并用EtOAc(50mL×2)萃取。将合并的有机萃取物用2N $Na_2S_2O_3$(20mL)和盐水(20mL)洗涤,经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物通过硅胶色谱法纯化,用0至33% EtOAc/己烷洗脱,以得到198(1.34g,70%)。^{1}H NMR(300MHz,氯仿-d)δ8.62(s,2H),6.48(d,J=1.1Hz,1H),4.12(d,J=14.2Hz,1H),4.01-3.67(m,2H),3.19(d,J=14.2Hz,1H),2.89-2.61(m,5H),2.57-2.30(m,2H),2.00-1.53(m,4H),1.29(t,J=7.5Hz,3H),1.17(d,J=6.2Hz,3H)。LCMS m/z 378.07$[M+H]^+$。

[0602] 化合物199

[0603] (2′S,4R)-1′-[(6-氯-嘧啶-3-吡啶基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](199)

[0604] 

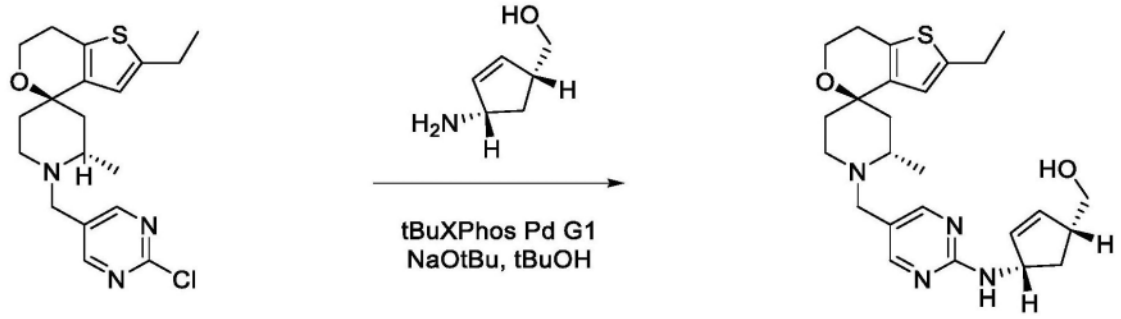
C5 C1 199

[0605] (2′S,4R)-1′-[(6-氯-嘧啶-3-吡啶基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](199)的制备

[0606] 在30℃下将(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸盐)S1(2g,4.99mmol)、2-氯-5-(氯甲基)吡啶(900mg,5.56mmol)、K_2CO_3(2.2g,15.92mmol)和NaI(750mg,5.00mmol)于THF(18mL)和DMF(2mL)中的混合物加热过夜。将混合物用H_2O(30mL)稀释并用EtOAc(50mL×2)萃取。将合并的有机萃取物用盐水(20mL)洗涤,经Na_2SO_4干燥,过滤并在真空中浓缩。将粗产物通过硅胶色谱法纯化,用0至33%EtOAc/己烷洗脱,以得到199(2.00g,92%)。^1H NMR(300MHz,氯仿-d)8.30(d,J=2.4Hz,1H),7.65(dd,J=8.2,2.4Hz,1H),7.23(d,J=8.2Hz,1H),6.45(d,J=1.1Hz,1H),4.06(d,J=13.8Hz,1H),3.84(tdd,J=11.3,8.8,4.9Hz,2H),3.11(d,J=13.8Hz,1H),2.87-2.55(m,5H),2.57-2.24(m,2H),1.96-1.58(m,4H),1.23(t,J=7.5Hz,3H),1.12(d,J=6.1Hz,3H)。LCMS m/z 377.13$[M+H]^+$。

[0607] 化合物200

[0608] [(1R,4S)-4-[[5-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]环戊-2-烯-1-基]甲醇(200)

[0609] 

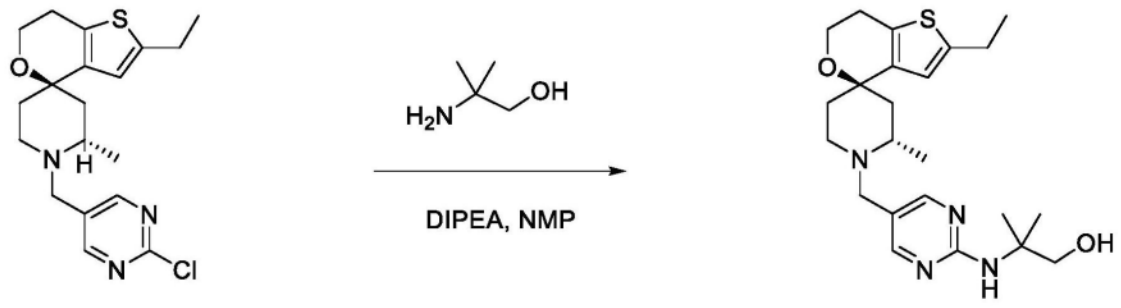
198 200

[0610] [(1R,4S)-4-[[5-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]环戊-2-烯-1-基]甲醇(200)的制备

[0611] 将(2′S,4R)-1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](14.5mg,0.037mmol)、((1R,4S)-4-氨基环戊-2-烯-1-基)甲醇(5.89mg,0.052mmol)、tBuXPhos Pd G1(2.41mg,0.0037mmol)于tBuOH(560μL)中的混合物用N_2脱气,并且然后添加2M NaOtBu于tBuOH(48μL)中的溶液。将所得混合物在85℃下加热3小时。在冷却至环境温度后,将反应物用MeOH淬灭。在真空中去除溶剂,并将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA),得到200(2.2mg,8.3%)。LCMS m/z 455.58$[M+H]^+$。

[0612] 化合物201

[0613] 2-[[5-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]-2-甲基-丙-1-醇(201)

[0614] 

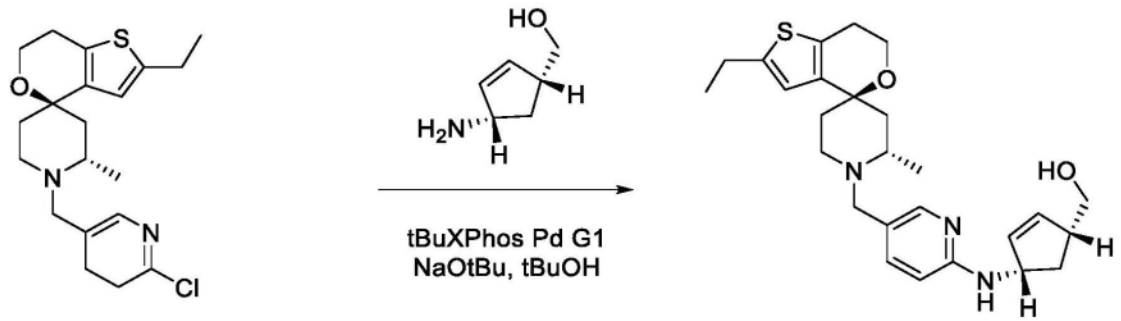
198 201

[0615] 2-[[5-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]-2-甲基-丙-1-醇(201)的制备

[0616] 向2-氨基-2-甲基-丙-1-醇(50mg,0.56mmol)和(2′S,4R)-1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]198(30mg,0.069mmol)于NMP(2mL)中的混合物中添加DIPEA(51mg,0.39mmol)。将反应物在230℃下在微波中加热6小时。在冷却至rt后,将反应物用DCM稀释,用H_2O(x3)洗涤。将有机层分离并在真空中浓缩。将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA),得到呈TFA盐的201(3.6mg,9%)。^1H NMR(300MHz,甲醇-d4)δ8.24(s,2H),6.49(d,J=1.0Hz,1H),3.97(d,J=13.6Hz,1H),3.92-3.81(m,2H),3.67(s,2H),3.21(d,J=13.6Hz,1H),2.78-2.61(m,6H),2.44(td,J=10.9,5.3Hz,1H),1.87-1.66(m,4H),1.38(s,6H),1.27-1.20(m,6H)。LCMS m/z 431.49$[M+H]^+$。

[0617] 化合物202

[0618] 5-[[(2′S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]-N-甲基-吡啶-2-胺(202)

[0619] 

199 202

[0620] 5-[[(2′S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]-N-甲基-吡啶-2-胺(202)的制备

[0621] 将(2′S)-1′-[(6-氯-3-吡啶基)甲基]-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]199(15mg,0.038mmol)、((1R,4S)-4-氨基环戊-2-烯-1-基)甲醇(5.21mg,0.046mmol)、tBuXPhos Pd G1(2.50mg,0.0038mmol)于tBuOH(500μL)中的混合物用N_2脱气,并且然后添加2M NaOtBu于tBuOH(42μL)中的溶液。将所得混合物在60℃下加热3小时。在冷却至环境温度后,将反应物用MeOH淬灭。在真空中去除溶剂,并将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1% TFA),得到202(11.9mg,49%)。^1H NMR

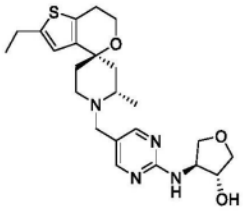
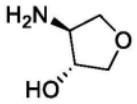
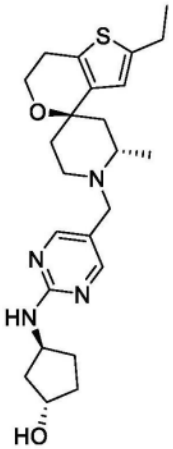
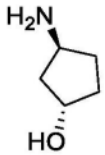
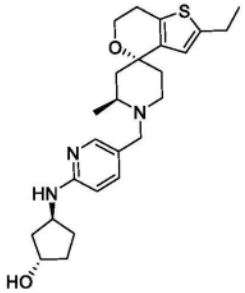
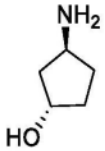
(300MHz,氯仿-d)δ8.29(dd,J＝18.9,9.3Hz,1H),7.99(s,1H),7.03(d,J＝9.6Hz,1H),6.49(s,1H),6.12-6.02(m,1H),5.95(s,1H),5.91-5.81(m,1H),4.84-4.62(m,2H),4.45(s,1H),4.02-3.49(m,6H),3.26-2.88(m,3H),2.77(q,J＝7.7Hz,4H),2.58(dt,J＝14.1,8.7Hz,1H),2.36(q,J＝13.4,12.3Hz,2H),2.12-1.91(m,2H),1.83(dt,J＝14.2,3.2Hz,1H),1.60(dd,J＝6.5,3.6Hz,3H),1.27(t,J＝7.5Hz,3H)。

[0622] 化合物203-231

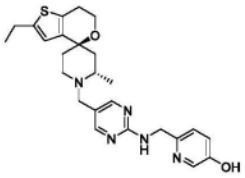
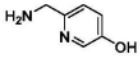
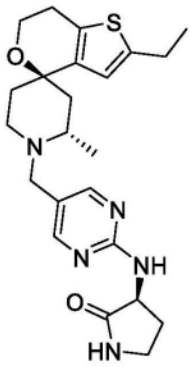
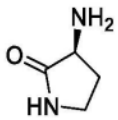
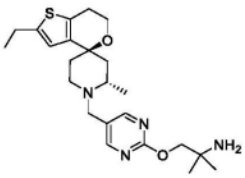
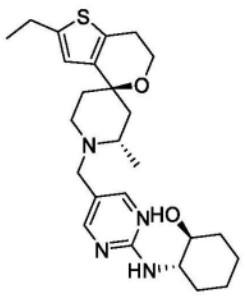
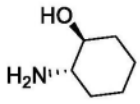
[0623] 化合物203-231(参见表4)由198或199使用适当的胺按照200-202的一般方法制备。除非另有说明,否则所有胺均从商业来源获得。表4和随附脚注中注明了对方法的任何修改。

[0624] 表4:化合物203-231的结构和物理化学数据

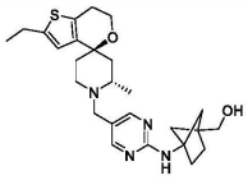
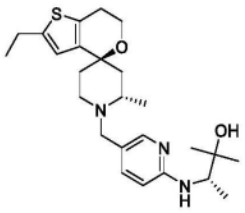
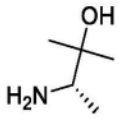
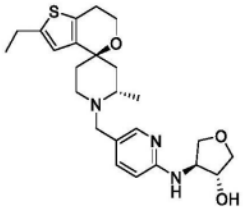
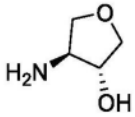
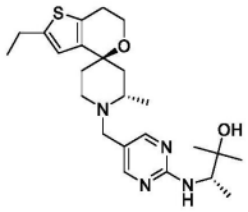
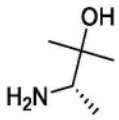
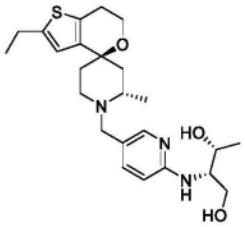
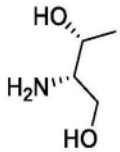
[0625]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
203			**化合物 200**	LCMS *m/z* [M+H]$^+$ 445.35
204			**化合物 200**	LCMS *m/z* [M+H]$^+$ 443.33
205			**化合物 202**	1H NMR (300 MHz, 氯仿-d) δ 8.26 (d, J = 9.4 Hz, 1H), 7.88 (s, 1H), 6.96 (d, J = 9.5 Hz, 1H), 6.50 (s, 1H), 4.76 (d, J = 13.5 Hz, 1H), 4.54 (d, J = 5.7 Hz, 1H), 4.20 (s, 1H), 4.06 - 3.78 (m, 2H), 3.64 - 3.46 (m, 1H), 3.19 (d, J = 11.5 Hz, 1H), 2.98 (t, J = 12.4 Hz, 1H), 2.77 (q, J = 7.8 Hz, 5H), 2.40 (dd, J = 16.1, 9.5 Hz, 3H), 2.30 - 2.12 (m, 2H), 1.98 (dt, J = 19.6, 10.7 Hz,

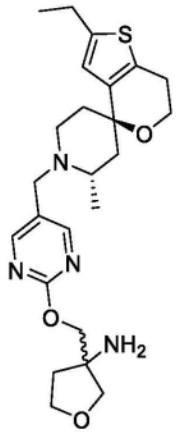
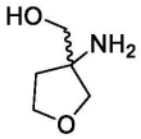
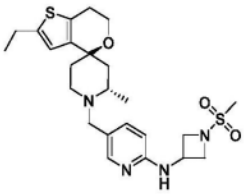
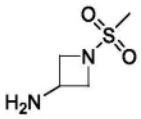
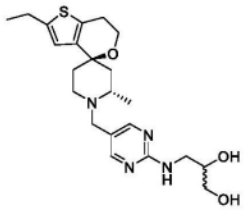
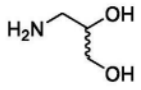
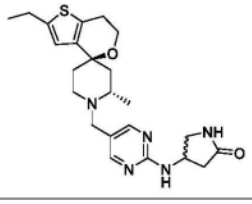
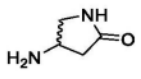
[0626]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				3H), 1.83 - 1.68 (m, 2H), 1.61 (d, J = 6.4 Hz, 4H), 1.27 (t, J = 7.5 Hz, 4H)。LCMS *m/z* [M+H]$^+$ 442.53
206			**化合物 200**	LCMS *m/z* [M+H]$^+$ 466.1
207			**化合物 201**	1H NMR (300 MHz, 氯仿-d) δ 8.42 (s, 2H), 6.54 (s, 1H), 5.32 (d, J = 3.2 Hz, 1H), 4.54 (s, 2H), 3.86 (d, J = 16.6 Hz, 3H), 3.51 (d, J = 3.3 Hz, 5H), 3.44 - 3.13 (m, 4H), 3.13 - 2.60 (m, 6H), 2.60 - 2.19 (m, 2H), 2.03 (d, J = 18.1 Hz, 3H), 1.27 (dd, J = 8.7, 6.2 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 442.2
208			**化合物 200**	1H NMR (300 MHz, 甲醇-d4) δ 8.56 (s, 2H), 6.48 (d, J = 1.1 Hz, 1H), 4.21 (s, 2H), 4.10 (d, J = 13.8 Hz, 1H), 3.87 (td, J = 5.7, 4.3 Hz, 2H), 2.79 - 2.56 (m, 7H), 2.45 (td, J = 11.4, 4.2 Hz, 1H), 1.87 - 1.67 (m, 4H), 1.27 (d, J = 4.1 Hz, 6H), 1.25 - 1.20 (m, 6H)。LCMS *m/z* [M+H]$^+$ 431.4
209			**化合物 200**	LCMS *m/z* [M+H]$^+$ 457.24

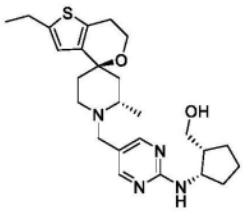
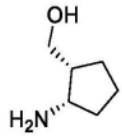
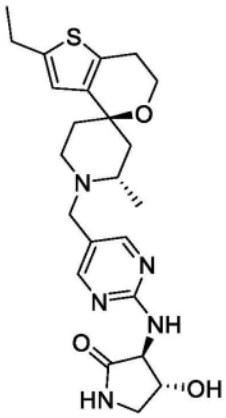
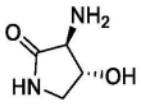
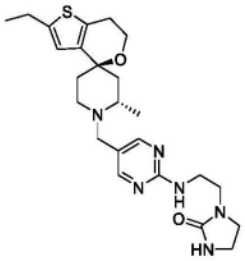
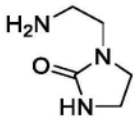
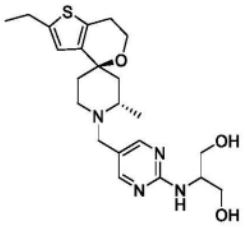
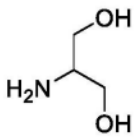
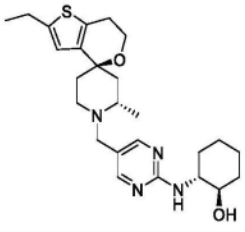
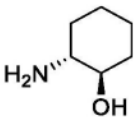
[0627]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
210			**化合物 200**	LCMS *m/z* [M+H]$^+$ 469.26
211			**化合物 202**	1H NMR (300 MHz, 氯仿-d) δ 8.13 (s, 2H), 7.15 (d, J = 9.6 Hz, 1H), 6.42 (s, 1H), 4.74 (d, J = 13.4 Hz, 1H), 4.01 - 3.80 (m, 2H), 3.78 - 3.57 (m, 3H), 3.19 (dd, J = 35.8, 12.3 Hz, 2H), 2.92 - 2.67 (m, J = 6.1 Hz, 4H), 2.41 - 1.96 (m, 4H), 1.61 (s, 3H), 1.41 - 1.18 (m, 12H)。LCMS *m/z* [M+H]$^+$ 444.25
212			**化合物 202**	1H NMR (300 MHz, 甲醇-d4) δ 8.15 (s, 1H), 7.86 (d, J = 9.2 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.49 (s, 1H), 4.75 (d, J = 13.7 Hz, 1H), 4.35 - 3.60 (m, 10H), 2.76 (d, J = 7.1 Hz, 5H), 2.19 - 1.99 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.5 Hz, 4H)。LCMS *m/z* [M+H]$^+$ 444.21
213			**化合物 200**	LCMS *m/z* [M+H]$^+$ 445.29
214			**化合物 202**	1H NMR (300 MHz, 甲醇-d4) δ 8.14 - 7.91 (m, 2H), 7.20 (d, J = 9.3 Hz, 1H), 6.50 (s, 1H), 5.50 (s, 1H), 4.77 (d, J = 13.6 Hz, 1H), 4.11 - 3.56 (m, 7H), 2.76 (d, J = 7.1 Hz, 4H), 2.21 - 1.95 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H), 1.35 - 1.18 (m, 7H), 0.88 (s, 1H)。LCMS *m/z* [M+H]$^+$ 446.27

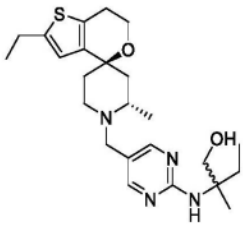
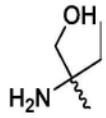
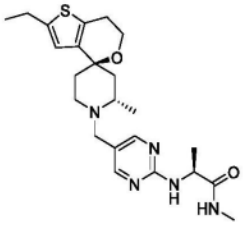
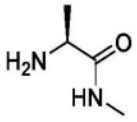
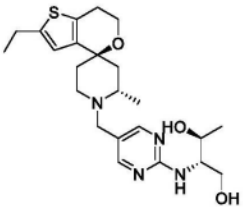
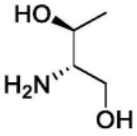
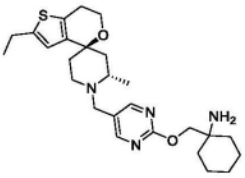
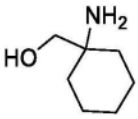
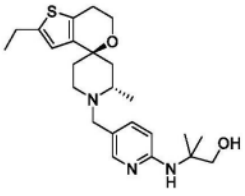
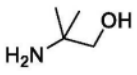
[0628]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
215			**化合物 200**	LCMS *m/z* [M+H]$^+$ 459.58
216			**化合物 202**	1H NMR (300 MHz, 甲醇-d4) δ 8.26 - 8.15 (m, 2H), 7.18 (dd, J = 9.1, 0.9 Hz, 1H), 6.58 (d, J = 1.1 Hz, 1H), 4.83 (d, J = 6.6 Hz, 1H), 4.67 (tt, J = 7.2, 5.5 Hz, 1H), 4.39 - 4.30 (m, 2H), 4.07 (d, J = 13.6 Hz, 1H), 4.03 - 3.90 (m, 4H), 3.71 (ddd, J = 12.0, 6.4, 3.0 Hz, 1H), 3.27 - 3.16 (m, 2H), 3.01 (s, 3H), 2.80 - 2.71 (m, 4H), 2.39 - 2.23 (m, 2H), 2.17 - 1.96 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 491.19
217			**化合物 200**	LCMS *m/z* [M+H]$^+$ 433.24
218			**化合物 200**	LCMS *m/z* [M+H]$^+$ 442.32

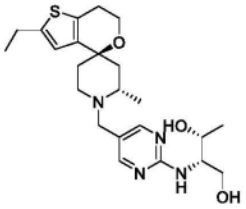
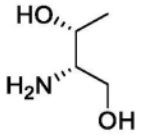
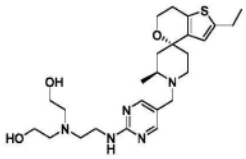
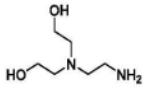
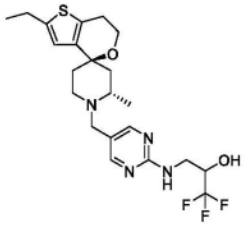
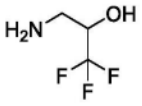
[0629]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
219			**化合物 200**	LCMS *m/z* [M+H]$^+$ 457.24
220			**化合物 200**	1H NMR (400 MHz, 甲醇-d4) δ 8.90 (d, J = 36.8 Hz, 2H), 6.59 (t, J = 1.0 Hz, 1H), 4.88 (d, J = 13.9 Hz, 1H), 4.81 - 4.52 (m, 2H), 4.23 - 3.61 (m, 6H), 3.33 (d, J = 2.6 Hz, 1H), 3.21 (dd, J = 9.9, 7.6 Hz, 1H), 2.86 - 2.71 (m, 4H), 2.38 - 1.97 (m, 4H), 1.62 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H)。[3] LCMS *m/z* [M+H]$^+$ 458.27 [3]
221			**化合物 200**	LCMS *m/z* [M+H]$^+$ 471.09
222			**化合物 200**	LCMS *m/z* [M+H]$^+$ 433.24
223			**化合物 200**	LCMS *m/z* [M+H]$^+$ 457.28

[0630]

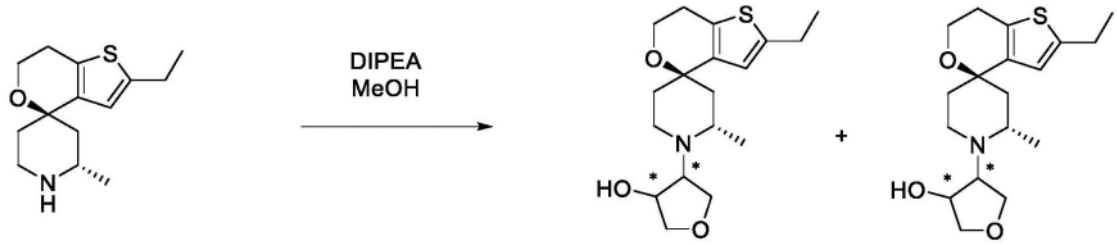
化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
224			**化合物 201**	1H NMR (300 MHz, 甲醇-d4) δ 8.42 (s, 2H), 6.48 (s, 1H), 4.66 (d, J = 13.8 Hz, 1H), 4.11 - 3.52 (m, 6H), 2.76 (q, J = 7.3, 6.6 Hz, 5H), 2.22 - 1.90 (m, 6H), 1.74 (dtd, J = 14.9, 7.7, 5.4 Hz, 1H), 1.56 (d, J = 6.4 Hz, 3H), 1.33 (s, 3H), 1.24 (t, J = 7.5 Hz, 3H), 1.08 - 0.75 (m, 3H)。LCMS *m/z* [M+H]$^+$ 445.26
225			**化合物 201**	LCMS *m/z* [M+H]$^+$ 444.21
226			**化合物 201**	1H NMR (300 MHz, 甲醇-d4) δ 8.42 (d, J = 3.0 Hz, 2H), 6.47 (s, 1H), 4.67 (d, J = 13.9 Hz, 1H), 4.45 - 3.49 (m, 7H), 2.78 (dt, J = 14.2, 6.5 Hz, 5H), 2.65 (s, 1H), 2.46 - 1.88 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H), 1.44 - 0.98 (m, 6H)。LCMS *m/z* [M+H]$^+$ 447.24
227			**化合物 200**	LCMS *m/z* [M+H]$^+$ 471.09
228			**化合物 202**	1H NMR (300 MHz, 甲醇-d4) δ 8.33 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.7, 2.5 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.48 (s, 1H), 4.80 (d, J = 13.6 Hz, 1H), 4.38 (s, 2H), 4.15 (d, J = 13.5 Hz, 1H), 3.92 (h, J = 5.9 Hz, 2H), 3.76 - 3.56 (m, 1H), 3.21 (td, J = 11.8, 7.6 Hz, 2H), 2.82 - 2.68 (m,

[0631]

化合物	结构	胺	方法	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
				4H), 2.21 - 1.97 (m, 4H),1.59 (d, J = 6.5 Hz, 3H), 1.46 (s, 6H), 1.25 (q, J = 7.5, 6.9 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 430.6
229			**化合物 201**	1H NMR (300 MHz, 甲醇-d4) δ 8.45 (s, 2H), 6.48 (s, 1H), 4.68 (d, J = 13.8 Hz, 1H), 4.18 - 3.86 (m, 5H), 3.86 - 3.42 (m, 4H), 2.91 - 2.59 (m, 5H), 2.34 - 1.91 (m, 5H), 1.56 (d, J = 6.4 Hz, 3H), 1.37 - 1.13 (m, 7H)。LCMS *m/z* [M+H]$^+$ 447.24
230			**化合物 200**	LCMS *m/z* [M+H]$^+$ 490.31
231			**化合物 200**	LCMS *m/z* [M+H]$^+$ 471.19

[0632] 化合物232

[0633] 4-[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(232)和4-[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(233)

[0634] 

C1 232 233

[0635] 4-[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(232)和4-[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(233)的制备

[0636] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸盐)S1(36mg,0.088mmol)于MeOH(1mL)中的溶液中添加DIPEA(100μL,0.57mmol)和3,6-二氧杂双环[3.1.0]己烷(43mg,0.50mmol)。将混合物在微波中在150℃加热6小时。冷

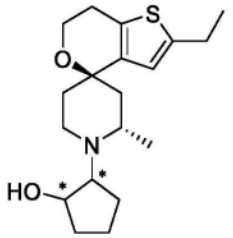
却至环境温度后,在真空中去除挥发物,并将粗产物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.2%甲酸)以得到232(11.5mg,38%)和对应反式非对映异构体233(10mg,33%),化合物232:^{1}H NMR(300MHz,氯仿-d)δ9.16(s,1H),6.51(d,J=1.1Hz,1H),4.91(t,J=6.6Hz,1H),4.36(dd,J=10.2,7.2Hz,1H),4.21(d,J=11.9Hz,1H),4.12(d,J=5.9Hz,1H),4.05-3.79(m,2H),3.60(dd,J=10.2,5.9Hz,1H),3.51-3.31(m,1H),2.92-2.72(m,4H),2.59(s,4H),2.44-2.24(m,1H),2.21-1.99(m,2H),1.46(d,J=6.6Hz,3H),1.29(t,J=7.5Hz,3H)。LCMS m/z 338.21[M+H]$^+$。化合物233:^{1}H NMR(300MHz,氯仿-d)δ8.56(s,1H),6.54(d,J=1.0Hz,1H),4.73(t,J=6.3Hz,1H),4.35-4.01(m,3H),3.99-3.79(m,2H),3.60(dd,J=9.8,5.9Hz,1H),3.49(d,J=10.3Hz,1H),3.18(d,J=10.9Hz,1H),2.98(t,J=12.4Hz,1H),2.86-2.71(m,5H),2.40-2.20(m,1H),2.13(d,J=12.0Hz,1H),1.98(d,J=14.4Hz,2H),1.43(d,J=6.4Hz,3H),1.28(t,J=7.6Hz,3H)。LCMS m/z 338.21[M+H]$^+$。

[0637] 化合物234-263

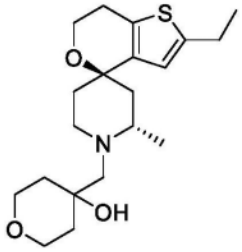
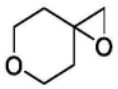
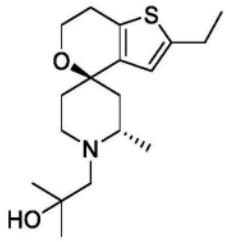
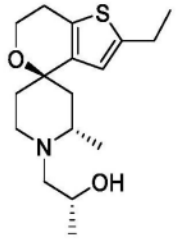
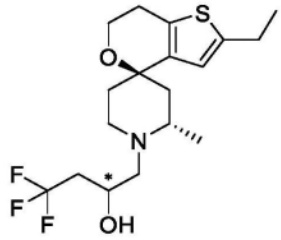
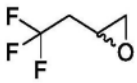
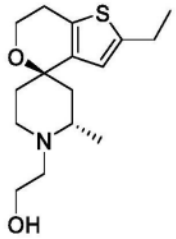
[0638] 化合物234-263(参见表5)由C1使用适当的环氧化物制备,采用232和233所述的环氧化物开环方法。除非另有说明,否则所有环氧化物均从商业来源获得。表5和随附脚注中注明了对方法的任何修改。

[0639] 表5:化合物234-263的结构和物理化学数据

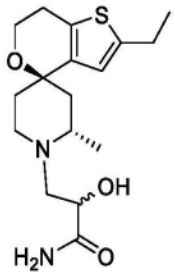
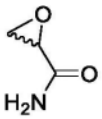
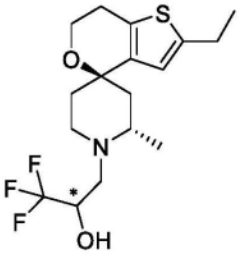
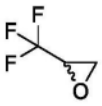
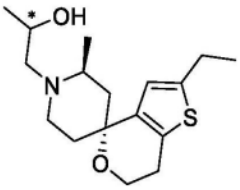
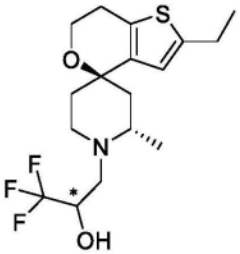
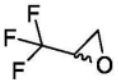
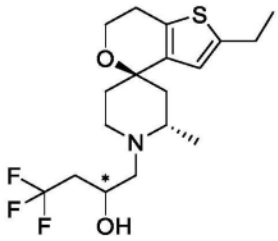
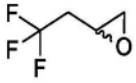
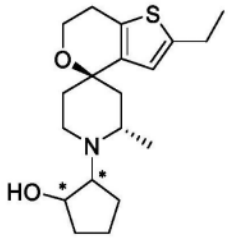
[0640]

化合物	结构	环氧化物	^{1}H NMR;LCMS *m/z*[M+H]$^+$。
234			LCMS *m/z* [M+H]$^+$ 336.22

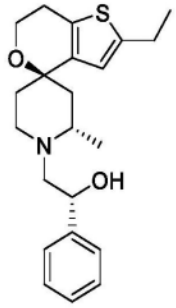
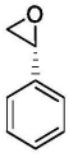
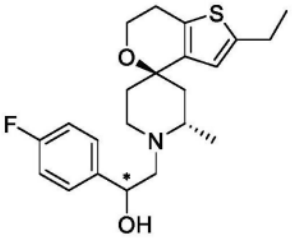
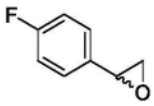
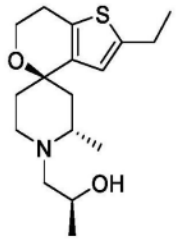
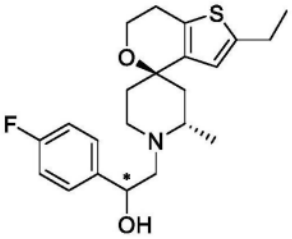
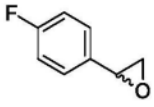
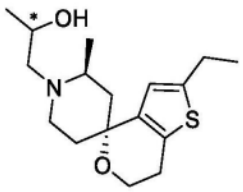
[0641]

化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
235			1H NMR (300 MHz, 氯仿-d) δ 8.45 (s, 1H), 6.55 (s, 1H), 4.01 - 3.69 (m, 6H), 3.49 - 3.14 (m, 3H), 2.89 - 2.69 (m, 5H), 2.65 (s, 1H), 2.45 (s, 2H), 1.98 (q, J = 19.4, 17.1 Hz, 3H), 1.82 - 1.49 (m, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.29 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 366.25
236			1H NMR (300 MHz, 氯仿-d) δ 8.67 (s, 1H), 6.55 (s, 1H), 4.01 - 3.76 (m, 2H), 3.58 (s, 1H), 3.33 - 3.01 (m, 3H), 2.77 (dd, J = 9.5, 6.0 Hz, 4H), 2.66 - 2.48 (m, 1H), 2.45 - 2.12 (m, 2H), 2.04 - 1.78 (m, 2H), 1.48 - 1.10 (m, 12H)。LCMS *m/z* [M+H]$^+$ 324.26
237			1H NMR (300 MHz, 氯仿-d) δ 8.57 (s, 1H), 6.53 (d, J = 1.0 Hz, 1H), 3.90 (tdd, J = 11.1, 8.6, 4.7 Hz, 3H), 3.51 - 3.36 (m, 1H), 3.33 - 3.13 (m, 2H), 2.92 - 2.71 (m, 5H), 2.67 (d, J = 15.6 Hz, 1H), 2.53 - 2.24 (m, 2H), 2.12 - 1.79 (m, 2H), 1.43 (d, J = 6.4 Hz, 3H), 1.33 - 1.16 (m, 6H)。LCMS *m/z* [M+H]$^+$ 310.22
238			LCMS *m/z* [M+H]$^+$ 378.17
239			1H NMR (300 MHz, 氯仿-d) δ 8.25 (s, 1H), 6.58 (s, 1H), 4.06 (td, J = 4.4, 3.6, 1.5 Hz, 2H), 4.02 - 3.84 (m, 3H), 3.69 (d, J = 3.6 Hz, 1H), 3.60 (s, 1H), 3.37 (s, 1H), 3.05 (d, J = 13.9 Hz, 1H), 2.92 - 2.70 (m, 4H), 2.62 - 2.20 (m, 2H), 2.14 - 1.93 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 296.18

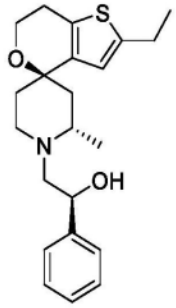
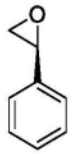
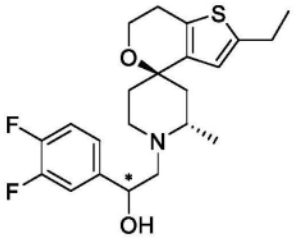
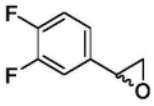
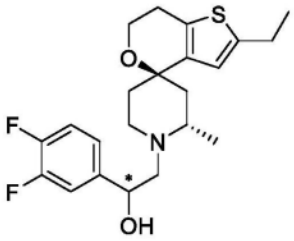
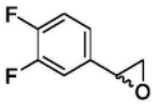
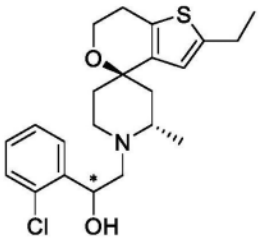
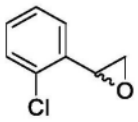
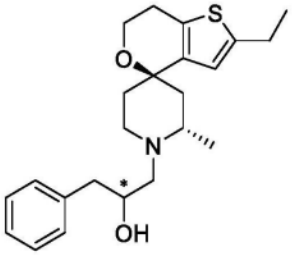
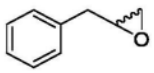
[0642]

化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
240			1H NMR (300 MHz, 氯仿-d) δ 6.52 (s, 1H), 5.53 (s, 1H), 4.70 (d, J = 9.7 Hz, 1H), 4.09 - 3.78 (m, 3H), 3.67 (d, J = 11.9 Hz, 1H), 3.50 (s, 1H), 3.30 (t, J = 12.9 Hz, 1H), 3.01 - 2.89 (m, 1H), 2.78 (t, J = 7.0 Hz, 4H), 2.36 (d, J = 13.2 Hz, 2H), 2.00 (d, J = 12.2 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.29 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 339.21
241			LCMS *m/z* [M+H]$^+$ 364.18
242			1H NMR (400 MHz, DMSO-d6): δ 6.59 (s, 1H), 4.07 (bs, 1H), 3.85-3.71 (m, 3H), 2.74-2.57 (m, 8H), 2.07-1.52 (m, 5H), 1.23-1.17 (t, J = 7.6 Hz, 3H), 1.04-1.03 (d, J = 5.2 Hz, 3H), 0.98 (s, 3H)。LCMS *m/z* [M+H]$^+$ 310.2
243			LCMS *m/z* [M+H]$^+$ 364.18
244			LCMS *m/z* [M+H]$^+$ 378.22
245			LCMS *m/z* [M+H]$^+$ 336.22

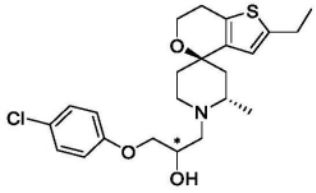
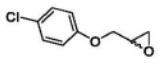
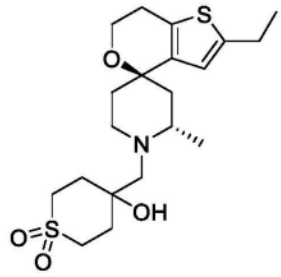
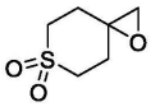
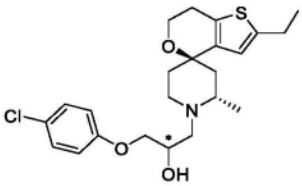
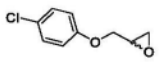
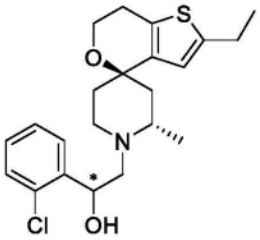
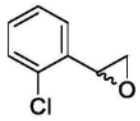
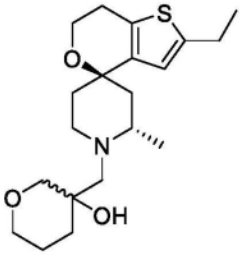
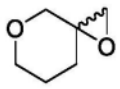
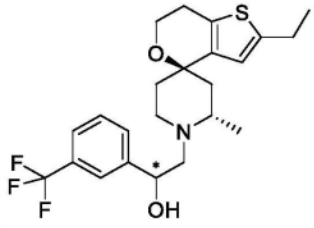
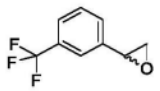
[0643]

化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
246			LCMS*m/z* [M+H]$^+$ 372.21
247			1H NMR (300 MHz, 氯仿-d) δ 8.56 (s, 1H), 6.54 (d, J = 1.0 Hz, 1H), 4.73 (t, J = 6.3 Hz, 1H), 4.35 - 4.01 (m, 3H), 3.99 - 3.79 (m, 2H), 3.60 (dd, J = 9.8, 5.9 Hz, 1H), 3.49 (d, J = 10.3 Hz, 1H), 3.18 (d, J = 10.9 Hz, 1H), 2.98 (t, J = 12.4 Hz, 1H), 2.86 - 2.71 (m, 5H), 2.40 - 2.20 (m, 1H), 2.13 (d, J = 12.0 Hz, 1H), 1.98 (d, J = 14.4 Hz, 2H), 1.43 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.6 Hz, 3H)。LCMS *m/z* [M+H]+ 338.21
248			LCMS *m/z* [M+H]$^+$ 390.23
249			LCMS *m/z* [M+H]$^+$ 310.22
250			LCMS *m/z* [M+H]$^+$ 390.23

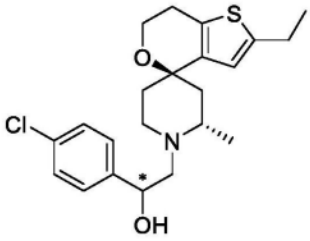
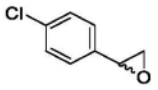
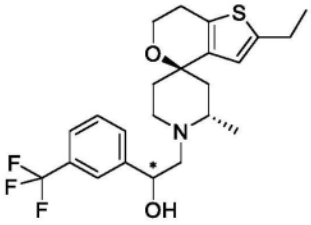
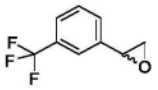
[0644]

化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
251			1H NMR (400 MHz, DMSO-d6): δ 6.59 (s, 1H), 4.33 (bs, 1H), 3.86-3.72 (m, 3H), 2.73-2.64 (m, 6H), 2.51-2.49 (m, 2H), 2.10-1.51 (m, 5H), 1.21-1.17 (t, J = 7.6 Hz, 3H), 1.06-1.05 (d, J = 6.0 Hz, 3H), 0.98-0.97 (d, J = 5.2 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 310.2
252			1H NMR (300 MHz, 氯仿-d) δ 8.40 (s, 1H), 7.63 - 7.39 (m, 5H), 6.44 (s, 1H), 4.57 (dd, J = 7.9, 5.1 Hz, 1H), 4.44 (dd, J = 12.2, 7.9 Hz, 1H), 4.19 (dd, J = 12.1, 5.0 Hz, 1H), 4.01 - 3.72 (m, 2H), 3.50 (d, J = 14.6 Hz, 1H), 3.46 - 3.37 (m, 1H), 3.27 (d, J = 11.9 Hz, 1H), 2.84 - 2.66 (m, 5H), 2.35 - 2.15 (m, 1H), 1.94 - 1.72 (m, 2H), 1.49 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.5 Hz, 3H)。LCMS *m/z* [M+H]$^+$ 372.25
253			LCMS *m/z* [M+H]$^+$ 408.2
254			LCMS *m/z* [M+H]$^+$ 408.2
255			LCMS *m/z* [M+H]$^+$ 406.17

[0645]

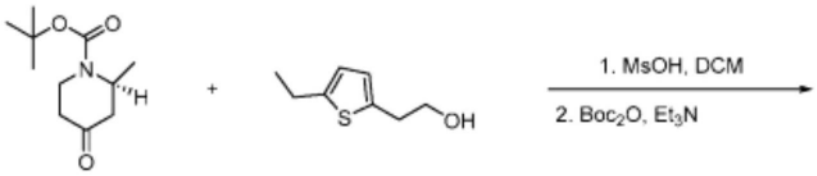
化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
256			LCMS *m/z* [M+H]$^+$ 386.21
257			LCMS *m/z* [M+H]$^+$ 436.15
258			1H NMR (300 MHz, 氯仿-d) δ 6.49 (s, 1H), 3.91 (hept, J = 5.8 Hz, 2H), 3.63 - 3.34 (m, 2H), 3.04 (d, J = 37.0 Hz, 5H), 2.90 (d, J = 14.9 Hz, 1H), 2.78 (t, J = 6.1 Hz, 4H), 2.48 (d, J = 14.0 Hz, 1H), 2.16 (q, J = 15.5, 14.8 Hz, 6H), 1.87 (d, J = 17.8 Hz, 3H), 1.30 (t, J = 7.5 Hz, 3H), 1.25 - 1.10 (m, 3H)。LCMS *m/z* [M+H]$^+$ 414.16
259			LCMS *m/z* [M+H]$^+$ 436.15
260			LCMS *m/z* [M+H]$^+$ 406.17
261			1H NMR (300 MHz, 氯仿-d) δ 8.39 (s, 1H), 6.58 (d, J = 8.1 Hz, 1H), 4.08 - 3.74 (m, 6H), 3.66 - 3.17 (m, 5H), 2.98 (d, J = 13.6 Hz, 1H), 2.79 (q, J = 7.6, 6.5 Hz, 4H), 2.46 (s, 2H), 2.15 - 1.72 (m, 4H), 1.69 - 1.52 (m, 1H), 1.46 (d, J = 6.4 Hz, 3H), 1.29 (td, J = 7.5, 1.0 Hz, 3H)。

[0646]

化合物	结构	环氧化物	^{1}H NMR；LCMS *m/z*[M+H]$^+$。
			LCMS *m/z* [M+H]$^+$ 366.25
262			LCMS *m/z* [M+H]$^+$ 440.17
263			LCMS *m/z* [M+H]$^+$ 406.17

[0647] 制备S9

[0648] (2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S9)



[0649]



C6 S9

[0650] 步骤1:(2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C6)

[0651] 将2-(5-乙基-2-噻吩基)乙醇(103mg,0.622mmol)、(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(144mg,0.675mmol)于DCM(1mL)中的溶液冷却至-78℃。逐滴添加MsOH(0.1mL,1.54mmol),并将所得溶液搅拌2小时。添加三氟甲磺酸(0.1mL,1.13mmol),并将反应物在-78℃下搅拌1小时。添加水(15mL)和DCM(15mL),并使用2N NaOH将pH调节至约10。将水层用DCM(3×15mL)萃取,并过滤以产生黄色凝胶。将粗产物溶解在DCM(1mL)中,并添加Et_3N(0.2mL,1.43mmol),随后添加boc酸酐(0.2mL,0.870mmol)。将反应混合物在rt下搅拌3小时。将溶液用DCM稀释并且用水(10mL)洗涤。将水层用DCM(2×10mL)萃取,经Na_2SO_4干燥,并过滤。通过硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生(2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C6(117mg,50%)。1H NMR(300MHz,甲醇-d4)δ6.46(s,1H),4.43-4.29(m,1H),3.97-3.83(m,3H),2.84-2.61(m,4H),1.94-1.76(m,4H),1.48(s,9H),1.33(d,J=7.1Hz,3H),1.24(t,J=7.5Hz,3H)。(在MeOH峰

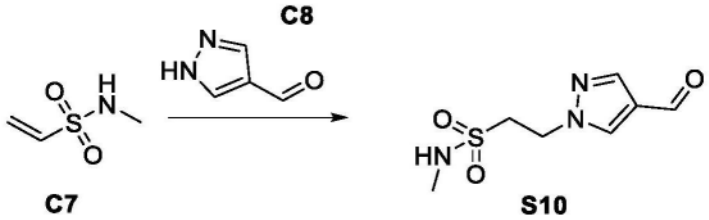
下1H)。

[0652] 步骤2:(2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S9

[0653] 向(2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C6(105mg,0.299mmol)于DCM(1mL)中的经搅拌的溶液中添加含4M HCl的二噁烷(0.16mL的4M,0.660mmol),并将反应物在rt下搅拌4小时。浓缩并通过制备型HPLC纯化(流动相A:-0.1% FA(水性),流动相B:-乙腈)以产生(2′S,4S)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S9(65mg,72%)。^{1}H NMR(300MHz,甲醇-d4)δ6.56(d,J=1.6Hz,1H),3.94(t,J=5.4Hz,2H),3.81-3.70(m,1H),3.50(td,J=12.4,3.6Hz,1H),3.19(dt,J=13.0,4.1Hz,1H),2.82-2.70(m,4H),2.15(td,J=14.7,14.2,4.8Hz,2H),2.02(d,J=15.2Hz,2H),1.55(d,J=7.1Hz,3H),1.25(t,J=7.5Hz,3H)。

[0654] 制备S10

[0655] 2-(4-甲酰基吡唑基-1-基)-N-甲基-乙磺酰胺(S10)

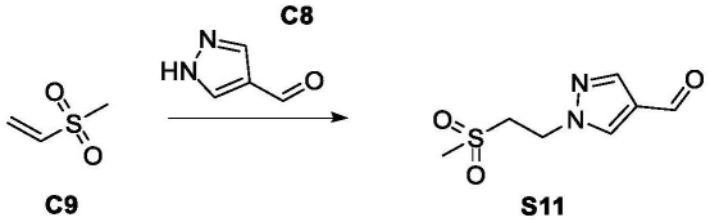
[0656] 

[0657] 步骤1:2-(4-甲酰基吡唑基-1-基)-N-甲基-乙磺酰胺(S10)

[0658] 将1H-吡唑-4-甲醛C8(250mg,2.60mmol)、N-甲基乙磺酰胺C7(350mg,2.88mmol)和碳酸钾(700mg,5.06mmol)于2-甲基四氢呋喃(10mL)中的溶液在60℃下搅拌。搅拌4小时后,将混合物冷却至室温,并将反应物用水(10mL)淬灭。将有机层用EtOAc(40mL)稀释。将层分离,并将水层用EtOAc(2×30mL)萃取,随后用DCM(2×20mL)萃取,经Na_2SO_4干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含0-10%甲醇的DCM),产生2-(4-甲酰基吡唑基-1-基)-N-甲基-乙磺酰胺S10(565mg,54%)。^{1}H NMR(400MHz,DMSO-d6)δδ9.80(s,1H),8.53(d,J=0.7Hz,1H),8.03(d,J=0.7Hz,1H),7.15(d,J=4.3Hz,1H),4.53(dd,J=7.4,6.5Hz,2H),3.60(dd,J=7.4,6.5Hz,2H),2.56(d,J=3.5Hz,3H)。LCMS m/z 218.42$[M+H]^+$。

[0659] 制备S11

[0660] 1-(2-甲基磺酰基乙基)吡唑-4-甲醛(S11)

[0661] 

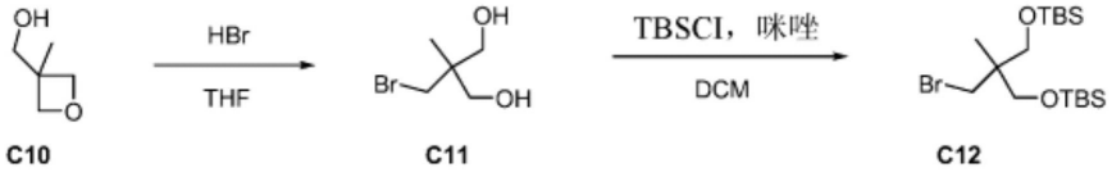
[0662] 步骤1:1-(2-甲基磺酰基乙基)吡唑-4-甲醛(S11)

[0663] 将1H-吡唑-4-甲醛C8(1g,10.4mmol)、1-甲基磺酰乙烯C9(1.2g,11.4mmol)和碳酸钾(2.4g,18.1mmol)于2-甲基四氢呋喃(20mL)中的溶液在60℃下搅拌。搅拌过夜后,将混合物冷却至室温,并将反应物用水(10mL)淬灭。将有机层用EtOAc(40mL)稀释。将层分离,并将水层用EtOAc(2×30mL)萃取,随后用DCM(2×20mL)萃取,经Na_2SO_4干燥,过滤并浓缩。通过硅

胶色谱法纯化(梯度:含0-10％甲醇的DCM),产生1-(2-甲基磺酰基乙基)吡唑-4-甲醛S11(1.3g,58％)。1H NMR(400MHz,氯仿-d)δ9.90(s,1H),8.10(d,J＝0.7Hz,1H),8.06(d,J＝0.6Hz,1H),4.75-4.63(m,2H),3.70(tdd,J＝6.0,1.4,0.7Hz,2H),2.66(t,J＝0.7Hz,3H)。LCMS m/z 203.34[M+H]$^+$。

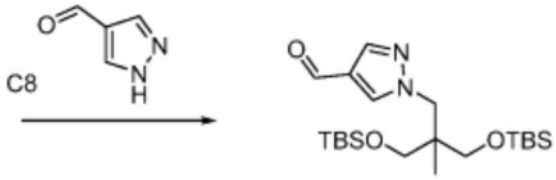
[0664] 制备S12

[0665] 1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛(S12)



C10 C11 C12

[0666]



S12

[0667] 步骤1:2-(溴甲基)-2-甲基-丙烷-1,3-二醇(C11)

[0668] 在0℃下向(3-甲基氧杂环丁烷-3-基)甲醇C10(10mL,100.3mmol)于THF(70mL)中的溶液中添加溴化氢(14mL的48％w/w,123.7mmol),并搅拌24小时。将混合物浓缩,并在二氯甲烷/甲醇中稀释。用饱和碳酸氢钠水溶液淬灭过量溴化氢。将层分离,并将有机层经Na_2SO_4干燥,过滤,并用甲醇冲洗并浓缩以产生2-(溴甲基)-2-甲基-丙烷-1,3-二醇C11(13.6g,74％)。^{1}H NMR(400MHz,甲醇-d4)δ3.47(d,J＝1.1Hz,6H),0.96(s,3H)。

[0669] 步骤2:[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷(C12)

[0670] 向2-(溴甲基)-2-甲基-丙烷-1,3-二醇C11(10g,54.1mmol)于DCM(200mL)中的溶液中添加咪唑(7.7g,113.1mmol),随后添加TBSCl(17g,112.8mmol)。5分钟后过滤固体,并用DCM洗涤。将滤液用庚烷(25mL)稀释,并过滤固体并用庚烷(10mL)洗涤。将滤液浓缩以产生[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷C12(22.2g,99％)。^{1}H NMR(400MHz,氯仿-d)δ3.44(s,4H),3.40(s,2H),0.94(s,3H),0.89(s,18H),0.04(d,J＝1.2Hz,12H)。

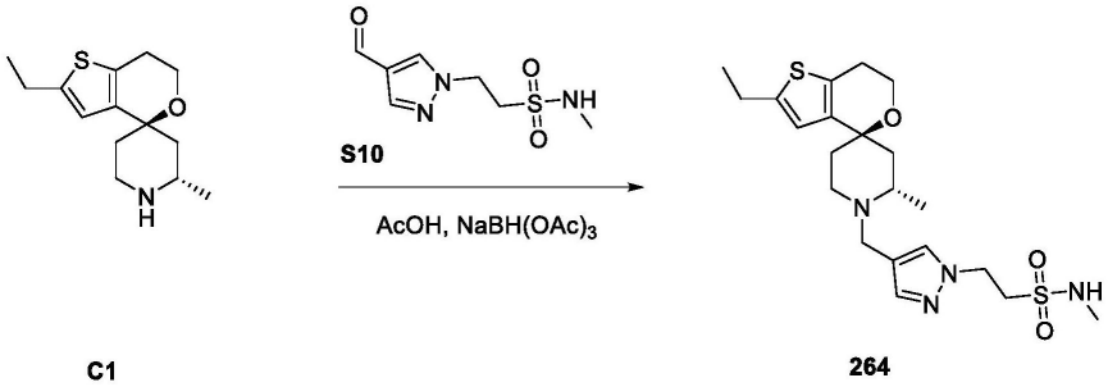
[0671] 步骤3:1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛(S12)

[0672] 向1H-吡唑-4-甲醛C8(2g,20.8mmol)于乙腈(20mL)中的溶液中添加碳酸钾(4g,28.9mmol)和[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷C12(9.5g,23.1mmol),并在110℃下搅拌35分钟。将混合物冷却至rt,过滤,用乙腈冲洗并浓缩。通过硅胶色谱法纯化(梯度:含30-60％ EtOAc的庚烷)以产生1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡

唑-4-甲醛(S12)(2.39g,23%)。^{1}H NMR(400MHz,氯仿-d)δ9.85(s,1H),7.98-7.91(m,2H),4.12(s,2H),3.43-3.29(m,4H),0.91(s,18H),0.84(s,3H),0.05(d,J=0.6Hz,12H)。LCMS m/z 427.31[M+H]$^+$。

[0673] 化合物264

[0674] 2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N-甲基-乙磺酰胺

[0675] 

C1 264

[0676] 步骤1:2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N-甲基-乙磺酰胺(264)

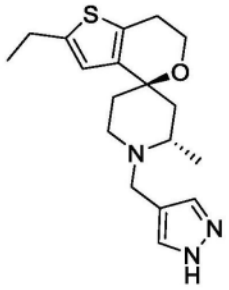
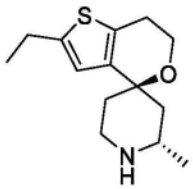
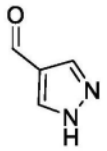
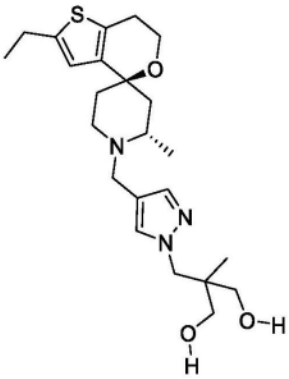
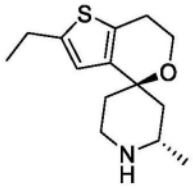
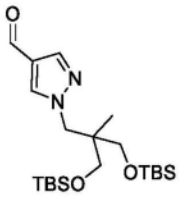
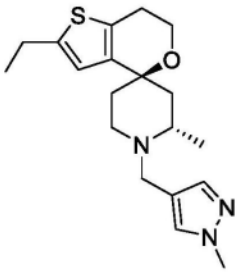
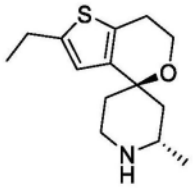
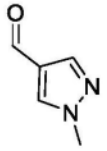
[0677] 将2-(4-甲酰基吡唑基-1-基)-N-甲基-乙磺酰胺S10(100mg,0.460mmol)、(2′S)-2-乙基-2′-甲基-螺[6,7二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C1(100mg,0.338mg)、乙酰氧基硼氢化钠(250mg,1.18mmol)和乙酸(0.025mL,0.439mmol)于1,2-二氯乙烷(5mL)中的混合物在50℃下搅拌过夜。将混合物用饱和碳酸氢钠和二氯甲烷(10mL)稀释,并将层分离。将有机层经Na_2SO_4干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含0-10%甲醇的DCM),产生2-[4-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N-甲基-乙磺酰胺(264)(71mg,45%)。^{1}HNMR(400MHz,氯仿-d)δ7.60-7.44(m,2H),6.54-6.41(m,1H),4.57(t,J=6.0Hz,3H),3.99-3.75(m,3H),3.75-3.42(m,5H),2.94-2.24(m,12H),2.09-1.65(m,4H),1.27(t,J=7.5Hz,3H),1.22(d,J=6.2Hz,3H)。LCMS m/zm/z453.46[M+H]$^+$。

[0678] 化合物265-277

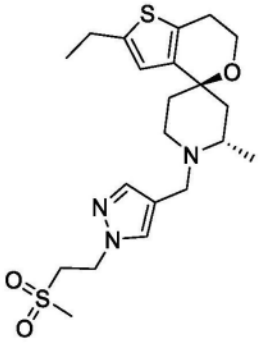
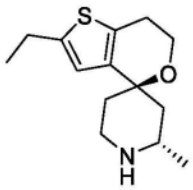
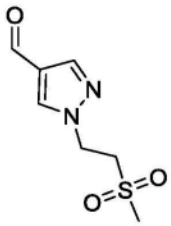
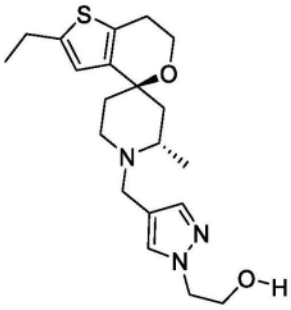
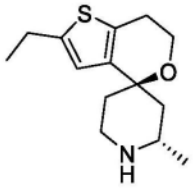
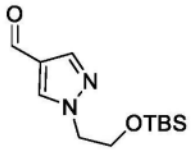
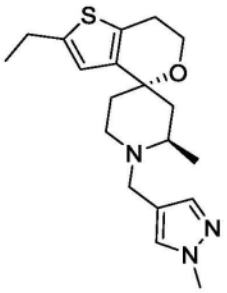
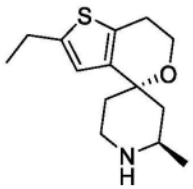
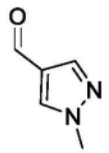
[0679] 使用化合物264的方法中所述的适当试剂,由选自C1、S5、S6或S9的中间体哌啶和适当的醛制备化合物265-277(表6)。醛通过上述方法制备或从商业来源获得。表6和随附脚注中注明了对方法的任何修改。

[0680] 表6:化合物265-277的结构和物理化学数据

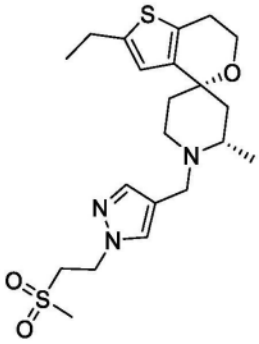
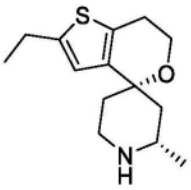
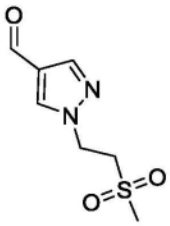
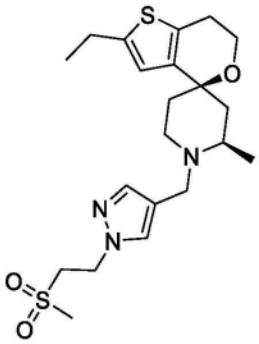
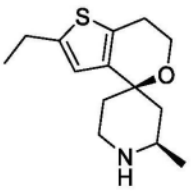
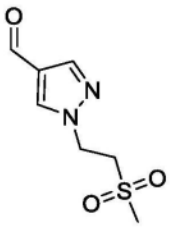
[0681]

化合物	结构	哌啶	醛	^{1}H NMR；LCMS m/zm/z $[M+H]^+$。
265				LCMS *m/zm/z* 332.07 $[M+H]^+$.
266				^{1}H NMR (400 MHz, 甲醇-d4) δ 8.00 (d, J = 0.7 Hz, 1H), 7.76 (d, J = 0.7 Hz, 1H), 6.86 - 6.54 (m, 1H), 4.53 (d, J = 14.1 Hz, 1H), 4.29 (d, J = 14.1 Hz, 1H), 4.22 (s, 2H), 3.98 - 3.80 (m, 2H), 3.55 - 3.33 (m, 5H), 3.29 - 3.21 (m, 1H), 2.84 - 2.63 (m, 4H), 2.25 - 2.04 (m, 4H), 2.03 (s, 1H), 1.55 (d, J = 6.5 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H), 0.85 (s, 3H)。LCMS *m/z* 433.87 $[M+H]^+$.
267				^{1}H NMR (300 MHz, 氯仿-d) δ 7.33 (d, J = 0.8 Hz, 1H), 7.21 (s, 1H), 6.40 (d, J = 1.1 Hz, 1H), 3.80 - 3.69 (m, 3H), 3.49 (d, J = 14.2 Hz, 1H), 2.74 - 2.56 (m, 5H), 2.53 - 2.35 (m, 2H), 1.89 - 1.69 (m, 3H), 1.61 (dd, J = 13.8, 11.3 Hz, 1H), 1.18 (t, J = 7.5 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H)。LCMS *m/z*

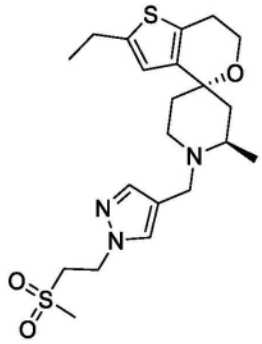
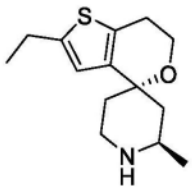
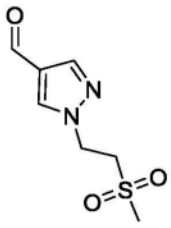
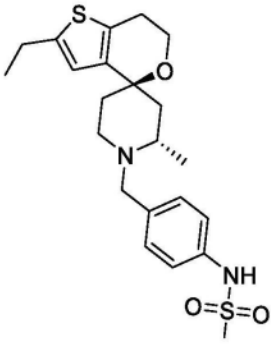
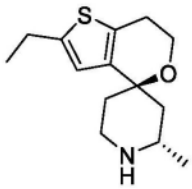
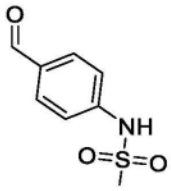
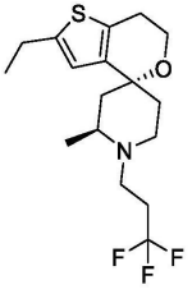
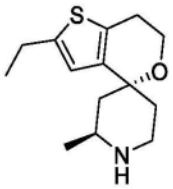
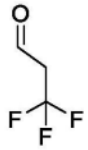
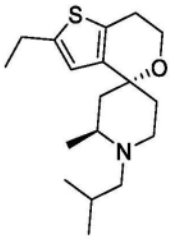
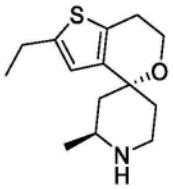
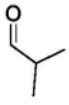
[0682]

化合物	结构	哌啶	醛	^{1}H NMR；LCMS m/zm/z $[M+H]^+$。
				346.45 $[M+H]^+$.
268				^{1}H NMR (400 MHz, 氯仿-d) δ 7.69 - 7.50 (m, 2H), 6.49 (q, J = 1.3 Hz, 1H), 4.68 - 4.55 (m, 2H), 4.35 (s, 1H), 3.99 - 3.75 (m, 3H), 3.75 - 3.62 (m, 3H), 2.84 - 2.58 (m, 6H), 2.48 (d, J = 0.8 Hz, 3H), 2.04 - 1.75 (m, 4H), 1.32 - 1.18 (m, 6H)。LCMS *m/z* 438.37 $[M+H]^+$.
269[1,2]				^{1}H NMR (400 MHz, 甲醇-d4) δ 8.02 (d, J = 0.7 Hz, 1H), 7.80 (d, J = 0.7 Hz, 1H), 6.57 - 6.51 (m, 1H), 4.57 (d, J = 14.1 Hz, 1H), 4.30 (dd, J = 5.7, 4.8 Hz, 2H), 4.24 (d, J = 14.1 Hz, 1H), 3.94 - 3.86 (m, 4H), 3.54 (p, J = 7.0 Hz, 1H), 3.38 - 3.31 (m, 1H), 3.29 - 3.21 (m, 1H), 2.80 - 2.70 (m, 4H), 2.22 - 2.01 (m, 4H), 1.55 (d, J = 6.4 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H)。LCMS *m/z* 375.74 $[M+H]^+$.
270[1]				LCMS *m/z* 346.47 $[M+H]^+$.

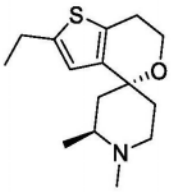
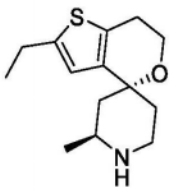
[0683]

化合物	结构	哌啶	醛	^{1}H NMR；LCMS m/zm/z $[M+H]^+$。
271[1]				^{1}H NMR (300 MHz, 氯仿-d) δ 7.54 (d, J = 0.7 Hz, 1H), 7.53 - 7.44 (m, 1H), 6.48 (d, J = 1.1 Hz, 1H), 4.71 - 4.50 (m, 2H), 4.01 - 3.80 (m, 2H), 3.72 - 3.58 (m, 2H), 3.54 (s, 2H), 3.05 (td, J = 5.7, 3.3 Hz, 1H), 2.89 - 2.61 (m, 5H), 2.55 - 2.40 (m, 4H), 2.03 - 1.87 (m, 2H), 1.87 - 1.72 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H)。
272[1]				^{1}H NMR (300 MHz, 氯仿-d) δ 7.55 (s, 1H), 7.48 (s, 1H), 6.49 (s, 1H), 4.58 (dd, J = 6.9, 5.3 Hz, 2H), 3.98 - 3.81 (m, 2H), 3.64 (t, J = 6.1 Hz, 2H), 3.56 (s, 2H), 3.06 (s, 1H), 2.89 - 2.62 (m, 5H), 2.57 - 2.39 (m, 1H), 2.47 (s, 3H), 1.96 (td, J = 14.0, 4.9 Hz, 2H), 1.89 - 1.71 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H)。LCMS *m/z* 438.23 $[M+H]^+$.

[0684]

化合物	结构	哌啶	醛	^{1}H NMR；LCMS m/zm/z $[M+H]^+$。
273				LCMS *m/z* 438.37 $[M+H]^+$.
274[1]				LCMS *m/z* 435.42 $[M+H]^+$.
275[1]				^{1}H NMR (400 MHz, DMSO-d6): δ 6.49 (s, 1H), 3.91-3.87 (m, 2H), 3.09-3.02 (m, 1H), 2.78-2.67 (m,8H), 2.55-2.51 (m, 2H), 1.91-1.63 (m, 4H), 1.26-1.22 (t, J = 11.6 Hz, 3H), 1.10-1.09 (d, J = 6.0 Hz, 3H)。LCMS *m/z* 348.53 $[M+H]^+$.
276[1]				^{1}H NMR (400 MHz, DMSO-d6): δ 6.60 (s, 1H), 3.86-3.79 (m, 2H), 3.32 (m, 1H), 2.77-2.37 (m,7H), 1.94-1.58 (m, 6H), 1.21-1.17 (t, J = 7.6 Hz, 3H), 1.00-0.99 (d, J = 6.4 Hz, 3H), 0.89-0.85 (t, J = 6.4 Hz, 6H)。LCMS *m/z*

[0685]

化合物	结构	哌啶	醛	^{1}H NMR；LCMS m/zm/z $[M+H]^+$。
				308.56 $[M+H]^+$.
277[1]				^{1}H NMR (400 MHz, DMSO-d6): δ 8.31 (s, 1H), 6.59 (s, 1H), 3.86-3.85 (m, 2H), 3.04-2.88 (m,3H), 2.76-2.67 (m, 4H), 2.57 (s, 3H), 2.02-1.74 (m, 4H), 1.23-1.14 (m, 6H)。LCMS *m/z* 266.1 $[M+H]^+$.

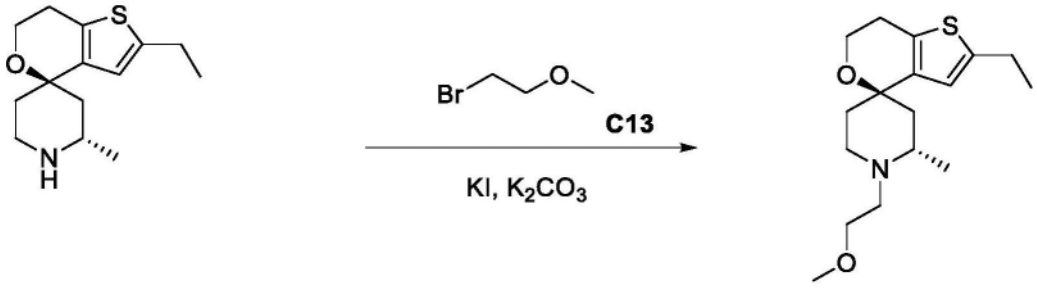
[0686] 脚注：

[0687] 1)用2当量聚合物负载的氰基硼氢化物代替乙酰氧基硼氢化钠进行还原胺化。

[0688] 还原胺化完成后,将产物与HCl和MeOH水溶液搅拌五分钟,以脱保护TBS基团。收集沉淀的白色固体并干燥,得到最终产物。

[0689] 化合物278

[0690] (2′S,4R)-2-乙基-1′-(2-甲氧基乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]

[0691] 

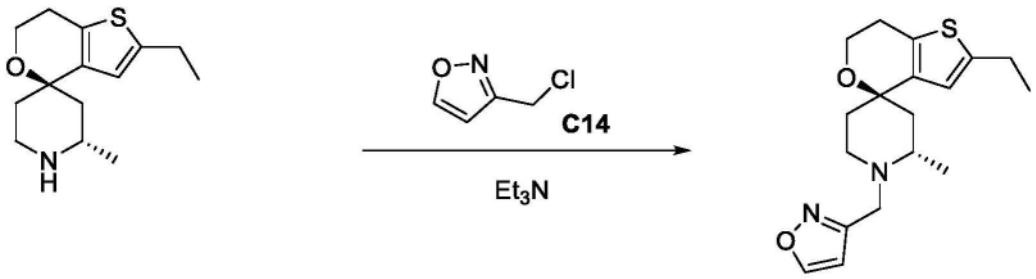
C1 278

[0692] 步骤1:(2′S,4R)-2-乙基-1′-(2-甲氧基乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](278)

[0693] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C1(100mg,0.236mmol)和1-溴-2-甲氧基-乙烷C13(99mg,0.712mmol)于含MeCN(8mL)的DMF(1mL)的经搅拌的溶液中添加碳酸钾(180mg,13.0mmol),随后添加KI(8mg,0.048mmol),并在60℃下搅拌48小时。将混合物用MeCN(20mL)稀释并过滤。将滤液浓缩并通过制备型HPLC纯化(条件:流动相A:-0.01M碳酸氢铵(水性),流动相B:-乙腈)并收集纯级分以产生(2′S,4R)-2-乙基-1′-(2-甲氧基乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]278(28mg,38%)。^{1}H NMR(400MHz,DMSO-d6):δ6.60(s,1H),3.83-3.79(q,J=5.2Hz,2H),3.42-3.39(t,J=6.0Hz,2H),3.23(s,3H),2.89-2.86(m,1H),2.73-2.63(m,5H),2.54-2.32(m,3H),1.70-1.49(m,4H),1.20-1.17(t,J=7.6Hz,3H),0.98-0.97(d,J=6.0Hz,3H)。LCMS m/z 310.2$[M+H]^+$。

[0694] 化合物279

[0695] (2′S,4R)-2-乙基-1′-(异噁唑-3-基甲基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]

[0696] 

C1 279

[0697] 步骤1:(2′S,4R)-2-乙基-1′-(异噁唑-3-基甲基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](279)

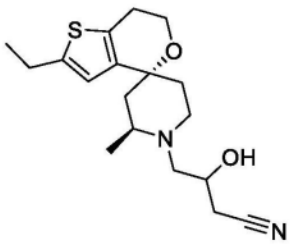
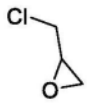
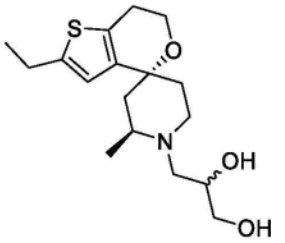
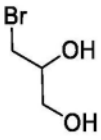
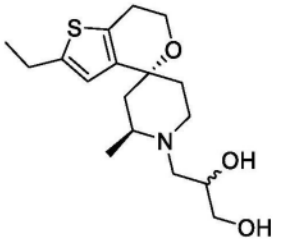
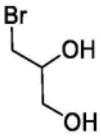
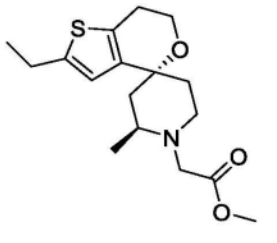
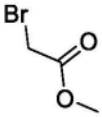
[0698] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C1(100mg,0.397mmol)于DMF(2mL)中的溶液中添加三乙胺(0.16mL,1.19mmol),随后添加3-(氯甲基)异噁唑C14(56mg,0.477mmol)。将混合物在室温下搅拌过夜。用EtOAc(20mL)稀释,用水(2×10mL)和盐水(2×5mL)洗涤。将有机层经无水Na_2SO_4干燥,过滤并浓缩。通过制备型HPLC纯化,产生(2′S,4R)-2-乙基-1′-(异噁唑-3-基甲基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]279(9mg,7%)。^{1}H NMR(400MHz,DMSO-d6)8.85(s,1H),6.60(s,1H),6.52(s,1H),3.91(d,J=14.55Hz,2H),3.80-3.76(m,2H),3.63(d,J=14.36Hz,1H),2.70(q,J=7.44Hz,14.92Hz 2H),2.62(bs,,2H),2.49-2.43(m,2H),1.77-1.69(m,3H),1.58(t,J=12.16Hz 1H),1.19(t,J=7.44Hz,3H),1.10(d,J=6.08Hz,3H)。LCMS m/z 333.0$[M+H]^+$。

[0699] 化合物280-298

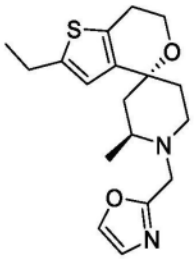
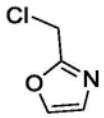
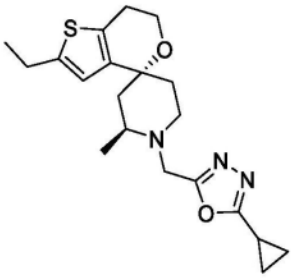
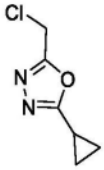
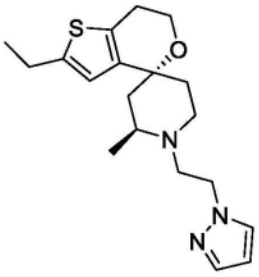
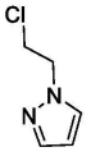
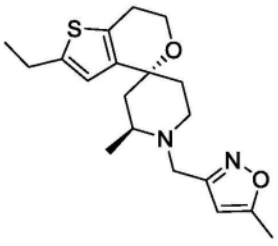
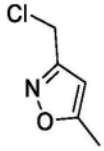
[0700] 使用化合物278和279所述的方法,由中间体C1和对应商业烷基卤化物制备化合物280-298。表7和随附脚注中注明了对方法的任何修改。

[0701] 表7:化合物280-298的结构和物理化学数据

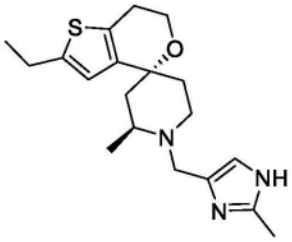
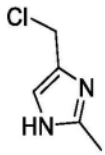
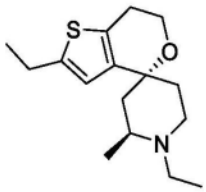
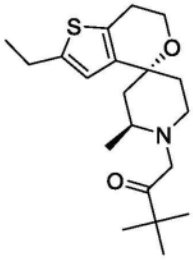
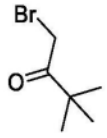
[0702]

化合物	结构	方法	烷基卤化物	^{1}H NMR；LCMS m/z $[M+H]^+$。
280		278[1]		^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.58 (s, 1H), 5.12 (br s, 1H), 3.85-3.78 (m, 3H), 2.73-2.54 (m, 10H), 2.16-2.12 (m, 1H), 1.82-1.79 (m, 1H), 1.66 (br d, J = 13.2 Hz, 2H), 1.51 (t, J =12.4 Hz, 1H), 1.19 (t, J =7.2 Hz, 3H), 0.97 (d, J =6 Hz, 3H)。LCMS *m/z* 335.2 $[M+H]^+$。
281		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.59 (s, 1H), 4.55 (s, 1H), 4.22 (s, 1H), 3.84-3.79 (m, 2H), 3.57 (m, 1H), 3.31 (m, 2H), 2.73-2.51 (m, 8H), 2.24-2.20 (m, 1H), 1.78-1.48 (m, 4H), 1.21-1.17 (t, J = 7.6 Hz, 3H), 0.98-0.97 (t, J = 6.0 Hz, 3H)。LCMS *m/z* 326.17 $[M+H]^+$。
282		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.59 (s, 1H), 4.40-4.62 (m, 2H), 3.84-3.80 (m, 2H), 3.57 (m, 1H), 3.41-3.27 (m, 2H), 2.79-2.64 (m, 6H), 2.50-2.45 (m, 2H), 2.07 (m, 1H), 1.81-1.49 (m, 4H), 1.21-1.17 (t, J = 7.6 Hz, 3H), 0.98-0.97 (t, J = 6.4 Hz, 3H)。LCMS *m/z* 326.17 [M+H]+。
283		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.61 (s, 1H), 3.84-3.80 (q, J = 5.6 Hz, 2H), 3.61 (s, 3H), 3.45-3.41 (m, 1H), 3.32-3.27 (m, 1H), 2.80-2.60 (m, 7H), 1.80-1.47 (m, 4H), 1.21-1.17 (t, J = 7.2 Hz, 3H), 0.96-0.94 (d, J = 6.4 Hz, 3H)。LCMS

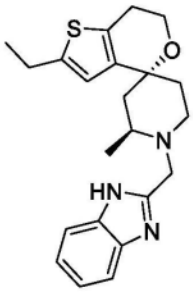
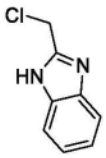
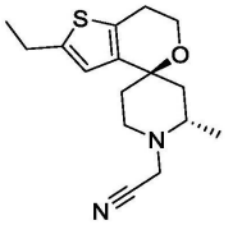
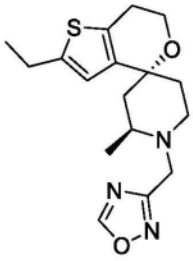
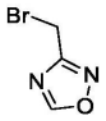
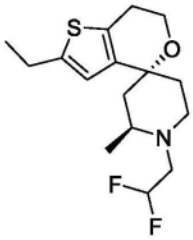
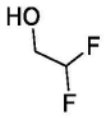
[0703]

化合物	结构	方法	烷基卤化物	^{1}H NMR；LCMS m/z $[M+H]^+$。
				m/z 324.49 $[M+H]^+$。
284		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.072 (d, J =0.8, 1H), 7.17 (d, J =0.8, 1H), 6.608 (s, 1H), 3.89-3.74 (m, 4H), 2.73-2.67 (m, 2H), 2.63-2.53 (m, 5H), 1.80-1.75 (m, 1H), 1.685 (d, J =13.6, 2H) , 1.54 (t, J =11.2 Hz, 1H), 1.18 (t, J =7.6 Hz, 3H), 1.095 (d, J =6.4 Hz, 3H)。LCMS *m/z* 333.2 $[M+H]^+$。
285		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.61 (s, 1H), 3.915 (q, J =15.6, Hz, 2H), 3.81-3.77 (m, 2H), 2.70(q, J =7.6, Hz, 2H), 2.64-2.59 (m, 5H), 2.24-2.22 (m, 1H), 1.85-1.75 (m, 1H), 1.70 (d, J =14, 2H) , 1.55 (t, J =11.2 Hz, 1H), 1.18 (t, J =7.6 Hz, 3H), 1.15-1.11 (m, 2H), 1.07 (d, J =6 Hz, 3H), 0.99-0.96 (m, 2H)。LCMS *m/z* 374.2 $[M+H]^+$。
286		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.742 (d, J =2, 1H), 7.415 (d, J =1.2, 1H), 6.59 (s, 1H), 6.20 (t, J =2 Hz, 1H), 4.18 (t, J =7.2 Hz, 2H) 3.83-3.80 (m, 2H), 3.12-3.08 (m, 1H), 2.73-2.56 (m, 8H), 1.78-1.65 (m, 3H), 1.47 (t, J =11.6 Hz, 1H), 1.19 (t, J =7.2 Hz, 3H), 0.928 (d, J =6 Hz, 3H)。LCMS *m/z* 346.1 $[M+H]^+$。
287		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.59 (s, 1H), 6.16 (s, 1H), 3.84-3.75 (m, 3H), 3.50(d, J=14.4 Hz, 1H), 2.70 (q, J = 7.44 Hz, J=14.92 Hz, 2H), 2.62 (bs,2H), ~2.50 (2H, 在

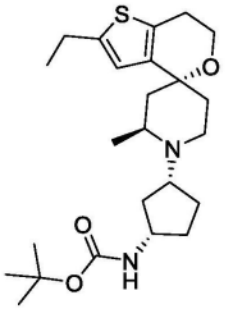
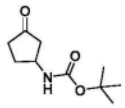
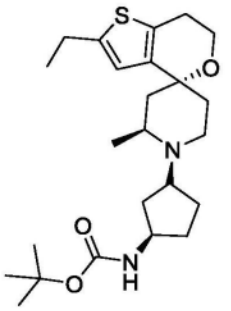
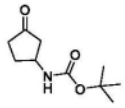
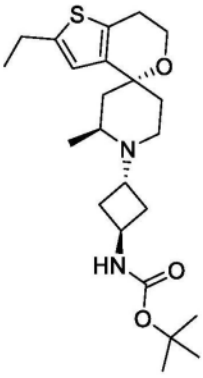
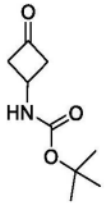
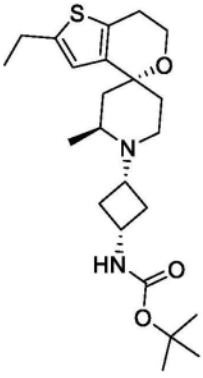
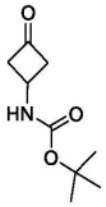
[0704]

化合物	结构	方法	烷基卤化物	^{1}H NMR；LCMS m/z [M+H]$^+$。
				DMSO 下) 2.38 (s, 3H), 1.76 -1.69 (m, 3H),1.54 (t, J =11.72 Hz 1H), 1.18 (t, J =7.52 Hz, 3H), 1.08 (d, J = 6.1 Hz, 3H)。LCMS *m/z* 347.0 [M+H]$^+$。
288		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.43 (bs, 1H), 6.66 (bs, 1H), 6.56 (s, 1H), 3.81 - 3.68 (m, 3H), 3.37-3.31 (m, 1H), 2.70 (q, J = 7.52 Hz, 15 Hz, 2H), 2.61 - 2.56 (m, 3H), 2.50-2.32 (m, 2H), 2.22 (s, 3H), 1.74 - 1.66 (m,3H), 1.53 (t, J = 11.68 Hz, 1H), 1.18 (t, J = 7.48 Hz, 3H), 1.11 (d, J = 6.08 Hz, 3H)。LCMS *m/z* 346.0 [M+H]$^+$。
289		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.25 (s, 1H), 6.59 (s, 1H), 3.86-3.49 (m, 2H), 2.84-2.81 (t, J = 6.4 Hz, 1H), 2.73-2.60 (m, 6H), 2.50-2.52 (m, 1H), 1.84-1.58 (m, 4H), 1.21-1.17 (t, J = 7.2 Hz, 3 H), 1.01-0.96 (m, 6H)。LCMS *m/z* 280.1 [M+H]$^+$。
290		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.61 (s, 1H), 3.84-3.69 (m, 3H), 3.38-3.33 (m, 1H), 2.82-2.58 (m, 7H), 1.77-1.33 (m, 4H), 1.21-1.17 (t, J = 7.2 Hz, 3H), 1.09 (s, 9H), 0.93-0.92 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 351.1 [M+H]$^+$。

[0705]

化合物	结构	方法	烷基卤化物	^{1}H NMR；LCMS m/z [M+H]$^+$。
291		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.14 (br s, 1H), 7.50 (br s, 2H), 7.14-7.12 (m, 2H), 6.56 (s, 1H), 4.06(d, J =14.4 Hz, 1H), 3.81-3.76 (m, 2H), 3.65 (d, J =14.8 Hz, 1H), 2.74-2.51 (m, 7H), 1.84-1.80 (m, 1H), 1.75-1.58 (m, 3H), 1.19 (t, J =7.6 Hz, 3H), 1.14 (d, J =6.4 Hz, 3H)。LCMS *m/z* 382.2 [M+H]$^+$。
292		278		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.60 (s, 1H), 3.95-3.83 (m, 3H), 3.71-3.67 (d, J = 16 Hz, 1H), 2.73-2.57 (m, 7H), 1.85-1.52 (m, 4H), 1.21-1.17 (t, J = 7.2 Hz, 3H), 0.99-0.98 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 291.26 [M+H]$^+$。
293		278		^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.56 (s, 1H), 6.60 (s, 1H), 3.93-3.92 (m, 2H), 3.79-3.75 (m, 2H), 2.73-2.67 (m, 2H), 2.62-2.60 (m, 5H), 1.81 - 1.75 (m, 1H), 1.69 (d, J = 13.2 Hz, 2H),1.58 - 1.52 (m, 1H), 1.20 (t, J = 10.96 Hz, 3H), 1.10 (d, J = 6.12 Hz, 3H)。LCMS *m/z* 334.0 [M+H]$^+$。
294		278[2]		^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.62 (s, 1H), 6.22-5.92 (tt, J = 16.0, 4.4 Hz, 1H), 3.86-3.79 (m, 2H), 3.08-3.03 (m, 1H), 2.76-2.54 (m, 8H), 1.80-1.48 (m, 4H), 1.21-1.17 (t, J = 7.2 Hz, 3H), 0.98-0.97 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 316.24 [M+H]$^+$。

[0706]

化合物	结构	方法	烷基卤化物	^{1}H NMR；LCMS m/z $[M+H]^+$。
295		264		LCMS *m/z* 435.53 $[M+H]^+$。
296		264		LCMS *m/z* 435.17 $[M+H]^+$。
297		264		LCMS *m/z* 421.36 $[M+H]^+$。
298		264		LCMS *m/z* 421.36 $[M+H]^+$。

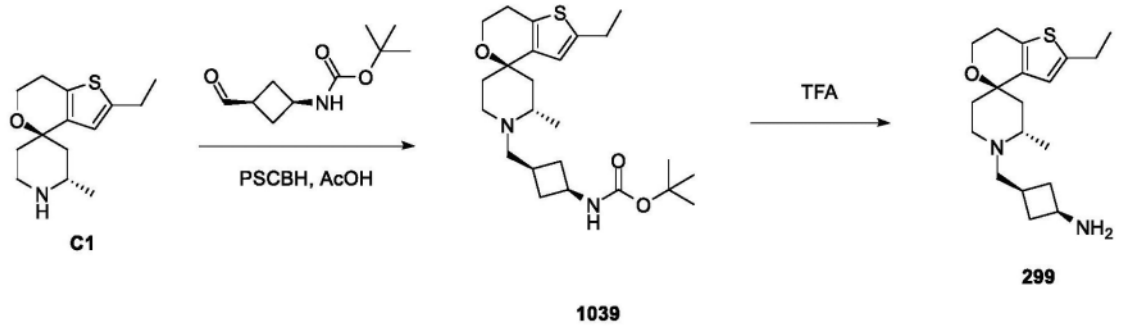
[0707] 脚注：

[0708] 1)在DMF中使用NaCN进行环氧化物开环

[0709] 2)在80℃下将醇与三氟甲磺酸酐搅拌,然后添加到反应混合物中

[0710] 3)通过手性SFC纯化分离化合物295-298立体异构体化合物299的制备

[0711] 3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(299)

[0712] 

[0713] 步骤1:N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(1039)的合成

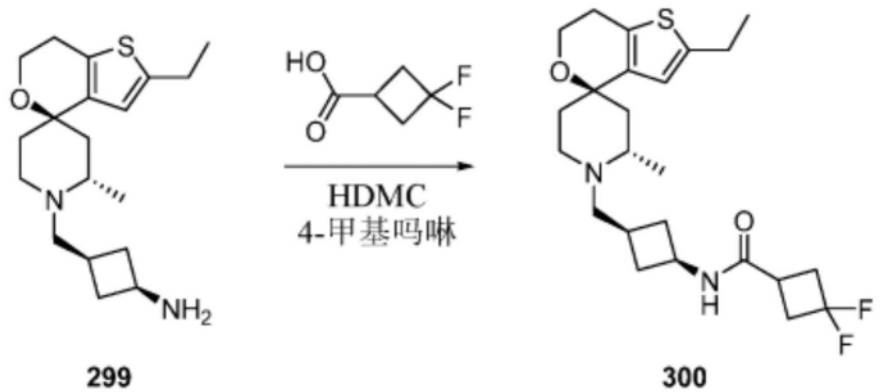
[0714] 向微波管中装入含(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]三氟甲烷磺酸盐(C1)(2.468g,6.163mmol)、N-(3-甲酰环丁基)氨基甲酸叔丁酯(6.54g,32.82mmol)、聚合物负载的氰基硼氢化物(11.4g的2mmol/g,22.80mmol)和乙酸(3mL,52.75mmol)的DCM(45mL)。在微波辐射下将反应加热至110℃,持续30分钟。冷却至室温后,过滤反应物,并将滤液用DCM(150mL)稀释。将有机相用1N NaOH(2×100mL)洗涤,经Na_2SO_4干燥,过滤,并在真空中蒸发。通过硅胶色谱法纯化(120g柱,含0-5% MeOH的DCM),得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(1042)(2.170g,79%)。^{1}H NMR(300MHz,氯仿-d)δ 6.49(s,1H),4.84-4.45(bs,1H),4.17-3.76(m,3H),2.90-2.72(m,5H),2.69-2.33(m,6H),2.28-2.15(m,1H),2.00-1.76(m,3H),1.76-1.62(m,1H),1.60-1.45(m,2H),1.45(s,9H),1.28(t,J=7.5Hz,3H),1.08(d,J=6.2Hz,3H)。ss LCMS m/z 435.4[M+H]$^+$。

[0715] 步骤3:3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(299)的合成

[0716] 将N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(1042)(2.04g,4.600mmol)溶解在含4M HCl溶液的二噁烷(10mL,40.00mmol)中,并将反应物在室温下搅拌2小时。将反应物在真空中浓缩以产生粗产物3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(盐酸盐)(299)(1.7g,96%)。LCMS m/z 334.68[M+H]$^+$。

[0717] 化合物300

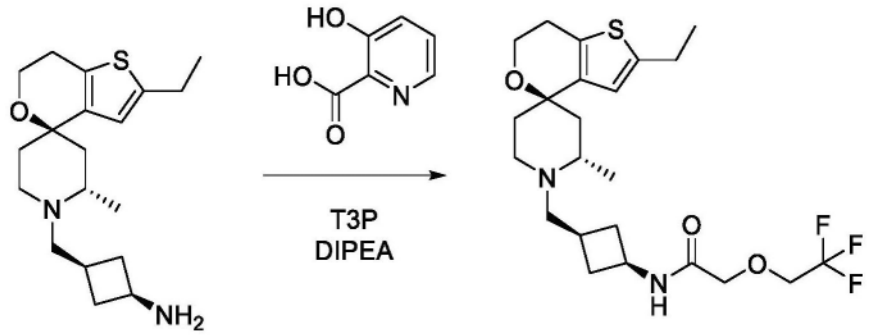
[0718] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-3,3-二氟-环丁烷甲酰胺(300)

[0719] 

[0720] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-3,3-二氟-环丁烷甲酰胺(300)的制备。将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(盐酸盐)299(20mg,0.05979mmol)和3,3-二氟环丁烷甲酸(8.1mg,0.05979mmol)溶解在DMF中,向其中添加HDMC(32.7mg,0.07175mmol)和4-甲基吗啉(20μL,0.1794mmol)。将反应物在室温下搅拌1小时。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-3,3-二氟-环丁烷甲酰胺(三氟乙酸盐)(300)(17mg,50%)。LCMS m/z 453.24$[M+H]^+$。

[0721] 化合物301

[0722] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-(2,2,2-三氟乙氧基)乙酰胺(301)

[0723] 

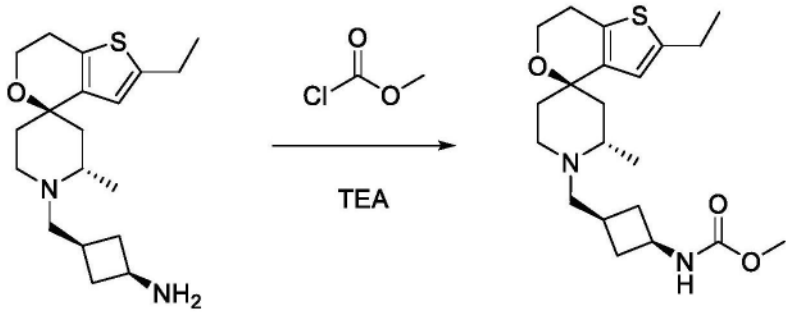
299 301

[0724] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-(2,2,2-三氟乙氧基)乙酰胺(301)的制备

[0725] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(盐酸盐)299(20mg,0.05979mmol)和2-(2,2,2-三氟乙氧基)乙酸(9.5mg,0.05979mmol)溶解在DMF(1mL)中,向其中添加T3P(38.5mg,0.1210mmol)和)和DIPEA(21μL,0.1206mmol)。将反应物在室温下搅拌过夜。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-(2,2,2-三氟乙氧基)乙酰胺(三氟乙酸盐)(6.8mg,24%)(301)。LCMS m/z 475.19$[M+H]^+$。

[0726] 化合物302

[0727] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸甲酯(302)

[0728] 

299 302

[0729] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸甲酯(302)的制备

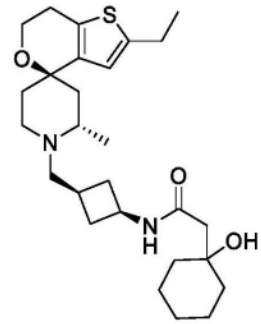
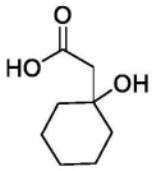
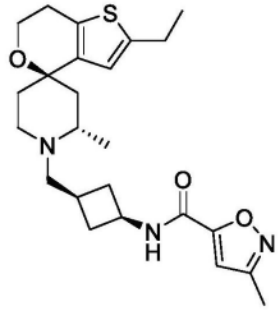
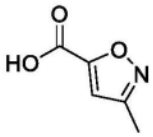
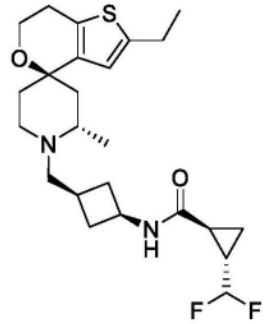
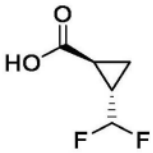
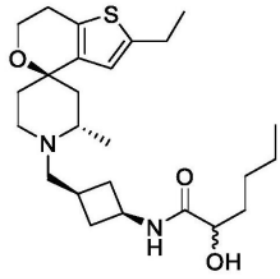
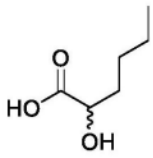
[0730] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(盐酸盐)299(18mg,0.03962mmol)溶解在DCM(1mL)中,向其中添加氯甲酸甲酯(5μL,0.06471mmol)和三乙胺(15μL,0.1076mmol)。将反应物在室温下搅拌2小时,然后将溶剂在真空中蒸发。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸甲酯(三氟乙酸盐)(302)(9.7mg,45%)。LCMS m/z393.23$[M+H]^+$。

[0731] 化合物303-384

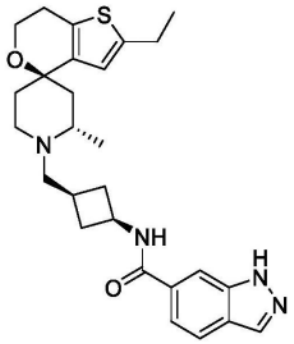
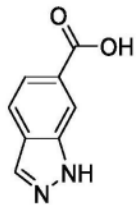
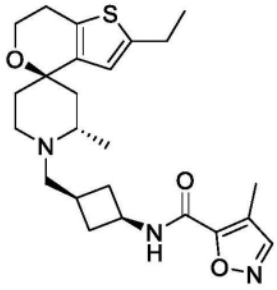
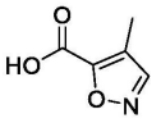
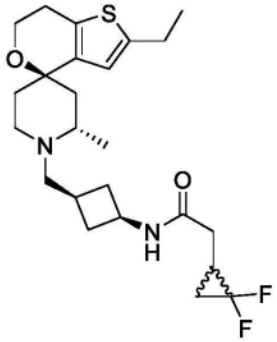
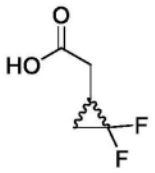
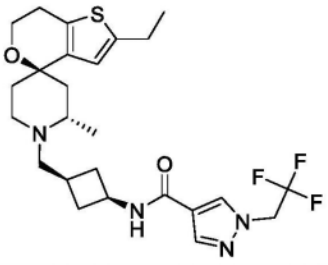
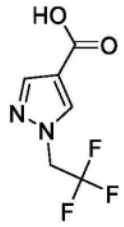
[0732] 使用适当的试剂和化合物300-302所述的酰胺形成方法,由中间体299制备化合物303-384(参见表8)。偶联配偶体从商业来源获得。表8和随附脚注中注明了对方法的任何修改。

[0733] 表8:化合物303-384的制备方法、结构和物理化学数据

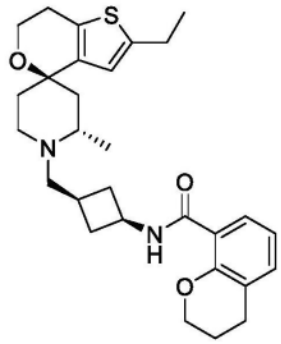
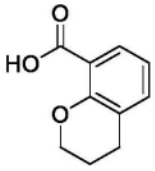
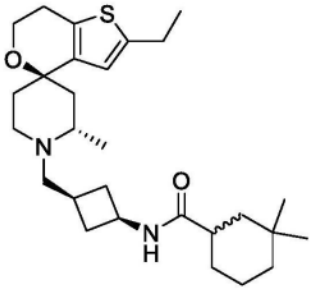
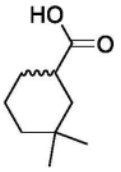
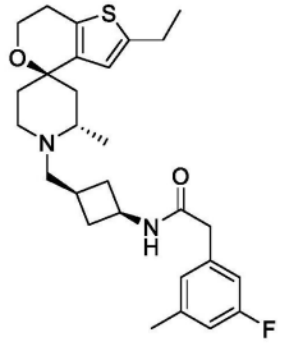
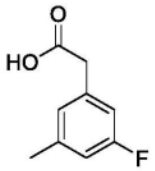
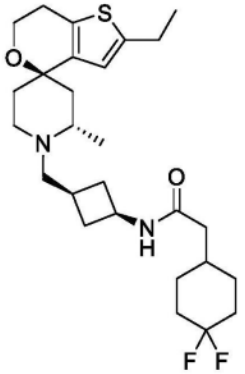
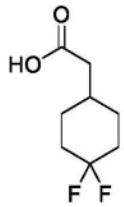
[0734]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
303			*化合物300*	LCMS *m/z* 475.32 $[M+H]^+$。
304			*化合物300*	LCMS *m/z* 444.18 $[M+H]^+$。
305			*化合物300*	LCMS *m/z* 453.20 $[M+H]^+$。
306			*化合物300*	LCMS *m/z* 449.30 $[M+H]^+$。

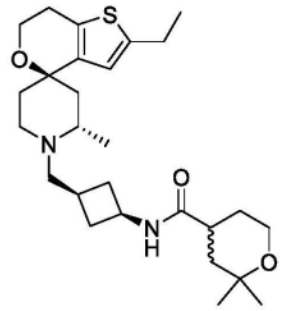
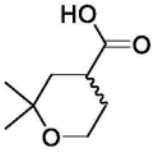
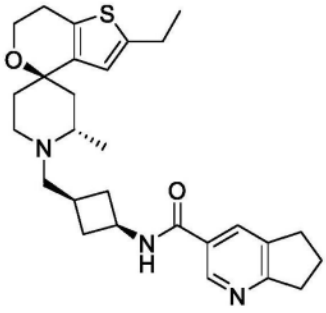
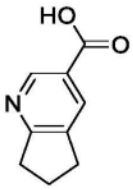
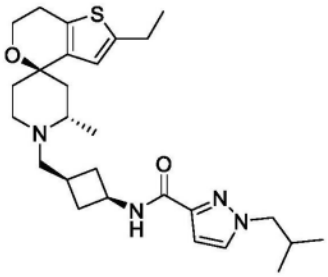
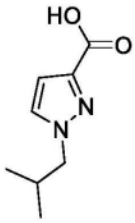
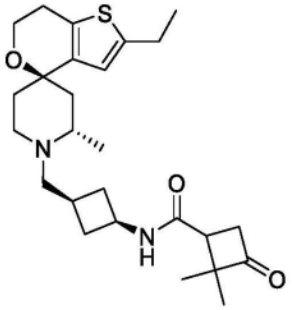
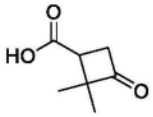
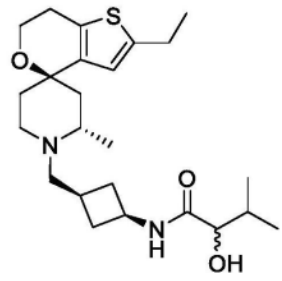
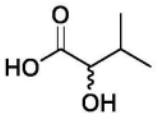
[0735]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
307			*化合物 300*	LCMS *m/z* 479.23 $[M+H]^+$。
308			*化合物 300*	LCMS *m/z* 444.21 $[M+H]^+$。
309			*化合物 300*	LCMS *m/z* 453.20 $[M+H]^+$。
310			*化合物 300*	LCMS *m/z* 455.19 $[M+H]^+$。

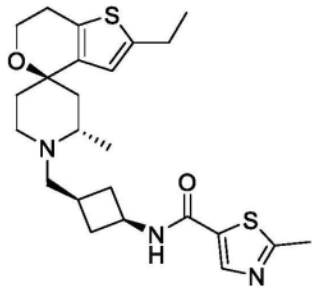
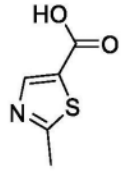
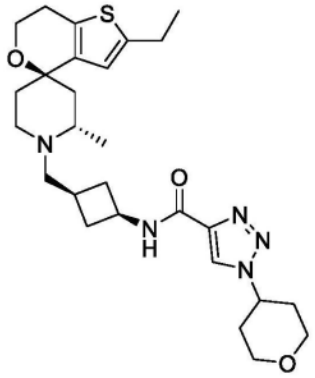
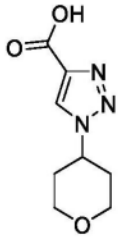
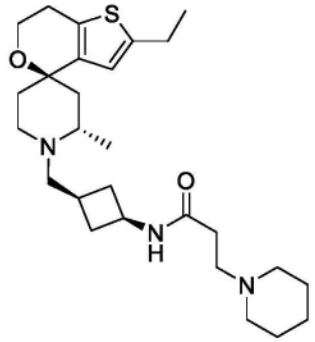
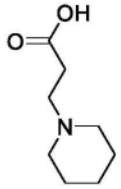
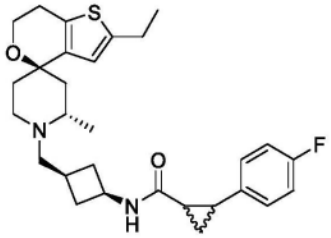
[0736]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
311			*化合物 300*	LCMS *m/z* 495.10 $[M+H]^+$。
312			*化合物 300*	LCMS *m/z* 473.30 $[M+H]^+$。
313			*化合物 300*	LCMS *m/z* 485.23 $[M+H]^+$。
314			*化合物 300*	LCMS *m/z* 495.29 $[M+H]^+$。

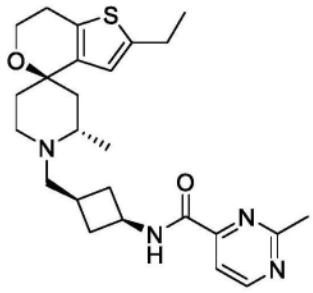
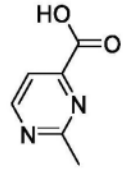
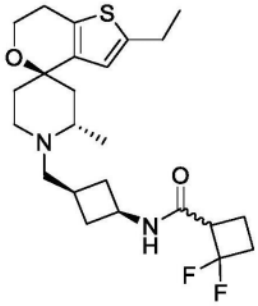
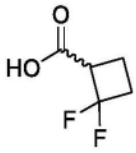
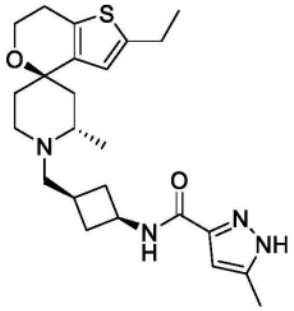
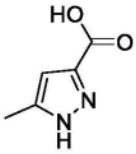
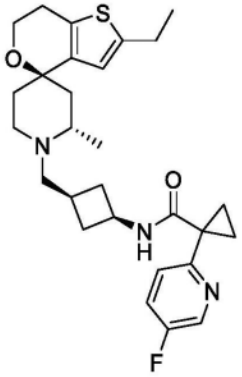
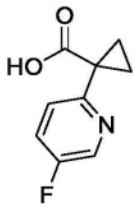
[0737]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
315			*化合物300*	LCMS *m/z* 475.29 $[M+H]^+$。
316			*化合物300*	LCMS *m/z* 480.24 $[M+H]^+$。
317			*化合物300*	LCMS *m/z* 485.29 $[M+H]^+$。
318			*化合物300*	LCMS *m/z* 459.26 $[M+H]^+$。
319			*化合物300*	LCMS *m/z* 435.26 $[M+H]^+$。

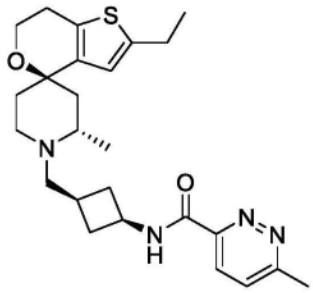
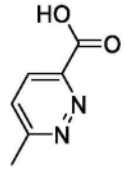
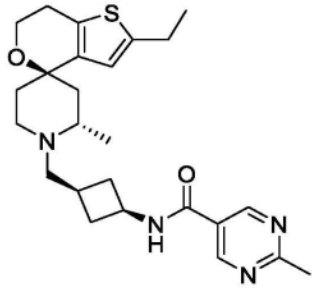
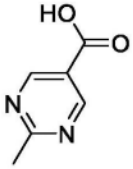
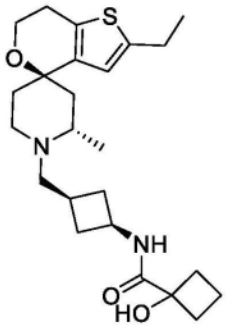
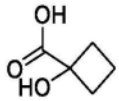
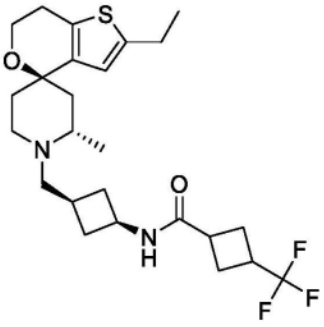
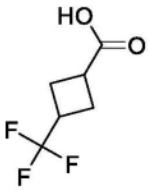
[0738]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
320			*化合物 300*	LCMS *m/z* 460.18 $[M+H]^+$。
321			*化合物 300*	LCMS *m/z* 514.25 $[M+H]^+$。
322			*化合物 300*	LCMS *m/z* 474.28 $[M+H]^+$。
323			*化合物 300*	LCMS *m/z* 497.25 $[M+H]^+$。

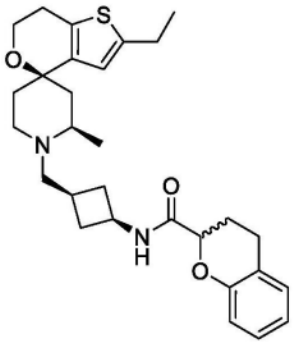
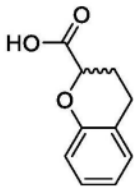
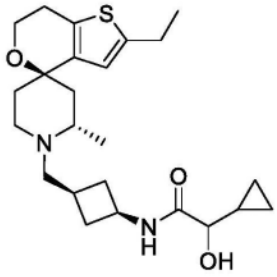
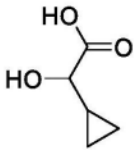
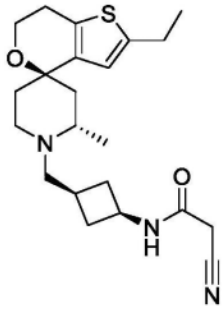
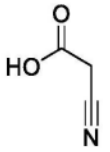
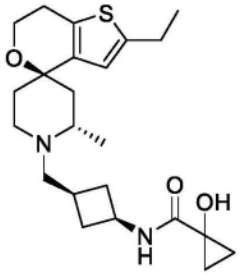
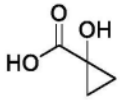
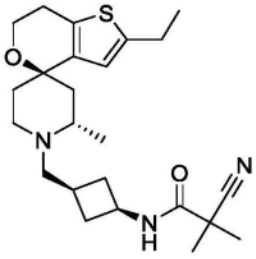
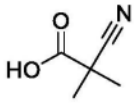
[0739]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
324			*化合物 300*	LCMS *m/z* 455.22 $[M+H]^+$。
325			*化合物 300*	LCMS *m/z* 453.20 $[M+H]^+$。
326			*化合物 300*	LCMS *m/z* 443.20 $[M+H]^+$。
327			*化合物 300*	LCMS *m/z* 498.22 $[M+H]^+$。

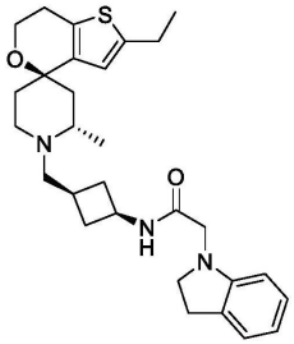
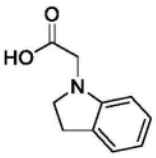
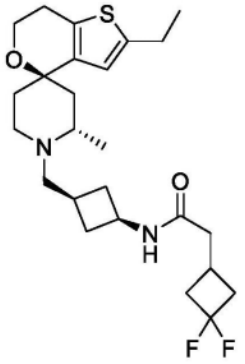
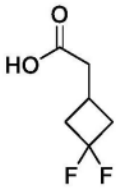
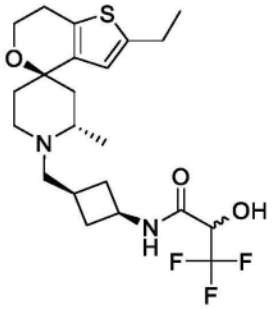
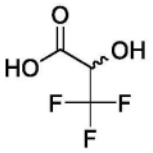
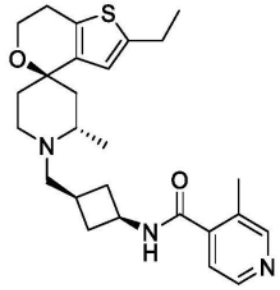
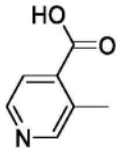
[0740]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
328			*化合物 300*	LCMS *m/z* 455.22 $[M+H]^+$。
329			*化合物 300*	LCMS *m/z* 455.22 $[M+H]^+$。
330			*化合物 300*	LCMS *m/z* 433.33 $[M+H]^+$。
331			*化合物 300*	LCMS *m/z* 485.39 $[M+H]^+$。

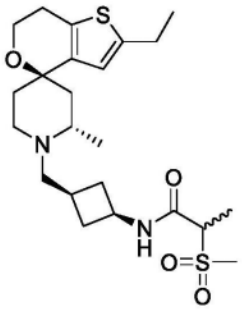
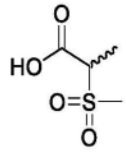
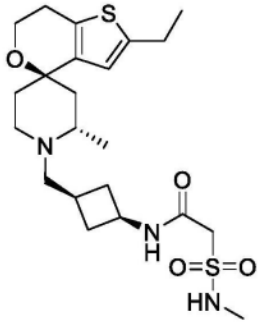
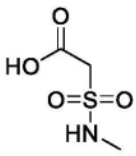
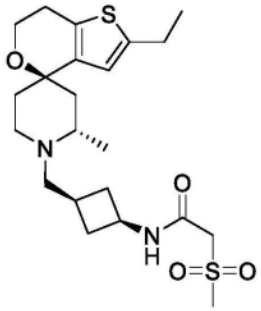
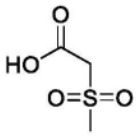
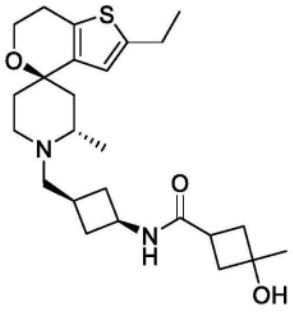
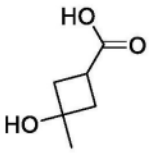
[0741]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
332			*化合物 300*	LCMS *m/z* 495.23 $[M+H]^+$。
333			*化合物 300*	LCMS *m/z* 433.27 $[M+H]^+$。
334			*化合物 300*	LCMS *m/z* 402.26 $[M+H]^+$。
335			*化合物 300*	LCMS *m/z* 419.26 $[M+H]^+$。
336			*化合物 300*	LCMS *m/z* 430.14 $[M+H]^+$。

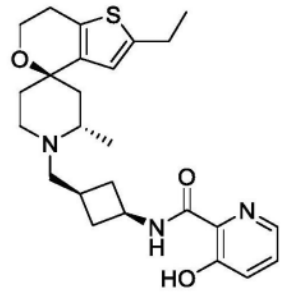
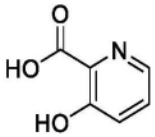
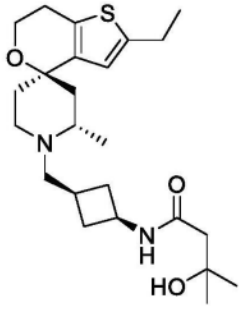
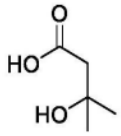
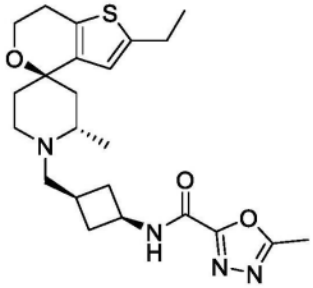
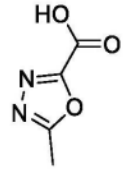
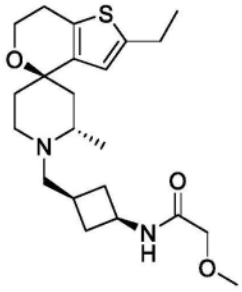
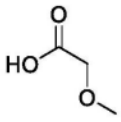
[0742]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
337			*化合物 300*	LCMS *m/z* 494.31 $[M+H]^+$。
338			*化合物 300*	LCMS *m/z* 467.24 $[M+H]^+$。
339			*化合物 300*	LCMS *m/z* 461.19 $[M+H]^+$。
340			*化合物 300*	LCMS *m/z* 454.05 $[M+H]^+$。

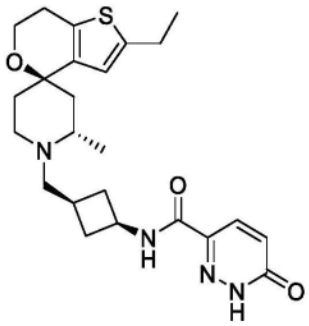
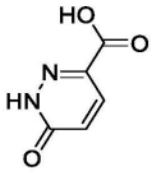
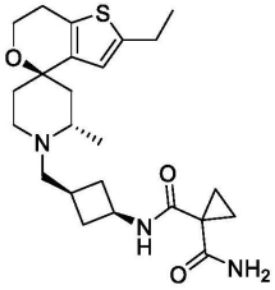
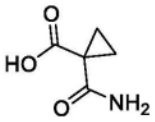
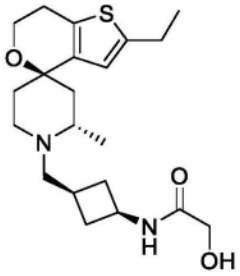
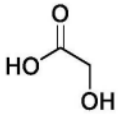
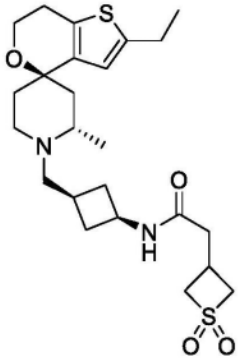
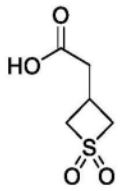
[0743]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
341			*化合物 300*	LCMS *m/z* 469.20 $[M+H]^+$。
342			*化合物 300*	LCMS *m/z* 470.21 $[M+H]^+$。
343			*化合物 300*	LCMS *m/z* 455.16 $[M+H]^+$。
344			*化合物 300*	LCMS *m/z* 447.24 $[M+H]^+$。

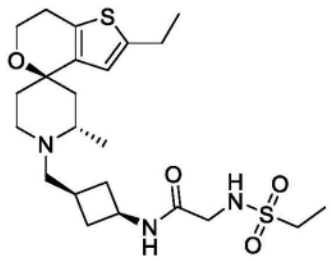
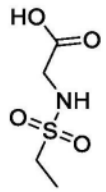
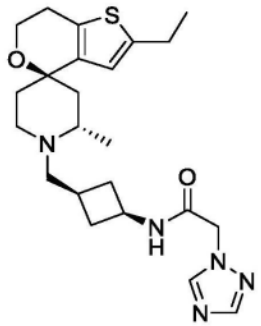
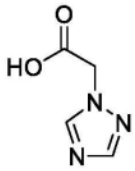
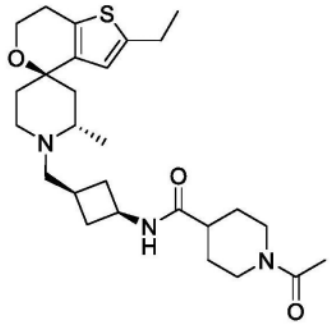
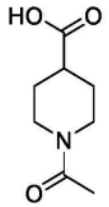
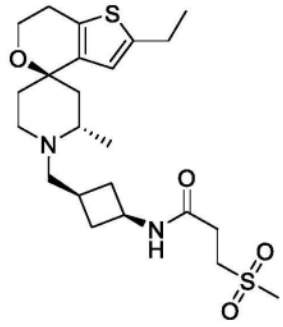
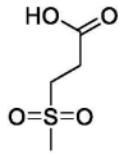
[0744]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
345			*化合物 300*	LCMS *m/z* 456.23 $[M+H]^+$。
346			*化合物 300*	LCMS *m/z* 435.29 $[M+H]^+$。
347			*化合物 300*	LCMS *m/z* 445.35 $[M+H]^+$。
348			*化合物 300*	LCMS *m/z* 407.21 $[M+H]^+$。

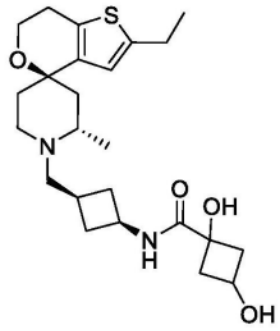
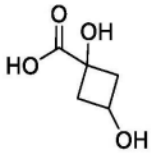
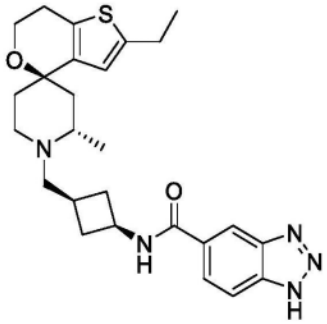
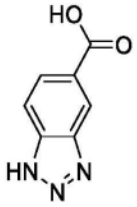
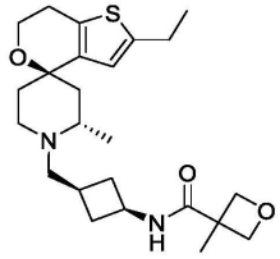
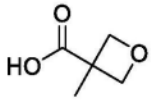
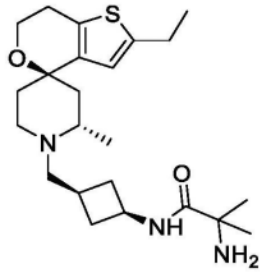
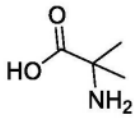
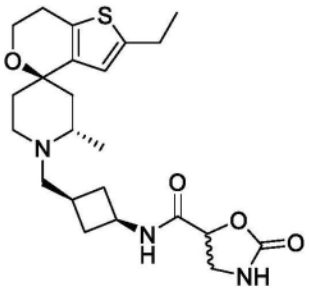
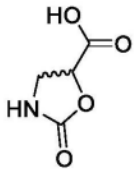
[0745]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
349			*化合物300*	LCMS *m/z* 457.21 $[M+H]^+$。
350			*化合物300*	LCMS *m/z* 446.23 $[M+H]^+$。
351			*化合物300*	LCMS *m/z* 393.20 $[M+H]^+$。
352			*化合物300*	LCMS *m/z* 481.19 $[M+H]^+$。

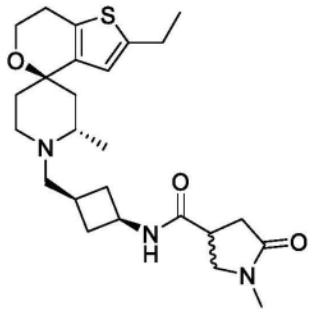
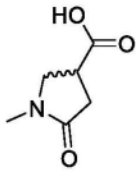
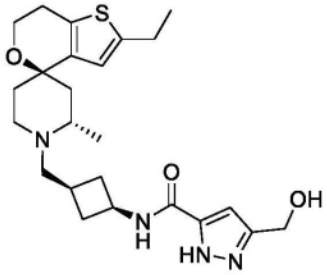
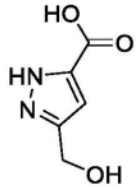
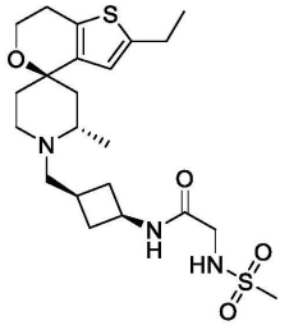
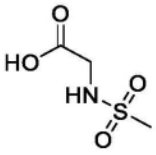
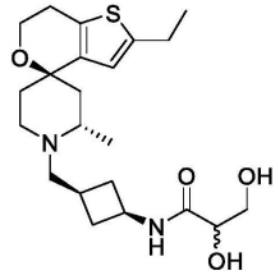
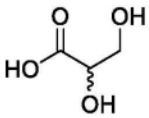
[0746]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
353			*化合物 300*	LCMS *m/z* 484.05 $[M+H]^+$。
354			*化合物 300*	LCMS *m/z* 444.21 $[M+H]^+$。
355			*化合物 300*	LCMS *m/z* 488.29 $[M+H]^+$。
356			*化合物 300*	LCMS *m/z* 469.20 $[M+H]^+$。

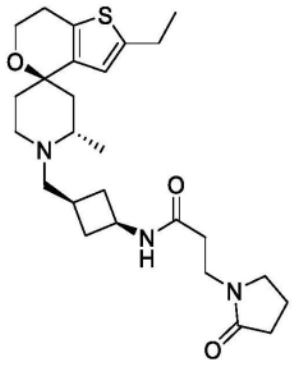
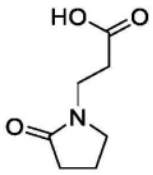
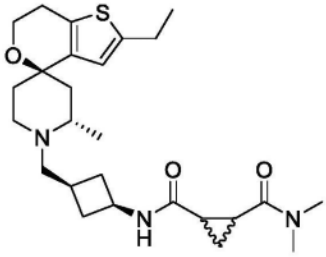
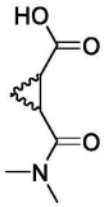
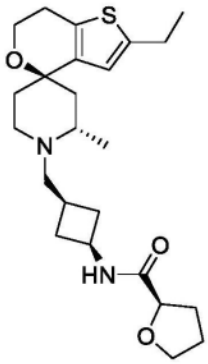
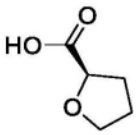
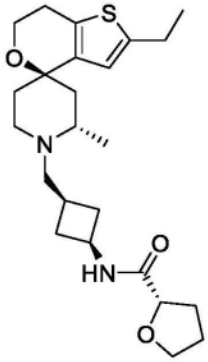
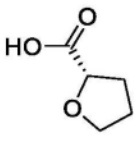
[0747]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
357			*化合物 300*	LCMS *m/z* 449.26 $[M+H]^+$。
358			*化合物 300*	LCMS *m/z* 480.21 $[M+H]^+$。
359			*化合物 300*	LCMS *m/z* 433.24 $[M+H]^+$。
360			*化合物 300*	LCMS *m/z* 420.40 $[M+H]^+$；
361			*化合物 300*	LCMS *m/z* 448.02 $[M+H]^+$。

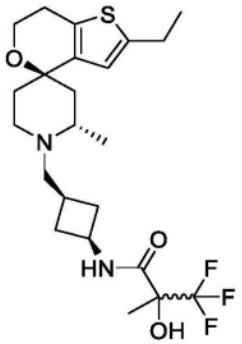
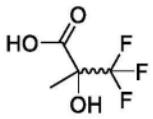
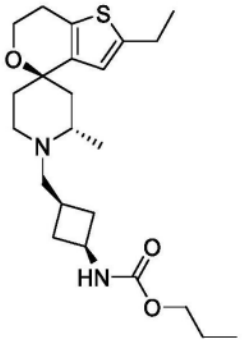
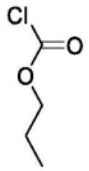
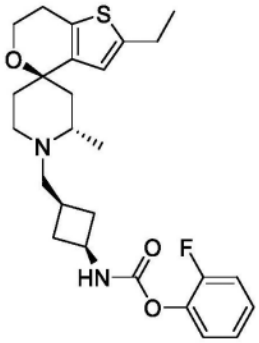
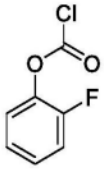
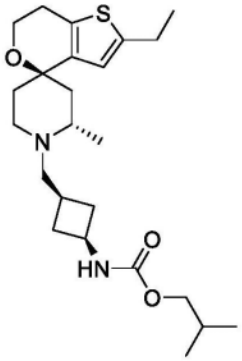
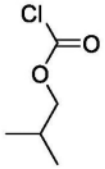
[0748]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
362			*化合物 300*	LCMS *m/z* 460.24 $[M+H]^+$。
363			*化合物 300*	LCMS *m/z* 459.07 $[M+H]^+$。
364			*化合物 300*	LCMS *m/z* 470.18 $[M+H]^+$。
365			*化合物 300*	LCMS *m/z* 423.20 $[M+H]^+$。

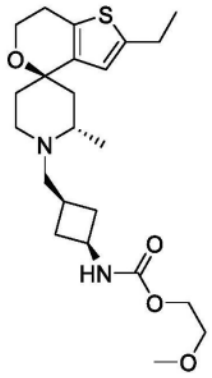
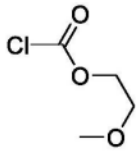
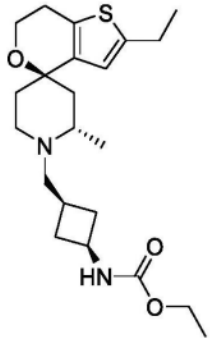
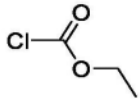
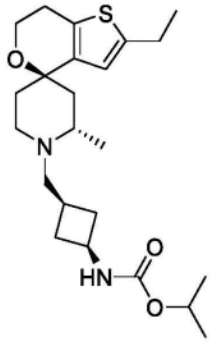
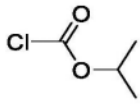
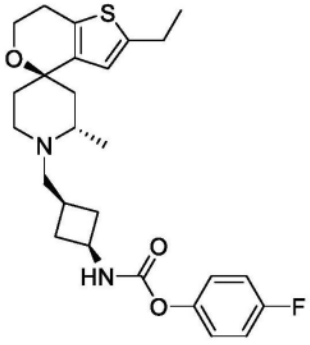
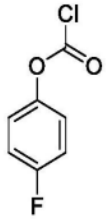
[0749]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
366			*化合物 300*	LCMS *m/z* 474.28 $[M+H]^+$。
367			*化合物 300*	LCMS *m/z* 474.28 $[M+H]^+$。
368			*化合物 301*	LCMS *m/z* 433.24 $[M+H]^+$。
369			*化合物 301*	LCMS *m/z* 433.07 $[M+H]^+$。

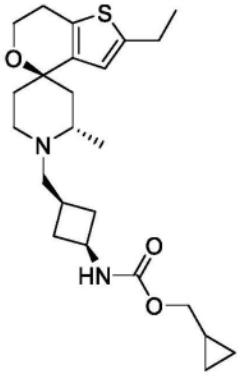
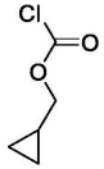
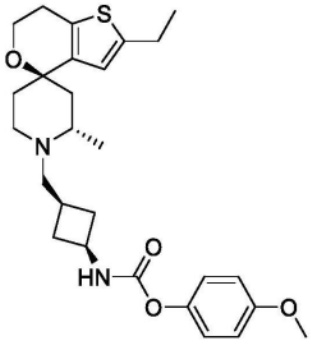
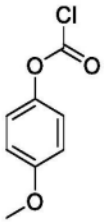
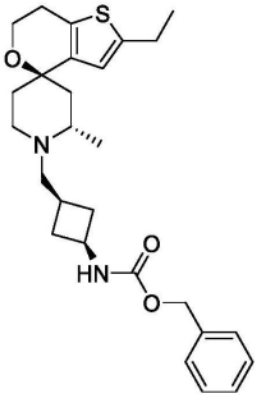
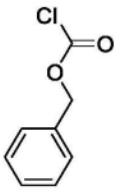
[0750]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
370			*化合物 301*	LCMS *m/z* 475.60 $[M+H]^+$。
371			*化合物 302*	LCMS *m/z* 421.25 $[M+H]^+$。
372			*化合物 302*	LCMS *m/z* 473.17 $[M+H]^+$。
373			*化合物 302*	LCMS *m/z* 435.29 $[M+H]^+$。

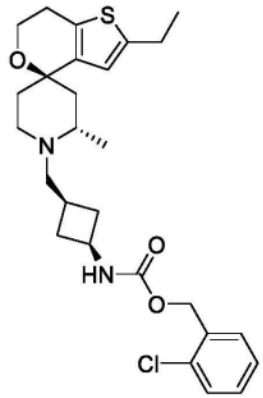
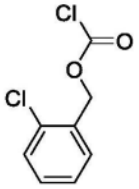
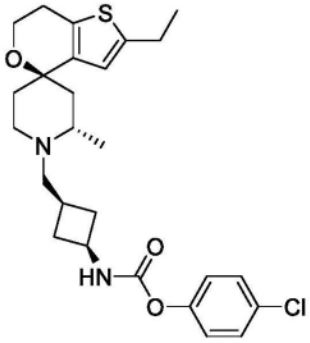
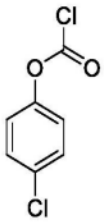
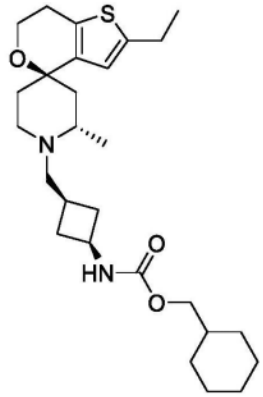
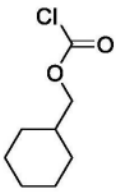
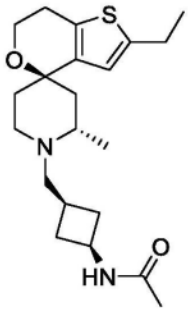
[0751]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
374			*化合物 302*	LCMS *m/z* 437.27 $[M+H]^+$。
375			*化合物 302*	LCMS *m/z* 407.24 $[M+H]^+$。
376			*化合物 302*	LCMS *m/z* 421.25 $[M+H]^+$。
377			*化合物 302*	LCMS *m/z* 473.21 $[M+H]^+$。

[0752]

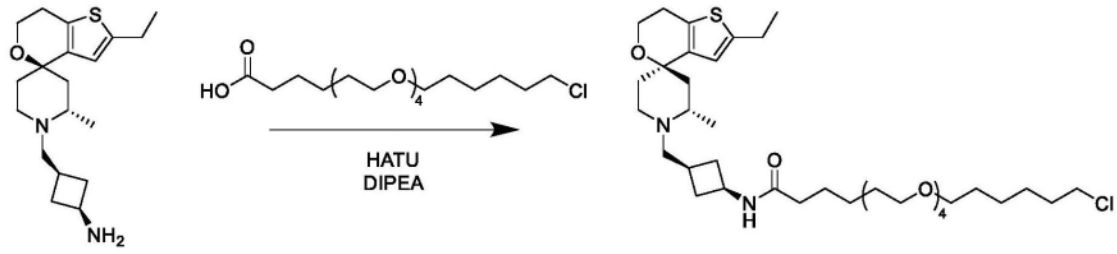
化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
378			*化合物 302*	LCMS *m/z* 433.24 $[M+H]^+$。
379			*化合物 302*	LCMS *m/z* 485.19 $[M+H]^+$。
380			*化合物 302*	LCMS *m/z* 469.23 $[M+H]^+$。

[0753]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
381			*化合物 302*	LCMS *m/z* 503.08 $[M+H]^+$。
382			*化合物 302*	LCMS *m/z* 489.17 $[M+H]^+$。
383			*化合物 302*	LCMS *m/z* 475.29 $[M+H]^+$。
384			*化合物 302*[1]	LCMS *m/z* 377.07 $[M+H]^+$。

[0754] 1)DIPEA用作碱化合物385

[0755] 6-[2-[2-[2-(6-氯己氧基)乙氧基]乙氧基]乙氧基]-N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]己酰胺(385)

[0756] 

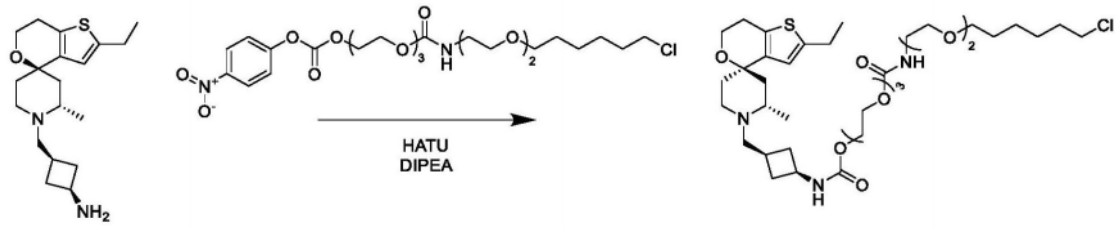
299 385

[0757] 6-[2-[2-[2-(6-氯己氧基)乙氧基]乙氧基]乙氧基]-N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]己酰胺(385)的制备

[0758] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(三氟乙酸盐)(299)(30mg,0.05333mmol)溶解在DMF(1mL)中,向其中添加6-[2-[2-[2-(6-氯己氧基)乙氧基]乙氧基]乙氧基]己酸(25mg,0.06529mmol)、DIPEA(50μL,0.2871mmol)和HATU(24mg,0.06312mmol),并将反应混合物在室温下搅拌1小时。通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1% TFA),得到产物6-[2-[2-[2-(6-氯己氧基)乙氧基]乙氧基]乙氧基]-N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]己酰胺(三氟乙酸盐)(385)(24mg,55%)。LCMS m/z 699.24[M+H]$^+$。

[0759] 化合物(386)

[0760] 2-[2-[2-[[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酰基氧基]乙氧基]乙氧基]N-[2-[2-(6-氯己氧基)乙氧基]乙基]氨基甲酸乙酯(386)

[0761] 

299 386

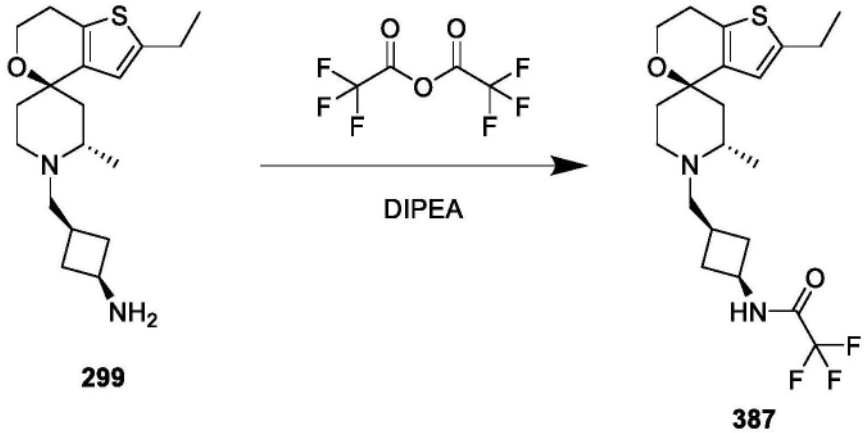
[0762] 2-[2-[2-[[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酰基氧基]乙氧基]乙氧基]N-[2-[2-(6-氯己氧基)乙氧基]乙基]氨基甲酸乙酯(386)的制备

[0763] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(三氟乙酸盐)(299)(49mg,0.08710mmol)溶解在DMF(1mL)中,向其中添加2-[2-[2-[2-[2-(6-氯己氧基)乙氧基]乙胺基甲酰基氧基]乙氧基]乙氧基](4-硝基苯基)碳酸乙酯(59mg,0.1044mmol)和DIPEA(75μL,0.4306mmol),并将反应物在室温下搅拌12小时。通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1%甲酸),得到产物2-[2-[2-[[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酰基氧基]乙氧基]乙氧基]N-[2-[2-(6-氯己氧基)乙氧基]乙基]氨基甲酸乙酯(甲酸盐)(386)(25mg,35%)。LCMS m/z 760.27[M+H]$^+$。

[0764] 化合物387

[0765] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-

[0766] 基]甲基]环丁基]-2,2,2-三氟-乙酰胺(387)

[0767] 

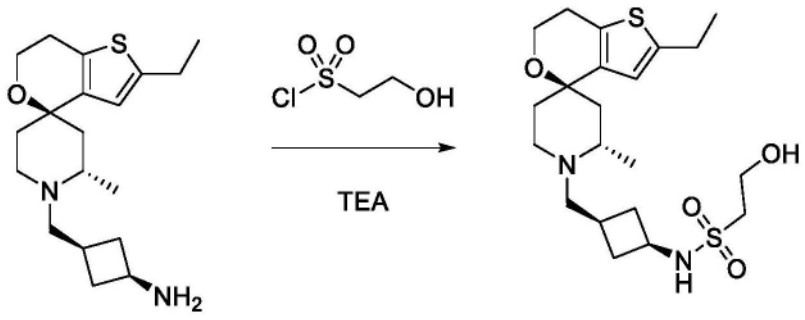
299 387

[0768] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2,2,2-三氟-乙酰胺(387)的制备

[0769] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(盐酸盐)(299)(20mg,0.05391mmol)溶解在DCM(1mL)中,向其中添加(2,2,2-三氟乙酰基)2,2,2-三氟乙酸盐(9μL,0.06475mmol)和DIPEA(19μL,0.1091mmol)。将反应物在室温下搅拌2小时,然后将溶剂蒸发。通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1% TFA),得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2,2,2-三氟-乙酰胺(387)(8.5mg,32%)。LCMS m/z 431.15$[M+H]^+$。

[0770] 化合物388

[0771] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-羟基-乙磺酰胺(388)

[0772] 

299 388

[0773] N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-羟基-乙磺酰胺(388)的制备

[0774] 将3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺和2-羟基乙磺酰氯溶解在DCM(1mL)中,向其中添加TEA(20μL,0.1435mmol)。将反应物在室温下搅拌2小时,然后将溶剂蒸发,并且将粗材料重新溶解在最

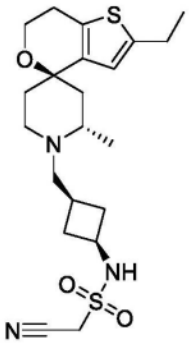
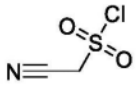
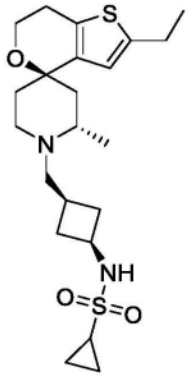
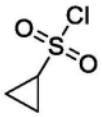
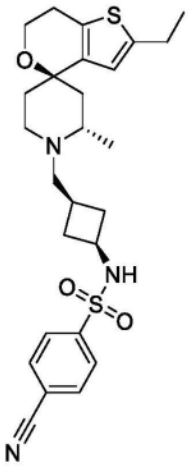
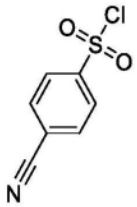
小MeOH中。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]-2-羟基-乙磺酰胺(三氟乙酸盐)(388)(5.6mg,20%)。LCMS m/z 443.14$[M+H]^+$。

[0775] 化合物389-417

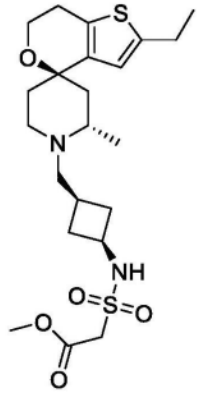
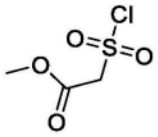
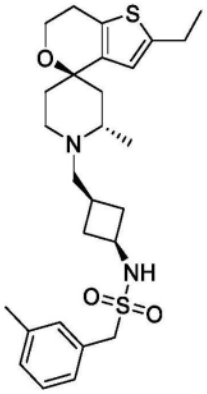
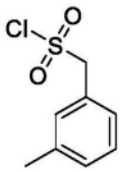
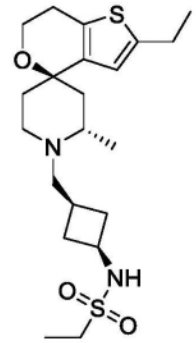
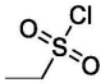
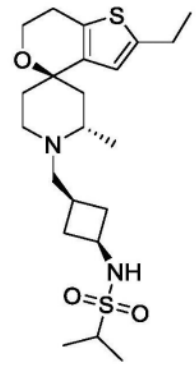
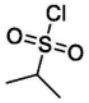
[0776] 使用388的偶联方法,由中间体299在单个步骤中制备了化合物389-417(参见表9)。磺酰氯从商业来源获得。

[0777] 表9:化合物389-417的结构和物理化学数据

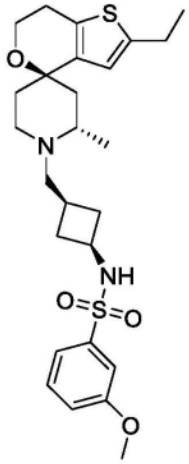
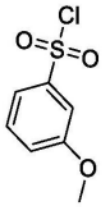
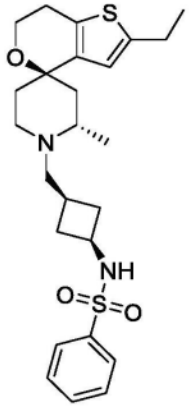
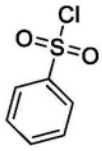
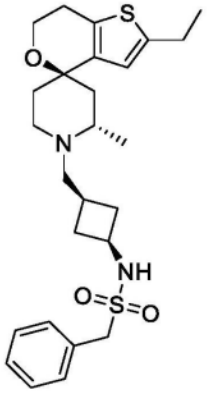
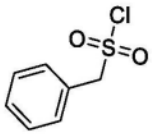
[0778]

化合物	结构	胺试剂	^{1}H NMR; LCMS m/z $[M+H]^+$。
389			LCMS *m/z* 438.15 $[M+H]^+$。
390			LCMS *m/z* 439.16 $[M+H]^+$。
391			LCMS *m/z* 500.01 $[M+H]^+$。

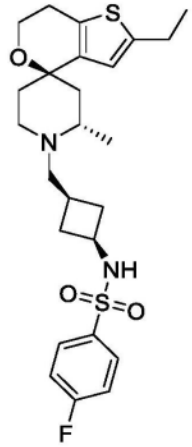
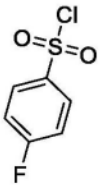
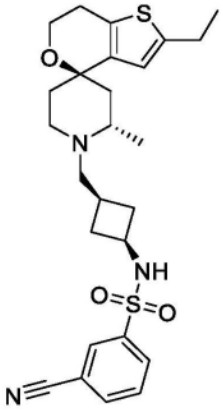
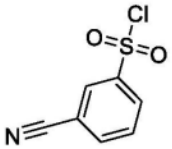
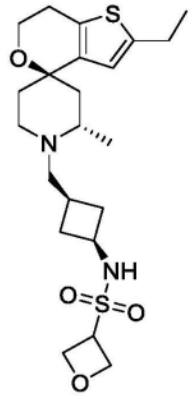
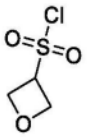
[0779]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
392			LCMS *m/z* 471.15 $[M+H]^+$。
393			LCMS *m/z* 503.37 $[M+H]^+$。
394			LCMS *m/z* 427.21 $[M+H]^+$。
395			LCMS *m/z* 441.28 $[M+H]^+$。

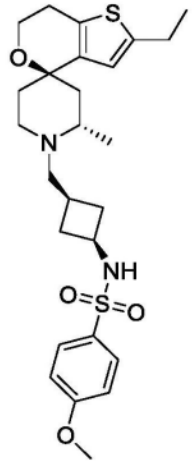
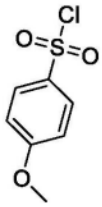
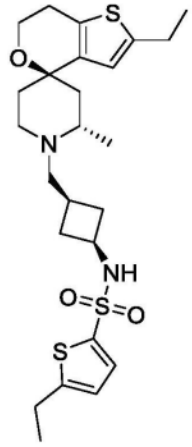
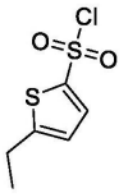
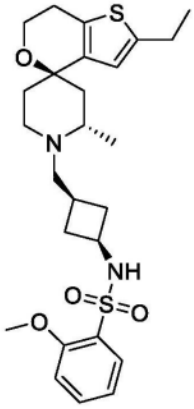
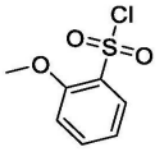
[0780]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
396			LCMS *m/z* 505.19 $[M+H]^+$。
397			LCMS *m/z* 475.19 $[M+H]^+$。
398			LCMS *m/z* 489.00 $[M+H]^+$。

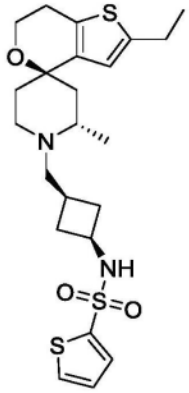
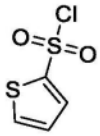
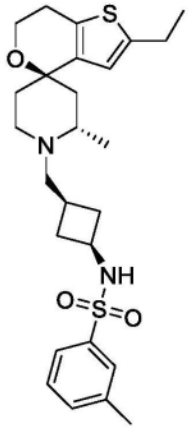
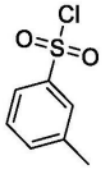
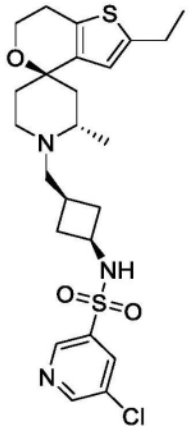
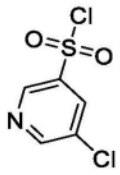
[0781]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
399			LCMS *m/z* 493.17 $[M+H]^+$。
400			LCMS *m/z* 500.18 $[M+H]^+$。
401			LCMS *m/z* 455.19 $[M+H]^+$。

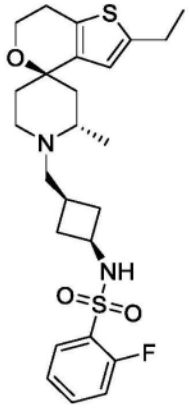
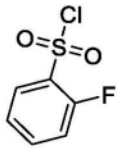
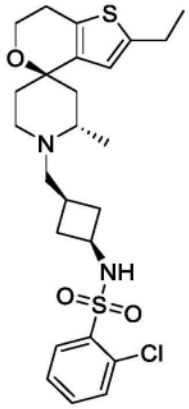
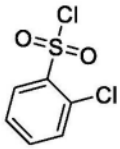
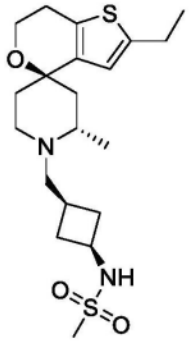
[0782]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
402			LCMS *m/z* 505.03 $[M+H]^+$。
403			LCMS *m/z* 509.13 $[M+H]^+$。
404			LCMS *m/z* 505.39 $[M+H]^+$。

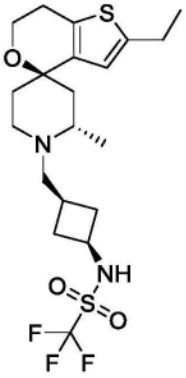
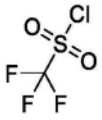
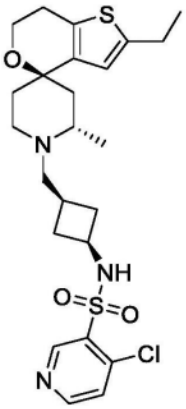
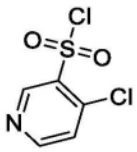
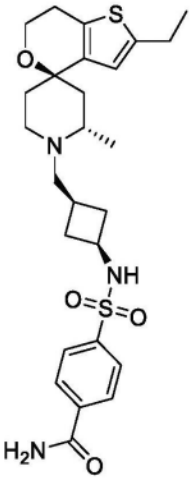
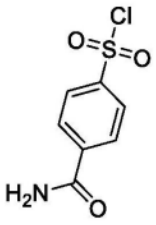
[0783]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
405			LCMS *m/z* 481.15 $[M+H]^+$。
406			LCMS *m/z* 489.17 $[M+H]^+$。
407			LCMS *m/z* 509.98 $[M+H]^+$。

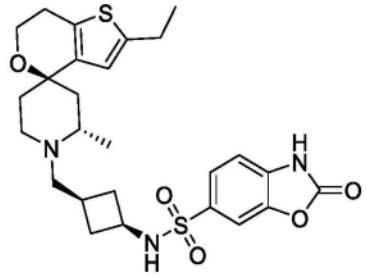
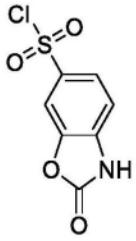
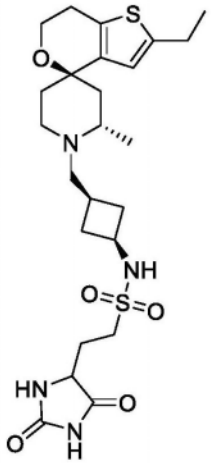
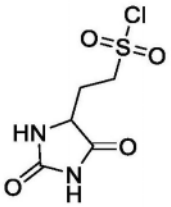
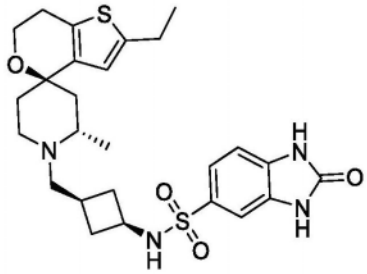
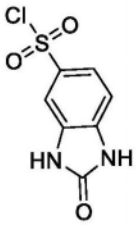
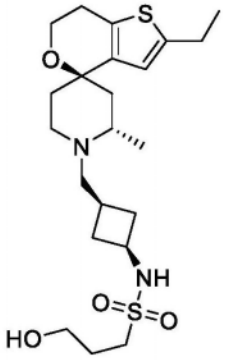
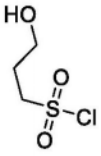
[0784]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
408			LCMS *m/z* 493.14 $[M+H]^+$。
409			LCMS *m/z* 509.13 $[M+H]^+$。
410			LCMS *m/z* 413.20 $[M+H]^+$。

[0785]

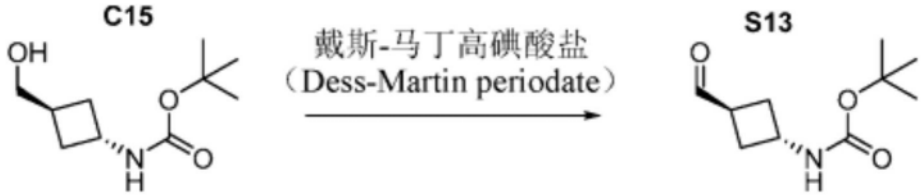
化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
411			LCMS *m/z* 467.21 $[M+H]^+$。
412			LCMS *m/z* 510.11 $[M+H]^+$。
413			LCMS *m/z* 518.29 $[M+H]^+$。

[0786]

化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
414			LCMS *m/z* 429.07 $[M+H]^+$。
415			LCMS *m/z* 525.39 $[M+H]^+$。
416			LCMS *m/z* 531.06 $[M+H]^+$。
417			LCMS *m/z* 457.28 $[M+H]^+$。

[0787] 制备S13

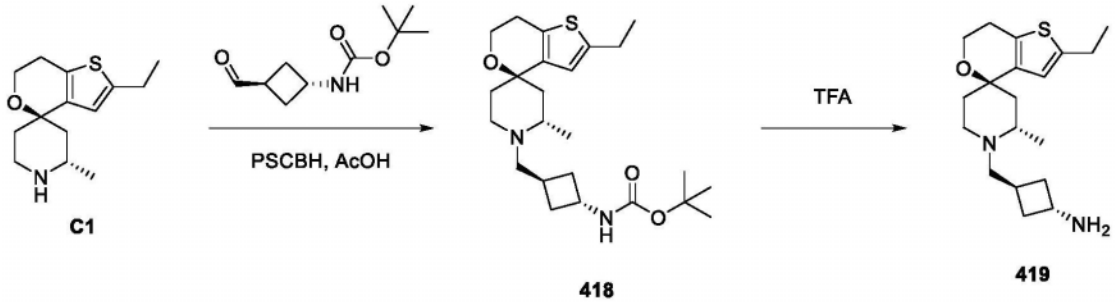
[0788] N-(3-甲酰环丁基)氨基甲酸叔丁酯(S13)

[0789] 

[0790] N-(3-甲酰环丁基)氨基甲酸叔丁酯(S13)的制备

[0791] N-[3-(羟甲基)环丁基]氨基甲酸叔丁酯(263mg,1.269mmol)溶解在DCM(4mL)中,向其中添加戴斯-马丁高碘酸盐(1.211g,2.855mmol)。将反应物在室温下搅拌3小时,然后用DCM洗脱液通过SiO_2塞过滤,并在真空中蒸发。通过硅胶色谱法纯化(4g柱,含0-40% EtOAc的庚烷),得到产物N-(3-甲酰环丁基)氨基甲酸叔丁酯(S13)(117mg,46%)。^{1}H NMR(300MHz,氯仿-d)δ9.84(d,J=1.9Hz,1H),4.75(s,1H),4.25-4.00(m,1H),3.12-2.94(m,1H),2.75-2.60(m,2H),2.28-2.07(m,2H),1.45(s,9H)。LCMS m/z200.14$[M+H]^+$。

[0792] 化合物419的制备3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(419)

[0793] 

[0794] 步骤1:N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(418)的合成

[0795] 向微波管中装入含(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]三氟甲烷磺酸盐(C1)(116mg,0.2887mmol)、N-(3-甲酰环丁基)氨基甲酸叔丁酯(S13)(110mg,0.5571mmol)、聚合物负载的氰基硼氢化物(455mg的2mmol/g,0.9104mmol)和乙酸(100μL,1.758mmol)的DCM(2mL)。在微波辐射下将反应加热至110℃,持续30分钟。冷却至室温后,过滤反应物,并将滤液用DCM(10mL)稀释。将有机相用1M NaOH(10mL)洗涤,经Na_2SO_4干燥,过滤,并在真空中蒸发。通过硅胶色谱法纯化(4g柱,含0-10% MeOH的DCM),得到产物N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(418)(19mg,15%)。^{1}H NMR(300MHz,氯仿-d)δ6.49(s,1H),4.91-4.55(bs,1H),4.31-4.03(m,1H),4.01-3.80(m,2H),3.07-2.88(m,1H),2.86

[0796] -1.59(m,17H),1.46(s,9H),1.28(t,J=7.5Hz,3H),1.10(d,J=6.2Hz,3H)。LCMS m/z 435.40$[M+H]^+$。

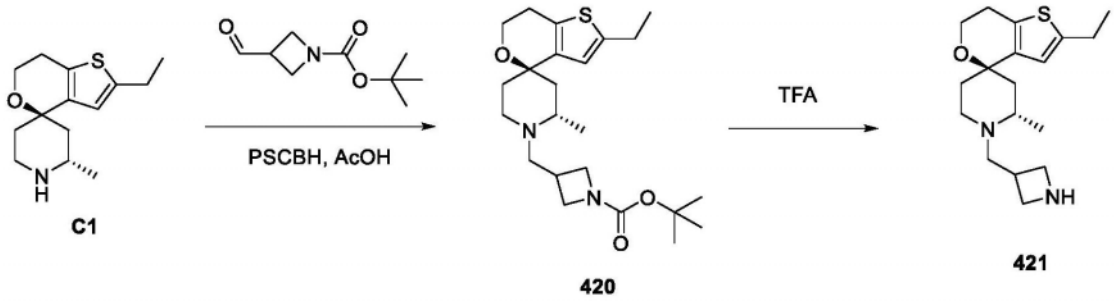
[0797] 步骤2:3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(三氟乙酸(2))(419)的合成

[0798] 将N-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(418)(16mg,0.03706mmol)溶解在DCM(300μL)中,向其中添加TFA(100μL,1.298mmol)。将反应物在室温下搅拌3小时,并且然后过滤反应混合物。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含

MeCN的H_2O,具有0.1%三氟乙酸,得到产物3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]环丁胺(三氟乙酸(2))(419)(13mg,62%)。LCMS m/z335.21[M+H]$^+$。

[0799] 化合物421的制备

[0800] (2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](421)

[0801] 

[0802] 步骤1:3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸叔丁酯(420)的合成

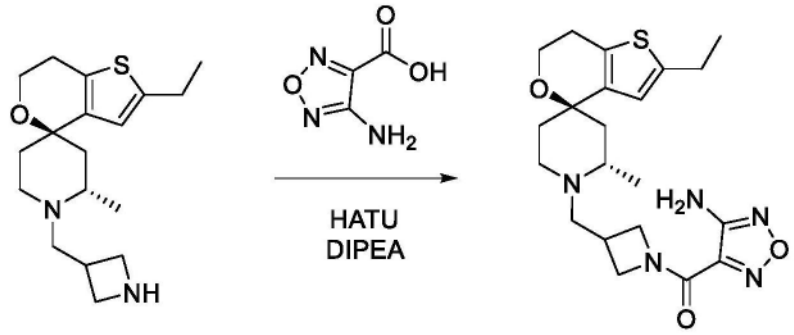
[0803] 向微波管中装入含(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]三氟甲烷磺酸盐(C1)(2.5g,6.243mmol)、3-甲酰基氮杂环丁烷-1-甲酸叔丁酯(4.65g,25.11mmol)、聚合物负载的氰基硼氢化物(12.5g的2mmol/g,25.00mmol)和乙酸(2.5mL,43.96mmol)的DCM(50mL)。在微波辐射下将反应加热至110℃,持续30分钟。冷却至室温后,过滤反应物,并将滤液在真空中浓缩。通过硅胶色谱法纯化(120g柱,含0-5% MeOH的DCM),得到产物3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸叔丁酯(420)(1.838g,67%)。^{1}H NMR(300MHz,氯仿-d)δ6.48(s,1H),4.05(td,J=8.4,4.3Hz,2H),3.98-3.82(m,2H),3.66(dd,J=8.6,5.7Hz,1H),3.59(dd,J=8.5,5.7Hz,1H),3.07(dd,J=12.9,7.8Hz,1H),2.86-2.70(m,5H),2.70-2.53(m,2H),2.53-2.40(m,2H),1.91-1.77(m,3H),1.70-1.58(m,1H),1.46(s,9H),1.28(t,J=7.5Hz,3H),1.09(d,J=6.2Hz,3H)。LCMS m/z 421.5[M+H]$^+$。

[0804] 步骤2:(2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](421)的合成

[0805] 将TFA(3.0mL,38.94mmol)添加到3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸叔丁酯(420)(1.8g,4.205mmol)于DCM(12mL)中的溶液中,并将反应物在室温下搅拌3小时。将所得溶液在真空中浓缩以产生粗产物(2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸(2)盐)(421)(3.657g,95%)。LCMS m/z 321.22[M+H]$^+$。

[0806] 化合物422

[0807] (4-氨基-1,2,5-噁二唑-3-基)-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-基]甲酮(422)

[0808] 

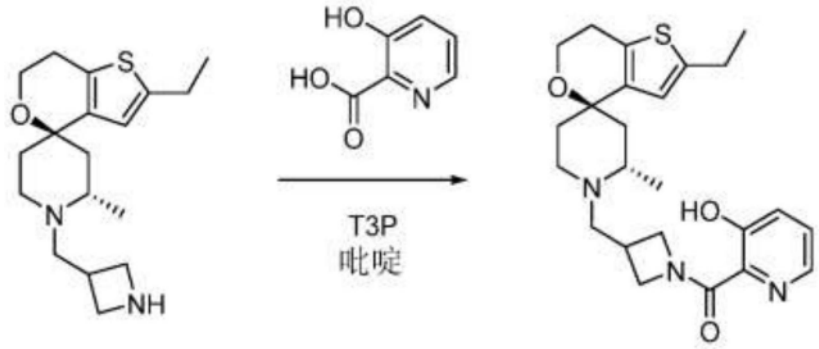
421 422

[0809] (4-氨基-1,2,5-噁二唑-3-基)-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-基]甲酮(422)的制备

[0810] 将(2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸(2)盐)421(34mg,0.03719mmol)溶解在DMF(300μL)和DIPEA(50μL,0.285mmol)中,向其中添加4-氨基-1,2,5-噁二唑-3-甲酸(16mg,0.1228mmol)和HATU(40mg,0.1052mmol)。将反应物在室温下搅拌16小时,然后将溶液用MeOH(500μL)稀释并过滤。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl,得到产物(4-氨基-1,2,5-噁二唑-3-基)-[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-基]甲酮(盐酸盐)(422)(7.4mg,49%)。LCMS m/z 432.19$[M+H]^+$。

[0811] 化合物423

[0812] [3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-基]-(3-羟基-2-吡啶基)甲酮(423)

[0813] 

421 423

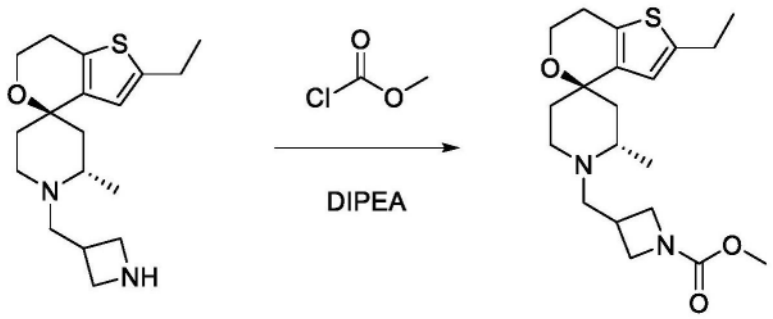
[0814] [3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-基]-(3-羟基-2-吡啶基)甲酮(423)的制备

[0815] 将(2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]421(20mg,0.0624mmol)溶解在DMF(2mL)和吡啶(50μL,0.6182mmol)中,向其中添加T3P(40mg,0.1257mmol)和3-羟基吡啶-2-甲酸(25mg,0.1797mmol)。将反应物在室温下搅拌过夜。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到[3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-

基]-(3-羟基-2-吡啶基)甲酮(2.8mg,10%)(423)。LCMS m/z 442.16[M+H]+。

[0816] 化合物424

[0817] 3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸甲酯(424)

[0818] 

421 424

[0819] 3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸甲酯(424)的制备

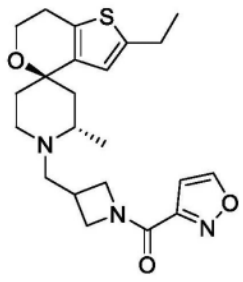
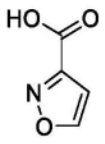
[0820] 将(2′S,4R)-1′-(氮杂环丁烷-3-基甲基)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸(2)盐)421(34mg,0.03719mmol)溶解在DMF(300μL)和DIPEA(50μL,0.285mmol)中,向其中添加氯甲酸甲酯(9.5μL,0.1228mmol)。将反应物在室温下搅拌10分钟,然后将其过滤。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有5mM HCl,得到产物3-[[(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]氮杂环丁烷-1-甲酸甲酯(盐酸盐)(424)(13.4mg,86%)。LCMS m/z379.22[M+H]+。

[0821] 化合物425-490

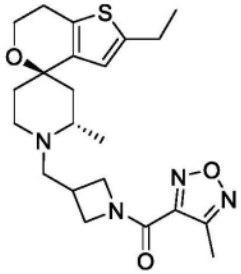
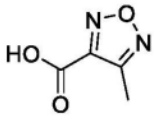
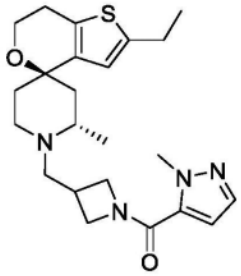
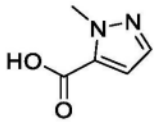
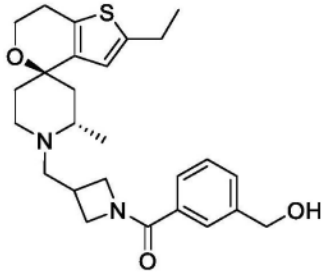
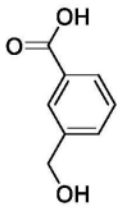
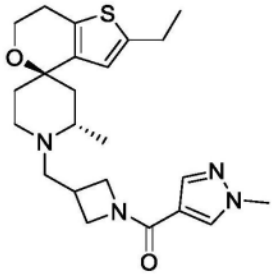
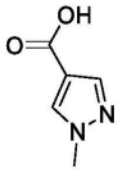
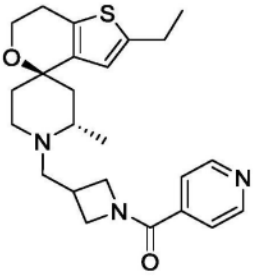
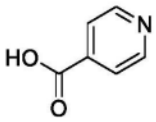
[0822] 使用适当的试剂和化合物422-424所述的酰胺形成方法,由中间体421制备化合物425-490(参见表10)。偶联配偶体从商业来源获得。

[0823] 表10:化合物425-490的制备方法、结构和物理化学数据

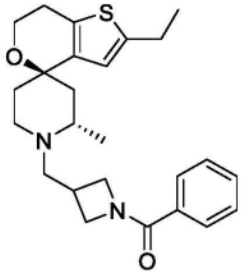
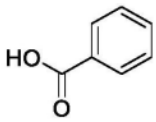
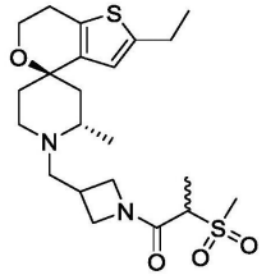
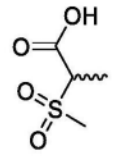
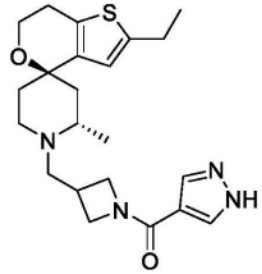
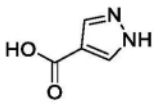
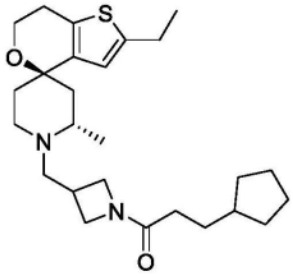
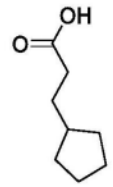
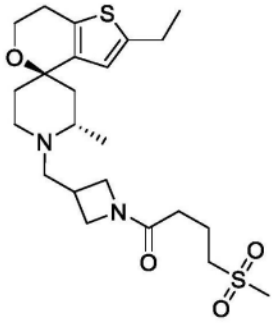
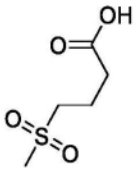
[0824]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR; LCMS m/z [M+H]$^+$。
425			*422*	LCMS *m/z* 416.2 [M+H]$^+$。

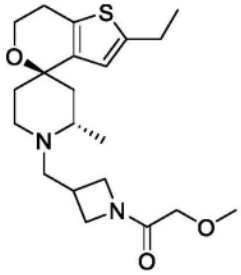
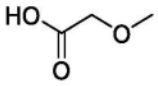
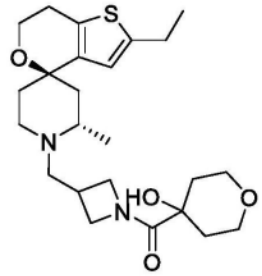
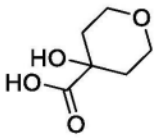
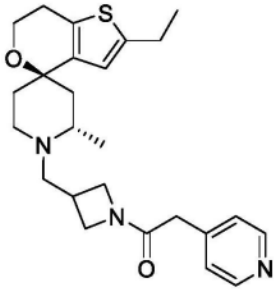
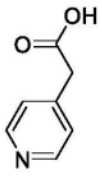
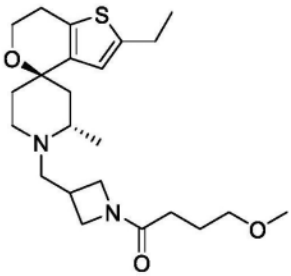
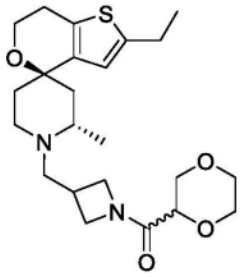
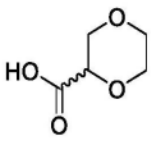
[0825]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
426			*422*	LCMS *m/z* 431.22 $[M+H]^+$。
427			*422*	LCMS *m/z* 429.23 $[M+H]^+$。
428			*422*	LCMS *m/z* 455.22 $[M+H]^+$。
429			*422*	LCMS *m/z* 429.23 $[M+H]^+$。
430			*422*	LCMS *m/z* 426.23 $[M+H]^+$。

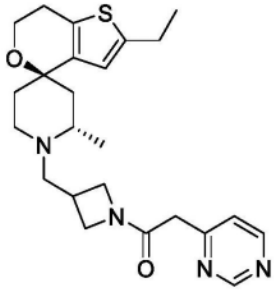
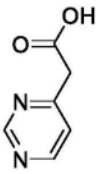
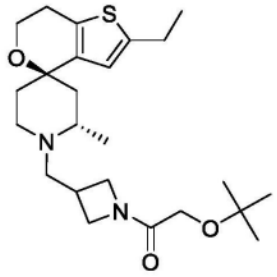
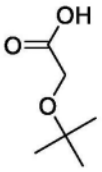
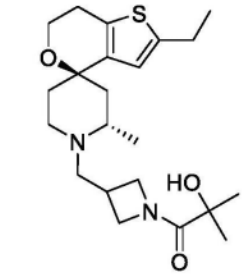
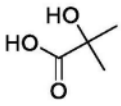
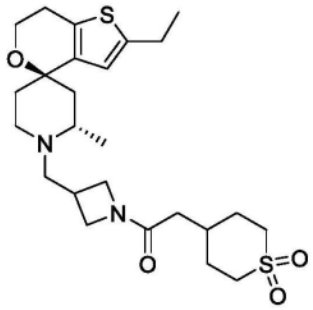
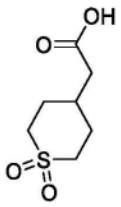
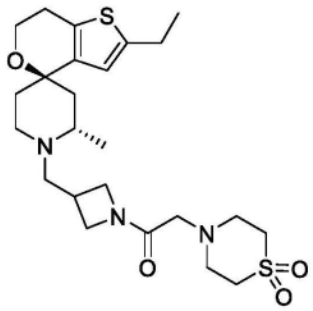
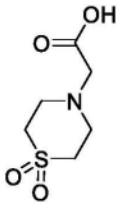
[0826]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
431			*422*	LCMS *m/z* 425.35 $[M+H]^+$。
432			*422*	LCMS *m/z* 455.19 $[M+H]^+$。
433			*422*	LCMS *m/z* 415.22 $[M+H]^+$。
434			*422*	LCMS *m/z* 445.13 $[M+H]^+$。
435			*422*	LCMS *m/z* 469.39 $[M+H]^+$。

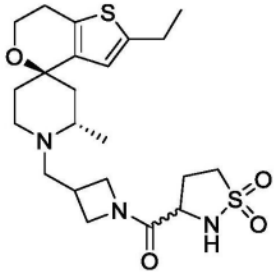
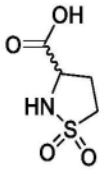
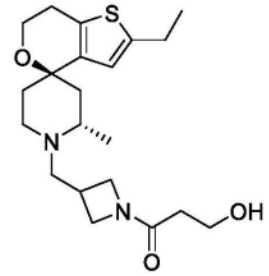
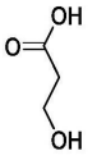
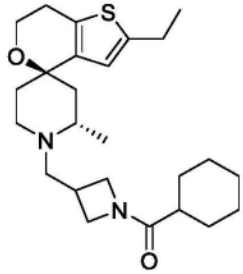
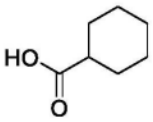
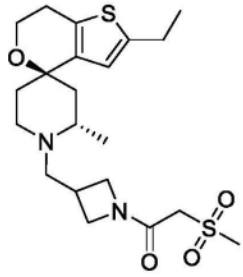
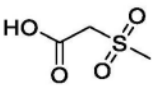
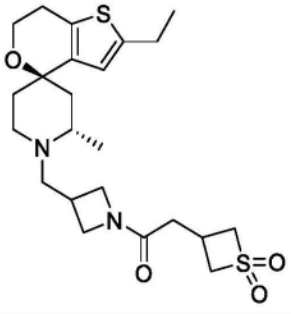
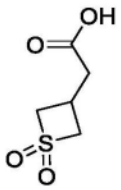
[0827]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
436			*422*	LCMS *m/z* 393.23 $[M+H]^+$。
437			*422*	LCMS *m/z* 449.23 $[M+H]^+$。
438			*422*	LCMS *m/z* 440.21 $[M+H]^+$。
439			*422*	LCMS *m/z* 421.28 $[M+H]^+$。
440			*422*	LCMS *m/z* 435.26 $[M+H]^+$.

