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(71)申请人 斯克里普斯研究学院
地址 美国加利福尼亚州

(72)发明人 库尔特内·米勒
帕特里克·格里芬
西奥多·卡梅内茨卡
加文·罗姆博 马修·舒尔曼
史蒂夫·扬 史蒂文·达迪
拉斯洛·雷德纳尔

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代理人 郑斌 韩晓帆

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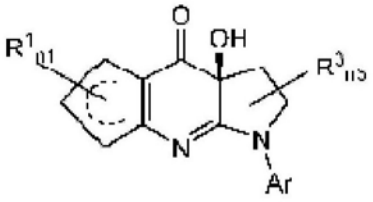
权利要求书72页 说明书154页 附图13页

(54)发明名称

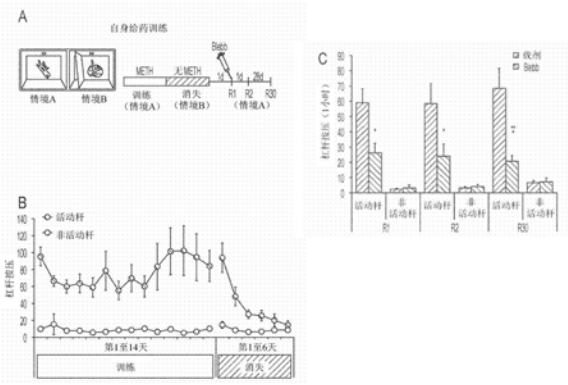
用于物质使用复发的非肌肉肌球蛋白II抑制剂

(57)摘要

本发明可提供化合物布雷他汀类似物，其相对于心肌球蛋白II而言是非肌肉肌球蛋白II的有效和选择性抑制剂。该化合物可用于治疗患者的疾病、病症或医学状况(包括调节肌球蛋白II ATP酶)的方法中，例如治疗物质滥用复发性病症或肾病、癌症和转移、良性前列腺增生、止血或血栓形成、神经损伤(包括视网膜损伤)、肺纤维化、肝纤维化、关节纤维化、伤口愈合、脊髓损伤、牙周炎、青光眼和免疫相关疾病(包括多发性硬化症)；或者其中所述疾病、病症或医疗状况包括成瘾，所述成瘾包括滥用或成瘾于《精神障碍诊断与统计手册》(DSM)中归类为物质相关性或成瘾性病症的任何事物，所述事物例如但不限于可卡因、阿片类物质、安非他命、乙醇、大麻/大麻药品、尼古丁以及包括赌博在内的活动。化合物为通式(I)，其具有如本文所限定的取代基。

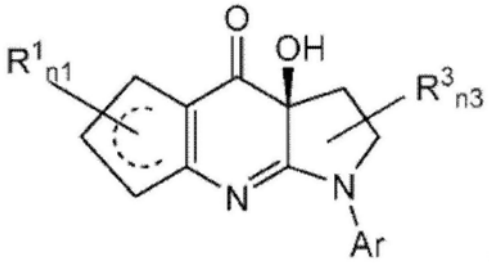


(I)



CN 112584832 A

1.式(I)化合物或其可药用盐：



(I)

其中

带有R^1的环是5元、6元或7元芳基或杂芳基环系统，其包含0、1或2个选自S、O、N和NR^1的杂原子；其中所述环可以与芳基、杂芳基、环烷基或杂环基环稠合；其中R^1可以设置在多环系统的任何一个或更多个环上；

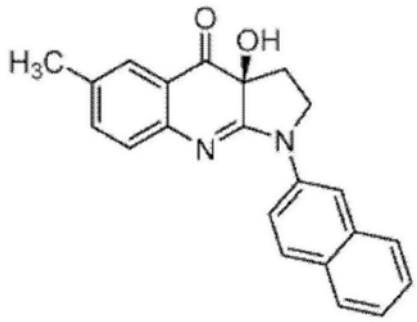
R^1在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、氰基、硝基或卤素；n1＝0、1、2或3；

Ar是单环或双环芳基或杂芳基环系统，其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代；

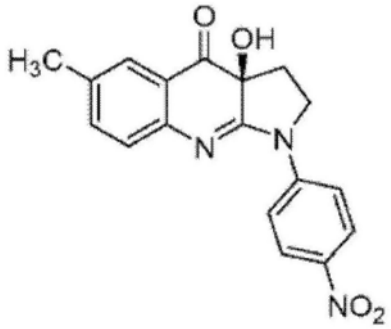
R^2在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、羟甲基、R_2NCH_2，其中R为H或烷基、氰基、硝基或卤素；

R^3在每次出现时独立地为(C1-C4)烷基、卤素或(C1-C4)卤代烷基；n3＝0、1、2、3或4；

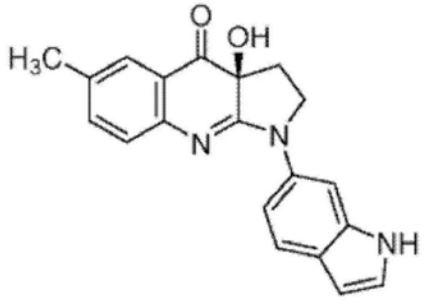
前提是所述化合物不是布雷他汀或任何下式的化合物：



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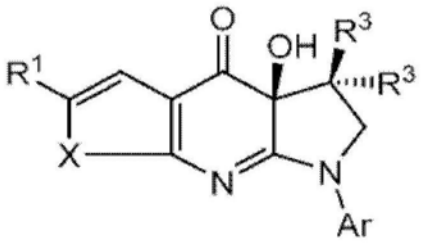


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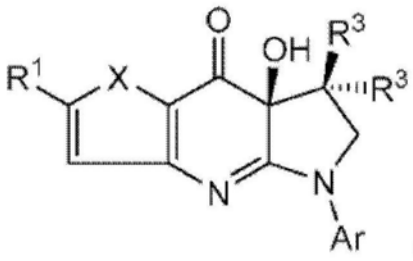
。

2.权利要求1所述的化合物，其中所述带有R^1的环为苯基、吡啶基或噻吩基。

3.式(IIa)或(IIb)的权利要求1所述的化合物或其可药用盐：

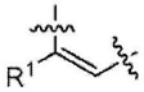


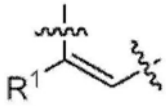
(IIa)



(IIb)

其中

X是S,或者X是式  的基团,其中波浪线表示键合点;

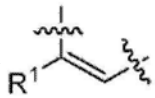
R^1在每次出现时独立地为H、(C1-C4)烷基、CF_3或卤素;前提是当X是式  的基团且Ar是未经取代的苯基时,至少一个R^1基团不为H或(C1-C4)烷基;

Ar是芳基或杂芳基,其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代;

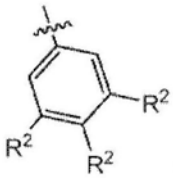
R^2在每次出现时独立地为卤素、氰基、硝基、CF_3、(C1-C4)烷基或(C1-C4)烷氧基;

R^3在每次出现时独立地为H或CH_3。

4.权利要求3所述的化合物,其中X是S。

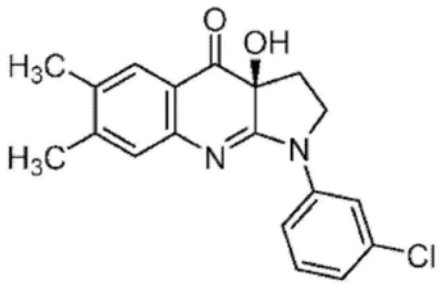
5.权利要求3所述的化合物,其中X是式  的基团,其中波浪线表示键合点。

6.权利要求5所述的化合物,其中式(I)的至少一个R^1基团是甲基、卤素或CF_3。

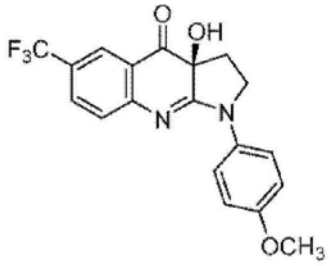
7.权利要求1所述的化合物,其中Ar是式  的基团,其中波浪线表示键合点。

8.权利要求1所述的化合物,其中Ar是吡唑基、噻吩基、异喹啉基、苯并噁唑基、喹唑啉基、异噁唑基、噌啉基、喹喔啉基、苯并异噁唑基、苯并噻二唑基、吡唑并吡啶基、咪唑并吡啶基、噻吩并吡啶基、二氢苯并噁嗪基、三唑并吡啶基、二氢吡啶并噁嗪基、四氢苯并氧氮杂䓬基、二氢苯并二氧杂芑基、二氢苯并噻嗪基、四氢喹啉基、四氢萘基或苯并二氢吡喃基环系统,其中的任一者均可以是未经取代的或者被1、2或3个R^2取代。

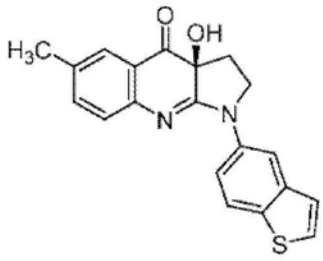
9.权利要求1所述的化合物,其中所述化合物是以下的任一个或其可药用盐:



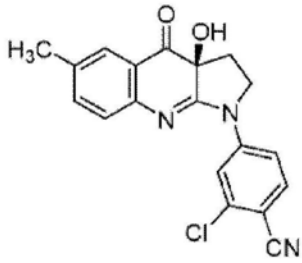
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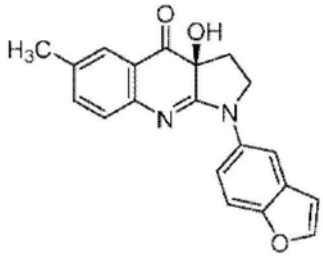
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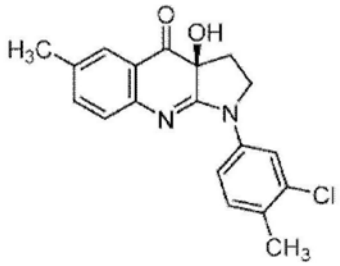
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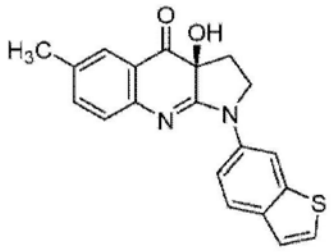
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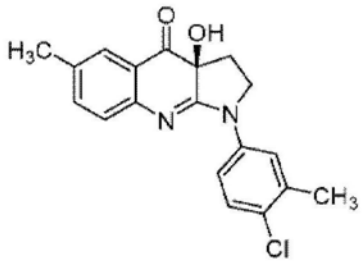
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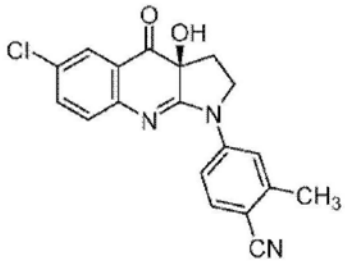
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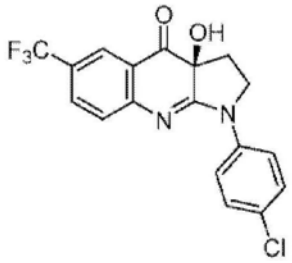
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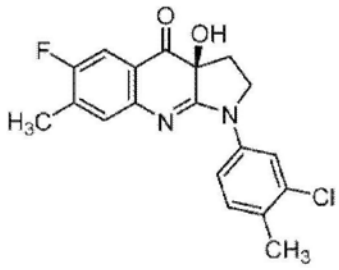
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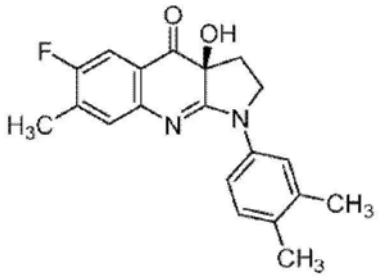
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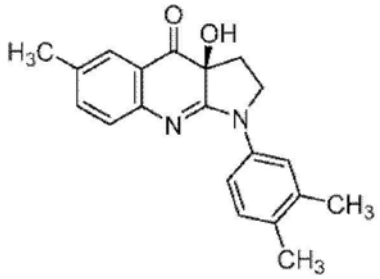
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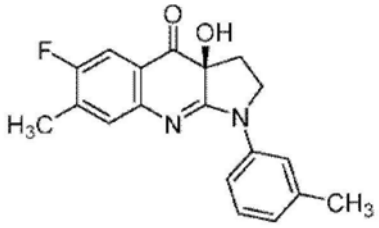
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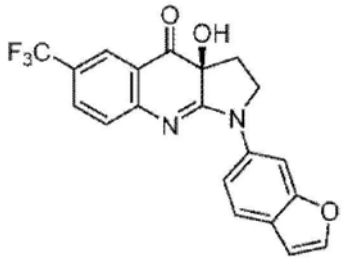
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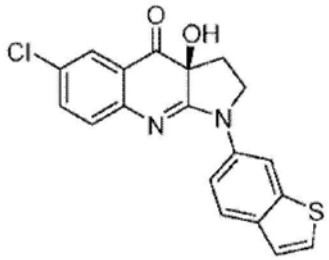
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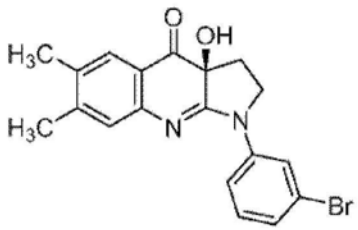
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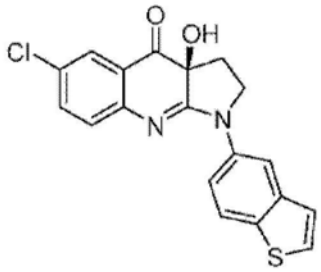
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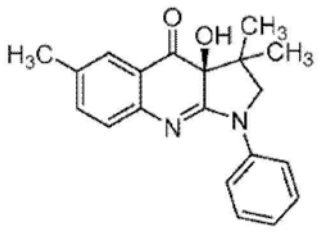
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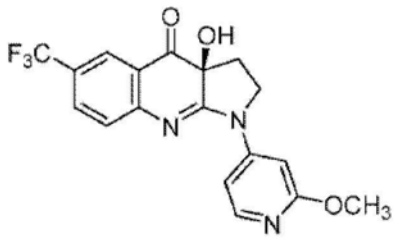
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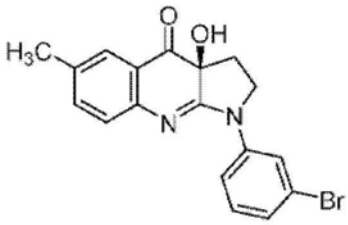
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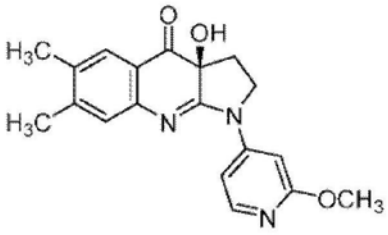
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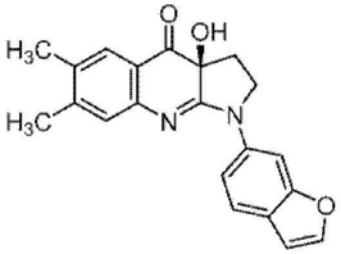
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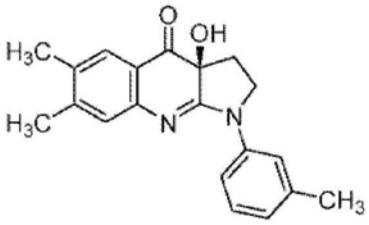
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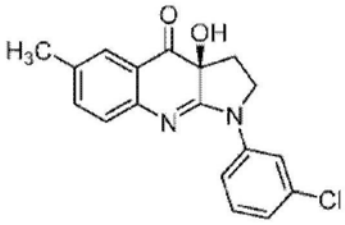
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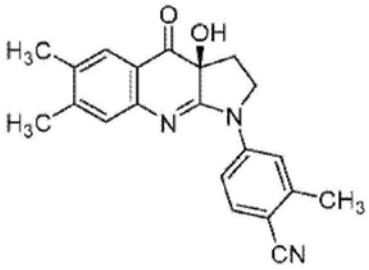
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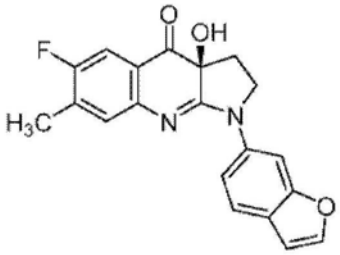
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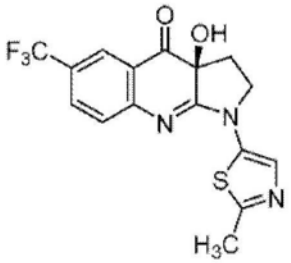
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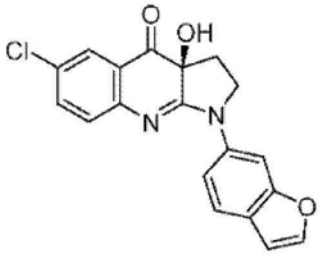
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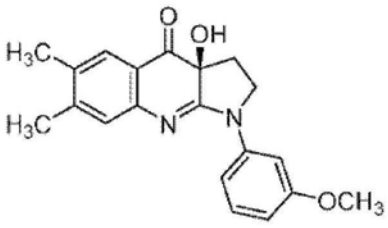
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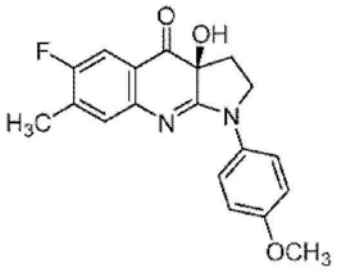
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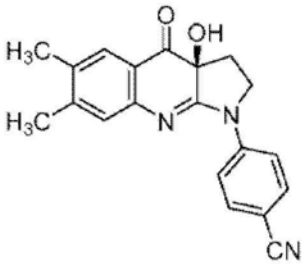
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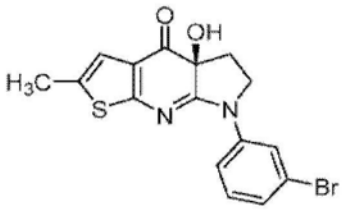
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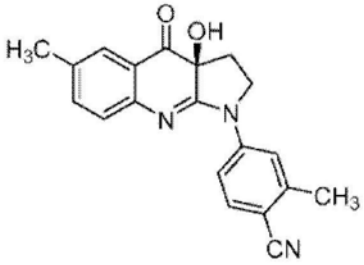
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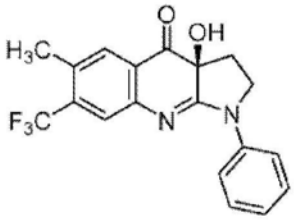
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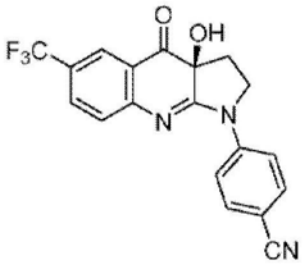
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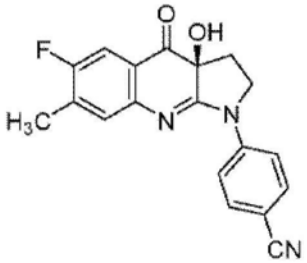
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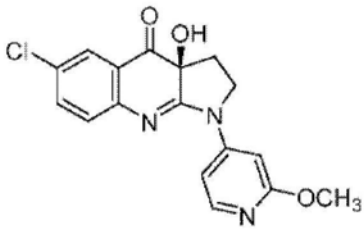
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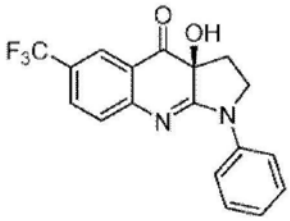
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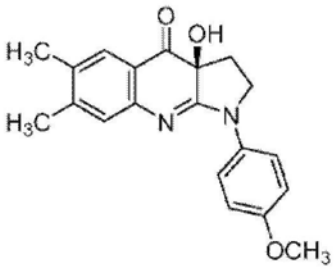
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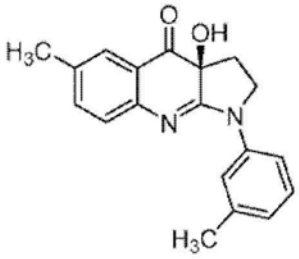
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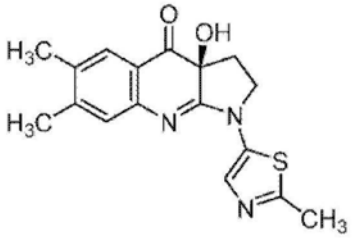
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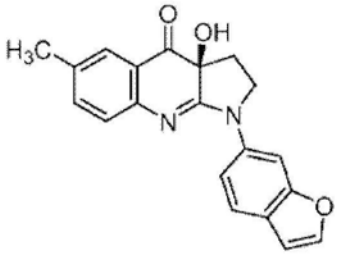
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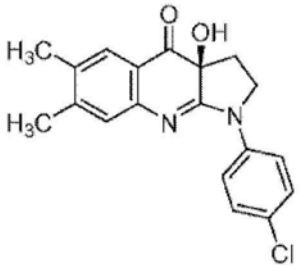
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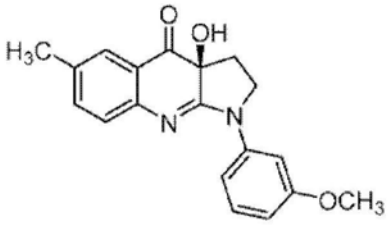
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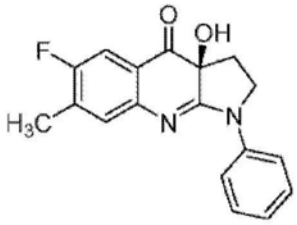
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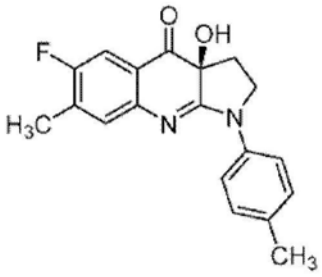
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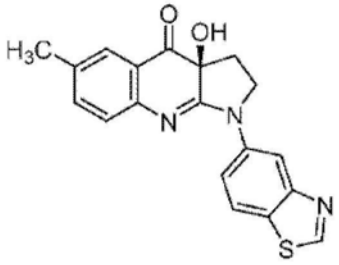
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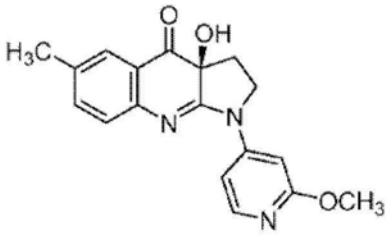
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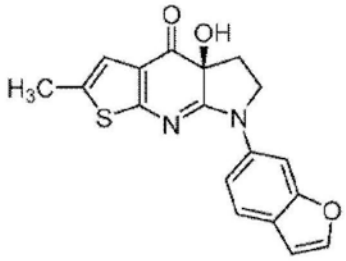
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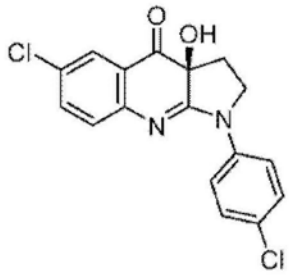
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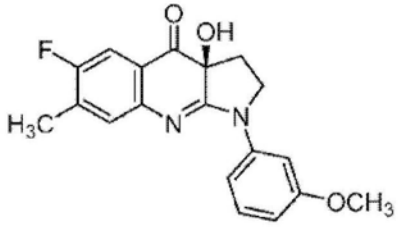
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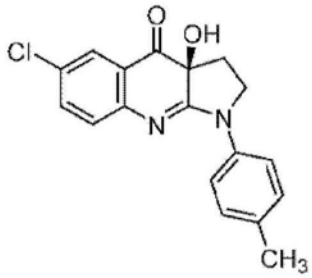
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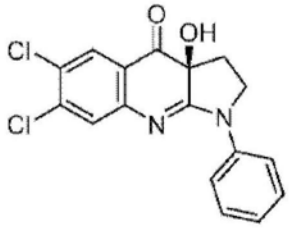
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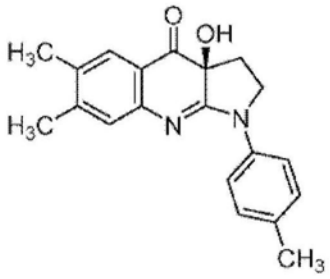
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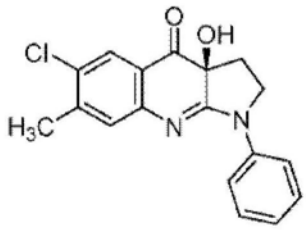
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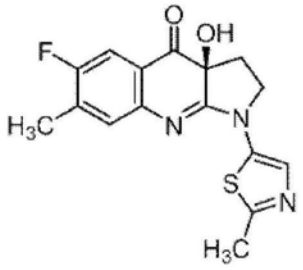
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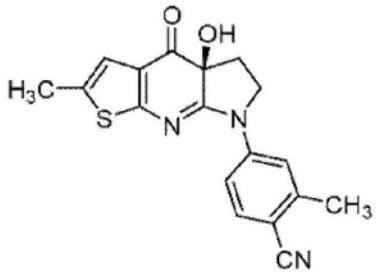
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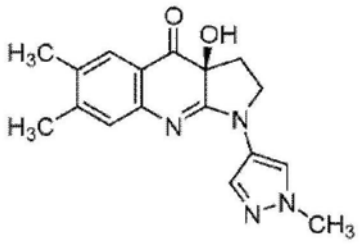
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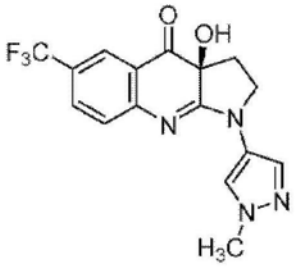
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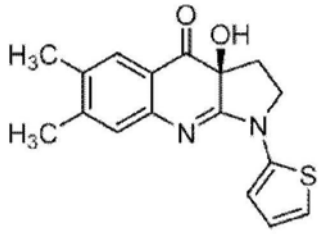
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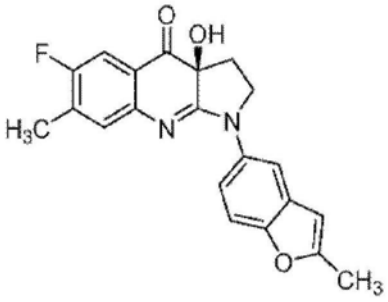
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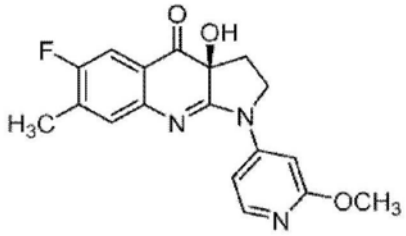
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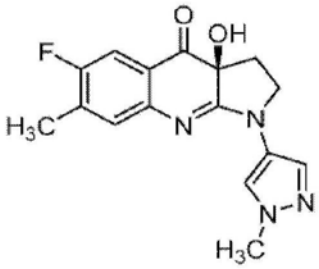
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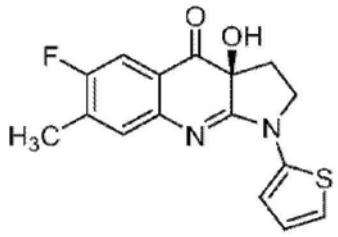
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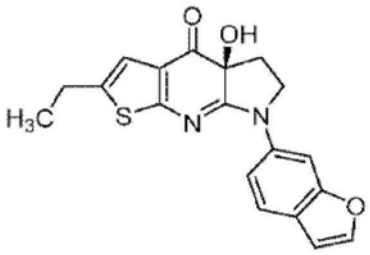
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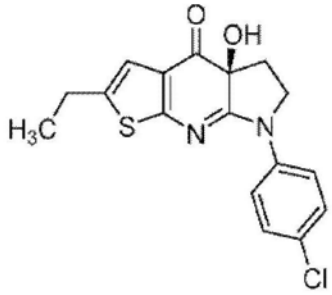
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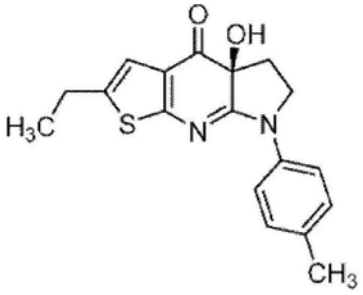
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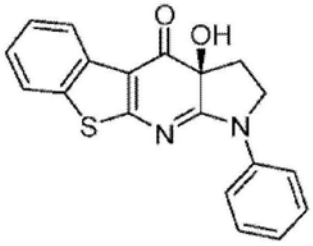
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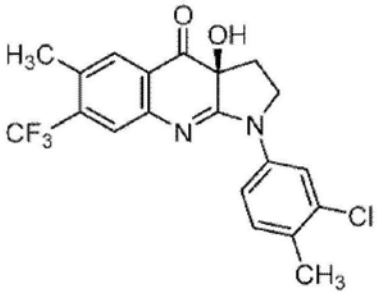
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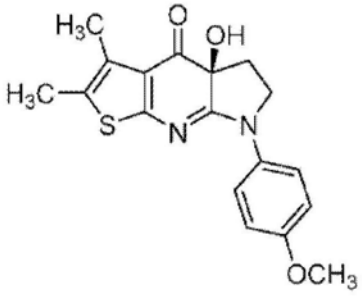
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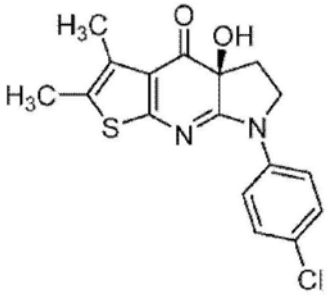
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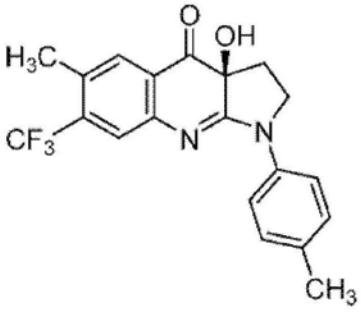
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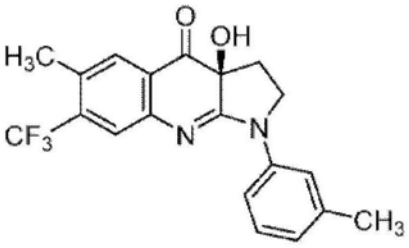
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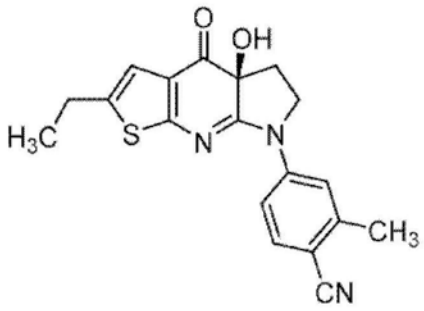
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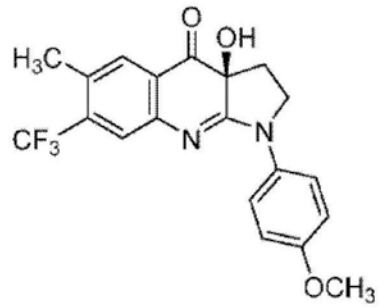
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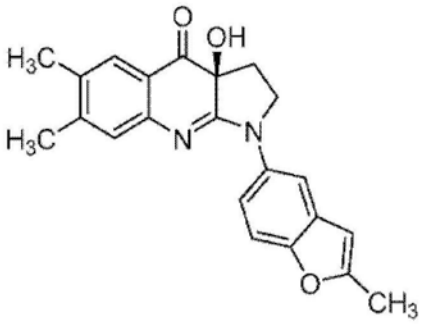
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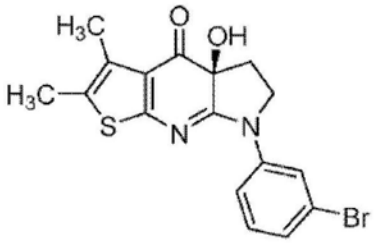
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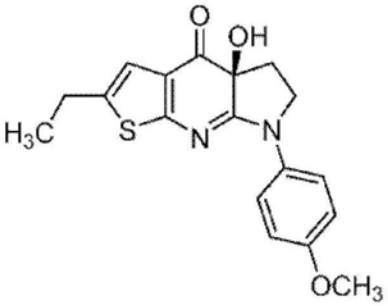
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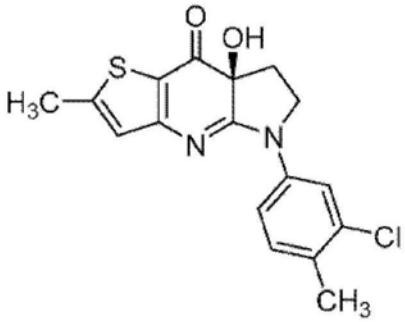
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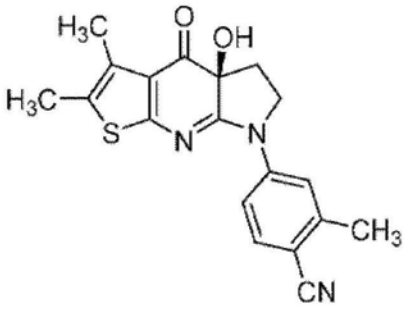
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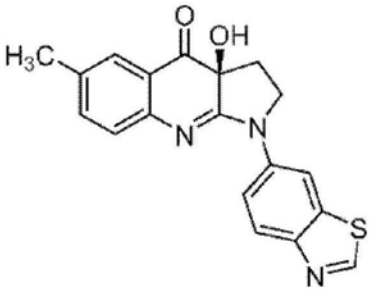


BPN-0026881

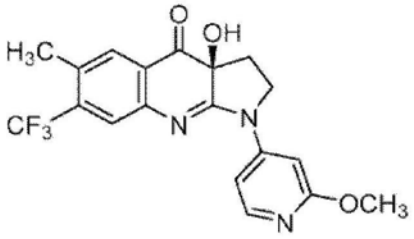


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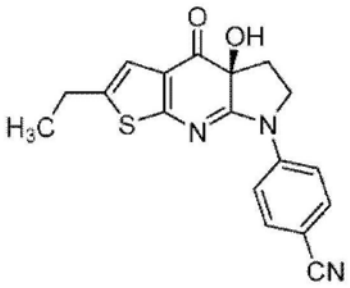




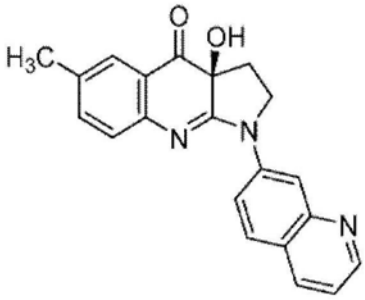
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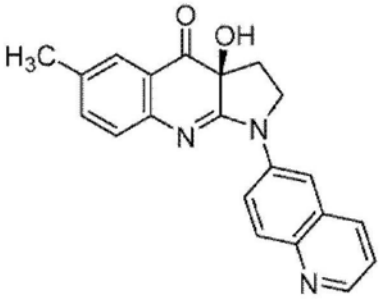
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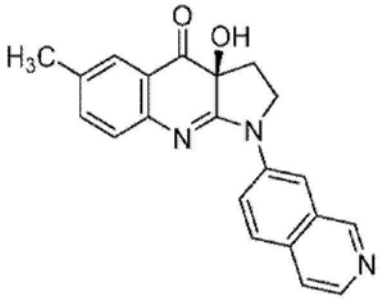
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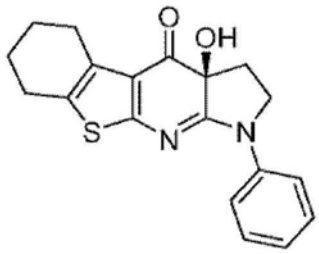
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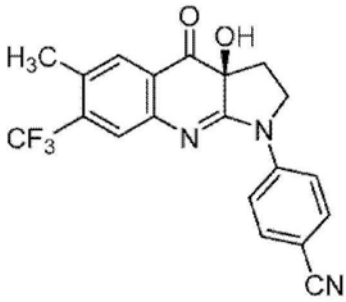
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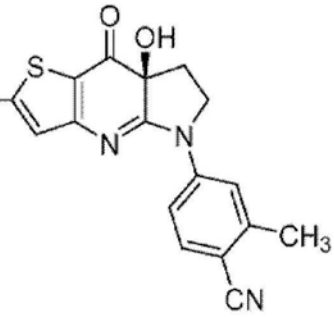
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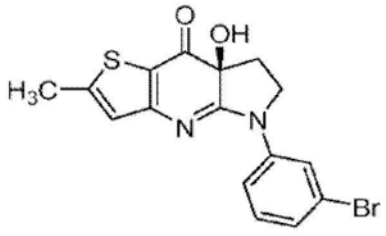


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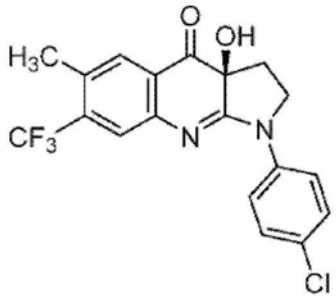