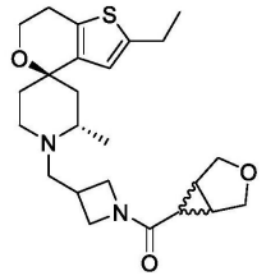
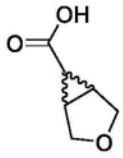
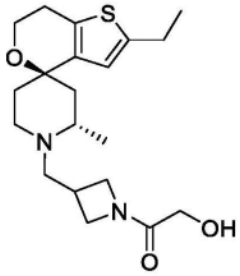
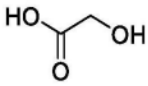
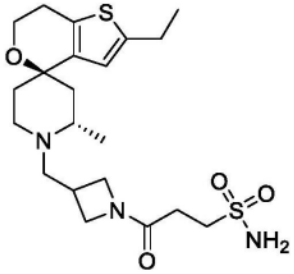
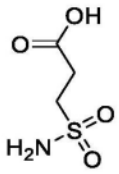
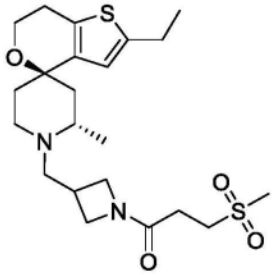
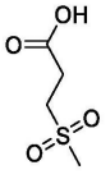
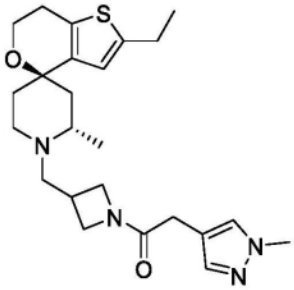
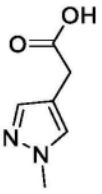
[0828]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
441			*422*	LCMS *m/z* 441.25 $[M+H]^+$。
442			*422*	LCMS *m/z* 435.42 $[M+H]^+$。
443			*422*	LCMS *m/z* 407.27 $[M+H]^+$。
444			*422*	LCMS *m/z* 495.23 $[M+H]^+$。
445			*422*	LCMS *m/z* 496.33 $[M+H]^+$。

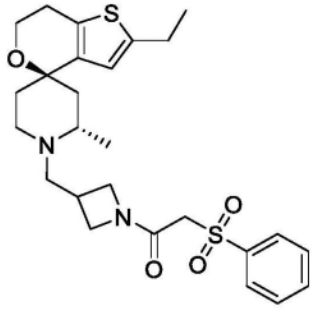
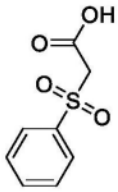
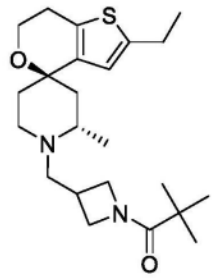
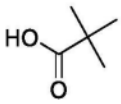
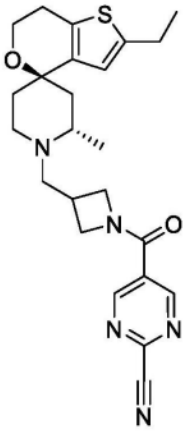
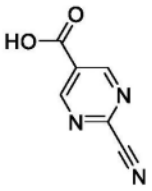
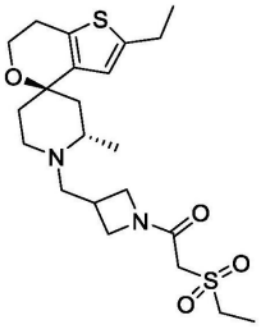
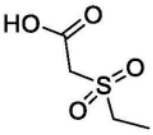
[0829]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
446			*422*	LCMS *m/z* 468.19 $[M+H]^+$。
447			*422*	LCMS *m/z* 393.23 $[M+H]^+$。
448			*422*	LCMS *m/z* 431.25 $[M+H]^+$。
449			*422*	LCMS *m/z* 441.18 $[M+H]^+$。
450			*422*	LCMS *m/z* 467.18 $[M+H]^+$。

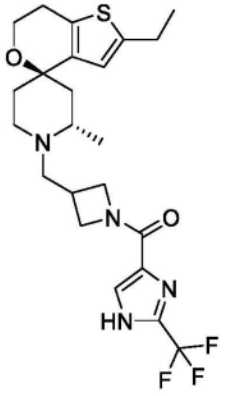
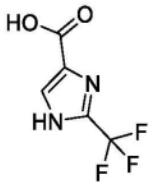
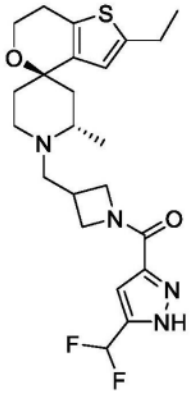
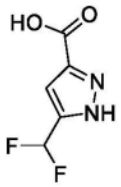
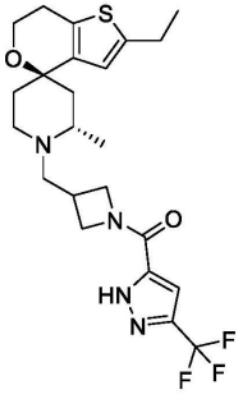
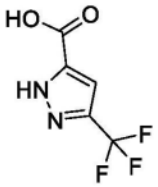
[0830]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
451			*422*	LCMS *m/z* 431.22 $[M+H]^+$。
452			*422*	LCMS *m/z* 379.22 $[M+H]^+$。
453			*422*	LCMS *m/z* 456.20 $[M+H]^+$。
454			*422*	LCMS *m/z* 455.22 $[M+H]^+$。
455			*422*	LCMS *m/z* 443.37 $[M+H]^+$。

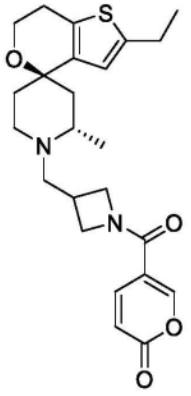
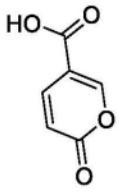
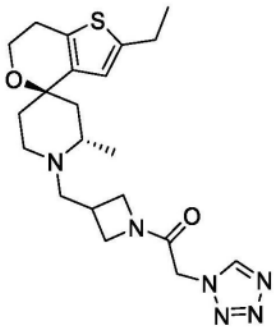
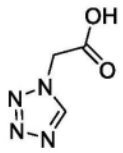
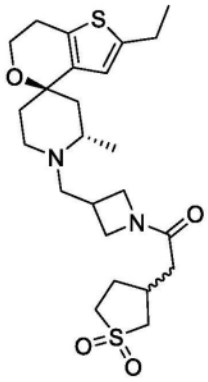
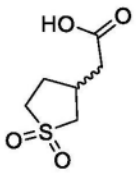
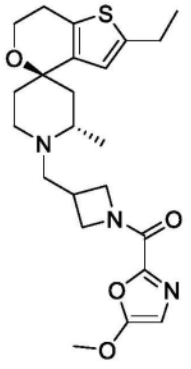
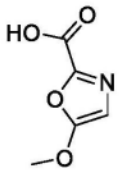
[0831]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
456			*422*	LCMS *m/z* 503.08 $[M+H]^+$。
457			*422*	LCMS *m/z* 405.25 $[M+H]^+$。
458			*423*	LCMS *m/z* 452.19 $[M+H]^+$。
459			*423*	LCMS *m/z* 455.00 $[M+H]^+$。

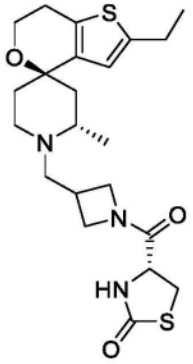
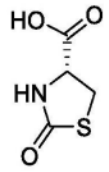
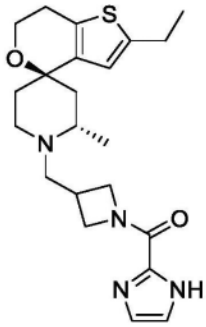
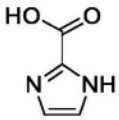
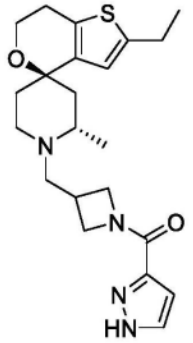
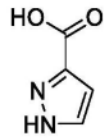
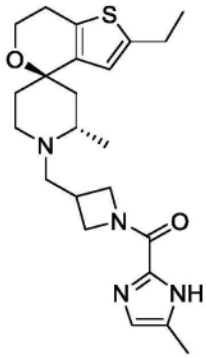
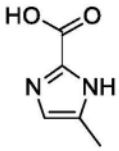
[0832]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
460			*423*	LCMS *m/z* 483.21 $[M+H]^+$。
461			*423*	LCMS *m/z* 465.35 $[M+H]^+$。
462			*423*	LCMS *m/z* 483.04 $[M+H]^+$。

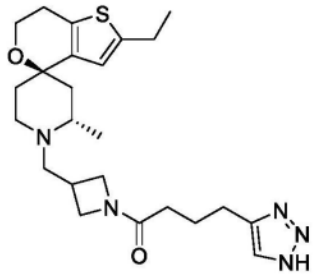
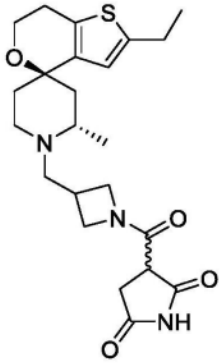
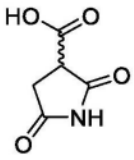
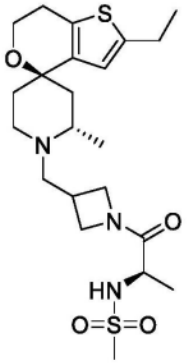
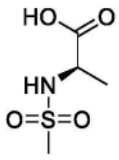
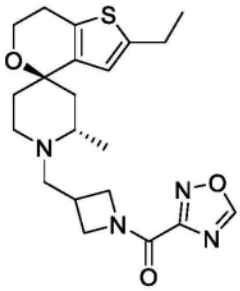
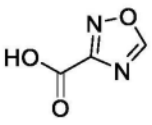
[0833]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
463			*423*	LCMS *m/z* 443.30 $[M+H]^+$。
464			*423*	LCMS *m/z* 431.31 $[M+H]^+$。
465			*423*	LCMS *m/z* 481.25 $[M+H]^+$。
466			*423*	LCMS *m/z* 446.17 $[M+H]^+$。

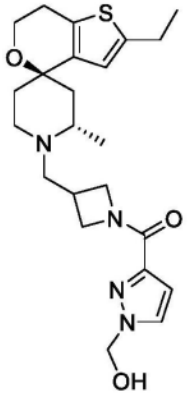
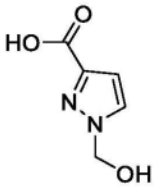
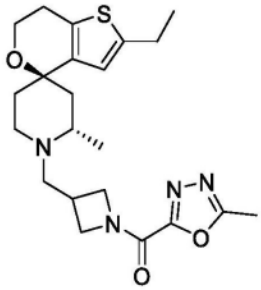
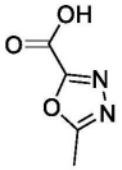
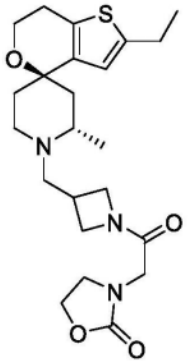
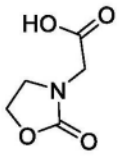
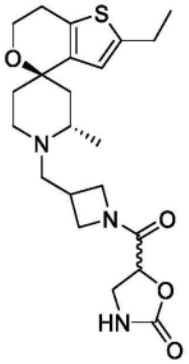
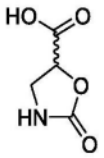
[0834]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
467			*423*	LCMS *m/z* 450.17 $[M+H]^+$。
468			*423*	LCMS *m/z* 415.33 $[M+H]^+$。
469			*423*	LCMS *m/z* 415.06 $[M+H]^+$。
470			*423*	LCMS *m/z* 429.28 $[M+H]^+$。

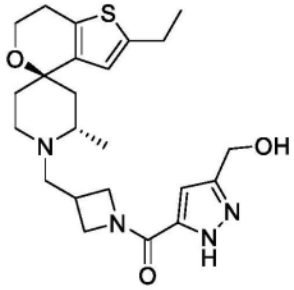
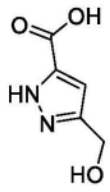
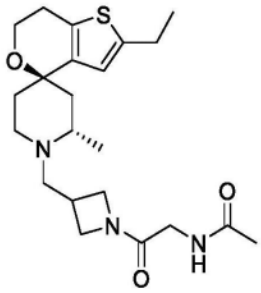
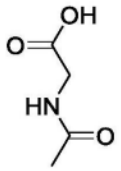
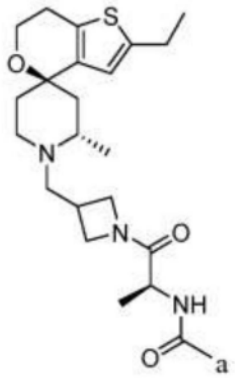
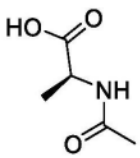
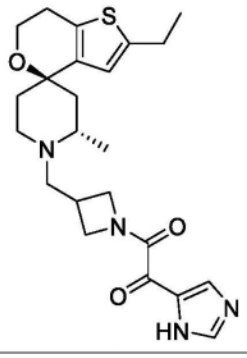
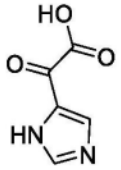
[0835]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
471			*423*	LCMS *m/z* 458.42 $[M+H]^+$。
472			*423*	LCMS *m/z* 446.30 $[M+H]^+$。
473			*423*	LCMS *m/z* 470.24 $[M+H]^+$。
474			*423*	LCMS *m/z* 417.05 $[M+H]^+$。

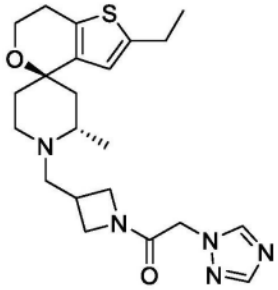
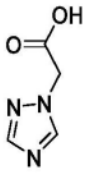
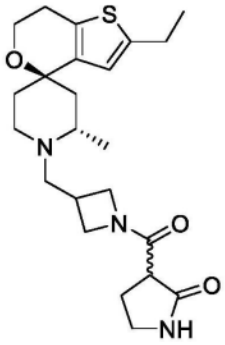
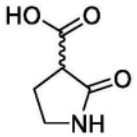
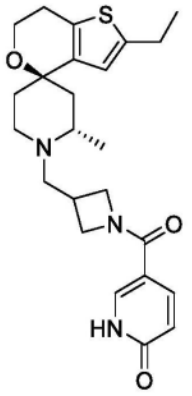
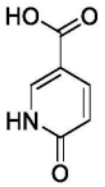
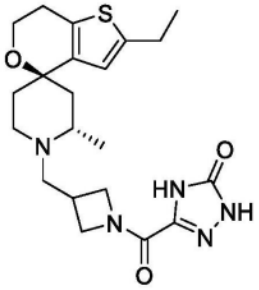
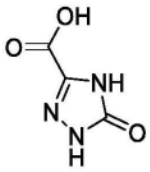
[0836]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
475			*423*	LCMS *m/z* 445.39 $[M+H]^+$。
476			*423*	LCMS *m/z* 431.18 $[M+H]^+$。
477			*423*	LCMS *m/z* 448.22 $[M+H]^+$。
478			*423*	LCMS *m/z* 450.17 $[M+H]^+$。

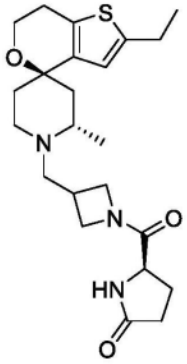
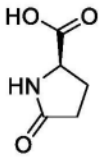
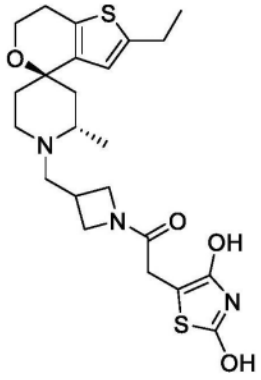
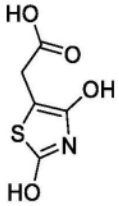
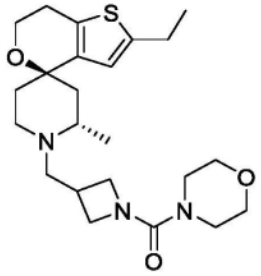
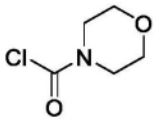
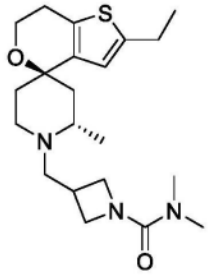
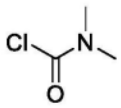
[0837]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
479			*423*	LCMS *m/z* 445.19 $[M+H]^+$。
480			*423*	^{1}H NMR (300 MHz, 甲醇-d_4) δ 6.68 - 6.35 (m, 1H), 4.48 (q, *J* = 8.3 Hz, 1H), 4.24 (q, *J* = 8.7, 8.3 Hz, 1H), 4.12 (dd, *J* = 9.0, 5.7 Hz, 1H), 4.08 - 3.79 (m, 6H), 3.75 - 3.49 (m, 2H), 3.35 (s, 7H), 2.02 (d, *J* = 8.9 Hz, 9H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 4H)。LCMS *m/z* 420.33 $[M+H]^+$。
481			*423*	LCMS *m/z* 434.25 $[M+H]^+$。
482			*423*	LCMS *m/z* 443.28 $[M+H]^+$。

[0838]

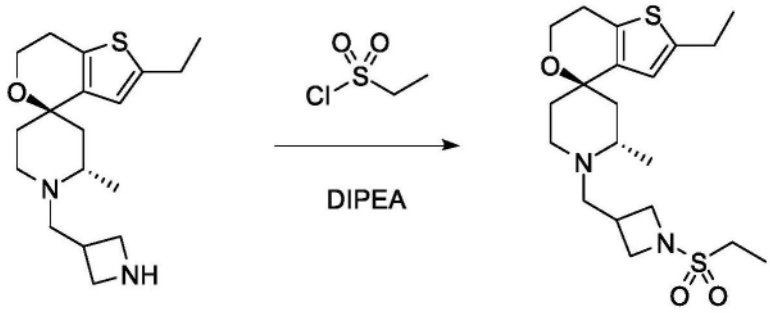
化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
483			*423*	LCMS *m/z* 430.04 $[M+H]^+$；
484			*423*	LCMS *m/z* 432.34 $[M+H]^+$。
485			*423*	LCMS *m/z* 442.16 $[M+H]^+$。
486			*423*	LCMS *m/z* 432.19 $[M+H]^+$。

[0839]

化合物	结构	酰胺偶联配偶体	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
487			*423*	LCMS *m/z* 432.25 $[M+H]^+$。
488			*423*	LCMS *m/z* 483.87 $[M+H]^+$。
489			*424*	LCMS *m/z* 434.25 $[M+H]^+$。
490			*424*	LCMS *m/z* 392.26 $[M+H]^+$。

[0840] 化合物491

[0841] (2′S,4R)-2-乙基-1′-[(1-乙基磺酰基氮杂环丁烷-3-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](491)

[0842] 

421 491

[0843] (2′S,4R)-2-乙基-1′-[(1-乙基磺酰基氮杂环丁烷-3-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](491)的制备

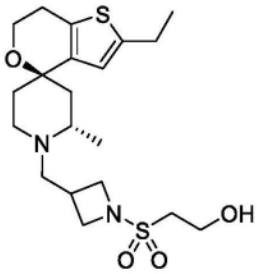
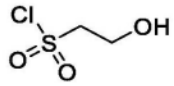
[0844] 将(2′S,4R)-1′-(氮杂环丁烷-3-乙磺酰氯)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸(2)盐)421(50mg,0.05502mmol)溶解在DMF(800μL)和DIPEA(100μL,0.5740mmol)中,向其中添加乙磺酰氯(14μL,0.1500mmol)。将反应物在室温下搅拌3小时,然后将其用MeOH(800μL)稀释并过滤。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有5mM HCl,得到产物(2′S,4R)-2-乙基-1′-[(1-乙基磺酰基氮杂环丁烷-3-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](盐酸盐)(491)(14.5mg,63%)。LCMS m/z 413.20$[M+H]^+$。

[0845] 化合物492-496

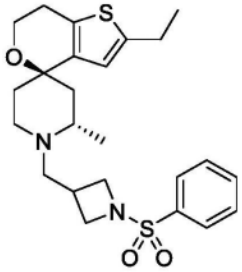
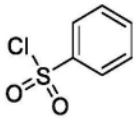
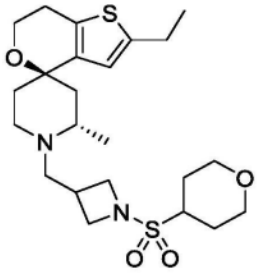
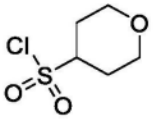
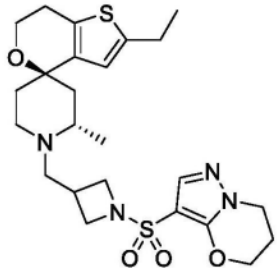
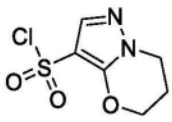
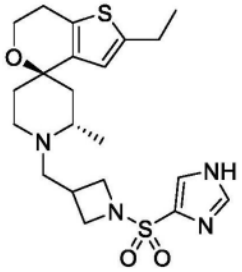
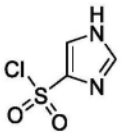
[0846] 使用491的偶联方法,由中间体421在单个步骤中制备了化合物492-496(参见表11)。磺酰氯从商业来源获得。

[0847] 表11:化合物492-496的结构和物理化学数据

[0848]

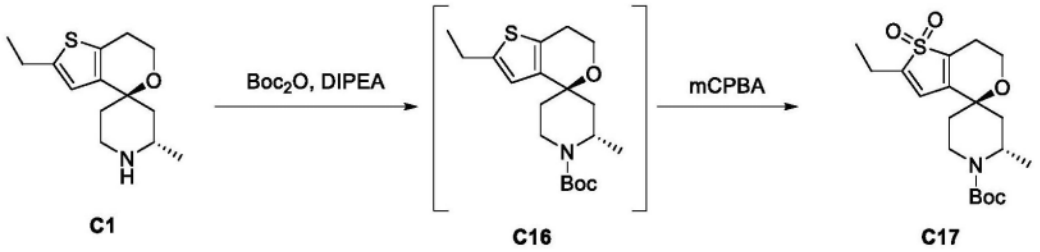
化合物	结构	胺试剂	^{1}H NMR; LCMS m/z $[M+H]^+$。
492			LCMS *m/z* 429.07$[M+H]^+$。

[0849]

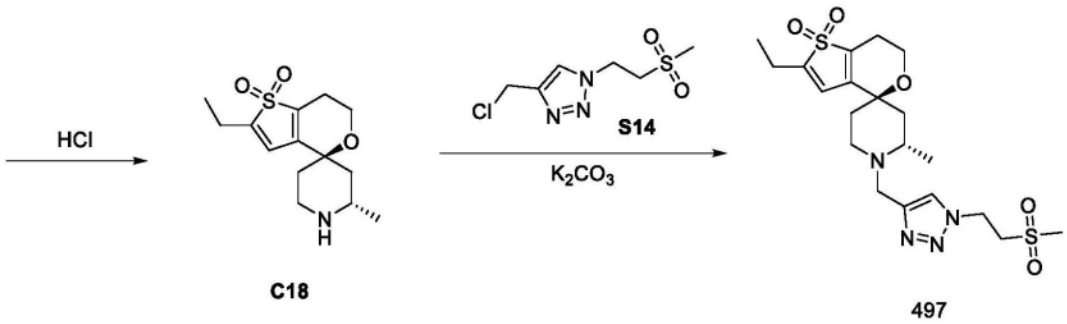
化合物	结构	胺试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
493			LCMS *m/z* 461.15 $[M+H]^+$。
494			LCMS *m/z* 469.26 $[M+H]^+$。
495			LCMS *m/z* 507.18 $[M+H]^+$。
496			LCMS *m/z* 451.25 $[M+H]^+$。

[0850] 化合物497

[0851] (2′S,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物



[0852]



[0853] 步骤1:(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C16)的合成

[0854] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](200mg,0.7956mmol)C1于DCM(6mL)中的混合物中添加Boc_2O(211μL,0.9185mmol)和DIPEA(160μL,0.9186mmol)。1小时后,将反应混合物用饱和氯化铵水溶液稀释。将层分离,并使有机层通过相分离器,并且无需进一步纯化即可用于下一步骤。

[0855] 步骤2:(2′S,4R)-2-乙基-2′-甲基-1,1-二氧代-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C17)的合成

[0856] 向来自先前步骤的(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C16于DCM(6mL)中的混合物中添加mCPBA(200mg,0.8692mmol),并将反应物在rt下搅拌。然后将混合物分成两半,并将一半混合物与mCPBA(300mg,1.74mmol)在回流下搅拌3小时。此时,将混合物冷却至rt,用饱和碳酸氢钠(20mL)和另外的DCM(20mL)稀释。将层分离,并将水层用DCM(10mL)洗涤,并且然后将合并的有机层用另外的饱和碳酸氢钠(10mL)洗涤,随后用盐水(10mL)洗涤。将有机层用硫酸钠干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含0-100%EtOAc的庚烷),得到(2′S,4R)-2-乙基-2′-甲基-1,1-二氧代-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C17(46mg,26%)。^1H NMR(400MHz,氯仿-d_3)δ6.14(t,J=2.1Hz,1H),4.01(tt,J=11.8,6.5Hz,1H),3.95-3.67(m,3H),3.24(ddd,J=14.0,9.3,5.4Hz,1H),2.63-2.40(m,4H),1.95-1.74(m,2H),1.70-1.56(m,2H),1.46(d,J=14.0Hz,9H),1.31-1.23(m,6H)。LCMS m/z383.85$[M+H]^+$。

[0857] 步骤3:(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物(C18)的合成

[0858] 向(2′S,4R)-2-乙基-2′-甲基-1,1-二氧代-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C17(46mg,0.12mmol)中添加含HCl(500μL的4M,2.000mmol)的二噁烷。将混合物在rt下搅拌。1小时后,将混合物在真空中浓缩,以提供(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物C18(盐酸盐)(33mg,

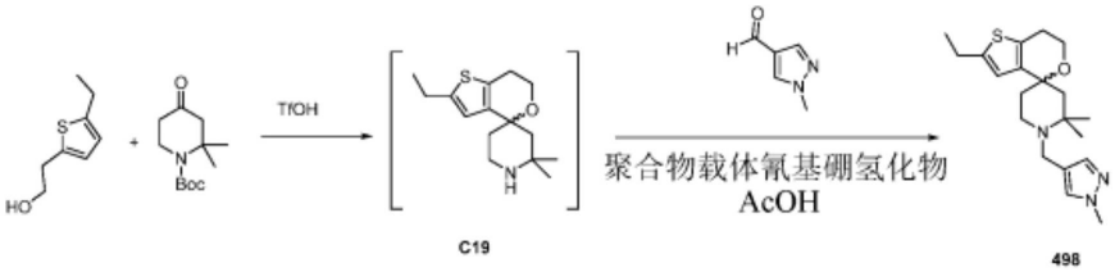
25%)。LCMS m/z 284.03[M+H]$^+$。其无需进一步纯化即可用于下一步骤。

[0859] 步骤4:(2′S,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物(497)的合成

[0860] 向(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物C(盐酸盐)(33mg,0.1032mmol)于乙腈(3mL)中的混合物中添加碳酸钾(30mg,0.2171mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(30mg,0.1155mmol)。搅拌60小时后,将反应混合物吹干,用水/DMSO稀释,并将混合物通过反相HPLC纯化(C18柱,梯度:含10-100% MeCN的水,具有TFA作为改性剂)。合并含产物的级分,浓缩,并用6N NaOH/DCM稀释。将层分离,并用另外的DCM萃取水层。使有机层通过相分离器并浓缩以产生(2′S,4R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]1,1-二氧化物497(12mg,23%)。^{1}H NMR(400MHz,氯仿-d_3)δ7.64(s,1H),6.24(t,J=2.2Hz,1H),4.92-4.83(m,2H),4.04(d,J=14.7Hz,1H),3.88(d,J=14.7Hz,1H),3.84-3.78(m,1H),3.78-3.70(m,3H),2.73(s,3H),2.63-2.46(m,6H),1.83-1.62(m,4H),1.61-1.48(m,1H),1.30-1.23(m,6H)。LCMS m/z 471.09[M+H]$^+$。

[0861] 化合物498

[0862] 2-乙基-2′,2′-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]

[0863] 

[0864] 步骤1:2-乙基-2′,2′-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](C19)的合成

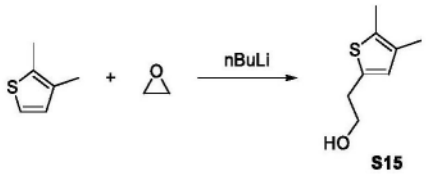
[0865] 向小瓶中添加2,2-二甲基-4-氧代-哌啶-1-甲酸叔丁酯(90.9mg,0.4mmol)、2-(5-乙基-2-噻吩基)乙醇(75mg,0.48mmol)和二噁烷(2mL)。然后在0℃下添加三氟甲磺酸(100μL,1.13mmol),并在rt下搅拌4小时。将反应混合物在真空中浓缩,以提供2-乙基-2′,2′-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C19,其无需纯化即可用于下一步骤。

[0866] 步骤2:2-乙基-2′,2′-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](498)的合成

[0867] 向含来自先前步骤的粗材料的DCM中添加AcOH(114μL,2.0mmol)、1-甲基吡唑-4-甲醛(88mg,0.8mmol)和聚合物负载的氰基硼氢化物(500mg,1mmol)。将反应混合物在110℃下在微波反应器中加热20分钟。然后将反应混合物过滤,在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为2-乙基-2′,2′-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸盐)(20.5mg,11%)。LCMS m/z360.23[M+H]$^+$。

[0868] 制备S15

[0869] 2-(4,5-二甲基-2-噻吩基)乙醇(S15)

[0870] 

S15

[0871] 2-(4,5-二甲基-2-噻吩基)乙醇(S15)的制备

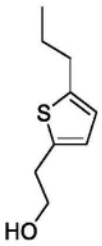
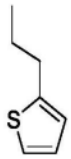
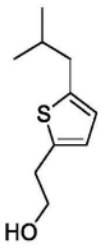
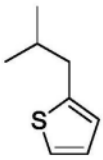
[0872] 在0℃下在15分钟内向2,3-二甲基噻吩(2g,17.826mmol)于Et_2O(50mL)中的溶液中添加n-BuLi(8.5564mL的2.5M,21.391mmol)。将混合物在rt下搅拌30分钟。冷却至0℃后,添加环氧乙烷(7.1303mL的3M,21.391mmol)的溶液。将反应物在0℃下搅拌3小时,然后用水淬灭并用EtOAc萃取。将有机层经无水硫酸钠干燥,过滤并在真空中浓缩。通过硅胶色谱法纯化(梯度:含20-25% EtOAc的己烷),得到2-(4,5-二甲基-2-噻吩基)乙醇S15(2g,67%)。^1H NMR(400MHz,DMSO-d_6)δ6.51(s,1H),4.71(s,1H),3.54(s,2H),2.77(t,J=6.4Hz,2H),2.21(s,3H),2.00(s,3H)。LCMS m/z157.1$[M+H]^+$。

[0873] 中间体S16-S17

[0874] 中间体S16-S17(参见表12)使用S15中描述的方法在单个步骤中制备对应噻吩。表11和随附脚注中注明了对方法的任何修改。

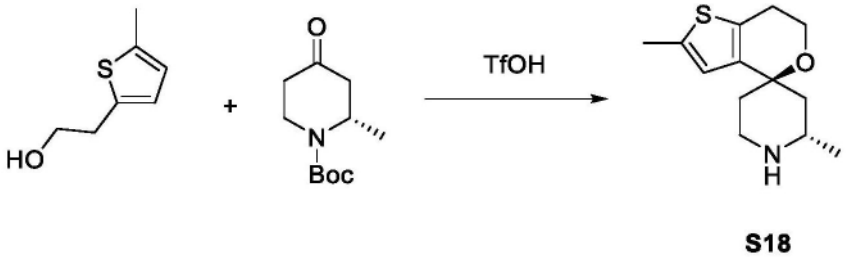
[0875] 表12:化合物S16-S17的结构和物理化学数据

[0876]

中间体	产物	噻吩试剂	^1H NMR; LCMS m/z $[M+H]^+$。
S16			^1H NMR (400MHz, DMSO-d_6) δ 6.65 (d, J = 3.24 Hz, 1H), 6.59 (d, J = 3.24 Hz, 1H), 3.84-3.79 (m, 2H), 2.9 (t, J = 8 Hz, 2H), 2.72 (t, J = 8 Hz, 1H), 1.71-1.63 (m, 3H), 0.49 (t, J = 7.08 Hz, 3H)。
S17			^1H NMR (400MHz, DMSO-d_6) δ 6.64 (d, J = 2.92 Hz, 1H), 6.58 (d, J = 2.96 Hz, 1H), 4.74 (s, 1H), 3.57 (t, J = 6.44 Hz, 2H), 2.84 (t, J = 6.8Hz, 2H), 2.56 (d, J = 6.96Hz, 2H), 1.82-1.72 (m, 1H), 0.88 (d, J = 6.56 Hz, 6H)。 LCMS *m/z* 185.1 $[M+H]^+$。

[0877] 制备S18

[0878] (2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S18)

[0879] 

S18

[0880] (2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S18)的制

备

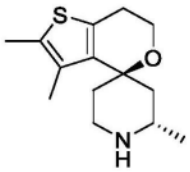
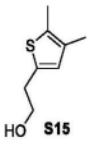
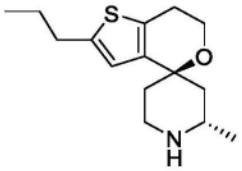
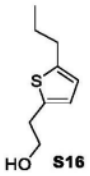
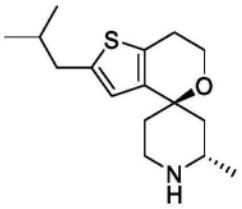
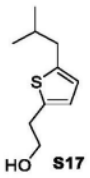
[0881] 向烧瓶中制备2-(5-甲基-2-噻吩基)乙醇(12.8g,85.50mmol)和(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(20g,93.78mmol,1.1当量)于二噁烷(158mL)中的溶液。用冰甲醇浴冷却烧瓶,使其平衡10分钟,达到约0℃的内部温度。在30分钟内通过加料漏斗逐滴添加三氟甲磺酸(17mL,192.1mmol,2.2当量)。添加后,将混合物用冰浴搅拌另外30分钟。然后将冰浴去除,并且使反应物温热至rt并搅拌过夜。将混合物用水和饱和碳酸氢钠水溶液(500mL)和EtOAc(400mL)的1:1混合物稀释。将层分离,将水层用EtOAc(200mL)重新萃取。将合并的有机层经硫酸钠干燥,过滤并在真空中浓缩。然后在rt下将固体悬浮在Et_2O(约250mL)中,并且然后加热至回流。在回流的同时溶解混合物,并且然后冷却。添加庚烷,随后添加更多Et_2O。一部分溶剂被去除。过滤固体,并用1:1Et_2O-庚烷(3×75mL)洗涤,并在高真空下进一步干燥。将固体悬浮在Et_2O(250mL)中,并搅拌并加热至回流30分钟。此时,将混合物冷却至0℃并搅拌10分钟,过滤,并且然后用冰冷的Et_2O冲洗,产生无色固体,将其在空气中干燥5分钟,并且然后在高真空下干燥过夜。(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲烷磺酸盐)S18(19.3g,57%)。^{1}H NMR(300MHz,氯仿-d)δ 7.78(bs,1H),7.48(bs,1H),6.52(d,J=1.3Hz,1H),3.89(hept,J=5.8Hz,2H),3.75-3.54(m,1H),3.40(dq,J=10.9,4.7,3.8Hz,2H),2.77(td,J=5.2,2.8Hz,2H),2.43(d,J=1.1Hz,3H),2.21(ddd,J=15.0,11.5,6.4Hz,1H),2.09-1.92(m,3H),1.42(d,J=6.6Hz,3H)。LCMS m/z 238.14$[M+H]^+$。

[0882] 关键中间体S19-S21

[0883] 中间体S19-S21(参见表13)由(S)-2-甲基-4-氧代哌啶-1-甲酸叔丁酯和适当的噻吩乙醇试剂S15-S17使用皮克泰-斯彭格勒(Pictet-Spengler)反应在单个步骤中制备,如中间体S18的制备。表13和随附脚注中注明了对方法的任何修改。

[0884] 表13:化合物S19-S21的结构和物理化学数据

[0885]

中间体	产物	噻吩乙醇试剂	^{1}H NMR；LCMS m/z [M+H]$^+$。
S19[1]			^{1}H NMR (400MHz, DMSO-d_6) δ 8.36 (bs, 2H), 3.88-3.78 (m, 2H), 3.43-3.39 (m, 1H), 3.23-3.09 (m, 2H), 2.68 (t, J = 5.12 Hz, 2H), 2.23-2.19 (m, 3H), 2.17-2.12 (m, 4H), 1.98 (t, J = 14.36 Hz, 1H), 1.84 (t, J = 18.84 Hz, 2H), 1.20 (d, J = 6.48Hz, 3H)；LCMS *m/z* 251.9 [M+H]$^+$。
S20[2]			^{1}H NMR (400MHz, DMSO-d_6) δ 8.57 (bs, 1H), 8.19 (d, J = 8 Hz, 1H), 6.45 (s, 1H), 3.84 (d, J = 4.12 Hz, 2H), 3.35 (bs, 1H), 3.22 (d, J = 12 Hz, 1H), 3.09 (bs, 1H), 2.69 (t, J = 6.4 Hz, 4H), 1.98-1.91 (m, 3H), 1.81-1.74 (m, 1H), 1.61 – 1.55 (m, 2H), 1.19 (d, J = 4 Hz, 3H), 0.922 (t, J = 7.2 Hz, 3H)；LCMS *m/z* 266.3 [M+H]$^+$。
S21[3]			^{1}H NMR (400MHz, DMSO-d_6) δ 8.50 (bs, 1H), 6.42 (s, 1H), 3.87 (d, J = 4.28 Hz, 2H), 3.32 (bs, 1H), 3.23-3.20 (m, 1H), 3.10 (bs, 1H), 2.70 (bs, 2H), 2.59 (d, J = 6.88 Hz,2H), 1.98-1.87 (m, 3H), 1.80 – 1.73 (m, 2H), 1.20 (d, J = 6.4Hz, 3H), 0.90 (d, J = 6.52 Hz, 6H)；LCMS *m/z* 279.8 [M+H]$^+$。

[0886] 脚注：

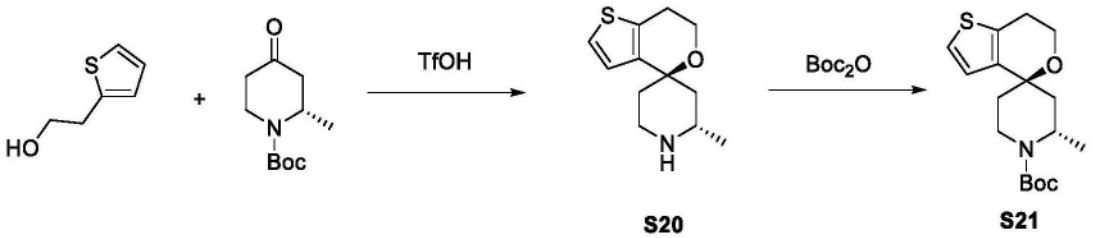
[0887] 1)使用(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(0.9当量)和三氟甲磺酸(2.8当量)。

[0888] 2)使用(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(0.8当量)和三氟甲磺酸(3.0当量)。

[0889] 3)使用(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(0.9当量)和三氟甲磺酸(2.8当量)。

[0890] 制备S21

[0891] (2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S21)

[0892] 

S20 S21

[0893] 步骤1：(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S20)

[0894] 将2-(2-噻吩基)乙醇(1.028g,7.618mmol)和(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(1.8g,8.440mmol)于二噁烷(15mL)中的溶液冷却冰浴。在5分钟内向溶液中添加三氟甲磺酸(2.5mL,28.25mmol)。将所得溶液缓慢温热至rt并搅拌过夜,然后将反应物用1N NaOH碱化至pH 8。用EtOAc分配混合物,并将合并的有机物用无水硫酸钠干燥,过滤并在真空中浓缩,以提供琥珀色粗油。通过HPLC纯化:含10-90% ACN的水(TFA改性剂)C18柱,随后冻干以得到(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲烷磺酸盐)(1.40g)。^{1}H NMR(300MHz,氯仿-d)δ7.13(d,J=5.2Hz,1H),6.87(d,J=5.3Hz,1H),3.97-3.86(m,2H),3.62(d,J=15.1Hz,1H),3.39(d,J=8.4Hz,2H),2.84(td,J=5.3,2.0Hz,2H),2.31-2.18(m,1H),2.07-1.97(m,3H),1.41(d,J=6.6Hz,3H)。LCMS m/z 224.18 $[M+H]^+$。

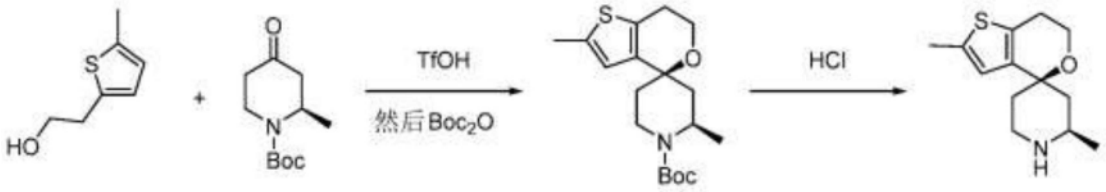
[0895] 步骤2:(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S21)

[0896] 将获得的材料溶解在DCM(20mL)中,并用Boc_2O(1.9mL,8.270mmol)处理,随后用DIPEA(2.7mL,15.50mmol)处理。将所得溶液在rt下搅拌过夜。将反应物在1N NaOH和DCM之间分配。将有机物通过相分离器管收集,在真空中浓缩,随后通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷),得到(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S21(786.4mg,32%)。^{1}H NMR(300MHz,氯仿-d)δ7.10(dd,J=5.2,0.7Hz,1H),6.73(d,J=5.2Hz,1H),4.06-3.95(m,1H),3.93-3.88(m,2H),3.81-3.72(m,1H),3.37(ddd,J=14.0,8.8,5.4Hz,1H),2.82(q,J=5.2Hz,2H),2.11

[0897] -1.93(m,2H),1.86-1.73(m,2H),1.50(s,9H),1.28(d,J=6.6Hz,3H)。

[0898] 制备S22

[0899] (2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S22)

[0900] 

C20 S22

[0901] 步骤1:(2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C20)的合成

[0902] 将2-(5-甲基-2-噻吩基)乙醇(107mg,0.7524mmol)和(2R)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(170mg,0.7971mmol)于DCM(1.4mL)中的溶液冷却至-78℃。向反应混合物中添加三氟甲磺酸(130μL,1.469mmol)并将反应物在-78℃下搅拌1.5小时。将反应物淬灭到饱和$NaHCO_3$(15mL)和DCM(15mL)的双相混合物中,并使用2N NaOH将水层pH调节至>10。然后将水层用DCM(3×15mL)萃取,并通过相分离筒过滤并浓缩。将粗材料溶解在DCM(1.4mL)和三乙胺(250μL,1.794mmol)中,并将二碳酸二叔丁酯(250μL,1.088mmol)以该顺序添加到反应物中。将反应物在rt下搅拌18小时。将溶液用DCM稀释并且用水(10mL)洗涤。将水层用DCM(2×10mL)萃取,经硫酸钠干燥,通过相分离过滤器过滤,并在真空中浓缩。将粗混合物浓缩,并通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),产生(2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C20(138.3mg,54%)。^{1}H NMR

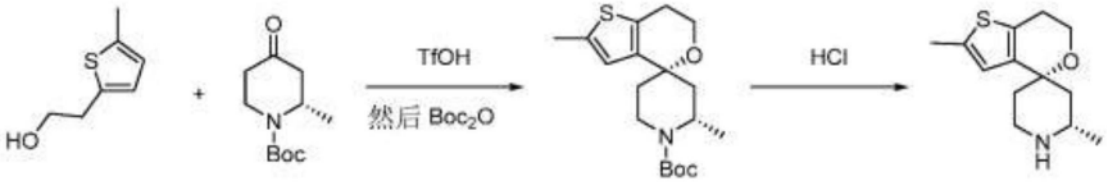
(300MHz,甲醇-d_4)δ6.42(d,J=1.2Hz,1H),4.35(d,J=7.2Hz,1H),3.99-3.82(m,3H),2.83-2.60(m,2H),2.37(s,3H),1.89(d,J=4.3Hz,2H),1.85-1.75(m,2H),1.48(s,9H),1.33(d,J=7.1Hz,3H)。

[0903] 步骤2:(2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S22)的合成

[0904] 向(2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C20(135mg,0.4000mmol)于DCM(1.3mL)中的经搅拌的溶液中添加含氯化氢的二噁烷(500μL的4M,2.000mmol),并将反应物在rt下搅拌2.5小时。将反应物在氮气流下浓缩。通过反相HPLC纯化。方法:C18Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1% HCl。(2′R,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](盐酸盐)S22(84.9mg,71%)。^{1}H NMR(300MHz,甲醇-d_4)δ6.52(s,1H),3.94(t,J=5.4Hz,2H),3.83-3.67(m,1H),3.50(td,J=12.5,3.9Hz,1H),3.19(dt,J=13.0,4.1Hz,1H),2.83-2.63(m,2H),2.41(d,J=1.1Hz,3H),2.24-1.96(m,4H),1.55(d,J=7.1Hz,3H)。LCMS m/z 238.0[M+H]$^+$。

[0905] 制备S23

[0906] (2′S,4S)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S23)

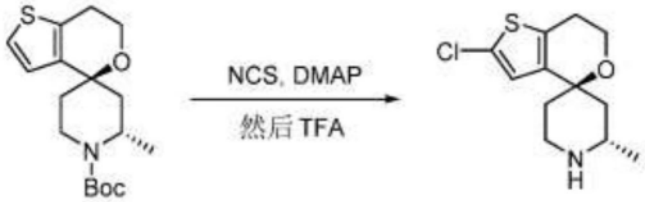
[0907] 

C21 S23

[0908] 使用与S22的制备相同的程序制备(2′S,4S)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S23。^{1}H NMR(300MHz,甲醇-d_4)δ6.51(s,1H),3.94(t,J=5.4Hz,2H),3.81-3.69(m,1H),3.50(td,J=12.2,3.6Hz,1H),3.19(dt,J=13.0,4.1Hz,1H),2.74(td,J=5.5,1.7Hz,2H),2.41(s,3H),2.22-1.96(m,4H),1.55(d,J=7.1Hz,3H)。LCMS m/z 238.0[M+H]$^+$。

[0909] 制备S24

[0910] (2′S)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S24)

[0911] 

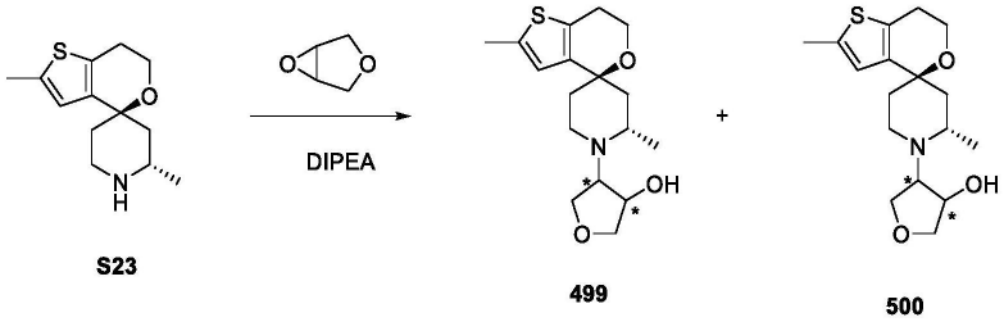
S21 S24

[0912] 将(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S21(286mg,0.8842mmol)于ACN(4.5mL)中的溶液用NCS(112mg,0.8387mmol)和DMAP(1.1mg,0.009004mmol)处理。将所得溶液搅拌过夜,然后通过硅胶色谱法纯化(梯度:含10-100% EtOAc的庚烷),得到(2′S)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(210mg,66%)。LCMS m/z 358.22[M+H]+。

[0913] 将产物溶解在DCM(4mL)中并用TFA(210μL,2.726mmol)处理。将所得溶液在rt下搅拌3小时,随后在真空中浓缩并用MeOH共蒸发,得到(2′S)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S24(三氟乙酸盐)(180mg,46%)。LCMS m/z 258.21[M+H]$^+$。

[0914] 化合物499[ENANT-1]和500[ENANT-2]

[0915] 4-[(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇

[0916] 

S23 499 500

[0917] 4-[(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(499[ENANT-1]和500[ENANT-2])的制备

[0918] 将(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲烷磺酸盐)S23(54mg,0.1397mmol)、DIPEA(210μL,1.206mmol,8.6当量)和3,6-二氧杂双环[3.1.0]己烷(43μL,0.60mmol,4.3当量)与n-BuOH(1ml)混合。并将所得混合物在210℃下加热1小时。将粗反应混合物蒸发。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%甲酸。将两种产物分离:

[0919] 4-[(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢呋喃-3-醇(499[ENANT-1])(甲酸)(16mg,62%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.44(s,1H),6.50(d,J=1.3Hz,1H),4.69(t,J=6.1Hz,1H),4.20(dd,J=9.6,6.6Hz,1H),4.15-4.02(m,3H),4.02-3.87(m,2H),3.61(dt,J=10.8,4.1Hz,1H),3.49(dd,J=9.6,5.5Hz,1H),3.30-3.21(m,1H),3.09(td,J=12.0,4.2Hz,1H),2.73(td,J=5.3,2.1Hz,2H),2.40(d,J=1.0Hz,3H),2.19-1.89(m,4H),1.40(d,J=6.4Hz,3H)。LCMS m/z 324.26[M+H]$^+$;和

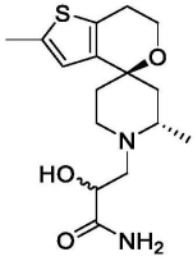
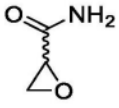
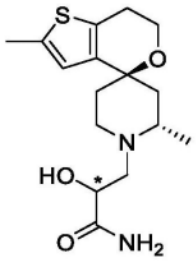
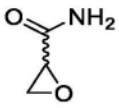
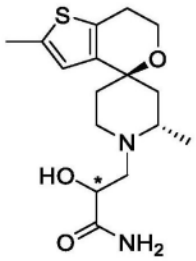
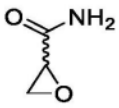
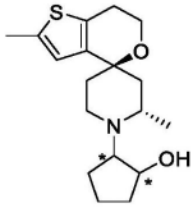
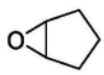
[0920] 4-[(2′S,4R)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]四氢-呋喃-3-醇(500[ENANT-2])(甲酸)(12mg,46%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.38(s,1H),6.53(q,J=1.1Hz,1H),4.70(t,J=5.3Hz,1H),4.30-4.07(m,2H),4.07-3.88(m,4H),3.70-3.48(m,2H),3.28-3.20(m,1H),3.15(dd,J=12.2,2.7Hz,1H),2.73(t,J=5.4Hz,2H),2.40(d,J=1.0Hz,3H),2.24-1.90(m,4H),1.36(d,J=6.5Hz,3H)。LCMS m/z 324.26[M+H]$^+$。

[0921] 化合物501-507

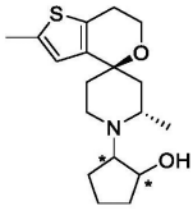
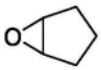
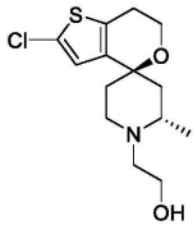
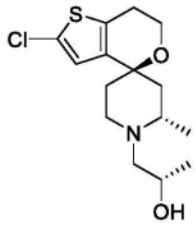
[0922] 如同化合物499和500的制备一样,由中间体S23或S24在单个步骤中制备化合物501-507(参见表14)。环氧化物从商业来源获得。表14和随附脚注中注明了对方法的任何修改。

[0923] 表14:化合物501-507的结构和物理化学数据

[0924]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
501			***S23***^{1}	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.28 (s, 1H), 6.44 (t, J = 1.3 Hz, 1H), 5.71 (s, 1H), 4.22 - 4.15 (m, 1H), 3.91 (qdd, J = 8.8, 4.9, 2.0 Hz, 2H), 3.36 - 2.58 (m, 6H), 2.43 (s, 3H), 1.97 - 1.77 (m, 3H), 1.66 (dd, J = 14.1, 11.2 Hz, 1H), 1.11 (dd, J = 11.3, 6.3 Hz, 3H)；LCMS *m/z* 325.18 $[M+H]^+$。
502			***S23***^{2}	^{1}H NMR (300 MHz, 甲醇-d_4) δ 6.47 (q, J = 1.1 Hz, 1H), 4.21 (dd, J = 7.6, 3.9 Hz, 1H), 3.89 (td, J = 5.5, 1.7 Hz, 2H), 3.33 (d, J = 8.4 Hz, 1H), 3.14 (dd, J = 14.0, 3.9 Hz, 1H), 2.94 - 2.81 (m, 2H), 2.74 - 2.60 (m, 3H), 2.38 (d, J = 1.1 Hz, 3H), 2.01 - 1.86 (m, 1H), 1.85 - 1.71 (m, 2H), 1.62 (dd, J = 14.1, 11.4 Hz, 1H), 1.13 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 325.18 $[M+H]^+$。
503			***S23***^{2}	^{1}H NMR (300 MHz, 甲醇-d_4) δ 6.48 (q, J = 1.1 Hz, 1H), 4.25 (dd, J = 9.2, 3.0 Hz, 1H), 3.90 (td, J = 5.5, 2.2 Hz, 2H), 3.33 (d, J = 8.4 Hz, 2H, 1H 在 MeOH 下), 3.07 - 2.74 (m, 3H), 2.70 (dt, J = 6.9, 3.4 Hz, 2H), 2.39 (d, J = 1.1 Hz, 3H), 2.04 - 1.59 (m, 4H), 1.13 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 325.18 $[M+H]^+$。
504			***S23***^{3}	1H NMR (300 MHz, 甲醇-d_4) δ 8.53 (s, 1H), 6.49 (s, 1H), 4.48 (q, J = 7.1 Hz, 1H), 4.09 - 3.75 (m, 3H), 3.39 (t, J = 4.5 Hz, 2H), 2.74 (t, J = 5.5 Hz, 2H), 3.31 (2H 在 MeOH 下) 2.40 (d, J = 1.0 Hz, 3H), 2.23 - 1.97 (m, 6H), 1.96 - 1.57 (m, 2H), 1.46 (d, J = 6.4

[0925]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				Hz, 3H)。LCMS *m/z* 322.27 $[M+H]^+$。
505			***S23***[3]	1H NMR (300 MHz, 甲醇-*d*4) δ 8.53 (s, 1H), 6.52 (t, J = 1.2 Hz, 1H), 4.40 (q, J = 6.9 Hz, 1H), 4.04 - 3.85 (m, 2H), 3.75 (q, J = 8.2 Hz, 1H), 3.52 (h, J = 6.6 Hz, 1H), 3.31 (4H 在 MeOH 下) 2.74 (t, J = 5.4 Hz, 2H), 2.41 (d, J = 1.1 Hz, 3H), 2.26 - 1.57 (m, 7H), 1.40 (d, J = 6.5 Hz, 3H)。LCMS *m/z* 322.27 $[M+H]^+$。
506			***S24***[4]	1H NMR (300 MHz, 氯仿-*d*) δ 6.60 (s, 1H), 4.01 - 3.83 (m, 2H), 3.70 (ddd, J = 10.7, 9.2, 4.0 Hz, 1H), 3.56 (ddd, J = 10.7, 5.1, 3.6 Hz, 1H), 3.12 (ddd, J = 13.9, 9.2, 5.1 Hz, 1H), 2.86 (dt, J = 11.7, 3.5 Hz, 1H), 2.80 - 2.63 (m, 3H), 2.60 - 2.48 (m, 1H), 2.27 (dt, J = 13.0, 3.8 Hz, 1H), 1.92 - 1.76 (m, 3H), 1.60 (t, J = 12.7 Hz, 1H), 1.09 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 302.12 $[M+H]^+$。
507			***S24***[4]	1H NMR (300 MHz, 氯仿-*d*) δ 6.72 (s, 1H), 4.20 (ddt, J = 9.0, 6.3, 4.1 Hz, 1H), 3.90 (tdd, J = 11.4, 8.8, 4.9 Hz, 2H), 3.56 (d, J = 11.4 Hz, 1H), 3.24 (ddt, J = 33.7, 25.3, 10.6 Hz, 3H), 2.79 - 2.59 (m, 3H), 2.39 - 2.09 (m, 2H), 1.97 (ddt, J = 15.2, 12.0, 3.0 Hz, 2H), 1.38 (d, J = 6.4 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 316.11 $[M+H]^+$。

[0926] 脚注：

[0927] 1)使用环氧乙烷-2-甲酰胺(1.6当量)和DIPEA(5.2当量)。使用IPA代替n-BuOH。将反应物在150℃下加热2小时。使用硅胶色谱法完成纯化(梯度:含0至20％ MeOH的DCM)。

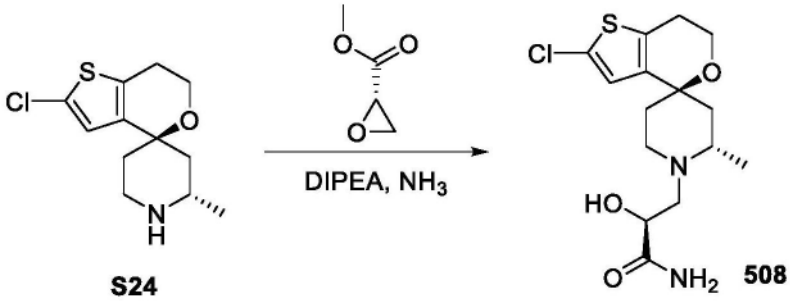
[0928] 2)将混合物通过手性SFC分离分离成组成对映异构体。柱:Daicel Chiralpak® OJ-H,10×250mm;流动相:30％ MeOH(含有5mM氨),70％二氧化碳。流速:15毫升/分钟。3)使用6-氧杂双环[3.1.0]己烷(4.2当量)和DIPEA(8.5当量)。将反应物在200℃下加热4小时。

[0929] 4)使用对应环氧乙烷(3.1当量)和DIPEA(5.0当量)。使用MeOH代替n-BuOH。将反应

物在90℃下加热2小时。使用硅胶色谱法完成纯化(梯度:含0至15% MeOH的DCM)。

[0930] 化合物508

[0931] (2S)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺(508)

[0932] 

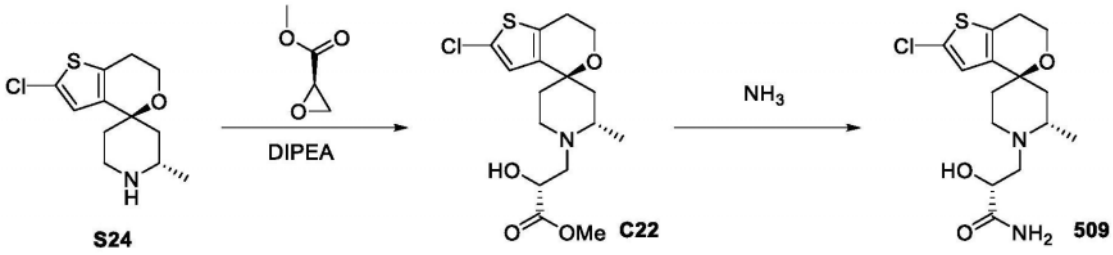
S24 508

[0933] (2S)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺(508)的制备

[0934] 将(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S24(78mg,0.3026mmol)和(2S)-环氧乙烷-2-甲酸甲酯(260μL,2.970mmol)添加到微波小瓶中,并添加含NH_3(400μL的7M,2.800mmol)的MeOH(1.5mL)。添加DIPEA(260μL,1.493mmol),并将反应物在120℃下加热3小时。添加另外的200μL(2S)-环氧乙烷-2-甲酸酯和NH_3(400μL的7M,2.800mmol)),并将反应物在120℃下搅拌7小时。将反应混合物在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。使用硅胶色谱法进行进一步纯化(梯度:含1-16% MeOH的DCM)以提供(2S)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺(8.5mg,7%)。^1H NMR(300MHz,氯仿-d)δ11.37(s,1H),8.30(s,1H),7.20(s,1H),6.68(s,1H),5.58(s,1H),4.69(d,J=9.8Hz,1H),4.07-3.84(m,2H),3.65(s,1H),3.49(d,J=11.8Hz,1H),3.29(s,0H),2.92(t,J=11.9Hz,1H),2.76(q,J=5.5Hz,2H),2.37(dd,J=32.2,15.7Hz,2H),2.00(dd,J=14.9,8.1Hz,2H),1.49(d,J=6.4Hz,3H)。LCMS m/z 345.21$[M+H]^+$。

[0935] 化合物509

[0936] (2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺

[0937] 

S24 C22 509

[0938] 步骤1:(2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯(C22)的合成

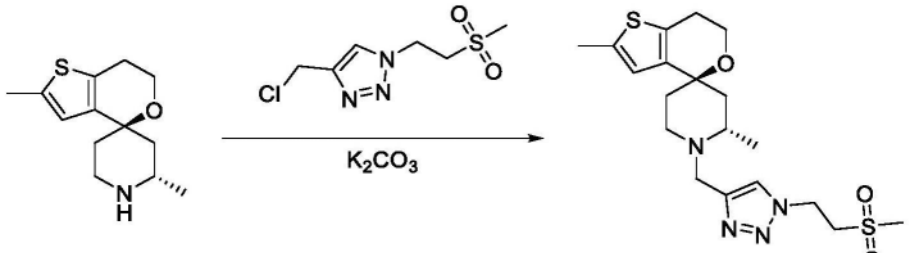
[0939] (2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯C22是按照508所述的环氧化物开环方法从S24和(2R)-环氧乙烷-2-甲酸酯开始制备的。

[0940] 步骤2:(2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺(509)的合成

[0941] 将(2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-丙酸甲酯(66mg,0.1834mmol)添加到微波小瓶中,并添加含NH_3(1.3mL的7M,9.100mmol)的MeOH(100μL)。将反应混合物在50℃下搅拌过夜。将反应混合物在真空中浓缩,并通过硅胶色谱法纯化(梯度:含0-12% MeOH的DCM)以提供(2R)-3-[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]-2-羟基-丙酰胺509(21.1mg,31%)。^{1}H NMR(300MHz,氯仿-d)δ7.01(d,J=3.9Hz,1H),6.59(s,1H),5.92(s,1H),4.19(dd,J=9.9,4.9Hz,1H),3.89(h,J=6.1Hz,2H),3.15-2.86(m,3H),2.80-2.59(m,3H),1.84(dt,J=14.9,4.7Hz,3H),1.65(dd,J=14.2,11.4Hz,1H),1.44(dd,J=17.0,7.0Hz,1H),1.10(d,J=6.2Hz,3H)。

[0942] 化合物510

[0943] (2′S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]

[0944] 

S23 510

[0945] (2′S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](510)的制备

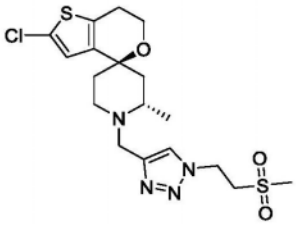
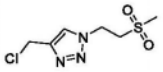
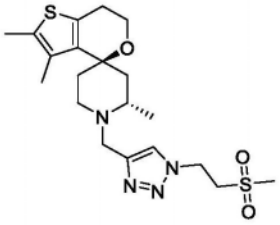
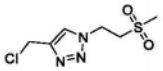
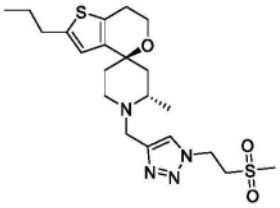
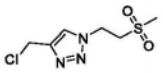
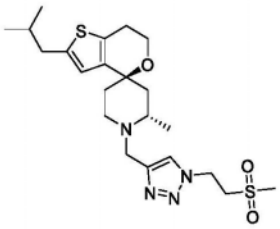
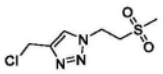
[0946] 在反应小瓶中添加(2′S)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲烷磺酸盐)S23(260mg,0.6148mmol)、4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(151mg,0.6751mmol)、K_2CO_3(255mg,1.845mmol)和DMF(1.5mL)。将反应混合物加热至60℃并搅拌6小时,然后冷却至rt并搅拌过夜。将反应物用DCM稀释,用$NaHCO_3$洗涤,并用DCM萃取。将合并的有机层在真空中浓缩,然后通过硅胶色谱法纯化(梯度:含0-10%MeOH的DCM)以提供(2′S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]510(157.4mg,57%)。^{1}H NMR(300MHz,氯仿-d)δ7.81(s,1H),6.45(d,J=1.3Hz,1H),4.87(t,J=6.4Hz,2H),4.17(d,J=14.7Hz,1H),3.96(d,J=14.5Hz,1H),3.89-3.78(m,2H),3.73(t,J=6.4Hz,2H),2.71(d,J=11.4Hz,8H),2.39(d,J=1.0Hz,3H),2.00(s,1H),1.85(d,J=10.0Hz,3H),1.31(d,J=6.3Hz,3H)。LCMS m/z 425.32$[M+H]^+$。

[0947] 化合物511-514

[0948] 使用与化合物510相同的烷基化方法,由适当的中间体哌啶和烷基卤化物在单个步骤中制备化合物511-514(参见表15)。烷基卤化物从商业来源获得或如前所述。表15和随附脚注中注明了对方法的任何修改。

[0949] 表15:化合物511-514的结构和物理化学数据

[0950]

化合物	结构	烷基卤化物	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
511			S24[1]	1H NMR (300 MHz, 甲醇-d_4) δ 8.11 (s, 1H), 6.73 (s, 1H), 4.94 (dd, J = 7.0, 6.1 Hz, 2H), 4.18 - 4.01 (m, 2H), 3.87 - 3.79 (m, 4H), 2.91 (d, J = 0.7 Hz, 3H), 2.80 (dd, J = 22.9, 9.4 Hz, 3H), 2.67 (td, J = 5.4, 1.7 Hz, 2H), 1.91 - 1.83 (m, 3H), 1.70 (dd, J = 14.3, 11.5 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 445.21 $[M+H]^+$。
512			S19[2]	LCMS *m/z* 439.13 $[M+H]^+$。
513			S20[2]	LCMS *m/z* 453.17 $[M+H]^+$。
514			S21[2]	LCMS *m/z* 467.18 $[M+H]^+$。

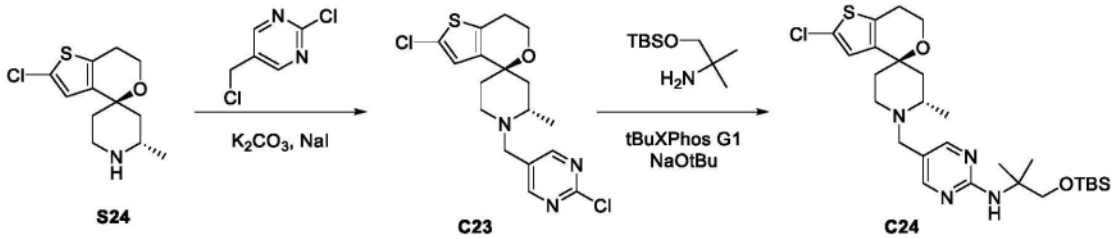
[0951] 脚注：

[0952] 1)通过硅胶色谱法纯化(梯度:含10-100% EtOAc的庚烷)。

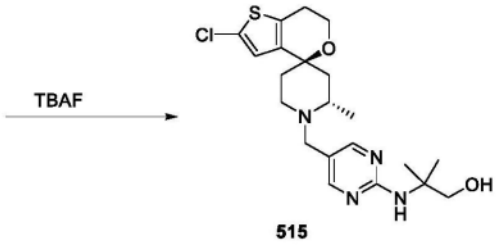
[0953] 2)通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。

[0954] 化合物515

[0955] 2-[[5-[[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]-2-甲基-丙-1-醇



[0956]



[0957] 步骤1:(2′S,4R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](C23)的合成

[0958] 向微波小瓶中装入(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S24(三氟甲烷磺酸盐)(250mg,0.6011mmol)、2-氯-5-(氯甲基)嘧啶(118mg,0.7239mmol)、K_2CO_3(965mg,1.930mmol)和NaI(91mg,0.6071mmol),随后装入THF(2.2mL)和DMF(250μL)。将所得混合物在40℃下加热过夜,然后在EtOAc与水之间分配。将有机层用盐水洗涤,经无水硫酸钠干燥,过滤,并在真空中浓缩。通过硅胶色谱法纯化(梯度:含10-100% EtOAc的庚烷),提供(2′S,4R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C23(143.7mg,59%)。LCMS m/z384.01$[M+H]^+$。

[0959] 步骤2:N-[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]-5-[[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-胺(C24)的合成

[0960] 将(2′S,4R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C23(143.7mg,0.3519mmol)、1-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙烷-2-胺(108mg,0.5310mmol)、tBuXPhos Pd G1(15mg,0.02303mmol)于t-BuOH(3.5mL)中的混合物在氮气下脱气10分钟,随后添加NaOtBu(388μL的2M,0.7760mmol)。将所得混合物密封并在60℃下加热45分钟。在EtOAc与水之间分配。将合并的有机物经无水硫酸钠干燥,过滤,并在真空中浓缩以得到N-[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]-5-[[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-胺。LCMS m/z 551.28$[M+H]^+$。

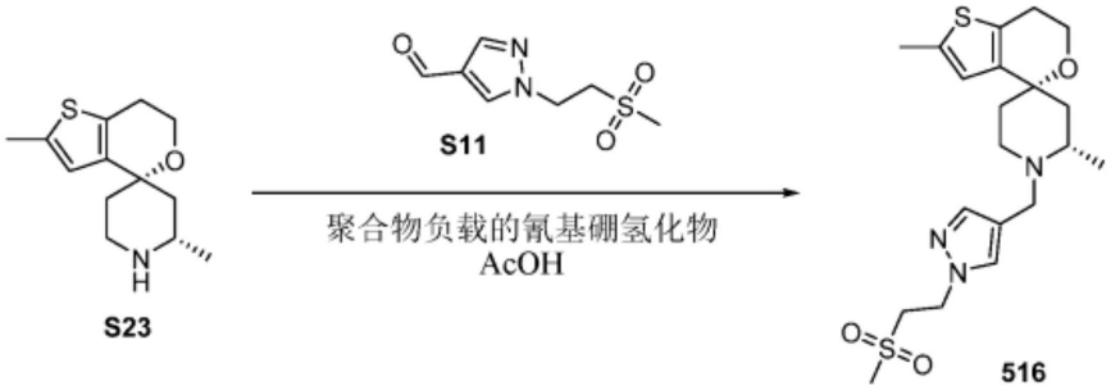
[0961] 步骤3:2-[[5-[[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]-2-甲基-丙-1-醇(515)的合成

[0962] 将来自步骤2的粗产物溶解在THF(3mL)中并用TBAF(含1.8mL的1M的THF,1.800mmol)处理。将反应在rt下搅拌2小时,然后在EtOAc与水之间分配。将合并的有机物经无水硫酸钠干燥,过滤并在真空中浓缩。通过HPLC纯化:含10-90% ACN的水(HCl改性剂)以得到2-[[5-[[(2′S,4R)-2-氯-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基]甲基]嘧啶-2-基]氨基]-2-甲基-丙-1-醇(盐酸盐)(6.3mg,4%)。^1H NMR(300MHz,甲醇-

d_4)δ8.43(s,2H),6.81(s,1H),4.56(s,1H),3.96(h,J＝6.1Hz,3H),3.69(s,2H),3.56(s,1H),3.18(s,2H),2.74(td,J＝5.3,1.9Hz,2H),2.09(dd,J＝23.2,8.1Hz,4H),1.56(s,3H),1.39(s,6H)。LCMS m/z 437.11[M+H]$^+$。

[0963] 化合物516

[0964] (2′S,4S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](516)

[0965] 

[0966] (2′S,4S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](516)的制备

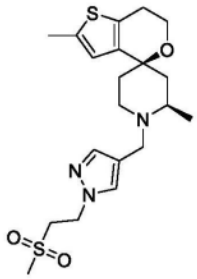
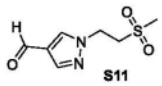
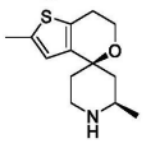
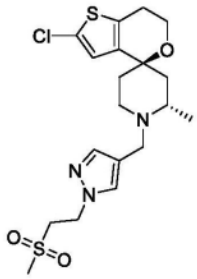
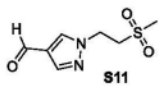
[0967] 将(2′S,4S)-2,2′-二甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S23(27.6mg,0.1163mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(41mg,0.2027mmol)溶解在DCM(750μL)中,并将乙酸(40μL,0.7034mmol)添加到溶液中,随后添加聚合物负载的氰基硼氢化物(186mg的2mmol/g,0.3720mmol)。将溶液在微波反应器中加热至90℃,持续95分钟。添加另外部分的聚合物负载的氰基硼氢化物(67mg,0.5930mmol),并将反应物在rt下搅拌过夜。将悬浮液在1.5mL的MeOH中搅拌10分钟,然后滤出树脂。去除溶剂,并且将残余物溶解在水(2mL)和DCM(2mL)中。用2M NaOH将水层的pH调节至pH>10。通过相分离器分离各相,将水层用DCM(2×10mL)萃取,并将合并的有机物在真空中浓缩。将粗残余物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生(2′S,4S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](32.1mg,62%)。^{1}H NMR(300MHz,氯仿-d)δ7.54(s,1H),7.49(s,1H),6.46(d,J＝1.3Hz,1H),4.58(t,J＝6.8Hz,2H),4.00-3.80(m,2H),3.64(t,J＝6.1Hz,2H),3.55(s,2H),3.06(q,J＝5.9,5.3Hz,1H),2.91-2.58(m,3H),2.56-2.43(m,1H),2.47(s,3H),2.40(s,3H),2.03-1.76(m,4H),1.17(d,J＝6.8Hz,3H)。

[0968] 化合物517-518

[0969] 化合物517-518(参见表16)由中间体S22和S24使用如化合物516的还原胺化步骤在单个步骤中制备。醛如前所述。表16和随附脚注中注明了对方法的任何修改。

[0970] 表16:化合物517-518的结构和物理化学数据

[0971]

化合物	产物	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
517		 S11	S22[1]  S22	^{1}H NMR (300 MHz, 甲醇-d_4) δ 7.74 (s, 1H), 7.58 (d, J = 0.7 Hz, 1H), 6.45 (d, J = 1.3 Hz, 1H), 4.62 (t, J = 6.5 Hz, 2H), 3.89 (dd, J = 5.9, 5.0 Hz, 2H), 3.68 (t, J = 6.4 Hz, 2H), 3.64 (d, J = 1.3 Hz, 2H), 3.08 (dq, J = 10.4, 6.5 Hz, 1H), 2.97 - 2.79 (m, 1H), 2.76 (s, 3H), 2.74 - 2.54 (m, 3H), 2.36 (d, J = 1.0 Hz, 3H), 2.06 - 1.69 (m, 4H), 1.24 (d, J = 6.8 Hz, 3H)。
518		 S11	S24[2]	^{1}H NMR (300 MHz, 甲醇-d_4) δ 8.02 (s, 1H), 7.74 (d, J = 0.7 Hz, 1H), 6.76 (d, J = 1.1 Hz, 1H), 5.49 (s, 1H), 4.76 - 4.66 (m, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.28 (d, J = 14.1 Hz, 1H), 3.97 - 3.84 (m, 2H), 3.72 (t, J = 6.2 Hz, 2H), 3.53 - 3.46 (m, 1H), 2.91 - 2.82 (m, 3H), 2.79

[0972]

化合物	产物	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
				- 2.69 (m, 2H), 2.25 - 1.91 (m, 4H), 1.54 (d, J = 6.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 1H)；LCMS *m/z* 443.99 [M+H]$^+$。

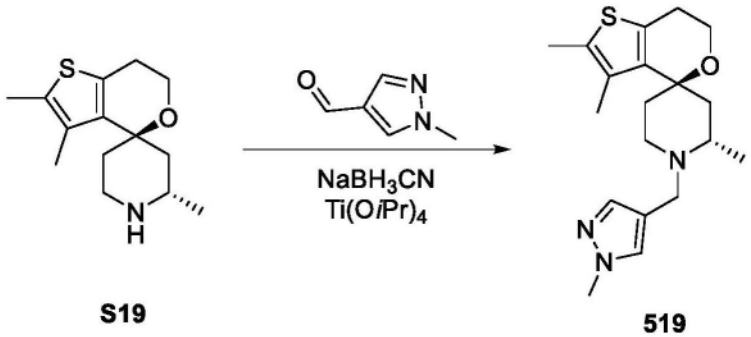
[0973] 脚注：

[0974] 1)使用了不同的试剂量:1-(2-甲基磺酰基乙基)吡唑-4-甲醛(2.2当量)、乙酸(7.0当量)、聚合物负载的氰基硼氢化物(4.7当量)。

[0975] 2)使用了不同的试剂量:1-(2-甲基磺酰基乙基)吡唑-4-甲醛(1.5当量)、乙酸(5.0当量)、聚合物负载的氰基硼氢化物(2.8当量)。将反应在110℃下进行1小时。

[0976] 化合物519

[0977] (2′S,4R)-2,2′,3-三甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](519)

[0978] 

S19 519

[0979] (2′S,4R)-2,2′,3-三甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](519)的制备

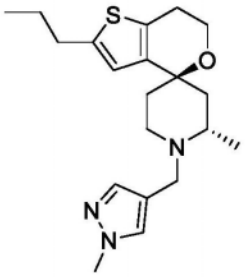
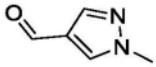
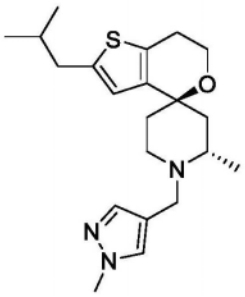
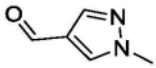
[0980] 向(2′S,4R)-2,2′,3-三甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S19(150mg,0.5967mmol)于MeOH(2mL)中的经搅拌的溶液中添加1-甲基吡唑-4-甲醛(131.41mg,1.1934mmol)和异丙醇钛(508.77mg,0.5283mL,1.7901mmol)并在50℃下搅拌2小时。将氰基硼氢化钠(112.49mg,1.7901mmol)添加到反应混合物中并在50℃下搅拌24小时。将反应混合物在真空中浓缩并用水(4ml)洗涤,并用EtOAc(3×5ml)萃取。将有机层经硫酸钠干燥并在真空中浓缩,并通过反相HPLC色谱法纯化。方法:YMC Triart Actus C18(250×20mm,5微米)。梯度:含MeCN的H_2O,具有20mM碳酸氢铵。将产物分离为(2′S,4R)-2,2′,3-三甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](56.3mg,27%)。1H NMR(400MHz,DMSO-d_6)δ7.57(s,1H),7.29(s,1H),3.80(bs,3H),3.77-3.65(m,3H),3.45(d,J=14.52Hz,1H),2.60(bs,2H),2.43-2.32(m,3H),2.21(s,3H),2.09(s,3H),2.02-1.97(m,1H),1.75(t,J=11.6Hz,1H),1.59(d,J=13.8Hz,2H),1.09(d,J=5.8Hz,3H)。LCMS m/z 346.3$[M+H]^+$。

[0981] 化合物520-521

[0982] 化合物520-521(参见表17)由选自中间体S20或S21的适当哌啶使用如化合物519的还原动画步骤在单个步骤中制备。醛从商业来源获得。表17和随附脚注中注明了对方法的任何修改。

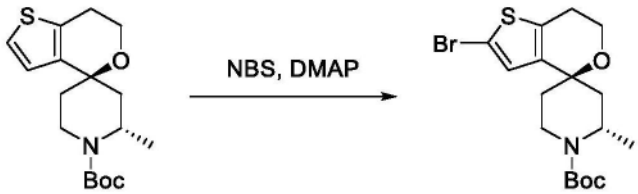
[0983] 表17:化合物520-521的结构和物理化学数据

[0984]

化合物	产物	醛 试剂	^{1}H NMR；LCMS m/z [M+H]$^+$。
520			^{1}H NMR (400MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.27 (s,1H), 6.57 (s, 1H), 3.79-3.65 (m, 6H), 3.39-3.31 (m, 1H), 3.30 (s, 3H), 2.66-2.61 (m, 4H), 2.40-2.32 (m, 2H), 1.73-1.65 (m, 2H), 1.59-1.52 (m, 2H), 1.08 (d, J=6.12 Hz, 3H), 0.90 (t, J=7.28 Hz, 3H)； LCMS *m/z* 360.3 [M+H]$^+$。
521			^{1}H NMR (400MHz,DMSO-d6) δ: 7.55 (s, 1H), 7.28 (s, 1H), 6.54 (s, 1H), 3.79-3.74 (m, 5H), 3.67 (d, J = 14.0 Hz, 1H), 3.41 (d, J = 14.0 Hz, 1H), 2.61 (bs, 2H), 2.54 (d, J = 6.92 Hz, 2H), 2.40-2.35 (m, 2H), 1.77-1.66 (m, 4H), 1.55-1.52 (m, 2H), 1.08 (d, J = 5.88 Hz, 3H), 0.88 (d, J = 6.56 Hz, 6H)； LCMS *m/z* 374.3 [M+H]$^+$。

[0985] 制备S25

[0986] (2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S25)

[0987] 

S21 S25

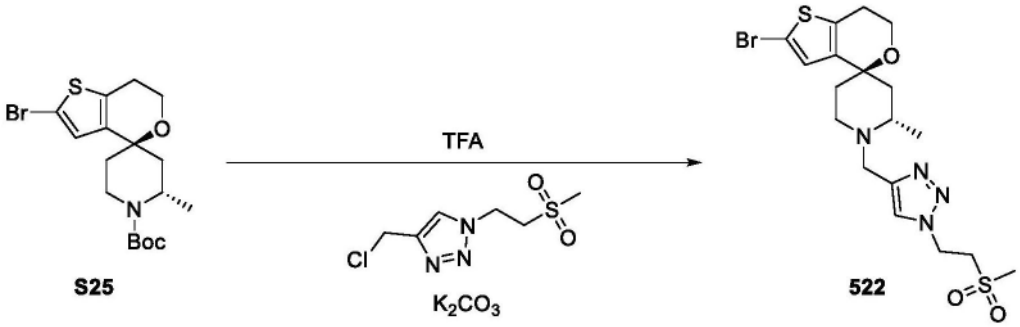
[0988] (2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S25)的制备

[0989] 在rt下向(2′S,4R)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S21(220mg,564.54μmol)于ACN(4mL)的搅拌溶液中添加NBS(100mg,561.85μmol)和DMAP(0.6mg,4.9113μmol)。然后将反应混合物加热至65℃并搅拌过夜。将反应混合物用1N NaOH(25mL)稀释,用EtOAc(2×50ml)萃取。将有机层用饱和硫代硫酸钠水溶液(50ml)洗涤,然后用盐水溶液(50ml)洗涤,经Na_2SO_4干燥。将有机层在真空中浓缩,以提供粗材料。将粗化合物通过硅胶色谱法纯化(梯度:含10-15%EtOAc的石油醚),产生(2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S25(140mg,59%)。^{1}H NMR(400MHz,氯仿-d)δ6.55(s,1H),5.30(s,1H),3.98-3.88(m,1H),3.87-3.85(m,1H),3.74-3.71(m,1H),3.32-3.28(m,1H),2.71-2.66(m,2H),1.96-1.91(m,2H),1.76-1.64(m,2H),1.48(s,9H),1.24(d,J=6.4Hz,3H)。LCMS m/z 404.24[M+H]$^+$。

[0990] 化合物522

[0991] (2′S,4R)-2-溴-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-

二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](522)

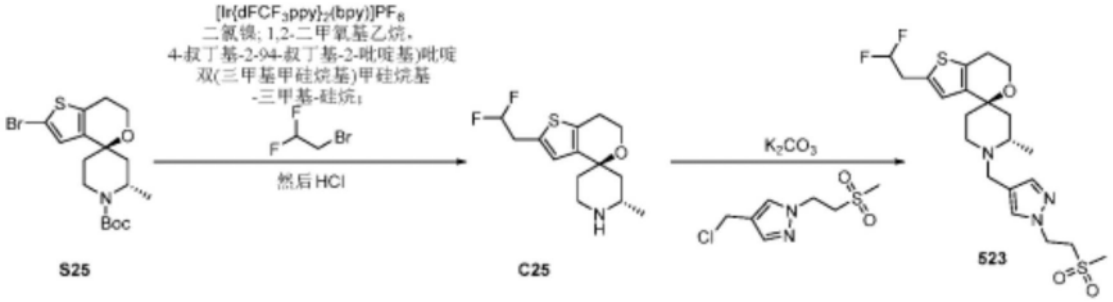
[0992] 

[0993] (2′S,4R)-2-溴-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](522)的制备

[0994] 向(2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S25(50mg,0.1156mmol)于DCM(1mL)中的混合物中添加三氟乙酸(200μL,2.596mmol)。搅拌5分钟后,将混合物干燥并重新溶解在乙腈(2mL)中,并向其中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(盐酸盐)(45mg,0.1730mmol)和碳酸钾(50mg,0.3618mmol)。将混合物在70℃下搅拌3小时。将混合物冷却至rt,用水(3mL)和EtOAc(5mL)稀释,将各层混合并去除水层。将有机层用饱和盐水洗涤,用硫酸镁干燥,过滤并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0-10% MeOH的DCM)以产生(2′S,4R)-2-溴-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]522(33mg,58%)。^{1}H NMR(400MHz,氯仿-d)δ7.55(s,1H),6.65(s,1H),4.83-4.75(m,2H),4.00-3.71(m,5H),3.66(t,J=6.3Hz,2H),2.68-2.55(m,6H),2.48(s,2H),1.80-1.71(m,3H),1.58(d,J=12.7Hz,1H),1.16(d,J=6.1Hz,3H)。LCMS m/z 488.97[M+H]$^+$。

[0995] 化合物523

[0996] (2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](523)

[0997] 

[0998] 步骤1:(2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](C25)的合成

[0999] 将[Ir{dFCFppy}$_2$(bpy)]PF$_6$(4mg,0.003962mmol)、4-叔丁基-2-(4-叔丁基-2-吡啶基)吡啶(10mg,0.03726mmol)和二氯镍;1,2-二甲氧基乙烷(10mg,0.04551mmol)添加到1打兰小瓶中,将其抽空并用氮气重新填充三次。在氮气下将双(三甲基甲硅烷基)甲硅烷基-三甲基-硅烷(190μL,0.6159mmol)、2,6-二甲基吡啶(90μL,0.7769mmol)、2-溴-1,1-二氟-乙烷(50μL)和(2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(150mg,0.3728mmol)溶解在1,2-二甲氧基乙烷(2mL)中。将反应物在Merck光反应

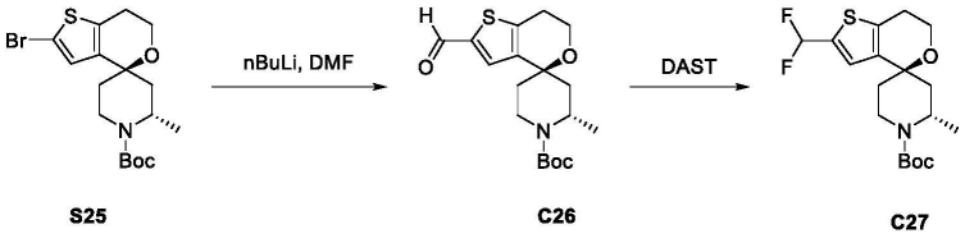
器中以100％ LED功率、4700RPM风扇辐照2小时。将反应物用3mL EtOAc和1mL水稀释。将反应物萃取，并将有机层干燥，然后蒸发掉挥发物。将粗残余物溶解在HCl(1000μL的4M，4.000mmol)中，并搅拌1小时，然后去除挥发物。通过反相HPLC纯化。方法：C18 Waters Sunfire柱(30×150mm，5微米)。梯度：含MeCN的H_2O，具有0.1％三氟乙酸。产生(2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C25(三氟乙酸盐)(33.2mg，22％)。1H NMR(400MHz，DMSO-d6)δ8.91(s,2H)，6.66(s,1H)，6.40-6.02(m,1H)，3.89(hept,J＝6.0,5.5Hz,2H)，3.70-3.37(m,3H)，3.12(dd,J＝54.9,12.4Hz,2H)，2.74(t,J＝5.4Hz,2H)，2.10-1.83(m,4H)，1.24(d,J＝6.4Hz,3H)。LCMS m/z 288.48$[M+H]^+$。

[1000] 步骤2：(2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](523)的合成

[1001] 将(2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]C25(30mg)溶解在ACN(1mL)中，并添加4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(盐酸盐)(17mg，0.06560mmol)和K_2CO_3(100mg，0.7236mmol)。在氮气下加热至65℃过夜。然后将反应物用水和DCM稀释，然后在相分离器上分离各层并将水层用DCM(x2)萃取。将有机层在真空中浓缩，并用硅胶色谱法纯化(梯度：含0-20％ MeOH的DCM)以产生(2′S,4R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](6.1mg，19％)。^{1}H NMR(400MHz，DMSO-d_6)δ7.71(s,1H)，7.39(s,1H)，6.77(s,1H)，6.19(tt,J＝56.2,4.2Hz,1H)，4.51(t,J＝6.8Hz,2H)，3.82-3.65(m,5H)，3.51-3.26(m,4H)，2.77(s,3H)，2.65(s,2H)，2.44-2.25(m,2H)，1.76-1.46(m,4H)，1.09(d,J＝6.1Hz,3H)。LCMS m/z474.02$[M+H]^+$。

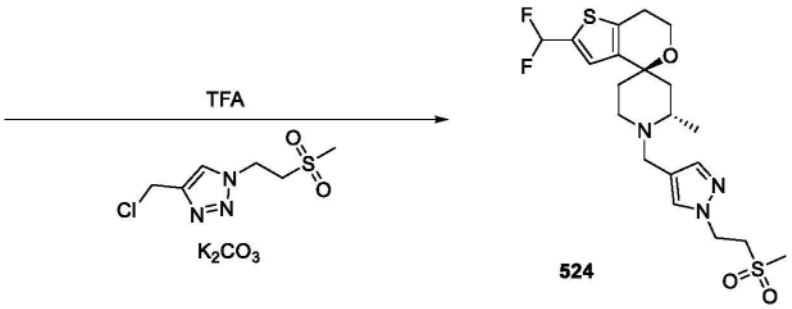
[1002] 化合物524

[1003] (2′S,4R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]



S25 C26 C27

[1004]



[1005] 步骤1：(2′S,4R)-2-甲酰基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C26)的合成

[1006] 将(2′S,4R)-2-溴-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S25(50mg,0.1243mmol)于THF(1mL)中的溶液冷却至-78℃。此时,逐滴添加含丁基锂(50μL的2.5M,0.1250mmol)的己烷。在此温度下搅拌60分钟后,添加DMF(10μL,0.1291mmol)。另外50分钟后,将混合物缓慢温热至rt。将反应物用饱和氯化铵淬灭,用1mL水和5mL EtOAc稀释。将层混合并分离,并且将有机层用饱和盐水洗涤。将有机层用硫酸钠干燥,过滤并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0-50%EtOAc的庚烷),提供(2′S,4R)-2-甲酰基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C26(29mg,65%)。^{1}H NMR(400MHz,氯仿-d)δ9.82(s,1H),7.42(s,1H),4.05-3.85(m,3H),3.76(ddd,J=13.8,6.1,4.8Hz,1H),3.37(ddd,J=14.0,8.9,5.4Hz,1H),2.96-2.80(m,2H),2.10(dddd,J=14.7,8.2,6.0,1.8Hz,1H),1.99(ddd,J=14.2,5.2,1.9Hz,1H),1.83-1.73(m,2H),1.49(s,9H),1.27(d,J=6.6Hz,3H)。LCMS m/z 351.93[M+H]$^+$。

[1007] 步骤2:(2′S,4R)-2-(二氟乙基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C27)的合成

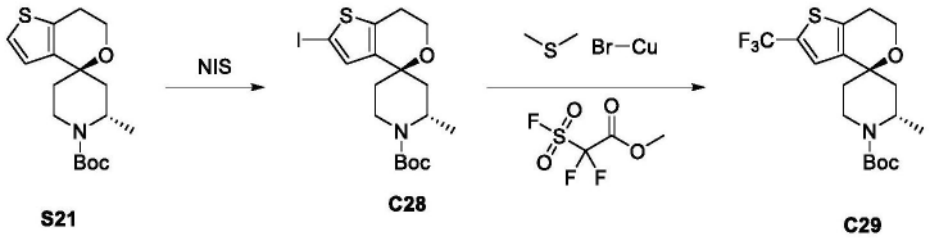
[1008] 将(2′S,4R)-2-甲酰基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C26(29mg,0.08040mmol)于DCM(500μL)中的混合物在rt下搅拌。将N-乙基-N-(三氟-λ4-硫醇基)乙胺(30μL,0.2271mmol)和混合物在回流下搅拌。搅拌20小时后,将混合物冷却至rt,用水稀释,并分离各层。用硫酸钠干燥有机层,过滤,浓缩,并通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷),提供(2′S,4R)-2-(二氟甲基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C27(18mg,59%)。^{1}H NMR(400MHz,氯仿-d)δ6.90(d,J=2.1Hz,1H),6.75(t,J=56.2Hz,1H),4.03-3.83(m,3H),3.74(ddd,J=13.9,6.0,4.8Hz,1H),3.33(ddd,J=14.1,8.9,5.4Hz,1H),2.88-2.72(m,2H),2.05(dddd,J=14.8,9.0,6.1,1.8Hz,1H),1.95(ddd,J=14.2,5.2,1.8Hz,1H),1.80-1.67(m,2H),1.48(s,9H),1.25(d,J=6.5Hz,3H)。LCMS m/z 373.99[M+H]$^+$。

[1009] 步骤3:(2′S,4R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](524)的合成

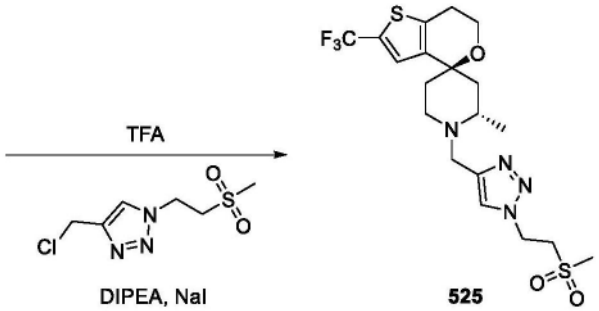
[1010] 向(2′S,4R)-2-(二氟甲基)-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C27(18mg,0.04775mmol)于DCM(400μL)中的混合物中添加三氟乙酸(40μL,0.5192mmol)(11:30)。搅拌60分钟后,将混合物干燥并重新溶解在乙腈(1,000μL)中,并向其中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(盐酸盐)(15mg,0.05766mmol)和碳酸钾(20mg,0.1447mmol),并将混合物在60℃下搅拌过夜。将混合物用EtOAc(5mL)和水(2mL)稀释,并将有机层混合并分离。然后将有机层用盐水洗涤,用硫酸镁干燥,过滤并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0-10%MeOH的DCM)以提供(2′S,4R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]524(10mg,45%)。^{1}H NMR(400MHz,氯仿-d)δ7.57(s,1H),6.90(t,J=2.1Hz,1H),6.68(t,J=56.1Hz,1H),4.86-4.74(m,2H),3.97(d,J=14.7Hz,1H),3.91-3.71(m,3H),3.71-3.62(m,2H),2.82-2.64(m,3H),2.62(d,J=0.7Hz,3H),2.52(dt,J=11.5,5.9Hz,2H),1.86-1.72(m,3H),1.61(t,J=12.6Hz,1H),1.17(d,J=6.2Hz,3H)。LCMS m/z 461.1[M+H]$^+$。

[1011] 化合物525

[1012] (2′S,4R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]



[1013]



[1014] 步骤1:(2′S)-2-碘代-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C28)的合成

[1015] 将(2′S)-2′-甲基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S21(200mg,0.6183mmol)溶解在CH_3CN(4mL)中,并添加NIS(168mg,0.7467mmol)。将反应混合物在rt下搅拌过夜,并且然后用1NNaOH/EtOAc稀释,并将有机层干燥并浓缩,将其用硅胶色谱法纯化(梯度:0至40% EtOAc/庚烷),提供(2′S)-2-碘代-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C28(222mg,80%)。LCMS m/z 449.94$[M+H]^+$。

[1016] 步骤2:(2′S)-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C29)的合成

[1017] 将(2′S)-2-碘代-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C28(215mg,0.4785mmol)溶解在DMF(4mL)中,并添加溴铜;甲基磺酰基甲烷(30mg,0.1459mmol)和2,2-二氟-2-氟磺酰基-甲酸乙酯(150μL,1.178mmol)。将反应混合物在微波中加热至100℃,持续40分钟。添加另外的2,2-二氟-2-氟磺酰基-甲酸乙酯(75μL,0.5891mmol),并将反应混合物再次在微波中加热至100℃,持续40分钟。将反应混合物用EtOAc/1N NaOH稀释,并通过Celite®过滤。将有机层干燥并浓缩成油,将其通过硅胶色谱法纯化(梯度:含0至25% EtOAc的庚烷),产生(2′S)-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯C28(87mg,46%)。1H NMR(300MHz,氯仿-d)δ 7.07(s,1H),4.07-3.96(m,1H),3.96-3.86(m,2H),3.84-3.70(m,1H),3.41-3.28(m,1H),2.88-2.78(m,2H),2.15-1.91(m,2H),1.83-1.67(m,2H),1.48(s,9H),1.28(d,J=6.5Hz,3H)。

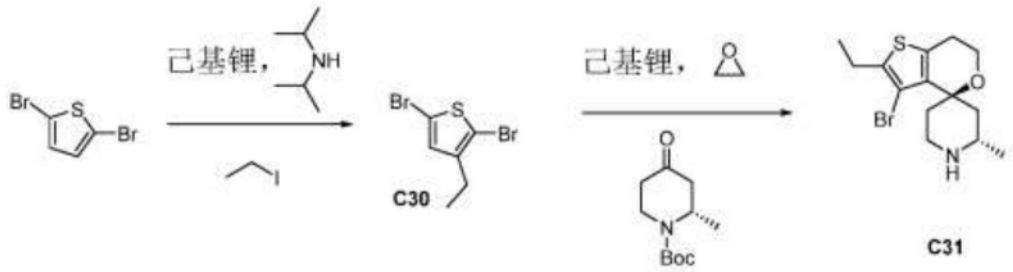
[1018] 步骤3:(2′S,4R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](525)的合成

[1019] 将(2′S)-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-

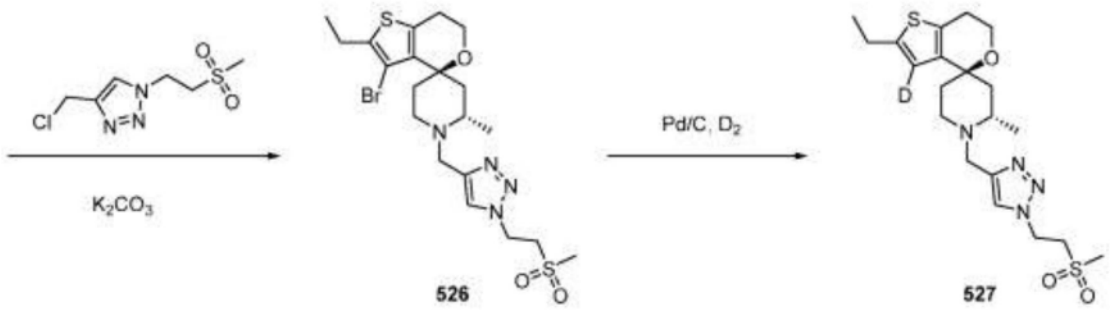
1′-甲酸叔丁酯C29(42mg,0.1073mmol)溶解在DCM(1mL)中,并添加TFA(500μL,6.490mmol)。20分钟后,去除溶剂并将残余物重新溶解在DCE(1mL)中,并添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(40mg,0.1788mmol)、NaI(3mg,0.02001mmol)和DIPEA(60μL,0.3445mmol)。将反应混合物加热至60℃,持续20小时。将反应混合物浓缩,溶解在1mL MeOH中并使用反相C18柱重新纯化(梯度:CH_3CN/H2O,TFA改性剂)。将纯级分用EtOAc/1N NaOH稀释并将有机层干燥并浓缩,产生(2′S,4R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]525(27mg,52%)。1H NMR(300MHz,氯仿-d)δ7.65(s,1H),7.14(s,1H),4.88(t,J=6.3Hz,2H),4.12-3.82(m,4H),3.75(t,J=6.3Hz,2H),2.91-2.75(m,3H),2.71(s,3H),2.66-2.51(m,2H),1.96-1.68(m,4H),1.25(d,J=6.2Hz,3H)。LCMS m/z 479.11$[M+H]^+$。

[1020] 化合物526和527

[1021] (2′S,4R)-3-溴-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](526)和(2′S,4R)-3-氘-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](527)



[1022]



[1023] 步骤1:3,5-二溴-2-乙基-噻吩(C30)的合成

[1024] 在0℃下在氮气下在5分钟内向N-异丙基丙-2-胺(1.2mL,8.562mmol)于THF(50mL)中的溶液中添加己基锂(4.2mL的2.3M,9.660mmol),并将反应物搅拌另外30分钟。将溶液冷却至-78℃后添加2,5-二溴噻吩(900μL,7.987mmol)。然后添加碘乙烷(1.3mL,16.25mmol)并搅拌过夜,缓慢温热至rt。将反应物用饱和氯化铵溶液淬灭,然后用DCM(3×100mL)萃取,并将合并的有机物用饱和碳酸氢盐溶液和饱和盐水溶液洗涤。将合并的有机层在真空中蒸发,产生3,5-二溴-2-乙基-噻吩(1.1g,52%)。^{1}H NMR(300MHz,氯仿-d)δ6.79(s,1H),2.68(q,J=7.5Hz,2H),1.18(t,J=7.5Hz,3H)。

[1025] 步骤2:(2′S)-3-溴-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌

啶](C31)的合成

[1026] 在-78℃下将3,5-二溴-2-乙基-噻吩C30(500mg,1.852mmol)溶解在THF(10mL)中。添加已基锂(900μL的2.3M,2.070mmol),并搅拌30分钟,然后添加环氧乙烷(1000μL的2.5M,2.500mmol)。将反应混合物温热至rt并搅拌2天。将反应物用饱和氯化铵溶液淬灭并且用DCM(x3)萃取。将合并的有机层在真空中浓缩,并通过硅胶色谱法纯化(梯度:含0至60%EtOAc的庚烷),产生2-(4-溴-5-乙基-2-噻吩基)乙醇(200mg,46%)。^{1}H NMR(300MHz,氯仿-d)δ6.62(s,1H),3.78(m,2H),2.91(t,J=6.1Hz,2H),2.73-2.61(m,2H),1.18(td,J=7.5,1.4Hz,3H)。

[1027] 将来自步骤2的材料溶解在二噁烷(5mL)中,并在氮气下添加(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(400mg,1.876mmol)。添加三氟甲磺酸(400μL,4.520mmol)并搅拌过夜。将反应混合物用饱和碳酸氢盐溶液淬灭,用DCM稀释,并在相分离器上萃取(x3)。将溶剂在正氮气压下蒸发,产生(2′S)-3-溴-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸(1))C31(510mg,37%)。LCMS m/z 330.05[M+H]$^+$。

[1028] 步骤3:(2′S,4R)-3-溴-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](526)的合成

[1029] 向(2′S)-3-溴-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟甲磺酸(1))C31(120mg,0.1593mmol)于DMF(1mL)中的溶液中添加K_2CO_3(88mg,0.6367mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(盐酸盐)(42mg,0.1615mmol)。将反应物在60℃下搅拌过夜。将反应混合物用水淬灭并用DCM(x3)萃取。将合并的有机层在真空中浓缩,并且然后通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生(2′S,4R)-3-溴-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]526(60mg,71%)。LCMS m/z 517.1[M+H]$^+$。

[1030] 步骤4:(2′S,4R)-3-氘-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](527)的合成

[1031] 含(2′S,4R)-3-溴-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]526(10mg)的MeOH(2mL),并在氮气下添加Pd/C(10mg,0.09397mmol)。将反应物在氘气下经受过夜。然后将烧瓶用氮气吹扫并过滤掉Pd/C以产生(2′S,4R)-3-氘-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]527(6.0mg,73%)。LCMS m/z 440.12[M+H]$^+$。

[1032] 制备S26

[1033] 1-(5-氯-2-噻吩基)丙-2-醇(S26)

[1034]



S26

[1035] 步骤1:1-(5-氯-2-噻吩基)丙-2-醇(S26)

[1036] 在-78℃下向2-氯噻吩(1.5g,12.6mmol)于THF(20mL)中的经搅拌的溶液中添加

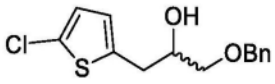
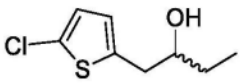
LDA(含9.45mL的2M溶液的THF,18.9mmol),并将反应混合物搅拌1小时。添加2-甲基环氧乙烷(731mg,12.6mmol),并继续在-78℃下搅拌2小时。将反应物用饱和NH_4Cl水溶液(50mL)淬灭,并用EtOAc(2×50mL)萃取。将合并的有机层用盐水(40mL)洗涤,经Na_2SO_4干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含5% EtOAc的庚烷),产生1-(5-氯-2-噻吩基)丙-2-醇S26(1.3g,52%)。^1H NMR(300MHz,DMSO-d6)δ6.90(d,J=3.6Hz,1H),6.70(d,J=3.9Hz,1H),4.82(d,J=4.8Hz,1H),3.77(m,1H),2.84-2.68(m,2H),1.06(d,J=5.7Hz,3H)。LCMS m/z 272.19$[M+H]^+$。

[1037] 中间体S27-S29

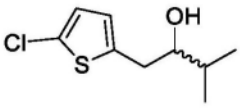
[1038] 中间体S27-S29(表18)由2-氯噻吩和适当的环氧化物制备,如化合物S26的方法所述。

[1039] 表18:噻吩核S27-S29的结构和LCMS数据

[1040]

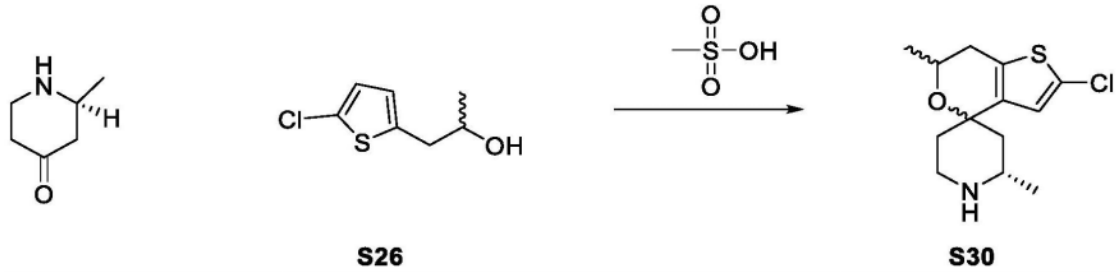
化合物	噻吩	环氧化物	^1H NMR; LCMS m/z $[M+H]^+$。
S27			^1H NMR (300 MHz, DMSO-*d6*) δ 7.35-7.28 (m, 5H), 6.90 (d, J = 3.6 Hz, 1H), 6.71 (d, J = 4.2 Hz, 1H), 5.12 (d, J = 5.1 Hz, 1H), 4.52 (s, 1H), 4.48 (s, 1H), 3.80-3.74 (m, 1H), 3.39-3.27 (m, 2H), 2.97 (dd, J = 14.7 HZ, 1H), 2.77-2.69 (m, 1H)。LCMS *m/z* 288.1 $[M+H]^+$。
S28			^1H NMR (400 MHz, $CDCl_3$) δ 6.895 (d, J = 4 Hz, 1H), 6.63-6.62 (m, 1H), 3.72-3.69 (m, 1H), 2.96-2.91 (m, 1H), 2.81-2.75 (m, 1H), 1.66-1.51 (m, 2H), 0.98 (t, J = 4.8 Hz, 3H)。LCMS *m/z* 288.24 $[M+H]^+$。

[1041]

S29			^1H NMR (300 MHz, DMSO-*d6*) δ 6.89 (d, J = 3.6 Hz, 1H), 6.725 (d, J = 3.6 Hz, 1H), 4.80 (d, J = 6 Hz, 1H), 3.34-3.30 (m, 1H), 2.87 (dd, J = 3.3, 15, 1H), 2.67 (dd, J = 8.4, 15, 1H), 1.59-1.45 (m, 1H), 0.86 (d, J = 6.6 Hz, 6H)。LCMS *m/z* 300.15 $[M+H]^+$。

[1042] 制备S30

[1043] (2′S)-2-氯-2′,6-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S30)

[1044] 

S26 S30

[1045] 步骤1:(2′S)-2-氯-2′,6-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S30)的合成

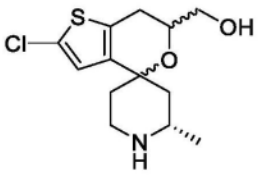
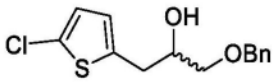
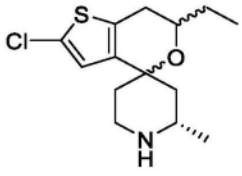
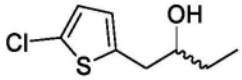
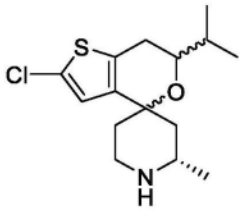
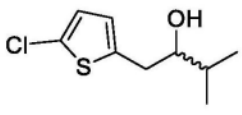
[1046] 在室温下向1-(5-氯-2-噻吩基)丙-2-醇S30(1.3g,0.0066mol)、(2S)-2-甲基哌啶-4-酮(三氟乙酸(1))(1.5g,0.0059mol)于甲苯(15mL)中的经搅拌的溶液中添加甲磺酸(701.58mg,0.4737mL,0.0073mol)。将反应混合物在120℃下搅拌4小时。使用Na_2CO_3的饱和水溶液将pH调节至8-9,并用乙酸乙酯(2×50mL)萃取。将合并的有机层用盐水(50mL)洗涤,经无水Na_2SO_4干燥,过滤并浓缩。通过反相HPLC纯化。方法Xbridge C18柱(19×150mm,5微米)。梯度:含MeCN的H2O,具有10mM碳酸氢铵,产生产物。将收集的级分冻干以得到(2′S)-2-氯-2′,6-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S30(370mg,20%)。^{1}H NMR(300MHz,DMSO-d6)δ6.92(s,1H),3.87(d,J=9.6Hz,1H),2.95-2.78(m,2H),2.71-2.62(m,2H),2.42-2.33(m,1H),1.91-1.79(m,2H),1.46-1.36(m,2H),1.23(d,J=6.3Hz,3H),1.15-1.07(m,1H),0.94-0.91(m,3H)。LCMS m/z 272.11$[M+1]^+$。

[1047] 化合物S31-S33

[1048] 化合物S31-S33(表19)由(2S)-2-甲基哌啶-4-酮和适当的噻吩试剂制备,如化合物S30的方法所述。

[1049] 表19:螺哌啶核S31-S33的结构和LCMS数据

[1050]

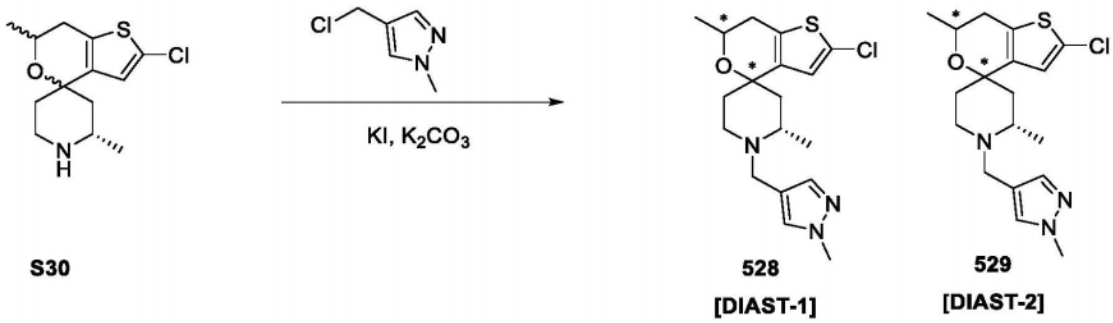
化合物	结构	噻吩	LCMS m/z $[M+H]^+$。
S31[1]			LCMS *m/z* 288.1 $[M+H]^+$。
S32			LCMS *m/z* 288.24 $[M+H]^+$。
S33			LCMS *m/z* 300.15 $[M+H]^+$。

[1051] 脚注:

[1052] 1)三氟甲磺酸(1当量)用作酸。

[1053] 化合物528

[1054] (2′S)-2-氯-2′,6-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](528[DIAST-1]和529[DIAST-2])

[1055] 

[1056] (2′S)-2-氯-2′,6-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](528和529)的制备

[1057] 向(2′S)-2-氯-2′,6-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S30(300mg,0.993mmol)和4-(氯甲基)-1-甲基-吡唑(115mg,0.792mmol)于MeCN(6mL)中的经搅拌的溶液中添加碳酸钾(691mg,5.0mmol),随后添加KI(33mg,0.198mmol),并在室温下搅拌16小时。完成后,蒸发溶剂。通过反相HPLC纯化。方法:XSelect苯基己基柱(19×250mm,5微米)。梯度:含MeCN的H2O,具有0.1%甲酸。随后通过SFC纯化产生两种非对映异构体:

[1058] (2′S)-2-氯-2′,6-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]528[DIAST-1](39.7mg,11%)。^{1}H NMR(400MHz,DMSO-d6)δ7.54(s,1H),7.28(s,1H),6.98(s,1H),3.82-3.79(m,4H),3.73(d,J=14Hz,1H),3.25(d,J=13.6Hz,1H),2.63(dd,J=3.2Hz and 16Hz,1H),2.55-2.45(m,2H),2.39-2.28(m,2H),1.87(dd,J=2.4Hz and 14Hz,1H),1.75-1.69(m,1H),1.57-1.56(m,1H),1.46-1.42(m,1H),1.18(d,J=6Hz,3H),1.07(d,J=6Hz,3H)。LCMS m/z 366.1[M+1]$^+$;和

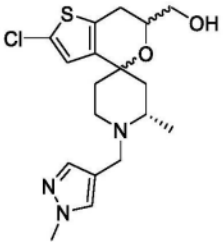
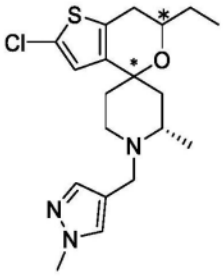
[1059] (2′S)-2-氯-2′,6-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]529[DIAST-2](10.3mg,3%)。^{1}H NMR(400MHz,DMSO-d6)δ7.54(s,1H),7.28(s,1H),6.98(s,1H),3.90-3.85(m,1H),3.79-3.72(m,4H),3.32-3.23(m,1H),2.64(dd,J=2.8Hz and 16Hz,1H),2.56-2.49(m,1H),2.41-2.32(m,3H),1.97-1.90(m,2H),1.44-1.34(m,2H),1.18(d,J=6Hz,3H),1.09(d,J=6Hz,3H)。LCMS m/z 366.1[M+1]$^+$。

[1060] 化合物530-533

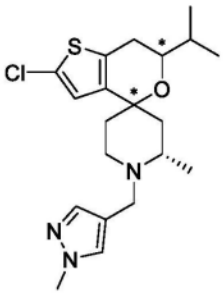
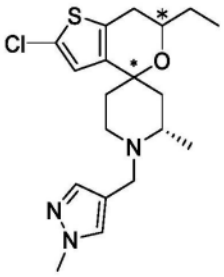
[1061] 使用化合物528和529的方法,由适当选择的哌啶和4-(氯甲基)-1-甲基-吡唑制备化合物530-533(表20)。

[1062] 表20:化合物530-533的结构和物理化学数据

[1063]

化合物	结构	哌啶	^{1}H NMR；LCMS m/z [M+H]$^+$。
530		S31[1]	^{1}H NMR (400 MHz, DMSO-d6) δ 7.54 (s, 1H), 7.27 (s, 1H), 6.98 (s, 1H), 4.7 (br s, 1H), 3.79-3.73 (m, 5H), 3.56-3.48 (m, 1H), 3.43-3.32 (m, 1H), 3.23 (d, J = 14 Hz, 1H), 2.66-2.60 (m, 2H), 2.46-2.32 (m, 3H), 1.73-1.41 (m, 4H), 1.09-1.06 (m, 3H)。LCMS *m/z* 382.2 [M+H]$^+$。
531		S32	^{1}H NMR (400 MHz, DMSO-d6) δ 7.59 (brs, 1H), 7.31 (brs, 1H), 6.95 (s, 1H), 3.79-3.76 (m, 4H), 3.68-3.58 (m, 1H), 3.42-3.32 (m, 1H), 2.64 (d, J = 16, 3H), 2.38-2.31 (m, 2H), 1.99 (brs, 2H), 1.52-1.44 (m, 4H), 1.19-1.15 (m, 3H), 0.83 (t, J = 4.8 Hz, 3H)。LCMS *m/z* 380.0 [M+H]$^+$。

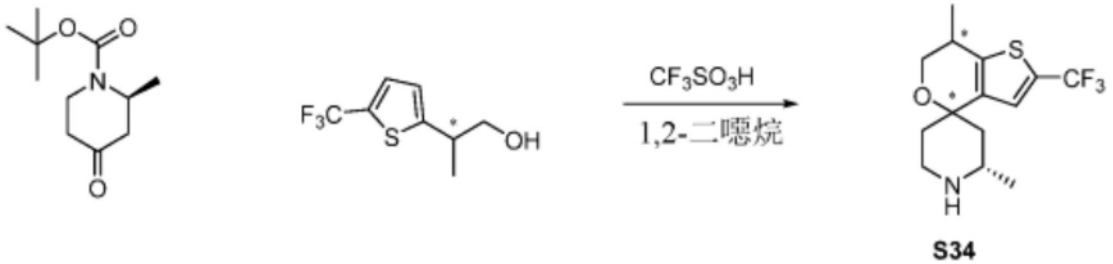
[1064]

化合物	结构	哌啶	^{1}H NMR；LCMS m/z [M+H]$^+$。
532		S33	^{1}H NMR (400 MHz, DMSO-d6) δ 7.53 (s, 1H), 7.27 (s, 1H), 6.97 (s, 1H), 3.77 (s, 3H), 3.69 (d, J = 14 Hz, 1H), 3.38-3.31- (m, 2H), 2.70-2.65 (m, 1H), 2.51-2.49 (m, 1H), 2.46-2.34 (m, 3H), 1.98-1.89 (m, 2H), 1.62-1.61 (m, 1H), 1.43-1.32 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H), 0.87-0.85 (m, 6H)。LCMS *m/z* 394.2 [M+H]$^+$。
533		S32	^{1}H NMR (400 MHz, DMSO-d6) δ 7.53 (s, 1H), 7.27 (s, 1H), 6.97 (s, 1H), 3.78 (s, 3H), 2.64 (d, J = 14, 1H), 3.61-3.52 (m, 1H), 3.38-3.31 (m, 1H), 2.64-2.60 (m, 1H), 2.51-2.49 (m, 2H), 2.38-2.31 (m, 2H), 1.88 (br d, 1H), 1.756 (t, J = 13.2 Hz, 1H), 1.61-1.42 (m, 4H), 1.07 (d, J = 6, 3H), 0.86 (t, J = 7.8 Hz, 3H)。LCMS *m/z* 380.0 [M+H]$^+$。

[1065] 制备S34

[1066] (2′S)-2′,7-二甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S34)

[1067]



S34

[1068] 步骤1：(2′S)-2′,7-二甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,

4′-哌啶](S34)的合成

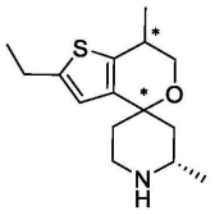
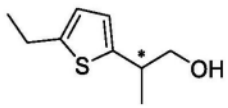
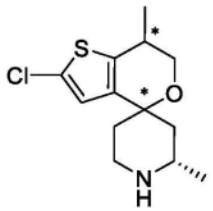
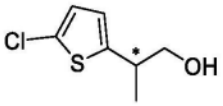
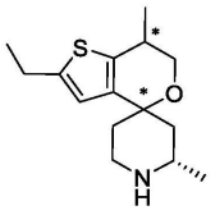
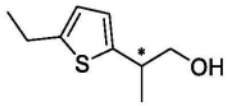
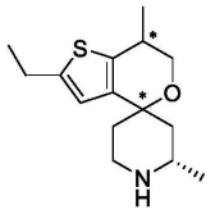
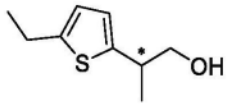
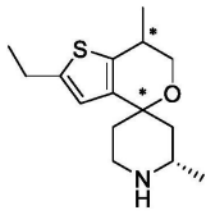
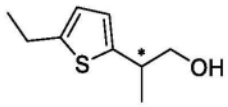
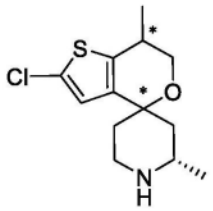
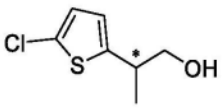
[1069] 将2-[5-(三氟甲基)-2-噻吩基]丙-1-醇(250mg,1.18mmol)和(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(362mg,1.69mmol)溶解在1,2-二噁烷(3mL)中。添加三氟甲磺酸(375μL,4.24mmol)并在rt下搅拌过夜。将反应物用$NaHCO_3$淬灭并蒸发溶剂。添加DCM和水,并将有机层通过相分离器收集。蒸发溶剂以产生(2′S)-2′,7-二甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S34)(600mg,146%)。LCMS m/z 306.24$[M+H]^+$。

[1070] 化合物S35-S41

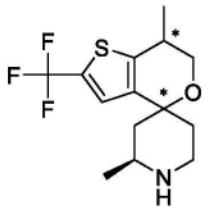
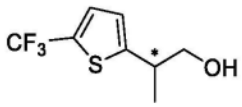
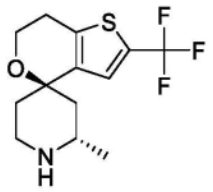
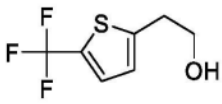
[1071] 使用化合物S34的方法,由(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯和适当的噻吩制备化合物S35-S41(表21)。

[1072] 表22:化合物S35-S41的结构和物理化学数据

[1073]

化合物	结构	噻吩	LCMS m/z [M+H]$^+$。
S35[1]			LCMS *m/z* 266.03 [M+H]$^+$。
S36			LCMS *m/z* 272.2 [M+H]$^+$。
S37[1]			LCMS *m/z* 266.03 [M+H]$^+$。
S38[1]			LCMS *m/z* 266.21 [M+H]$^+$。
S39[1]			LCMS *m/z* 266.21 [M+H]$^+$。
S40			LCMS *m/z* 272.2 [M+H]$^+$。

[1074]

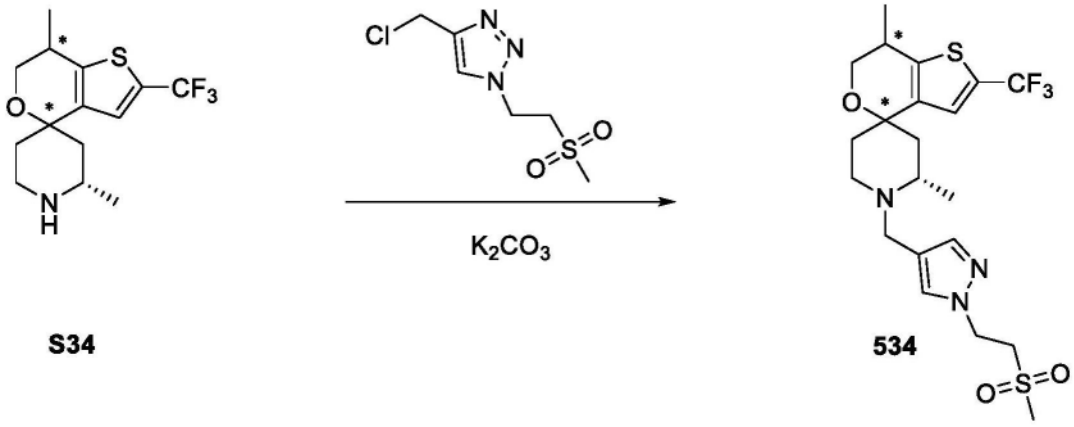
化合物	结构	噻吩	LCMS m/z [M+H]+。
S41			LCMS *m/z* 306.24 [M+H]+。
S42			LCMS *m/z* 292.38 [M+H]+。

[1075] 脚注：

[1076] 1)将(2′S)-2-乙基-2′,7-二甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]通过手性SFC分离分离成组成非对映异构体(顺式和反式)。柱:Phenomenex Lux® Cellulose-2,20x 250mm。流动相:40% MeOH(含有5mM氨),60% CO2化合物534

[1077] (2S,4R)-2,7′-二甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-2′-(三氟甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]

[1078]



S34 534

[1079] 步骤1:(2S,4R)-2,7′-二甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-2′-(三氟甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃](534)

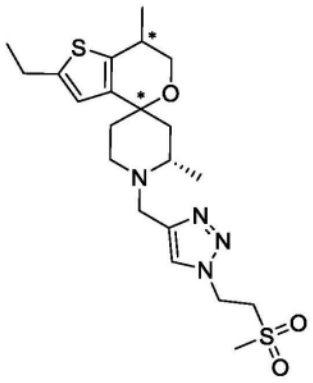
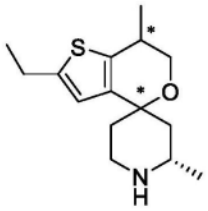
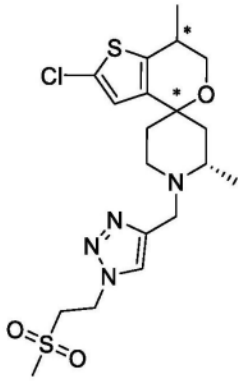
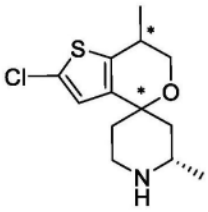
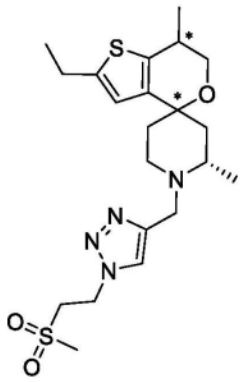
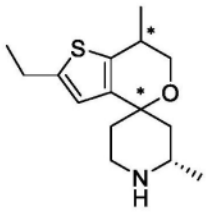
[1080] 向(2S,4R)-2,7′-二甲基-2′-(三氟甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]S34(71mg,0.111mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(25mg,0.111mmol)于DMF中的经搅拌的溶液中添加碳酸钾(15mg,0.111mmol)并将反应物在60℃下搅拌过夜。添加水和二氯甲烷,并将有机层通过相分离器收集。通过硅胶色谱法纯化(梯度:含0-20%甲醇的DCM),产生(2S,4R)-2,7′-二甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-2′-(三氟甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]534(10mg,18%)。LCMS m/z 493.56[M+H]+。

[1081] 化合物535-541

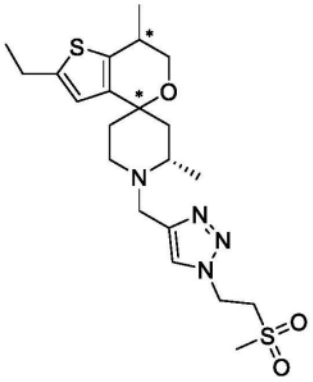
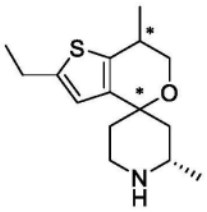
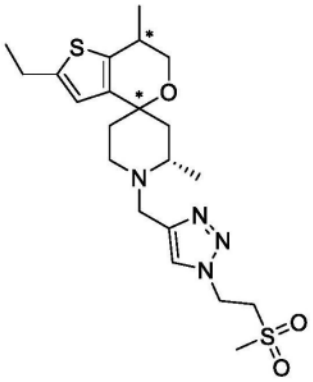
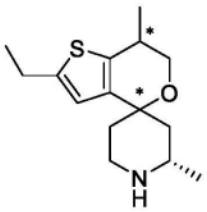
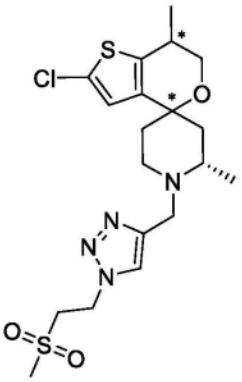
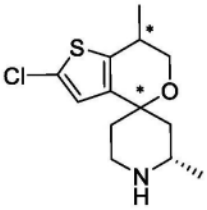
[1082] 使用化合物534的方法,由中间体哌啶和4-(氯甲基)-1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑制备化合物535-541(表23)。

[1083] 表23:化合物535-541的结构和物理化学数据

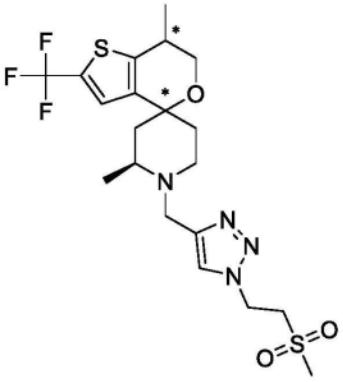
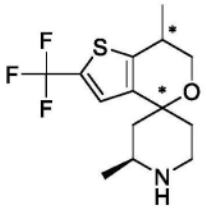
[1084]

化合物	结构	哌啶	^{1}H NMR；LCMS m/z $[M+H]^+$。
535			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.08 (s, 1H), 6.57 (s, 1H), 4.80 (m, 2H), 3.91 - 3.66 (m, 5H), 3.37 (m, 1H), 2.92 (s, 3H), 2.77 (m, 3H), 2.43 (m, 2H), 1.87 - 1.69 (m, 3H), 1.63 - 1.42 (m, 2H), 1.20 - 1.08 (m, 9H)。LCMS *m/z* 453.2 $[M+H]^+$。
536			LCMS *m/z* 459.17 $[M+H]^+$。
537			^{1}H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 6.57 (s, 1H), 4.80 (t, J = 6.9 Hz, 2H), 3.94 - 3.66 (m, 5H), 3.50 - 3.21 (m, 3H), 2.92 (s, 3H), 2.71 (m, 3H), 2.41 (m, 1H), 1.79 - 1.55 (m, 4H), 1.23 - 1.05 (m, 9H)。LCMS *m/z* 453.45 $[M+H]^+$。

[1085]

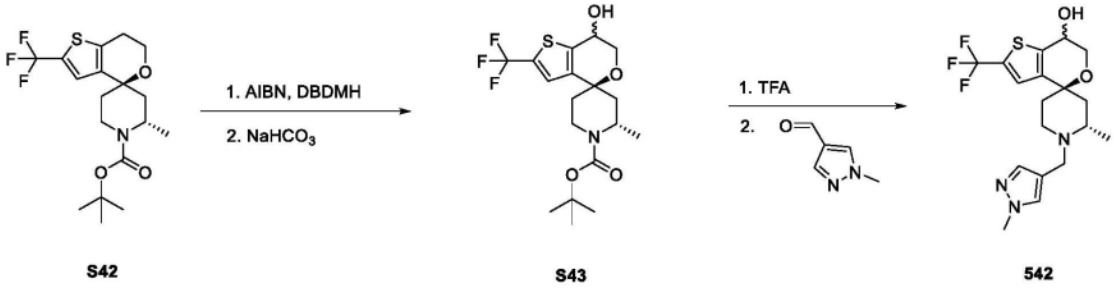
化合物	结构	哌啶	^{1}H NMR；LCMS m/z [M+H]$^+$。
538			^{1}H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 6.55 (s, 1H), 4.79 (t, J = 7.0 Hz, 2H), 3.91 - 3.77 (m, 3H), 3.76 - 3.62 (m, 2H), 3.43 (dd, J = 11.4, 6.0 Hz, 1H), 2.98 (d, J = 14.3 Hz, 5H), 2.91 - 2.64 (m, 4H), 1.96 - 1.61 (m, 4H), 1.22 - 1.08 (m, 9H)。LCMS *m/z* 493.17 [M+H]$^+$。
539			LCMS *m/z* 453.45 [M+H]$^+$。
540			LCMS *m/z* 459.12 [M+H]$^+$。

[1086]

化合物	结构	哌啶	^{1}H NMR；LCMS m/z [M+H]$^+$。
541			LCMS *m/z* 493.15 [M+H]$^+$。

[1087] 化合物542

[1088] (2′S,4R)-2′-甲基-1′-[(1-乙甲基吡唑基-4-基)甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-7-醇

[1089] 

S42 S43 542

[1090] 步骤1:(2′S,4R)-7-羟基-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S43)的合成

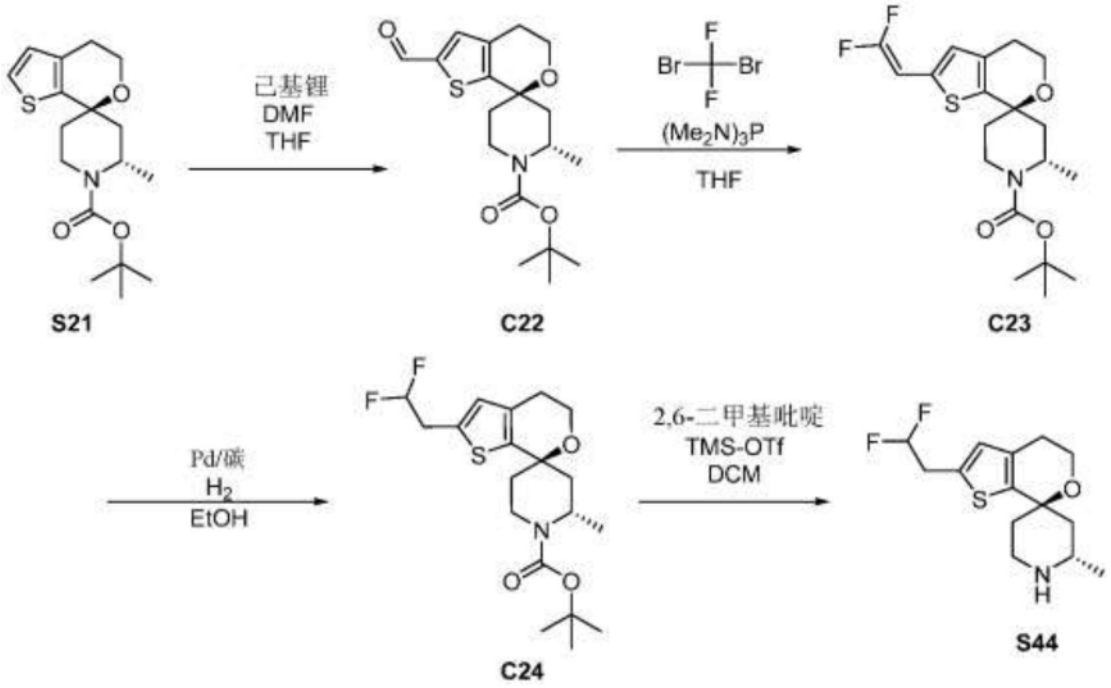
[1091] 将(2′S,4R)-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S42(670mg,1.71mmol)、1,3-二溴-5,5-二甲基-咪唑烷-2,4-二酮(390mg,1.36mmol)和2-(1-氰基-1-甲基-乙基)偶氮-2-甲基-丙腈(20mg,0.121mmol)合并在二氯甲烷(10mL)中,并将混合物在35℃下搅拌4小时。添加硫代硫酸钠,并用水和乙酸乙酯稀释反应混合物。将有机层浓缩,并通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),产生溴化物中间体(2′S,4R)-7-溴-2′-甲基-2-(三氟甲基)-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯。将中间体溶解在THF中,并用饱和$NaHCO_3$(2mL)处理,并将混合物加热至60℃过夜。将混合物用水和EtOAc稀释,并将有机层干燥并浓缩。通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷),得到(2′S,4R)-7-羟基-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯S43(48mg,7%)。^{1}H NMR(300MHz,氯仿-d)δ7.09(s,1H),4.74-4.61(m,1H),4.05-3.69(m,4H),3.44-3.24(m,1H),2.39(t,J=9.0Hz,1H),2.26-1.73(m,3H),1.50(s,9H),1.28(d,J=6.6Hz,3H)。

[1092] 步骤2:(2′S,4R)-2′-甲基-1′-[(1-甲基吡唑-4-基)甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-7-醇(542)

[1093] 将(2′S,4R)-7-羟基-2′-甲基-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(48mg,0.117mmol)溶解在二氯甲烷(1mL)中,并添加TFA(0.5mL,6.490mmol)。将反应混合物搅拌30分钟,然后浓缩成油。将油溶解在二氯甲烷(1mL)中,并添加1-甲基吡唑-4-甲醛(20mg,0.181mmol)、AcOH(35μL,0.615mmol)和(三甲基铵)甲基(氰基硼氢化物)(180mg的2mmol/g,0.3600mmol)树脂。将反应混合物在微波中加热至110℃,持续60分钟。将反应物过滤,并将滤液浓缩。通过二氧化硅色谱法纯化(梯度:含0-20%甲醇的DCM),产生(2′S,4R)-2′-甲基-1′-[(1-甲基吡唑-4-基)甲基]-2-(三氟甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-7′-醇542(23mg,48%)。^{1}H NMR(300MHz,氯仿-d)δ7.40(s,1H),7.30(s,1H),7.15(s,1H),4.76-4.58(m,1H),4.06-3.76(m,6H),3.62-3.48(m,1H),3.05-2.36(m,4H),2.09-1.69(m,3H),1.67-1.43(m,1H),1.23-1.14(m,3H)。LCMS m/z402.04$[M+H]^+$。

[1094] S44的制备(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S44)

[1095]



[1096] 步骤1:(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C22)的合成

[1097] 在20分钟的过程内在氮气下通过加料漏斗向(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S21(81.4g,251.7mmol)于THF(740mL)中的冷却至-78℃的溶液中添加己基锂于己烷中的溶液(120mL的2.6M,312.0mmol)。在完成添加己基锂后搅拌70分钟后,在5分钟的过程内添加DMF(100mL。1.291mol)。将溶液在-78℃下搅拌30分钟,然后将反应物温热至0℃并搅拌45分钟。然后将反应物通过添加饱和氯化铵水溶液(600mL)淬灭。将混合物在EtOAc(1L)与水(500mL)之间分配。将有机层分离,用饱和氯化铵水溶液、水和盐水(各600mL)洗涤。将有机层经硫酸镁干燥,过滤,并浓缩以产生呈粘性琥珀色油的(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C22(88g,99%),其无需进一步纯化即可使用。^{1}H NMR(300MHz,氯仿-d)δ9.83(s,1H),7.42(s,1H),4.01(ddd,J=11.5,6.7,5.3Hz,1H),3.94-3.82(m,2H),3.75(ddd,J=14.0,6.1,4.7Hz,1H),3.35(ddd,J=14.1,8.8,5.4Hz,1H),2.71(td,J=5.5,2.8Hz,2H),2.28-2.06(m,2H),1.90-1.65(m,2H),1.47(s,9H),1.26(d,J=6.6Hz,3H)。

[1098] 步骤2:(2′S,7R)-2-(2,2-二氟乙烯基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C23)的合成

[1099] 在45分钟的过程内通过加料漏斗向二溴(二氟)甲烷(33mL,361.3mmol)于THF(600mL)中的溶液中在干冰-丙酮冷却浴中添加N-[双(二甲基氨基)膦基]-N-甲基-甲胺(140mL,770.3mmol)。然后将干冰-丙酮浴用冰水浴替代并搅拌45分钟。在30分钟的过程内向反应物中添加(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C22(88g,250.4mmol)于THF(500mL)中的溶液,此时,去除冰水浴。2小时后,将反应物在冰水浴中冷却,然后在5分钟内通过添加水(300mL)淬灭。添加10%亚硫酸氢钠的水溶液(300mL)。将混合物搅拌30分钟,然后将有机层分离。将有机层用1M HCl水溶液(1L)洗涤。将有机层用MTBE(500mL)稀释,用饱和碳酸氢钠水溶液(1L)洗涤,随后用50%饱

和盐水溶液(1L)洗涤,经硫酸镁干燥,过滤并浓缩。将粗产物通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷,以得到呈粘性澄清淡黄色油的(2′S,7R)-2-(2,2-二氟乙烯基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C23(54g,56%)。^{1}H NMR(300MHz,氯仿-d)δ6.62(s,1H),5.44(dd,J=25.8,2.0Hz,1H),4.00(dp,J=12.2,6.4Hz,1H),3.86(t,J=5.5Hz,2H),3.74(ddd,J=13.9,6.0,4.7Hz,1H),3.32(ddd,J=14.1,8.9,5.4Hz,1H),2.71-2.51(m,2H),2.26-2.03(m,2H),1.91-1.65(m,2H),1.48(s,9H),1.25(d,J=6.5Hz,3H)。19F NMR(282MHz,氯仿-d)δ-80.93(d,J=28.1Hz),-87.47(d,J=27.9Hz)。

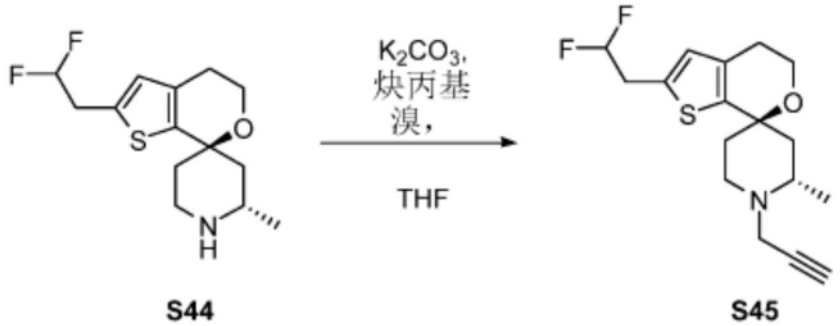
[1100] 步骤3:(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C24)的合成

[1101] 在氮气下向Pd/碳(8.2g的5%w/w,3.853mmol)于2L Parr瓶中添加(2′S,7R)-2-(2,2-二氟乙烯基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C23(54g,140.1mmol)于EtOH(700mL)中的溶液。将Parr振荡器装入50psi的H_2。24小时后,将反应混合物通过硅藻土垫过滤,并将滤液在氮气下用新鲜催化剂Pd/碳(10g的5%w/w,4.698mmol)处理。将Parr振荡器装入50psi的H_2,并将反应继续另外16小时。然后将反应物通过硅藻土垫过滤,用EtOH(200mL)洗涤。将滤液浓缩成黄色油,将其通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷)以得到呈澄清无色粘性油的(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(45.5g,84%)。^{1}H NMR(300MHz,氯仿-d)δ6.58(s,1H),5.90(tt,J=56.5,4.4Hz,1H),3.99(ddd,J=11.5,6.7,5.3Hz,1H),3.86(t,J=5.5Hz,2H),3.79-3.66(m,1H),3.40-3.16(m,3H),2.72-2.51(m,2H),2.24-2.03(m,2H),1.90-1.65(m,2H),1.48(s,9H),1.25(d,J=6.5Hz,3H)。19FNMR(282MHz,氯仿-d)δ-115.12。

[1102] 步骤4:(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S44)的合成

[1103] 在0℃(冰水浴)下在12分钟的过程内通过加料漏斗向(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(32g,82.58mmol)C23于二氯甲烷(300mL)中的溶液中添加2,6-二甲基吡啶(18mL,155.4mmol),随后添加三甲基甲硅烷基三氟甲磺酸酯(15.4mL,85.23mmol)。搅拌50分钟后,将反应物用1M氢氧化钠水溶液(150mL)淬灭并搅拌10分钟。然后将各层分离。将有机层用1M氢氧化钠水溶液(2×200mL)洗涤,经硫酸镁干燥,过滤并浓缩以得到呈粘性淡琥珀色油的(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(23.8g,100%)。^{1}H NMR(300MHz,氯仿-d)δ6.60(s,1H),5.90(tt,J=56.5,4.5Hz,1H),3.91(td,J=5.6,2.9Hz,2H),3.26(td,J=16.7,4.5Hz,2H),3.17-2.99(m,2H),2.92(ddd,J=12.1,4.8,2.0Hz,1H),2.63(td,J=5.5,2.9Hz,2H),2.01(dt,J=13.9,2.2Hz,2H),1.70(td,J=13.3,4.8Hz,1H),1.39(dd,J=13.6,11.3Hz,2H),1.06(d,J=6.4Hz,3H)。19F NMR(282MHz,氯仿-d)δ-115.07。LCMS m/z 288.1$[M+1]^+$。

[1104] S45的制备(2′S)-2-(2,2-二氟乙基)-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S45)

[1105] 

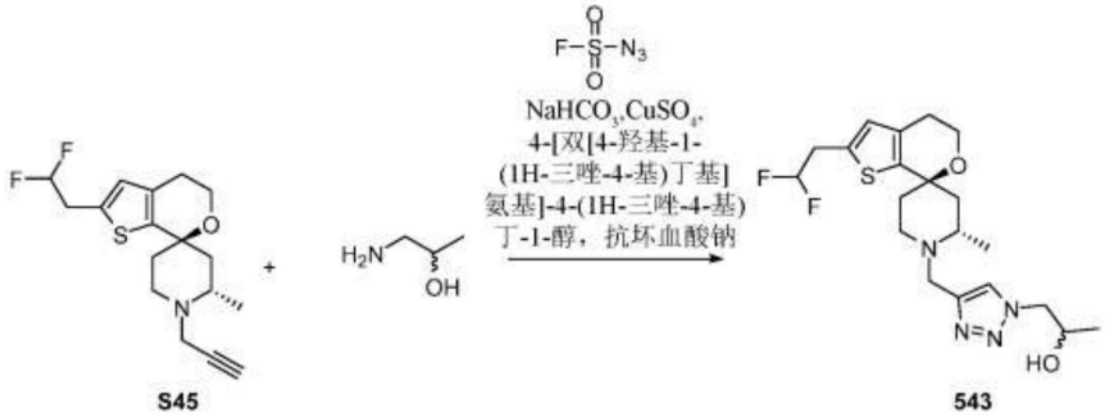
S44 S45

[1106] (2′S)-2-(2,2-二氟乙基)-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S45)的制备

[1107] 将(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(700mg,2.436mmol)和碳酸钾(440mg,3.184mmol)于四氢呋喃(14mL)中的混合物加热至50℃并搅拌。此时,添加含炔丙基溴(353μL,3.961mmol)的甲苯并将混合物在50℃下搅拌过夜。将反应物用饱和碳酸氢钠水溶液和DCM淬灭。将各层通过相分离器分离。将有机物在真空中浓缩。通过硅胶色谱法纯化(梯度:0-10% MeOH-DCM),产生(2′S)-2-(2,2-二氟乙基)-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S45)(537mg,67%)。1H NMR(400MHz,甲醇-d4)δ6.64(s,1H),5.96(tt,J=56.6,4.3Hz,1H),3.91(td,J=5.6,2.2Hz,2H),3.64(dd,J=17.4,2.4Hz,1H),3.41(dd,J=17.3,2.4Hz,1H),3.25(ddd,J=17.2,4.3,0.9Hz,2H),3.04-2.82(m,2H),2.77-2.54(m,4H),2.13-1.83(m,3H),1.61(dd,J=13.9,11.6Hz,1H),1.07(d,J=6.4Hz,3H)。LCMS m/z 326.04[M+1]$^+$。

[1108] 543的制备

[1109] 1-[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]丙-2-醇(543)

[1110] 

S45 543

[1111] 1-[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]丙-2-醇(543)的制备

[1112] 向含有1-氨基丙-2-醇(20.8mg,150μmol)溶解在DMSO(0.3mL)中的溶液中添加碳酸氢盐水溶液(钠盐)(0.25mL的1M溶液,0.25mmol)。向该混合物中添加0.550mL的氟磺酰基叠氮化物溶液(含约0.45M的MTBE,约250μmol,根据《自然(Nature)》,574,2019,86-89中的方案制备),并将反应物在室温下搅拌20分钟。将(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S45(30mg,0.092mmol)溶解在DMSO(1.0mL)中的溶液添加到反应物中。向该混合物中添加$CuSO_4$水溶液(0.085mL的0.1M溶

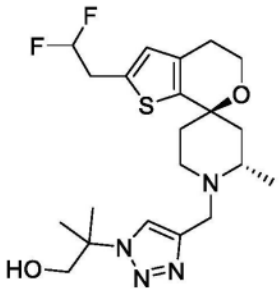
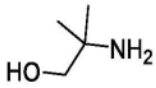
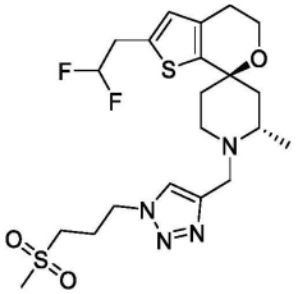
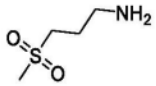
液,0.0085mmol)、4-[双[4-羟基-1-(1H-三唑-4-基)丁基]氨基]-4-(1H-三唑-4-基)丁-1-醇于DMSO(0.085mL的0.1M溶液,0.0085mmol)中的溶液和抗坏血酸钠水溶液(0.085mL的0.2M溶液,0.017mmol)。将所得反应混合物在露天下在50℃下加热过夜。添加另外部分的$CuSO_4$(0.1mL的0.1M水溶液,0.01mmol)和抗坏血酸钠(0.1mL的0.2M水溶液,0.02mmol),并将反应物在50℃下加热过夜。将反应物冷却至室温,用2mL水和1mL DCM稀释,并搅拌若干分钟。使混合物通过平行过滤板并用1mL DCM洗涤。使用有机层并蒸发。将所得残余物溶解在1mL DMSO中,并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有10mM氢氧化铵,产生1-[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]丙-2-醇(543)。^1H NMR(300MHz,甲醇-d4)δ7.94(s,1H),6.62(s,1H),5.95(tt,J=56.6,4.3Hz,1H),4.52-3.67(m,7H),3.24(dd,J=17.1,4.3Hz,2H),2.84-2.37(m,5H),2.12-1.78(m,3H),1.75-1.48(m,1H),1.34-0.95(m,6H)。LCMS m/z 427.16$[M+1]^+$。

[1113] 化合物544-548的制备

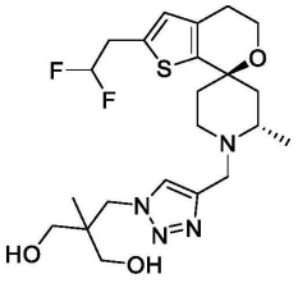
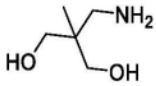
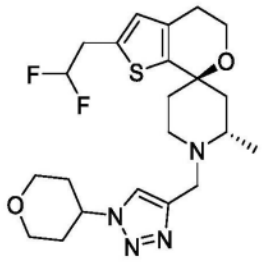
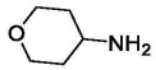
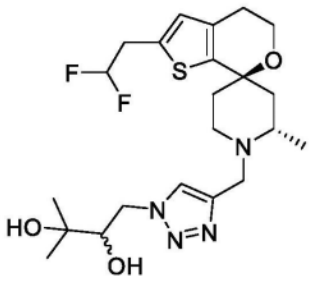
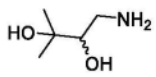
[1114] 使用适当的试剂,使用叠氮化物转移和点击化学方法,由中间体S45制备化合物544-548(参见表23),如化合物543所述。胺从商业来源购买。

[1115] 表23:化合物544-548的制备方法、结构和物理化学数据

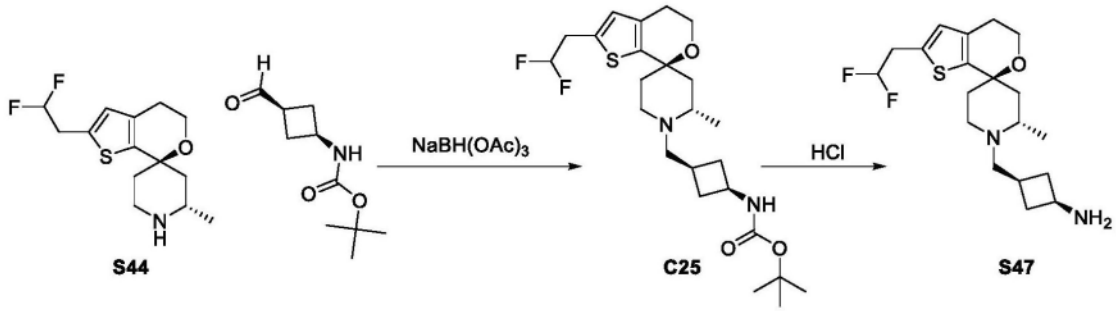
[1116]

化合物	*结构*	*胺*	*^1H NMR; LCMS m/z $[M+H]^+$。*
544			^{1}H NMR (300 MHz, 甲醇-d4) δ 8.01 (s, 1H), 6.63 (s, 1H), 5.95 (tt, J = 56.6, 4.3 Hz, 1H), 4.15 - 3.62 (m, 6H), 3.27 - 3.14 (m, 1H), 2.82 - 2.42 (m, 5H), 2.10 - 1.73 (m, 3H), 1.65 (s, 7H), 1.25 (d, J = 6.2 Hz, 3H)。 LCMS *m/z* 441.2 $[M+H]^+$
545			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.06 (s, 1H), 6.67 (s, 1H), 6.19 (tt, *J* = 56.4, 4.3 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 2H), 3.86 (d, *J* = 14.6 Hz, 1H), 3.77 (q, *J* = 5.4 Hz, 1H), 3.71 (d, *J* = 14.6 Hz, 1H), 3.42 – 3.25 (m, 3H), 3.10 (dd, *J* = 9.3, 6.4 Hz, 2H), 3.00 (s, 3H), 2.59 (d, *J* = 11.7 Hz, 1H), 2.55 – 2.34 (m, 4H), 2.31 – 2.20 (m, 2H), 1.90 (d, *J* = 13.3 Hz, 2H), 1.68 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.44 (t, *J* = 12.4 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H)。 LCMS *m/z* 489.12 $[M+H]^+$

[1117]

化合物	结构	胺	^1H NMR；LCMS m/z $[M+H]^+$。
546			^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.86 (s, 1H), 6.67 (s, 1H), 6.41 – 6.01 (m, 1H), 4.76 – 4.72 (m, 2H), 4.26 (s, 2H), 3.90 – 3.61 (m, 4H), 3.32 (s, 2H), 3.25 – 3.12 (m, 4H), 2.61 – 2.31 (m, 5H), 1.89 (d, *J* = 13.0 Hz, 2H), 1.67 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.49 – 1.38 (m, 1H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.66 (s, 3H)。LCMS *m/z* 471.19 $[M+H]^+$
547			^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.10 (s, 1H), 6.68 (s, 1H), 6.19 (tt, *J* = 56.3, 4.2 Hz, 1H), 4.72 (tt, *J* = 10.1, 4.9 Hz, 1H), 3.96 (d, *J* = 11.4 Hz, 2H), 3.86 (d, *J* = 14.5 Hz, 1H), 3.78 (hept, *J* = 5.6 Hz, 2H), 3.65 (d, *J* = 14.4 Hz, 1H), 3.49 (td, *J* = 11.4, 3.0 Hz, 2H), 3.40 – 3.25 (m, 2H), 2.59 (d, *J* = 11.9 Hz, 1H), 2.55 – 2.37 (m, 4H), 2.08 – 1.96 (m, 4H), 1.90 (d, *J* = 13.2 Hz, 2H), 1.67 (td, *J* = 13.1, 4.5 Hz, 1H), 1.44 (t, *J* = 12.4 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H)。LCMS *m/z* 453.21 $[M+H]^+$
548			^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (d, J = 3.5 Hz, 1H), 6.68 (s, 1H), 6.19 (tt, J = 56.4, 4.2 Hz, 1H), 5.13 (d, J = 6.0 Hz, 1H), 4.68 – 4.56 (m, 2H), 4.12 (dd, J = 13.5, 10.2 Hz, 1H), 3.85 (d, J = 15.2 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.67 (dd, J = 14.4, 4.4 Hz, 1H), 3.55 (d, J = 7.6 Hz, 1H), 3.42 – 3.22 (m, 2H), 2.60 (d, J = 11.4 Hz, 1H), 2.54 – 2.30 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.71 – 1.61 (m, 1H), 1.44 (t, J = 12.4 Hz, 1H), 1.16 – 1.06 (m, 9H)。LCMS *m/z* 471.19 $[M+H]^+$

[1118] S46的制备3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁胺(S46)

[1119] 

[1120] 步骤1:N-[3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯(C25)的合成

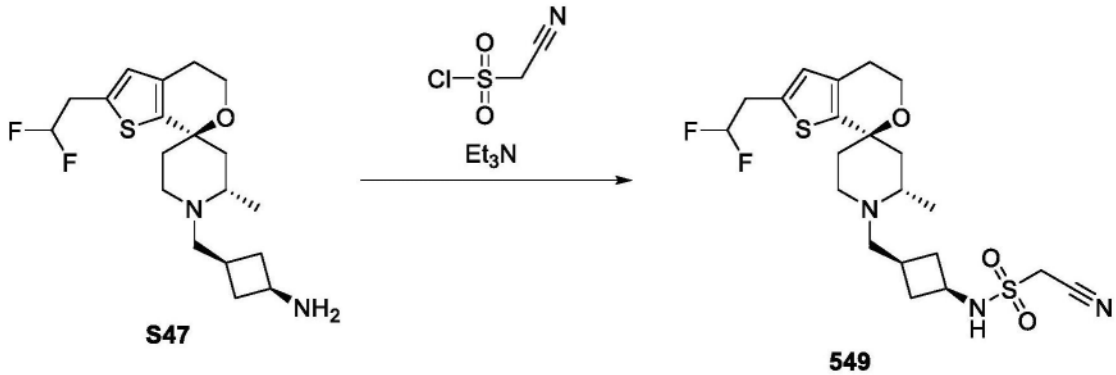
[1121] 向N-(3-甲酰基环丁基)氨基甲酸叔丁酯(177mg,0.8883mmol)和(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(170mg,0.5916mmol)于DCM(5mL)中的溶液中添加三乙酰氧基硼氢化物(钠盐)(376mg,1.774mmol)。将反应混合物在室温下搅拌2小时。将反应物用$NaHCO_3$(饱和)淬灭,并将混合物用DCM(3×5mL)萃取。将合并的有机物用H_2O和盐水恭敬地洗涤,并且然后经Na_2SO_4干燥。将溶剂在真空中去除以得到N-[3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯C25(270mg,87%)。LCMS m/z 471.68$[M+H]^+$。

[1122] 步骤2:3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁胺(S47)的合成

[1123] 将N-[3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁基]氨基甲酸叔丁酯C25用含HCl(3mL的4M,12.00mmol)的二噁烷处理。将反应混合物在室温下搅拌1小时。将溶剂去除以得到3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁胺(189mg,83%)。LCMS m/z 371.18$[M+H]^+$。

[1124] 化合物549

[1125] 1-氰基-N-((1R,3s)-3-(((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)甲基)环丁基)甲磺酰胺(549)

[1126] 

[1127] 1-氰基-N-((1R,3s)-3-(((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)甲基)环丁基)甲磺酰胺(549)的合成

[1128] 将3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]环丁胺S47(20mg)和氰基甲磺酰氯(7.2mg,0.052mmol)在DCM

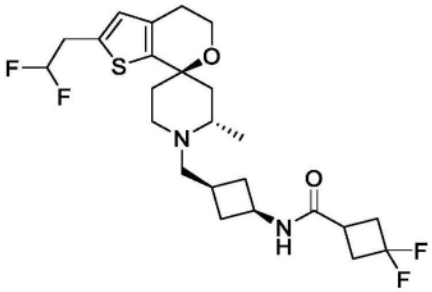
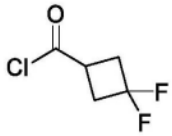
(1mL)中混合,向其中添加Et_3N(22uL)。将混合物在室温下搅拌2小时。去除溶剂。将所得残余物重新溶解在MeOH中,并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有0.1%三氟乙酸,以得到3-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]-N-氧代-环丁胺(4.7mg)。LCMS m/z 474.02$[M+H]^+$。

[1129] 化合物550-558的制备

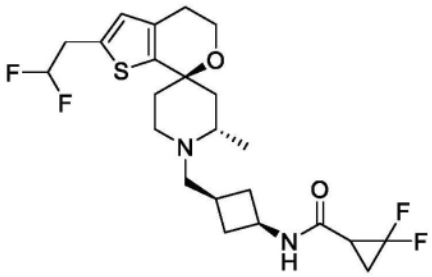
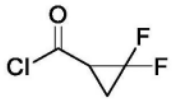
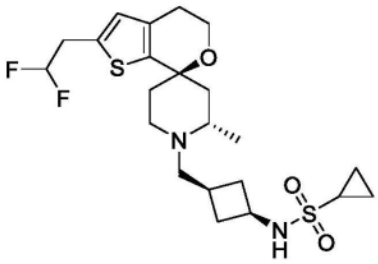
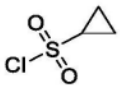
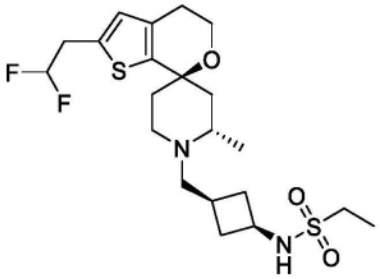
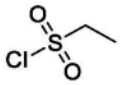
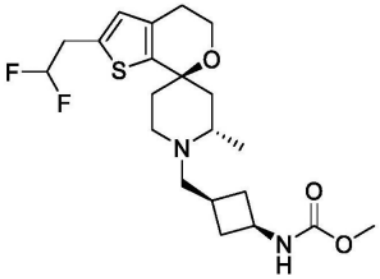
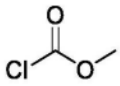
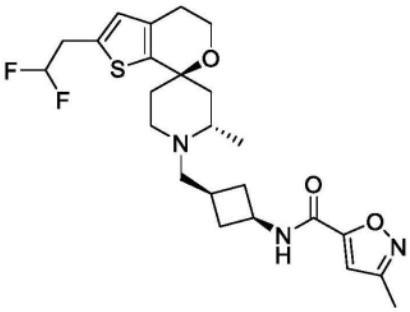
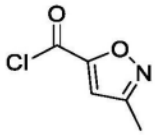
[1130] 使用适当的酰氯或磺酰氯试剂,按照化合物549所述的方法,由中间体S47制备化合物550-558(参见表24)。酰氯或磺酰氯从商业来源购买。

[1131] 表24:化合物550-558的制备方法、结构和物理化学数据

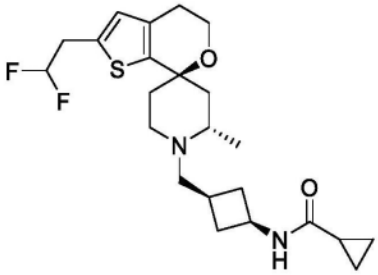
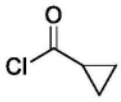
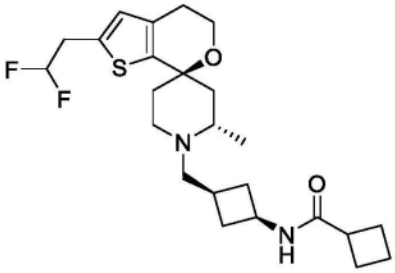
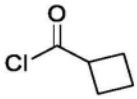
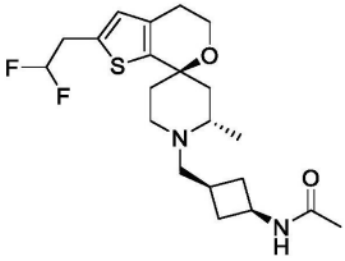
[1132]

化合物	结构	酰氯或磺酰氯磺酰氯	^{1}H NMR; LCMS m/z $[M+H]^+$。
550			LCMS *m/z* 489.13 $[M+H]^+$

[1133]

化合物	结构	酰氯或磺酰氯磺酰氯	^{1}H NMR；LCMS m/z $[M+H]^+$。
551			LCMS *m/z* 475.16 $[M+H]^+$
552			LCMS *m/z* 475.13 $[M+H]^+$
553			LCMS *m/z* 463.11 $[M+H]^+$
554			LCMS *m/z* 429.16 $[M+H]^+$
555			LCMS *m/z* 480.14 $[M+H]^+$

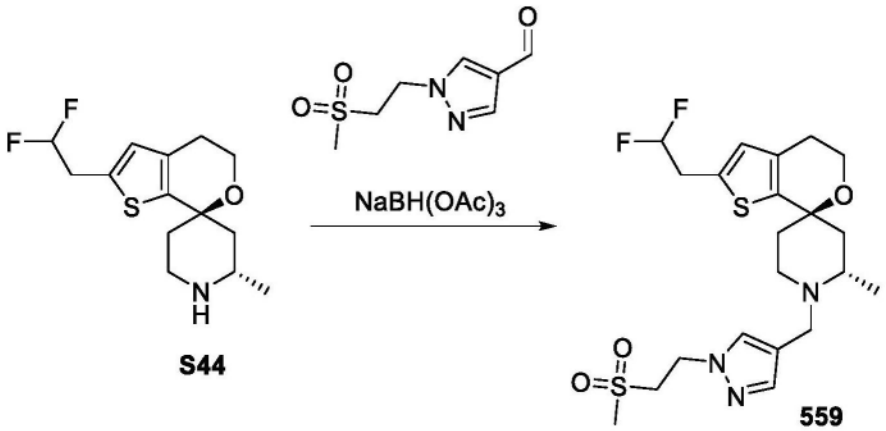
[1134]

化合物	结构	酰氯或磺酰氯磺酰氯	^{1}H NMR；LCMS m/z $[M+H]^+$。
556			LCMS *m/z* 439.13 $[M+H]^+$
557			LCMS *m/z* 453.2 $[M+H]^+$
558			LCMS *m/z* 413.17 $[M+H]^+$

[1135] 化合物559

[1136] (2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]

[1137]



S44 559

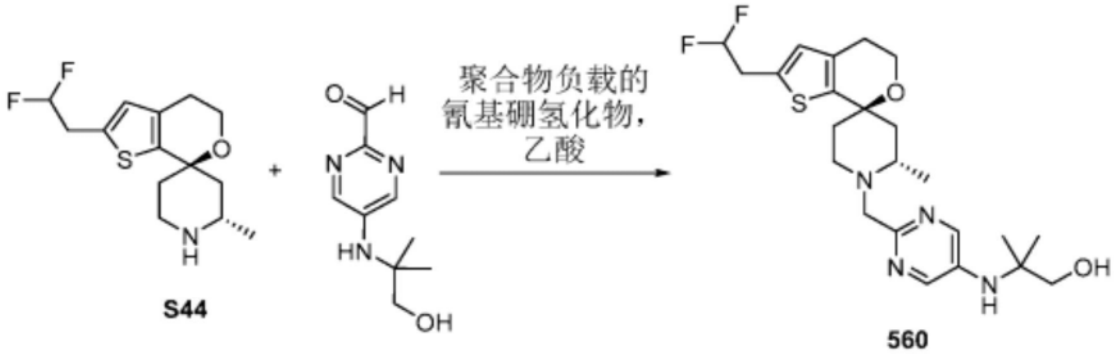
[1138] (2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](559)的制备

[1139] 将(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(295mg,0.8864mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(323mg,1.597mmol)溶解在THF(4mL)中。向该溶液中添加三乙酰氧基硼氢化物(钠盐)(470mg,2.218mmol)并将反应物加热至60℃并搅拌4小时。然后将反应物冷却至室温,此时将反应物

用盐水(20mL)淬灭并用EtOAc(20mL)萃取。将有机物干燥,过滤,并在减压下去除溶剂。将所得残余物通过反相柱色谱法纯化(Isco 150g金C-18,梯度:5-95% ACN/水0.2% FA改性剂)以产生(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]559(142.9mg,31%)。^{1}H NMR(400MHz,甲醇-d4)δ8.42(s,1H),7.98(d,J=0.8Hz,1H),7.71(d,J=0.7Hz,1H),6.69(d,J=2.6Hz,1H),5.97(tt,J=56.6,4.2Hz,1H),4.75-4.65(m,2H),4.46(d,J=14.1Hz,1H),4.23(d,J=14.1Hz,1H),3.89(dt,J=6.2,5.3Hz,2H),3.76-3.66(m,3H),2.85(d,J=0.7Hz,3H),2.63(td,J=5.4,1.5Hz,2H),2.36-2.13(m,3H),2.13-1.89(m,2H),1.50(d,J=6.5Hz,3H)。LCMS m/z 474.38[M+H]$^+$。

[1140] 化合物560

[1141] 2-[[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]′-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇

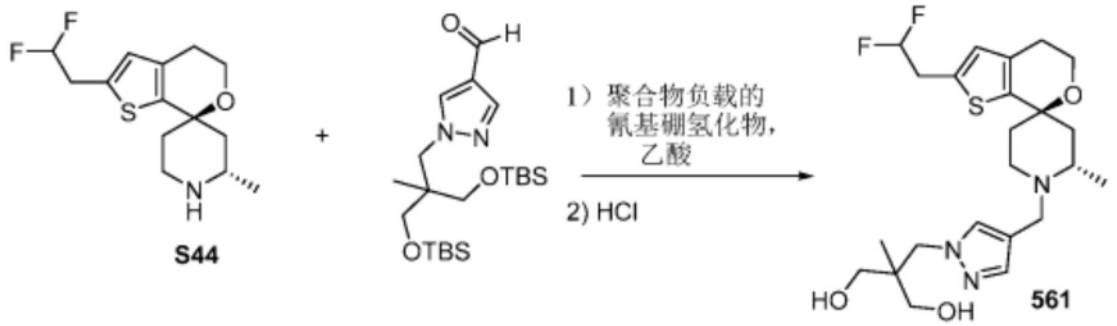
[1142] 

[1143] 2-[[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇(560)的制备

[1144] 将(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(55mg,0.19mmol)放在微波小瓶中,添加5-((1-氰基-2-甲基丙-2-基)氨基)嘧啶-2-甲醛(37mg,0.19mmol)、乙酸(52uL,0.92mmol)、二氯甲烷(1.6mL),并添加聚合物负载的氰基硼氢化物(295mg,0.59mmol)。将溶液加盖并在微波反应器中加热至95℃,持续120分钟。添加MeOH,并将溶液搅拌十分钟以洗涤珠粒。将溶液过滤,并将溶剂在真空中去除。通过反相HPLC纯化。C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有10mM氢氧化铵,产生产物2-[[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇。^{1}H NMR(300MHz,氯仿-d)δ8.23(s,2H),6.60(d,J=9.5Hz,2H),5.92(tt,J=56.5,4.4Hz,1H),5.24(s,1H),4.05-3.59(m,6H),3.28(td,J=16.7,4.5Hz,2H),3.06(d,J=13.6Hz,1H),2.64(hept,J=4.4Hz,4H),2.39(td,J=12.2,11.7,2.6Hz,1H),2.01(ddt,J=14.2,5.3,2.8Hz,2H),1.91-1.68(m,2H),1.38(s,7H),1.21(d,J=6.1Hz,4H)。LCMS m/z467.18[M+H]$^+$。

[1145] 化合物561

[1146] 2-[[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇

[1147] 

[1148] 2-[[4-[[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇(561)的制备

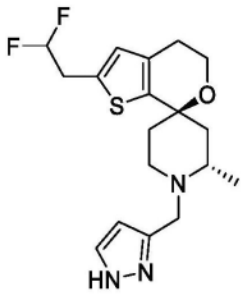
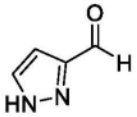
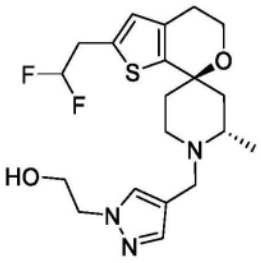
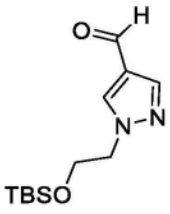
[1149] 向含(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(55mg,0.19mmol)的微波通过中添加1 1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛(82mg,0.19mmol)、乙酸(52uL,0.92mmol)、二氯甲烷(1.6mL)和聚合物负载的氰基硼氢化物(295mg,0.59mmol)。将溶液加盖并在微波反应器中加热至95℃,持续120分钟。添加MeOH,并将溶液搅拌十分钟以洗涤珠粒。将反应物用含HCl 4M(0.5mL)的二噁烷搅拌10分钟。将溶液过滤,并在真空中去除溶剂。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)(基本方法)产生产物(2′S,7R)-2-(2,2-二氟乙基)-1′-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]。1H NMR(300MHz,氯仿-d)δ7.46(s,1H),7.37(s,1H),6.61(s,1H),5.92(tt,J＝56.4,4.5Hz,1H),4.26(s,2H),4.00-3.74(m,3H),3.74-3.06(m,9H),2.86-2.41(m,5H),2.16-1.64(m,5H),1.21(d,J＝6.2Hz,3H),0.84(s,3H)。ESI-MS m/z 470.24。

[1150] 化合物562-593

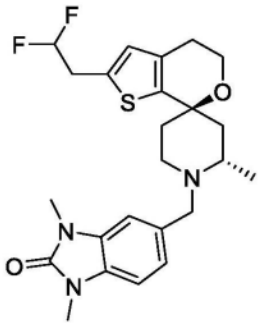
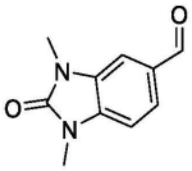
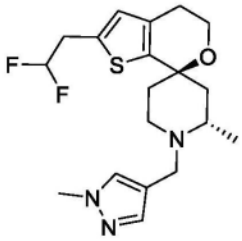
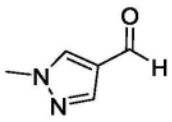
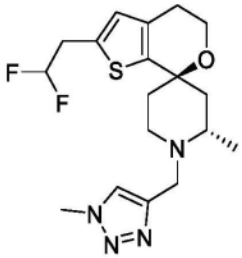
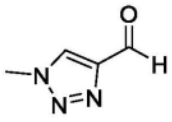
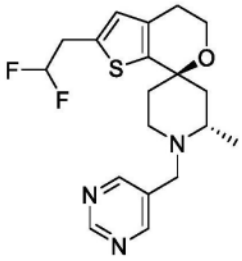
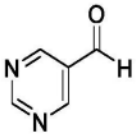
[1151] 化合物562-593由还原胺化步骤制备,在一些实例中使用中间体S44的化合物559-561和相关醛或酮的方法进行脱保护步骤。醛或酮从商业来源获得或如上所述合成。表25和随附脚注中注明了对方法的任何修改。

[1152] 表25:化合物562-593的制备方法、结构和物理化学数据。

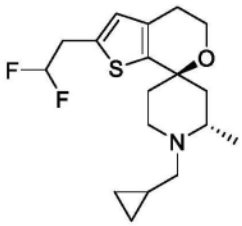
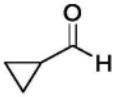
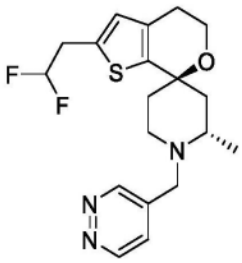
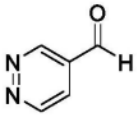
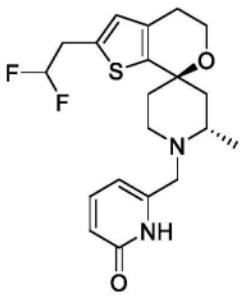
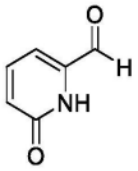
[1153]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
562			*560*[4]	^{1}H NMR (300 MHz, 甲醇-*d4*) δ 7.59 (s, 2H), 6.62 (s, 1H), 5.95 (tt, J = 56.6, 4.3 Hz, 1H), 4.03 - 3.71 (m, 3H), 3.65 (d, J = 14.2 Hz, 1H), 3.24 (dd, J = 17.1, 4.3 Hz, 2H), 2.80 - 2.38 (m, 5H), 2.11 - 1.56 (m, 4H), 1.23 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 368.19.
563			*561*	^{1}H NMR (300 MHz, 甲醇-*d4*) δ 7.55 (dd, J = 49.3, 2.8 Hz, 2H), 6.62 (d, J = 2.8 Hz, 1H), 5.95 (ddt, J = 60.8, 56.7, 4.0 Hz, 1H), 4.21 (dt, J = 8.3, 3.7 Hz, 2H), 3.86 (td, J = 9.9, 8.8, 4.1 Hz, 5H), 3.56 (dd, J = 14.1, 2.9 Hz, 1H), 3.23 (dd, J = 17.1, 4.0 Hz, 2H), 2.85 - 2.35 (m, 5H), 2.12 - 1.52 (m, 4H), 1.21 (d, J = 5.8 Hz, 3H)。LCMS *m/z* 412.22

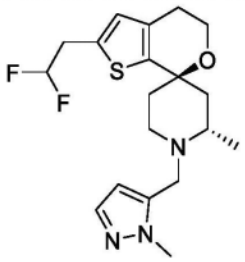
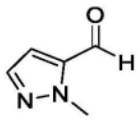
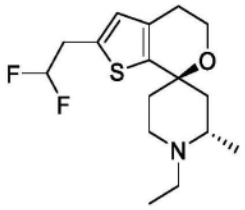
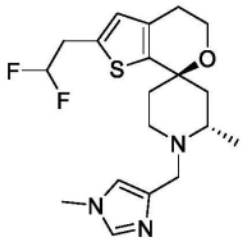
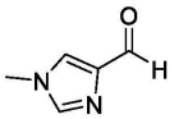
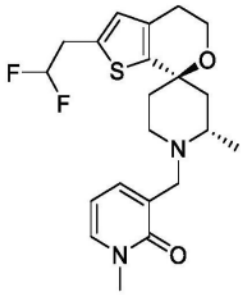
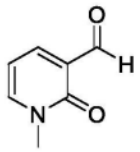
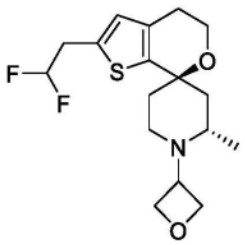
[1154]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
564			*560*[4]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.19 - 6.97 (m, 2H), 6.91 (d, J = 7.9 Hz, 1H), 6.61 (s, 1H), 5.91 (tt, J = 56.5, 4.5 Hz, 1H), 4.25 (d, J = 12.9 Hz, 1H), 3.90 (tdd, J = 11.6, 8.9, 5.1 Hz, 2H), 3.44 (d, J = 8.2 Hz, 6H), 3.38 - 3.02 (m, 3H), 2.65 (ddt, J = 18.1, 15.9, 8.0 Hz, 4H), 2.35 (td, J = 12.2, 2.7 Hz, 1H), 2.14 - 1.68 (m, 4H), 1.25 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 462.18
565			*559*[1,4]	LCMS *m/z* 382.19
566			*559*[1,4]	LCMS *m/z* 383.18
567			*559*[2,4]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 9.13 (s, 1H), 8.73 (s, 2H), 6.61 (s, 1H), 5.91 (tt, J = 56.5, 4.5 Hz, 1H), 4.21 - 4.09 (m, 1H), 4.00 - 3.81 (m, 2H), 3.40 - 3.15 (m, 3H), 2.85 - 2.38 (m, 5H), 2.01 (ddt, J = 16.3, 13.9, 2.9 Hz, 2H), 1.89 - 1.64 (m, 2H), 1.19 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 380.02

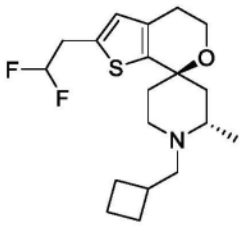
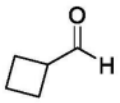
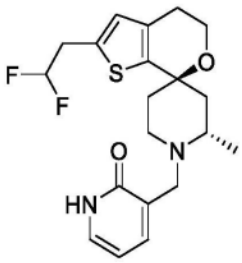
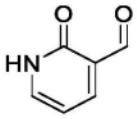
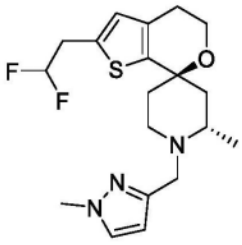
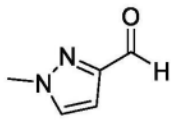
[1155]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
568			*559*[1,4]	LCMS *m/z* 342.19
569			*559*[2,4]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 9.23 (dd, J = 2.3, 1.2 Hz, 1H), 9.12 (dd, J = 5.2, 1.2 Hz, 1H), 7.53 (dd, J = 5.3, 2.2 Hz, 1H), 6.61 (s, 1H), 5.92 (tt, J = 56.5, 4.4 Hz, 1H), 4.20 - 4.07 (m, 1H), 4.01 - 3.78 (m, 2H), 3.40 - 3.15 (m, 3H), 2.87 - 2.58 (m, 3H), 2.56 - 2.42 (m, 2H), 2.08 - 1.93 (m, 2H), 1.91 - 1.80 (m, 1H), 1.79 - 1.64 (m, 1H), 1.13 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 380.02
570			*559*[2]	1H NMR (300 MHz, 氯仿-d) δ 9.85 (s, 1H), 7.34 (dd, J = 9.2, 6.7 Hz, 1H), 6.62 (s, 1H), 6.44 (d, J = 9.1 Hz, 1H), 6.19 - 5.70 (m, 2H), 4.04 - 3.81 (m, 3H), 3.30 (tdd, J = 16.7, 4.5, 0.9 Hz, 2H), 3.14 (d, J = 15.6 Hz, 1H), 2.79 (dtd, J = 12.4, 6.2, 2.5 Hz, 1H), 2.73 - 2.52 (m, 4H), 2.08 - 1.82 (m, 3H), 1.67 (dd, J = 14.0, 11.3 Hz, 1H), 1.07 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 395.06

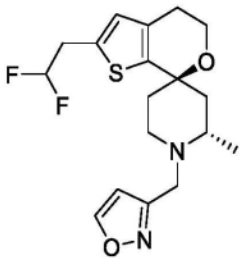
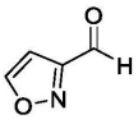
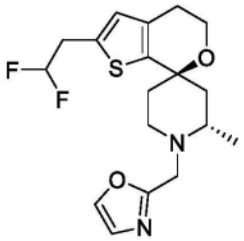
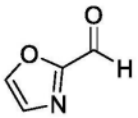
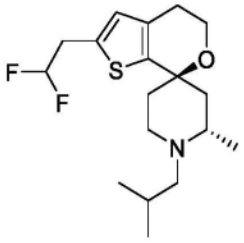
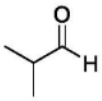
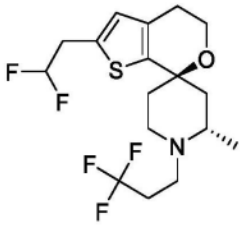
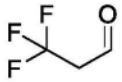
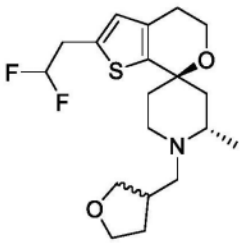
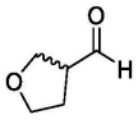
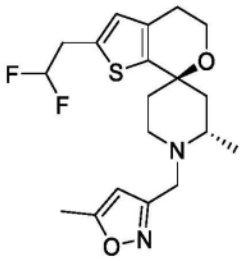
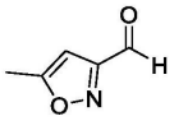
[1156]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
571			*559*[1,4]	LCMS *m/z* 382
572			*559*[1,4]	LCMS *m/z* 316.45
573			*559*[1,4]	LCMS *m/z* 382.19
574			*559*[2,4]	1H NMR (300 MHz, 氯仿-d) δ 7.57 (d, J = 6.8 Hz, 1H), 7.23 (dd, J = 6.7, 2.1 Hz, 1H), 6.61 (s, 1H), 6.21 (t, J = 6.8 Hz, 1H), 5.92 (tt, J = 56.5, 4.5 Hz, 1H), 3.98 - 3.88 (m, 2H), 3.58 (s, 3H), 3.39 - 3.17 (m, 3H), 2.89 - 2.49 (m, 5H), 2.12 - 1.83 (m, 3H), 1.73 (t, J = 12.4 Hz, 2H), 1.15 (d, J = 6.1 Hz, 3H)。LCMS *m/z* 409.02
575			*559*[1,4]	1H NMR (300 MHz, 乙腈-d3) δ 6.68 (s, 1H), 6.35 - 5.78 (m, 1H), 4.69 - 4.42 (m, 4H), 3.87 (td, J = 5.6, 1.6 Hz, 2H), 3.67 (p, J = 7.2 Hz, 1H), 3.33 (tdd, J = 17.7, 4.2, 0.9 Hz, 2H), 2.68 - 2.54 (m, 2H), 2.44 (dddd, J = 24.8, 12.9, 5.4, 2.6 Hz,

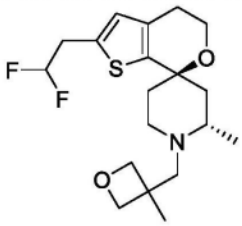
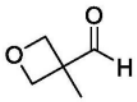
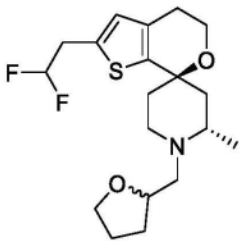
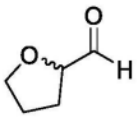
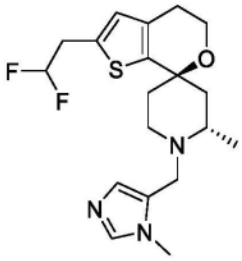
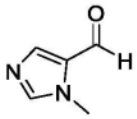
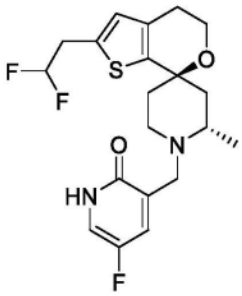
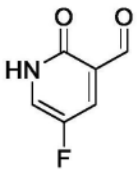
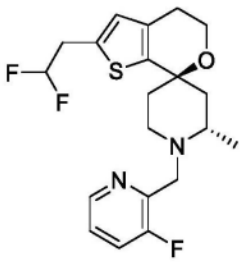
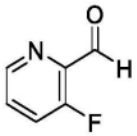
[1157]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				2H), 2.29 - 2.11 (m, 2H), 1.94 - 1.70 (m, 2H), 1.57 (dd, J = 13.7, 11.4 Hz, 1H), 0.85 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 344.59
576			*559*[1,4]	LCMS *m/z* 356.18
577			*559*[1,4]	1H NMR (300 MHz, 乙腈-d3) δ 7.48 (dddd, J = 6.5, 5.4, 2.5, 1.6 Hz, 1H), 7.16 (td, J = 6.5, 6.0, 2.1 Hz, 1H), 6.54 (s, 1H), 6.15 (t, J = 6.7 Hz, 1H), 5.90 (tt, J = 56.5, 4.2 Hz, 1H), 3.83 - 3.33 (m, 3H), 3.28 - 3.11 (m, 2H), 3.07 (d, J = 15.5 Hz, 1H), 2.72 - 2.29 (m, 4H), 1.91 - 1.84 (m, 1H), 1.79 (d, J = 3.0 Hz, 1H), 1.69 (ddd, J = 13.6, 12.4, 4.5 Hz, 1H), 1.52 (dd, J = 13.7, 11.3 Hz, 1H), 1.12 - 1.01 (m, 1H), 1.01 - 0.89 (m, 3H)。LCMS *m/z* 395.06
578			*559*[1,4]	LCMS *m/z* 382.19

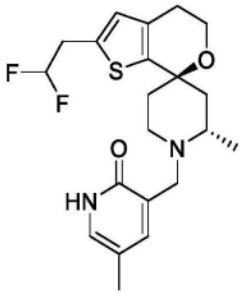
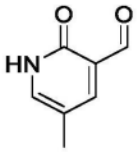
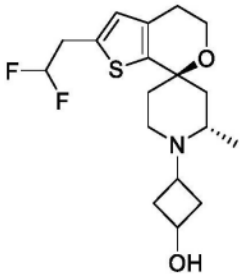
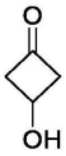
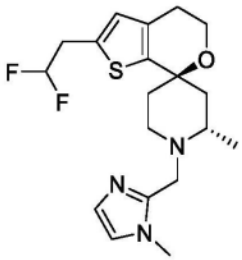
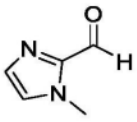
[1158]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
579			*按照 559[1,4]*	LCMS *m/z* 369.14
580			*按照 559[1,4]*	LCMS *m/z* 369.14
581			*559[1,4]*	LCMS *m/z* 344.17
582			*559[1,4]*	LCMS *m/z* 384.14
583			*559[1,4]*	LCMS *m/z* 372.21
584			*559[1,4]*	LCMS *m/z* 383.18

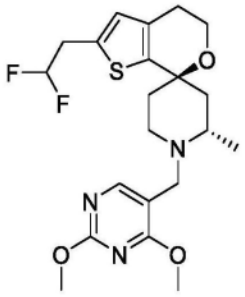
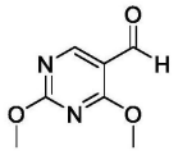
[1159]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
585			*559*[1,4]	LCMS *m/z* 372.21
586			*559*[1,4]	LCMS *m/z* 372.17
587			*559*[1,4]	LCMS *m/z* 382.19
588			*559*[1,4]	1H NMR (300 MHz, 氯仿-d) δ 7.68 (d, J = 3.1 Hz, 1H), 7.37 (dd, J = 7.9, 3.1 Hz, 1H), 6.63 (s, 1H), 5.93 (tt, J = 56.4, 4.4 Hz, 1H), 4.30 - 4.09 (m, 1H), 4.06 - 3.81 (m, 2H), 3.42 - 3.18 (m, 3H), 2.87 (ddt, J = 12.5, 6.2, 3.0 Hz, 1H), 2.80 - 2.55 (m, 4H), 2.21 - 1.86 (m, 3H), 1.75 (dd, J = 14.1, 11.4 Hz, 1H), 1.19 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 412.75
589			*559*[1,4]	1H NMR (300 MHz, 氯仿-d) δ 8.46 (dt, J = 4.6, 1.5 Hz, 1H), 7.39 (ddd, J = 9.6, 8.3, 1.4 Hz, 1H), 7.22 (dd, J = 8.4, 4.3 Hz, 1H), 6.60 (s, 1H), 5.91 (tt, J = 56.5, 4.5 Hz, 1H), 4.24 (dd, J = 13.1, 2.7

[1160]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
				Hz, 1H), 4.06 - 3.79 (m, 2H), 3.62 (dd, J = 13.1, 2.5 Hz, 1H), 3.38 - 3.17 (m, 2H), 2.86 - 2.49 (m, 5H), 2.07 - 1.72 (m, 4H), 1.30 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 396.99
590			*559*[1,4]	1H NMR (300 MHz, 氯仿-d) δ 7.43 (d, J = 2.4 Hz, 1H), 7.08 (s, 1H), 6.54 (s, 1H), 5.84 (tt, J = 56.5, 4.5 Hz, 1H), 3.94 - 3.76 (m, 3H), 3.32 - 3.09 (m, 3H), 2.79 - 2.42 (m, 5H), 2.07 (d, J = 1.0 Hz, 3H), 2.01 - 1.57 (m, 5H), 1.07 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 409.15
591			*559*[1,4]	1H NMR (300 MHz, 氯仿-d) δ 6.61 (s, 1H), 5.92 (tt, J = 56.5, 4.5 Hz, 1H), 4.07 - 3.82 (m, 3H), 3.27 (tdd, J = 16.6, 4.4, 0.9 Hz, 2H), 2.87 - 2.74 (m, 1H), 2.70 - 2.61 (m, 3H), 2.61 - 2.48 (m, 3H), 2.36 - 2.29 (m, 1H), 2.15 - 1.99 (m, 2H), 1.98 - 1.84 (m, 4H), 1.70 (dd, J = 14.0, 11.5 Hz, 1H), 1.08 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 358.59
592			*559*[1,4]	LCMS *m/z* 382.19

[1161]

化合物	结构	醛 或酮	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
593			*559*[1,4]	1H NMR (300 MHz, 氯仿-d) δ 9.78 (s, 1H), 7.35 (dd, J = 9.2, 6.7 Hz, 1H), 6.63 (s, 1H), 6.45 (d, J = 9.2 Hz, 1H), 6.21 - 5.67 (m, 2H), 4.02 - 3.82 (m, 2H), 3.43 - 3.21 (m, 2H), 3.15 (d, J = 15.6 Hz, 1H), 2.81 (ddd, J = 11.4, 6.2, 2.4 Hz, 1H), 2.74 - 2.48 (m, 4H), 2.12 - 1.83 (m, 3H), 1.68 (dd, J = 14.0, 11.3 Hz, 1H), 1.38 - 1.16 (m, 1H), 1.07 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 440.03

[1162] 脚注：

[1163] 1.使用DCM代替THF作为溶剂,并将反应在室温下进行2小时。

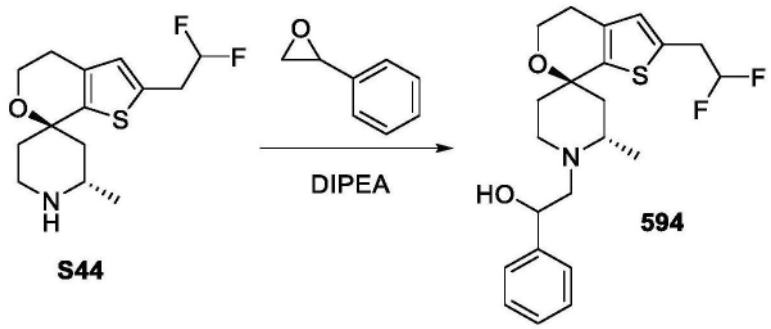
[1164] 2.使用DCM代替THF作为溶剂,并且除标准试剂外还使用Et_3N(1当量)。将反应物在50 C下搅拌30分钟。在添加三乙酰氧基硼氢化钠之前,将其冷却至室温后添加到反应物中并搅拌过夜,然后淬灭反应物。另外地,将化合物通过硅胶纯化(Redi-Sep筒,4g),用含0-10％ DCM的MeOH(具有7N NH_3)洗脱以得到产物。

[1165] 3.使用DCM代替THF作为溶剂,并且除标准试剂外还使用DIPEA(1当量)。将反应物在回流下搅拌30分钟。在添加三乙酰氧基硼氢化钠之前,将其冷却至室温后添加到反应物中并搅拌过夜,然后淬灭反应物。另外地,将化合物通过硅胶纯化(Redi-Sep筒,4g),用含0-10％ DCM的MeOH(具有7N NH_3)洗脱以得到产物。

[1166] 4.未使用HCl进行TBS脱保护。

[1167] 化合物594

[1168] 2-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-1苯基-乙醇(594)

[1169] 

[1170] 2-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-1-苯基-乙醇(594)的制备

[1171] 向(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(9.8mg,0.02875mmol)于甲醇(1ml)中的溶液中在微波小瓶中添加胡宁

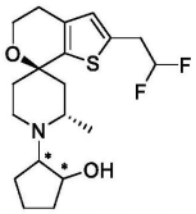
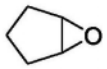
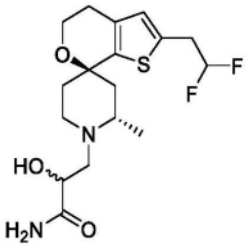
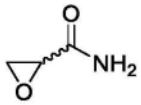
氏碱(Hunig's base)(40μL,0.2296mmol)和2-苯基环氧乙烷(10μL,0.08748mmol)。将反应在微波中在100℃下进行15分钟。蒸发溶剂。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有0.2%三氟乙酸,得到2-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-1-苯基-乙醇594(6.5mg,55%)。LCMS m/z 408.16[M+1]$^+$。

[1172] 化合物595-609

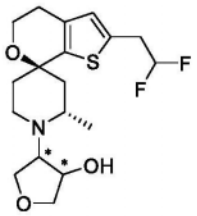
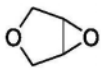
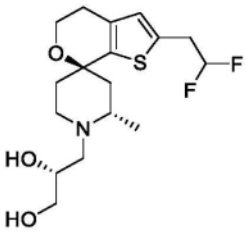
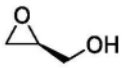
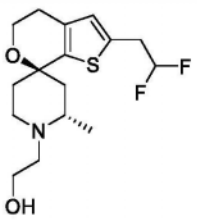
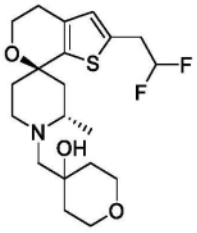
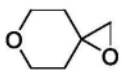
[1173] 化合物595-609和中间体S48和S49由环氧化物开环步骤制备,如由中间体S44和相关环氧化物制备化合物594所述。环氧化物从商业来源获得。表26和随附脚注中注明了对方法的任何修改。

[1174] 表26:化合物595-609和中间体S48和S49的制备方法、结构和物理化学数据

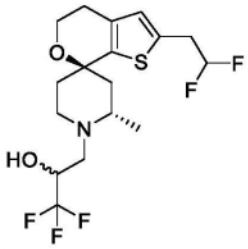
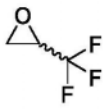
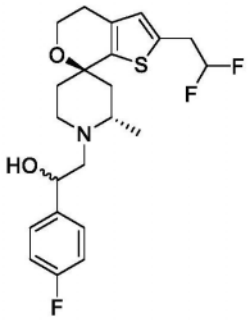
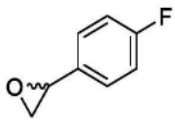
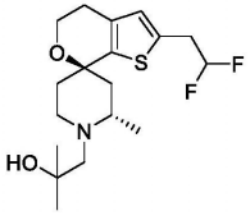
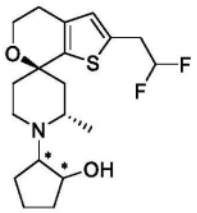
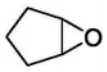
[1175]

化合物	结构	环氧化物	方法	^{1}H NMR; LCMS m/z [M+H]$^+$。
595			*化合物594*[1,2,3,5,6]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 8.52 (s, 1H), 6.64 (s, 1H), 5.92 (tt, J = 56.4, 4.4 Hz, 1H), 4.55 (q, J = 6.5 Hz, 1H), 4.02 - 3.71 (m, 3H), 3.53 - 3.07 (m, 4H), 2.79 - 2.61 (m, 2H), 2.48 (tt, J = 13.2, 2.8 Hz, 2H), 2.31 - 1.63 (m, 6H), 1.45 (d, J = 6.5 Hz, 3H)。LCMS *m/z* 372.21 [M+1]$^+$
596			*化合物594*	LCMS *m/z* 375.15 [M+1]$^+$

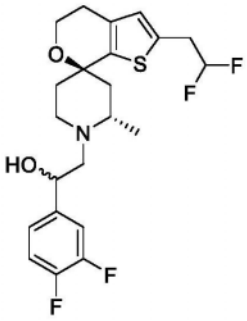
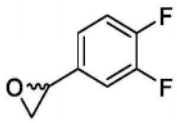
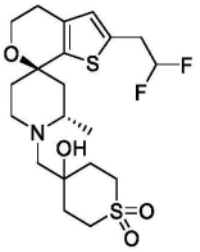
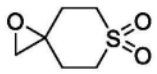
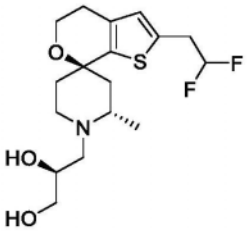
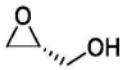
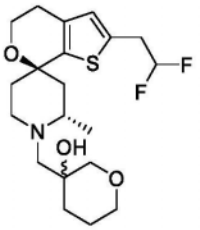
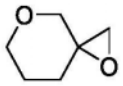
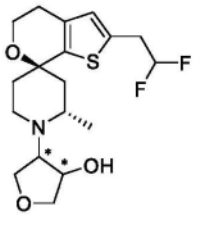
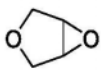
[1176]

化合物	结构	环氧化物	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
597			*化合物 594*[1,2,4,6]	^{1}H NMR (300 MHz, 氯仿-d) δ 6.62 (s, 1H), 5.92 (tt, J = 56.5, 4.5 Hz, 1H), 4.67 (ddd, J = 5.4, 3.4, 1.7 Hz, 1H), 4.24 - 4.00 (m, 2H), 4.00 - 3.78 (m, 4H), 3.68 (dd, J = 10.0, 3.4 Hz, 1H), 3.27 (tdd, J = 16.7, 4.5, 0.9 Hz, 2H), 2.98 (dtd, J = 12.4, 6.2, 2.4 Hz, 1H), 2.87 (ddd, J = 11.6, 4.4, 2.6 Hz, 1H), 2.71 - 2.41 (m, 3H), 2.06 (ddt, J = 14.2, 5.7, 2.9 Hz, 2H), 1.95 - 1.77 (m, 2H), 1.69 (dd, J = 13.9, 11.3 Hz, 1H), 1.23 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 374.2 $[M+1]^+$.
598			*化合物 594*	LCMS *m/z* 362.19 $[M+1]^+$
599			*化合物 594*	LCMS *m/z* 332.16 $[M+1]^+$
600			*化合物 594*	LCMS *m/z* 402.19 $[M+1]^+$

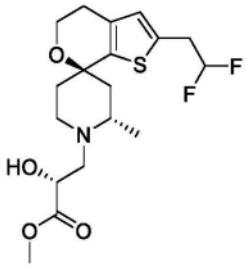
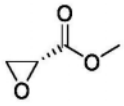
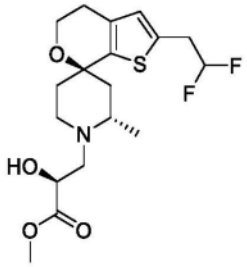
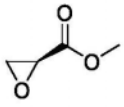
[1177]

化合物	结构	环氧化物	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
601			*化合物 594*	LCMS *m/z* 400.12 $[M+1]^+$
602			*化合物 594*	LCMS *m/z* 426.17 $[M+1]^+$
603			*化合物 594*	LCMS *m/z* 360.2 $[M+1]^+$
604			*化合物 594*[1,2,3,6]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 6.63 (s, 1H), 5.92 (tt, J = 56.4, 4.4 Hz, 1H), 4.56 (d, J = 6.7 Hz, 1H), 4.04 - 3.84 (m, 2H), 3.71 (d, J = 7.3 Hz, 1H), 3.48 (s, 1H), 3.28 (tdd, J = 16.5, 4.5, 0.9 Hz, 2H), 3.12 (s, 2H), 2.67 (td, J = 5.4, 1.7 Hz, 2H), 2.13 (d, J = 12.1 Hz, 4H), 2.04 - 1.59 (m, 4H), 1.40 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 372.21 $[M+1]^+$

[1178]

化合物	结构	环氧化物	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
605			*化合物 594*	LCMS *m/z* 444.14 $[M+1]^+$
606			*化合物 594*	LCMS *m/z* 450.15 $[M+1]^+$
607			*化合物 594*	LCMS *m/z* 362.19 $[M+1]^+$
608			*化合物 594*	LCMS *m/z* 402.19 $[M+1]^+$
609			*化合物 594*[1,2,4,6]	^{1}H NMR (300 MHz, 氯仿-d) δ 6.62 (s, 1H), 5.92 (tt, J = 56.5, 4.5 Hz, 1H), 4.50 (ddd, J = 6.4, 5.1, 2.9 Hz, 1H), 4.11 (ddd, J = 11.3, 9.6, 5.3 Hz, 2H), 4.01 - 3.83 (m, 2H), 3.78 (dd, J = 9.6, 6.8 Hz, 1H), 3.74 - 3.55 (m, 2H), 3.40 - 3.19 (m, 2H), 2.93 - 2.76 (m, 2H), 2.72 - 2.50 (m, 3H), 2.20 - 1.59 (m, 4H), 1.15 (d, J =

[1179]

化合物	结构	环氧化物	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				6.3 Hz, 3H)。LCMS *m/z* 374.2 [M+1]$^+$。
S48			*化合物 594*[7,8]	LCMS *m/z* 390.13 [M+1]$^+$
S49			*化合物 594*[7,8]	LCMS *m/z* 390.13 [M+1]$^+$

[1180] 脚注：

[1181] 1.IPA(1mL)用作溶剂，

[1182] 2.在150℃下加热两小时后添加另外3当量环氧化物。

[1183] 3.将反应物在微波中加热至150℃，持续八小时

[1184] 4.将产物通过硅胶色谱法重新纯化(梯度:含0-20％ MeOH的DCM)

[1185] 5.产物作为甲酸盐提交

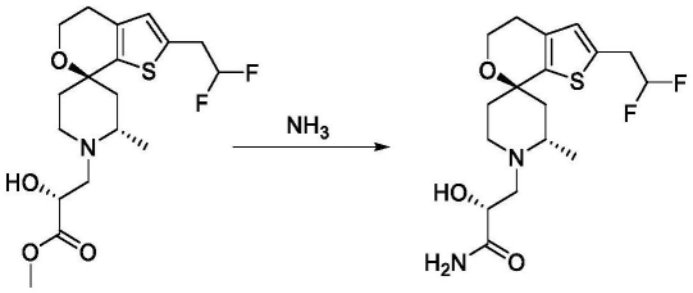
[1186] 6.纯化期间分离出两种非对映异构体

[1187] 7.将反应物在微波中加热至90℃，持续1.5小时

[1188] 8.完全反应后，将溶剂在真空中去除，用MeOH和DCM冲洗，并将粗反应物伸缩至下一反应。

[1189] 化合物610

[1190] (2R)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(610)

[1191] 

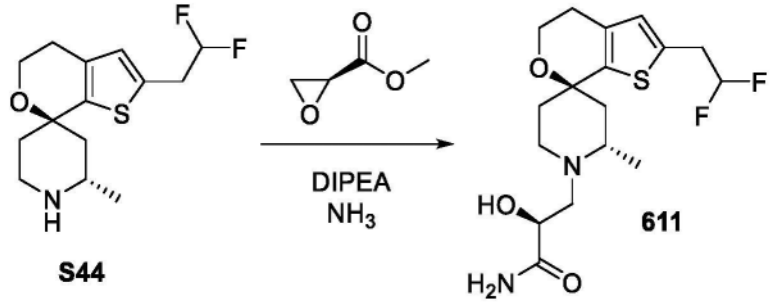
[1192] (2R)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(610)的制备

[1193] 将(2R)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]

吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯S48(96mg,0.2465mmol)添加到微波烧瓶中。添加NH_3(1.5mL的7M,10.50mmol)于MeOH(100μL)中的溶液,并将反应物在50℃下搅拌过夜。将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-10% MeOH的DCM),提供期望产物610。^{1}H NMR(300MHz,氯仿-d)δ6.94(d,J=4.2Hz,1H),6.58(s,1H),6.13-5.61(m,2H),3.93-3.76(m,2H),3.24(td,J=16.8,4.4Hz,2H),2.91(dd,J=12.9,9.9Hz,1H),2.80(ddq,J=11.5,7.0,2.5Hz,2H),2.62(tdd,J=13.1,10.3,3.7Hz,4H),1.99-1.86(m,2H),1.86-1.69(m,1H),1.56(dd,J=14.0,11.4Hz,1H),1.03(d,J=6.2Hz,3H)。LCMS m/z 375.14[M+1]$^+$。

[1194] 化合物611

[1195] (2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(611)

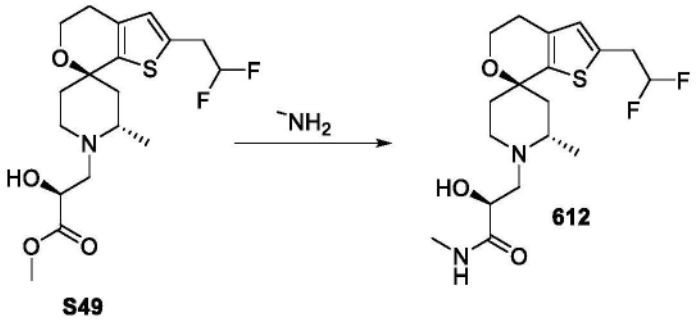
[1196] 

[1197] (2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(611)的制备

[1198] 将(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S44(108mg,0.3758mmol)和(2S)-环氧乙烷-2-甲酸甲酯)700μL,7.995mmol)添加到微波小瓶中并放入含NH_3(4mL的7M,28.00mmol)的MeOH。添加DIPEA(980μL,5.626mmol),并将反应物在120℃下搅拌6小时。将溶剂在真空中去除,并将产物用MeOH和DCM(2x)冲洗。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)纯化,随后通过硅胶色谱法纯化(梯度:含0-20% MeOH的二氯甲烷),产生产物(2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺611(17.8mg,12%)。^{1}H NMR(300MHz,氯仿-d)δ7.29(s,1H),6.61(s,1H),6.11-5.66(m,2H),4.38(s,1H),3.87(hept,J=5.9Hz,2H),3.61(s,1H),3.26(td,J=16.7,4.4Hz,4H),3.11(s,1H),2.77(dd,J=13.5,8.2Hz,1H),2.63(q,J=5.2Hz,2H),1.29(d,J=6.4Hz,3H)。LCMS m/z375.14[M+1]$^+$。

[1199] 化合物612

[1200] (2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺(612)

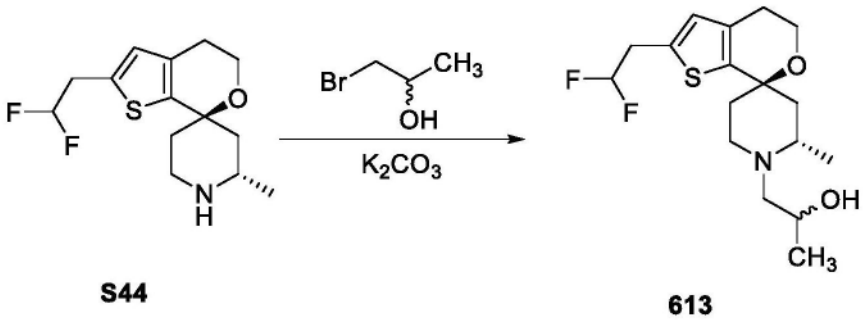
[1201] 

[1202] (2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺(612)的制备

[1203] 将(S)-3-((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)-2-羟基丙酸甲酯49(95mg,0.2439mmol)放入二噁烷(1.9mL)中并添加到微波烧瓶中。添加甲胺(250μL的40%w/v,3.220mmol)和水(45μL,2.498mmol),并将反应物加热至80℃并搅拌过夜。将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有0.1%三氟乙酸,产生(2S)-3-[(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺(三氟乙酸(2))612(60.1mg,39%)。^{1}H NMR(300MHz,氯仿-d)δ7.41(d,J=5.8Hz,1H),6.64(d,J=4.2Hz,1H),5.91(tt,J=56.3,4.4Hz,1H),4.81-4.46(m,1H),4.02(s,OH),3.89(dp,J=10.6,5.9Hz,2H),3.68(d,J=12.1Hz,1H),3.53(s,1H),3.27(td,J=16.7,4.4Hz,3H),3.13-2.92(m,1H),2.86(d,J=4.9Hz,2H),2.71-2.60(m,2H),2.46-2.26(m,1H),2.26-2.07(m,2H),1.48(d,J=6.4Hz,2H)。LCMS m/z 389.28[M+1]$^+$。

[1204] 化合物613

[1205] 1-((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)丙-2-醇(613)

[1206] 

[1207] 1-((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)丙-2-醇(613)的制备

[1208] 向1-溴丙-2-醇(16.51mg,0.1188mmol)和(2′S,7R)-2-(2,2-二氟乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(27mg,0.07921mmol)于DMF(2mL)中的溶液中添加K_2CO_3(32.84mg,0.2376mmol)。将反应物在110℃下搅拌72小时,然后冷却至室温并过滤。将粗反应混合物通过反相HPLC纯化(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸)以得到1-((2S,4R)-2′-(2,2-二氟乙基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)丙-2-醇(613)(8.8mg,31.5%)。1H NMR(300MHz,乙腈-d3)δ6.68(d,J=1.1Hz,1H),6.04(tt,J=56.5,4.2Hz,1H),

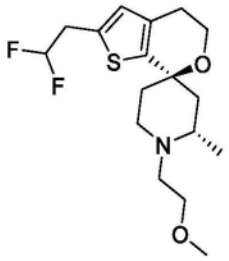
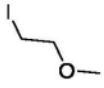
3.89(tt,J＝5.7,1.8Hz,2H),3.84-3.63(m,1H),3.33(tdt,J＝17.7,4.2,0.8Hz,3H),2.91-2.36(m,6H),2.14-2.03(m,1H),2.03-1.98(m,1H),1.93-1.77(m,2H),1.56(ddd,J＝20.6,13.7,11.3Hz,1H),1.13-0.97(m,6H)。LCMS m/z 345.44[M+H]$^+$。

[1209] 化合物614-624

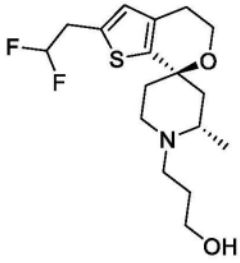
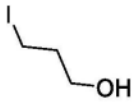
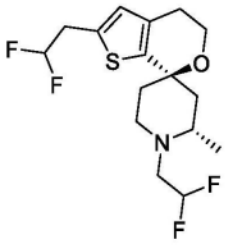
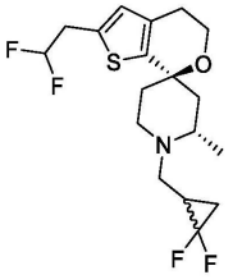
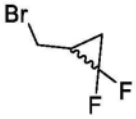
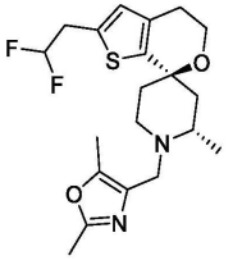
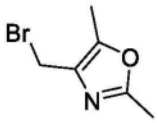
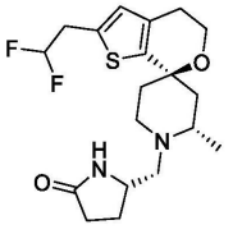
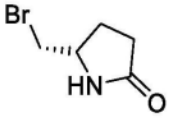
[1210] 使用化合物613的方法,由中间体S44和适当的胺试剂制备化合物614-624(表27)。烷基卤化物从商业来源获得。表27和随附脚注中注明了对方法的任何修改。

[1211] 表27:化合物614-624的结构和物理化学数据

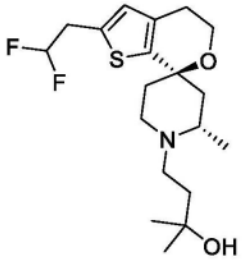
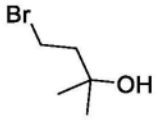
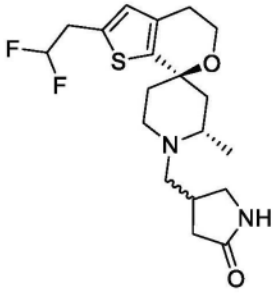
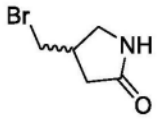
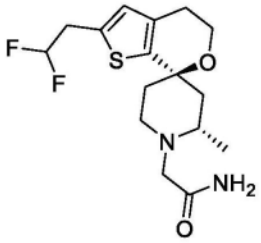
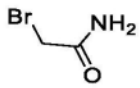
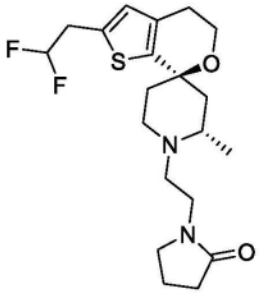
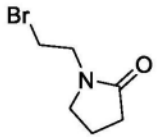
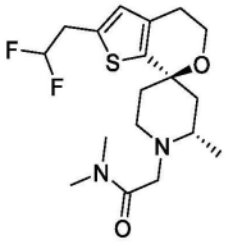
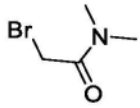
[1212]

化合物	结构	烷基卤化物	^{1}H NMR；LCMS m/z [M+H]$^+$。
614			LCMS *m/z* 346.2 [M+H]$^+$。

[1213]

化合物	结构	烷基卤化物	^{1}H NMR；LCMS m/z $[M+H]^+$。
615			LCMS *m/z* 346.2 $[M+H]^+$。
616			LCMS *m/z* 352.17 $[M+H]^+$。
617			LCMS *m/z* 378.15 $[M+H]^+$。[1]
618			LCMS *m/z* 397.17 $[M+H]^+$。[1]
619			LCMS *m/z* 385.02 $[M+H]^+$。[1]

[1214]

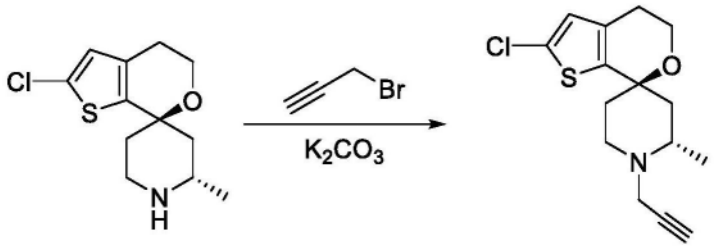
化合物	结构	烷基卤化物	^{1}H NMR；LCMS m/z $[M+H]^+$。
620			LCMS *m/z* 374.18 $[M+H]^+$。[1]
621			LCMS *m/z* 385.15 $[M+H]^+$。[1]
622			LCMS *m/z* 345.12 $[M+H]^+$。[1]
623			LCMS *m/z* 398.66 $[M+H]^+$。[1]
624			LCMS *m/z* 373.17 $[M+H]^+$。[1]

[1215] 脚注：

[1216] [1]将反应物在90℃下搅拌18小时。

[1217] 化合物625

[1218] (2′S,7R)-2-氯-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]

[1219] 

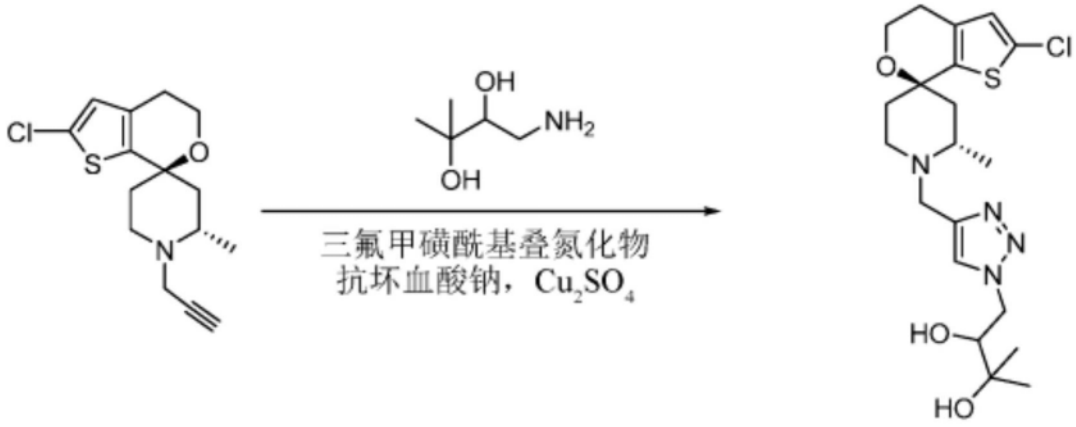
S50 625

[1220] (2′S,7R)-2-氯-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](625)的制备

[1221] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)S50(500mg,1.345mmol)和炔丙基溴(267mg,1.796mmol)和碳酸钾(250mg,1.809mmol)于乙腈(10mL)中的混合物加热至70℃,持续2分钟。将混合物冷却至室温,过滤并浓缩。将粗材料在二氯甲烷(10mL)和2M NaOH中稀释。将各层混合,通过相分离器并浓缩。通过硅胶色谱法纯化(含1-10% MeOH的二氯甲烷),得到(2′S,7R)-2-氯-2′-甲基-1′-丙-2-炔基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]625(228mg,57%)。^{1}H NMR(400MHz,氯仿-d)δ6.54(s,1H),3.96-3.82(m,2H),3.61(dd,J=17.4,2.4Hz,1H),3.38(dd,J=17.4,2.4Hz,1H),2.87(ddd,J=12.8,11.5,2.7Hz,1H),2.78(dqd,J=12.5,6.3,2.6Hz,1H),2.63(ddd,J=11.4,4.7,2.4Hz,1H),2.60-2.49(m,2H),2.22(t,J=2.4Hz,1H),2.10-2.01(m,1H),1.98(dt,J=13.8,2.8Hz,1H),1.84(ddd,J=13.9,12.8,4.6Hz,1H),1.55(dd,J=13.8,11.5Hz,1H),1.05(d,J=6.3Hz,3H)。LCMS m/z 296.36$[M+H]^+$。

[1222] 化合物626

[1223] 1-(4-(((2R,4S)-2′-氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)甲基)-1H-1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇

[1224] 

625 626

[1225] 1-(4-(((2R,4S)-2′-氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)甲基)-1H-1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇(626)的制备

[1226] 向1-氨基-3-甲基-丁烷-2,3-二醇(40mg,0.3357mmol)于MeOH(3mL)中的混合物中添加含$CuSO_4$(0.25mg,0.001566mmol)的水(0.125mL),随后添加含碳酸氢钠(45mg)的水(0.375mL)和三氟甲磺酸叠氮化物(1.25mL的0.452M,0.5650mmol)于二氯甲烷中的溶液并将溶液搅拌1小时。向反应物中添加含(2′S,7R)-2-氯-2′-甲基-1′-丙-2-炔基-螺[4,5-二

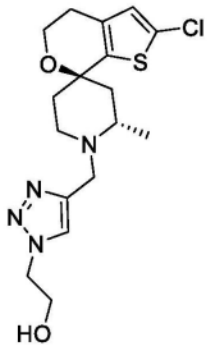
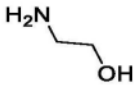
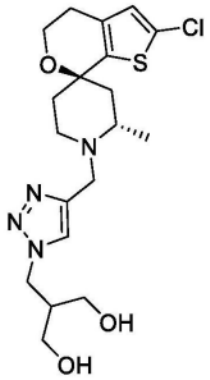
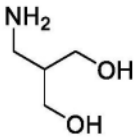
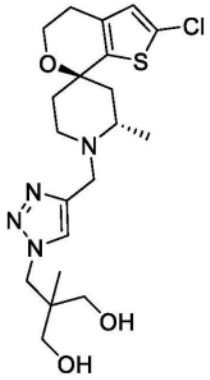
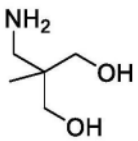
氢噻吩并[2,3-c]吡喃-7,4′-哌啶]625(50mg,0.1671mmol)的甲醇(0.5mL)、含抗坏血酸钠(35mg,0.1987mmol)的水(0.25mL)和含1-(1-苄基三唑-4-基)-N,N-双[(1-苄基三唑-4-基)甲基]甲胺(2mg,0.003769mmol)的甲醇(0.2mL),并将混合物加热至60℃并搅拌17小时。将反应物浓缩并通过反相HPLC纯化(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸)以得到1-(4-(((2R,4S)-2′-氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-基)甲基)-1H-1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇(626)(51mg,69%)。^{1}H NMR(400MHz,氯仿-d)δ7.80(s,1H),6.59(s,1H),4.73-4.60(m,1H),4.34(td,J=13.8,13.3,9.4Hz,1H),3.95-3.78(m,4H),2.75(d,J=78.1Hz,4H),2.65-2.54(m,2H),2.22(d,J=10.7Hz,1H),2.04(d,J=7.0Hz,3H),1.79(s,2H),1.47-1.27(m,9H)。LCMS m/z 441.11$[M+H]^+$。

[1227] 化合物627-629

[1228] 使用化合物626的方法,由中间体S50和适当的胺试剂制备化合物627-629(表28)。胺从商业来源获得。表28和随附脚注中注明了对方法的任何修改。

[1229] 表28:化合物627-629的结构和物理化学数据

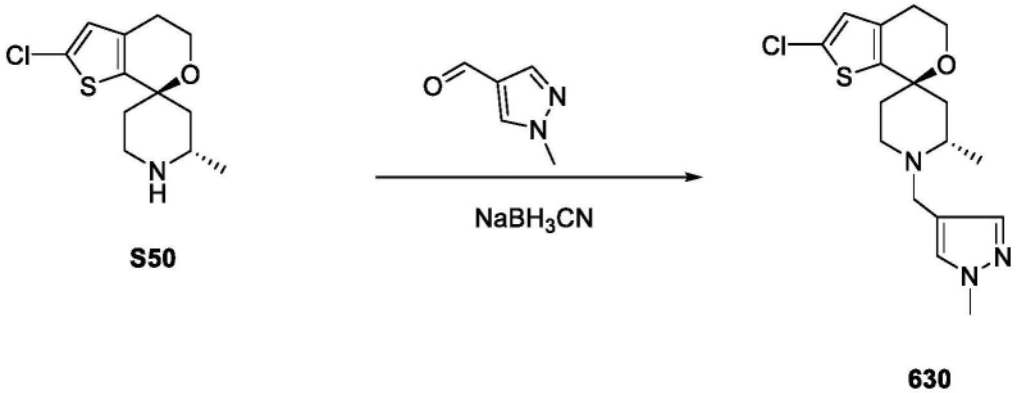
[1230]

化合物	结构	胺	^{1}H NMR；LCMS m/z [M+H]$^+$。
627			^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.77 (s, 1H), 6.59 (s, 1H), 4.56 - 4.48 (m, 2H), 4.20 (d, J = 14.1 Hz, 1H), 4.14 - 4.07 (m, 2H), 3.95 - 3.81 (m, 3H), 2.80 (d, J = 60.8 Hz, 4H), 2.67 - 2.53 (m, 2H), 2.05 (d, J = 12.9 Hz, 2H), 1.96 (s, 1H), 1.34 (d, J = 6.0 Hz, 3H)。LCMS *m/z* 382.99 [M+H]$^+$。
628			^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.69 (s, 1H), 6.58 (s, 1H), 4.64 (d, J = 7.0 Hz, 2H), 4.14 (d, J = 14.6 Hz, 1H), 3.93 - 3.81 (m, 3H), 3.81 - 3.61 (m, 4H), 2.80 (d, J = 11.7 Hz, 1H), 2.67 (d, J = 9.7 Hz, 2H), 2.63 - 2.50 (m, 2H), 2.32 (tp, J = 7.0, 4.8 Hz, 1H), 2.04 (ddt, J = 11.2, 5.8, 2.8 Hz, 2H), 1.92 (d, J = 14.7 Hz, 1H), 1.74 (s, 1H), 1.30 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 427.07 [M+H]$^+$。
629			^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.76 - 7.56 (m, 1H), 6.58 (d, J = 1.4 Hz, 1H), 4.63 - 4.44 (m, 2H), 4.12 (d, J = 14.7 Hz, 1H), 3.87 (td, J = 14.1, 12.2, 8.4 Hz, 3H), 3.61 (dd, J = 11.3, 7.7 Hz, 2H), 3.43 (t, J = 10.0 Hz, 2H), 3.07 (s, 1H), 2.84 - 2.49 (m, 5H), 2.03 (t, J = 11.1 Hz, 2H), 1.91 (d, J = 13.9 Hz, 3H), 1.29 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 1.6 Hz, 3H)。LCMS *m/z* 441.07 [M+H]$^+$。

[1231] 化合物630#MZ48

[1232] (2R,4S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]

[1233]



S50 630

[1234] 步骤1:(2R,4S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](630)的合成

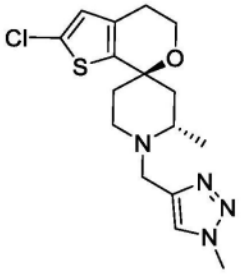
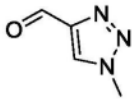
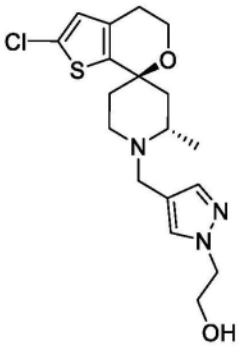
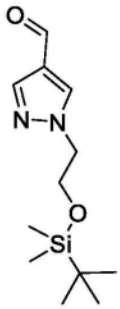
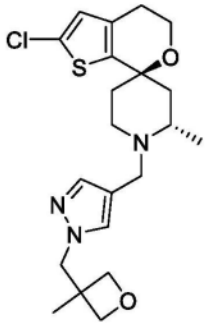
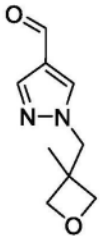
[1235] 将1-甲基吡唑-4-甲醛(12mg,0.109mmol)和乙酸(15L,0.266mmol)添加到(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(14mg,0.0290mmol)于DMF(2mL)中的溶液中。添加$NaBH_3CN$(81mg,0.162mmol),并将反应混合物在110℃下搅拌30分钟。通过制备型HPLC纯化(流动相A:-0.1% TFA(水性),流动相B:-乙腈),产生(2R,4S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]630(13mg,67%)。^1H NMR(300MHz,氯仿-d)δ11.80(s,1H),7.67(s,1H),7.52(s,1H),6.58(s,1H),4.51(d,J=14.2Hz,1H),3.95(s,4H),3.89-3.75(m,2H),3.31(d,J=13.0Hz,2H),3.02(d,J=9.6Hz,1H),2.63-2.48(m,2H),2.39-2.23(m,2H),2.23-2.06(m,2H),1.56(d,J=6.5Hz,3H)。LCMS m/z352.12$[M+H]^+$。

[1236] 化合物631-693

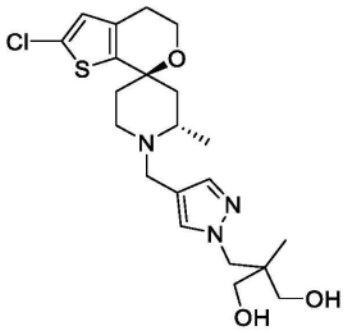
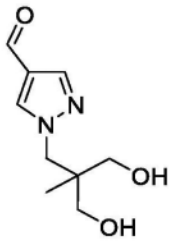
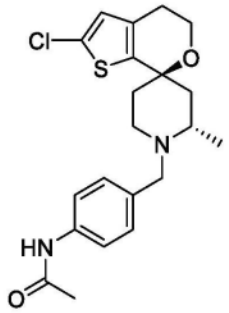
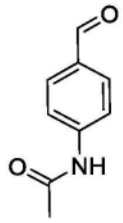
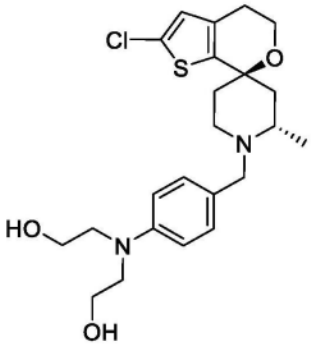
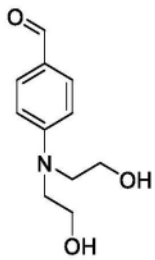
[1237] 使用化合物630的方法,由中间体S50和适当的醛试剂制备化合物631-693(表29)。醛通过上述方法制备或从商业来源获得。表29和随附脚注中注明了对方法的任何修改。

[1238] 表29:化合物631-693的结构和物理化学数据

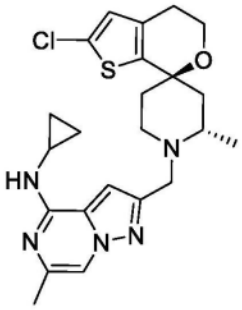
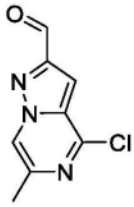
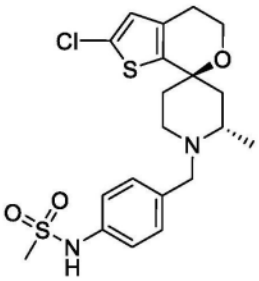
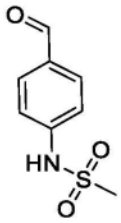
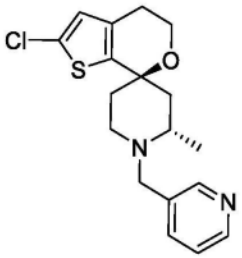
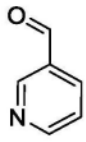
[1239]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
631			
632[1]			^{1}H NMR (400 MHz, 甲醇-d4) δ 8.03 (d, J = 0.7 Hz, 1H), 7.81 (d, J = 0.8 Hz, 1H), 6.73 (s, 1H), 4.59 (d, J = 14.1 Hz, 1H), 4.31 (dd, J = 5.7, 4.8 Hz, 2H), 4.23 (d, J = 14.1 Hz, 1H), 3.98 - 3.85 (m, 4H), 3.56 (ddd, J = 12.2, 6.4, 3.0 Hz, 1H), 3.41 - 3.34 (m, 1H), 3.26 (dd, J = 12.8, 3.1 Hz, 1H), 2.61 (td, J = 5.3, 1.4 Hz, 2H), 2.34 (dt, J = 14.9, 3.0 Hz, 1H), 2.27 (dd, J = 15.0, 2.9 Hz, 1H), 2.12 - 1.99 (m, 3H), 1.56 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 382.0 $[M+H]^+$。
633			^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.41 (d, J = 0.7 Hz, 1H), 7.29 (s, 1H), 6.54 (s, 1H), 4.69 (dd, J = 6.2, 1.9 Hz, 2H), 4.38 (d, J = 6.1 Hz, 2H), 4.29 (s, 2H), 3.88 - 3.77 (m, 3H), 3.50 (d, J = 14.1 Hz, 1H), 2.67 (ddd, J = 11.6, 4.6, 2.5 Hz, 1H), 2.61 - 2.49 (m, 3H), 2.45 (td, J = 12.4, 11.7, 2.7 Hz, 1H), 1.98 (ddt, J = 15.2, 13.1, 2.9 Hz, 2H), 1.79 (td, J = 13.3, 4.5 Hz, 1H), 1.62 (dd, J = 13.9, 11.4 Hz, 1H), 1.22 (s, 3H), 1.18 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 422.13 $[M+H]^+$。

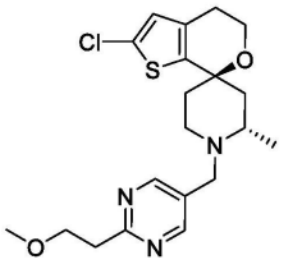
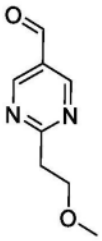
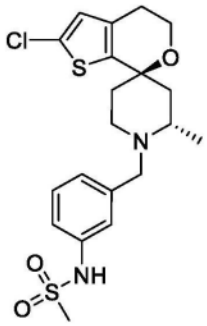
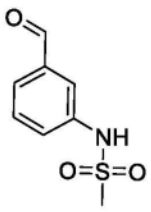
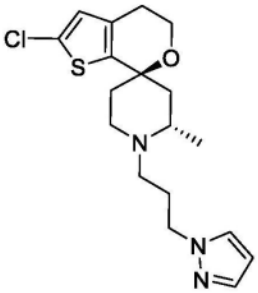
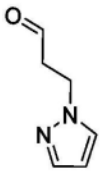
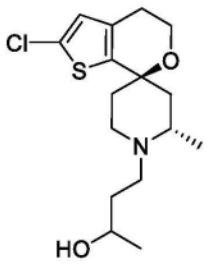
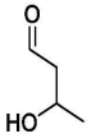
[1240]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
634			^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.45 (dd, J = 12.4, 0.7 Hz, 2H), 6.58 (d, J = 17.0 Hz, 1H), 4.32 - 4.19 (m, 2H), 3.93 (td, J = 11.5, 10.7, 5.4 Hz, 1H), 3.88 - 3.78 (m, 2H), 3.60 - 3.45 (m, 4H), 3.40 - 3.29 (m, 2H), 2.71 (d, J = 28.2 Hz, 2H), 2.63 - 2.47 (m, 3H), 2.10 - 1.68 (m, 5H), 1.26 (d, J = 6.2 Hz, 3H), 0.84 (d, J = 10.1 Hz, 3H)。LCMS *m/z* 440.12 [M+H]$^+$。
635			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.14 (s, 1H), 9.56 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 6.92 (s, 1H), 4.64 (d, J = 12.9 Hz, 1H), 4.10 (dd, J = 13.0, 7.4 Hz, 1H), 3.88 (ddt, J = 19.1, 12.0, 5.7 Hz, 2H), 3.04 (dd, J = 28.7, 10.3 Hz, 2H), 2.57 (s, 2H), 2.29 (d, J = 14.7 Hz, 1H), 2.16 (d, J = 14.9 Hz, 1H), 2.06 (s, 3H), 2.00 - 1.85 (m, 2H), 1.48 (d, J = 6.5 Hz, 3H)。LCMS *m/z* 405.35 [M+H]$^+$。
636			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.29 (s, 1H), 7.29 - 7.21 (m, 2H), 6.92 (s, 1H), 6.73 (d, J = 8.5 Hz, 2H), 4.78 (s, 1H), 4.53 (d, J = 12.8 Hz, 1H), 3.98 (dd, J = 13.1, 7.3 Hz, 1H), 3.87 (dq, J = 18.2, 6.2 Hz, 2H), 3.54 (t, J = 6.2 Hz, 4H), 3.46 - 3.43 (m, 6H), 3.02 (d, J = 15.8 Hz, 2H), 2.57 (s, 2H), 2.28 (d, J = 14.9 Hz, 1H), 2.17 (d, J = 14.8 Hz, 1H), 1.89 (dt, J = 22.5, 11.6 Hz, 2H), 1.46 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 451.36 [M+H]$^+$。

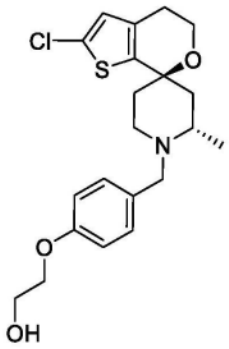
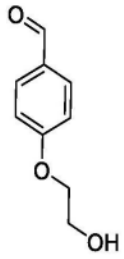
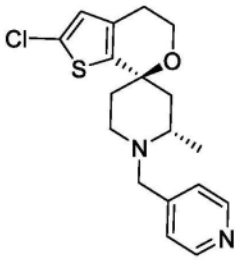
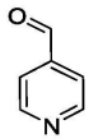
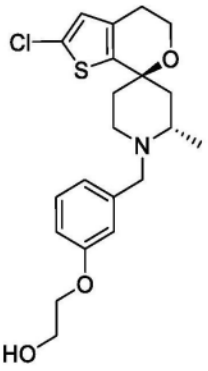
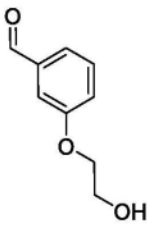
[1241]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
637			^{1}H NMR (400 MHz, 甲醇-*d4*) δ 7.65 - 7.61 (m, 1H), 6.82 (d, J = 0.9 Hz, 1H), 6.65 (s, 1H), 4.10 (d, J = 14.2 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.89 - 3.76 (m, 2H), 2.91 (tt, J = 7.2, 3.8 Hz, 1H), 2.86 - 2.68 (m, 3H), 2.54 (td, J = 5.5, 2.6 Hz, 2H), 2.33 (d, J = 1.0 Hz, 3H), 2.09 - 1.98 (m, 2H), 1.89 - 1.77 (m, 1H), 1.64 (dd, J = 14.1, 11.6 Hz, 1H), 1.30 (d, J = 6.3 Hz, 3H), 0.90 - 0.79 (m, 2H), 0.68 - 0.59 (m, 2H)。LCMS *m/z* 458.18 [M+H]$^+$。
638			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.05 (s, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.92 (s, 1H), 4.67 (d, J = 12.8 Hz, 1H), 4.10 (dd, J = 13.0, 7.6 Hz, 1H), 3.87 (dp, J = 17.4, 5.9 Hz, 2H), 3.51 (s, 1H), 3.11 (s, 1H), 3.06 (s, 3H), 3.03 - 2.97 (m, 1H), 2.58 (s, 2H), 2.30 (d, J = 15.1 Hz, 1H), 2.16 (d, J = 15.3 Hz, 1H), 1.93 (dd, J = 23.3, 10.9 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 441.29 [M+H]$^+$。
639			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.89 (s, 1H), 8.73 (d, J = 2.3 Hz, 1H), 8.68 (dd, J = 4.9, 1.6 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 7.9, 4.8 Hz, 1H), 6.93 (s, 1H), 4.80 (d, J = 13.2 Hz, 1H), 4.22 (d, J = 13.1 Hz, 1H), 3.88 (dp, J = 22.6, 6.0, 5.6 Hz, 2H), 3.62 (dd, J = 6.0, 2.2 Hz, 1H), 3.16 (s, 1H), 3.01 (d, J = 8.8 Hz, 1H), 2.66 - 2.56 (m, 2H), 2.40 - 2.26 (m, 1H), 2.16 (d, J = 15.6 Hz, 1H), 2.02 - 1.82 (m, 2H), 1.50 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 349.31 [M+H]$^+$。

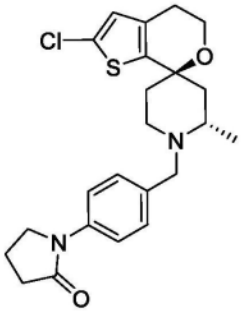
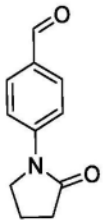
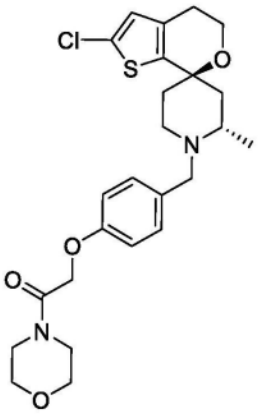
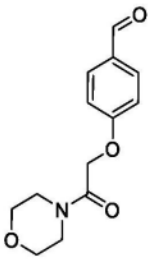
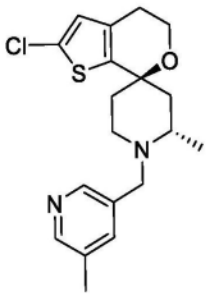
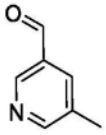
[1242]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
640			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.87 (s, 2H), 6.93 (s, 1H), 4.79 (d, J = 13.3 Hz, 1H), 4.19 (s, 1H), 3.89 (dd, J = 11.6, 6.0 Hz, 3H), 3.83 (t, J = 6.5 Hz, 2H), 3.68 - 3.60 (m, 1H), 3.23 (s, 3H), 3.15 (t, J = 6.5 Hz, 2H), 2.59 (s, 2H), 2.32 (d, J = 13.2 Hz, 1H), 2.25 - 1.99 (m, 2H), 1.91 (d, J = 16.5 Hz, 2H), 1.48 (d, J = 6.1 Hz, 3H)。LCMS *m/z* 408.33 [M+H]$^+$。
641			LCMS *m/z* 441.33 [M+H]$^+$。
642			LCMS *m/z* 366.3 [M+H]$^+$。
643			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.37 (s, 1H), 8.32 (d, J = 12.7 Hz, 1H), 6.94 (s, 1H), 4.82 (s, 1H), 3.91 (d, J = 5.1 Hz, 2H), 3.69 (s, 1H), 3.16 (s, 2H), 2.59 (t, J = 5.5 Hz, 2H), 2.24 (t, J = 18.2 Hz, 2H), 2.07 - 1.83 (m, 2H), 1.71 (s, 1H), 1.28 (t, J = 5.7 Hz, 3H), 1.22 (t, J = 7.3 Hz, 2H), 1.18 - 1.13 (m, 1H), 1.14 - 1.08 (m, 2H)。LCMS *m/z* 330.31 [M+H]$^+$。

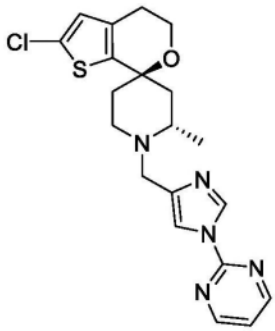
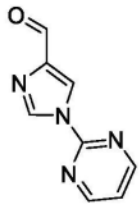
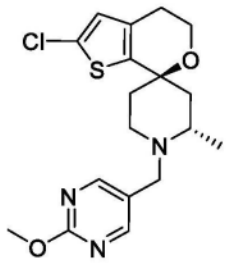
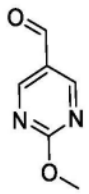
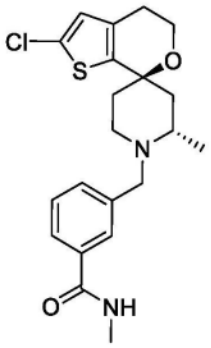
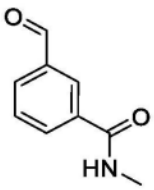
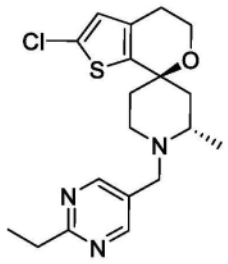
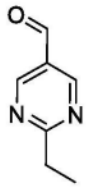
[1243]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
644			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.47 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 6.92 (s, 1H), 4.90 (s, 1H), 4.65 (d, J = 12.9 Hz, 1H), 4.09 (dd, J = 13.0, 7.5 Hz, 1H), 4.02 (t, J = 5.0 Hz, 2H), 3.87 (dp, J = 17.2, 5.9, 5.4 Hz, 2H), 3.72 (t, J = 4.8 Hz, 2H), 3.47 (s, 1H), 3.04 (dd, J = 30.4, 8.7 Hz, 2H), 2.58 (s, 2H), 2.29 (d, J = 15.1 Hz, 1H), 2.16 (d, J = 14.8 Hz, 1H), 1.91 (dd, J = 23.6, 11.4 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 408.33 $[M+H]^+$。
645			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.09 (s, 1H), 8.71 (d, J = 5.0 Hz, 2H), 7.58 (d, J = 4.9 Hz, 2H), 6.92 (s, 1H), 4.78 (d, J = 13.4 Hz, 1H), 4.18 (d, J = 12.9 Hz, 1H), 3.88 (dp, J = 22.5, 5.8, 5.3 Hz, 2H), 3.14 (dd, J = 7.5, 4.1 Hz, 1H), 3.05 - 2.92 (m, 1H), 2.60 - 2.56 (m, 2H), 2.31 (d, J = 15.2 Hz, 1H), 2.14 (d, J = 15.0 Hz, 1H), 1.95 (q, J = 16.0, 15.4 Hz, 2H), 1.46 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 348.9 $[M+H]^+$。
646			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.59 (s, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.17 - 6.98 (m, 3H), 6.92 (s, 1H), 4.91 (s, 1H), 4.71 (d, J = 12.8 Hz, 1H), 4.10 (dd, J = 13.0, 8.0 Hz, 1H), 4.02 (t, J = 5.0 Hz, 2H), 3.88 (dp, J = 22.7, 5.9, 5.4 Hz, 2H), 3.77 - 3.65 (m, 2H), 3.53 (s, 1H), 3.12 (q, J = 11.6, 11.2 Hz, 1H), 3.00 - 2.86 (m, 1H), 2.58 (s, 2H), 2.37 - 2.23 (m, 1H), 2.17 (d, J = 15.0 Hz, 1H), 1.93 (dt, J = 25.9, 12.7 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 408.33 $[M+H]^+$。

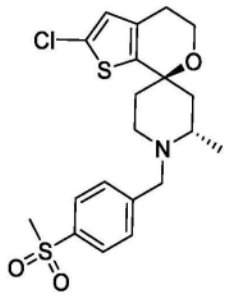
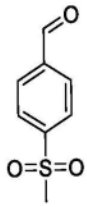
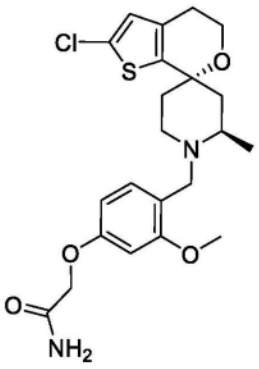
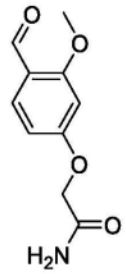
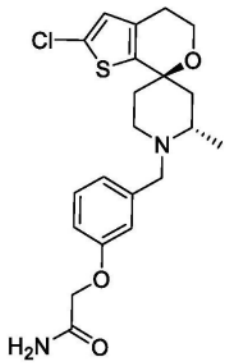
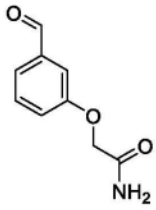
[1244]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
647			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.58 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 4.70 (d, J = 12.9 Hz, 1H), 4.14 (dd, J = 13.0, 7.4 Hz, 1H), 3.87 (dt, J = 14.9, 6.5 Hz, 4H), 3.09 (t, J = 11.7 Hz, 1H), 3.00 (s, 1H), 2.93 (dd, J = 15.9, 9.7 Hz, 1H), 2.58 (s, 2H), 2.52 (s, 1H), 2.30 (d, J = 15.2 Hz, 1H), 2.16 (d, J = 15.4 Hz, 1H), 2.07 (p, J = 7.6 Hz, 2H), 1.91 (dt, J = 24.7, 13.8 Hz, 2H), 1.48 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 431.35 [M+H]$^+$。
648			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.56 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.02 (s, 2H), 6.92 (s, 1H), 4.89 (s, 2H), 4.80 - 4.56 (m, 1H), 4.09 (dd, J = 13.0, 7.5 Hz, 1H), 3.88 (dq, J = 18.3, 6.2 Hz, 2H), 3.61 (s, 3H), 3.57 (s, 4H), 3.18 - 2.95 (m, 3H), 2.58 (s, 2H), 2.39 - 2.23 (m, 1H), 2.17 (d, J = 14.7 Hz, 1H), 1.92 (q, J = 16.3, 15.3 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 491.41 [M+H]$^+$。
649			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.54 (s, 2H), 7.83 (s, 1H), 6.93 (s, 1H), 4.77 (d, J = 13.0 Hz, 1H), 4.16 (d, J = 13.1 Hz, 1H), 3.94 - 3.80 (m, 2H), 3.55 (s, 1H), 3.14 (s, 1H), 3.01 (d, J = 9.6 Hz, 1H), 2.58 (s, 2H), 2.36 (s, 3H), 2.15 (d, J = 15.1 Hz, 1H), 1.92 (dt, J = 23.3, 13.2 Hz, 2H), 1.49 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 363.31 [M+H]$^+$。

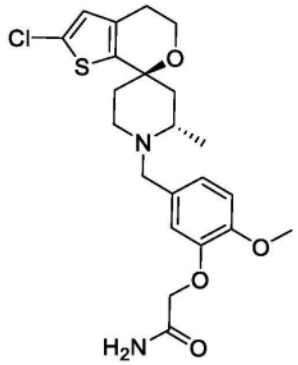
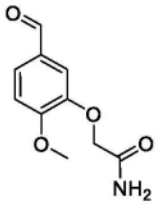
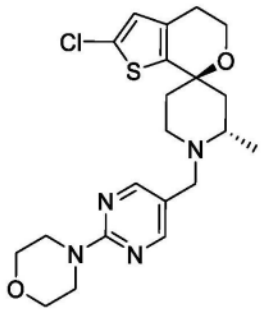
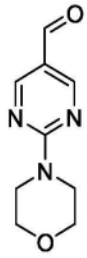
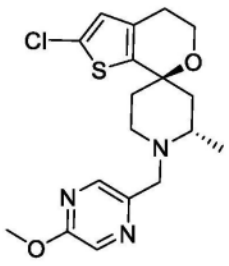
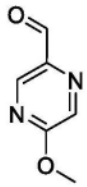
[1245]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
650			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.88 (s, 1H), 8.93 (d, J = 4.9 Hz, 2H), 8.76 (d, J = 1.3 Hz, 1H), 8.26 (s, 1H), 7.57 (t, J = 4.9 Hz, 1H), 6.92 (s, 1H), 4.51 (d, J = 14.0 Hz, 1H), 4.40 (d, J = 14.1 Hz, 1H), 3.84 (p, J = 6.0 Hz, 2H), 3.39 (d, J = 13.5 Hz, 1H), 3.27 (s, 1H), 2.56 (s, 2H), 2.24 (dd, J = 25.6, 14.7 Hz, 2H), 1.97 (q, J = 14.5, 13.8 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 416.28 [M+H]$^+$。
651			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.74 (s, 2H), 6.93 (d, J = 2.0 Hz, 1H), 4.74 (d, J = 13.3 Hz, 1H), 4.15 (d, J = 11.5 Hz, 1H), 3.96 (s, 3H), 3.90 (dt, J = 11.4, 5.7 Hz, 3H), 3.13 (s, 2H), 2.59 (s, 2H), 2.32 (d, J = 14.1 Hz, 1H), 2.16 (d, J = 14.9 Hz, 1H), 1.99 - 1.81 (m, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 380.33 [M+H]$^+$。
652			LCMS *m/z* 405.35 [M+H]$^+$。
653			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.87 (s, 2H), 6.93 (s, 1H), 4.79 (d, J = 13.1 Hz, 1H), 4.19 (s, 1H), 3.99 - 3.83 (m, 3H), 3.13 (d, J = 33.9 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 2.59 (s, 2H), 2.32 (d, J = 14.8 Hz, 1H), 2.15 (d, J = 15.1 Hz, 1H), 1.91 (q, J = 15.7, 15.3 Hz, 2H), 1.49 (d, J = 6.3 Hz, 3H), 1.30 (t, J = 7.6 Hz, 3H)。LCMS *m/z* 378.35

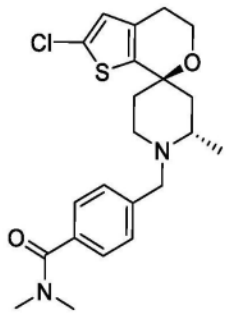
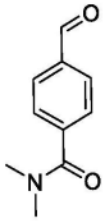
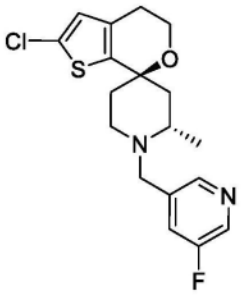
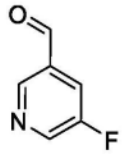
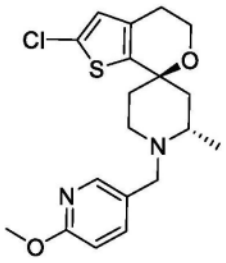
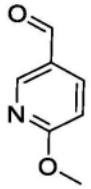
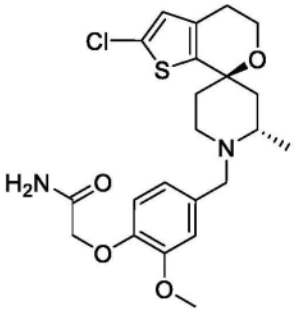
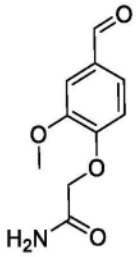
[1246]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
			$[M+H]^+$。
654			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.85 (s, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 6.93 (s, 1H), 4.88 (d, J = 12.9 Hz, 1H), 4.28 (s, 1H), 3.89 (ddt, J = 18.8, 13.0, 6.6 Hz, 2H), 3.58 (s, 1H), 3.27 (s, 3H), 3.03 - 2.77 (m, 2H), 2.58 (s, 2H), 2.39 - 2.23 (m, 1H), 2.15 (d, J = 14.8 Hz, 1H), 1.93 (dt, J = 28.2, 13.9 Hz, 2H), 1.49 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 426.26 $[M+H]^+$。
655			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.62 (s, 1H), 7.42 (s, 1H), 7.36 (s, 1H), 7.18 (d, J = 1.9 Hz, 1H), 7.06 - 7.00 (m, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.92 (s, 1H), 4.75 - 4.61 (m, 1H), 4.47 (s, 2H), 4.04 (dd, J = 13.0, 8.0 Hz, 1H), 3.90 (dq, J = 13.4, 6.2 Hz, 2H), 3.83 (s, 3H), 3.10 (q, J = 11.3 Hz, 1H), 2.95 (dd, J = 13.9, 8.1 Hz, 1H), 2.58 (s, 2H), 2.30 (d, J = 15.1 Hz, 1H), 2.16 (d, J = 14.8 Hz, 1H), 1.93 (dt, J = 26.4, 12.6 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 451.31 $[M+H]^+$。
656			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.58 (s, 1H), 7.56 (s, 1H), 7.47 - 7.40 (m, 2H), 7.12 (d, J = 11.4 Hz, 2H), 7.06 (s, 1H), 7.02 (d, J = 12.4 Hz, 1H), 6.93 (s, 1H), 4.70 (d, J = 13.9 Hz, 1H), 4.48 (s, 2H), 4.11 (dd, J = 12.9, 7.8 Hz, 1H), 3.92 - 3.83 (m, 2H), 2.99 - 2.87 (m, 1H), 2.58 (s, 2H), 2.37 - 2.21 (m, 1H), 2.16 (d, J = 15.0 Hz, 1H), 1.92 (dt, J = 24.7, 12.8 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 421.33 $[M+H]^+$。

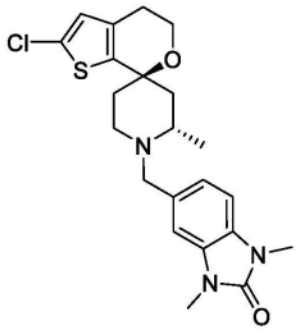
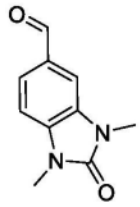
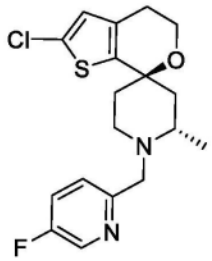
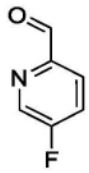
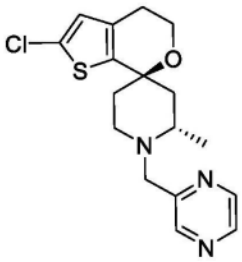
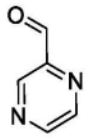
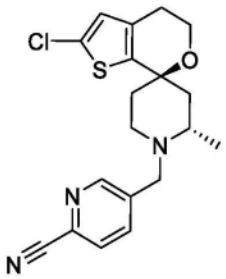
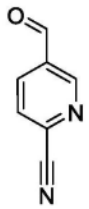
[1247]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
657			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.46 (s, 1H), 7.29 (d, J = 18.9 Hz, 1H), 7.10 (s, 3H), 6.93 (s, 1H), 4.71 - 4.60 (m, 1H), 4.47 (s, 2H), 4.05 (dd, J = 12.8, 7.5 Hz, 1H), 3.89 (dq, J = 12.6, 6.2 Hz, 2H), 3.82 (s, 3H), 3.53 - 3.47 (m, 1H), 3.06 (t, J = 11.6 Hz, 1H), 2.93 (dd, J = 13.1, 7.0 Hz, 1H), 2.58 (s, 2H), 2.30 (d, J = 15.3 Hz, 1H), 2.15 (d, J = 15.0 Hz, 1H), 1.98 - 1.78 (m, 2H), 1.47 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 451.31 [M+H]$^+$。
658			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.67 (s, 1H), 8.49 (s, 2H), 6.93 (s, 1H), 4.60 (d, J = 13.5 Hz, 1H), 4.04 (dd, J = 13.5, 7.0 Hz, 1H), 3.88 (dq, J = 11.9, 5.8 Hz, 3H), 3.74 (d, J = 4.9 Hz, 3H), 3.66 (t, J = 4.6 Hz, 4H), 3.10 (d, J = 20.3 Hz, 2H), 2.58 (t, J = 5.6 Hz, 2H), 2.31 (d, J = 15.2 Hz, 1H), 2.17 (d, J = 14.9 Hz, 1H), 1.90 (t, J = 13.2 Hz, 2H), 1.46 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 435.37 [M+H]$^+$。
659			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.46 (d, J = 1.4 Hz, 1H), 8.41 (s, 1H), 6.92 (s, 1H), 4.71 (d, J = 13.7 Hz, 1H), 4.39 (s, 1H), 3.96 (s, 3H), 3.86 (tq, J = 11.6, 5.8 Hz, 2H), 3.58 (s, 1H), 3.18 (s, 2H), 2.57 (t, J = 5.6 Hz, 2H), 2.27 (d, J = 14.8 Hz, 1H), 2.14 (d, J = 14.8 Hz, 1H), 2.06 - 1.86 (m, 2H), 1.45 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 380.29 [M+H]$^+$。

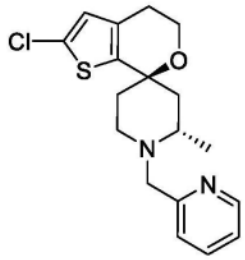
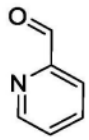
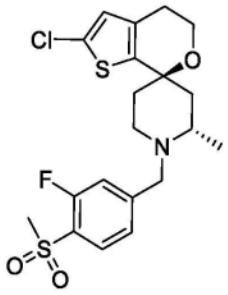
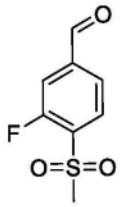
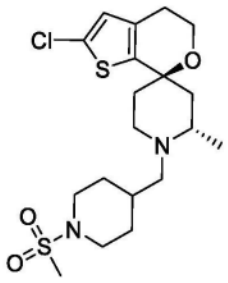
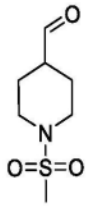
[1248]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
660			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.59 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H), 6.92 (s, 1H), 4.78 (d, J = 12.9 Hz, 1H), 4.19 (dd, J = 13.0, 7.7 Hz, 1H), 3.88 (dp, J = 17.3, 6.0, 5.5 Hz, 3H), 3.56 (s, 1H), 3.00 (s, 4H), 2.90 (s, 3H), 2.58 (s, 2H), 2.46 - 2.24 (m, 1H), 2.16 (d, J = 15.4 Hz, 1H), 2.03 - 1.80 (m, 2H), 1.49 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 419.3 [M+H]$^+$。
661			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.71 (s, 1H), 8.61 (s, 1H), 7.95 (d, J = 9.6 Hz, 1H), 6.93 (s, 1H), 4.85 (d, J = 13.1 Hz, 1H), 4.24 (s, 1H), 3.91 (ddt, J = 18.2, 11.9, 6.2 Hz, 3H), 3.19 (s, 1H), 3.02 (d, J = 17.4 Hz, 1H), 2.58 (d, J = 5.5 Hz, 2H), 2.37 - 2.24 (m, 1H), 2.15 (d, J = 15.4 Hz, 1H), 1.92 (q, J = 15.3, 14.0 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 367.33 [M+H]$^+$。
662			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.31 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.5, 2.5 Hz, 1H), 6.94 (d, J = 11.8 Hz, 2H), 4.70 (d, J = 13.1 Hz, 1H), 4.13 (d, J = 12.8 Hz, 1H), 3.88 (s, 6H), 3.07 (d, J = 25.8 Hz, 2H), 2.57 (d, J = 5.9 Hz, 2H), 2.31 (d, J = 15.0 Hz, 1H), 2.16 (d, J = 15.2 Hz, 1H), 1.91 (q, J = 15.8, 14.9 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 379.34 [M+H]$^+$。
663			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.42 (s, 1H), 7.36 (s, 1H), 7.18 (s, 1H), 7.06 - 7.00 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.92 (s, 1H), 4.74 - 4.63 (m, 1H), 4.47 (s, 2H), 4.03 (dd, J = 12.9, 7.9 Hz, 1H), 4.00 - 3.84 (m, 3H), 3.83 (s, 3H), 2.96 (dd, J = 22.1, 8.7 Hz, 2H), 2.58 (s, 2H), 2.39 -

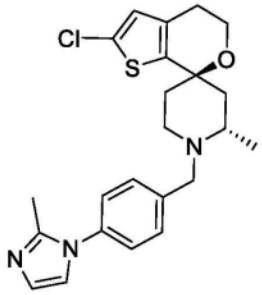
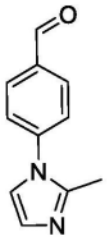
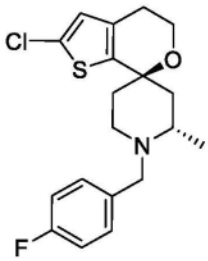
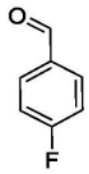
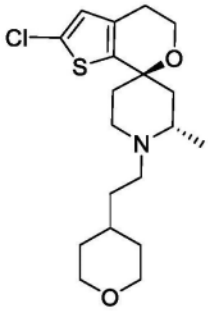
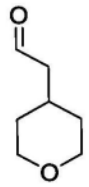
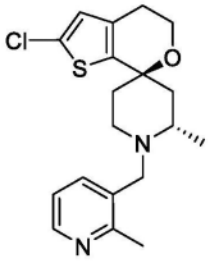
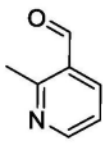
[1249]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
			2.24 (m, 1H), 2.16 (d, J = 14.9 Hz, 1H), 1.93 (dt, J = 26.6, 13.1 Hz, 2H), 1.48 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 451.31 $[M+H]^+$。
664			LCMS *m/z* 432.35 $[M+H]^+$。
665			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.74 (d, J = 3.0 Hz, 1H), 7.91 (t, J = 8.6 Hz, 1H), 7.72 - 7.60 (m, 1H), 6.92 (s, 1H), 4.78 (d, J = 14.0 Hz, 1H), 4.41 (s, 1H), 3.87 (dq, J = 11.9, 5.8 Hz, 2H), 3.60 (s, 1H), 3.18 (d, J = 29.0 Hz, 2H), 2.64 - 2.56 (m, 2H), 2.26 (d, J = 14.6 Hz, 1H), 2.07 (dt, J = 43.7, 15.7 Hz, 3H), 1.42 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 367.29 $[M+H]^+$。
666			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.83 (s, 1H), 8.79 (d, J = 11.4 Hz, 2H), 6.92 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.88 (dq, J = 12.0, 5.8 Hz, 2H), 3.64 (s, 1H), 3.23 (s, 2H), 2.58 (s, 2H), 2.28 (d, J = 15.1 Hz, 1H), 2.21 - 1.92 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 350.31 $[M+H]^+$。
667			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.89 (s, 1H), 8.21 (s, 2H), 6.96 (d, J = 28.7 Hz, 1H), 4.90 (d, J = 8.2 Hz, 1H), 4.29 (s, 1H), 3.89 (d, J = 11.8 Hz, 2H), 3.59 (s, 1H), 3.20 (s, 1H), 2.98 - 2.87 (m, 1H), 2.58 (s, 2H), 2.35 (d, J = 17.1 Hz, 1H), 2.12 (s, 1H),

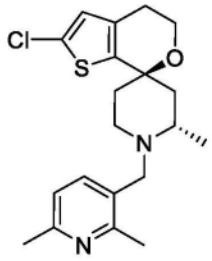
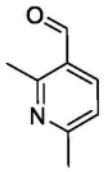
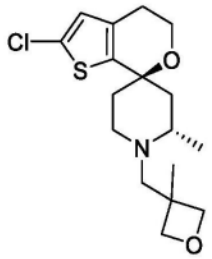
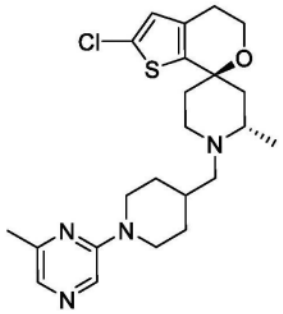
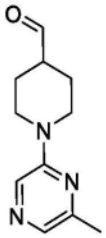
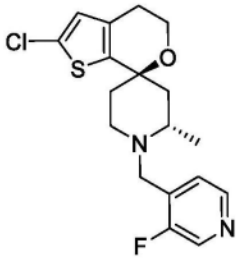
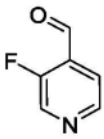
[1250]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
			1.88 (s, 2H), 1.48 (s, 3H)。LCMS *m/z* 374.33 [M+H]$^+$。
668			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.72 (d, J = 4.8 Hz, 1H), 7.95 (td, J = 7.8, 1.8 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.50 (dd, J = 7.6, 4.9 Hz, 1H), 6.92 (s, 1H), 4.79 (d, J = 14.2 Hz, 1H), 4.41 (d, J = 14.3 Hz, 1H), 3.88 (ddq, J = 17.4, 11.6, 5.4 Hz, 2H), 3.64 (s, 1H), 3.25 (s, 1H), 3.19 - 3.09 (m, 1H), 2.60 - 2.56 (m, 2H), 2.25 (dt, J = 14.7, 3.0 Hz, 1H), 2.20 - 1.96 (m, 3H), 1.40 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 349.31 [M+H]$^+$。
669			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.98 (s, 1H), 7.76 (dd, J = 16.3, 8.8 Hz, 1H), 7.62 (s, 1H), 6.92 (s, 1H), 4.88 (s, 1H), 4.25 (s, 1H), 3.88 (dd, J = 15.0, 9.3 Hz, 2H), 3.37 (s, 3H), 3.32 (s, 1H), 3.00 - 2.85 (m, 2H), 2.59 (s, 2H), 2.35 (d, J = 16.5 Hz, 1H), 2.13 (s, 1H), 1.94 (s, 2H), 1.48 (s, 3H)。LCMS *m/z* 444.27 [M+H]$^+$。
670			^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.93 (d, J = 4.4 Hz, 1H), 3.91 (q, J = 5.4 Hz, 2H), 3.69 - 3.57 (m, 2H), 3.56 - 3.49 (m, 1H), 3.29 (d, J = 11.4 Hz, 1H), 3.15 (dd, J = 12.1, 8.4 Hz, 1H), 2.98 (d, J = 13.9 Hz, 1H), 2.87 (s, 3H), 2.69 (d, J = 14.4 Hz, 2H), 2.60 (t, J = 5.4 Hz, 2H), 2.22 (dd, J = 25.4, 14.7 Hz, 2H), 2.15 - 1.87 (m, 4H), 1.74 (d, J = 13.1 Hz, 1H), 1.32 (d, J = 6.2 Hz, 4H), 1.27 (s, 1H)。LCMS *m/z* 433.3 [M+H]$^+$。

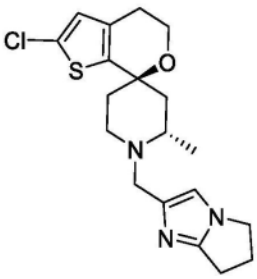
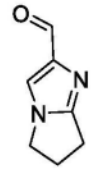
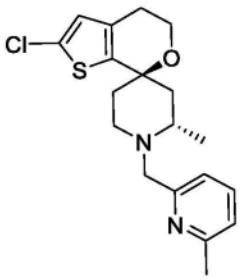
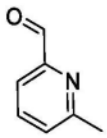
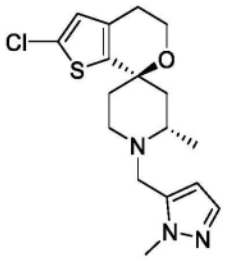
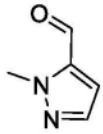
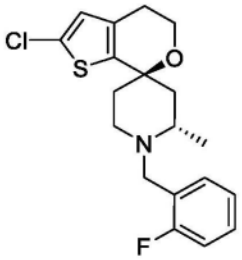
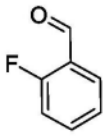
[1251]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
671			LCMS *m/z* 428.33 $[M+H]^+$。
672			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.59 - 7.50 (m, 2H), 7.34 (t, J = 8.6 Hz, 2H), 6.92 (s, 1H), 4.73 (d, J = 12.9 Hz, 1H), 4.32 - 3.98 (m, 1H), 3.88 (dtd, J = 17.4, 11.5, 5.4 Hz, 2H), 3.52 (s, 1H), 3.12 (d, J = 12.2 Hz, 1H), 3.03 - 2.87 (m, 1H), 2.59 (d, J = 6.0 Hz, 2H), 2.31 (d, J = 15.2 Hz, 1H), 2.16 (d, J = 15.5 Hz, 1H), 1.91 (dt, J = 25.7, 13.7 Hz, 2H), 1.48 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 366.29 $[M+H]^+$。
673			^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.94 (s, 1H), 3.90 (q, J = 5.4 Hz, 2H), 3.86 - 3.82 (m, 2H), 3.44 (d, J = 12.4 Hz, 1H), 3.27 (dd, J = 13.3, 10.5 Hz, 4H), 3.19 (d, J = 11.3 Hz, 1H), 3.15 - 3.03 (m, 1H), 2.59 (t, J = 5.5 Hz, 2H), 2.30 - 2.18 (m, 2H), 2.00 (t, J = 12.3 Hz, 1H), 1.94 - 1.81 (m, 1H), 1.58 (t, J = 13.9 Hz, 5H), 1.29 (d, J = 6.3 Hz, 3H), 1.26 - 1.19 (m, 2H)。LCMS *m/z* 370.35 $[M+H]^+$。
674			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.58 (d, J = 5.0 Hz, 1H), 7.99 (s, 1H), 7.44 (s, 1H), 6.93 (s, 1H), 4.83 (d, J = 13.3 Hz, 1H), 4.24 (s, 1H), 3.93 (dd, J = 14.0, 5.9 Hz, 2H), 3.74 (s, 1H), 3.01 (d, J = 9.5 Hz, 1H), 2.93 (q, J = 6.6 Hz, 1H), 2.65 (s, 3H), 2.61 - 2.57 (m, 2H), 2.38 - 2.27 (m, 1H), 2.13 (d, J = 14.9 Hz, 1H), 1.95 (dt, J = 29.4, 13.1 Hz, 2H),

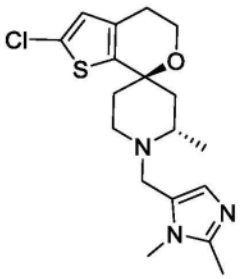
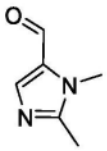
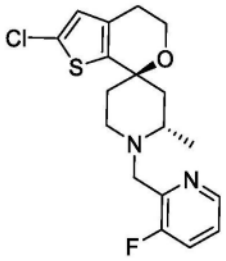
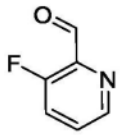
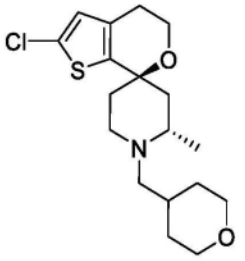
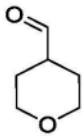
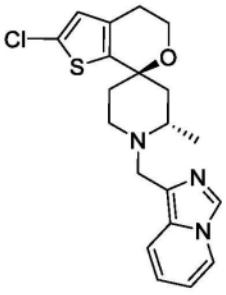
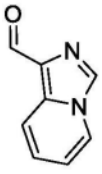
[1252]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
			1.51 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 363.31 [M+H]$^+$。
675			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.98 (s, 1H), 7.39 (s, 1H), 6.93 (s, 1H), 4.79 (s, 1H), 4.23 (s, 1H), 3.92 (dq, J = 17.9, 6.0 Hz, 5H), 3.73 (s, 1H), 3.23 (s, 1H), 3.00 (s, 1H), 2.64 (s, 3H), 2.60 (s, 2H), 2.30 (s, 1H), 2.12 (d, J = 15.0 Hz, 1H), 2.07 - 1.80 (m, 2H), 1.50 (s, 3H)。LCMS *m/z* 377.35 [M+H]$^+$。
676			^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.93 (d, J = 1.8 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 4.39 (d, J = 6.2 Hz, 1H), 4.27 (d, J = 5.9 Hz, 1H), 4.19 (d, J = 6.2 Hz, 1H), 3.91 (d, J = 7.0 Hz, 3H), 3.22 (d, J = 10.8 Hz, 1H), 2.88 (d, J = 13.7 Hz, 1H), 2.59 (s, 2H), 2.11 (ddd, J = 58.3, 31.1, 14.8 Hz, 5H), 1.49 (s, 3H), 1.31 (d, J = 6.4 Hz, 3H)。LCMS *m/z* 342.32 [M+H]$^+$。
677			LCMS *m/z* 447.38 [M+H]$^+$。
678			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.74 (s, 1H), 8.56 (s, 1H), 7.68 (s, 1H), 6.92 (s, 1H), 3.90 (d, J = 5.7 Hz, 2H), 3.11 (s, 2H), 2.98 - 2.84 (m, 1H), 2.57 (d, J = 5.7 Hz, 2H), 2.13 (s, 2H), 1.92 (s, 2H), 1.44 (s, 2H), 1.16 (t, J = 7.2 Hz, 3H)。LCMS *m/z* 367.29 [M+H]$^+$。

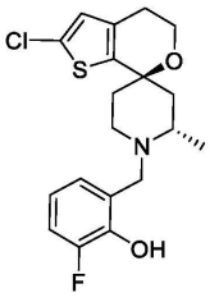
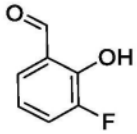
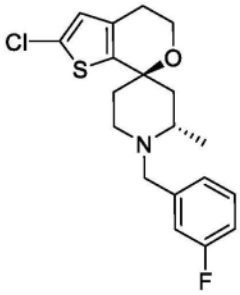
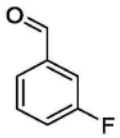
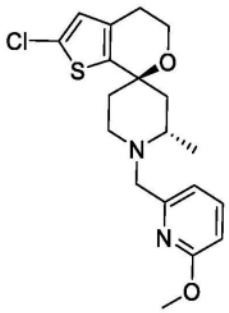
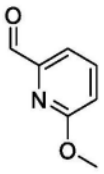
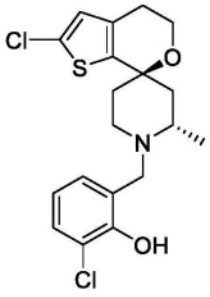
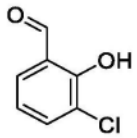
[1253]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
679			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.46 (s, 1H), 6.92 (s, 1H), 4.45 (d, J = 14.2 Hz, 1H), 4.22 (d, J = 14.2 Hz, 1H), 4.05 (d, J = 7.1 Hz, 2H), 3.87 (dd, J = 11.8, 6.0 Hz, 2H), 3.42 (s, 1H), 3.28 (s, 1H), 3.16 (t, J = 12.8 Hz, 1H), 2.86 (t, J = 7.7 Hz, 2H), 2.63 - 2.55 (m, 4H), 2.22 (dd, J = 27.8, 15.0 Hz, 2H), 2.02 - 1.86 (m, 2H), 1.42 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 378.35 $[M+H]^+$。
680			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.05 - 9.45 (m, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.37 (dd, J = 12.4, 7.7 Hz, 2H), 6.93 (s, 1H), 4.71 (d, J = 13.8 Hz, 1H), 4.34 (d, J = 13.8 Hz, 1H), 4.00 - 3.84 (m, 2H), 3.26 (t, J = 12.7 Hz, 1H), 3.12 (d, J = 12.4 Hz, 1H), 2.58 (s, 2H), 2.56 (s, 3H), 2.25 (d, J = 14.7 Hz, 1H), 2.20 - 1.94 (m, 3H), 1.41 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 363.36 $[M+H]^+$。
681			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.50 (d, J = 1.9 Hz, 1H), 6.91 (s, 1H), 6.63 (d, J = 1.9 Hz, 1H), 4.75 (d, J = 14.4 Hz, 1H), 4.32 (dd, J = 14.6, 7.9 Hz, 1H), 3.96 (s, 3H), 3.88 (dp, J = 17.3, 5.8 Hz, 2H), 3.60 (s, 1H), 3.09 (d, J = 23.4 Hz, 2H), 2.58 (s, 2H), 2.36 - 2.09 (m, 4H), 1.51 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 352.34 $[M+H]^+$。
682			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.51 (s, 1H), 7.66 - 7.58 (m, 2H), 7.39 - 7.28 (m, 2H), 6.93 (s, 1H), 4.77 (d, J = 13.4 Hz, 1H), 4.24 (s, 1H), 3.90 (dtd, J = 17.6, 11.6, 5.5 Hz, 2H), 3.63 (s, 1H), 3.19 (s, 1H), 3.07 (s, 1H), 2.59 (d, J = 5.9 Hz, 2H), 2.30 (d, J = 16.1 Hz, 1H), 2.16 (d, J =

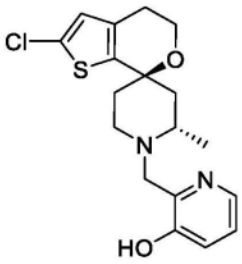
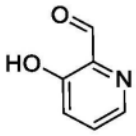
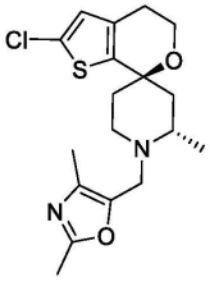
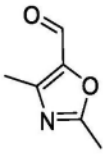
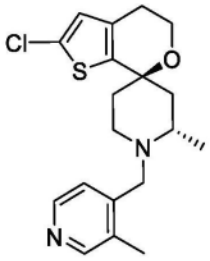
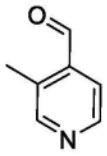
[1254]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
			14.9 Hz, 1H), 1.94 (d, J = 15.4 Hz, 2H), 1.48 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 366.34 $[M+H]^+$。
683			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.70 (s, 1H), 6.92 (s, 1H), 3.90 (d, J = 7.8 Hz, 4H), 3.74 (s, 4H), 2.98 - 2.81 (m, 1H), 2.58 (s, 6H), 2.01 (d, J = 70.4 Hz, 4H), 1.41 (s, 3H)。LCMS *m/z* 366.34 $[M+H]^+$。
684			LCMS *m/z* 367.33 $[M+H]^+$。
685			^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.93 (d, J = 4.4 Hz, 1H), 3.96 - 3.81 (m, 4H), 3.55 (s, 1H), 3.32 (ddd, J = 12.1, 9.7, 5.3 Hz, 3H), 3.24 (d, J = 10.7 Hz, 1H), 3.16 (q, J = 11.5 Hz, 1H), 2.97 - 2.88 (m, 1H), 2.59 (t, J = 5.4 Hz, 2H), 2.22 (dd, J = 27.0, 14.8 Hz, 2H), 2.02 (dt, J = 36.1, 13.1 Hz, 3H), 1.75 (d, J = 12.9 Hz, 1H), 1.54 (d, J = 13.1 Hz, 1H), 1.31 (d, J = 6.4 Hz, 3H), 1.29 - 1.19 (m, 2H)。LCMS *m/z* 356.36 $[M+H]^+$。
686			LCMS *m/z* 388.33 $[M+H]^+$。

[1255]

化合物	结构	醛	^{1}H NMR；LCMS m/z [M+H]$^+$。
687			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.63 (s, 1H), 9.14 (s, 1H), 7.31 (t, J = 9.6 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 5.4 Hz, 2H), 4.68 (d, J = 13.1 Hz, 1H), 4.10 (d, J = 13.1 Hz, 1H), 3.89 (dp, J = 17.2, 5.9, 5.4 Hz, 2H), 3.58 (s, 1H), 3.12 (d, J = 33.2 Hz, 2H), 2.58 (d, J = 5.9 Hz, 2H), 2.26 (d, J = 14.8 Hz, 1H), 2.13 (d, J = 14.7 Hz, 1H), 1.99 (t, J = 14.2 Hz, 2H), 1.47 (d, J = 6.2 Hz, 3H)。LCMS *m/z* 382.28 [M+H]$^+$。
688			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.59 - 7.50 (m, 1H), 7.37 (td, J = 20.0, 9.6 Hz, 3H), 6.92 (s, 1H), 4.77 (d, J = 13.0 Hz, 1H), 4.16 (s, 1H), 3.88 (dp, J = 17.3, 5.9 Hz, 2H), 3.54 (s, 1H), 3.14 (s, 1H), 3.00 (s, 1H), 2.59 (d, J = 5.9 Hz, 2H), 2.31 (d, J = 15.3 Hz, 1H), 2.15 (d, J = 15.4 Hz, 1H), 1.94 (dd, J = 24.6, 12.9 Hz, 2H), 1.48 (s, 3H)。LCMS *m/z* 366.34 [M+H]$^+$。
689			^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.83 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 6.96 - 6.82 (m, 2H), 4.59 (d, J = 13.9 Hz, 1H), 4.43 (s, 1H), 3.91 (s, 3H), 3.87 (q, J = 5.9 Hz, 2H), 3.67 (s, 1H), 2.58 (d, J = 5.8 Hz, 2H), 2.24 (dd, J = 28.5, 14.8 Hz, 2H), 2.00 (d, J = 15.4 Hz, 2H), 1.44 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 379.34 [M+H]$^+$。
690			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.29 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 6.92 (s, 1H), 4.69 (s, 1H), 4.09 (s, 1H), 3.89 (dp, J = 17.3, 5.9 Hz, 2H), 3.42 (d, J = 41.8 Hz, 2H), 3.15 (s, 1H), 3.00 (s, 1H),

[1256]

化合物	结构	醛	^{1}H NMR；LCMS m/z $[M+H]^+$。
			2.58 (d, J = 6.5 Hz, 2H), 2.25 (d, J = 14.8 Hz, 1H), 2.12 (d, J = 14.8 Hz, 1H), 1.98 (t, J = 13.4 Hz, 2H), 1.53 - 1.37 (m, 3H)。LCMS *m/z* 398.26 $[M+H]^+$。
691			^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.85 (s, 1H), 8.16 (dd, J = 3.9, 2.1 Hz, 1H), 7.39 - 7.31 (m, 2H), 6.92 (s, 1H), 4.64 (d, J = 14.5 Hz, 1H), 4.36 (d, J = 14.4 Hz, 1H), 3.89 (qt, J = 11.6, 5.5 Hz, 2H), 3.71 (s, 1H), 3.27 (d, J = 8.1 Hz, 2H), 2.58 (t, J = 5.6 Hz, 2H), 2.28 - 2.00 (m, 4H), 1.38 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 365.34 $[M+H]^+$。
692			^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.96 (s, 1H), 6.93 (s, 1H), 4.65 (d, J = 15.0 Hz, 1H), 4.47 (d, J = 15.3 Hz, 1H), 3.87 (dt, J = 12.4, 5.8 Hz, 2H), 3.24 (d, J = 12.2 Hz, 1H), 3.11 (s, 1H), 2.61 - 2.56 (m, 2H), 2.40 (s, 3H), 2.25 (dd, J = 29.2, 14.9 Hz, 2H), 2.14 (s, 3H), 1.93 (q, J = 13.7, 13.1 Hz, 2H), 1.42 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 367.33 $[M+H]^+$。
693			^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.56 (d, J = 11.6 Hz, 2H), 7.56 (s, 1H), 6.93 (s, 1H), 4.79 (s, 1H), 4.25 (s, 1H), 3.94 - 3.89 (m, 3H), 3.25 (s, 1H), 2.93 (q, J = 6.8 Hz, 1H), 2.60 (s, 2H), 2.42 (s, 3H), 2.38 - 2.20 (m, 1H), 2.04 (d, J = 50.1 Hz, 3H), 1.48 (s, 3H)。LCMS *m/z* 363.31 $[M+H]^+$。

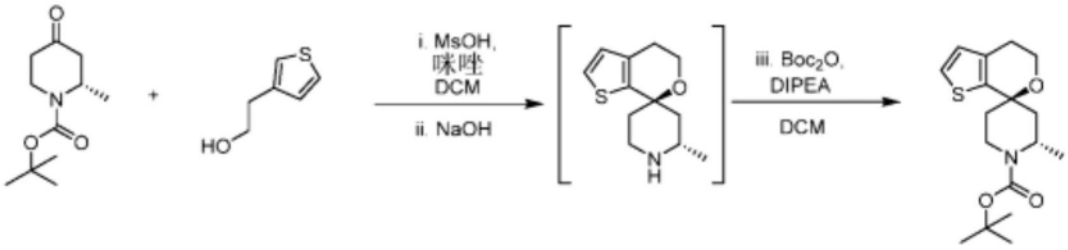
[1257] 脚注

[1258] 1.第二步:使用含HCl的甲醇对TBS基团进行脱保护

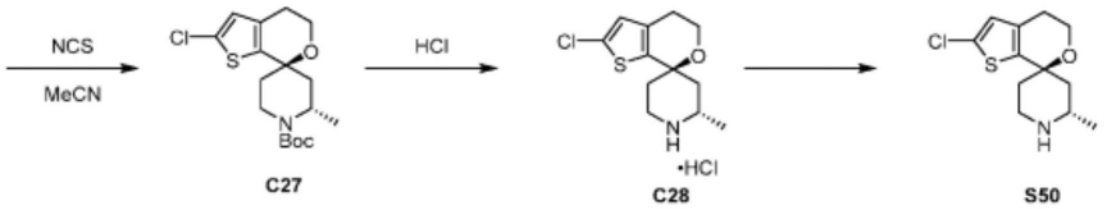
[1259] 2.第二步:SnAr使用环丙胺(2.5当量)、含碳酸钾(4当量)的DMF(0.5mL)在90℃下过夜。将反应物在DCM和水中稀释,并将水层通过相分离器收集。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有5mM HCl,随后通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有10mM氢氧化铵,产生产物。

[1260] S50的制备

[1261] (2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S50)



[1262]



[1263] 步骤1(i):(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯的合成

[1264] 向(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(25g,117.2mmol)于DCM(500mL)中的混合物中添加MsOH(24mL,369.8mmol),并将混合物在室温下搅拌40分钟。将混合物真空-氮气吹扫五次以去除溶解的异丁烯。

[1265] 步骤1(ii):(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]的合成

[1266] 然后向混合物中添加2-(3-噻吩基)乙醇(16.5g,128.7mmol),并将反应物搅拌过夜。将混合物浓缩至约50mL,并用水(300mL)和二乙醚(600mL)重新稀释。去除有机层。将水层用NaOH水溶液(64mL的6M,384.0mmol)调节至pH 14,并且然后添加DCM(600mL)以萃取游离碱。将有机层用pH 14水(2×200mL)、pH 14盐水(200mL)洗涤,用$MgSO_4$干燥,过滤并浓缩以产生(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](24900mg,95%)。LCMS m/z 224.54$[M+H]^+$。

[1267] 步骤1(iii):(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C26)的合成

[1268] 向来自前两步产物的于DCM(500mL)中的混合物中添加DIPEA(20mL,114.8mmol),随后添加Boc_2O(27mL,117.5mmol)。将反应物搅拌45分钟。添加咪唑(1g,14.69mmol)以淬灭过量Boc_2O。然后添加2N HCl(100mL),并将混合物搅拌20分钟。分离各层,并将有机层用1N HCl(100mL)洗涤。使有机层通过相分离器,并浓缩以产生呈黄色油的(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(37300mg,91%)。LCMS m/z 323.11$[M+H]^+$。

[1269] 步骤2:(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C27)的合成

[1270] 将(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C26(16g,49.47mmol)溶解在乙腈(150mL)中,并添加NCS(13.2g,98.85mmol)。将反应物在65℃下加热并搅拌过夜。将反应物用1NNaOH/EtOAc稀释,用硫代硫酸钠溶液和盐水洗涤并经Na_2SO_4干燥并浓缩成油。通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),产生产物。(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯

(15.4g,83%)。LCMS m/z 358.14[M+H]$^+$。

[1271] 步骤3:(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(C28)的合成

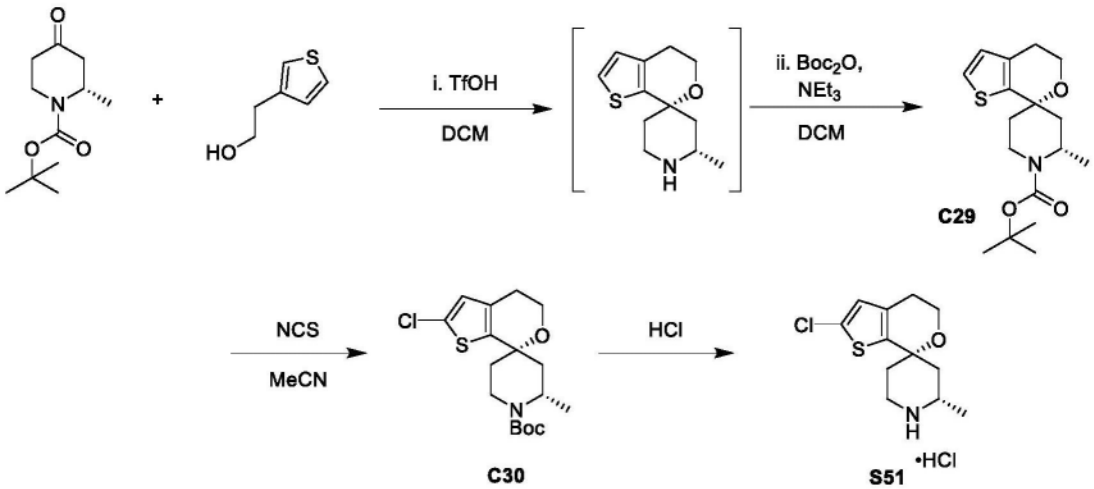
[1272] 在室温下将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(9500mg,26.37mmol)于含HCl(25mL的4M,100.0mmol)的二噁烷中的溶液中的混合物搅拌过夜。搅拌过夜后,混合物凝结成固体团块。向混合物中添加二乙醚(总计200mL),将混合物过滤并用另外的醚冲洗并干燥以产生(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(C28)(7.4757g,94%)。^{1}H NMR(400MHz,DMSO-d6)δ9.25-8.93(m,2H),6.92(s,1H),3.96-3.81(m,2H),3.38-3.26(m,1H),3.23-3.12(m,1H),3.04(q,J=12.2Hz,1H),2.58(t,J=5.5Hz,2H),2.13(t,J=15.0Hz,2H),2.01(td,J=14.1,13.7,4.6Hz,1H),1.84(dd,J=14.3,12.1Hz,1H),1.25(d,J=6.5Hz,3H)。LCMS m/z 258.09[M+H]$^+$。

[1273] 步骤4:(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S50)的合成

[1274] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](2.70g)溶解在水中,并向混合物中添加饱和碳酸氢钠,随后通过NaOH调节至pH>10。此时,将产物油出并溶解在DCM(10mL)中,并将水层用另外的DCM(10mL)萃取。将合并的有机层经Na_2SO_4干燥,过滤并浓缩以产生(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(2280mg,93%)。^{1}H NMR(400MHz,氯仿-d)δ6.57(s,1H),3.98-3.81(m,2H),3.18-3.00(m,2H),2.94(ddd,J=12.2,4.8,2.1Hz,1H),2.67-2.51(m,2H),2.07-1.94(m,2H),1.66(d,J=4.8Hz,1H),1.38(dd,J=13.7,11.4Hz,1H),1.09(d,J=6.4Hz,3H)。LCMS m/z 258.09[M+H]$^+$。

[1275] S51的制备(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S51)的制备

[1276]



[1277] 步骤1(i):(2′S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]的合成

[1278] 将2-(3-噻吩基)乙醇(1.275g,9.946mmol)和(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(2.217g,10.40mmol)于DCM(18mL)中的溶液冷却至-78℃。向反应物中添加三氟甲磺酸(1.5mL,16.95mmol)并将反应物在-78℃下搅拌1.5小时。将反应物淬灭到饱和NaHCO3

(75mL)和DCM(50mL)的双相混合物中,并使用2N NaOH将水层pH调节至>10。然后将水层用DCM(3×75mL)萃取,并通过SPE筒过滤,并浓缩以产生粗产物(2′S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]。

[1279] 步骤1(ii):(2′S,7S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C29)的合成

[1280] 将来自先前步骤的粗产物溶解在DCM(20mL)中,并添加三乙胺(3.1mL,22.24mmol),随后添加碳酸叔丁氧基羰基叔丁酯(3.1mL,13.49mmol)。将反应物在室温下搅拌18小时。将溶液用DCM稀释并且用水(50mL)洗涤。将水层用DCM(2×50mL)萃取,经Na_2SO_4干燥,通过SPE过滤器过滤,并在真空下浓缩。通过硅胶色谱法纯化(含0至30% EtOAc的庚烷),产生(2′S,7S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C29(2.95g,92%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.21(d,J=5.1Hz,1H),6.77(d,J=5.1Hz,1H),4.37(p,J=7.0Hz,1H),4.03-3.84(m,3H),3.39-3.21(m,1H),2.68(td,J=5.5,2.6Hz,2H),2.16-1.65(m,4H),1.48(s,9H),1.34(d,J=7.2Hz,3H)。

[1281] 步骤2:(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C30)的合成

[1282] 在室温下向(2′S,7S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C29(239mg,0.7389mmol)于MeCN(3mL)中的溶液中添加NCS(138mg,1.033mmol),随后添加DMAP(5mg,0.04093mmol)。将反应物加热至55℃,持续24小时。将反应物冷却至rt并搅拌过夜,然后将反应物用15%亚硫酸氢钠水溶液(10mL)淬灭。搅拌15分钟,然后在盐水(20mL)与DCM(20mL)之间分配。将水层分离并用DCM(2×20mL)萃取,将合并的有机层经Na_2SO_4干燥,通过相分离器过滤并浓缩。通过硅胶色谱法纯化(含0至30% EtOAc的庚烷),得到粗混合物,剩余一些起始材料。

[1283] 通过将粗材料溶解在MeCN(2.5mL)中并添加N-氯代琥珀酰亚胺(50mg,0.3744mmol)和DMAP(5mg,0.04093mmol),使粗材料再次经受反应条件。将反应物加热至60℃,持续6小时,然后冷却至室温并用15%亚硫酸氢钠水溶液(10mL)淬灭。搅拌15分钟,然后在盐水与DCM(各20mL)之间分配。将水层分离并用DCM(2×20mL)萃取,将合并的有机层经Na_2SO_4干燥,通过相分离器过滤并浓缩。通过硅胶色谱法纯化(含0至30% EtOAc的庚烷),以得到(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C30(170mg,63%)。^{1}H NMR(300MHz,甲醇-d_4)δ6.66(s,1H),4.35(q,J=6.9Hz,1H),4.03-3.85(m,3H),3.27(s,1H),2.69-2.50(m,2H),2.14-1.94(m,2H),1.80(dd,J=14.5,6.6Hz,1H),1.68(ddd,J=13.7,12.9,4.7Hz,1H),1.47(s,9H),1.32(d,J=7.1Hz,3H)。

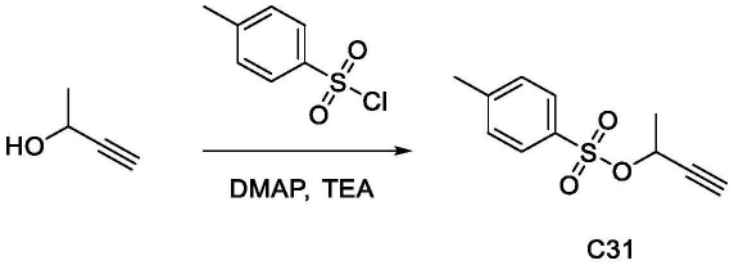
[1284] 步骤3:(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S51)的合成

[1285] 向(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C30(170mg,0.4750mmol)于二噁烷(2mL)中的经搅拌的溶液中添加含HCl(600μL的4M,2.400mmol)的二噁烷并将反应物在室温下搅拌20小时。将反应浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl并冻干,得到产物(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S51(盐酸盐)(108.2mg,75%)。^{1}H NMR(300MHz,甲醇-d_4)δ6.77(s,1H),3.98(t,J=5.8Hz,2H),

3.72(h,J＝6.3Hz,1H),3.53(ddd,J＝13.8,9.7,4.0Hz,1H),3.29-3.16(m,1H),2.70-2.60(m,2H),2.25-2.05(m,4H),1.52(d,J＝7.0Hz,3H)。LCMS m/z 258.0[M+H]$^+$。

[1286] C31的制备

[1287] 4-甲基苯磺酸1-甲基丙-2-炔酯(C31)

[1288] 

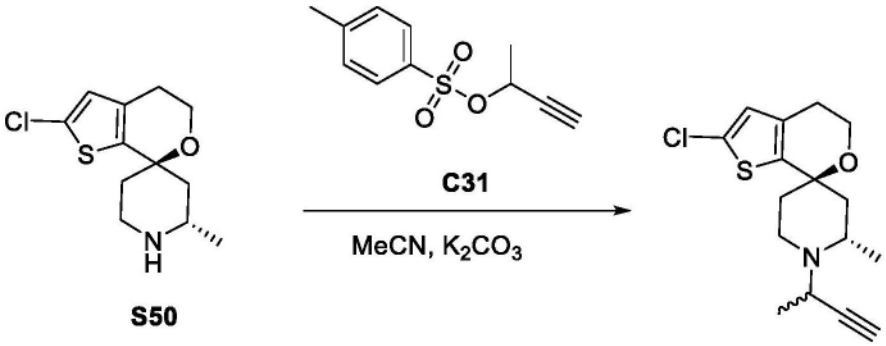
C31

[1289] 4-甲基苯磺酸1-甲基丙-2-炔酯(C31)的合成

[1290] 在0℃下向丁-3-炔-2-醇(1.5g,0.0214mol)于DCM(15mL)中的经搅拌的溶液中添加DMAP(1g,0.0082mol)、TEA(726.00mg,1mL,0.0072mol)和4-甲基苯磺酰氯(0.45g,0.0024mol)。将反应混合物在0℃下搅拌30分钟并在室温下搅拌1小时。然后,将反应混合物过滤。将滤液用饱和$CuSO_4$溶液(200mL)、饱和$NaHCO_3$溶液(200mL)和盐水(200mL)洗涤。将有机层经Na_2SO_4干燥并在减压下浓缩。通过硅胶色谱法纯化(梯度:含10-30% EtOAc的石油醚),得到4-甲基苯磺酸1-甲基丙-2-炔酯C31(1.2g,25%)。^{1}H NMR(400MHz,氯仿-d)δppm 7.83-7.80(m,2H),7.34-7.26(m,2H),5.19-5.13(m,1H),2.44-2.41(m,4H),1.58-1.56(m,3H)。

[1291] 化合物694

[1292] (2′S,7R)-2-氯-2′-甲基-1′-(1-甲基丙-2-炔基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](694)

[1293] 

S50

694

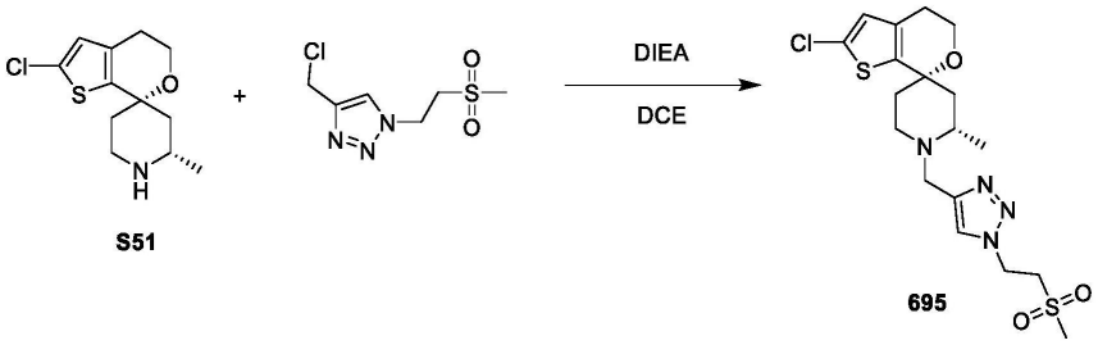
[1294] (2′S,7R)-2-氯-2′-甲基-1′-(1-甲基丙-2-炔基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](694)的制备

[1295] 在室温下向(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸(1))(S50)(500mg,0.0012mol)于MeCN(10mL)中的经搅拌的溶液中添加K_2CO_3(415mg,0.0030mol)和4-甲基苯磺酸1-甲基丙-2-炔酯(C31)(403mg,0.0018mol)。将反应混合物在80℃下搅拌16小时。将反应混合物冷却至室温并在减压下浓缩。将反应混合物冷却至室温,并用水(50ml)淬灭,并用EtOAc(2×100mL)萃取。将合并的有机层经$_2SO_4$干燥,过滤并在减压下浓缩。通过硅胶色谱法纯化(含0-30% EtOAc的己烷),随后通过反相色谱法纯

化(柱:-xselectPhenyl hexyle(250*19)mm,5u,.梯度:含0-20% MeCN的水,具有0.1%甲酸),得到(2′S,7R)-2-氯-2′-甲基-1′-(1-甲基丙-2-炔基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]694(28mg,8%)。^{1}H NMR(400MHz,DMSO-d6)δppm 6.84(s,1H),3.99-3.96(m,1H),3.86-3.82(m,2H),3.11-3.11(m,1H),2.93-2.90(m,1H),2.69-2.67(m,1H),2.58-2.49(m,2H),2.01-1.90(m,2H),1.64-1.62(m,1H),1.44-1.38(m,1H),1.11(d,J=6.8Hz,3H),0.98(d,J=6.4Hz,3H)。LCMS m/z 310.0[M+H]$^+$。

[1296] 化合物695

[1297] (2′S,7S)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](695)

[1298] 

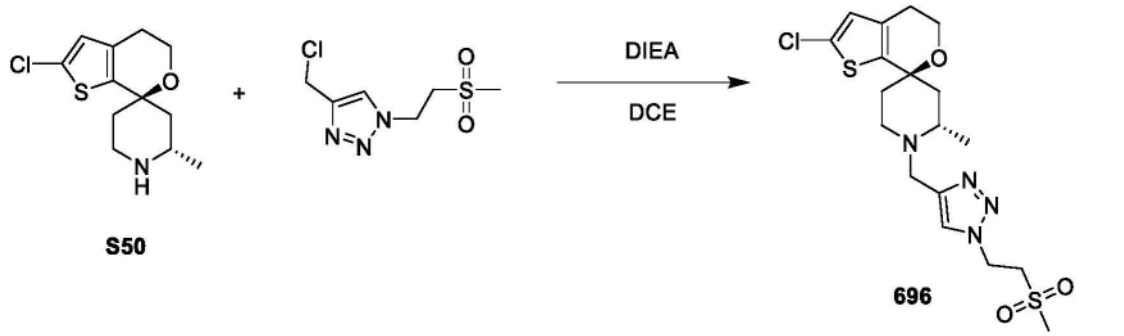
S51 695

[1299] (2′S,7S)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](695)的制备

[1300] 将(2′S,7S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](35mg,0.1358mmol)(S51)溶解在DCE(1mL)中,并添加DIEA(50μL,0.2871mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(34mg,0.1520mmol)。将反应混合物在密封的管中在60℃下加热过夜。添加另外的4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(10mg,0.04471mmol)并将反应物在60℃下加热过夜。将反应混合物浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7S)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](695)。(三氟乙酸盐)(32mg,41%)。^{1}H NMR(300MHz,氯仿-d)δ8.26(s,1H),6.60(s,1H),4.94(t,J=6.8Hz,2H),4.41(d,J=19.1Hz,2H),3.93(t,J=5.1Hz,2H),3.81-3.65(m,3H),3.56-3.37(m,2H),2.95(s,3H),2.69-2.58(m,2H),2.38-2.09(m,4H),1.70(d,J=7.1Hz,3H)。LCMS m/z 445.31[M+H]$^+$。

[1301] 化合物696

[1302] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](696)

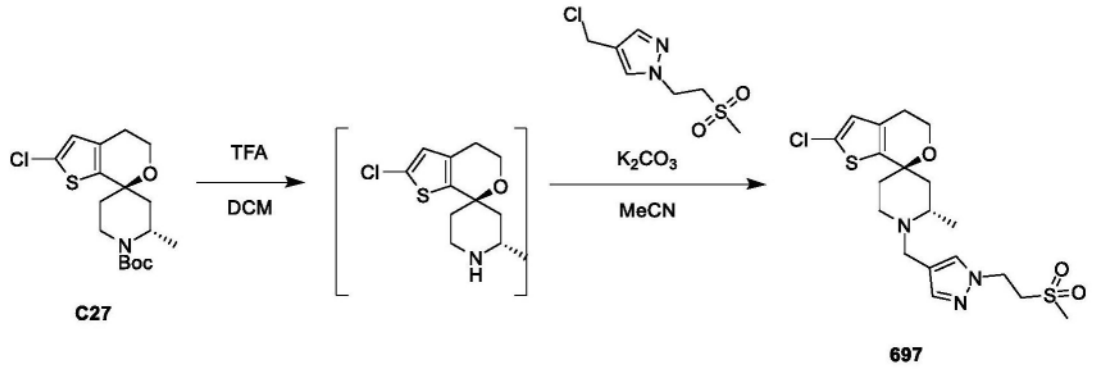
[1303] 

[1304] 2′S)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](696)的合成

[1305] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](48mg,0.1862mmol)溶解在DCE(1mL)中,并添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(45mg,0.2012mmol)和DIEA(65μL,0.3732mmol)。将反应混合物在密封管中加热至60℃过夜。添加另外的4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(15mg,0.06706mmol)并继续加热24小时。将反应混合物浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(696)(46mg,43%)。^{1}H NMR(300MHz,氯仿-d)δ8.28(s,1H),6.61(s,1H),4.97(td,J=6.6,4.0Hz,2H),4.78(d,J=14.0Hz,1H),4.26(d,J=14.0Hz,1H),3.97-3.65(m,4H),3.65-3.55(m,1H),3.40-3.18(m,2H),2.95(s,3H),2.69-2.56(m,2H),2.28-2.09(m,4H),1.62(d,J=6.5Hz,3H)。LCMS m/z 445.21$[M+H]^+$。

[1306] 化合物697

[1307] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](697)

[1308] 

[1309] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](697)的制备

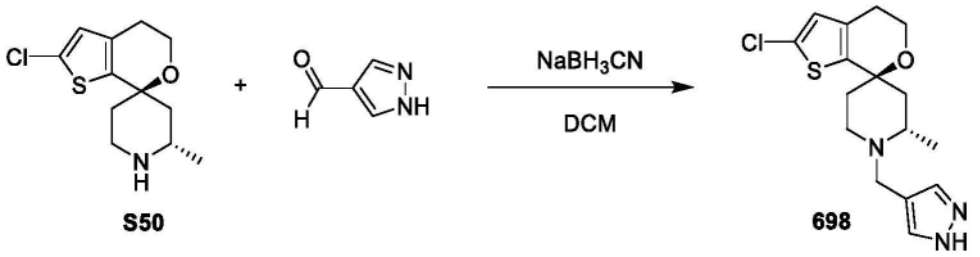
[1310] i.向(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(65mg,0.1780mmol)于DCM(1mL)中的溶液中添加TFA(200μL,2.596mmol),并将混合物回流5分钟。此时,UPLC显示完全转化,并将混合物浓缩至干燥,在DCM中稀释并再次浓缩。

[1311] ii.将来自第一步骤的油用乙腈(1.5mL)稀释,并添加K_2CO_3(75mg,0.5427mmol),随

后添加4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(盐酸盐)(90mg,0.3473mmol)。将混合物在70℃下搅拌。将混合物搅拌过夜。将混合物冷却至室温,并用水(10mL)和EtOAc(15mL)稀释。分离各相,并将有机层用水(2×10mL)和盐水(10mL)洗涤,并将有机层用$MgSO_4$干燥,过滤并浓缩。通过硅胶色谱法纯化(含0-20% MeOH的DCM)。得到(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](697)(41.6mg,51%)。^{1}H NMR(400MHz,氯仿-d)δ7.51(d,J=0.7Hz,1H),7.47(s,1H),6.57(s,1H),4.64-4.56(m,2H),3.89-3.75(m,3H),3.71-3.59(m,3H),2.69-2.43(m,8H),2.00(tt,J=14.2,2.9Hz,2H),1.82(td,J=13.3,4.6Hz,1H),1.62(dd,J=13.8,11.4Hz,1H),1.20(d,J=6.2Hz,3H)。LCMS m/z 444.04$[M+H]^+$。

[1312] 化合物698

[1313] (2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](698)

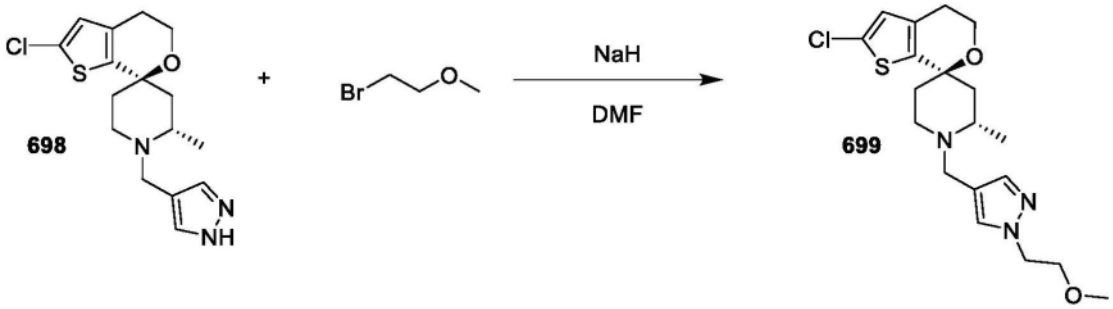
[1314] 

[1315] (2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](698)的制备

[1316] 将1H-吡唑-4-甲醛(150mg,1.561mmol)、(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(三氟甲烷磺酸盐)(350mg,0.8603mmol)、氰基硼氢化物(钠盐)(1000mg的2mmol/g,2.000mmol)于DCM(10mL)中的混合物在110℃下搅拌。将混合物冷却至室温,过滤并在减压下浓缩。通过硅胶色谱法纯化(含0-20% MeOH的DCM),以得到产物。(2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](72mg,25%)。^{1}H NMR(400MHz,氯仿-d)δ7.56(s,2H),6.50(s,1H),4.05(s,1H),3.88-3.71(m,3H),3.70-3.57(m,1H),2.82(s,2H),2.66-2.47(m,4H),2.01-1.91(m,3H),1.28(d,J=6.3Hz,3H)。LCMS m/z 337.88$[M+H]^+$。

[1317] 化合物699

[1318] (2S,7R)-2′-氯-1-((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](699)

[1319] 

[1320] (2S,7R)-2′-氯-1-((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)-2-甲基-4′,5′-二

氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](699)的制备

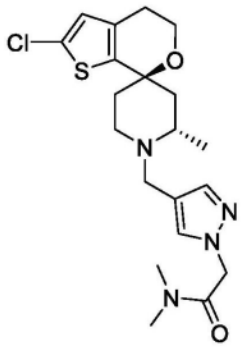
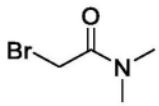
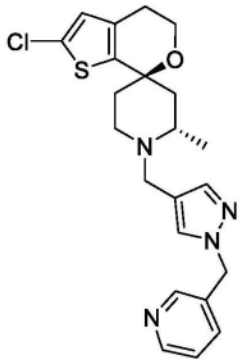
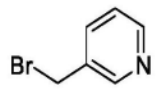
[1321] 向(2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]698(20mg)于DMF(1mL)中的混合物中添加NaH(3mg,60%w/w),随后添加1-溴-2-甲氧基-乙烷(16mL)。将反应物在室温下搅拌80分钟,并且然后加热至60℃并搅拌5小时。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl,得到产物(HCl盐)EA#6(18.8mg,73.3%)。^{1}H NMR(400MHz,DMSO-d6)δ 10.94(s,1H),7.95(s,1H),7.65(s,1H),6.91(s,1H),4.35(d,J=14.3Hz,1H),4.28(t,J=5.3Hz,2H),4.18(dd,J=14.0,5.3Hz,1H),3.82(hept,J=6.0Hz,2H),3.68(t,J=5.2Hz,2H),3.21(s,5H),3.16(d,J=14.3Hz,1H),2.98(d,J=15.3Hz,1H),2.56(s,1H),2.18(q,J=14.1,13.1Hz,4H),1.45(d,J=6.3Hz,3H)。LCMS m/z 396.14$[M+H]^+$。

[1322] 化合物700-707

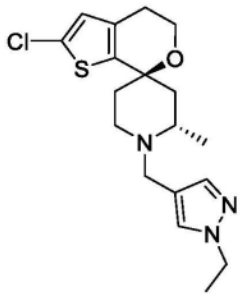
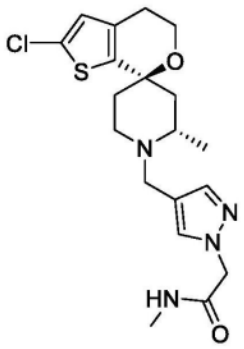
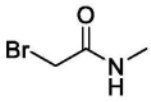
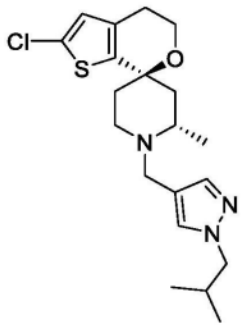
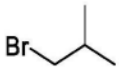
[1323] 化合物700-707(参见表30)由698的烷基化和相关烷基卤化物在单个步骤中制备,如化合物699所述。烷基卤化物从商业来源获得。表30和随附脚注中注明了对方法的任何修改。

[1324] 表30:化合物700-707的制备方法、结构和生理化学数据

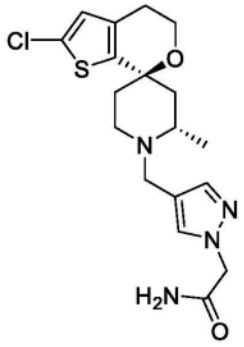
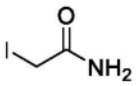
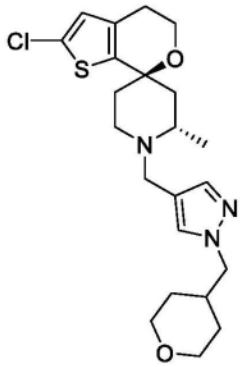
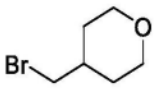
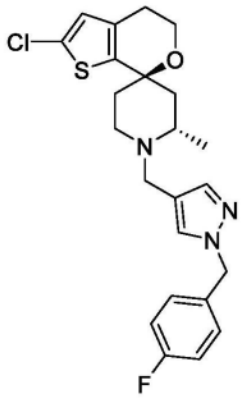
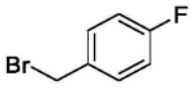
[1325]

化合物	结构	烷基卤化物	方法	^{1}H NMR; LCMS m/z $[M+H]^+$。
700			*699*[2]	LCMS *m/z* 423.36 $[M+H]^+$。
701			*699*	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.32 (s, 1H), 8.69 (d, J = 7.9 Hz, 2H), 8.18 (s, 1H), 8.00 (s, 1H), 7.72 (d, J = 7.6 Hz, 2H), 6.91 (s, 1H), 5.54 (s, 2H), 4.37 (d, J = 13.9 Hz, 1H), 4.17 (dd, J = 14.1, 5.5 Hz, 2H), 3.84 (q, J = 6.1 Hz, 3H), 3.26 (s, 1H), 2.99 (d, J = 6.4 Hz, 1H), 2.32 - 2.05 (m, 4H), 1.47 (d, J = 6.5 Hz, 3H)。 LCMS *m/z* 429.18 $[M+H]^+$。

[1326]

化合物	结构	烷基卤化物	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
702			*699*[1]	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 7.97 (s, 1H), 7.63 (s, 1H), 6.91 (s, 1H), 4.34 (d, J =13.9 Hz, 1H), 4.16 (q, J = 7.2 Hz, 3H), 3.92 – 3.74 (m, 2H), 3.31 – 3.15 (m, 2H), 3.08 (d, J = 19.2 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.17 (dd, J = 20.6, 9.2 Hz, 4H), 1.46 (d, J = 6.4 Hz, 3H), 1.36 (d, J = 7.3 Hz, 3H)。LCMS *m/z* 366.34 $[M+H]^+$。
703			*699*	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.89 (s, 1H), 8.14 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.65 (s, 1H), 6.91 (s, 1H), 4.81 (s, 2H), 4.38 (d, J = 13.9 Hz, 1H), 4.18 (d, J = 14.2 Hz, 1H), 3.85 (tt, J = 12.2, 5.9 Hz, 2H), 3.32 – 3.11 (m, 3H), 3.00 (s, 1H), 2.62 (d, J = 4.6 Hz, 3H), 2.19 (q, J = 14.3 Hz, 4H), 1.46 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 409.11 $[M+H]^+$。
704			*699*[1]	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.15 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 6.92 (s, 1H), 4.38 (d, J = 13.7 Hz, 1H), 4.22 (dd, J = 13.8, 5.3 Hz, 1H), 3.95 (d, J = 7.2 Hz, 2H), 3.82 (h, J = 6.3 Hz, 2H), 3.38 - 3.12 (m, 2H), 3.01 (d, J = 11.8 Hz, 1H), 2.55 (t, J = 5.3 Hz, 2H), 2.21 (dd, J = 25.4, 14.3 Hz, 1H), 2.15 - 2.03 (m, 1H), 1.97 (dd, J = 14.6, 12.0 Hz, 1H), 1.43 (d, J = 6.4 Hz, 2H), 0.83 (d, J = 6.7 Hz, 3H), -0.14 (s, 6H)。LCMS *m/z*

[1327]

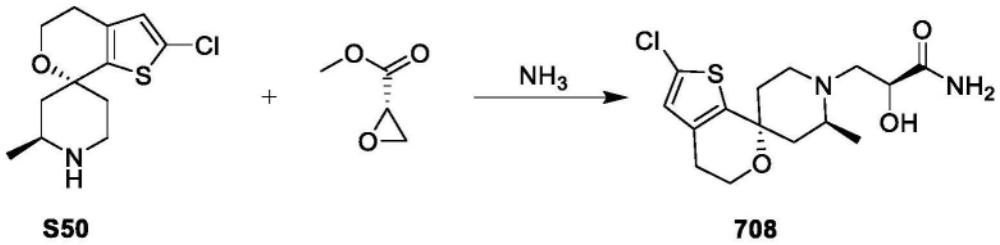
化合物	结构	烷基卤化物	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
				394.33 $[M+H]^+$。
705			*699*	LCMS *m/z* 394.92 $[M+H]^+$。
706			*699*[1]	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.19 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 6.90 (s, 1H), 4.32 (d, J = 14.0 Hz, 1H), 4.18 (dd, J = 14.1, 5.1 Hz, 1H), 4.04 (d, J = 7.2 Hz, 2H), 3.81 (q, J = 8.7, 6.2 Hz, 4H), 3.28 - 3.03 (m, 5H), 3.01 - 2.86 (m, 1H), 2.17 (q, J = 14.4 Hz, 4H), 2.05 (d, J = 6.8 Hz, 1H), 1.46 (d, J = 6.3 Hz, 3H), 1.33 - 1.17 (m, 5H)。LCMS *m/z* 436.37 $[M+H]^+$。
707			*699*[1]	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.96 (s, 1H), 8.08 (s, 1H), 7.68 (s, 1H), 7.30 (dd, J = 8.5, 5.6 Hz, 2H), 7.19 (t, J = 8.8 Hz, 2H), 6.91 (s, 1H), 5.36 (s, 2H), 4.35 (d, J = 14.0 Hz, 1H), 4.27 - 4.10 (m, 1H), 3.84 (tt, J = 12.1, 6.7 Hz, 2H), 3.29 - 3.13 (m, 2H), 3.00 (s, 1H), 2.18 (q, J = 15.0 Hz, 4H), 1.45 (d, J = 6.3 Hz, 3H)。LCMS *m/z* 446.3 $[M+H]^+$。

[1328] 脚注：

[1329] 1.将反应在室温下搅拌10分钟。

[1330] 2.用甲酸改性剂纯化。将产物分离为甲酸盐化合物708

[1331] (2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺

[1332] 

S50 708

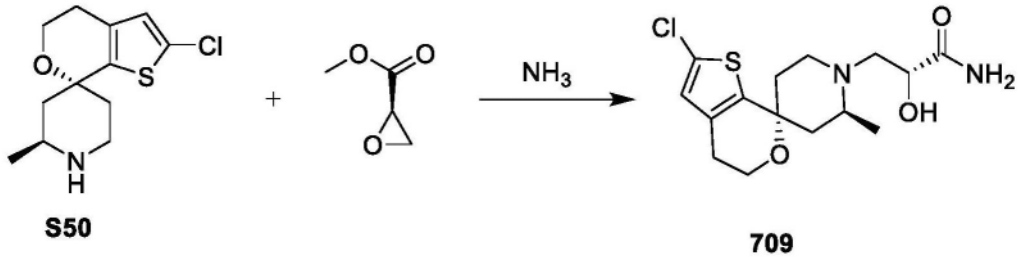
[1333] (2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(708)的制备

[1334] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(99.1mg,0.3844mmol)和(2S)-环氧乙烷-2-甲酸甲酯(100μL,1.142mmol)添加到微波小瓶中,并加入NH_3(3.5mL的7M,24.50mmol)和MeOH(99μL)。添加DIPEA(340μL,1.952mmol),并将反应物在120℃下搅拌4小时。添加另外的70μL环氧乙烷和800μL NH3/MeOH,并将反应物在120℃下加热2小时。添加另外的50μL环氧乙烷和500μL NH3/MeOH,并将反应物在120℃下加热另外2小时。将反应混合物通过旋转蒸发器浓缩,然后在水/DCM中稀释,并将有机物萃取(3x DCM,3x EtOAc),并通过旋转蒸发器浓缩。将材料通过正相色谱法纯化(12g HP硅胶,含0-100％90:10MeOH/DCM的DCM)以得到期望产物708(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(10.2mg,7％)。^{1}H NMR(300MHz,氯仿-d)δ7.34(s,1H),6.58(s,1H),5.66(s,1H),4.03(dd,J＝7.8,5.8Hz,1H),3.95-3.76(m,2H),3.18(dd,J＝13.3,7.8Hz,1H),2.89(dtd,J＝11.5,6.3,2.3Hz,1H),2.82-2.72(m,2H),2.62-2.49(m,3H),2.02(d,J＝2.3Hz,1H),1.97(q,J＝2.8Hz,1H),1.77(ddd,J＝13.8,10.5,6.7Hz,1H),1.52(dd,J＝14.0,11.4Hz,1H),1.10(d,J＝6.3Hz,3H)。LCMS m/z 345.08$[M+1]^+$。

[1335] 化合物709

[1336] (2R)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-

[1337] 基]-2-羟基-丙酰胺

[1338] 

S50 709

[1339] (2R)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(709)的制备

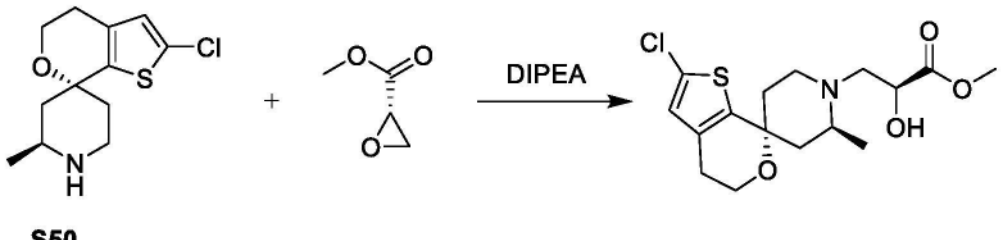
[1340] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(107.5mg,0.4170mmol)和(2R)-环氧乙烷-2-甲酸甲酯(360μL,4.112mmol)添加到微波小瓶中,并加入含NH_3(4.7mL的7M,32.90mmol)的MeOH(4.7mL)。添加DIPEA(750μL,4.306mmol),并将反应物在120℃下搅拌5小时。添加另外的200μL环氧乙烷和500μL NH3,并将反应物在120℃下搅拌另外4小时。将材料通过旋转蒸发器浓缩并用MeOH/DCM(2x)冲洗。剩余的固体不溶于DCM以装载到柱上,因此添加柠檬酸进行酸化,并用EtOAc(3x)萃取有机物。将有机层

通过旋转蒸发器干燥并将材料通过正相色谱法纯化(40g硅胶,0-20% MeOH/DCM),得到产物(2R)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酰胺(36.9mg,22%)。^{1}H NMR(300MHz,氯仿-d)δ6.93(d,J=4.4Hz,1H),6.56(s,1H),5.88(s,1H),4.07(d,J=7.1Hz,3H),3.95-3.77(m,2H),2.92(dd,J=12.9,9.9Hz,1H),2.85-2.75(m,2H),2.70-2.42(m,4H),1.98(p,J=2.7Hz,1H),1.73(td,J=13.4,4.6Hz,1H),1.51(dd,J=14.0,11.3Hz,1H),1.04(d,J=6.2Hz,3H)。LCMS m/z 345.03[M+1]$^+$。

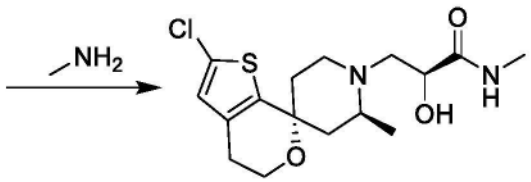
[1341] 化合物710

[1342] (2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺

[1343]



S50 C32



710

[1344] 步骤1:(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯(C32)的合成

[1345] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S50(176mg,0.6828mmol)加入到MeOH(3.5mL)中,并添加到微波小瓶中。添加(2S)-环氧乙烷-2-甲酸甲酯(250μL,2.855mmol)和DIPEA(600μL,3.445mmol),并将反应物在90℃下加热1小时。将反应混合物通过旋转蒸发器浓缩,并通过正相色谱法纯化(24g硅胶,0-80% EtOAc/庚烷),得到(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯C32(147.5mg,57%)。LCMS m/z 360.02[M+1]$^+$。

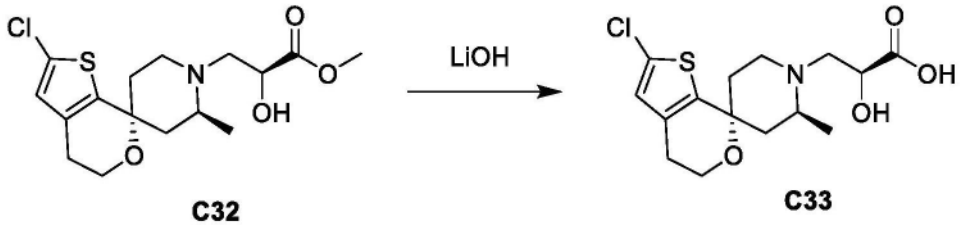
[1346] 步骤2:(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺甲基(710)的合成

[1347] 将(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸酯C32(35.7mg,0.09920mmol)加入到微波烧瓶中的二噁烷(700μL)中。添加甲胺(100μL的40%w/v,1.288mmol)和水(17μL,0.9436mmol),并将反应物加热至80℃,持续3小时。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。得到产物(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N-甲基-丙酰胺710(22.4mg,62%)。1H NMR(300MHz,氯仿-d)δ10.65(s,1H),7.46(s,1H),6.61(s,1H),4.70(dd,J=9.7,3.1Hz,1H),4.04(d,J=13.7Hz,1H),3.89(p,J=5.8Hz,3H),3.66(d,J=12.0Hz,1H),3.53(s,1H),3.32(q,J=11.6,10.9Hz,1H),2.87(d,J=4.9Hz,3H),2.63(q,J=5.2Hz,3H),2.32(q,J=13.7,12.7Hz,1H),2.17(d,J=

15.6Hz,2H),1.49(dd,J＝6.5,2.2Hz,4H)。LCMS m/z 359.42[M+1]$^+$。

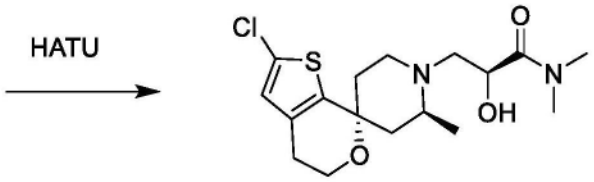
[1348] 化合物711

[1349] (2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N,N-二甲基-丙酰胺



C32 C33

[1350]



711

[1351] 步骤1:(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸(C33)的合成

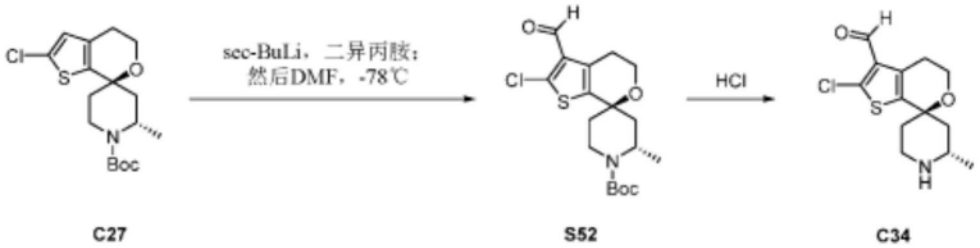
[1352] (2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸甲酯C32(107mg,0.2973mmol)和LiOH(31.6mg,1.320mmol)于MeOH(1.1mL)和THF(1mL)中的溶液,并在rt下搅拌2小时。将反应混合物通过旋转蒸发器浓缩,并且粗材料无需纯化即可使用。(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸(锂盐)C33(147mg,98%)。LCMS m/z 344[M+1]$^+$。

[1353] 步骤2:(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N,N-二甲基-丙酰胺(711)的合成

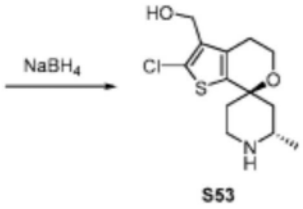
[1354] 将(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-丙酸C33(锂盐)(147mg,0.2917mmol)、N-甲基甲胺(500μL的2M,1.000mmol)和HATU(379.5mg,0.9981mmol)加入到DMF(2mL)中。添加DIPEA(200μL,1.148mmol),并将反应物搅拌2小时。添加另外500μL DMF以冲洗烧瓶侧面。添加另外含332mg HATU的500μL DMF和300μL二甲胺溶液,并将反应物搅拌过夜。将反应混合物通过旋转蒸发器浓缩。添加过量水,并将有机物用DCM萃取,并通过旋转蒸发器浓缩。通过硅胶色谱法纯化(0-20% MeOH/DCM),随后通过硅胶色谱法纯化(0-15% MeOH/DCM)得到(2S)-3-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2-羟基-N,N-二甲基-丙酰胺711(7.6mg,6%)。^{1}H NMR(300MHz,氯仿-d)δ6.60(s,1H),4.69(dd,J＝7.4,4.0Hz,1H),4.14(q,J＝7.1Hz,1H),4.03-3.79(m,2H),3.33-2.94(m,11H),2.80-2.50(m,3H),2.24-2.08(m,1H),2.05-1.88(m,2H),1.71(dd,J＝14.1,11.6Hz,1H),1.33-1.07(m,4H)。LCMS m/z 373.12[M+1]$^+$。

[1355] 制备S53

[1356] [(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S53)



[1357]



[1358] 步骤1:(2′S,7R)-2-氯-3-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(S52)的合成-LDA溶液的制备:

[1359] 将二异丙胺(3mL,21.41mmol)于Et_2O(3mL)中的溶液在烘箱干燥的烧瓶中用氮气吹扫并冷却至-20℃。此时,逐滴添加仲丁基锂(15mL的1.333M,19.99mmol)。将反应混合物在该温度下搅拌30分钟。

[1360] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(6.3g,17.49mmol)于THF(100mL)中的溶液在烘箱干燥的烧瓶中用氮气吹扫并冷却至-78℃。此时,将来自先前步骤的LDA的混合物在2分钟的过程内转移。将混合物在该温度下搅拌5分钟。此时,添加DMF(5mL,64.57mmol)。5分钟后,向该混合物中添加饱和氯化铵水溶液(25mL),并将混合物温热至室温。然后将混合物用Et_2O(200mL)稀释,随后用水(200mL)稀释。将有机层用另外的水(2×200mL)和盐水(200mL)洗涤。将有机层用硫酸钠干燥,过滤并在真空中浓缩。将混合物通过硅胶色谱法纯化(梯度:含0-25% EtOAc的庚烷),产生(2′S,7R)-2-氯-3-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(5.0g,73%)。^1H NMR(400MHz,氯仿-d)δ10.09(s,1H),4.01(tt,J=11.6,6.5Hz,1H),3.95-3.80(m,2H),3.74(dt,J=14.0,5.5Hz,1H),3.36(ddd,J=13.9,8.6,5.3Hz,1H),2.99-2.84(m,2H),2.21(dddd,J=14.6,8.3,5.9,1.9Hz,1H),2.12(ddd,J=14.1,5.1,2.0Hz,1H),1.76(dt,J=14.5,5.2Hz,1H),1.67(dd,J=14.2,10.9Hz,1H),1.50(s,9H),1.29(d,J=6.5Hz,3H)。LCMS m/z 385.96$[M+H]^+$。