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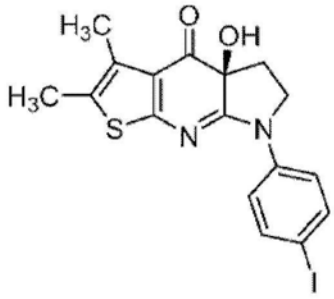
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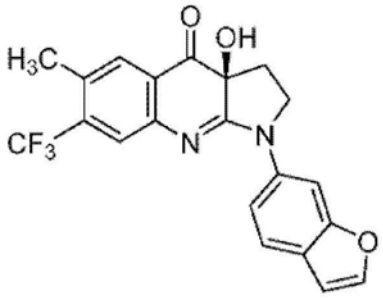
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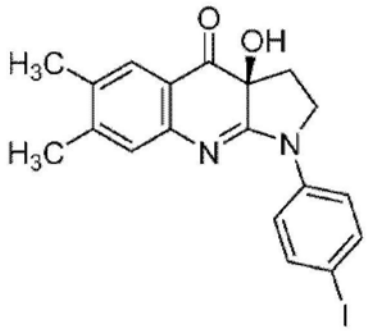
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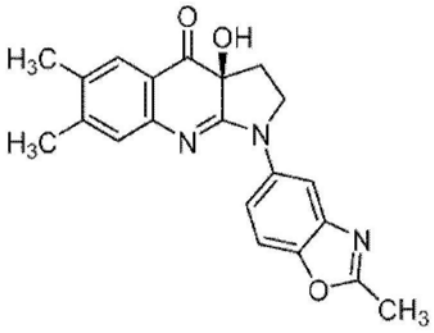
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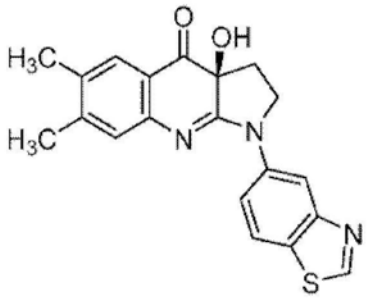
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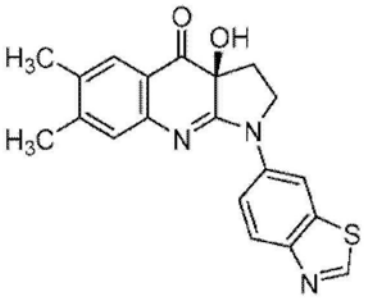


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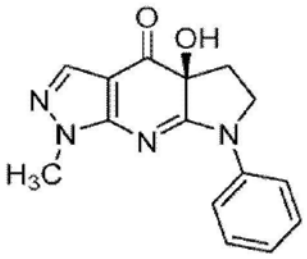


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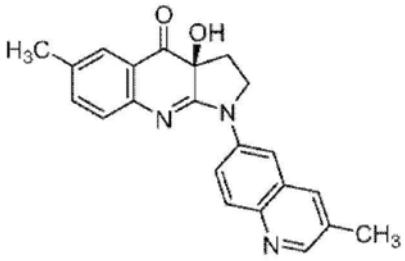




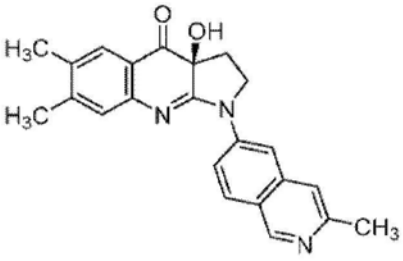
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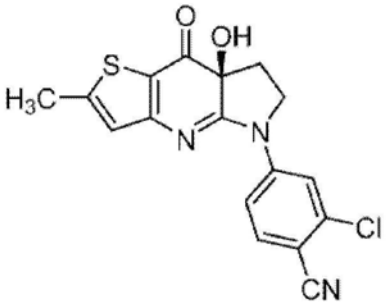
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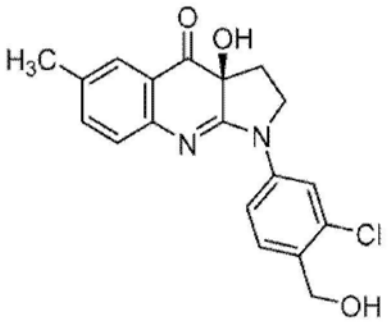
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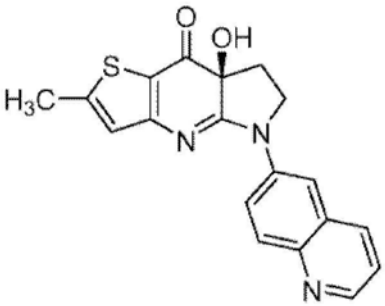
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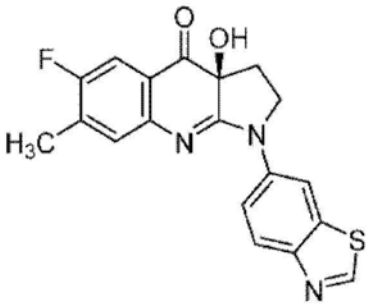
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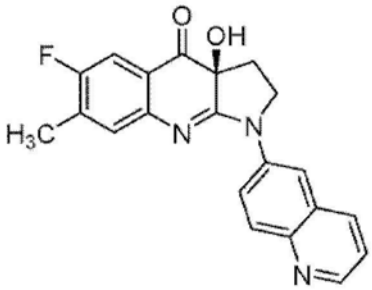
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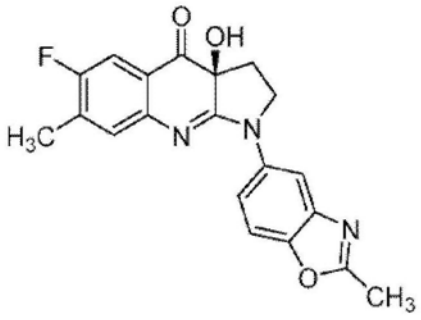


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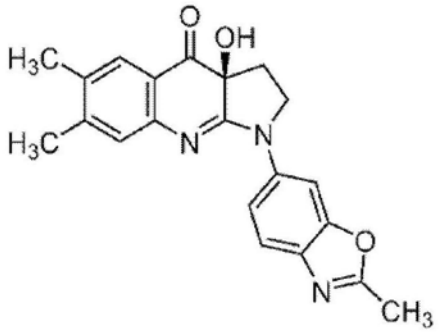
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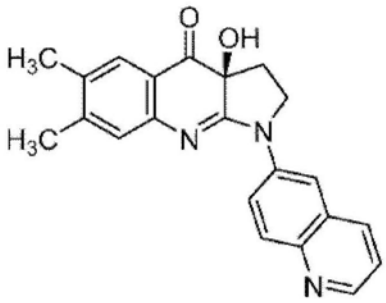




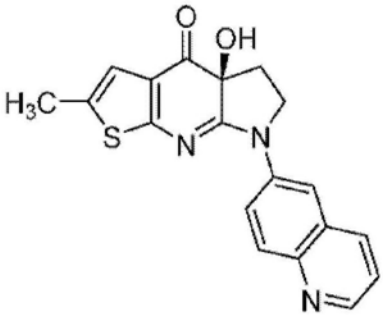
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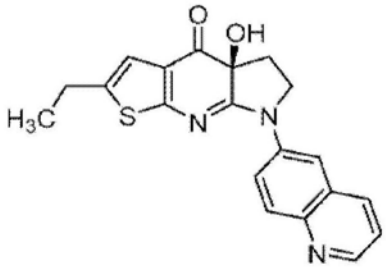
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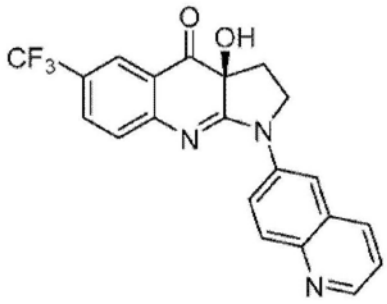
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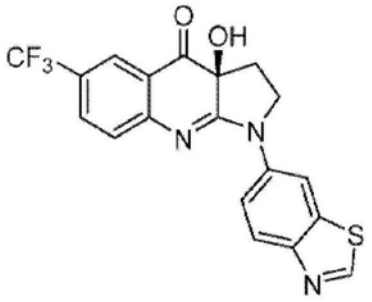
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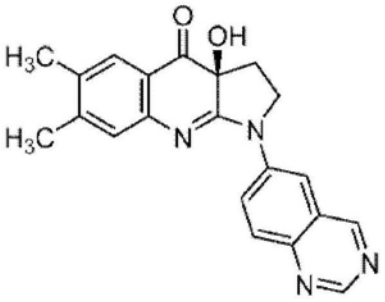
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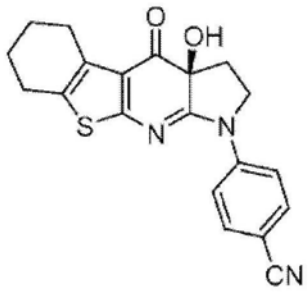
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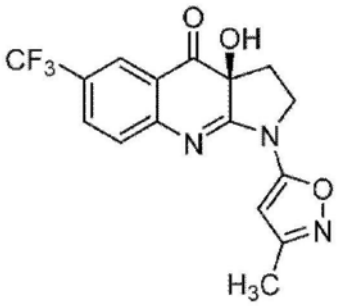
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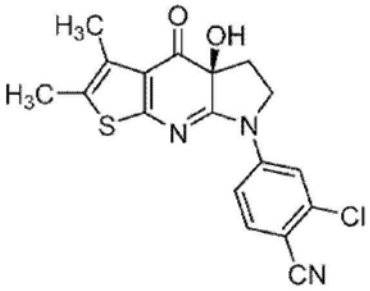
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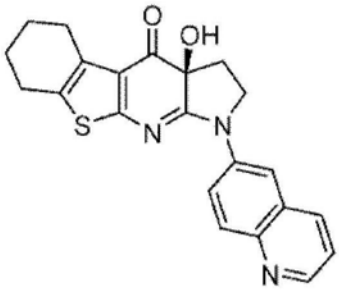
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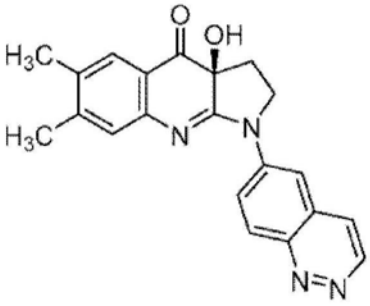
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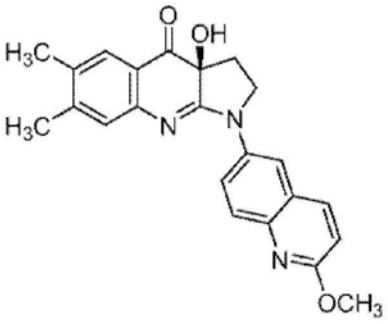
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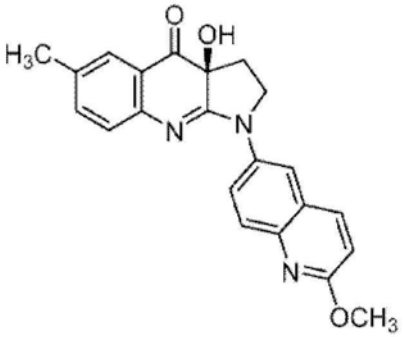
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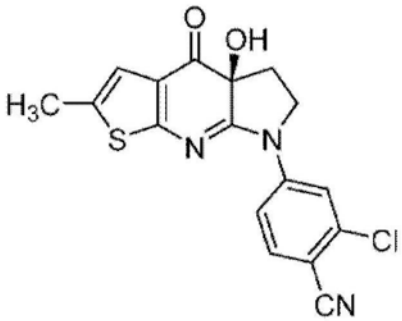
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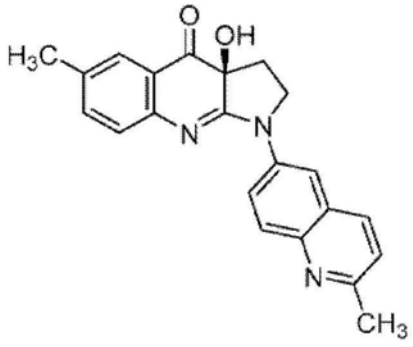
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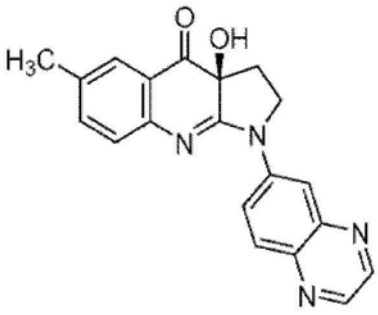
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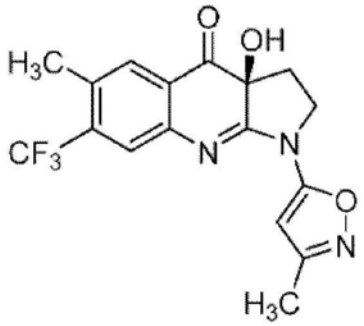
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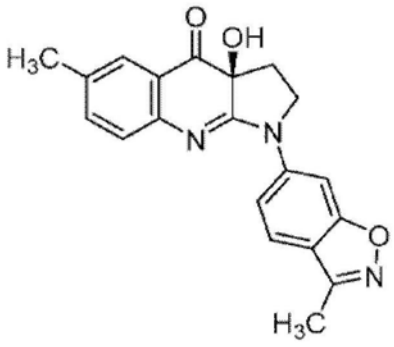
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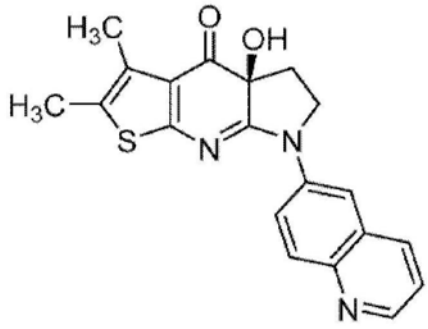
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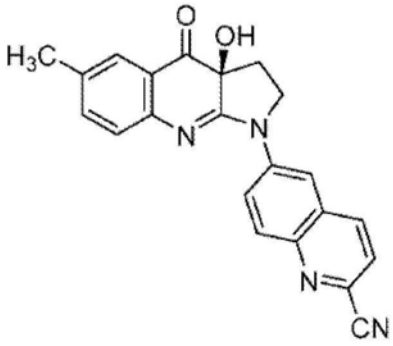
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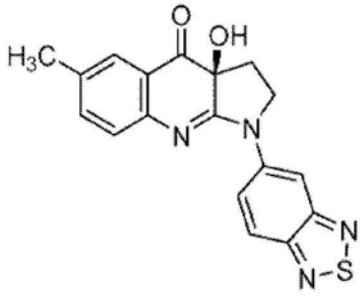
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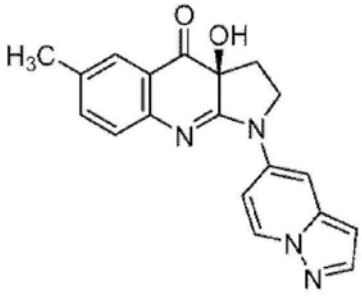


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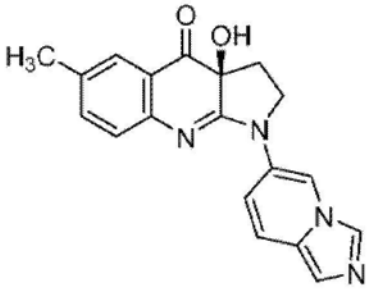


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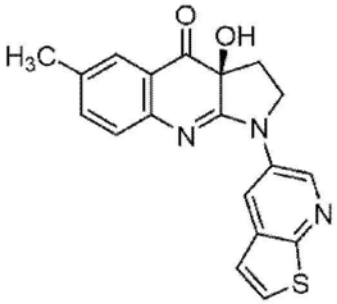




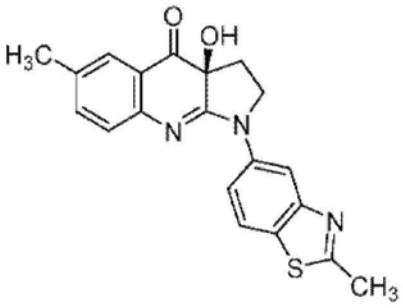
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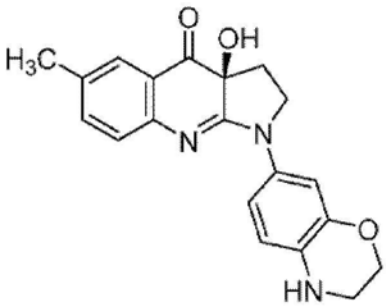
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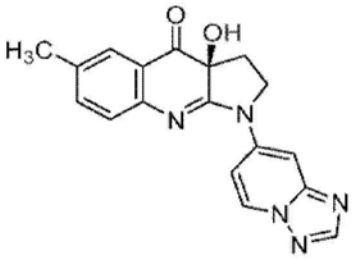


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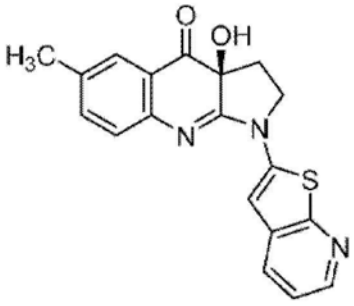


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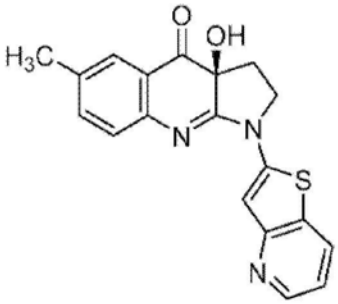
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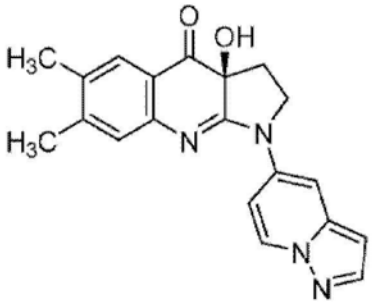


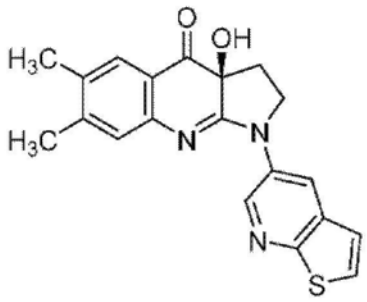
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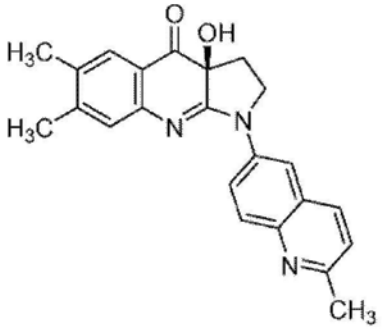
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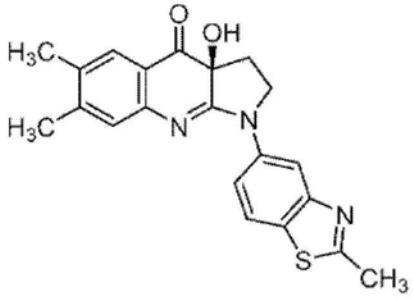