[1361] 步骤2:(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛(C34)的合成

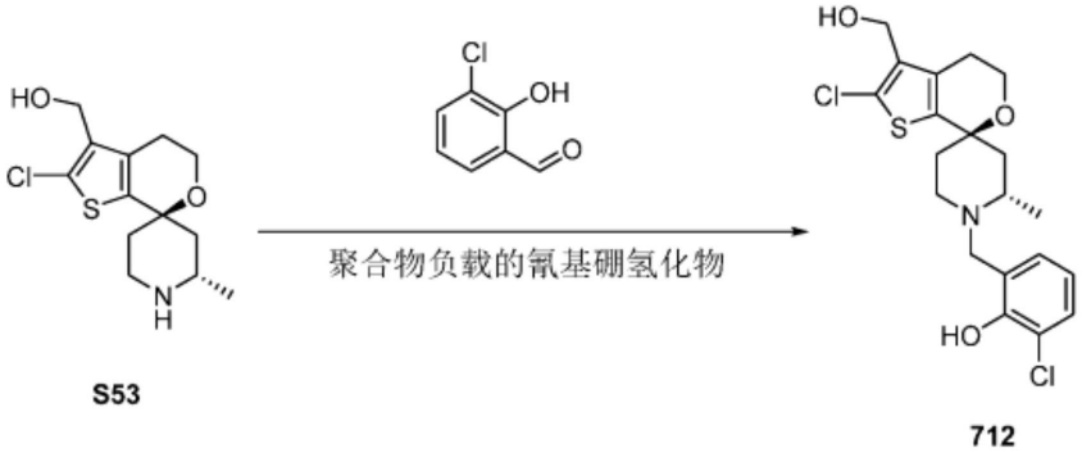
[1362] 在室温下搅拌(2′S,7R)-2-氯-3-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S52(3.0g,7.649mmol)于HCl(7.5mL的4M,30.00mmol)的二噁烷溶液中的混合物。5分钟后,添加Et_2O(15mL),并将悬浮液在室温下搅拌。30分钟后,将混合物过滤,用Et_2O冲洗,并浓缩以产生(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛(盐酸盐)(2.369g,96%)。LCMS m/z 286.05$[M+H]^+$。

[1363] 步骤3:[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S53)的合成

[1364] 向溶解在水(40mL)中的(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛(盐酸盐)C34(2.369g,7.35mmol)中添加$NaBH_4$(100mg,2.643mmol)。然后添加HCl水溶液(7.5mL的1M,7.500mmol)直到pH=1。搅拌5分钟后,然后将混合物pH用NaOH(2.5mL的6M,15.00mmol)调节至约pH=12。将混合物用DCM(2×25mL)萃取,用硫酸钠干燥,过滤并浓缩以提供呈白色无定型固体的[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(1.88g,82%)。^1H NMR(400MHz,DMSO-d_6)δ5.03(t,J=5.4Hz,1H),4.31(d,J=5.2Hz,2H),3.86(td,J=5.7,3.0Hz,2H),2.95-2.78(m,2H),2.78-2.68(m,1H),2.59(t,J=5.5Hz,2H),1.93-1.80(m,2H),1.49(td,J=13.0,4.8Hz,1H),1.18(dd,J=13.4,11.2Hz,1H),0.94(d,J=6.4Hz,3H)。LCMS m/z 288.08$[M+H]^+$。

[1365] 化合物712

[1366] 2-氯-6-[[(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]苯酚(712)

[1367] 

S53 712

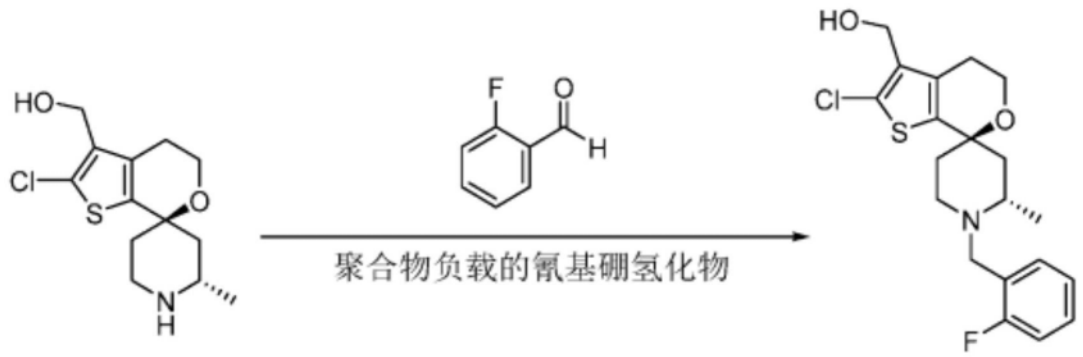
[1368] 标准方法#A:使用聚合物负载的氰基硼氢化物进行还原胺化

[1369] 向1打兰小瓶中添加聚合物负载的氰基硼氢化物(75mg的2mmol/g,0.15mmol),随后添加溶液含3-氯-2-羟基-苯甲醛(15.7mg,0.1mmol)的DMF(400uL)和[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S53(16mg,0.056mmol)于DMF(400uL)中的溶液。将小瓶密封并在85℃下加热过夜。然后将小瓶冷却至室温。将所得悬浮液通过聚丙烯过滤板过滤。将含0.1wt%TFA(400uL)的水添加到反应小瓶中,将其搅拌若干分钟以冲洗珠粒。将DMSO(200uL)添加到所得滤液中。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。2-氯-6-[[(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]苯酚(三氟乙酸盐)(2.8mg,9.2%)。LCMS m/z 428.29$[M+H]^+$。

[1370] 化合物713

[1371] (2′S,7R)-2-氯-1′-[(2-氟苯基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-

[1372] 哌啶](713)

[1373] 

S53 713

[1374] 标准方法#B:使用聚合物负载的氰基硼氢化物和乙酸进行还原胺化

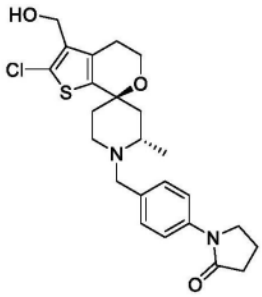
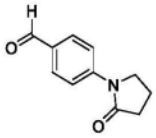
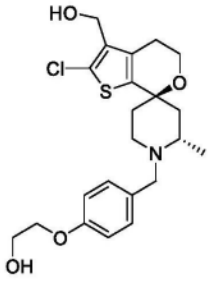
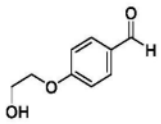
[1375] 将[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S53(20mg,0.068mmol)和AcOH(2μL)于DMF(0.7mL)中的储备溶液添加到2-氟苯甲醛(25μL,0.237mmol)于DMF(0.7mL)中的混合物中。向该混合物中添加聚合物负载的氰基硼氢化物(75mg的2mmol/g,0.15mmol),并将混合物加热至85℃。搅拌过夜后,将混合物冷却至室温,过滤并将聚合物用另外的DMF冲洗。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。(2′S,7R)-2-氯-1′-[(2-氟苯基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(19.3mg,56%)。^{1}H NMR(400MHz,氯仿-d)δ7.74-7.65(m,1H),7.48(q,J=6.3Hz,1H),7.31(s,1H),7.21-7.14(m,1H),4.63(d,J=13.4Hz,1H),4.57(s,2H),4.13(d,J=13.2Hz,1H),3.91(dq,J=21.8,5.9Hz,2H),3.52(s,1H),3.22(d,J=12.1Hz,1H),3.05(t,J=12.6Hz,1H),2.71(q,J=5.5,5.1Hz,2H),2.53-2.37(m,2H),2.22-2.03(m,2H),1.68(d,J=6.5Hz,3H)。LCMS m/z 396.32$[M+H]^+$。

[1376] 化合物714-758

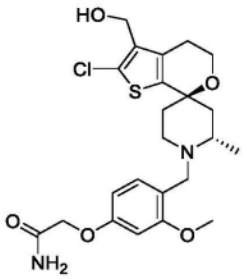
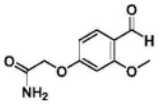
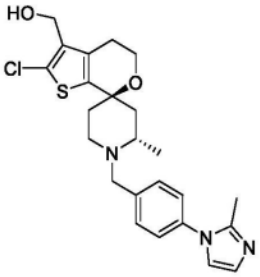
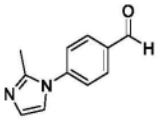
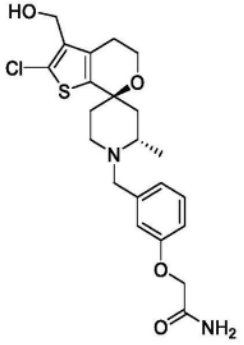
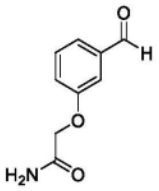
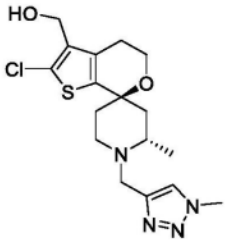
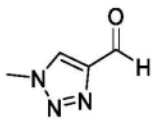
[1377] 使用712的制备或713的制备的方法,由中间体S53制备化合物714-758(参见表31)。醛可商购获得或如前所述。表31和随附脚注中注明了对方法的任何修改。

[1378] 表31:化合物714-758的结构和物理化学数据

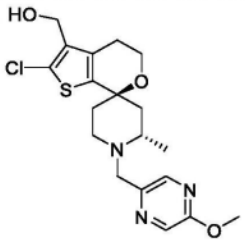
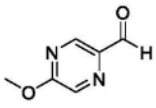
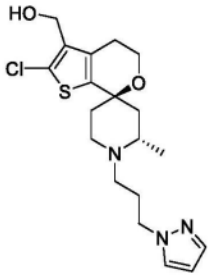
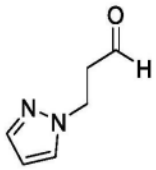
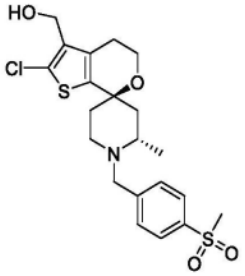
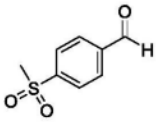
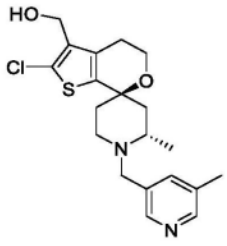
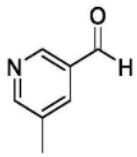
[1379]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
714			**712**	LCMS *m/z* 461.38 $[M+H]^+$
715			**712**	LCMS *m/z* 438.31 $[M+H]^+$

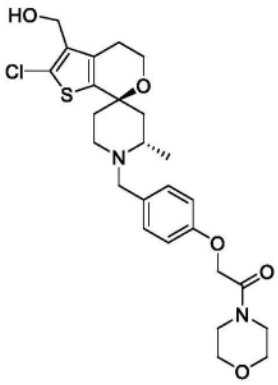
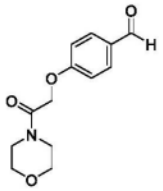
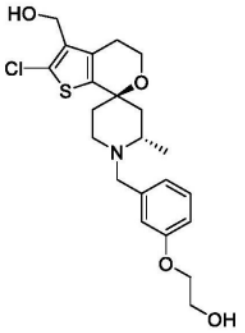
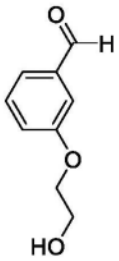
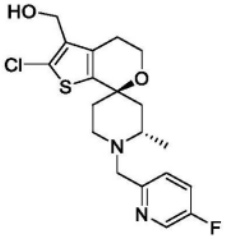
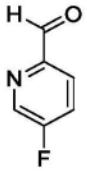
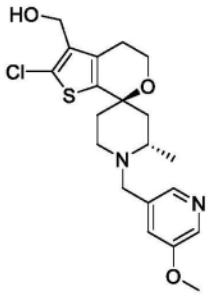
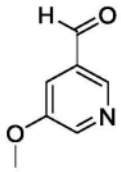
[1380]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
716			**712**	LCMS *m/z* 481.34 $[M+H]^+$
717			**712**	LCMS *m/z* 458.36 $[M+H]^+$
718			**712**	LCMS *m/z* 451.31 $[M+H]^+$
719			**712**	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.31 (s, 1H), 5.09 (s, 1H), 4.62 (d, *J* = 14.2 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 4.32 (s, 2H), 4.11 (s, 3H), 3.87 (q, *J* = 6.0 Hz, 2H), 3.33 (d, *J* = 12.6 Hz, 2H), 3.17 (d, *J* = 11.9 Hz, 1H), 2.61 (t, *J* = 5.5 Hz, 2H), 2.38 - 2.08 (m, 2H), 2.05 - 1.82 (m, 2H), 1.45 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 383.36 $[M+H]^+$

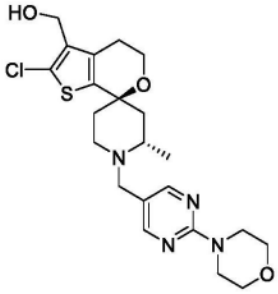
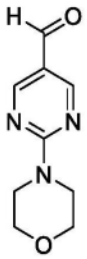
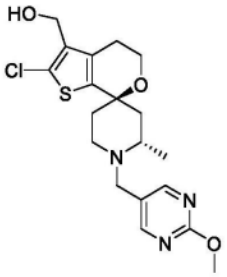
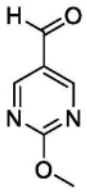
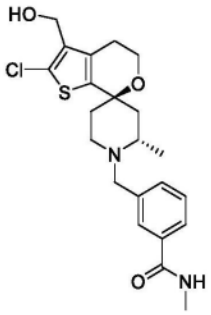
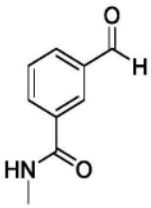
[1381]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
720			**712**	LCMS *m/z* 410.32 [M+H]$^+$
721			**712**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 6.28 (t, *J* = 2.1 Hz, 1H), 5.03 (d, *J* = 6.1 Hz, 1H), 4.33 (s, 2H), 4.23 (t, *J* = 6.7 Hz, 2H), 3.92 (h, *J* = 6.4 Hz, 2H), 3.41 (s, 2H), 3.34 - 3.13 (m, 2H), 3.03 (t, *J* = 14.0 Hz, 1H), 2.64 (t, *J* = 5.5 Hz, 2H), 2.31 - 2.07 (m, 4H), 1.99 (t, *J* = 12.1 Hz, 1H), 1.91 - 1.82 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 396.36 [M+H]$^+$
722			**712**	LCMS *m/z* 456.28 [M+H]$^+$
723			**712**	LCMS *m/z* 393.34 [M+H]$^+$

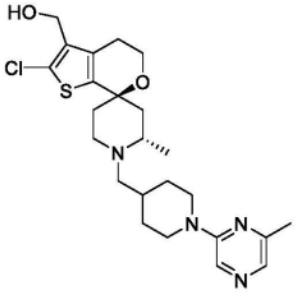
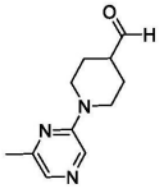
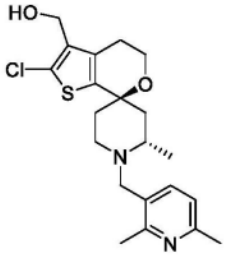
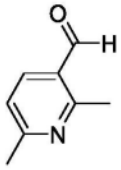
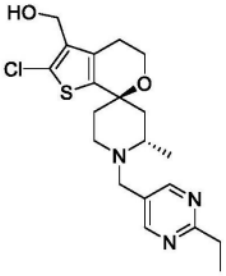
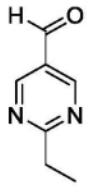
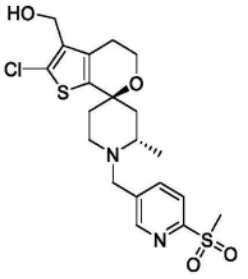
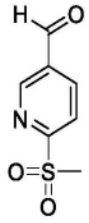
[1382]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
724			**712**	LCMS *m/z* 521.43 $[M+H]^+$
725			**712**	LCMS *m/z* 438.31 $[M+H]^+$
726			**712**	LCMS *m/z* 397.31 $[M+H]^+$
727			**712**	LCMS *m/z* 409.32 $[M+H]^+$

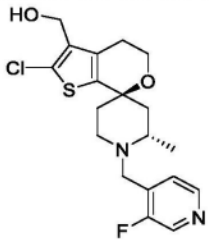
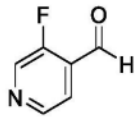
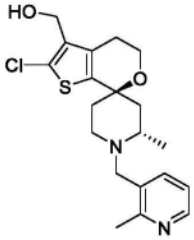
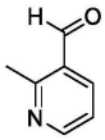
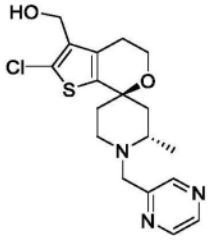
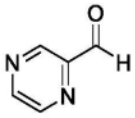
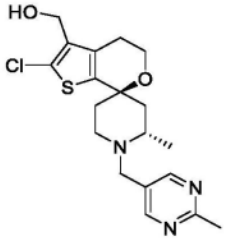
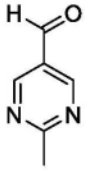
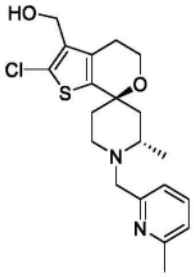
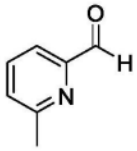
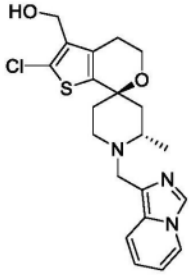
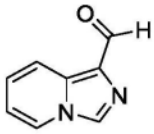
[1383]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
728			**712**	LCMS *m/z* 465.4 [M+H]$^+$
729			**712**	LCMS *m/z* 410.32 [M+H]$^+$
730			**712**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.00 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 4.81 (d, *J* = 12.8 Hz, 1H), 4.32 (s, 2H), 4.20 (dd, *J* = 13.2, 8.1 Hz, 1H), 3.91 (dp, *J* = 23.3, 6.0 Hz, 2H), 3.57 (s, 1H), 3.04 - 2.84 (m, 2H), 2.81 (d, *J* = 4.4 Hz, 3H), 2.63 (s, 3H), 2.29 (d, *J* = 15.0 Hz, 1H), 2.15 (d, *J* = 15.2 Hz, 1H), 1.90 (dt, *J* = 32.3, 12.3 Hz, 2H), 1.50 (d, *J* = 6.2 Hz, 3H)；LCMS *m/z* 435.37 [M+H]$^+$

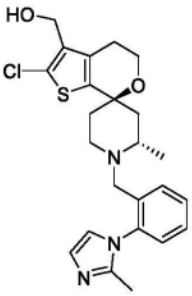
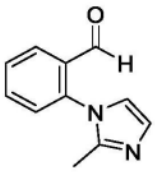
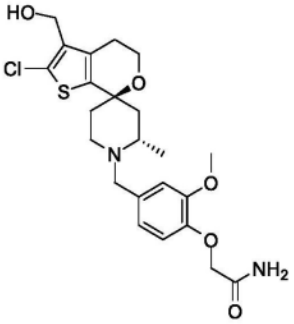
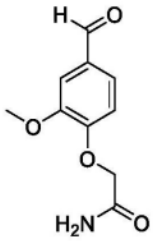
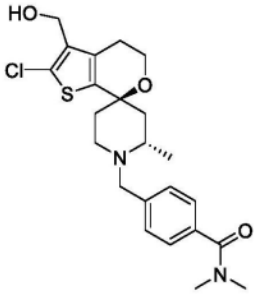
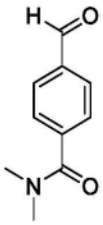
[1384]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
731			**712**	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.14 (s, 1H), 7.70 (s, 1H), 4.39 (s, 2H), 4.34 (s, 2H), 3.94 (s, 3H), 3.57 (d, J = 12.3 Hz, 1H), 3.46 (s, 1H), 3.24 (d, J = 55.0 Hz, 2H), 2.90 (dt, J = 25.8, 12.9 Hz, 4H), 2.68 - 2.62 (m, 2H), 2.29 (s, 3H), 2.26 - 1.84 (m, 6H), 1.70 (d, J = 12.8 Hz, 1H), 1.30 (d, J = 6.4 Hz, 3H), 1.24 (d, J = 7.4 Hz, 1H)；LCMS m/z 477.45 [M+H]$^+$
732			**712**	LCMS m/z 407.38 [M+H]$^+$
733			**712**	LCMS m/z 408.37 [M+H]$^+$
734			**712**	LCMS m/z 457.28 [M+H]$^+$

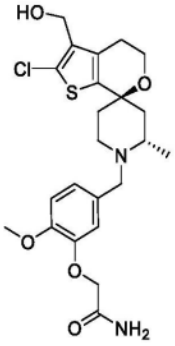
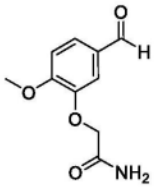
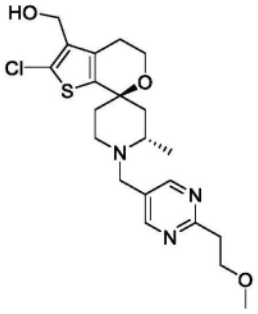
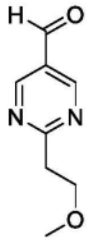
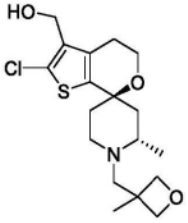
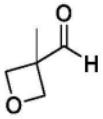
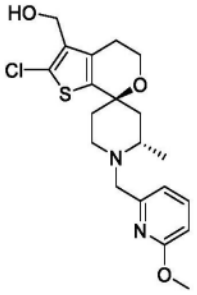
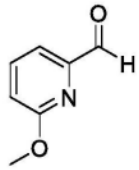
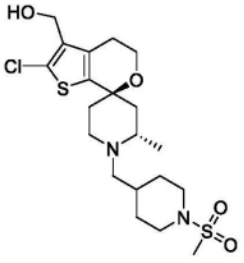
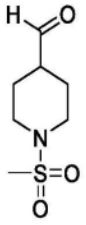
[1385]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
735			**712**	LCMS *m/z* 397.31 [M+H]$^+$
736			**712**	LCMS *m/z* 393.34 [M+H]$^+$
737			**712**	LCMS *m/z* 380.33 [M+H]$^+$
738			**712**	LCMS *m/z* 394.33 [M+H]$^+$
739			**712**	LCMS *m/z* 393.34 [M+H]$^+$
740			**712**	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.75 (s, 1H), 8.42 (d, *J* = 7.1 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 6.79 (t, *J* = 6.7 Hz, 1H), 4.79 (d, *J* = 14.1 Hz, 1H), 4.63

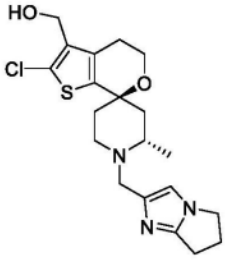
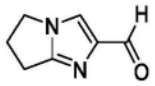
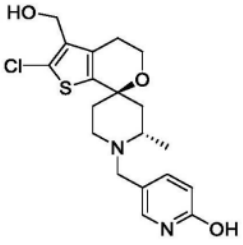
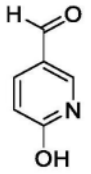
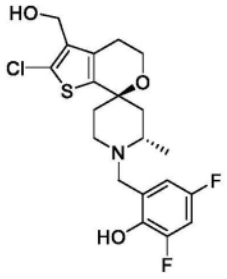
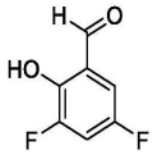
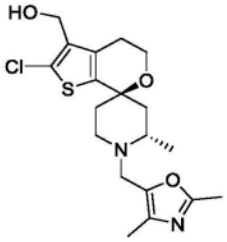
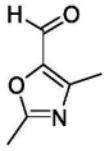
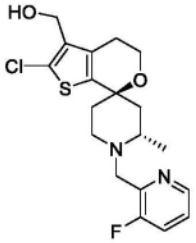
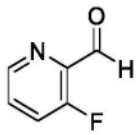
[1386]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
				(d, *J* = 14.1 Hz, 1H), 3.92 (d, *J* = 4.9 Hz, 1H), 3.85 (d, *J* = 5.3 Hz, 1H), 3.51 (s, 1H), 3.37 (s, 1H), 3.26 (d, *J* = 21.4 Hz, 1H), 3.12 (s, 1H), 2.64 (d, *J* = 6.7 Hz, 2H), 2.59 (s, 2H), 2.25 (d, *J* = 15.2 Hz, 1H), 2.16 (d, *J* = 15.0 Hz, 2H), 1.93 (d, *J* = 14.8 Hz, 2H), 1.55 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 418.35 $[M+H]^+$
741			**712**	LCMS *m/z* 458.4 $[M+H]^+$
742			**712**	LCMS *m/z* 481.34 $[M+H]^+$
743			**712**	LCMS *m/z* 449.37 $[M+H]^+$

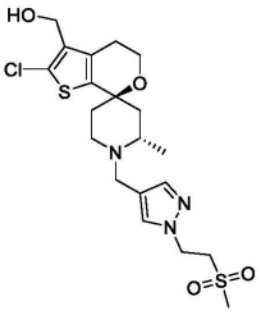
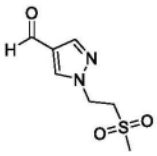
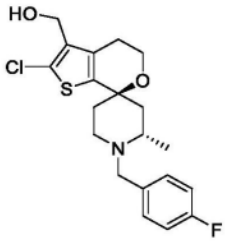
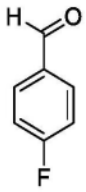
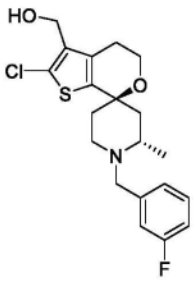
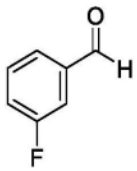
[1387]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
744			**712**	LCMS *m/z* 481.34 $[M+H]^+$
745			**712**	LCMS *m/z* 438.35 $[M+H]^+$
746			**712**	LCMS *m/z* 372.34 $[M+H]^+$
747			**712**	LCMS *m/z* 409.32 $[M+H]^+$
748			**712**	LCMS *m/z* 463.37 $[M+H]^+$

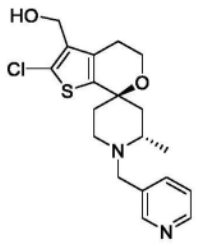
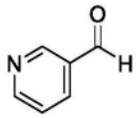
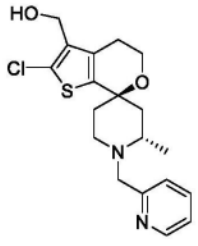
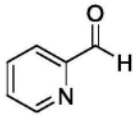
[1388]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
749			**712**	LCMS *m/z* 408.37 [M+H]$^+$
750			**712**	LCMS *m/z* 395.32 [M+H]$^+$
751			**712**	LCMS *m/z* 430.32 [M+H]$^+$
752			**712**	LCMS *m/z* 397.31 [M+H]$^+$
753			**712**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.58 (d, J = 4.7 Hz, 1H), 7.93 (t, J = 9.2 Hz, 1H), 7.64 (dt, J = 8.7, 4.5 Hz, 1H), 4.84 (d, J = 14.8 Hz, 1H), 4.55 (d, J = 15.0 Hz, 1H), 4.33 (s, 2H), 3.98 - 3.86 (m, 2H), 3.76 (s, 2H), 3.27 (s, 2H), 2.65 (d, J = 5.8 Hz, 2H), 2.26 (d, J = 14.7 Hz, 1H), 2.14 (d, J = 13.6 Hz, 3H), 1.41 (d, J =

[1389]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				6.3 Hz, 3H)； LCMS *m/z* 397.36 [M+H]$^+$
754			**712**[1]	^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.60 - 7.48 (m, 1H), 7.46 (s, 1H), 4.59 (t, *J* = 6.0 Hz, 2H), 4.54 (s, 2H), 3.96 - 3.70 (m, 3H), 3.70 - 3.50 (m, 3H), 2.65 (ddt, *J* = 9.1, 5.6, 3.3 Hz, 3H), 2.51 (ddd, *J* = 19.3, 10.7, 4.3 Hz, 2H), 2.46 (s, 3H), 1.98 (tt, *J* = 14.2, 2.9 Hz, 2H), 1.80 (td, *J* = 13.3, 4.5 Hz, 1H), 1.60 (dd, *J* = 13.9, 11.4 Hz, 1H), 1.19 (d, *J* = 6.2 Hz, 3H)； LCMS *m/z* 474.16 [M+H]$^+$
755			**713**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 7.58 (s, 2H), 7.34 (t, *J* = 8.6 Hz, 2H), 5.10 (s, 1H), 4.73 (d, *J* = 12.9 Hz, 1H), 4.32 (s, 2H), 4.16 (s, 1H), 4.01 - 3.78 (m, 2H), 3.52 (s, 1H), 3.12 (s, 1H), 2.99 (d, *J* = 7.3 Hz, 1H), 2.68 - 2.57 (m, 2H), 2.29 (d, *J* = 15.0 Hz, 1H), 2.15 (d, *J* = 15.3 Hz, 1H), 1.92 (dd, *J* = 25.7, 13.1 Hz, 2H), 1.58 - 1.39 (m, 3H)； LCMS *m/z* 395.9 [M+H]$^+$
756			**713**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.47 - 7.31 (m, 3H), 5.10 (s, 1H), 4.77 (d, *J* = 12.7 Hz, 1H), 4.32 (s, 2H), 4.16 (s, 1H), 3.97 - 3.86 (m, 2H), 3.55 (s, 1H), 3.15

[1390]

化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				(s, 1H), 3.00 (s, 1H), 2.63 (d, *J* = 5.7 Hz, 2H), 2.29 (d, *J* = 15.0 Hz, 1H), 2.15 (d, *J* = 15.2 Hz, 1H), 1.94 (dd, *J* = 25.0, 13.4 Hz, 2H), 1.48 (s, 3H)； LCMS *m/z* 395.87 [M+H]$^+$
757			**713**	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.93 (s, 1H), 8.73 (d, *J* = 2.3 Hz, 1H), 8.68 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.80 (d, *J* = 13.1 Hz, 1H), 4.32 (s, 2H), 4.22 (d, *J* = 13.1 Hz, 1H), 3.97 - 3.86 (m, 2H), 3.21 - 3.10 (m, 2H), 3.00 (t, *J* = 6.0 Hz, 1H), 2.64 (t, *J* = 5.6 Hz, 2H), 2.30 (d, *J* = 15.0 Hz, 1H), 2.15 (d, *J* = 14.9 Hz, 1H), 1.92 (dt, *J* = 22.9, 13.5 Hz, 2H), 1.50 (d, *J* = 6.4 Hz, 3H)； LCMS *m/z* 378.9 [M+H]$^+$
758			**713**	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.14 - 9.65 (m, 1H), 8.72 (d, *J* = 4.8 Hz, 1H), 7.95 (td, *J* = 7.7, 1.8 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.50 (dd, *J* = 7.6, 4.9 Hz, 1H), 5.10 (s, 1H), 4.79 (d, *J* = 14.2 Hz, 1H), 4.42 (d, *J* = 14.2 Hz, 1H), 4.33 (s, 2H), 3.91 (dtd, *J* = 17.4, 11.5, 5.3 Hz, 2H), 3.64 (s, 1H), 3.12 (d, *J* = 12.4 Hz, 1H), 2.63 (d, *J* = 5.5 Hz, 2H), 2.23 (d, *J* = 14.7 Hz, 1H),

[1391]

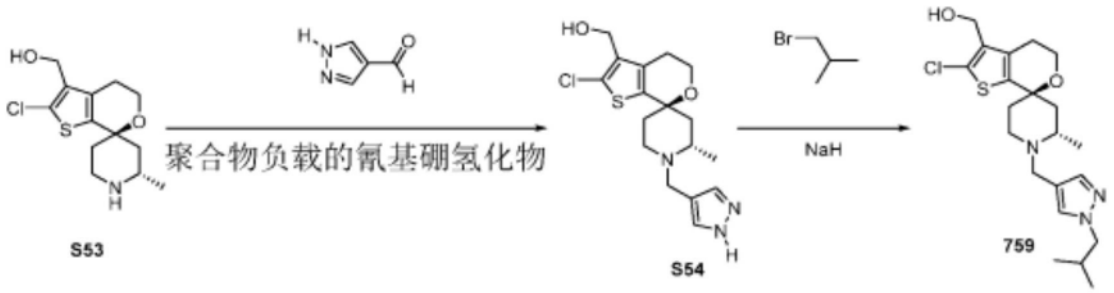
化合物	结构	醛 试剂	方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				2.06 (dt, *J* = 27.5, 12.6 Hz, 3H), 1.40 (d, *J* = 6.3 Hz, 3H)； LCMS *m/z* 378.9 [M+H]$^+$

[1392] 脚注：

[1393] 1)使用$NaBH_3CN$代替聚合物负载的氰基硼氢化物。在DCM中在95℃下加热反应物。使用硅胶色谱法完成纯化(梯度:含0至20％ MeOH的DCM)。

[1394] 化合物759

[1395] [(2′S,7R)-2-氯-1′-[(1-异丁基吡唑-4-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(759)

[1396] 

[1397] 步骤1:[(2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S54)的合成

[1398] [(2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S54根据标准方法A制备,具有如下修改:使用聚合物负载的氰基硼氢化物(2.0当量),并且DCM用作溶剂。通过硅胶色谱法进行纯化(梯度:含0-20％ MeOH的DCM)以产生标题化合物。^{1}H NMR(400MHz,DMSO-d_6)δ12.68(s,1H),7.49(d,J＝73.3Hz,2H),5.02(t,J＝5.4Hz,1H),4.31(t,J＝5.7Hz,2H),3.81(q,J＝5.6Hz,2H),3.72(s,1H),3.50(s,1H),3.17(d,J＝5.2Hz,1H),2.56(t,J＝5.5Hz,3H),2.38(s,1H),1.92(d,J＝6.4Hz,2H),1.63(s,1H),1.42(s,1H),1.12(s,3H)。LCMS m/z 368.05[M+H]$^+$。

[1399] 步骤2:[(2′S,7R)-2-氯-1′-[(1-异丁基吡唑-4-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(759)的合成-标准方法#C:N-烷基化吡唑

[1400] 向[(2′S,7R)-2-氯-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S54(20mg,0.05320mmol)于DMF(1000μL)中的混合物中添加NaH(含3.5mg的60％分散体的矿物油,0.08751mmol),随后添加1-溴-2-甲基-丙烷(20μL,0.1839mmol)。搅拌过夜后,将混合物用C18柱纯化(梯度:含10-100％ MeCN的水,0.1％ TFA改性剂)。将含产物级分合并并浓缩,在饱和碳酸氢钠/DCM中重新稀释以去除TFA。使有机层通过相分离器并浓缩以产生[(2′S,7R)-2-氯-1′-[(1-异丁基吡唑-4-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(11mg,48％)。^{1}H NMR(400MHz,氯仿-d)δ7.39(d,J＝0.8Hz,1H),7.31-7.26(m,1H),4.52(s,2H),3.86(d,J＝7.3Hz,5H),3.53(d,J＝14.2Hz,1H),2.66(dtd,J＝10.4,5.3,3.3Hz,3H),2.54(ddt,J＝11.2,6.1,2.9Hz,1H),2.47(td,J＝12.0,11.5,2.5Hz,1H),2.18(hept,J＝6.8Hz,1H),1.95(d,J＝13.7Hz,

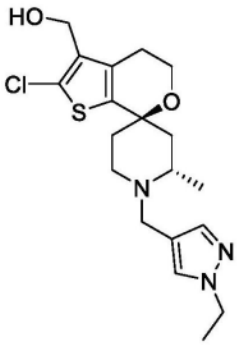
3H),1.78(td,J=13.4,4.4Hz,1H),1.60(dd,J=13.8,11.4Hz,1H),1.18(d,J=6.2Hz,3H),0.89(dd,J=6.7,0.9Hz,6H)。LCMS m/z 424.23[M+H]$^+$。

[1401] 化合物760-761

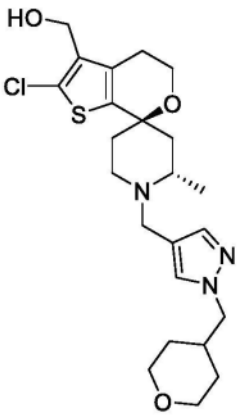
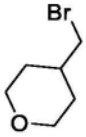
[1402] 使用如化合物759的制备中的方法,由中间体S54在单个步骤中制备化合物760-761(参见表32)。烷基卤化物从商业来源获得。表32和随附脚注中注明了对方法的任何修改。

[1403] 表32:化合物760-761的结构和物理化学数据

[1404]

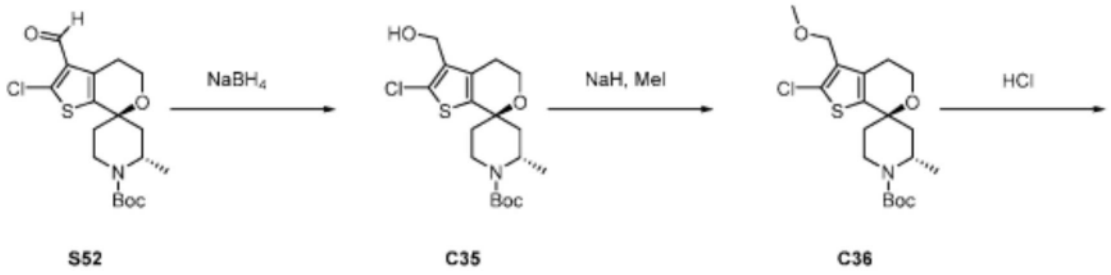
化合物	结构	烷基卤化物试剂	方法	^{1}H NMR; LCMS m/z [M+H]$^+$。
760			759	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.97 (s, 1H), 7.63 (s, 1H), 4.32 (s, 2H), 4.16 (q, J = 6.9 Hz, 3H), 3.86 (q, J = 6.6, 6.2 Hz, 2H), 3.27 - 3.04 (m, 3H), 2.98 (d, J = 13.7 Hz, 1H), 2.61 (t, J = 5.4 Hz, 2H), 2.27 - 2.05 (m, 4H), 1.46 (d, J = 6.3 Hz, 3H), 1.37 (t, J = 7.2 Hz, 4H); LCMS m/z 396.36 [M+H]$^+$。

[1405]

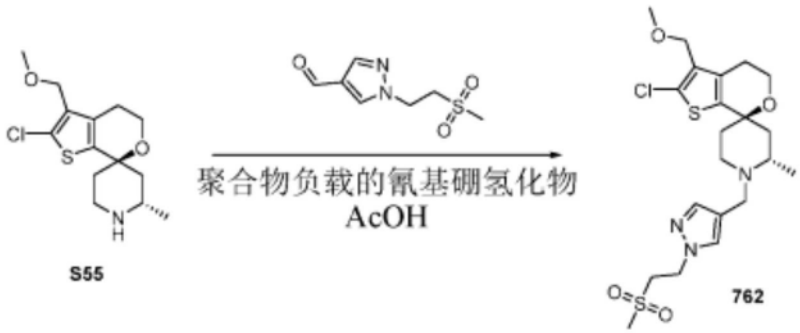
化合物	结构	烷基卤化物试剂	方法	^{1}H NMR; LCMS m/z [M+H]$^+$。
761			759	^{1}H NMR (400MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 4.32 (s, 2H), 4.19 (dd, J = 14.1, 5.2 Hz, 1H), 4.04 (d, J = 7.1 Hz, 2H), 3.91 - 3.73 (m, 4H), 3.29 - 3.11 (m, 5H), 2.61 (d, J = 5.3 Hz, 2H), 2.28 - 1.94 (m, 5H), 1.45 (d, J = 6.3 Hz, 3H), 1.36 (d, J = 12.9 Hz, 2H), 1.27 - 1.15 (m, 3H); LCMS m/z 466.39 [M+H]$^+$。

[1406] 化合物762

[1407] (2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](762)



[1408]



[1409] 步骤1:(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C35)的合成

[1410] 向(2′S,7R)-2-氯-3-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S52(400mg,1.023mmol)于四氢呋喃(8mL)中的混合物中添加$NaBH_4$(13μL,0.3247mmol),随后添加MeOH(160μL)并将反应物加热至50℃。10分钟后,将混合物用饱和碳酸氢钠水溶液和EtOAc淬灭。将有机层分离,用水和盐水冲洗。将有机层用硫酸钠干燥,过滤并浓缩以提供(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯。LCMS m/z 387.9$[M+H]^+$。物质无需进一步纯化即可用于下一步骤。

[1411] 步骤2:(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C36)的合成

[1412] 将(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C35(400mg,1.031mmol)溶解在THF(11mL)中并添加MeI(192μL,3.084mmol)和NaH(74mg,3.084mmol)。将混合物在室温下搅拌48。然后添加饱和NH_4Cl水溶液以淬灭反应物,并将溶液用DCM萃取,用硫酸钠干燥并过滤以产生粗产物。通过硅胶色谱法纯化(梯度:含0-20% EtOAc的庚烷),产生(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(340mg,82%)。LCMS m/z402.04$[M+H]^+$。

[1413] 步骤3:(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S55)的合成

[1414] 将(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C36(113mg,0.2811mmol)溶解在HCl(703μL的4M,2.812mmol)中。20分钟后,去除溶剂以提供(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]。LCMS m/z 302.22$[M+H]^+$。物质无需进一步纯化即可用于下

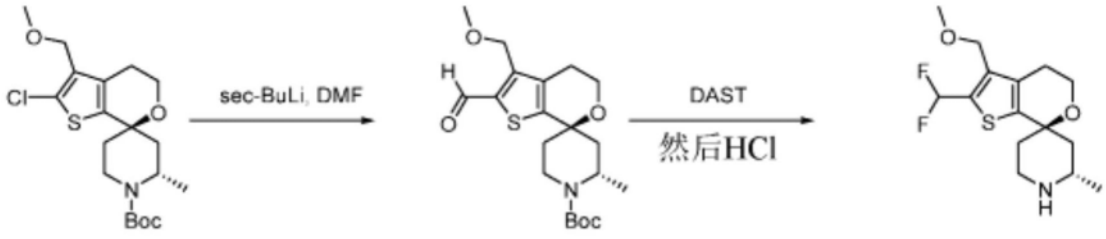
一步骤。

[1415] 步骤4:(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](762)的合成

[1416] 将(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S55(70mg,0.17mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(57mg,0.2819mmol)溶解在DCM(3mL)中。将乙酸(50.7mg,0.8443mmol)添加到溶液中。将溶液转移到微波管中并添加聚合物负载的氰基硼氢化物(253mg的2mmol/g,0.5060mmol)。将管加盖并在微波反应器中加热至110℃,持续45分钟。将氢硼化物树脂过滤掉并将溶剂在真空中去除。通过反相HPLC纯化。方法:C18Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(38.2mg,37%)。^{1}H NMR(300MHz,氯仿-d)δ 7.84(s,1H),7.64(s,1H),4.81-4.51(m,3H),4.34(s,2H),4.10-3.60(m,5H),3.35(s,3H),2.99(s,4H),2.86-2.61(m,5H),2.45-2.05(m,4H),1.58(d,J=6.5Hz,3H)。LCMS m/z488.21 $[M+H]^+$。

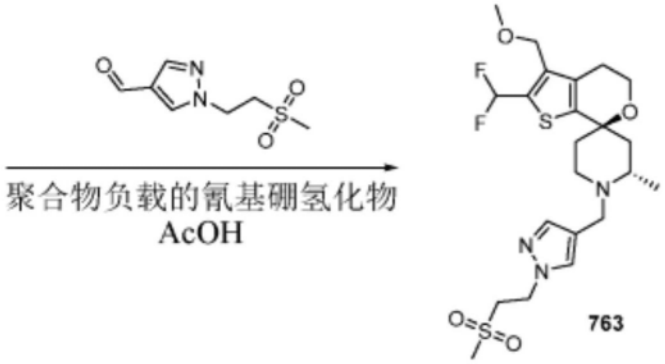
[1417] 化合物763

[1418] (2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](763)



S55 C37 C38

[1419]



[1420] 步骤1:(2′S,7R)-2-甲酰基-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C37)的合成

[1421] 将(2′S,7R)-2-氯-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S55(226mg,0.5615mmol)于THF(5mL)中的混合物在烘箱干燥的

小瓶中冷却至-70℃。此时,逐滴添加含仲丁基锂(570μL的1.25M,0.7125mmol)环己烷并在该温度下搅拌。20分钟后,添加N,N-二甲基甲酰胺(222μL,2.867mmol)。使混合物温热至室温。将反应混合物在该温度下搅拌过夜。向该混合物中添加饱和氯化铵水溶液(6mL),并将混合物温热至室温。此时,将混合物用Et_2O稀释,随后用水稀释。用盐水洗涤有机层。将有机层用$MgSO_4$干燥,过滤并在真空中浓缩。将混合物通过硅胶色谱法纯化(梯度:含0-25%EtOAc的庚烷)以产生(2′S,7R)-2-甲酰基-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(75mg,34%)。^{1}H NMR(300MHz,甲醇-d_4)δ10.13(s,1H),4.68(s,2H),4.11-3.73(m,4H),3.41(s,3H),2.65(t,J=5.6Hz,2H),2.43-2.01(m,2H),1.99-1.60(m,2H),1.48(s,10H),1.22(d,J=6.5Hz,3H)。LCMS m/z 396.05$[M+H]^+$。

[1422] 步骤2:(2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C38)的合成

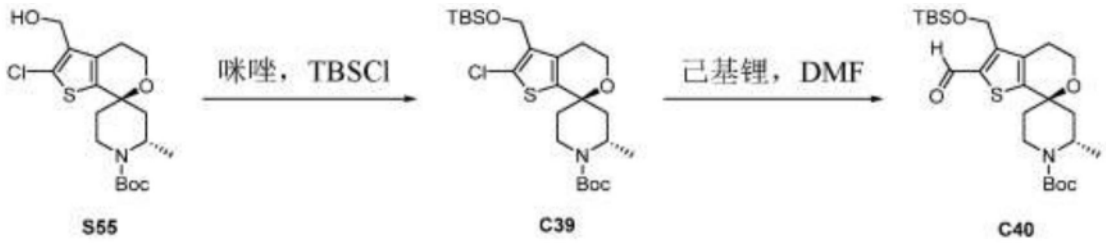
[1423] 向(2′S,7R)-2-甲酰基-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C37(70mg,0.1763mmol)于DCM(700μL)中的溶液中添加DAST(116μL,0.8780mmol),并将反应物加热至40℃。4小时后,添加另外的DAST(116μL,0.8780mmol)。搅拌过夜后,将溶液用DCM稀释并用饱和$NaHCO_3$溶液洗涤,用DCM(2x)萃取并用盐水洗涤。去除溶剂以产生粗产物。将粗材料重新溶解在二噁烷(2mL)中,并添加HCl(1.3mL的4M,5.200mmol)。30分钟后,去除溶剂并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(43mg,55%)。^{1}H NMR(300MHz,氯仿-d)δ9.48(s,1H),8.80(s,1H),7.04(t,J=55.5Hz,1H),4.43(d,J=1.3Hz,2H),4.34-3.88(m,4H),3.65(s,1H),3.41(s,5H),2.67(t,J=5.4Hz,2H),2.28-1.93(m,4H),1.38(d,J=6.5Hz,3H)。LCMS m/z318.25$[M+H]^+$。

[1424] 步骤3:(2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](763)的合成

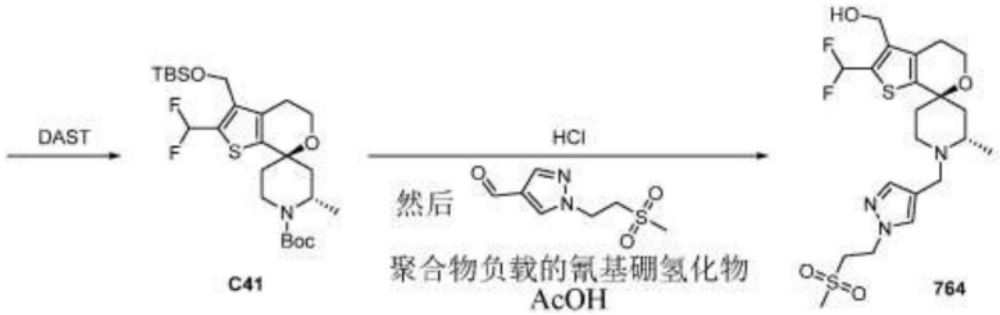
[1425] 将(2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)C38(11.1mg,0.02496mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(6.5mg,0.03214mmol)溶解在DCM(2mL)中。将乙酸(4.5mg,0.07494mmol)添加到溶液中。将溶液转移到微波管(5mL)中并添加聚合物负载的氰基硼氢化物(62mg的2mmol/g,0.1240mmol)。将溶液加盖并在微波反应器中加热至110℃,持续45分钟。将溶液过滤,将溶剂去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7R)-2-(二氟甲基)-3-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(5.4mg,26%)。LCMS m/z 504.09$[M+H]^+$。

[1426] 化合物764

[1427] [(2′S,7R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(764)



[1428]



[1429] 步骤1:(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C39)的合成

[1430] 向(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S55(396mg,1.021mmol)于DCM(8mL)中的溶液中添加咪唑(400mg,5.876mmol)和TBSCl(649mg,4.306mmol)。将混合物搅拌40分钟并且然后将其用1N HCl淬灭,用DCM稀释并通过相分离器分离。将混合物通过硅胶色谱法纯化(梯度:含0-10% EtOAc的庚烷),以提供(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(385mg,65%)。LCMS m/z502.31$[M+H]^+$。

[1431] 步骤2:(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C40)的合成

[1432] 将(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C39(1070mg,2.070mmol)于THF(25mL)中的混合物在火焰干燥的烧瓶中冷却至-78℃。此时,逐滴添加含己基锂(1.8mL的2.3M,4.140mmol)的己烷并在该温度下搅拌10分钟。此时,添加N,N-二甲基甲酰胺(500μL,6.457mmol)并将混合物搅拌另外10分钟。将混合物用约7M氯化铵水溶液(3mL)淬灭。使混合物温热至室温。将反应物用Et_2O(100mL)和水(100mL)稀释。将有机层分离并用水(2×100mL)和盐水(100mL)洗涤,用硫酸钠干燥并浓缩。将混合物通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),以提供(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(771mg,75%)。^1H NMR(400MHz,氯仿-d)δ10.22(s,1H),4.93-4.81(m,2H),4.01(tt,J=11.7,6.4Hz,1H),3.96-3.85(m,2H),3.76(ddd,J=13.9,6.1,4.6Hz,1H),3.34(ddd,J=14.1,9.0,5.3Hz,1H),2.69-2.55(m,2H),2.26-2.16(m,1H),2.11(ddd,J=14.2,5.2,1.9Hz,1H),1.83(ddd,J=14.5,5.3,4.6Hz,1H),1.75(dd,J=14.3,11.0Hz,1H),1.48(s,9H),1.26(d,J=6.6Hz,3H),0.90(s,9H),0.10(d,J=0.8Hz,6H)。LCMS m/z 496.21$[M+H]^+$。

[1433] 步骤3:(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-(二氟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C41)的合成

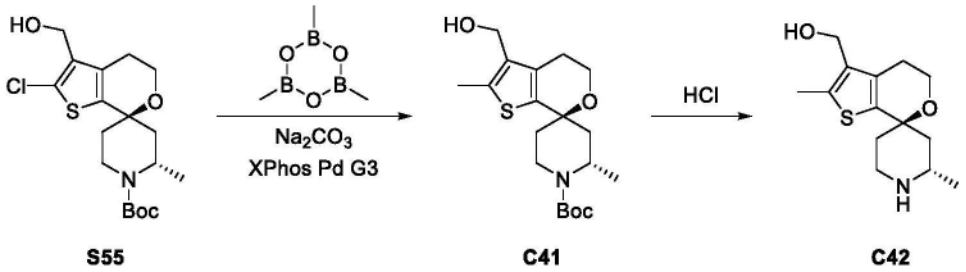
[1434] 向(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C40(100mg,0.1990mmol)于DCM(500μL)中的混合物中添加DAST(75μL,0.5677mmol)并将混合物加热至40℃。1小时后,添加另外的DAST(75μL,0.5677mmol)并将反应物搅拌过夜。在0℃下将混合物缓慢添加到碳酸氢钠水溶液的搅拌饱和溶液中。萃取后,添加另外的DCM(20mL)并将有机层分离并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0-20% EtOAc的庚烷),以提供(2′S,7R)-3-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-(二氟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯。物质无需进一步纯化即可用于下一步骤。

[1435] 步骤4:[(2′S,7R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(764)的合成

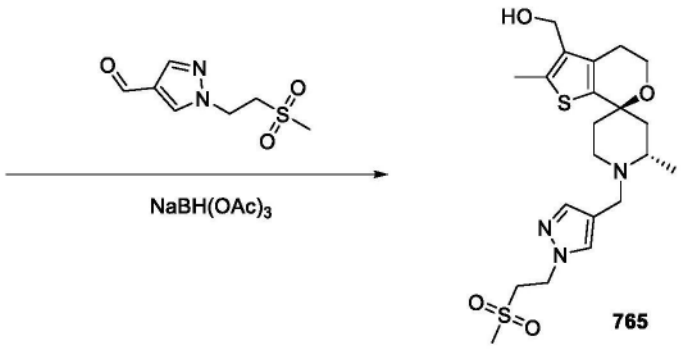
[1436] 向来自先前步骤的产物(C41)中添加HCl(含550μL的4M的二噁烷,2.200mmol)。25分钟后,将混合物用Et_2O稀释并且然后浓缩。添加DCM,将其再次浓缩,并且然后用DCM(1mL)稀释。添加甲醇(0.1mL)产,随后添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(75mg,0.3193mmol)和聚合物负载的氰基硼氢化物(150mg的2mmol/g,0.3000mmol)。将混合物加热至80℃。4小时又35分钟后,将混合物冷却至室温,过滤并将聚合物用另外的甲醇冲洗。将混合物浓缩,通过硅胶色谱法纯化(梯度:含0-10%MeOH的DCM)以产生[(2′S,7R)-2-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(17.4mg,18%)。^1H NMR(400MHz,氯仿-d)δ7.43(d,J=0.7Hz,1H),7.39(s,1H),6.99(t,J=55.8Hz,1H),4.57(t,J=1.3Hz,2H),4.52(dd,J=6.6,5.5Hz,2H),3.87-3.71(m,3H),3.60-3.50(m,3H),2.63-2.53(m,3H),2.53-2.40(m,2H),2.38(d,J=1.6Hz,3H),1.98-1.88(m,2H),1.85-1.77(m,2H),1.61(dd,J=13.9,11.4Hz,1H),1.12(d,J=6.2Hz,3H)。LCMS m/z 490.09$[M+H]^+$。

[1437] 化合物765

[1438] [(2′S,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(765)



[1439]



[1440] 步骤1:(2′S,7R)-3-(羟甲基)-2,2′-二甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C41)的合成

[1441] 向1打兰小瓶中添加(2′S,7R)-2-氯-3-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S55(97mg,0.2501mmol)、碳酸钠(138mg,1.302mmol)、XPhos Pd G3(21mg,0.02481mmol)并将小瓶用N_2吹扫15分钟。然后添加二噁烷(700μL)、水(700μL,经脱气的)和2,4,6-三甲基-1,3,5,2,4,6-三氧杂三硼烷(110μL,0.7869mmol)。将反应混合物在80℃下搅拌。3小时后,将反应物用饱和$NaHCO_3$溶液淬灭并且用EtOAc(x4)萃取。将合并的有机层经Na_2SO_4干燥,过滤,并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0至60% EtOAc的庚烷)以产生(2′S,7R)-3-(羟甲基)-2,2′-二甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(74.7mg,81%)。

[1442] 步骤2:[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(C42)的合成

[1443] 向含(2′S,7R)-3-(羟甲基)-2,2′-二甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C41(74.7mg,0.203mmol)的DCM(1mL)中添加HCl(650μL的4M,2.600mmol),并将反应物置于室温下。3小时后,将反应物用饱和$NaHCO_3$溶液淬灭并用DCM(x6)萃取。将合并的有机层经Na_2SO_4干燥,过滤并浓缩以提供粗材料[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(43.4mg,65%)。

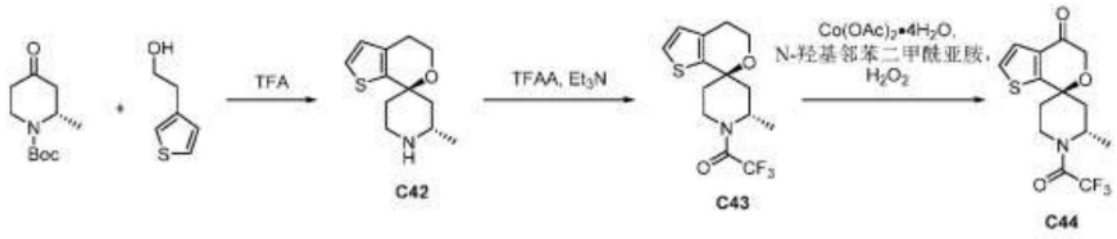
[1444] 步骤3:[(2′S,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(765)的合成

[1445] 向来自步骤2的粗材料(C42)和含1-(2-甲基磺酰基乙基)吡唑-4-甲醛(76mg,0.3758mmol)的DCM(970μL)中添加三乙酰氧基(钠代)硼(126mg,0.5973mmol)。16小时后,将反应物用饱和$NaHCO_3$溶液淬灭并用EtOAc(x4)萃取。将合并的有机层经Na_2SO_4干燥,过滤,并浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0至20% MeOH的DCM)以产生[(2′S,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡

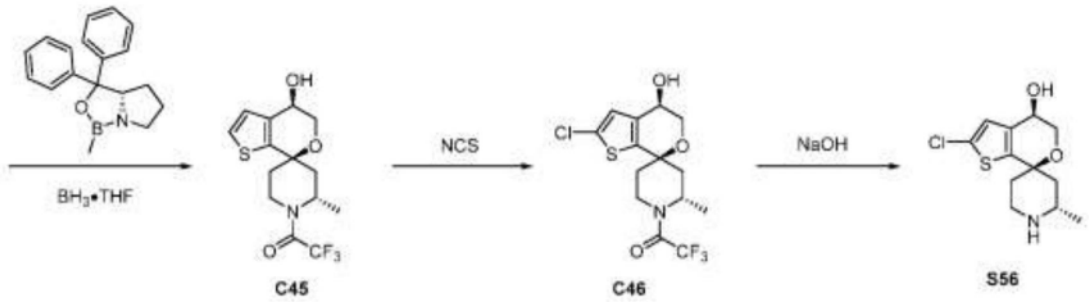
喃-7,4′-哌啶]-3-基]甲醇(30.8mg,25%,经3个步骤)。^{1}H NMR(300MHz,氯仿-d)δ7.50(s,1H),7.45(s,1H),4.66-4.53(m,2H),4.49(s,2H),3.83(dd,J=13.5,8.5Hz,3H),3.73-3.56(m,3H),2.71-2.47(m,4H),2.45(s,3H),2.42(s,3H),2.09-1.76(m,3H),1.66(t,J=12.8Hz,3H),1.19(d,J=6.2Hz,3H)。LCMS m/z 454.17[M+H]$^+$。

[1446] 制备S56

[1447] (2′S,4S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S56)



[1448]



[1449] 步骤1:(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C42)的合成

[1450] 向配备有氮气入口、加料漏斗、机械搅拌器和内部温度探针的3颈圆底烧瓶中装入(2S)-2-甲基-4-氧代-p哌啶-1-甲酸叔丁酯(144.1g,675.7mmol)于DCM(1.30L)中的溶液。将溶液冷却至5℃,并且以将内部温度保持在10℃以下的速率逐滴添加TFA(1.10L)。搅拌所得溶液,直至通过TLC和1H NMR观察到起始材料完全消耗。然后用室内真空将容器抽空5分钟,并且然后用氮气(气球)吹扫。将混合物冷却至-62℃,这使得溶液变成粘稠浆料。逐滴添加2-(3-噻吩基)乙醇(91.2g,711.4mmol),确保内部温度不超过-55℃。冷却浴过夜后,使混合物温热至环境温度。

[1451] 搅拌过夜后,将混合物浓缩并在DCM(1L)中摄取并在真空中浓缩。将残余物在DCM(500mL)中摄取并搅拌添加2M氢氧化钠水溶液知道水层达到pH 7-8。将各层分离,并将水相用DCM(2×100mL)萃取。将合并的有机萃取物用盐水洗涤,经硫酸钠干燥,过滤并浓缩以提供(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](150.9g,100%)。LCMS m/z 224.04[M+H]$^+$。材料无需进一步纯化即可用于下一步骤。

[1452] 步骤2:2,2,2-三氟-1-[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(C43)的合成

[1453] 向配备有氮气入口、加料漏斗、机械搅拌器和内部温度探针的3颈圆底烧瓶装入含(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]C42(150.9g)的DCM(1.3L)并冷却至5℃。将Et_3N(0.300L,2.152mol)和TFAA(0.100L,719.4mmol)依序逐滴添加到溶液

中。20分钟后,去除冷却浴。胺完全消耗后,将反应物用10％柠檬酸水溶液(400mL)淬灭,并将各层分离。将水部分用DCM(100mL)萃取。将合并的有机层用饱和碳酸氢钠水溶液(300mL)洗涤两次,经硫酸钠干燥,过滤并浓缩。将粗残余物在庚烷(1L)中摄取两次并浓缩以得到黄色油。随后将油在含5％乙酸异丙酯的庚烷中摄取并加热指导溶液均匀。一旦达到均匀性,关闭搅拌以使不溶性物质沉淀,将溶液插入侧臂锥形烧瓶中,并冷却至室温。此时,引入种子(来自同一批次的试验作物),并在环境条件下轻轻搅拌溶液过夜。将收集的固体通过硅胶色谱法纯化(梯度:含0-15％叔丁基甲醚的庚烷)以得到呈油的标题化合物,其静置后固化为白色固体。2,2,2-三氟-1-[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(142.3g,63％)。^{1}H NMR(300MHz,氯仿-d)δ7.16(d,J＝5.0Hz,1H),6.75(d,J＝5.0Hz,1H),4.50-4.27(m,1H),3.85(t,J＝5.5Hz,3H),3.44(s,1H),2.66(t,J＝5.5Hz,2H),2.31(ddd,J＝14.3,6.3,1.9Hz,2H),1.99(ddd,J＝14.8,6.0,2.4Hz,1H),1.83(dd,J＝14.4,10.8Hz,1H),1.30(d,J＝6.5Hz,3H)。^{19}F NMR(282MHz,氯仿-d)δ-69.75。LCMS m/z 320.1[M+H]$^{+}$。

[1454] 步骤3:(2S,4R)-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(C44)的合成

[1455] 在空气中向2,2,2-三氟-1-[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮C43(5000mg,14.87mmol)于乙腈(300mL)中的混合物中添加N-羟基邻苯二甲酰亚胺(3.3g,20.23mmol)和二乙酸钴(II)四水合物(200mg,0.8029mmol),并且然后添加过氧化氢水溶液(3.2mL的30％w/w,31.33mmol)。将黄色混合物在50℃下搅拌。30小时后,将混合物冷却至室温并浓缩至约2vol。将固体用MTBE(100mL)稀释,沉淀出棕褐色固体,过滤并用另外的MTBE冲洗。将绿色滤液用饱和碳酸氢钠水溶液(100mL)洗涤。将各层分开,并用另外3次碳酸氢钠溶液洗涤有机层,直到有机层显示出很少至没有NHPI。将有机层用盐水(100mL)最后一次洗涤,用硫酸钠干燥,过滤并浓缩至干燥以产生4.9g粗材料。将粗材料使用硅胶色谱法纯化(梯度:含0-30％ EtOAc的庚烷)以产生(2S,4R)-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(2.78g,53％)。^{1}HNMR(400MHz,DMSO-d_6)δ7.61(d,J＝5.2Hz,1H),7.31(d,J＝5.2Hz,1H),4.39(d,J＝17.2Hz,1H),4.32-4.08(m,2H),3.74(s,2H),2.56(d,J＝14.7Hz,1H),2.42-2.26(m,1H),2.10(d,J＝15.1Hz,2H),1.20(s,3H)。LCMS m/z 334.01[M+H]$^{+}$。

[1456] 步骤4:2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙烯酮(C45)的合成

[1457] 在0℃下向(3aS)-1-甲基-3,3-二苯基-3a,4,5,6-四氢吡咯并[1,2-c][1,3,2]噁唑硼烷(1250μL的1M,1.250mmol)于MTBE(40mL)中的甲苯溶液中的混合物中添加硼烷四氢呋喃(12mL的1M,12.00mmol)。10分钟后,通过加料漏斗添加(2S,4R)-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮C44(2800mg,8.182mmol)于MTBE(20mL)中的溶液。总计50分钟后,添加另外的硼烷(3mL的1M,3.00mmol)。10分钟后,将混合物用1N HCl水溶液(50mL)淬灭。将有机层用盐水洗涤,用硫酸钠干燥并过滤。将混合物浓缩,并通过硅胶色谱法纯化(梯度:含0-60％EtOAc的庚烷)以提供2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(2.31g,83％)。^{1}H NMR(400MHz,氯仿-d)δ7.23(d,J＝5.1Hz,1H),7.00(d,J＝5.1Hz,1H),4.55(dt,J

＝9.2,2.8Hz,1H),4.48(d,J＝18.4Hz,1H),3.96-3.79(m,3H),3.49(d,J＝5.5Hz,1H),2.39(s,1H),2.29(dd,J＝14.5,6.4Hz,1H),1.99(d,J＝9.3Hz,1H),1.97-1.88(m,1H),1.88-1.77(m,1H),1.32(d,J＝6.5Hz,3H)。LCMS m/z 335.99[M+H]$^+$。

[1458] 步骤5:1-[(2′S,4S,7R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮(C46)的合成

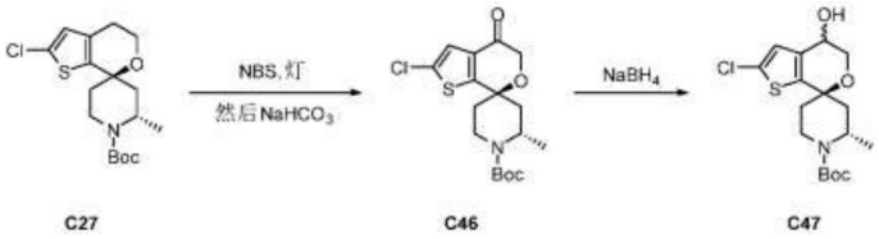
[1459] 向2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮C45(2.31g,6.89mmol)于MeCN(30mL)中的混合物中添加NCS(1200mg,8.987mmol),并将混合物在氮气下加热至70℃。3小时后,将反应物冷却至rt,用1M亚硫酸氢钠淬灭,并且然后用EtOAc(50mL)和水(30mL)稀释。将有机层用盐水洗涤(2×50mL)洗涤,用硫酸钠干燥并过滤。将有机层浓缩,并通过硅胶色谱法纯化(梯度:含0-50%EtOAc的庚烷)以提供1-[(2′S,4S,7R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮(1.44g,47%)。LCMS m/z 378.67[M+H]$^+$。

[1460] 步骤6:(2′S,4S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S56)的合成

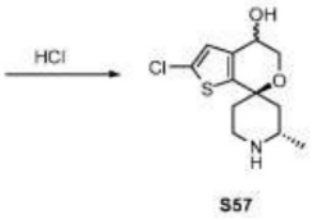
[1461] 向1-[(2′S,4S,7R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮C45(2700mg,7.302mmol)于MeOH(26mL)中的混合物中添加NaOH水溶液(10mL的2M,20.00mmol)。7分钟后,将混合物浓缩至最小体积并用HCl(20mL的1M,20.00mmol)淬灭至约10的pH。此时,将混合物用pH 10.5缓冲液(50mL)和DCM(100mL)稀释。将各层混合并分离,并测定水层,并通过UPLC发现仍具有产物。用氢氧化钠溶液将混合物的pH调节至pH 12,并且然后用DCM(100mL)萃取。将有机层于第一有机层合并,用硫酸镁干燥,过滤冲洗并通过相分离器以产生(2′S,4S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1.93g,95%)。^{1}H NMR(400MHz,DMSO-d_6)δ6.94(s,1H),5.35(d,J＝6.4Hz,1H),4.35(ddd,J＝6.4,5.2,4.2Hz,1H),3.86(dd,J＝11.8,4.2Hz,1H),3.58(dd,J＝11.8,5.2Hz,1H),2.85(ddd,J＝11.0,6.3,2.3Hz,1H),2.78(dd,J＝12.3,2.5Hz,1H),2.73-2.63(m,1H),1.97(dt,J＝13.3,2.5Hz,1H),1.92-1.76(m,2H),1.45(ddd,J＝13.4,12.3,4.9Hz,1H),1.15(dd,J＝13.3,11.2Hz,1H),0.94(d,J＝6.4Hz,3H)。LCMS m/z 274.07[M+H]$^+$。

[1462] 制备S57

[1463] (2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S57)



[1464]



[1465] 步骤1:(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C46)的合成

[1466] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(3g,6.433mmol)和NBS(1.67g,9.383mmol)溶解在氯苯(40mL)中,并在100W灯泡下辐照。30小时后,将溶液用硫酸氢钠水溶液淬灭,用DCM淬灭,并通过硅胶塞过滤。将溶剂在真空中去除。将所得固体溶解在DMSO(30mL)中并将$NaHCO_3$(786mg,9.356mmol)添加到溶液中。将所得混合物加热至50℃并搅拌过夜。然后将溶液用H_2O淬灭并将溶液用DCM(x3)萃取并用盐水洗涤。将产物通过硅胶色谱法纯化(梯度:含0-20% EtOAc的己烷)以提供(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(300mg,11%)。LCMS m/z 371.83$[M+H]^+$。

[1467] 步骤2:(2S,4R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C47)的合成

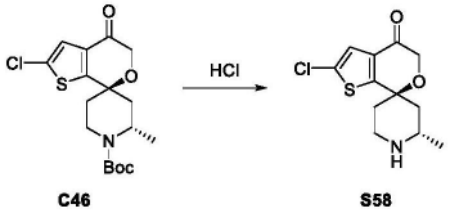
[1468] 将(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(2g,5.378mmol)溶解在DCM(80mL)中,并在N_2下添加MeOH(20mL),随后添加$NaBH_4$(1.3mL,32.47mmol)。将反应物在室温下搅拌1小时。然后将其用水洗涤,并用DCM萃取。将合并的有机层用HCl洗涤,用盐水洗涤并在真空中去除溶剂。然后将粗材料通过硅胶色谱法纯化(梯度:含0-40% EtOAc的己烷)以提供(2S,4R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(350mg,16%)。^1H NMR(300MHz,氯仿-d)δ 6.80(d,J=5.4Hz,1H),4.48-4.34(m,1H),4.10-3.64(m,4H),3.29(ddt,J=14.1,8.9,5.4Hz,1H),2.49-2.02(m,3H),1.89-1.58(m,2H),1.45(s,9H),1.24(dd,J=6.6,3.6Hz,3H)。LCMS m/z 374.26$[M+H]^+$。

[1469] 步骤3:(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S57)的合成

[1470] 将(2S,4R)-2-氯-4-羟基-2′-甲基-螺[5,6-二氢-4H-苯并噻吩-7,4′-哌啶]-1′-甲酸叔丁酯C47(240mg,0.6453mmol)溶解在二噁烷(3.6mL)中并添加HCl(3.2mL的4M,12.80mmol)。将溶液搅拌过夜。然后将溶剂在真空中去除以提供(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(176mg,100%)。LCMS m/z 274.03$[M+H]^+$。

[1471] 制备S58

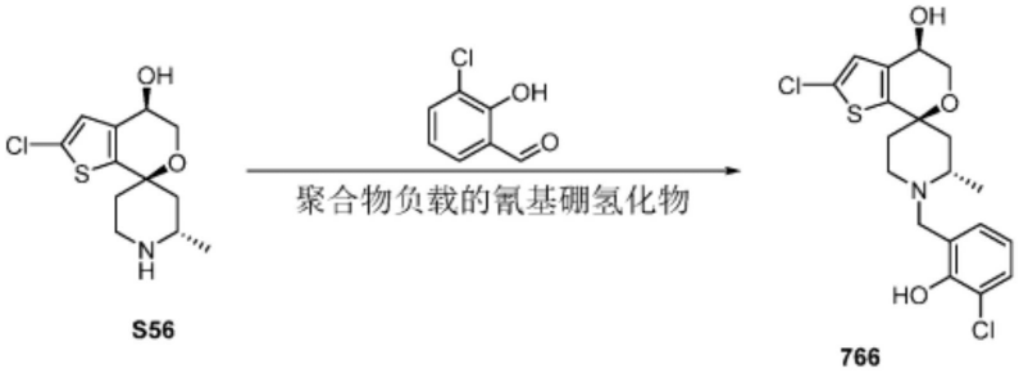
[1472] (2S,4R)-2′-氯-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(S58)

[1473] 

[1474] 将(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(20mg,0.05378mmol)溶解在具有HCl(200μL的4M,0.8000mmol)的二噁烷(520μL)中。将溶液在室温下搅拌过夜。将溶剂在真空中去除以产生(2S,4R)-2′-氯-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(盐酸盐)(14.64mg,31%)。LCMS m/z 272.38[M+H]$^+$。

[1475] 化合物766

[1476] (2′S,4R,7R)-2-氯-1′-[(3-氯-2-羟基-苯基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(766)

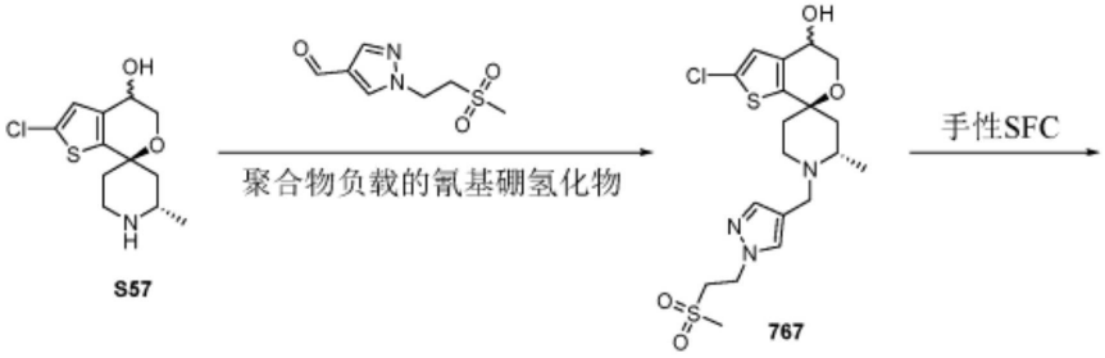
[1477] 

[1478] 标准方法#A:使用聚合物负载的氰基硼氢化物进行还原胺化

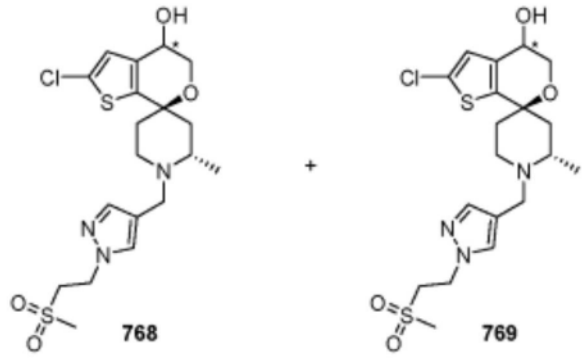
[1479] 向含有3-氯-2-羟基-苯甲醛溶液(400μL,含0.25M的DMF,0.1mmol)的1打兰小瓶中装入聚合物负载的氰基硼氢化物(75mg,0.15mmol,负载2mmol/g),随后添加(2′S,4S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S56(400μL,含0.14M的DMF,0.056mmol;具有催化量的TFA)。将小瓶密封并在85℃下加热过夜。然后将小瓶冷却至室温。将所得悬浮液通过25微米聚丙烯过滤板过滤。将TFA(400μL,含0.1wt%的水)添加到反应小瓶中,将其搅拌若干分钟以冲洗珠粒。使另外的水洗涤液通过过滤板。将DMSO(200μL)添加到所得滤液中。将所得粗溶液通过0.45微米注射器过滤器过滤。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2′S,4R,7R)-2-氯-1′-[(3-氯-2-羟基-苯基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(4.5mg,15%)。LCMS m/z414.29[M+H]$^+$。

[1480] 化合物767-769

[1481] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(767,768,769)



[1482]



[1483] 步骤1:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(767)的合成-标准方法#B:在微波反应器中使用聚合物负载的氰基硼氢化物和乙酸进行还原胺化

[1484] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S57(109mg,0.3981mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(161mg,0.7961mmol)溶解在DCM(2.94mL)中,并将乙酸(120mg,1.998mmol)添加到溶液中。将溶液转移到微波管(5mL)中并添加聚合物负载的氰基硼氢化物(594mg的2mmol/g,1.188mmol)。将反应混合物加盖并在微波反应器中加热至110℃,持续140分钟。将溶液过滤并通过硅胶色谱法纯化(梯度:含0-60% EtOAc的己烷)以产生(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(90.9mg,49%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.74(s,1H),7.55(s,1H),6.85(d,J=0.7Hz,1H),4.63(t,J=6.4Hz,2H),4.41(dt,J=6.9,3.8Hz,1H),4.07-3.60(m,6H),2.87-2.48(m,7H),2.10(t,J=9.6Hz,2H),1.96-1.42(m,2H),1.26(dd,J=6.3,4.1Hz,3H)。LCMS m/z 460.11$[M+H]^+$。

[1485] 步骤2:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(768和769)的合成

[1486] 将(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇767通过手性SFC分离分离成组成对映异构体。柱:Daicel Chiralpak®IC,10×250mm;流动相:40% MeOH(含有5mM氨),60%二氧化碳。流速:15毫升/分钟。获得两种产物:

[1487] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(24.2mg,26%)。^{1}H NMR(400MHz,甲醇-d_4)δ8.00(s,1H),7.73(d,J=0.7Hz,1H),6.92(s,1H),4.70(dd,J=6.9,5.4Hz,2H),4.54(d,J=14.1Hz,1H),4.45(t,J=3.5Hz,1H),4.28(d,J=14.1Hz,1H),3.94(dd,J=12.3,3.4Hz,

1H),3.81-3.69(m,3H),3.57(dd,J＝10.4,6.4Hz,1H),3.40-3.21(m,2H),2.87(s,3H),2.37(ddd,J＝21.0,15.0,3.0Hz,2H),2.03-1.82(m,2H),1.54(d,J＝6.5Hz,3H)。LCMS m/z 460.06[M+H]$^+$;和

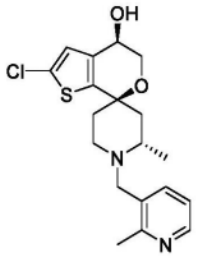
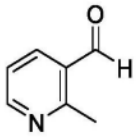
[1488] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(23.6mg,25%)。^{1}H NMR(400MHz,甲醇-d_4)δ7.74(s,1H),7.54(d,J＝0.8Hz,1H),6.85(s,1H),4.63(t,J＝6.4Hz,2H),4.42(t,J＝4.0Hz,1H),3.99-3.56(m,6H),2.88-2.50(m,6H),2.20-1.73(m,3H),1.53(dd,J＝14.3,11.6Hz,1H),1.24(d,J＝6.3Hz,3H)。LCMS m/z460.11[M+H]$^+$。

[1489] 化合物770-812

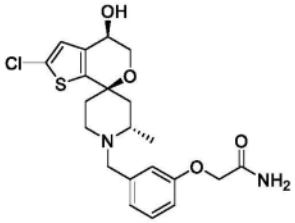
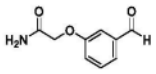
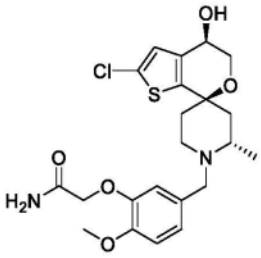
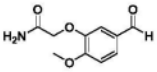
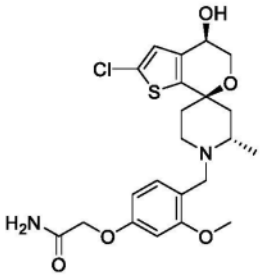
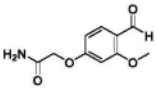
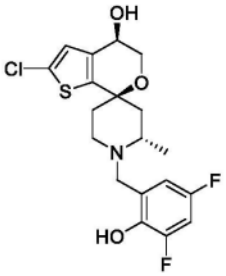
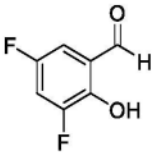
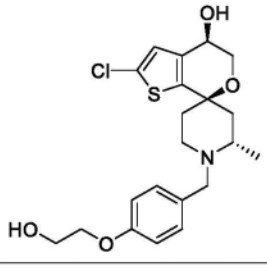
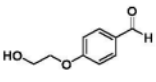
[1490] 化合物770-812(参见表33)由中间体S56和S57使用如化合物766-769所述的方法在单个步骤中制备。醛从商业来源获得或如前所述。表33和随附脚注中注明了对方法的任何修改。

[1491] 表33:化合物770-812的结构和物理化学数据

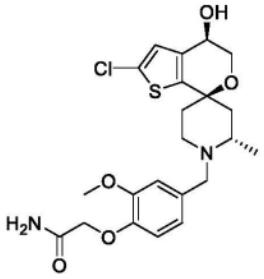
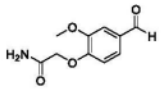
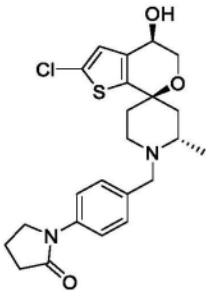
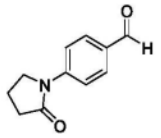
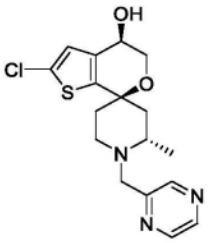
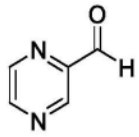
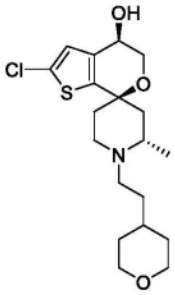
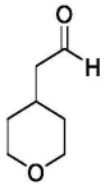
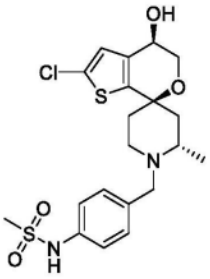
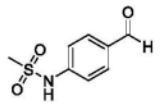
[1492]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
770			S56，化合物 766	LCMS *m/z* 379.34 [M+H]$^+$。

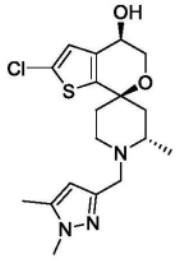
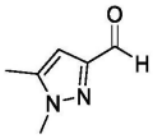
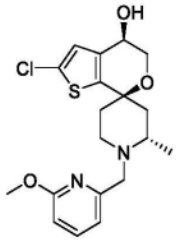
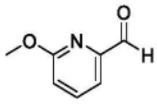
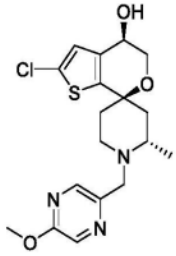
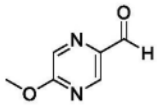
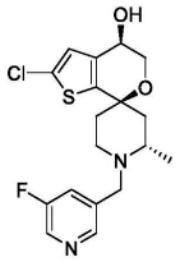
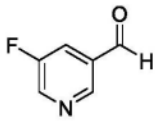
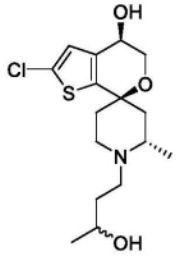
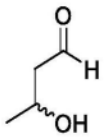
[1493]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
771			S56，化合物 766	LCMS *m/z* 437.36 $[M+H]^+$。
772			S56，化合物 766	LCMS *m/z* 467.39 $[M+H]^+$。
773			S56，化合物 766	LCMS *m/z* 467.39 $[M+H]^+$。
774			S56，化合物 766	LCMS *m/z* 416.28 $[M+H]^+$。
775			S56，化合物 766	LCMS *m/z* 424.36 $[M+H]^+$。

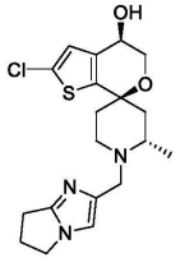
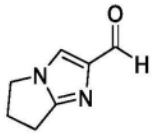
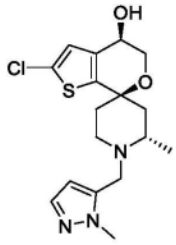
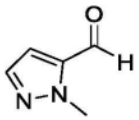
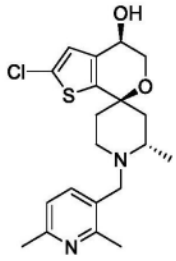
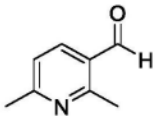
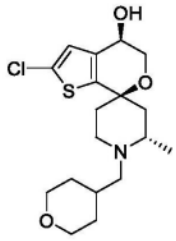
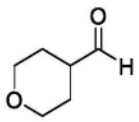
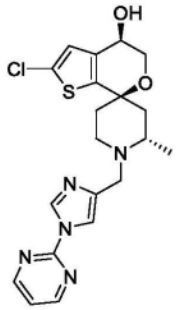
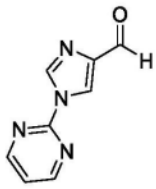
[1494]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
776			S56，化合物 766	LCMS *m/z* 467.39 $[M+H]^+$。
777			S56，化合物 766	LCMS *m/z* 447.38 $[M+H]^+$。
778			S56，化合物 766	LCMS *m/z* 366.29 $[M+H]^+$。
779			S56，化合物 766	LCMS *m/z* 386.38 $[M+H]^+$。
780			S56，化合物 766	LCMS *m/z* 457.36 $[M+H]^+$。

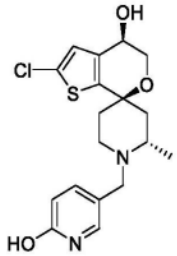
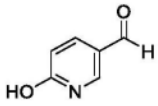
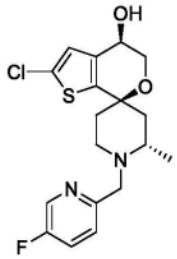
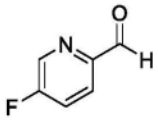
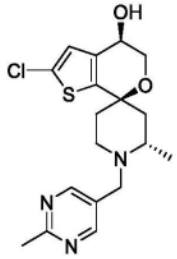
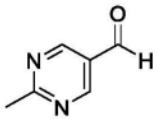
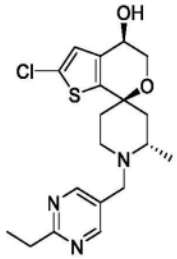
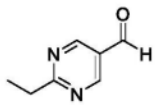
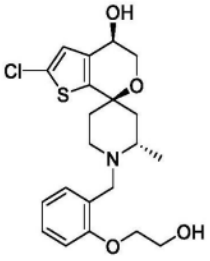
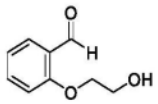
[1495]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
781			S56，化合物 766	LCMS *m/z* 382.36 $[M+H]^+$。
782			S56，化合物 766	LCMS *m/z* 395.32 $[M+H]^+$。
783			S56，化合物 766	LCMS *m/z* 396.32 $[M+H]^+$。
784			S56，化合物 766	LCMS *m/z* 383.31 $[M+H]^+$。
785			S56，化合物 766	LCMS *m/z* 346.33 $[M+H]^+$。

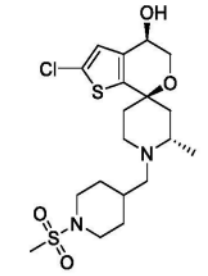
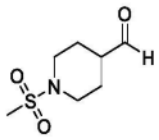
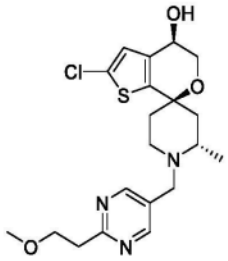
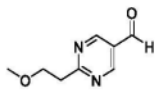
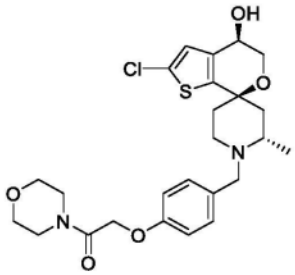
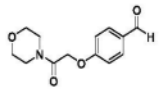
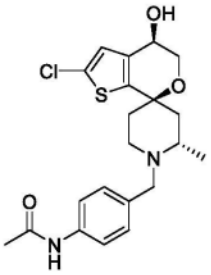
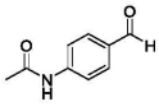
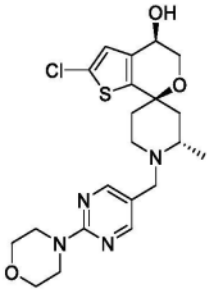
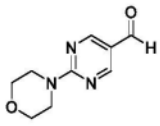
[1496]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
786			S56，化合物 766	LCMS *m/z* 394.33 $[M+H]^+$。
787			S56，化合物 766	LCMS *m/z* 368.32 $[M+H]^+$。
788			S56，化合物 766	LCMS *m/z* 393.34 $[M+H]^+$。
789			S56，化合物 766	LCMS *m/z* 372.34 $[M+H]^+$。
790			S56，化合物 766	LCMS *m/z* 432.35 $[M+H]^+$。

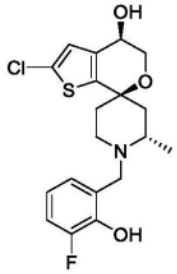
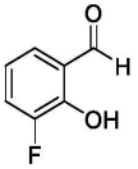
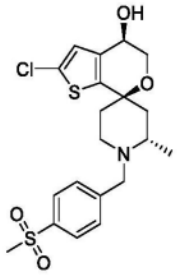
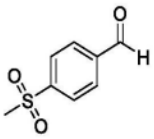
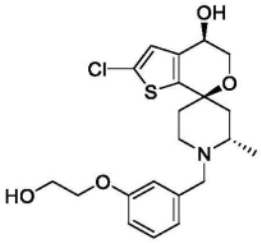
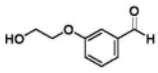
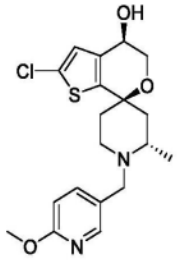
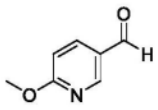
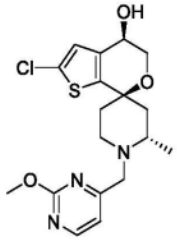
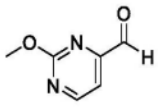
[1497]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
791			S56，化合物 766	LCMS *m/z* 381.33 $[M+H]^+$。
792			S56，化合物 766	LCMS *m/z* 383.31 $[M+H]^+$。
793			S56，化合物 766	LCMS *m/z* 380.33 $[M+H]^+$。
794			S56，化合物 766	LCMS *m/z* 394.33 $[M+H]^+$。
795			S56，化合物 766	LCMS *m/z* 424.36 $[M+H]^+$。

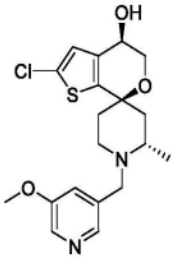
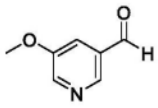
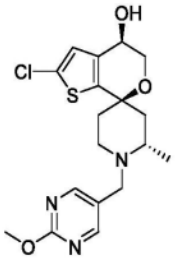
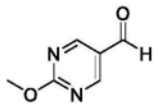
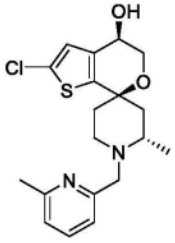
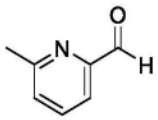
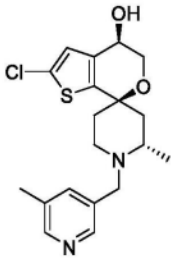
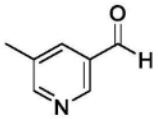
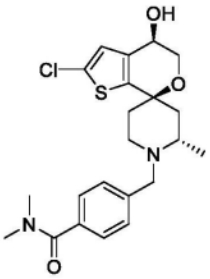
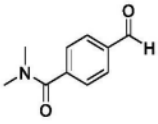
[1498]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
796			S56，化合物 766	LCMS *m/z* 449.37 $[M+H]^+$。
797			S56，化合物 766	LCMS *m/z* 424.36 $[M+H]^+$。
798			S56，化合物 766	LCMS *m/z* 507.43 $[M+H]^+$。
799			S56，化合物 766	LCMS *m/z* 421.33 $[M+H]^+$。
800			S56，化合物 766	LCMS *m/z* 451.36 $[M+H]^+$。

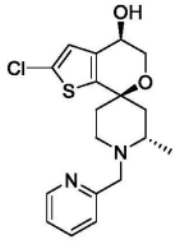
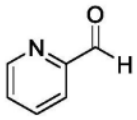
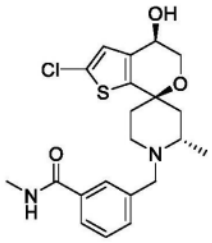
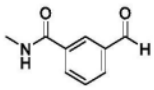
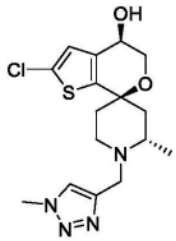
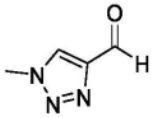
[1499]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
801			S56，化合物 766	LCMS *m/z* 398.31 $[M+H]^+$。
802			S56，化合物 766	LCMS *m/z* 442.28 $[M+H]^+$。
803			S56，化合物 766	LCMS *m/z* 424.31 $[M+H]^+$。
804			S56，化合物 766	LCMS *m/z* 395.37 $[M+H]^+$。
805			S56，化合物 766	LCMS *m/z* 396.32 $[M+H]^+$。

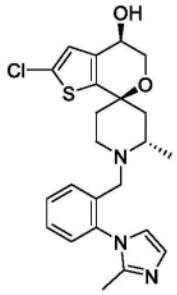
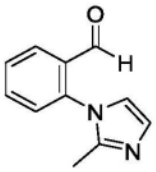
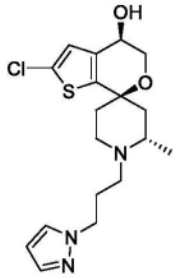
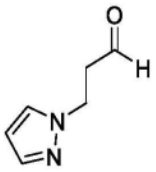
[1500]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
806			S56，化合物 766	LCMS *m/z* 395.32 $[M+H]^+$。
807			S56，化合物 766	LCMS *m/z* 396.32 $[M+H]^+$。
808			S56，化合物 766	LCMS *m/z* 379.3 $[M+H]^+$。
809			S56，化合物 766	LCMS *m/z* 379.34 $[M+H]^+$。
810			S56，化合物 766	LCMS *m/z* 435.37 $[M+H]^+$。

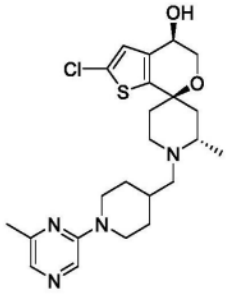
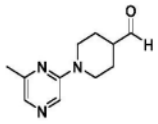
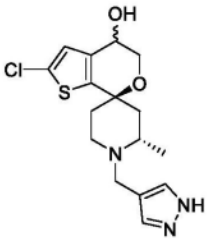
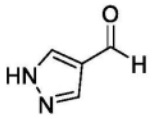
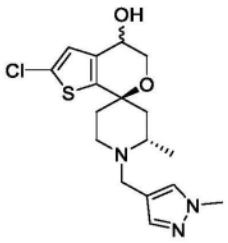
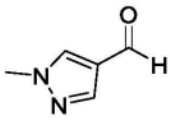
[1501]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
811			S56，化合物 766	LCMS *m/z* 365.34 $[M+H]^+$。
812			S56，化合物 766	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (d, *J* = 10.6 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 7.99 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 3.5 Hz, 1H), 5.49 (s, 1H), 4.81 (d, *J* = 12.8 Hz, 1H), 4.38 (d, *J* = 4.4 Hz, 1H), 4.19 (dd, *J* = 12.8, 8.3 Hz, 1H), 3.89 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.67 (dd, *J* = 12.0, 4.7 Hz, 1H), 3.59 (s, 1H), 3.18 - 3.09 (m, 1H), 2.98 - 2.88 (m, 1H), 2.80 (d, *J* = 4.4 Hz, 3H), 2.44 - 2.07 (m, 2H), 1.88 (dt, *J* = 50.4, 13.6 Hz, 2H), 1.51 (d, *J* = 6.4 Hz, 3H)；LCMS *m/z* 421.33 $[M+H]^+$。
813			S56，化合物 766	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.30 (s, 1H), 7.01 (s, 1H), 5.43 (s, 1H), 4.62 (d, *J* = 14.3 Hz, 1H), 4.50 (d, *J* = 13.9 Hz, 1H), 4.37 (s, 1H), 4.11

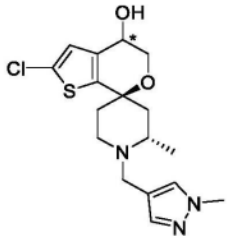
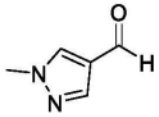
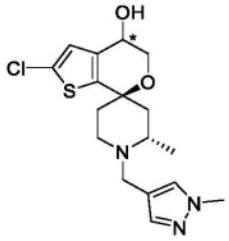
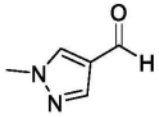
[1502]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
				(s, 3H), 3.85 (dd, *J* = 11.8, 4.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.38 - 3.26 (m, 2H), 3.23 - 3.08 (m, 1H), 2.26 (dd, *J* = 55.6, 14.7 Hz, 2H), 1.92 (t, *J* = 13.4 Hz, 2H), 1.46 (d, *J* = 6.4 Hz, 3H)；LCMS *m/z* 369.36 $[M+H]^+$。
814			S56，化合物 766	LCMS *m/z* 444.36 $[M+H]^+$。
815			S56，化合物 766	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.02 (s, 1H), 6.28 (t, *J* = 2.0 Hz, 1H), 5.48 (s, 1H), 4.43 - 4.36 (m, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 3.91 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.66 (dd, *J* = 12.0, 4.9 Hz, 1H), 3.37 - 3.21 (m, 2H), 3.16 (q, *J* = 11.2 Hz, 1H), 3.09 - 2.98 (m, 1H), 2.39 - 2.01 (m, 4H), 2.03 - 1.75 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 382.36 $[M+H]^+$。

[1503]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z $[M+H]^+$。
816			S56，化合物 766	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.14 (s, 1H), 7.70 (s, 1H), 7.03 (s, 1H), 4.47 - 4.32 (m, 4H), 3.93 (dd, J = 12.0, 4.0 Hz, 1H), 3.68 (dd, J = 11.8, 4.9 Hz, 1H), 3.56 (d, J = 12.3 Hz, 1H), 3.51 - 3.43 (m, 1H), 3.21 (dt, J = 55.8, 11.3 Hz, 2H), 3.03 - 2.80 (m, 4H), 2.30 (d, J = 22.5 Hz, 1H), 2.29 (s, 3H), 2.23 - 1.93 (m, 3H), 1.94 - 1.64 (m, 2H), 1.31 (d, J = 6.3 Hz, 3H), 1.29 - 1.12 (m, 2H)；LCMS m/z 463.41 $[M+H]^+$。
817			S57，化合物 767[1]	^{1}H NMR (400 MHz, 氯仿-d) δ 7.51 (s, 2H), 6.80 (d, J = 2.0 Hz, 1H), 4.39 (dt, J = 12.2, 2.8 Hz, 1H), 3.87 (ddt, J = 26.6, 14.4, 11.0 Hz, 3H), 3.58 (dd, J = 14.2, 5.7 Hz, 1H), 2.78 - 2.38 (m, 3H), 2.12 - 1.99 (m, 1H), 1.97 - 1.46 (m, 3H), 1.21 (t, J = 3.3 Hz, 3H)；LCMS m/z 353.95 $[M+H]^+$。
818			S57，化合物 767[2]	^{1}H NMR (300 MHz, 甲醇-d4) δ 7.88 (s, 1H), 7.66 (d, J = 0.8 Hz, 1H), 6.91 (s, 1H), 4.60 - 4.39 (m, 2H), 4.26 (d, J = 14.1 Hz,

[1504]

化合物	结构	醛 试剂	起始材料， 标准方法	^{1}H NMR；LCMS m/z [M+H]$^+$。
				1H), 4.05 - 3.89 (m, 4H), 3.76 (ddd, *J* = 12.2, 9.3, 3.9 Hz, 1H), 3.69 - 3.41 (m, 1H), 3.44 - 3.32 (m, 1H), 2.49 - 2.26 (m, 2H), 2.16 - 1.77 (m, 2H), 1.54 (dd, *J* = 6.5, 3.6 Hz, 3H)一些与溶剂峰重叠；LCMS *m/z* 368.15 [M+H]$^+$。
819			S57，化合物 768-769[23]	^{1}H NMR (300 MHz，甲醇-*d*$_4$) δ 7.57 (s, 1H), 7.42 (d, *J* = 0.8 Hz, 1H), 6.84 (s, 1H), 4.39 (t, *J* = 3.7 Hz, 1H), 3.99 - 3.47 (m, 7H), 2.76 - 2.42 (m, 3H), 2.15 - 1.98 (m, 2H), 1.81 - 1.51 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H)。
820			S57，化合物 768-769[3]	^{1}H NMR (300 MHz，甲醇-*d*$_4$) δ 7.57 (s, 1H), 7.43 (d, *J* = 0.8 Hz, 1H), 6.85 (s, 1H), 4.41 (t, *J* = 4.1 Hz, 1H), 4.00 - 3.55 (m, 7H), 2.88 - 2.38 (m, 3H), 2.15 - 1.97 (m, 2H), 1.82 (td, *J* = 13.3, 4.6 Hz, 1H), 1.51 (dd, *J* = 14.1, 11.5 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H)。

[1505] 脚注：

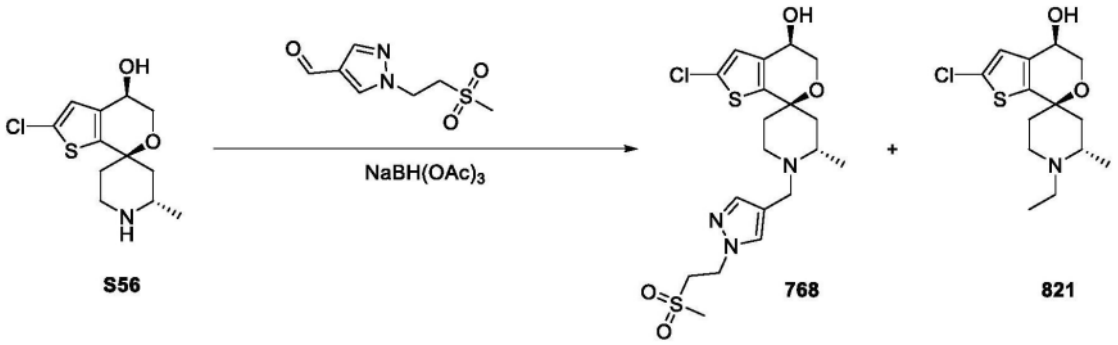
[1506] 1)使用了不同的试剂量：1H-吡唑-4-甲醛(1.1当量)，乙酸(2.6当量)。用C18柱反相HPLC进行纯化(梯度：含0-60％ MeCN的水，具有TFA改性剂)。

[1507] 2)使用了不同的试剂量：1-甲基吡唑-4-甲醛(1.5当量)。通过反相HPLC纯化。方法：C18 Waters Sunfire柱(30×150mm，5微米)。梯度：含MeCN的H_2O，具有0.1％三氟乙酸。

[1508] 3)将外消旋混合物818通过手性SFC分离分离成组成对映异构体。柱：Daicel Chiralpak®IC，10×250mm；流动相：40％ MeOH(含有5mM氨)，60％二氧化碳。流速：15毫升/分钟。

[1509] 化合物821

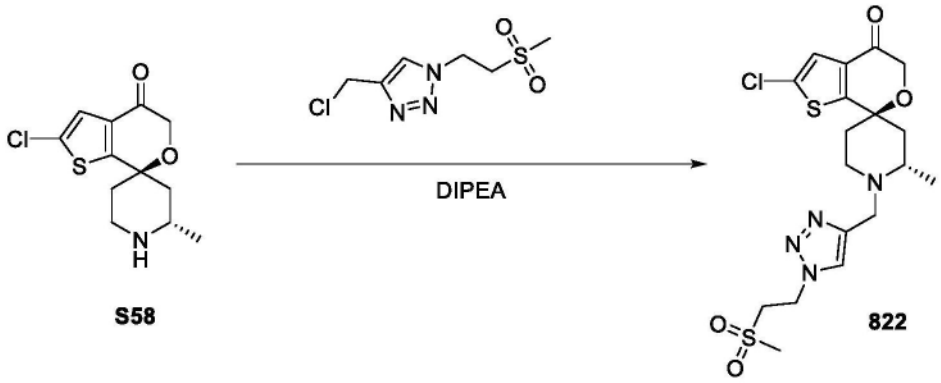
[1510] (2′S,4S,7R)-2-氯-1′-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(821)的合成

[1511] 

[1512] 在rt下向(2′S,4S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S56(48g,175.3mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(36.5g,180.5mmol)于THF(750mL)中的悬浮液中添加三乙酰氧基硼氢化钠(73g,344.4mmol)。将反应混合物加热至55℃。2小时后,添加另外的1-(2-甲基磺酰基乙基)吡唑-4-甲醛(1.0g,4.945mmol)。1小时后,使用冰水浴将反应物冷却至室温,并且然后用饱和碳酸氢钠水溶液(1.3L)。将双相混合物用碳酸钾(29g)处理,然后去除冰水浴。将混合物用EtOAc(300mL)处理,并在室温下搅拌过夜。16小时后,分离各层。将有机层用盐水(800mL)洗涤。将水层用EtOAc(1L)萃取,并将萃取物用盐水(500mL)洗涤,然后与原始有机层合并。将合并的有机层用$MgSO_4$干燥,过滤浓缩。通过硅胶色谱法纯化(梯度:含0-100% EtOAc的庚烷,具有5% Et_2NH改性剂)以得到期望产物混合杂质。将其进一步通过SFC纯化。柱:PYR,4.6×150mm;流动相:20% MeOH(含有0.2% Et_2NH),80%二氧化碳。流速:5毫升/分钟。分离两种产物:主产物是呈黄色泡沫的(2′S,4S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(76g,94%)。并且次峰鉴定为呈棕色油的(2′S,4S,7R)-2-氯-1′-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(2.9g,5%)。^{1}HNMR(400MHz,氯仿-d)δ6.80(s,1H),4.40(t,J=2.8Hz,1H),4.00-3.83(m,2H),2.89(dq,J=13.2,7.3Hz,1H),2.81-2.63(m,2H),2.58-2.47(m,2H),2.11(dq,J=14.3,2.8Hz,1H),1.94(dt,J=13.7,2.9Hz,1H),1.75(ddd,J=14.4,13.0,4.6Hz,1H),1.67(dd,J=13.8,11.4Hz,1H),1.09(d,J=6.3Hz,3H),1.04(t,J=7.2Hz,3H)。LCMS m/z 301.98$[M+H]^+$。

[1513] 化合物822

[1514] (2S,4R)-2′-氯-2-甲基-1-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(822)

[1515] 

[1516] 标准方法#C:SN2烷基化

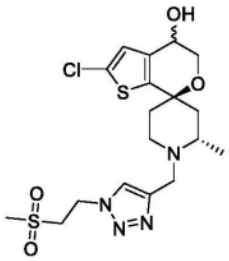
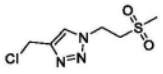
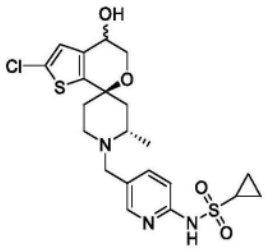
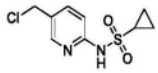
[1517] 将4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(9mg,0.04024mmol)和(2S,4R)-2′-氯-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮S58(11mg,0.04048mmol)溶解在DCE(300μL)中,并将DIPEA(15.7mg,0.1215mmol)添加到微波小瓶中。将小瓶加盖并将反应混合物加热至65℃并搅拌24小时。将溶液用MeOH淬灭并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有0.1%三氟乙酸。将产物分离为(2S,4R)-2′-氯-2-甲基-1-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(三氟乙酸盐)(4.3mg,16%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.35(s,1H),7.26(s,1H),5.10-4.94(m,2H),4.85-4.56(m,2H),4.49-4.31(m,2H),4.08-3.76(m,2H),3.65-3.45(m,1H),3.42(dd,J=13.9,11.2Hz,2H),3.01(s,3H),2.68-2.45(m,2H),2.26-1.92(m,2H),1.61(d,J=6.5Hz,3H)。

[1518] 化合物823-824

[1519] 使用标准方法#C,由中间体S58在单个步骤中制备了化合物823-824(参见表34)。烷基卤化物从商业来源获得或如前所述。表34和随附脚注中注明了对方法的任何修改。

[1520] 表34:化合物823-824的结构和物理化学数据

[1521]

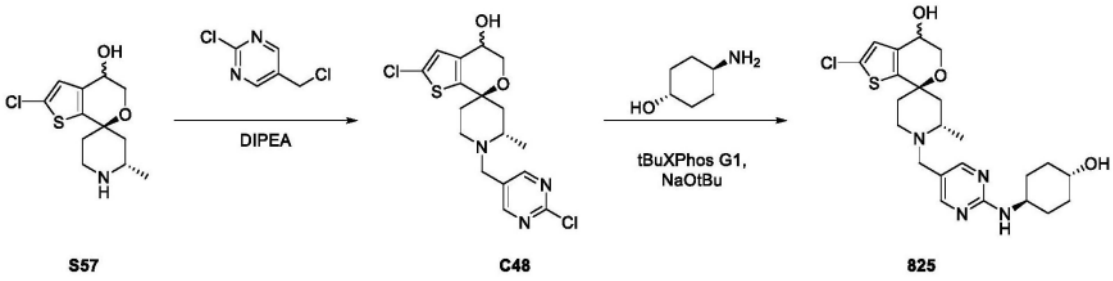
化合物	产物	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
823			S58	^{1}H NMR (300 MHz, 甲醇-d_4) δ 8.32 (s, 1H), 6.91 (s, 1H), 5.11 - 4.94 (m, 2H), 4.72 - 4.33 (m, 3H), 4.03 - 3.66 (m, 4H), 3.38 (s, 1H), 2.99 (d, J = 0.6 Hz, 3H), 2.43 - 1.80 (m, 4H), 1.54 (d, J = 6.4 Hz, 3H)。一些峰与溶剂峰重叠；LCMS m/z 461.38 [M+H]$^+$。
824			S58[1]	^{1}H NMR (300 MHz, 甲醇-d_4) δ 8.09 (d, J = 2.3 Hz, 1H), 7.74 (dd, J = 8.6, 2.4 Hz, 1H), 7.16 (dt, J = 8.6, 0.9 Hz, 1H), 6.85 (d, J = 0.9 Hz, 1H), 4.42 (dt, J = 9.3, 3.9 Hz, 1H), 4.08 (d, J = 13.5 Hz, 1H), 3.95 (ddd, J = 12.5, 9.0, 3.7 Hz, 1H), 3.84 - 3.65 (m, 1H), 3.22 (d, J = 13.5 Hz, 1H), 2.91 (td, J = 8.1, 4.1 Hz, 1H), 2.86 - 2.55 (m, 2H), 2.55 - 2.34 (m, 1H), 2.20 - 1.96 (m, 2H), 1.87 - 1.49 (m, 2H), 1.27 - 0.95 (m, 8H)；LCMS m/z 484.01 [M+H]$^+$。

[1522] 脚注：

[1523] 1)使用(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1.5当量)和N-[5-(氯甲基)-2-吡啶基]环丙烷磺酰胺(1.0当量)。将反应在60℃下在2小时内完成。使用硅胶色谱法进行纯化(梯度:含1-20% MeOH的DCM)。

[1524] 化合物825

[1525] (2′S,7R)-2-氯-1′-[[2-[(4-羟基环己基)氨基]嘧啶-5-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(825)

[1526] 

S57 C48 825

[1527] 步骤1:(2′S,7R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C48)的合成

[1528] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S57(73mg,0.2666mmol)溶解在DCE(2mL)中,并添加2-氯-5-(氯甲基)嘧啶(43mg,

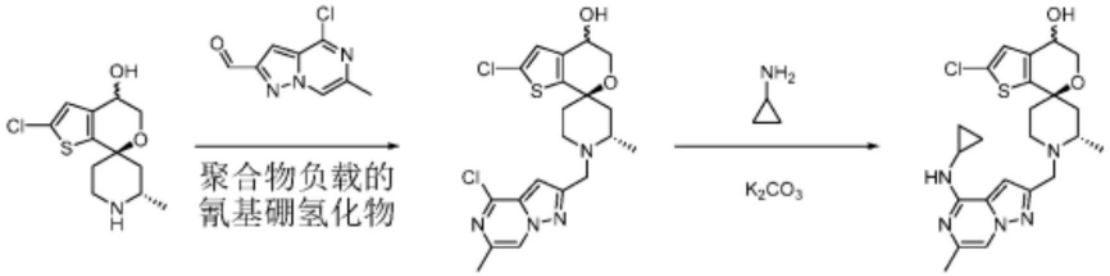
0.2638mmol)和DIPEA(103mg,0.7969mmol)。当反应完成时,将反应混合物用DCM和水稀释并在相分离器中分离。然后将粗产物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生(2′S,7R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(76mg,64%)。LCMS m/z 400.01[M+H]$^+$。

[1529] 步骤2:(2′S,7R)-2-氯-1′-[[2-[(4-羟基环己基)氨基]嘧啶-5-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(825)的合成

[1530] 放入装有(2′S,7R)-2-氯-1′-[(2-氯嘧啶-5-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C48(76mg,0.1633mmol)、4-氨基环己醇(22.57mg,0.1960mmol)、tBuXPhos G1(10.6mg,0.01628mmol)和tBuOH(2.27mL)的烧瓶中。将反应物用N_2脱气,然后添加NaOtBu(34.5mg,0.3590mmol)。将烧瓶密封并在60℃下加热40分钟,并且然后用MeOH淬灭。去除溶剂并将产物重新溶解在DCM中,并用树脂搅拌过夜以去除过量钯。将树脂过滤掉并将产物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)。通过反相HPLC完成进一步纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。产物分离为(2′S,7R)-2-氯-1′-[[2-[(4-羟基环己基)氨基]嘧啶-5-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(3.1mg,4%)。LCMS m/z 481.19[M+H]$^+$。

[1531] 化合物826

[1532] 2-氯-1′-[[4-(环丙基氨基)-6-甲基-吡唑并[1,5-a]吡嗪-2-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(826)

[1533] 

S57 C49 826

[1534] 步骤1:(2′S,7R)-2-氯-1′-[(4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C49)的合成

[1535] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S57(39.5mg,0.1356mmol)和4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-甲醛(27.8mg,0.1421mmol)溶解在DCM(1mL)中,并将乙酸(60μL,1.055mmol)添加到溶液中,随后添加聚合物负载的氰基硼氢化物(280mg的2mmol/g,0.5600mmol)。将溶液加盖并加热至70℃,持续75分钟。添加另外部分的4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-甲醛(15mg,0.07668mmol)并将溶液重新加盖搅拌过夜。将悬浮液在MeOH(1.5mL)中搅拌10分钟,然后滤出树脂(两次)。去除溶剂,并将残余物溶解在水(2mL)和DCM(2mL)中。用2M NaOH将水层的pH调节至pH>10。通过相分离器分离各相,将水层用DCM(2×10mL)萃取,并将合并的有机物在真空下浓缩。将粗残余物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生(2′S,7R)-2-氯-1′-[(4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(31mg,48%)。^{1}H NMR(400MHz,氯仿-d)δ8.10(q,J=1.0Hz,1H),6.80(d,J

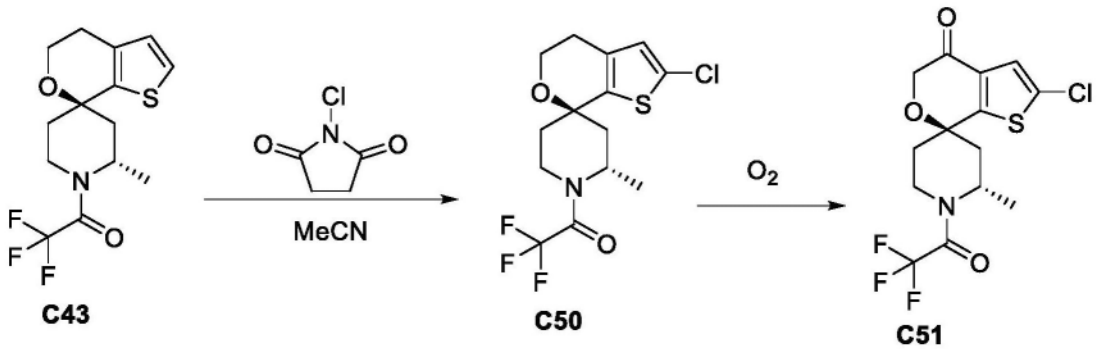
=2.1Hz,1H),6.75(s,1H),4.45-4.34(m,1H),4.19(dd,J=14.2,3.0Hz,1H),3.99-3.71(m,3H),2.84-2.56(m,2H),2.50(d,J=1.0Hz,3H),2.12-1.91(m,4H),1.81-1.67(m,1H),1.54(s,1H),1.26(t,J=6.4Hz,3H)。LCMS m/z 453.04[M+H]$^+$。

[1536] 步骤2:2-氯-1′-[[4-(环丙基氨基)-6-甲基-吡唑并[1,5-a]吡嗪-2-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(826)的合成

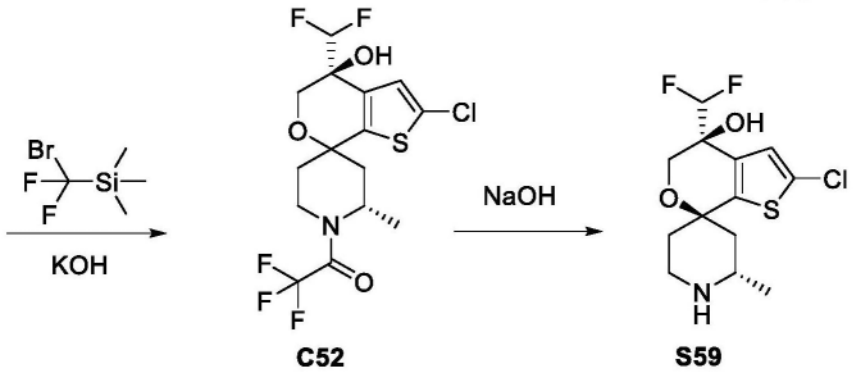
[1537] 将化合物2-氯-1′-[(4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C49(11.1mg,0.02448mmol)溶解在DMF(0.8mL)和环丙胺(20μL,0.2886mmol)中。向其中添加K_2CO_3(13.56mg,0.09811mmol)并将反应物加热至45℃,持续90分钟,然后加热至80℃并搅拌过夜。然后将反应物在水和DCM中稀释,分离各层,将水溶液用DCM(2x)萃取并使合并的有机物通过相分离器。将反应物浓缩并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有10mM氢氧化铵。产物分离为2-氯-1′-[[4-(环丙基氨基)-6-甲基-吡唑并[1,5-a]吡嗪-2-基]甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(2.8mg,23%)。^{1}H NMR(400MHz,甲醇-d_4)δ7.65(q,J=1.1Hz,1H),6.86(d,J=0.9Hz,2H),4.40(dt,J=8.9,3.9Hz,1H),4.22(d,J=14.2Hz,1H),4.03(d,J=14.3Hz,1H),3.91(ddd,J=12.2,9.6,3.6Hz,1H),3.75-3.63(m,1H),2.91(tt,J=7.1,3.7Hz,2H),2.85-2.75(m,1H),2.33(d,J=1.0Hz,3H),2.21-2.07(m,2H),1.99-1.54(m,3H),1.36(t,J=5.7Hz,3H),0.86(td,J=7.0,4.9Hz,2H),0.68-0.59(m,2H)。LCMS m/z 474.12[M+H]$^+$。

[1538] 制备S59

[1539] (2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S59)



[1540]



[1541] 步骤1:1-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮酮(C50)

[1542] 向在室温下在氮气气氛下搅拌15分钟的2,2,2-三氟-1-[(2′S,7R)-2′-甲基螺[4,

5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮C43(440g,1.378mol)于MeCN(3.6L)中的溶液中添加DMAP(9.2g,75.31mmol),随后添加1-氯吡咯烷-2,5-二酮(262g,1.962mol)。将所得反应混合物温热到70℃并搅拌14小时。将反应混合物冷却至室温并用10％亚硫酸氢钠水溶液(约1L)淬灭,并搅拌20分钟。将混合物在水(约1L)与乙酸乙酯(约2L)之间分配。将水层用乙酸乙酯(约1L)萃取。将合并的有机相依次用1:1水:盐水、1:1:1水:盐水:1M HCl水溶液和盐水(各自约1L),用$MgSO_4$干燥,过滤并浓缩。硅胶纯化(柱:Combiflash Torrent,2×1600g。梯度:含0-40％EtOAc的庚烷)。得到1-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮C50(418g,75％)。^{1}H NMR(300MHz,氯仿-d)δ6.57(s,1H),4.36(s,1H),3.96-3.68(m,3H),3.39(s,1H),2.56(t,J＝5.5Hz,2H),2.30(ddd,J＝14.2,6.3,1.8Hz,2H),1.99-1.79(m,1H),1.73(dd,J＝14.4,10.6Hz,1H),1.29(d,J＝6.5Hz,3H)。19F NMR(282MHz,氯仿-d)δ-69.80。LCMS m/z 354.12 $[M+1]^+$。

[1543] 步骤2:(2S,4R)-2′-氯-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(C51)

[1544] 向1-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮C50(6g,16.96mmol)于乙腈(60mL)中的混合物中添加N-羟基苯邻二甲酰亚胺(1.7g,10.42mmol)和二乙酸钴四水合(270mg,1.084mmol)并且然后将混合物用氧气气球真空吹扫三次。将反应混合物加热至45℃并搅拌6小时。将反应物冷却至室温。将混合物用氮气吹扫三次并且然后用MTBE(100mL)和饱和碳酸氢盐(100mL)稀释。分离各层,并将有机层用水(2×50mL)和盐水(50mL)洗涤。将有机层用硫酸钠干燥,过滤并浓缩。通过硅胶色谱法纯化(0-30％ EtOAc:庚烷),产生产物(2S,4R)-2′-氯-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(2700mg,42％)。^{1}H NMR(400MHz,氯仿-d)δ7.19(s,1H),4.38(d,J＝6.1Hz,1H),4.35-4.20(m,2H),3.95(s,1H),3.46(s,1H),2.60-2.43(m,2H),2.00-1.90(m,1H),1.85(dd,J＝14.5,10.6Hz,1H),1.34(d,J＝6.5Hz,3H)。LCMS m/z 367.96$[M+1]^+$。

[1545] 步骤3:1-[(2′S,4S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮(C52)

[1546] 在室温下向(2S,4R)-2′-氯-2-甲基-1-(2,2,2-三氟乙酰基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮C51(11.3g,30.73mmol)于MeCN(115mL)中的溶液中添加DMPU(7.5mL,62.26mmol),随后添加PPh_3(9.7g,36.98mmol),随后添加[溴(二氟)甲基]-三甲基-硅烷(10.8g,53.18mmol)。将所得溶液在55℃下加热1小时。将反应物冷却至室温,并添加KOH(140mL的1M,140.0mmol)。观察到部分脱保护。将反应物搅拌30分钟,然后添加饱和$NaHCO_3$(300mL)水溶液直到达到8-9的pH。将反应物用EtOAc(500mL,200mL)萃取。将合并的有机萃取物用$MgSO_4$干燥,过滤并浓缩。将粗产物溶解在DCM(200mL)中,并用Et_3N(13mL,93.27mmol)处理,随后用TFAA(4.5mL,32.37mmol)处理。将反应物搅拌45分钟。将反应物用饱和$NaHCO_3$水溶液(200mL)淬灭。分离各层,将水层用DCM(100mL)重新萃取并将合并的有机物用$MgSO_4$干燥,过滤并浓缩。通过硅胶色谱法(含0-30％ EtOAc的庚烷)产生产物和少量的其它非对映异构体。通过硅胶色谱法进一步纯化(梯度:0-60％ EtOAc:庚烷),产生呈灰白色固体的产物1-[(2′S,4S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-

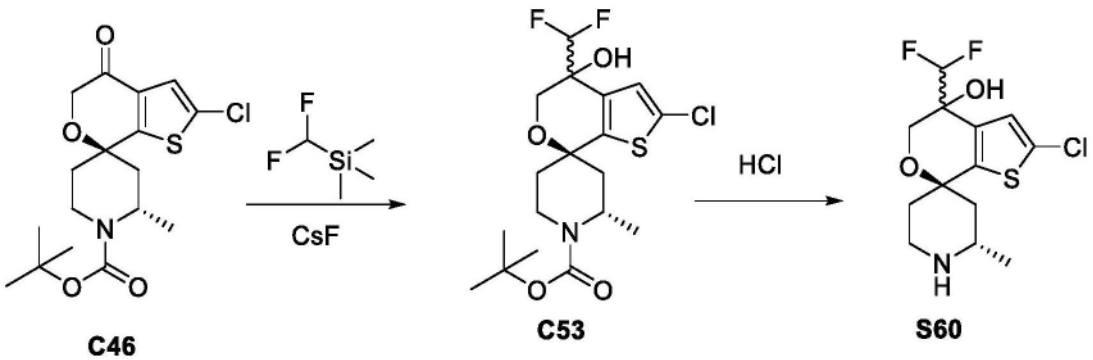
c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮(5.4g,42%)。^{1}H NMR(400MHz,氯仿-d)δ 6.91(d,J=1.3Hz,1H),5.87(dd,J=55.6,54.8Hz,1H),4.34(s,1H),3.99(d,J=12.2Hz,1H),3.88(s,1H),3.69(ddd,J=12.2,3.8,1.2Hz,1H),3.42(s,1H),2.60(d,J=1.1Hz,1H),2.49-2.38(m,1H),2.30(q,J=11.7,8.4Hz,1H),2.02-1.91(m,1H),1.73(dd,J=14.7,10.8Hz,1H),1.30(d,J=6.5Hz,3H)。19F NMR(376MHz,氯仿-d)δ-69.80,-130.52(d,J=280.4Hz),-135.69(d,J=280.1Hz)。

[1547] 步骤4:(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S59)

[1548] 向1-[(2′S,4S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮C52(3.23g,7.694mmol)于MeOH(50mL)中的溶液中添加NaOH水溶液(12mL的2M,24.00mmol)。将反应物搅拌2小时。将溶剂在真空中去除,并将残余物在2-MeTHF与饱和碳酸氢钠水溶液(各200mL)之间分配。将有机层分离并用饱和碳酸氢钠水溶液洗涤,随后用盐水(各150mL)洗涤。将合并的有机萃取物用$MgSO_4$干燥,过滤并浓缩。将残余物溶解在EtOAc(100mL回流)以产生略微浑浊的溶液。添加庚烷(35mL)并将所得溶液/悬浮液加热至回流,持续30秒。使溶液在室温下静置。18小时后,将晶体通过过滤分离,用庚烷(20mL)洗涤,并干燥以产生呈奶油色晶体的(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1.9g,76%)。^{1}H NMR(300MHz,DMSO-d6)δ7.05(s,1H),6.22(s,1H),6.09(t,J=55.1Hz,1H),3.93(d,J=12.2Hz,1H),3.66(dd,J=12.1,2.8Hz,1H),3.34(s,1H),3.03-2.80(m,3H),2.19-2.07(m,1H),1.87(dd,J=13.8,2.5Hz,1H),1.67(dt,J=13.5,8.2Hz,1H),1.27(dd,J=13.8,11.4Hz,1H),1.02(d,J=6.3Hz,3H)。19F NMR(282MHz,DMSO-d6)δ-128.66(d,J=277.3Hz),-134.33(d,J=277.4Hz)。LCMS m/z 324.06[M+1]$^+$。

[1549] 制备S60

[1550] (2′S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S60)

[1551] 

C46 C53 S60

[1552] 步骤1:(2′S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C53)

[1553] 在氮气下向(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(1.05g,2.823mmol)于1,2-二甲氧基乙烷(30mL)中的溶液中添加氟化铯(430mg,2.831mmol)和1,4,7,10,13,16-六氧杂环十八烷(750mg,2.838mmol)。向混合物中添加二氟甲基(三甲基)硅烷(2.3mL,16.85mmol)并将所得混合物在室温下搅拌过夜。

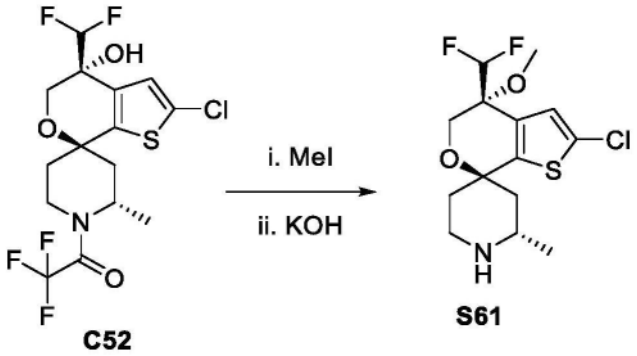
将TBAF(2.5mL的1M,2.500mmol)添加到反应物中并将溶液在室温下搅拌另外30分钟。通过在水与二氯甲烷之间分配来淬灭反应物。将有机物通过相分离器收集并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),得到(2′S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(440mg,34%)。^{1}H NMR(300MHz,氯仿-d)δ6.89(d,J=1.4Hz,1H),5.88(t,J=55.3Hz,1H),4.04-3.91(m,2H),3.80-3.67(m,2H),3.40-3.23(m,1H),2.46(d,J=1.0Hz,1H),2.33-2.01(m,2H),1.85-1.60(m,2H),1.47(s,9H),1.26(dd,J=6.6,5.2Hz,3H)。LCMS m/z 424.29[M+1]$^+$。

[1554] 步骤2:(2′S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S60)

[1555] 将(2′S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C53(440mg,0.9582mmol)于1,4-二噁烷(5mL)中的溶液用HCl(5mL的4M,20.00mmol)处理并在室温下搅拌过夜。将溶液在真空中浓缩以得到(2′S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(盐酸盐)(340mg,86%)。LCMS m/z 323.97[M+1]$^+$。

[1556] 制备S61

[1557] (2′S,4S,7R)-2-氯-4-(二氟甲基)-4-甲氧基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶](S61)

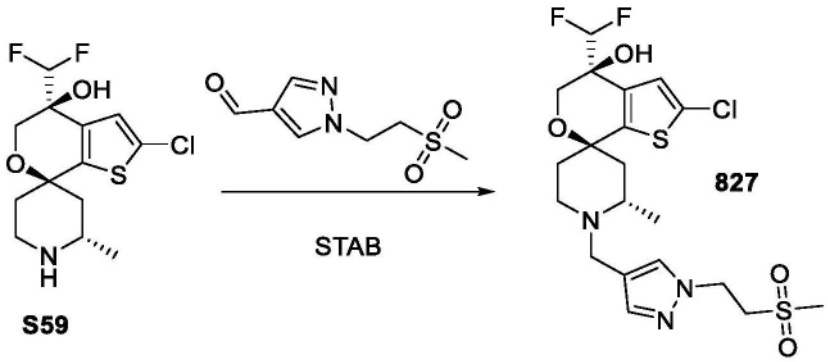
[1558] 

[1559] (2′S,4S,7R)-2-氯-4-(二氟甲基)-4-甲氧基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶](S61)的制备

[1560] 在氮气下向1-[(2′S,4S,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮C52(50mg,0.1191mmol)和碳酸二铯(40mg,0.1228mmol)于DMF(1mL)中的溶液中添加MeI(10μL,0.1606mmol)。将反应物搅拌过夜。将反应物用水淬灭并用DCM萃取。将溶剂在真空中去除。添加氢氧化钾水溶液(500μL的2M,1.000mmol)(100μL,5.551mmol),并将反应物搅拌过夜。将反应物用DCM稀释并通过相分离器萃取(3x)。将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl。(2′S,4S,7R)-2-氯-4-(二氟甲基)-4-甲氧基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(14mg,31%)。LCMS m/z 338.21[M+1]$^+$。^{1}H NMR(300MHz,DMSO-d6)δ8.95(s,1H),8.69(s,1H),7.17(s,1H),6.32(t,J=54.4Hz,1H),4.09(s,2H),3.33(s,2H),3.18(s,3H),3.04(s,1H),2.22(m,2H),1.92(m,2H),1.25(d,J=6.4Hz,3H)。

[1561] 化合物827

[1562] (2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(827)

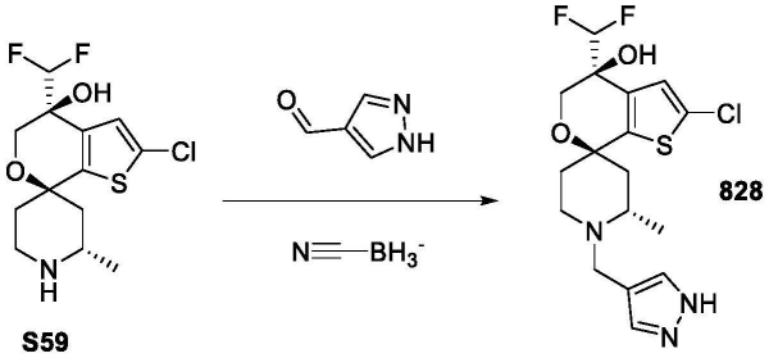
[1563] 

[1564] (2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(827)

[1565] 在室温下向1-(2-甲基磺酰基乙基)吡唑-4-甲醛(1.23g,6.082mmol)和(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S59(1.79g,5.528mmol)于THF(26mL)中的溶液中添加三乙酰氧基硼氢化物(钠盐)(2.50g,11.80mmol)。将反应物加热至50℃并搅拌3小时。将反应物在冰水浴中冷却并用饱和碳酸氢钠水溶液(100mL)仔细淬灭。将所得混合物在室温下搅拌1小时,并且然后添加EtOAc和水(各50mL)。将反应物搅拌另外1小时。将双相混合物用EtOAc(100mL)萃取。将有机层用盐水(100mL)洗涤,并将合并的有机物用$MgSO_4$干燥,过滤并浓缩。通过硅胶色谱法纯化(0-15%[含2M NH_3的MeOH]/DCM),随后通过硅胶色谱法第二次纯化(0-15%[含2M NH_3的MeOH]/DCM)。将产物(1.65g,3.24mmol)悬浮在水(20mL)中并用1M HCl水溶液(3.5mL)处理。将混合物在旋转蒸发器(无真空)上旋转,在60℃下水浴10分钟以产生澄清溶液。将溶液通过注射器过滤器(聚醚砜膜)过滤,将合并的溶液和洗涤液冷冻并冻干以产生呈白色固体的(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇827(盐酸盐)(1.77g,58%)。^{1}H NMR(400MHz,氯仿-d)δ7.46(d,J=0.7Hz,1H),7.44(d,J=0.7Hz,1H),6.88(d,J=1.1Hz,1H),5.84(t,J=55.3Hz,1H),4.58(t,J=6.0Hz,2H),3.95(d,J=12.1Hz,1H),3.79(d,J=14.4Hz,1H),3.74-3.67(m,1H),3.67-3.60(m,2H),3.57(d,J=14.4Hz,1H),3.26(s,1H),2.65(ddd,J=11.4,4.4,2.5Hz,1H),2.54-2.36(m,2H),2.45(s,3H),2.10-2.00(m,1H),1.98-1.76(m,2H),1.56(dd,J=14.1,11.4Hz,1H),1.18(d,J=6.2Hz,3H)。19F NMR(376MHz,氯仿-d)δ-129.99(d,J=279.9Hz),-135.47(d,J=279.9Hz)。LCMS m/z 510.02$[M+1]^+$。

[1566] 化合物828

[1567] (2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(828)

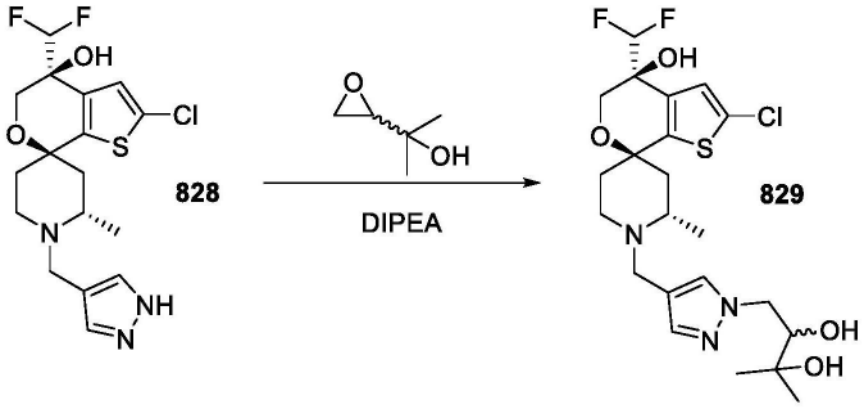
[1568] 

[1569] (2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(828)

[1570] 在微波小瓶中向(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S59(150mg,0.4633mmol)于二氯甲烷(4mL)中的溶液中添加1H-吡唑-4-甲醛(45mg,0.4683mmol)、乙酸(134mg,2.231mmol)和聚合物负载的氰基硼氢化物(231mg的2mmol/g,0.4620mmol)。将溶液加盖并在微波反应器中加热至95℃,持续120分钟。添加MeOH,并将溶液搅拌十分钟以从聚合物载体珠粒去除产物。将溶液过滤,并将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),梯度:含MeCN的H_2O 10mM氢氧化铵,得到(2′S,4S,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(131mg,54%)。^{1}H NMR(300MHz,甲醇-d4)δ7.63(s,2H),6.96(s,1H),5.89(t,J=55.2Hz,1H),4.00(dd,J=15.0,13.2Hz,2H),3.72(dd,J=19.6,13.1Hz,2H),2.99-2.54(m,3H),2.24(d,J=14.3Hz,1H),2.13-1.80(m,3H),1.62(dd,J=14.4,11.6Hz,1H),1.30(d,J=6.3Hz,3H)。LCMS m/z 404.03$[M+1]^+$。

[1571] 化合物829

[1572] 1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(829)

[1573] 

[1574] 1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(829)

[1575] 在微波小瓶中向(2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-(1H-吡唑-4-基甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇828(85mg,0.2105mmol)和2-(环氧乙烷-2-基)丙-2-醇(34mg,0.3329mmol)于MeOH(1.45mL)中的溶液中添加DIPEA(183μL,1.051mmol)。将反应物在90℃下搅拌1小时。将反应转移到微波中并在120℃下运行七小时。

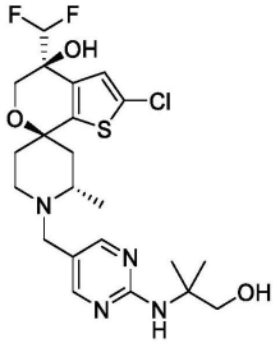
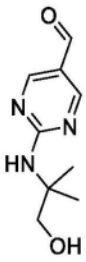
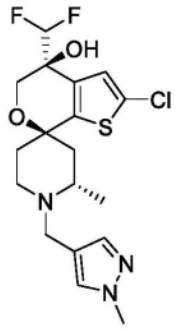
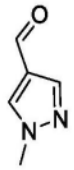
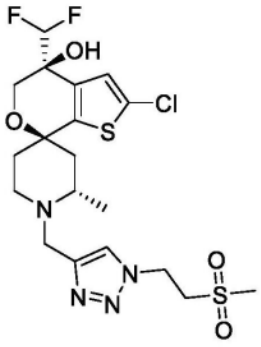
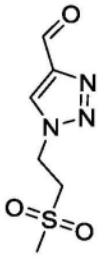
将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,产生1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(三氟乙酸盐)(16mg,12%)^{1}H NMR(300MHz,甲醇-d4)δ7.68(s,1H),7.50(s,1H),6.96(s,1H),5.89(t,J=55.3Hz,1H),4.44(dd,J=13.9,2.3Hz,1H),4.18-3.90(m,3H),3.71(td,J=10.9,9.9,3.0Hz,3H),2.97-2.58(m,3H),2.24(dt,J=14.3,2.9Hz,1H),1.94(dtd,J=26.7,13.9,3.6Hz,2H),1.62(dd,J=14.3,11.6Hz,1H),1.29(d,J=6.3Hz,3H),1.23(d,J=8.3Hz,6H)。LCMS m/z 506.14$[M+1]^+$。

[1576] 化合物830-835

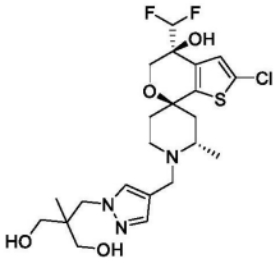
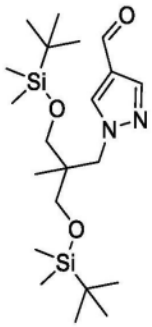
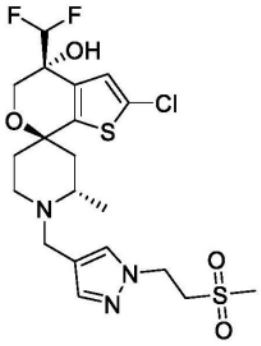
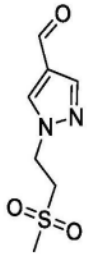
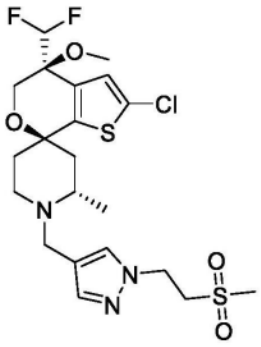
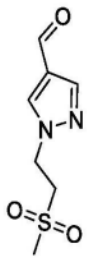
[1577] 化合物830-835由如化合物829所述的还原胺化步骤与相关的醛和哌啶制备。醛和哌啶通过上述方法制备或从商业来源获得。表35和随附脚注中注明了对方法的任何修改。

[1578] 表35:化合物830-835的制备方法、结构和物理化学数据。

[1579]

化合物	产物	醛和哌啶试剂	方法	^{1}H NMR
830		S59：	*829*	^{1}H NMR (300 MHz, 甲醇-*d4*) δ 8.23 (s, 2H), 6.95 (s, 1H), 5.90 (t, *J* = 55.2 Hz, 1H), 3.98 (t, *J* = 12.7 Hz, 2H), 3.84 - 3.59 (m, 3H), 3.22 - 2.98 (m, 1H), 2.72 - 2.53 (m, 2H), 2.41 (td, *J* = 12.2, 2.8 Hz, 1H), 2.20 (dt, *J* = 14.3, 2.8 Hz, 1H), 2.03 - 1.67 (m, 2H), 1.56 (dd, *J* = 14.2, 11.4 Hz, 1H), 1.37 (s, 6H), 1.24 (d, *J* = 6.2 Hz, 3H)。LCMS *m/z* 503.05 $[M+1]^+$。
831		S59：	*829*[1,2]	^{1}H NMR (300 MHz, 甲醇-*d4*) δ 7.87 (s, 1H), 7.66 (s, 1H), 7.03 (s, 1H), 5.94 (t, *J* = 55.2 Hz, 1H), 4.55 (d, *J* = 14.0 Hz, 1H), 4.27 (d, *J* = 14.1 Hz, 1H), 4.05 (d, *J* = 12.2 Hz, 1H), 3.94 (s, 4H), 3.74 (d, *J* = 12.3 Hz, 1H), 3.47 (s, 2H), 2.54 (d, *J* = 14.7 Hz, 1H), 2.26 (d, *J* = 15.5 Hz, 1H), 2.13 - 1.71 (m, 2H), 1.54 (d, *J* = 6.5 Hz, 3H)。LCMS *m/z* 418.14 $[M+1]^+$。
832		S59：	*829*[1,2]	LCMS *m/z* 511.11 $[M+1]^+$。

[1580]

化合物	产物	醛 和哌啶 试剂	方法	^{1}H NMR
833		S59： 	*829*[3]	^{1}H NMR (400 MHz, 甲醇-*d4*) δ 7.62 (d, *J* = 0.7 Hz, 1H), 7.45 (d, *J* = 0.8 Hz, 1H), 6.94 (d, *J* = 0.9 Hz, 1H), 5.89 (t, *J* = 55.2 Hz, 1H), 4.13 (s, 2H), 3.89 (dd, *J* = 41.8, 13.2 Hz, 2H), 3.66 (dd, *J* = 13.2, 6.8 Hz, 2H), 3.43 - 3.32 (m, 4H), 2.80 - 2.43 (m, 3H), 2.18 (dt, *J* = 14.2, 2.9 Hz, 1H), 2.03 - 1.69 (m, 2H), 1.54 (dd, *J* = 14.2, 11.5 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.82 (s, 3H)。LCMS *m/z* 506.14 [M+1]$^+$。
834		S60： 	*829*[1,4,5]	^{1}H NMR (300 MHz, 甲醇-*d4*) δ 7.75 (s, 1H), 7.55 (d, *J* = 0.7 Hz, 1H), 6.95 (d, *J* = 1.0 Hz, 1H), 5.90 (t, *J* = 55.2 Hz, 1H), 4.64 (dd, *J* = 6.9, 5.9 Hz, 2H), 3.94 (dd, *J* = 13.2, 8.2 Hz, 2H), 3.79 - 3.60 (m, 4H), 2.85 - 2.57 (m, 6H), 2.22 (dd, *J* = 14.4, 3.1 Hz, 1H), 2.06 - 1.96 (m, 1H), 1.84 - 1.63 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H)。LCMS *m/z* 510.11 [M+1]$^+$。
835		S61： 	*829*[1,6,7]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.51 (s, 1H), 7.46 (s, 1H), 6.83 (s, 1H), 5.79 (t, *J* = 55.1 Hz, 1H), 4.61 (t, *J* = 6.0 Hz, 2H), 4.09 - 3.95 (m, 2H), 3.84 (d, *J* = 14.4 Hz, 1H), 3.66 (t, *J* = 6.1 Hz, 2H), 3.57 (d, *J* = 14.4 Hz, 1H), 3.27 (s, 3H), 2.72 - 2.64 (m, 1H), 2.64 - 2.51 (m, 1H), 2.48 (d, *J* = 1.0 Hz, 3H), 2.47 - 2.33 (m, 1H), 2.13 - 1.91 (m, 2H), 1.83 - 1.60 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H)。LCMS *m/z*

[1581]

化合物	产物	醛 和哌啶 试剂	方法	^{1}H NMR
				523.99 $[M+1]^+$。

[1582] 脚注：

[1583] 1.在110℃下将反应物在微波中加热45分钟。

[1584] 2.通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1％三氟乙酸,产生产物。

[1585] 3.将珠粒用MeOH洗涤并过滤后,添加含4M HCl的二噁烷(10当量)。将反应物搅拌十分钟以去除TBS保护基团。

[1586] 4.反应完成后,将溶液过滤,并将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-100％ EtOAc的庚烷)产生产物。

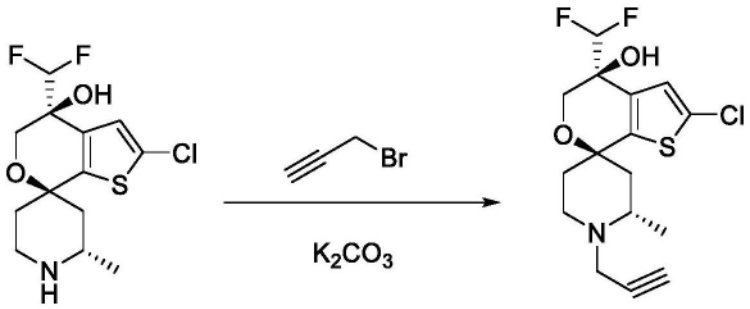
[1587] 5.SFC纯化得到在苄位具有R立体化学的化合物。

[1588] 6.反应完成后,将溶液过滤,并将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-20％ MeOH的DCM)产生产物。

[1589] 7.反应中省略乙酸,因为哌啶起始材料是HCl盐。

[1590] 制备S62

[1591] (2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-丙-2-炔基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S62)

[1592] 

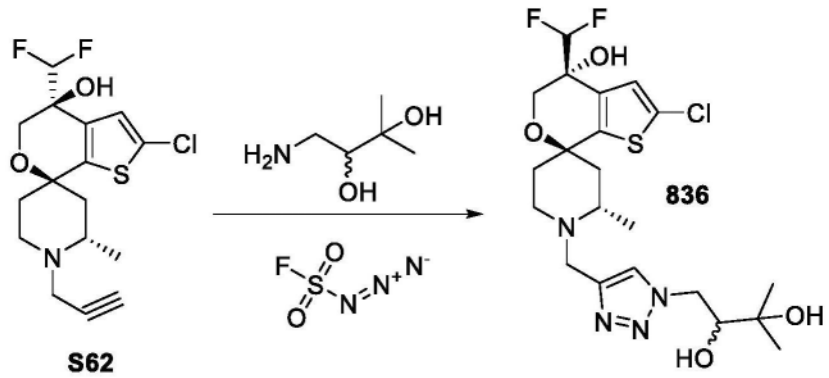
S59 S62

[1593] (2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-丙-2-炔基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S62)的制备

[1594] 将(2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S59(320mg,0.9883mmol)和碳酸钾(178mg,1.288mmol)于四氢呋喃(6.4mL)中的溶液加热至50℃并搅拌。此时,添加含炔丙基溴(191mg,1.284mmol)的甲苯并搅拌混合物。搅拌过夜后,将混合物用碳酸氢钠水溶液和DCM淬灭,并将有机层通过相分离器收集。将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:0-20％ MeOH:DCM),产生(2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-丙-2-炔基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(223mg,61％)。^{1}H NMR(300MHz,氯仿-d)δ6.91(d,J＝1.3Hz,1H),5.91(t,J＝55.3Hz,1H),4.07(d,J＝12.2Hz,1H),3.90-3.75(m,1H),3.67(dd,J＝17.4,2.4Hz,1H),3.42(dd,J＝17.5,2.4Hz,1H),3.02-2.62(m,3H),2.48(s,1H),2.26(t,J＝2.4Hz,1H),2.13(dt,J＝14.1,2.8Hz,1H),2.03-1.85(m,2H),1.11(d,J＝6.3Hz,3H)。LCMS m/z 362.0$[M+1]^+$。

[1595] 化合物836

[1596] 1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-3-甲基-丁烷-2,3-二醇(836)

[1597] 

[1598] 1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-3-甲基-丁烷-2,3-二醇(836)的制备

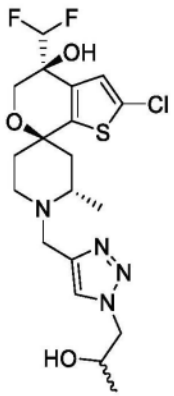
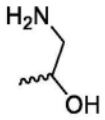
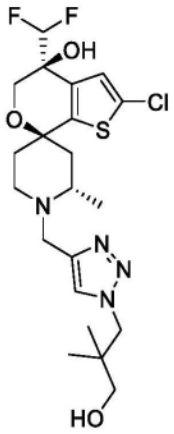
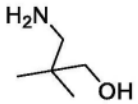
[1599] 向1-氨基-3-甲基-丁烷-2,3-二醇(大约29.64mg,0.2487mmol)于DMSO(300.0μL)中的溶液中添加碳酸氢盐(钠盐)水溶液(大约250.0μL的1M,0.2500mmol)和550uL氟磺酰基叠氮化物溶液(含约0.45M的MTBE,约250μmol)。将所得溶液在室温下搅拌20分钟。添加溶解在DMSO(999.9μL)中的(2′S,4R,7R)-2-氯-4-(二氟甲基)-2′-甲基-1′-丙-2-炔基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S62(30mg,0.08291mmol)(30mg)的溶液,随后添加$CuSO_4$水溶液(大约84.98μL的0.1M,0.008498mmol)、4-[双[4-羟基-1-(1H-三唑-4-基)丁基]氨基]-4-(1H-三唑-4-基)丁-1-醇(大约84.98μL的0.1M,0.008498mmol)于DMSO中的溶液和(2R)-2-[(1S)-1,2-二羟乙基]-4-羟基-5-氧代-2H-呋喃-3-抗坏血酸醇钠水溶液(钠盐)(大约85.00μL的0.2M,0.01700mmol)。将反应物在50℃下加热过夜。添加另外100uL 0.1M$CuSO_4$和100uL 0.2M抗坏血酸钠,并继续加热过夜。将反应物冷却至室温,用水(2mL)和DCM(1mL)稀释,并搅拌若干分钟。使混合物通过平行过滤板并用DCM(1mL)洗涤。使用有机层并蒸发。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),梯度:含MeCN的H_2O,10mM氢氧化铵,得到1-[4-[[(2′S,4R,7R)-2-氯-4-(二氟甲基)-4-羟基-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-3-甲基-丁烷-2,3-二醇(2.3,5.5%)。^{1}H NMR(300MHz,甲醇-d4)δ8.91(s,1H),7.91(s,1H),6.85(t,J=55.2Hz,1H),5.72(d,J=14.0Hz,1H),5.24(t,J=11.9Hz,1H),5.08-4.41(m,5H),3.65(dd,J=35.8,11.8Hz,3H),3.33-2.70(m,3H),2.50(t,J=12.9Hz,1H),2.35-1.97(m,9H)。LCMS m/z 507.13$[M+1]^+$。

[1600] 化合物837-841

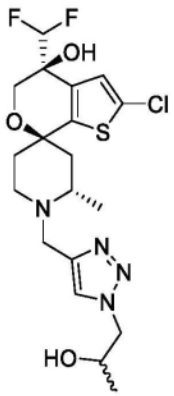
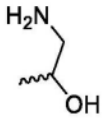
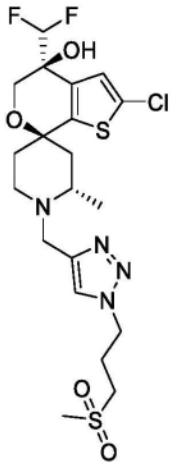
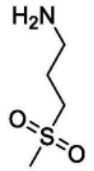
[1601] 化合物837-841(参见表36)由点击化学步骤制备,如化合物836与相关胺所述。胺通过上述方法制备或从商业来源获得。表36和随附脚注中注明了对方法的任何修改。

[1602] 表36:化合物837-841的制备方法、结构和物理化学数据。

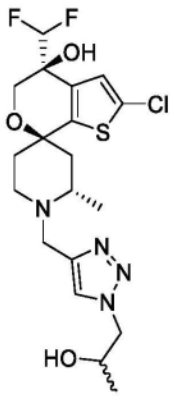
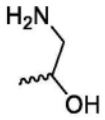
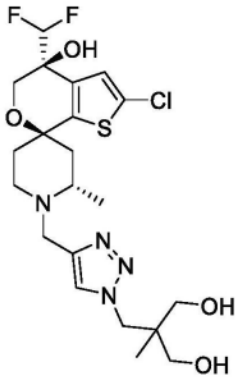
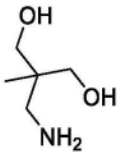
[1603]

化合物	结构	胺试剂	方法	^{1}H NMR
837			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.4 Hz, 1H), 7.02 (s, 1H), 6.19 (s, 1H), 5.98 (d, *J* = 55.1 Hz, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.34 – 4.16 (m, 2H), 4.02 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.7 Hz, 1H),3.60 (d, *J* = 12.1 Hz, 1H), 2.62 (d, *J* = 11.5 Hz, 1H), 2.41 (q, *J* = 11.0, 10.1 Hz, 2H), 2.09 (d, *J* = 13.7 Hz, 1H), 1.86 (d, *J* = 13.4 Hz,1H), 1.72 (td, *J* = 12.9, 4.4 Hz, 1H), 1.47 – 1.30 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.04 (dd, *J* = 6.3, 4.0 Hz, 3H)。LCMS *m/z* 463.11 $[M+1]^+$。
838			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.02 (s, 1H), 6.20 (s,1H), 5.98 (t, *J* = 55.1 Hz, 1H), 5.14 (t, *J* = 5.5 Hz, 1H), 3.87 (d, *J* = 12.2Hz, 1H), 3.86 (d, *J* = 14.4 Hz, 1H), 3.66 – 3.59 (m, 4H), 2.63 (d, *J* =11.5 Hz, 1H), 2.46 – 2.33 (m, 2H), 2.10 (d, *J* = 14.0 Hz, 1H), 1.86 (d, *J* = 13.4 Hz, 1H), 1.72 (td, *J* = 13.0, 4.6 Hz, 1H), 1.54 (s, 6H), 1.36 (dd, *J* = 13.8, 11.2 Hz, 1H), 1.16 (d, *J* = 6.2 Hz, 3H)。LCMS *m/z* 477.11 $[M+1]^+$。

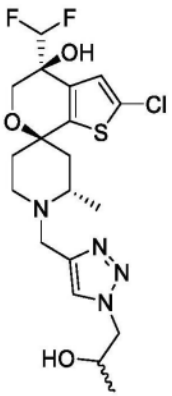
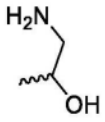
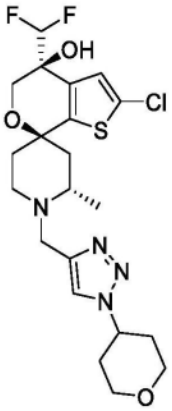
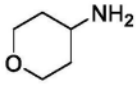
[1604]

化合物	结构	胺试剂	方法	^{1}H NMR
837			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.4 Hz, 1H), 7.02 (s, 1H), 6.19 (s, 1H), 5.98 (d, *J* = 55.1 Hz, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.34 – 4.16 (m, 2H), 4.02 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.7 Hz, 1H),3.60 (d, *J* = 12.1 Hz, 1H), 2.62 (d, *J* = 11.5 Hz, 1H), 2.41 (q, *J* = 11.0, 10.1 Hz, 2H), 2.09 (d, *J* = 13.7 Hz, 1H), 1.86 (d, *J* = 13.4 Hz,1H), 1.72 (td, *J* = 12.9, 4.4 Hz, 1H), 1.47 – 1.30 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.04 (dd, *J* = 6.3, 4.0 Hz, 3H)。LCMS *m/z* 463.11 $[M+1]^+$。
839			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.02 (s, 1H), 6.21 (s, 1H), 6.04 (t, *J* = 55.1 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 2H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.85 (d, *J* = 14.6 Hz, 1H), 3.73 (d, *J* = 14.6 Hz, 1H), 3.60 (d, *J* = 12.3 Hz, 1H), 3.15 – 3.06 (m, 2H), 2.99 (s, 3H), 2.62 (d, *J* = 11.5 Hz, 1H), 2.47 – 2.19 (m, 4H), 2.10 (d, *J* = 13.8 Hz, 1H), 1.86 (d, *J* = 13.3 Hz, 1H), 1.73 (td, *J* = 13.0, 4.6 Hz, 1H), 1.35 (dd, *J* = 13.8, 11.3 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H)。LCMS *m/z* 525.1 $[M+1]^+$。

[1605]

化合物	结构	胺试剂	方法	^{1}H NMR
837			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.4 Hz, 1H), 7.02 (s, 1H), 6.19 (s, 1H), 5.98 (d, *J* = 55.1 Hz, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.34 – 4.16 (m, 2H), 4.02 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.7 Hz, 1H),3.60 (d, *J* = 12.1 Hz, 1H), 2.62 (d, *J* = 11.5 Hz, 1H), 2.41 (q, *J* = 11.0, 10.1 Hz, 2H), 2.09 (d, *J* = 13.7 Hz, 1H), 1.86 (d, *J* = 13.4 Hz,1H), 1.72 (td, *J* = 12.9, 4.4 Hz, 1H), 1.47 – 1.30 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.04 (dd, *J* = 6.3, 4.0 Hz, 3H)。LCMS *m/z* 463.11 $[M+1]^+$。
840			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.02 (s, 1H), 6.19 (s, 1H), 6.05 (t, *J* = 55.1 Hz, 1H), 4.74 (s, 2H), 4.26 (s, 2H), 3.88 – 3.79 (m, 2H), 3.76 (d, *J* = 14.6 Hz, 1H), 3.59 (d, *J* = 12.2 Hz, 1H), 3.21 (s, 4H), 2.59 (d, *J* = 12.0 Hz, 1H), 2.41 (dd, *J* = 23.7, 11.4 Hz, 2H), 2.08 (d, *J* = 13.8 Hz, 1H), 1.86 (d, *J* = 13.4 Hz, 1H), 1.71 (td, *J* = 13.0, 4.4 Hz, 1H), 1.36 (dd, *J* = 13.8, 11.3 Hz, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.65 (s, 3H)。LCMS *m/z* 507.17 $[M+1]^+$。

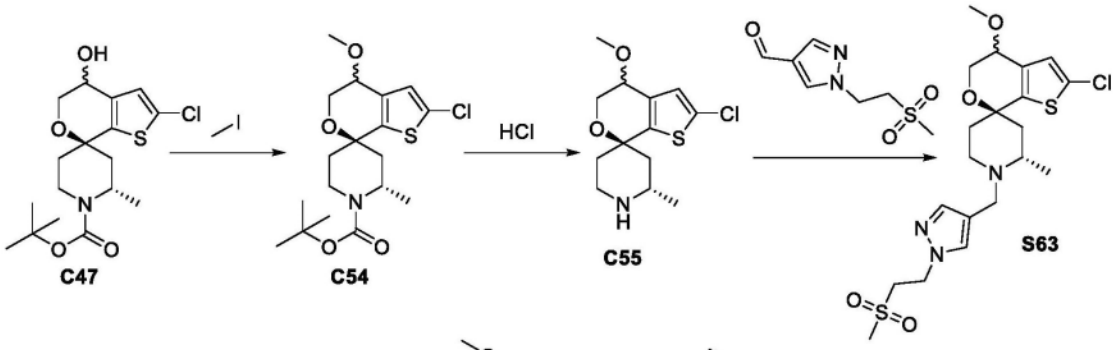
[1606]

化合物	结构	胺试剂	方法	^{1}H NMR
837			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.4 Hz, 1H), 7.02 (s, 1H), 6.19 (s, 1H), 5.98 (d, *J* = 55.1 Hz, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.34 – 4.16 (m, 2H), 4.02 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.7 Hz, 1H),3.60 (d, *J* = 12.1 Hz, 1H), 2.62 (d, *J* = 11.5 Hz, 1H), 2.41 (q, *J* = 11.0, 10.1 Hz, 2H), 2.09 (d, *J* = 13.7 Hz, 1H), 1.86 (d, *J* = 13.4 Hz,1H), 1.72 (td, *J* = 12.9, 4.4 Hz, 1H), 1.47 – 1.30 (m, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.04 (dd, *J* = 6.3, 4.0 Hz, 3H)。LCMS *m/z* 463.11 $[M+1]^+$。
841			*化合物836*	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.02 (s, 1H), 6.20 (s,1H), 6.05 (t, *J* = 55.3 Hz, 1H), 4.72 (tt, *J* = 10.1, 4.9 Hz, 1H), 3.96 (d, *J* = 11.5 Hz, 2H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.85 (d, *J* = 14.6 Hz, 1H), 3.69 (d, *J* = 14.6 Hz, 1H), 3.61 (d, *J* = 12.2 Hz, 1H), 3.49 (td, *J* = 11.5, 2.9 Hz, 2H), 2.62 (d, *J* = 11.7 Hz, 1H), 2.40 (q, *J* = 9.7, 7.3 Hz, 2H), 2.14 – 1.90 (m, 5H), 1.86 (d, *J* = 13.3 Hz, 1H), 1.72 (td, *J* = 12.9, 4.5 Hz, 1H), 1.36 (dd, *J* = 13.9, 11.3 Hz, 1H), 1.15 (d, *J* = 6.1 Hz, 3H)。LCMS *m/z* 489.12 $[M+1]^+$。

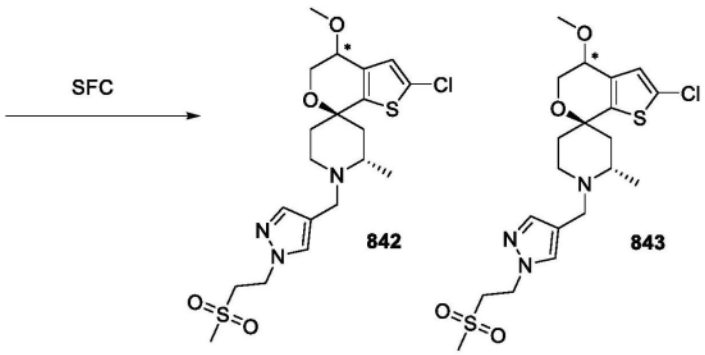
[1607] 化合物(842)[DIAST-1]和(843)[DIAST-2]

[1608] (2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](842)[DIAST-1]和(843)[DIAST-2]

[1609]



[1610]



[1611] 步骤1:(2′S,7R)-2-氯-4-甲氧基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C54)

[1612] 向(2′S,7R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C47(100mg,0.2675mmol)的经搅拌的四氢呋喃(2.5mL)溶液中添加NaH(43mg的60%w/w,1.075mmol)和碘甲烷(151mg,1.064mmol)。将混合物在室温下搅拌并放置过夜。早晨添加饱和NH_4Cl水溶液以淬灭反应物,并将溶液用DCM萃取。将有机物用盐水洗涤,用硫酸钠干燥,并将溶剂通过旋转蒸发去除以产生(2′S,7R)-2-氯-4-甲氧基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C54。LCMS m/z 387.99$[M+1]^+$。将粗反应混合物直接伸缩至下一步骤。

[1613] 步骤2:(2′S,7R)-2-氯-4-甲氧基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C55)

[1614] 向C54于二噁烷(500μL)中的溶液中添加含HCl(1.34mL的4M,5.360mmol)的二噁烷。将反应物在室温下搅拌三小时。将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7R)-2-氯-4-甲氧基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(79.9mg,74%)。LCMS m/z 288.1$[M+1]^+$。

[1615] 步骤3:(2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S63)

[1616] 在5mL微波小瓶中向(2′S,7R)-2-氯-4-甲氧基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](22mg,0.07644mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(23mg,0.1137mmol)于二氯甲烷(2mL)中的溶液中添加乙酸(22μL,0.3869mmol)和聚合物负载的氰基硼氢化物(114mg的2mmol/g,0.2280mmol)。将管加盖并在微波反应器中加热至110℃,持续一个半小时。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯

度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(18.9mg,41%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.03-7.93(m,1H),7.72(s,1H),6.95(s,1H),4.75-4.63(m,2H),4.61-4.49(m,1H),4.29(d,J=14.1Hz,1H),4.15(dt,J=4.5,2.6Hz,1H),4.09-3.81(m,2H),3.72(t,J=6.2Hz,2H),3.41(d,J=0.6Hz,3H),3.31(m,2H)2.87(dd,J=1.4,0.8Hz,3H),2.54-1.77(m,3H),1.53(dd,J=6.5,2.2Hz,3H)。LCMS m/z 474.11[M+1]$^+$。

[1617] 步骤3:(2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](842)[DIAST-1]和(843)[DIAST-2]

[1618] 将外消旋混合物S63(43mg,0.09071mmol)通过手性SFC分离分离成组成非对映异构体。(2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(842)[DIAST-1](6mg,22%)。^{1}H NMR(400MHz,甲醇-d_4)δ7.75(d,J=0.7Hz,1H),7.55(d,J=0.8Hz,1H),6.88(s,1H),4.63(t,J=6.4Hz,2H),4.09(t,J=2.6Hz,1H),4.02-3.56(m,6H),3.39(s,3H),2.90-2.49(m,6H),2.17(dt,J=14.3,2.8Hz,1H),2.00(dt,J=13.9,2.9Hz,1H),1.79-1.59(m,2H),1.26(d,J=6.3Hz,3H)。

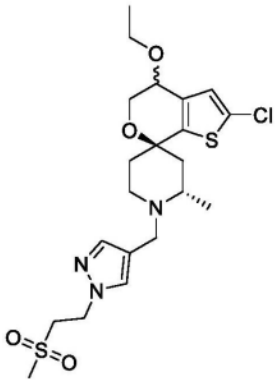
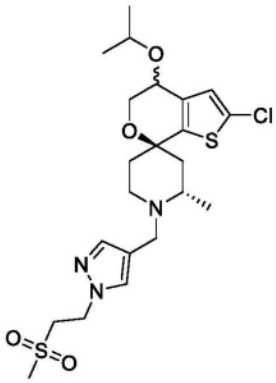
[1619] (2′S,7R)-2-氯-4-甲氧基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(843)[DIAST-2](12mg,45%)。^{1}H NMR(400MHz,甲醇-d_4)δ7.72(d,J=0.8Hz,1H),7.53(d,J=0.8Hz,1H),6.87(s,1H),4.62(t,J=6.4Hz,2H),4.11(t,J=2.8Hz,1H),4.00-3.65(m,6H),3.39(s,3H),2.87-2.47(m,6H),2.13(dt,J=14.3,2.9Hz,1H),2.09-1.81(m,2H),1.45(dd,J=14.3,11.6Hz,1H),1.22(d,J=6.3Hz,3H)。

[1620] 化合物844-846

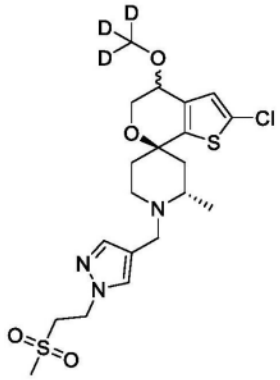
[1621] 化合物844-846由中间体C47和相关烷基卤化物通过中间体S63所述的烷基化、脱保护和还原胺化步骤制备。烷基卤化物从商业来源获得。表37和随附脚注中注明了对方法的任何修改。

[1622] 表37:化合物844-846的制备方法、结构和物理化学数据。

[1623]

化合物	结构	烷基卤化物	方法	^{1}H NMR
844			*方法* ***S63***[1,2]	^{1}H NMR (300 MHz, 甲醇-d_4) δ 8.20 - 7.96 (m, 1H), 7.72 (d, *J* = 0.7 Hz, 1H), 6.93 (s, 1H), 4.82 - 4.64 (m, 2H), 4.53 (d, *J* = 14.1 Hz, 1H), 4.37 - 4.18 (m, 2H), 4.15 - 3.84 (m, 2H), 3.82 - 3.55 (m, 4H), 3.51 - 3.35 (m, 1H), 3.22 (td, *J* = 13.0, 2.9 Hz, 1H), 2.87 (d, *J* = 1.5 Hz, 3H), 2.52 - 1.75 (m, 5H), 1.53 (dd, *J* = 6.5, 3.2 Hz, 3H), 1.20 (td, *J* = 7.0, 0.7 Hz, 3H)。LCMS *m/z* 488.11 $[M+1]^+$
845			*方法* ***S63***[1,2,3]	^{1}H NMR (300 MHz, 甲醇-d_4) δ 7.99 (s, 1H), 7.72 (s, 1H), 6.89 (s, 1H), 4.76 - 4.59 (m, 2H), 4.53 (d, *J* = 14.1 Hz, 1H), 4.43 - 4.18 (m, 2H), 4.08 - 3.77 (m, 3H), 3.72 (t, *J* = 6.2 Hz, 2H), 3.42 (d, *J* = 37.3 Hz, 2H), 2.87 (d, *J* = 1.2 Hz, 3H), 2.65 (s, 1H), 2.53 - 2.20 (m, 2H), 2.13 - 1.70 (m, 2H), 1.53 (dd, *J* = 6.5, 3.2 Hz, 3H), 1.30 - 1.08

[1624]

化合物	结构	烷基卤化物	方法	^{1}H NMR
				(m, 6H)。LCMS *m/z* 502.1 [M+1]+
846			*方法* ***S63***[1,2]	1H NMR (300 MHz, 甲醇-d_4) δ 8.01 (d, *J* = 1.4 Hz, 1H), 7.74 (s, 1H), 6.97 (s, 1H), 4.78 – 4.67 (m, 2H), 4.55 (d, *J* = 14.1 Hz, 1H), 4.31 (d, *J* = 14.1 Hz, 1H), 4.17 (dt, *J* = 4.5, 2.6 Hz, 1H), 4.13 – 3.88 (m, 2H), 3.74 (t, *J* = 6.2 Hz, 2H), 3.31 (m, 2H) 2.89 (dd, *J* = 1.4, 0.7 Hz, 3H), 2.60 – 1.75 (m, 4H), 1.55 (dd, *J* = 6.5, 2.2 Hz, 3H)。LCMS *m/z* 477.11 $[M+1]^+$

[1625] 脚注

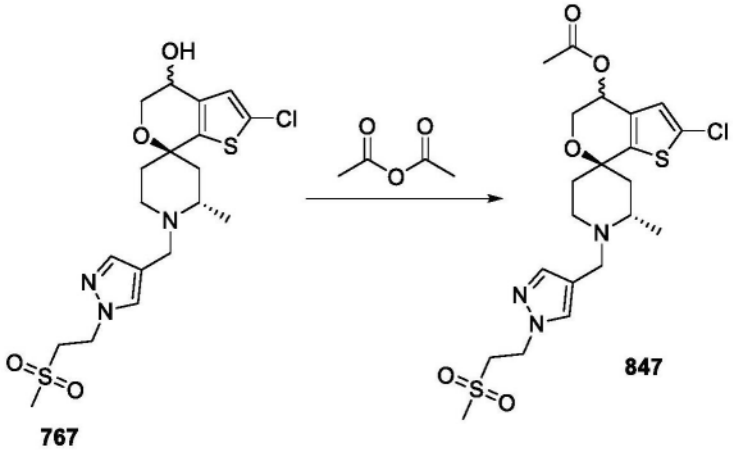
[1626] 1.通过硅胶色谱法纯化(梯度:含0-40% EtOAc的庚烷)产生产物(步骤1)

[1627] 2.在伸缩到还原胺化步骤(步骤2)之前,未纯化脱保护产物。

[1628] 3.将反应物加热至60℃,持续三天。

[1629] 化合物847的制备

[1630] [(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]乙酸酯(847)

[1631] 

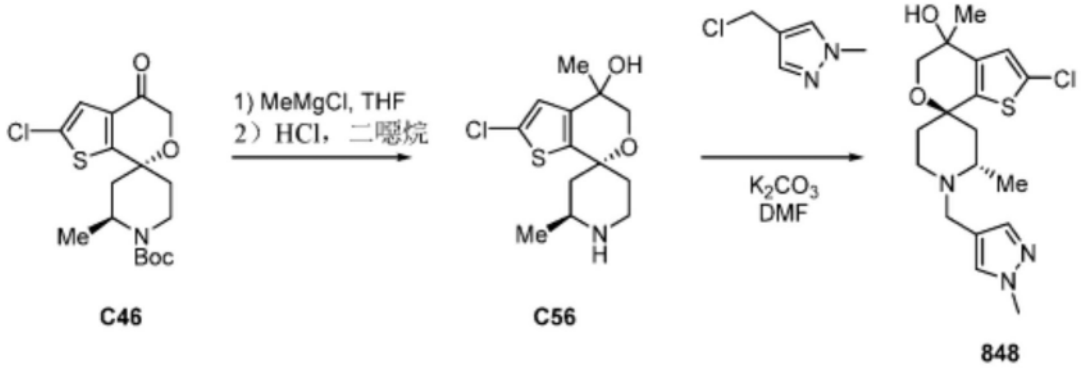
[1632] [(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]乙酸酯(847)

[1633] 向(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇767(45mg,0.09782mmol)于吡啶(1.4mL)中的溶液中添加乙酸酐(1.4mL,14.84mmol),并将反应物在rt下搅拌。在真空中去除溶剂。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生产物[(2′S,7R)-2-氯-2′-甲基-1′-

[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]乙酸酯(29.1mg,59%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.87-7.68(m,1H),7.55(t,J=0.9Hz,1H),6.84(d,J=1.2Hz,1H),5.52-5.47(m,1H),4.63(t,J=6.4Hz,2H),4.14-3.56(m,6H),2.93-2.41(m,6H),2.36-2.10(m,1H),2.06-1.38(m,6H),1.26(dd,J=6.3,4.0Hz,3H)。LCMS m/z 502.11[M+1]$^+$。

[1634] 制备848

[1635] (2′S,7R)-2-氯-2′,4-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(848)

[1636] 

[1637] 步骤1:(2′S,7R)-2-氯-2′,4-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C56)的合成

[1638] 在0℃下向(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(107mg,0.288mmol)于THF(2.7mL)中的溶液中添加含3.0M MeMgCl的THF(191μL,0.573mmol)。20分钟后,将反应物用饱和氯化铵水溶液淬灭并用EtOAc萃取。将有机层用盐水洗涤,经无水硫酸钠干燥,过滤,并在真空中浓缩。通过硅胶色谱法(含0至60% EtOAc的己烷),产生溶解在二噁烷(2.7mL)中的材料和含4M HCl的二噁烷(720μL,2.88mmol)。4小时后,将粗混合物浓缩并使用于下一步骤无需进一步纯化(28mg,产率:20%)。LCMS m/z 288.03[M+H]$^+$。

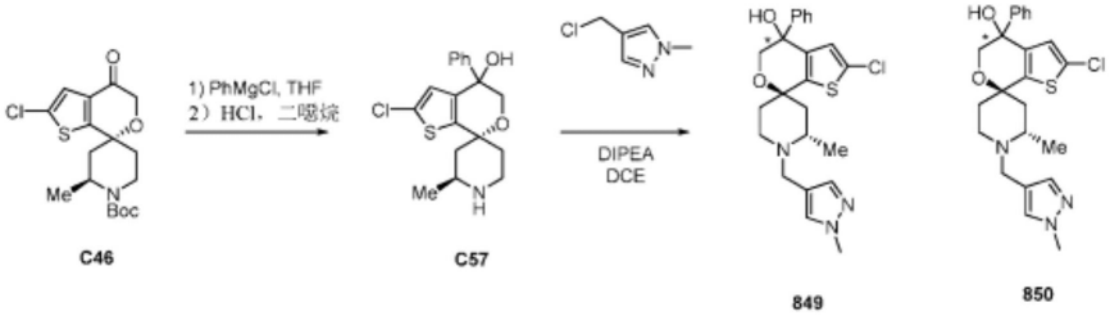
[1639] 步骤2:(2′S,7R)-2-氯-2′,4-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(848)的合成

[1640] 向(2′S,7R)-2-氯-2′,4-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C56(28mg,0.097mmol)于DMF(420μL)中的溶液中添加4-(氯甲基)-1-甲基-吡唑(15mg,0.11mmol)和K_2CO_3(40mg,0.29mmol)。将反应物在60℃下搅拌3小时并且然后用水和DCM淬灭。将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(含0至20% MeOH的DCM),产生呈60:40比率的非对映异构体的(2′S,7R)-2-氯-2′,4-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(8.7mg,产率:46%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.57(s,1H),7.43(d,J=0.8Hz,1H),6.90(d,J=1.5Hz,1H),3.91-3.77(m,4H),3.67-3.53(m,3H),2.79-2.45(m,3H),2.19-1.94(m,2H),1.87-1.67(m,1H),1.55(ddd,J=13.3,11.5,1.6Hz,1H),1.38(d,J=3.8Hz,3H),1.22(dd,J=6.3,2.1Hz,3H)。LCMS m/z 382.09[M+H]$^+$。

[1641] 制备849和850

[1642] (2′S,7R)-2-氯-2′-甲基-1′-[(1-甲基吡唑-4-基)甲基]-4-苯基-螺[5H-噻吩并

[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(849和850)

[1643] 

[1644] 步骤1:(2′S,7R)-2-氯-2′-甲基-4-苯基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C57)的合成

[1645] 在0℃下向(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(158mg,0.425mmol)于THF(4mL)中的溶液中添加含2.0M PhMgCl的THF(420μL,0.84mmol)。2小时后,将反应物用饱和氯化铵水溶液淬灭并用EtOAc萃取。将有机层用盐水洗涤,经无水硫酸钠干燥,过滤,并在真空中浓缩。通过硅胶色谱法纯化(含0至60% EtOAc的己烷),产生两种纯非对映异构产物级分。将每种级分溶解在二噁烷(2mL)和含4M HCl的二噁烷(106μL,0.42mmol)中。搅拌过夜后,将反应物用饱和碳酸氢钠水溶液淬灭,并用DCM萃取。将粗混合物浓缩并使用于下一步骤无需进一步纯化(C57,25.3mg,产率:74%)。LCMS m/z 349.99[M+H]$^+$。

[1646] 步骤2:(2′S,7R)-2-氯-2′-甲基-1′-[(1-甲基吡唑-4-基)甲基]-4-苯基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(849和850)的合成

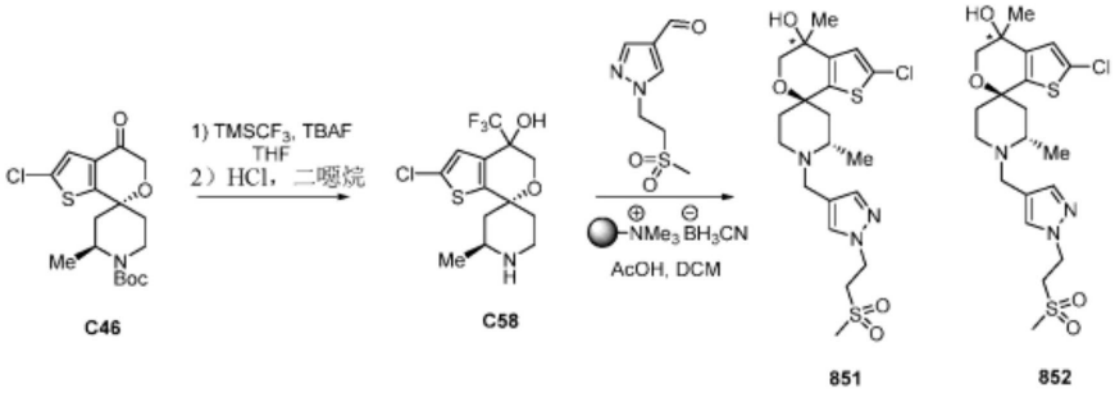
[1647] 向(2′S,7R)-2-氯-2′-甲基-4-苯基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C57(20mg,0.044mmol)于DCE(540μL)中的溶液中添加4-(氯甲基)-1-甲基-吡唑(6.9mg,0.053mmol)和DIPEA(17mg,0.13mmol)。将反应物在60℃下搅拌3小时并且然后用水和DCM淬灭。将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(含0至20% MeOH的DCM),随后通过反相HPLC纯化(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸),产生产物:

[1648] 化合物849[DIAST 1]:(3mg,产率:12%)。^{1}H NMR(300MHz,DMSO-d_6)δ9.73(s,1H),7.91(d,J=3.7Hz,1H),7.59(d,J=3.5Hz,1H),7.45-7.09(m,5H),6.71(d,J=7.0Hz,1H),4.42(d,J=13.8Hz,1H),4.30-4.08(m,1H),3.39-2.78(m,3H),2.48-2.15(m,2H),1.99(tt,J=26.9,13.1Hz,2H),1.44(dd,J=10.5,6.3Hz,3H)。LCMS m/z 444.12[M+H]$^+$。[溶剂后面的一些质子峰]

[1649] 化合物850[DIAST 2]:(7mg,产率:28%)。^{1}H NMR(300MHz,DMSO-d_6)δ7.91(d,J=3.6Hz,1H),7.59(d,J=3.5Hz,1H),7.47-7.09(m,5H),6.71(d,J=7.2Hz,1H),4.43(d,J=13.9Hz,1H),4.19(dd,J=14.0,5.1Hz,1H),3.96-3.80(m,6H),3.30(t,J=13.5Hz,2H),3.02(d,J=16.3Hz,1H),2.44-2.20(m,1H),1.96(td,J=29.4,26.8,16.1Hz,2H),1.44(dd,J=10.5,6.3Hz,3H)。LCMS m/z 444.28[M+H]$^+$。

[1650] 制备851和852

[1651] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(851和852)

[1652] 

[1653] 步骤1:(2′S,7R)-2-氯-2′-甲基-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C58)的合成

[1654] 在0℃下向(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯46(128mg,0.344mmol)、$TMSCF_3$(62μL,0.42mmol)和THF(3.5mL)的溶液中添加含1M TBAF的THF(35μL,0.035mmol)。在室温下搅拌30分钟后,添加另外部分的含1M TBAF的THF(172μL,0.172mmol)。将反应物用水和DCM淬灭。将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(含0至30% EtOAc的己烷),产生两种纯非对映异构产物级分。将每种级分溶解在二噁烷(1mL)和含4M HCl的二噁烷(1mL,4mmol)中。1小时后,将粗混合物浓缩并使用于下一步骤无需进一步纯化(C58:63.5mg,产率:54%)。LCMS m/z 341.93$[M+H]^+$。

[1655] 步骤2:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(851和852)的合成

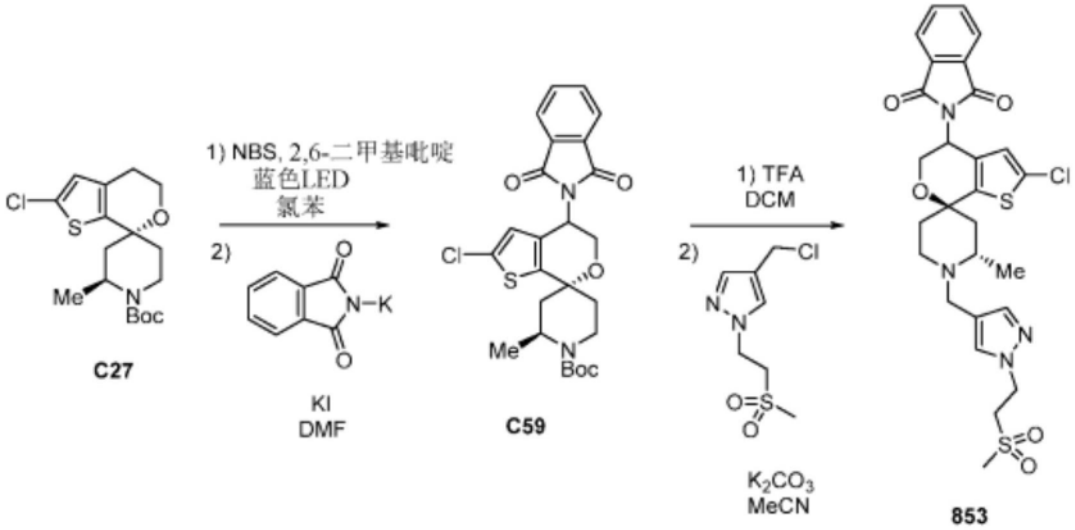
[1656] 向含有(2′S)-2-氯-2′-甲基-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C58(63.0mg,0.175mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(53.5mg,0.26mmol)、AcOH(52.4mg,0.87mmol)和DCM(3.3mL)溶液的微波管中添加约2mmol/g(262mg)氰基硼氢化物/Amberlite树脂。将管密封并在微波反应器中在110℃下加热45分钟。将反应物过滤并将回收的树脂在DCM中剧烈搅拌以收集任何另外的产物。将合并的有机层在真空中浓缩。通过硅胶色谱法纯化(含0至20% MeOH的DCM),产生产物:

[1657] 化合物851[DIAST 1]:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(59.1mg,产率:62%)。^1H NMR(300MHz,$CDCl_3$)δ7.42(d,J=10.0Hz,2H),6.93(d,J=1.1Hz,1H),4.54(td,J=5.9,3.2Hz,2H),4.09(d,J=12.4Hz,1H),3.90-3.41(m,5H),2.73-2.34(m,6H),2.08-1.89(m,2H),1.80(td,J=12.9,4.2Hz,1H),1.59(dd,J=14.2,11.4Hz,1H),1.18(d,J=6.2Hz,3H);和

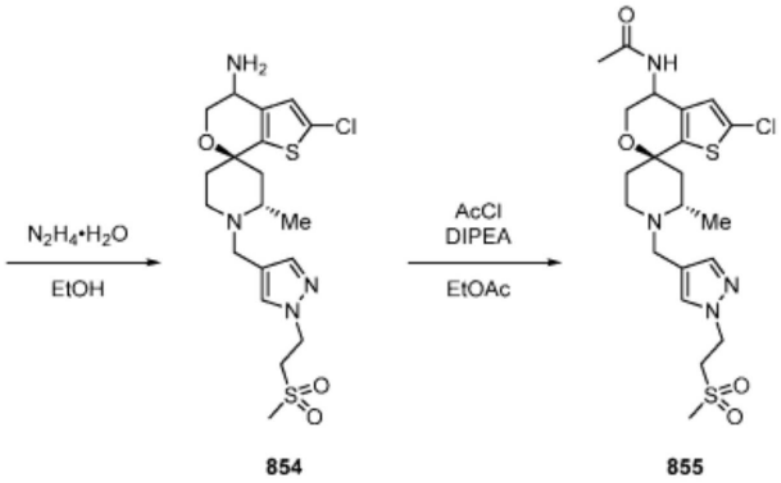
[1658] 化合物852[DIAST 2]:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-4-(三氟甲基)螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(23mg,产率:63%)。^1H NMR(300MHz,甲醇-d_4)δ7.82-7.68(m,1H),7.53(d,J=0.8Hz,1H),6.96(d,J=1.0Hz,1H),4.63(t,J=6.4Hz,2H),4.05(d,J=12.5Hz,1H),3.92-3.57(m,5H),2.90-2.45(m,6H),2.17(dt,J=14.2,2.8Hz,1H),2.02-1.76(m,2H),1.54(dd,J=14.2,11.5Hz,1H),1.23(d,J=6.3Hz,3H)。LCMS m/z 527.99$[M+H]^+$。

[1659] 制备853,854和855

[1660] N-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]乙酰胺(853,854,855)



[1661]



[1662] 步骤1:(2′S,7R)-2-氯-4-(1,3-二氧代异吲哚啉-2-基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C59)的合成

[1663] 向(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(1.12g,3.07mmol)和2,6-二甲基吡啶(0.6mL,5.2mmol)于氯苯(20mL)中的混合物中添加NBS(875mg,4.9mmol)。将反应物在蓝色LED辐照5分钟。将反应物过滤并用EtOAc冲洗。将滤液用EtOAc稀释,并用水和盐水洗涤。将有机层经无水硫酸镁干燥,过滤并在真空中浓缩。向粗材料中添加邻苯二甲酰亚胺钾盐(600mg,3.2mmol)、KI(50mg,0.3mmol)和DMF(10mL)。将反应物在100℃下搅拌15分钟。将反应物冷却至室温并用水和二乙醚稀释。将水层用二乙醚萃取。将合并的有机层用水和盐水洗涤,并在真空中浓缩。通过硅胶色谱法纯化(含0至50% EtOAc的庚烷),产生呈澄清油的产物(362mg,产率:17%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.83-7.73(m,2H),7.72-7.63(m,2H),6.39(d,J=9.1Hz,1H),5.34-5.23(m,1H),4.19(ddd,J=28.2,11.5,7.9Hz,1H),3.99-3.80(m,2H),3.76-3.57(m,1H),3.28(tdd,J=14.4,8.8,5.4Hz,1H),2.58-2.37(m,1H),2.19-1.99(m,1H),1.86-1.74(m,1H),1.65(ddd,J=24.2,14.4,10.9Hz,1H),1.40(d,J=0.7Hz,9H),1.26-1.21(m,3H)。LCMS m/z 501.88[M+

H]$^+$。

[1664] 步骤2:2-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]异吲哚啉-1,3-二酮(853)的合成

[1665] 向(2′S,7R)-2-氯-4-(1,3-二氧代异吲哚啉-2-基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C59(132mg,0.23mmol)于DCM(2mL)中的溶液中添加TFA(175μL,2.3mmol)。将溶液在室温下搅拌20分钟。将溶液在真空中浓缩,重新溶解在DCM中,并再次浓缩。将粗油溶解在MeCN(2mL)中,并用K_2CO_3(100mg,0.72mmol)处理,随后用4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(盐酸盐)853(100mg,0.39mmol)处理。将反应物在70℃下搅拌2小时。将混合物冷却至室温,并用水和EtOAc稀释。去除水层,并将有机层用水和盐水洗涤。将有机层经无水硫酸钠干燥,过滤并在真空中浓缩。通过硅胶色谱法纯化(含0至50% EtOAc的庚烷),产生呈澄清油的产物(118mg,产率:71%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.95-7.82(m,2H),7.82-7.70(m,2H),7.55(s,2H),6.49(d,J=5.7Hz,1H),5.37(dt,J=13.3,6.9Hz,1H),4.62(s,2H),4.26(dt,J=12.2,6.7Hz,1H),4.03-3.78(m,2H),3.66(d,J=6.0Hz,3H),2.60(d,J=91.0Hz,6H),2.05(d,J=17.3Hz,3H),1.32(d,J=37.8Hz,4H)。LCMS m/z 588.98[M+H]$^+$。

[1666] 步骤3:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-胺(854)的合成

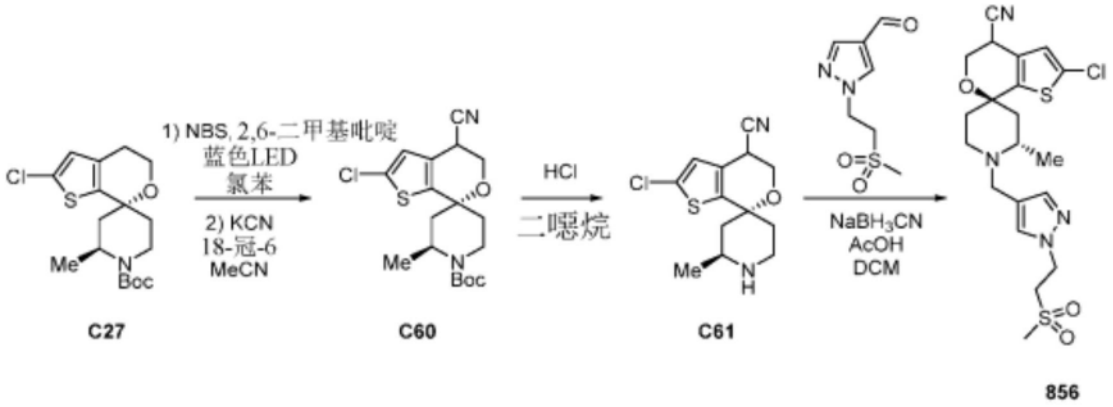
[1667] 向2-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]异吲哚啉-1,3-二酮853(100mg,0.16mmol)于EtOH(5mL)中的混合物中添加一水合肼(76μL,1.6mmol)。将反应物在80℃下搅拌。1小时后,将反应物冷却至0℃,过滤,并用冰冷EtOH冲洗。将滤液在真空中浓缩。通过反相色谱法纯化(柱:C18。梯度:含10-100% MeCN的水,具有0.1%三氟乙酸),得到呈TFA盐的产物。将经纯化的材料用饱和碳酸氢钠水溶液和DCM处理。将水层用DCM萃取,并将合并的有机层在真空中浓缩以递送呈澄清油的产物(40mg,产率:55%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.43(d,J=0.7Hz,1H),7.38(s,1H),6.69(s,1H),4.52(dd,J=6.7,5.2Hz,2H),3.82(dd,J=11.7,3.6Hz,1H),3.74(d,J=14.4Hz,1H),3.63-3.44(m,5H),2.62-2.32(m,6H),1.97-1.87(m,2H),1.68(td,J=13.2,4.5Hz,1H),1.56(dd,J=13.6,11.3Hz,1H),1.13(d,J=6.2Hz,3H)。LCMS m/z 459.03[M+H]$^+$。

[1668] 步骤4:N-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]乙酰胺(855)的合成

[1669] 向(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-胺854(32mg,0.070mmol)和DIPEA(25μL,0.14mmol)于EtOAc(1mL)中的混合物中添加乙酰氯(8μL,0.11mmol)。将反应物在室温下搅拌1小时并且然后通过添加饱和氯化铵水溶液淬灭。去除水层,并将有机层经无水硫酸钠干燥,过滤并在真空中浓缩。通过硅胶色谱法纯化(含0至20% MeOH的DCM),产生呈白色泡沫的产物(11mg,产率:30%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.43(d,J=0.8Hz,1H),7.39(s,1H),6.67(d,J=1.5Hz,1H),5.77(t,J=7.9Hz,1H),4.82-4.70(m,1H),4.52(t,J=6.0Hz,2H),3.91-3.65(m,3H),3.57(td,J=6.0,2.1Hz,2H),3.50(d,J=14.4Hz,1H),2.68-2.43(m,2H),2.43-2.26(m,4H),2.10-1.39(m,7H),1.14(t,J=6.2Hz,3H)。LCMS m/z 501.03[M+H]$^+$。

[1670] 制备856

[1671] (2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-甲腈(三氟乙酸盐)(856)

[1672] 

[1673] 步骤1:(2′S)-2-氯-4-氰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C60)的合成

[1674] 向(2′S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(1g,2.8mmol)和2,6-二甲基吡啶(536mg,5.0mmol)于氯苯(28mL)中的混合物中添加NBS(795mg,4.5mmol)。将反应物在蓝色LED辐照30分钟。将反应物用亚硫酸氢钠淬灭并用DCM萃取。将合并的有机层用盐水洗涤并在真空中浓缩。将溴化粗材料与KCN(127mg,2.0mmol)和含18-冠-6(516mg,2.0mmol)的MeCN(10mL)合并并在60℃下搅拌过夜。将反应物冷却至室温并用EtOAc稀释。将反应物用水和饱和碳酸氢钠水溶液洗涤。将有机层经无水硫酸钠干燥,过滤并在真空中浓缩。通过硅胶色谱法纯化(含0至40% EtOAc的己烷),产生产物(245mg,产率:23%)。LCMS m/z 382.72$[M+H]^+$。

[1675] 步骤2:(2′S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-甲腈(盐酸盐)(C61)的合成

[1676] 将(2′S)-2-氯-4-氰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C60(202mg,0.53mmol)和4M HCl于二噁烷(0.5mL,2.0mmol)中的溶液在室温下搅拌4小时。将反应物在真空中浓缩,重新溶解在MeOH中,并且然后再次浓缩。通过反相色谱法纯化(柱:C18。梯度:含10-90% MeCN的水,具有盐酸),得到产物(31.9mg,产率:18%)。LCMS m/z 283.06$[M+H]^+$。

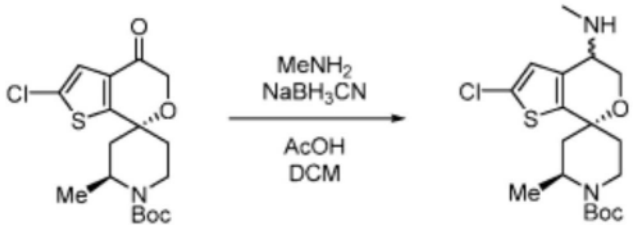
[1677] 步骤3:(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-甲腈(三氟乙酸盐)(856)的合成

[1678] 向1-(2-甲基磺酰基乙基)吡唑-4-甲醛C61(7.9mg,0.028mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(8.5mg,0.042mmol)于DCM(2mL)中的溶液中添加AcOH(8μL,0.14mmol),随后添加固体负载的$NaBH_3CN$(0.084mmol)。将反应物在微波反应器中加热至110℃。1小时后,将反应物冷却,过滤并在真空中浓缩。通过反相HPLC(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸),产生产物(5.1mg,产率:31%)。LCMS m/z 468.94$[M+H]^+$。

[1679] 制备857

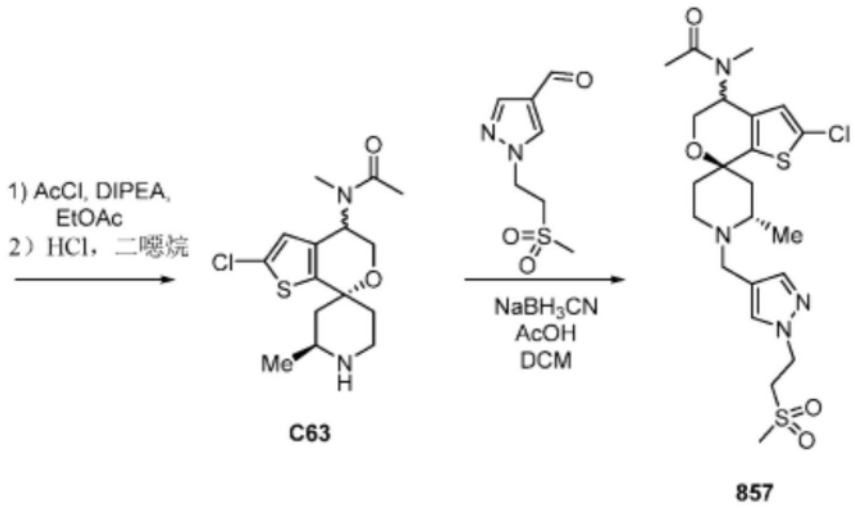
[1680] N-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺

[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]-N-甲基-乙酰胺(857)



C46 C62

[1681]



C63 857

[1682] 步骤1:(2′S,7R)-2-氯-2′-甲基-4-(甲基氨基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C62)的合成

[1683] 将(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C46(200mg,0.54mmol)、2M $MeNH_2$(1mL,2mmol)和固体负载的$NaBH_3CN$(1mmol)于DCM(3mL)中的混合物在90℃下在微波反应器中搅拌。2小时后,添加AcOH(40μL,0.70mmol)。3小时后,将反应物冷却,过滤并在真空中浓缩。通过反相色谱法纯化(柱:C18。梯度:含10-100% MeCN的水,具有0.1%三氟乙酸),得到产物。将分离的产物在饱和碳酸氢钠水溶液和DCM中搅拌。将有机层分离并在真空中浓缩以产生呈淡黄色油的产物(112mg,产率:52%)。^1H NMR(400MHz,$CDCl_3$)δ6.67(d,J=7.8Hz,1H),4.01-3.75(m,3H),3.70-3.59(m,1H),3.33-3.19(m,2H),2.42(d,J=1.4Hz,3H),2.27-1.92(m,3H),1.82-1.54(m,2H),1.41(s,9H),1.19(d,J=6.6Hz,3H)。LCMS m/z 386.96$[M+H]^+$。

[1684] 步骤2:N-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]-N-甲基-乙酰胺(盐酸盐)(C63)的合成

[1685] 向(2′S,7R)-2-氯-2′-甲基-4-(甲基氨基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C62(105mg,0.26mmol)和DIPEA(0.1mL,0.57mmol)于EtOAc(2mL)中的混合物中添加乙酰氯(20μL,0.28mmol)。将反应搅拌1小时并且然后在真空中浓缩。向粗材料中添加DCM和1M HCl。去除水层,并将有机层用1M HCl洗涤。将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(含0至100% EtOAc的庚烷),产生呈澄清油的乙酰化产物(95mg,产率:85%)。^1H NMR(400MHz,$CDCl_3$)δ6.64(s,1H),5.53(ddd,J=10.8,4.1,1.9Hz,1H),4.10-3.98(m,2H),3.96-3.68(m,3H),3.34(ddt,J=17.1,8.6,4.5Hz,1H),2.87(d,J=

3.7Hz,3H),2.24(h,J=8.1Hz,2H),2.16(s,3H),2.05-1.91(m,1H),1.78(dd,J=13.9,10.9Hz,1H),1.58(dd,J=14.6,11.0Hz,1H),1.50(s,9H),1.30-1.25(m,3H)。LCMS m/z 429.05[M+H]$^+$。

[1686] 将乙酰化产物在含4M HCl的二噁烷(250μL,1mmol)中搅拌过夜。将反应物在真空中浓缩并将脱保护产物从乙醚中结晶为白色固体(76mg,产率:97%)。^{1}H NMR(400MHz,甲醇-d_4)δ6.77(s,1H),5.51(q,J=3.6Hz,1H),4.13(ddd,J=12.7,7.0,4.5Hz,1H),3.96(ddd,J=12.7,4.4,3.0Hz,1H),3.66(s,3H),3.65-3.44(m,2H),3.42-3.35(m,1H),2.89(d,J=3.1Hz,3H),2.47-2.39(m,1H),2.31-2.26(m,1H),2.15(s,3H),2.11-1.99(m,1H),1.93-1.65(m,2H)。LCMS m/z 328.92[M+H]$^+$。

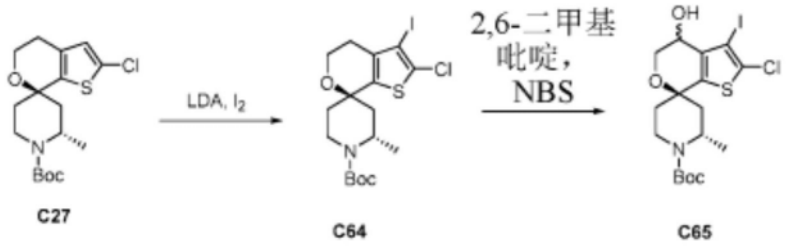
[1687] 步骤3:N-[(2′S,7R)-2-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]-N-甲基-乙酰胺(857)的合成

[1688] 将N-[(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-基]-N-甲基-乙酰胺C63(20mg,0.054mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(30mg,0.15mmol)、固体负载的$NaBH_3CN$(0.15mmol)和AcOH(4μL,0.07mmol)于DCM(1mL)中的混合物在95℃下在微波反应器中搅拌。3小时后,将反应物冷却并过滤。将树脂用甲醇冲洗并将合并的有机层在真空中浓缩。通过硅胶色谱法纯化(含0至12% MeOH的DCM),产生呈澄清油的产物(10mg,产率:35%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.51(s,1H),7.47(s,1H),6.60(dd,J=13.6,2.3Hz,1H),5.51(ddd,J=11.2,4.2,2.0Hz,1H),4.67-4.56(m,2H),4.00(ddd,J=12.7,6.8,4.2Hz,1H),3.92-3.77(m,2H),3.73-3.62(m,2H),3.58(d,J=14.4Hz,1H),2.91-2.63(m,4H),2.48(d,J=3.4Hz,5H),2.18-2.12(m,3H),2.07-1.81(m,2H),1.84-1.44(m,2H),1.22(t,J=6.3Hz,3H)。LCMS m/z 514.94[M+H]$^+$。

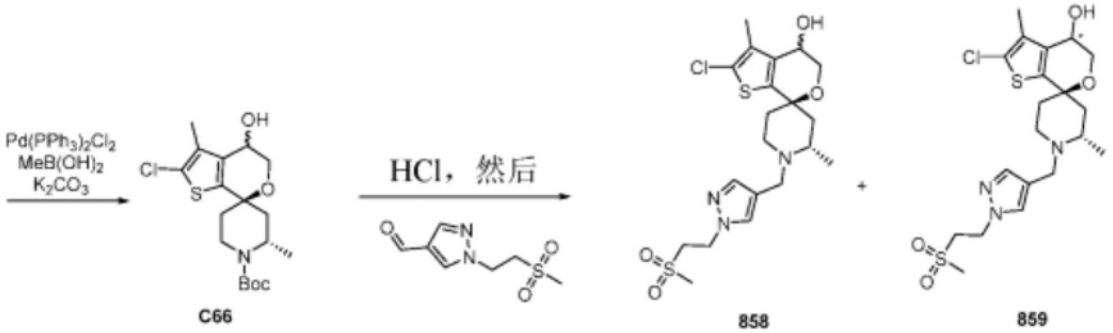
[1689] 化合物858和859

[1690] (2′S,7R)-2-氯-2′,3-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(858)和

[1691] (2′S,7R)-2-氯-2′,3-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(859)



[1692]



[1693] 步骤1:(2S,4R)-2′-氯-3′-碘代-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C64)的合成

[1694] 在0℃下在氮气气氛下向二异丙胺(220μL,1.6mmol)于THF(3mL)中的溶液中逐滴添加n-BuLi(660μL的2.2M,1.5mmol)。将混合物搅拌30分钟并在-78℃下转移到(2′S)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(500mg,1.397mmol)于THF(3mL)中的溶液中。然后,添加含碘(500mg,2.0mmol)的THF(0.5mL),并将混合物搅拌5分钟,并用氯化铵水溶液淬灭。将混合物温热至室温并用乙酸乙酯稀释。将有机层分离并在真空中浓缩。将残余物通过硅胶色谱法(梯度:含0-15% EtOAc的庚烷),得到产物。(2′S)-2-氯-3-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(380mg,56%)。^{1}H NMR(300MHz,氯仿-d)δ4.00(ddd,J=11.4,6.6,5.1Hz,1H),3.91(td,J=5.4,1.1Hz,2H),3.73(ddd,J=14.0,6.0,4.9Hz,1H),3.32(ddd,J=14.0,8.7,5.4Hz,1H),2.49(td,J=5.5,3.3Hz,2H),2.24-2.01(m,2H),1.82-1.71(m,1H),1.66(dd,J=14.1,10.9Hz,1H),1.49(s,9H),1.30-1.23(m,3H)。LCMS m/z 484.07[M+H]$^+$。

[1695] 步骤2:(2S,4R)-2′-氯-4′-羟基-3′-碘代-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C65)的合成

[1696] 向(2′S)-2-氯-3-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C64(380mg,0.79mmol)于氯苯(10mL)中的溶液中添加2,6-二甲基吡啶(220μL,1.9mmol)。将混合物用氮气吹扫并添加NBS(220mg,1.2mmol)。将混合物在蓝色LED下辐照40分钟。接下来,将混合物过滤,并将滤液在真空中浓缩。将残余物溶解于THF(5mL)中并添加饱和碳酸氢钠溶液。将混合物加热至70℃,持续60小时,并且随后用乙酸乙酯稀释。将水层萃取三次,并将合并的有机层经硫酸钠干燥,过滤并在真空中浓缩。将残余物通过硅胶色谱法纯化(梯度:含0-35% EtOAc的庚烷),得到产物。(2′S)-2-氯-4-羟基-3-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(90mg,22%)。^{1}H NMR(300MHz,氯仿-d)δ4.32(s,1H),4.20-3.86(m,3H),3.76(tdd,J=11.0,8.7,5.1Hz,1H),3.45-3.21(m,1H),2.32-2.11(m,2H),2.10-1.86(m,1H),1.79-1.52(m,2H),1.49(s,9H),1.29-1.24(m,3H)。LCMS m/z 499.88[M+H]$^+$。

[1697] 步骤3:(2S,4R)-2′-氯-4′-羟基-2,3′-二甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C66)的合成

[1698] 在室温下向(2′S,7R)-2-氯-4-羟基-3-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C65(171mg,0.342mmol)于DME(4mL)中的溶液中添加水(855μL)、$CH_3B(OH)_2$(123mg,2.06mmol)、K_2CO_3(95mg,0.69mmol)和双(三苯基膦)二氯化钯(II)(24mg,0.034mmol)。将混合物在60℃下加热36小时。将混合物在水与DCM之间分配,并将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生产物。(2′S,7R)-2-氯-4-羟基-2′,3-二甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(90mg,61%)。LCMS m/z 384.75[M+H]$^+$。

[1699] 步骤4:(2S,4R)-2′-氯-2,3′-二甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[p哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-醇(858)和(2′S,7R)-2-氯-2′,3-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(859)的合成

[1700] 向(2′S,7R)-2-氯-4-羟基-2′,3-二甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C66(90mg,0.23mmol)于1,4-二噁烷(855μL)中的溶液中添加含HCl(855μL的4M,3.420mmol)的1,4-二噁烷。将混合物搅拌30分钟并在真空中浓缩。向残余物中添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(84mg,0.42mmol)、乙酸(60mg,1mmol)、二氯甲烷(2mL)和聚合物负载的氰基硼氢化物(310mg的2mmol/g,0.6200mmol)。将混合物加热至95℃,持续120分钟。接下来,添加MeOH,并将混合物搅拌10分钟,过滤并在真空中浓缩。通过反相HPLC(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸),产生产物。(2′S,7R)-2-氯-2′,3-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(31mg,25%)作为异构体的混合物。

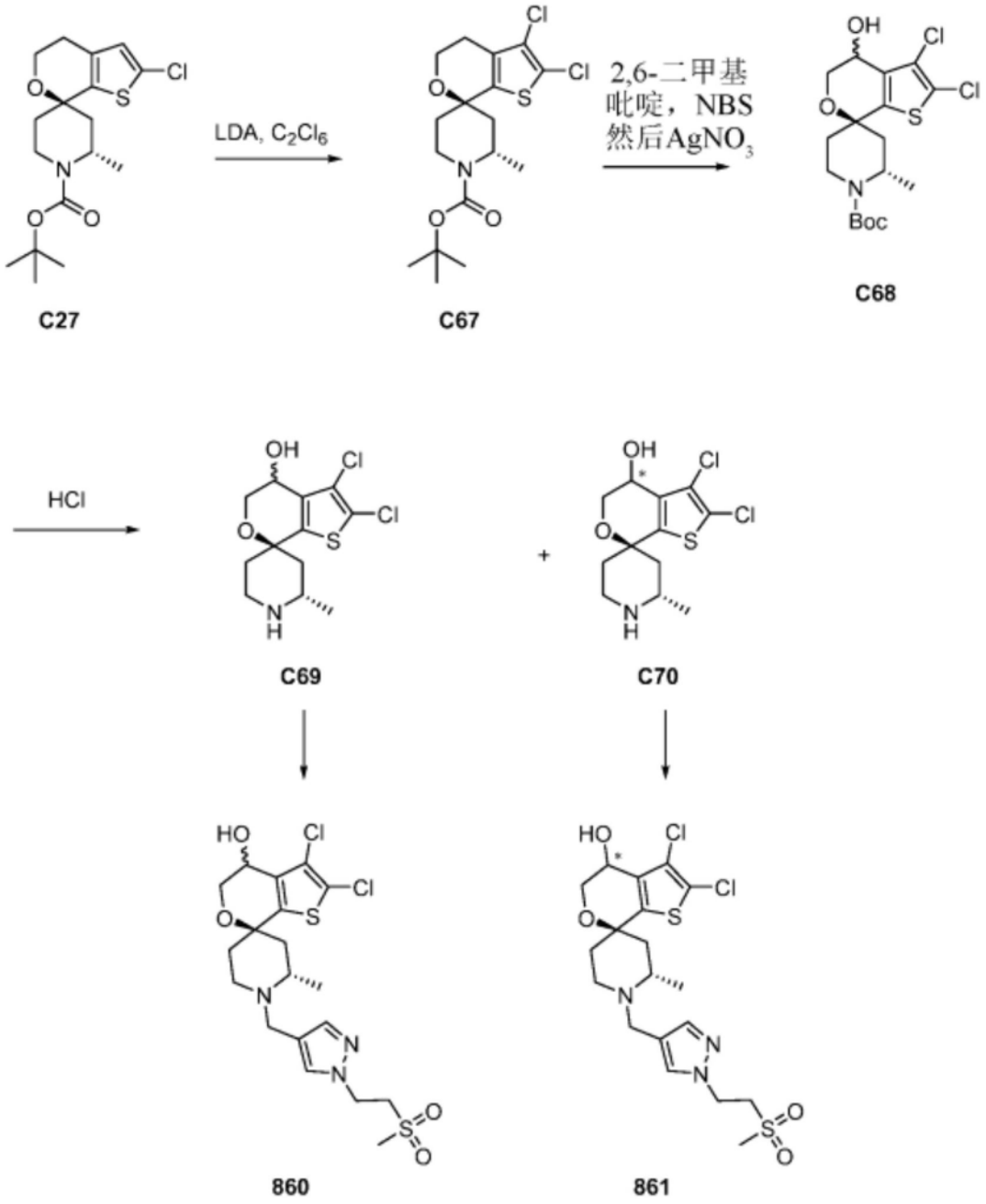
[1701] ^{1}H NMR(400MHz,甲醇-d_4)δ8.00(dd,J=1.7,0.8Hz,1H),7.73(d,J=0.8Hz,1H),4.76-4.64(m,2H),4.53(dd,J=14.1,1.8Hz,1H),4.38(dt,J=4.1,2.1Hz,1H),4.28(d,J=14.1Hz,1H),4.07-3.83(m,2H),3.72(t,J=6.2Hz,2H),3.65-3.33(m,2H),3.22(td,J=13.0,2.9Hz,1H),2.89-2.82(m,3H),2.57-1.72(m,7H),1.53(dd,J=6.5,5.1Hz,3H)。LCMS m/z 474.3$[M+H]^+$;和

[1702] (2′S,7R)-2-氯-2′,3-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(6mg,10%)作为单个对映异构体。^{1}H NMR(400MHz,甲醇-d_4)δ8.00(d,J=0.8Hz,1H),7.72(d,J=0.9Hz,1H),4.76-4.61(m,2H),4.53(d,J=14.1Hz,1H),4.39(t,J=2.1Hz,1H),4.29(d,J=14.1Hz,1H),4.03-3.83(m,2H),3.72(t,J=6.2Hz,2H),3.53-3.32(m,3H),2.87(d,J=0.6Hz,3H),2.50(dt,J=15.2,3.0Hz,1H),2.35-1.92(m,5H),1.77(dd,J=15.3,12.1Hz,1H),1.52(d,J=6.5Hz,3H)。

[1703] 化合物860和861

[1704] (2′S,7R)-2,3-二氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(860)和(2S,4R)-2′,3′-二氯-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-4′13-螺[哌啶-4,7′-噻吩并[3,2-d]吡喃]-4′(5′H)-醇(861)

[1705]



[1706] 步骤1:(2S,4R)-2′,3′-二氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C67)的合成

[1707] 在0℃下在氮气气氛下向二异丙胺(176μL,1.26mmol)于THF(2.4mL)中的溶液中逐滴添加sec-BuLi(840μL的1.3M,1.1mmol)。将混合物在-78℃下搅拌30分钟并转移到(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(400mg,1.1mmol)于THF(2.4mL)中的溶液中。将混合物搅拌2分钟,并添加含六氯乙烷(370mg,1.6mmol)的THF(0.5mL)。将混合物搅拌5分钟,并用氯化铵水溶液淬灭。将混合物温热至室温并用DCM稀释。将有机层分离并在真空中浓缩。将残余物通过硅胶色谱法(梯度:含0-20% EtOAc的庚烷),得到产物。(2′S,7R)-2,3-二氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(165mg,34%)。LCMS m/z 392.4$[M+H]^+$。

[1708] 步骤2:(2S,4R)-2′,3′-二氯-4-羟基-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并

[2,3-c]吡喃]-1-甲酸叔丁酯(C68)的合成

[1709] 向(2′S)-2,3-二氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C67(480mg,1.0mmol)于氯苯(12.6mL)中的溶液中添加2,6-二甲基吡啶(342μL,2.95mmol)。将混合物用氮气吹扫15分钟并添加NBS(291mg,1.64mmol)。将混合物用蓝色LED辐照40分钟并用硫酸氢钠淬灭。将混合物用DCM萃取,并将有机相用盐水洗涤并在真空中浓缩。将残余物溶解在丙酮(6.24mL)和水(6.24mL)中,并添加硝酸银(226mg,1.33mmol)。1小时后,将混合物在真空中浓缩,并在DCM与水之间分配。将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生产物。(2S,4R)-2′,3′-二氯-4′-羟基-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(90mg,21%)。LCMS m/z 407.75[M+H]$^+$。

[1710] 步骤3:(2S,4R)-2′,3′-二氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-醇(C69)的合成

[1711] 向(2′S)-2,3-二氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C68(90mg,21%)于1,4-二噁烷(2.4mL)中的溶液中添加HCl(917μL的4M,3.668mmol)。将混合物搅拌5小时,在真空中浓缩,并通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1% TFA),得到随后在DCM与1M NaOH溶液之间分配的产物。将有机层收集并在真空中浓缩以产生产物。(2′S,7S)-2,3-二氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(35.1mg,50%)作为异构体的混合物。LCMS m/z 329.74[M+H]$^+$;(2′S,7R)-2,3-二氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(8mg,25%)作为单个立体异构体。^{1}H NMR(400MHz,甲醇-d_4)δ4.40(dd,J=2.3,1.6Hz,1H),4.00(dd,J=12.6,2.3Hz,1H),3.92(dd,J=12.6,1.7Hz,1H),3.13(td,J=12.7,2.9Hz,1H),3.08-2.87(m,2H),2.21(dt,J=14.2,2.7Hz,1H),1.99(dq,J=13.7,2.6Hz,1H),1.78(td,J=13.1,4.8Hz,1H),1.20(dd,J=14.2,11.5Hz,1H),1.09(d,J=6.5Hz,3H)。LCMS m/z 307.94[M+H]$^+$。

[1712] 步骤4a:(2′S,7R)-2,3-二氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(860)的合成

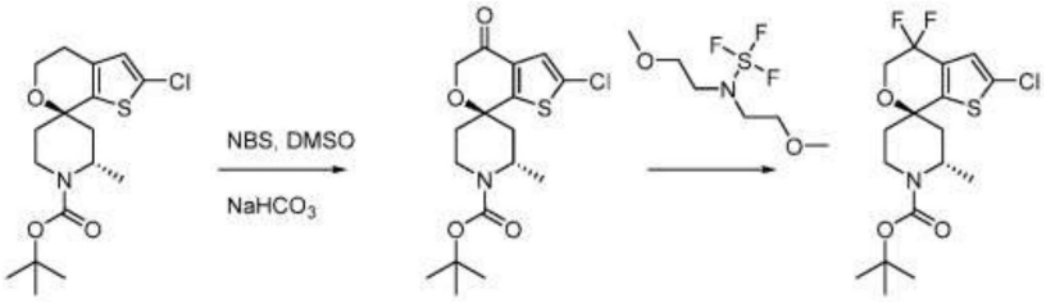
[1713] 向(2S,4R)-2′,3′-二氯-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-醇C69(8mg,0.03mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(10.5mg,0.0519mmol)、乙酸(7.5mg,0.12mmol)于二氯甲烷(2mL)中的溶液中添加聚合物负载的氰基硼氢化物(40mg的2mmol/g,0.080mmol)。将混合物在微波反应器中加热至95℃,持续120分钟。然后,添加MeOH,并将混合物搅拌10分钟,过滤并在真空中浓缩。通过反相HPLC(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸),得到在DCM与pH 10缓冲液之间分配的产物。将有机层分离并在真空中浓缩以得到产物。(2′S,7R)-2,3-二氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(8.3mg,65%)。^{1}H NMR(400MHz,甲醇-d_4)δ8.00(d,J=2.5Hz,1H),7.73(s,1H),4.70(dd,J=7.0,5.2Hz,2H),4.61-4.46(m,1H),4.42(dt,J=3.3,1.8Hz,1H),4.29(d,J=14.1Hz,1H),4.06-3.87(m,2H),3.72(t,J=6.2Hz,2H),3.54-3.33(m,2H),2.87(dd,J=5.1,2.4Hz,3H),2.64-1.71(m,4H),1.54(t,J=6.3Hz,3H)。LCMS m/z 494.1[M+H]$^+$。

[1714] 步骤4b:(2S,4R)-2′,3′-二氯-2-甲基-1-((1-(2-(甲基磺酰基乙基)乙基)-1H-吡唑-4-基)甲基)-4′13-螺[哌啶-4,7′-噻吩并[3,2-d]吡喃]-4′(5′H)-醇(861)的合成

[1715] 向(2′S,7R)-2,3-二氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇6C69(11mg,0.036mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(14mg,0.069mmol)和乙酸(10mg,0.2mmol)于二氯甲烷(2.75mL)中的溶液中添加聚合物负载的氰基硼氢化物(55mg的2mmol/g,0.11mmol)。将混合物在微波反应器中加热至95℃,持续120分钟。然后,添加MeOH,并将混合物搅拌10分钟,过滤并在真空中浓缩。通过反相HPLC(方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸),产生产物。(2′S,7R)-2,3-二氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(甲酸盐)(7.8mg,40%)。^{1}H NMR(400MHz,甲醇-d_4)δ7.98(d,J=0.7Hz,1H),7.72(d,J=0.7Hz,1H),4.73-4.63(m,2H),4.53-4.20(m,3H),3.93(d,J=1.8Hz,2H),3.78-3.66(m,2H),3.57(ddd,J=12.0,6.4,3.0Hz,1H),3.19(td,J=13.0,2.9Hz,1H),2.85(s,3H),2.41(dt,J=15.2,2.9Hz,1H),2.28(dt,J=14.5,3.1Hz,1H),2.06(dd,J=14.6,12.0Hz,1H),1.88(ddd,J=15.1,13.2,4.4Hz,1H),1.53(d,J=6.5Hz,3H)。LCMS m/z 494.39$[M+H]^+$。

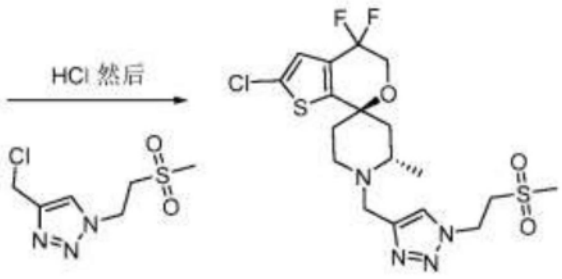
[1716] 化合物862

[1717] (2S,4R)-2′-氯-4′,4′-二氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](JMA5)



C27 C70 C71

[1718]



862

[1719] 步骤1:(2S,4R)-2′-氯-2-甲基-4′-氧代-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C70)的合成

[1720] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(900mg,1.8mmol)和NBS(400mg,2.2mmol)于氯苯(12mL)中的溶液在100W灯泡下辐照过夜。添加另外的NBS(83mg,0.47mmol),并将混合物搅拌另外5小时。接下来,添加硫

酸氢钠,并将混合物用DCM萃取,通过二氧化硅垫过滤,并在真空中浓缩。将残余物溶解在DMSO(36mL)中,并添加碳酸氢钠(236mg,2.81mmol)。将混合物加热至50℃过夜。然后,添加水并将混合物用DCM(x3)萃取,用盐水洗涤,并在真空中浓缩。将残余物通过硅胶色谱法(梯度:含0-20% EtOAc的庚烷)以得到产物。(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(80mg,8%)。LCMS m/z 372.1[M+H]$^+$。

[1721] 步骤2:(2S,4R)-2′-氯-4′,4′-二氟-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C71)的合成

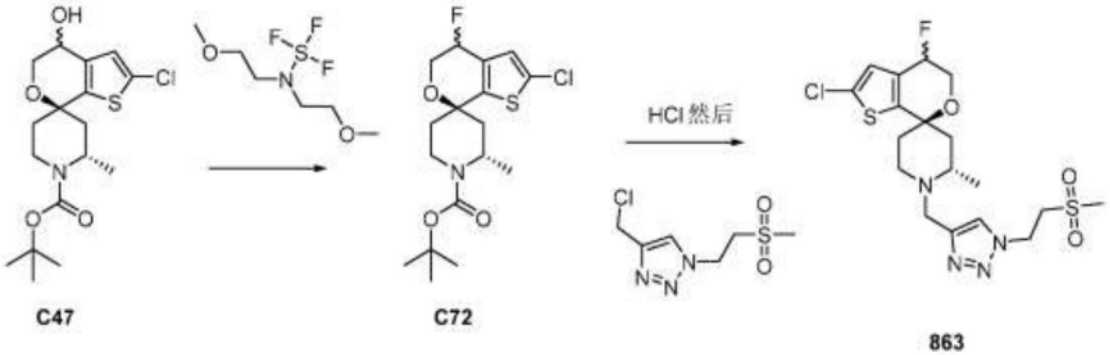
[1722] 在65℃下向(2S,4R)-2′-氯-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C70(80mg,0.2mmol)于甲苯(2mL)中的溶液中逐滴添加Deoxo-fluor(119mg,0.538mmol)。使混合物搅拌过夜然后添加另外的Deoxo-fluor(238mg,1.08mmol)。将混合物加热至76℃,并搅拌24小时。然后,将混合物用DCM稀释,并用$NaHCO_3$和盐水洗涤。将有机层在真空中浓缩,并将残余物通过硅胶色谱法纯化(梯度:含0-25% EtOAc的庚烷),得到产物。(2′S,7R)-2-氯-4,4-二氟-2′-甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(8mg,9%)。LCMS m/z 391.63[M+H]$^+$。

[1723] 步骤3:(2S,4R)-2′-氯-4′,4′-二氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](862)的合成

[1724] 向(2S,4R)-2′-氯-4′,4′-二氟-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C71(8mg,0.02mmol)于1,4-二噁烷(0.3mL)中的溶液中添加HCl(0.051mL,含4M的1,4-二噁烷)。将混合物搅拌过夜并在真空中浓缩。向残余物中添加4-(氯甲基)-1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑(9mg,0.04mmol)、DCE(0.2mL)和DIPEA(7.8mg,0.060mmol)。将混合物加热至60℃过夜。然后,将混合物在DCM与1M NaOH之间分配,并将有机层分离并在真空中浓缩。通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1% TFA),得到产物。(2S,4R)-2′-氯-4′,4′-二氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](2.4mg,20%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.33(s,1H),7.14(s,1H),5.06-4.95(m,2H),4.77-4.54(m,2H),4.10(t,J=10.4Hz,2H),3.90-3.78(m,2H),3.66-3.34(m,3H),3.01(s,3H),2.56-2.35(m,2H),2.17-1.90(m,2H),1.58(d,J=6.5Hz,3H)。LCMS m/z 480.99[M+H]$^+$。

[1725] 化合物863

[1726] (2S,4R)-2′-氯-4′-氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](863)

[1727] 

[1728] 步骤1:(2S,4R)-2′-氯-4′-氟-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]

吡喃]-1-甲酸叔丁酯(C72)的合成

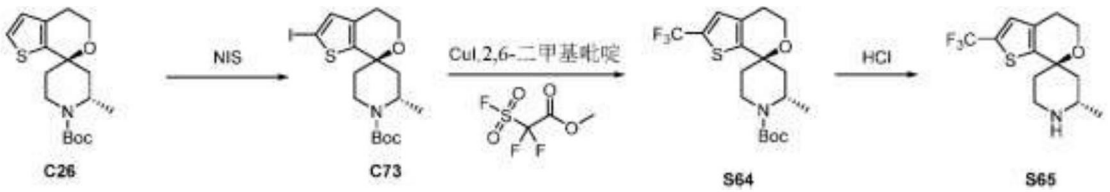
[1729] 在-78℃下向(2′S,7R)-2-氯-4-羟基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C47(82mg,0.22mmol)于DCM(7.2mL)中的溶液中添加2-甲氧基-N-(2-甲氧基乙基)-N-(三氟-λ³,4-硫烷基)乙胺(126mg,0.57mmol)。将混合物搅拌1小时,并用饱和氯化铵溶液淬灭。将有机层分离并在真空中浓缩以得到产物。(2′S,7R)-2-氯-4-氟-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(80mg,72%)。LCMS m/z 376.29$[M+H]^+$。

[1730] 步骤2:(2S,4R)-2′-氯-4′-氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](863)的合成

[1731] 向(2′R)-2-氯-4-氟-2′-甲基-5,6-二氢-4H-螺[苯并[b]噻吩-7,4′-哌啶]-1′-外消旋甲酸叔丁酯C72(90mg,0.24mmol)于1,4-二噁烷(3.6mL)中的溶液中添加HCl(0.6mL,含4M的1,4-二噁烷)。将混合物搅拌过夜并在真空中浓缩。向残余物中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)-三唑(62mg,0.028mmol)、DCE(2.6mL)和DIPEA(92mg,0.71mmol)。将混合物加热至60℃过夜。然后,将混合物在DCM与1M NaOH之间分配,并将有机层分离并在真空中浓缩。通过反相色谱法纯化(柱:C18。梯度:含0-100% MeCN的水,具有0.1% TFA),得到产物。(2S,4R)-2′-氯-4′-氟-2-甲基-1-((1-(2-(甲基磺酰基)乙基)-1H-1,2,3-三唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](46mg,30%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.34(d,J=2.7Hz,1H),7.00(d,J=0.7Hz,1H),5.23(ddt,J=51.1,3.4,2.0Hz,1H),5.11-4.94(m,2H),4.63(q,J=14.4Hz,2H),4.19-3.91(m,2H),3.83(t,J=6.3Hz,2H),3.66-3.37(m,2H),3.00(d,J=0.6Hz,3H),2.65-1.78(m,5H),1.57(dd,J=6.5,5.4Hz,3H)。LCMS m/z 463.11$[M+H]^+$。

[1732] 制备S64和S65

[1733] (2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]′-1′-甲酸叔丁酯(S64)和(1r,3r)-3-[5,7-二氟-2-(4-氟苯基)-1H-吲哚-3-基]环丁胺(S65)

[1734] 

[1735] 步骤1:(2′S,7R)-2-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C73)的合成

[1736] 在配备有机械搅拌器和温度探针以及氮气入口/出口的3颈RBF中,在10分钟内向(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C26(227g,701.8mmol)于DCM(2.5L)和AcOH(680mL)中的溶液中添加NIS(206g,869.8mmol)。将所得反应混合物在室温下搅拌30小时。将反应混合物用2N NaOH水溶液(约8L)碱化直到pH=11。将有机相分离,用10%亚硫酸氢钠水溶液(1L)、水(600mL)、盐水(2L)洗涤,并经$MgSO_4$干燥,过滤并在减压下浓缩。将粗残余物通过Combiflash Torrent纯化,3kg isco柱线性梯度(含0%至40%乙酸乙酯的庚烷),收集含有期望产物的级分,在减压下浓缩以得到呈澄清浅黄色粘性油的(2′S,7R)-2-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌

啶]-1′-甲酸叔丁酯(295g,85％)。1H NMR(300MHz,氯仿-d)δ6.89(s,1H),3.98(dt,J＝11.5,5.8Hz,1H),3.83(t,J＝5.5Hz,2H),3.71(dt,J＝14.0,5.5Hz,1H),3.32(ddd,J＝14.0,8.7,5.4Hz,1H),2.71-2.53(m,2H),2.20(d,J＝7.1Hz,2H),1.86-1.61(m,2H),1.48(s,9H),1.25(d,J＝6.6Hz,3H)。

[1737] 步骤2:(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(S64)的合成

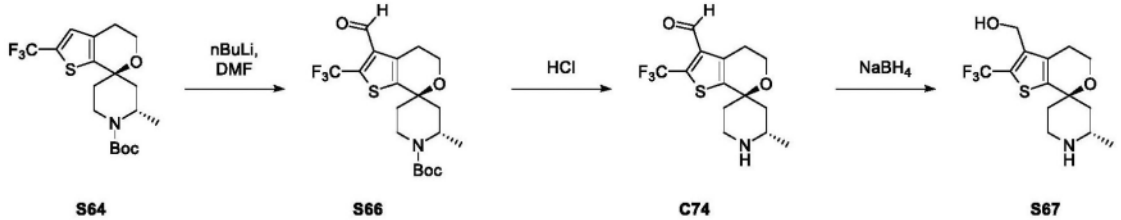
[1738] 在配备有机械搅拌器、温度探针、加热夹套的4颈RBF中,N_2扫描6NNaOH水溶液洗涤器,在30分钟的过程内向(2′S,7R)-2-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C73(295g,649.9mmol)、2,6-二甲基吡啶(18mL,155.4mmol)和CuI(127g,666.8mmol)于DMF(4L)中的预加热至85℃的溶液/悬浮液中逐滴添加2,2-二氟-2-氟磺酰基-乙酸甲酯(165mL,1.296mol)。2小时后,HPLC分析显示约50％转化,在85℃下在20分钟内添加另外1.3当量的2,2-二氟-2-氟磺酰基-乙酸甲酯(110mL,864.0mmol)。并将反应混合物在该温度下搅拌2小时,此时HPLC分析显示约80％转化。在85℃下在20分钟内添加另外0.8当量的2,2-二氟-2-氟磺酰基-乙酸甲酯(67mL,526.3mmol)。并将反应混合物在该温度下搅拌12小时,此时HPLC分析显示约98％转化为期望产物。将反应混合物冷却至环境温度,并用MTBE(4L)处理,观察红色沉淀物,将其通过Celite®床过滤,并将固体用MTBE(3×1L)洗涤。将合并的滤液用1:1水:氢氧化铵(冰冷,4L)洗涤,将有机相分离。将有机相用1:1水:氢氧化铵(冰冷,2L)、盐水(1L)、1M HCl水溶液(1L)、盐水(1L)再次洗涤,经$MgSO_4$干燥,过滤并浓缩。将粗残余物通过Combiflash Torrent纯化,1.5kg isco柱线性梯度(含0％至50％乙酸乙酯的庚烷),收集含有期望产物的级分,在减压下浓缩以得到呈澄清浅黄色粘性油的(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(230g,90％)。^{1}H NMR(300MHz,氯仿-d)δ7.09(d,J＝1.4Hz,1H),4.01(ddd,J＝11.5,6.8,5.2Hz,1H),3.94-3.80(m,2H),3.80-3.64(m,1H),3.35(ddd,J＝14.0,8.7,5.4Hz,1H),2.66(td,J＝5.5,3.3Hz,2H),2.30-2.06(m,2H),1.88-1.61(m,2H),1.48(s,9H),1.27(d,J＝6.5Hz,3H)。^{19}F NMR(282MHz,氯仿-d)δ-55.35。

[1739] 步骤3:(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S65)的合成

[1740] 将含(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S64(466mg,1.190mmol)的MeOH(5ml)和HCl(3mL的4M,12.00mmol)在50℃下搅拌40分钟。将反应混合物蒸发以提供(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(310mg,78％)。LCMS m/z 292.01[M+1]$^+$。

[1741] 制备67

[1742] [(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S67)

[1743] 

[1744] 步骤1:(2′S,7R)-3-甲酰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(S66)的合成

[1745] 在-78℃(干冰/丙酮浴)下在N_2在30分钟内向(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S64(230g,575.8mmol)于THF(2.6L)中的溶液中添加n-BuLi(340mL的1.75M,595.0mmol)。5分钟后,将等分试样(0.3mL)用CD_3OD(1mL)淬灭,将溶液浓缩;1H NMR显示在7.09ppm的芳香族质子处几乎完全氘化。添加完成后,将反应混合物在-78℃下搅拌总计30分钟,然后在6分钟内通过加料漏斗添加DMF(270mL,3.487mol)。在-78℃下搅拌然后将冷却浴用冰水浴替代。在冰水浴中45分钟后,将反应物用水(500mL)淬灭。将反应混合物在MTBE(2L)与水(1L)之间分配。将有机层分离并依次用水(3×500mL)然后盐水(1L)洗涤,使用$MgSO_4$干燥,过滤并浓缩。将残余物通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷),收集含有期望产物的级分,在减压下浓缩以得到呈澄清浅黄色泡沫的(2′S,7R)-3-甲酰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(215g,89%)。^{1}H NMR(300MHz,氯仿-d)δ10.18(d,J=1.4Hz,1H),4.01(ddd,J=11.5,6.8,5.2Hz,1H),3.89(td,J=5.6,2.2Hz,2H),3.75(dt,J=14.0,5.5Hz,1H),3.38(ddd,J=14.0,8.6,5.3Hz,1H),3.04-2.87(m,2H),2.24(dddd,J=10.5,8.3,6.1,3.0Hz,1H),2.14(ddd,J=14.1,5.1,1.9Hz,1H),1.84-1.63(m,2H),1.48(s,9H),1.28(d,J=6.6Hz,3H)。^{19}F NMR(282MHz,氯仿-d)δ-50.49。

[1746] 步骤2:(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛(C74)的合成

[1747] 在20℃下在配备有机械搅拌器、温度探针和加料漏斗的3颈RBF中,向(2′S,7R)-3-甲酰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S66(215g,512.6mmol)于DCM(1.6L)中的溶液中在25分钟的过程内逐滴添加含HCl(600mL的4M,2.400mol)溶液的二噁烷。将反应混合物搅拌3小时,并且然后在冰水浴中冷却至0℃,然后在20分钟的过程内起初缓慢地用2M NaOH水溶液(1.2L,直到pH=11.5)处理。将反应混合物搅拌5分钟,并且然后添加氯化钠(400g)。搅拌另外15分钟,然后分离各层。将水层用DCM(2×200mL)重新萃取。将合并的有机物干燥($MgSO_4$),过滤并浓缩以得到呈粘稠琥珀色油的(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛(179g,100%)。^{1}H NMR(300MHz,氯仿-d)δ10.19(t,J=1.3Hz,1H),3.93(td,J=5.7,3.8Hz,2H),3.21-3.03(m,2H),3.03-2.87(m,3H),2.06(dd,J=13.9,2.2Hz,2H),1.79-1.63(m,1H),1.39(dd,J=13.4,11.3Hz,1H),1.08(d,J=6.4Hz,3H)。^{19}F NMR(282MHz,氯仿-d)δ-50.41。LCMS m/z 319.99$[M+1]^+$。将该材料无需进行进一步纯化即可用于下一步骤。

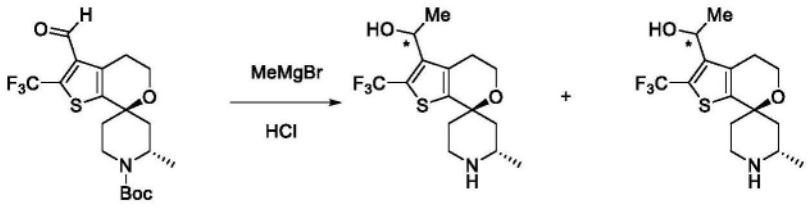
[1748] 步骤3:[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S67)的合成

[1749] 在配备有机械搅拌器、温度探针和冰水冷却浴的3颈RBF中,在0℃(冰水浴)下向(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲醛C74(179g,510.1mmol)于MeOH(1.5L)和水(25mL)中的混合物中的溶液中分三份添加$NaBH_4$(13.5g,356.8mmol)(颗粒,10-40网),并观察到气体逸出。将所得反应混合物在2小时内在0℃至rt下搅拌。将反应混合物在真空中浓缩以去除大部分甲醇。将残余物溶解在1M HCl水溶液(1.15L)中,搅拌15分钟,然后用DCM(1.0L)处理。搅拌双相溶液并用2M NaOH水溶液

(600mL)缓慢碱化至约pH 10。搅拌10分钟后,分离各层。将水层用DCM(2×400mL)萃取。将合并的有机物用$MgSO_4$干燥,过滤并浓缩。将粗残余物用庚烷(1.5L)处理,使用旋转蒸发器(无真空)在95℃下旋转45分钟,并且并非所有物质都进入到溶液中。然后将反应混合物在室温下放置30分钟,并冷却至0℃(在旋转蒸发器上,无真空,冰水浴),持续15分钟。将所得悬浮液过滤,用庚烷(2×200mL)洗涤。在抽吸下干燥40分钟并在真空烘箱中在50℃下干燥1小时以得到呈白色结晶固体的[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(146g,89%)。^{1}H NMR(300MHz,DMSO-d_6)δ5.22(t,J=5.3Hz,1H),4.52-4.37(m,2H),3.89(td,J=5.7,2.3Hz,2H),2.96-2.79(m,2H),2.76(dd,J=4.9,2.0Hz,1H),2.66(t,J=5.5Hz,2H),1.91(ddt,J=13.8,8.0,2.4Hz,3H),1.54(td,J=12.8,4.8Hz,1H),1.23(dd,J=13.4,11.2Hz,1H),0.94(d,J=6.3Hz,3H)。^{19}F NMR(282MHz,DMSO-d_6)δ-51.03。LCMS m/z322.03[M+1]$^+$。

[1750] 制备S68和S69

[1751] 1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]乙醇(S68和S69)

[1752] 

S66 S68 S69

[1753] 向(2′S,7R)-3-甲酰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S66(500mg,1.192mmol)于THF(10mL)中的混合物中添加溴(甲基)镁(500μL的3.4M,1.700mmol)的THF溶液。20分钟后,将混合物用饱和氯化铵水溶液(1mL)和乙醚(3mL)稀释,并将有机层去除,浓缩并在庚烷中最小稀释用于使用硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]乙醇(盐酸盐)(400mg,90%)。将产物用二噁烷稀释,将HCl(5mL的4M,20.00mmol)和混合物在rt下搅拌。50分钟后,将混合物在真空中浓缩并将混合物通过手性SFC分离分离成组成对映异构体。柱:Daicel Chiralpak®AD-H,20×250mm;流动相:20%异丙醇(含有5mM氨),80%二氧化碳。流速:75毫升/分钟。获得两种对映异构体:

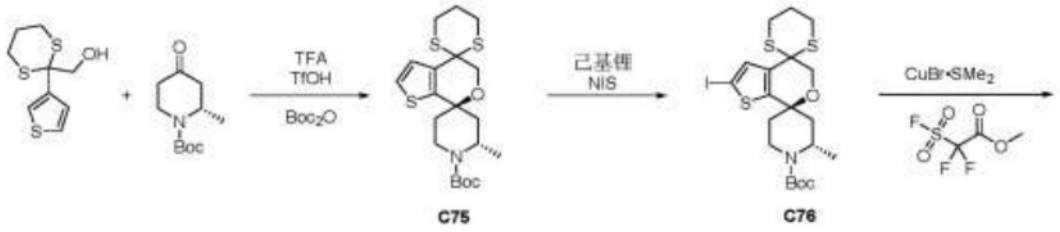
[1754] 1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]乙醇(152mg,75%)。^{1}H NMR(400MHz,氯仿-d)δ5.33-5.23(m,1H),4.02-3.83(m,2H),3.46(d,J=11.9Hz,1H),3.32-3.18(m,2H),3.05(dt,J=16.3,4.8Hz,1H),2.82(ddd,J=16.4,7.1,4.9Hz,1H),2.23-2.09(m,3H),1.87(t,J=12.9Hz,1H),1.53(d,J=6.7Hz,3H),1.38(d,J=6.4Hz,3H)。LCMS m/z 336.03[M+1]$^+$;和

[1755] 1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]乙醇(152mg,75%)。^{1}H NMR(400MHz,氯仿-d)δ5.27(q,J=6.6Hz,1H),3.95(t,J=5.5Hz,2H),3.15(td,J=12.5,2.6Hz,2H),3.01(tt,J=10.2,5.1Hz,2H),2.80(dt,J=16.2,5.5Hz,1H),2.08(ddt,J=14.1,5.2,2.6Hz,2H),1.83-1.74(m,1H),1.53(d,J=

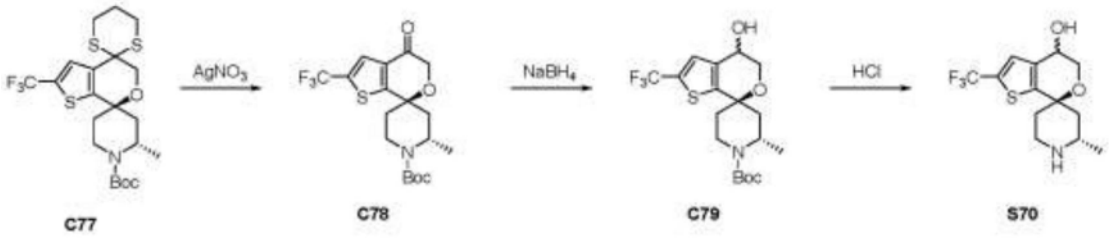
6.7Hz,3H),1.47-1.38(m,1H),1.28(s,1H),1.12(d,J=6.4Hz,3H)。LCMS m/z 336.03[M+1]$^+$。

[1756] 制备S70

[1757] (2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S70)



[1758]



[1759] 步骤1:(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(C75)的合成

[1760] 在室温下将(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(2.5g,11.72mmol)溶解在DCM(5mL)和TFA(5mL,64.90mmol)中,持续20分钟。去除溶剂,并将残余物溶解在二噁烷(40mL)中,并添加到[2-(3-噻吩基)-1,3-二噻烷-2-基]甲醇(3.0g,12.91mmol)中。将该反应混合物冷却至0℃并添加三氟甲磺酸(2.1mL,23.73mmol)。将反应混合物温热至室温。40分钟后,将其倒入EtOAc/2N NaOH(各200mL)中并将有机层干燥,并在真空中浓缩。然后将粗材料溶解在DCM(40mL)和Boc_2O(2.8g,12.83mmol)中,添加DIPEA(5mL,28.71mmol)。将该反应混合物在室温下搅拌3小时,并且然后用H_2O洗涤,干燥并在真空中浓缩,将其通过硅胶色谱法纯化(梯度:含0至30% EtOAc的庚烷)以提供(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(1.6g,32%)。LCMS m/z428.06[M+1]$^+$。

[1761] 步骤2:(6"S,7′R)-2′-碘代-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(C76)的合成

[1762] 将(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸酯C75(800mg,1.871mmol)溶解在THF(15mL)中并冷却至-78℃。向该溶液中添加己基锂(1.6mL的2M,3.200mmol)并将反应混合物在-78℃下搅拌15分钟,此时逐滴添加含NIS(420mg,1.867mmol)的THF(5mL)。将反应混合物在-78℃下搅拌30分钟,然后用H_2O淬灭,并用硫代硫酸钠溶液(80ml)和EtOAc(80ml)稀释。将有机层干燥并在真空中浓缩,将其通过硅胶色谱法纯化(梯度:含0至20% EtOAc的庚烷)以产生与约40mol%的起始材料混合的产物(通过1H NMR)。(6"S,7′R)-2′-碘代-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(700mg,41%校正产率)。LCMS m/z 553.92[M+1]$^+$。此材料无需进一步纯化即可结转。

[1763] 步骤3:(6”S,7′R)-6”-甲基-2′-(三氟甲基)-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯(C77)的合成

[1764] 在微波小瓶中用溴化铜甲基硫烷基甲烷(100mg,0.4864mmol)将(6”S,7′R)-2′-碘代-6”-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯C76(700mg,0.7588mmol)溶解在DMF(5mL)中,并添加2,2-二氟-2-氟磺酰基-乙酸甲酯(300μL,2.356mmol)。将管密封并加热至100℃,持续50分钟。将反应混合物用EtOAc/H2O(各50mL)稀释并通过Celite®过滤。将有机层干燥并在真空中浓缩,将其通过硅胶色谱法纯化(梯度:含0至20% EtOAc的庚烷)以产生成灰白色泡沫的产物:(6”S,7′R)-6”-甲基-2-(三氟甲基)-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯(180mg,48%)。LCMS m/z 496.12[M+1]$^+$。

[1765] 步骤4:(2S,4R)-2′-甲基-4′-氧代-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C78)的合成

[1766] 将(6”S,7′R)-6”-甲基-2′-(三氟甲基)-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯C77(180mg,0.3305mmol)溶解在EtOH(3mL)中,并添加溶解在H_2O(1.5mL)中的硝酸银(170mg,1.001mmol)。将反应混合物在密封的管上加热至50℃,持续4小时。将反应混合物用1NNaOH/EtOAc(各20mL)稀释并通过Celite®过滤。将有机层干燥并浓缩成油,将其通过硅胶色谱法纯化(梯度:含0至50% EtOAc的庚烷)以提供呈油的产物:(2S,4R)-2′-甲基-4′-氧代-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(70mg,52%)。LCMS m/z 405.91[M+1]$^+$。

[1767] 步骤5:(2′S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C79)的合成

[1768] 将(2S,4R)-2-甲基-4′-氧代-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C78(85mg,0.2097mmol)溶解在MeOH(2mL)中并添加$NaBH_4$(10mg,0.2643mmol)。3小时后,将反应混合物用EtOAc/H_2O(各20mL)稀释,并将有机层干燥,并在真空中浓缩以产生产物:(2′S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(82mg,96%)。^{1}H NMR(300MHz,氯仿-d)δ7.42-7.32(m,1H),4.60-4.48(m,1H),4.19-3.70(m,4H),3.46-3.28(m,1H),2.38-2.09(m,3H),2.00-1.65(m,2H),1.50(s,9H),1.34-1.24(m,3H)。LCMS m/z 408.16[M+1]$^+$。

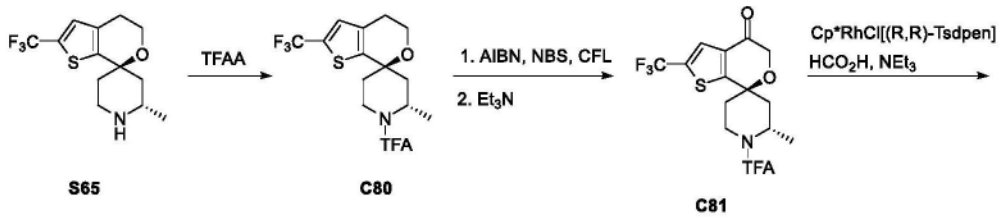
[1769] 步骤6:(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S70)的合成

[1770] 将(2′S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C79(82mg,0.2013mmol)溶解在含HCl(1mL的4M,4.0mmol)的二噁烷中。30分钟后,去除溶剂并将残余物用Et_2O研磨以产生白色固体(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(盐酸盐)(68mg,92%)。^{1}H NMR(300MHz,DMSO-d_6)δ8.94(s,2H),7.62(s,1H),5.60(d,J=6.2Hz,1H),4.52(q,J=5.4Hz,1H),4.05-3.89(m,1H),3.76-3.60(m,1H),3.26-3.03(m,2H),2.36-1.75(m,4H),1.33-1.17(m,3H)。LCMS m/z 308.57[M+1]$^+$。

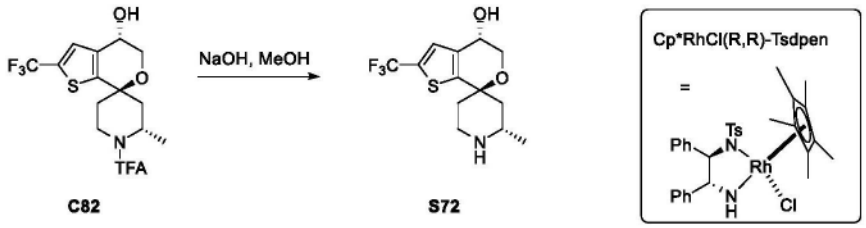
[1771] 制备S71

[1772] (2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌

啶]-4-醇(S71)



[1773]



[1774] 步骤1:2,2,2-三氟-1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(C80)的合成

[1775] 向(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](2.74g,9.4mmol)和DIPEA(2.0mL,11.5mmol)于DCM(25mL)中的冷却至0℃的混合物中逐滴添加(2,2,2-三氟乙酰基)2,2,2-三氟乙酸酯(1.45mL,10.4mmol)。1小时后,将混合物用1N HCl淬灭,并将混合物温热至RT。将各层混合并分离。将水层用DCM(x2)萃取。将有机层用盐水洗涤,用硫酸钠干燥,过滤并浓缩。将粗材料用硅胶色谱法纯化(梯度:含0至30%EtOAc的庚烷)以提供2,2,2-三氟-1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(3.59g,95%)。1H NMR(400MHz,CDCl3)δ7.11(t,J=1.2Hz,1H),4.39(s,1H),3.87(t,J=5.5Hz,3H),3.44(s,1H),2.67(t,J=5.5Hz,2H),2.34(ddd,J=14.4,6.3,1.8Hz,2H),2.07-1.89(m,1H),1.80(dd,J=14.3,10.7Hz,1H),1.31(d,J=6.5Hz,3H)。LCMS m/z 388.25[M+1]$^+$。

[1776] 步骤2:(2S,4R)-2-甲基-1-(2,2,2-三氟乙酰基)-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(C81)的合成

[1777] 在250mL烧瓶中添加含2,2,2-三氟-1-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(3.40g,8.5mmol)的MeCN(56mL)。将反应混合物用N2流脱气30分钟。然后向烧瓶中添加1-溴吡咯烷-2,5-二酮(1.97g,11.1mmol)和2-[(E)-(1-氰基-1-甲基-乙基)偶氮]-2-甲基-丙腈(35mg,0.21mmol)。然后使反应小瓶经受CFL(100W)辐照。5小时后,将反应混合物用10wt%亚硫酸氢钠水溶液(200mL)淬灭,搅拌5分钟,用DCM(x3)萃取。将合并的有机层用饱和$NaHCO_3$溶液和盐水洗涤。将水层用DCM(x1)反萃取。经MgSO4干燥,在真空中浓缩。在真空下干燥以提供粗材料1-[(2′S,7R)-4-溴-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]-2,2,2-三氟-乙酮。干燥过夜后,将材料溶解在DMSO(48mL)中,随后在配备有冷凝器的250mL烧瓶中添加Et3N(8.3mL,60mmol)。将反应混合物加热至75℃,持续3小时。将反应混合物冷却至RT,在MTBE、饱和$NaHCO_3$溶液之间分配。将有机相分离,将水层用MTBE(x2)萃取。将合并的有机相用饱和$NaHCO_3$水溶液洗涤,经$MgSO_4$干燥,过滤并在减压下浓缩以得到粗材料。将粗材料用硅胶色谱法纯化(梯度:含0至30% EtOAc的庚烷)以提供(2S,4R)-2-甲基-1-(2,2,2-三氟乙

酰基)-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(2.10g,58%)。1H NMR(300MHz,CDCl3)δ7.72(q,J=1.2Hz,1H),4.53-4.18(m,3H),4.01(s,1H),3.49(s,1H),2.68-2.36(m,2H),2.19-1.83(m,2H),1.36(d,J=6.5Hz,3H)。LCMS m/z402.15[M+1]$^+$。

[1778] 步骤3:2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(C82)的合成

[1779] 烧瓶A:向100mL烧瓶中添加1,2,3,4,5-五甲基环戊烷四氯化铑(II)(13.1mg,0.021mmol)和N-[(1R,2R)-2-氨基-1,2-二苯基-乙基]-4-甲基-苯磺酰胺(15.8mg,0.043mmol),用N2吹扫10分钟,随后添加MeCN(15mL)。将该催化剂混合物在RT下搅拌1小时。一次性添加TEA(1.40mL,10.04mmol)和甲酸(950μL,25.18mmol)(从奥克伍德公司(Oakwood)获得的5:2商业溶液,2.1mL)并且反应物立即变成鲜红色,并观察到一些起泡。立即将RBF放入冰浴中并冷却至0℃。

[1780] 烧瓶B:将(2S,4R)-2-甲基-1-(2,2,2-三氟乙酰基)-2′-(三氟甲基)螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(1.77g,4.16mmol)溶解在MeCN(15mL)中,在冰浴中冷却。

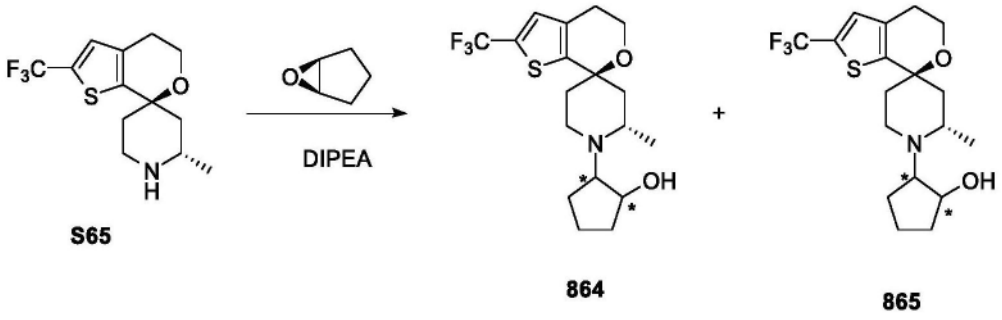
[1781] 然后在0℃下将烧瓶B的内容物添加到烧瓶A中并将反应物在0℃下搅拌。4小时后,将反应混合物用饱和$NaHCO_3$水溶液淬灭,使达到RT。将反应混合物用MTBE(x2)萃取。将合并的有机相用1N HCl、盐水洗涤,经硫酸钠干燥,过滤并在减压下浓缩。粗材料含有一些水,并将其重新溶解在DCM中,经硫酸钠干燥,过滤并在减压下浓缩。将混合物浓缩并直接上样到硅胶柱上进行纯化(0-40% EtOAc:庚烷)以提供:2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(1.702g,100%)。1H NMR(300MHz,CDCl3)δ7.36(q,J=1.2Hz,1H),4.55(dt,J=9.1,3.1Hz,1H),4.52-4.34(m,1H),4.04-3.63(m,3H),3.44(s,1H),2.62-2.21(m,2H),2.20-2.01(m,1H),1.97-1.67(m,2H),1.33(d,J=6.5Hz,3H)。LCMS m/z 404.22[M+1]$^+$。

[1782] 步骤4:(2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S72)的合成

[1783] 向含2,2,2-三氟-1-[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]乙酮(1.69g,4.17mmol)的MeOH(15mL)中添加氢氧化钠(12.5mL的1M,12.5mmol)。将反应混合物在RT下搅拌。3小时后,将反应混合物在水与MTBE之间分配,并且然后将有机相分离。将水相用MTBE(x2)萃取。将合并的有机相用盐水洗涤,经$MgSO_4$干燥,通过介质烧结漏斗过滤并在减压下浓缩。将粗材料用硅胶色谱法纯化(梯度:含0至20% MeOH的DCM(非常容易变的!))以提供(2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1.16g,86%)。1H NMR(300MHz,CDCl3)δ7.38(q,J=1.2Hz,1H),4.55(t,J=2.9Hz,1H),4.14-3.85(m,2H),3.19(dtd,J=18.5,7.3,6.8,2.5Hz,1H),3.07(dd,J=12.4,2.6Hz,1H),2.96(ddd,J=12.1,4.8,2.2Hz,1H),2.08(ddt,J=22.6,13.4,2.6Hz,2H),1.80-1.40(m,2H),1.11(d,J=6.4Hz,3H)。LCMS m/z 308.14[M+1]$^+$。

[1784] 化合物864和865

[1785] 2-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]环戊醇(864和865)

[1786] 

[1787] 标准方法#A:环氧化物开环

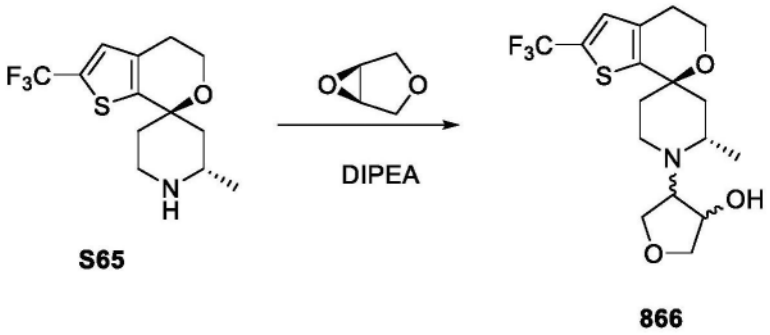
[1788] 将含(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)S65(60mg,0.1815mmol)、DIPEA(270μL,1.550mmol)和6-氧杂双环[3.1.0]己烷(67μL)的n-BuOH(1ml)在210℃下加热4小时。将粗反应混合物蒸发。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%甲酸。将两种产物分离:

[1789] 化合物864:2-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]环戊醇((甲酸(1))864(6mg,15%)。LCMS m/z 376.27[M+1]$^+$;和

[1790] 化合物865:2-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]环戊醇(甲酸(1))865(4.7mg,11%)。LCMS m/z 376.27[M+1]$^+$。

[1791] 化合物866

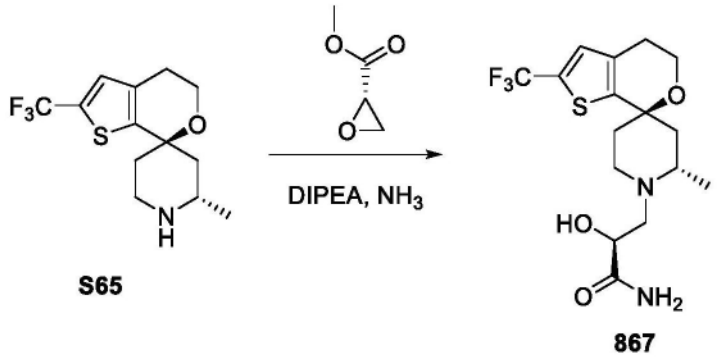
[1792] 4-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]四氢呋喃-3-醇(866)

[1793] 

[1794] 4-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]四氢呋喃-3-醇(甲酸(1))S65由(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)和3,6-二氧杂双环[3.1.0]己烷使用标准方法#A制备。^{1}H NMR(300MHz,甲醇-d_4)8.43(s,1H),7.29(t,J=1.2Hz,1H),4.60(td,J=5.3,4.4,1.6Hz,1H),4.22-4.09(m,2H),4.04-3.92(m,2H),3.53(dd,J=9.9,4.4Hz,1H),3.31(dq,J=3.3,1.7Hz,2H),3.13(td,J=12.5,2.8Hz,1H),2.99(ddd,J=12.3,4.6,2.4Hz,1H),2.72(t,J=5.5Hz,2H),2.38-2.19(m,2H),2.17-1.81(m,2H),1.30(d,J=6.5Hz,3H)。LCMS m/z378.26[M+1]$^+$。

[1795] 化合物867

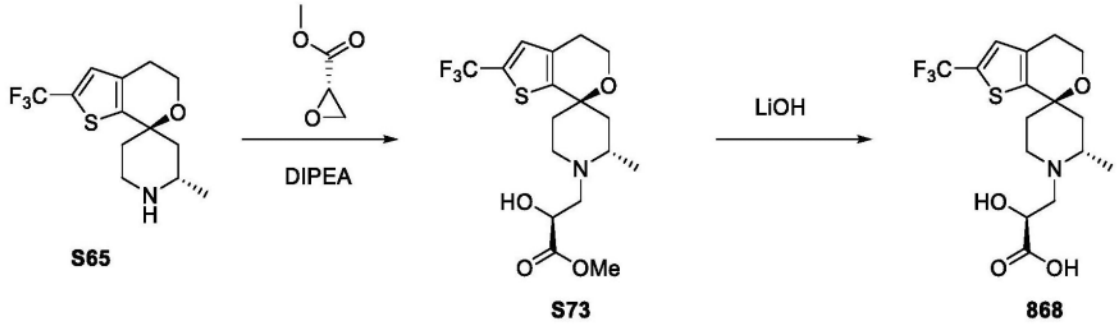
[1796] (2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙烯酰胺(867)

[1797] 

[1798] 将(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S65(88mg,0.2599mmol)和(2S)-环氧乙烷-2-甲酸甲酯(500μL,5.711mmol)添加到微波小瓶中并加入含NH_3(2.5mL的7M,17.50mmol)的MeOH(2.5mL)。添加DIPEA(700μL,4.019mmol)并将反应物在120℃下搅拌3小时。将溶液转移到另外的微波小瓶中。添加另外的(2S)-环氧乙烷-2-甲酸甲酯(300μL)和NH_3/MeOH(500μL)并将反应物在120℃下搅拌2小时。将反应物用水和柠檬酸淬灭,直到pH达到6。将有机物用EtOAc(4x)萃取并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)得到与杂质混合的产物。通过反相HPLC进一步纯化。方法:C18Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H2O,具有0.1%三氟乙酸。将产物分离为(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酰胺(三氟乙酸盐)(39.7mg,31%)。^{1}H NMR指示差向异构体的混合物(85:15)。^{1}H NMR(300MHz,氯仿-d)δ7.32(s,1H),7.14(s,1H),6.29(s,1H),4.73(dd,J=10.1,2.7Hz,1H),4.07-3.82(m,3H),3.72(d,J=12.0Hz,1H),3.53(s,1H),3.33(d,J=9.6Hz,1H),2.95(t,J=11.9Hz,1H),2.73(q,J=5.6,5.1Hz,2H),2.52-2.26(m,2H),2.18(t,J=13.1Hz,2H),1.51(d,J=6.4Hz,3H)。LCMS m/z 379.21$[M+1]^+$。

[1799] 化合物868

[1800] (2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸(868)

[1801] 

[1802] 步骤1:(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸甲酯(S73)的合成

[1803] 将(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](132.3mg,0.4541mmol)S65和(2S)-环氧乙烷-2-甲酸甲酯(120μL,1.371mmol)添加到微波烧瓶中,并加入MeOH(2.6mL)。添加DIPEA(400μL,2.296mmol)并将反应物在90℃下搅拌3小时。将反应混合物在真空中浓缩,并用MeOH/DCM(3x)冲洗以提供产物(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]

丙酸甲酯(244mg,100%)。LCMS m/z 394.13[M+1]$^+$。

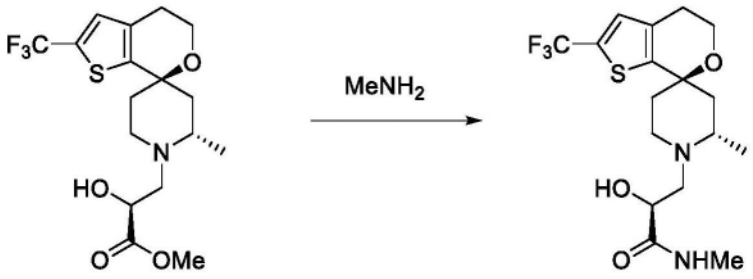
[1804] 步骤2:(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸(868)的合成

[1805] 将(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸甲酯S73(244mg,0.6202mmol)和LiOH(42.9mg,1.791mmol)添加到圆底烧瓶中。然后将反应混合物溶解在MeOH(3mL)、THF(3mL)中,并将反应混合物在室温下搅拌4小时。将反应混合物在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸(84.3mg,36%)。^{1}H NMR(300MHz,氯仿-d)δ10.98(s,1H),7.16-7.14(m,1H),4.80(d,J=9.3Hz,1H),3.95(td,J=11.0,5.4Hz,3H),3.73(d,J=12.0Hz,1H),3.60(s,1H),3.39(t,J=12.5Hz,1H),3.09(dd,J=13.9,9.5Hz,1H),2.73(q,J=5.1Hz,2H),2.45-2.26(m,1H),2.23(s,1H),2.18(s,1H),1.50(d,J=6.4Hz,3H)。材料是基于^{1}H NMR的90:10的差向异构体的混合物。LCMS m/z 380.25[M+1]$^+$。

[1806] 化合物869

[1807] (2S)-2-羟基N-甲基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-

[1808] c]吡喃-7,4′-哌啶]-1-基]丙酰胺(869)

[1809] 

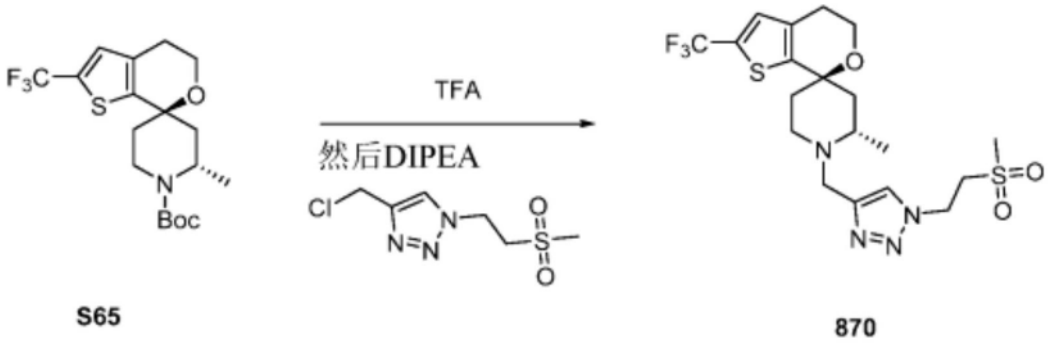
S73 869

[1810] 在微波烧瓶中将(2S)-2-羟基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸甲酯S73(70mg,0.1779mmol)溶解在二噁烷(1.4mL)中。添加甲胺(180μL的40%w/v,2.318mmol)和水(30μL,1.665mmol),并将反应物加热至80℃,持续3小时,然后在室温下搅拌过夜。将反应混合物通过旋转蒸发器浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2S)-2-羟基-N-甲基-3-[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酰胺(三氟乙酸盐)(40.8mg,41%)。^{1}H NMR(300MHz,氯仿-d)δ7.39(s,1H),7.16(s,1H),4.72(dd,J=10.1,2.9Hz,1H),4.08(d,J=13.7Hz,1H),3.96(p,J=6.0Hz,2H),3.71(d,J=12.2Hz,1H),3.53(s,1H),3.37(t,J=11.8Hz,1H),2.91(dd,J=10.7,5.1Hz,3H),2.75(d,J=3.2Hz,2H),2.55-2.29(m,2H),2.19(t,J=14.2Hz,2H),1.52(d,J=6.5Hz,3H)。材料是基于^{1}H NMR的85:15的差向异构体的混合物。LCMS m/z 393.21[M+1]$^+$。

[1811] 化合物870

[1812] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲

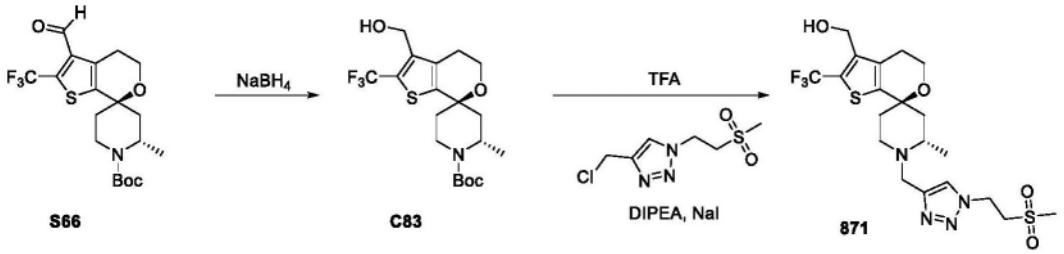
基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](870)

[1813] 

[1814] 将(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S65(30mg,0.07664mmol)溶解在DCM(2mL)中,并添加TFA(1mL,12.98mmol)。20分钟后,去除溶剂并将残余物溶解在DCE(1mL)中并添加到4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(25mg,0.1118mmol)中。然后添加DIPEA(30μL,0.1722mmol),并将反应混合物在密封管中加热至60℃。24小时后,添加另外的4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(15mg,0.06706mmol),并继续加热24小时。将反应混合物通过硅胶色谱法纯化(梯度:含0-10% MeOH的DCM),产生产物。通过反相HPLC进一步纯化(C18,TFA改性剂,15.5g)。将纯级分合并,并用1NNaOH/EtOAc稀释,并将有机层干燥并浓缩以产生呈白色固体的产物。(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](14mg,36%)。^{1}H NMR(300MHz,氯仿-d)δ7.68(s,1H),7.10(s,1H),4.87(t,J=6.4Hz,2H),4.13-4.02(m,1H),3.90-3.82(m,2H),3.79-3.67(m,2H),2.80-2.53(m,8H),2.12-1.97(m,3H),1.97-1.82(m,1H),1.71(t,J=12.7Hz,1H),1.28-1.20(m,3H)。LCMS m/z 479.15[M+1]$^+$。

[1815] 化合物871

[1816] [(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇

[1817] 

[1818] 步骤1:(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C83)的合成

[1819] 将(2′S,7R)-3-甲酰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S66(45mg,0.1073mmol)溶解在MeOH(3mL)中,并添加$NaBH_4$(10mg,0.2643mmol)。15分钟后,将反应混合物用EtOAc和H_2O稀释。将有机层干燥并浓缩呈油,将其通过二氧化硅色谱法纯化(梯度:0至60% EtOAc/庚烷,12g二氧化硅)以产生呈无色油的产物。(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(32mg,71%)。^{1}H NMR(300MHz,氯仿-d)δ4.70-4.63(m,2H),4.10-3.97(m,1H),3.94(td,J=5.7,1.5Hz,2H),3.83-3.69(m,1H),3.43-3.28(m,1H),

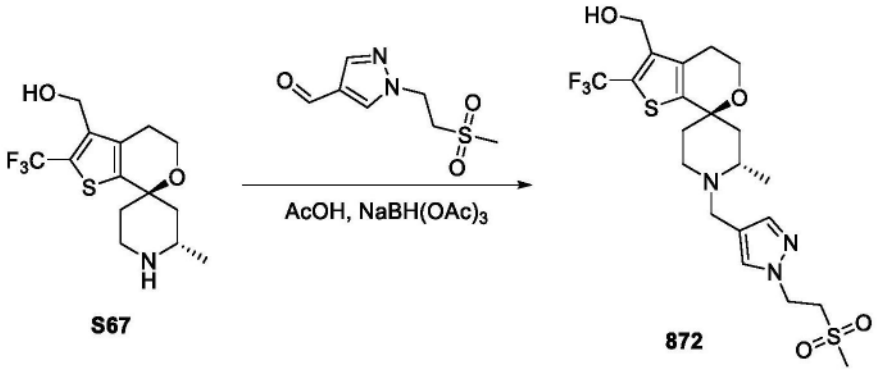
2.77-2.67(m,2H),2.31-2.08(m,2H),1.88-1.61(m,3H),1.51(s,9H),1.28(d,J＝6.5Hz,3H)。LCMS m/z 422.65[M+1]$^+$。

[1820] 步骤2:[(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(871)的合成

[1821] 将(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C83(32mg,0.07592mmol)溶解在DCM(1mL)和TFA(0.5mL,6.490mmol)中。15分钟后,去除溶剂,并将残余物重新溶解在DCE(0.5mL)中,并添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(盐酸盐)(25mg,0.1112mmol)、碘化钠(3mg,0.02001mmol)和DIPEA(80μL,0.4593mmol)。将反应混合物在密封管中加热至60℃,持续24小时。将反应混合物浓缩,溶解在MeOH中并上样到C18柱(15.5g)上,并用具有TFA改性剂的CH_3CN/H_2O洗脱。将含有产物的级分合并,用EtOAc/1N NaOH稀释,并将有机层干燥,浓缩,并通过二氧化硅色谱法进一步纯化(0至15% MeOH/DCM,4g二氧化硅)以产生呈无色油的产物。[(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(9.7mg,25%)。^{1}H NMR(300MHz,氯仿-d)δ7.66(s,1H),4.88(t,J＝6.3Hz,2H),4.66(d,J＝1.3Hz,2H),4.06(d,J＝14.7Hz,1H),4.03-3.84(m,3H),3.75(t,J＝6.3Hz,2H),2.84-2.49(m,7H),2.20-1.83(m,5H),1.69(dd,J＝13.9,11.3Hz,1H),1.26(d,J＝6.2Hz,3H)。LCMS m/z 509.13[M+1]$^+$。

[1822] 化合物872

[1823] [(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(872)

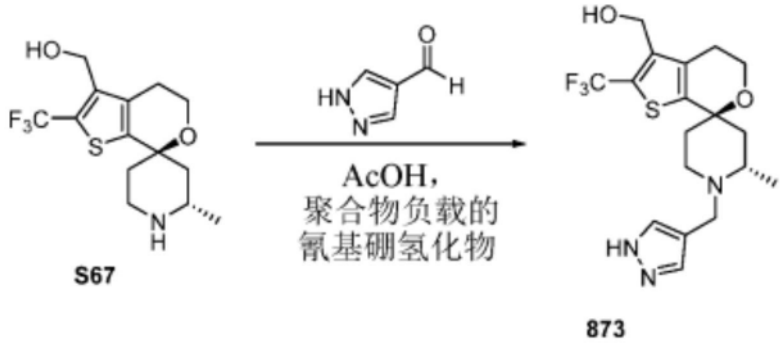
[1824] 

[1825] 向[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S67(20g,62.05mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(13.6g,67.25mmol)于THF(350mL)中的溶液中添加AcOH(4mL,70.34mmol),随后添加三乙酰氧基硼氢化钠(30g,141.5mmol)。将所得悬浮液温热至55℃。2小时后,将反应物在冰水浴中冷却,并且然后用1M HCl水溶液(约350mL)淬灭,直到pH＝1。在室温下搅拌25分钟,然后用MTBE(约400mL)萃取,将MTBE萃取物丢弃。将水溶液用DCM(约400mL)处理,在搅拌下将水层通过添加2M NaOH水溶液(约270mL)碱化至pH11。将各层分离,并将水层用DCM(2×100mL)萃取。将有机萃取物用$MgSO_4$干燥,过滤并浓缩。将粗残余物用MTBE(570mL)处理,并将泡沫加入溶液中。当其溶解时,观察到晶体并立即过滤。将收集的晶体用MTBE(2×60mL)洗涤,在抽吸下干燥20分钟以得到呈白色结晶固体的期望产物29.2g。将材料用IPA(80mL)处理,加热至回流,持续30分钟,然后使其缓慢冷却至室温,搅拌过夜。14小时后,过滤浆料,将收集的固体

用IPA(2×20mL)洗涤。将收集的固体在抽吸下干燥2小时,然后转移到旋转蒸发器中。将材料在30mbar下干燥,将浴温度在1小时的过程内从25℃缓慢升高至70℃。将固体在90℃下在真空烘箱中进一步干燥14小时以得到呈白色结晶固体的[(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(27g,85%)。^{1}HNMR(400MHz,DMSO-d_6)δ7.72(d,J=0.7Hz,1H),7.40(d,J=0.7Hz,1H),5.23(t,J=5.3Hz,1H),4.51(t,J=6.8Hz,2H),4.43(dd,J=5.4,1.5Hz,2H),3.83(q,J=5.9Hz,2H),3.75-3.61(m,3H),3.48(s,1H),2.77(s,3H),2.63(t,J=5.6Hz,2H),2.60-2.53(m,1H),2.47-2.29(m,2H),2.00-1.89(m,2H),1.74-1.63(m,1H),1.47(dd,J=13.5,11.3Hz,1H),1.10(d,J=6.1Hz,3H)。^{19}F NMR(376MHz,DMSO-d_6)δ-51.03。LCMS m/z 508.24[M+1]$^{+}$。

[1826] 化合物873

[1827] [(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(873)

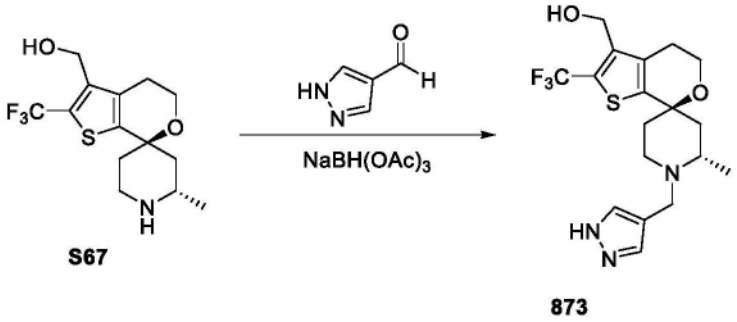
[1828] 

[1829] 标准方法#B1:还原胺化

[1830] 将[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S67(44mg,0.137mmol)添加到微波小瓶中,并添加1H-吡唑-4-甲醛(26.3mg,0.274mmol)、乙酸(37.5μL,0.659mmol)和DCM(1.9mL)。添加聚合物负载的氰基硼氢化物(211mg,0.422mmol)。将溶液加盖并在微波反应器中加热至95℃,持续120分钟。添加MeOH并将溶液搅拌10分钟以洗涤珠粒。将溶液过滤,并将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有10mM氢氧化铵。将产物分离为[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(9.3mg,17%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.59(s,2H),4.57(s,2H),4.10-3.74(m,3H),3.66(d,J=14.2Hz,1H),2.85-2.41(m,5H),2.20-1.54(m,4H),1.24(d,J=6.3Hz,3H)。LCMS m/z 402.19[M+1]$^{+}$。

[1831] 制备化合物873的替代性途径

[1832] [(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(873)

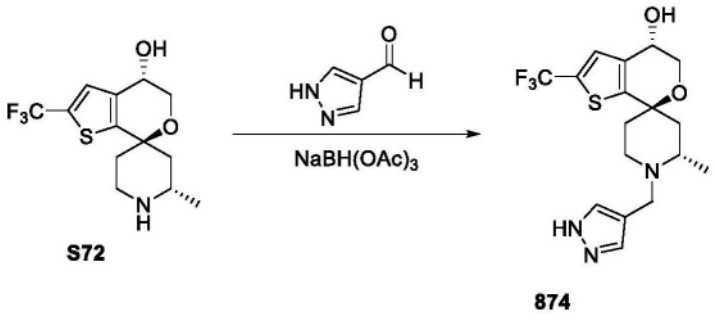
[1833] 

[1834] 标准方法#B2:使用三乙酰氧基硼氢化钠进行还原胺化

[1835] 向1H-吡唑-4-甲醛(600mg,6.244mmol)于THF(15mL)中的溶液中添加[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S67(1g,3.112mmol),添加三乙酰氧基硼氢化钠(887mg,4.205mmol)。将混合物在50℃下搅拌45分钟。然后将其在冰水浴中冷却并用饱和碳酸氢钠水溶液淬灭,然后添加EtOAc。将水层用EtOAc萃取,并将有机层用盐水洗涤。将有机层分离并用Na_2SO_4干燥,过滤并将溶剂在真空中去除。将粗材料通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(1.05g,82%)。LCMS m/z 402.1$[M+1]^+$。

[1836] 化合物874

[1837] (2′S,4S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(874)

[1838] 

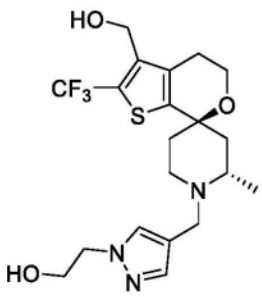
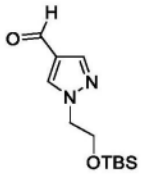
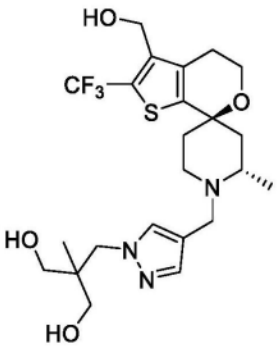
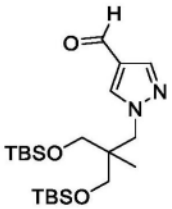
[1839] 向(2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇S72(1.0g,3.17mmol)和1H-吡唑-4-甲醛(333mg,3.47mmol)于THF(14mL)中的溶液中添加三乙酰氧基硼氢化钠(1.46g,6.89mmol),并将混合物加热至55℃。3.5小时后,将混合物冷却至RT,用乙酸乙酯稀释并用饱和碳酸氢钠水溶液淬灭。将有机层分离,用盐水洗涤,用硫酸镁干燥,过滤并浓缩。将混合物最小稀释在DCM中并上样到硅胶柱上进行纯化(0-20% MeOH:DCM)以提供期望产物,含有约35mol%MeOH。将固体在真空下加热至55℃,持续20小时,这将MeOH含量降低至4.5mol%(和非常少量的DCM)。将最终产物分离为(2′S,4S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1.12g,87%)。1HNMR(300MHz,CDCl3)δ7.53(s,2H),7.34(q,J=1.2Hz,1H),4.50(t,J=2.7Hz,1H),4.08-3.79(m,3H),3.59(d,J=14.2Hz,1H),2.83-2.59(m,2H),2.45(td,J=12.3,2.6Hz,1H),2.10(dd,J=14.1,3.0Hz,1H),2.00(dt,J=13.6,2.9Hz,1H),1.82-1.69(m,2H),1.23(d,J=6.2Hz,3H)。LCMS m/z 388.2$[M+1]^+$。

[1840] 化合物875-886

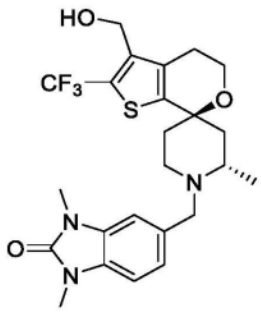
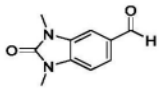
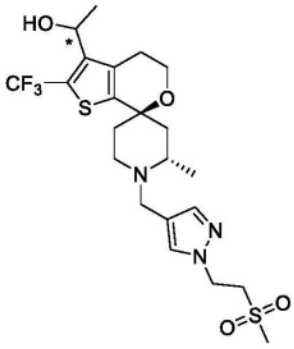
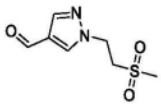
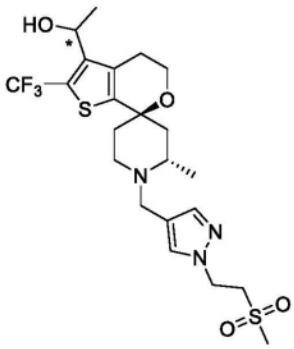
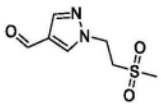
[1841] 化合物875-886(参见表38)由中间体S67、S69、S70和S72使用标准方法#B1或B2在单个步骤中制备。醛从商业来源获得或如前所述。表38和随附脚注中注明了对方法的任何修改。

[1842] 表38:化合物875-886的结构和物理化学数据

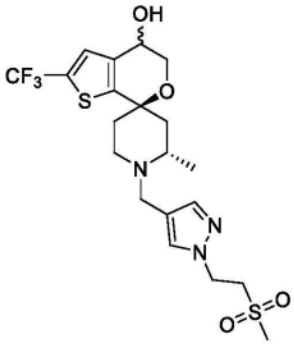
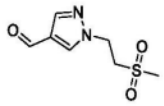
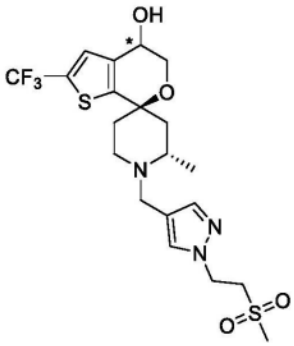
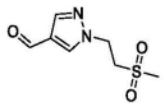
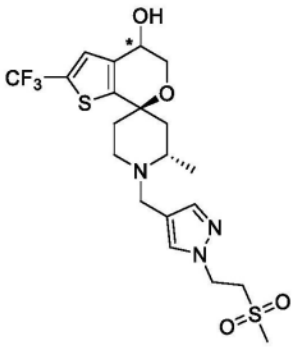
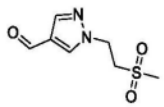
[1843]

化合物	结构	醛 试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
875			**S67**[1]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.44 (s, 1H), 7.36 (s, 1H), 4.73 - 4.57 (m, 2H), 4.21 (dd, *J* = 5.6, 3.9 Hz, 2H), 4.06 - 3.79 (m, 5H), 3.50 (d, *J* = 14.2 Hz, 1H), 3.24 (s, 1H), 2.71 (td, *J* = 5.5, 1.7 Hz, 3H), 2.65 - 2.40 (m, 2H), 2.02 (ddt, *J* = 11.5, 6.5, 2.9 Hz, 2H), 1.84 (td, *J* = 12.8, 4.5 Hz, 2H), 1.76 - 1.59 (m, 1H), 1.19 (d, *J* = 6.1 Hz, 3H)；LCMS *m/z* 446.07 $[M+H]^+$
876			**S67**[1]	^{1}H NMR (300 MHz, 甲醇-d_4) δ 7.63 (s, 1H), 7.46 (d, *J* = 3.9 Hz, 1H), 4.57 (s, 2H), 4.14 (d, *J* = 3.8 Hz, 2H), 3.86 (d, *J* = 24.2 Hz, 3H), 3.67 (d, *J* = 14.3 Hz, 1H), 3.38 (t, *J* = 4.2 Hz, 4H), 2.65 (d, *J* = 31.3 Hz, 5H), 2.21 - 1.53 (m, 4H), 1.23 (d, *J* = 5.8 Hz, 3H), 0.83 (q, *J* = 2.5 Hz, 3H)；LCMS *m/z* 504.15 $[M+H]^+$

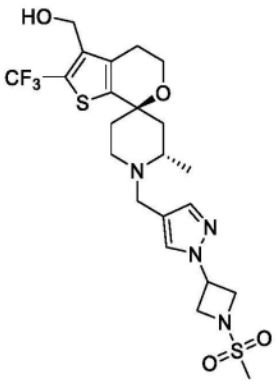
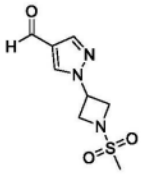
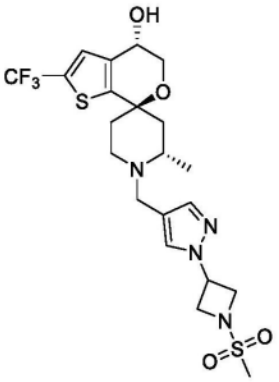
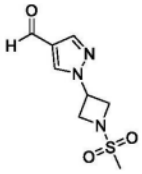
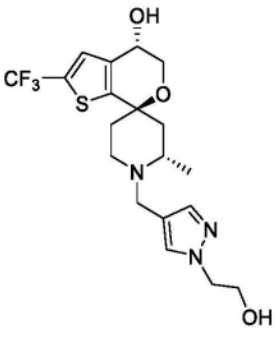
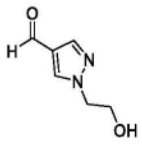
[1844]

化合物	结构	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
877			**S67**[2]	^{1}H NMR (300 MHz, 氯仿-d) δ 7.14 - 6.97 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 4.66 (d, *J* = 4.5 Hz, 2H), 4.26 (d, *J* = 12.9 Hz, 1H), 3.98 (qt, *J* = 11.7, 5.6 Hz, 2H), 3.45 (d, *J* = 7.9 Hz, 6H), 3.14 (d, *J* = 12.9 Hz, 1H), 2.85 - 2.57 (m, 4H), 2.51 - 2.25 (m, 1H), 2.13 - 1.94 (m, 3H), 1.89 - 1.68 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 3H)；LCMS *m/z* 496.2 [M+H]$^+$
878			**S69**[3]	^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.52 (d, *J* = 0.8 Hz, 1H), 7.50 (s, 1H), 5.31 - 5.19 (m, 1H), 4.68 - 4.52 (m, 2H), 3.96 - 3.76 (m, 3H), 3.72 - 3.60 (m, 3H), 3.00 (dt, *J* = 16.3, 4.7 Hz, 1H), 2.83 - 2.66 (m, 2H), 2.61 (s, 1H), 2.54 (d, *J* = 11.4 Hz, 1H), 2.48 (s, 3H), 2.08 - 2.01 (m, 2H), 1.90 (dd, *J* = 13.1, 4.3 Hz, 1H), 1.72 (d, *J* = 12.7 Hz, 1H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H)；LCMS *m/z* 522.19 [M+H]$^+$
879			**S69**[3]	^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.53 (s, 1H), 7.51 (s, 1H), 5.26 (q, *J* = 6.7 Hz, 1H), 4.66 - 4.57 (m, 2H), 3.94 - 3.81 (m, 3H), 3.74 - 3.58 (m, 3H), 2.98 (dt, *J* = 16.4, 5.6 Hz, 1H), 2.75 (dq, *J* = 16.3, 5.3 Hz, 2H), 2.55 (t, *J* = 12.7 Hz, 2H), 2.49 (s, 3H), 2.10 - 1.99 (m, 2H), 1.93 (t, *J* = 12.9 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.28 (t, *J* = 3.6 Hz, 1H), 1.24 (dd, *J* = 6.1, 2.0 Hz, 3H)；LCMS *m/z*

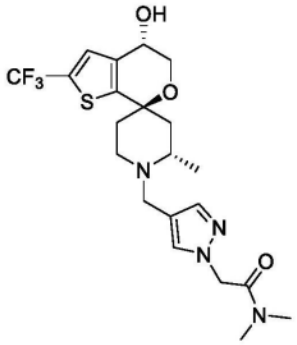
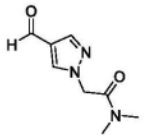
[1845]

化合物	结构	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
				522.14 [M+H]$^+$
880			**S70**[4]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.52 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 4.62 (t, *J* = 6.0 Hz, 2H), 4.53 (d, *J* = 8.3 Hz, 1H), 4.02 - 3.78 (m, 3H), 3.73 - 3.50 (m, 3H), 2.82 - 2.49 (m, 3H), 2.48 (s, 3H), 2.17 - 1.90 (m, 4H), 1.86 - 1.70 (m, 1H), 1.26 - 1.17 (m, 3H)；LCMS *m/z* 494.27 [M+H]$^+$
881			**S70**[4,5]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.43 (s, 1H), 7.39 (s, 1H), 7.27 (s, 1H), 4.60 - 4.48 (m, 2H), 4.43 (t, *J* = 2.7 Hz, 1H), 3.87 - 3.74 (m, 3H), 3.64 - 3.46 (m, 3H), 2.67 - 2.46 (m, 2H), 2.40 (s, 4H), 2.13 - 1.78 (m, 3H), 1.78 - 1.58 (m, 2H), 1.14 (d, *J* = 6.2 Hz, 3H)；LCMS *m/z* 494.19 [M+H]$^+$
882			**S70**[4,5]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.51 (s, 1H), 7.47 (s, 1H), 7.37 (s, 1H), 4.61 (t, *J* = 6.0 Hz, 2H), 4.54 (t, *J* = 3.2 Hz, 1H), 4.02 - 3.74 (m, 3H), 3.74 - 3.52 (m, 3H), 2.81 - 2.64 (m, 1H), 2.64 - 2.43 (m, 5H), 2.16 - 1.92 (m, 4H), 1.67 - 1.45 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H)；LCMS *m/z* 494.19 [M+H]$^+$

[1846]

化合物	结构	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
883			**S67**[6]	1H NMR (300 MHz, MeOD) δ 7.93 (s, 1H), 7.73 (s, 1H), 5.28 (t, J = 7.1 Hz, 1H), 4.59 (s, 2H), 4.46 - 4.24 (m, 5H), 4.05 (d, J = 14.4 Hz, 1H), 3.96 (d, J = 3.0 Hz, 2H), 3.24 - 3.00 (m, 3H), 3.07 (s, 3H), 2.75 (t, J = 5.5 Hz, 2H), 2.26 (t, J = 14.2 Hz, 2H), 2.07 - 1.77 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 535.34 [M+H]$^+$
884			**S72**[6]	1H NMR (300 MHz, MeOD) δ 7.94 (s, 1H), 7.74 (s, 1H), 7.48 (s, 1H), 5.36 - 5.21 (m, 1H), 4.56 (t, J = 3.7 Hz, 1H), 4.44 - 4.32 (m, 6H), 4.15 - 4.03 (m, 1H), 3.97 (dd, J = 12.2, 3.4 Hz, 1H), 3.85 - 3.75 (m, 1H), 3.45 - 3.35 (m, 1H), 3.25 - 3.09 (m, 1H), 3.07 (s, 3H), 2.32 (d, J = 14.7 Hz, 2H), 1.94 (d, J = 13.6 Hz, 2H), 1.46 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 521.34 [M+H]$^+$
885			**S72**[6]	1H NMR (300 MHz, MeOD) δ 8.40 (s, 1H), 7.88 (s, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.49 (q, J = 1.2 Hz, 1H), 4.56 (t, J = 3.6 Hz, 1H), 4.45 (d, J = 14.1 Hz, 1H), 4.26 (t, J = 5.2 Hz, 2H), 4.14 (d, J = 14.0 Hz, 1H), 4.06 - 3.76 (m, 4H), 3.59 - 3.39 (m, 1H), 3.29 - 3.02 (m, 3H), 2.46 - 2.22 (m, 2H), 2.10 - 1.85 (m, 2H), 1.50 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 432.22 [M+H]$^+$

[1847]

化合物	结构	醛 试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
886			S72[6]	1H NMR (300 MHz, MeOD) δ 8.38 (s, 1H), 7.83 (s, 1H), 7.64 (s, 1H), 7.49 (d, J = 1.3 Hz, 1H), 5.18 (s, 2H), 4.57 (t, J = 3.7 Hz, 1H), 4.46 (d, J = 14.0 Hz, 1H), 4.10 (d, J = 14.0 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.3, 3.9 Hz, 1H), 3.13 (s, 5H), 2.98 (s, 3H), 2.37 (t, J = 15.6 Hz, 2H), 2.11 - 1.83 (m, 2H), 1.49 (d, J = 6.4 Hz, 3H); LCMS *m/z* 473.26 [M+H]$^+$

[1848] 脚注：

[1849] 1)添加HCl以在反应结束时去除TBS保护基团。

[1850] 2)0.1％三氟乙酸改性剂用于反向纯化。

[1851] 3)试剂的化学计量修改如下:1.5当量的对应醛,0.24当量的乙酸和2.0当量的聚合物负载的氰基硼氰化物。将反应在85℃下进行过夜。

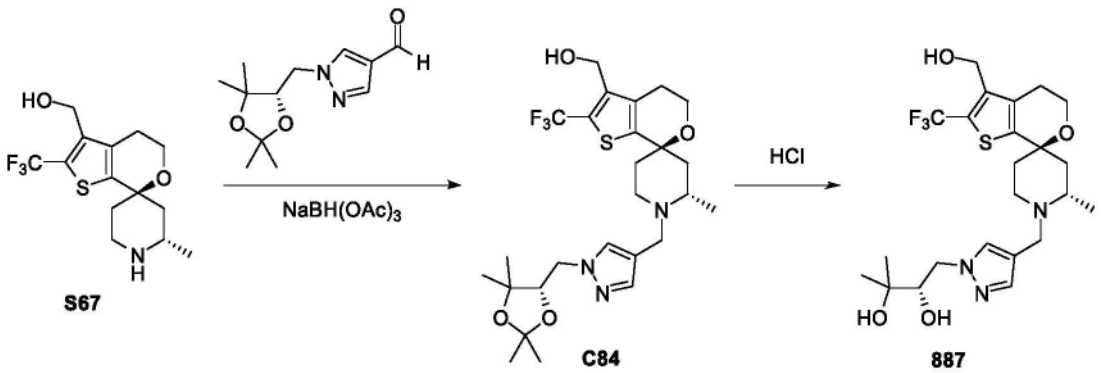
[1852] 4)试剂的化学计量修改如下:2.0当量的对应醛和2.2当量的聚合物负载的氰基硼氰化物。将反应在85℃下进行16小时。将产物使用硅胶色谱法分离(梯度:含0至100％EtOAc的庚烷,1％ Et_3N)。

[1853] 5)通过手性SFC分离从880获得对映异构体。柱:Daicel Chiralpak®IB,10×250mm;流动相:20％ MeOH(含有5mM氨),80％二氧化碳。流速:15毫升/分钟。

[1854] 6)按照标准程序B2,用三乙酰氧基硼氢化钠作为还原剂。

[1855] 化合物887

[1856] (2S)-1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(887)

[1857] 

[1858] 步骤1:[(2′S,7R)-2′-甲基-1′-[[1-[[(4S)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(C84)的合成

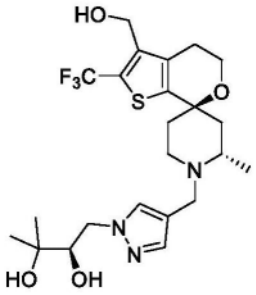
[1859] 向[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(41mg,0.1199mmol)和1-[[(4S)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-甲醛(31mg,0.1301mmol)于THF(500μL)中的溶液中添加三乙酰氧基硼氢化钠(55mg,0.2595mmol)并将混合物加热至50℃,持续2.5小时。将混合物冷却至rt,用乙酸乙酯稀释,并用饱和碳酸氢钠水溶液淬灭。将有机层分离,用盐水洗涤,用硫酸镁干燥,过滤并浓缩。将混合物用硅胶色谱法纯化(含0-100% EtOAc/EtOH 3:1的庚烷)以提供[(2′S,7R)-2′-甲基-1′-[[1-[[(4S)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(59.6mg,78%)。LCMS m/z 544.36[M+1]$^+$。

[1860] 步骤2:(2S)-1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(887)的合成

[1861] 向20mL小瓶中的[(2′S,7R)-2′-甲基-1′-[[1-[[(4S)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(59.6mg,0.1020mmol)中添加THF(500μL),随后添加氯化氢(85μL的6M,0.5100mmol)。将反应物在RT下搅拌20小时。将反应混合物浓缩并通过反相HPLC纯化。方法:Waters XSelect CSH C18OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.1%三氟乙酸。将产物分离为(2S)-1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(三氟乙酸盐)(51.6mg,68%)。1H NMR(300MHz,CDCl3)δ11.56(s,1H),7.78(s,1H),7.57(s,1H),4.65(s,2H),4.60(d,J=13.9Hz,1H),4.40(dd,J=13.9,2.4Hz,1H),4.14(dd,J=13.8,9.4Hz,1H),4.02-3.71(m,4H),3.46(d,J=12.0Hz,2H),3.04(s,1H),2.81-2.69(m,2H),2.37-2.22(m,2H),2.22-2.06(m,2H),1.59(d,J=6.4Hz,3H),1.29(d,J=7.4Hz,6H)。LCMS m/z 504.41[M+1]$^+$。

[1862] 化合物888

[1863] (2R)-1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(888)

[1864] 

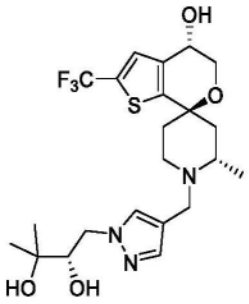
888

[1865] 标题化合物以与化合物887相同的方式由[(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇和1-[[(4R)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-甲醛制备。1H NMR(300MHz,MeOD)δ7.97-7.86(m,1H),7.69(s,1H),4.66-4.53(m,3H),4.49(dd,J=13.8,2.3Hz,1H),4.27(d,J=14.0Hz,1H),4.17-3.89(m,3H),3.72(dd,J=9.9,2.3Hz,1H),3.66-3.49(m,1H),3.38(d,J=5.7Hz,2H),2.77

(t,J＝5.5Hz,2H),2.51-2.26(m,2H),2.16-1.89(m,2H),1.55(d,J＝6.4Hz,3H),1.25(d,J＝7.5Hz,6H)。LCMS m/z 504.37[M+1]$^+$。

[1866] 化合物889

[1867] (2S)-1-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(889)

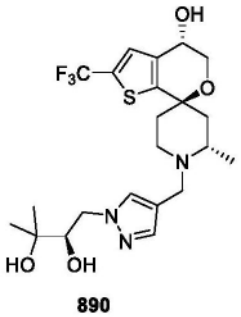
[1868] 

889

[1869] 标题化合物以与化合物887相同的方式由(2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S72)和1-[[(4S)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-甲醛制备。1H NMR(300MHz,MeOD)δ7.92(s,1H),7.69(s,1H),7.50(d,J＝1.3Hz,1H),4.67-4.55(m,2H),4.50(dd,J＝13.8,2.3Hz,1H),4.28(d,J＝14.1Hz,1H),4.13-3.93(m,2H),3.83(dd,J＝12.3,3.8Hz,1H),3.70(dd,J＝9.9,2.2Hz,1H),3.62(s,1H),3.41(d,J＝11.0Hz,2H),2.44(t,J＝16.6Hz,2H),2.12-1.86(m,2H),1.56(d,J＝6.4Hz,3H),1.25(d,J＝7.6Hz,6H)。LCMS m/z 490.37[M+1]$^+$。

[1870] 化合物890

[1871] (2R)-1-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁烷-2,3-二醇(890)

[1872] 

890

[1873] 标题化合物以与化合物887相同的方式制备(2′S,4S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(S72)和1-[[(4R)-2,2,5,5-四甲基-1,3-二氧戊环-4-基]甲基]吡唑-4-甲醛。1H NMR(300MHz,MeOD)δ7.96-7.88(m,1H),7.69(s,1H),7.50(d,J＝1.2Hz,1H),4.58(dd,J＝8.6,5.0Hz,2H),4.49(dd,J＝13.9,2.3Hz,1H),4.28(d,J＝14.0Hz,1H),4.16-3.94(m,2H),3.84(dd,J＝12.3,3.8Hz,1H),3.72(dd,J＝9.8,2.3Hz,1H),3.62(s,1H),3.46-3.32(m,2H),2.44(t,J＝16.2Hz,2H),2.13-1.84(m,2H),1.56(d,J＝6.5Hz,3H),1.25(d,J＝7.6Hz,6H)。LCMS m/z 490.37[M+1]$^+$。

[1874] 制备S74

[1875] 叔丁基-二甲基-[[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺

[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲氧基]硅烷(S74)

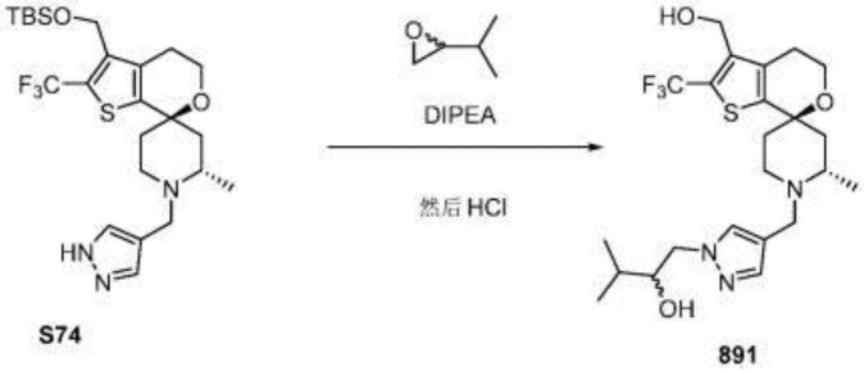
[1876] 

873 S74

[1877] 向具有[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇873(1.05g,2.563mmol)的烧瓶中添加DCM(21mL)、咪唑(175mg,2.571mmol)和TBSCl(1.15mL,6.608mmol)。将反应混合物在室温下搅拌3小时。将混合物用1N HCl(30mL)和DCM稀释。分离水层,并将有机层用盐水洗涤。将合并的有机层浓缩。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生产物。叔丁基-二甲基-[[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲氧基]硅烷(700mg,53%)。^{1}H NMR(300MHz,氯仿-d)δ7.54(s,2H),4.64(d,J=1.3Hz,2H),4.02-3.76(m,3H),3.61(d,J=14.2Hz,1H),2.82-2.41(m,5H),2.03(ddt,J=11.0,5.6,2.8Hz,2H),1.95-1.79(m,1H),1.70(t,J=12.6Hz,1H),1.22(d,J=6.2Hz,3H),0.89(s,9H),0.06(s,6H)。LCMS m/z 516.14[M+1]$^+$。

[1878] 化合物891

[1879] 1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁-2-醇(891)

[1880] 

S74 891

[1881] 标准方法#C:环氧化物开环

[1882] 将叔丁基-二甲基-[[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲氧基]硅烷S74(50mg,0.0968mmol)和2-异丙基环氧乙烷(16.7mg,0.194mmol)添加到微波小瓶中并溶解在MeOH(850μL)中。添加DIPEA(84μL,0.483mmol),并将反应物在120℃下加热3.5小时。将HCl(含4N的二恶烷,0.5ml)添加到反应混合物中,并将反应混合物搅拌30分钟。去除溶剂并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),具有10mM氢氧化铵。将产物分离为1-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-3-甲基-丁-2-二醇(3.7mg,8%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.63(s,1H),7.46(s,1H),4.57(d,J=1.4Hz,2H),4.23(dd,J=14.0,3.6Hz,1H),4.08-

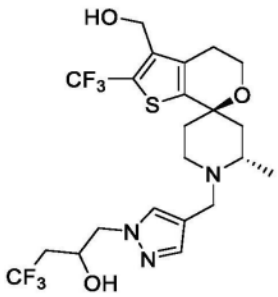
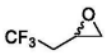
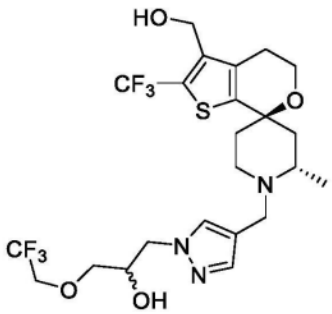
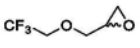
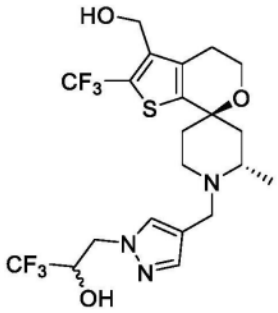
3.79(m,4H),3.76-3.54(m,2H),2.84-2.48(m,5H),2.05(d,J＝12.3Hz,2H),1.86(dt,J＝14.0,6.9Hz,1H),1.71-1.51(m,2H),1.23(d,J＝6.2Hz,3H),0.99(dd,J＝6.8,4.3Hz,6H)。LCMS m/z 488.21[M+1]$^+$。

[1883] 化合物892-895

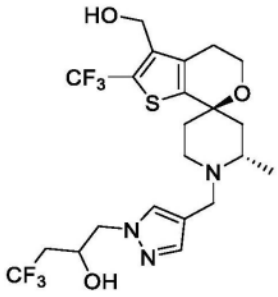
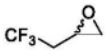
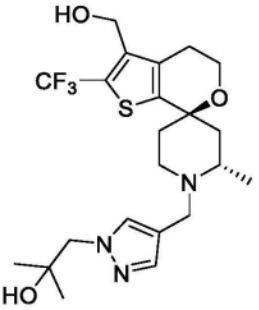
[1884] 化合物892-895(参见表39)由中间体S74或873使用如化合物891的制备的标准方法#C在单个步骤中制备。环氧化物从商业来源获得。表39和随附脚注中注明了对方法的任何修改。

[1885] 表38:化合物892-895的结构和物理化学数据

[1886]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
892			*S74*	^{1}H NMR (300 MHz, 甲醇-d_4) δ 7.70 (s, 1H), 7.53 (s, 1H), 4.62 - 4.52 (m, 2H), 4.42 - 4.10 (m, 3H), 4.10 - 3.83 (m, 3H), 3.76 - 3.61 (m, 1H), 2.95 - 2.62 (m, 5H), 2.43 - 2.05 (m, 4H), 1.89 (td, *J* = 13.3, 4.5 Hz, 1H), 1.71 (t, *J* = 12.8 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 528.17 [M+H]$^+$
893			*S74*	^{1}H NMR (300 MHz, 甲醇- d_4) δ 7.62 (s, 1H), 7.48 (s, 1H), 4.57 (d, *J* = 1.2 Hz, 2H), 4.39 - 3.45 (m, 11H), 2.91 - 2.44 (m, 5H), 2.19 - 1.52 (m, 4H), 1.23 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 558.15 [M+H]$^+$
894			*S74*	^{1}H NMR (300 MHz, 甲醇- d_4) δ 7.70 (s, 1H), 7.53 (s, 1H), 4.58 (d, *J* = 1.4 Hz, 2H), 4.52 - 4.14 (m, 3H), 4.10 - 3.80 (m, 3H), 3.67 (dd, *J* = 14.3, 2.5 Hz, 1H), 2.85 - 2.35 (m, 5H), 2.21 - 1.63 (m, 4H), 1.26 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 514.17 [M+H]$^+$

[1887]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
892			*S74*	^{1}H NMR (300 MHz, 甲醇-d_4) δ 7.70 (s, 1H), 7.53 (s, 1H), 4.62 - 4.52 (m, 2H), 4.42 - 4.10 (m, 3H), 4.10 - 3.83 (m, 3H), 3.76 - 3.61 (m, 1H), 2.95 - 2.62 (m, 5H), 2.43 - 2.05 (m, 4H), 1.89 (td, *J* = 13.3, 4.5 Hz, 1H), 1.71 (t, *J* = 12.8 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 528.17 $[M+H]^+$
895			*873*[1]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.77 (s, 1H), 7.56 (s, 1H), 4.58 (s, 2H), 4.25 - 3.84 (m, 6H), 3.14 - 2.61 (m, 5H), 2.19 (d, *J* = 14.2 Hz, 2H), 1.96 (ddd, *J* = 17.3, 12.9, 6.3 Hz, 1H), 1.81 (t, *J* = 13.2 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.16 (s, 6H)；LCMS *m/z* 474.2 $[M+H]^+$

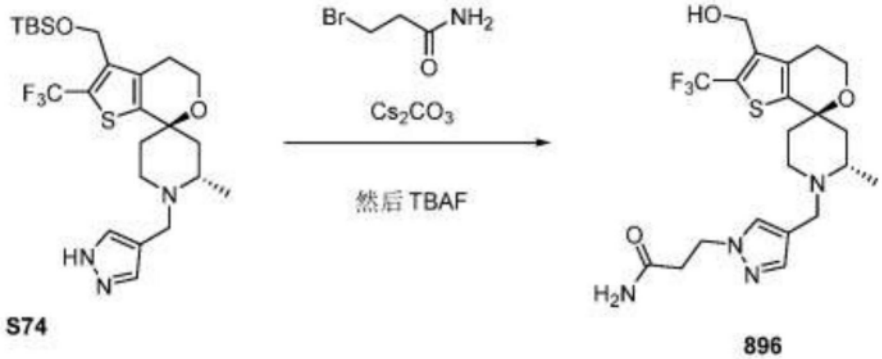
[1888] 脚注：

[1889] 1)使用2,2-二甲基环氧乙烷(1当量)。未进行HCl脱保护,因为起始材料不具有甲硅烷基保护基团。将反应物在85℃下加热16小时。

[1890] 化合物896

[1891] 3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酰胺(896)

[1892]



[1893] 向叔丁基-二甲基-[[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲氧基]硅烷S74(30mg,0.05386mmol)在1打兰小瓶中添加3-溴丙酰胺(16mg,0.1053mmol),随后添加碳酸铯(53mg,0.1627mmol)和DMF(200μL)。将反应混合物加热至80℃。2小时后,将反应混合物用0.4mL的DMF稀释,并用四丁胺(氟离子(1))(110μL的1M,0.1100mmol)处理。90分钟后,将反应物浓缩以去除过量

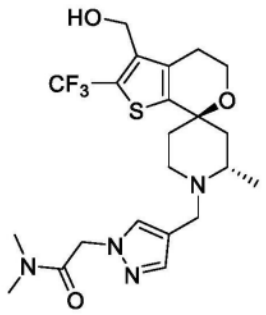
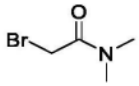
THF并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),具有10mM氢氧化铵。将产物分离为3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酰胺(13.8mg,53%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.60(s,1H),7.46(s,1H),4.58(d,J=1.4Hz,2H),4.41(t,J=6.6Hz,2H),3.92(td,J=5.7,2.4Hz,2H),3.84(d,J=14.3Hz,1H),3.60(d,J=14.2Hz,1H),2.85-2.66(m,5H),2.66-2.47(m,2H),2.22-1.96(m,2H),1.85(td,J=13.2,4.4Hz,1H),1.65(dd,J=14.1,11.5Hz,1H),1.23(d,J=6.2Hz,3H)。LCMS m/z 473.21[M+1]$^+$。

[1894] 化合物897-910

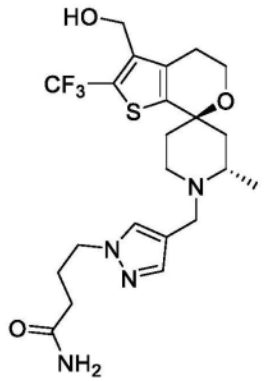
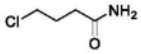
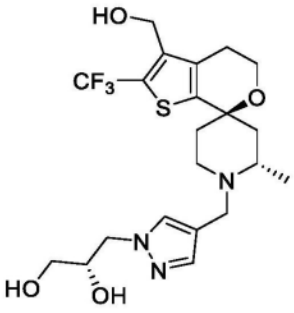
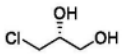
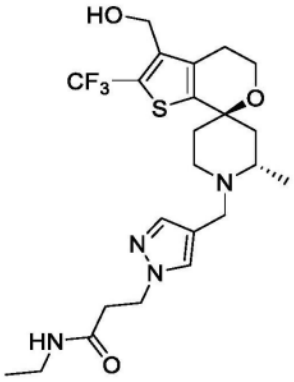
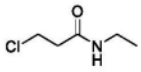
[1895] 化合物897-910(参见表40)由中间体S74或873使用896的制备中所述的方法在单个步骤中制备。烷基卤化物从商业来源获得。表40和随附脚注中注明了对方法的任何修改。

[1896] 表40:化合物897-910的结构和物理化学数据

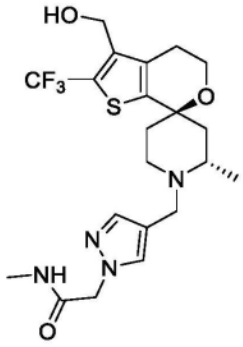
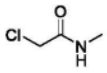
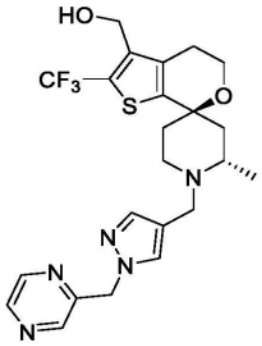
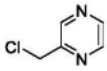
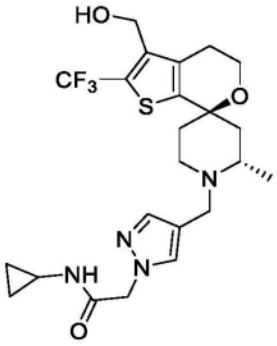
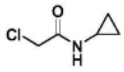
[1897]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
897			*S74*[1]	^{1}H NMR (300 MHz, 氯仿-*d*) δ 7.48 (d, *J* = 7.3 Hz, 2H), 4.97 (s, 2H), 4.64 (s, 2H), 3.90 (hept, *J* = 6.0 Hz, 3H), 3.57 (s, 1H), 3.08 (s, 3H), 2.99 (s, 3H), 2.86 - 2.35 (m, 5H), 2.02 (s, 2H), 1.88 (s, 1H), 1.22 (s, 4H), 0.83 (s, 1H)； LCMS *m/z* 487.18 [M+H]$^+$

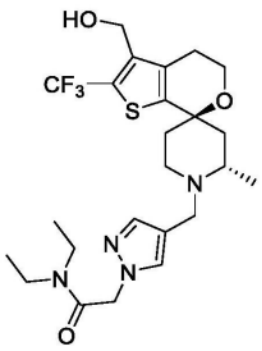
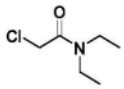
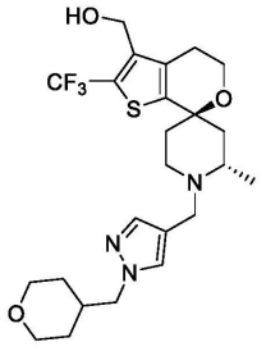
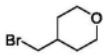
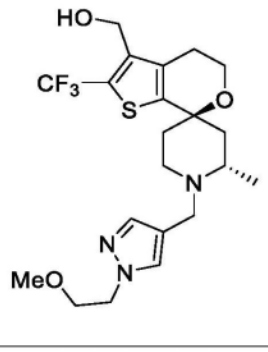
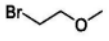
[1898]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
898			*S74*[2]	^{1}H NMR (300 MHz, 甲醇- d_4) δ 7.63 (s, 1H), 7.47 (s, 1H), 4.58 (d, *J* = 1.3 Hz, 2H), 4.19 (t, *J* = 6.4 Hz, 2H), 4.09 - 3.77 (m, 3H), 3.64 (d, *J* = 14.2 Hz, 1H), 2.81 - 2.47 (m, 5H), 2.34 - 1.99 (m, 6H), 1.86 (td, *J* = 13.2, 4.5 Hz, 1H), 1.65 (dd, *J* = 14.0, 11.5 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H)；LCMS *m/z* 487.16 $[M+H]^+$
899			*S74*[3]	1H NMR (300 MHz, MeOD) δ 7.97 (s, 1H), 7.75 (d, J = 3.9 Hz, 1H), 4.69 - 4.52 (m, 3H), 4.47 - 4.12 (m, 3H), 3.98 (h, J = 7.0, 6.1 Hz, 3H), 3.58 (s, 1H), 3.51 (d, J = 5.3 Hz, 2H), 3.37 (d, J = 5.5 Hz, 2H), 2.77 (t, J = 5.5 Hz, 2H), 2.51 - 2.24 (m, 2H), 2.08 (q, J = 15.2, 14.3 Hz, 2H), 1.56 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 476.13 $[M+H]^+$
900			*S74*[3]	1H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 7.76 (t, J = 6.3 Hz, 1H), 7.69 (s, 1H), 7.44 (s, 1H), 4.25 (s, 2H), 4.14 (q, J = 6.5 Hz, 3H), 3.96 (dd, J = 14.2, 5.3 Hz, 1H), 3.69 (ddt, J = 16.6, 12.0, 5.7 Hz, 2H), 3.02 (dd, J = 32.6, 12.9 Hz, 2H), 2.91 - 2.72 (m, 3H), 2.56 - 2.44 (m, 2H), 2.41 (t, J = 6.7 Hz, 2H), 2.15 - 1.87 (m, 4H), 1.26 (d, J = 6.3 Hz, 3H), 0.76 (t, J = 7.2 Hz, 3H)；LCMS *m/z* 501.22 $[M+H]^+$

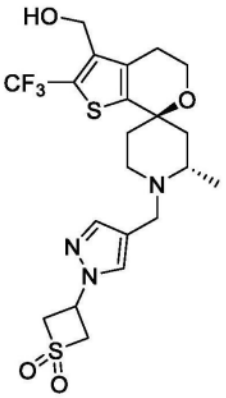
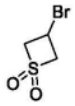
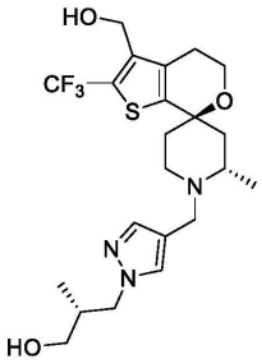
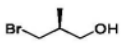
[1899]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
901			*S74*[3]	1H NMR (300 MHz, MeOD) δ 7.96 (s, 1H), 7.72 (s, 1H), 4.90 (s, 2H), 4.62 (d, J = 12.7 Hz, 3H), 4.24 (d, J = 14.0 Hz, 1H), 3.99 (q, J = 5.4 Hz, 2H), 3.62 (s, 1H), 3.39 (d, J = 14.8 Hz, 2H), 2.78 (s, 5H), 2.48 - 2.26 (m, 2H), 2.13 - 1.94 (m, 2H), 1.56 (d, J = 6.5 Hz, 3H)；LCMS *m/z* 473.12 $[M+H]^+$
902			*S74*[3]	1H NMR (300 MHz, MeOD) δ 8.61 (s, 1H), 8.58 (d, J = 2.6 Hz, 1H), 8.52 (s, 1H), 8.16 (s, 1H), 7.76 (s, 1H), 5.60 (s, 2H), 4.64 - 4.55 (m, 3H), 4.30 (d, J = 14.1 Hz, 1H), 3.99 (p, J = 6.0, 5.4 Hz, 2H), 3.57 (s, 1H), 3.38 (d, J = 4.9 Hz, 1H), 2.77 (t, J = 5.5 Hz, 2H), 2.51 - 2.25 (m, 2H), 2.24 - 1.95 (m, 2H), 1.70 - 1.60 (m, 1H), 1.57 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 494.09 $[M+H]^+$
903			*S74*[3]	1H NMR (400 MHz, DMSO) δ 10.60 (d, J = 18.6 Hz, 1H), 8.21 (t, J = 3.5 Hz, 1H), 7.76 (s, 1H), 7.46 (s, 1H), 4.58 (s, 2H), 4.27 (s, 2H), 4.21 (d, J = 13.9 Hz, 1H), 4.02 (dd, J = 14.2, 5.4 Hz, 1H), 3.72 (dq, J = 10.5, 6.0 Hz, 2H), 3.04 (d, J = 12.8 Hz, 2H), 2.84 (d, J = 10.3 Hz, 1H), 2.47 (dt, J = 15.0, 4.5 Hz, 3H), 2.05 (q, J = 14.1, 12.6 Hz, 4H), 1.28 (d, J = 6.3 Hz, 3H), 0.45 (t, J = 6.3 Hz, 2H), 0.31 - 0.19 (m, 2H)；LCMS

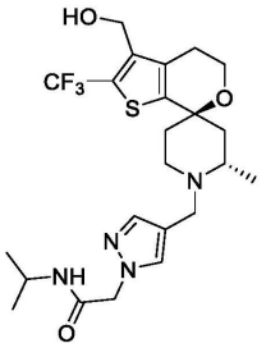
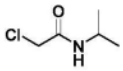
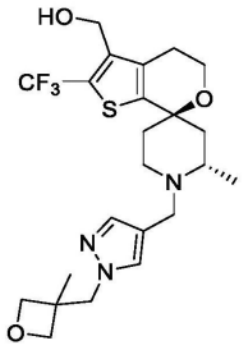
[1900]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				m/z 499.19 $[M+H]^+$
904			***S74***[3]	1H NMR (300 MHz, MeOD) δ 7.93 (s, 1H), 7.71 (s, 1H), 5.20 (s, 2H), 4.71 - 4.53 (m, 3H), 4.24 (d, J = 14.0 Hz, 1H), 4.00 (q, J = 5.5 Hz, 2H), 3.74 - 3.56 (m, 1H), 3.44 (dt, J = 19.9, 7.2 Hz, 6H), 2.77 (t, J = 5.5 Hz, 2H), 2.54 - 2.30 (m, 2H), 2.17 - 1.93 (m, 2H), 1.56 (d, J = 6.3 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H)；LCMS *m/z* 515.11 $[M+H]^+$
905			***S74***[3]	1H NMR (400 MHz, DMSO) δ 10.66 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 4.26 (s, 2H), 4.17 (d, J = 13.9 Hz, 1H), 4.02 (dd, J = 14.2, 5.0 Hz, 1H), 3.85 (d, J = 7.1 Hz, 2H), 3.66 (td, J = 13.0, 11.2, 5.1 Hz, 4H), 3.06 (t, J = 11.1 Hz, 4H), 2.82 (q, J = 4.7, 4.2 Hz, 1H), 2.48 (t, J = 5.5 Hz, 2H), 2.04 (q, J = 14.0, 13.3 Hz, 4H), 1.86 (ddd, J = 11.4, 7.5, 4.2 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.21 - 1.12 (m, 2H), 1.05 (tt, J = 12.1, 6.0 Hz, 2H)；LCMS *m/z* 500.23 $[M+H]^+$
906			***S74***[3]	1H NMR (300 MHz, MeOD) δ 7.96 (s, 1H), 7.72 (s, 1H), 4.64 - 4.51 (m, 3H), 4.36 (t, J = 5.0 Hz, 2H), 4.27 (d, J = 14.1 Hz, 1H), 4.09 - 3.87 (m, 2H), 3.75 (t, J = 5.1 Hz, 2H), 3.66 - 3.49 (m, 1H), 3.37 (d, J = 4.9 Hz, 2H), 3.30 (s, 3H), 2.77 (t, J = 5.5 Hz, 2H), 2.36 (dd, J =

[1901]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				19.0, 16.0 Hz, 2H), 2.06 (q, J = 13.4 Hz, 2H), 1.56 (d, J = 6.4 Hz, 3H); LCMS *m/z* 460.16 $[M+H]^+$
907			*S74*[3]	1H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 8.08 (s, 1H), 7.74 (s, 1H), 5.34 (td, J = 9.2, 4.6 Hz, 1H), 4.83 - 4.65 (m, 2H), 4.57 (dd, J = 15.1, 5.3 Hz, 2H), 4.35 (d, J = 19.2 Hz, 3H), 4.10 (dd, J = 14.0, 5.7 Hz, 1H), 3.82 (dp, J = 17.1, 5.7 Hz, 2H), 3.14 (d, J = 12.5 Hz, 2H), 2.99 - 2.92 (m, 1H), 2.60 (q, J = 7.0, 5.4 Hz, 2H), 2.25 - 1.93 (m, 4H), 1.38 (d, J = 6.3 Hz, 3H)； LCMS *m/z* 506.12 $[M+H]^+$
908			*S74*[3]	1H NMR (400 MHz, DMSO) δ 10.50 (s, 1H), 7.95 (s, 1H), 7.65 (s, 1H), 4.46 (s, 2H), 4.38 (d, J = 13.9 Hz, 1H), 4.20 (ddd, J = 19.4, 13.5, 5.5 Hz, 2H), 3.98 - 3.82 (m, 3H), 3.25 (dd, J = 15.9, 8.7 Hz, 4H), 3.02 (s, 1H), 2.68 (t, J = 5.5 Hz, 2H), 2.31 - 2.01 (m, 6H), 1.46 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H); LCMS *m/z* 474.27 $[M+H]^+$

[1902]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
909			*S74*[3]	1H NMR (400 MHz, DMSO) δ 9.76 (s, 1H), 7.28 - 7.06 (m, 1H), 6.96 (s, 1H), 6.65 (s, 1H), 3.79 (s, 2H), 3.41 (d, J = 13.8 Hz, 1H), 3.22 (dd, J = 14.0, 5.3 Hz, 1H), 2.98 - 2.87 (m, 2H), 2.86 - 2.80 (m, 1H), 2.24 (d, J = 12.7 Hz, 3H), 2.13 - 2.01 (m, 2H), 1.69 (t, J = 5.5 Hz, 2H), 1.33 - 1.10 (m, 4H), 0.48 (d, J = 6.3 Hz, 3H), 0.09 (d, J = 6.5 Hz, 6H)； LCMS *m/z* 501.22 $[M+H]^+$
910			*S74*[3]	1H NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 8.65 (s, 2H), 4.64 (d, J = 13.9 Hz, 1H), 4.55 (d, J = 12.0 Hz, 2H), 4.46 (s, 2H), 4.31 (dd, J = 12.2, 2.3 Hz, 2H), 4.28 - 4.20 (m, 1H), 3.95 (dq, J = 11.3, 6.1 Hz, 2H), 3.22 (s, 3H), 3.11 (s, 2H), 2.70 (d, J = 5.7 Hz, 2H), 2.34 (dd, J = 14.4, 9.4 Hz, 3H), 2.20 (d, J = 14.6 Hz, 1H), 1.51 (d, J = 6.3 Hz, 3H), 1.27 (s, 3H)；LCMS *m/z* 486.19 $[M+H]^+$

[1903] 脚注：

[1904] 1)将反应在室温下进行22小时。

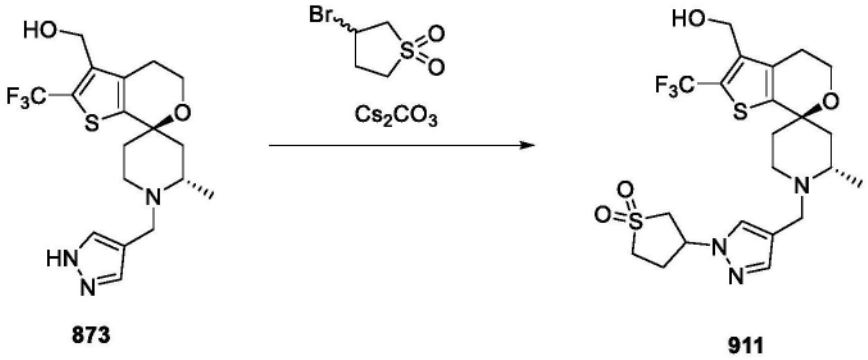
[1905] 2)将反应物在80℃下加热72小时。

[1906] 3)通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,

[1907] 5微米。梯度:乙腈于水中,含5mM盐酸。

[1908] 化合物911

[1909] [(2′S,7R)-1′-[[1-(1,1-二氧硫杂环戊烷-3-基)吡唑-4-基]甲基]-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(911)

[1910] 

873 911

[1911] 标准方法E:用烷基卤化物N烷基化

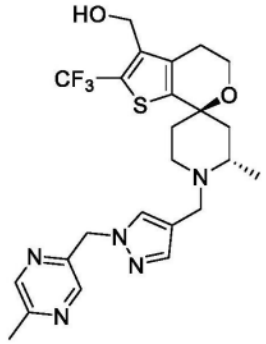
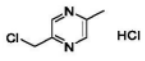
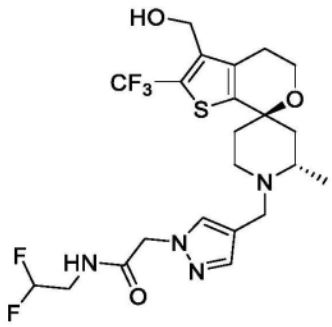
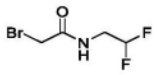
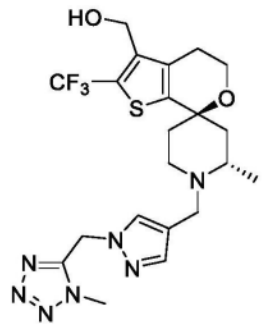
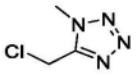
[1912] 向具有3-溴四氢噻吩1,1-二氧化物(22mg,0.11mmol)的2打兰小瓶中添加碳酸铯(64mg,0.20mmol)。将[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(32mg,0.079mmol)添加为DMF(0.4mL)中的溶液。将小瓶在80℃下加热40小时。通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。将产物分离为[(2′S,7R)-1′-[[1-(1,1-二氧硫杂环戊烷-3-基)吡唑-4-基]甲基]-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(17mg,41%)。1HNMR(400MHz,MeOD)δ 7.85(s,1H),7.61(s,1H),5.26(p,J=7.5Hz,1H),4.58(d,J=1.3Hz,2H),4.09(d,J=14.3Hz,1H),3.94(h,J=6.1Hz,2H),3.82(d,J=14.2Hz,1H),3.67(dd,J=13.8,8.1Hz,1H),3.60-3.53(m,1H),3.53-3.40(m,1H),3.25(dt,J=13.6,8.0Hz,1H),2.94(d,J=11.5Hz,2H),2.88-2.46(m,5H),2.15(d,J=14.6Hz,2H),1.92(td,J=13.5,4.4Hz,1H),1.82-1.62(m,1H),1.33(d,J=6.3Hz,3H)。LCMS m/z 520.44$[M+1]^+$。

[1913] 化合物912-928

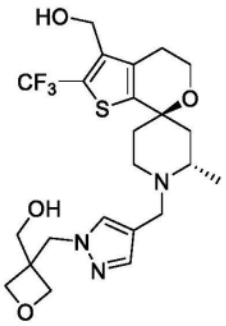
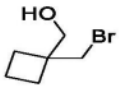
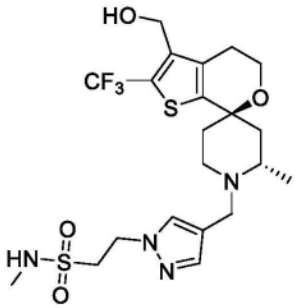
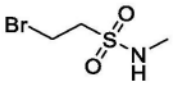
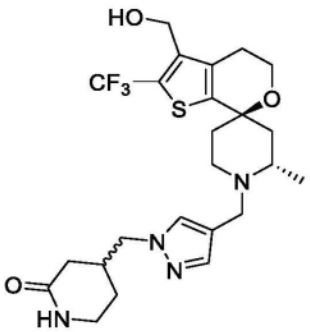
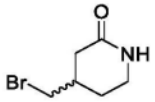
[1914] 化合物912-928(参见表41)由中间体S74或873使用标准方法E(化合物911)在单个步骤中制备。烷基卤化物从商业来源获得。表41和随附脚注中注明了对方法的任何修改。

[1915] 表41:化合物912-928的结构和物理化学数据

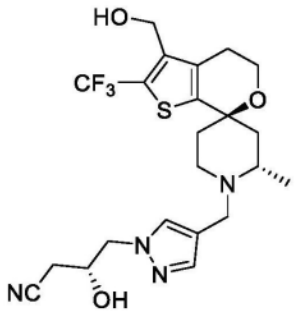
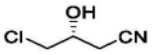
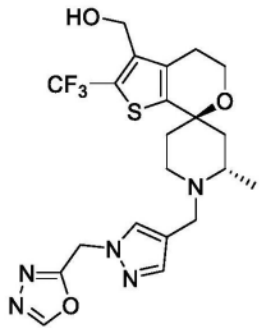
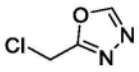
[1916]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
912			*S74*[1]	LCMS *m/z* 508.43 $[M+H]^+$
913			*S74*	1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.64 (s, 1H), 5.91 (tt, J = 55.8, 3.8 Hz, 1H), 4.95 (s, 2H), 4.59 (d, J = 1.5 Hz, 2H), 4.35 (d, J = 13.8 Hz, 1H), 4.12 - 3.81 (m, 3H), 3.61 (td, J = 15.3, 3.8 Hz, 2H), 3.29 - 2.94 (m, 3H), 2.75 (t, J = 5.5 Hz, 2H), 2.26 (t, J = 15.4 Hz, 2H), 2.10 - 1.70 (m, 2H), 1.43 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 523.42 $[M+H]^+$
914			*S74*	1H NMR (400 MHz, MeOD) δ 7.93 (s, 1H), 7.61 (s, 1H), 5.78 (s, 2H), 4.58 (s, 2H), 4.14 (s, 1H), 4.10 (s, 3H), 3.92 (dq, J = 11.9, 5.6 Hz, 3H), 2.94 (d, J = 46.3 Hz, 3H), 2.73 (t, J = 5.5 Hz, 2H), 2.16 (s, 2H), 1.92 (s, 1H), 1.76 (d, J = 13.2 Hz, 1H), 1.35 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 498.4 $[M+H]^+$

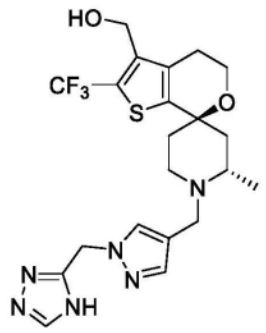
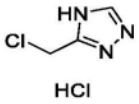
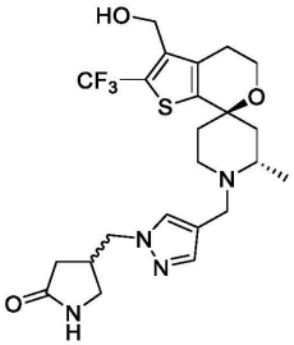
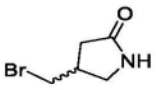
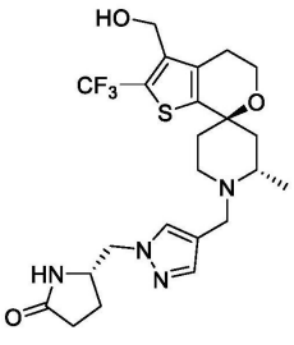
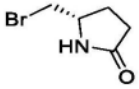
[1917]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
915			*S74*	1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.61 (s, 1H), 4.65 (d, J = 6.4 Hz, 2H), 4.61 - 4.54 (m, 2H), 4.50 (s, 2H), 4.43 (d, J = 6.4 Hz, 2H), 4.29 (d, J = 14.2 Hz, 1H), 4.07 (d, J = 14.1 Hz, 1H), 3.94 (hept, J = 5.9, 5.5 Hz, 2H), 3.60 (s, 2H), 3.29 - 2.97 (m, 3H), 2.75 (t, J = 5.5 Hz, 2H), 2.24 (t, J = 13.8 Hz, 2H), 1.99 (td, J = 13.7, 4.7 Hz, 1H), 1.87 (dd, J = 14.5, 11.9 Hz, 1H), 1.43 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 502.42 $[M+H]^+$
916			*S74*	1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.67 (s, 1H), 4.66 - 4.52 (m, 4H), 4.39 (d, J = 14.1 Hz, 1H), 4.14 (d, J = 14.0 Hz, 1H), 3.95 (hept, J = 5.9 Hz, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.39 (s, 1H), 3.27 - 3.04 (m, 2H), 2.75 (t, J = 5.5 Hz, 2H), 2.67 (s, 3H), 2.42 - 2.16 (m, 2H), 2.13 - 1.85 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 523.37 $[M+H]^+$
917			*S74*	1H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 4.59 (s, 2H), 4.31 (d, J = 14.1 Hz, 1H), 4.23 - 4.12 (m, 2H), 4.09 (d, J = 14.4 Hz, 1H), 3.95 (q, J = 5.6 Hz, 2H), 3.36 (s, 2H), 3.24 (dd, J = 12.1, 4.4 Hz, 2H), 3.11 (d, J = 24.2 Hz, 2H), 2.75 (t, J = 5.5 Hz, 2H),