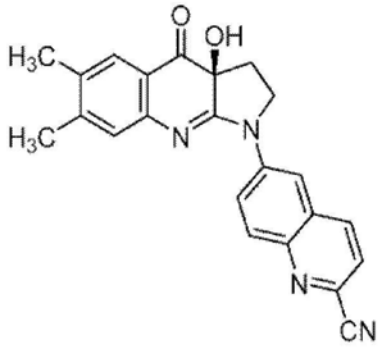
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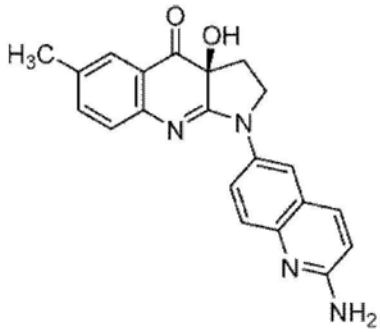
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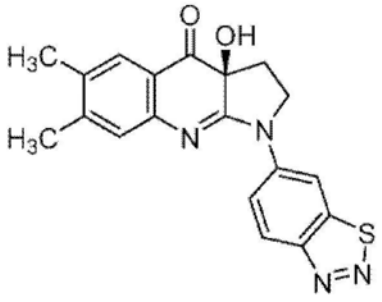
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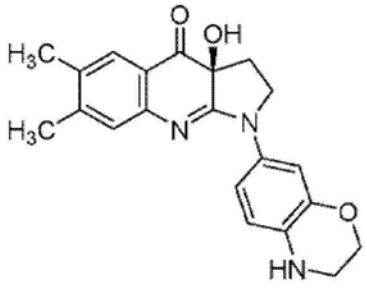
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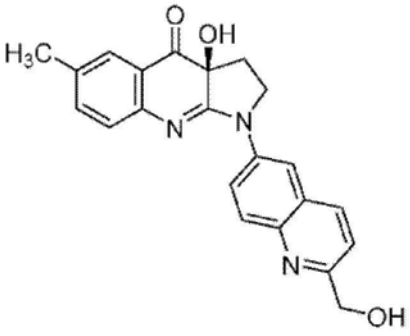
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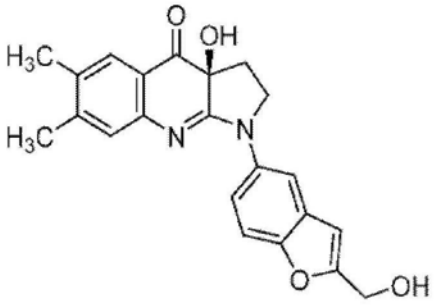
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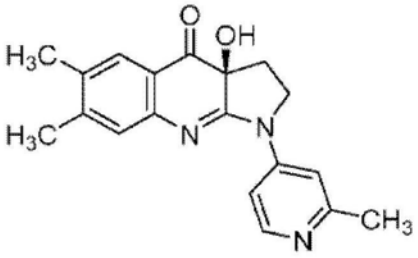
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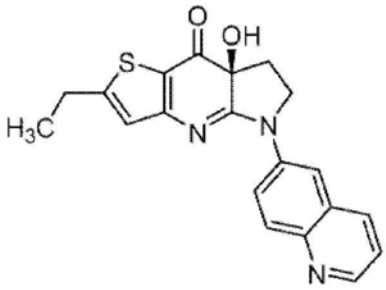
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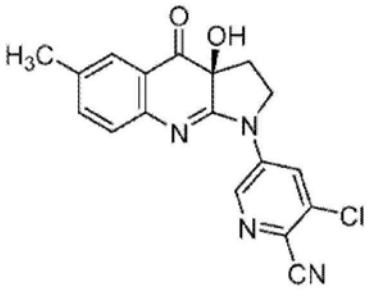
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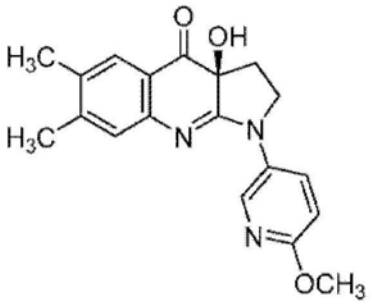
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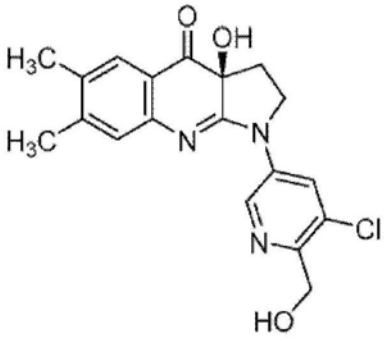
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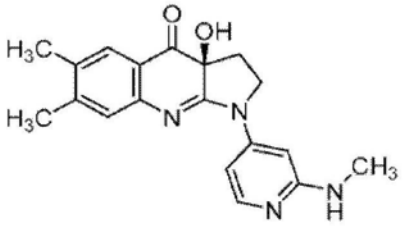
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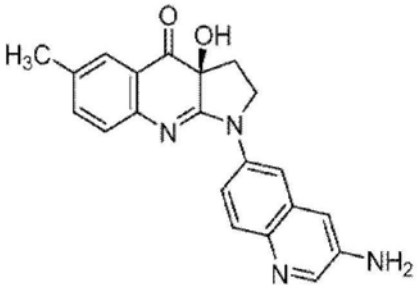
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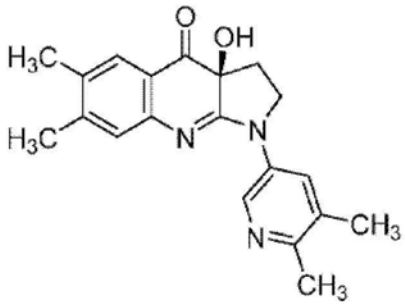
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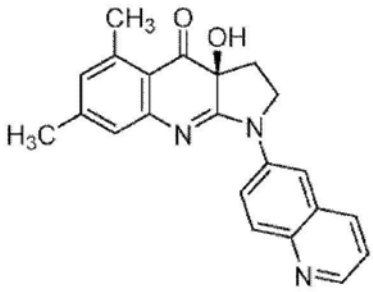
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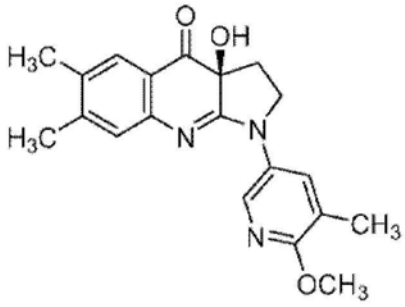
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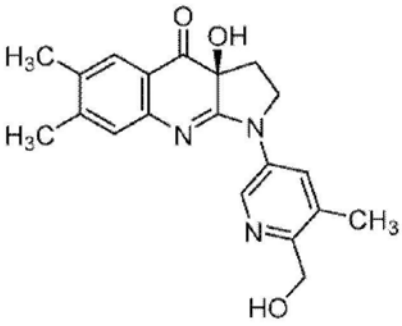
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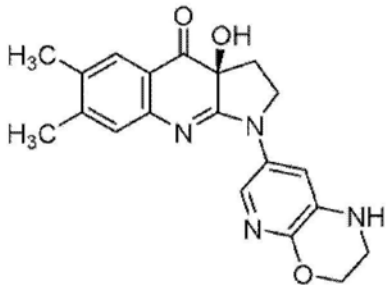
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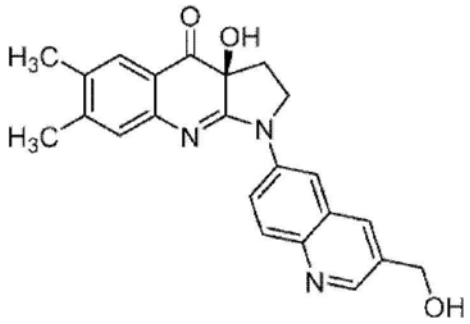
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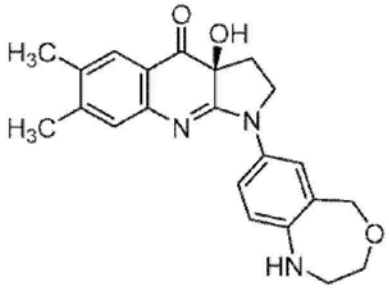
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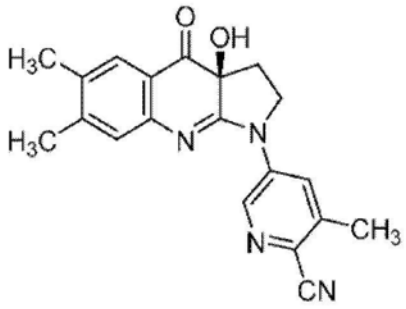
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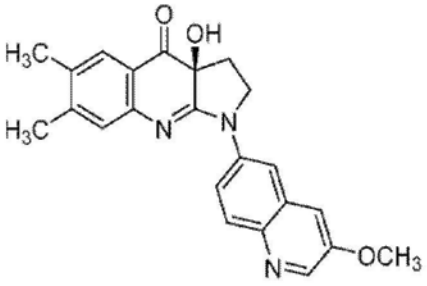
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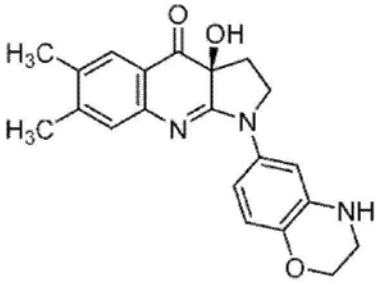
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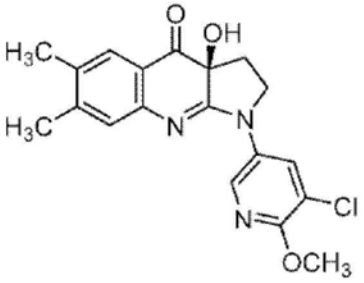
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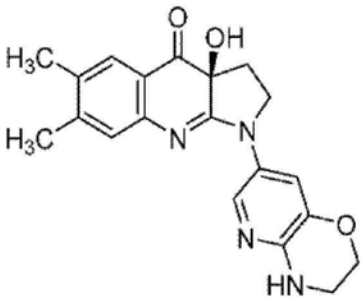
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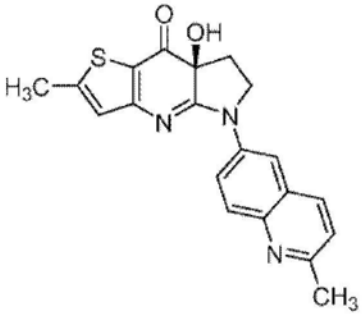
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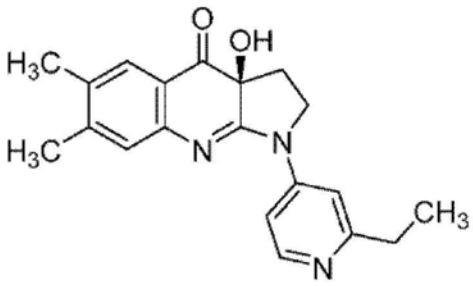
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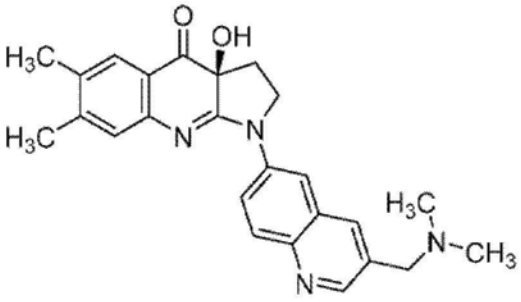
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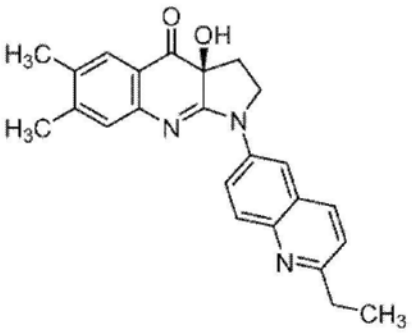
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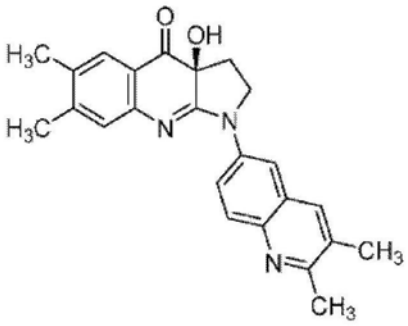
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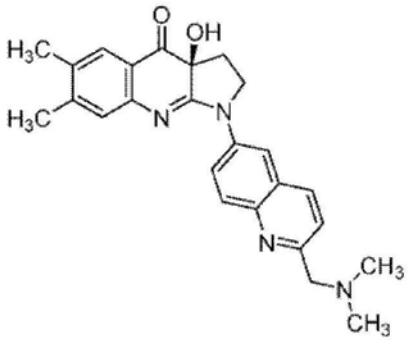
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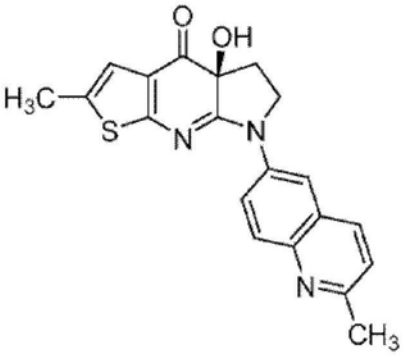
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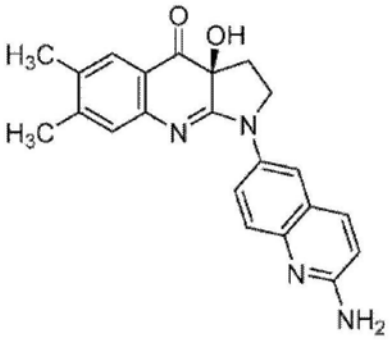
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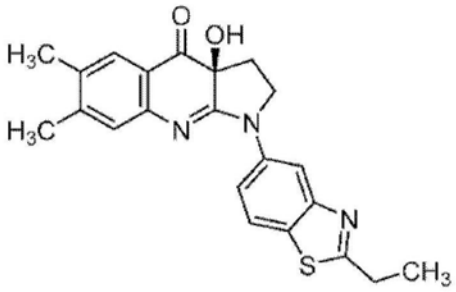
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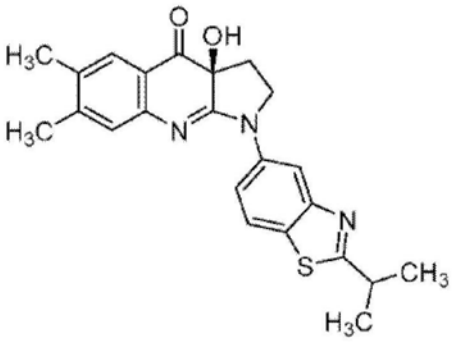
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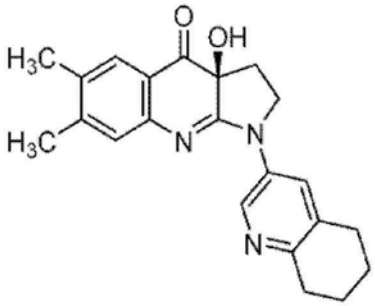
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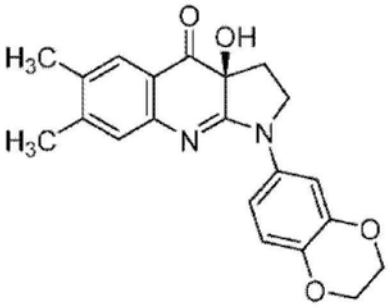


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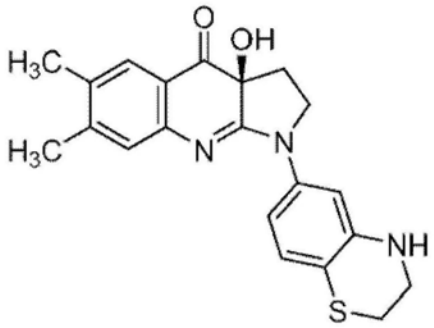


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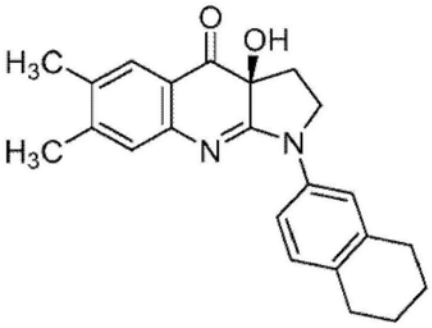




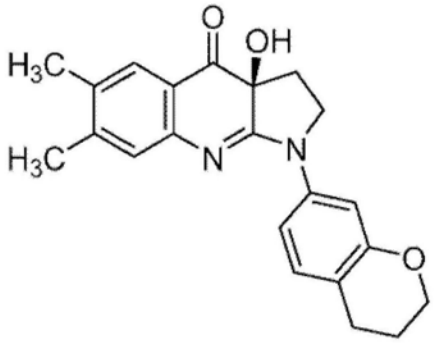
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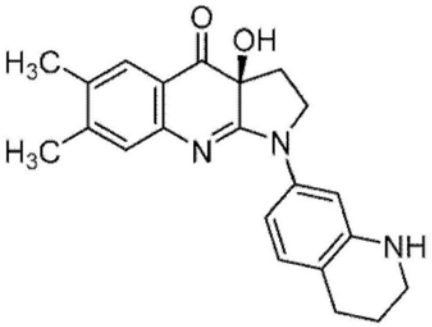
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BPN-0028922



BPN-0028923

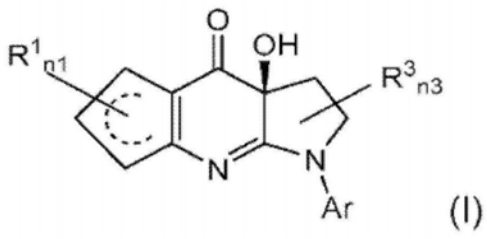


BPN-0028924

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10.抑制非肌肉肌球蛋白II的方法,其包括使所述非肌肉肌球蛋白II与有效量或浓度的式(I)化合物或其可药用盐接触:



(I)

其中

带有R^1的环是5元、6元或7元芳基或杂芳基环系统,其包含0、1或2个选自S、O、N和NR^1的杂原子;其中所述环可以与芳基、杂芳基、环烷基或杂环基环稠合;其中R^1可以设置在多环系统的任何一个或更多个环上;

R^1在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、氰基、硝基或卤素;n1=0、1、2或3;

Ar是单环或双环芳基或杂芳基环系统,其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代;

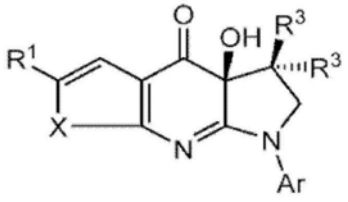
R^2在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、羟甲基、R_2NCH_2,其中R为H或烷基、氰基、硝基或卤素;

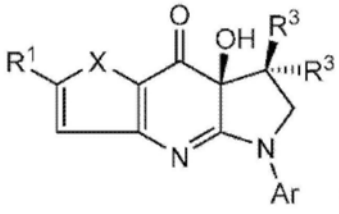
R^3在每次出现时独立地为(C1-C4)烷基、卤素或(C1-C4)卤代烷基;n3=0、1、2、3或4;

前提是所述化合物不是布雷他汀。

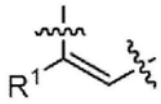
11.权利要求10所述的方法，其中对于式(I)化合物，所述带有R^1的环为苯基、吡啶基或噻吩基。

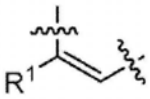
12.权利要求10所述的方法，其中式(I)化合物为式(IIa)或(IIb)或者其可药用盐：


(IIa)


(IIb)

其中

X是S，或者X是式  的基团，其中波浪线表示键合点；

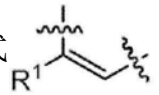
R^1在每次出现时独立地为H、(C1-C4)烷基、CF_3或卤素；前提是当X是式  的基团且Ar是未经取代的苯基时，至少一个R^1基团不为H或(C1-C4)烷基；

Ar是芳基或杂芳基，其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代；

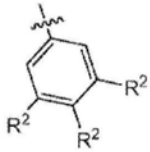
R^2在每次出现时独立地为卤素、氰基、硝基、CF_3、(C1-C4)烷基或(C1-C4)烷氧基；

R^3在每次出现时独立地为H或CH_3。

13.权利要求12所述的方法，其中X是S。

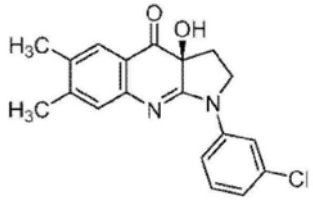
14.权利要求12所述的方法，其中X是式  的基团，其中波浪线表示键合点。

15.权利要求14所述的方法，其中式(I)的至少一个R^1基团是甲基、卤素或CF_3。

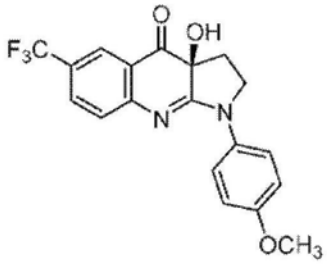
16.权利要求10所述的方法，其中Ar是式  的基团，其中波浪线表示键合点。

17.权利要求10所述的方法，其中Ar是吡唑基、噻吩基、异喹啉基、苯并噁唑基、喹唑啉基、异噁唑基、噌啉基、喹喔啉基、苯并异噁唑基、苯并噻二唑基、吡唑并吡啶基、咪唑并吡啶基、噻吩并吡啶基、二氢苯并噁嗪基、三唑并吡啶基、二氢吡啶并噁嗪基、四氢苯并氧氮杂䓬基、二氢苯并二氧杂芑基、二氢苯并噻嗪基、四氢喹啉基、四氢萘基或苯并二氢吡喃基环系统，其中的任一者均可以是未经取代的或者被1、2或3个R^2取代。

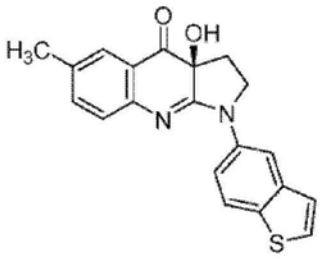
18.权利要求10所述的方法，其中所述化合物是以下的任一个或其可药用盐：



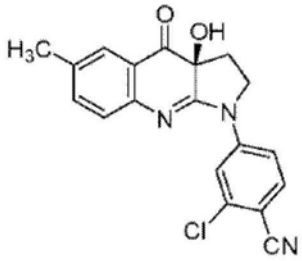
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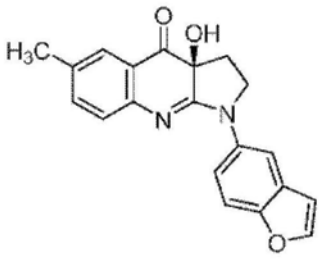
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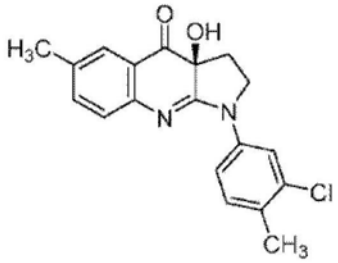
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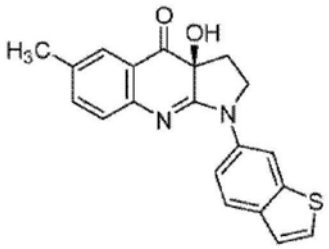
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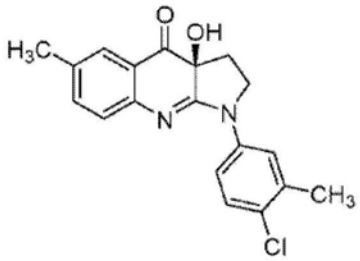
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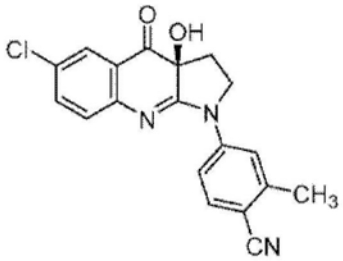
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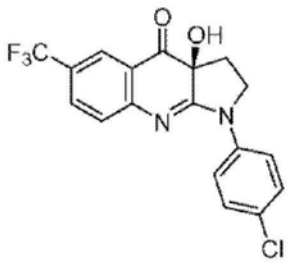
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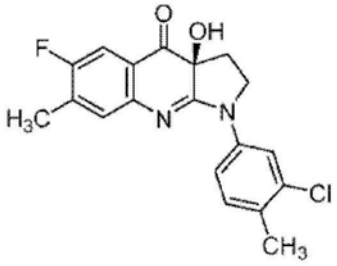
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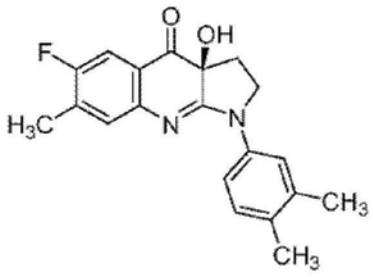
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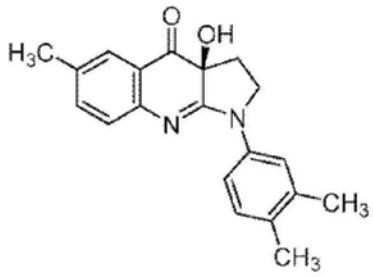
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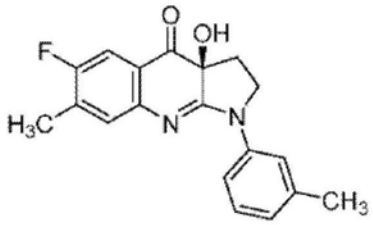
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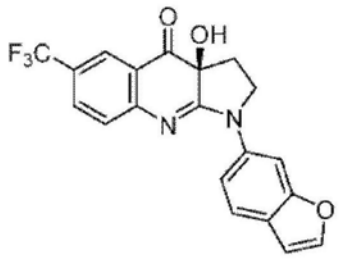
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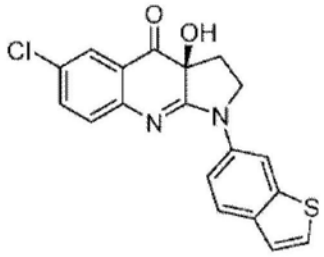
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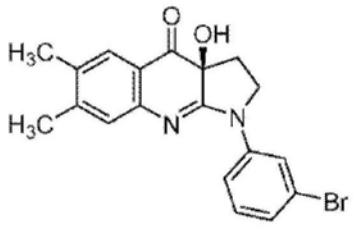
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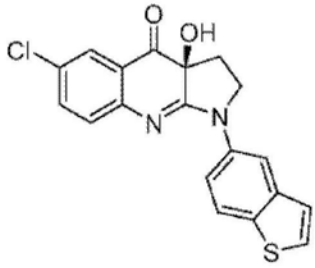
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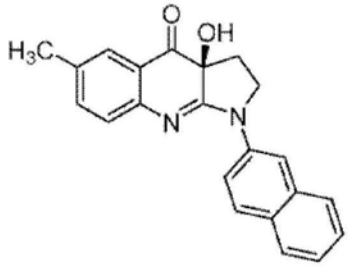
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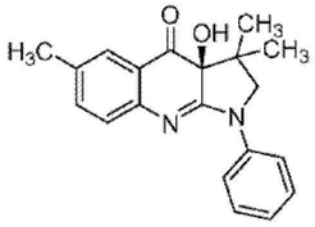
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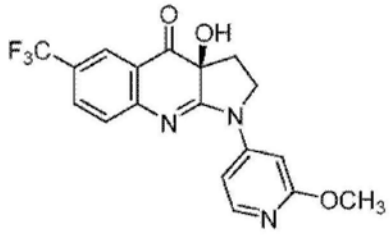
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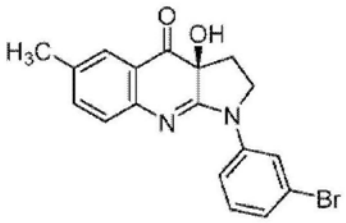
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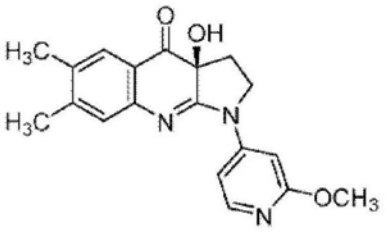
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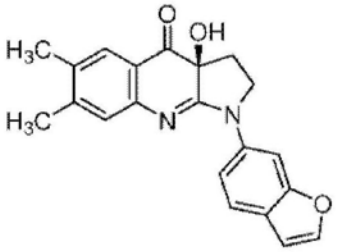
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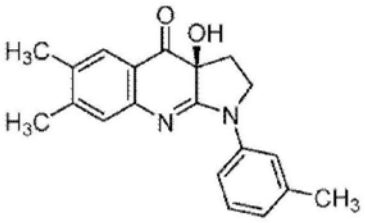
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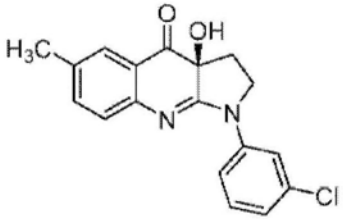
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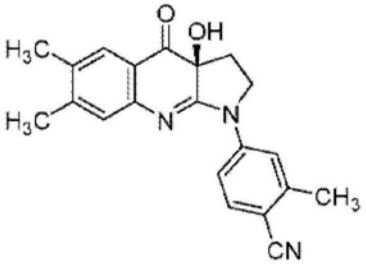
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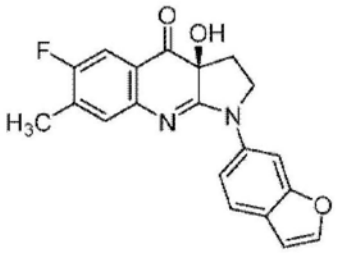
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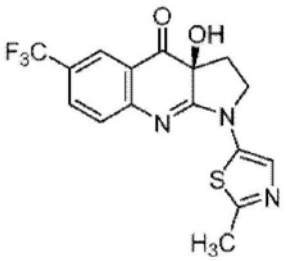
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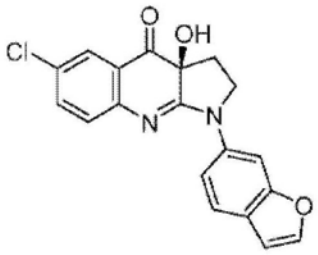
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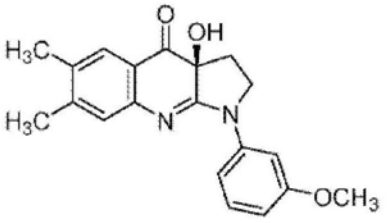
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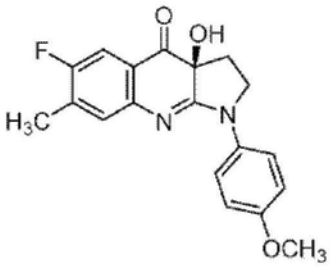
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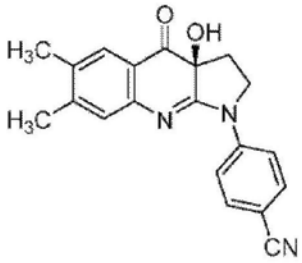
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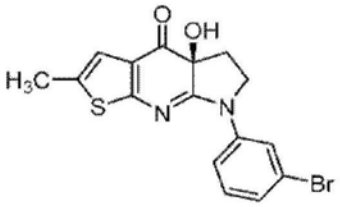
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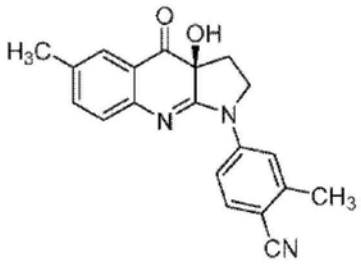
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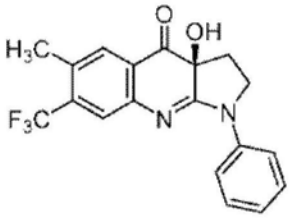
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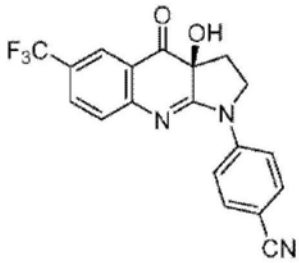
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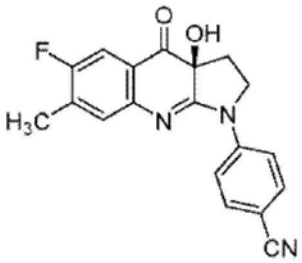
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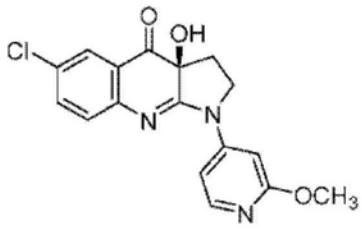
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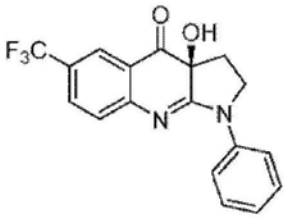
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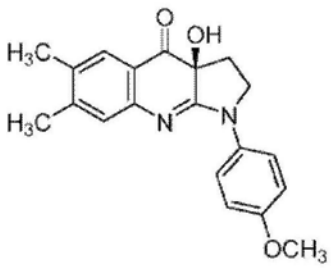
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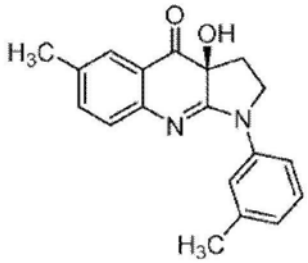
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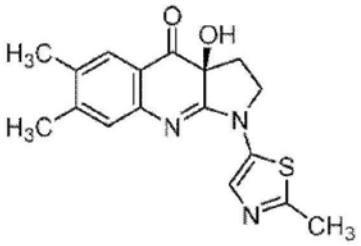
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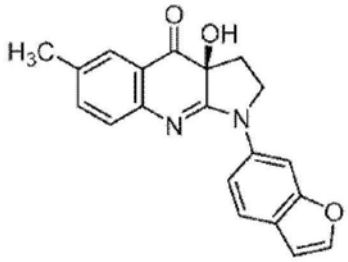
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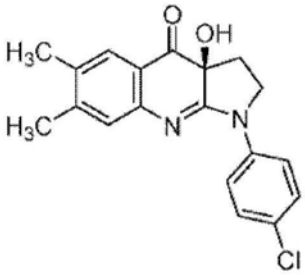
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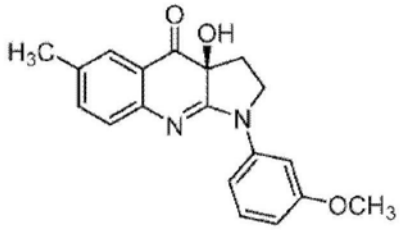
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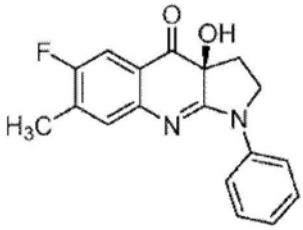
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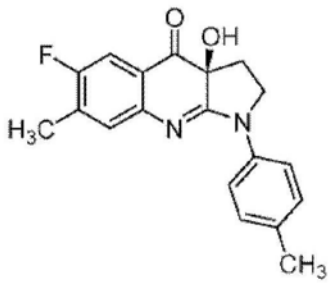
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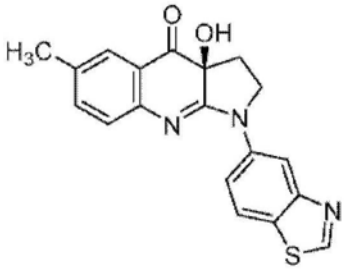
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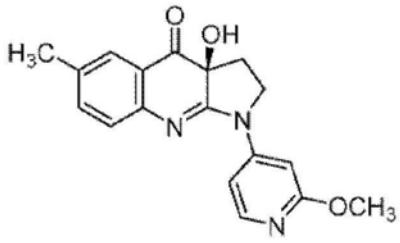
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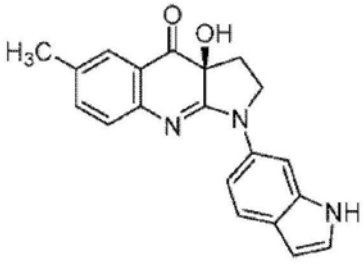
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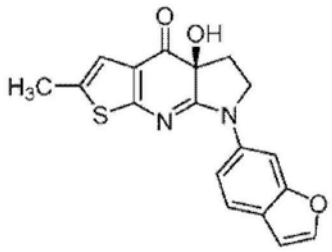
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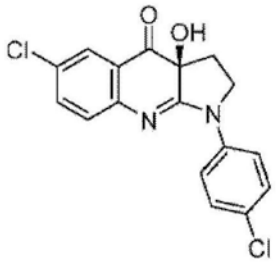
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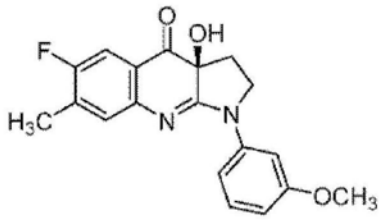
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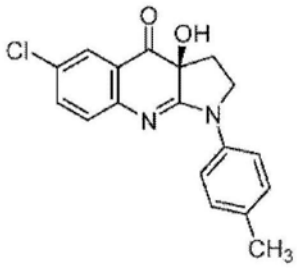
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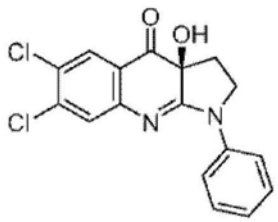
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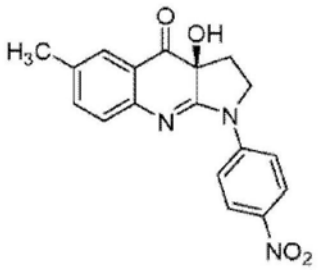
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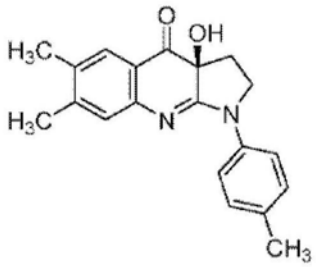
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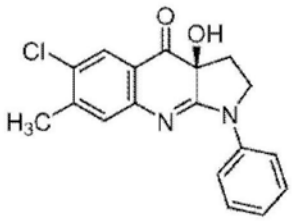
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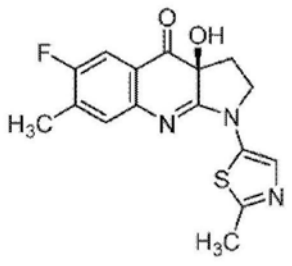
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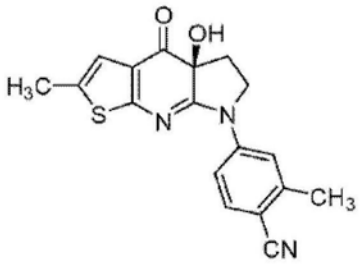