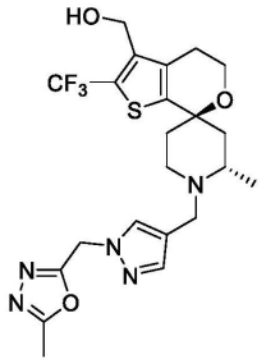
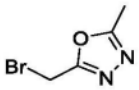
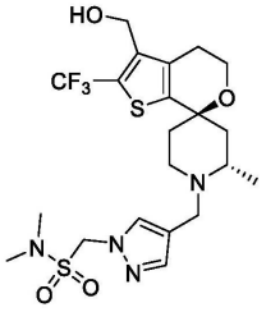
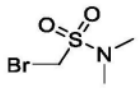
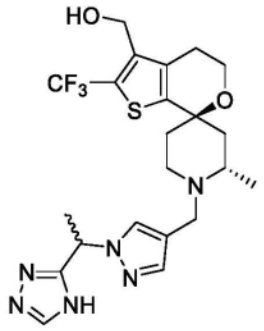
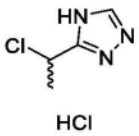
[1918]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				2.46 (s, 1H), 2.32 - 2.17 (m, 3H), 2.17 - 1.94 (m, 2H), 1.94 - 1.76 (m, 2H), 1.51 (td, J = 12.6, 12.0, 5.5 Hz, 1H), 1.44 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 513.39 $[M+H]^+$
918			*S74*	1H NMR (400 MHz, MeOD) δ 8.47 (s, 1H), 7.94 (s, 1H), 7.68 (s, 1H), 4.77 - 4.61 (m, 1H), 4.59 (s, 2H), 4.29 (d, J = 13.8 Hz, 1H), 4.11 - 3.74 (m, 5H), 3.25 - 2.83 (m, 6H), 2.74 (t, J = 5.5 Hz, 2H), 2.22 (t, J = 13.5 Hz, 2H), 1.96 (t, J = 11.9 Hz, 1H), 1.84 (t, J = 13.2 Hz, 1H), 1.41 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 485.31 $[M+H]^+$
919			*S74*	1H NMR (400 MHz, MeOD) δ 8.97 (s, 1H), 8.41 (s, 1H), 8.01 (s, 1H), 7.67 (s, 1H), 5.75 (s, 2H), 4.59 (s, 2H), 4.33 (d, J = 14.2 Hz, 1H), 4.03 (d, J = 14.3 Hz, 1H), 3.96 (q, J = 5.5 Hz, 2H), 3.24 (s, 1H), 3.18 - 2.99 (m, 2H), 2.75 (t, J = 5.5 Hz, 2H), 2.25 (t, J = 14.9 Hz, 2H), 2.04 - 1.91 (m, 1H), 1.91 - 1.74 (m, 1H), 1.43 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 484.32 $[M+H]^+$

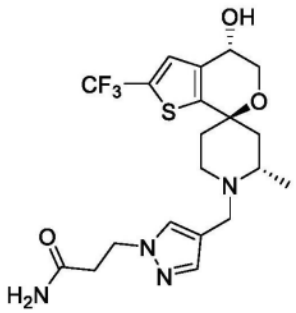
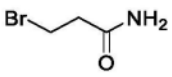
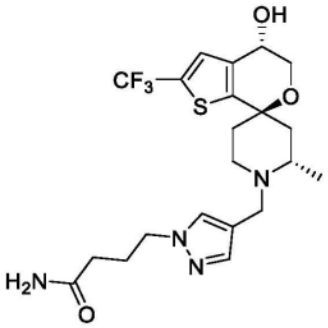
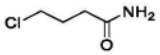
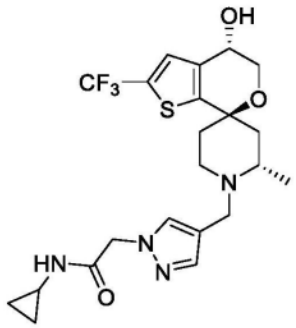
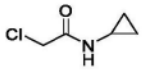
[1919]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
920			*S74*[1]	1H NMR (400 MHz, MeOD) δ 8.44 (s, 1H), 8.33 (s, 1H), 7.69 (s, 2H), 5.36 (s, 2H), 4.58 (s, 2H), 4.16 - 3.99 (m, 2H), 3.99 - 3.84 (m, 2H), 3.04 - 2.89 (m, 3H), 2.72 (t, J = 5.6 Hz, 2H), 2.11 (d, J = 14.1 Hz, 2H), 1.99 - 1.86 (m, 1H), 1.80 - 1.68 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 483.33 $[M+H]^+$
921			*S74*	1H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.87 (s, 1H), 7.62 (s, 1H), 4.59 (s, 2H), 4.27 (d, J = 7.1 Hz, 3H), 4.06 (d, J = 14.2 Hz, 1H), 3.96 (q, J = 5.4 Hz, 2H), 3.47 (dd, J = 10.3, 7.8 Hz, 1H), 3.23 (dd, J = 10.3, 5.4 Hz, 2H), 3.05 (t, J = 8.2 Hz, 3H), 2.75 (t, J = 5.5 Hz, 2H), 2.42 (dd, J = 17.1, 8.8 Hz, 1H), 2.25 (t, J = 14.3 Hz, 2H), 2.16 (dd, J = 17.0, 6.4 Hz, 1H), 1.98 (t, J = 14.5 Hz, 1H), 1.86 (t, J = 13.2 Hz, 1H), 1.43 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 499.35 $[M+H]^+$
922			*S74*	1H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 4.66 - 4.52 (m, 2H), 4.34 (d, J = 14.1 Hz, 1H), 4.29 (d, J = 4.6 Hz, 2H), 4.15 - 4.05 (m, 2H), 3.96 (h, J = 6.2 Hz, 2H), 3.28 - 2.99 (m, 3H), 2.75 (t, J = 5.5 Hz, 2H), 2.45 - 2.08 (m, 4H), 2.08 - 1.95 (m,

[1920]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				2H), 1.94 - 1.68 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 499.35 $[M+H]^+$
923			***S74***	LCMS *m/z* 498.32 $[M+H]^+$
924			***S74***	LCMS *m/z* 523.33 $[M+H]^+$
925			***S74***[1,2]	1H NMR (400 MHz, MeOD) δ 8.47 (s, 1H), 8.03 (s, 1H), 7.69 (s, 1H), 5.81 (d, J = 6.9 Hz, 1H), 4.63 (s, 1H), 4.60 (s, 2H), 4.21 (d, J = 13.8 Hz, 1H), 3.99 (t, J = 5.9 Hz, 2H), 3.69 - 3.54 (m, 4H), 2.77 (t, J = 5.5 Hz, 2H), 2.46 - 2.26 (m, 2H), 2.10 - 1.98 (m, 2H), 1.96 (d, J = 7.1 Hz, 3H), 1.55 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 497.37 $[M+H]^+$

[1921]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
926			*S74*	1H NMR (300 MHz, MeOD) δ 7.83 (s, 1H), 7.64 (s, 1H), 7.49 (d, J = 1.3 Hz, 1H), 4.56 (t, J = 3.6 Hz, 1H), 4.52 - 4.36 (m, 3H), 4.15 (d, J = 14.1 Hz, 1H), 3.98 (dd, J = 12.3, 3.4 Hz, 1H), 3.82 (dd, J = 12.3, 3.8 Hz, 1H), 3.41 (d, J = 21.1 Hz, 1H), 3.27 - 3.05 (m, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.37 (t, J = 14.2 Hz, 2H), 2.03 - 1.85 (m, 2H), 1.49 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 459.31 $[M+H]^+$
927			*S74*[3]	1H NMR (300 MHz, MeOD) δ 7.82 (s, 1H), 7.60 (s, 1H), 7.47 (d, J = 1.4 Hz, 1H), 4.55 (t, J = 3.6 Hz, 1H), 4.35 - 4.15 (m, 3H), 4.04 (d, J = 14.2 Hz, 1H), 3.97 (dd, J = 12.3, 3.5 Hz, 1H), 3.79 (dd, J = 12.3, 3.9 Hz, 1H), 3.29 - 3.20 (m, 1H), 3.14 (d, J = 10.0 Hz, 1H), 3.00 (dd, J = 13.3, 10.7 Hz, 1H), 2.31 (t, J = 12.9 Hz, 2H), 2.17 (dq, J = 12.3, 6.5 Hz, 4H), 2.05 - 1.83 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 473.21 $[M+H]^+$
928			*S74*[4]	1H NMR (300 MHz, MeOD) δ 7.87 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 4.84 (s, 2H), 4.57 (t, J = 3.6 Hz, 1H), 4.45 (d, J = 14.1 Hz, 1H), 4.10 (d, J = 14.2 Hz, 1H), 3.99 (dd, J = 12.3, 3.5 Hz, 1H), 3.83 (dd, J = 12.3, 3.9 Hz, 1H), 3.52

[1922]

化合物	结构	烷基卤化物试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
				- 3.38 (m, 1H), 3.29 - 3.21 (m, 1H), 3.14 (d, J = 12.2 Hz, 1H), 2.70 (dt, J = 7.2, 3.5 Hz, 1H), 2.37 (t, J = 14.8 Hz, 2H), 1.97 (d, J = 13.8 Hz, 2H), 1.49 (d, J = 6.4 Hz, 3H), 0.74 (td, J = 7.2, 5.1 Hz, 2H), 0.59 - 0.45 (m, 2H)；LCMS *m/z* 485.36 [M+H]$^+$

[1923] 脚注：

[1924] 1)使用3.5当量的Cs2CO3。

[1925] 2)通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:乙腈于水中,含5mM盐酸。

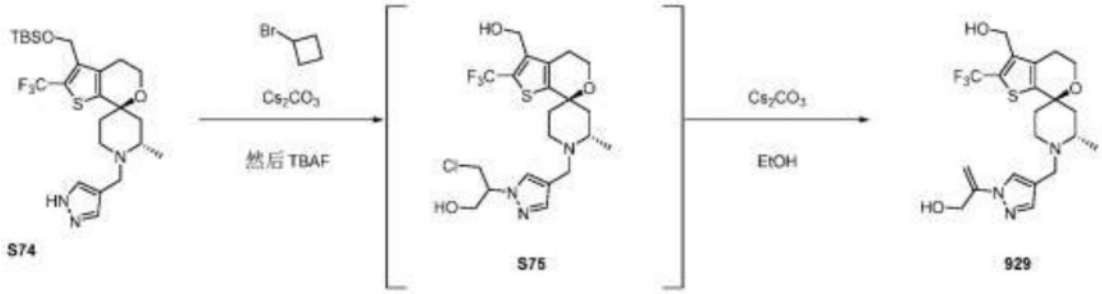
[1926] 3)在90℃下26小时后,添加另外的4-氯丁酰胺(15.2mg,0.125mmol)和碳酸铯(60mg,0.18mmol),并将反应物在90℃下加热另外24小时。

[1927] 4)将反应在90℃下进行4小时。

[1928] 化合物929

[1929] 3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酰胺(929)

[1930]

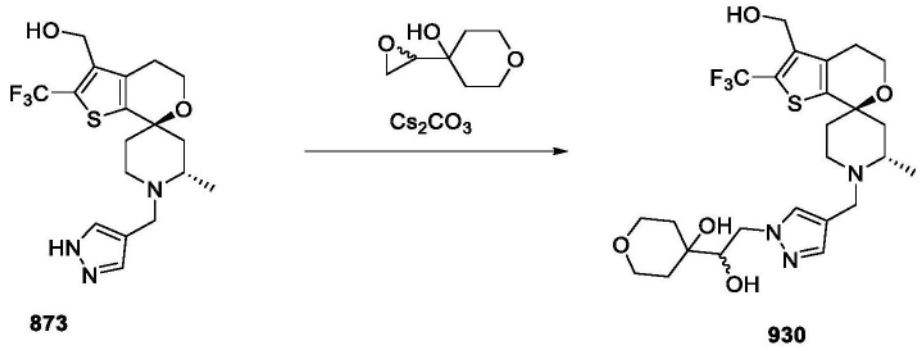


[1931] 向叔丁基-二甲基-[[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲氧基]硅烷S74(30mg,0.058mmol)在1打兰小瓶中添加3-溴氧杂环丁烷(16mg,0.12mmol),随后添加碳酸铯(57mg,0.17mmol)和DMF(200μL)。将反应混合物加热至80℃。2小时后,将反应混合物用0.4mL的DMF稀释,并用四丁基氟化铵溶液(110μL的1M,0.1100mmol)处理。90分钟后,将反应物浓缩以去除过量THF并通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:乙腈于水中,含5mM盐酸。分离开环产物3-氯-2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙-1-醇S75(36mg,0.11mmol)。将中间体用碳酸铯(36mg,0.11mmol)处理。然后在RT下添加EtOH(400μL)。加热至70℃,持续5小时,并将反应物用饱和NaHCO3溶液淬灭,并用EtOAc(x4)萃取。将合并的有机层经Na2SO4干燥,过滤并浓缩。将粗材料通过硅胶色谱法纯化(柱:4g柱X2,梯度:含0-16％ MeOH的DCM),基于1H NMR,得到了意想不到的产物烯丙醇而不是氧杂环

丁烷。乙烯基质子1H-1H偶联可以在400MHz仪器上观察到,显示J＝1.5Hz。将产物分离为2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙-2-烯-1-醇(7.5mg,48％)。1H NMR(400MHz,CDCl3)δ7.77(s,1H),7.54(s,1H),5.21(d,J＝1.5Hz,1H),4.94-4.86(m,1H),4.70-4.60(m,2H),4.56(d,J＝0.7Hz,2H),4.02-3.84(m,3H),3.53(d,J＝14.2Hz,1H),2.86-2.59(m,4H),2.53(t,J＝11.9Hz,1H),2.04(ddd,J＝11.7,9.8,2.9Hz,2H),1.90(t,J＝13.5Hz,1H),1.83-1.70(m,1H),1.24(d,J＝6.3Hz,3H)。LCMS m/z 458.31[M+H]$^+$。

[1932] 化合物930

[1933] 4-[1-羟基-2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢-噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙基]四氢吡喃-4-醇(930)

[1934] 

[1935] 标准方法F:使用碳酸铯作为碱用环氧化物进行N-烷基化

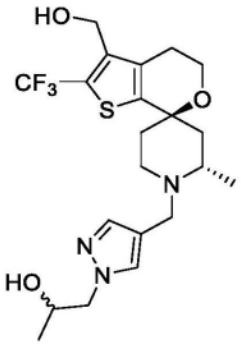
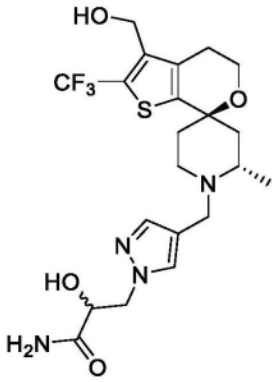
[1936] 向1打兰小瓶中的4-(环氧乙烷-2-基)四氢-2H-吡喃-4-醇(36mg,0.25mmol)中添加碳酸铯(171mg,0.53mmol)。然后将[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(84mg,0.21mmol)添加到1mL的DMF中。将反应小瓶加热至60℃,持续14小时,并且之后加热至90℃,持续另外14小时。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),具有10mM氢氧化铵。将产物分离为4-[1-羟基-2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙基]四氢吡喃-4-醇(37mg,30％)。1H NMR(300MHz,CDCl3)δ7.48(s,1H),7.40(s,1H),4.66(s,2H),4.25(d,J＝5.3Hz,1H),4.08(s,1H),3.87(dtd,J＝29.8,15.6,13.4,8.9Hz,8H),3.60-3.40(m,1H),2.75(q,J＝7.5,6.2Hz,3H),2.52(d,J＝11.7Hz,2H),2.01(s,1H),1.77(ddd,J＝38.7,26.9,10.8Hz,7H),1.22(d,J＝6.2Hz,3H)。LCMS m/z 546.4[M+1]$^+$。

[1937] 化合物931-942

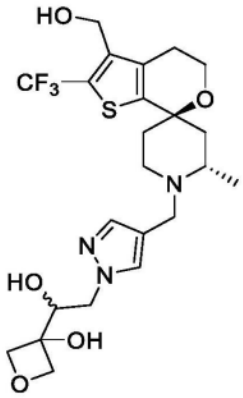
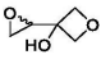
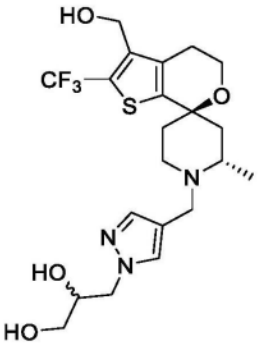
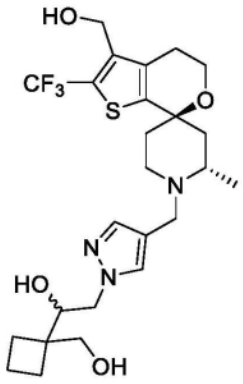
[1938] 化合物931-942(参见42)由中间体873使用标准方法F在单个步骤中制备。环氧化物从商业来源获得。表42和随附脚注中注明了对方法的任何修改。

[1939] 表42:化合物931-942的结构和物理化学数据

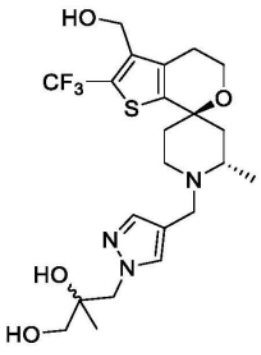
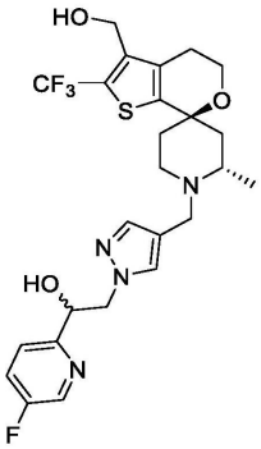
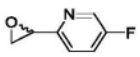
[1940]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
931			**S74^I**	1H NMR (300 MHz, CDCl3) δ 7.46 (s, 1H), 7.39 (s, 1H), 4.64 (s, 2H), 4.29 - 4.07 (m, 2H), 3.93 (qd, J = 12.9, 12.1, 7.0 Hz, 4H), 3.56 (d, J = 14.8 Hz, 1H), 2.92 - 2.34 (m, 4H), 2.01 (d, J = 8.3 Hz, 2H), 1.91 - 1.81 (m, 1H),1.81 - 1.67 (m, 2H), 1.22 (d, J = 6.3 Hz, 6H); LCMS *m/z* 460.29 $[M+H]^+$
932			**S74^I**	1H NMR (300 MHz, CDCl3) δ 7.46 (d, J = 3.2 Hz, 1H), 7.38 (s, 1H), 6.74 (s, 1H), 5.47 (s, 1H), 5.30 (s, 1H), 4.64 (s, 2H), 4.47 (s, 3H), 4.03 - 3.73 (m, 3H), 3.60 (t, J = 14.1 Hz, 1H), 2.71 (s, 3H), 2.51 (s, 2H), 1.87 (s, 1H), 1.67 (s, 1H), 1.20 (d, J = 6.2 Hz, 3H); LCMS *m/z* 489.27 $[M+H]^+$

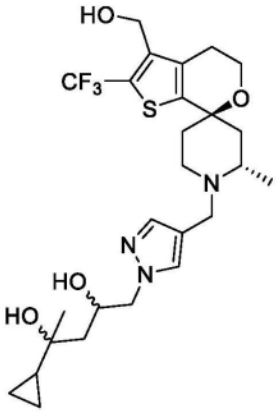
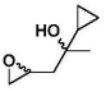
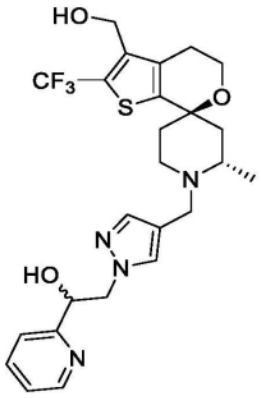
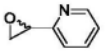
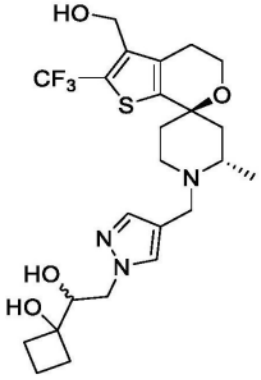
[1941]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
933			**S74**	1H NMR (300 MHz, CDCl3) δ 7.45 (s, 1H), 7.38 (s, 1H), 4.74 - 4.56 (m, 3H), 4.53 (d, J = 6.9 Hz, 1H), 4.50 - 4.43 (m, 1H), 4.39 (dd, J = 7.2, 3.7 Hz, 1H), 4.35 - 4.15 (m, 3H), 4.05 - 3.71 (m, 5H), 3.55 (dd, J = 14.3, 3.4 Hz, 1H), 2.77 - 2.62 (m, 3H), 2.62 - 2.38 (m, 2H), 2.00 (d, J = 10.3 Hz, 2H), 1.84 (td, J = 13.3, 4.5 Hz, 1H), 1.19 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 518.36 $[M+H]^+$
934			**S74**	LCMS *m/z* 476.33 $[M+H]^+$
935			**S74**	1H NMR (300 MHz, CDCl3) δ 7.44 (s, 1H), 7.40 (s, 1H), 4.64 (d, J = 5.4 Hz, 2H), 4.32 (s, 1H), 4.24 - 4.05 (m, 3H), 3.92 (d, J = 5.3 Hz, 2H), 3.82 (s, 2H), 3.62 - 3.47 (m, 1H), 2.89 (s, 1H),2.79 - 2.35 (m, 4H), 2.13 - 1.59 (m, 11H), 1.20 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 530.42 $[M+H]^+$

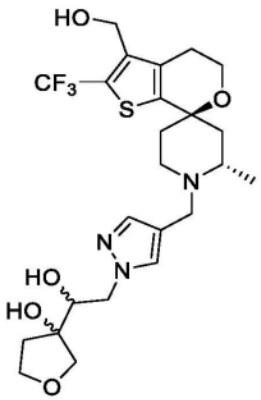
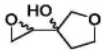
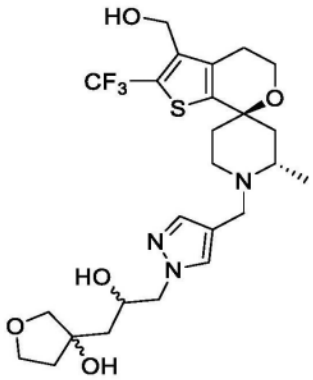
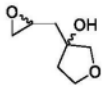
[1942]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z [M+H]$^+$。
936			S74	1H NMR (300 MHz, CDCl3) δ 7.47 (s, 1H), 7.38 (s, 1H), 4.64 (s, 2H), 4.24 (d, J = 14.0 Hz, 1H), 4.06 (d, J = 14.0 Hz, 1H), 3.96 - 3.79 (m, 3H), 3.66 (s, 1H), 3.53 (dd, J = 14.3, 4.3 Hz, 1H), 3.43 (d, J = 12.0 Hz, 1H), 3.29 (d, J = 11.8 Hz, 1H), 2.89 (s, 1H), 2.70 (s, 3H), 2.61 - 2.38 (m, 2H), 2.02 (t, J = 11.4 Hz, 2H), 1.84 (td, J = 13.3, 4.5 Hz, 1H), 1.68 (d, J = 12.7 Hz, 1H), 1.19 (d, J = 6.2 Hz, 3H), 1.14 (s, 3H)；LCMS *m/z* 490.37 [M+H]$^+$
937			S74	1H NMR (300 MHz, CDCl3) δ 8.39 (d, J = 2.6 Hz, 1H), 7.42 (s, 1H), 7.39 (s, 2H), 7.22 (d, J = 4.3 Hz, 1H), 5.14 (s, 1H), 4.94 (s, 1H), 4.64 (s, 2H), 4.51 (ddd, J = 13.8, 3.6, 2.2 Hz, 1H), 4.39 (ddd, J = 13.8, 6.5, 4.5 Hz, 1H), 3.91 (hept, J = 6.0 Hz, 2H), 3.76 (d, J = 2.3 Hz, 1H), 3.49 (dd, J = 14.3, 3.9 Hz, 1H), 2.72 (dt, J = 6.6, 3.3 Hz, 2H), 2.66 - 2.27 (m, 3H), 2.00 (t, J = 10.3 Hz, 2H), 1.82 (td, J = 13.2, 4.4 Hz, 1H), 1.74 - 1.64 (m, 1H), 1.16 (dd, J = 6.2, 3.1 Hz, 3H)；LCMS *m/z* 541.39 [M+H]$^+$

[1943]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
938			**S74**	LCMS *m/z* $[M+H]^+$
939			**S74**	1H NMR (300 MHz, CDCl3) δ 8.54 (dt, J = 4.8, 1.4 Hz, 1H), 7.66 (td, J = 7.7, 1.7 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.25 - 7.12 (m, 2H), 5.14 (s, 1H), 5.01 (s, 1H), 4.64 (s, 2H), 4.51 (ddd, J = 13.8, 3.7, 1.9 Hz, 1H), 4.38 (ddd, J = 13.9, 6.8, 2.1 Hz, 1H), 3.90 (hept, J = 5.9 Hz, 2H), 3.79 (d, J = 14.2 Hz, 1H), 3.47 (dd, J = 14.2, 3.7 Hz, 1H), 2.72 (dt, J = 6.2, 2.9 Hz, 2H), 2.65 - 2.31 (m, 3H), 2.00 (ddd, J = 10.7, 5.5, 2.8 Hz, 2H), 1.91 - 1.44 (m, 3H), 1.15 (dd, J = 6.2, 1.8 Hz, 3H)；LCMS *m/z* 523.37 $[M+H]^+$
940			**S74**	1H NMR (300 MHz, CDCl3) δ 7.75 (d, J = 4.9 Hz, 1H), 7.52 (d, J = 3.3 Hz, 1H), 4.64 (s, 2H), 4.48 (t, J = 13.6 Hz, 1H), 4.34 (ddd, J = 14.1, 7.7, 2.9 Hz, 1H), 4.21 (dt, J = 14.1, 9.1 Hz, 1H), 4.01 (td, J = 8.9, 8.5, 2.8 Hz, 1H), 3.95 - 3.83 (m, 2H),

[1944]

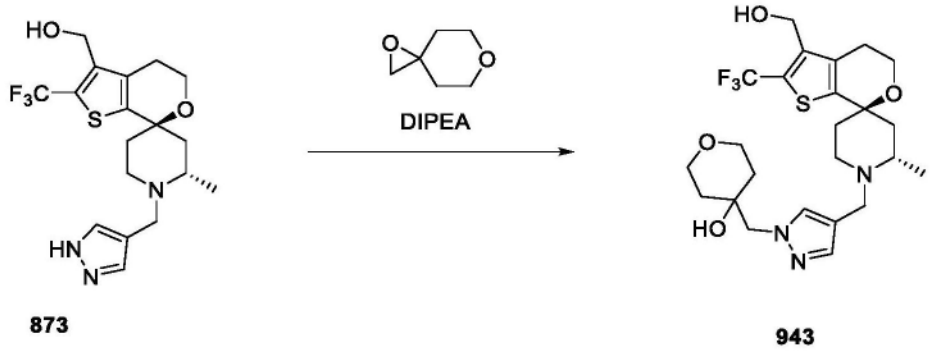
化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				3.77 (t, J = 14.7 Hz, 1H), 3.32 (d, J = 11.6 Hz, 2H), 2.74 (t, J = 5.5 Hz, 5H), 2.40 - 2.18 (m, 3H), 2.07 (d, J = 37.7 Hz, 5H), 1.86 (d, J = 5.9 Hz, 1H), 1.64 (t, J = 8.5 Hz, 1H), 1.53 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 516.42 $[M+H]^+$
941			**S74**	1H NMR (300 MHz, DMSO) δ 7.59 (s, 1H), 7.33 (s, 1H), 5.40 - 4.60 (m, 2H), 4.43 (s, 2H), 4.29 (ddd, J = 13.8, 6.3, 2.6 Hz, 1H), 3.95 (ddd, J = 13.3, 9.0, 3.5 Hz, 1H), 3.88 - 3.58 (m, 9H), 2.62 (q, J = 5.7 Hz, 4H), 2.36 (d, J = 11.7 Hz, 2H), 1.93 (t, J = 16.4 Hz, 3H), 1.79 - 1.58 (m, 2H), 1.49 (t, J = 12.4 Hz, 1H), 1.11 (d, J = 6.1 Hz, 3H)；LCMS *m/z* 532.4 $[M+H]^+$
942			**S74**	1H NMR (300 MHz, DMSO) δ 7.58 (d, J = 2.0 Hz, 1H), 7.34 (s, 1H), 4.43 (s, 2H), 4.24 - 3.93 (m, 3H), 3.93 - 3.62 (m, 6H), 3.61 - 3.42 (m, 6H), 2.63 (t, J = 5.7 Hz, 3H), 2.39 (t, J = 11.9 Hz, 1H), 2.11 - 1.91 (m, 2H), 1.91 - 1.39 (m, 6H), 1.12 (d, J = 6.1 Hz, 3H)；LCMS *m/z* 546.44 $[M+H]^+$

[1945] 脚注：

[1946] 1)将反应在80℃下进行18小时。

[1947] 化合物943

[1948] 4-[[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]四氢吡喃-4-醇(943)

[1949] 

[1950] 标准方法G:使用DIPEA作为碱用环氧化物进行N-烷基化

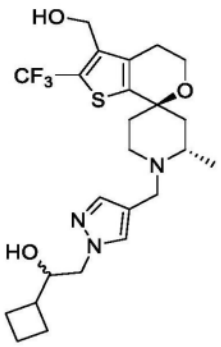
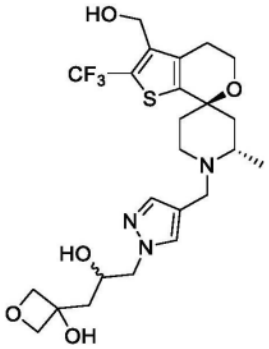
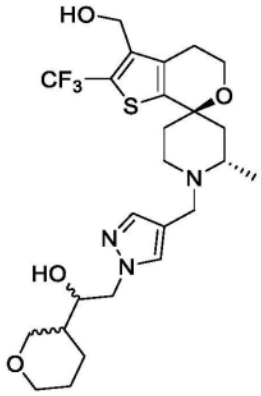
[1951] 向1打兰小瓶中添加[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(63mg,0.16mmol)、1,6-二氧杂螺[2.5]辛烷(28mg,0.25mmol)、N-乙基-N-异丙基-丙-2-胺(135μL,0.78mmol)和EtOH(1mL)。将反应小瓶加热至100℃,持续1小时,并且之后加热至90℃,持续另外105小时。通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。将产物分离为4-[[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]四氢吡喃-4-醇(50mg,52%)。1H NMR(300MHz,MeOD)δ8.30(d,J=2.7Hz,2H),7.91(s,1H),7.67(s,1H),4.72-4.56(m,2H),4.52(d,J=14.1Hz,1H),4.25(d,J=14.1Hz,1H),4.19(s,2H),4.05-3.86(m,2H),3.86-3.67(m,4H),3.53(s,1H),3.42-3.33(m,1H),3.30-3.15(m,1H),2.77(t,J=5.5Hz,2H),2.33(dd,J=18.9,15.8Hz,2H),2.16-1.87(m,2H),1.71(dt,J=15.6,7.8Hz,2H),1.53(d,J=6.4Hz,3H),1.47-1.30(m,2H)。LCMS m/z 516.42[M+1]$^+$。

[1952] 化合物944-980

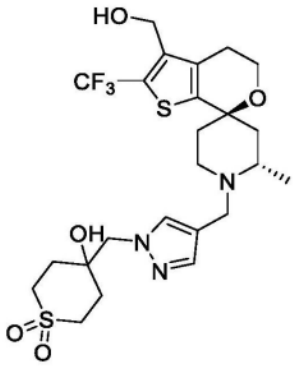
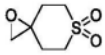
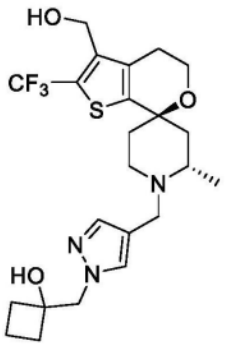
[1953] 化合物944-980(参见43)由中间体873使用标准方法G在单个步骤中制备。环氧化物从商业来源获得。表43和随附脚注中注明了对方法的任何修改。

[1954] 表43:化合物944-980的结构和物理化学数据

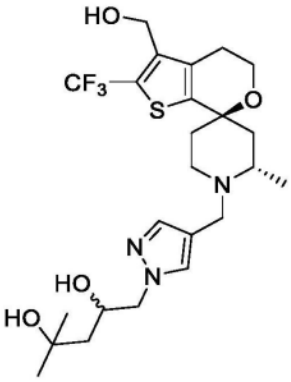
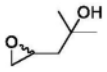
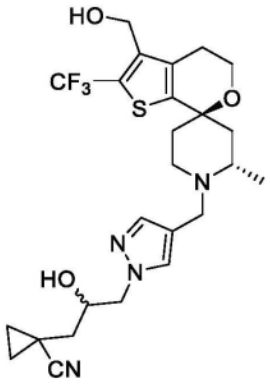
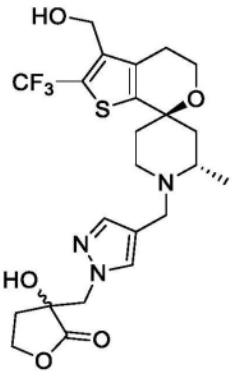
[1955]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
944			**873**	1H NMR (300 MHz, CDCl3) δ 7.45 (s, 1H), 7.39 (s, 1H), 4.64 (s, 2H), 4.12 (d, J = 10.9 Hz, 1H), 4.04 - 3.83 (m, 5H), 3.58 (dd, J = 14.2, 4.2 Hz, 1H), 2.75 (d, J = 22.7 Hz, 4H), 2.54 (d, J = 12.9 Hz, 1H), 2.30 (s, 1H), 2.09 - 1.77 (m, 10H), 1.26 (d, J = 6.1 Hz, 3H)；LCMS *m/z* 500.35 $[M+H]^+$
945			**873**	1H NMR (300 MHz, CDCl3) δ 8.38 (s, 1H), 7.67 (d, J = 3.2 Hz, 1H), 7.50 (s, 1H), 4.86 - 4.59 (m, 4H), 4.53 (dd, J = 6.5, 3.5 Hz, 1H), 4.49 - 4.39 (m, 2H), 4.39 - 4.19 (m, 2H), 4.09 (td, J = 13.0, 7.8 Hz, 1H), 3.91 (p, J = 6.3 Hz, 2H), 3.60 (dd, J = 13.8, 9.4 Hz, 1H), 3.25 (s, 2H), 2.84 (d, J = 12.3 Hz, 1H), 2.74 (t, J = 5.6 Hz, 2H), 2.13 (t, J = 17.3 Hz, 7H), 1.92 (q, J = 12.2 Hz, 1H), 1.49 (dd, J = 6.5, 2.5 Hz, 3H)；LCMS *m/z* 532.45 $[M+H]^+$
946			**873**	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.68 (s, 1H), 4.64 - 4.55 (m, 2H), 4.51 (d, J = 14.2 Hz, 1H), 4.40 - 4.21 (m, 2H), 4.14 (dd, J = 14.0, 8.0 Hz, 1H), 3.98 (q, J = 9.8, 5.5 Hz, 3H), 3.92 - 3.76 (m, 3H), 3.51 (dt, J = 7.4, 6.4 Hz, 2H), 3.45 - 3.32 (m, 4H), 2.76 (t, J = 5.5 Hz, 2H), 2.33 (dd, J = 19.3, 16.0 Hz, 2H), 2.20 - 1.82 (m, 3H), 1.79 - 1.56 (m, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.40 (dd, J =

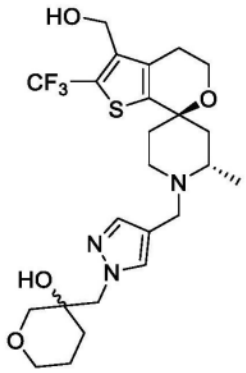
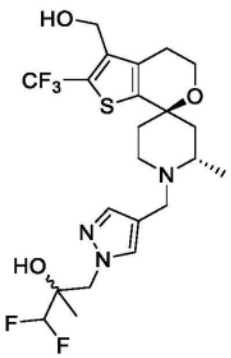
[1956]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				10.3, 5.6 Hz, 1H)；LCMS *m/z* 530.42 $[M+H]^+$
947			**873**	1H NMR (300 MHz, MeOD) δ 7.92 (s, 1H), 7.70 (s, 1H), 4.59 (d, J = 1.5 Hz, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.34 - 4.18 (m, 3H), 4.12 - 3.85 (m, 2H), 3.53 (q, J = 6.8 Hz, 1H), 3.36 (d, J = 3.6 Hz, 2H), 3.26 (d, J = 2.7 Hz, 1H), 3.04 - 2.83 (m, 2H), 2.76 (t, J = 5.5 Hz, 2H), 2.41 - 2.24 (m, 2H), 2.23 - 1.82 (m, 7H), 1.53 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 564.42 $[M+H]^+$
948			**873**	1H NMR (300 MHz, MeOD) δ 7.94 (s, 1H), 7.66 (s, 1H), 4.59 (d, J = 1.4 Hz, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.29 (s, 2H), 4.24 (d, J = 14.1 Hz, 1H), 3.97 (td, J = 5.7, 3.7 Hz, 2H), 3.54 (d, J = 10.9 Hz, 1H), 3.36 (dd, J = 10.2, 2.7 Hz, 1H), 3.29 - 3.20 (m, 1H), 2.76 (t, J = 5.5 Hz, 2H), 2.49 - 2.22 (m, 2H), 2.22 - 2.09 (m, 2H), 2.09 - 1.94 (m, 4H), 1.89 - 1.68 (m, 1H), 1.68 - 1.58 (m, 1H), 1.53 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 486.35 $[M+H]^+$

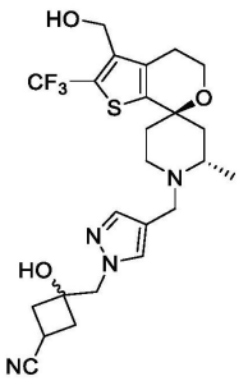
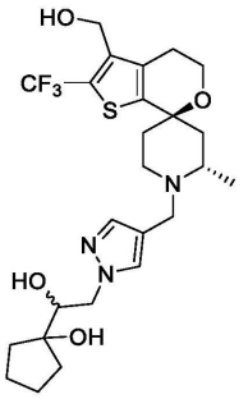
[1957]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
949			**873**	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.68 (s, 1H), 4.67 - 4.56 (m, 2H), 4.53 (d, J = 14.0 Hz, 1H), 4.38 - 4.17 (m, 3H), 4.09 (dd, J = 14.0, 7.7 Hz, 1H), 3.97 (t, J = 4.9 Hz, 2H), 3.55 (s, 1H), 3.43 - 3.21 (m, 2H), 2.76 (t, J = 5.5 Hz, 2H), 2.34 (dd, J = 19.5, 16.1 Hz, 2H), 2.16 - 1.91 (m, 2H), 1.64 - 1.58 (m, 2H), 1.53 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 8.9 Hz, 6H)；LCMS *m/z* 518.45 $[M+H]^+$
950			**873**	1H NMR (300 MHz, MeOD) δ 7.92 (s, 1H), 7.69 (s, 1H), 4.68 - 4.58 (m, 2H), 4.53 (d, J = 14.0 Hz, 1H), 4.41 - 4.08 (m, 4H), 3.98 (q, J = 5.5 Hz, 2H), 3.54 (s, 1H), 3.37 (d, J = 9.6 Hz, 1H), 2.76 (t, J = 5.5 Hz, 3H), 2.34 (t, J = 18.0 Hz, 3H), 2.17 - 1.84 (m, 2H), 1.72 (dd, J = 14.4, 3.2 Hz, 1H), 1.54 (dd, J = 6.9, 3.6 Hz, 4H), 1.44 - 1.10 (m, 3H), 1.10 - 0.98 (m, 1H), 0.98 - 0.86 (m, 1H)； LCMS *m/z* 525.45 $[M+H]^+$
951			**873**	1H NMR (300 MHz, MeOD) δ 7.93 (d, J = 2.1 Hz, 1H), 7.69 (s, 1H), 4.59 (d, J = 1.3 Hz, 2H), 4.56 - 4.44 (m, 3H), 4.42 - 4.16 (m, 3H), 4.08 (ddd, J = 14.4, 8.5, 6.3 Hz, 1H), 4.02 - 3.87 (m, 2H), 3.52 (dt, J = 9.2, 3.5 Hz, 2H), 3.24 (d, J = 12.4 Hz, 1H), 2.76 (t, J = 5.5 Hz, 2H), 2.60 - 2.43 (m, 1H), 2.33

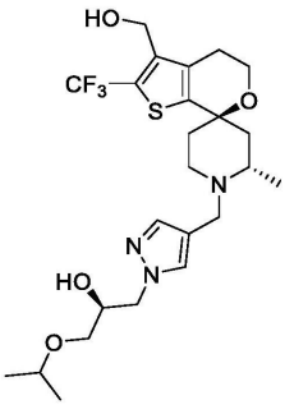
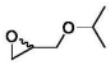
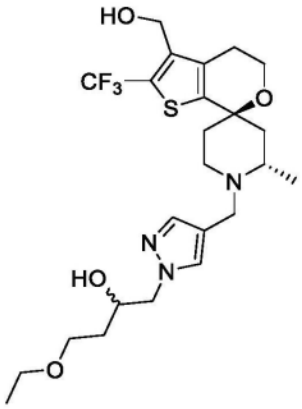
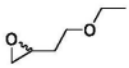
[1958]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				(t, J = 16.3 Hz, 2H), 2.20 (ddd, J = 13.9, 7.8, 6.3 Hz, 1H), 2.15 - 1.89 (m, 2H), 1.52 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 516.38 $[M+H]^+$
952			**873**	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.66 (s, 1H), 4.68 - 4.56 (m, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.37 - 4.14 (m, 3H), 3.97 (h, J = 6.2 Hz, 2H), 3.83 - 3.40 (m, 6H), 3.40 - 3.32 (m, 1H), 3.24 (s, 1H), 2.77 (q, J = 6.9, 5.5 Hz, 2H), 2.33 (t, J = 16.9 Hz, 2H), 2.20 - 1.90 (m, 2H), 1.75 (d, J = 5.5 Hz, 3H), 1.66 - 1.55 (m, 2H), 1.53 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 516.42 $[M+H]^+$
953			**873**	1H NMR (300 MHz, CDCl3) δ 7.64 (d, J = 6.3 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 5.74 - 5.19 (m, 1H), 4.67 (s, 2H), 4.48 - 4.30 (m, 1H), 4.22 (t, J = 13.8 Hz, 2H), 4.08 - 3.82 (m, 2H), 3.73 (dd, J = 14.1, 6.3 Hz, 1H), 3.07 (s, 2H), 2.80 - 2.69 (m, 3H), 2.24 - 2.08 (m, 6H),1.44 (t, J = 6.3 Hz, 3H), 1.24 (d, J = 14.7 Hz, 3H)；LCMS *m/z* 510.25 $[M+H]^+$

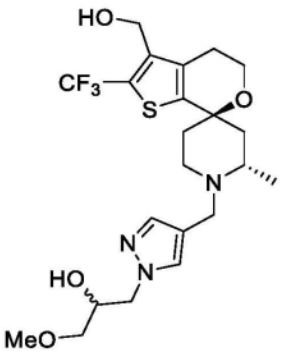
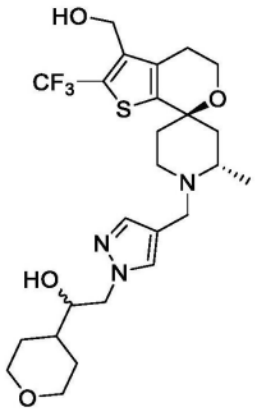
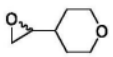
[1959]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
954			**873**	1H NMR (300 MHz, MeOD) δ 7.92 (s, 1H), 7.68 (d, J = 4.9 Hz, 1H), 4.59 (d, J = 1.5 Hz, 2H), 4.51 (dd, J = 14.1, 8.1 Hz, 1H), 4.31 (d, J = 22.2 Hz, 2H), 4.23 (d, J = 14.1 Hz, 1H), 3.98 (hept, J = 6.2, 5.6 Hz, 2H), 3.57 - 3.44 (m, 1H), 3.28 - 3.19 (m, 1H), 2.87 (q, J = 8.7 Hz, 1H), 2.76 (t, J = 5.5 Hz, 2H), 2.73 - 2.54 (m, 3H), 2.54 - 2.42 (m, 1H), 2.42 - 2.21 (m, 5H), 2.17 - 1.86 (m, 2H), 1.52 (dd, J = 6.4, 1.9 Hz, 3H)；LCMS *m/z* 511.41 $[M+H]^+$
955			**873**	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.68 (s, 1H), 4.71 - 4.57 (m, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.49 - 4.40 (m, 1H), 4.24 (d, J = 14.1 Hz, 1H), 4.15 (dd, J = 13.8, 9.8 Hz, 1H), 3.98 (h, J = 6.2 Hz, 2H), 3.88 - 3.75 (m, 1H), 3.73 - 3.55 (m, 1H), 3.51 - 3.42 (m, 1H), 3.34 (s, 1H), 2.76 (t, J = 5.5 Hz, 2H), 2.51 - 2.17 (m, 2H), 2.13 - 1.91 (m, 2H), 1.91 - 1.57 (m, 11H), 1.53 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 530.46 $[M+H]^+$

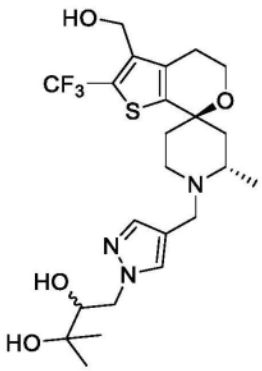
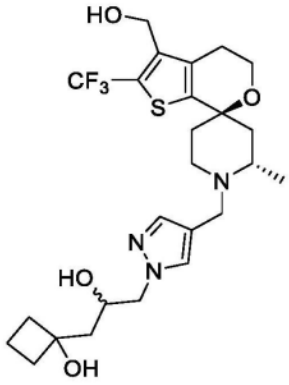
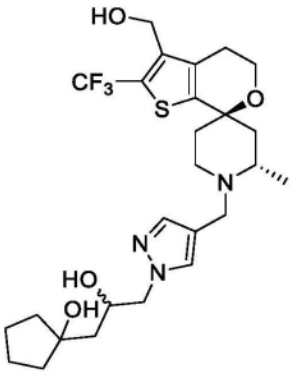
[1960]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
956			**873**	1H NMR (300 MHz, MeOD) δ 7.90 (s, 1H), 7.68 (s, 1H), 4.59 (d, J = 1.5 Hz, 2H), 4.52 (d, J = 14.1 Hz, 1H), 4.35 (dd, J = 13.8, 3.7 Hz, 1H), 4.29 - 4.11 (m, 2H), 4.07 (dt, J = 7.9, 4.4 Hz, 1H), 3.97 (td, J = 5.7, 3.6 Hz, 2H), 3.63 (h, J = 6.0 Hz, 1H), 3.55 (d, J = 8.3 Hz, 1H), 3.42 (d, J = 5.2 Hz, 2H), 3.38 - 3.33 (m, 1H), 3.29 - 3.14 (m, 1H), 2.76 (t, J = 5.5 Hz, 2H), 2.33 (dd, J = 19.7, 15.7 Hz, 2H), 2.13 - 1.90 (m, 2H), 1.53 (d, J = 6.4 Hz, 3H), 1.17 (dd, J = 6.1, 1.2 Hz, 6H)；LCMS *m/z* 518.45 $[M+H]^+$
957			**873**	1H NMR (300 MHz, MeOD) δ 7.89 (s, 1H), 7.67 (s, 1H), 4.67 - 4.56 (m, 2H), 4.50 (d, J = 14.0 Hz, 1H), 4.35 - 4.06 (m, 4H), 3.97 (q, J = 5.5 Hz, 2H), 3.59 (t, J = 6.2 Hz, 3H), 3.54 - 3.41 (m, 4H), 2.76 (t, J = 5.4 Hz, 2H), 2.33 (t, J = 17.3 Hz, 2H), 2.15 - 1.87 (m, 2H), 1.86 - 1.69 (m, 1H), 1.61 (dd, J = 13.9, 8.0 Hz, 1H), 1.51 (d, J = 6.4 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H)；LCMS *m/z* 518.49 $[M+H]^+$

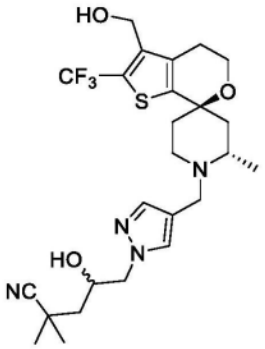
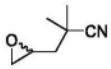
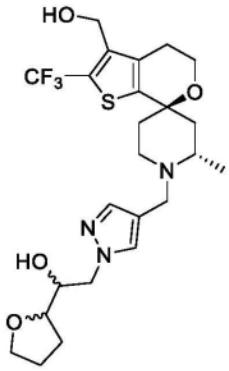
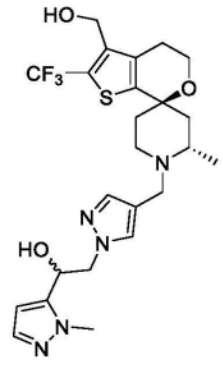
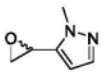
[1961]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
958			**873**	1H NMR (400 MHz, MeOD) δ 7.62 (s, 1H), 7.47 (s, 1H), 4.64 - 4.47 (m, 2H), 4.26 (dd, J = 13.6, 4.3 Hz, 1H), 4.18 - 3.99 (m, 2H), 3.91 (td, J = 5.7, 3.8 Hz, 2H), 3.85 (d, J = 14.1 Hz, 1H), 3.62 (dd, J = 14.2, 2.8 Hz, 1H), 3.36 (d, J = 1.2 Hz, 3H), 3.34 - 3.32 (m, 2H), 2.87 - 2.46 (m, 5H), 2.17 - 1.91 (m, 2H), 1.86 (td, J = 13.4, 4.5 Hz, 1H), 1.65 (dd, J = 14.1, 11.5 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 490.41 $[M+H]^+$
959			**873**	1H NMR (400 MHz, MeOD) δ 7.64 (d, J = 1.3 Hz, 1H), 7.47 (s, 1H), 4.57 (d, J = 1.2 Hz, 2H), 4.26 (dd, J = 14.0, 3.7 Hz, 1H), 4.08 (ddd, J = 14.0, 8.0, 2.5 Hz, 1H), 4.03 - 3.88 (m, 4H), 3.85 (dd, J = 14.3, 2.8 Hz, 1H), 3.71 (s, 1H), 3.62 (dd, J = 14.3, 5.4 Hz, 1H), 3.45 - 3.35 (m, 2H), 2.85 - 2.52 (m, 5H), 2.16 - 1.96 (m, 2H), 1.86 (td, J = 13.4, 4.5 Hz, 1H), 1.73 (d, J = 12.6 Hz, 1H), 1.70 - 1.61 (m, 1H), 1.61 - 1.35 (m, 4H), 1.23 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 530.46 $[M+H]^+$

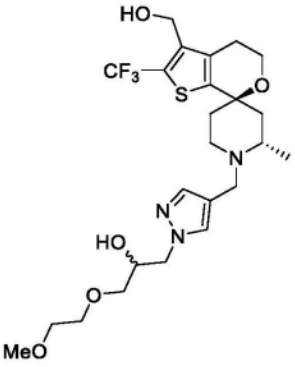
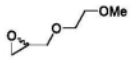
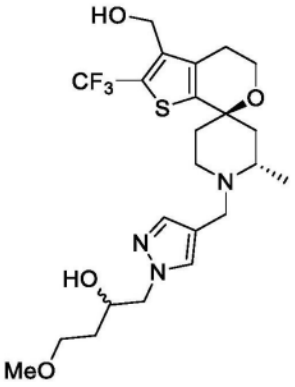
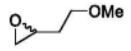
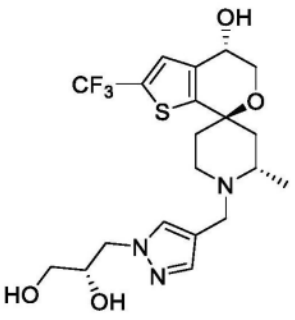
[1962]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
960			**873**	1H NMR (400 MHz, MeOD) δ 7.64 (s, 1H), 7.46 (s, 1H), 4.66 - 4.55 (m, 2H), 4.44 (dd, J = 14.0, 2.3 Hz, 1H), 4.02 (ddd, J = 14.0, 9.7, 1.6 Hz, 1H), 3.96 - 3.89 (m, 2H), 3.86 (dd, J = 14.2, 4.3 Hz, 1H), 3.68 (ddd, J = 9.8, 2.3, 1.3 Hz, 1H), 3.60 (dd, J = 14.2, 8.9 Hz, 1H), 2.80 - 2.52 (m, 5H), 2.05 (ddt, J = 14.2, 5.8, 2.9 Hz, 2H), 1.85 (td, J = 13.5, 13.0, 3.9 Hz, 1H), 1.65 (dd, J = 14.1, 11.4 Hz, 1H), 1.28 - 1.17 (m, 9H)；LCMS *m/z* 504.41 $[M+H]^+$
961			**873**	1H NMR (400 MHz, MeOD) δ 7.64 (s, 1H), 7.47 (d, J = 0.8 Hz, 1H), 4.57 (d, J = 1.2 Hz, 2H), 4.33 - 4.16 (m, 2H), 4.16 - 4.02 (m, 1H), 3.97 - 3.80 (m, 3H), 3.61 (dd, J = 14.2, 3.0 Hz, 1H), 2.80 - 2.48 (m, 5H), 2.05 (q, J = 7.7 Hz, 6H), 1.85 (td, J = 13.3, 4.5 Hz, 1H), 1.77 - 1.57 (m, 4H), 1.50 (dt, J = 11.1, 9.0 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 530.46 $[M+H]^+$
962			**873**	1H NMR (400 MHz, MeOD) δ 7.63 (s, 1H), 7.47 (d, J = 0.8 Hz, 1H), 4.57 (d, J = 1.2 Hz, 2H), 4.28 (tt, J = 8.2, 4.1 Hz, 1H), 4.18 (dd, J = 13.9, 4.3 Hz, 1H), 4.08 (ddd, J = 13.9, 7.2, 1.9 Hz, 1H), 3.99 - 3.74 (m, 3H), 3.60 (dd, J = 14.2, 3.2 Hz, 1H), 2.88 - 2.48 (m, 5H), 2.05 (ddd, J = 11.5, 6.6, 3.1 Hz,

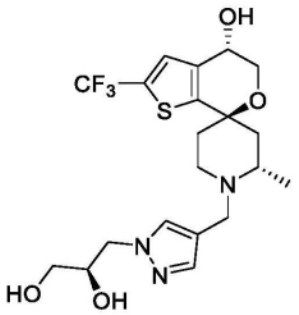
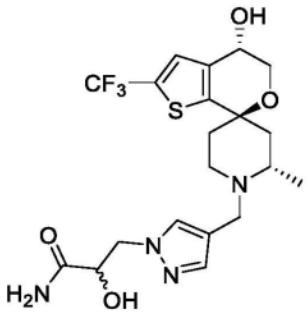
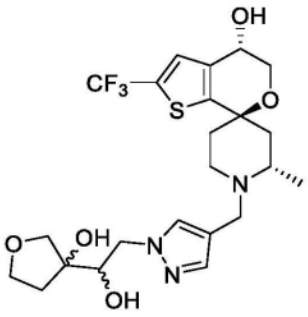
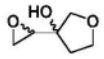
[1963]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				2H), 1.96 - 1.43 (m, 12H), 1.23 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 544.46 $[M+H]^+$
963			**873**	LCMS *m/z* 527.44 $[M+H]^+$
964			**873**	1H NMR (400 MHz, MeOD) δ 7.63 (s, 1H), 7.47 (d, J = 0.9 Hz, 1H), 4.57 (d, J = 1.3 Hz, 2H), 4.31 - 4.12 (m, 2H), 4.00 - 3.81 (m, 5H), 3.81 - 3.66 (m, 2H), 3.61 (dd, J = 14.2, 6.2 Hz, 1H), 2.82 - 2.47 (m, 5H), 2.05 (ddt, J = 14.4, 9.6, 2.8 Hz, 2H), 1.99 - 1.73 (m, 5H), 1.73 - 1.59 (m, 1H), 1.23 (d, J = 6.3 Hz, 3H)；LCMS *m/z* 516.42 $[M+H]^+$
965			**873**	1H NMR (400 MHz, MeOD) δ 7.52 (d, J = 13.9 Hz, 1H), 7.48 (s, 1H), 7.39 - 7.34 (m, 1H), 6.28 (t, J = 1.6 Hz, 1H), 5.34 - 5.01 (m, 1H), 4.58 (d, J = 1.3 Hz, 2H), 4.53 - 4.35 (m, 2H), 4.00 - 3.85 (m, 2H), 3.84 - 3.74 (m, 4H), 3.59 (dd, J = 14.3, 1.3 Hz, 1H), 2.79 - 2.33 (m, 5H), 2.04 (ddd, J = 13.9, 7.7, 2.6 Hz, 2H), 1.84 (td, J = 13.3, 4.5 Hz, 1H), 1.63 (ddd, J = 14.2, 11.5, 2.9 Hz, 1H), 1.20 (dd, J = 10.4, 6.2 Hz, 3H)；

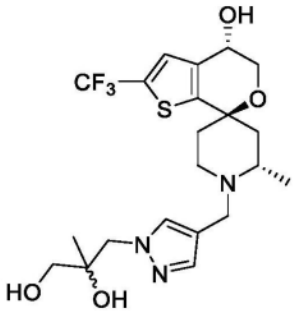
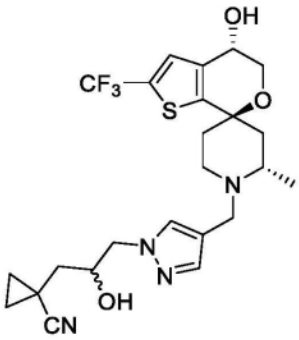
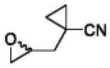
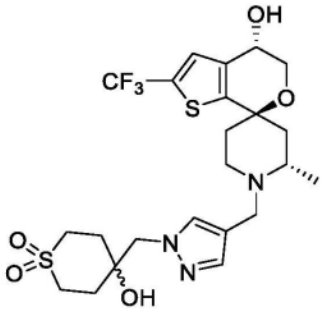
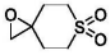
[1964]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				LCMS *m/z* 526.44 $[M+H]^+$
966			**873**	LCMS *m/z* 534.43 $[M+H]^+$
967			**873**	1H NMR (400 MHz, MeOD) δ 7.63 (s, 1H), 7.46 (s, 1H), 4.57 (d, J = 1.2 Hz, 2H), 4.21 - 4.12 (m, 1H), 4.08 (ddt, J = 10.0, 3.4, 1.9 Hz, 2H), 3.99 - 3.79 (m, 3H), 3.60 (dd, J = 14.2, 2.1 Hz, 1H), 3.57 - 3.43 (m, 2H), 3.32 (s, 3H), 2.83 - 2.50 (m, 5H), 2.05 (ddt, J = 12.2, 5.8, 2.9 Hz, 2H), 1.85 (td, J = 13.3, 4.5 Hz, 1H), 1.77 - 1.50 (m, 3H), 1.23 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 504.41 $[M+H]^+$
968			**873**	1H NMR (300 MHz, MeOD) δ 7.64 (s, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 4.51 (t, J = 3.8 Hz, 1H), 4.28 (dd, J = 14.1, 4.4 Hz, 1H), 4.11 (dd, J = 14.0, 7.4 Hz, 1H), 4.00 - 3.80 (m, 3H), 3.75 (dd, J = 12.2, 4.1 Hz, 1H), 3.61 (d, J = 14.2 Hz, 1H), 3.48 (dd, J = 5.4, 1.6 Hz, 2H), 2.73 (s, 2H), 2.55 (s, 1H), 2.11 (s, 2H), 1.88 - 1.60 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 462.33 $[M+H]^+$

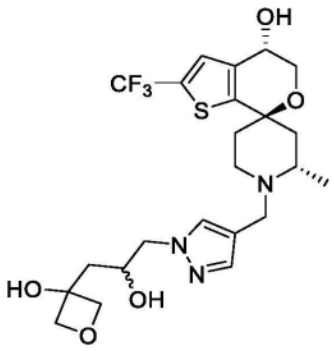
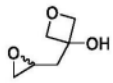
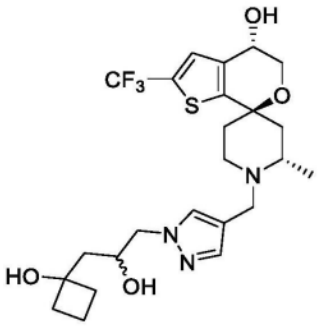
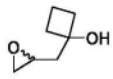
[1965]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
969			**873**	1H NMR (300 MHz, MeOD) δ 7.65 (s, 1H), 7.48 (s, 1H), 7.43 (s, 1H), 4.51 (t, J = 3.8 Hz, 1H), 4.29 (dd, J = 14.0, 4.3 Hz, 1H), 4.12 (dd, J = 13.9, 7.3 Hz, 1H), 4.01 - 3.82 (m, 3H), 3.75 (dd, J = 12.2, 4.1 Hz, 1H), 3.63 (d, J = 13.9 Hz, 1H), 3.48 (dd, J = 5.3, 1.8 Hz, 2H), 2.74 (s, 2H), 2.56 (s, 1H), 2.14 (d, J = 13.9 Hz, 2H), 1.72 (d, J = 12.3 Hz, 2H), 1.26 (d, J = 6.2 Hz, 3H)；LCMS *m/z* 462.29 $[M+H]^+$
970			**873**	1H NMR (300 MHz, CDCl3) δ 7.45 (d, J = 2.1 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 1.3 Hz, 1H), 6.79 (s, 1H), 5.57 (s, 1H), 5.30 (s, 1H), 4.63 - 4.36 (m, 4H), 4.00 - 3.75 (m, 3H), 3.64 - 3.44 (m, 1H), 2.83 - 2.52 (m, 2H), 2.52 - 2.33 (m, 1H), 2.18 - 2.04 (m, 1H), 1.99 (dt, J = 13.8, 3.1 Hz, 1H), 1.77 (d, J = 11.8 Hz, 3H), 1.20 (dd, J = 6.2, 1.0 Hz, 3H)；LCMS *m/z* 475.24 $[M+H]^+$
971			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.94 (s, 1H), 7.71 (s, 1H), 7.50 (s, 1H), 4.58 (dd, J = 8.2, 4.6 Hz, 2H), 4.42 (t, J = 13.2 Hz, 1H), 4.36 - 4.05 (m, 2H), 4.05 - 3.50 (m, 8H), 3.47 - 3.24 (m, 2H), 2.44 (t, J = 16.2 Hz, 2H), 2.23 - 1.72 (m, 4H), 1.56 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 518.32 $[M+H]^+$

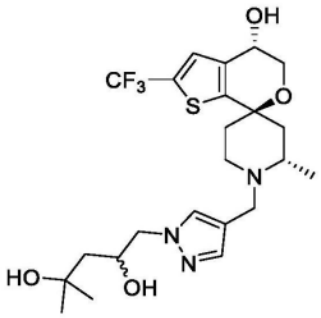
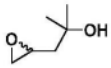
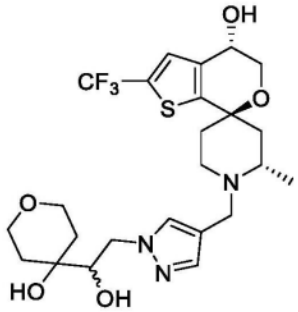
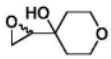
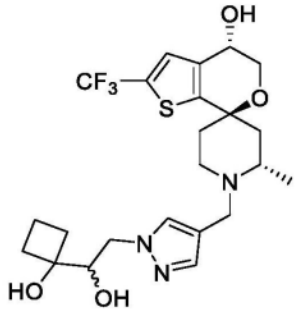
[1966]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
972			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.90 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 4.57 (t, J = 3.6 Hz, 1H), 4.51 (d, J = 14.1 Hz, 1H), 4.25 (d, J = 10.7 Hz, 3H), 3.98 (dd, J = 12.4, 3.5 Hz, 1H), 3.82 (dd, J = 12.4, 3.8 Hz, 1H), 3.62 - 3.44 (m, 1H), 3.34 (s, 2H), 3.30 - 3.10 (m, 2H), 2.40 (t, J = 14.9 Hz, 2H), 2.01 (t, J = 13.3 Hz, 2H), 1.53 (d, J = 6.4 Hz, 3H), 1.09 (s, 3H)；LCMS *m/z* 476.11 $[M+H]^+$
973			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.68 (s, 1H), 7.50 (s, 1H), 4.58 (d, J = 3.6 Hz, 1H), 4.52 (d, J = 14.1 Hz, 1H), 4.36 - 4.06 (m, 4H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.2, 3.9 Hz, 1H), 3.68 - 3.46 (m, 1H), 3.21 (d, J = 11.7 Hz, 2H), 2.40 (t, J = 15.8 Hz, 2H), 2.15 - 1.85 (m, 2H), 1.85 - 1.66 (m, 1H), 1.53 (d, J = 6.4 Hz, 4H), 1.38 - 1.11 (m, 2H), 1.11 - 0.88 (m, 2H)；LCMS *m/z* 511.32 $[M+H]^+$
974			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.69 (s, 1H), 7.50 (d, J = 1.4 Hz, 1H), 4.57 (t, J = 3.6 Hz, 1H), 4.51 (d, J = 14.1 Hz, 1H), 4.32 - 4.17 (m, 3H), 3.98 (dd, J = 12.3, 3.4 Hz, 1H), 3.82 (dd, J = 12.3, 3.9 Hz, 1H), 3.64 - 3.45 (m, 1H), 3.41 - 3.14 (m, 4H), 2.92 (d, J = 13.8 Hz, 2H), 2.40 (t, J = 14.3 Hz, 2H), 2.15 (t, J =

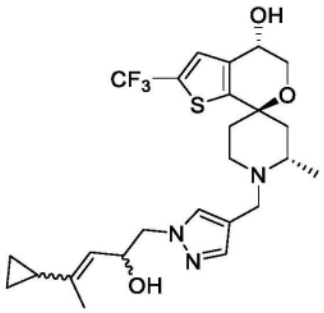
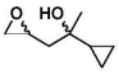
[1967]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				13.3 Hz, 2H), 2.08 - 1.81 (m, 4H), 1.53 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 550.16 $[M+H]^+$
975			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.91 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 4.66 - 4.45 (m, 3H), 4.38 (dd, J = 14.3, 3.3 Hz, 1H), 4.32 - 4.16 (m, 2H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 10.8, 5.5 Hz, 2H), 3.67 - 3.40 (m, 4H), 3.20 (d, J = 12.6 Hz, 2H), 2.40 (t, J = 15.1 Hz, 2H), 2.11 - 1.81 (m, 3H), 1.74 (ddd, J = 13.5, 9.9, 4.7 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 518.32 $[M+H]^+$
976			**873**[1]	1H NMR (300 MHz, MeOD) δ 7.93 (s, 1H), 7.69 (s, 1H), 7.50 (s, 1H), 4.60 (d, J = 13.7 Hz, 2H), 4.36 - 4.19 (m, 3H), 4.13 (dd, J = 12.8, 6.9 Hz, 1H), 3.99 (dd, J = 12.2, 3.3 Hz, 1H), 3.83 (dd, J = 12.3, 3.7 Hz, 1H), 3.64 (s, 1H), 3.41 (d, J = 12.1 Hz, 2H), 2.44 (t, J = 16.4 Hz, 2H), 2.09 (t, J = 8.8 Hz, 4H), 1.98 (d, J = 18.0 Hz, 2H), 1.86 - 1.63 (m, 3H), 1.56 (d, J = 6.4 Hz, 4H)； LCMS *m/z* 516.33 $[M+H]^+$

[1968]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
977			**873**^{I}	1H NMR (300 MHz, MeOD) δ 7.92 (s, 1H), 7.69 (s, 1H), 7.50 (s, 1H), 4.71 - 4.52 (m, 2H), 4.40 - 4.20 (m, 3H), 4.10 (dd, J = 14.0, 7.8 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.3, 3.8 Hz, 1H), 3.61 (d, J = 11.5 Hz, 1H), 3.42 (d, J = 12.3 Hz, 2H), 2.44 (t, J = 16.1 Hz, 2H), 2.11 - 1.77 (m, 2H), 1.68 - 1.45 (m, 5H), 1.26 (d, J = 8.7 Hz, 6H)；LCMS *m/z* 504.32 $[M+H]^+$
978			**873**^{I}	1H NMR (300 MHz, MeOD) δ 7.92 (s, 1H), 7.69 (s, 1H), 7.50 (d, J = 1.3 Hz, 1H), 4.66 - 4.41 (m, 3H), 4.28 (d, J = 14.1 Hz, 1H), 4.13 (dd, J = 13.9, 9.8 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.91 - 3.72 (m, 5H), 3.67 (dt, J = 9.8, 2.8 Hz, 2H), 3.38 (d, J = 12.4 Hz, 2H), 2.42 (t, J = 16.2 Hz, 2H), 2.11 - 1.67 (m, 4H), 1.55 (d, J = 6.3 Hz, 4H), 1.44 (d, J = 13.7 Hz, 1H)；LCMS *m/z* 532.32 $[M+H]^+$
979			**873**^{I}	1H NMR (300 MHz, MeOD) δ 7.66 (s, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 4.52 (t, J = 3.8 Hz, 1H), 4.31 (dd, J = 14.1, 3.2 Hz, 1H), 4.10 (dd, J = 14.1, 8.9 Hz, 1H), 4.02 - 3.81 (m, 3H), 3.80 - 3.61 (m, 2H), 2.76 (s, 2H), 2.59 (t, J = 12.0 Hz, 1H), 2.46 - 2.26 (m, 1H), 2.24 - 1.90 (m, 5H), 1.90 - 1.52 (m, 4H), 1.27 (d, J = 6.2 Hz,

[1969]

化合物	结构	环氧化物试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
				3H)； LCMS *m/z* 502.25 $[M+H]^+$
980			*873*[1,2]	1H NMR (300 MHz, MeOD) δ 8.91 (s, 1H), 8.62 (s, 1H), 7.50 (s, 1H), 4.84 - 4.63 (m, 3H), 4.59 (t, J = 3.7 Hz, 2H), 4.41 (td, J = 13.9, 13.1, 7.3 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 4.01 (dd, J = 12.3, 3.4 Hz, 1H), 3.86 (dd, J = 12.3, 3.9 Hz, 1H), 3.65 (d, J = 25.8 Hz, 1H), 3.45 - 3.34 (m, 1H), 2.59 - 1.93 (m, 7H), 1.77 (d, J = 10.2 Hz, 1H), 1.63 (d, J = 3.0 Hz, 1H), 1.57 (d, J = 6.5 Hz, 3H), 1.42 (d, J = 3.2 Hz, 2H), 1.03 - 0.48 (m, 4H)； LCMS *m/z* 512.19 $[M+H]^+$

[1970] 脚注：

[1971] 1)将反应在90℃下进行86小时。

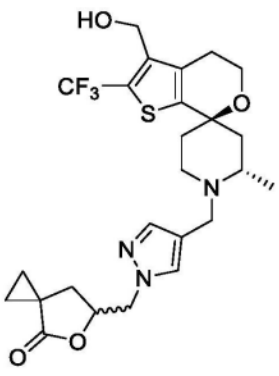
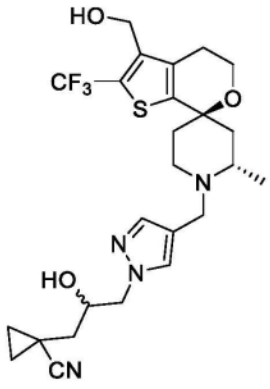
[1972] 2)将脱水产物分离为主要产物,其为1.2:1的烯烃异构体混合物。

[1973] 化合物981-984

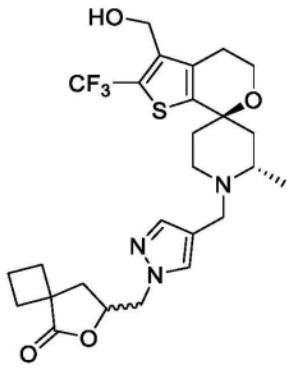
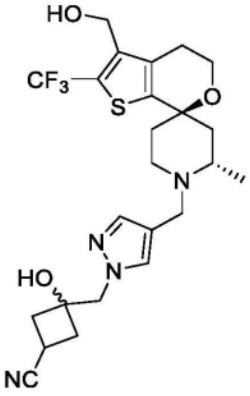
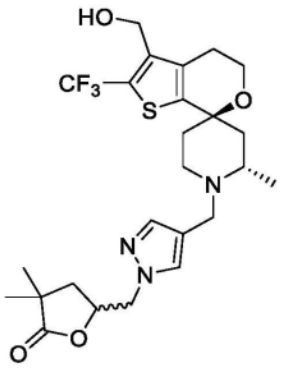
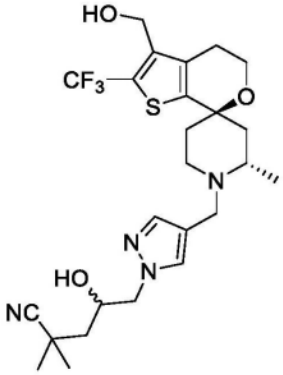
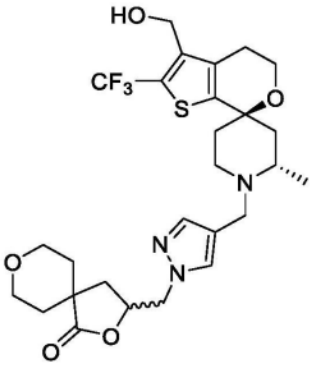
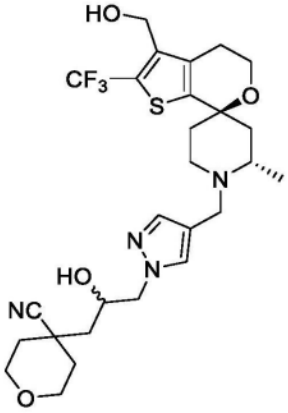
[1974] 化合物981-984(参见表44)由对应腈类似物分离为副产物,这是由纯化步骤中甲酸介导的环化引起的。

[1975] 表44:化合物981-984的结构和物理化学数据

[1976]

化合物	结构	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
981			1H NMR (400 MHz, MeOD) δ 7.91 (d, J = 3.1 Hz, 1H), 7.70 (s, 1H), 5.16 - 4.95 (m, 1H), 4.61 - 4.54 (m, 3H), 4.46 (dd, J = 14.7, 5.8 Hz, 1H), 4.40 (d, J = 14.2 Hz, 1H), 4.22 (dd, J = 14.2, 2.6 Hz, 1H), 4.04 - 3.87 (m, 2H), 3.27 - 3.05 (m, 1H), 2.76 (t, J = 5.5 Hz, 2H),

[1977]

化合物	结构	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
			2.66 (s, 3H), 2.51 (ddd, J = 13.3, 8.5, 2.0 Hz, 1H), 2.40 - 2.20 (m, 3H), 2.11 - 1.88 (m, 2H), 1.49 (t, J = 6.8 Hz, 3H), 1.18 - 0.97 (m, 3H), 0.97 - 0.85 (m, 1H)；LCMS *m/z* 526.27 $[M+H]^+$
982			LCMS *m/z* 540.31 $[M+H]^+$
983			1H NMR (300 MHz, CDCl3) δ 7.92 (s, 1H), 7.70 (s, 1H), 4.64 - 4.56 (m, 3H), 4.56 - 4.34 (m, 2H), 4.20 (d, J = 14.1 Hz, 1H), 3.97 (s, 2H), 3.24 (s, 3H), 2.76 (t, J = 5.5 Hz, 2H), 2.66 (s, 1H), 2.44 - 2.10 (m, 3H), 2.11 - 1.79 (m, 3H), 1.49 (d, J = 6.4 Hz, 3H), 1.25 (s, 4H), 1.17 (d, J = 3.6 Hz, 3H)；LCMS *m/z* 528.29 $[M+H]^+$
984			1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.67 (s, 1H), 4.58 (d, J = 14.6 Hz, 3H), 4.41 (dd, J = 14.8, 6.5 Hz, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 4.04 - 3.81 (m, 5H), 3.71 - 3.53 (m, 2H), 3.48 (d, J = 20.4 Hz, 1H), 3.19 - 3.05 (m, 1H), 2.75 (t, J = 5.4 Hz, 2H), 2.66 (s, 2H),

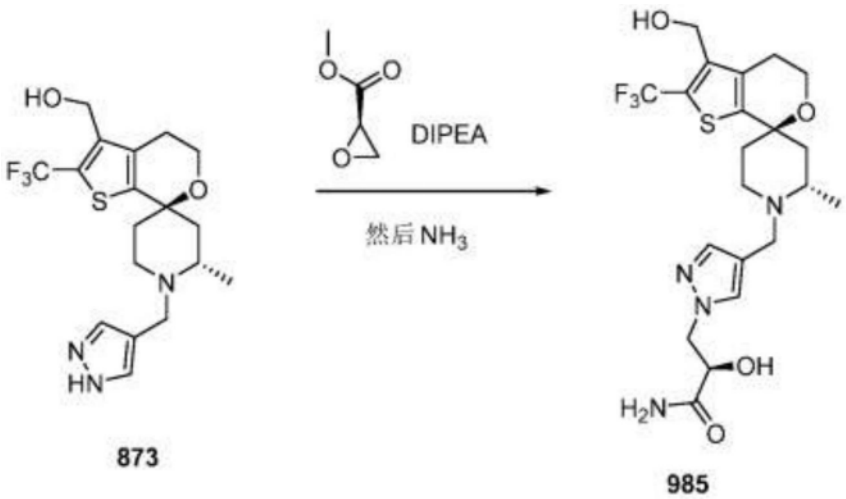
[1978]

化合物	结构	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
			2.57 (dd, J = 13.4, 6.9 Hz, 1H), 2.27 (s, 2H), 2.08 - 1.76 (m, 4H), 1.64 (d, J = 13.5 Hz, 1H), 1.45 (dd, J = 6.5, 3.8 Hz, 3H), 1.34 - 1.22 (m, 1H); LCMS *m/z* 570.29 $[M+H]^+$

[1979] 化合物985

[1980] (2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酰胺(985)

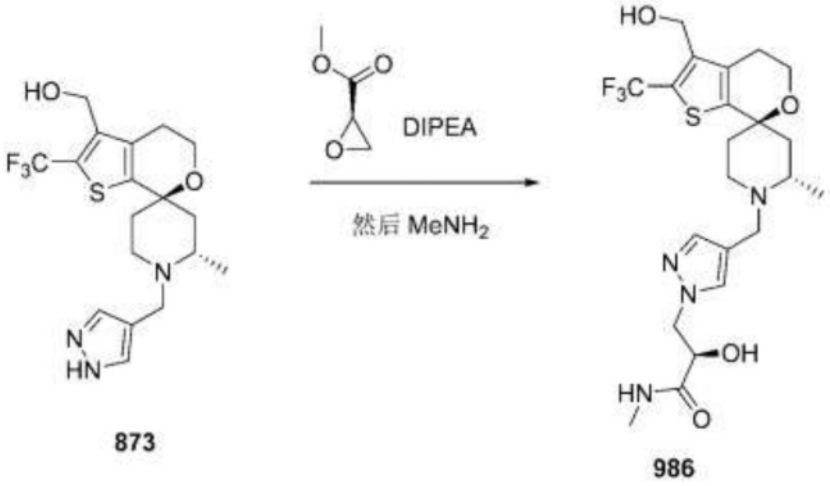
[1981]



[1982] 向2打兰小瓶中添加[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(102mg,0.24mmol)、(2R)-环氧乙烷-2-甲酸甲酯(34μL,0.39mmol)、EtOH(1.5mL)和DIPEA(220μL,1.26mmol)。将反应小瓶加热至90℃,持续60小时。添加另外的(2R)-环氧乙烷-2-甲酸甲酯(1当量,21uL),并将反应小瓶继续在90℃下加热24小时。然后将反应混合物浓缩并溶解在MeOH(0.3mL)中。将1/3溶液(0.1mL)转移到1打兰小瓶中,并用含氨的MeOH(1.2mL的4M,4.8mmol)处理。将反应混合物在RT下搅拌20小时。将反应混合物通过旋转蒸发器浓缩。通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。将产物分离为(2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙烯酰胺(甲酸盐)(3.6mg,7%)。1H NMR(300MHz,CD3CN)δ8.27(s,3H),7.89(s,1H),7.66(s,1H),4.60(s,2H),4.52(dd,J=12.7,6.8Hz,2H),4.46-4.31(m,2H),4.22(d,J=14.1Hz,1H),3.98(d,J=4.3Hz,2H),3.53(s,1H),2.77(t,J=5.5Hz,2H),2.34(t,J=16.6Hz,2H),1.98(d,J=11.8Hz,2H),1.51(d,J=6.4Hz,3H)。LCMS m/z 489.16$[M+1]^+$。

[1983] 化合物986

[1984] (2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N-甲基-丙酰胺(986)

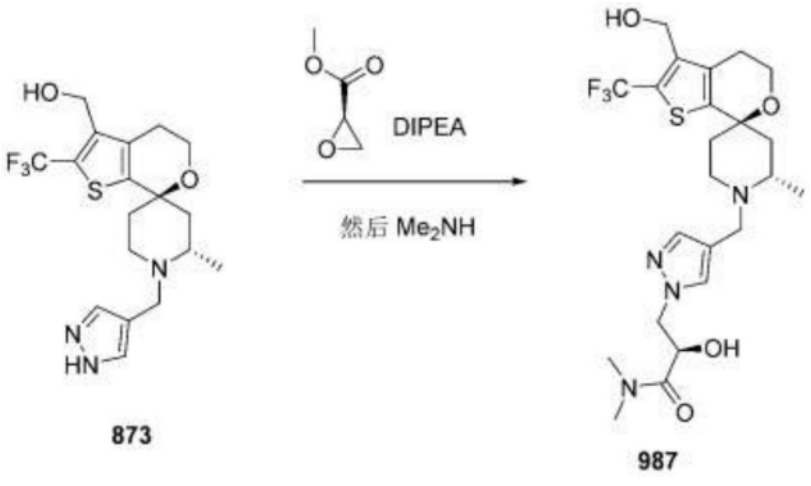
[1985] 

873 986

[1986] 在第二步中,使用含甲胺的EtOH(600μL的8M,4.8mmol)作为亲核试剂,按照与985类似的程序制备标题化合物。并且第二步花费4小时。通过反相HPLC纯化。方法:Waters XSelect CSH制备型苯基己基柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。通过硅胶色谱法进行后续纯化(梯度:含0-12% MeOH的DCM)产生并且然后SFC纯化最终提供期望产物(2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N-甲基-丙酰胺(1.9mg,5%)。1H NMR(300MHz,CDCl3)δ7.44(s,1H),7.36(s,1H),6.88(d,J=5.4Hz,1H),4.64(s,2H),4.59-4.27(m,3H),4.04-3.75(m,3H),3.53(d,J=14.2Hz,1H),2.79(d,J=4.9Hz,3H),2.69(q,J=9.3,7.2Hz,3H),2.57(s,1H),2.47(t,J=11.8Hz,1H),2.12-1.95(m,2H),1.85(td,J=13.1,4.3Hz,1H),1.76-1.66(m,1H),1.19(d,J=6.0Hz,3H)。LCMS m/z 503.33[M+1]$^+$。

[1987] 化合物987

[1988] (2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N,N-二甲基-丙酰胺(987)

[1989] 

873 987

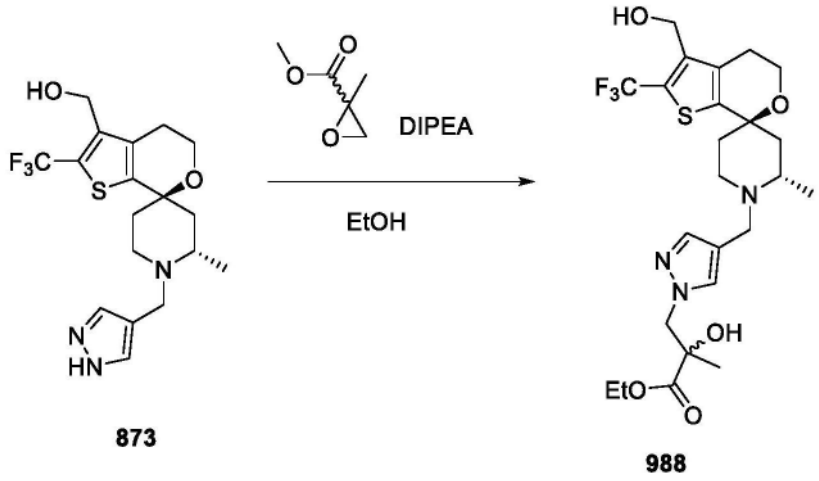
[1990] 在第二步中,使用含N-甲基甲胺的MeOH(2.4mL的2M,4.8mmol)作为亲核试剂,按照与985类似的程序制备标题化合物。并且将第二步在RT下进行24小时。通过硅胶色谱法纯化(梯度:含0-12% MeOH的DCM),产生产物和起始材料的混合物。通过反相HPLC进行后续纯化。方法:Waters XSelect CSH制备型苯基己基柱;30×150mm,5微米。梯度:含乙腈的水,具

有0.2%甲酸。将产物分离为(2R)-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N,N-二甲基-丙酰胺(甲酸盐)(7.7mg,14%)。1H NMR(300MHz,MeOD)δ7.85(s,1H),7.64(s,1H),4.85-4.81(m,1H),4.59(s,2H),4.52-4.27(m,3H),4.11(d,J＝14.2Hz,1H),4.04-3.91(m,2H),3.44-3.32(m,1H),3.26-3.01(m,5H),2.94(s,3H),2.75(t,J＝5.5Hz,2H),2.29(t,J＝13.0Hz,2H),2.12-1.82(m,2H),1.46(d,J＝6.4Hz,3H)。LCMS m/z 517.02[M+1]$^+$。

[1991] 化合物988

[1992] 2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酸乙酯(988)

[1993]



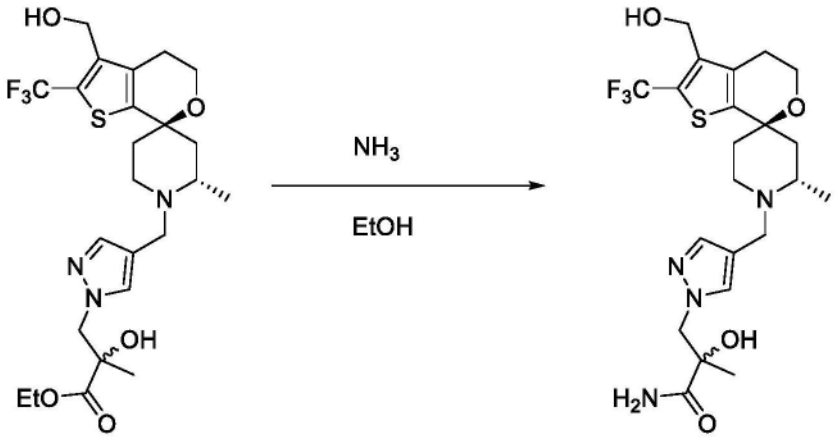
873 988

[1994] 向2打兰小瓶中添加[(2′S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(124mg,0.30mmol)、2-甲基环氧乙烷-2-甲酸甲酯(51μL,0.48mmol)、EtOH(1.5mL)和DIPEA(270μL,1.55mmol)。将反应小瓶在90℃下加热20小时。将反应物浓缩并通过硅胶色谱法纯化(梯度:含0-14% MeOH的二氯甲烷)以提供2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-螺-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-基-丙酸乙酯(100mg,59%)。1H NMR(300MHz,CDCl3)δ7.41(s,1H),7.35(s,1H),4.64(d,J＝4.7Hz,2H),4.47(d,J＝13.8Hz,1H),4.29(d,J＝8.4Hz,1H),4.24-4.11(m,3H),4.08-3.66(m,3H),3.51(d,J＝14.3Hz,1H),2.80-2.37(m,5H),1.99(d,J＝10.4Hz,2H),1.83(t,J＝12.0Hz,1H),1.65(t,J＝12.5Hz,1H),1.47(s,3H),1.32-1.22(m,3H),1.18(d,J＝6.1Hz,3H)。LCMS m/z 532.26[M+1]$^+$。

[1995] 化合物989

[1996] 2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酰胺(989)

[1997]



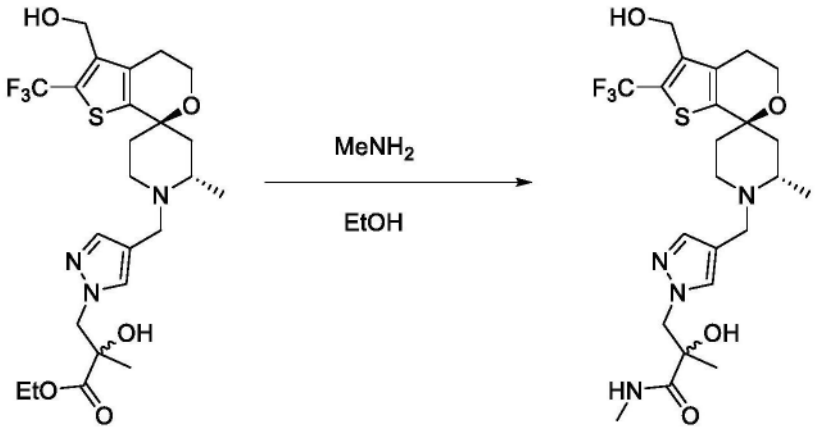
988 989

[1998] 向2打兰小瓶中添加2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酸乙酯(25mg,0.047mmol)、EtOH(0.1mL)和含氨的MeOH(750μL的4M,3.0mmol)。将反应混合物在RT下搅拌20小时并且然后加热至60℃,持续60小时。将反应物浓缩并通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。将产物分离为2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酰胺(甲酸盐)(12mg,29%)。1H NMR(300MHz,MeOD)δ7.82(d,J=2.2Hz,1H),7.61(s,1H),4.59(s,2H),4.50(d,J=14.1Hz,1H),4.39(d,J=14.0Hz,1H),4.26(d,J=14.0Hz,1H),4.14(d,J=14.1Hz,1H),3.96(q,J=5.2Hz,2H),3.43-3.33(m,1H),3.16(d,J=14.2Hz,2H),2.75(t,J=5.5Hz,2H),2.29(t,J=13.4Hz,2H),2.15-1.78(m,2H),1.46(d,J=6.4Hz,3H),1.38(s,3H)。LCMS m/z 503.29[M+1]$^+$。

[1999] 化合物990

[2000] 2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-N,2-二甲基-丙酰胺(990)

[2001]



988 990

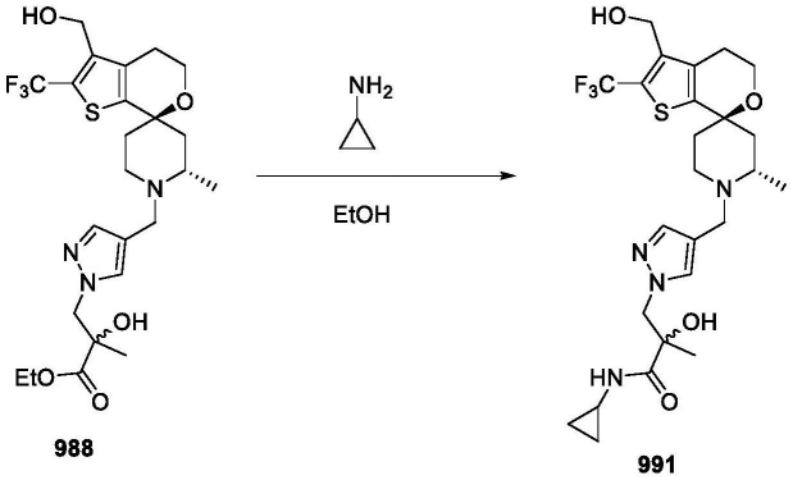
[2002] 在第二步中,使用含甲胺的EtOH(600μL的8M,4.8mmol)作为亲核试剂,按照与989类似的程序制备标题化合物。并且第二步花费36小时。将最终产物分离为2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-

哌啶]-1′-基]甲基]吡唑-1-基]-N,2-二甲基-丙酰胺(甲酸盐)(16.9mg,34%)。1H NMR(300MHz,MeOD)δ7.84(d,J=2.8Hz,1H),7.63(s,1H),4.59(s,2H),4.49(d,J=14.0Hz,2H),4.25(dd,J=13.9,4.7Hz,2H),3.98(t,J=5.0Hz,2H),3.48(s,1H),3.29-3.16(m,2H),2.76(t,J=5.5Hz,2H),2.66(s,3H),2.33(t,J=16.8Hz,2H),2.14-1.88(m,2H),1.52(d,J=6.4Hz,3H),1.37(s,3H)。LCMS m/z 517.33[M+1]$^+$。

[2003] 化合物991

[2004] N-环丙基-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酰胺(991)

[2005]

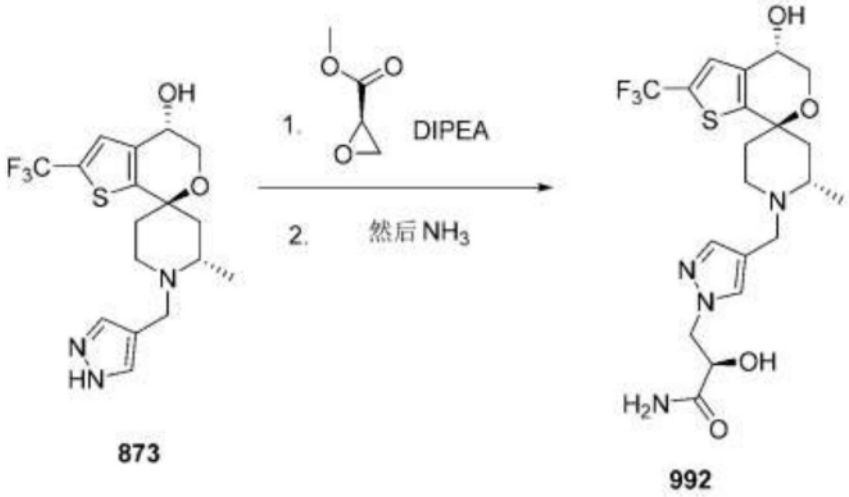


988 991

[2006] 在第二步中,使用环丙胺(210μL,3.03mmol)作为亲核试剂,按照与989类似的程序制备标题化合物。通过硅胶色谱法纯化(梯度:含0-20%MeOH的二氯甲烷)以提供N-环丙基-2-羟基-3-[4-[[(2′S,7R)-3-(羟甲基)-2′-螺-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]-2-甲基-丙酰胺(5.8mg,14%)。1H NMR(300MHz,CDCl3)δ7.45(s,1H),7.37(s,1H),6.87(s,1H),5.62(s,1H),4.64(s,2H),4.54(dd,J=13.7,8.5Hz,1H),4.11(dd,J=13.5,8.9Hz,1H),3.92(dq,J=15.4,9.8,7.6Hz,3H),3.49(s,4H),2.70(d,J=5.9Hz,3H),2.65-2.42(m,3H),2.01(d,J=12.5Hz,2H),1.95-1.67(m,2H),1.36(t,J=4.2Hz,3H),0.39(d,J=11.2Hz,1H),0.33-0.17(m,1H)。LCMS m/z 543.2[M+1]$^+$。

[2007] 化合物992

[2008] (2R)-2-羟基-3-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酰胺(992)

[2009] 

873 992

[2010] 步骤1:(2R)-2-羟基-3-[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]丙酸乙酯的合成

[2011] 向2打兰小瓶中添加(2′S,4S,7R)-2′-甲基-1′-(1H-吡唑-4-基甲基)-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(93mg,0.23mmol)、(2R)-环氧乙烷-2-甲酸甲酯(40μL,0.46mmol)、EtOH(1mL)和DIPEA(210μL,1.21mmol)。将反应物加热至90℃,持续29小时,并添加另外20uL环氧化物和100uL DIPEA。将反应小瓶加热另外20小时。将反应物浓缩并通过硅胶色谱法纯化(梯度:含0-14% MeOH的二氯甲烷)以提供(2R)-2-羟基-3-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酸乙酯(62.7mg,54%)。1H NMR(300MHz,CDCl3)δ7.41(s,1H),7.38(s,1H),7.34(d,J=1.4Hz,1H),4.65-4.33(m,4H),4.24(q,J=7.1Hz,2H),4.01-3.72(m,3H),3.54(d,J=14.3Hz,1H),3.47(s,1H),2.73-2.57(m,2H),2.43(td,J=12.3,2.6Hz,1H),2.13-2.01(m,1H),1.95(dt,J=13.7,3.0Hz,1H),1.86-1.65(m,2H),1.29(t,J=7.1Hz,3H),1.18(d,J=6.2Hz,3H)。LCMS m/z 504.13[M+1]$^+$。

[2012] 步骤2:(2R)-2-羟基-3-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙烯酰胺(992)的合成

[2013] 将来自步骤1的(2R)-2-羟基-3-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙酸乙酯(62.7mg)溶解在EtOH(0.4mL)中。然后将EtOH(100μL)(1/4)转移到2打兰小瓶中。添加含氨的MeOH(570μL的4M,2.280mmol)。将反应混合物在RT下搅拌。14小时后,将反应混合物浓缩并通过反相HPLC纯化。方法:Waters XSelect CSH制备型苯基己基柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。将产物分离为(2R)-2-羟基-3-[4-[[(2′S,4S,7R)-4-羟基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]丙烯酰胺(12mg,37%)。1H NMR(300MHz,MeOD)δ7.85(s,1H),7.63(s,1H),7.48(s,1H),4.63-4.44(m,2H),4.44-4.28(m,3H),4.13(d,J=14.1Hz,1H),3.98(dd,J=12.3,3.5Hz,1H),3.82(dd,J=12.3,3.9Hz,1H),3.41(s,1H),3.26-3.03(m,2H),2.35(t,J=14.2Hz,2H),2.06-1.83(m,2H),1.48(d,J=6.4Hz,3H)。LCMS m/z 475.2[M+1]$^+$。

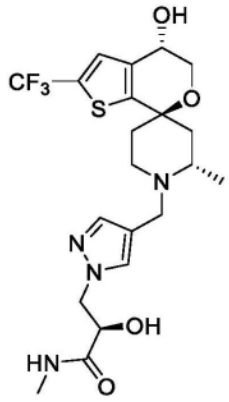
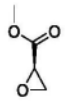
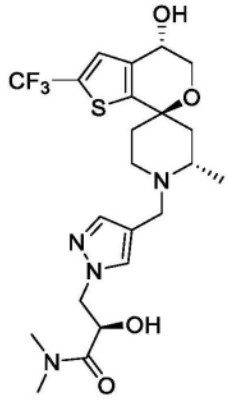
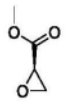
[2014] 化合物993-999

[2015] 化合物993-999(参见表45)由中间体873按照制备化合物992的程序制备。环氧化

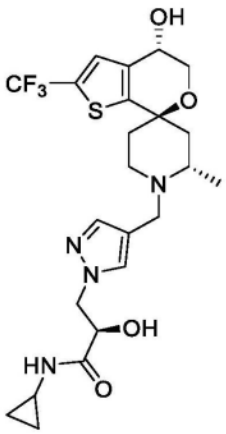
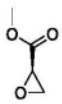
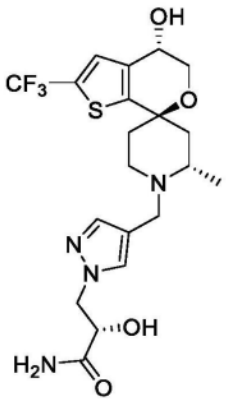
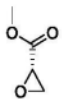
物和胺从商业来源获得。表45和随附脚注中注明了对方法的任何修改。

[2016] 表45:化合物993-999的结构和物理化学数据

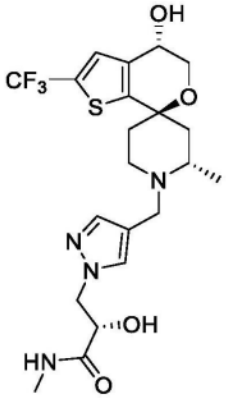
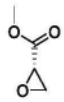
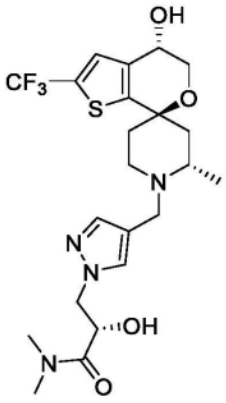
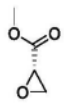
[2017]

化合物	结构	环氧化物试剂	胺试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
993			$MeNH_2$	*873*	1H NMR (300 MHz, MeOD) δ 7.83 (s, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 4.60 - 4.46 (m, 2H), 4.45 - 4.25 (m, 3H), 4.12 (d, J = 14.1 Hz, 1H), 3.98 (dd, J = 12.3, 3.5 Hz, 1H), 3.81 (dd, J = 12.3, 3.9 Hz, 1H), 3.40 (s, 1H), 3.28 - 3.00 (m, 2H), 2.73 (s, 3H), 2.35 (t, J = 14.7 Hz, 2H), 1.96 (t, J = 13.2 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H); LCMS *m/z* 489.25 $[M+H]^+$
994			Me_2NH	*873*[1]	1H NMR (300 MHz, MeOD) δ 7.65 (s, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 4.84 - 4.80 (m, 1H), 14.52 (s, 1H), 4.39 (dd, J = 14.0, 5.0 Hz, 1H), 4.27 (dd, J = 14.1, 7.1 Hz, 1H), 3.95 (dd, J = 12.4, 3.6 Hz, 2H), 3.76 (dd, J = 12.1, 4.0 Hz, 2H), 3.03 (s, 3H), 2.93 (s, 3H), 2.73 (d, J = 44.6 Hz, 3H), 2.17 (d, J = 14.2 Hz, 2H), 1.76 (d, J = 12.5 Hz, 2H), 1.29 (d, J = 6.1 Hz, 3H)； LCMS *m/z* 503.33 $[M+H]^+$

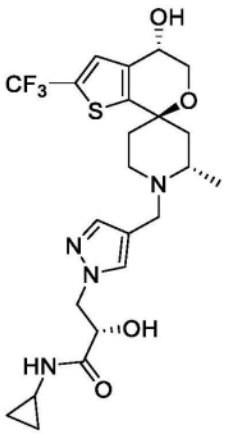
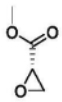
[2018]

化合物	结构	环氧化物试剂	胺试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
995				*873*[2]	1H NMR (300 MHz, MeOD) δ 7.87 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 4.57 (t, J = 3.7 Hz, 1H), 4.54 - 4.41 (m, 2H), 4.35 (d, J = 10.6 Hz, 2H), 4.21 (d, J = 14.0 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.3, 3.9 Hz, 1H), 3.54 (s, 1H), 3.38 - 3.31 (m, 1H), 3.22 (t, J = 12.3 Hz, 1H), 2.62 (dt, J = 7.3, 3.9 Hz, 1H), 2.40 (t, J = 15.7 Hz, 2H), 2.17 - 1.85 (m, 2H), 1.53 (d, J = 6.4 Hz, 3H), 0.72 (td, J = 7.0, 4.8 Hz, 2H), 0.49 (p, J = 4.4 Hz, 2H)；LCMS *m/z* 515.3 $[M+H]^+$
996			NH_3	*873*[3]	1H NMR (300 MHz, MeOD) δ 7.90 (s, 1H), 7.67 (s, 1H), 7.49 (s, 1H), 4.63 - 4.55 (m, 1H), 4.55 - 4.47 (m, 2H), 4.38 (d, J = 11.5 Hz, 2H), 4.24 (d, J = 14.1 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.3, 3.8 Hz, 1H), 3.56 (s, 1H), 3.35 (s, 1H), 3.29 - 3.15 (m, 1H), 2.40 (t, J = 14.9 Hz, 2H), 2.21 - 1.93 (m, 2H), 1.54 (d, J = 6.4 Hz, 3H)；LCMS *m/z* 475.29 $[M+H]^+$

[2019]

化合物	结构	环氧化物试剂	胺试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
997			$MeNH_2$	*873*[3]	1H NMR (300 MHz, MeOD) δ 7.88 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 4.64 - 4.44 (m, 3H), 4.44 - 4.29 (m, 2H), 4.24 (d, J = 14.1 Hz, 1H), 3.99 (dd, J = 12.3, 3.4 Hz, 1H), 3.83 (dd, J = 12.4, 3.8 Hz, 1H), 3.54 (s, 1H), 3.35 (s, 1H), 3.29 - 3.16 (m, 1H), 2.73 (s, 3H), 2.40 (t, J = 15.0 Hz, 2H), 2.18 - 1.89 (m, 2H), 1.54 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 488.12 $[M+H]^+$
998			Me_2NH	*873*[3,4]	1H NMR (300 MHz, MeOD) δ 7.86 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 4.86 - 4.80 (m, 1H),4.57 (t, J = 3.5 Hz, 1H), 4.45 (dd, J = 13.8, 5.5 Hz, 2H), 4.31 (dd, J = 14.1, 7.0 Hz, 1H), 4.15 (d, J = 14.0 Hz, 1H), 3.98 (dd, J = 12.4, 3.5 Hz, 1H), 3.82 (dd, J = 12.3, 3.9 Hz, 1H), 3.45 (s, 1H), 3.28 - 3.12 (m, 2H), 3.11 (s, 3H), 2.94 (s, 3H), 2.37 (t, J = 15.4 Hz, 2H), 1.98 (t, J = 13.2 Hz, 2H), 1.50 (d, J = 6.4 Hz, 3H)； LCMS *m/z* 503.33 $[M+H]^+$

[2020]

化合物	结构	环氧化物试剂	胺试剂	起始材料	^{1}H NMR；LCMS m/z $[M+H]^+$。
999				*873*[3,4]	1H NMR (300 MHz, MeOD) δ 7.78 (s, 1H), 7.59 (s, 1H), 7.48 (s, 1H), 4.84 - 4.79 (m, 1H),4.55 (d, J = 3.7 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.34 (d, J = 9.5 Hz, 3H), 4.10 - 3.92 (m, 2H), 3.81 (dd, J = 12.3, 3.8 Hz, 1H), 3.07 (d, J = 30.8 Hz, 2H), 2.63 (dd, J = 7.5, 3.7 Hz, 1H), 2.32 (t, J = 13.7 Hz, 2H), 1.90 (t, J = 13.0 Hz, 2H), 1.44 (d, J = 6.4 Hz, 3H), 0.71 (d, J = 6.2 Hz, 2H), 0.49 (d, J = 3.9 Hz, 2H)；LCMS *m/z* 515.38 $[M+H]^+$

[2021] 脚注：

[2022] 1)反应时间为30小时。通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有10mM氢氧化铵。

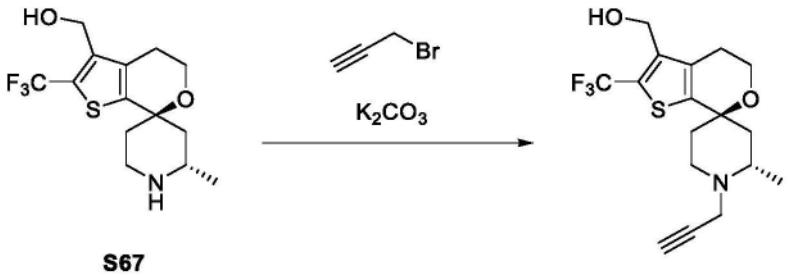
[2023] 2)将反应在60℃下进行26小时。

[2024] 3)通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.2%甲酸。

[2025] 4)将反应在60℃下进行4天。

[2026] 制备S76

[2027] [(2′S,7R)-2′-甲基-1′-丙-2-炔基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(S76)

[2028] 

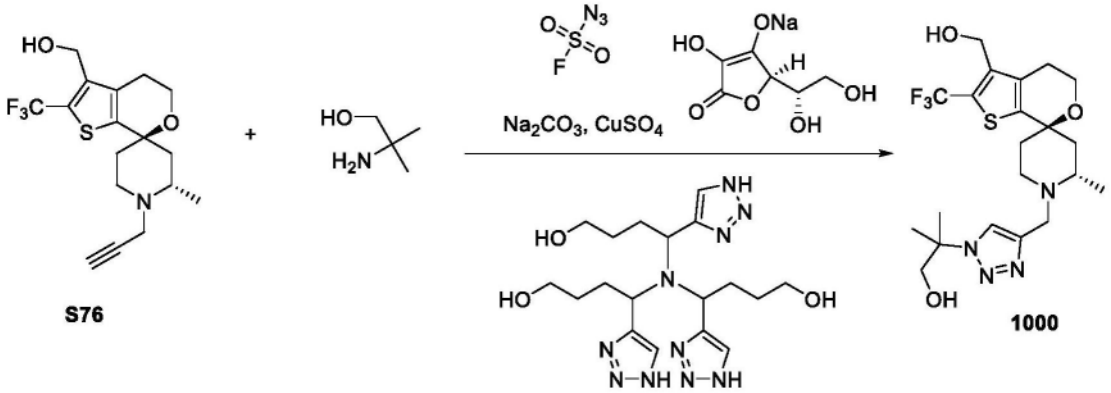
S67 S76

[2029] 将[(2′S)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S67(740mg,2.303mmol)和碳酸钾(330mg,2.388mmol)于THF(15mL)中的混合物加热至50℃。添加含炔丙基溴(285μL,3.198mmol)的甲苯,并将混合物在50℃下搅拌。24小时后,将反应物用$NaHCO_3$水溶液和DCM淬灭。将有机层通过相分离器分离。将溶剂在真空中去除。将经浓缩的油在最小DCM中重新稀释并上样到SiO_2柱上进行纯化(梯度:含0-20% MeOH

的DCM)以产生[(2′S,7R)-2′-甲基-1′-丙-2-炔基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇(600mg,72%)。^{1}H NMR(300MHz,氯仿-d)δ4.62-4.35(m,2H),3.80(hept,J=6.0Hz,2H),3.49(dd,J=17.4,2.4Hz,1H),3.24(dd,J=17.4,2.4Hz,1H),2.87-2.43(m,5H),2.17-1.65(m,4H),1.47(dd,J=13.7,11.4Hz,2H),0.92(d,J=6.3Hz,3H)。

[2030] 化合物1000

[2031] 2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-2-甲基-丙烷-1-醇(1000)

[2032] 

[2033] 标准方法H:制备叠氮化物的点击化学

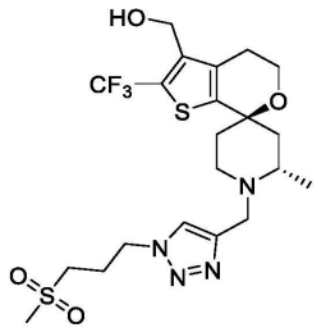
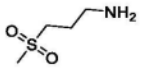
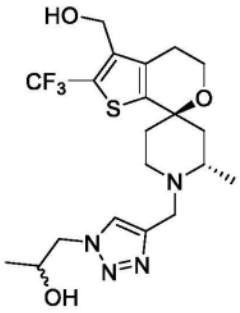
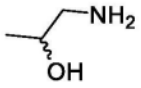
[2034] 向含有2-氨基-2-甲基-丙-1-醇(22.3mg,0.25mmol)的1打兰小瓶中添加Na_2CO_3水溶液(250μL,1M,0.25mmol)。将氟磺酰基叠氮化物溶液(550uL,含约0.45M的MTBE,约250umol,根据《自然》,574,2019,86-89.中的方案制备)添加到小瓶中。将所得溶液在室温下搅拌20分钟。将[(2′S,7R)-2′-甲基-1′-丙-2-炔基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-基]甲醇S76(30mg,0.835mmol)溶解在DMSO(1mL)中,并添加到反应小瓶中。将$CuSO_4$水溶液(85uL,0.1M,8.5umol)添加到反应小瓶中。添加4-[双[4-羟基-1-(1H-三唑-4-基)丁基]氨基]-4-(1H-三唑-4-基)丁-1-醇于DMSO(85uL,0.1M,8.5umol)中的溶液,随后添加(2R)-2-[(1S)-1,2-二羟乙基]-4-羟基-5-氧代-2H-呋喃-3-抗坏血酸醇钠水溶液(85uL,0.2M,17umol)。将所得反应混合物在露天下在50℃下加热过夜。添加另外的$CuSO_4$(100uL,0.1M)和抗坏血酸钠(100uL,0.2M),并继续加热过夜。将小瓶冷却至室温,用水(2mL)和DCM(1mL)稀释,并搅拌若干分钟。使混合物通过过滤板,并用DCM(1mL)洗涤,并将有机层蒸发。将所得残余物溶解在DMSO(1mL)中并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米),具有10mM氢氧化铵作为改性剂。将产物分离为2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-2-甲基-丙-1-醇(6.9mg,17%)。^{1}H NMR(400MHz,DMSO-d_6)δ7.98(s,1H),5.21(d,J=33.7Hz,2H),4.43(s,2H),3.92-3.79(m,3H),3.64-3.57(m,3H),2.67-2.60(m,3H),2.50-2.34(m,2H),1.96(d,J=13.2Hz,2H),1.71(dt,J=13.6,7.0Hz,1H),1.54(s,6H),1.49(t,J=12.6Hz,1H),1.15(d,J=6.2Hz,3H)。LCMS m/z 475.16[M+1]$^+$。

[2035] 化合物1001-1005

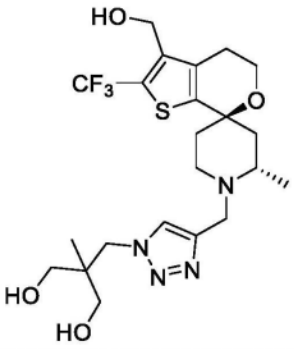
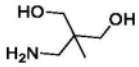
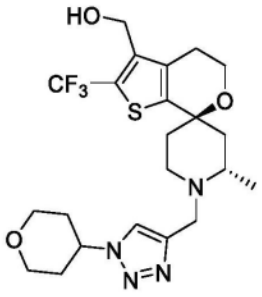
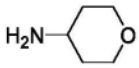
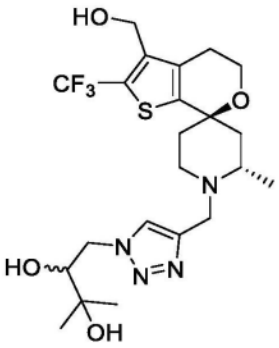
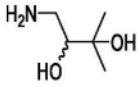
[2036] 化合物1001-1005(参见46)由中间体S76使用标准方法H单个步骤中制备。胺从商业来源获得。表46和随附脚注中注明了对方法的任何修改。

[2037] 表46:化合物1001-1005的结构和物理化学数据

[2038]

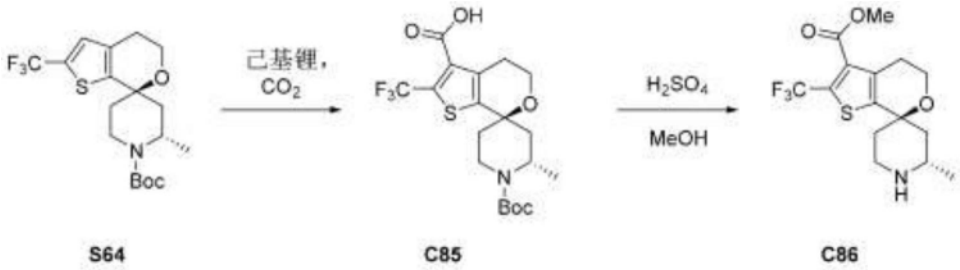
化合物	产物	胺试剂	^{1}H NMR；LCMS m/z [M+H]$^+$。
1001			^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 5.24 (s, 1H), 4.48 (t, J = 7.0 Hz, 2H), 4.43 (d, J = 3.7 Hz, 2H), 3.91 – 3.69 (m, 4H), 3.15 – 3.07 (m, 2H), 3.00 (d, J = 1.6 Hz, 3H), 2.63 (t, J = 5.7 Hz, 3H), 2.50 – 2.39 (m, 2H), 2.26 (p, J = 6.9 Hz, 2H), 1.96 (d, J = 13.1 Hz, 2H), 1.72 (dt, J = 13.3, 6.8 Hz, 1H), 1.49 (dd, J = 24.3, 12.0 Hz, 1H), 1.14 (d, J = 6.1 Hz, 3H)；LCMS m/z 523.16 [M+H]$^+$
1002			^{1}H NMR (300 MHz，甲醇-d_4) δ 7.94 (s, 1H), 4.67 - 3.62 (m, 9H), 2.91 - 2.36 (m, 5H), 2.23 - 1.52 (m, 4H), 1.42 - 0.87 (m, 6H)；LCMS m/z 461.12 [M+H]$^+$

[2039]

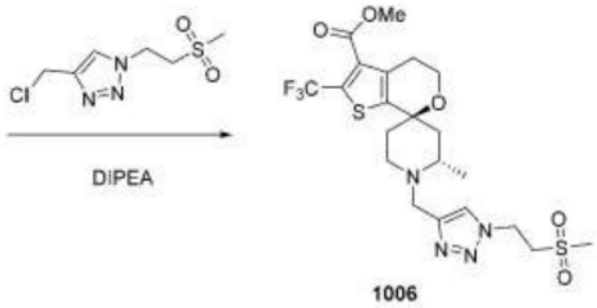
化合物	产物	胺试剂	^{1}H NMR；LCMS m/z [M+H]$^+$。
1003			^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 5.24 (s, 1H), 4.75 (s, 2H), 4.43 (s, 2H), 4.26 (s, 2H), 3.91 – 3.68 (m, 4H), 3.28 – 3.15 (m, 4H), 2.63 (t, J = 5.6 Hz, 2H), 2.60 – 2.33 (m, 3H), 1.95 (t, J = 10.1 Hz, 2H), 1.70 (td, J = 13.0, 4.4 Hz, 1H), 1.47 (dd, J = 13.7, 11.2 Hz, 1H), 1.14 (d, J = 6.1 Hz, 3H), 0.66 (s, 3H)；LCMS m/z 505.19 [M+H]$^+$
1004			^{1}H NMR (300 MHz, 甲醇-d_4) δ 8.03 (s, 1H), 4.77 (ddd, J = 15.8, 9.1, 7.0 Hz, 1H), 4.57 (d, J = 1.4 Hz, 2H), 4.16 - 3.76 (m, 6H), 3.76 - 3.48 (m, 2H), 2.88 - 2.52 (m, 5H), 2.27 - 1.77 (m, 7H), 1.64 (dd, J = 13.9, 11.4 Hz, 1H), 1.26 (d, J = 6.2 Hz, 3H)；LCMS m/z 487.17 [M+H]$^+$
1005			^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 3.3 Hz, 1H), 5.22 (s, 1H), 5.11 (d, J = 6.4 Hz, 1H), 4.70 - 4.51 (m, 2H), 4.42 (s, 2H), 4.21 - 4.03 (m, 1H), 3.84 (dt, J = 11.0, 6.4 Hz, 3H), 3.68 (dd, J = 14.5, 3.7 Hz, 1H), 3.53 (d, J = 7.3 Hz, 1H), 2.62 (t, J = 5.7 Hz, 3H), 2.44 (d, J = 11.9 Hz, 2H), 1.95 (d, J = 13.2 Hz, 2H), 1.79 - 1.62 (m, 1H), 1.47 (t, J = 12.4 Hz, 1H), 1.20 - 1.01 (m, 9H)；LCMS m/z 505.19 [M+H]$^+$

[2040] 化合物1006

[2041] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯(1006)



[2042]



[2043] 步骤1:(2′S)-1′-叔丁氧基羰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸(C85)的合成

[2044] 将(2′S)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(530mg,1.151mmol)S64溶解在THF(10mL)中并冷却至-78℃,并添加己基锂(800μL的2.3M,1.840mmol)。将反应混合物在-78℃下搅拌3分钟,并将CO_2鼓泡通过。10分钟后,将反应物温热至rt。将反应混合物用EtOAc和1N NaOH稀释,并将水层用6N HCl酸化并用EtOAc萃取。将合并的有机层在真空中浓缩,并通过硅胶色谱法纯化(梯度:含0至50%EtOAc的庚烷,具有1% AcOH)以产生呈黄色油的产物。通过C18反相HPLC进一步纯化(CH_3CN/H_2O,TFA改性剂),提供纯级分,将其用0.5N HCl/EtOAc稀释并将有机层干燥并浓缩以产生呈白色固体的产物。(2′S)-1′-叔丁氧基羰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸(226mg,45%)。^{19}F NMR(282MHz,DMSO-d_6)δ-52.52(d,J=1.3Hz),LCMS m/z 436.43$[M+1]^+$。

[2045] 步骤2:(2′S)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯(C86)的合成

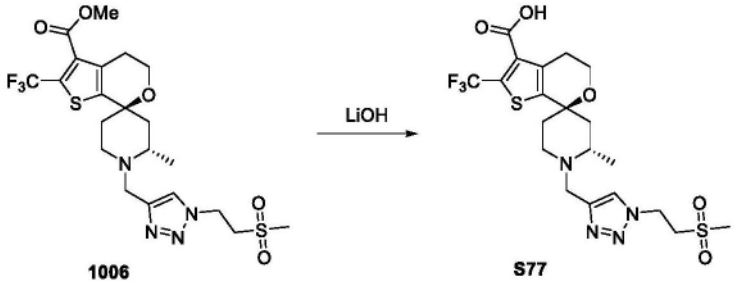
[2046] 将(2′S)-1′-叔丁氧基羰基-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸C85(224mg,0.5144mmol)溶解在MeOH(8mL)中并添加H_2SO_4(200μL,3.752mmol)。将反应混合物加热至60℃,持续24小时,并在室温下搅拌48小时。将反应混合物用EtOAc/1N NaOH稀释并将有机层干燥并在真空中浓缩以提供(2′S)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯(162mg,90%)。^1H NMR(300MHz,氯仿-d)δ3.95(td,J=5.7,3.6Hz,2H),3.91(s,3H),3.18-3.04(m,2H),2.95(dd,J=12.4,4.0Hz,1H),2.88(t,J=5.6Hz,2H),2.06(d,J=13.5Hz,2H),1.72(td,J=13.2,4.7Hz,1H),1.40(dd,J=13.4,11.3Hz,1H),1.09(d,J=6.4Hz,3H)。LCMS m/z 349.65$[M+1]^+$。

[2047] 步骤3:(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯(1006)的合成

[2048] 将(2′S)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯C86(160mg,0.4580mmol)溶解在具有DIPEA(160μL,0.9186mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(120mg,0.5365mmol)的1,2-二氯乙烷(2mL)中。将管密封,并且将反应混合物加热至在60℃,持续72小时。将反应混合物通过反相HPLC纯化(柱:C18,TFA改性剂)。将纯级分合并,并用1N NaOH和EtOAc稀释,并将有机层干燥并浓缩以产生呈白色固体的产物。(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯(155mg,59%)。^{1}H NMR(300MHz,氯仿-d)δ7.65(s,1H),4.93-4.81(m,2H),4.13-3.99(m,1H),3.98-3.80(m,6H),3.75(t,J=6.3Hz,2H),2.85(t,J=5.5Hz,2H),2.82-2.55(m,6H),2.12-1.97(m,2H),1.97-1.79(m,1H),1.75-1.67(m,1H),1.26(d,J=6.2Hz,3H)。LCMS m/z 537.54[M+1]$^+$。

[2049] 制备S77

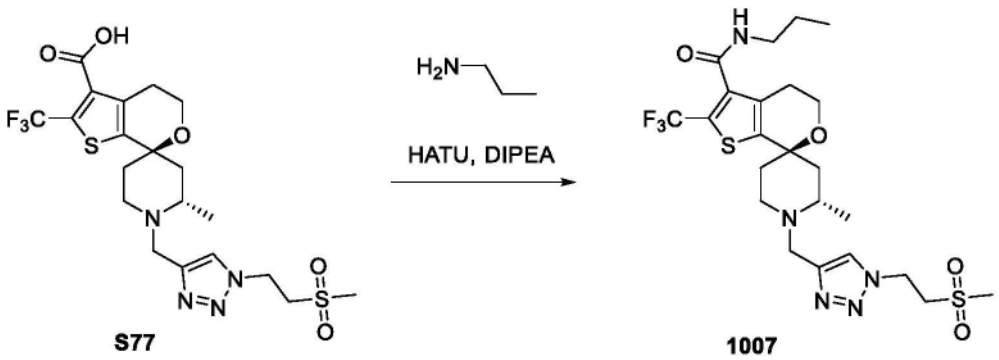
[2050] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸(S77)

[2051] 

[2052] 将(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸甲酯1006(122mg,0.2137mmol)溶解在THF(2mL)和MeOH(2mL)中,并添加LiOH(220μL的1M,0.2200mmol)。将反应混合物搅拌24小时。添加更多LiOH(80μL的1M,0.08000mmol)并将反应混合物搅拌过夜。添加另外的LiOH(100μL的1M,0.1000mmol)并将反应混合物搅拌6小时。然后将反应混合物在真空中浓缩,以提供粗反应物。(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸(锂离子(1))(112mg,98%)。LCMS m/z 523.18[M+1]$^+$。

[2053] 化合物1007

[2054] 2-[4-[[(2′S,7R)-3-(羟甲基)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]三唑-1-基]-2-甲基-丙-1-醇(1007)

[2055] 

[2056] 标准方法I:与HATU酰胺偶联

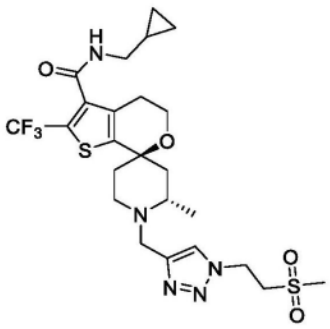
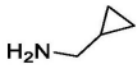
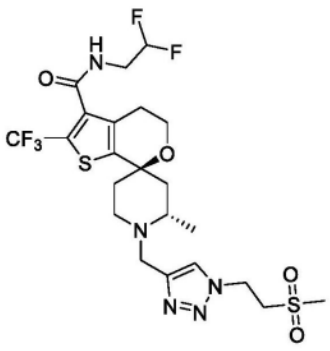
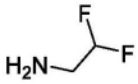
[2057] 将(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酸(锂离子(1))S77(18mg,0.034mmol)和丙-1-胺(13.9μL,0.169mmol)溶解在DMF(1mL)中,并添加HATU(15mg,0.0.039mmol),随后添加DIPEA(5.8μL,0.034mmol)。将反应混合物在rt下搅拌过夜。将反应混合物过滤。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将最终产物分离为(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-N-丙基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-3-甲酰胺(三氟乙酸盐)(8.8mg,47%)。LCMS m/z 564.31$[M+1]^+$。

[2058] 化合物1008-1009

[2059] 化合物1008-1009(参见表47)由中间体S77使用标准方法I(如在化合物1007的制备中所述的方法)在单个步骤中制备。胺从商业来源获得。表47和随附脚注中注明了对方法的任何修改。

[2060] 表47:化合物1008-1009的结构和物理化学数据

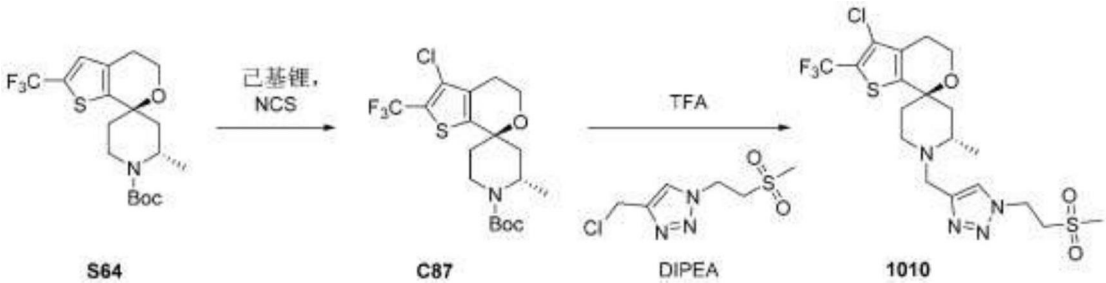
[2061]

化合物	结构	胺试剂	^{1}H NMR; LCMS m/z $[M+H]^+$。
1008			LCMS *m/z* 576.37 $[M+H]^+$
1009			LCMS *m/z* 586.3 $[M+H]^+$

[2062] 化合物1010

[2063] (2′S,7R)-3-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(1010)

[2064]



[2065] 步骤1:(2′S,7R)-3-氯-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C87)的合成

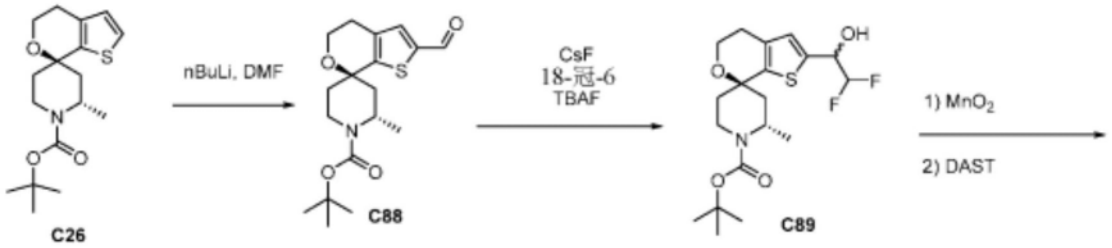
[2066] 将(2′S,7R)-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S64(150mg,0.3832mmol)溶解在THF(5mL)中并冷却至-78℃,并添加己基锂(250μL的2M,0.5000mmol)。将反应混合物搅拌5分钟并添加溶解在1mL THF中的NCS(80mg,0.5991mmol)。将反应混合物温热至室温。将反应混合物用1N NaOH/EtOAc稀释并将有机层干燥并浓缩。将粗材料通过反相HPLC纯化(柱:C18)。将纯级分用1N NaOH和EtOAc稀释,并将有机层干燥并浓缩以产生呈油的产物(2′S,7R)-3-氯-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(17mg,10%)。^{1}H NMR(300MHz,氯仿-d)δ3.96-3.84(m,1H),3.84-3.76(m,2H),3.69-3.55(m,1H),3.28-3.14(m,1H),2.46(t,J=5.5Hz,2H),2.13-1.91(m,2H),1.74-1.50(m,2H),1.36(s,9H),1.14(d,J=6.7Hz,3H)。

[2067] 步骤2:(2′S,7R)-3-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(1010)的合成

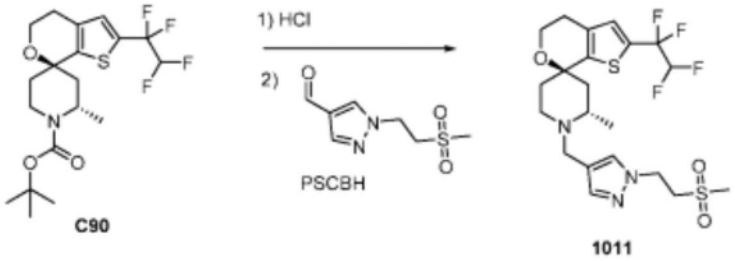
[2068] 将(2′S,7R)-3-氯-2′-甲基-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C87(17mg,0.03992mmol)溶解在DCM(1mL)中,并添加TFA(0.5mL,6.490mmol)。20分钟后,将反应混合物浓缩并重新溶解在DCE(1mL)中。向该溶液中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(13mg,0.05812mmol),随后添加DIPEA(30μL,0.1722mmol)。将反应混合物在60℃下加热过夜。添加另外的4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(8mg,0.03577mmol)并将反应混合物加热至60℃过夜。将反应混合物用硅胶色谱法纯化(梯度:含0至10% MeOH的DCM)。通过反相HPLC进一步纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。分离出呈白色固体的产物:(2′S,7R)-3-氯-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]-2-(三氟甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(9mg,35%)。^{1}H NMR(300MHz,氯仿-d)δ8.25(s,1H),4.97(q,J=6.5Hz,2H),4.74(d,J=14.0Hz,1H),4.26(d,J=13.9Hz,1H),4.06-3.79(m,2H),3.79-3.63(m,2H),3.63-3.45(m,1H),3.42-3.14(m,2H),2.95(s,3H),2.68-2.59(m,2H),2.49-2.26(m,2H),2.23-2.07(m,2H),1.64(d,J=6.4Hz,3H)。LCMS m/z 513.14$[M+1]^{+}$。

[2069] 化合物1011

[2070] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1011)



[2071]



[2072] 步骤1:(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C88)的合成

[2073] 在-78℃下在氮气气氛下在20分钟的过程内添加(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C26(81.4g,252mmol)于THF(740mL)中的溶液中添加丁基锂(120mL的2.6M,310mmol)。搅拌70分钟后,在5分钟的过程内添加DMF(100mL,1.3mol)。将混合物在-78℃下搅拌30分钟并在0℃下搅拌另外45分钟。通过添加饱和氯化铵水溶液(600mL)淬灭反应物。向混合物中添加EtOAc(1L)和水(500mL),并将有机层分离并用饱和氯化铵水溶液(600mL)、水(600mL)和盐水(600mL)洗涤。将有机层经硫酸镁干燥,过滤并在真空中浓缩以产生呈琥珀色油的产物(88g,99%)。^{1}H NMR(300MHz,氯仿-d)δ9.83(s,1H),7.42(s,1H),4.01(ddd,J=11.5,6.7,5.3Hz,1H),3.94-3.82(m,2H),3.75(ddd,J=14.0,6.1,4.7Hz,1H),3.35(ddd,J=14.1,8.8,5.4Hz,1H),2.71(td,J=5.5,2.8Hz,2H),2.28-2.06(m,2H),1.90-1.65(m,2H),1.47(s,9H),1.26(d,J=6.6Hz,3H)。LCMS m/z 252.08[M-Boc]$^+$。

[2074] 步骤2:(2′S,7R)-2-(2,2-二氟-1-羟基-乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C89)的合成

[2075] 在氮气气氛下,将氟化铯(295mg,1.94mmol)和1,4,7,10,13,16-六氧杂环十八烷(515mg,1.95mmol)添加到(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C88(680mg,1.9mmol)于1,2-二甲氧基乙烷(27mL)中的溶液中,随后添加二氟甲基(三甲基)硅烷(972mg,7.83mmol)。将所得混合物在室温下搅拌3小时。接下来,添加四丁基氟化铵(2mL的1M,2mmol),并将混合物搅拌另外30分钟。将混合物在水与二氯甲烷之间分配,收集有机层并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-60%EtOAc的庚烷),产生产物(471mg,60%)。^{1}H NMR(300MHz,氯仿-d)δ6.79(d,J=2.7Hz,1H),5.81(td,J=55.9,4.5Hz,1H),5.01(td,J=10.4,4.4Hz,1H),4.06-3.68(m,3H),3.39-3.08(m,1H),2.73-2.54(m,2H),2.26-2.03(m,2H),1.91-1.67(m,2H),1.49(d,J=1.3Hz,9H),1.32-1.23(m,4H)。LCMS m/z 403.7[M+H]$^+$。

[2076] 步骤3:(2′S,7R)-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C90)的合成

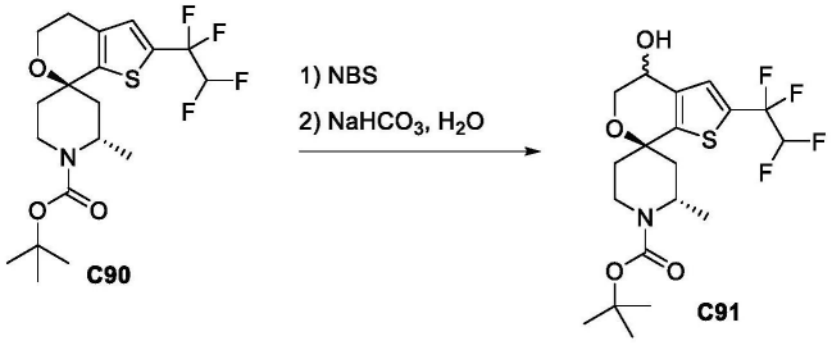
[2077] 向(2′S,7R)-2-(2,2-二氟-1-羟基-乙基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C89(471mg,1.17mmol)于DCM(5mL)中的溶液中添加MnO_2(985mg,11.3mmol)。将混合物搅拌过夜,并通过Celite®垫过滤,并将滤液在真空中浓缩。将残余物溶解在DCM(2mL)中并添加二乙氨基三氟化硫(770μL,5.8mmol)。将混合物在40℃下搅拌3小时。添加水,并将有机层分离并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),得到产物(221mg,45%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.13(t,J=1.4Hz,1H),6.30(tt,J=53.4,3.1Hz,1H),4.07(dt,J=11.2,6.2Hz,1H),3.90(t,J=5.5Hz,2H),3.84-3.62(m,1H),2.68(t,J=5.5Hz,2H),2.38-2.09(m,2H),1.95-1.64(m,2H),1.48(s,9H),1.22(d,J=6.5Hz,3H)。注:其中一个质子共振被与残留NMR溶剂相对应的信号所掩盖。LCMS m/z424.32[M+H]$^+$。

[2078] 步骤4:(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1011)的合成

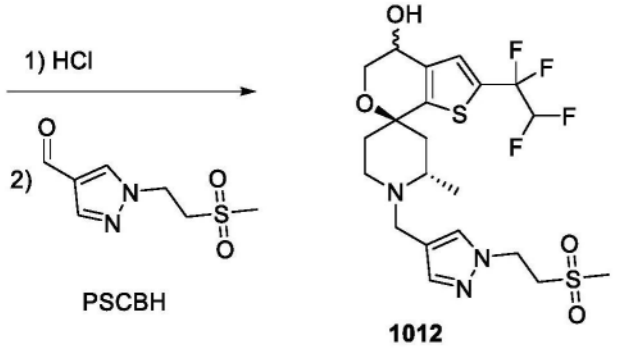
[2079] 向(2′S)-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C90(36mg,0.085mmol)于1,4-二噁烷(200μL)中的溶液中添加HCl(含430μL的4M的1,4-二噁烷,1.7mmol)。将混合物在室温下搅拌30分钟并在真空中浓缩。将残余物溶解在DCM(2mL)中,并添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(25mg,0.12mmol),随后添加乙酸(24mg,0.40mmol)和聚合物负载的氰基硼氰化物(127mg,0.254mmol)。将混合物在微波反应器中在95℃下加热45分钟并过滤。将滤液在真空中浓缩并通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生产物。(11mg,23%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.77(s,1H),7.57(s,1H),7.14(d,J=1.4Hz,1H),6.30(tt,J=53.4,3.0Hz,1H),4.64(t,J=6.4Hz,2H),4.06-3.57(m,6H),2.92-2.58(m,7H),2.21-2.02(m,2H),2.01-1.82(m,2H),1.72(dd,J=14.0,11.6Hz,1H),1.28(d,J=6.3Hz,3H)。LCMS m/z 510.12[M+H]$^+$。

[2080] 化合物1012

[2081] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1012)



[2082]



[2083] 步骤1:(2′S)-4-羟基-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C91)的合成

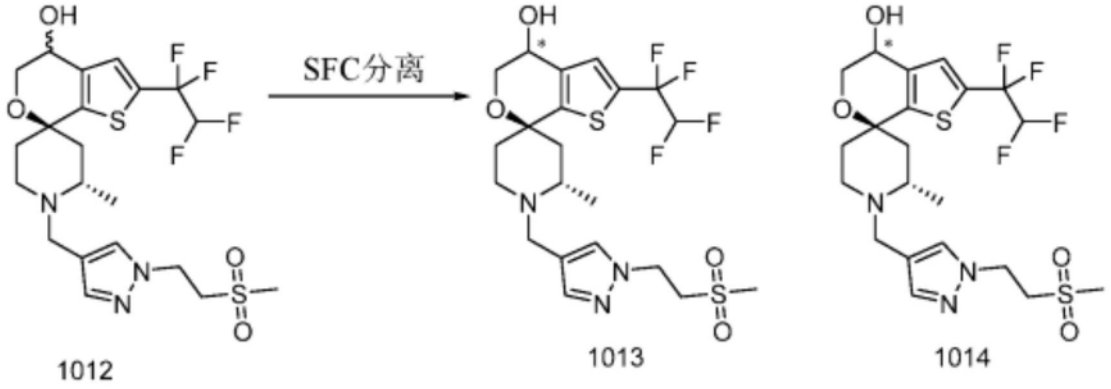
[2084] 在氩气气氛向(2′S)-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C90(230mg,0.54mmol)于氯苯(6mL)中的溶液中添加N-溴代琥珀酰亚胺(193mg,1.08mmol)和2,6-二甲基吡啶(140μL,1.2mmol)。将溶液用蓝色LED辐照30分钟。将反应物用硫酸氢钠淬灭,并将水层用DCM萃取。将有机层用盐水洗涤并在真空中浓缩。将残余物溶解在THF(6mL)中,并且添加含碳酸氢钠(680mg,8.1mmol)的水(6mL)。将混合物在60℃下加热3天。然后将混合物用水稀释并用DCM萃取。通过硅胶色谱法纯化(梯度:含0-23%乙酸乙酯的庚烷),产生呈白色固体的产物(53mg,22%)。LCMS m/z 440.3[M+H]$^+$。

[2085] 步骤2:(2′S)-4-羟基-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(1012)的合成

[2086] 向(2′S)-4-羟基-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C91(53mg,0.12mmol)于1,4-二噁烷(0.7mL)中的溶液中添加含HCl(2mL的4M,8mmol)的1,4-二噁烷。将反应物搅拌30分钟并在真空中浓缩。将残余物溶解在DCM(2mL)中并添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(33mg,0.16mmol),随后添加聚合物负载的氰基硼氰化物(170mg的2mmol/g,0.34mmol)。将混合物在微波反应器中加热至95℃,持续45分钟。将溶液过滤,并将滤液在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生产物(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(14mg,21%)。^{1}H NMR(300Mhz,甲醇-d_4)δ7.73(s,1H),7.54(s,1H),7.33(d,J=1.5Hz,1H),6.32(tt,J=53.7,3.0Hz,1H),4.66-4.47(m,3H),4.00-3.55(m,6H),3.37-3.31(m,2H),2.85-2.46(m,5H),2.20-1.52(m,4H),1.24(dd,J=6.1,4.5Hz,3H)。LCMS m/z 526.1[M+H]$^+$。

[2087] 化合物1013

[2088] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1013)

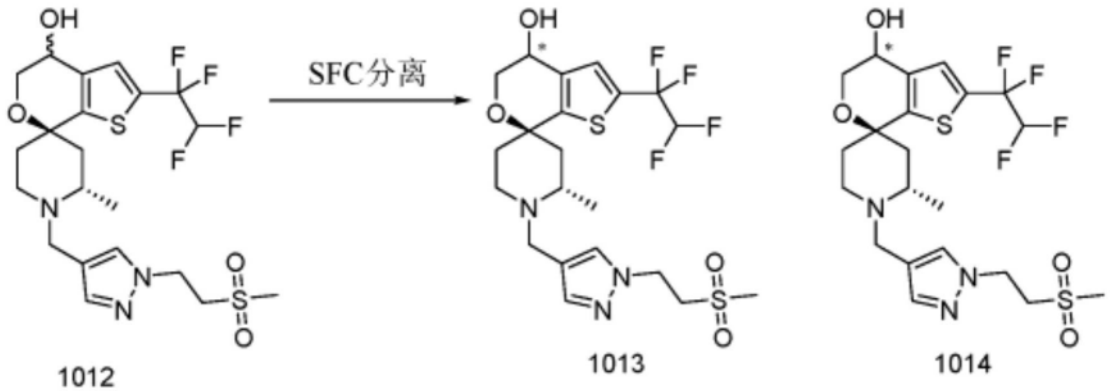
[2089] 

1012 1013 1014

[2090] 将(2′S)-4-羟基-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯1012(10mg,0.02mmol)的异构混合物通过手性SFC分离(2.7mg,27%)分离。柱:Daicel Chiralpak®IB,10×250mm;流动相:20%甲醇(含有5mM氨),80%二氧化碳。流速:15毫升/分钟。^{1}H NMR(300MHz,甲醇-d_4)δ7.73(d,J=0.8Hz,1H),7.54(d,J=0.7Hz,1H),7.33(t,J=1.4Hz,1H),6.32(tt,J=53.4,3.0Hz,1H),4.63(dd,J=6.8,5.9Hz,2H),4.53(t,J=4.1Hz,1H),4.01-3.58(m,6H),2.83-2.46(m,6H),2.22-1.99(m,2H),1.98-1.80(m,2H),1.59(dd,J=14.0,11.5Hz,1H),1.23(d,J=6.3Hz,3H)。

[2091] 化合物1014

[2092] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1014)

[2093] 

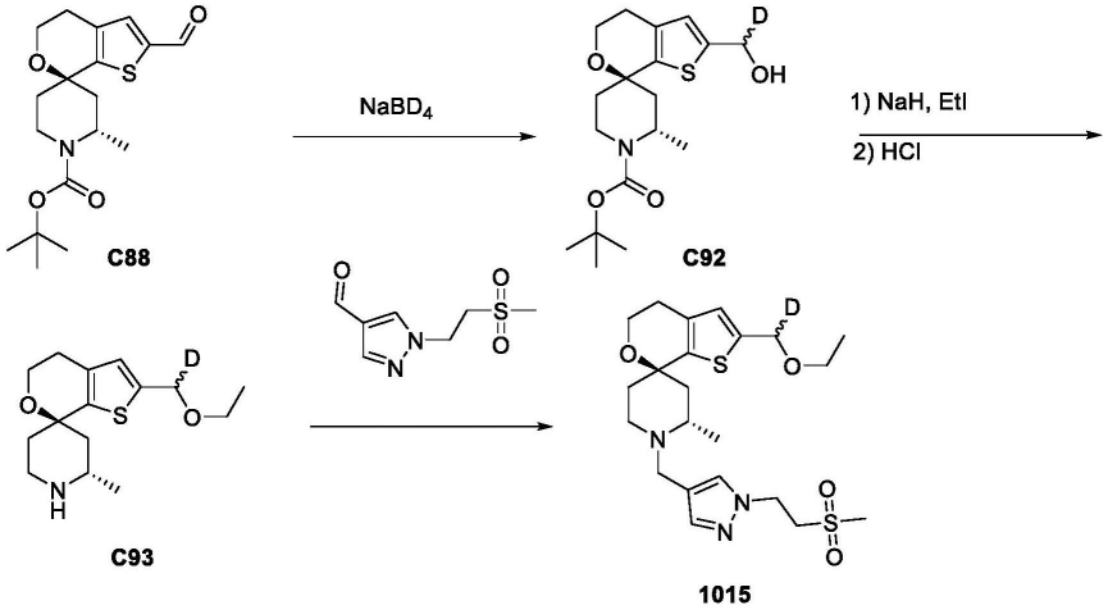
1012 1013 1014

[2094] 将(2′S)-4-羟基-2′-甲基-2-(1,1,2,2-四氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯JMA2(10mg,0.02mmol)的异构混合物通过手性SFC分离(2mg,20%)分离。柱:Daicel Chiralpak®IB,10×250mm;流动相:20%甲醇(含有5mM氨),80%二氧化碳。流速:15毫升/分钟。^{1}H NMR(300MHz,甲醇-d_4)δ7.72(s,1H),7.53(d,J=0.7Hz,1H),7.33(d,J=1.4Hz,1H),6.32(tt,J=53.4,3.0Hz,1H),4.63(t,J=6.4Hz,2H),4.51(t,J=3.7Hz,1H),4.00-3.59(m,6H),2.80-2.48(m,5H),2.19-1.60(m,4H),1.25(d,J=6.2Hz,3H)。

[2095] 化合物1015

[2096] (2′S,7R)-2-[氘(乙氧基)甲基]-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-

基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1015)



[2097]

[2098] 步骤1:(2′S,7R)-2-[氘(羟基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C92)的合成

[2099] 向(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C88(600mg,1.7mmol)于乙醇(16mL)中的溶液中添加硼氘化钠(65mg,1.7mmol)。将混合物在室温下搅拌过夜。将混合物用水和DCM稀释,并将水层用DCM萃取。将有机层经硫酸钠干燥,过滤并在真空中浓缩以得到产物(605mg,100%)。LCMS m/z 354.45 $[M+H]^+$。

[2100] 步骤2:(2′S,7R)-2-[氘(乙氧基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C93)的合成

[2101] 向(2′S,7R)-2-[氘(羟基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C92(60mg,0.17mmol)于THF(1.6mL)中的溶液中添加碘乙烷(41μL,0.51mmol)和NaH(12mg,0.50mmol)。将混合物在室温下搅拌5天。然后,添加饱和氯化铵水溶液,并将混合物用DCM萃取。将有机层经硫酸钠干燥,过滤并在真空中浓缩。将残余物溶解1,4-二噁烷(667μL)中并添加含HCl(655μL的4M,2.62mmol)的1,4-二噁烷。搅拌30分钟后,将混合物在真空中浓缩。然后将残余物通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有0.1%三氟乙酸)以得到产物(8.3mg,25%)。^1H NMR(300MHz,甲醇-d_4)δ6.74(d,J=0.8Hz,1H),4.57(s,1H),3.95(td,J=5.5,2.0Hz,2H),3.68-3.45(m,3H),3.37(dd,J=12.7,9.8Hz,1H),2.70-2.62(m,3H),2.25(ddt,J=14.9,12.1,2.8Hz,2H),1.99(ddd,J=15.1,12.7,5.6Hz,1H),1.81(dd,J=14.9,12.3Hz,1H),1.32(dd,J=6.6,2.0Hz,3H),1.18(td,J=7.1,1.9Hz,3H)。LCMS m/z 283.26$[M+H]^+$。

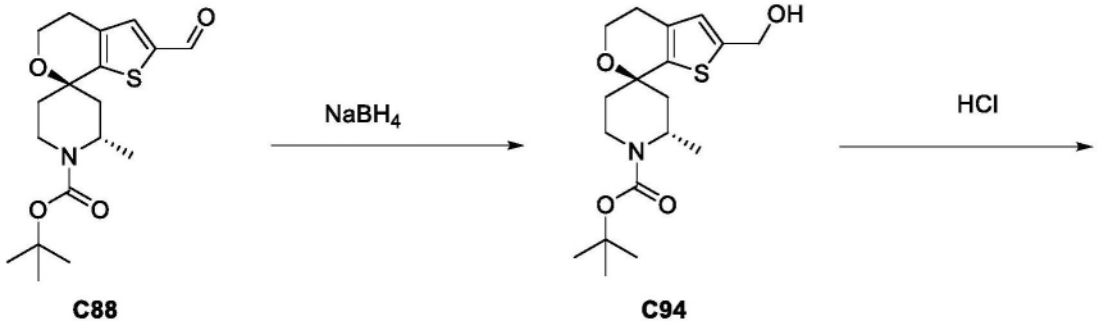
[2102] 步骤3:(2′S,7R)-2-[氘(乙氧基)甲基]-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1015)的合成

[2103] 向(2′S,7R)-2-[氘(乙氧基)甲基]-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]C93(85mg,0.27mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(78mg,0.39mmol)于二氯甲烷(3.5mL)中的溶液中添加聚合物负载的氰基硼氰化物(400mg的2mmol/g,

0.80mmol)。将混合物在微波反应器中加热至95℃,持续45分钟。然后将混合物过滤并在MeOH中搅拌30分钟。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生产物(45mg,20%)。^{1}H NMR(300MHz,甲醇-d_4)7.74(s,1H),7.55(d,J=0.8Hz,1H),6.68(d,J=0.8Hz,1H),4.75-4.42(m,3H),3.93-3.76(m,3H),3.76-3.57(m,4H),3.51(q,J=7.0Hz,2H),3.33(d,J=8.4Hz,6H),2.79-2.52(m,9H),1.97-1.58(m,2H)。LCMS m/z 469.2[M+1]$^+$

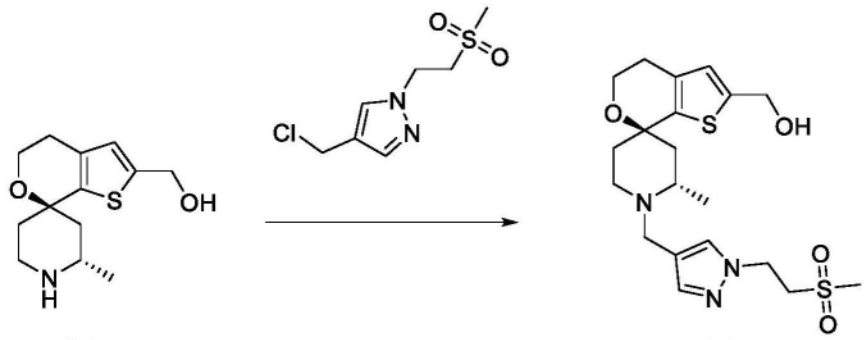
[2104] 化合物1016

[2105] [(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇(1016)



C88 C94

[2106]



C95 1016

[2107] 步骤1:(2′S,7R)-2-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C94)的合成

[2108] 在0℃下向(2′S,7R)-2-甲酰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C88(460mg,1.3mmol)于MeOH(10mL)中的溶液中添加$NaBH_4$(60mg,1.6mmol)。搅拌1小时后,将混合物在饱和氯化铵水溶液与乙酸乙酯之间分配。将有机层分离并在真空中浓缩以产生产物(434mg,91%)。^{1}H NMR(300MHz,氯仿-d)δ6.67(s,1H),4.81-4.73(m,2H),4.07-3.95(m,1H),3.88(t,J=5.5Hz,2H),3.81-3.69(m,1H),3.41-3.28(m,1H),2.63(q,J=5.4Hz,2H),2.27-2.04(m,2H),1.91-1.68(m,3H),1.51(s,9H),1.28(d,J=6.6Hz,3H)。LCMS m/z 354.04[M+H]$^+$

[2109] 步骤2:[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇(C95)的合成

[2110] 向(2′S,7R)-2-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C94(28mg,0.077mmol)于1,4-二噁烷中的溶液中添加HCl(含1mL的4M的1,4-二噁烷,4mmol)。使混合物在室温下搅拌40分钟并在真空中浓缩。用二乙醚研磨并通过反相色谱法纯化(C18柱;梯度:含MeCN的H_2O,具有10mM氢氧化铵),得到产物(5mg,24%)。^{1}H NMR(400MHz,氯仿-d)δ6.69(s,1H),4.77(s,2H),4.00-3.86(m,2H),3.19-3.05(m,2H),

3.00-2.86(m,1H),2.74-2.58(m,2H),2.08-1.96(m,3H),1.85-1.73(m,1H),1.54

[2111] -1.42(m,1H),1.09(d,J＝6.4Hz,3H)。LCMS m/z 254.1[M+H]$^+$

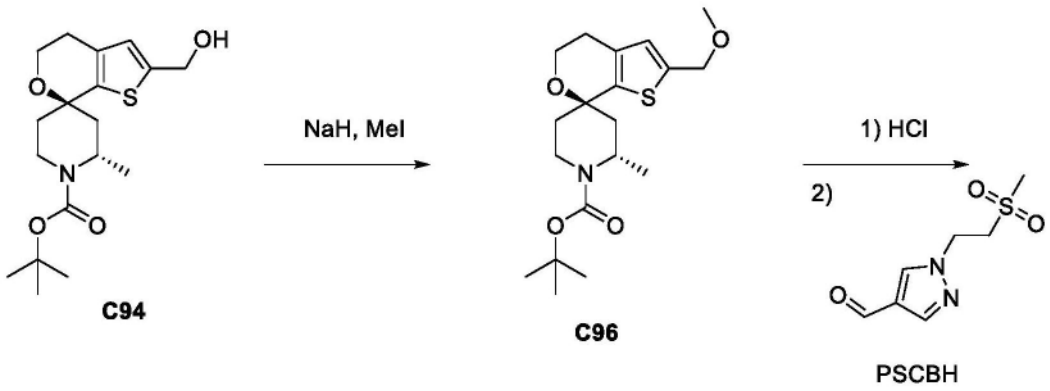
[2112] 步骤3:[(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇(1016)的合成

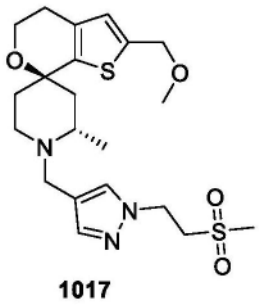
[2113] 向[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇C95(35mg,0.14mmol)于乙腈(1mL)中的溶液中添加碳酸钾(74mg,0.54mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑氯化氢(36mg,0.14mmol)。将反应混合物在70℃下加热12小时。然后将混合物在水与乙酸乙酯之间分配,并将有机层分离并在真空中浓缩。将残余物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生呈白色固体的产物(13mg,19%)。^{1}H NMR(400MHz,氯仿-d)δ7.54(s,2H),6.68(s,1H),4.75(s,2H),4.66-4.57(m,2H),3.94-3.79(m,3H),3.72-3.60(m,3H),2.79-2.52(m,6H),2.50(s,3H),2.05-1.93(m,3H),1.90-1.75(m,1H),1.26(d,J＝6.4Hz,3H)。LCMS m/z 440.17[M+H]$^+$

[2114] 化合物1017

[2115] (2′S,7R)-2-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1017)

[2116]





[2117] 步骤1:(2′S,7R)-2-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C96)的合成

[2118] 向(2′S,7R)-2-(羟甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C94(220mg,0.62mmol)于THF(5mL)中的溶液中添加NaH(26mg的60%w/w,0.65mmol)。将混合物搅拌直到停止起泡,并添加MeI(40μL,0.6mmol)。将混合物在室温下搅拌2小时。将混合物用水(2mL)淬灭,并用二乙醚(10mL)萃取。将有机层用水(2×2mL)和盐水(2mL)洗涤,经硫酸钠干燥,过滤并在真空中浓缩。将混合物物通过硅胶色谱法纯化(含0-30% EtOAc的庚烷),以产生呈无色油的产物(143mg,63%)。^{1}H NMR(400MHz,氯仿-d)。δ6.66(s,1H),4.54(d,J＝0.8Hz,2H),4.01(dq,J＝11.9,6.5,5.9Hz,1H),3.91-3.88(m,1H),

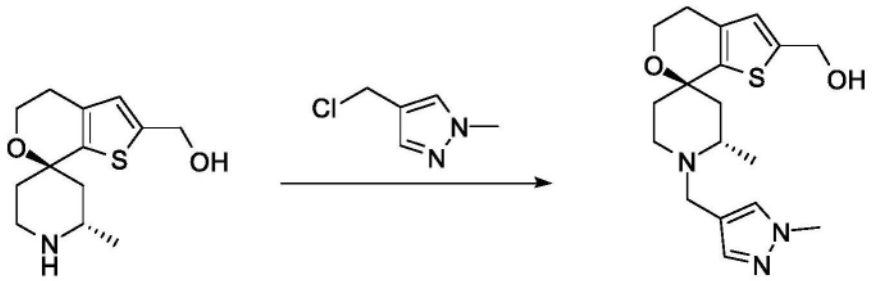
3.75(dt,J＝13.9,5.5Hz,1H),3.41(s,3H),3.36(ddd,J＝13.9,8.7,5.3Hz,1H),2.72-2.54(m,2H),2.24-2.06(m,2H),1.87(dt,J＝14.5,5.2Hz,1H),1.77(dd,J＝14.3,11.0Hz,1H),1.51(s,9H),1.28(d,J＝6.6Hz,4H)。LCMS m/z 368.0[M+H]$^+$。

[2119] 步骤2:(2′S,7R)-2-(甲氧基甲基)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1017)的合成

[2120] 向(2′S,7R)-2-(甲氧基甲基)-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C96(143mg,0.373mmol)于二乙醚(4mL)中的混合物中添加含HCl(500μL的4M,2.000mmol)的1,4-二噁烷,并将混合物加热至回流,持续4小时。将混合物冷却至0℃,并通过过滤将沉淀物收集。用二乙醚冲洗固体并在真空中干燥。将固体溶解在DCM(2mL)和MeOH(0.2mL)中,并添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(80mg,0.3mmol)和聚合物负载的氰基硼氢化钠(170mg的2mmol/g,0.34mmol)。将混合物在95℃下搅拌过夜。然后将混合物冷却至室温并过滤。将残余物用MeOH(2mL)冲洗,并将合并的滤液在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-10％ MeOH的DCM),得到呈白色固体的产物(30.7mg,45％)。^{1}H NMR(400MHz,氯仿-d)δ7.49(d,J＝0.8Hz,1H),7.44(s,1H),6.63(d,J＝0.7Hz,1H),4.63-4.53(m,2H),4.49(d,J＝0.8Hz,2H),3.88-3.76(m,3H),3.66-3.56(m,3H),3.36(s,3H),2.67-2.46(m,5H),2.43(d,J＝1.6Hz,3H),2.01-1.81(m,3H),1.68(dd,J＝13.8,11.4Hz,1H),1.18(d,J＝6.2Hz,3H)。LCMS m/z 454.08[M+H]$^+$。

[2121] 化合物1018

[2122] [(2′S,7R)-2′-甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇(1018)

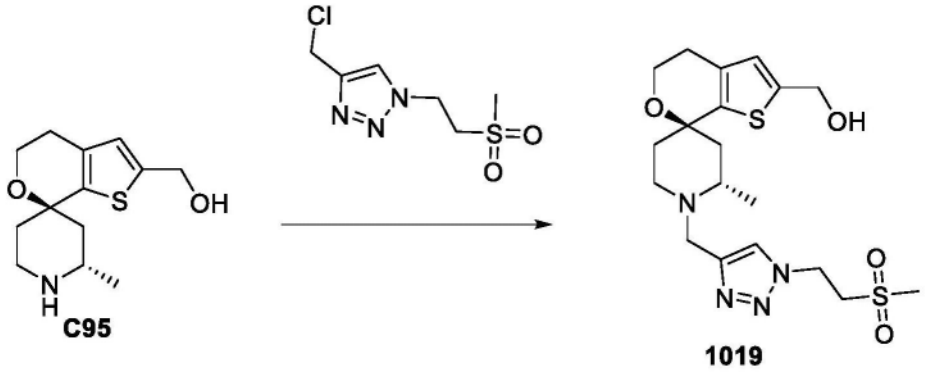
[2123] 

C95 1018

[2124] 向[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇C95(35mg,0.14mmol)于乙腈(1mL)中的溶液中添加碳酸钾(70mg,0.5mmol)和4-(氯甲基)-1-甲基-吡唑(19mg,0.15mmol)。将混合物加热至70℃,持续12小时。将混合物在水与乙酸乙酯之间分配,并将有机层分离并在真空中浓缩。将残余物通过硅胶色谱法(梯度:含0-20％ MeOH的DCM),以产生呈油的产物(11mg,21％)。^{1}H NMR(400MHz,氯仿-d)δ7.43(s,1H),7.37(s,1H),6.66(s,1H),4.75(s,2H),3.96-3.78(m,6H),3.59(d,J＝14.2Hz,1H),2.75(d,J＝11.4Hz,1H),2.72-2.51(m,4H),2.07-1.92(m,3H),1.83(t,J＝12.9Hz,1H),1.25(d,J＝6.4Hz,3H)。LCMS m/z 348.01[M+H]$^+$。

[2125] 化合物1019

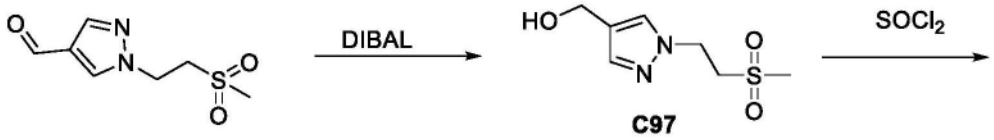
[2126] [(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇(1019)

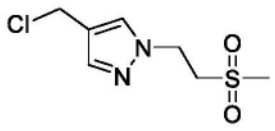
[2127] 

[2128] 向[(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-基]甲醇C95(35mg,0.14mmol)于乙腈(1mL)中的溶液中添加碳酸钾(73mg,0.53mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑氯化氢(34mg,0.13mmol)。将混合物加热至70℃,持续4小时并且然后在水与乙酸乙酯之间分配。将有机层分离并在真空中浓缩。将残余物通过硅胶色谱法(梯度:含0-20% MeOH的DCM),产生呈白色固体的产物(18mg,28%)。^{1}H NMR(400Mhz,氯仿-d)δ7.59(s,1H),6.69(s,1H),4.95(t,J=6.6Hz,2H),4.77(s,2H),4.02(d,J=14.5Hz,1H),3.95-3.78(m,3H),3.76-3.70(m,2H),2.75(s,3H),2.73-2.49(m,5H),2.11-1.88(m,3H),1.81-1.64(m,2H),1.24(d,J=6.2Hz,3H)。LCMS m/z 441.07[M+H]$^{+}$。

[2129] 制备S78

[2130] 4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(S78)



[2131] 

S78

[2132] 步骤1:[1-(2-甲基磺酰基乙基)吡唑-4-基]甲醇(C97)的合成

[2133] 在0℃下向1-(2-甲基磺酰基乙基)吡唑-4-甲醛(2g,9mmol)于THF(20mL)中的溶液中添加含DIBAL-H的己烷(27.6mL的1M,0.0276mol)。使混合物在室温下搅拌16小时。然后,将混合物冷却至-78℃,并缓慢添加MeOH(25mL)。将混合物在真空中浓缩并将残余物悬浮在EtOAc(250mL)中。通过Celite®垫过滤,随后在真空中浓缩,得到呈无色固体的产物(1.6g,80%)。^{1}H NMR(300MHz,DMSO-d_6)δ7.68(s,1H),7.40(s,1H),4.84(t,J=5.1Hz,1H),4.48(t,J=7.2Hz,2H),4.33(d,J=5.7Hz,2H),3.65(t,J=6.9Hz,2H),2.82(s,3H)。LCMS m/z 205.01[M+H]$^{+}$。

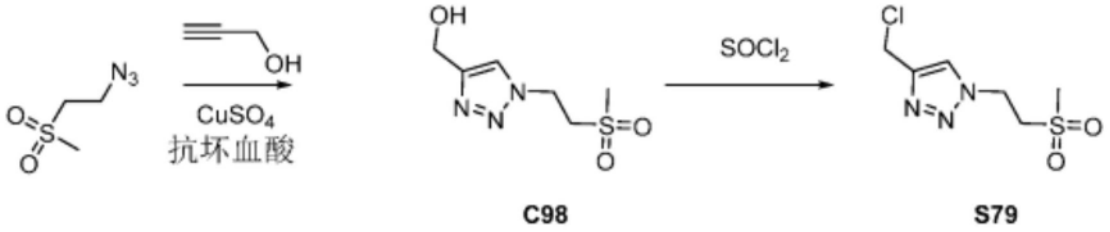
[2134] 步骤2:4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(S78)的合成

[2135] 在0℃下向[1-(2-甲基磺酰基乙基)吡唑-4-基]甲醇C97(40mg,0.2mmol)于DCM(2mL)中的溶液中添加$SOCl_2$(0.5mL,0.007mol)。允许混合物温热到室温并且搅拌2小时。将混合物在真空中浓缩,并将残余物用二乙醚研磨以得到呈白色固体的产物(42mg,99%)。^{1}H NMR(300MHz,DMSO-d_6)δ7.91(s,1H),7.56(s,1H),4.69(s,2H),4.51(t,J=6.9Hz,2H),3.67

(t,J＝7.2Hz,2H),2.85(s,3H)作为灰白色固体。

[2136] 制备S79

[2137] 4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S79)

[2138] 

C98 S79

[2139] 步骤1:[1-(2-甲基磺酰基乙基)三唑-4-基]甲醇(C98)的合成

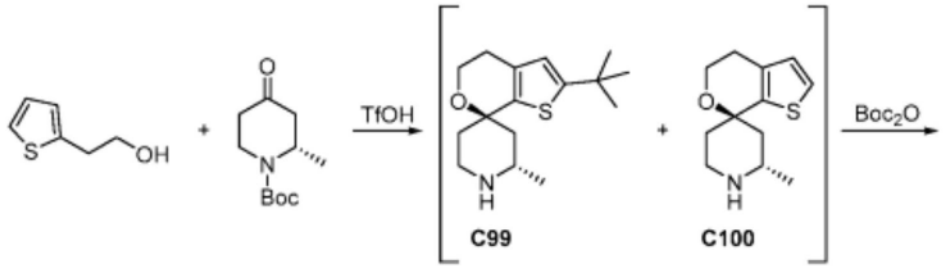
[2140] 将丙-2-炔-1-醇(500μL,8.5mmol)、1-叠氮基-2-甲基磺酰基-乙烷(1200mg,8.04mmol)、$CuSO_4$(16mg,0.10mmol)、1-(1-苄基三唑-4-基)-N,N-双[(1-苄基三唑-4-基)甲基]甲胺(100mg,0.19mmol)和抗坏血酸(1500mg,8.52mmol)于MeOH(40mL)中和水(10mL)的混合物加热至50℃,持续3小时。然后将混合物冷却至室温并在真空中浓缩。将残余物通过通过硅胶色谱法纯化(梯度:含0-10％ MeOH的DCM),产生呈黄色固体的产物(1210mg,70％)。^{1}H NMR(400MHz,DMSO-d_6)δ8.04(s,1H),5.21(d,J＝6.8Hz,1H),4.81(t,J＝7.0Hz,2H),4.54(d,J＝4.5Hz,2H),3.80(t,J＝6.9Hz,2H),2.96(s,3H)。LCMS m/z 206.4$[M+H]^+$。

[2141] 步骤2:4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S79)的合成

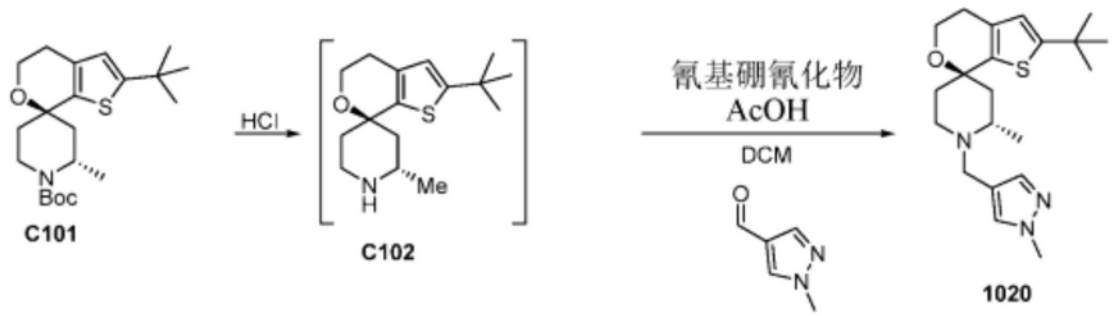
[2142] 向[1-(2-甲基磺酰基乙基)三唑-4-基]甲醇C98(2000mg,9.78mmol)于二氯甲烷(74mL)和DMF(1mL)中的溶液中添加亚硫酰氯(1mL,14mmol)。将混合物搅拌30分钟并在真空中浓缩。将残余物用二乙醚(50mL)研磨,并将悬浮液过滤并用另外的二乙醚冲洗以得到呈黄色固体的产物(1600mg,73％)。^{1}H NMR(400MHz,氯仿-d)δ7.80(s,1H),4.93-4.82(m,2H),4.73(d,J＝0.6Hz,2H),3.74(ddd,J＝7.1,5.5,0.7Hz,2H),2.77(t,J＝0.6Hz,3H)。LCMS m/z 224.4$[M+H]^+$。

[2143] 制备1020

[2144] (2S,4R)-2′-(叔丁基)-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](1020)



[2145]



[2146] 步骤1:(2S,4R)-2′-(叔丁基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C101)的合成

[2147] 在0℃下向(S)-2-甲基-4-氧代哌啶-1-甲酸叔丁酯(750mg,3.517mmol)和2-(3-噻吩基)乙醇(676mg,5.273mmol)于二噁烷(11mL)中的溶液中添加三氟甲磺酸(1.6g,10.66mmol)。使所得溶液在室温下搅拌3小时,此后,将其用DCM稀释并用2M Na_2CO_3洗涤。将水层用DCM萃取,并将合并的有机层经硫酸钠干燥,然后过滤并浓缩。将含有C99和C100的粗混合物溶解在DCM(16mL)中,并向该溶液中添加碳酸叔丁氧基羰基叔丁酯(460mg,2.108mmol)。使所得溶液在室温下搅拌三小时,此后将粗产物通过住色谱法纯化以产生(2S,4R)-2′-(叔丁基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(82mg,23%)。1H NMR(300MHz,氯仿-d)δ7.15(d,J=5.1Hz,1H),6.76(d,J=5.1Hz,1H),4.03(ddd,J=11.4,6.6,5.1Hz,1H),3.90(t,J=5.5Hz,2H),3.76(ddd,J=13.9,6.0,4.9Hz,1H),3.37(ddd,J=14.0,8.8,5.4Hz,1H),2.69(td,J=5.5,3.4Hz,2H),2.25-2.08(m,2H),1.92-1.77(m,2H),1.50(s,9H),1.32-1.25(m,5H)。LCMS m/z 380.33$[M+H]^+$。