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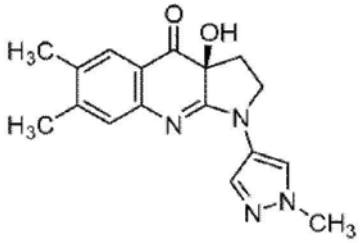


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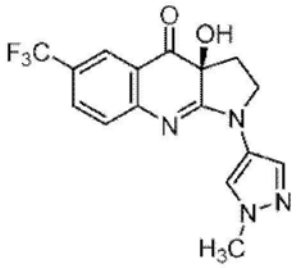




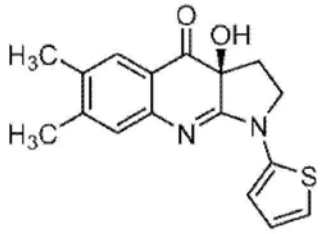
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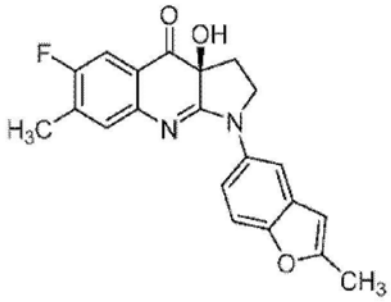
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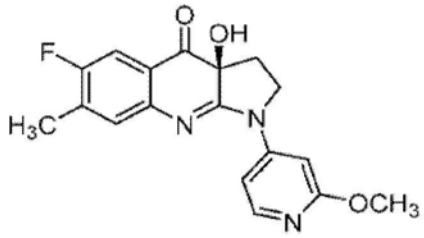
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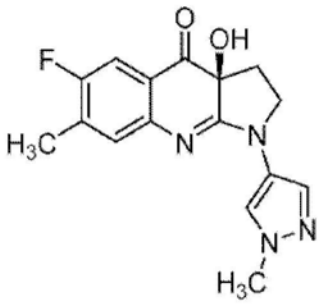
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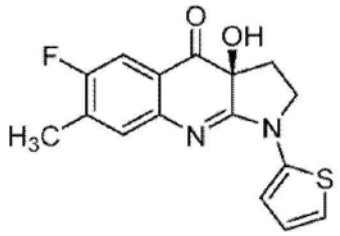
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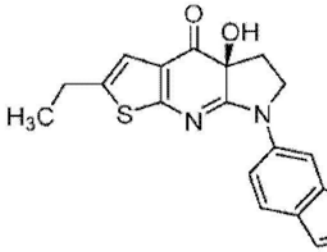
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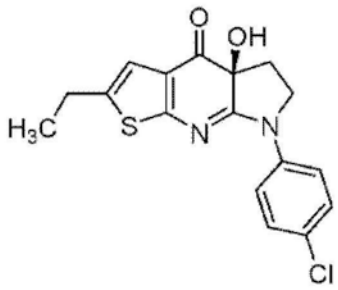


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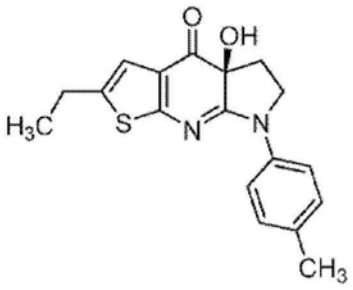


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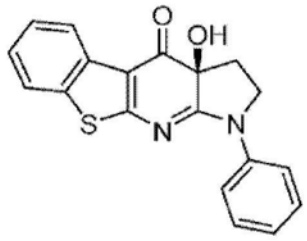
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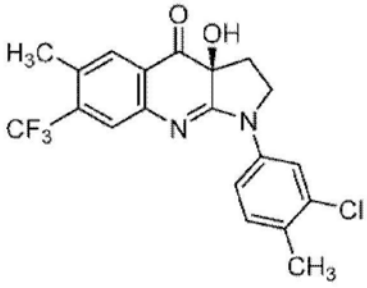
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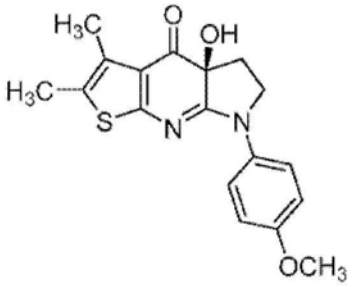
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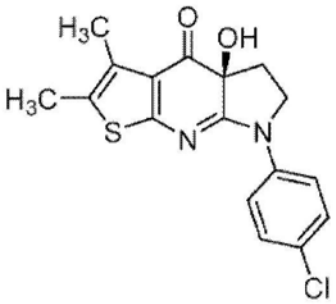
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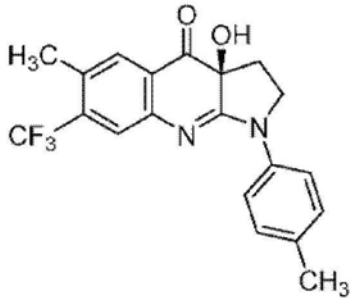
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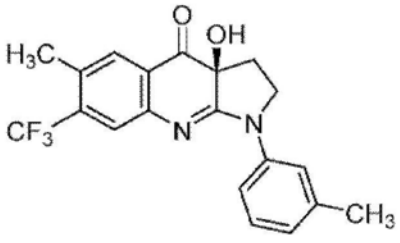
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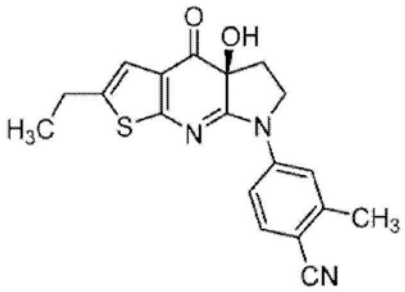
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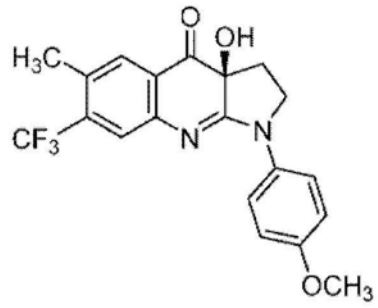
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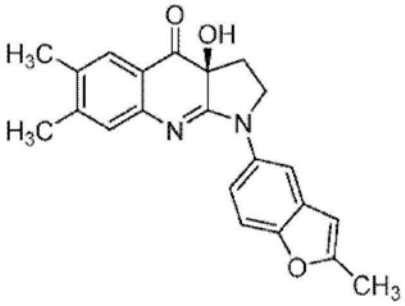
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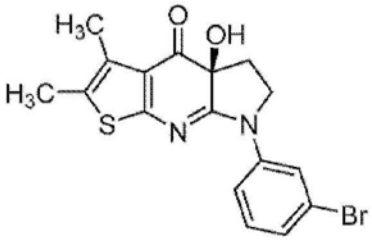
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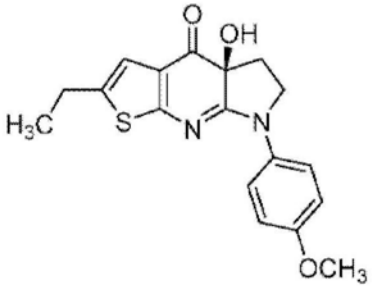
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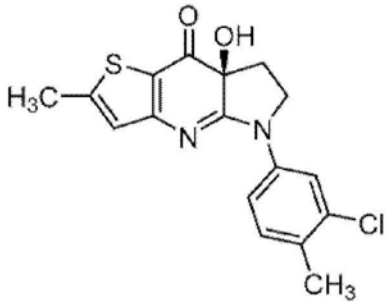
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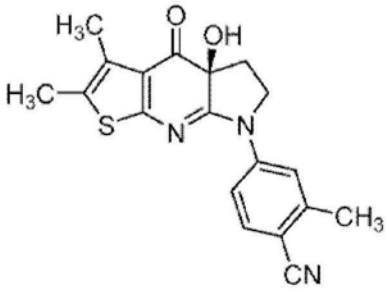
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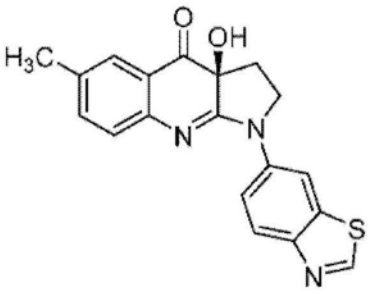
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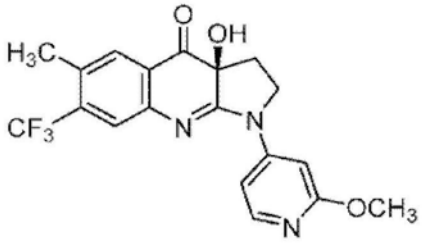
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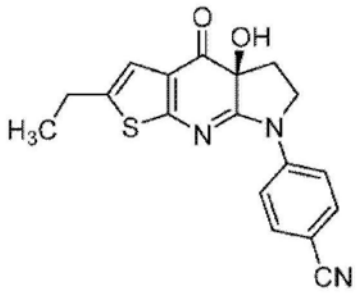
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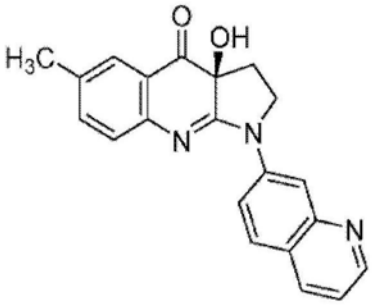
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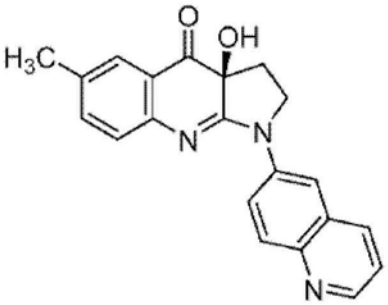
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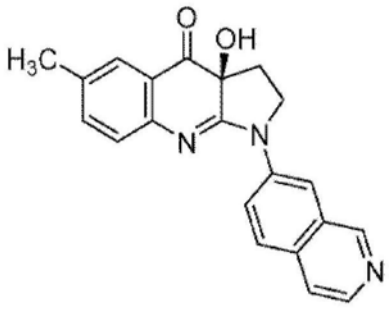
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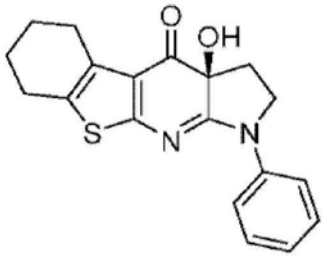
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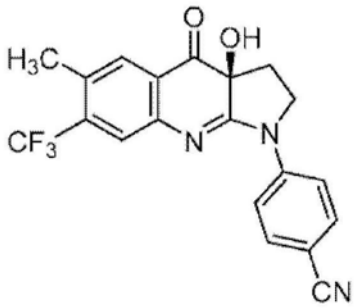
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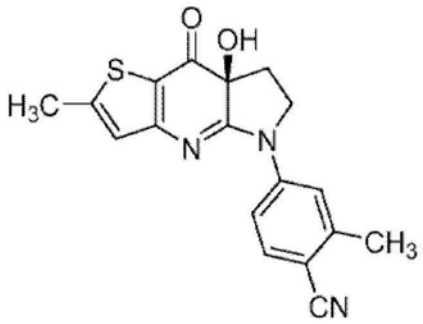
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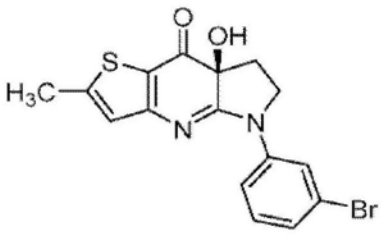
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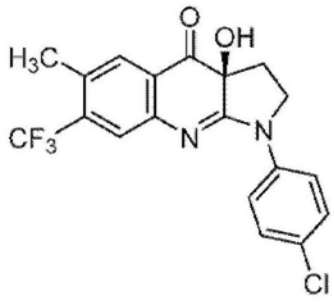
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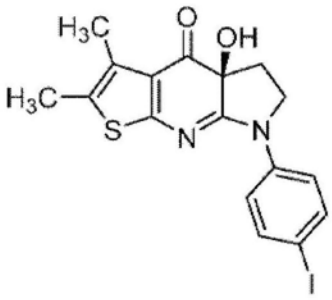
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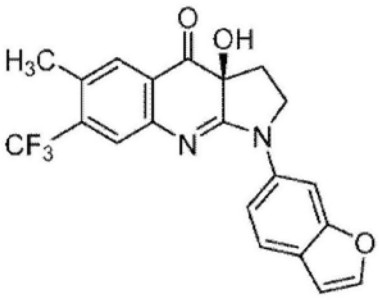
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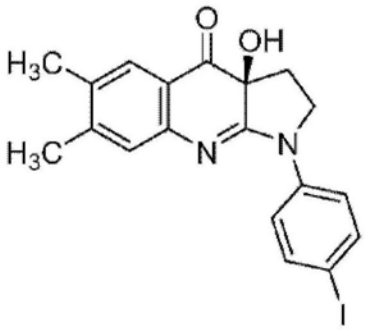
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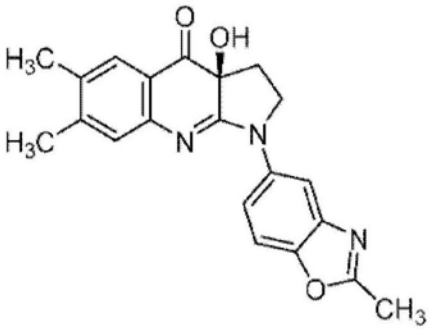
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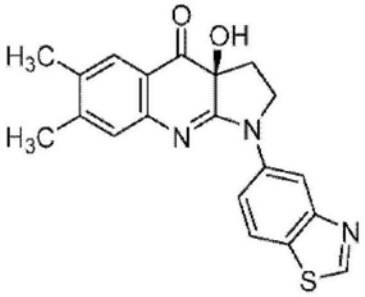
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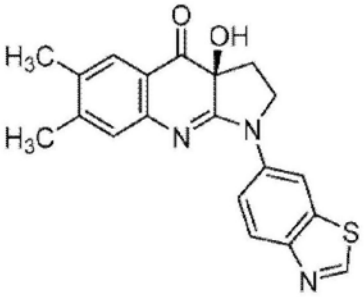


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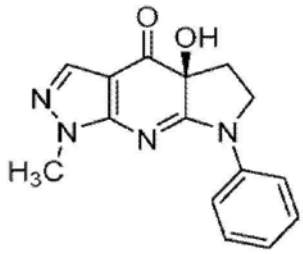


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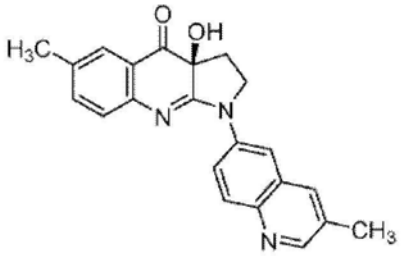




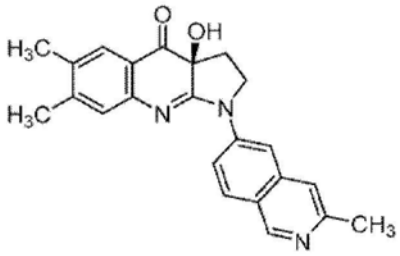
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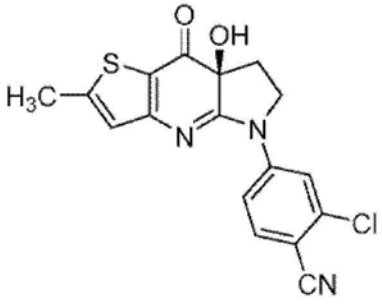
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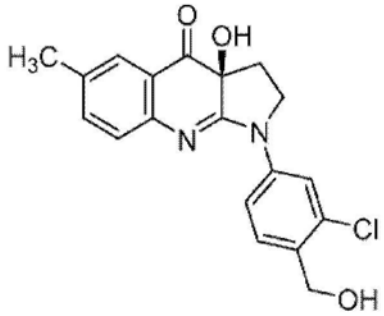
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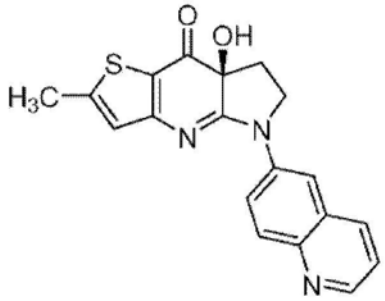
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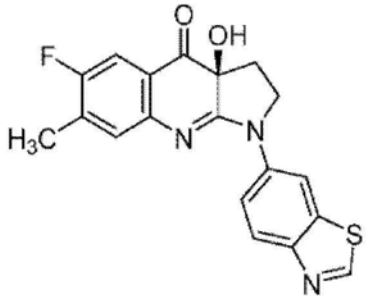
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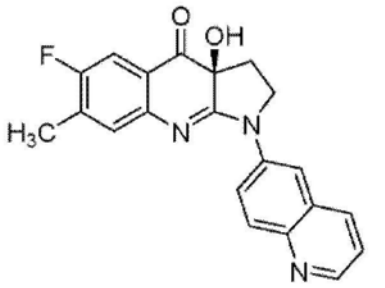
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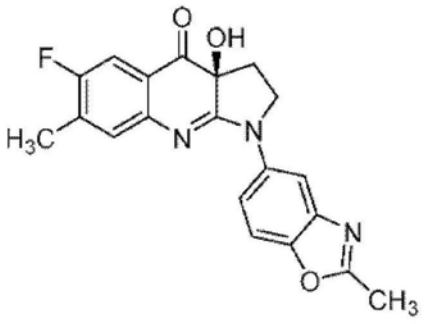


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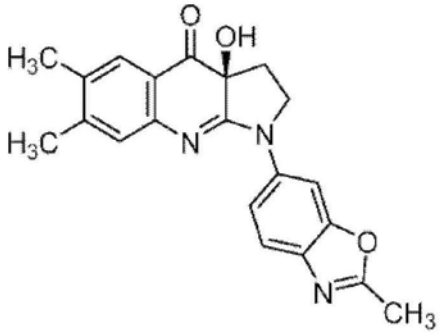
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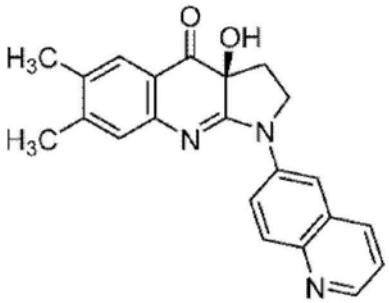