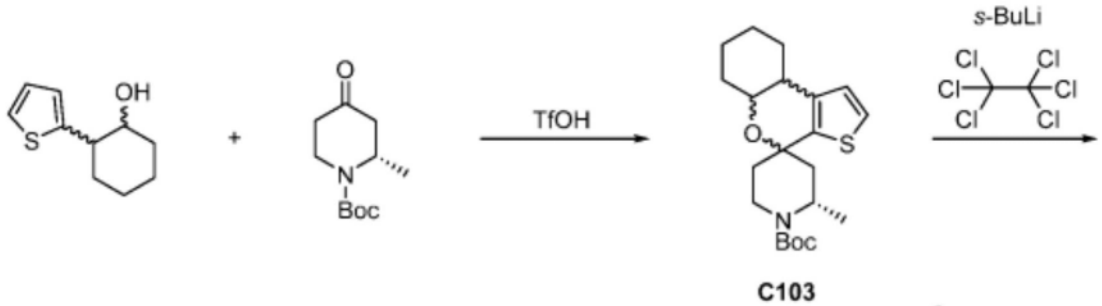
[2148] 步骤2:(2S,4R)-2′-(叔丁基)-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](1020)的合成

[2149] 向(2S,4R)-2′-(叔丁基)-2-甲基-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C101(60mg,0.142mmol)于二噁烷(0.9mL)中的溶液中添加4M HCl(395μL,1.580mmol)。使所得溶液在室温下搅拌过夜,然后在真空中浓缩。将粗材料溶解在二氯甲烷(2.5mL)中,并向该溶液中添加1-甲基吡唑-4-甲醛(35mg,0.318mmol)、乙酸(47mg,0.783mmol)和聚合物负载的氰基硼氰化物(2mmol/g)(236mg,0.472mmol)。将所得溶液在微波反应器中加热至110℃,持续35分钟,此后将溶液冷却至室温。将溶液过滤,并将溶剂在真空中去除。将粗产物通过反相HPLC纯化:含ACN的水(TFA改性剂)C18柱,随后冻干以得到(2S,4R)-2′-(叔丁基)-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](三氟乙酸盐)(15.3mg,18%)。^{1}H NMR(300MHz,氯仿-d)δ11.92(s,1H),7.66(s,1H),7.53(d,J=0.8Hz,1H),6.48(s,1H),4.51(d,J=14.2Hz,1H),4.04(dd,J=14.1,4.0Hz,1H),3.97(s,3H),3.84(q,J=5.8Hz,2H),3.34(d,J=12.1Hz,2H),3.08(t,J

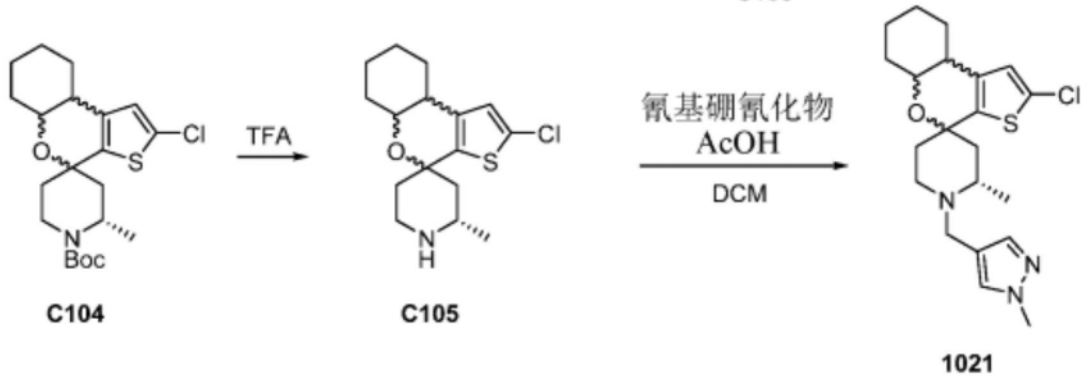
＝11.4Hz,1H),2.62(q,J＝5.1Hz,2H),2.40-2.27(m,2H),2.20-2.08(m,2H),1.58(d,J＝6.5Hz,3H),1.35(s,9H)。LCMS m/z 374.2[M+H]$^+$。

[2150] 制备1021

[2151] (2S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](1021)



[2152]



[2153] 步骤1:(2S)-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯]-1-甲酸叔丁酯(C103)的合成

[2154] 向(S)-2-甲基-4-氧代哌啶-1-甲酸叔丁酯(335mg,1.571mmol)和2-(3-噻吩基)环己醇(270mg,1.481mmol)于DCM(1.8mL)中的溶液中添加TFA(1.8mL)。使所得溶液搅拌30分钟,然后在真空中浓缩。将残余物溶解在二噁烷(4.5mL)中并冷却至0℃。在5分钟内向该溶液中逐滴添加三氟甲磺酸(680.00mg,0.4mL,4.531mmol)并使溶液温热至室温并搅拌3小时。将反应物用NaOH水溶液(1N,50mL)淬灭,然后用EtOAc(50mL)稀释。将水层分离并用EtOAc(2×300mL)进一步萃取。将合并的有机层经无水硫酸钠干燥,过然后滤并浓缩。将残余物溶解在DCM(2.5mL)中,并向该溶液中添加DIEA(408mg,0.55mL,3.158mmol)和boc酸酐(360mg,1.650mmol)。将所得溶液在室温下搅拌过夜,然后用DCM(25mL)稀释并且依次用水和盐水洗涤。将有机层经硫酸钠干燥,然后过滤并浓缩以得到(2S)-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯]-1-甲酸叔丁酯。粗产物无需进一步纯化即可使用。

[2155] 步骤2:(2S)-2′-氯-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](C105)的合成

[2156] 在-78℃下在5分钟内向(2S)-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯]-1-甲酸叔丁酯C103(535mg,1.417mmol)于THF(7.0mL)中的溶液中逐滴添加sec-BuLi(2.0mL的1.4M,2.800mmol)。将所得溶液在该相同温度下搅拌1小时,然后逐滴添加1,1,1,2,2,2-六氯乙烷(500mg,2.112mmol)于THF(3.0mL)中的溶液。将反应混合

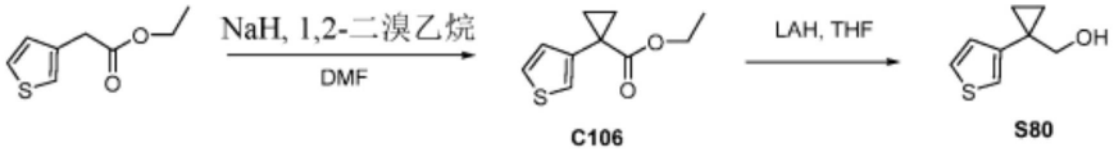
物在-78℃下搅拌1小时,然后用饱和氯化铵溶液(5mL)淬灭,并用乙酸乙酯(50mL)和水(50mL)稀释。将有机层分离并经硫酸钠干燥,然后过滤并浓缩以得到(2R)-2′-氯-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯]-1-甲酸叔丁酯,其无需进一步纯化即可使用。向(2R)-2′-氯-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯]-1-甲酸叔丁酯(50mg,0.073mmol)于DCM(0.5mL)中的溶液中添加TFA(29.6mg,0.02mL,0.260mmol),并将所得溶液在室温下搅拌2小时。将反应混合物浓缩,并将粗产物通过反相HPLC纯化以得到呈白色粉末的(2S)-2′-氯-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](4.2mg,14%)。LCMS m/z 312.3[M+H]$^+$。

[2157] 步骤3:(2S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](1021)的合成

[2158] 向(2S)-2′-(叔丁基)-2-甲基-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](C105)(62mg,0.199mmol)和1-甲基-1H-吡唑-4-甲醛(28mg,0.254mmol)于二氯甲烷(1.0mL)中的溶液中添加乙酸(53mg,0.879mmol)和聚合物负载的氰基硼氰化物(2mmol/g)(250mg,0.500mmol)。将所得溶液在微波反应器中加热至110℃,持续20分钟,此后将溶液冷却至室温。将溶液过滤,并将溶剂在真空中去除。将粗产物通过反相HPLC纯化:含ACN的水(TFA改性剂)C18柱,随后冻干以得到呈白色粉末的((2S)-2′-氯-2-甲基-1-((1-甲基-1H-吡唑-4-基)甲基)-5a′,6′,7′,8′,9′,9a′-六氢螺[哌啶-4,4′-噻吩并[2,3-c]色烯](1021)(三氟乙酸盐)(8.9mg,11%)。将产物用未知的绝对立体化学分离为非对映异构体的混合物。^{1}H NMR(500MHz,DMSO-d6)δ9.61(s,1H),7.92(s,1H),7.60(s,1H),7.01(d,J=1.8Hz,1H),4.48-4.39(m,1H),4.22-4.14(m,1H),3.87(s,3H),3.32-3.21(m,2H),3.16-3.03(m,1H),2.30-2.19(m,2H),2.11-1.89(m,2H),1.89-1.66(m,4H),1.46-1.40(m,3H),1.33(q,J=11.4,11.4,11.2Hz,3H),1.17-1.02(m,1H)。水峰下隐藏着另外的质子。LCMS m/z 405.3[M+H]$^+$。

[2159] S80的制备

[2160] (1-(噻吩-3-基)环丙基)甲醇(S80)

[2161] 

[2162] 步骤1:1-(噻吩-3-基)环丙烷-1-甲酸乙酯(C106)的合成

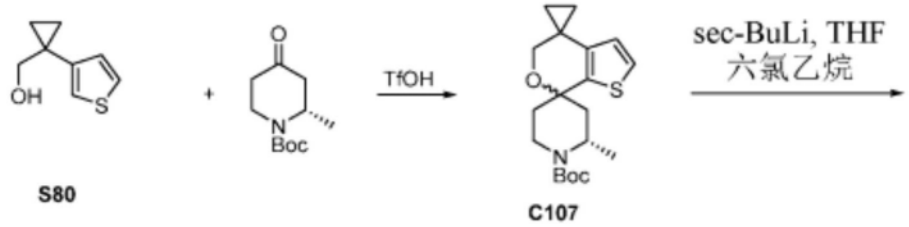
[2163] 将2-(3-噻吩基)乙酸乙酯(2.84g,2.5mL,16.70mmol)和1,2-二溴乙烷(6.97g,3.2mL,37.13mmol)溶解在DMF(80mL)中,然后添加NaH(1.9g,60%w/w,47.50mmol),并将混合物在0℃下搅拌30分钟,然后使温热至室温过夜。然后将反应物冷却至0℃,并添加另外的1,2-二溴乙烷(4.36g,2mL,23.21mmol),随后添加NaH(950mg,60%w/w,23.752mmol)。将混合物在0℃下搅拌30分钟,并且然后温热至室温。搅拌16小时后,通过添加1M HCl(100mL)将反应物淬灭,并用水(400mL)稀释。将水层用EtOAc(75mL)萃取三次,并将有机层用盐水(5×50mL)洗涤5次。将有机层经Na_2SO_4干燥并浓缩以提供呈无色油的1-(3-噻吩基)环丙基甲酸乙酯(2.0g,46%),其无需进一步纯化即可继续进行。

[2164] 步骤2:(1-(噻吩-3-基)环丙基)甲醇(S80)的合成

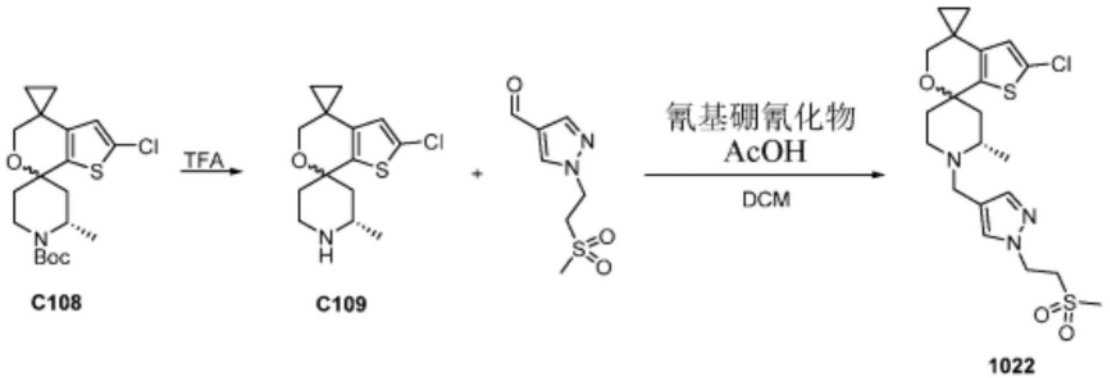
[2165] 将1-(3-噻吩基)环丙基甲酸乙酯(3.27g,16.69mmol)溶解在冷却至0℃的THF(65mL)中,然后添加氢化铝锂(9.15mL的2M,18.30mmol),并使反应物温热以在0℃下搅拌40分钟。然后,添加50mL的Et20。添加0.5mL的DI水,随后添加0.5mL的15% NaOH,然后缓慢添加1.5mL的DI水(费雪操作法(Fieser workup))。将固体过滤掉并将滤液干燥上样氘硅胶上并使用含0-30%乙酸乙酯的己烷通过快速柱色谱法纯化以产生呈无色油的[1-(3-噻吩基)环丙基]甲醇(500mg,17%)。^{1}H NMR(250MHz,CDC13)δ7.35-7.22(m,1H),7.21-7.08(m,1H),7.08-6.93(m,1H),3.71(s,2H),0.89(d,J=8.4Hz,4H)。

[2166] 制备1022

[2167] (2"S)-2′-氯-2"-甲基-1"-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶](1022)



[2168]



[2169] 步骤1:(2"S)-2"-甲基-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(C107)的合成

[2170] 将[1-(3-噻吩基)环丙基]甲醇S80(150mg,0.9726mmol)溶解在DCM(1mL)中,然后添加(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(245mg,1.1488mmol)和TFA(1mL),并使反应物在室温下搅拌20分钟。去除挥发物,并将粗残余物溶解在二噁烷(2mL)中并冷却至0℃。添加TfOH(424.00mg,0.25mL,2.8252mmol)并使混合物在室温下搅拌3小时。通过添加1M NaOH(5mL)来淬灭反应物。将水层用EtOAc(3×5mL)萃取三次。将有机层经Na_2SO_4干燥并浓缩。将粗残余物溶解在DCM(6mL)中,然后添加Boc_20(237mg,1.0859mmol)和DIEA(259.70mg,0.35mL,2.0094mmol)并使反应物搅拌过夜。将粗反应混合物直接上样到硅胶上并使用含0-30% EtOAc的己烷通过快速柱色谱法纯化以产生呈无色晶体的(2"S)-2"-甲基-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(255mg,68%)。ESI-MS m/z计算值:349.1712,实测值:350.2$(M+1)^+$。

[2171] 步骤2:2′-氯-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(C108)的合成

[2172] 将(2"S)-2"-甲基-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-

1”-甲酸叔丁酯(110mg,0.327mmol)溶解在THF(1.5mL)中并冷却至-78℃,然后逐滴添加sec-buli(0.5mL的1.4M,0.7000mmol)。将反应物在该温度下搅拌1小时,然后添加含1,1,1,2,2,2-六氯乙烷(155mg,0.6547mmol)的THF(0.6mL),并将反应物搅拌30分钟。通过添加NH_4Cl(2mL)淬灭反应物。将反应物用水和EtOAc(各5mL)稀释,然后将水层用EtOAc(2×5mL)萃取两次。将有机层经Na_2SO_4干燥并浓缩。将粗材料通过反相HPLC纯化纯化以产生呈无色白色固体的C18H24ClNO3S(28.6mg,22%)。ESI-MS m/z计算值:369.1165,实测值:370.3$(M+1)^+$。

[2173] 步骤3:2′-氯-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶](C109)的合成

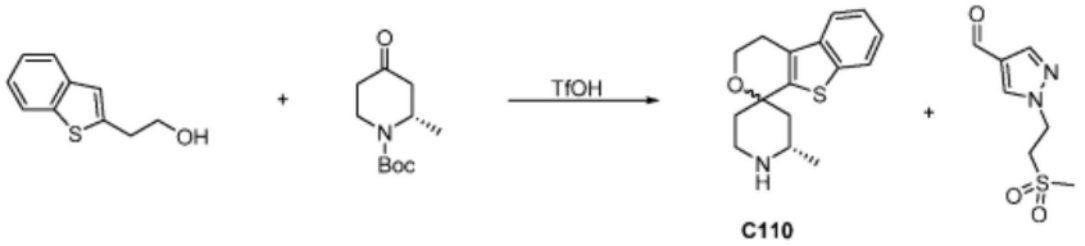
[2174] 向2′-氯-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯C108(28.6mg,0.0773mmol)于DCM(0.5mL)中的溶液中添加TFA(148.00mg,0.1mL,1.298mmol)并在室温下搅拌2小时。在减压下去除挥发物以得到粗产物2′-氯-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶],29mg的粗产物无需进一步纯化即可用于下一步骤。ESI-MS m/z计算值:269.0641,实测值:270.3$(M+1)^+$。

[2175] 步骤4:(2”R)-2′-氯-2”-甲基-1”-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶](1022)的合成

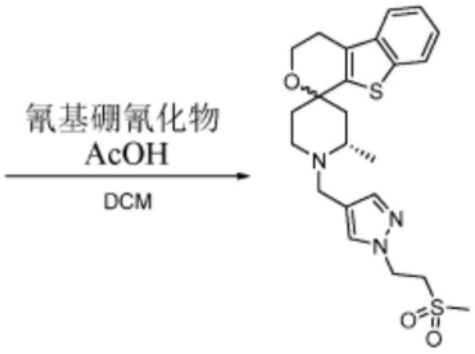
[2176] 向(2”S)-2′-氯-2”-甲基-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]C109(81.6mg,0.213mmol)于DCM(5mL)中的溶液中添加TFA(1.48g,1mL,12.98mmol),并将所得溶液在室温下搅拌1小时。将反应混合物在真空中浓缩1小时,然后将残余物溶解在DCM(3mL)中。向所得溶液中添加乙酸(84.48mg,0.08mL,1.407mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(80mg,0.396mmol)和聚合物负载的氰基硼氰化物(182mg,2mmol/g,0.364mmol)。将所得溶液在微波反应器中加热至110℃,持续30分钟,此后将溶液冷却至室温。将溶液过滤,并将溶剂在真空中去除。将粗产物通过反相HPLC纯化:含ACN的水(TFA改性剂),C18柱,随后冻干以得到呈黄色凝胶的(2”R)-2′-氯-2”-甲基-1”-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-5′H-二螺[环丙烷-1,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶](1022)(25.3mg,17%)(三氟乙酸盐)。^1H NMR(500MHz,DMSO-d_6)δ9.61(s,1H),7.92(s,1H),7.60(s,1H),7.01(d,J=1.8Hz,1H),4.48-4.39(m,1H),4.22-4.14(m,1H),3.87(s,3H),3.32-3.21(m,2H),3.16-3.03(m,1H),2.30-2.19(m,2H),2.11-1.89(m,2H),1.89-1.66(m,4H),1.46-1.40(m,3H),1.33(q,J=11.4,11.4,11.2Hz,3H),1.17-1.02(m,1H)。一些质子在水峰下。LCMS m/z470.5$[M+H]^+$。

[2177] 制备1023

[2178] (2′S)-2′-甲基-1′-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-3,4-二氢螺[苯并[4,5]噻吩并[2,3-c]吡喃-1,4′-哌啶](1023)



[2179]



[2180] 步骤1:(1R,2′S)-2′-甲基-3,4-二氢螺[苯并[4,5]噻吩并[2,3-c]吡喃-1,4′-哌啶](C110)的合成

[2181] 将(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(298mg,1.40mmol)和2-(苯并噻吩-3-基)甲醇(300mg,1.683mmol)于二噁烷(4mL)中的溶液冷却至0℃。向溶液中逐滴添加三氟甲磺酸(376μL,4.25mmol)。使所得溶液温热至室温并搅拌3小时,此后将反应物用DCM稀释,随后用2M碳酸钠水溶液稀释。将有机层分离并且将水层用DCM萃取。将合并的有机层经无水硫酸钠干燥,过然后滤并浓缩。将粗产物通过反相HPLC纯化:含5-95% ACN的水(TFA改性剂),C18柱,随后冻干以得到呈白色固体的(2′S,4R)-2-乙基-2′-甲基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](C110)(TFA盐)(412.5mg,76%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.90-7.79(m,1H),7.79-7.62(m,1H),7.45-7.26(m,2H),4.12(qd,J=5.8,2.2Hz,2H),3.87-3.33(m,3H),2.88(td,J=5.5,1.0Hz,2H),2.39-1.87(m,4H),1.56(d,J=7.0Hz,1H),1.35(d,J=6.6Hz,2H)。LCMS m/z 274.19[M+H]$^+$。

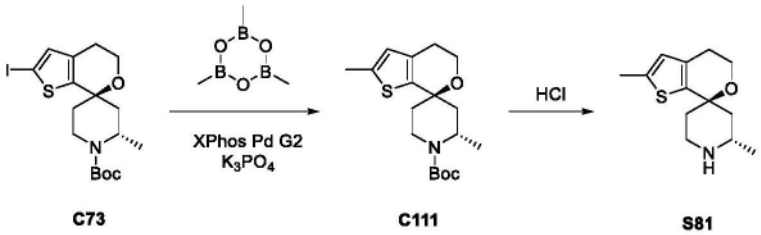
[2182] 步骤2:(2′S)-2′-甲基-1′-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-3,4-二氢螺[苯并[4,5]噻吩并[2,3-c]吡喃-1,4′-哌啶](1023)

[2183] 向(2′S)-2′-甲基螺[3,4-二氢苯并噻吩[2,3-c]吡喃-1,4′-哌啶](三氟乙酸盐)(C110)(88mg,0.227mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(68.5mg,0.339mmol)于二氯甲烷(2.4mL)中的溶液中添加乙酸(68mg,1.13mmol)和聚合物负载的氰基硼氰化物(2mmol/g)(340mg,0.680mmol)。将所得溶液在微波反应器中加热至110℃,持续45分钟,此后将溶液冷却至室温。将溶液过滤,并将溶剂在真空中去除。将粗产物通过反相HPLC纯化:含ACN的水(TFA改性剂),C18柱,随后冻干以得到(2′S)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[3,4-二氢苯并噻吩[2,3-c]吡喃-1,4′-哌啶](三氟乙酸盐)(37mg,28%)。将产物用未知的绝对立体化学分离为非对映异构体的混合物。^{1}H NMR(500MHz,DMSO-d_6)δ9.57(s,1H),8.05(d,J=40.9Hz,1H),7.70(d,J=27.5Hz,1H),6.73(d,J=19.0Hz,1H),4.64-4.55(m,2H),4.20(d,J=5.4Hz,2H),3.85(d,J=12.0Hz,1H),3.70(t,J

=6.8,6.8Hz,2H),3.65-3.54(m,1H),3.41-3.29(m,1H),3.21(d,J=12.9Hz,1H),2.92(s,3H),2.39(d,J=15.6Hz,1H),2.31-2.19(m,1H),2.11-1.99(m,2H),1.52-1.39(m,3H),1.02-0.92(m,1H),0.92-0.82(m,2H)。另外的质子在水峰下。LCMS m/z470.5[M+H]$^+$。

[2184] 制备S81

[2185] (2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S81)

[2186] 

[2187] 步骤1:(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C111)的合成

[2188] 向20mL闪烁小瓶中添加(2′S,7R)-2-碘代-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C73(1.19g,2.648mmol)、K_3PO_4(1.78g,8.386mmol)、XPhos Pd G2(113mg,0.1436mmol),并将小瓶用N_2吹扫15分钟。然后添加二噁烷(8.8mL)和2,4,6-四甲基-1,3,5,2,4,6-三氧杂三硼烷(1.1mL,7.869mmol)。将反应混合物在80℃下搅拌。4小时后,将反应物冷却至rt,并用水洗涤,并用EtOAc(3×10mL)萃取。将合并的有机层经Na_2SO_4干燥并通过Celite®塞过滤。将粗材料用150g HP二醇柱纯化并用含0至10% EtOAc的庚烷洗脱以提供(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(421mg,44%)。^{1}H NMR(300MHz,氯仿-d_3)δ6.41(s,1H),4.00(dt,J=11.6,5.9Hz,1H),3.87(t,J=5.5Hz,2H),3.73(dt,J=13.7,5.5Hz,1H),3.35(ddd,J=14.0,8.7,5.4Hz,1H),2.59(q,J=5.1,4.5Hz,2H),2.44(d,J=1.1Hz,3H),2.30-2.04(m,2H),1.96-1.68(m,2H),1.50(s,9H),1.28(d,J=6.6Hz,3H)。

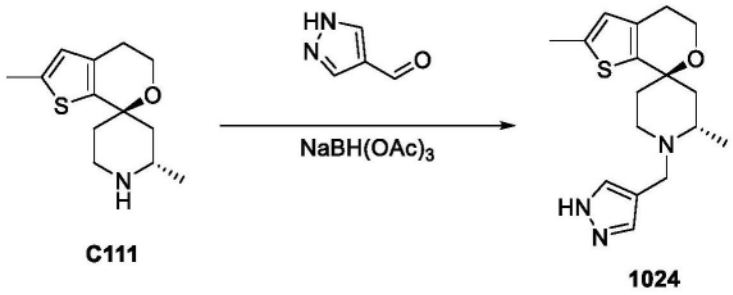
[2189] 步骤2:(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S81)的合成

[2190] 在rt下向50mL烧瓶中添加(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C111(494mg,1.464mmol)和二噁烷(6mL)。然后添加HCl(含1.8mL的4M的二噁烷,7.200mmol)。18小时后,将反应物用饱和$NaHCO_3$溶液淬灭并用EtOAc(x4)萃取。将合并的有机层经Na_2SO_4干燥,过滤,并浓缩。将粗材料通过硅胶柱色谱法纯化(梯度:含0至20% MeOH的DCM)以提供(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](291mg,69%)。LCMS m/z 238.11[M+H]$^+$。

[2191] 化合物1024

[2192] (2′S,7R)-2,2′-二甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-

[2193] 7,4′-哌啶](1024)

[2194] 

[2195] 标准方法:使用三乙酰氧基硼氢化钠进行还原胺化

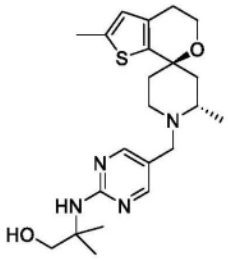
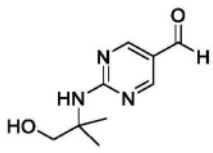
[2196] 向1打兰小瓶中添加(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]C111(30mg,0.1037mmol)、1H-吡唑-4-甲醛(20mg,0.2081mmol),随后添加DCM(500μL)。然后最后添加三乙酰氧基硼氢化钠(66mg,0.3129mmol)。在室温下16小时后,将反应混合物用饱和$NaHCO_3$溶液淬灭并用EtOAc(x8)萃取。将合并的有机层经$MgSO_4$干燥,过滤,并在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.2%甲酸。将产物分离为(2′S,7R)-2,2′-二甲基-1′-(1H-吡唑-4-基甲基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](17.4mg,51%)。LCMS m/z 318.21$[M+H]^+$。^1H NMR(300MHz,氯仿-d_3)δ7.54(s,2H),6.39(s,1H),4.01-3.72(m,3H),3.61(d,J=14.1Hz,1H),2.88-2.46(m,6H),2.41(s,3H),1.88(s,3H),1.71(t,J=12.8Hz,1H),1.22(d,J=6.2Hz,3H)。

[2197] 化合物1025-1026

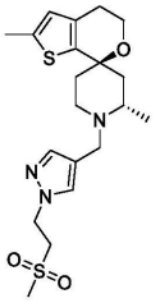
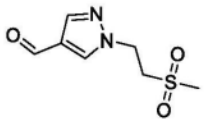
[2198] 化合物1025-1026(参见表48)由中间体C111使用标准方法,如在化合物1024的制备中所述的方法在单个步骤中制备。醛从商业来源获得或如前所述。表48和随附脚注中注明了对方法的任何修改。

[2199] 表48:化合物1025-1026的结构和物理化学数据

[2200]

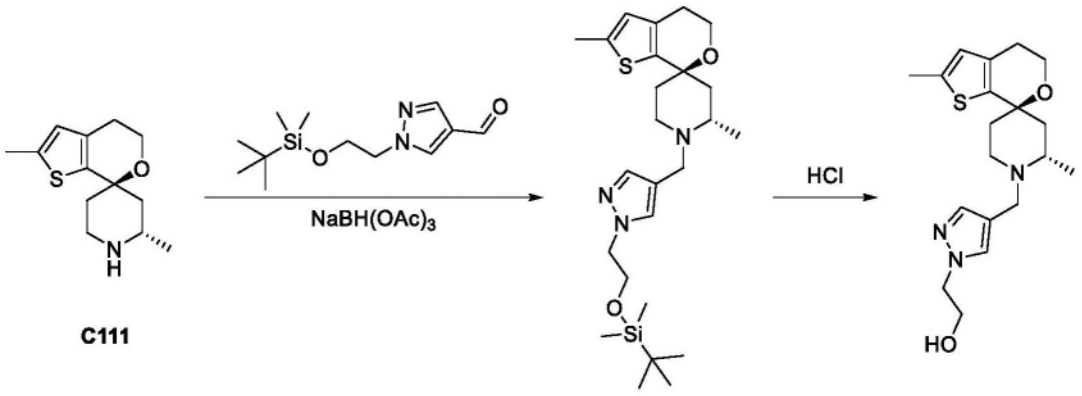
化合物	结构	醛 试剂	^1H NMR; LCMS m/z $[M+H]^+$。
1025			^1H NMR (300 MHz, 氯仿-d_3) δ 8.21 (s, 2H), 6.52 (s, 1H), 6.40 (d, J = 1.2 Hz, 1H), 5.21 (s, 1H), 3.99 - 3.80 (m, 3H), 3.67 (s, 2H), 3.04 (d, J = 13.6 Hz, 1H), 2.59 (q, J = 5.9, 5.3 Hz, 4H), 2.42 (d, J = 1.1 Hz, 3H), 2.35 (d, J = 11.9 Hz, 1H), 1.98 (d, J = 14.9 Hz, 2H), 1.89 - 1.73 (m, 1H), 1.73 - 1.60 (m, 1H), 1.36 (s, 6H), 1.18 (d, J =

[2201]

化合物	结构	醛 试剂	^{1}H NMR；LCMS m/z $[M+H]^+$。
			6.1 Hz, 3H)； LCMS *m/z* 417.23 $[M+H]^+$。
1026			^{1}H NMR (300 MHz, 氯仿-d_3) δ 7.62 (s, 1H), 7.55 (s, 1H), 6.40 (s, 1H), 4.62 (t, *J* = 6.1 Hz, 2H), 4.11 (d, *J* = 14.4 Hz, 1H), 3.81 (dd, *J* = 10.0, 4.9 Hz, 3H), 3.64 (t, *J* = 6.2 Hz, 2H), 3.04 - 2.83 (m, 2H), 2.81 - 2.65 (m, 1H), 2.65 - 2.56 (m, 2H), 2.54 (s, 3H), 2.41 (s, 3H), 2.14 (td, *J* = 13.6, 12.4, 4.6 Hz, 1H), 2.01 (d, *J* = 7.9 Hz, 3H), 1.36 (d, *J* = 6.4 Hz, 3H)； LCMS *m/z* 424.11 $[M+H]^+$。

[2202] 化合物1027

[2203] 2-[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙醇(1027)

[2204] 

C111 C112 1027

[2205] 步骤1:叔丁基-[2-[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙氧基]-二甲基-硅烷(C112)的合成

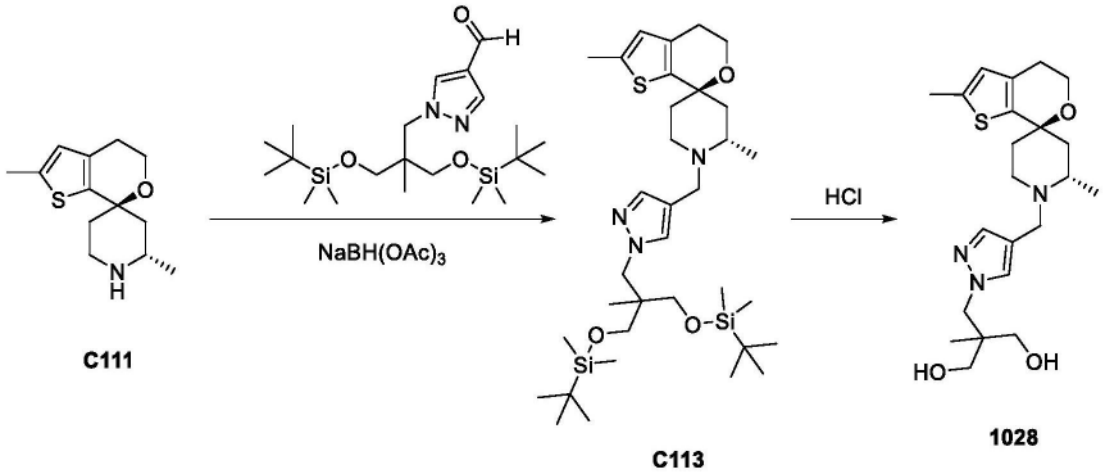
[2206] 向1打兰小瓶中添加(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]C111(30mg,0.1037mmol)、1-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]吡唑-4-甲醛(66mg,0.2594mmol),随后添加DCM(500μL)。然后添加三乙酰氧基硼氢化钠(77mg,0.3650mmol)。19小时后,将反应物用饱和$NaHCO_3$溶液淬灭并用EtOAc(x5)萃取。将合并的有机层经Na_2SO_4干燥,过滤,并在真空中浓缩。将粗材料通过硅胶色谱法纯化(梯度:含0至10% MeOH的DCM)以提供叔丁基-[2-[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙氧基]-二甲基-硅烷(64mg,114%)。LCMS m/z 476.22$[M+H]^+$。

[2207] 步骤2:2-[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙醇(1027)的合成

[2208] 向步骤1中的经分离的产物C112中添加MeOH(600μL),随后添加HCl(44μL的11.7M,0.5148mmol)。30分钟后,将反应混合物浓缩并通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。发现一部分产物转化为对应的三氟乙酸酯。将其溶解在DCM(1mL)中,用1N NaOH(1mL)处理。80分钟后,将混合物分离并将水层用DCM(x4)萃取。将合并的有机层经Na_2SO_4干燥,过滤并在真空中浓缩以提供2-[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]乙醇(25.0mg,57%)。^{1}H NMR(300MHz,氯仿-d_3)δ7.45(s,1H),7.39(s,1H),6.40(d,J=1.2Hz,1H),4.22(dd,J=5.6,3.9Hz,2H),4.00(dd,J=5.5,4.1Hz,2H),3.96-3.79(m,3H),3.54(d,J=14.1Hz,1H),2.75(d,J=11.9Hz,1H),2.70-2.46(m,4H),2.41(d,J=1.2Hz,3H),2.11-1.81(m,4H),1.80-1.64(m,1H),1.23(t,J=6.2Hz,3H)。LCMS m/z 362.09[M+H]$^+$。

[2209] 化合物1028

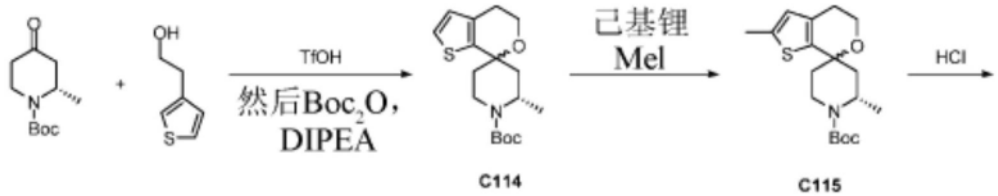
[2210] 2-[[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷-1,3-二醇(1028)

[2211] 

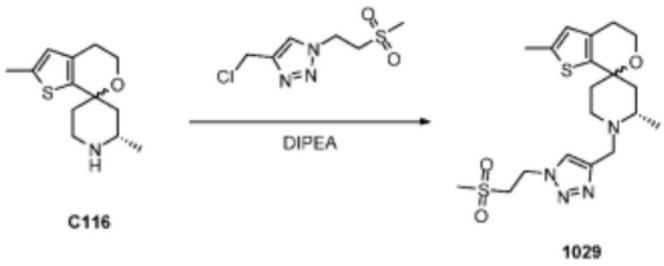
[2212] 2-[[4-[[(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-基]甲基]吡唑-1-基]甲基]-2-甲基-丙烷1,3-二醇1028根据如化合物1027的制备中所述的程序制备,除了在步骤2中使用HCl(10当量)之外。LCMS m/z420.19[M+H]$^+$。^{1}H NMR(300MHz,氯仿-d_3)δ7.44(s,1H),7.39(s,1H),6.40(d,J=1.3Hz,1H),4.24(d,J=2.1Hz,2H),3.99-3.78(m,3H),3.53(td,J=12.0,4.2Hz,4H),3.34(dd,J=11.3,3.1Hz,2H),2.78-2.46(m,5H),2.41(d,J=1.1Hz,3H),2.09-1.80(m,4H),1.72(t,J=12.8Hz,1H),1.21(d,J=6.3Hz,3H),0.82(s,3H)。

[2213] 化合物1029

[2214] (2′S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1029)



[2215]



[2216] 步骤1:(2′S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C114)的合成

[2217] 将(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(332mg,1.557mmol)溶解在二噁烷(6mL)中并在冰浴中冷却并添加三氟甲磺酸(721mg,4.804mmol)。然后将反应混合物在rt下搅拌15分钟并添加2-(3-噻吩基)乙醇(200mg,1.560mmol)。将反应混合物在室温下搅拌3小时并且然后用1NNaOH/EtOAc稀释。将有机层用盐水洗涤,干燥并浓缩成油。将粗材料溶解在DCM(9mL)中。添加DIPEA(410mg,3.172mmol)和Boc_2O(370mg,1.695mmol)。2小时后,将反应混合物在真空中浓缩,并通过硅胶色谱法纯化(梯度:含0至20% EtOAc的己烷)以提供(2′S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(314mg,41%)。LCMS m/z 323.27$[M+H]^+$。

[2218] 步骤2:(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C115)的合成

[2219] 在烧瓶中溶解含(2′S)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C114(100mg,0.3092mmol)的THF(2.6mL)并冷却至-78℃。向反应混合物中逐滴添加己基锂(403μL的2.3M,0.9269mmol)并将反应混合物在-78℃下搅拌30分钟。然后添加MeI(38.5μL,0.6184mmol)并将反应物温热至rt并搅拌过夜。将反应物用氯化铵溶液淬灭并用EtOAc萃取,用盐水洗涤并用硫酸钠干燥。将合并的有机层在真空中浓缩以产生(2′S,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(190mg,78%)。LCMS m/z 338.15$[M+H]^+$。

[2220] 步骤3:(2′S)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C116)的合成

[2221] 将(2′S)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C115(190mg,0.2421mmol)溶解在二噁烷(3mL)中并添加HCl(605μL的4M,2.420mmol)。将溶液搅拌过夜。将溶液在真空中浓缩以提供(2′S)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶],其无需进一步纯化即可用于下一步骤。LCMS m/z 238.09$[M+H]^+$。

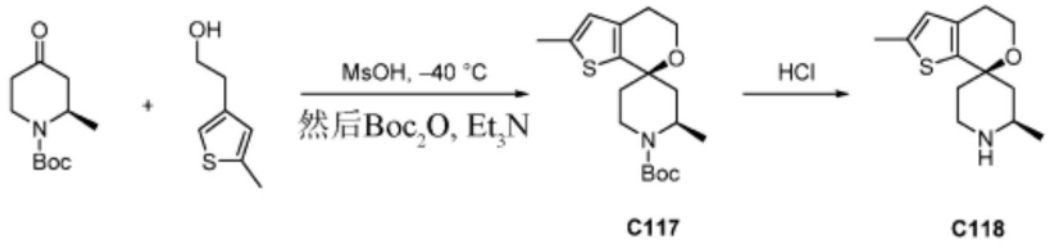
[2222] 步骤4:(2′S)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,

5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1029)的合成

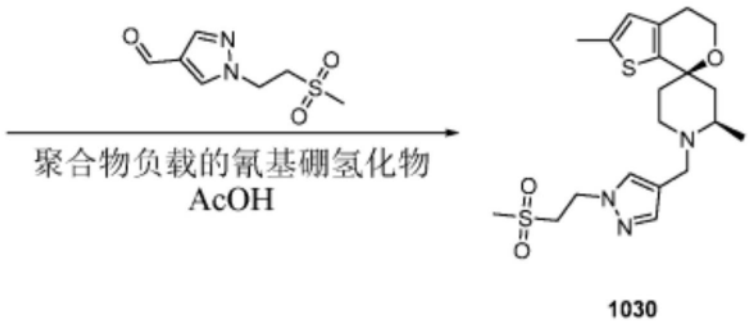
[2223] 将(2′S)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](57.47mg,0.24mmol;使用未优化的条件制备,并作为非对映异构体的混合物分离)溶解在DCE(3mL)中,并添加DIPEA(42μL,0.2411mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(54mg,0.2414mmol)。将溶液在65℃下搅拌。24小时后,将溶液冷却并在DCM与1N NaOH之间分配。将有机层通过相分离器管收集然后在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2′S)-2,2′-二甲基1-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(35.6mg,26%,4:1dr)。LCMS m/z 425.19$[M+H]^+$。^1H NMR(300MHz,甲醇-d_4)δ8.33(s,1H),6.47(d,J=1.4Hz,1H),5.10-4.91(m,2H),4.77-4.39(m,2H),3.91-3.77(m,4H),3.45-3.34(m,2H),3.03-2.93(m,3H),2.59(q,J=5.8Hz,2H),2.41(d,J=1.2Hz,3H),2.33-1.88(m,4H),1.65(d,J=7.1Hz,1H),1.56(d,J=6.4Hz,3H)。

[2224] 化合物1030

[2225] (2′S,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1030)



[2226]



1030

[2227] 步骤1:(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C117)的合成

[2228] 将(2R)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(252mg,1.182mmol)和2-(5-甲基-3-噻吩基)乙醇(165mg,1.160mmol)于DCM(1.5mL)中的溶液冷却至-40℃。向反应物中添加MsOH(220μL,3.390mmol)并将反应物在-40℃下搅拌2.5小时并使其温热至0℃。将反应混合物淬灭到饱和$NaHCO_3$溶液(15mL)和DCM(15mL)的双相混合物中,并将水层pH用2N NaOH调节至>10。然后将水层用DCM(3×15mL)萃取,并通过SPE筒过滤并浓缩成浅黄色凝胶。将粗材料溶解在DCM(1.5mL)中并添加Et_3N(330μL,2.368mmol)、Boc_2O(330μL,1.436mmol)。将反应混

合物在室温下搅拌20小时。将溶液用DCM稀释并且用水(10mL)洗涤。将水层用DCM(2×10mL)萃取,经硫酸钠干燥,通过SPE过滤器过滤,并在真空中浓缩。将所得残余物通过硅胶色谱法纯化(梯度:含0至30% EtOAc的庚烷)以在螺环中心产生两个非对映异构体。将期望产物分离为(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(313.5mg,80%)。1H NMR(300MHz,甲醇-d_4)δ6.42(d,J=1.2Hz,1H),4.35(p,J=7.0Hz,1H),3.97-3.81(m,3H),3.37-3.19(m,1H),2.69-2.47(m,2H),2.39(d,J=1.1Hz,3H),2.05(dd,J=14.5,2.1Hz,1H),1.95(dd,J=13.9,2.6Hz,1H),1.89-1.63(m,2H),1.48(s,9H),1.33(d,J=7.1Hz,3H)。

[2229] 步骤2:(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C118)的合成

[2230] 向(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C117(205mg,0.6074mmol)于DCM(2mL)中的经搅拌的溶液中添加HCl(0.5mL的4M的二噁烷,2.00mmol),并将反应物在室温下搅拌3小时。将反应混合物在氮气流下浓缩,并进行反相纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl。浓缩后,将产物分离(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(98.3mg,57%)。LCMS m/z 238.0$[M+H]^+$。1H NMR(300MHz,甲醇-d_4)δ6.52(t,J=1.2Hz,1H),3.95(t,J=5.6Hz,2H),3.72(dq,J=11.7,6.6Hz,1H),3.52(dt,J=13.2,6.5Hz,1H),3.28-3.19(m,1H),2.62(t,J=5.5Hz,2H),2.43(d,J=1.1Hz,3H),2.24-1.99(m,4H),1.50(d,J=6.9Hz,3H)。

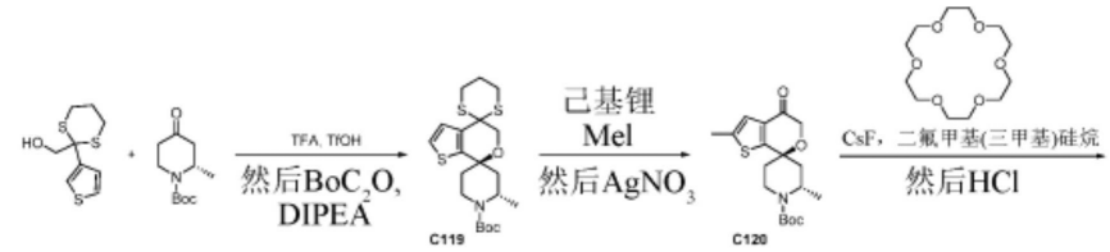
[2231] 步骤3:(2′R,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1030)的合成

[2232] 将(2′R,7R)-2,2′-二甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)C118(36mg,0.1315mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(28mg,0.1385mmol)溶解在DCM(1mL)中。将乙酸(50μL,0.8792mmol)添加到溶液中,随后添加聚合物负载的氰基硼氢化物(252mg的2mmol/g,0.5040mmol)。将溶液加盖并在微波反应器中加热至90℃,持续60分钟。将悬浮液在MeOH(1.5mL)中搅拌10分钟,然后滤出树脂(两次)。去除溶剂,并将残余物溶解在水(2mL)和DCM(2mL)中。用2M NaOH将水层的pH调节至pH>10。通过相分离器分离各相,将水层用DCM(2×10mL)萃取,并将合并的有机物在真空中浓缩。将粗残余物通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生(2′R,7R)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](55.5mg,95%)。^{1}H NMR(300MHz,甲醇-d_4)δ7.75(s,1H),7.57(d,J=0.8Hz,1H),6.46(d,J=1.1Hz,1H),4.64(t,J=6.6Hz,2H),3.91(t,J=5.6Hz,2H),3.80-3.64(m,4H),2.88(dd,J=13.0,6.5Hz,2H),2.77(d,J=0.8Hz,3H),2.73-2.62(m,1H),2.57(t,J=5.6Hz,2H),2.38(d,J=1.1Hz,3H),2.05-1.76(m,4H),1.24(d,J=6.4Hz,3H)。

[2233] 化合物1031

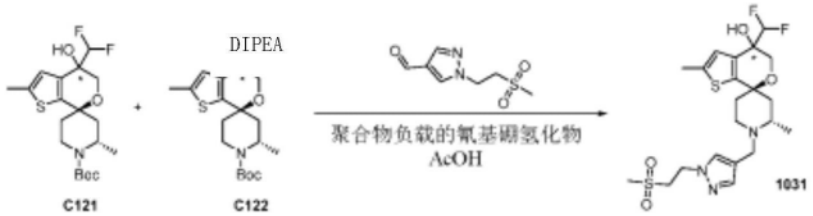
[2234] (2′S,7R)-4-(二氟甲基)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]

[2235] 螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1031)



然后 BoC_2O，　　然后 $AgNO_3$，　　然后 HCl

[2236]



聚合物负载的氰基硼氢化物

AcOH

[2237] 步骤1:(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(C119)的合成

[2238] 将(2S)-2-甲基-4-氧代-哌啶-1-甲酸叔丁酯(524mg,2.457mmol)溶解在DCM(21mL)中并添加TFA(1.13mL,14.67mmol)并搅拌30分钟。将溶剂在真空中去除。将[2-(3-噻吩基)-1,3-二噻烷-2-基]甲醇(600mg,2.453mmol)添加到相同反应烧瓶中,随后添加二噁烷(14mL)。将反应混合物冷却至0℃。逐滴添加三氟甲磺酸(434μL,4.905mmol)同时剧烈搅拌,并将反应物温热至rt。20分钟后,将反应混合物用DCM稀释,并用Na_2CO_3洗涤,并用DCM(x3)萃取。收集有机层,用硫酸钠干燥,过滤并去除溶剂以产生粗材料:(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]

[2239] 将粗材料溶解在DCM(21mL)中,并添加碳酸叔丁氧基羰基叔丁酯(733μL,3.191mmol)和DIPEA(728μL,4.180mmol)。将溶液在rt下搅拌4小时。将反应物通过硅胶柱色谱法纯化(梯度:含0至50% EtOAc的己烷)以产生(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯(250mg,20%)。LCMS m/z 428.15$[M+H]^+$。

[2240] 步骤2:(2S,4R)-2,2′-二甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C120)的合成

[2241] 在-78℃下向(6"S,7′R)-6"-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4"-哌啶]-1"-甲酸叔丁酯C119(250mg,0.5846mmol)于THF(10mL)中的溶液中逐滴添加己基锂(838μL的2.3M,1.927mmol)。将反应物在-78℃下搅拌1小时并添加MeI(36μL,0.5783mmol)作为THF中的溶液。搅拌1小时后,将反应物用NH_4Cl水溶液淬灭,并在DCM与NH_4Cl溶液之间分配。将水层用DCM(x3)萃取,并将合并的有机层用盐水洗涤,用硫酸钠干燥并将溶剂在真空中去除。

[2242] 将粗产物溶解在EtOH(10mL)中,并添加硝酸银(57μL,1.460mmol)并加热至50℃。2小时后,将溶液在DCM与水之间分配,并将有机层通过相分离器收集。将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-60%EtOAc的庚烷)以产生产物(2S,4R)-2,2′-二甲基-4′-

氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(145mg,65%)。LCMS m/z 352.42 $[M+H]^+$。^{1}HNMR(400MHz,甲醇-d_4)δ6.98(q,J=1.2Hz,1H),4.28(s,2H),4.13-3.99(m,1H),3.88-3.72(m,1H),3.41-3.31(m,1H),2.54-2.27(m,5H),1.98-1.76(m,2H),1.48(s,9H),1.24(d,J=6.5Hz,3H)。

[2243] 步骤3:(2′S,7R)-4-(二氟甲基)-2,2′-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(C121和C122)的合成

[2244] 在N_2下,将氟化铯(109mg,0.7176mmol)和1,4,7,10,13,16-六氧杂环十八烷(189mg,0.7151mmol)添加到(2S,4R)-2,2′-二甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯C120(250mg,0.7113mmol)于1,2-二甲氧基乙烷(6mL)中的溶液中。向混合物中添加二氟甲基(三甲基)硅烷(357mg,2.874mmol)并将所得混合物在室温下搅拌。搅拌60小时后,添加另外的二氟甲基(三甲基)硅烷(357mg,2.874mmol)并将溶液搅拌24小时。将反应物通过在水与DCM之间分配而淬灭,并通过相分离器管收集有机物,并在真空中浓缩以产生粗产物。

[2245] 将其溶解在二噁烷(2mL)中,并添加HCl(含2mL的4M的二噁烷,8.000mmol)。1小时后,将溶剂在真空中去除并将粗材料通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.2%甲酸。用pH 10缓冲液中和后分离出两种非对映异构体:

[2246] (2′S,7R)-4-(二氟甲基)-2,2′-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(33mg,30%)。^{1}H NMR(300MHz,甲醇-d_4)δ6.74(t,J=1.3Hz,1H),5.89(t,J=55.4Hz,1H),4.00(d,J=11.9Hz,1H),3.70(ddd,J=12.0,3.2,1.7Hz,1H),3.14-2.80(m,3H),2.43(d,J=1.2Hz,3H),2.15(dt,J=14.0,2.6Hz,1H),1.97-1.66(m,2H),1.35(dd,J=14.0,11.5Hz,1H),1.08(d,J=6.4Hz,3H);和

[2247] (2′S,7R)-4-(二氟甲基)-2,2′-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(31mg,28%)。^{1}H NMR(300MHz,甲醇-d_4)δ6.74(s,1H),5.89(t,J=55.4Hz,1H),4.01(d,J=12.0Hz,1H),3.74-3.60(m,1H),3.15-2.80(m,3H),2.43(d,J=1.1Hz,3H),2.12(d,J=14.2Hz,1H),1.94(d,J=13.8Hz,1H),1.78-1.57(m,1H),1.53-1.36(m,1H),1.08(d,J=6.4Hz,3H)。

[2248] 步骤4:(2′S,7R)-4-(二氟甲基)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基-乙基)吡唑-4-基]甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1031)的合成

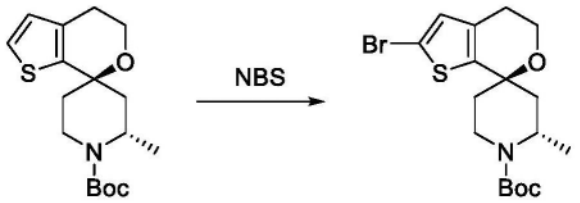
[2249] 将(2′S)-4-(二氟甲基)-2,2′-二甲基-螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇C122(20mg,0.06593mmol)添加到微波小瓶中并添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(26.67mg,0.1319mmol)、乙酸(19mg,0.3164mmol)和DCM(2mL)。添加聚合物负载的氰基硼氢化物(98mg的2mmol/g,0.1960mmol)。将反应小瓶在微波反应器中加热至95℃,持续2小时。添加MeOH,并将溶液搅拌10分钟以洗涤珠粒。将溶液过滤,并将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM),产生(2′S,7R)-4-(二氟甲基)-2,2′-二甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[5H-噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(8.2mg,25%)。LCMS m/z 490.18 $[M+H]^+$。^{1}H NMR(300MHz,甲醇-d_4)δ7.71(d,J=0.8Hz,1H),7.53(d,J=0.8Hz,1H),6.82-6.62(m,1H),5.86(t,J=55.4Hz,1H),4.62(t,J=6.4Hz,2H),3.97-3.54(m,6H),2.77-2.32(m,9H),2.12(dd,J=14.3,2.7Hz,1H),2.00-1.80

(m,2H),1.58(dd,J＝14.2,11.6Hz,1H),1.22(d,J＝6.3Hz,3H)。

[2250] 制备S82

[2251] (2′S,7R)-2-溴-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯

[2252] (S82)

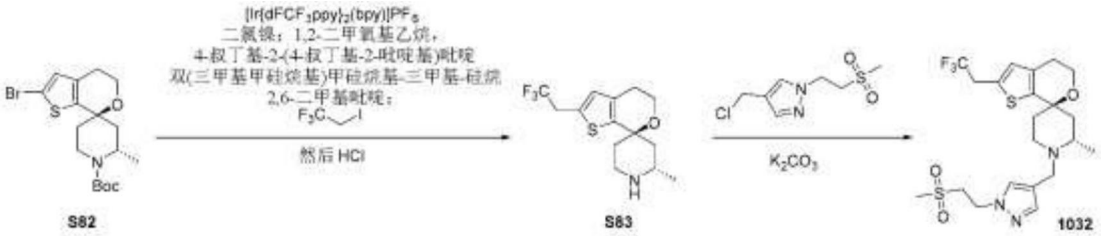
[2253] 

C26 S82

[2254] 在氮气下向烧瓶中添加含(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C26(860mg,2.659mmol)的THF(15mL)和NBS(465mg,2.613mmol)。将反应混合物搅拌过夜,之后用饱和碳酸氢盐溶液淬灭并将有机溶剂蒸发。将水层用DCM萃取。将合并的有机层浓缩,并通过硅胶色谱法纯化(梯度:含0-20% EtOAc的庚烷),产生(2′S,7R)-2-溴-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(905mg,81%)。LCMS m/z 402.08$[M+H]^+$。

[2255] 化合物1032

[2256] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1032)

[2257] 

[2258] 步骤1:(2′S,7R)-2′-甲基-2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](S83)的合成

[2259] 将二氯镍;1,2-二甲氧基乙烷(3.2mg,0.014mmol)、4-叔丁基-2-(4-叔丁基-2-吡啶基)吡啶(3.9mg,0.014mmol)和$[Ir\{dFCFppy\}_2(bpy)]PF_6$(1.4mg,0.0014mmol)称入1打兰小瓶中。将反应用隔板加盖并泵送/吹扫(x3)。向其中添加含(2′S,7R)-2-溴-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S82(60mg,0.14mmol)的DME(1mL),并搅拌10分钟。然后添加2,6-二甲基吡啶(31mg,0.29mmol)、双(三甲基甲硅烷基)甲硅烷基-三甲基-硅烷(36mg,0.14mmol)和1,1,1-三氟-2-碘代-乙烷(60mg,0.29mmol)。将反应混合物在Merck光反应器中(100% LED功率/4700RPM风扇/1700RPM搅拌)辐照2小时。然后将反应物用DCM稀释并用1N HCl洗涤。将有机层在真空中浓缩并添加HCl(二噁烷溶液)。2小时后,将反应混合物浓缩。将粗材料通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将最终产物分离为(2′S,7R)-2′-甲基-2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](2.4mg,5.5%)。LCMS m/z 306.09$[M+H]^+$。^1H NMR(400MHz,DMSO-d_6)δ8.73(s,1H),8.32(s,1H),6.85

(s,1H),4.09-3.82(m,5H),3.28-3.03(m,2H),2.61(m,2H),2.16(m,2H),1.89(m,1H),1.74(m,1H),1.21(d,J=6.5Hz,3H)。

[2260] 步骤2:(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]-2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1032)的合成

[2261] 在氮气下将(2′S,7R)-2′-甲基-2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]S83(20mg,0.048mmol)溶解在MeCN(2mL)中。然后添加4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(12.4mg,0.048mmol)和K_2CO_3(19.9mg,0.144mmol)。将反应混合物加热至70℃过夜。然后,将反应物用水淬灭并用DCM(x3)萃取。将合并的有机层浓缩,并通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]2-(2,2,2-三氟乙基)螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](4.2mg,18%)。LCMS m/z 492.12$[M+H]^+$。^{1}H NMR(400MHz,DMSO-d_6)δ7.72(s,1H),7.40(s,1H),6.77(s,1H),4.51(t,J=6.8Hz,2H),3.90-3.62(m,7H),3.46(d,J=14.3Hz,1H),2.77(s,3H),2.45-2.30(m,5H),1.91(d,J=13.2Hz,2H),1.66(dt,J=13.9,6.9Hz,1H),1.44(t,J=12.5Hz,1H),1.10(d,J=6.1Hz,3H)。

[2262] 化合物1033

[2263] (2′S,7R)-2-环丁基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-

[2264] 二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1033)

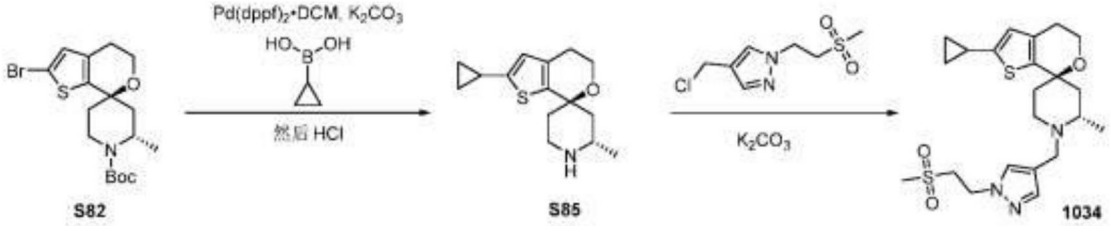
[2265] 

[2266] (2′S,7R)-2-环丁基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]根据如化合物1032的制备中的程序制备。LCMS m/z 464.21$[M+H]^+$。^{1}H NMR(400MHz,DMSO-d_6)δ7.72(s,1H),7.40(s,1H),6.52(s,1H),4.51(t,J=6.8Hz,2H),3.84-3.43(m,7H),2.77(s,3H),2.56-2.26(m,7H),2.11-1.59(m,7H),1.50-1.39(m,1H),1.09(d,J=6.2Hz,3H)。

[2267] 化合物1034

[2268] (2′S,7R)-2-环丙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-

[2269] 二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1034)

[2270] 

[2271] 步骤1:(2′S,7R)-2-环丙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌

啶](S85)的合成

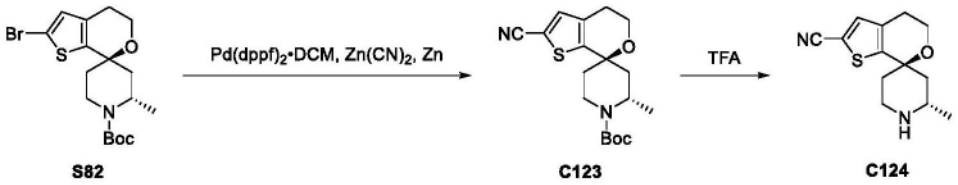
[2272] 在氮气下将(2′S,7R)-2-溴-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S82(120mg,0.2871mmol)、环丙基硼酸(30mg,0.3493mmol)、Pd(dppf)Cl_2(23.5mg,0.02871mmol)和K_2CO_3(80mg,0.5788mmol)添加到DME(2mL)中。将反应混合物用氮气喷射5分钟,之后加热至回流过夜。然后将反应混合物用EtOAc稀释并由水(x2)萃取。将合并的有机层在真空中浓缩并且然后用HCl(含1000μL的4M的二噁烷,4.000mmol)并搅拌过夜。将反应混合物在真空中浓缩。将粗材料通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有5mM HCl。将产物分离为(2′S,7R)-2-环丙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(14.6mg,16%)。LCMS m/z 264.1$[M+H]^+$。^{1}H NMR(400MHz,DMSO-d_6)δ8.68(s,1H),8.28(s,1H),6.54(s,1H),3.85(m,2H),3.42-3.04(m,4H),2.17-2.00(m,3H),1.90-1.64(m,2H),1.20(d,J=6.5Hz,4H),1.01-0.92(m,2H),0.65-0.58(m,2H)。

[2273] 步骤2:(2′S,7R)-2-环丙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1034)的合成

[2274] 向(2′S,7R)-2-环丙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](盐酸盐)(11.5mg,0.038mmol)于ACN(1mL)中的溶液中添加K_2CO_3(40mg,0.2894mmol)和4-(氯甲基)-1-(2-甲基磺酰基乙基)吡唑(10mg,0.04491mmol)。将反应混合物在70℃下搅拌过夜,之后用水稀释并用DCM萃取。将合并的有机层浓缩,并通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生(2′S,7R)-2-环丙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](9.2mg,7%)。LCMS m/z 450.48$[M+H]^+$。^{1}H NMR(400MHz,DMSO-d_6)δ7.71(s,1H),7.39(s,1H),6.46(s,1H),4.51(t,J=6.8Hz,2H),3.79-3.64(m,5H),3.50-3.25(m,2H),2.77(s,3H),2.49-2.26(m,2H),2.05-1.78(m,3H),1.70-1.36(m,4H),1.08(d,J=6.2Hz,3H),0.92(dd,J=8.2,2.3Hz,2H),0.60(dd,J=4.9,2.1Hz,2H)。

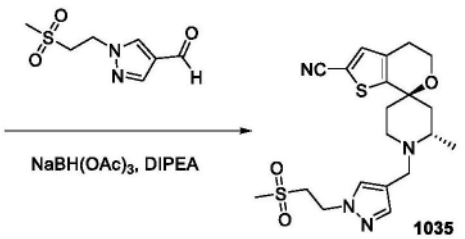
[2275] 化合物1035

[2276] (2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(1035)



S82 C123 C124

[2277]



[2278] 步骤1:(2′S,7R)-2-氰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌

啶]-1′-甲酸叔丁酯(C123)的合成

[2279] 向2打兰小瓶中装入(2′S,7R)-2-溴-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯S82(100mg,0.2485mmol)、Pd(dppf)Cl_2(21mg,0.02572mmol)、双氰锌(24μL,0.3781mmol)、Zn(5mg,0.07644mmol)。添加DMA(2.4mL),并将反应混合物用N_2吹扫5分钟。将反应物在90℃下加热20小时。将反应混合物用EtOAc稀释并用NH_4OH(2.5M)淬灭。将有机层分离,并将水层用EtOAc(x3)萃取,并将合并的有机萃取物在真空中浓缩。将粗产物通过硅胶色谱法纯化(梯度:含0-50% EtOAc的己烷),产生(2′S,7R)-2-氰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(110mg,127%)。LCMS m/z 348.95$[M+H]^+$。假设定量产率,该产物无需进一步纯化即可继续进行。

[2280] 步骤2:(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(C124)的合成

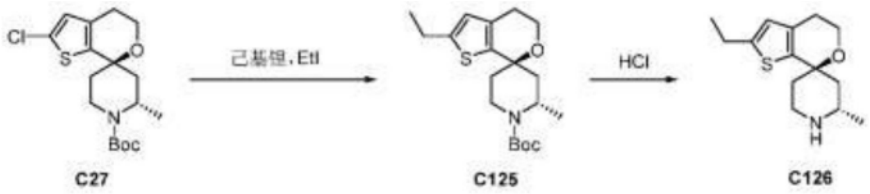
[2281] 向2打兰小瓶中装入(2′S,7R)-2-氰基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C123(86mg,0.2468mmol)并向DCM(0.8mL)中添加TFA(200μL,2.596mmol)。将所得黄色溶液在rt下搅拌。将挥发物在真空中去除以得到粗产物:(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(三氟乙酸盐)(89mg,95%)。LCMS m/z 249.0$[M+H]^+$。^{1}HNMR(300MHz,甲醇-d_4)δ7.54(s,1H),4.00(td,J=5.7,2.1Hz,2H),3.62(s,1H),3.45-3.30(m,2H),2.77(t,J=5.5Hz,2H),2.41-2.18(m,2H),1.99(ddd,J=14.9,12.0,5.9Hz,1H),1.82(dd,J=14.7,12.2Hz,1H),1.34(d,J=6.6Hz,3H)。该产物无需进一步纯化即可继续进行。

[2282] 步骤3:(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(1035)的合成

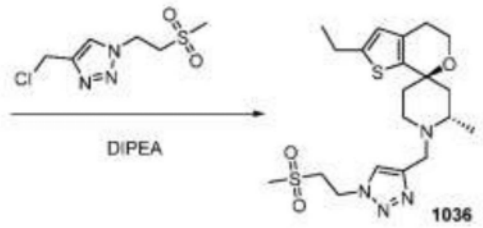
[2283] 向2打兰小瓶中装入(2′S,7R)-2′-甲基螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(三氟乙酸盐)C124(35mg,0.09659mmol)和DCM(1mL)。添加1-(2-甲基磺酰基乙基)吡唑-4-甲醛(39mg,0.1928mmol),随后添加三乙酰氧基硼氢化钠(61mg,0.2892mmol)。将所得混合物在rt下搅拌。添加N-乙基-N-异丙基-丙-2-胺(34μL,0.1952mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(20mg,0.10mmol),并将反应物在rt下搅拌过夜。将反应物用饱和$NaHCO_3$溶液缓慢淬灭,用DCM萃取并将合并的有机萃取物在真空中浓缩。将粗材料通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2′S,7R)-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-2-甲腈(三氟乙酸盐)(35.4mg,63%)。LCMS m/z 435.0$[M+H]^+$。^{1}H NMR(300MHz,甲醇-d_4)δ8.00(s,1H),7.73(s,1H),7.54(s,1H),4.76-4.66(m,2H),4.56(d,J=14.1Hz,1H),4.30(d,J=14.1Hz,1H),3.94(q,J=5.1Hz,2H),3.73(t,J=6.2Hz,2H),3.55(s,1H),3.44-3.33(m,3H),2.88(s,3H),2.74(t,J=5.5Hz,2H),2.49-2.26(m,1H),2.11-1.89(m,2H),1.54(d,J=6.4Hz,3H)。

[2284] 化合物1036

[2285] (2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1036)



[2286]



[2287] 步骤1:(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C125)的合成

[2288] 将(2′S,7R)-2-氯-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C27(110mg,0.3074mmol)溶解在THF(4mL)中并冷却至-78℃。逐滴添加己基锂(400μL的2.3M,0.9200mmol)并使溶液搅拌60分钟。将碘乙烷(25μL,0.3126mmol)添加到溶液中并将其温热至rt。12小时后,将反应物用氯化铵水溶液淬灭,并用EtOAc萃取,用盐水洗涤,并用硫酸钠干燥。将合并的有机层在真空中浓缩以提供(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(120mg,25%)。LCMS m/z352.52[M+H]$^+$。

[2289] 步骤2:(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C126)的合成

[2290] 将(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯C125(120mg,0.3414mmol)溶解在二噁烷(4.3mL)中,并添加HCl(850μL的4M,3.400mmol)。将溶液搅拌过夜。12小时后,将溶液在真空中浓缩以提供(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](85.82mg,100%),其无需进一步纯化即可用于下一步。LCMS m/z 252.46[M+H]$^+$。

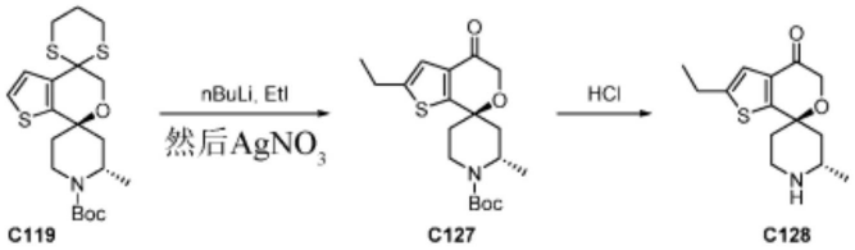
[2291] 步骤3:(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1046)的合成

[2292] 将(2′S,7R)-2-乙基-2′-甲基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]C126(85.82mg,0.34mmol)溶解在DCE(4.3mL)中,并添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(76mg,0.3398mmol)和DIPEA(60μL,0.3445mmol)。将所得溶液在rt下搅拌并加热至65℃。24小时后,将溶液冷却并在DCM与1N NaOH之间分配。将有机层通过相分离器管收集然后在真空中浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](三氟乙酸盐)(41mg,43%)。LCMS m/z 439.2[M+H]$^+$。^{1}HNMR(300MHz,甲醇-d_4)δ8.33(s,1H),6.63-6.40(m,1H),5.07-4.91(m,2H),4.74-4.48(m,2H),4.00-3.74(m,4H),3.55(d,J=11.3Hz,

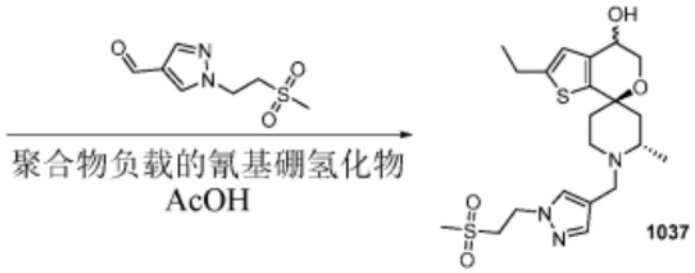
1H),3.46-3.35(m,2H),3.06-2.93(m,3H),2.77(dt,J＝8.3,7.0Hz,2H),2.61(dt,J＝10.7,7.1Hz,2H),2.37-1.95(m,4H),1.76-1.45(m,3H),1.25(t,J＝7.5Hz,3H)。

[2293] 化合物1037

[2294] (2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1037)



[2295]



[2296] 步骤1:(2S,4R)-2′-乙基-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(C127)的合成

[2297] 在-78℃下向(6”S,7′R)-6”-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯C119(600mg,1.403mmol)于THF(16mL)中的溶液中逐滴添加n-BuLi(582μL的2.41M,1.403mmol)。将反应物搅拌1小时,此时在-78℃下添加碘乙烷(224μL,2.801mmol)作为THF中的溶液。搅拌1小时后,将反应混合物温热至rt。将反应物用NH_4Cl水溶液淬灭,并在DCM与NH_4Cl水溶液之间分配。将水层用DCM(x3)萃取,并将合并的有机层用盐水洗涤,用硫酸钠干燥并将溶剂在真空中去除以提供(6”S,7′R)-2′-乙基-6”-甲基-5′H-二螺[1,3-二噻烷-2,4′-噻吩并[2,3-c]吡喃-7′,4”-哌啶]-1”-甲酸叔丁酯。

[2298] 将粗材料溶解在乙醇(24mL)中,并添加硝酸银(137μL,3.510mmol)并将反应物加热至50℃。2小时后,将溶液在DCM与水之间分配,并将有机层通过相分离器收集。将溶剂在真空中去除。通过硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生产物(2S,4R)-2′-乙基-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲酸叔丁酯(150mg,29%)。LCMS m/z 366.33$[M+H]^+$。^1H NMR(300MHz,甲醇-d_4)δ7.01(t,J＝1.1Hz,1H),4.29(s,2H),4.06(dq,J＝12.4,6.2Hz,1H),3.81(ddd,J＝14.4,6.8,3.3Hz,1H),3.40-3.35(m,1H),2.84(qd,J＝7.5,1.2Hz,2H),2.48-2.21(m,2H),2.03-1.71(m,2H),1.48(s,11H),1.37-1.13(m,7H)。

[2299] 步骤2:(2S,4R)-2′-乙基-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(C128)的合成

[2300] 将(2S,4R)-2′-乙基-2-甲基-4′-氧代-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-1-甲

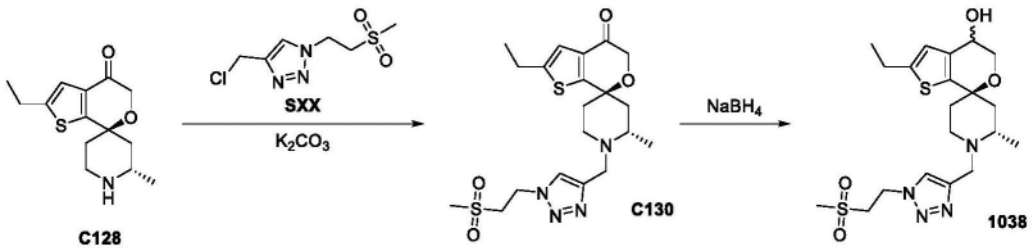
酸叔丁酯C127(90mg,0.2462mmol)溶解在二噁烷(500μL)中,并添加HCl(含620μL的4M的二噁烷,2.480mmol)。将反应混合物在rt下搅拌30分钟。将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸。将产物分离为(2S,4R)-2′-乙基-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(三氟乙酸盐)(72mg,77%)。LCMS m/z 266.28$[M+H]^+$。^{1}H NMR(300MHz,甲醇-d_4)δ7.08(t,J=1.1Hz,1H),4.39(d,J=0.7Hz,2H),3.61(ddp,J=9.3,6.4,2.7Hz,1H),3.45-3.34(m,2H),2.86(qd,J=7.5,1.1Hz,2H),2.59-2.36(m,2H),2.19-1.85(m,2H),1.44-1.17(m,6H)。

[2301] 步骤3:(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1037)的合成

[2302] 将(2S,4R)-2′-乙基-2-甲基-螺[哌啶-4,7-噻吩并[2,3-c]吡喃]-4′酮(三氟乙酸盐)C128(31mg,0.08171mmol)和1-(2-甲基磺酰基乙基)吡唑-4-甲醛(25mg,0.1236mmol)溶解在DCM(2mL)中,并将乙酸(23mg,0.3830mmol)添加到溶液中。将溶液转移到微波管(5mL)中并添加聚合物负载的氰基硼氢化物(122mg的2mmol/g,0.2440mmol)。将溶液加盖并在微波反应器中加热至95℃,持续2小时。将溶液过滤,并将溶剂在真空中去除。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,产生(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(16mg,31%)。LCMS m/z 454.34$[M+H]^+$。^{1}H NMR(300MHz,甲醇-d_4)δ7.99(s,1H),7.72(d,J=0.8Hz,1H),6.73(q,J=1.0Hz,1H),4.78-4.64(m,2H),4.64-4.38(m,2H),4.28(d,J=14.1Hz,1H),4.02-3.63(m,4H),3.36(dd,J=5.0,2.3Hz,1H),3.28-3.16(m,1H),2.92-2.63(m,6H),2.46-2.23(m,2H),2.16-1.73(m,2H),1.53(dd,J=6.5,4.1Hz,3H),1.26(t,J=7.5Hz,3H)。

[2303] 化合物1038

[2304] (2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1038)

[2305] 

[2306] 步骤1:(2S,4R)-2′-乙基-2-甲基-1-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(C130)的合成

[2307] 向(2S,4R)-2′-乙基-2-甲基-螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(三氟乙酸盐)C128(10mg,0.02636mmol)于乙腈(429.9μL)中的溶液中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(盐酸盐)(10mg,0.03844mmol)和碳酸钾(11.4mg,0.08249mmol)。将混合物在70℃下搅拌3小时。将混合物冷却至rt,用水和DCM稀释,并且后来将有机物通过相分离器收集。将有机层收集,并将溶剂在真空中去除以产生粗产物(2S,4R)-2′-乙基-2-甲基-1-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮(11.9mg,100%)。LCMS m/z 453.22$[M+H]^+$。材料无需进一步纯化即可用于下一步。

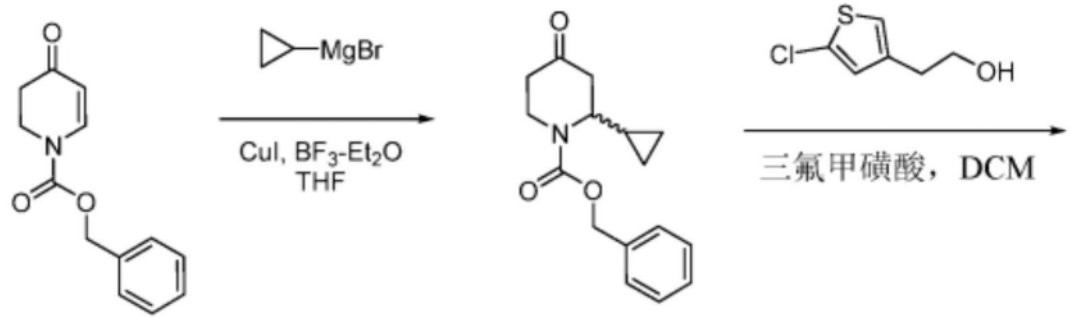
[2308] 步骤2:(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1038)的合成

[2309] 在N_2下将(2S,4R)-2′-乙基-2-甲基-1-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[哌啶-4,7′-噻吩并[2,3-c]吡喃]-4′-酮C130(15.8mg,0.03491mmol)溶解在DCM(630μL)和甲醇(158μL)中,随后添加$NaBH_4$(7.8mg,0.2073mmol)。在rt下搅拌1小时后,将反应混合物用水和DCM洗涤,并将有机层通过相分离器收集。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,得到(2′S,7R)-2-乙基-2′-甲基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(三氟乙酸盐)(2.3mg,12%)。LCMS m/z 455.33$[M+H]^+$。^1H NMR(300MHz,甲醇-d_4)δ8.06(s,1H),6.67(d,J=1.3Hz,1H),4.92(t,J=6.6Hz,3H),4.40(dd,J=6.6,3.5Hz,1H),4.11-3.61(m,6H),2.93-2.54(m,9H),2.14-1.50(m,3H),1.25(q,J=4.2,3.6Hz,6H)。

[2310] 化合物1040

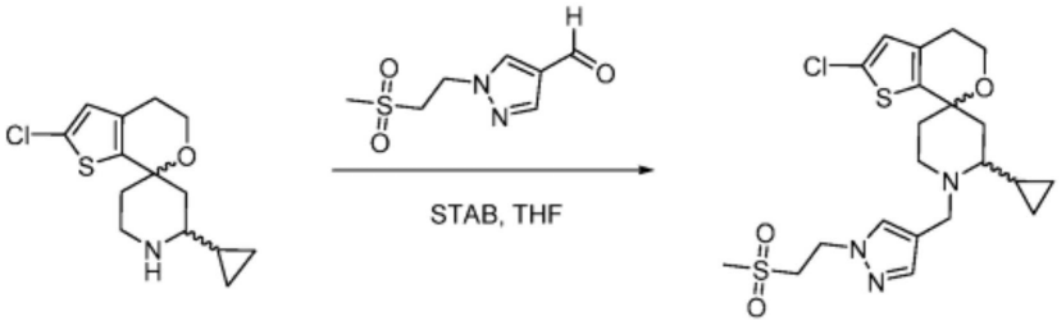
[2311] 2-氯-2′-环丙基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并

[2312] [2,3-c]吡喃-7,4′-哌啶](1040)



C169

[2313]



C170 1040

[2314] 步骤1:2-环丙基-4-氧代-哌啶-1-甲酸苄酯(C169)的合成

[2315] 在-78℃下在氮气气氛下向圆底烧瓶中添加含CuI(1.62g,8.506mmol)的THF(11mL)。添加溴(环丙基)镁(9mL的1M,9.000mmol),并将混合物在-78℃下搅拌30分钟,然后添加二乙基氧鎓(三氟)硼酊(80μL,0.6482mmol)。将混合物在-78℃下搅拌另外10分钟,并添加含4-氧代-2,3-二氢哌啶-1-甲酸苄酯(1g,4.324mmol)的4mL THF。在-78℃下继续搅拌

5小时。将反应物用饱和NH_4Cl淬灭。将有机层用CH_2Cl_2(3x)通过相分离器萃取并浓缩。将粗产物通过正相快速柱色谱法纯化(梯度:含0-50% EtOAc/庚烷)以提供2-环丙基-4-氧代-哌啶-1-甲酸苄酯(603mg,37%)。^1H NMR(300MHz,氯仿-d)δ7.23(d,J=11.5Hz,5H),5.12-4.96(m,2H),4.30(dd,J=14.1,7.0Hz,1H),3.83(t,J=8.2Hz,1H),3.43-3.27(m,1H),2.53(dd,J=14.4,6.8Hz,1H),2.46-2.16(m,3H),0.80(dddd,J=10.1,8.0,5.0,3.1Hz,1H),0.56-0.11(m,4H)。ESI-MS m/z 274.07$[M+H]^+$。

[2316] 步骤2:2-氯-2′-环丙基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](C170)的合成

[2317] 在0℃下将2-环丙基-4-氧代-哌啶-1-甲酸苄酯(580mg,2.122mmol)溶解在CH_2Cl_2(12mL)中,并用三氟甲磺酸(750μL,8.476mmol)处理。将溶液搅拌10分钟,然后添加2-(5-氯-3-噻吩基)乙醇(300μL)。使反应温热至环境温度,并搅拌20分钟。将反应物用$NaHCO_3$淬灭并用CH_2Cl_2(3x)通过相分离器萃取。将粗产物通过正相快速柱色谱法纯化(梯度:0-80% EtOAc/Hep)以提供2-氯-2′-环丙基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](332.8mg,50%)作为对应反式对映异构体的混合物。^1H NMR(300MHz,氯仿-d)δ6.60(s,1H),3.95-3.74(m,2H),3.35(ddd,J=23.5,12.0,4.8Hz,2H),2.71-2.52(m,3H),2.31(d,J=14.6Hz,1H),2.18-1.95(m,3H),1.09(dq,J=12.7,7.7,5.7Hz,1H),0.77-0.52(m,3H),0.29(d,J=7.0Hz,1H)。ESI-MS m/z284.06$[M+H]^+$。

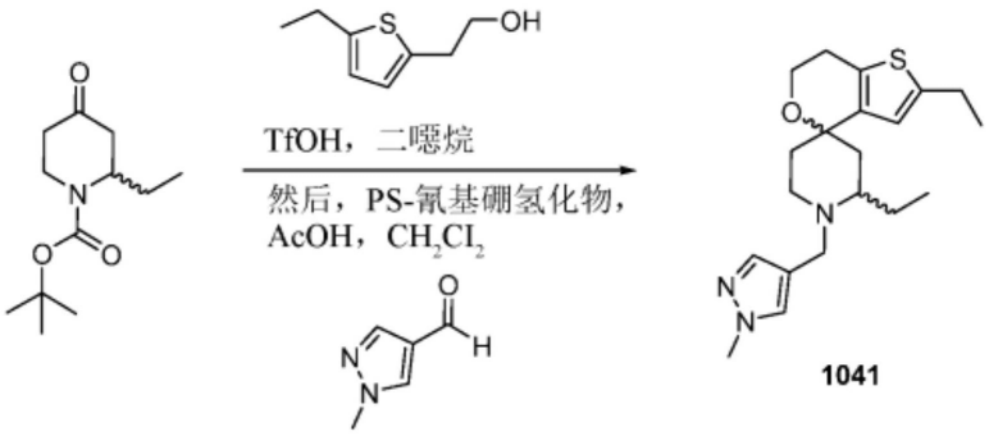
[2318] 步骤3:2-氯-2′-环丙基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1040)的合成

[2319] 将2-氯-2′-环丙基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](59mg,0.2039mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(62mg,0.3066mmol)和三乙酰氧基硼氢化物(钠盐)(144mg,0.6794mmol)添加到微波小瓶中,并溶解在THF(1.4mL)中。将反应物在55℃下搅拌2小时。将反应混合物用$NaHCO_3$淬灭并用CH_2Cl_2(3x)通过相分离器萃取。将粗产物通过正相色谱法纯化(梯度:0-6% MeOH/DCM)。以提供期望的2-氯-2′-环丙基-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]甲腈(三氟乙酸盐)(42.2mg,31%)。^1H NMR(300MHz,MeOD)δ7.96(s,1H),7.71(s,1H),6.75(s,1H),5.10(d,J=13.8Hz,1H),4.71(t,J=6.2Hz,2H),4.07(d,J=13.8Hz,1H),3.93(q,J=5.4Hz,2H),3.72(t,J=6.2Hz,2H),3.19(t,J=12.3Hz,1H),2.90(s,3H),2.64(q,J=4.7Hz,2H),2.47(d,J=14.9Hz,1H),2.27(d,J=15.9Hz,1H),2.09-1.98(m,1H),1.92-1.81(m,1H),1.35-1.21(m,1H),1.02(d,J=8.3Hz,2H),0.90-0.70(m,2H),0.35(dd,J=9.5,4.8Hz,1H)。ESI-MS m/z 470.41$[M+H]^+$。

[2320] 化合物1041

[2321] 2,2′-二乙基-1-((1-甲基-1H-吡唑-4-基)甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并

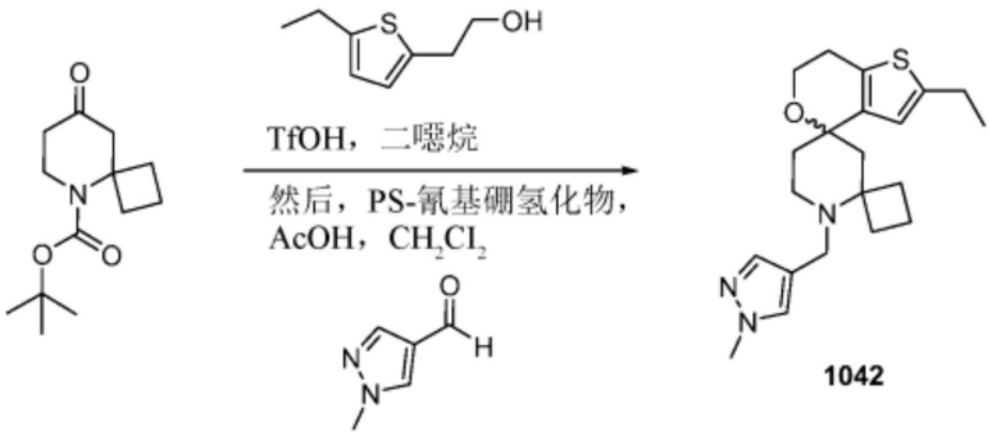
[2322] [3,2-c]吡喃](1041)

[2323] 

[2324] 向微波小瓶中用搅拌棒添加2-乙基-4-氧代-哌啶-1-甲酸叔丁酯(90mg,0.4mmol)、含2-(5-乙基-2-噻吩基)乙醇(75mg,0.48mmol)的二噁烷(2.0mL)。添加三氟甲磺酸(0.1mL,1.13mmol)并将反应物在环境温度下搅拌2小时。此时将反应物浓缩,并将粗中间体重新溶解在CH_2Cl_2(2.0mL)中。向溶液中添加与10% DVB(30-50网)(2.6-3.0mmol/g)交联的(聚苯乙烯基甲基)三甲基胺氰基硼氢化物(500mg,1.0mmol)、乙酸(0.13mL,2.0mmol)和1-甲基吡唑-4-甲醛(88mg,0.8mmol)。将微波小瓶加盖并在微波条件下辐照至110℃,持续20分钟。然后将混合物过滤,浓缩。通过反相HPLC纯化。方法:C18 Waters Sunfire柱(30×150mm,5微米)。梯度:含MeCN的H_2O,具有0.1%三氟乙酸,提供2,2′-二乙基-1-((1-甲基-1H-吡唑-4-基)甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃](13.7mg,7%)。ESI-MS m/z360.23$[M+H]^+$。

[2325] 化合物1042

[2326] 2”-乙基-1′-((1-甲基-1H-吡唑-4-基)甲基)-6”,7”-二氢二螺[环丁烷-1,2′-哌啶-4′,4”-噻吩并[3,2-c]吡喃](1042)

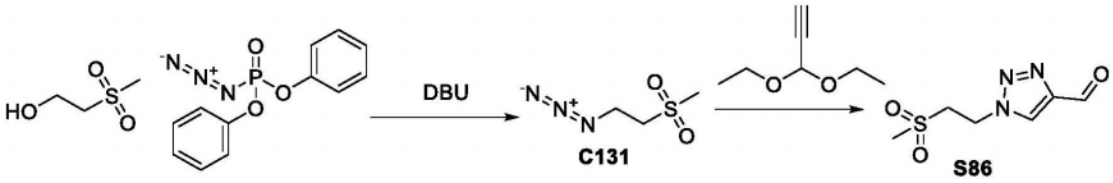
[2327] 

[2328] 化合物1042按照化合物1041所述的方法,使用氧代-哌啶中间体8-氧代-5-氮杂螺[3.5]壬烷-5-甲酸叔丁酯制备。这提供了产物2”-乙基-1′-((1-甲基-1H-吡唑-4-基)甲基)-6”,7”-二氢二螺[环丁烷-1,2′-哌啶-4′,4”-噻吩并[3,2-c]吡喃](12mg,6%)。ESI-MS m/z 372.22$[M+H]^+$。

[2329] 共同中间体的制备:

[2330] 制备S86

[2331] 1-(2-甲基磺酰基乙基)三唑-4-甲醛(S86)

[2332] 

[2333] 步骤1:1-叠氮基-2-甲基磺酰基-乙烷(C131)

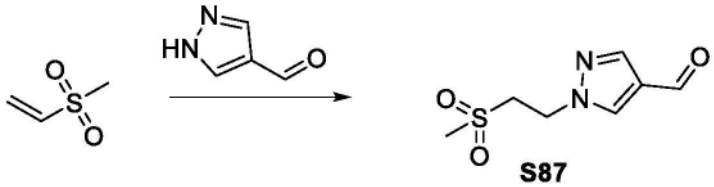
[2334] 将2-甲基磺酰基乙醇(5g,0.0403mol)和二苯基磷酰基叠氮化物(8.8614g,0.0322mol)于甲苯(50.000mL)中的溶液在0℃下搅拌10分钟,并在0℃下在10分钟内逐滴添加DBU(5.5262g,5.4285mL,0.0363mol),并将反应物在室温下搅拌16小时。将反应混合物用水(25mL)和乙酸乙酯(100mL)淬灭并搅拌20分钟。将有机层分离并将水层用乙酸乙酯(100mL×2)再次萃取。将有机层经硫酸钠干燥并浓缩。通过硅胶色谱法纯化(梯度:含0-100%乙酸乙酯的石油醚),产生1-叠氮基-2-甲基磺酰基-乙烷C131(5.2g,86%)。^{1}H NMR(400MHz,DMSO-d6)δ=3.77-3.73(t,J=8.8Hz,2H),3.44-3.42(t,J=8.8Hz,2H),3.03(s,3H)。

[2335] 步骤2:1-(2-甲基磺酰基乙基)三唑-4-甲醛(S86)

[2336] 将3,3-二乙氧基丙-1-炔(555μL,3.897mmol)、1-叠氮基-2-甲基磺酰基-乙烷C131(600mg,4.022mmol)、CuSO4(15mg,0.09398mmol)、1-(1-苄基三唑-4-基)-N,N-双[(1-苄基三唑-4-基)甲基]甲胺(100mg,0.1885mmol)和抗坏血酸钠(700mg,3.974mmol)于MeOH(12mL)/水(3mL)中的混合物加热至60℃,持续2小时。将反应物冷却至室温,浓缩并在EtOAc(100mL)和水(50mL)中稀释。分开各层并将水层用EtOAc(50mL)萃取。将各层合并并浓缩,在1N HCl(20mL)中稀释,并搅拌过夜。此时,将溶液浓缩以产生1-(2-甲基磺酰基乙基)三唑-4-甲醛(盐酸盐)S86(553mg,59%)。^{1}H NMR(400MHz,甲醇-d4)δ8.07(s,1H),5.58-5.45(m,1H),4.89-4.82(m,2H),3.76-3.67(m,2H),3.24(s,3H)。LCMS m/z 204.47$[M+H]^+$。

[2337] 制备S87

[2338] 1-(2-甲基磺酰基乙基)吡唑-4-甲醛(S87)

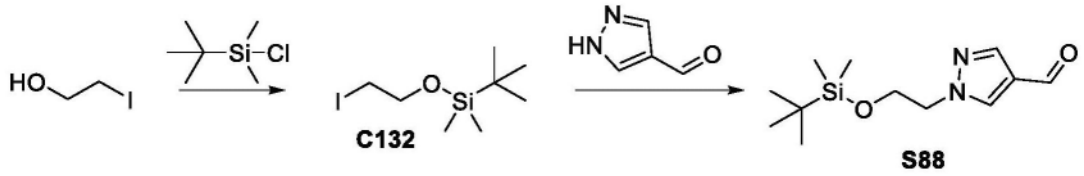
[2339] 

[2340] 步骤1:1-(2-甲基磺酰基乙基)吡唑-4-甲醛(S87)

[2341] 将1H-吡唑-4-甲醛(10g,104.1mmol)、1-甲基磺酰乙烯(10mL,114.2mmol)和碳酸钾(25g,180.9mmol)于四氢呋喃(200mL)中的溶液在60℃下搅拌。搅拌过夜后,将混合物冷却至室温并且浓缩到干燥。将产物悬浮在二乙醚(100mL)中以研磨产物并搅拌2小时。将产物过滤并干燥过夜以产生1-(2-甲基磺酰基乙基)吡唑-4-甲醛S87(20280mg,83%)。1HNMR(400MHz,DMSO-d6)δ9.80(s,1H),8.54(d,J=0.7Hz,1H),8.05(d,J=0.7Hz,1H),4.64(t,J=6.8Hz,2H),3.80-3.67(m,2H),2.96(d,J=0.7Hz,3H)。LCMS m/z 203.01$[M+H]^+$。

[2342] 制备S88

[2343] 1-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]吡唑-4-甲醛(S88)

[2344] 

[2345] 步骤1:叔丁基-(2-碘乙氧基)-二甲基-硅烷(C132)

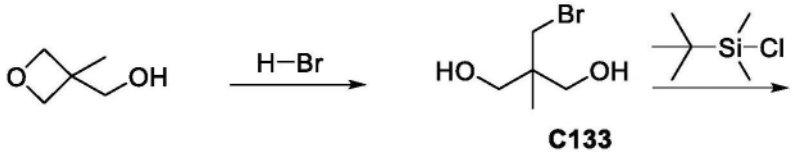
[2346] 在0℃下向2-碘乙醇(2g,0.0116mol)和咪唑(1.58g,0.0232mol)于DCM(40mL)中的经搅拌的溶液中添加叔丁基-氯-二甲基-硅烷(1.9g,0.0126mol)。将反应物温热至室温并搅拌4小时。将反应混合物用DCM(100mL)稀释,用饱和$NaHCO_3$和盐水洗涤,经Na_2SO_4干燥并在减压下浓缩以产生叔丁基-(2-碘乙氧基)-二甲基-硅烷C132(2.5g,68%),^{1}H NMR(400MHz,氯仿-d)δ3.83(t,J=6.8Hz,2H),3.20(t,J=6.8Hz,2H),0.90(s,9H),0.08(s,6H)。

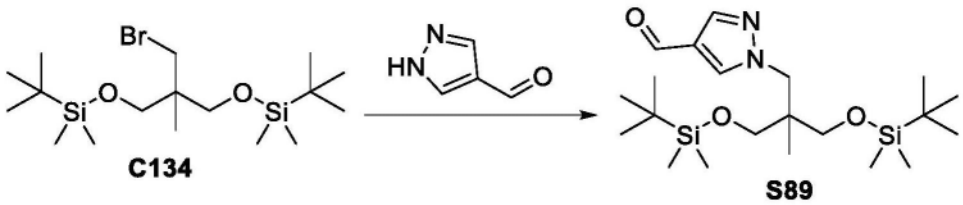
[2347] 步骤2:1-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]吡唑-4-甲醛(S88)

[2348] 向1H-吡唑-4-甲醛(20g,208.1mmol)和K_2CO_3(115g,832.1mmol)于MeCN(200mL)中的溶液中添加叔丁基-(2-碘乙氧基)-二甲基-硅烷C132(65g,227.1mmol)。将反应物加热至80℃。将反应物搅拌5小时。将反应物冷却至50℃并搅拌16小时。将反应混合物温热、过滤,并且用MeCN(200mL)洗涤固体。丢弃固体。浓缩滤液。将残余物在EtOAc(400mL)与水(400mL)之间分配。将有机层分离,用水(400mL)和盐水(400mL)洗涤,经$MgSO_4$干燥,过滤并浓缩。通过硅胶色谱法纯化(800g柱,含0-80%EtOAc的己烷),得到呈淡黄色油的产物1-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]吡唑-4-甲醛S88(46g,87%)。^{1}H NMR(300MHz,氯仿-d)δ9.86(s,1H),7.98(s,2H),4.25(dd,J=5.5,4.5Hz,2H),3.96(dd,J=5.5,4.5Hz,2H),0.83(s,9H),-0.06(s,6H)。LCMS m/z 255.14$[M+H]^+$。

[2349] 制备S89

[2350] 1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛(S89)



[2351] 

[2352] 步骤1:2-(溴甲基)-2-甲基-丙烷-1,3-二醇(C133)

[2353] 在0℃下向(3-甲基氧杂环丁烷-3-基)甲醇(10mL,100.3mmol)于THF(70mL)中的混合物中添加溴化氢(14mL的48%w/w,123.7mmol)。搅拌24小时后,将混合物浓缩至最小体积,在DCM/甲醇中稀释,并将过量HBr用饱和碳酸氢钠淬灭。将各层分来并将有机层用硫酸钠干燥,过滤,用甲醇冲洗,并浓缩以产生2-(溴甲基)-2-甲基-丙烷-1,3-二醇C133(13.6682g,74%)。^{1}H NMR(400MHz,甲醇-d4)δ3.47(d,J=1.1Hz,6H),0.96(s,3H)。

[2354] 步骤2:[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷(C134)

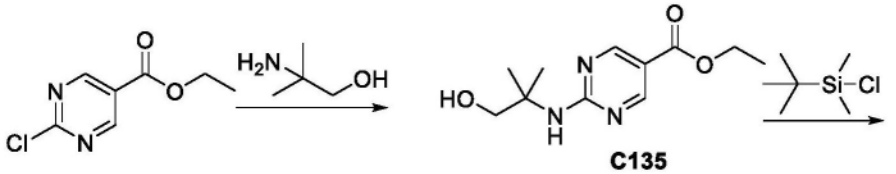
[2355] 向2-(溴甲基)-2-甲基-丙烷-1,3-二醇C133(10g,54.09mmol)于DCM(200mL)中的混合物中添加咪唑(7.7g,113.1mmol),随后添加TBSCl(17g,112.8mmol)。5分钟后,混合物沉淀出白色结晶固体。将混合物过滤,用DCM冲洗,并浓缩。将混合物用庚烷(25mL)稀释,以进一步沉淀出咪唑/咪唑HCl,过滤,并固体再用庚烷(10mL)冲洗。将混合物浓缩,将其沉淀出另外的固体。将混合物稀释并用庚烷(50mL)再浓缩两次以得到[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷C134(22246mg,100%)。^{1}H NMR(400MHz,氯仿-d)δ3.44(s,4H),3.40(s,2H),0.94(s,3H),0.89(s,18H),0.04(d,J=1.2Hz,12H)。

[2356] 步骤3:1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛(S89)

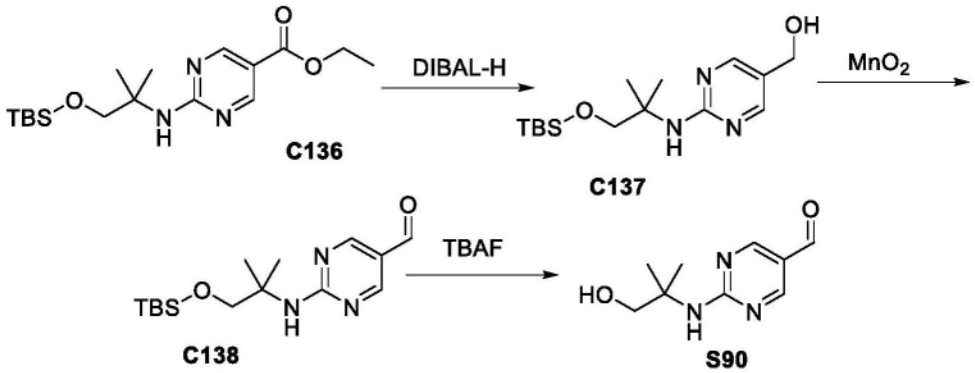
[2357] 向小瓶中添加含1H-吡唑-4-甲醛(2g,20.81mmol)、碳酸二钾(4g,28.94mmol)和[2-(溴甲基)-3-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙氧基]-叔丁基-二甲基-硅烷C134(9.5g,23.08mmol)的DMF(20mL)。将混合物加热至130℃。3小时后,将混合物冷却至室温,用水(100mL)和庚烷(100mL)稀释。将各层混合,并将水层用庚烷(2×100mL)洗涤。将合并的有机层用水(100mL)、盐水(100mL)洗涤,并将有机层用硫酸钠干燥并浓缩。通过硅胶色谱法纯化(梯度:0-60% EtOAc:庚烷),产生产物1-[3-[叔丁基(二甲基)甲硅烷基]氧基-2-[[叔丁基(二甲基)甲硅烷基]氧基甲基]-2-甲基-丙基]吡唑-4-甲醛S89(2390mg,23%)。^{1}H NMR(400MHz,氯仿-d)δ9.85(s,1H),7.98-7.91(m,2H),4.12(s,2H),3.43-3.29(m,4H),0.91(s,18H),0.84(s,3H),0.05(d,J=0.6Hz,12H)。LCMS m/z 427.31$[M+H]^+$。

[2358] 制备S90

[2359] 2-[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲醛(S90)



[2360]



[2361] 步骤1:2-[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲酸乙酯(C135)

[2362] 在室温下向2-氯嘧啶-5-甲酸乙酯(25g,0.1340mol)于乙醇(750mL)中的经搅拌的溶液中添加2-氨基-2-甲基-丙-1-醇(14.333g,15.412mL,0.1608mol),随后添加DIPEA(34.637g,46.681mL,0.2680mol)。将反应物在80℃下搅拌8小时。将反应物温热至室温,并

在减压下浓缩。通过硅胶色谱法纯化(洗脱液:含70% EtOAc的石油醚),得到2-[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲酸乙酯C135(18g,55%)。^{1}H NMR(400MHz,DMSO-d6)δ8.70(s,2H),7.39(s,1H),4.86(t,J=6Hz,1H),4.25(q,J=6.8Hz,2H),3.52(d,J=6Hz,2H),1.32(s,6H),1.28(t,J=6.8Hz,3H)。LCMS m/z 240.27[M+H]$^+$。

[2363] 步骤2:2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲酸乙酯(C136)

[2364] 在室温下向2-[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲酸乙酯C135(10g,0.0410mol)和叔丁基-氯-二甲基-硅烷(9.2694g,0.0615mol)于DCM(500mL)中的经搅拌的溶液中添加咪唑(8.3735g,0.1230mol),随后添加DMAP(1.0018g,0.0082mol),并搅拌16小时。将反应物在减压下浓缩。将粗产物用水(500mL)和戊烷(500mL)稀释。将有机层分离,用水洗涤,经Na_2SO_4干燥并在减压下浓缩以产生2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲酸乙酯C136(14.9g,100%)。^{1}H NMR(400MHz,DMSO-d6)δ8.70(s,2H),7.46(s,1H),4.25(q,J=7.2Hz,2H),3.77(s,2H),1.30(s,6H),1.28(t,J=7.6Hz,3H),0.82(s,9H),-0.06(s,6H)。LCMS m/z 354.3[M+H]$^+$。

[2365] 步骤3:[2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-基]甲醇(C137)

[2366] 在-78℃下在氮气球压下向2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲酸乙酯C136(15g,0.0411mol)于THF(600mL)中的经搅拌的溶液中缓慢添加DIBAL-H(1M于甲苯中)(205.50mL的1M,0.2055mol)。将反应物在-78℃下搅拌30分钟。在室温下搅拌4小时。在0℃下将反应混合物用饱和NH_4Cl(500mL)淬灭并将化合物用EtOAc(2×500mL)萃取。将有机层用1N HCl(100mL)、盐水洗涤,经Na_2SO_4干燥,并在减压下浓缩。通过硅胶色谱法纯化(洗脱液:含50% EtOAc的石油醚),得到[2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-基]甲醇C137(6g,46%)。^{1}H NMR(400MHz,DMSO-d6)δ8.19(s,2H),6.25(s,1H),4.99(t,J=5.6Hz,1H),4.27(d,J=5.6Hz,2H),3.71(s,2H),1.30(s,6H),0.84(s,9H),-0.03(s,6H)。LCMS m/z 312.23[M+H]$^+$。

[2367] 步骤4:2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲醛(C138)

[2368] 在室温下向[2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-基]甲醇C137(120mg,271.55μmol)于DCM(10mL)中的经搅拌的溶液中添加MnO_2(851.98mg,0.0098mol),并搅拌6小时。将反应物通过Celite®过滤,并用DCM(10mL)洗涤。将滤液在减压下浓缩以得到2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲醛C138(90mg,99%)。^{1}H NMR(400MHz,DMSO-d6)δ9.71(s,1H),8.71(d,J=11.6Hz,2H),7.72(s,1H),3.78(s,2H),1.34(s,6H),0.84(s,9H),-0.05(s,6H)。LCMS m/z 310.22[M+H]$^+$。

[2369] 步骤5:2-[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲醛(S90)

[2370] 在室温下向2-[[2-[叔丁基(二甲基)甲硅烷基]氧基-1,1-二甲基-乙基]氨基]嘧啶-5-甲醛C138(2.9g,0.0087mol)于THF(20mL)中的经搅拌的溶液中添加TBAF(1M于THF中)(21.700mL的1M,0.0217mol),并搅拌2小时。将反应物用EtOAc(100mL)稀释,用盐水溶液洗涤,经Na_2SO_4干燥并在减压下浓缩以得到粗化合物。将粗化合物用戊烷洗涤并干燥以得到2-

[(2-羟基-1,1-二甲基-乙基)氨基]嘧啶-5-甲醛S90(1.47g,86%)。^{1}H NMR(400MHz,DMSO-d6)δ9.72(s,1H),8.71(d,J=13.2Hz,2H),7.64(s,1H),4.87(t,J=6Hz,1H),3.54(d,J=6Hz,2H),1.33(s,6H)。LCMS m/z 196.35[M+H]$^+$。

[2371] 制备S91

[2372] 4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-甲醛(S91)

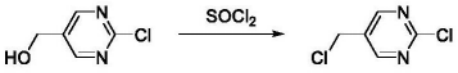
[2373] 

S91

[2374] 向烘箱干燥的小瓶中添加4-氯-6-甲基-吡唑并[1,5-a]哌嗪-2-甲酸乙酯(381mg,1.590mmol),然后将其在氮气气氛下溶解在DCM(10mL)中。将该溶液冷却至-78℃。在30分钟内向该混合物中缓慢添加含氢化二异丁基铝(1.8mL的1M,1.800mmol)溶液的DCM。搅拌1小时后,添加另外部分的含氢化二异丁基铝(2.4mL的1M,2.400mmol)溶液的DCM,并将反应物搅拌60分钟,并且然后用MeOH(1mL)淬灭,随后用盐水淬灭,并用DCM稀释并搅拌过夜。然后将其用DCM和水进一步稀释并通过相分离器。将水层用DCM(3×30mL)萃取,并将其也通过相分离器。将合并的有机层在真空中浓缩并将混合物通过硅胶色谱法纯化(洗脱液:含0-60%EtOAc的庚烷)以得到4-氯-6-甲基-吡唑并[1,5-a]吡嗪-2-甲醛(237mg,76%)。1H NMR(300MHz,氯仿-d)δ10.20(s,1H),8.22-8.12(m,1H),7.34(d,J=1.0Hz,1H),2.56(d,J=1.1Hz,3H)。LCMS m/z 195.99[M+H]$^+$。

[2375] 制备S92

[2376] (2-氯嘧啶-5-基)甲醇(S92)

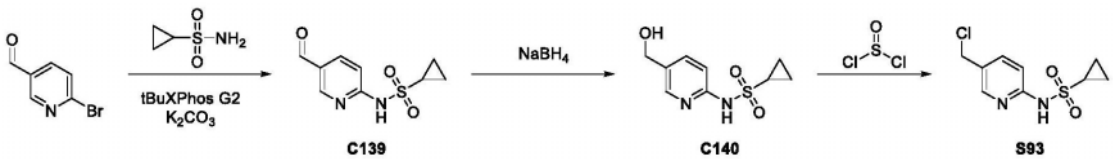
[2377] 

S92

[2378] 在50mL圆底烧瓶中装入(2-氯吡啶-5-基)甲醇(1g,6.918mmol)和亚硫酰氯(12.5mL,171.4mmol)。向悬浮液中添加DMF(32.5μL,0.4197mmol),并将所得混合物在回流下加热大约5小时。将反应冷却至rt然后在真空中浓缩。然后在高真空下将其用DCM(2x)共蒸发并将其干燥到恒定质量以得到2-氯-5-(氯甲基)嘧啶(1.08g,92%)。1H NMR(300MHz,氯仿-d)δ8.67(s,2H),4.57(d,J=0.6Hz,2H)。LCMS m/z 162.95[M+H]$^+$。

[2379] 制备S93

[2380] N-[5-(氯甲基)-2-吡啶基]环丙烷磺酰胺(S93)

[2381] 

C139 C140 S93

[2382] 步骤1:N-(5-甲酰基吡啶-2-基)环丙烷磺酰胺(C139)的合成

[2383] 将6-溴吡啶-3-甲醛(70mg,0.3763mmol)、环丙烷磺酰胺(137mg,1.131mmol)、K_2CO_3(107mg,0.7742mmol)和tBuXPhos G2(15mg,0.01888mmol)于2-MeTHF(3.5mL)中的混合物加热至80℃并搅拌过夜。将反应物冷却至rt并且然后用EtOAc和1N HCl稀释。将溶液用EtOAc

萃取并用盐水洗涤。将粗材料通过硅胶色谱法纯化(梯度:含0-20% MeOH的DCM)以产生产物N-(5-甲酰基吡啶-2-基)环丙烷磺酰胺(46mg,27%)。LCMS m/z226.97[M+H]$^+$。

[2384] 步骤2:N-[5-(羟甲基)-2-吡啶基]环丙烷磺酰胺(C140)的合成

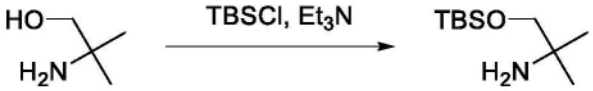
[2385] 然后将N-(5-甲酰基吡啶-2-基)环丙烷磺酰胺(46mg,0.20mmol)溶解在THF(1.9mL)中,并添加$NaBH_4$(28mg,0.7401mmol)。将溶液搅拌过夜。将反应物用水洗涤,用DCM萃取,用HCl洗涤,并用盐水洗涤。将水层在真空中去除。将产物重新溶解在DCM中并将水性盐过滤掉以产生N-[5-(羟甲基)-2-吡啶基]环丙烷磺酰胺(19mg,57%)。LCMS m/z 229.22[M+H]$^+$。

[2386] 步骤3:N-[5-(氯甲基)-2-吡啶基]环丙烷磺酰胺(S93)的合成

[2387] 将N-[5-(羟甲基)-2-吡啶基]环丙烷磺酰胺(19mg,0.083mmol)溶解在亚硫酰氯(450mg,3.782mmol)中并将反应物在60℃下搅拌2小时。在真空中去除溶剂,并且粗产物无需进一步纯化即可使用。N-[5-(氯甲基)-2-吡啶基]环丙烷磺酰胺(20mg,51%)。LCMS m/z 246.92[M+H]$^+$。

[2388] 制备S94

[2389] 1-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙-2-胺(S94)

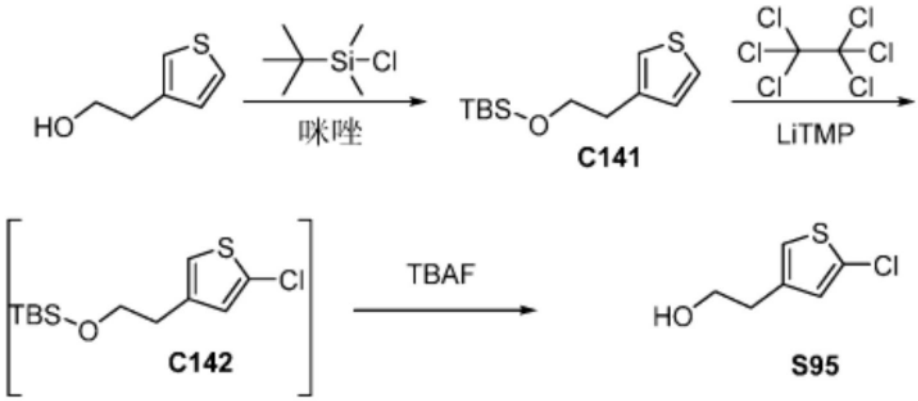
[2390] 

S94

[2391] 将2-氨基-2-甲基-丙-1-醇(2.5g,28.05mmol)于DCM(85mL)中的0℃溶液用叔丁基-氯-二甲基-硅烷(5mL,26.87mmol)处理随后添加Et_3N(5.9mL,42.33mmol)。将所得溶液在rt下搅拌过夜。通过用水(2x)分配来处理反应物。将有机层用盐水洗涤,经无水硫酸钠干燥,过滤并在真空中浓缩以得到1-[叔丁基(二甲基)甲硅烷基]氧基-2-甲基-丙-2-胺(3.61g,63%)。1H NMR(300MHz,氯仿-d)δ3.20(d,J=28.3Hz,2H),1.00(d,J=2.3Hz,4H),0.88-0.83(m,9H),0.80(s,2H),-0.01(d,J=5.1Hz,6H)。

[2392] 制备S95

[2393] 2-(5-氯-3-噻吩基)乙醇(S95)

[2394] 

[2395] 步骤1:叔丁基-二甲基-[2-(3-噻吩基)乙氧基]硅烷(C141)

[2396] 向2-(3-噻吩基)乙醇(18g,140.4mmol)于DMF(100mL)中的溶液中依次添加咪唑(12g,176.3mmol)和叔丁基-氯-二甲基-硅烷(24g,159.2mmol)。观察到放热。将反应混合物在室温下搅拌3小时。反应停滞在90%转化。将反应物用MTBE(500mL)稀释并用水(200mL)、

0.5N HCl、(200mL)、水(200mL)和盐水(200mL)洗涤。将有机层干燥,过滤并在真空中浓缩。将有机层溶解于庚烷中并使其穿过硅胶塞;将其用1-5% MTBE/庚烷洗涤。去除溶剂以得到叔丁基-二甲基-[2-(3-噻吩基)乙氧基]硅烷(C141)(34g,99%)。^{1}H NMR(400MHz,氯仿-d)δ 7.28-7.13(m,1H),7.04-6.91(m,2H),3.80(t,J=6.9Hz,2H),2.90-2.75(m,2H),0.88(s,9H),-0.00(s,6H)。

[2397] 步骤2:叔丁基-[2-(5-氯-3-噻吩基)乙氧基]-二甲基-硅烷(C142)

[2398] 向冷却至0℃的2,2,6,6-四甲基哌啶(36mL,213.3mmol)于四氢呋喃(200mL)中的溶液中添加己基锂溶液(92mL的2.3M,211.6mmol)。将反应物在-78℃下搅拌30分钟。在20分钟内将叔丁基-二甲基-[2-(3-噻吩基)乙氧基]硅烷(34g,138.8mmol)于THF(150mL)中的溶液添加到反应物中。将反应物在-30℃下搅拌45分钟。将反应物冷却至-78℃。分份添加1,1,1,2,2,2-六氯乙烷(54g,228.1mmol)。将反应物升温至室温并搅拌过夜。将反应物用饱和氯化铵(125mL)淬灭,用水(100mL)稀释,用EtOAc(500mL)萃取,并用EtOAc(100mL)反萃取。将有机层用0.5N HCl(200mL)、水(300mL)和盐水(200mL)洗涤。将有机层经硫酸钠干燥,过滤并且浓缩以得到粗产物(C142)。

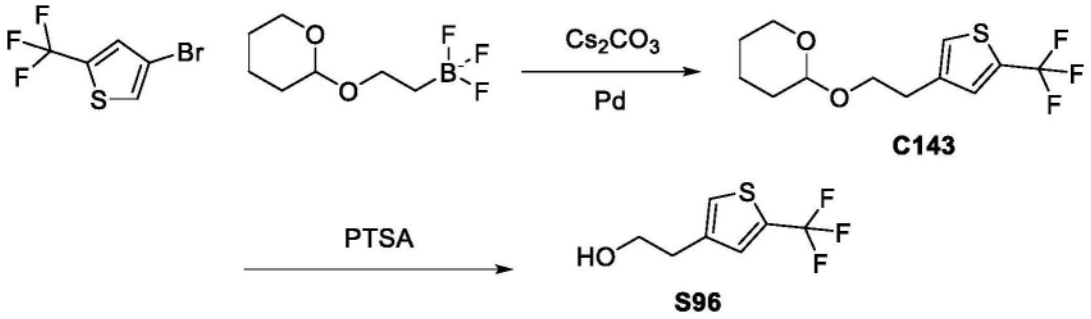
[2399] 步骤3:2-(5-氯-3-噻吩基)乙醇(S95)

[2400] 向叔丁基-[2-(5-氯-3-噻吩基)乙氧基]-二甲基-硅烷(C142)(12.5g,42.89mmol)于2-Me-THF(120mL)中的溶液中添加TBAF(63mL的1M,63.00mmol)(于THF中的溶液)。将反应物在室温下搅拌过夜。将反应物分配于EtOAc(400mL)与水(400mL)之间。分离各层,并将有机层用EtOAc(200mL)萃取,经硫酸钠干燥,过滤,并在真空中浓缩以去除溶剂。通过硅胶色谱法纯化(梯度:含0-50% EtOAc的庚烷),产生产物2-(5-氯-3-噻吩基)乙醇(S95)(4.5g,58%)。^{1}H NMR(300MHz,氯仿-d)δ6.82(d,J=0.9Hz,2H),3.89-3.71(m,2H),2.79(t,J=6.4Hz,2H),2.05(s,1H)。LCMS m/z 162.91[M+H]$^+$。

[2401] 制备S96

[2402] 2-[5-(三氟甲基)-3-噻吩基]乙醇(S96)

[2403]



[2404] 步骤1:2-[2-[5-(三氟甲基)-3-噻吩基]乙氧基]四氢吡喃(C143)

[2405] 向4-溴-2-(三氟甲基)噻吩(9g,38.96mmol)、二环己基-[2-(2,6-二异丙氧基苯基)苯基]磷烷;甲磺酸酯;N-甲基-2-苯基-苯胺;钯(2+)(1.8g,2.117mmol)和三氟(2-四氢吡喃-2-基氧基乙基)硼化钾(钾离子(1))(10g,42.36mmol)的混合物中添加甲苯(75mL)和水(25mL)。使氮气穿过反应物顶部,之后添加碳酸二铯(40g,122.8mmol)。添加回流冷凝器,并将反应物在100℃下加热48小时。将反应物用EtOAc(150mL)和水(100mL)稀释。分离两层并将水层用EtOAc(100mL)萃取。将合并的有机物用盐水洗涤,经硫酸钠干燥,过滤,并在真空中浓缩。通过硅胶色谱法纯化(梯度:含0-20% EtOAc的庚烷)产生产物。2-[2-[5-(三氟

甲基)-3-噻吩基]乙氧基]四氢吡喃(C143)(9g,82%)。^{1}H NMR(300MHz,氯仿-d)δ7.37(t,J=1.3Hz,1H),7.22(d,J=1.5Hz,1H),4.62(dd,J=4.2,2.8Hz,1H),3.96(dt,J=9.6,6.7Hz,1H),3.75(ddd,J=11.3,8.0,3.4Hz,1H),3.62(dt,J=9.6,6.5Hz,1H),3.55-3.41(m,1H),2.93(t,J=6.6Hz,2H),1.83(ddd,J=14.2,6.6,3.4Hz,1H),1.73(td,J=9.0,4.2Hz,1H),1.66-1.50(m,4H)。

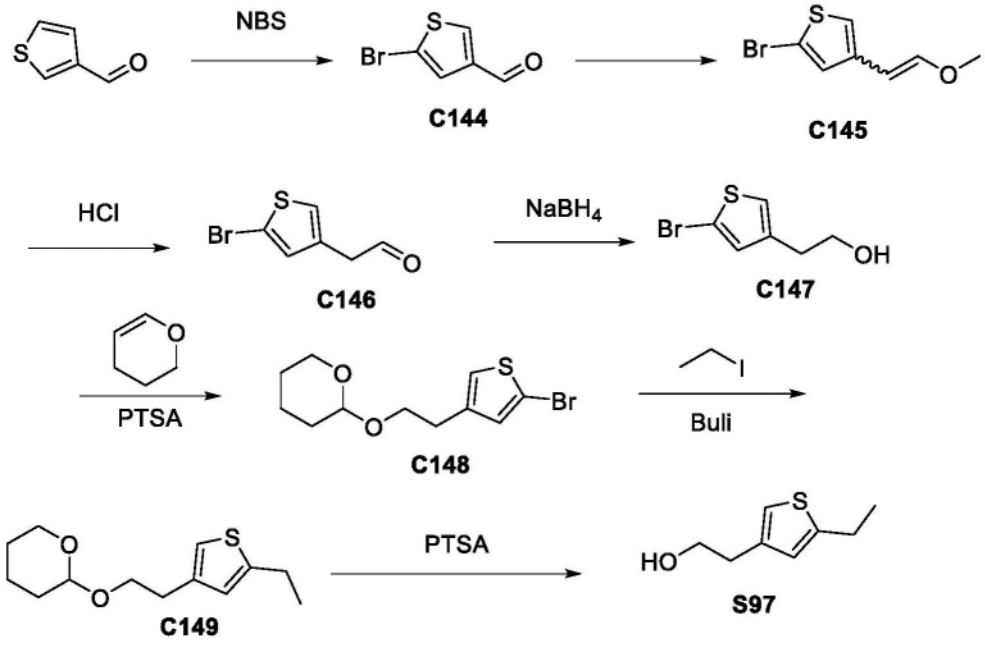
[2406] 步骤2:2-[5-(三氟甲基)-3-噻吩基]乙醇(S96)

[2407] 在室温下向2-[2-[5-(三氟甲基)-3-噻吩基]乙氧基]四氢吡喃(C143)(1.8g,6.100mmol)于MeOH(25mL)中的经搅拌的溶液中添加4-甲基苯磺酸(水(1))(1.2g,6.309mmol)。将反应混合物在室温下搅拌1小时。将反应混合物用水(100mL)稀释并用MTBE(2×100mL)萃取。将有机层用稀的$NaHCO_3$(10mL $NaHCO_3$和10mL水)和盐水(10mL)洗涤,经硫酸钠干燥,过滤,并在真空下蒸发,以得到粗化合物。通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷),产生产物2-[5-(三氟甲基)-3-噻吩基]乙醇(S96)(820mg,69%)。^{1}H NMR(400MHz,氯仿-d)δ7.35(p,J=1.3Hz,1H),7.23(dt,J=1.7,0.9Hz,1H),3.85(td,J=7.1,6.5,2.7Hz,2H),2.87(td,J=6.4,0.8Hz,2H),2.06(d,J=4.3Hz,1H)。

[2408] 制备S97

[2409] 2-(5-乙基-3-噻吩基)乙醇(S97)

[2410]



[2411] 步骤1:5-溴噻吩-3-甲醛(C144)

[2412] 在0℃下,向噻吩-3-甲醛(50g,40.717mL,0.4458mol)于DMF(500mL)中的经搅拌的溶液中添加NBS(119.02g,0.6687mol)。将反应混合物在室温下搅拌16小时。将反应混合物用冰冷水(600ml)淬灭并用EtOAc(2×600ml)萃取。将有机层在Na_2SO_4上干燥,过滤,并浓缩。通过硅胶色谱法纯化(梯度:含0-2% EtOAc的石油醚),产生产物5-溴噻吩-3-甲醛(C144)(39.2g,44%)。^{1}H NMR(400MHz,氯仿-d)δ9.77(s,1H),7.99(d,J=1.2Hz,1H),7.505(d,J=1.6Hz,1H)。

[2413] 步骤2:2-溴-4-[(E)-2-甲氧基乙烯基]噻吩(C145)

[2414] 在0℃下向(甲氧基甲基)三苯基氯化磷(115.1g,0.3358mol)于二乙醚(450.00mL)

中的经搅拌的溶液中逐滴添加叔丁醇钾(1M于THF中)(381mL的1M,0.3810mol)。将反应物在0℃下搅拌1小时。添加5-溴噻吩-3-甲醛(C144)(45g,0.2215mol)于二乙醚(90mL)中的溶液,并且然后将反应混合物在室温下搅拌30分钟。在0℃下将反应混合物用NH_4Cl溶液(900mL)淬灭,用EtOAc(2×700mL)萃取,并将有机层经Na_2SO_4干燥,过滤并浓缩。通过硅胶色谱法纯化(洗脱液:石油醚),得到产物2-溴-4-[(E)-2-甲氧基乙烯基]噻吩(C145)(44.1g,82%)。^1H NMR(400MHz,氯仿-d)δ7.25(d,J=2Hz,1H),7.18(d,J=0.8Hz,1H),7.00(d,J=1.8Hz,1H),6.91(d,J=12.8Hz,1H),6.97(d,J=1.2Hz,1H),6.05(d,J=6.8Hz,1H),5.72(d,J=12.8Hz,1H),5.22(d,J=6.4Hz,1H),3.77(d,J=2.8Hz,3H),3.64(d,J=5.2Hz,3H)NMR示出E和Z异构体的1:1混合物。

[2415] 步骤3:2-(5-溴-3-噻吩基)乙醛(C146)

[2416] 在0℃下向2-溴-4-[(E)-2-甲氧基乙烯基]噻吩(C145)(14.1g,0.0602mol)于1,4-二噁烷(141.00mL)的经搅拌的溶液中添加HCl(4M于二噁烷中)(60.200mL的4M,0.2408mol)。将反应混合物在室温下搅拌30分钟。在0℃下将反应混合物用饱和$NaHCO_3$淬灭并用EtOAc萃取。将有机层经Na_2SO_4干燥,过滤并浓缩以得到2-(5-溴-3-噻吩基)乙醛(C146)(13.1g,89%)。^1H NMR(400MHz,氯仿-d)δ9.72(t,J=2.4Hz,1H),7.04(s,1H),6.94(d,J=1.2Hz,1H),3.66(d,J=1.6Hz,2H)。

[2417] 步骤4:2-(5-溴-3-噻吩基)乙醇(C147)

[2418] 在0℃下向2-(5-溴-3-噻吩基)乙醛(C146)(38.5g,0.1524mol)于MeOH(390mL)的经搅拌的溶液中添加$NaBH_4$(13.3g,0.3515mol)。将反应物搅拌1小时。将反应混合物用冰水(400mL)淬灭并在真空中浓缩以去除MeOH。将粗残余物用水(500ml)稀释,并用EtOAc(3×300ml)萃取。将分离的有机层经Na_2SO_4干燥,过滤并浓缩。用中性氧化铝通过柱色谱法纯化(洗脱液:含35% EtOAc的石油醚),得到呈淡黄色液体的产物2-(5-溴-3-噻吩基)乙醇(C147)(30.2g,84%)。^1H NMR(300MHz,DMSO-d_6)δ7.20(t,J=0.9Hz,1H),7.10(d,J=1.2Hz,1H),4.64(q,J=5.2Hz,1H),3.59-3.55(m,2H),2.67(t,J=6.8Hz,2H)。

[2419] 步骤5:2-[2-(5-溴-3-噻吩基)乙氧基]四氢吡喃(C148)

[2420] 在室温下向2-(5-溴-3-噻吩基)乙醇(C147)(8g,0.0328mol)于THF(80。mL)中的经搅拌的溶液中添加3,4-二氢-2H-吡喃(3.7696g,3.8mL,0.0448mol)和PTSA(259mg,0.0015mol)。然后将反应混合物在室温下搅拌16小时。将反应混合物用饱和的水性K_2CO_3(300mL)淬灭并用EtOAc(2×600mL)萃取。将有机层经Na_2SO_4干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含0-5% EtOAc的石油醚),产生产物2-[2-(5-溴-3-噻吩基)乙氧基]四氢吡喃(10.1g,90%)。^1H NMR(400MHz,氯仿-d)δ6.95(d,J=1.6Hz,1H),6.92(d,J=0.8,1H),4.59(t,J=2.8Hz,1H),3.94-3.74(m,2H),3.60-3.46(m,2H),2.85(q,J=6.4Hz,2H),1.80-1.61(m,6H)。LCMS m/z 291.03$[M+H]^+$。

[2421] 步骤6:2-[2-(5-乙基-3-噻吩基)乙氧基]四氢吡喃(C149)

[2422] 在-76℃下向2-[2-(5-溴四氢噻吩-3-基)乙氧基]四氢吡喃(C148)(25g,0.0719mol)于THF(250.00mL)的经搅拌的溶液中添加n-BuLi(2.5M于己烷中)(46.1mL的2.5M,0.1153mol)。将反应物搅拌1小时。在-76℃下添加碘乙烷(24.832g,12.8mL,0.1592mol)。然后将反应物温度缓慢增加到室温,并且然后搅拌16小时。将反应混合物用NH_4Cl溶液(500mL)淬灭,并用EtOAc(2×300mL)萃取。将有机层经Na_2SO_4干燥,过滤并浓缩。

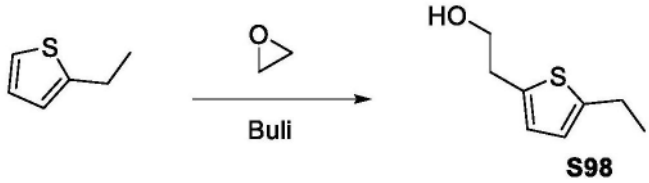
通过硅胶色谱法纯化(梯度:含0-3% EtOAc的石油醚),产生产物2-[2-(5-乙基-3-噻吩基)乙氧基]四氢吡喃(C149)(13.2g,59%)。LCMS m/z 241.21[M+H]$^+$。

[2423] 步骤7:2-(5-乙基-3-噻吩基)乙醇(S97)

[2424] 在室温下向2-[2-(5-乙基-3-噻吩基)乙氧基]四氢吡喃(C149)(4.4g,0.0142mol)于MeOH(44.000mL)的经搅拌的溶液中添加PTSA(3.0g,0.0174mol),并将反应物搅拌2小时。将反应混合物用饱和$NaHCO_3$溶液(150mL)淬灭,用EtOAc(2×150mL)萃取,经Na_2SO_4干燥,过滤并浓缩。用中性氧化铝通过柱色谱法纯化(洗脱液:含10% EtOAc的石油醚),得到产物2-(5-乙基-3-噻吩基)乙醇(S97)(1.1g,45%)。^{1}H NMR(400MHz,DMSO-d_6)δ6.90(d,J=1.2Hz,1H),6.71(d,J=1.2Hz,1H),4.62-4.58(m,1H),3.59-3.55(m,2H),2.77-2.71(m,2H),2.64(t,J=7.2,2H),1.22-1.85(m,3H)。

[2425] 制备S98

[2426] 2-(5-乙基-2-噻吩基)乙醇(S98)

[2427] 

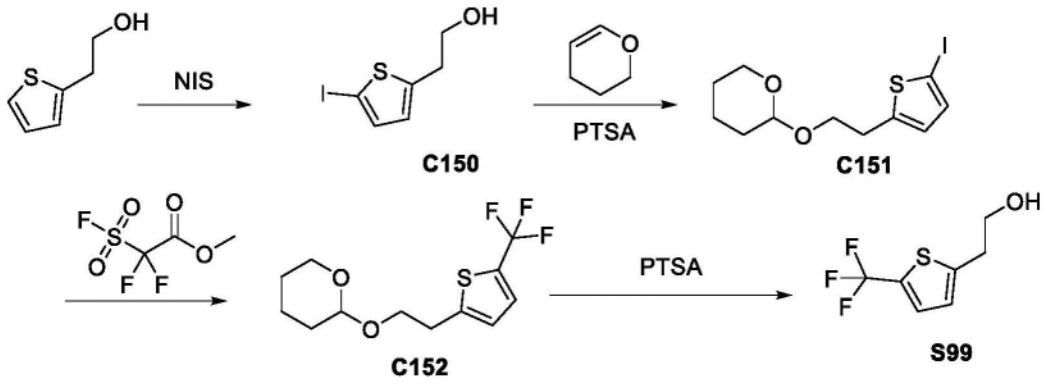
S98

[2428] 步骤1:2-(5-乙基-2-噻吩基)乙醇(S98)

[2429] 在0℃下在45分钟内向2-乙基噻吩(54g,466.9mmol)于无水THF(1L)中的溶液中添加含n-BuLi的己烷(255mL的2.2M,561.0mmol)。得到浅黄色/橙色溶液。添加期间的温度范围为0-10℃。将混合物在室温下搅拌30分钟。冷却到0℃后,在30分钟内添加环氧乙烷(200mL的2.9M,580.0mmol)的溶液。将反应物在0℃搅拌2小时并且然后温热至室温。将反应混合物用水(700mL)和饱和NH_4Cl(200mL)淬灭并蒸发THF。将产物用EtOAc(1×400mL;2×150mL)萃取。将有机层经无水硫酸钠干燥,过滤并在真空中浓缩。将粗产物在真空中干燥。将有机层通过硅胶塞,用DCM(1000mL)、80% EtOAc/庚烷(2×200mL)和DCM(2×250mL)洗涤以得到2-(5-乙基-2-噻吩基)乙醇(S98)(71.25g,93%)。^{1}H NMR(300MHz,氯仿-d)δ6.69(dt,J=3.4,0.9Hz,1H),6.64(dt,J=3.3,1.0Hz,1H),3.84(t,J=6.3Hz,2H),3.08-2.97(m,2H),2.82(qd,J=7.5,1.0Hz,2H),1.31(t,J=7.5Hz,4H)。

[2430] 制备S99

[2431] 2-[5-(三氟甲基)-2-噻吩基]乙醇(S99)

[2432] 

[2433] 步骤1:2-(5-碘代-2-噻吩基)乙醇(C150)

[2434] 在0℃下向NIS(104.83g,0.4680mol)于DCM(1000mL)中的经搅拌的溶液中添加2-(2-噻吩基)乙醇(50g,0.3900mol)。将反应物温热至室温并搅拌16小时。将反应混合物用DCM(500mL)稀释,用饱和硫代硫酸钠、盐水洗涤,经Na_2SO_4干燥并在真空中浓缩。通过柱色谱法纯化(洗脱液:含20% EtOAc的石油醚),得到产物2-(5-碘代-2-噻吩基)乙醇(C150)(62g,56%)。^{1}H NMR(400MHz,氯仿-d)δ7.08(d,J=3.6Hz,1H),6.57-6.56(m,1H),3.82(q,J=6Hz,2H),3.05(q,J=6.4Hz,2H)。LCMS m/z 254.89$[M+H]^+$。

[2435] 步骤2:2-[2-(5-碘代-2-噻吩基)乙氧基]四氢吡喃(C151)

[2436] 在室温下向2-(5-碘代-2-噻吩基)乙醇(C150)(15g,0.0525mol)和3,4-二氢-2H-吡喃(6.6284g,0.0788mol)于THF(60mL)的经搅拌的溶液中添加PTSA(1.3604g,1.2714mL,0.0079mol)。将反应物在氩气球压下搅拌16小时。将反应混合物在减压下浓缩。通过硅胶色谱法纯化(洗脱液:含5%EtOAc的石油醚),产生产物2-[2-(5-碘代-2-噻吩基)乙氧基]四氢吡喃(C151)(12.8g,68%)。^{1}H NMR(400MHz,DMSO-d_6)δ7.14(d,J=3.6Hz,1H),6.64(d,J=3.6Hz,1H),4.59(t,J=3.6Hz,1H),3.80-3.76(m,1H),3.74-3.67(m,1H),3.54-3.50(m,1H),3.48-3.41(m,1H),3.03(t,J=6Hz,2H),1.75-1.69(m,1H),1.61-1.59(m,1H),1.51-1.42(m,4H)。

[2437] 步骤3:2-[2-[5-(三氟甲基)-2-噻吩基]乙氧基]四氢吡喃(C152)

[2438] 向2-[2-(5-碘代-2-噻吩基)乙氧基]四氢吡喃(C151)(10g,0.0219mol)和2,2-二氟-2-氟磺酰基-乙酸甲酯(12.63g,0.0657mol)于DMF(40mL)中的经搅拌的溶液中添加99%溴化铜(I)二甲基硫醚复合物(2.241g,0.0109mol)。将反应物在100℃下搅拌16小时。将反应物温热至室温,用EtOAc(100mL)稀释,过滤并用EtOAc(50mL)洗涤。将滤液用发盐水溶液洗涤,经Na_2SO_4干燥,并在减压下浓缩。用中性氧化铝通过柱色谱法纯化(洗脱液:含5% EtOAc的石油醚),得到产物(C152)2-[2-[5-(三氟甲基)-2-噻吩基]乙氧基]四氢吡喃(2.9g,41%)。^{1}H NMR(400MHz,氯仿-d)δ7.25(s,1H),6.82-6.81(m,1H),4.63(t,J=3.6Hz,1H),4.00-3.95(m,1H),3.78-3.75(m,1H),3.64-3.58(m,1H),3.51-3.48(m,1H),3.12(d,J=6.4Hz,2H),1.90-1.80(m,1H),1.73-1.64(m,1H),1.65-1.51(m,4H)。

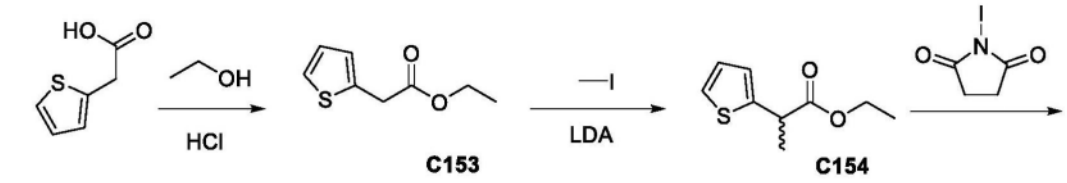
[2439] 步骤4:2-[5-(三氟甲基)-2-噻吩基]乙醇(S99)

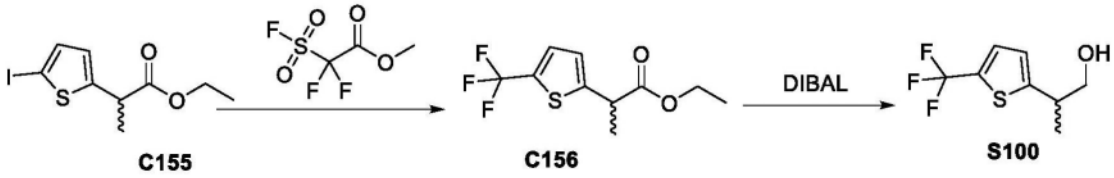
[2440] 在室温下向2-[2-[5-(三氟甲基)-2-噻吩基]乙氧基]四氢吡喃(C152)(5.8g,0.0170mol)于MeOH(100mL)中的经搅拌的溶液中添加PTSA(2.93g,0.0170mol)。将反应物搅拌16小时。将反应混合物在减压下浓缩。用中性氧化铝通过柱色谱法纯化(洗脱液:含10% EtOAc的石油醚),得到产物2-[5-(三氟甲基)-2-噻吩基]乙醇S99(2.3g,61%)^{1}H NMR(400MHz,DMSO-d_6)δ7.52-7.51(m,1H),6.99-6.98(m,1H),4.92(t,J=4.8Hz,1H),3.65-3.61(m,2H),2.98(t,J=6Hz,2H)。^{19}F NMR(376.22MHz,DMSO-d6)δ-53.53(s,3F)。

[2441] 制备S100

[2442] 2-[5-(三氟甲基)-2-噻吩基]丙-1-醇(S100)

[2443]





[2444] 步骤1:2-(2-噻吩基)乙酸乙酯乙醇(C153)

[2445] 在室温下向2-(2-噻吩基)乙酸(100g,703.35mmol)于乙醇(2000mL)中的经搅拌的溶液中添加HCl(水性)(50mL的36%w/v,493.68mmol)。将反应混合物在70℃下搅拌12小时。将混合物浓缩并将所得粗产物用EtOAc(1000ml)稀释,用5% Na_2CO_3水溶液(3×200ml)和盐水(200ml)洗涤。将有机层干燥并浓缩以得到期望产物2-(2-噻吩基)乙酸乙酯(C153)(100g,82%)。^{1}H NMR(氯仿-d,400MHz):δ=7.222-7.206(dd,J=1.2Hz,J=3.6Hz,1H),6.969-6.948(m,2H),4.213-4.160(q,J=7.2Hz,2H),3.828(s,2H),1.295-1.259(t,J=7.2Hz,3H)。LCMS m/z 171.26$[M+H]^+$。

[2446] 步骤2:2-(2-噻吩基)丙酸乙酯(C154)

[2447] 在-78℃下向2-(2-噻吩基)乙酸乙酯(C153)(1.36g,7.989mmol)于THF(20mL)中的溶液中添加(二异丙胺)锂(8mL的1M,8.000mmol)。15分钟后,添加MeI(500μL,8.032mmol),并将反应混合物在-78℃下搅拌2小时。将反应物用饱和NH_4Cl(50mL)淬灭,并用EtOAc萃取。将有机层干燥并浓缩成油,将其通过二氧化硅色谱法纯化(梯度:含0至25% EtOAc的庚烷)以得到产物2-(2-噻吩基)丙酸乙酯(C20)(1.04g,71%)。^{1}H NMR(300MHz,氯仿-d)δ7.25-7.17(m,1H),7.02-6.93(m,2H),4.18(d,J=7.2Hz,2H),4.02(q,J=7.1Hz,1H),1.60(d,J=7.2Hz,3H),1.28(t,J=7.1Hz,3H)。

[2448] 步骤3:2-(5-碘代-2-噻吩基)丙酸乙酯(C155)

[2449] 向2-(2-噻吩基)丙酸乙酯C154(35g,143.99mmol)于乙酸(350mL)中的经搅拌的溶液中添加N-碘代琥珀酰亚胺(38.875g,172.79mmol)。将反应混合物在100℃下搅拌一小时。将混合物浓缩,并将所得粗产物用EtOAc(700ml)稀释,用水(300ml)、饱和碳酸氢钠溶液(300ml)、饱和硫代硫酸钠溶液(300ml)和盐水溶液(250ml)依序洗涤。将有机层经Na_2SO_4干燥,过滤并浓缩以得到粗产物。通过硅胶色谱法纯化(洗脱液:含3% EtOAc的石油醚),产生产物2-(5-碘代-2-噻吩基)丙酸乙酯(C155)(30g,42%)。^{1}H NMR(氯仿-d,400MHz):δ=7.08(d,J=4Hz,1H),6.62(d,J=4Hz,1H),4.191-4.130(m,2H),3.979-3.925(m,1H),1.552-1.513(m,3H),1.277-1.240(m,3H)。LCMS m/z 309.9$[M+H]^+$。

[2450] 步骤4:2-[5-(三氟甲基)-2-噻吩基]丙酸乙酯(C156)

[2451] 在氮气气氛下向2-(5-碘代-2-噻吩基)丙酸乙酯(C155)(5g,9.9629mmol)和2,2-二氟-2-(氟磺酰基)乙酸甲酯(9.5700g,49.814mmol)于DMF(50mL)中的经搅拌的溶液中添加CuI(2.2768g,11.955mmol)。将反应混合物在100℃下搅拌12小时。将混合物通过Celite®过滤并将Celite®垫用二乙醚(2×100ml)洗涤。将滤液用冷水(100ml)淬灭。将两层分离并

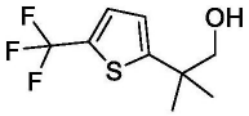
将水层用二乙醚(2×50ml)萃取。将总有机层用盐水(30ml)洗涤,干燥并浓缩。通过硅胶色谱法纯化(洗脱液:含3% EtOAc的石油醚),产生产物2-[5-(三氟甲基)-2-噻吩基]丙酸乙酯(C156)(2g,58%)。^{1}H NMR(氯仿-d,400MHz):δ=7.290-7.261(m,1H),6.918-6.903(m,1H),4.213-4.147(m,2H),3.996-3.961(m,1H),1.565-1.525(m,3H),1.277-1.267(m,3H)。LCMS m/z252.1[M]。

[2452] 步骤5:2-[5-(三氟甲基)-2-噻吩基]丙-1-醇(S100)

[2453] 在0℃下向2-[5-(三氟甲基)-2-噻吩基]丙酸乙酯(12g,41.701mmol)于THF(250mL)中的经搅拌的溶液中逐滴添加DIBAL-H(35.584mL的25%w/v,62.552mmol)。将反应混合物在0℃下搅拌2小时。在0℃下将混合物用饱和NH_4Cl溶液(300ml)缓慢淬灭并将悬浮液通过Celite®过滤并将Celite®垫用EtOAc(2×200ml)洗涤。将滤液分离成层。将水层用EtOAc(2×200ml)萃取。将总有机层用盐水(200ml)洗涤,经硫酸钠干燥并浓缩。通过硅胶色谱法纯化(洗脱液:含3% EtOAc的石油醚)产生粗产物。将粗化合物通过手性SFC纯化进一步纯化以产生外消旋2-[5-(三氟甲基)-2-噻吩基]丙-1-醇(3.64g)。^{1}H NMR(400MHz,氯仿-d)δ7.52(m,1H),7.00(m,1H),4.97(t,J=5.6Hz,1H),3.51(t,J=6.0Hz,2H)3.17(m,1H),1.27(d,J=6.8Hz,3H)。LCMS m/z 210.0[M]。

[2454] 制备S101

[2455] 2-甲基-2-[5-(三氟甲基)-2-噻吩基]丙-1-醇(S101)

[2456] 

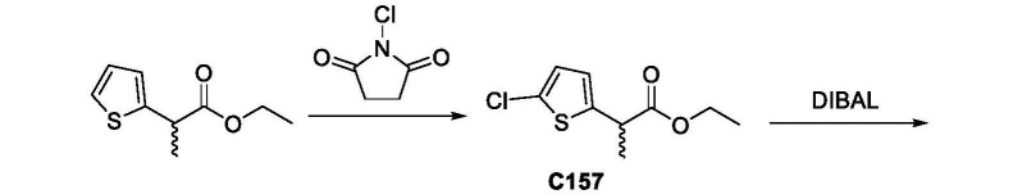
S101

[2457] S8是在步骤2中由于过度烷基化而在S100的SFC纯化期间作为副产物获得的。

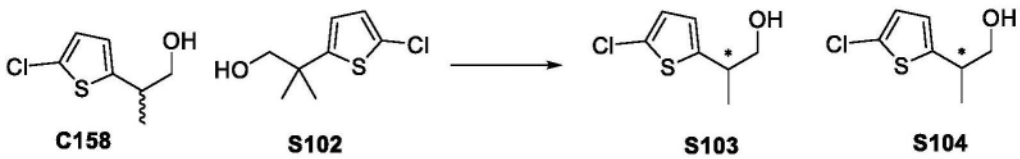
[2458] 制备S102、S103和S104

[2459] 2-甲基-2-[5-(氯)-2-噻吩基]丙-1-醇(S102)

[2460] 2-[5-(氯)-2-噻吩基]丙-1-醇(S103 ENANT-1、S104 ENANT-2)

[2461] 

C157



C158 S102 S103 S104

[2462] 步骤1:2-(5-氯-2-噻吩基)丙酸乙酯(C157)

[2463] 向2-(2-噻吩基)丙酸乙酯(1g,4.1139mmol)于乙酸(10mL)中的经搅拌的溶液中添加N-氯代琥珀酰亚胺(549.34mg,4.1139mmol)。将反应混合物在100℃下搅拌1小时。将混合物浓缩,并将所得粗产物用EtOAc(25ml)稀释,用水(10ml)、饱和碳酸氢钠溶液(10ml)、饱和硫代硫酸钠溶液(10ml)和盐水溶液(10ml)洗涤。将有机层经Na_2SO_4干燥,过滤并浓缩以得到粗产物。通过硅胶色谱法纯化(洗脱液:含3% EtOAc的石油醚),产生产物2-(5-氯-2-噻吩

基)丙酸乙酯(C157)(700mg,60%)。^{1}H NMR(氯仿-d,400MHz):δ=6.751-6.731(m,1H),6.712-6.697(m,1H),4.195-4.139(m,2H),3.876-3.729(q,J=6.4Hz,1H),1.545-1.527(t,J=2.8Hz,3H),1.300-1.221(m,3H)。LCMS m/z 218.0[M]。

[2464] 步骤2:2-(5-氯-2-噻吩基)-2-甲基-丙-1-醇和2-(5-氯-2-噻吩基)丙-1-醇(S102)和(C158)

[2465] 在0℃下向2-(5-氯-2-噻吩基)丙酸乙酯(C157)(25g,86.877mmol)于THF(500mL)中的经搅拌的溶液中逐滴添加DIBAL-H(74.135mL的25%w/v,130.32mmol)。将反应混合物在0℃下搅拌2小时。在0℃下将混合物用饱和NH_4Cl溶液(300ml)缓慢淬灭并将悬浮液通过Celite®过滤并将Celite®垫用EtOAc(2×200ml)洗涤。将滤液分离成两层。将水层用EtOAc(2×200ml)萃取。将合并的有机层用盐水(200ml)洗涤,经硫酸钠干燥并浓缩。通过硅胶色谱法纯化(洗脱液:含3% EtOAc的石油醚),产生(S102)2-(5-氯-2-噻吩基)-2-甲基-丙-1-醇(410mg,2%)。^{1}H NMR(氯仿-d,400MHz):δ=6.762-6.752(d,J=4Hz,1H),6.671-6.649(t,J=4Hz,1H),3.540-3.523(d,J=6.8Hz,2H),1.466-1.433(t,J=6.8Hz,1H),1.339(s,6H)。LCMS m/z 190.0[M];和2-(5-氯-2-噻吩基)丙-1-醇(C158)(12g,72%)。^{1}H NMR(氯仿-d,400MHz):δ=6.763-6.754(d,J=3.6Hz,1H),6.663-6.652(dd,J=4.4Hz,1H),3.712-3.606(m,2H),3.154-3.103(m,1H),1.570-1.522(m,1H),1.338-1.306(t,J=6Hz,3H)。LCMS m/z 176.0[M]。

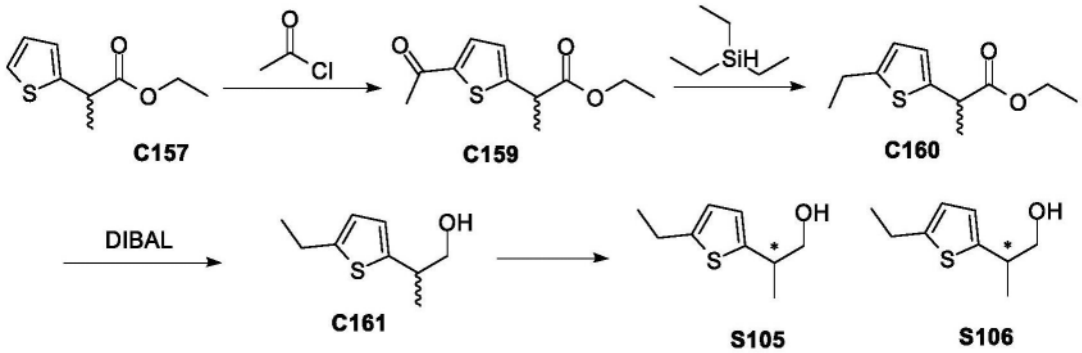
[2466] 步骤3:2-(5-氯-2-噻吩基)丙-1-醇(S103)和(S104)

[2467] 外消旋化合物2-(5-氯-2-噻吩基)丙-1-醇(C158)(12g,62.492mmol)使用SFC纯化纯化成两个单一对映异构体以得到:

[2468] 2-(5-氯-2-噻吩基)丙-1-醇(S103)(4g,35%)。^{1}H NMR(氯仿-d,400MHz):δ=6.762-6.753(d,J=3.6Hz,1H),6.662-6.651(dd,J=3.6Hz,1H),3.731-3.610(m,2H),3.170-3.103(m,1H),1.523-1.492(t,J=5.2Hz,1H),1.324-1.307(d,J=6.8Hz,3H)。LCMS m/z 176.0[M];和2-(5-氯-2-噻吩基)丙-1-醇(S104)(3.75g,34%)。^{1}H NMR(氯仿-d,400MHz):δ=6.763-6.753(d,J=4Hz,1H),6.662-6.651(dd,J=3.6Hz,1H),3.731-3.611(m,2H),3.154-3.104(q,J=6.8Hz,1H),1.511-1.480(t,J=5.6Hz,1H),1.325-1.307(d,J=7.2Hz,3H)。LCMS m/z 176.0[M]。

[2469] 制备S105和S106

[2470] 2-(5-乙基-2-噻吩基)丙-1-醇(S105 ENANT-1)和(S106 ENANT-2)

[2471] 

[2472] 步骤1:2-(5-乙酰基-2-噻吩基)丙酸乙酯(C159)

[2473] 在0℃下向2-(2-噻吩基)丙酸乙酯(C159)(80g,336.92mmol)于DCM(1500mL)中的

经搅拌的溶液中逐滴添加乙酰氯(39.671g,35.934mL,505.38mmol),随后在0℃下添加$AlCl_3$(67.388g,505.38mmol)。将反应混合物在0℃下搅拌2小时。将混合物用冰水(1000ml)缓慢淬灭,将两个层分离,并用DCM(2×500ml)进一步萃取水层。将总有机层用盐水(500ml)洗涤,经硫酸钠干燥并通过硅胶色谱法纯化(梯度:含0-5% EtOAc的石油醚),产生产物2-(5-乙酰基-2-噻吩基)丙酸乙酯(C159)(60g,73%)。^{1}H NMR(氯仿-d,400MHz):δ=7.559-7.543(t,J=4.0Hz,1H),6.991-6.980(m,1H),4.200-4.140(m,2H),4.015-3.962(q,J=7.2Hz,1H),2.525(s,3H),1.603-1.585(d,J=7.2Hz,3H),1.277-1.230(m,3H)。LCMS m/z 227.1[M+H]$^+$。

[2474] 步骤2:2-(5-乙酰基-2-噻吩基)丙酸乙酯(C160)

[2475] 在0℃下向2-(5-乙酰基-2-噻吩基)丙酸乙酯C159(60g,245.79mmol)于TFA(400mL)中的经搅拌的溶液中逐滴添加三乙基硅烷(42.870g,58.887mL,368.69mmol)。将反应混合物在室温下搅拌4小时。将反应物浓缩并用冰水(500ml)淬灭,并用EtOAc(3×500ml)萃取。将总有机物用盐水(250ml)洗涤,经硫酸钠干燥并浓缩以得到产物。通过硅胶色谱法纯化(梯度:含0-3% EtOAc的石油醚),产生产物2-(5-乙基-2-噻吩基)丙酸乙酯(C160)(50g,82)。^{1}H NMR(氯仿-d,400MHz):δ=6.735-6.725(dd,J=3.6Hz,1H),6.615-6.601(m,1H),4.186-4.127(m,2H),3.930-3.876(q,J=7.2Hz,1H),2.824-2.766(m,2H),1.550-1.532(d,J=7.2Hz,3H)1.303-1.229(m,6H)。LCMS m/z213.2[M+H]$^+$。

[2476] 步骤3:2-(5-乙基-2-噻吩基)丙-1-醇(C161)

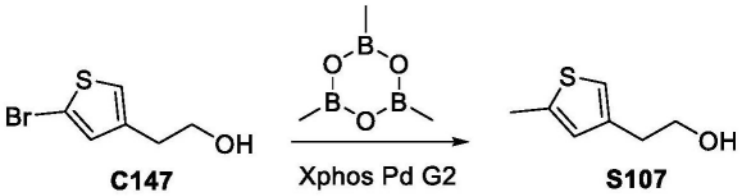
[2477] 在0℃下向2-(5-乙基-2-噻吩基)丙酸乙酯(C160)(50g,200.18mmol)于THF(1000mL)中的经搅拌的溶液中逐滴添加DIBAL-H(25%于甲苯中)(227.75mL的25%w/v,400.36mmol)。将反应混合物在0℃下搅拌2小时。在0℃下将混合物用饱和NH_4Cl溶液(500ml)缓慢淬灭并用EtOAc(2×500ml)萃取。将总有机层用盐水(250ml)洗涤,经硫酸钠干燥并浓缩。通过硅胶色谱法纯化(梯度:含0-5% EtOAc的石油醚),产生产物2-(5-乙基-2-噻吩基)丙-1-醇(C161)(31g,89%)。^{1}H NMR(氯仿-d,400MHz):δ=6.686-6.677(d,J=3.6Hz,1H),6.635-6.621(m,1H),3.724-3.601(m,2H),3.184-3.134(q,J=6.8Hz,1H),2.831-2.772(m,2H),1.609-1.548(m,1H),1.350-1.276(m,6H)。LCMS m/z 171.02[M+H]$^+$。

[2478] 步骤4:2-(5-乙基-2-噻吩基)丙-1-醇(S105)和(S106)

[2479] 外消旋化合物2-(5-乙基-2-噻吩基)丙-1-醇(31g,178.06mmol)使用SFC纯化纯化成两个单一对映异构体。2-(5-乙基-2-噻吩基)丙-1-醇(S105)(13.45g,43%)。^{1}H NMR(氯仿-d,400MHz):δ=6.686-6.678(d,J=3.2Hz,1H),6.632-6.624(d,J=3.2Hz,1H),3.730-3.607(m,2H),3.187-3.137(q,J=6.8Hz,1H),2.831-2.775(m,2H),1.535-1.470(m,1H),1.352-1.271(m,6H)。LCMS m/z 171.1[M+H]$^+$;和2-(5-乙基-2-噻吩基)丙-1-醇(S106)(11.35g,37%)。^{1}H NMR(氯仿-d,400MHz):δ=6.686-6.677(d,J=3.6Hz,1H),6.632-6.623(d,J=3.6Hz,1H),3.729-3.606(m,2H),3.203-3.119(m,1H),2.830-2.773(q,J=7.6Hz,2H),1.542-1.478(m,1H),1.329-1.271(m,6H)。LCMS m/z 171.1[M+H]$^+$。

[2480] 制备S107

[2481] 2-(5-甲基-3-噻吩基)乙醇(S107)

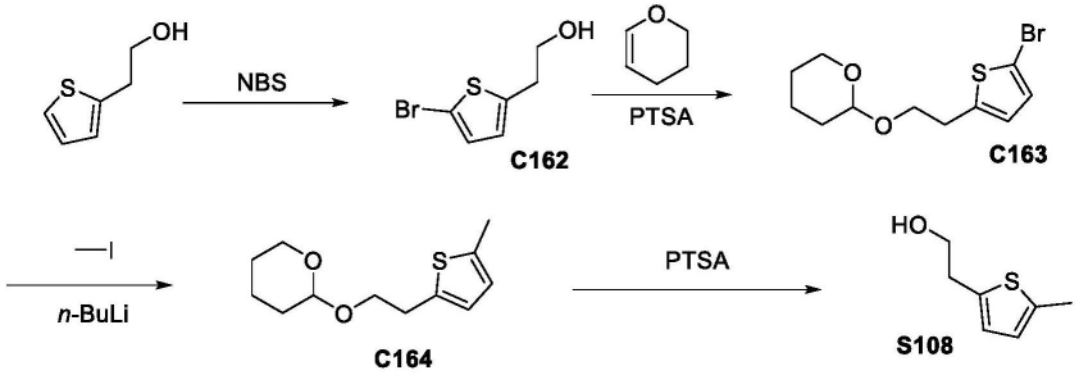
[2482] 

[2483] 步骤1:2-(5-甲基-3-噻吩基)乙醇(S107)

[2484] 在室温下在密封管中向2-(5-溴-3-噻吩基)乙醇(C147)(2.5g,0.0098mol)于1,4-二噁烷(16.000mL)中的经搅拌的溶液中添加$K_2CO_3$4.9 g,0.0355mol)。将反应混合物用氩气脱气10分钟。添加Xphos Pd G2(457mg,580.83μmol)并再次脱气5分钟。添加三甲基环三硼氧烷(50%溶液于THF中)(24.605mL的50%w/v,0.0980mol)并加热至80℃,持续16小时。将反应混合物用水(200ml)稀释并用乙酸乙酯(3×150ml)萃取。将分离的有机层经Na_2SO_4干燥,过滤,并在减压下浓缩。通过柱色谱法纯化(洗脱液:含20% EtOAc的石油醚),得到呈黄色液体的产物S1072-(5-甲基-3-噻吩基)乙醇(950mg,66%)。^{1}H NMR(400MHz,DMSO-d_6)δ 6.87(d,J=0.8Hz,1H),6.68(s,1H),4.59(t,J=5.2Hz,1H),3.58-3.53(m,2H),2.63(t,J=7.2Hz,2H),2.38(d,J=0.8Hz,3H)。

[2485] 制备S108

[2486] 2-(5-甲基-2-噻吩基)乙醇(S108)

[2487] 

[2488] 步骤1:2-(5-溴-2-噻吩基)乙醇(C162)

[2489] 在-10℃下将2-(2-噻吩基)乙醇(15g,0.1170mol)于DMF(150.00mL)中的溶液逐滴添加到NBS(20.824g,0.1170mol)于DMF中的溶液中。将反应物在室温下搅拌16小时。将反应混合物用水(300mL)淬灭,并用乙酸乙酯(200mL×3)萃取。将有机层用6% KOH溶液、冰水(150mL×2)和盐水(150mL)洗涤。将有机层经硫酸钠干燥并浓缩。通过柱色谱法纯化(洗脱液:含10% EtOAc的石油醚),得到产物2-(5-溴-2-噻吩基)乙醇(C162)(20.5g,79%)2-(5-溴-2-噻吩基)乙醇(20.5g,79%)。^{1}H NMR(400MHz,氯仿-d):δ6.89(d,J=3.6Hz,1H),6.64-6.28(m,1H),3.82(t,J=6.0Hz,2H),2.99(t,J=6.0Hz,2H)。

[2490] 步骤2:2-[2-(5-溴-2-噻吩基)乙氧基]四氢吡喃(C163)

[2491] 向2-(5-溴-2-噻吩基)乙醇(C162)(20g,0.0869mol)和3,4-二氢-2H-吡喃(10.969g,0.1304mol)于THF(80.000mL)的经搅拌的溶液中添加PTSA(603mg,0.5636mL,0.0035mol),并将反应物在室温下搅拌24小时。将反应混合物用乙酸乙酯稀释,用饱和碳酸氢钠和溶液(50mL)、水和盐水洗涤。将有机层分离,经硫酸钠干燥并浓缩。通过硅胶色谱法纯化(梯度:含0-5% EtOAc的石油醚),产生产物2-[2-(5-溴-2-噻吩基)乙氧基]四氢吡喃

(C163)(18.5g,64%)。^{1}H NMR(400MHz,氯仿-d):δ6.86(d,J=3.6Hz,1H),6.61-6.60(m,1H),4.62(t,J=3.6Hz,1H),3.99-3.50(m,4H),3.05-3.01(m,2H),1.73-1.50(m,6H)。

[2492] 步骤3:2-[2-(5-甲基-2-噻吩基)乙氧基]四氢吡喃(C164)

[2493] 在-78℃下向2-[2-(5-溴-2-噻吩基)乙氧基]四氢吡喃(C163)(19g,0.0555mol)于THF(380.00mL)中的溶液中逐滴添加n-BuLi(33.320mL的2.5M,0.0833mol)。将反应物在-78℃下搅拌一小时。在-78℃下添加碘甲烷(15.755g,6.9101mL,0.1110mol)并使反应混合物在室温下搅拌16小时。将反应混合物用饱和NH_4Cl溶液淬灭并用水稀释。将水层用乙酸乙酯(2×250mL)萃取。通过硅胶色谱法纯化(洗脱液:100%石油醚),产生产物2-[2-(5-甲基-2-噻吩基)乙氧基]四氢吡喃(C32)(19g,130%)。^{1}H NMR(400MHz,氯仿-d):δ6.61(d,J=3.2Hz,1H),6.55-6.54(m,1H),4.63(m,1H),3.96-3.50(m,4H),3.03(t,J=2.8Hz,2H),2.42(s,3H),1.72-1.42(m,6H)。

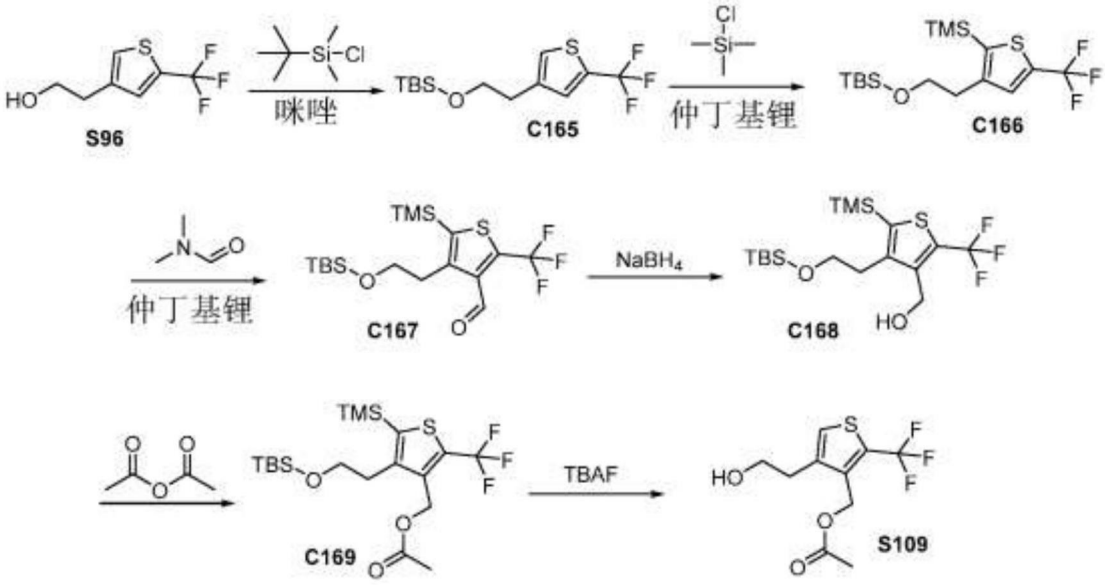
[2494] 步骤4:2-(5-甲基-2-噻吩基)乙醇(S108)

[2495] 在室温下向2-[2-(5-甲基-2-噻吩基)乙氧基]四氢吡喃(14g,0.0532mol)于MeOH(280.00mL)中的溶液中添加PTSA(10.9g,10.187mL,0.0633mol)。将反应物搅拌24小时。将反应混合物用乙酸乙酯(500mL)稀释并且然后用水(200mL)洗涤。将有机层用饱和碳酸氢钠(100mL×2)水溶液洗涤。将水层用乙酸乙酯(100ml×2)再次萃取。将合并的有机层经硫酸钠干燥。通过硅胶色谱法纯化(梯度:含0-15% EtOAc的石油醚),产生产物2-(5-甲基-2-噻吩基)乙醇(6.56g,82%)。^{1}H NMR(400MHz,DMSO-d_6):δ6.61(d,J=3.6Hz,1H),6.58-6.57(d,J=4.0Hz,1H),4.73(t,J=5.2Hz,1H),3.58-3.53(m,2H),2.82(t,J=6.8Hz,2H),2.36(s,3H)。

[2496] 制备S109

[2497] [4-(2-羟乙基)-2-(三氟甲基)-3-噻吩基]乙酸甲酯(S109)

[2498]



[2499] 步骤1:叔丁基-二甲基-[2-[5-(三氟甲基)-3-噻吩基]乙氧基]硅烷(C165)

[2500] 向2-[5-(三氟甲基)-3-噻吩基]乙醇(S96)(500mg,2.498mmol)于DCM(10mL)中的混合物中添加咪唑(190mg,2.791mmol),随后添加TBSCl(420mg,2.787mmol),其立即沉淀出白色固体。将固体过滤,并将有机层用1N HCl(10mL)、盐水(10mL)洗涤,用硫酸镁干燥,过滤

并浓缩。通过硅胶色谱法纯化(梯度:含0-30% EtOAc的庚烷)产生产物。将含产物级分合并并浓缩。假设产率是定量的,吡嗪粗产物被伸缩到下一步。

[2501] 步骤2:叔丁基-二甲基-[2-[5-(三氟甲基)-2-三甲基硅烷基-3-噻吩基]乙氧基]硅烷(C166)

[2502] 将来自步骤1的THF(10mL)中的混合物冷却至-78℃,并添加仲丁基锂(2.3mL的1.4M,3.220mmol),随后添加TMSCl(3mL的1M,3.000mmol)。5分钟后,将黄色混合物用饱和氯化铵水溶液淬灭。将混合物用水(10mL)和TBME(10mL)稀释。将有机层用盐水洗涤,用硫酸镁干燥,过滤并浓缩。通过硅胶色谱法纯化(梯度:含0-10% EtOAc的庚烷),产生产物叔丁基-二甲基-[2-[5-(三氟甲基)-2-三甲基甲硅烷基-3-噻吩基]乙氧基]硅烷(C166)(400mg,42%)。^{1}H NMR(300MHz,氯仿-d)δ7.41(d,J=1.2Hz,1H),3.80-3.75(m,2H),2.87(t,J=6.8Hz,2H),0.87(s,9H),0.36(s,9H),-0.00(d,J=2.2Hz,6H)。

[2503] 步骤3:4-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]-2-(三氟甲基)-5-三甲基甲硅烷基-噻吩-3-甲醛(C167)

[2504] 向冷却至-78℃叔丁基-二甲基-[2-[5-(三氟甲基)-2-三甲基甲硅烷基-3-噻吩基]乙氧基]硅烷C166(400mg,1.024mmol)于THF(10mL)中的混合物中添加仲丁基锂(1.2mL的1.4M,1.680mmol),随后添加N,N-二甲基甲酰胺(3mL的1M,3.000mmol)。5分钟后,将黄色混合物用饱和氯化铵水溶液淬灭。将混合物用乙酸乙酯(20mL)和水(20mL)稀释并分离。将有机层用盐水(20mL)洗涤,用硫酸镁干燥,过滤,并浓缩。通过硅胶色谱法纯化(洗脱液:100%庚烷)产生产物。将混合物浓缩,用庚烷(5mL)稀释并用水(5mL)洗涤。使有机层通过相分离器,浓缩并伸缩直接用于下一步。