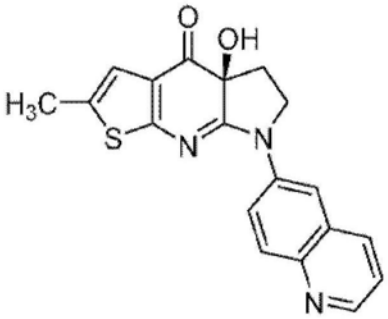
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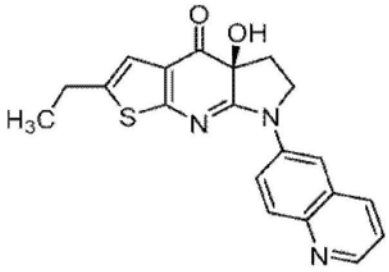
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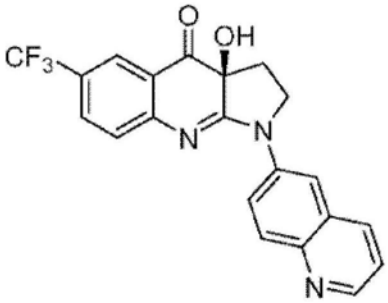
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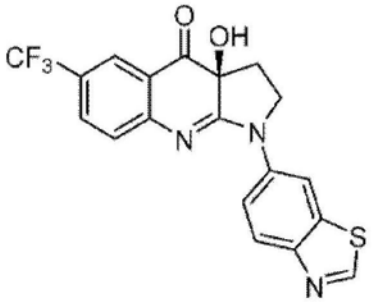
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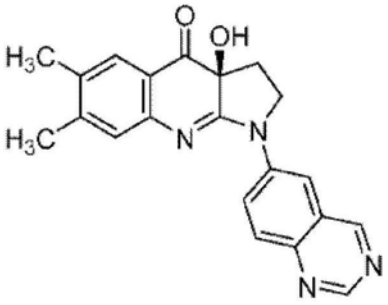
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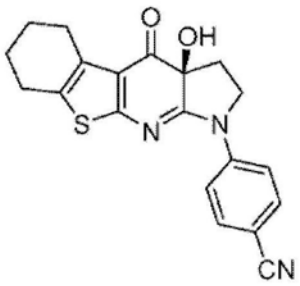
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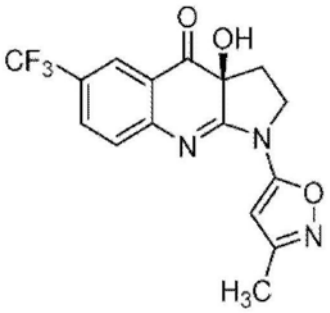
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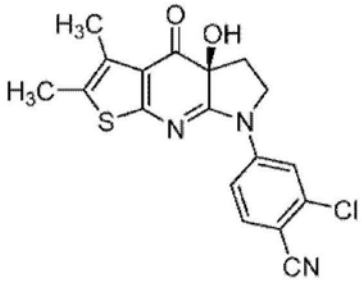
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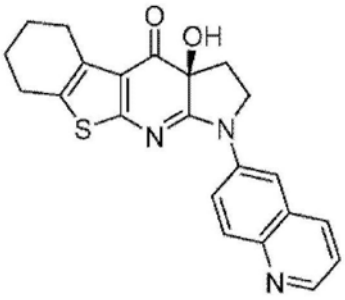
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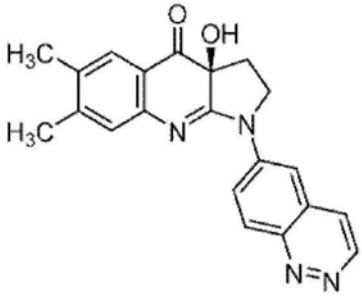
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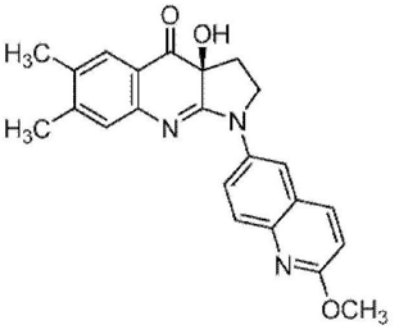
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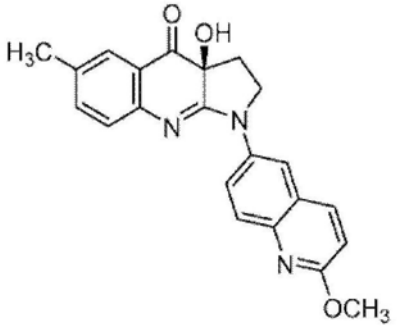
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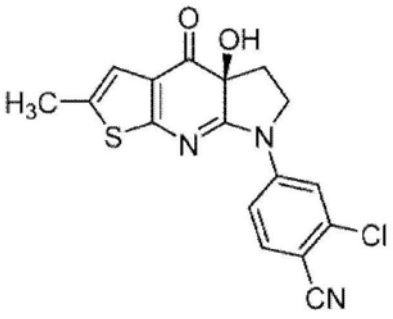
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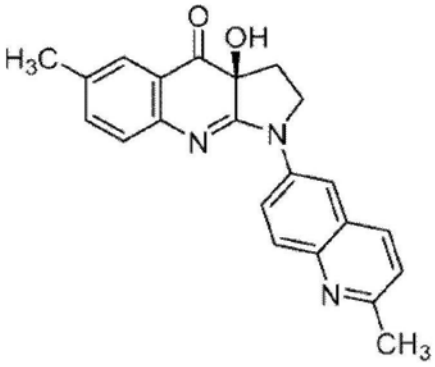
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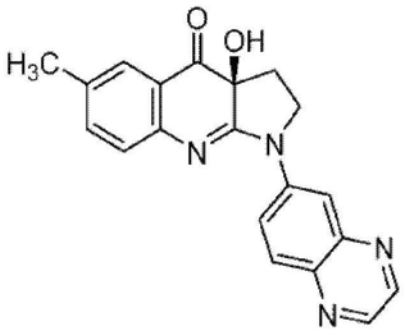
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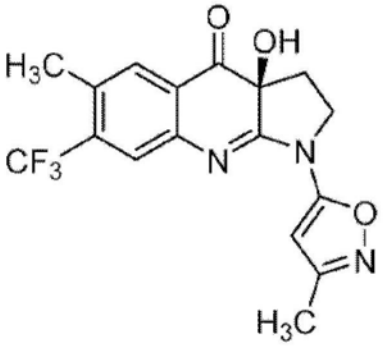
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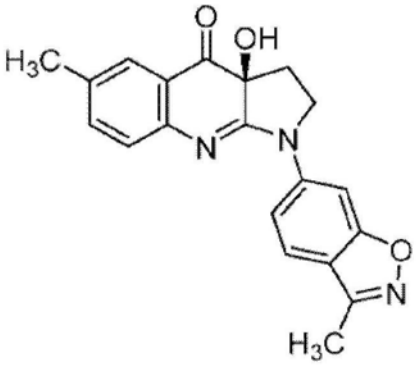
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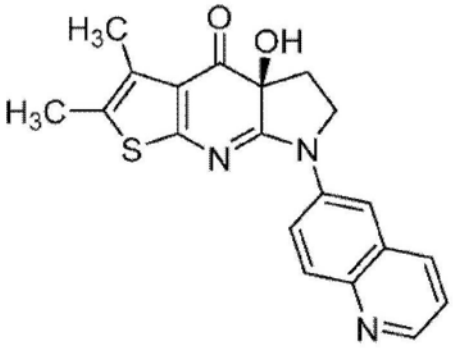
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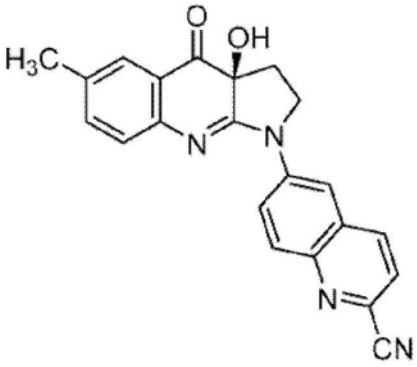
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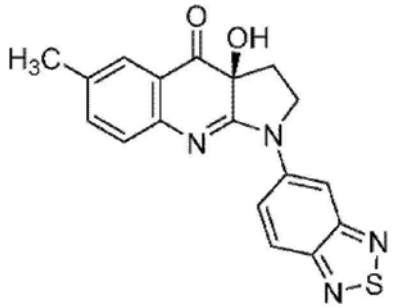
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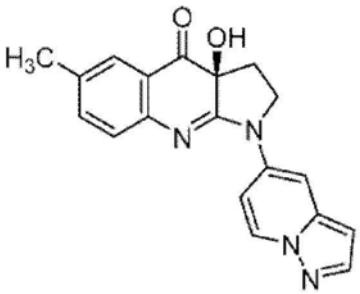
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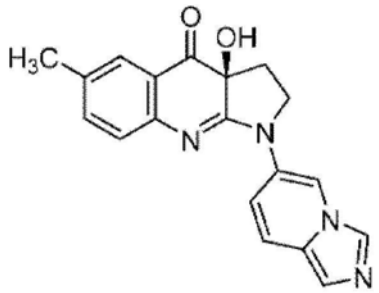
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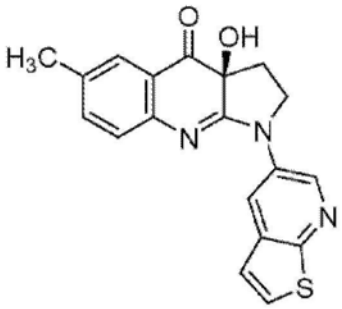
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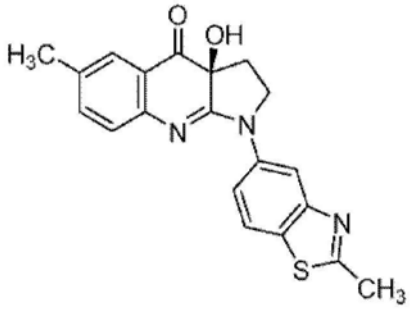
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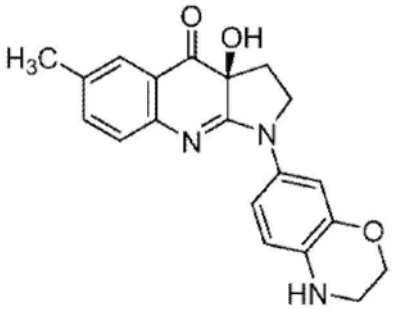
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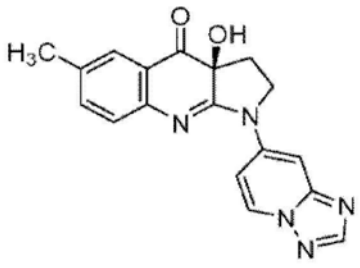
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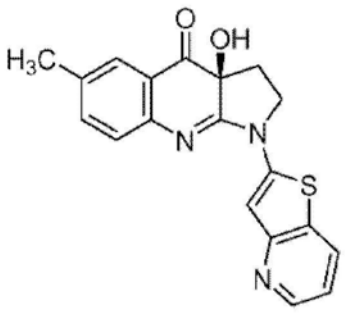
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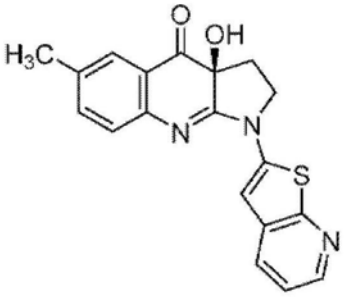
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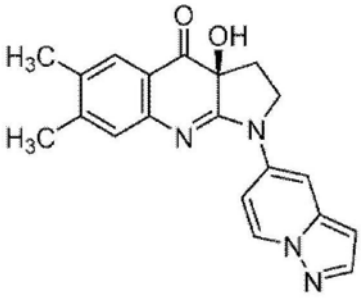
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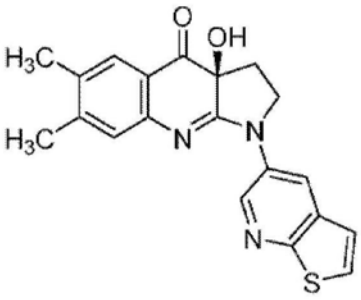
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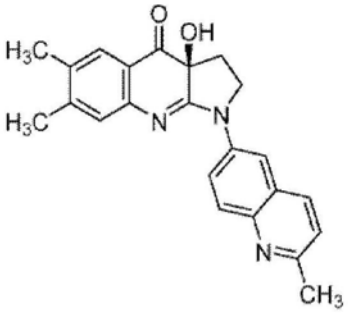
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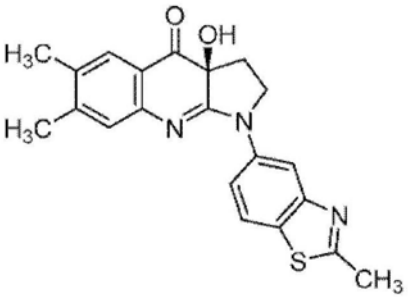
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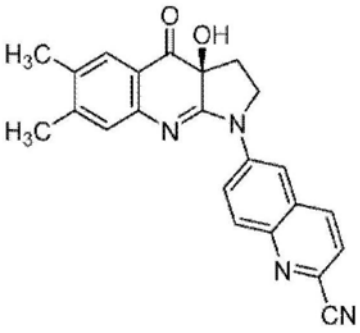
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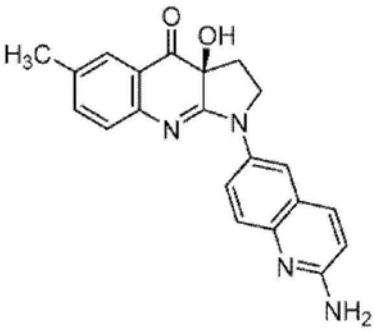
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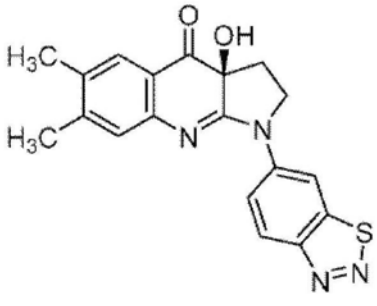
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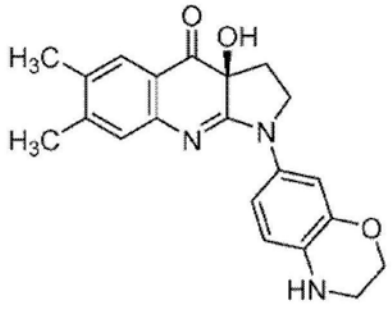
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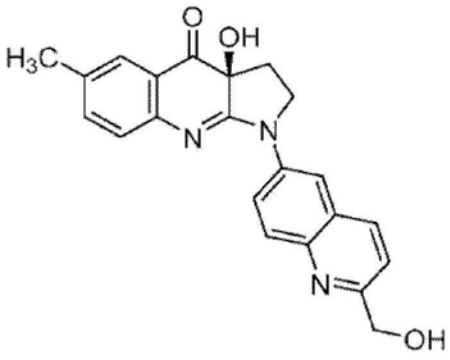
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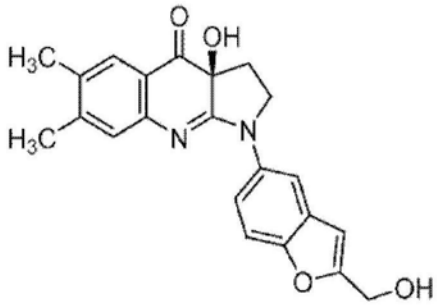
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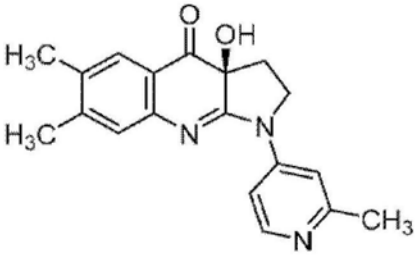
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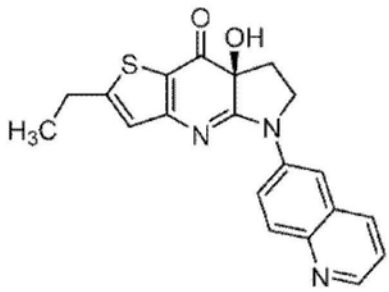
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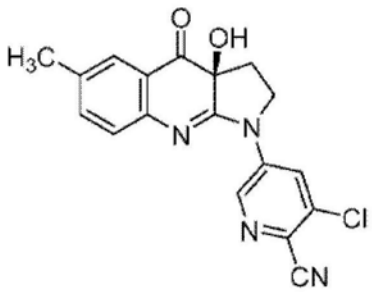
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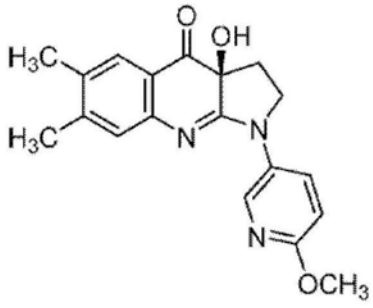
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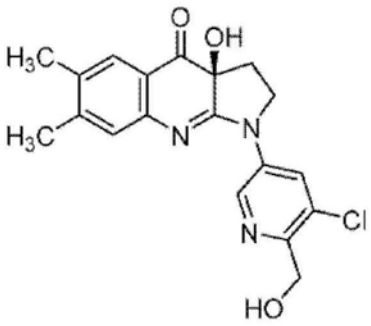
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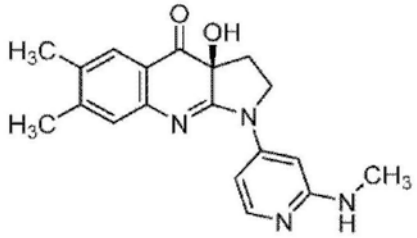
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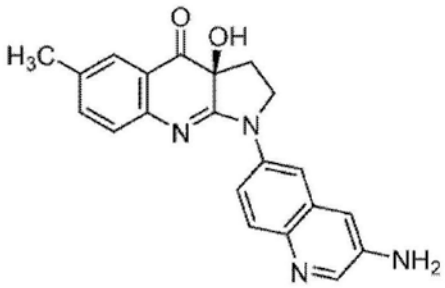
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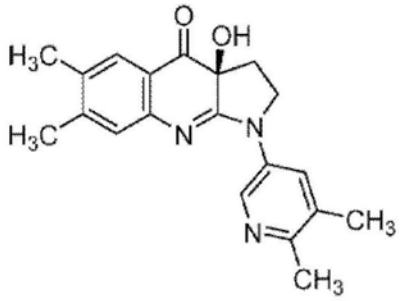
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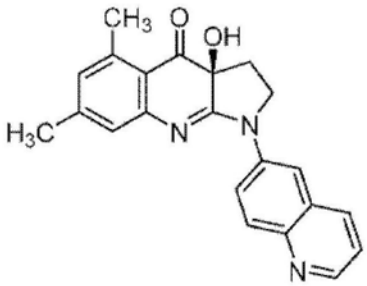
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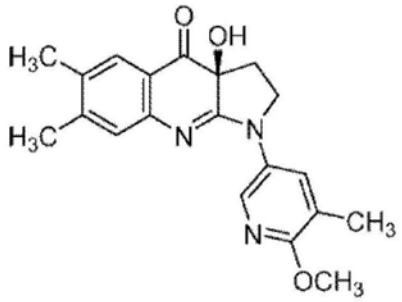
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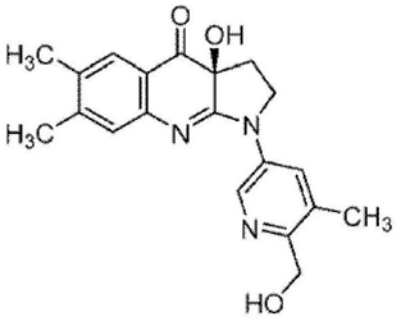
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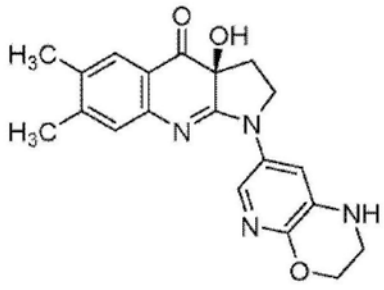
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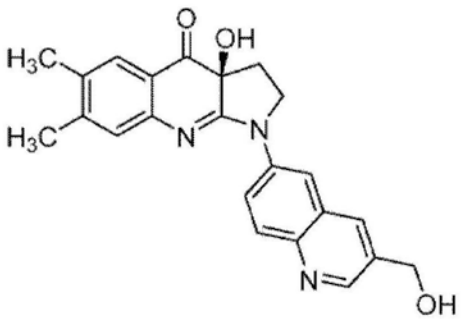
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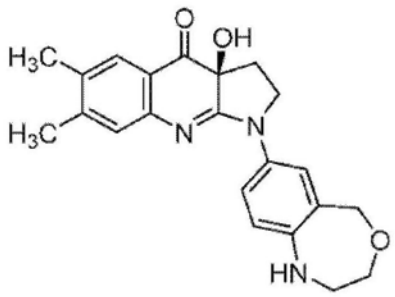
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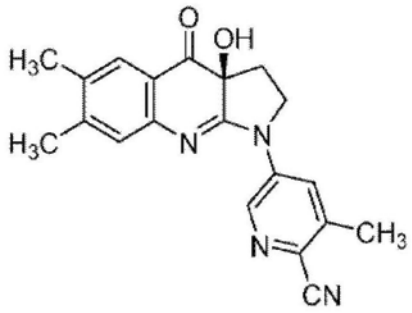
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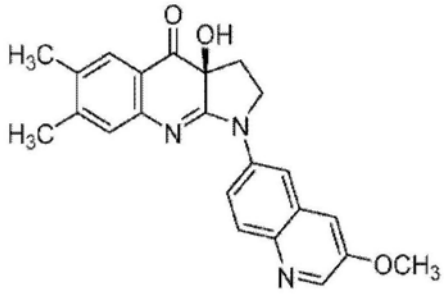
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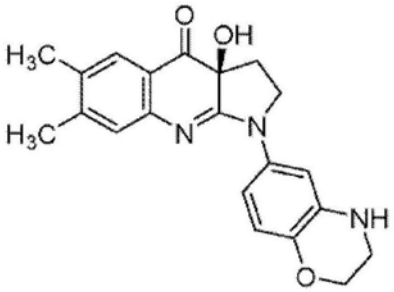
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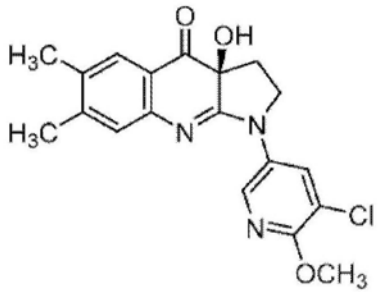
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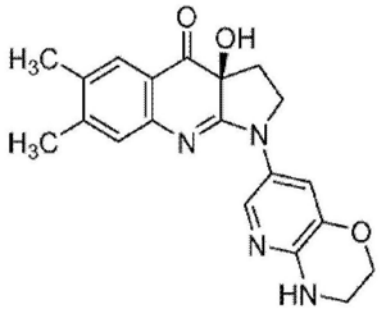
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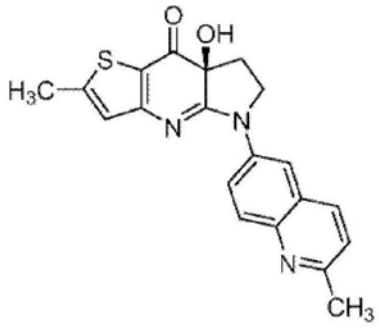
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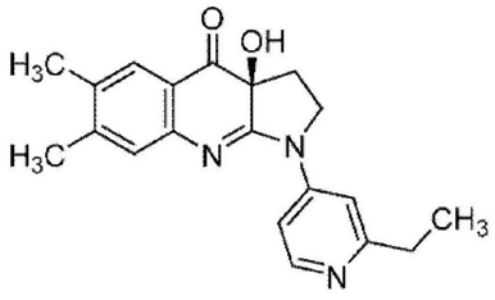
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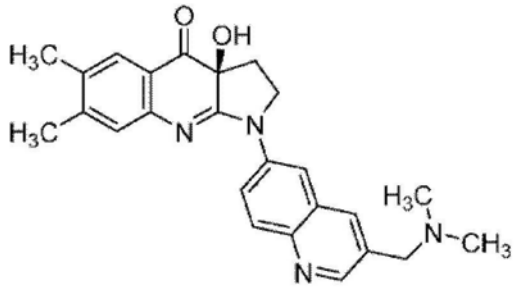
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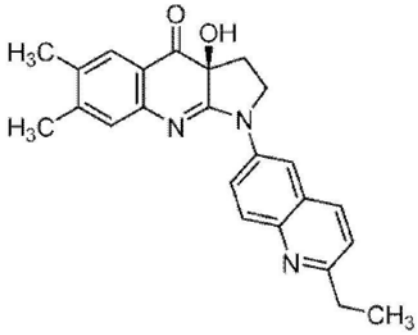
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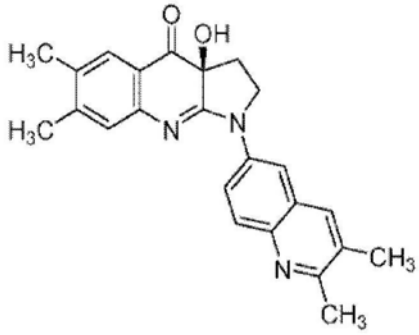
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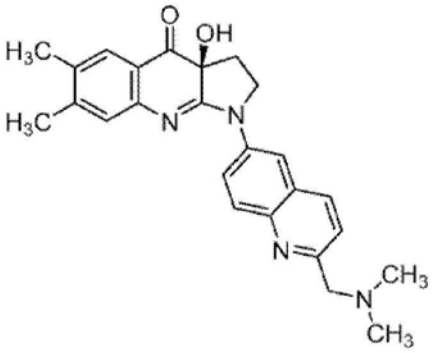
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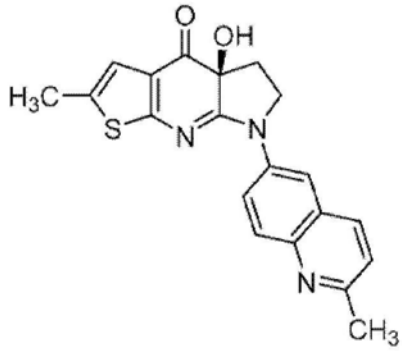
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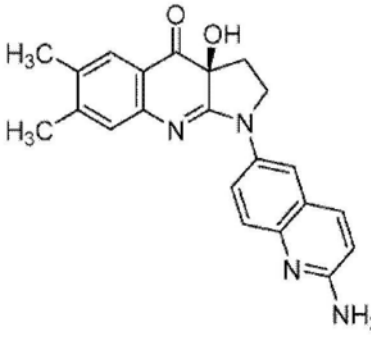
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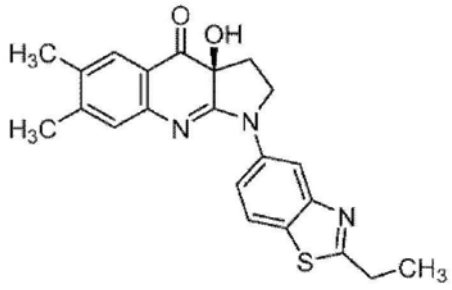
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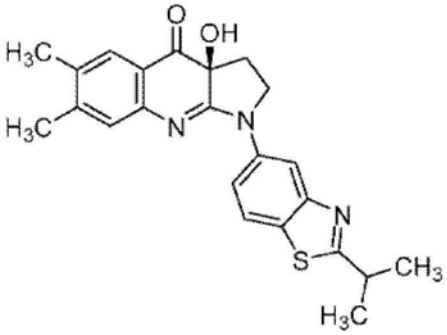