[2505] 步骤4:[4-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]-2-(三氟甲基)-5-三甲基甲硅烷基-3-噻吩基]甲醇(C168)

[2506] 将(C167)在MeOH(1mL)中稀释并向混合物中添加$NaBH_4$(7mg,0.1850mmol)。10分钟后,将混合物浓缩,并在庚烷(2mL)和水(2mL)中重新稀释。去除有机层用并用另外的庚烷萃取水层。使有机层通过相分离器并浓缩。通过硅胶色谱法纯化(梯度:含0-10% EtOAc的庚烷),产生产物(C168)。^{1}H NMR(300MHz,氯仿-d)δ4.65(d,J=6.3Hz,2H),4.00-3.72(m,2H),3.34(t,J=6.3Hz,1H),2.97(t,J=6.1Hz,2H),0.82(s,10H),0.36(s,9H)。

[2507] 步骤5:[4-[2-[叔丁基(二甲基)甲硅烷基]氧基乙基]-2-(三氟甲基)-5-三甲基甲硅烷基-3-噻吩基]乙酸甲酯(C169)

[2508] 向含(C168)的DCM(4mL)中添加DMAP(2mg,0.01637mmol)和DIPEA(50μL,0.2871mmol),随后添加Ac2O(30μL,0.3180mmol)。将混合物浓缩,用庚烷(5mL)稀释并用水(5mL)洗涤。使有机层通过相分离器并浓缩以产生产物。

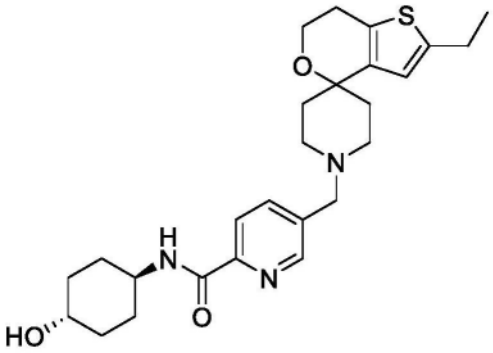
[2509] 步骤6:[4-(2-羟乙基)-2-(三氟甲基)-3-噻吩基]乙酸甲酯(S109)

[2510] 将来自步骤5的(C169)用EtOAc(2mL)稀释并向混合物中添加TBAF(1mL的1M,1.000mmol)的THF溶液,并搅拌混合物。5分钟后,观察到TBS基团的完全脱保护。将反应物搅拌48小时。将混合物用另外的EtOAc(3mL)稀释,用水洗涤,通过相分离器并浓缩。通过硅胶色谱法纯化(梯度:含0-60% EtOAc的庚烷),产生产物[4-(2-羟乙基)-2-(三氟甲基)-3-噻吩基]乙酸甲酯(35mg,12%)。^{1}H NMR(300MHz,氯仿-d)δ7.26(s,1H),5.14(d,J=1.1Hz,2H),3.86(t,J=6.4Hz,2H),2.97-2.74(m,2H),2.07(s,3H),1.80(s,1H)。LCMS m/z 269.21

$[M+H]^+$。

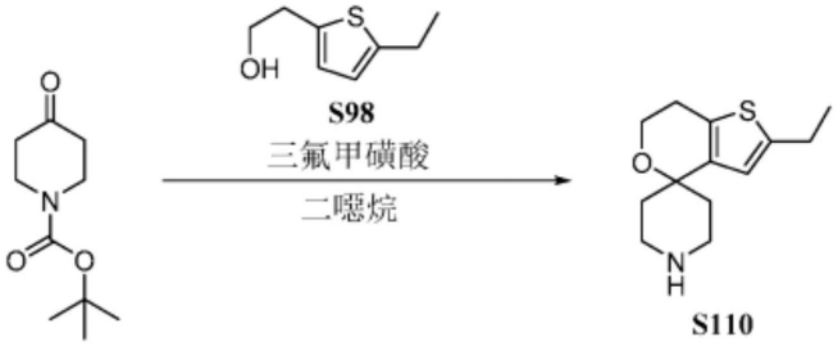
[2511] 化合物1043

[2512] 5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-N-((1r,4r)-4-羟基环已基)吡啶酰胺(1043)

[2513] 

1043

[2514] 步骤1:2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S110)

[2515] 

[2516] 在0℃下向2-(5-乙基-2-噻吩基)乙醇(S98)(3g,18.22mmol)和4-氧代哌啶-1-甲酸叔丁(3.3g,16.56mmol)于1,4-二噁烷(50mL)中的经搅拌的溶液中添加三氟甲磺酸(4.5mL,50.85mmol)。将反应混合物在搅拌下缓慢温热至室温。将反应物用水稀释,然后用2M Na_2CO_3调节至pH 8并用乙酸乙酯萃取。将合并的有机物经无水硫酸钠干燥,过滤并在真空中浓缩。用TFA改性剂进行反相纯化,随后冻干过夜,提供无定形白色固体2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S110,三氟乙酸盐)(5.21g,29%)。ESI-MS m/z计算值:237.11873,实测值:237.82(M+1)+。

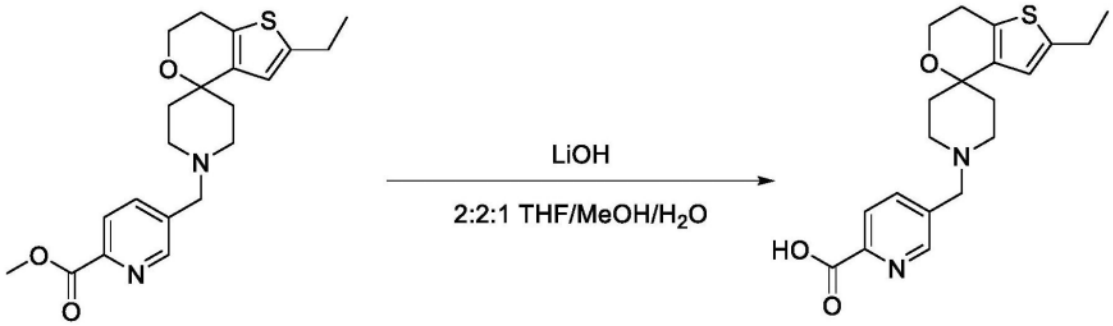
[2517] 步骤2:5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]哌啶-2-甲酸叔丁酯(S111)

[2518] 

[2519] 将2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](3.3g,13.90mmol)于二氯

甲烷(95mL)中的溶液用5-甲酰基哌啶-2-甲酸叔丁酯(S110)(3.5g,21.19mmol)和三乙酰氧基硼氢化钠(5.9g,27.84mmol)处理。将所得溶液在室温下搅拌过夜。将反应物通过在饱和$NaHCO_3$之间分配淬灭,将有机物经无水硫酸钠干燥,过滤并在真空中浓缩。通过HPLC纯化:含10-90%ACN的水(TFA改性剂),C18柱,然后冻干过夜,得到5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]哌啶-2-甲酸甲酯(三氟乙酸盐)(2.3207g,32%)。^{1}H NMR(300MHz,氯仿-d)δ8.77(dd,J=2.1,1.0Hz,1H),8.29-8.18(m,2H),6.45(d,J=1.0Hz,1H),4.33(s,2H),4.05(s,3H),3.90(t,J=5.3Hz,2H),3.41(d,J=11.5Hz,2H),3.19(t,J=12.1Hz,2H),2.82-2.71(m,4H),2.38(td,J=14.2,13.7,4.3Hz,2H),2.05-1.96(m,2H),1.27(t,J=7.5Hz,3H)。ESI-MS m/z计算值:386.1664,实测值:387.47(M+1)$^+$。

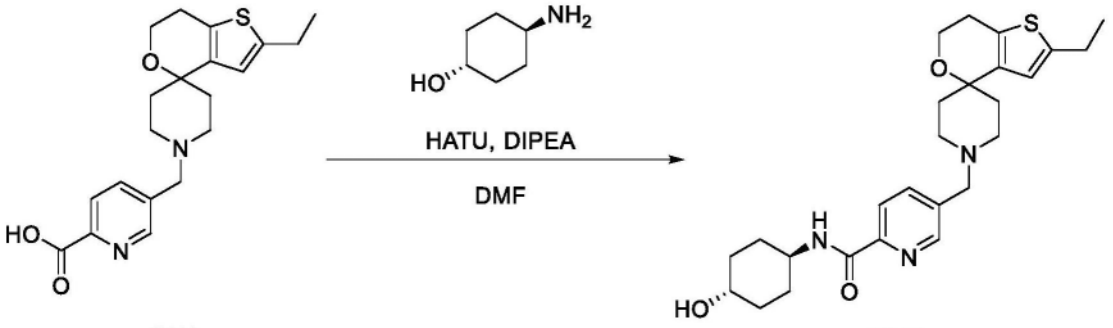
[2520] 步骤3:5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]哌啶-2-甲酸(S112)的合成

[2521] 

S111 S112

[2522] 将5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]哌啶-2-甲酸甲酯(三氟乙酸盐)(2.3091g,4.532mmol)于THF(9mL)/MeOH(9mL)/水(4.5mL)中的溶液用LiOH(220mg,9.187mmol)处理,并在环境温度下搅拌大约3小时。将反应物在真空中浓缩以去除有机物。将剩余水用1N HCl酸化至pH 3并用乙酸乙酯分配。将合并的有机物经无水硫酸钠干燥,过滤并在真空中浓缩。从乙腈/水冻干过夜以得到5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′哌啶]-1′-基)甲基]哌啶-2-甲酸(467.9mg,26%)。^{1}HNMR(300MHz,氯仿-d)δ8.81(s,1H),8.27(d,J=11.9Hz,2H),6.43(s,1H),4.37(s,2H),3.92(t,J=5.2Hz,2H),3.53(s,2H),3.26(s,2H),2.85-2.70(m,4H),2.35(s,2H),2.05(d,J=13.8Hz,2H),1.27(t,J=7.5Hz,3H)。ESI-MS m/z计算值:372.15076,实测值:373.48(M+1)$^+$。

[2523] 步骤4:5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-N-((1r,4r)-4-羟基环己基)吡啶酰胺(1043)的合成

[2524] 

S112 1043

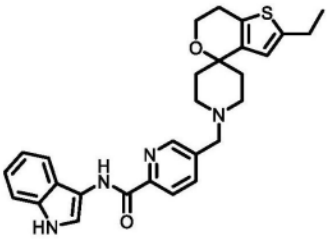
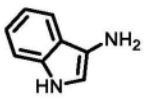
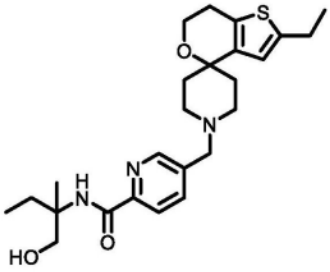
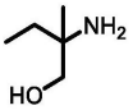
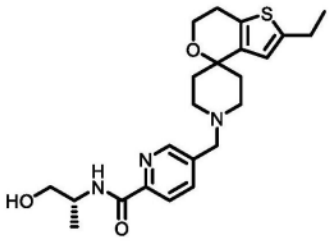
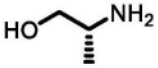
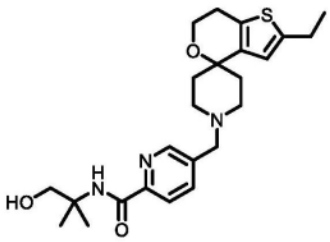
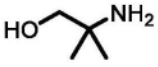
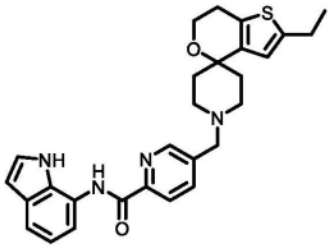
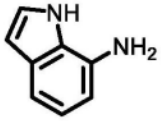
[2525] 将5-[(2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]吡啶-

2-甲酸(15mg,0.038mmol)、HATU(22mg,0.057mmol)和DIPEA(12mg,0.095mmol)于DMF(1mL)中的溶液中添加到含有反式-4-氨基环己醇(8.8mg,0.076mmol)的小瓶中。将所得溶液在环境温度下搅拌16小时,过滤并用TFA改性剂通过HPLC直接纯化以提供5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-N-((1r,4r)-4-羟基环己基)吡啶酰胺(5mg,28%)。ESI-MS m/z计算值:470.24,实测值:470.247(M+1)$^+$。

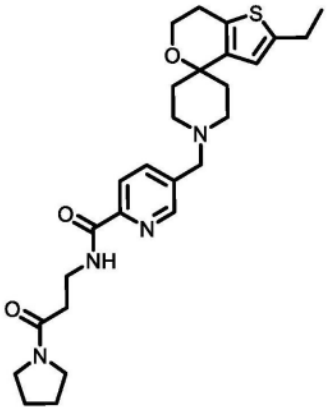
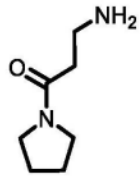
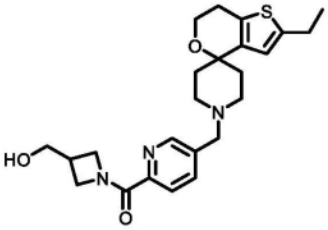
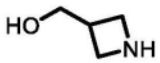
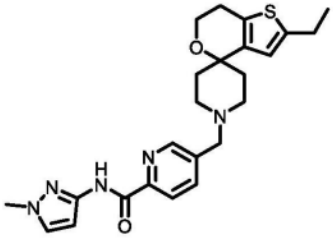
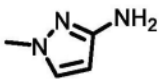
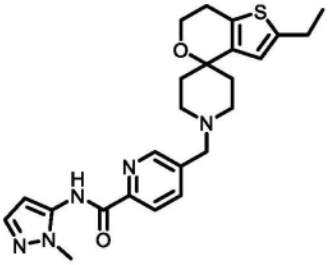
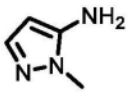
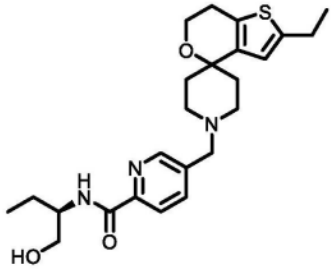
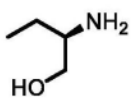
[2526] 采用与化合物1043所述相同的方法,使用适当的胺由S112制备化合物1044-1065(参见表49)。

[2527] 表49:化合物1025-1026的结构和物理化学数据

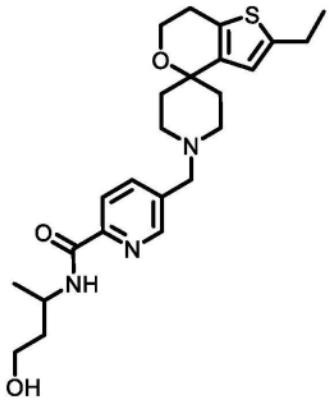
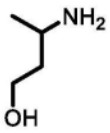
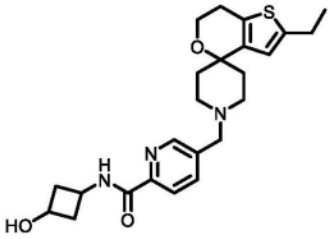
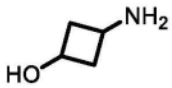
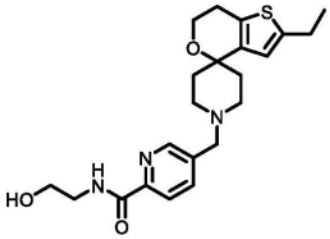
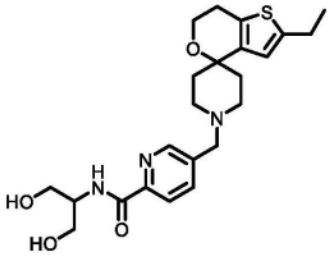
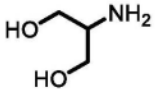
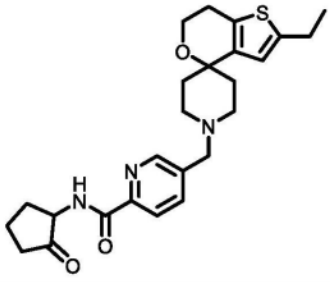
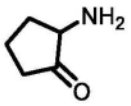
[2528]

化合物	产物	胺	^{1}H NMR; LCMS m/z [M+H]$^+$。
1044			ESI-MS m/z 计算值: 486.628, 实测值: 487.217 (M+1)+。
1045			ESI-MS m/z 计算值: 457.629, 实测值: 458.248 (M+1)+。
1046			ESI-MS m/z 计算值: 429.576, 实测值: 430.215 (M+1)+。
1047			ESI-MS m/z 计算值: 443.602, 实测值: 444.232 (M+1)+。
1048			ESI-MS m/z 计算值: 486.628, 实测值: 487.217 (M+1)+。

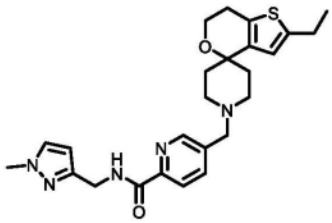
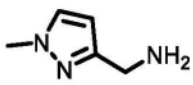
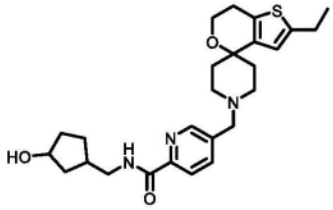
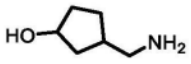
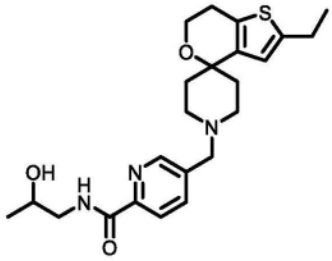
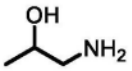
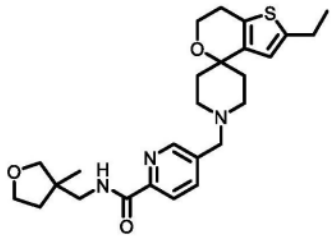
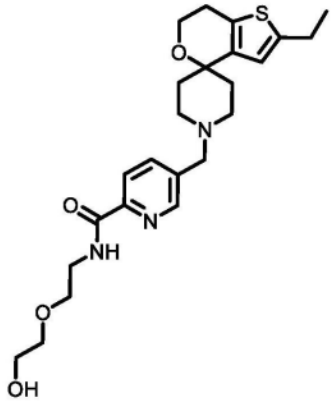
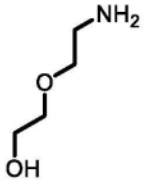
[2529]

化合物	产物	胺	^{1}H NMR；LCMS m/z $[M+H]^+$。
1049			ESI-MS m/z 计算值：496.665，实测值：497.258 (M+1)+。
1050			ESI-MS m/z 计算值：441.586，实测值：442.216 (M+1)+。
1051			ESI-MS m/z 计算值：451.584，实测值：452.212 (M+1)+。
1052			ESI-MS m/z 计算值：451.584，实测值：452.212 (M+1)+。
1053			ESI-MS m/z 计算值：443.602，实测值：444.232 (M+1)+。

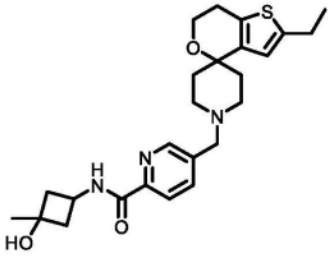
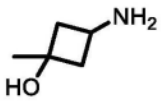
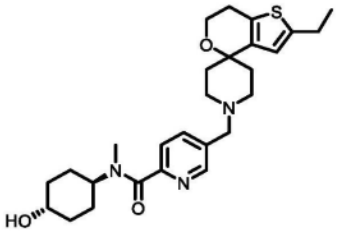
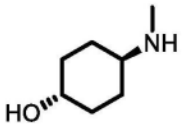
[2530]

化合物	产物	胺	^{1}H NMR；LCMS m/z $[M+H]^+$。
1054			ESI-MS m/z 计算值：443.602，实测值：444.232 (M+1)+。
1055			ESI-MS m/z 计算值：441.586，实测值：442.216 (M+1)+。
1056			ESI-MS m/z 计算值：415.549，实测值：416.201 (M+1)+。
1057			ESI-MS m/z 计算值：445.575，实测值：446.211 (M+1)+。
1058			ESI-MS m/z 计算值：453.597，实测值：454.216 (M+1)+。

[2531]

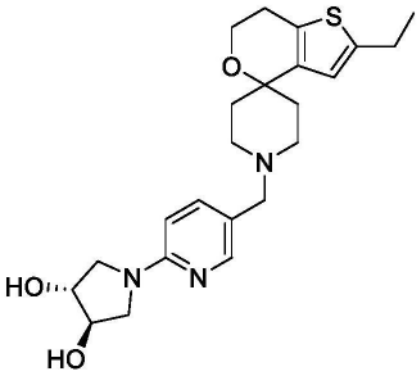
化合物	产物	胺	^{1}H NMR；LCMS m/z $[M+H]^+$。
1059			ESI-MS m/z 计算值：465.611，实测值：466.227 (M+1)+。
1060			ESI-MS m/z 计算值：469.639，实测值：470.248 (M+1)+。
1061			ESI-MS m/z 计算值：429.576，实测值：430.216 (M+1)+。
1062			ESI-MS m/z 计算值：469.639，实测值：470.248 (M+1)+。
1063			ESI-MS m/z 计算值：459.602，实测值：460.227 (M+1)+。

[2532]

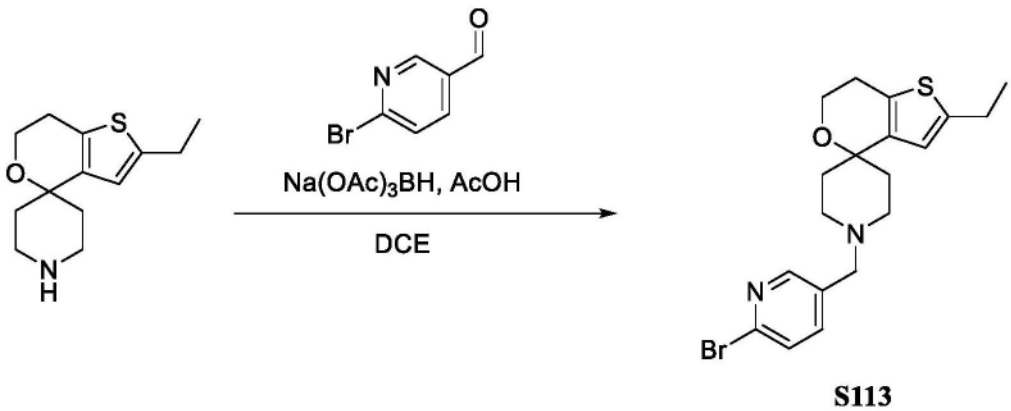
化合物	产物	胺	^{1}H NMR；LCMS m/z $[M+H]^+$。
1064			ESI-MS m/z 计算值：455.613，实测值：456.232 (M+1)+。
1065			ESI-MS m/z 计算值：483.666，实测值：484.263 (M+1)+。

[2533] 化合物1066

[2534] (3R,4R)-1-(5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)吡啶-2-基)吡咯烷-3,4-二醇(1066)

[2535] 

[2536] 步骤1:1′-[(6-溴-3-吡啶基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S113)的合成

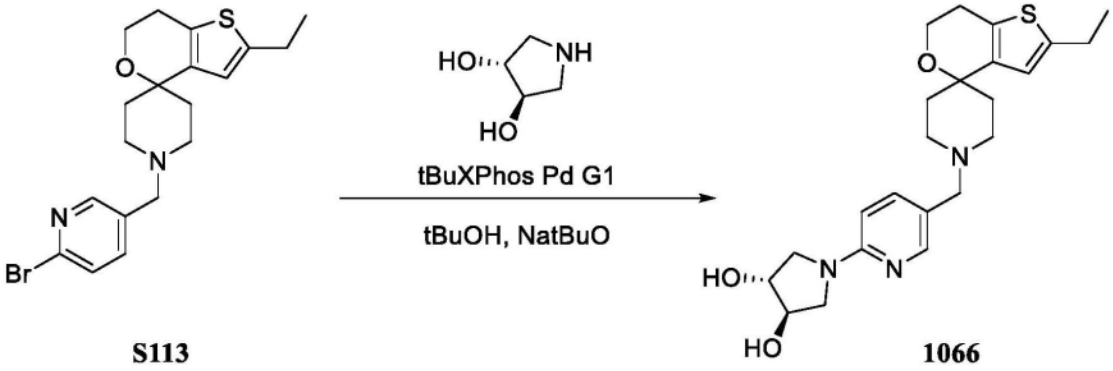
[2537] 

S113

[2538] 将2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](2.5g,10.53mmol)、6-溴吡啶-3-甲醛(1.9g,10.21mmol)和AcOH(640μL,11.25mmol)于二氯甲烷(45mL)中的溶液在室温下搅拌10分钟,随后添加Na(OAc)$_3$BH(6.6g,31.14mmol)。将所得混合物在室温下搅拌

过夜,然后在真空中浓缩。通过快速柱色谱法纯化(含0-10% MeOH的DCM),提供1′-[(6-溴-3-吡啶基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](2.06g,48%)。^{1}H NMR(300MHz,氯仿-d)δ8.34-8.28(m,1H),7.58(dd,J=8.1,2.5Hz,1H),7.44(dd,J=8.1,0.7Hz,1H),6.47(d,J=1.1Hz,1H),3.90(t,J=5.4Hz,2H),3.50(s,2H),2.80-2.71(m,4H),2.70-2.60(m,2H),2.40(td,J=11.5,3.3Hz,2H),1.97-1.81(m,4H),1.27(t,J=7.5Hz,3H)。ESI-MS m/z计算值:406.07144,实测值:407.1(M+1)$^+$。

[2539] 步骤2:(3R,4R)-1-(5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)吡啶-2-基)吡咯烷-3,4-二醇(1066)的合成

[2540] 

S113 1066

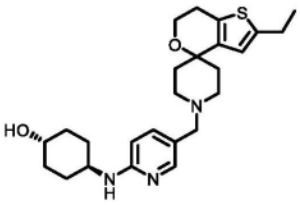
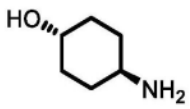
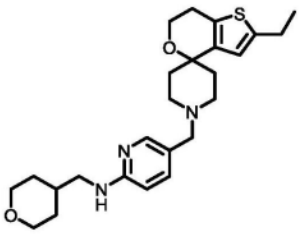
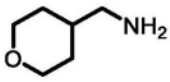
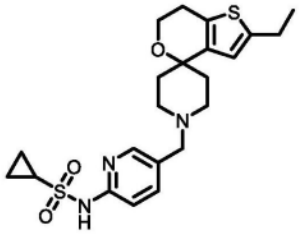
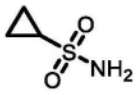
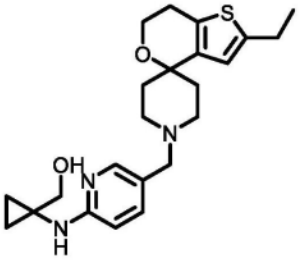
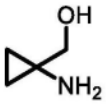
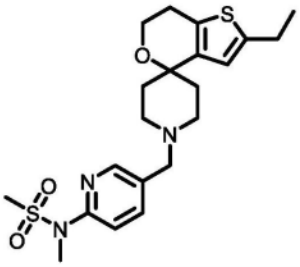
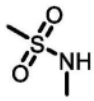
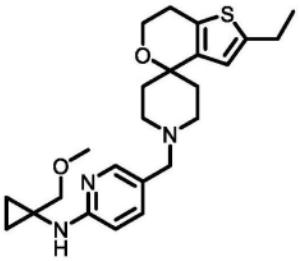
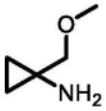
[2541] 将含有1′-[(6-溴-3-吡啶基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](15mg,0.04mmol)、(3R,4R)-吡咯烷-3,4-二醇(4.4mg,0.042mmol)、tBuXPhos Pd G1(1.2mg,0.0018mmol)和tBuOH(0.5mL)的小瓶用2-甲基丙-2-醇酯(钠盐)(39uL,2M)处理,在氮气下密封,并在80℃下搅拌3小时。将反应物通过添加甲醇淬灭并用TFA改性剂通过反相HPLC纯化以得到(3R,4R)-1-(5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)吡啶-2-基)吡咯烷-3,4-二醇(6mg,28%)。ESI-MS m/z计算值:429.576,实测值:430.216(M+1)$^+$。

[2542] 化合物1067-1072

[2543] 采用与化合物1066所述相同的方法,使用适当的胺由S113制备化合物1067-1072(参见表50)。

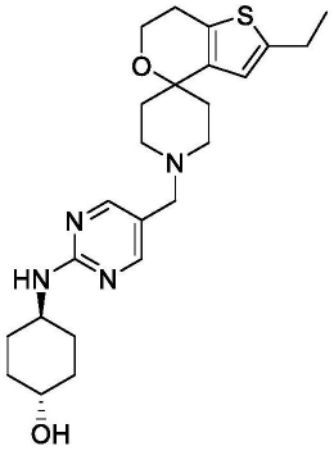
[2544] 表50:化合物1067-1072的结构和物理化学数据

[2545]

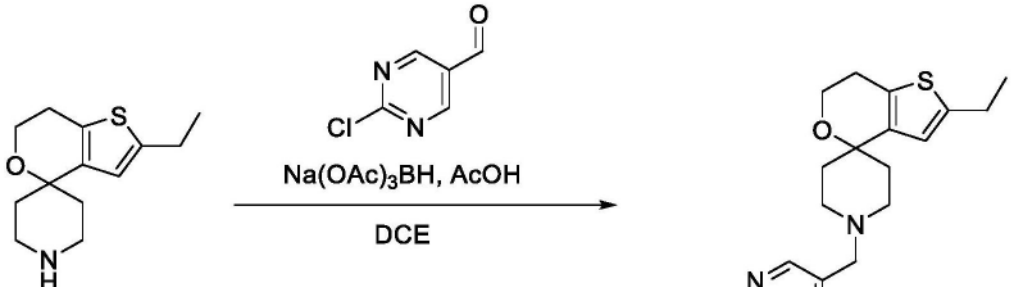
化合物	产物	胺	^{1}H NMR；LCMS m/z [M+H]$^+$。
1067			ESI-MS m/z 计算值：441.629，实测值：442.253 (M+1)+。
1068			ESI-MS m/z 计算值：441.629，实测值：442.253 (M+1)+。
1069			ESI-MS m/z 计算值：447.614，实测值：448.172 (M+1)+。
1070			ESI-MS m/z 计算值：413.576，实测值：414.221 (M+1)+。
1071			ESI-MS m/z 计算值：435.603，实测值：436.172 (M+1)+。
1072			ESI-MS m/z 计算值：427.603，实测值：428.237 (M+1)+。

[2546] 化合物1073

[2547] (1r,4r)-4-((5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)嘧啶-2-基)氨基)环己烷-1-醇(1073)

[2548] 

[2549] 步骤1:1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S114)的合成

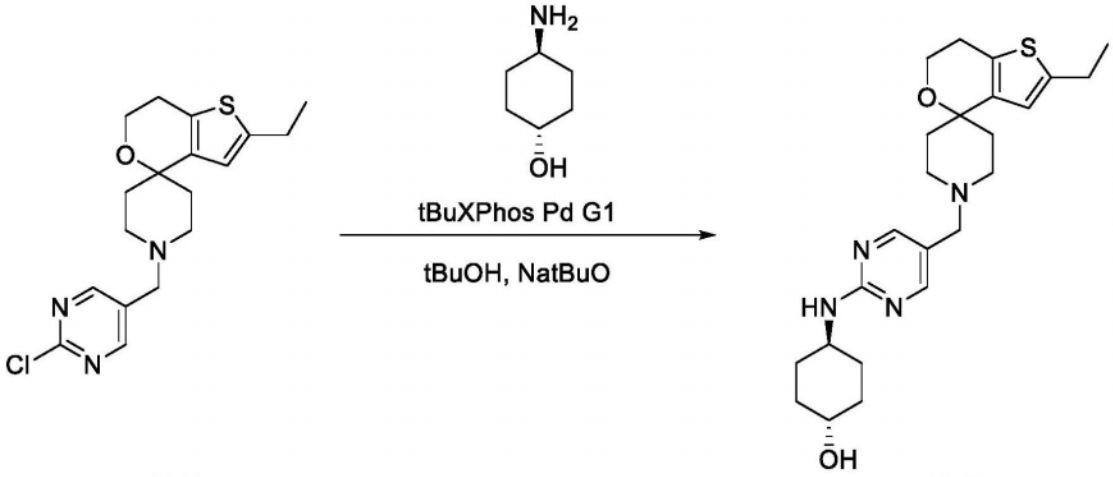
[2550] 

S114

[2551] 在反应小瓶中添加含2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](2.5g,10.53mmol)、2-氯嘧啶-5-甲醛(1.7g,11.93mmol)和AcOH(600μL,10.55mmol)的DCE(42mL)。添加三乙酰氧基硼氢化物(钠盐)(6.7g,31.61mmol),并将反应物在环境温度下搅拌过夜。然后将反应物用水淬灭,用DCM萃取三次,并在真空中浓缩。将粗残余物通过反相HPLC纯化(HCl改性剂)以提供1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](1.2g,29%)。ESI-MS m/z计算值:363.11722,实测值:363.73(M+1)$^+$。

[2552] 步骤2:(1r,4r)-4-((5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)嘧啶-2-基)氨基)环己烷-1-醇(1073)的合成

[2553]



S114 1073

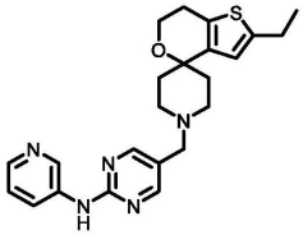
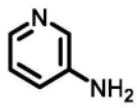
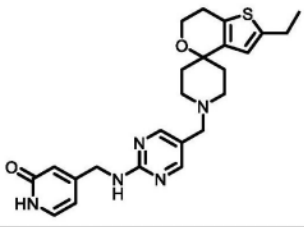
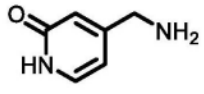
[2554] 将含有1′-[(2-氯嘧啶-5-基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](15mg,0.04mmol)、反式-4-氨基环己醇(5.5mg,0.047mmol)、tBuXPhos Pd G1(1.2mg,0.002mmol)和tBuOH(0.5mL)的小瓶用2-甲基丙-2-醇酯(钠盐)(39uL,2M)处理,在氮气下密封,并在80℃下搅拌3小时。将反应物通过添加甲醇淬灭并用TFA改性剂通过反相HPLC纯化以得到呈TFA盐的(1r,4r)-4-((5-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)嘧啶-2-基)氨基)环己-1-醇(15mg,67%)。ESI-MS m/z计算值:442.24,实测值:443.24$(M+1)^+$。

[2555] 化合物1074-1078

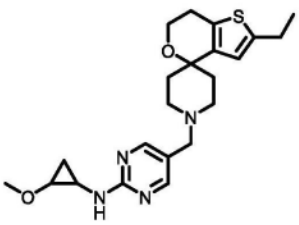
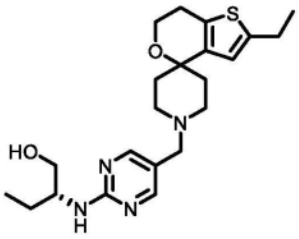
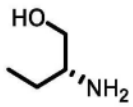
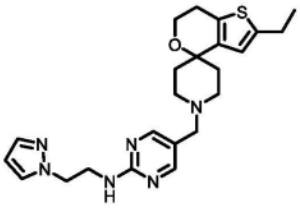
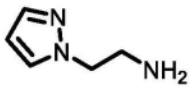
[2556] 采用与化合物1073所述相同的方法,使用适当的胺由S114制备化合物1074-1078(参见表51)。

[2557] 表51:化合物1074-1078的结构和物理化学数据

[2558]

化合物	产物	胺	^{1}H NMR；LCMS m/z[M+H]$^+$。
1074			ESI-MS m/z 计算值：421.558，实测值：422.201 (M+1)+。
1075			ESI-MS m/z 计算值：451.584，实测值：452.212 (M+1)+。

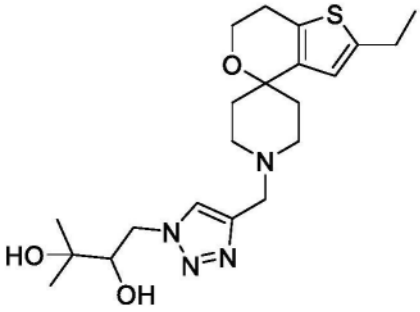
[2559]

1076			ESI-MS m/z 计算值：414.564，实测值：415.217 (M+1)+。
1077			ESI-MS m/z 计算值：416.58，实测值：417.232 (M+1)+。
1078			ESI-MS m/z 计算值：438.589，实测值：439.228 (M+1)+。

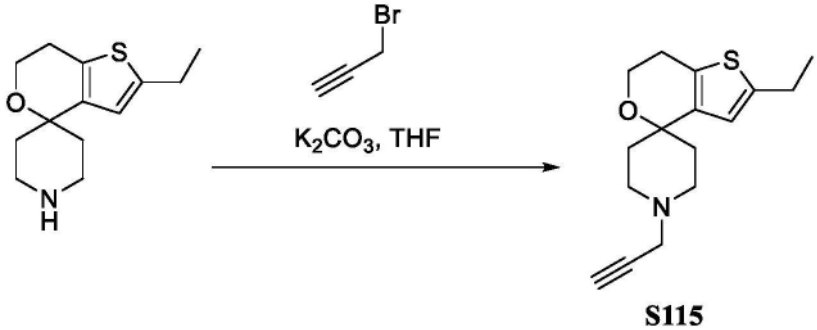
[2560] 化合物1079

[2561] 1-(4-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-1H-

[2562] 1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇(1079)

[2563] 

[2564] 步骤1:2-乙基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S115)的合成

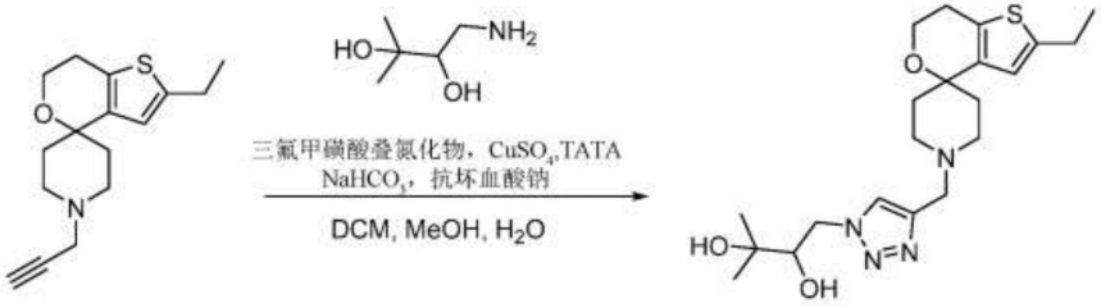
[2565] 

S115

[2566] 将2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](2500mg,10.53mmol)和碳酸钾(1.5g,10.85mmol)于四氢呋喃(50mL)中的混合物加热至50℃并搅拌。此时,添加含炔丙基溴(1.735g,11.67mmol)的甲苯并在该温度下搅拌混合物。4小时后,将混合物冷却至室

温,并用水(100mL)和EtOAc(100mL)稀释。分离各层,并将有机层用水(2×50mL)洗涤。将有机层用硫酸镁干燥,过滤,并浓缩。通过快速柱色谱法纯化(0-10% MeOH:DCM),提供产生2-乙基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S115)(1072mg,36%)。^{1}H NMR(400MHz,氯仿-d)δ6.45(d,J=1.1Hz,1H),3.91(t,J=5.4Hz,2H),3.31(d,J=2.5Hz,2H),2.85-2.65(m,6H),2.65-2.49(m,2H),2.26(t,J=2.4Hz,1H),2.05-1.92(m,2H),1.92-1.81(m,2H),1.26(t,J=7.5Hz,3H)。ESI-MS m/z计算值:275.1344,实测值:276.43(M+1)$^+$。

[2567] 步骤2:1-(4-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-1H-1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇(1079)的合成

[2568] 

S115 1079

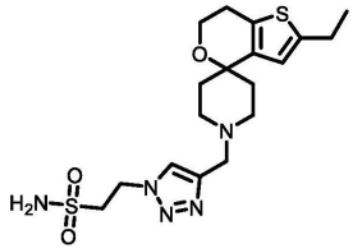
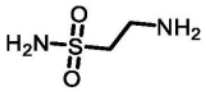
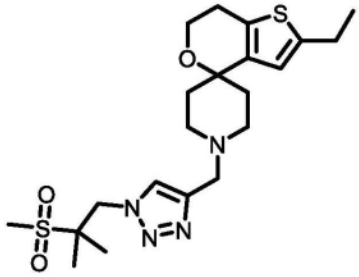
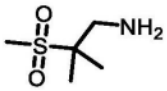
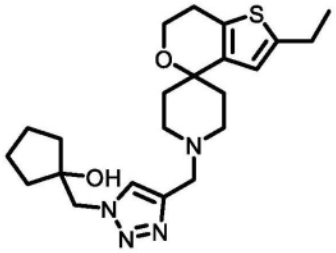
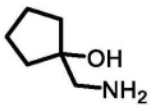
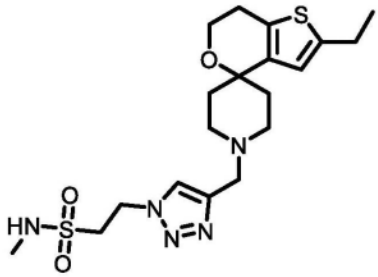
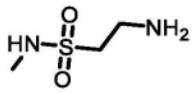
[2569] 向1-氨基-3-甲基丁烷-2,3-二醇(10mg,0.084mmol)于MeOH(600μL)中的混合物中添加含CuSO4(0.15mg)的水(75μL),随后添加含碳酸氢钠(6.5mg,0.08mmol)的水(75μL)和三氟甲磺酸叠氮化物(0.25mL的0.452M)于DCM中的溶液。将该混合物搅拌1小时。1小时后,将含2-乙基-1′-丙-2-炔基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](10mg,0.036mmol)的MeOH(100μL)、含抗坏血酸钠(7mg,0.039mmol)的水(50μL)和含TBTA(1mg,0.002mmol)的MeOH(100μL)以及混合物加热至50℃并搅拌过夜。此时,将混合物干燥并重新溶解在DMSO中以用TFA改性剂进行反相HPLC纯化。将含产物的级分在DCM中稀释,并用饱和碳酸氢钠洗涤以去除TFA盐。将有机层干燥以产生1-(4-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)-1H-1,2,3-三唑-1-基)-3-甲基丁烷-2,3-二醇(11.8mg,61%)。^{1}H NMR(400MHz,DMSO-d6)δ9.97(s,1H),8.23(s,1H),6.43(s,1H),5.20(s,1H),4.84-4.59(m,2H),4.51(s,2H),4.21(dd,J=13.8,10.0Hz,1H),3.87(t,J=5.3Hz,2H),3.54(d,J=9.9Hz,1H),3.34(s,2H),3.18(d,J=10.2Hz,2H),2.82-2.64(m,4H),2.10(t,J=13.5Hz,2H),1.98(d,J=14.4Hz,2H),1.20(t,J=7.5Hz,3H),1.16(s,3H),1.11(s,3H)。ESI-MS m/z计算值:420.22,实测值:421.227(M+1)$^+$。

[2570] 化合物1080-1125,1183

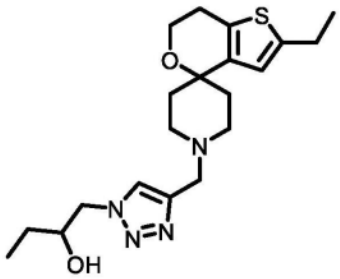
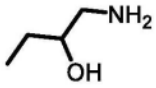
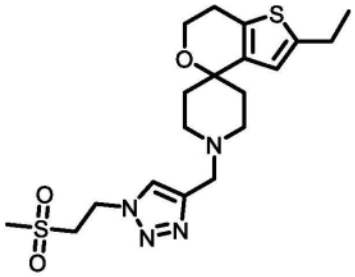
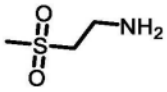
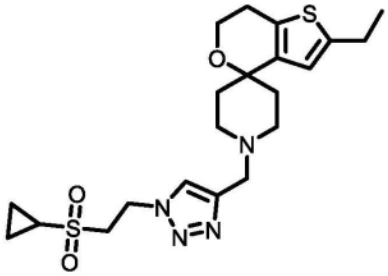
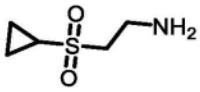
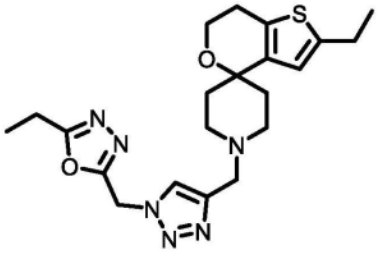
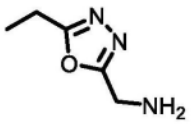
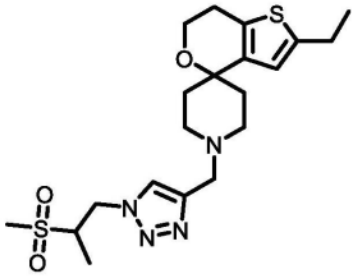
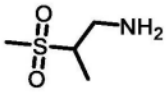
[2571] 采用与化合物1079所述相同的方法,使用适当的胺由S115制备化合物1080-1125和化合物1183(参见表52)。

[2572] 表52:化合物1080-1125,1183的结构和物理化学数据

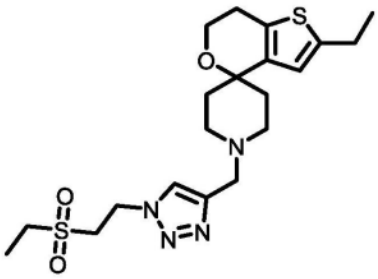
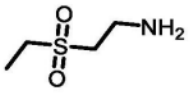
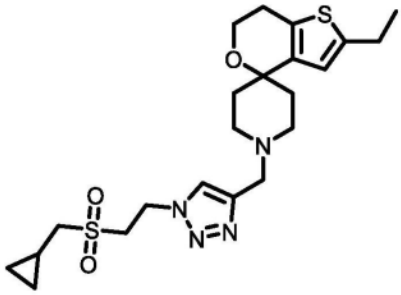
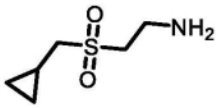
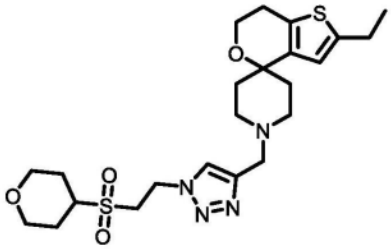
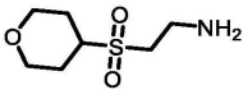
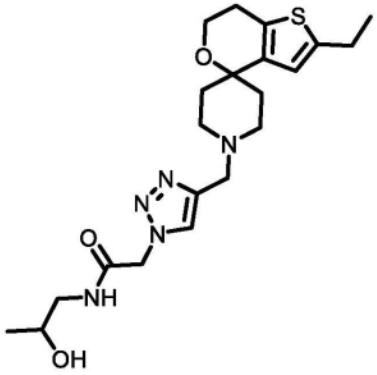
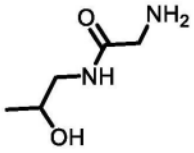
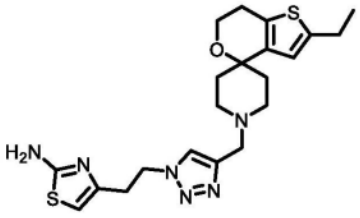
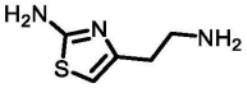
[2573]

化合物	产物	胺	LCMS m/z[M+H]+。
1080			ESI-MS m/z 计算值：425.156，实测值：426.163 (M+1)+。
1081			ESI-MS m/z 计算值：452.192，实测值：453.199 (M+1)+。
1082			ESI-MS m/z 计算值：416.225，实测值：417.232 (M+1)+。
1083			ESI-MS m/z 计算值：439.171，实测值：440.179 (M+1)+。

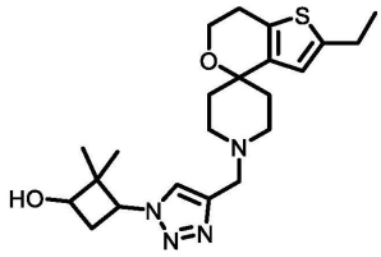
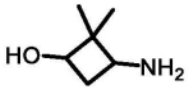
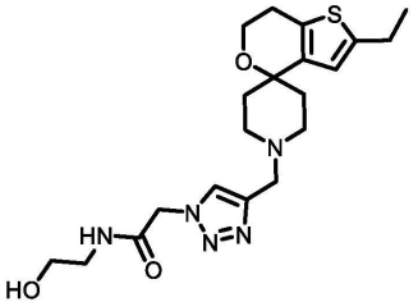
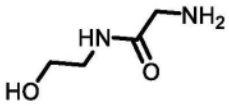
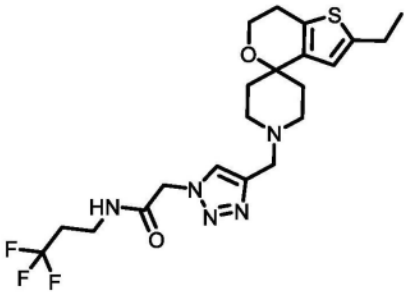
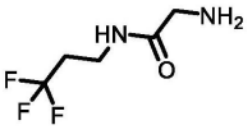
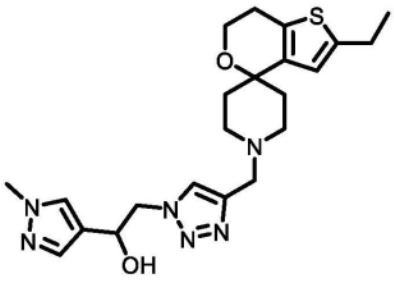
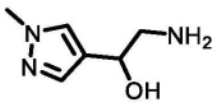
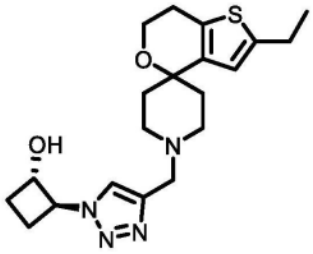
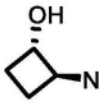
[2574]

化合物	产物	胺	LCMS m/z[M+H]+。
1084			ESI-MS m/z 计算值：390.209，实测值：391.216 (M+1)+。
1085			ESI-MS m/z 计算值：424.16，实测值：425.168 (M+1)+。
1086			ESI-MS m/z 计算值：450.176，实测值：451.183 (M+1)+。
1087			ESI-MS m/z 计算值：428.199，实测值：429.207 (M+1)+。
1088			ESI-MS m/z 计算值：438.176，实测值：439.184 (M+1)+。

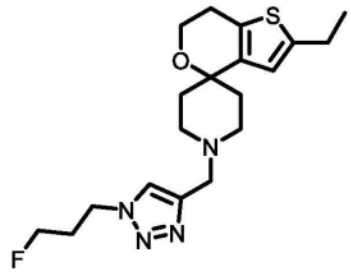
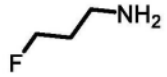
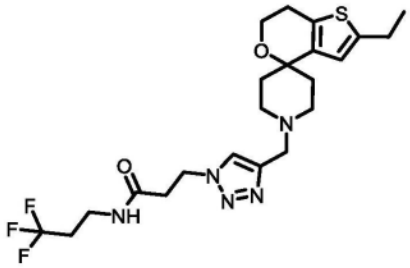
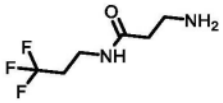
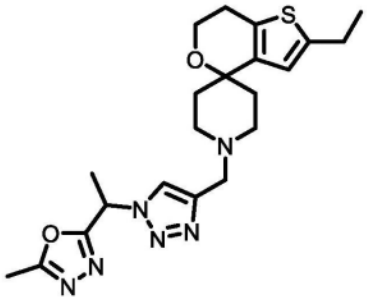
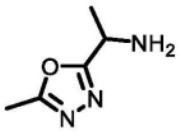
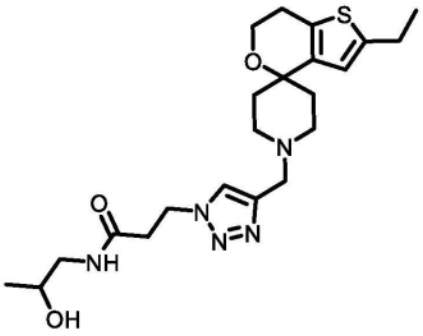
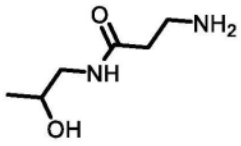
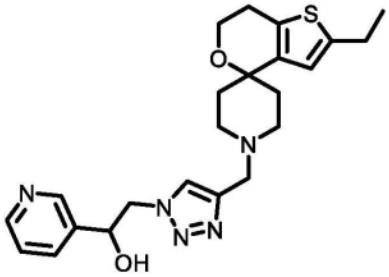
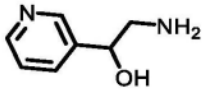
[2575]

化合物	产物	胺	LCMS m/z[M+H]+。
1089			ESI-MS m/z 计算值：438.176，实测值：439.183 (M+1)+。
1090			ESI-MS m/z 计算值：464.192，实测值：465.199 (M+1)+。
1091			ESI-MS m/z 计算值：494.202，实测值：495.21 (M+1)+。
1092			ESI-MS m/z 计算值：433.215，实测值：434.222 (M+1)+。
1093			ESI-MS m/z 计算值：444.177，实测值：445.184 (M+1)+。

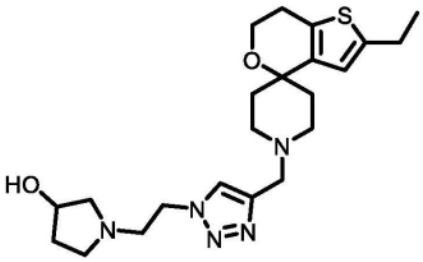
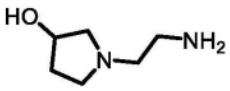
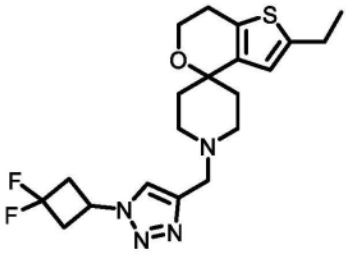
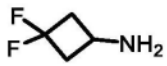
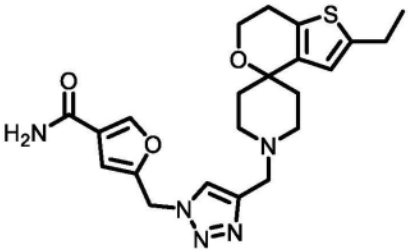
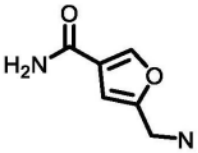
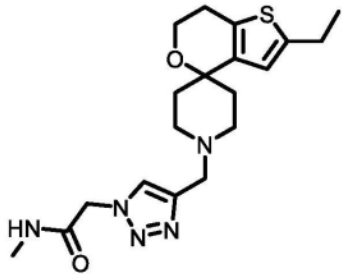
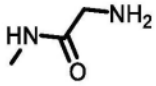
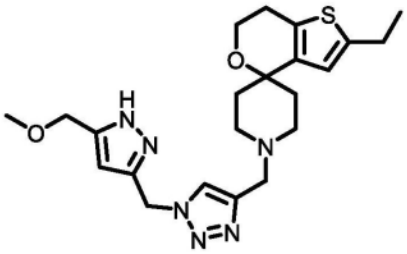
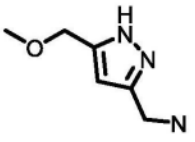
[2576]

化合物	产物	胺	LCMS m/z[M+H]+。
1094			ESI-MS m/z 计算值：416.225，实测值：417.232 (M+1)+。
1095			ESI-MS m/z 计算值：419.199，实测值：420.206 (M+1)+。
1096			ESI-MS m/z 计算值：471.192，实测值：472.199 (M+1)+。
1097			ESI-MS m/z 计算值：442.215，实测值：443.223 (M+1)+。
1098			ESI-MS m/z 计算值：388.193，实测值：389.2 (M+1)+。

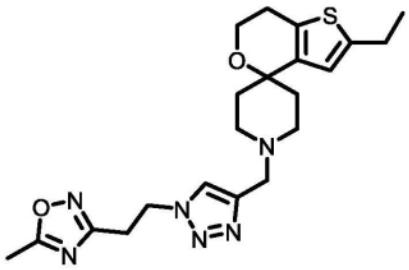
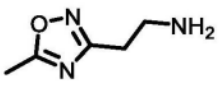
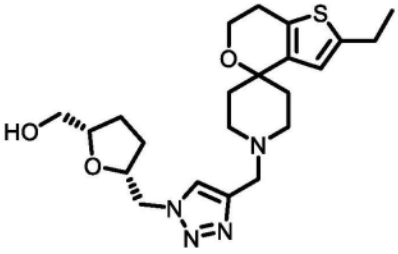
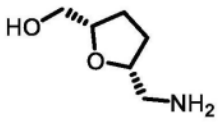
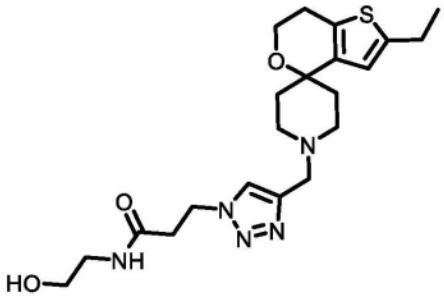
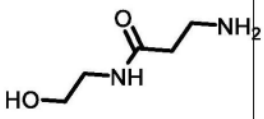
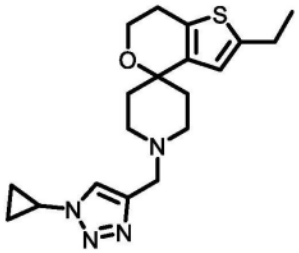
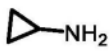
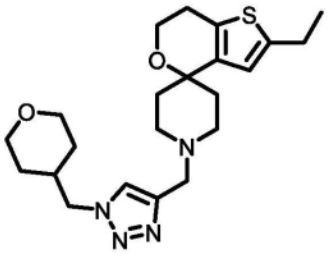
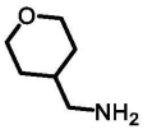
[2577]

化合物	产物	胺	LCMS m/z[M+H]+。
1099			ESI-MS m/z 计算值：378.189，实测值：379.196 (M+1)+。
1100			ESI-MS m/z 计算值：485.207，实测值：486.214 (M+1)+。
1101			ESI-MS m/z 计算值：428.199，实测值：429.207 (M+1)+。
1102			ESI-MS m/z 计算值：447.23，实测值：448.238 (M+1)+。
1103			ESI-MS m/z 计算值：439.204，实测值：440.212 (M+1)+。

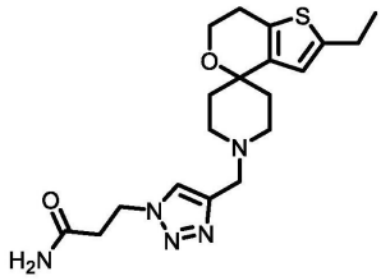
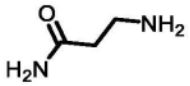
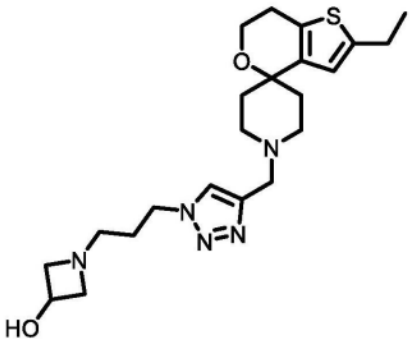
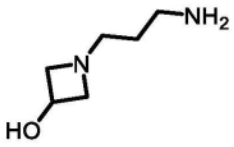
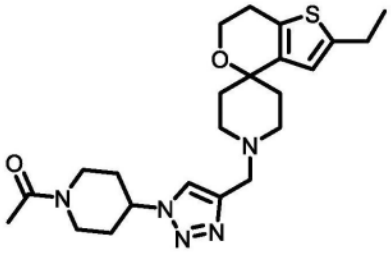
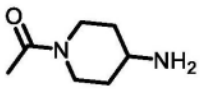
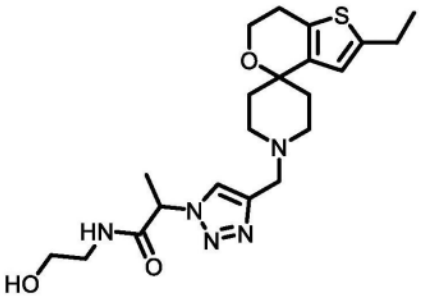
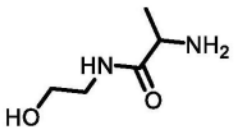
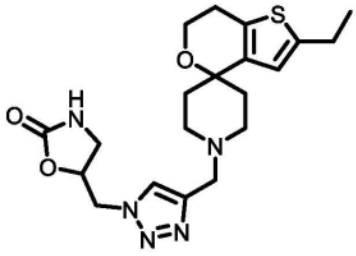
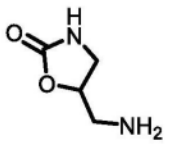
[2578]

化合物	产物	胺	LCMS m/z[M+H]+。
1104			ESI-MS m/z 计算值：431.235，实测值：432.243 (M+1)+。
1105			ESI-MS m/z 计算值：408.18，实测值：409.187 (M+1)+。
1106			ESI-MS m/z 计算值：441.183，实测值：442.191 (M+1)+。
1107			ESI-MS m/z 计算值：389.189，实测值：390.196 (M+1)+。
1108			ESI-MS m/z 计算值：442.215，实测值：443.223 (M+1)+。

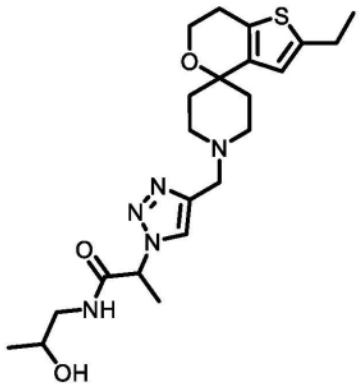
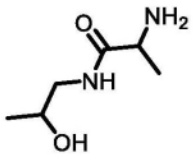
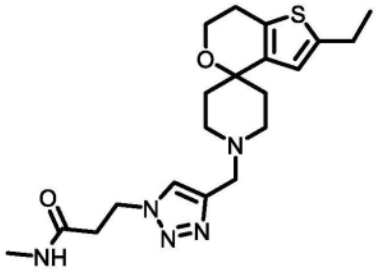
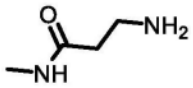
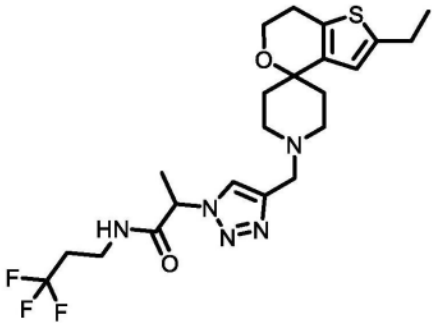
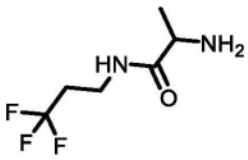
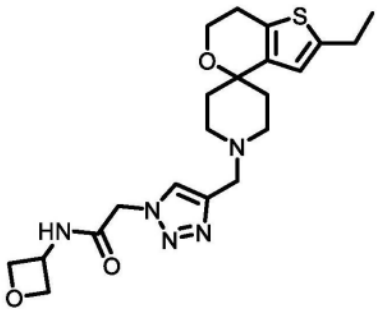
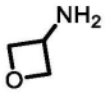
[2579]

化合物	产物	胺	LCMS m/z[M+H]+。
1109			ESI-MS m/z 计算值：428.199，实测值：429.207 (M+1)+。
1110			ESI-MS m/z 计算值：432.22，实测值：433.227 (M+1)+。
1111			ESI-MS m/z 计算值：433.215，实测值：434.222 (M+1)+。
1112			ESI-MS m/z 计算值：358.183，实测值：359.19 (M+1)+。
1113			ESI-MS m/z 计算值：416.225，实测值：417.232 (M+1)+。

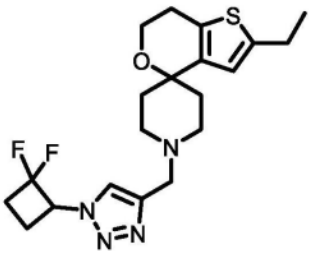
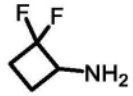
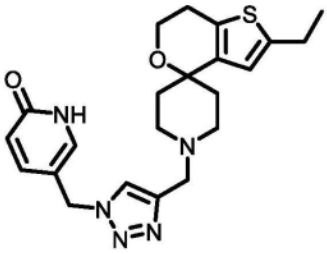
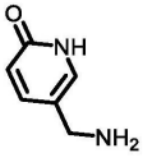
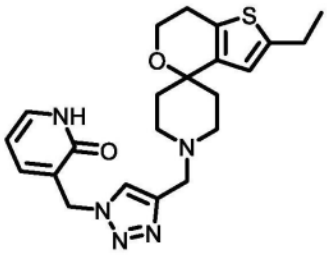
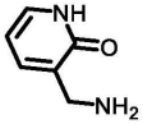
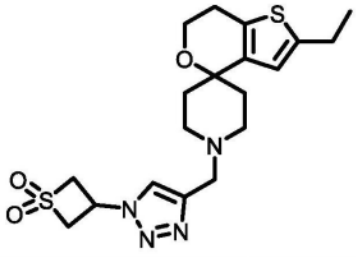
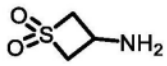
[2580]

化合物	产物	胺	LCMS m/z[M+H]+。
1114			ESI-MS m/z 计算值：389.189，实测值：390.196 (M+1)+。
1115			ESI-MS m/z 计算值：431.235，实测值：432.243 (M+1)+。
1116			ESI-MS m/z 计算值：443.235，实测值：444.243 (M+1)+。
1117			ESI-MS m/z 计算值：433.215，实测值：434.222 (M+1)+。
1118			ESI-MS m/z 计算值：417.183，实测值：418.191 (M+1)+。

[2581]

化合物	产物	胺	LCMS m/z[M+H]+。
1119			ESI-MS m/z 计算值：447.23，实测值：448.238 (M+1)+。
1120			ESI-MS m/z 计算值：403.204，实测值：404.211 (M+1)+。
1121			ESI-MS m/z 计算值：485.207，实测值：486.215 (M+1)+。
1122			ESI-MS m/z 计算值：431.199，实测值：432.207 (M+1)+。

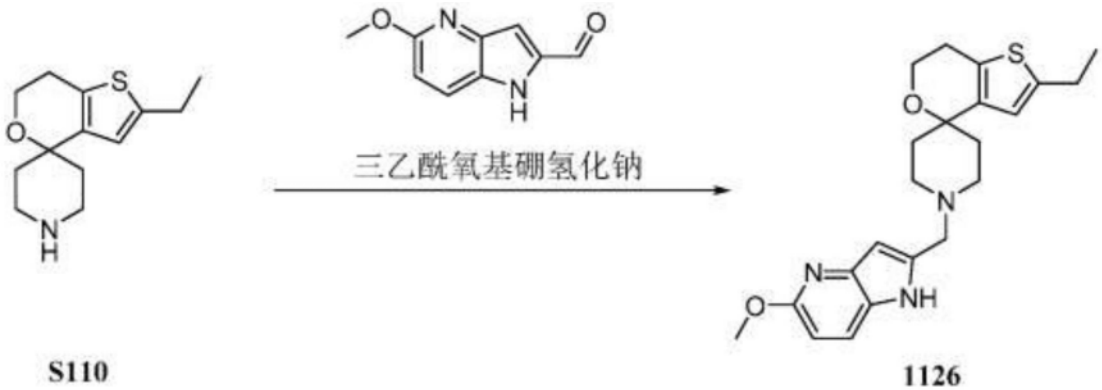
[2582]

化合物	产物	胺	LCMS m/z[M+H]+。
1123			ESI-MS m/z 计算值：408.18，实测值：409.187 (M+1)+。
1124			ESI-MS m/z 计算值：425.189，实测值：426.196 (M+1)+。
1125			ESI-MS m/z 计算值：425.189，实测值：426.196 (M+1)+。
1183			ESI-MS m/z 计算值：422.145，实测值：423.152 (M+1)+。

[2583] 化合物1126

[2584] 2′-乙基-1-((5-甲氧基-1H-吡咯并[3,2-b]哌啶-2-基)甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃](1126)的合成

[2585]



S110 1126

[2586] 将2-乙基螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸盐)(15mg,0.06mmol)和5-甲氧基-1H-吡咯并[3,2-b]哌啶-2-甲醛(16mg,0.09mmol)于二氯甲烷(1mL)

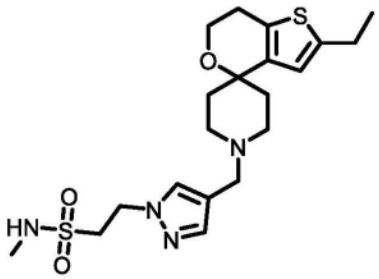
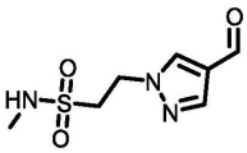
中的溶液在室温下搅拌15分钟,随后添加三乙酰氧基硼氢化钠(13mg,0.06mmol)。将所得溶液在室温下搅拌过夜,然后浓缩,并通过反相HPLC用含10-90% ACN的水(TFA改性剂)以得到2′-乙基-1-((5-甲氧基-1H-吡咯并[3,2-b]哌啶-2-基)甲基)-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃](15.2mg,62%)。^{1}H NMR(400MHz,DMSO-d6)δ7.80(d,J=8.8Hz,1H),6.70-6.60(m,2H),6.44(s,1H),4.53(s,2H),3.86(s,3H),3.34(d,J=12.1Hz,2H),3.18(d,J=12.4Hz,2H),2.77-2.66(m,4H),2.11(t,J=13.1Hz,2H),1.99(d,J=14.4Hz,2H),1.19(t,J=7.5Hz,3H)。ESI-MS m/z计算值:397.18,实测值:398.32(M+1)$^{+}$。

[2587] 化合物1127-1157,S116

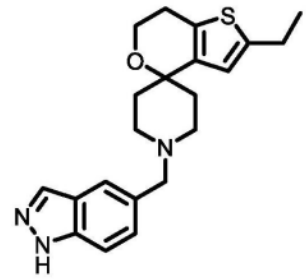
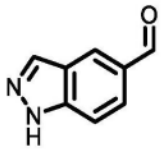
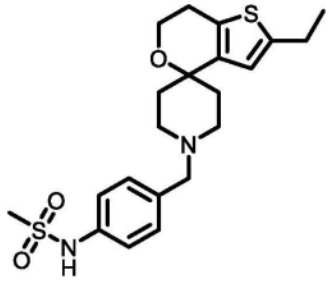
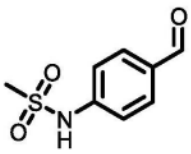
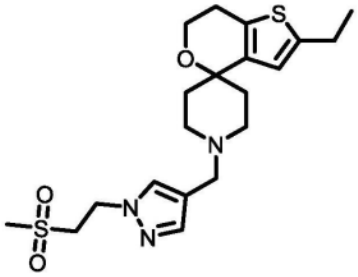
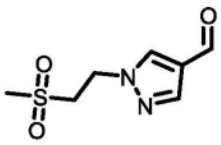
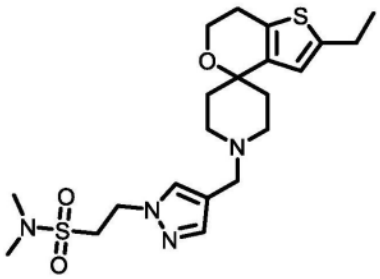
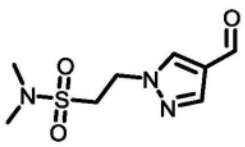
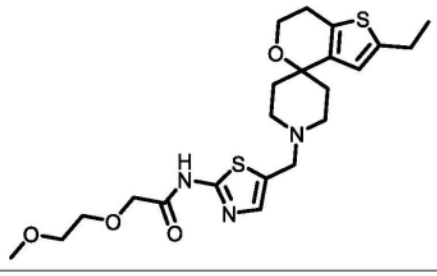
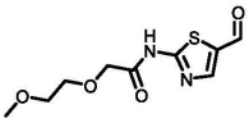
[2588] 采用与化合物1126所述相同的方法,使用适当的醛由S110制备化合物1127-1157和化合物S116(参见表53)。

[2589] 表53:化合物1127-1157,S116的结构和物理化学数据

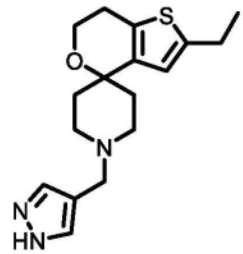
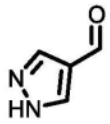
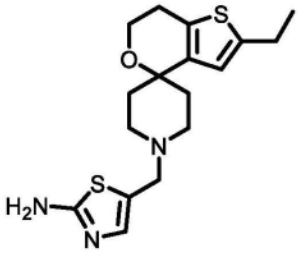
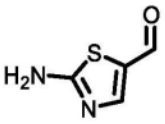
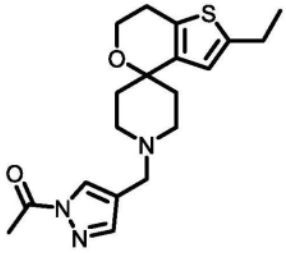
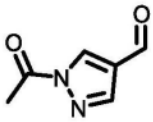
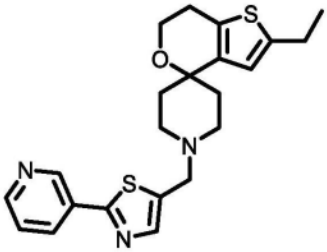
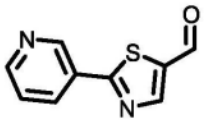
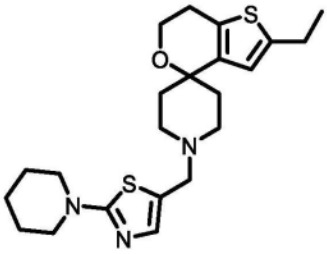
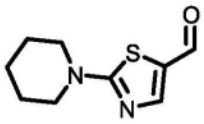
[2590]

化合物	产物	醛	LCMS m/z[M+H]+。
1127			ESI-MS m/z 计算值：438.176，实测值：439.183 (M+1)+。

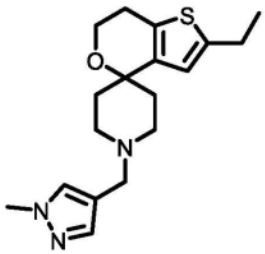
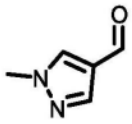
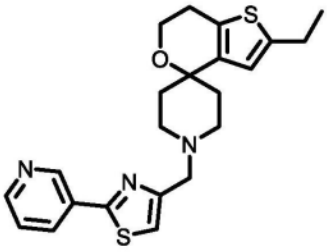
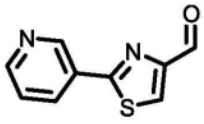
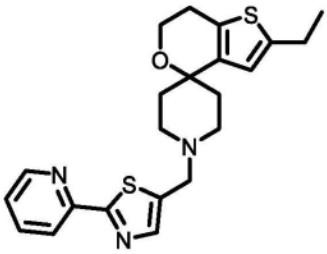
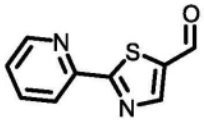
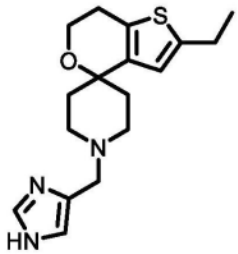
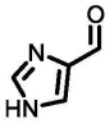
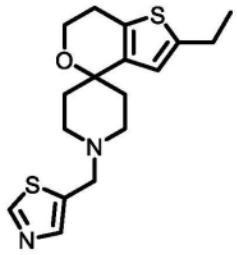
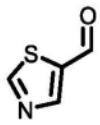
[2591]

化合物	产物	醛	LCMS m/z[M+H]+。
1128			ESI-MS m/z 计算值：367.172，实测值：368.179 (M+1)+。
1129			ESI-MS m/z 计算值：420.154，实测值：421.161 (M+1)+。
1130			ESI-MS m/z 计算值：423.165，实测值：424.172 (M+1)+。
1131			ESI-MS m/z 计算值：452.192，实测值：453.199 (M+1)+。
1132			ESI-MS m/z 计算值：465.176，实测值：466.184 (M+1)+。

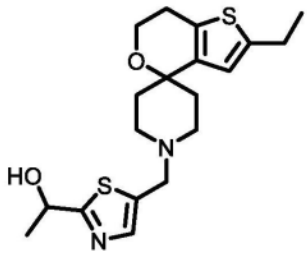
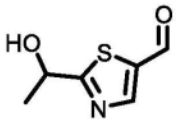
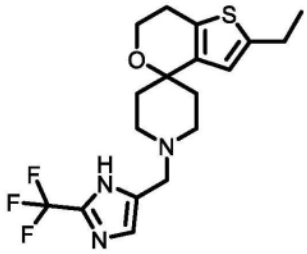
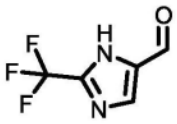
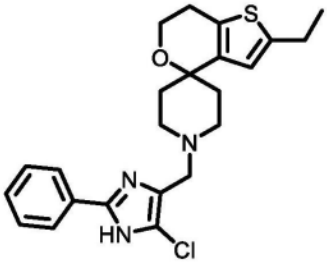
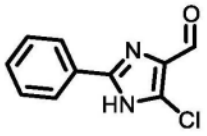
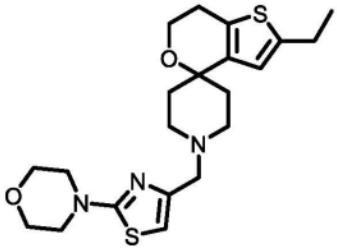
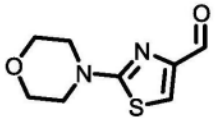
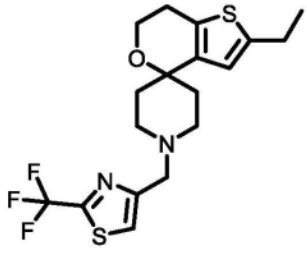
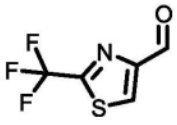
[2592]

化合物	产物	醛	LCMS m/z[M+H]+。
1133			ESI-MS m/z 计算值：317.156，实测值：318.164 (M+1)+。
1134			ESI-MS m/z 计算值：349.128，实测值：350.136 (M+1)+。
1135			ESI-MS m/z 计算值：359.167，实测值：360.174 (M+1)+。
1136			ESI-MS m/z 计算值：411.144，实测值：412.151 (M+1)+。
1137			ESI-MS m/z 计算值：417.191，实测值：418.198 (M+1)+。

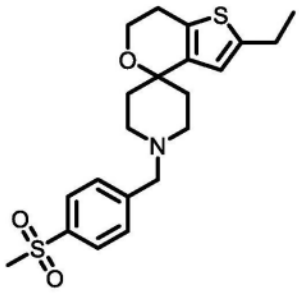
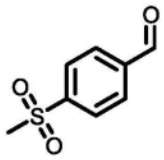
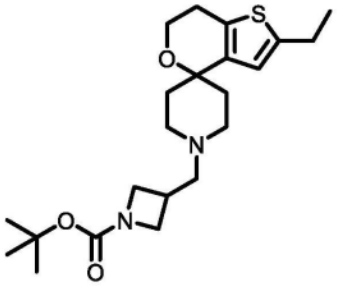
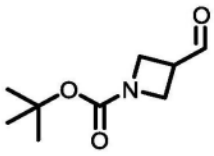
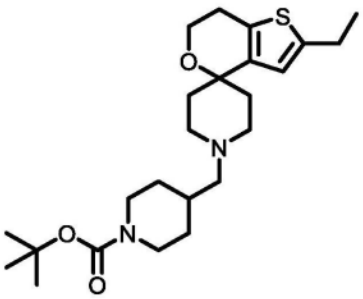
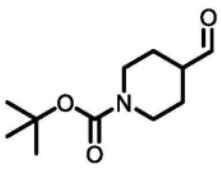
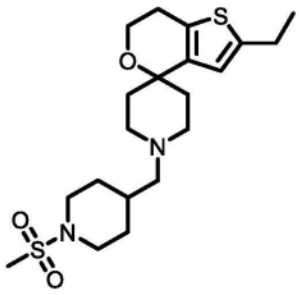
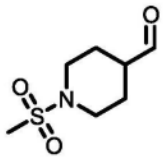
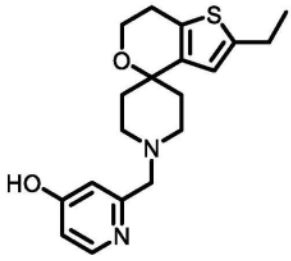
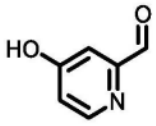
[2593]

化合物	产物	醛	LCMS m/z[M+H]+。
1138			ESI-MS m/z 计算值：331.172，实测值：332.18 (M+1)+。
1139			ESI-MS m/z 计算值：411.144，实测值：412.151 (M+1)+。
1140			ESI-MS m/z 计算值：411.144，实测值：412.151 (M+1)+。
1141			ESI-MS m/z 计算值：317.156，实测值：318.163 (M+1)+。
1142			ESI-MS m/z 计算值：334.117，实测值：335.125 (M+1)+。

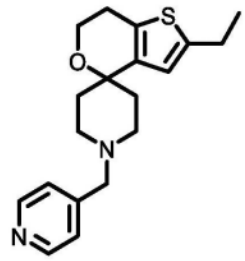
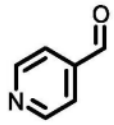
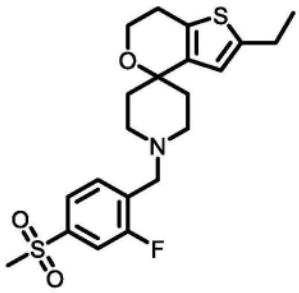
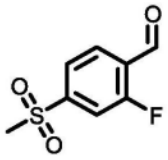
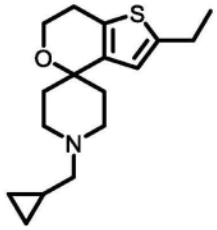
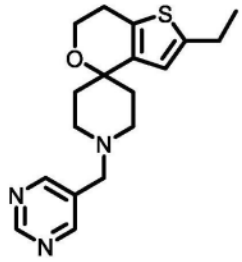
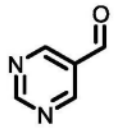
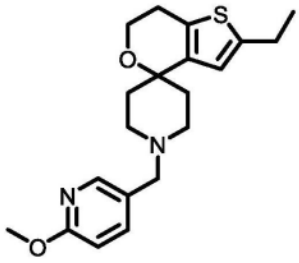
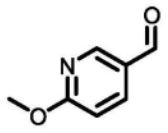
[2594]

化合物	产物	醛	LCMS m/z[M+H]+。
1143			ESI-MS m/z 计算值：378.144，实测值：379.151 (M+1)+。
1144			ESI-MS m/z 计算值：385.144，实测值：386.151 (M+1)+。
1145			ESI-MS m/z 计算值：427.149，实测值：428.156 (M+1)+。
1146			ESI-MS m/z 计算值：419.17，实测值：420.177 (M+1)+。
1147			ESI-MS m/z 计算值：402.105，实测值：403.112 (M+1)+。

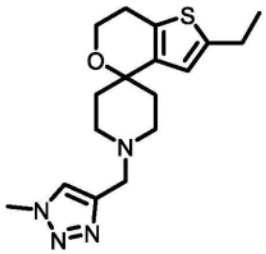
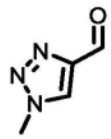
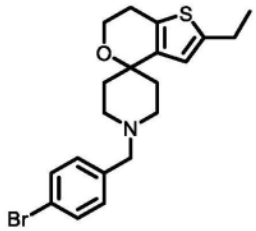
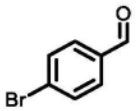
[2595]

化合物	产物	醛	LCMS m/z[M+H]+。
1148			ESI-MS m/z 计算值：405.143，实测值：406.151 (M+1)+。
1149			ESI-MS m/z 计算值：406.229，实测值：407.236 (M+1)+。
1150			ESI-MS m/z 计算值：434.26，实测值：435.268 (M+1)+。
1151			ESI-MS m/z 计算值：412.185，实测值：413.193 (M+1)+。
1152			ESI-MS m/z 计算值：344.156，实测值：345.163 (M+1)+。

[2596]

化合物	产物	醛	LCMS m/z[M+H]+。
1153			ESI-MS m/z 计算值：328.161，实测值：329.168 (M+1)+。
1154			ESI-MS m/z 计算值：423.134，实测值：424.141 (M+1)+。
1155			ESI-MS m/z 计算值：291.166，实测值：292.173 (M+1)+。
1156			ESI-MS m/z 计算值：329.156，实测值：330.164 (M+1)+。
1157			ESI-MS m/z 计算值：358.171，实测值：359.179 (M+1)+。

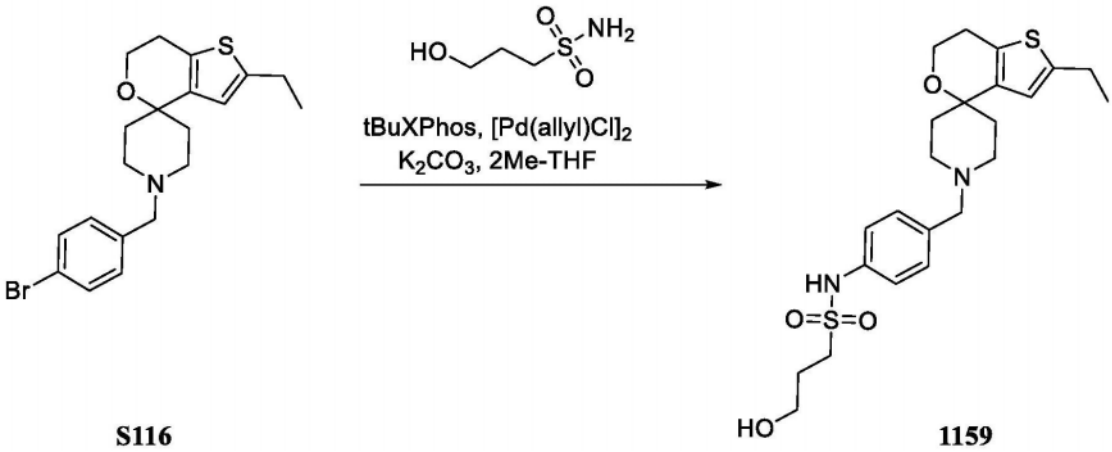
[2597]

化合物	产物	醛	LCMS m/z[M+H]+。
1158			ESI-MS m/z 计算值：332.167，实测值：333.174 (M+1)+。
S116			ESI-MS m/z 计算值：406.38，实测值：406.26 (M+1)+。

[2598] 化合物1159

[2599] N-(4-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)苯基)-3-羟基丙烷-1-磺酰胺(1159)

[2600]



S116 1159

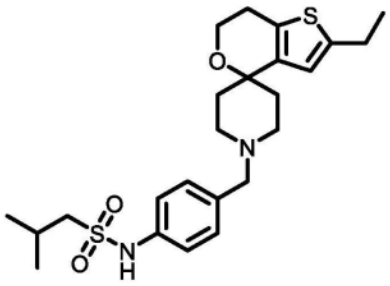
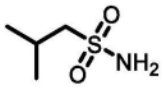
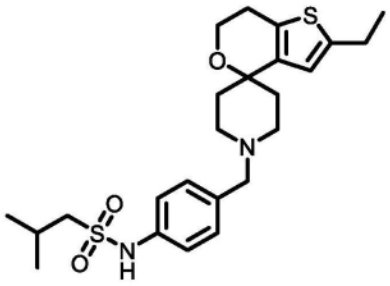
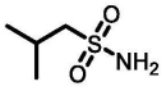
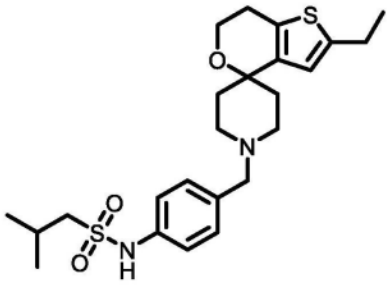
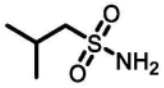
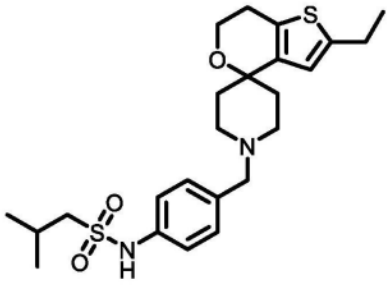
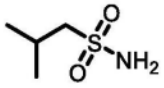
[2601] 将1′-[(4-溴苯基)甲基]-2-乙基-螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]S115(20mg,0.05mmol)、3-羟基丙烷-1-磺酰胺(7.7mg,0.05mmol)、K_2CO_3(14mg,0.1mmol)、二叔丁基-[2-(2,4,6-三异丙基苯基)苯基]膦(2mg,0.005mmol)和烯丙基(氯)钯(0.45mmol)于2-MeTHF(1mL)中的混合物加热至80℃。将反应物冷却至室温并且然后用EtOAc和1N HCl稀释。将有机层分离并浓缩,并且然后在DMSO中重新稀释并通过反相色谱法纯化(TFA改性剂)。将含产物级分浓缩以产生N-(4-((2′-乙基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-基)甲基)苯基)-3-羟基丙烷-1-磺酰胺(7.8mg,34%)。

[2602] 化合物1160-1164

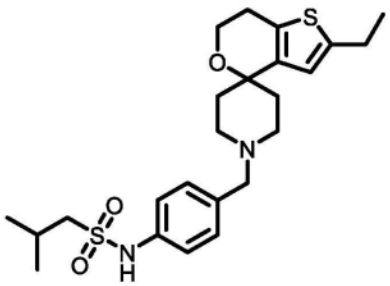
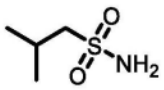
[2603] 采用与化合物1159所述相同的方法,使用适当的醛由S116制备化合物1160-1164(参见表54)。

[2604] 表54:化合物1160-1164的结构和物理化学数据

[2605]

化合物	产物	胺	LCMS m/z[M+H]+。
1161			ESI-MS m/z 计算值：478.196，实测值：479.204 (M+1)+。
1161			ESI-MS m/z 计算值：478.196，实测值：479.204 (M+1)+。
1161			ESI-MS m/z 计算值：478.196，实测值：479.204 (M+1)+。
1161			ESI-MS m/z 计算值：478.196，实测值：479.204 (M+1)+。

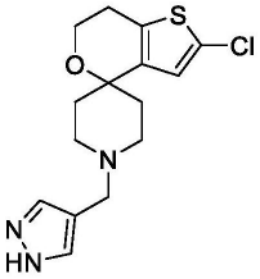
[2606]

化合物	产物	胺	LCMS m/z[M+H]+。
1161			ESI-MS m/z 计算值：478.196，实测值：479.204 (M+1)+。

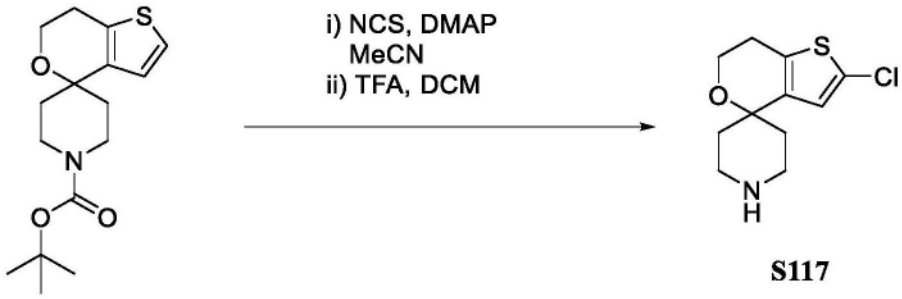
[2607] 化合物1165

[2608] 2-氯-1′-(1H-吡唑-4-基甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]

(1165)

[2609] 

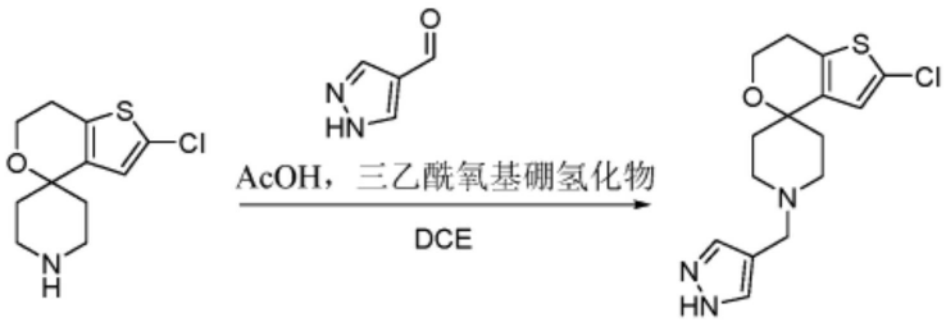
[2610] 步骤1:2-氯螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](S117)的合成

[2611] 

S117

[2612] 将螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(5300mg,17.13mmol)溶解在CH_3CN(100mL)中,并添加DMAP(180mg,1.473mmol)和N-氯代琥珀酰亚胺(2.6g,19.47mmol)。将反应混合物加热至65℃,持续5小时,浓缩,在DCM(10mL)中摄取,过滤并通过快速柱色谱法纯化(0-50% EtOAc/庚烷)以提供成白色固体的产物。将所得2-氯螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯溶解在DCM(100mL)中,随后在氮气下添加TFA(20mL,259.6mmol)并搅拌过夜。将反应混合物干燥成粗残余物,溶解在DCM中,并用饱和碳酸氢盐溶液中和直至气体逸出停止。将有机层浓缩以产生2-氯螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](2.84g,42%)。^1H NMR(300MHz,氯仿-d)δ6.69(s,1H),3.96(m,2H),3.44-3.20(m,4H),2.77(t,J=5.3Hz,2H),2.28-1.92(m,4H)。

[2613] 步骤2:2-氯-1′-(1H-吡唑-4-基甲基)螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](1165)的合成

[2614] 

S117 1165

[2615] 向烧瓶中添加2-氯螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸盐)(400mg,1.1mmol)、1H-吡唑-4-甲醛(105mg,1.1mmol)、乙酸(70μL,1.231mmol)和1,2-二氯乙烷(10mL)。将混合物在室温下搅拌,此时添加三乙酰乙基硼氢化物(钠盐)(680mg,3.208mmol),并搅拌过夜。将混合物用饱和碳酸氢钠(25mL)淬灭,并将各层分离,并将水层用DCM(50mL)洗涤。将有机层合并并浓缩以提供2-氯-1′-(1H-吡唑-4-基甲基)螺[6,7-二氢

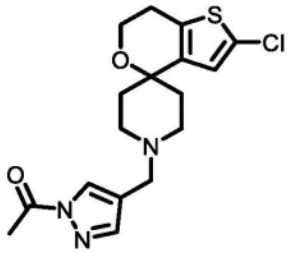
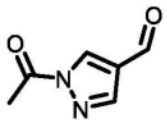
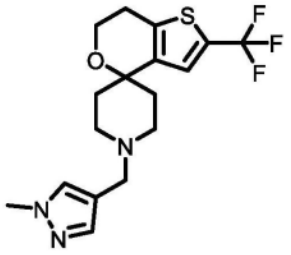
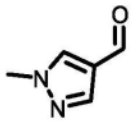
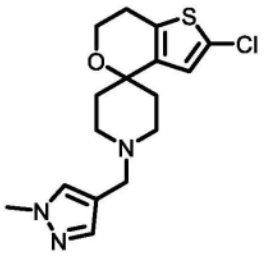
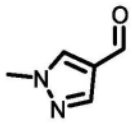
噻吩并[3,2-c]吡喃-4,4′-哌啶](360mg,94%)。^{1}H NMR(400MHz,氯仿-d)δ7.57(s,2H),6.62(s,1H),3.93(t,J=5.4Hz,2H),3.54(s,2H),2.81-2.75(m,2H),2.72(t,J=5.4Hz,2H),2.37(td,J=11.4,4.0Hz,2H),1.96-1.85(m,4H)。ESI-MS m/z calc。323.0859,found 324.26(M+1)$^{+}$。

[2616] 化合物1166-1168

[2617] 采用与化合物1165所述相同的方法,使用适当的醛由S117制备化合物1166-1168(参见表55)。

[2618] 表55:化合物1166-1168的结构和物理化学数据

[2619]

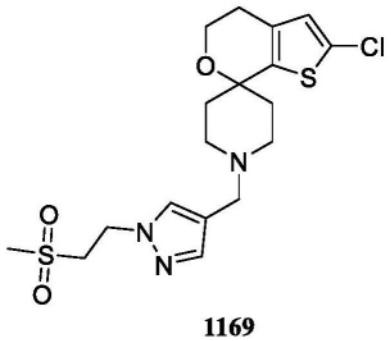
化合物	产物	醛	LCMS m/z[M+H]+。
1166			ESI-MS m/z 计算值：365.096，实测值：366.104 (M+1)+。
1167			ESI-MS m/z 计算值：371.128，实测值：372.135 (M+1)+。
1168			ESI-MS m/z 计算值：337.102，实测值：338.109 (M+1)+。

[2620] 化合物1169

[2621] 2′-氯-1-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-

[2622] 噻吩并[2,3-c]吡喃](1169)

[2623]



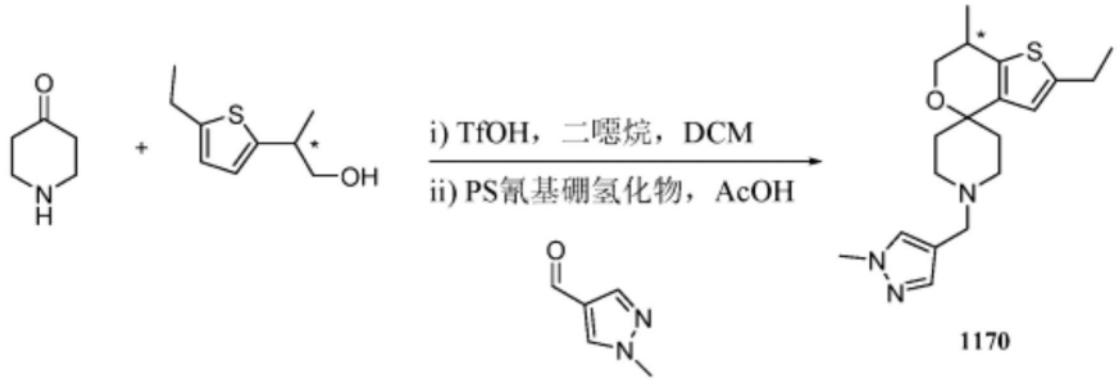
1169

[2624] 2′-氯-1-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](1169)是如化合物697的合成所述制备的,其中4-氧代哌啶-1-甲酸叔丁酯用于代替(S)-2-甲基-4-氧代哌啶-1-甲酸叔丁酯。将产物分离为2′-氯-1-((1-(2-(甲基磺酰基)乙基)-1H-吡唑-4-基)甲基)-4′,5′-二氢螺[哌啶-4,7′-噻吩并[2,3-c]吡喃](20.6mg,17%)。^{1}H NMR(400MHz,氯仿-d)δ7.50(d,J=0.7Hz,1H),7.45(s,1H),6.58(s,1H),4.65-4.50(m,2H),3.88(t,J=5.4Hz,2H),3.69-3.59(m,2H),3.46(s,2H),2.74-2.62(m,4H),2.46(d,J=0.8Hz,3H),2.32(td,J=10.9,4.6Hz,2H),1.84(dd,J=11.0,3.9Hz,4H)。ESI-MS m/z计算值:429.98,实测值:430.13(M+1)$^+$。

[2625] 化合物1170

[2626] 2-乙基-7-甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-

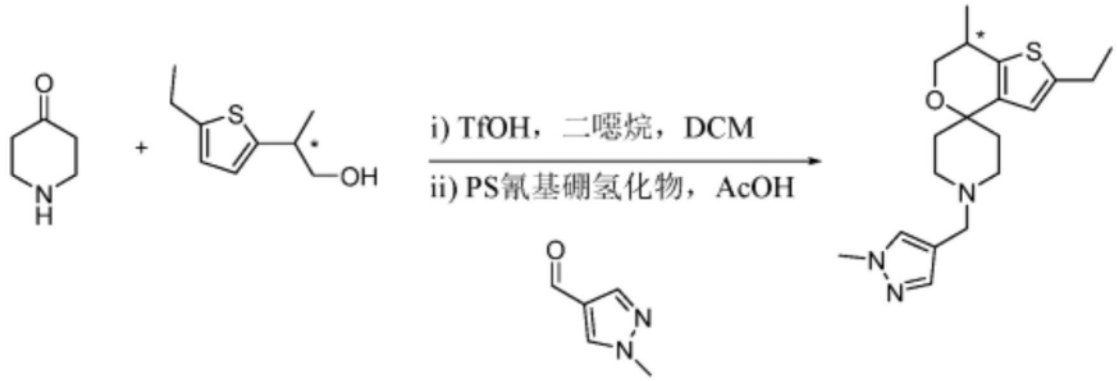
[2627] 哌啶](1170)

[2628] 

[2629] 将S105 2-(5-乙基-2-噻吩基)丙-1-醇和哌啶-4-酮(51mg,0.30mmol)和4-氧代哌啶-1-甲酸叔丁酯(50mg,0.25mmol)于二噁烷(1.2mL)中的溶液在冰浴中冷却至略高于冰点。向溶液中添加三氟甲磺酸(67uL,0.75mmol)并将所得溶液在室温下搅拌1.5小时。将反应物用水淬灭,并用2N Na_2CO_3调节至pH 8。将溶液用乙酸乙酯萃取,并将合并的有机物经无水硫酸钠干燥,过滤并在真空中浓缩。

[2630] 向粗反应混合物中添加1-甲基吡唑-4-甲醛(55mg,0.5mmol)、聚合物负载的(三甲基铵基)甲基(氰基硼氢化物)(376mg,0.75mmol,2mmol/g负载)和含AcOH(71uL,1.25mmol)的CH_2Cl_2(2mL)。将反应物在微波反应器中在95C下辐照1小时。将反应物过滤,用MeOH洗涤并在真空中浓缩。将粗残余物通过反相HPLC纯化(HCl改性剂)以提供期望产物。2-乙基-7-甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](40mg,41%)。ESI-MS m/z计算值:345.187,实测值:346.195(M+1)$^+$。

[2631] 2-乙基-7-甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](1171)的合成

[2632] 

[2633] 将S106 2-(5-乙基-2-噻吩基)丙-1-醇和哌啶-4-酮(51mg,0.30mmol)和4-氧代哌啶-1-甲酸叔丁酯(50mg,0.25mmol)于二噁烷(1.2mL)中的溶液在冰浴中冷却至略高于冰点。向溶液中添加三氟甲磺酸(67uL,0.75mmol)并将所得溶液在室温下搅拌1.5小时。将反应物用水淬灭,并用2N Na_2CO_3调节至pH 8。将溶液用乙酸乙酯萃取,并将合并的有机物经无水硫酸钠干燥,过滤并在真空中浓缩。

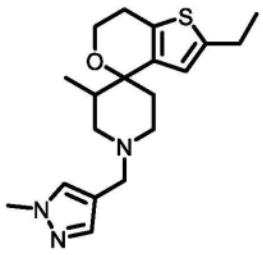
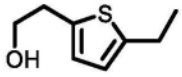
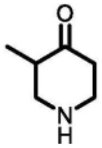
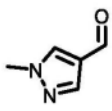
[2634] 向粗反应混合物中添加1-甲基吡唑-4-甲醛(55mg,0.5mmol)、聚合物负载的(三甲基铵基)甲基(氰基硼氢化物)(376mg,0.75mmol,2mmol/g负载)和含AcOH(71uL,1.25mmol)的CH_2Cl_2(2mL)。将反应物在微波反应器中在95C下辐照1小时。将反应物过滤,用MeOH洗涤并在真空中浓缩。将粗残余物通过反相HPLC纯化(HCl改性剂)以提供期望产物。2-乙基-7-甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](50mg,51%)。ESI-MS m/z计算值:345.187,实测值:346.195$(M+1)^+$。

[2635] 化合物1172-1176

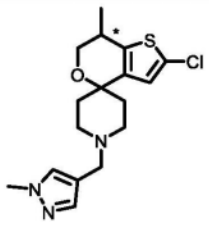
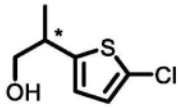
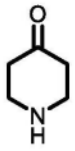
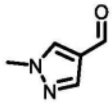
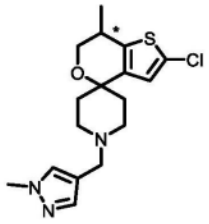
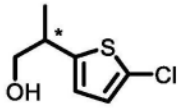
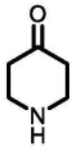
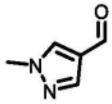
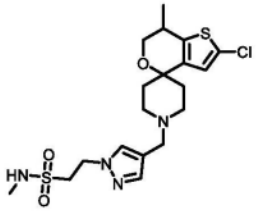
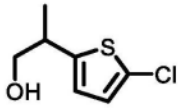
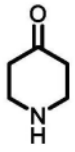
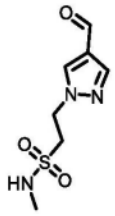
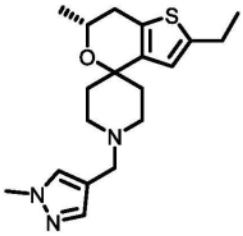
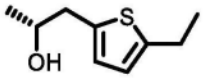
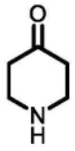
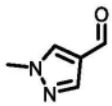
[2636] 化合物1172-1176(参见56)使用适当的噻吩乙醇、哌啶酮和醛采用化合物1171所述的方法制备。

[2637] 表56:化合物1172-1176的结构和物理化学数据

[2638]

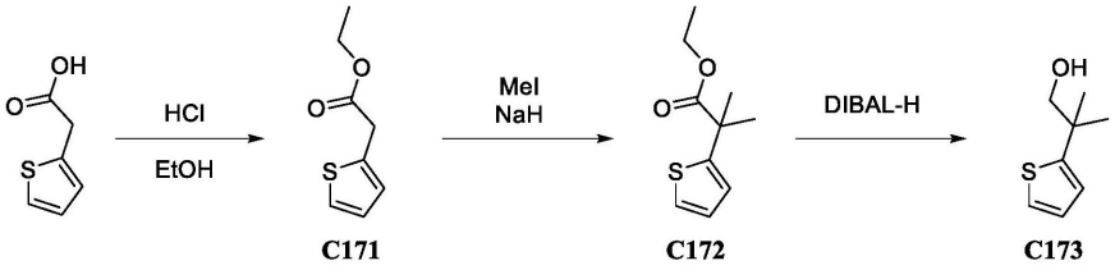
化合物	产物	噻吩乙醇	哌啶酮	醛	LCMS m/z[M+H]+。
1170					ESI-MS m/z 计算值：345.187，实测值：346.195 (M+1)+。

[2639]

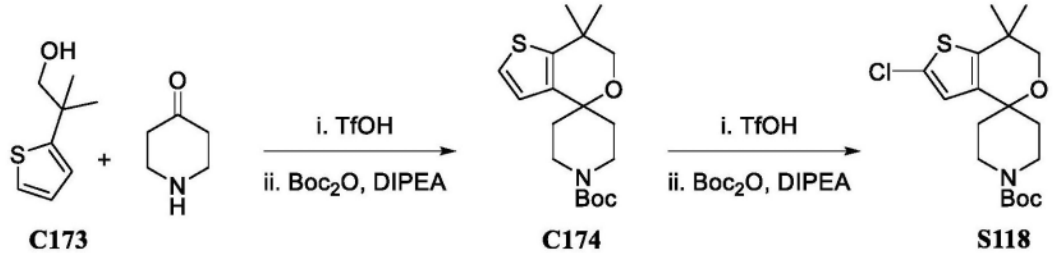
化合物	产物	噻吩乙醇	哌啶酮	醛	LCMS m/z[M+H]+。
1171					ESI-MS m/z 计算值：351.117，实测值：352.124 (M+1)+。
1172					ESI-MS m/z 计算值：351.117，实测值：352.124 (M+1)+。
1173					ESI-MS m/z 计算值：458.121，实测值：459.129 (M+1)+。
1174					ESI-MS m/z 计算值：345.187，实测值：346.195 (M+1)+。

[2640] 化合物S118

[2641] 2′-氯-7′,7′-二甲基-6′,7′-二氢螺[哌啶-4,4′-噻吩并[3,2-c]吡喃]-1-甲酸叔丁酯(S118)



[2642]



[2643] 步骤1:2-(2-噻吩基)乙酸乙酯(C171)的合成

[2644] 在rt下向2-(2-噻吩基)乙酸(100g,703.35mmol)于EtOH(2000mL)中的经搅拌的溶液中添加HCl(水性)(50mL的36%w/v,493.68mmol)。将反应混合物在70℃下搅拌12小时。反应完成后,将混合物浓缩并将所得粗产物用EtOAc(1000ml)稀释,用5% Na_2CO_3水溶液(3×200ml)、盐水(200ml)洗,将有机层干燥并浓缩以得到呈黄色油的2-(2-噻吩基)乙酸乙酯(C171)(100g,82%)。^{1}H NMR(氯仿-d,400MHz):δ=7.222-7.206(dd,J=1.2Hz,J=3.6Hz,1H),6.969-6.948(m,2H),4.213-4.160(q,J=7.2Hz,2H),3.828(s,2H),1.295-1.259(t,J=7.2Hz,3H)。LCMS m/z 171.26$[M+H]^+$。

[2645] 步骤2:2-甲基-2-(2-噻吩基)丙酸乙酯(C172)的合成

[2646] 在0℃下向2-(2-噻吩基)乙酸乙酯(C171)(100mg,531.87μmol)于THF(15mL)中的经搅拌的溶液中添加NaH(108mg,60%w/w,0.0027mol),搅拌30分钟。然后在0℃下向反应混合物中添加MeI(440.00mg,0.2mL,0.0031mol)并是反应物温热至rt,并且然后将反应物搅拌6小时。此时,将反应混合物用冷水(50ml)淬灭,萃取到EtOAC(2×100ml)中。将合并的有机层经Na_2SO_4干燥,在减压下浓缩以得到呈黄色液体的2-甲基-2-(2-噻吩基)丙酸乙酯(C172)(40mg,36%)。^{1}H NMR(400MHz,氯仿-d)δppm:7.20-7.18(m,1H),6.96-6.92(m,2H),4.16-4.10(m,2H),1.69-1.53(m,6H),1.26-1.08(m,3H)。

[2647] 步骤3:2-甲基-2-(2-噻吩基)丙-1-醇(C173)的合成

[2648] 在rt下向2-甲基-2-(2-噻吩基)丙酸乙酯(C172)(500mg,0.0017mol)于THF(10mL)中的经搅拌的溶液中。然后将反应混合物冷却至0℃,此时逐滴添加含DiBAL-H的己烷(5.10mL的1M,0.0051mol),持续10分钟。使反应混合物温热至rt并且然后搅拌3小时。然后将反应混合物冷却至0℃,用饱和NH_4Cl(100mL)缓慢淬灭,并且然后用EtOAc(300mL)萃取。将合并的有机层经Na_2SO_4干燥,在减压下浓缩以得到呈无色液体的粗产物2-甲基-2-(2-噻吩基)丙-1-醇(C173)(272mg,99%)。^{1}H NMR(DMSO-d_6):δ7.31-7.29(m,1H),6.94-6.87(m,2H),4.89-4.84(m,1H),3.39-3.36(m,2H),1.35(s,6H)。

[2649] 步骤4:7,7-二甲基螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C174)的合成

[2650] 将2-甲基-2-(2-噻吩基)丙-1-醇(C173)(250mg,1.600mmol)和哌啶-4-酮(盐酸盐)(217mg,1.600mmol)于二噁烷(6mL)中的溶液在冰浴中冷却并添加三氟甲磺酸(430μL,4.859mmol)。将反应混合物温热至rt,并搅拌2小时。此时没见过混合物用1N NaOH(80mL)和EtOAc(80mL)稀释,并将有机层干燥并浓缩成白色固体,将其重新悬浮在DCM(10mL)中,并添加DIEA(500μL,2.871mmol)和Boc_2O(400mg,1.833mmol),并在rt下搅拌2小时。将反应混合物浓缩成油,将其通过二氧化硅色谱法纯化(0至80% EtOAc/庚烷,24g二氧化硅)以产生呈白色固体的7,7-二甲基螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C174)(401mg,74%)。^{1}H NMR(300MHz,氯仿-d)δ7.11(d,J=5.2Hz,1H),6.69(d,J=5.2Hz,1H),4.11-3.82(m,2H),3.59(s,2H),3.27-3.04(m,2H),1.88-1.72(m,4H),1.51(s,9H),1.32(s,6H)。

[2651] 步骤5:2-氯-7,7-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S118)的合成

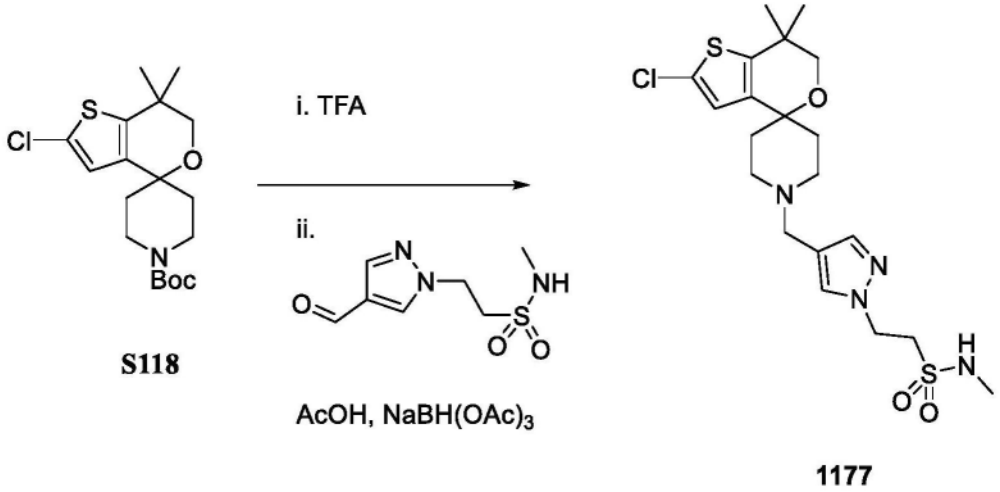
[2652] 向7,7-二甲基螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(C174)(196mg,0.5808mmol)于乙腈(5mL)中的溶液中添加N-氯代琥珀酰亚胺(85mg,0.6365mmol)

和DMAP(7mg,0.05730mmol)。将反应混合物在rt下搅拌2小时,并且然后将反应物加热至65℃并搅拌18小时。此时,将反应混合物浓缩成固体,将其用1N NaOH(20mL)和EtOAc(20mL)稀释。将有机层用1N硫代硫酸钠水溶液洗涤,并且然后用硫酸钠干燥并浓缩成固体,将其通过二氧化硅色谱法纯化(0至50% EtOAc/庚烷)以产生呈白色固体的2-氯-7,7-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S118)(165mg,76%)。^{1}H NMR(300MHz,氯仿-d)δ6.49(s,1H),4.08-3.84(m,2H),3.58(s,2H),3.23-2.98(m,2H),1.88-1.61(m,4H),1.50(s,9H),1.28(s,6H)。LCMS m/z 371.29$[M+H]^+$。

[2653] 化合物1177

[2654] 2-[4-[(2-氯-7,7′-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]吡唑-1-基]-N-甲基-乙磺酰胺(1177)

[2655]

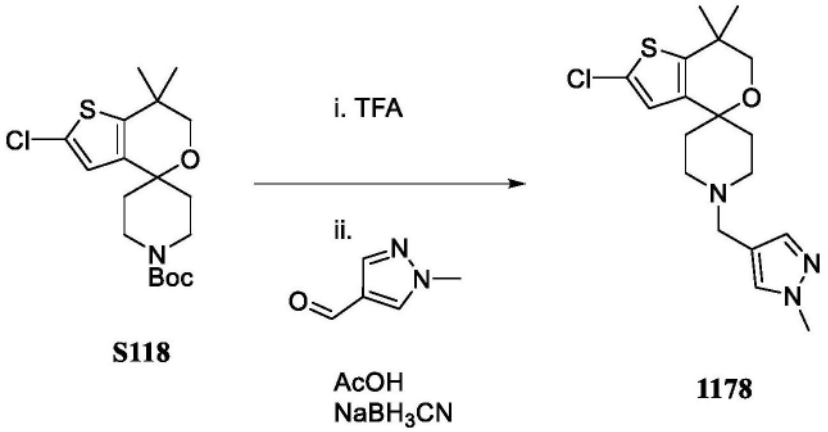


[2656] 将2-氯-7,7-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(25mg,0.0672mmol)(S118)和TFA(30μL,0.389mmol)于二氯甲烷(1mL)中的混合物在rt下搅拌过夜。此时,将混合物吹干,用DCM(5mL)稀释,并再次吹干。向混合物中添加2-(4-甲酰基吡唑-1-基)-N-甲基-乙磺酰胺(17mg,0.0783mmol)、乙酸(4μL,0.0703mmol)和三乙酰氧基硼氢化钠(40mg,0.189mmol)和1,2-二氯乙烷(1,500μL)并在rt下搅拌过夜。1小时后,将混合物加热至50℃,并搅拌18小时。此时,将混合物加热至65℃,并用另外的1,2-二氯乙烷(2mL)和另外的三乙酰氧基硼氢化钠(40mg,0.189mmol)稀释2小时。此时,将混合物浓缩并且然后在DMSO(1mL)中稀释。通过反相HPLC纯化。方法:Waters XSelect CSH C18 OBD制备型柱;30×150mm,5微米。梯度:含乙腈的水,具有0.1%三氟乙酸。将含产物的级分浓缩以产生呈澄清油的2-[4-[(2-氯-7,7-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-基)甲基]吡唑-1-基]-N-甲基-乙磺酰胺(三氟乙酸盐)(1177)(13.3mg,33%)。^{1}H NMR(400MHz,氯仿-d)δ11.54(s,1H),7.89(s,1H),7.58(s,1H),6.54(s,1H),5.32(s,1H),4.67-4.49(m,2H),4.11(d,J=4.3Hz,2H),3.60-3.52(m,4H),3.46(d,J=11.8Hz,2H),3.11(q,J=11.1Hz,2H),2.70(s,3H),2.28(td,J=14.2,4.2Hz,2H),2.06-1.98(m,2H),1.28(s,6H)。LCMS m/z 473.11$[M+H]^+$。

[2657] 化合物1178

[2658] 2-氯-7,7-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶](1178)

[2659]

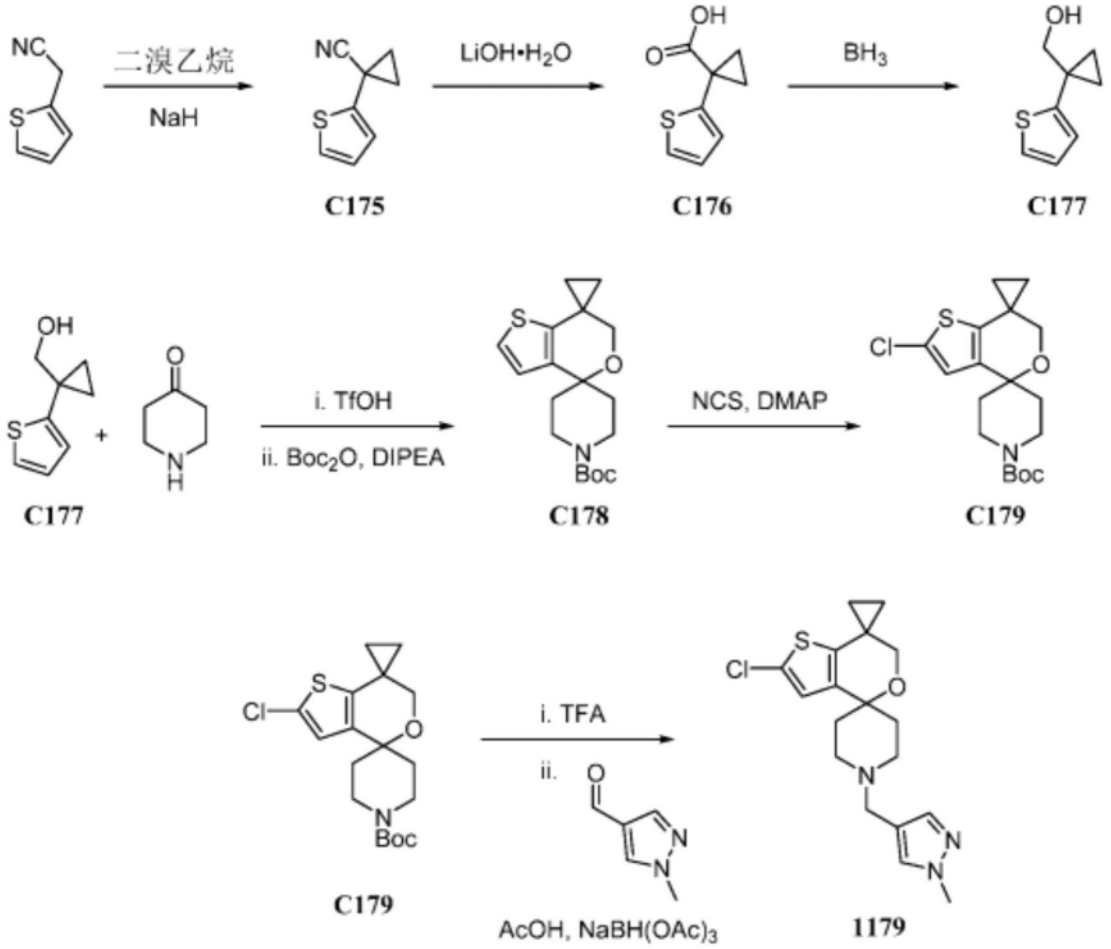


[2660] 向2-氯-7,7-二甲基-螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶]-1′-甲酸叔丁酯(S118)(60mg,0.1613mmol)于DCM(1mL)中的溶液中添加TFA(700μL,9.09mmol)。20分钟后,将反应混合物浓缩成油并重新溶解在DCM(2mL)中,并添加1-甲基吡唑-4-甲醛(35mg,0.318mmol),随后添加HOAc(50μL,0.8792mmol)和聚苯乙烯负载的氰基硼氢化物(200mg的2mmol/g,0.400mmol)。将反应混合物在微波中在110℃下加热60分钟,过滤掉树脂并将滤液浓缩。将获得的油通过反相色谱法纯化(C18,5-100% MeCN:H_2O,0.1wt%TFA改性剂)。将含产物级分浓缩并用EtOAc/1N NaOH稀释。将有机层分离,用硫酸镁干燥,过滤并浓缩以产生呈澄清油的2-氯-7,7-二甲基-1′-[(1-甲基吡唑-4-基)甲基]螺[6H-噻吩并[3,2-c]吡喃-4,4′-哌啶](1178)(29mg,47%)。^1H NMR(300MHz,氯仿-d)δ7.43(s,1H),7.32(s,1H),6.55(s,1H),3.90(s,3H),3.55(s,2H),3.48(s,2H),2.82-2.65(m,2H),2.45-2.25(m,2H),1.94-1.79(m,4H),1.27(s,6H)。LCMS m/z 365.89$[M+H]^+$。

[2661] 化合物1179

[2662] 2′-氯-1”-[(1-甲基-1H-吡唑-4-基)甲基]-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶](1179)

[2663]



[2664] 步骤1:1-(2-噻吩基)环丙烷甲腈(C175)的合成

[2665] 在0℃下向2-(2-噻吩基)乙腈(2g,0.0162mol)于DMF(30mL)中的经搅拌的溶液中添加NaH(60%含矿物质)(1.95g,60%w/w,0.0488mol)并搅拌5分钟。然后向反应混合物中添加1,2-二溴乙烷(4.679g,2.2mL,0.0244mol)。将反应物温热至室温并搅拌2小时。此时,将反应混合物用饱和NH_4Cl水溶液淬灭并用EtOAc(2×100mL)萃取。将有机层用冷盐水溶液洗涤,经Na_2SO_4干燥,并在减压下浓缩以得到粗化合物。将其通过柱色谱法纯化(二氧化硅,20% EtOAc:石油醚)。将收集的级分在减压下浓缩以得到呈淡黄色油的1-(2-噻吩基)环丙烷甲腈(C175)(1.2g,47%)。^1H NMR(300MHz,DMSO-d_6):δ7.49(dd,J=5.1Hz,1.2Hz,1H),7.09(dd,J=3.6Hz,1.2Hz,1H),7.00(t,J=3.6Hz,1H),1.80(t,J=5.1Hz,2H),1.49(t,J=4.8Hz,2H)。

[2666] 步骤2:1-(2-噻吩基)环丙烷甲酸(C176)的合成

[2667] 在室温下向1-(2-噻吩基)环丙烷甲腈(C175)(4g,0.0263mol)于乙醇(15mL)中的经搅拌的溶液中添加含LiOH一水合物(3.5g,0.0826mol)的水(10mL)。将反应混合物在100℃下搅拌16小时。然后将反应混合物在减压下浓缩。将粗混合物溶解在冰冷水(20ml)中并用1N HCl(pH 3-4)酸化以得到固体。将固体过滤,并用过量水洗涤,并在真空中干燥一点点呈灰白色固体的1-(2-噻吩基)环丙烷甲酸(C176)(3g,67%)。^1H-NMR(300MHz,DMSO-d_6)δ12.52(s,1H),7.37-7.35(m,1H),6.93-6.89(m,2H),1.58-1.55(m,2H),1.28-1.24(m,2H)。LCMS m/z 169.24$[M+H]^+$。

[2668] 步骤3:[1-(2-噻吩基)环丙基]甲醇(C177)的合成

[2669] 将1-(2-噻吩基)环丙烷甲酸(C176)(1g,5.945mmol)于THF(24mL)中的溶液冷却至0℃,并逐滴添加硼烷四氢呋喃(7.2mL的1M,7.200mmol)。1小时后,将反应物用H_2O淬灭,并用EtOAc(60mL)和饱和NH_4Cl(60mL)水溶液稀释。将有机层用1N NaOH(60mL)、盐水(60mL)洗涤,用硫酸钠干燥并浓缩成油。将粗油通过硅胶色谱法纯化(含0-60% EtOAc的庚烷)以得到呈澄清油的[1-(2-噻吩基)环丙基]甲醇(C177)(840mg,85%)。^1H NMR(300MHz,氯仿-d)δ7.15(dd,J=4.1,2.3Hz,1H),6.95-6.90(m,2H),3.69(d,J=6.2Hz,2H),1.02-0.92(m,4H)。LCMS m/z 154.94$[M+H]^+$。

[2670] 步骤4:6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1”-甲酸叔丁酯(C178)的合成

[2671] 将[1-(2-噻吩基)环丙基]甲醇(C177)(235mg,1.524mmol)和哌啶-4-酮(盐酸盐)(207mg,1.527mmol)于二噁烷(5mL)中的溶液在冰浴中冷却。添加三氟甲磺酸(400μL,4.520mmol)并将反应混合物温热至rt并搅拌2小时。将反应混合物用1N NaOH(60mL)和EtOAc(60mL)稀释,并将有机层用盐水洗涤,干燥并浓缩成油,将其用DCM(10mL)稀释,并添加DIPEA(500μL,2.871mmol)和Boc_2O(330mg,1.512mmol)。1小时后,将反应混合物浓缩并通过硅胶色谱法纯化(0至60% EtOAc/庚烷)以产生6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1”-甲酸叔丁酯(C178)(333mg,65%)。^1H NMR(400MHz,氯仿-d)δ7.00(d,J=5.2Hz,1H),6.73(d,J=5.2Hz,1H),4.16-3.87(m,2H),3.72(s,2H),3.26-3.02(m,2H),2.02-1.74(m,4H),1.46(s,9H),1.06-1.00(m,2H),1.00-0.95(m,2H)。

[2672] 步骤5:2′-氯-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1”-甲酸叔丁酯(C179)的合成

[2673] 向6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1”-甲酸叔丁酯(C178)(330mg,0.984mmol)于乙腈(5mL)中的溶液中添加NCS(150mg,1.123mmol)和DMAP(10mg,0.08185mmol)。将反应混合物加热至50℃,持续16小时,并且然后冷却至rt并搅拌2天。此时,将混合物用1NNaOH(50mL)和EtOAc(50mL)稀释,将有机层用硫代硫酸钠溶液(50mL)、盐水(50mL)洗涤,经Na_2SO_4干燥并浓缩成油,将其通过硅胶色谱法纯化(0至50% EtOAc/庚烷)以产生呈粘性白色固体的2′-氯-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1”-甲酸叔丁酯(C179)(269mg,74%)。^1H NMR(300MHz,氯仿-d)δ6.54(s,1H),4.09-3.88(m,2H),3.70(s,2H),3.12(t,J=12.8Hz,2H),1.99-1.85(m,2H),1.76(td,J=13.4,4.8Hz,2H),1.50(s,9H),1.04-0.95(m,2H),0.95-0.84(m,2H)。

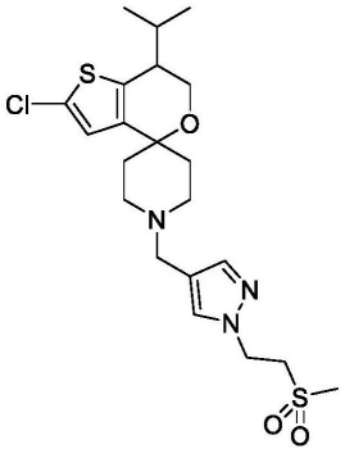
[2674] 步骤6:2′-氯-1”-[(1-甲基-1H-吡唑-4-基)甲基]-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶](1179)的合成

[2675] 向2′-氯-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶]-1′-甲酸叔丁酯(C179)(67mg,0.181mmol)于DCM(1mL)中的溶液中添加TFA(500μL,6.49mmol)。20分钟后,将溶剂蒸发,并将粗混合物溶解在DCE(1.5mL)中,并添加1-甲基吡唑-4-甲醛(35mg,0.318mmol),随后添加AcOH(52μL,0.914mmol)和三乙酰氧基硼氢化物(钠盐)(60mg,0.283mmol),并将反应混合物加热至60℃。2小时后,添加另外三乙酰氧基硼氢化物(钠盐)(50mg,0.236mmol),并将反应混合物加热至60℃并搅拌18小时。此时,将反应混合物用1N NaOH(20mL)和EtOAc(20mL)稀释,并将有机层用Na_2SO_4干燥并浓缩成油,将其通过C18柱色谱法纯化(10-100%MeCN:水,0.1wt%TFA改性剂)。将纯级分用1N NaOH(5mL)处理,并用EtOAc

(50mL)萃取。将有机层浓缩以产生呈黄色油的2′-氯-1”-[(1-甲基-1H-吡唑-4-基)甲基]-6′H-二螺[环丙烷-1,7′-噻吩并[3,2-c]吡喃-4′,4”-哌啶](1179)(16mg,23%)。^{1}H NMR(300MHz,氯仿-d)δ7.43(s,1H),7.32(s,1H),6.59(s,1H),3.90(s,3H),3.67(s,2H),3.48(s,2H),2.85-2.66(m,2H),2.45-2.25(m,2H),1.97-1.87(m,4H),1.02-0.93(m,2H),0.93-0.84(m,2H)。LCMS m/z 364.36[M+H]$^+$。

[2676] 化合物1180

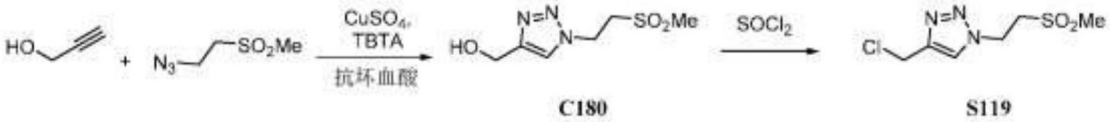
[2677] 2-氯-4-异丙基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶

[2678] 

1180

[2679] 根据用于合成化合物1177的类似化学策略合成化合物(1180)。将2-氯-4-异丙基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶](1180)(4.3mg,18%)分离为白色固体。^{1}H NMR(300MHz,甲醇-d_4)δ8.03(s,1H),6.72(s,1H),4.92(t,J=6.6Hz,2H),3.91-3.77(m,4H),3.75(s,2H),2.95-2.86(m,4H),2.82-2.66(m,2H),2.57(dt,J=7.4,3.6Hz,1H),2.54-2.39(m,2H),2.05-1.66(m,5H),0.99(dd,J=13.9,6.8Hz,6H)。ESI-MS m/z计算值:472.137,实测值:473.145(M+1)$^+$。

[2680] 4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S119)的制备

[2681] 

C180 S119

[2682] 步骤1:[1-(2-甲基磺酰基乙基)三唑-4-基]甲醇(C180)的合成

[2683] 将丙-2-炔-1-醇(500μL,8.464mmol)、1-叠氮基-2-甲基磺酰基-乙烷(1200mg,8.044mmol)、$CuSO_4$(16mg,0.100mmol)、1-(1-苄基三唑-4-基)-N,N-双[(1-苄基三唑-4-基)甲基]甲胺(TBTA)(100mg,0.189mmol)、(2R)-2-[(1S)-1,2-二羟乙基]-3,4-二羟基-2H-呋喃-5-酮(1500mg,8.517mmol)于MeOH(40mL)/水(10mL)中的混合物加热至50℃(11:00)。3小时后,TLC指示叠氮化物的完全消耗。将反应冷却至rt并浓缩。将混合物稀释直到完全溶解在MeOH中,并且然后添加二氧化硅,并将混合物浓缩成干燥固体。将固体上样到SiO2柱上进行纯化(0-10% MeOH:DCM)以产生呈黄色固体的[1-(2-甲基磺酰基乙基)三唑-4-基]甲醇(C180)(1210mg,70%)。^{1}HNMR(400MHz,DMSO-d_6)δ8.04(s,1H),5.21(d,J=6.8Hz,1H),4.81(t,J=7.0Hz,2H),4.54(d,J=4.5Hz,2H),3.80(t,J=6.9Hz,2H),2.96(s,3H)。LCMS m/z

206.4[M+H]$^+$。

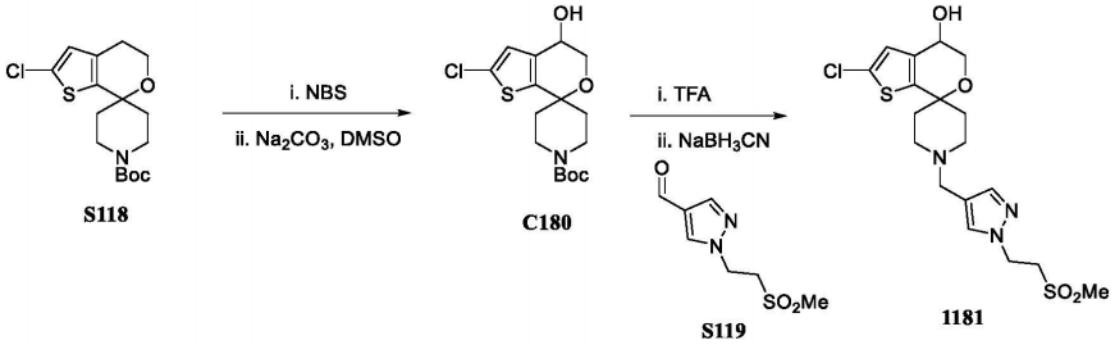
[2684] 步骤2:4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S119)的合成

[2685] 将来自第一步的固体用DCE(30mL)稀释,随后用DMF(5mL)稀释,并向该加热至50℃的混合物中添加亚硫酰氯(550μL,7.540mmol),这立即产生澄清黄色溶液。将混合物在该温度下搅拌(1:30)。搅拌30分钟后,将混合物浓缩至最小体积,并在二乙醚(20mL)中稀释以沉淀出黄色固体,将其过滤并用另外的醚冲洗以产生呈黄色固体的4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S119)(928mg,74%)。^{1}H NMR(400MHz,氯仿-d)δ7.80(s,1H),4.92-4.86(m,2H),4.74(d,J=0.6Hz,2H),3.74(ddd,J=7.1,5.6,0.7Hz,2H),2.77(t,J=0.7Hz,3H)。LCMS m/z 224.36[M+H]$^+$。

[2686] 化合物1181

[2687] 2-氯-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1181)

[2688]



[2689] 步骤1:2-氯-4-羟基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C180)的合成

[2690] 将2-氯螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(S118)(358mg,0.8329mmol)于乙酸乙酯(10mL)中的混合物搅拌,并吹扫并在氩气下超声处理15分钟。此时,添加含1-溴吡咯烷-2,5-二酮(175mg,0.9832mmol)的乙酸乙酯(5mL),并将混合物搅拌至溶解,并立即通过商业光反应器(450nm蓝色LED,4分钟停留时间,30℃,2mL光反应器,0.5毫升/分钟泵速)。将混合物用亚硫酸氢钠(10mL)混合以消耗过量NBS,分离,并将水层用乙酸乙酯(10mL)萃取,并将合并的有机层用硫酸钠干燥,过滤并浓缩。向粗混合物中添加碳酸氢钠(42mg,0.500mmol)和DMSO(1mL),并将混合物在50℃下搅拌3小时。此时,将混合物冷却至rt,用EtOAc(20mL)和水(5mL)稀释。将各层分离并浓缩至最小体积,并上样到C18柱并纯化(40-100% MeCN:水,0.1wt%TFA改性剂)。将含产物级分合并并浓缩以产生呈白色固体的2-氯-4-羟基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯(C180)(18mg,15%)。^{1}H NMR(400MHz,氯仿-d)δ6.77(s,1H),4.90-4.63(m,1H),4.39(t,J=2.9Hz,1H),4.00-3.78(m,4H),3.07(dt,J=45.4,12.4Hz,2H),2.06-1.90(m,1H),1.90-1.78(m,1H),1.70(td,J=13.1,4.9Hz,1H),1.53(ddd,J=14.2,12.7,4.8Hz,1H),1.41(s,9H)。LCMS m/z 360.48[M+H]$^+$。

[2691] 步骤2:2-氯-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1181)的合成

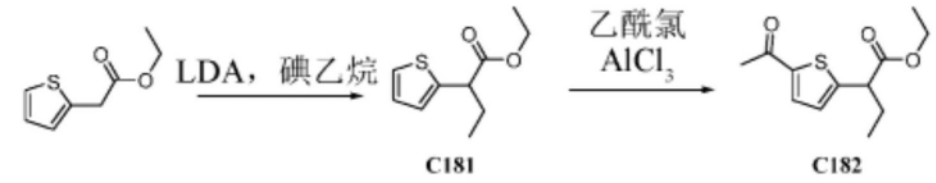
[2692] 向2-氯-4-羟基-螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-1′-甲酸叔丁酯

(C180)(18mg,0.0400mmol)于二氯甲烷(500μL)中的混合物中添加含氯化氢(100μL的4M,0.400mmol)的二噁烷。此时,添加二乙醚(2×3mL)以沉淀产物并倾析以去除二噁烷。将混合物干燥并重新溶解在二氯甲烷(2,000μL)中并转移到5mL微波小瓶中。添加聚苯乙烯负载的氰基硼氢化物(100mg的2mmol/g,0.200mmol)、1-(2-甲基磺酰基乙基)吡唑-4-甲醛(S119)(10.34mg,0.0440mmol)和乙酸(10μL,0.176mmol),并将混合物加盖,密封并加热至110℃,持续20分钟。此时,UPLC指示完全转化,并将混合物过滤,浓缩,最小重新溶解在DCM中,并上样到SiO2柱(0-10% MeOH:DCM)上。将含产物级分合并并浓缩以产生呈白色固体的2-氯-1′-[[1-(2-甲基磺酰基乙基)吡唑-4-基]甲基]螺[4,5-二氢噻吩并[2,3-c]吡喃-7,4′-哌啶]-4-醇(1181)(7mg,38%)。^{1}H NMR(400MHz,氯仿-d)δ7.51(s,1H),7.46(s,1H),6.82(s,1H),4.63-4.54(m,2H),4.41(t,J=2.8Hz,1H),3.94(dd,J=12.4,2.9Hz,1H),3.86(dd,J=12.3,2.8Hz,1H),3.64(t,J=6.1Hz,2H),3.48(s,2H),2.71(d,J=15.7Hz,2H),2.49(s,4H),2.32(t,J=12.0Hz,1H),1.96(s,2H),1.76(d,J=12.0Hz,1H),0.85(d,J=18.7Hz,2H)。LCMS m/z 446.07[M+H]$^+$。

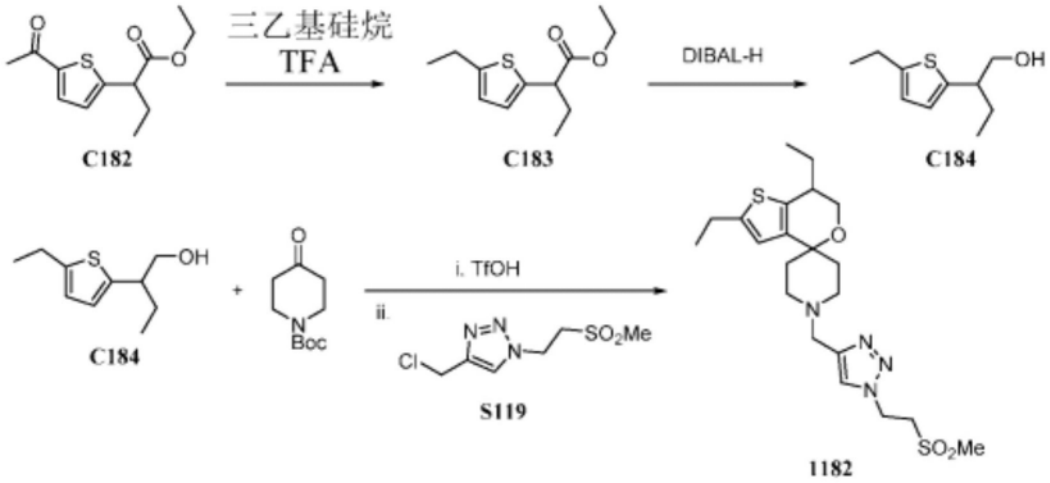
[2693] 化合物1182

[2694] 2,7-二乙基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并

[2695] [3,2-c]吡喃-4,4′-哌啶](1182)



[2696]



[2697] 步骤1:2-(2-噻吩基)丁酸乙酯(C181)的合成

[2698] 在-40℃下向2-(2-噻吩基)乙酸乙酯(441μL,2.94mmol)于THF(10mL)中的经搅拌的溶液中逐滴添加LDA(2.9mL的2M,5.800mmol)。将反应混合物在-40℃下搅拌1小时,并且然后逐滴添加碘乙烷(280μL,3.501mmol)。将反应物在-40℃下搅拌2小时,并且然后在rt下搅拌30分钟。此时,将混合物用饱和NH_4Cl水溶液(1000ml)缓慢淬灭并用二乙醚(3×500ml)萃取。将总有机层用盐水(500ml)洗涤,将有机层经硫酸钠干燥并浓缩以得到粗产物,将粗产物通过正相柱色谱法进一步纯化(含0-30%乙酸乙酯的庚烷)。分离的产物是呈黄色油的

2-(2-噻吩基)丁酸乙酯(C181)(370mg,23%)的混合物。^{1}H NMR(300MHz,氯仿-d)δ7.13-7.00(m,1H),6.85(q,J=2.2Hz,2H),4.17-3.93(m,2H),3.69-3.56(m,1H),2.15-1.87(m,2H),1.78(dp,J=13.5,7.3Hz,1H),1.29-1.05(m,3H),0.86(t,J=7.4Hz,2H),0.72(t,J=7.4Hz,1H)。LCMS m/z 227.1[M+H]$^+$。

[2699] 步骤2:2-(5-乙酰基-2-噻吩基)丁酸乙酯(C182)的合成

[2700] 在0℃下向2-(2-噻吩基)丁酸乙酯(C181)(360mg,1.089mmol)于DCM(3mL)中的经搅拌的溶液中逐滴添加乙酰氯(128mg,1.631mmol),此后在0℃下分批添加AlCl3(218mg,1.635mmol)。将反应混合物在0℃下搅拌2小时。此时,将混合物用冰水(20mL)缓慢淬灭,并用DCM(20mL)萃取。将总有机层用盐水(20mL)洗涤,经硫酸钠干燥并浓缩以得到粗化合物,将其通过硅胶柱色谱法进一步纯化(含4g 0-20%乙酸乙酯的庚烷)。将纯级分合并并浓缩以得到呈黄色油的2-(5-乙酰基-2-噻吩基)丁酸乙酯(C182)(130mg,83%)。^{1}H NMR(300MHz,氯仿-d)δ7.56(d,J=3.9Hz,1H),6.99(dd,J=3.9,0.6Hz,1H),4.19(m,2H),3.76(t,J=7.6Hz,1H),2.53(s,3H),2.26-2.03(m,1H),2.02-1.81(m,1H),1.27(t,J=7.1Hz,3H),0.96(t,J=7.4Hz,3H)。

[2701] 步骤3:2-(5-乙基-2-噻吩基)丁酸乙酯(C183)的合成

[2702] 在0℃下向2-(5-乙酰基-2-噻吩基)丁酸乙酯(C182)(130mg,0.541mmol)于TFA(780μL)中的经搅拌的溶液中逐滴添加三乙基硅烷(130μL,0.814mmol)。将溶液温热至rt。4小时后,添加另外当量的三乙基硅烷(130μL,0.814mmol)。1小时后,将混合物浓缩并用冰水(20mL)淬灭,并用EtOAc(20mL)萃取。将总有机物用盐水(20mL)洗涤,经硫酸钠干燥并浓缩以得到粗产物。将粗产物通过硅胶柱色谱法进一步纯化(含0-20%乙酸乙酯的庚烷)以得到呈黄色油的2-(5-乙基-2-噻吩基)丁酸乙酯(C183)(74mg,60%)。LCMS m/z 227.1[M+H]$^+$。

[2703] 步骤4:2-(5-乙基-2-噻吩基)丁-1-醇(C184)的合成

[2704] 在0℃下向2-(5-乙基-2-噻吩基)丁酸乙酯(C183)(74mg,0.3237mmol)于THF(1.46mL)中的经搅拌的溶液中逐滴添加DIBAL-H(809μL的1M,0.809mmol)。将反应物搅拌4小时。此时,将反应物用饱和NH_4Cl(5mL)淬灭并用EtOAc(5mL)萃取。然后将有机物用盐水(5mL)洗涤,经硫酸钠干燥并浓缩以产生呈黄色油的2-(5-乙基-2-噻吩基)丁-1-醇(C184)(49mg,81%)。^{1}H NMR(300MHz,氯仿-d)δ6.66-6.36(m,2H),3.78-3.34(m,2H),3.00-2.56(m,3H),1.86-1.32(m,3H),1.22(t,J=7.5Hz,3H),0.84(t,J=7.4Hz,3H)。LCMS m/z 185.08[M+H]$^+$。

[2705] 步骤5:2,7-二乙基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](1182)的合成

[2706] 向冷却至0℃的2-(5-乙基-2-噻吩基)丁-1-醇(C184)(49mg,0.266mmol)和4-氧代哌啶-1-甲酸叔丁酯(48mg,0.241mmol)于二噁烷(960μL)中的溶液中逐滴添加三氟甲磺酸(111mg,0.740mmol)。将冰浴去除,并将反应搅拌3小时。将反应用饱和碳酸氢钠水溶液淬灭,然后用EtOAc(5mL)稀释,并将水层用另外的EtOAc(3×5mL)萃取。将合并的有机层蒸发至干燥。

[2707] 向粗反应混合物中添加4-(氯甲基)-1-(2-甲基磺酰基乙基)三唑(S119)(110mg,0.492mmol),其溶解在DCE(2.6mL)中。逐滴添加DIPEA(128μL,0.735mmol)。将所得溶液在rt下搅拌1小时,并且然后将其加热至65℃并且然后搅拌18小时。24小时后,将溶液冷却并在

DCM(10mL)与1NNaOH(10mL)之间分配。将有机层通过相分离器管收集然后在真空中浓缩。将产物通过硅胶色谱法纯化(0-20乙酸乙酯:庚烷)以产生呈黄色油的2,7-二乙基-1′-[[1-(2-甲基磺酰基乙基)三唑-4-基]甲基]螺[6,7-二氢噻吩并[3,2-c]吡喃-4,4′-哌啶](三氟乙酸盐)(1182)(15.5mg,11%)。^{1}H NMR(300MHz,甲醇-d_4)δ8.30(s,1H),6.48(s,1H),4.99(t,J=6.4Hz,2H),4.51(s,2H),3.95(dd,J=11.6,4.1Hz,1H),3.83(t,J=6.3Hz,2H),3.70(dd,J=11.6,5.2Hz,1H),3.50-3.35(m,3H),3.00(s,3H),2.77(q,J=7.5Hz,3H),2.10(dd,J=14.0,8.6Hz,4H),1.82-1.48(m,2H),1.25(t,J=7.4Hz,3H),1.02(t,J=7.4Hz,3H)。ESI-MS m/z计算值:452.192,实测值:453.199$(M+1)^+$。

[2708] 实例2:用于检测和测量化合物的APOL1抑制剂特性的测定

[2709] MultiTox-Fluor多重细胞毒性测定

[2710] 该MultiTox-Fluor多重细胞毒性测定是单一试剂添加、均匀的荧光测定,可同时测量培养孔中活细胞和死细胞的数量。所述测定通过检测两种不同的蛋白酶活性来测量细胞活力和细胞毒性。活细胞蛋白酶活性限于完整的活细胞,并使用荧光、细胞渗透肽甘氨酰基-苯丙氨酰基氨基氟香豆素(GF-AFC)底物进行测量。底物进入完整的细胞,在那里它被裂解产生与活细胞数量成比例的荧光信号。这种活细胞蛋白酶活性标记在膜完整性丧失和泄漏到周围培养基中时变得失活。使用第二种不渗透细胞的荧光肽底物(双AAF-R110底物)测量从失去膜完整性的细胞中释放的死细胞蛋白酶。使用死细胞与活细胞的比率来使数据归一化。

[2711] 简言之,在湿润37℃温育箱中在10.03μM、3.24μM、1.13μM、0.356μM、0.129μM、0.042μM、0.129μM、0.0045μM、0.0015μM、0.0005μM的3-(2-(4-氟苯基)-1H-吲哚-3-基)-N-((3S,4R)-4-羟基-2-氧代吡咯烷-3-基)丙烯酰胺的存在下,一式两份地将tet诱导的转基因APOL1 T-REx-HEK293细胞系与50ng/mL tet一起温育持续24小时以诱导APOL1。将MultiTox试剂添加到每个孔中,并放回温育箱中再放置持续30分钟。在EnVision酶标仪上读取板。使用死细胞与活细胞的比率来进行归一化,并使用Genedata Screener(瑞士巴塞尔(Basel,Switzerland))软件导入、分析和拟合数据。使用对照、无tet(100%活力)和50ng/mL tet处理(0%活力)的百分比对数据进行归一化,并使用Smart Fit进行拟合。用于MultiTox测定的试剂、方法和完整方案如下所述。

[2712] 表49:Multi-Tox测定中使用的试剂

[2713]

试剂	目录号	供应商
384 孔，透明，平底组织培养处理的，多聚-D 赖氨酸包被的	356663	康宁公司（Corning）（纽约州康宁市（Corning, NY））
384 孔圆底聚丙烯板	3656	柯仕达公司（CoStar）（纽约州康宁市）
通用板盖	250002	赛默飞世尔公司（Thermo Fisher）（沃尔瑟姆（Waltham））
用于 Bravo 384 孔的 Axygen 30 µL 吸头	VT-384-31UL-R-S	康宁公司（纽约州康宁市）
MultiTox-Fluor 多重细胞毒性测定	G9202	普洛麦格公司（ProMega）（威斯康星州麦迪逊市（Madison, WI））
225 cm^2 烧瓶，斜颈，经过处理，通气盖	431082	康宁公司（纽约州康宁市）
杜氏磷酸盐缓冲盐水（DPBS），不含钙和镁	14190-136；	赛默飞世尔公司（沃尔瑟姆）
杜氏改良伊格尔氏培养基（DMEM），高葡萄糖，无谷氨酰胺，无丙酮酸钠	11960-077；	赛默飞世尔公司（沃尔瑟姆）
胎牛血清（FBS），不含四环素，美国采购	631368	宝生物（Takara）（日本草津市（Kusatsu, Japan））
l-谷氨酰胺，200 mM	25030-081；	赛默飞世尔公司（沃尔瑟姆）
青霉素-链霉素，10,000 单位/mL	15140-122；	赛默飞世尔公司（沃尔瑟姆）
杀稻瘟素 S HCl，10 mg/mL	A11139-03	赛默飞世尔公司（沃尔瑟姆）
盐酸四环素	T7660 - 5G	西格玛公司（Sigma）（密苏里州圣路易斯（St. Louis, MO））
二盐酸嘌呤霉素，10 mg/mL	A11138-03	赛默飞世尔公司（沃尔瑟姆）

[2714]

试剂	目录号	供应商
胰蛋白酶-EDTA	25300-054	赛默飞世尔公司（沃尔瑟姆）

[2715] 表50:Multi-Tox测定中使用的设备

[2716]

仪器	型号	供应商	位置
Bravo	16050-101	安捷伦科技公司（Agilent Technologies）	美国加利福尼亚州圣克拉拉（Santa Clara, CA）
Multidrop Combi	不适用	赛默飞世尔科技公司（Thermo Scientific）	马萨诸塞州沃尔瑟姆（Waltham, MA）
EnVision	不适用	珀金埃尔默公司（PerkinElmer）	马萨诸塞州沃尔瑟姆

[2717] Multi-Tox测定方案

[2718] 将含有tet诱导型表达系统(T-REx™;加利福尼亚州卡尔斯巴德的英杰公司(Invitrogen,Carlsbad,CA))和腺相关病毒位点1pAAVS1-Puro-APOL1G0或pAAVS1-Puro-APOL1 G1或pAAVS1-Puro-APOL1 G2克隆G0 DC2.13、G1 DC3.25和G2 DC4.44的人胚肾(HEK293)细胞系在T-225烧瓶中细胞生长培养基(DMEM、10％无Tet FBS、2mM L-谷氨酰胺、100单位/mL青霉素-链霉素、5μg/mL杀稻瘟素S HCl、1μg/mL嘌呤霉素二盐酸盐)中在约90％融合下生长。用DPBS洗涤细胞,并且然后用胰蛋白酶消化以从烧瓶中解离。用培养基淬灭胰蛋白酶,然后以200g使细胞沉淀,并重悬于新鲜细胞测定培养基(DMEM、2％无Tet FBS、2mM L-谷氨酰胺、100单位/mL青霉素-链霉素)中。将细胞计数并稀释到1.17×10^6个细胞/毫升。使用Multidrop分配器将20μL细胞(23,400/孔)分配到384孔聚-D-赖氨酸涂布板的每个孔中。然后将板在室温下温育持续一小时。

[2719] 需要四环素来诱导APOL1表达。在细胞测定培养基中将1mg/mL tet水储备液稀释至250ng/mL(5X)。使用Multidrop分配器将60μL细胞测定培养基(无tet对照)分配到第1列和第24列,并将60μL 5X tet在384-PP圆形底板中分配到第2列至第23列。

[2720] 使用模板384_APOL1细胞_DR10n2_50uM_v3订购全球化合物档案库中的即用型测定板。分配200nL于DMSO中的化合物。在MultiTox测定中,最终最高浓度为10μM,10点3倍稀释,一式两份。

[2721] 将20μL从5X tet板转移到ARP并混合,然后将5μL 5X tet和化合物转移到细胞板并使用Bravo混合。将细胞板放置在潮湿37℃5％ CO_2温育箱中持续24小时。

[2722] 根据制造商的方案进行MultiTox-Fluor多重细胞毒性测定。在将细胞与tet和化合物一起温育持续24小时后,使用Multidrop分配器将25μL 1xMultiTox试剂添加到每个孔中;将板置于板振荡器(600rpm)上持续2分钟,然后短暂离心并放回37℃温育箱中持续30分钟。使用EnVision读板器读取细胞活力(激发:400nm,发射:486nm)和细胞毒性(激发:485nm,发射:535nm)。报道了死细胞(细胞毒性)与活细胞(活力)的比率。在Genedata中导出并分析数据。使用对照、无tet(100％活力)和50ng/mL tet处理(0％活力)的百分比对数据进行归一化,并使用Genedata中的Smart Fit设置进行拟合。

[2723] 化合物1至1183的效力数据

[2724] 式I化合物可用作APOL1活性的抑制剂。下表5说明了使用上述程序的化合物1至1183的IC_{50}。上述程序也可以用于测定任何式I化合物的效力。在下表51中,以下含义适用。IP_{50}(即,细胞增殖的IC_{50}),“+++”意指＜0.1μM;“++”意指0.1-0.5μM(包含端值);“+”意指>

0.5-1.0μM。N.D.＝未确定。

[2725] 表51:化合物1至1042的效力数据

[2726]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
1	+++	41	+++	81	++
2	+++	42	+++	82	++
3	+++	43	++	83	++
4	+++	44	+++	84	+++
5	+++	45	+++	85	+++
6	+++	46	++	86	+++
7	+++	47	++	87	++
8	+++	48	+++	88	+++
9	+	49	+++	89	+++
10	+	50	+++	90	++
11	+++	51	++	91	+++

[2727]

12	+++	52	+++	92	+
13	+++	53	+	93	+
14	++	54	+++	94	++
15	++	55	++	95	+++
16	++	56	+++	96	+++
17	+++	57	+++	97	+++
18	+++	58	++	98	++
19	++	59	+++	99	+++
20	++	60	+++	100	++
21	+++	61	++	101	++
22	+++	62	+++	102	+++
23	+++	63	+++	103	++
24	+++	64	+++	104	++
25	+++	65	++	105	+
26	+++	66	++	106	++
27	+++	67	+++	107	+++
28	++	68	++	108	++
29	+++	69	+++	109	++
30	++	70	+++	110	++
31	++	71	+++	111	++
32	+++	72	+++	112	+++
33	+++	73	+++	113	+++
34	+++	74	++	114	++
35	++	75	+++	115	+++
36	++	76	++	116	++
37	+++	77	+	117	+++
38	++	78	++	118	++
39	++	79	++	119	+++
40	++	80	++	120	++
化合物编号	**IP_{50}**	**化合物编号**	**IP_{50}**	**化合物编号**	**IP_{50}**
121	+++	161	+++	201	+++
122	++	162	+++	202	+++
123	+++	163	+	203	+++
124	+++	164	+	204	+++
125	+++	165	+++	205	+++

[2728]

126	+++	166	+	206	+++
127	+	167	+++	207	+++
128	++	168	+	208	+++
129	++	169	+++	209	+++
130	++	170	+	210	+++
131	++	171	++	211	+++
132	++	172	++	212	+++
133	+++	173	++	213	+++
134	+++	174	++	214	+++
135	++	175	+	215	+++
136	+++	176	++	216	+++
137	+++	177	+	217	+++
138	+++	178	++	218	+++
139	+++	179	+++	219	+++
140	+++	180	+++	220	+++
141	++	181	++	221	+++
142	++	182	++	222	+++
143	+++	183	+++	223	+++
144	++	184	+++	224	+++
145	+++	185	+++	225	+++
146	+++	186	++	226	+++
147	+	187	++	227	+++
148	++	188	++	228	+++
149	+	189	+++	229	+++
150	++	190	+++	230	+++
151	+++	191	+++	231	++
152	++	192	+	232	+++
153	+++	193	+	233	++
154	+++	194	+	234	+++
155	+++	195	++	235	++
156	+++	196	++	236	++
157	+++	197	++	237	++
158	+++	198	++	238	++
159	++	199	+++	239	++
160	+++	200	+++	240	++

[2729]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
241	++	281	++	321	++
242	++	282	+	322	++
243	++	283	+	323	+++
244	++	284	+	324	+++
245	++	285		325	+++
246	+++	286	+	326	+++
247	++	287	+++	327	++
248	++	288	+++	328	++
249	+++	289	++	329	++
250	++	290	+	330	+++
251	+++	291	++	331	++
252	+++	292	++	332	++
253	++	293	+	333	+++
254	+++	294	+	334	++
255	+	295	++	335	+++
256	++	296	++	336	++
257	++	297	+	337	+++
258	+	298	+	338	+++
259	+++	299	++	339	+++
260	+	300	+++	340	+++
261	++	301	++	341	+++
262	+	302	+++	342	+++
263	+	303	+++	343	+++
264	+++	304	+++	344	+++
265	+++	305	+++	345	++
266	+++	306	+++	346	+++
267	+++	307	+++	347	++
268	+++	308	+++	348	++
269	+++	309	+++	349	+++
270	++	310	++	350	++
271	+++	311	++	351	++
272	++	312	+++	352	+++
273	++	313	+++	353	+++

274	+++	314	+++	354	++
275	+	315	+++	355	+++
276	+	316	+++	356	+++
277	+	317	++	357	+++
278	++	318	+++	358	+++
279	+++	319	+++	359	++
280	++	320	+++	360	++

[2730]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
361	++	401	+++	441	+++
362	++	402	+++	442	+++
363	+++	403	+++	443	+++
364	++	404	+++	444	+++
365	++	405	+++	445	+++
366	++	406	+++	446	+++
367	++	407	+++	447	++
368	++	408	+++	448	++
369	++	409	+++	449	++
370	++	410	+++	450	++
371	+++	411	++	451	++
372	+	412	+++	452	++
373	++	413	+++	453	++
374	++	414	+++	454	++
375	+++	415	++	455	++
376	+++	416	++	456	++
377	+++	417	+	457	++
378	++	418	++	458	++
379	+++	419	+	459	+++
380	++	420	+++	460	+++
381	++	421	+	461	+++
382	+++	422	+++	462	+++
383	++	423	+++	463	++
384	++	424	+	464	+++
385	++	425	+++	465	+++
386	+++	426	+++	466	+++

387	++	427	+++	467	+++
388	+++	428	+++	468	+++
389	+++	429	+++	469	+++
390	+++	430	+++	470	+++
391	+++	431	+++	471	+++
392	+	432	+++	472	+++
393	+++	433	+++	473	++
394	+++	434	+++	474	+++
395	+++	435	+++	475	+++
396	+++	436	+++	476	+++
397	+++	437	+++	477	+++
398	+++	438	+++	478	++
399	+++	439	+++	479	+++
400	+++	440	+++	480	++

[2731]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
481	++	521	+++	561	+++
482	+++	522	+++	562	+++
483	++	523	+++	563	+++
484	+++	524	+++	564	+++
485	+++	525	+++	565	+++
486	++	526	++	566	+++
487	++	527	+++	567	+++
488	+++	528	++	568	+++
489		529	+++	569	+++
490	+	530	+++	570	++
491	++	531	++	571	++
492	++	532	++	572	++
493	+	533	+	573	++
494	++	534	+++	574	+
495	+	535	+++	575	+
496	+	536	+++	576	++
497	++	537	+++	577	++
498	+	538	+	578	+++
499	+++	539		579	+++

[2732]

500	+++	540	+++	580	++
501	++	541	+++	581	++
502	++	542	+++	582	+
503	++	543	+++	583	++
504	++	544	+	584	+++
505	+++	545	+++	585	++
506	++	546	+++	586	+
507	++	547	+++	587	++
508	++	548	+++	588	+
509	++	549	+++	589	+
510	+++	550	+++	590	+
511	+++	551	+++	591	+
512	++	552	+++	592	+
513	++	553	+++	593	+++
514	++	554	+++	594	+++
515	+++	555	+++	595	+++
516	+++	556	+++	596	+++
517	++	557	+++	597	+++
518	+++	558	+++	598	++
519	+++	559	+++	599	++
520	+++	560	+++	600	++

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
601	+++	641	++	681	+
602	+++	642	+	682	++
603	++	643	+	683	+
604	++	644	+++	684	+
605	++	645	++	685	+
606	++	646	+++	686	+
607	++	647	+++	687	+
608	++	648	+++	688	+
609	+++	649	++	689	+
610	+++	650	++	690	+
611	+++	651	+++	691	
612	++	652	++	692	

613	++	653	++	693	+
614	++	654	++	694	+
615	++	655	+++	695	+
616	+	656	++	696	++
617	+++	657	+++	697	+++
618	+	658	+++	698	+++
619	++	659	++	699	+++
620	++	660	++	700	+++
621	+++	661	++	701	+++
622	+	662	+++	702	+++
623	+	663	+++	703	+++
624	+	664	+++	704	++
625	+	665	++	705	++
626	+++	666	++	706	+++
627	++	667	++	707	+++
628	++	668	+	708	++
629	++	669	++	709	++
630	+++	670	++	710	+
631	+++	671	+++	711	++
632	+++	672	++	712	+
633	+++	673	+	713	++
634	+++	674	+	714	+++
635	+++	675	++	715	+++
636	+++	676	++	716	++
637	+++	677	+	717	++
638	+++	678	+	718	++
639	+++	679	+	719	++
640	++	680	+	720	++

[2733]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
721	+	761	++	801	+
722	++	762	+++	802	++
723	++	763	+++	803	++
724	+++	764	+++	804	+++
725	++	765	+++	805	+

	726	+	766	+	806	++
	727	++	767	+++	807	++
	728	+++	768	+++	808	+
	729	+++	769	+++	809	++
	730	++	770	++	810	++
	731	+	771	++	811	+
	732	+	772	+++	812	++
	733	++	773	+++	813	++
	734	++	774	+	814	
	735	+	775	+++	815	+
	736	+	776	+++	816	+
	737	+	777	+++	817	+++
	738	++	778	+	818	+++
	739	+	779	+	819	+++
	740	+	780	+++	820	+++
	741		781	+	821	++
	742	+++	782	+	822	++
[2734]	743	++	783	++	823	++
	744	+++	784	++	824	+++
	745	++	785	+	825	+++
	746	+	786	+	826	+++
	747		787	+	827	+++
	748	++	788	++	828	+++
	749		789	+	829	+++
	750	+++	790	++	830	+++
	751		791	+++	831	+++
	752		792	++	832	+++
	753		793	++	833	+++
	754	+++	794	++	834	+++
	755	++	795		835	+++
	756	++	796	++	836	+++
	757	+++	797	++	837	+++
	758	+	798	+++	838	+
	759	++	799	+++	839	+++
	760	++	800	+++	840	+++

[2735]

化合物编号	IP50	化合物编号	IP50	化合物编号	IP50
841	+++	881	+++	921	+++
842	+++	882	+++	922	+++
843	+++	883	+++	923	+++
844	++	884	+++	924	+++
845	++	885	+++	925	++
846	+++	886	+++	926	+++
847	+++	887	+++	927	+++
848	+++	888	+++	928	+++
849	++	889	+++	929	+++
850	++	890	+++	930	+++
851	+++	891	+++	931	+++
852	+++	892	+++	932	+++
853	++	893	+++	933	+++
854	+++	894	+++	934	+++
855	+++	895	+++	935	+++
856	+++	896	+++	936	+++
857	+++	897	+++	937	+++
858	+++	898	+++	938	+++
859	+++	899	++	939	+++
860	+++	900	+++	940	+++
861	++	901	+++	941	+++
862	++	902	+++	942	+++
863	++	903	+++	943	+++
864	++	904	+++	944	+++
865	++	905	+++	945	+++
866	++	906	+++	946	+++
867	++	907	+++	947	+++
868		908	+++	948	+++
869	+	909	+++	949	+++
870	+++	910	++	950	+++
871	+++	911	+++	951	+
872	+++	912	+++	952	+++
873	+++	913	+++	953	+++

874	+++	914	+++	954	+++
875	+++	915	+++	955	+++
876	+++	916	+++	956	+++
877	+++	917	+++	957	+++
878	+++	918	+++	958	+++
879	+++	919	+++	959	+++
880	+++	920	++	960	+++

[2736]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
961	+++	1001	++	1041	+++
962	+++	1002	+++	1042	++
963	+++	1003	+++	1043	+++
964	+++	1004	++	1044	+++
965	+++	1005	+++	1045	+++
966	+++	1006	++	1046	+++
967	+++	1007	+	1047	+++
968	+++	1008	+	1048	+++
969	+++	1009	+	1049	+++
970	+++	1010	+++	1050	+++
971	+++	1011	+++	1051	+++
972	+++	1012	+++	1052	+++
973	+++	1013	+++	1053	+++
974	+++	1014	+++	1054	+++
975	+++	1015	+++	1055	+++
976	+++	1016	++	1056	++
977	+++	1017	++	1057	++
978	+++	1018	++	1058	++
979	+++	1019	+	1059	++
980	++	1020	+	1060	++
981	+++	1021	++	1061	++
982	+++	1022	+++	1062	++
983	+++	1023	+	1063	++
984	+++	1024	+++	1064	++
985	+++	1025	+++	1065	+
986	+++	1026	+++	1066	+++

987	+++	1027	+++	1067	+++
988	+++	1028	+++	1068	+++
989	+++	1029	++	1069	++
990	+++	1030	++	1070	++
991	+++	1031	+++	1071	++
992	+++	1032	+++	1072	++
993	++	1033	+++	1073	+++
994	+++	1034	+++	1074	+++
995	+++	1035	+++	1075	++
996	+++	1036	+++	1076	++
997	+++	1037	+++	1077	++
998	+++	1038	+++	1078	++
999	+++	1039	+++	1079	++
1000	+	1040	+++	1080	++

[2737]

化合物编号	IP_{50}	化合物编号	IP_{50}	化合物编号	IP_{50}
1081	++	1121	+	1161	++
1082	++	1122	+	1162	++
1083	+	1123	+	1163	++
1084	+	1124	+	1164	++
1085	+	1125	+	1165	++
1086	+	1126	+++	1166	++
1087	+	1127	+++	1167	++
1088	+	1128	+++	1168	+
1089	+	1129	++	1169	++
1090	+	1130	++	1170	++
1091	+	1131	++	1171	+
1092	+	1132	++	1172	+
1093	+	1133	++	1173	++
1094	+	1134	++	1174	++
1095	+	1135	++	1175	++
1096	+	1136	++	1176	+
1097	+	1137	++	1177	+++
1098	+	1138	++	1178	+++
1099	+	1139	+	1179	+++

[2738]

1100	+	1140	+	1180	+
1101	+	1141	+	1181	+
1102	+	1142	+	1182	+
1103	+	1143	+	1183	+
1104	+	1144	+		
1105	+	1145	+		
1106	+	1146	+		
1107	+	1147	+		
1108	+	1148	+		
1109	+	1149	+		
1110	+	1150	+		
1111	+	1151	+		
1112	+	1152	+		
1113	+	1153	+		
1114	+	1154	+		
1115	+	1155	+		
1116	+	1156	+		
1117	+	1157	++		
1118	+	1158	+		
1119	+	1159	+++		
1120	+	1160	++		

[2739] 其它实施例

[2740] 本公开仅提供了所公开的主题的非限制性示例性实施例。所属领域的技术人员将从本公开以及权利要求书中容易地认识到,在不脱离如以下权利要求书中限定的本公开的精神和范围的情况下,可在其中进行各种改变、修改和变化。