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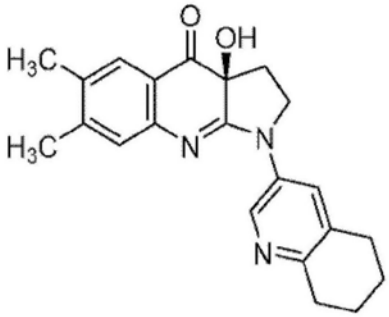


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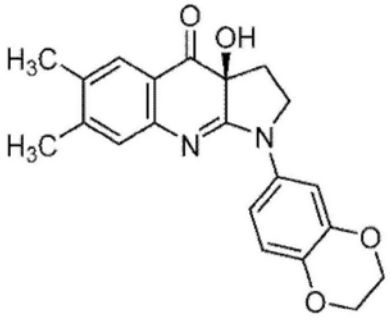




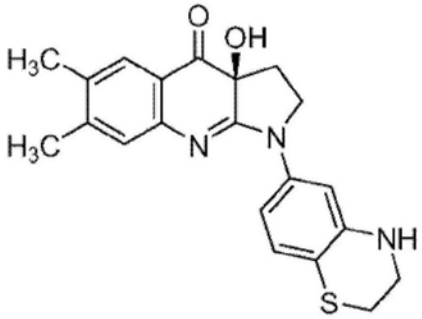
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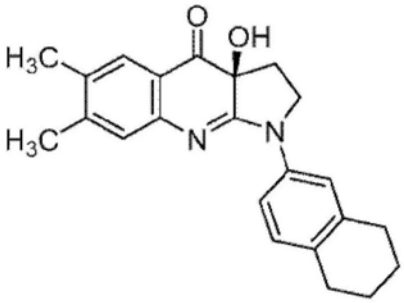
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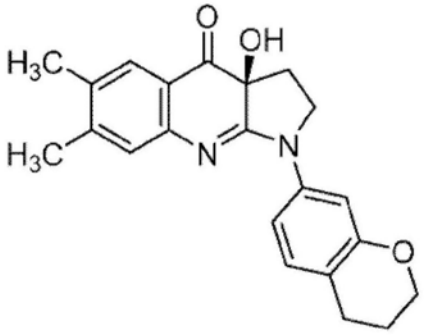
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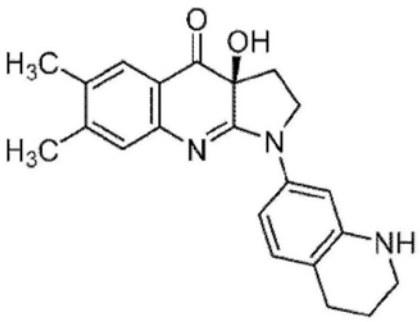
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BPN-0028922



BPN-0028923



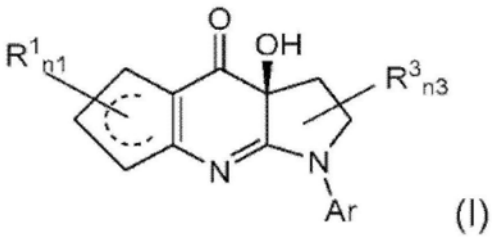
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19.权利要求10所述的方法,其中所述化合物在摩尔基础上相对于来源于心肌的肌球蛋白II在抑制非肌肉肌球蛋白II中更有效。

20.包括调节肌球蛋白II ATP酶的治疗患者的疾病、病症或医学状况的方法,所述方法包括向所述患者施用有效剂量的式(I)化合物或其可药用盐:



(I)

其中

带有R^1的环是5元、6元或7元芳基或杂芳基环系统，其包含0、1或2个选自S、O、N和NR^1的杂原子；其中所述环可以与芳基、杂芳基、环烷基或杂环基环稠合；其中R^1可以设置在多环系统的任何一个或更多个环上；

R^1在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、氰基、硝基或卤素；n1＝0、1、2或3；

Ar是单环或双环芳基或杂芳基环系统，其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代；

R^2在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、羟甲基、R_2NCH_2，其中R为H或烷基、氰基、硝基或卤素；

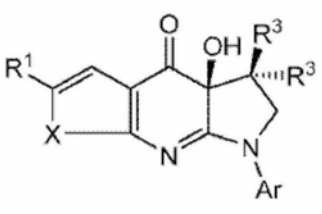
R^3在每次出现时独立地为(C1-C4)烷基、卤素或(C1-C4)卤代烷基；n3＝0、1、2、3或4；

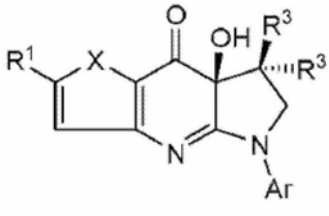
前提是所述化合物不是布雷他汀。

21.权利要求20所述的方法，其中所述疾病、病症或医学状况选自肾病、癌症和转移，包括肝癌、胰腺腺癌、乳腺癌、肺癌、胶质母细胞瘤、良性前列腺增生、止血或血栓形成、神经损伤(包括视网膜损伤)、肺纤维化、肝纤维化、关节纤维化、伤口愈合、脊髓损伤、牙周炎、青光眼和免疫相关疾病(包括多发性硬化症)；或者其中所述疾病、病症或医学状况选自病毒感染(包括疱疹病毒)、高血压、肺动脉高压、慢性呼吸系统疾病、心血管疾病、勃起功能障碍、血栓形成性疾病、膀胱过度活动症、心肌病、痉挛、骨骼肌病和精神障碍(包括物质使用)、焦虑性障碍(包括恐惧症)和应激障碍(包括创伤后应激障碍)；或者其中所述疾病、病症或医疗状况包括成瘾，所述成瘾包括滥用或成瘾于《精神障碍诊断与统计手册》(DSM)中归类为物质相关性或成瘾性病症的任何事物，所述事物例如但不限于可卡因、阿片类药物、安非他命、乙醇、大麻/大麻药品、尼古丁以及包括赌博在内的活动。

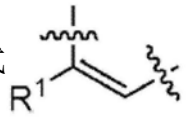
22.权利要求20所述的方法，其中所述带有R^1的环是苯基、吡啶基或噻吩基。

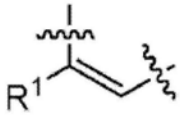
23.权利要求20所述的方法，其中式(I)化合物为式(IIa)或(IIb)或者其可药用盐：


(IIa)


(IIb)

其中

X是S，或者X是式  的基团，其中波浪线表示键合点；

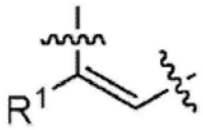
R^1在每次出现时独立地为H、(C1-C4)烷基、CF_3或卤素；前提是当X是式  的基团且Ar是未经取代的苯基时，至少一个R^1基团不为H或(C1-C4)烷基；

Ar是芳基或杂芳基，其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代；

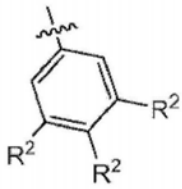
R^2在每次出现时独立地为卤素、氰基、硝基、CF_3、(C1-C4)烷基或(C1-C4)烷氧基；

R^3在每次出现时独立地为H或CH_3。

24.权利要求23所述的方法，其中X是S。

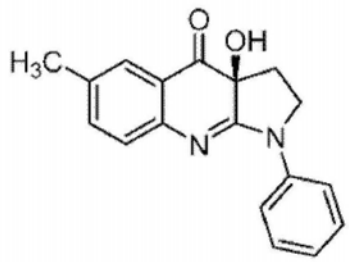
25.权利要求23所述的方法，其中X是式  的基团，其中波浪线表示键合点。

26.权利要求25所述的方法，其中式(I)的至少一个R^1基团是甲基、卤素或CF_3。

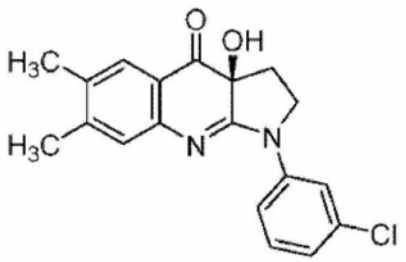
27.权利要求20所述的方法，其中Ar是式  的基团，其中波浪线表示键合点。

28.权利要求20所述的方法，其中Ar是吡唑基、噻吩基、异喹啉基、苯并噁唑基、喹唑啉基、异噁唑基、噌啉基、喹喔啉基、苯并异噁唑基、苯并噻二唑基、吡唑并吡啶基、咪唑并吡啶基、噻吩并吡啶基、二氢苯并噁嗪基、三唑并吡啶基、二氢吡啶并噁嗪基、四氢苯并氧氮杂䓬基、二氢苯并二氧杂芑基、二氢苯并噻嗪基、四氢喹啉基、四氢萘基或苯并二氢吡喃基环系统，其中的任一者均可以是未经取代的或者被1、2或3个R^2取代。

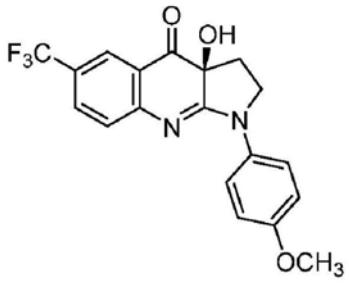
29.权利要求20所述的方法，其中所述化合物是以下的任一个或其可药用盐：



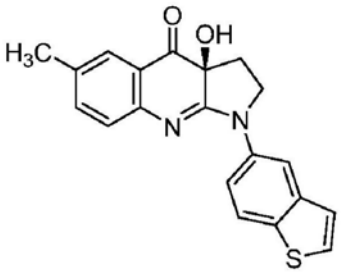
BPN-0024998（ 布雷他汀 ）



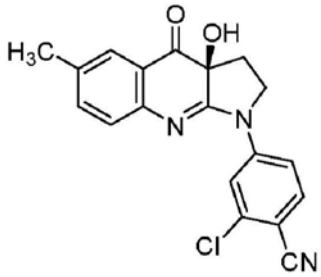
BPN-0026500



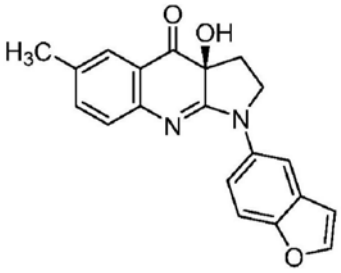
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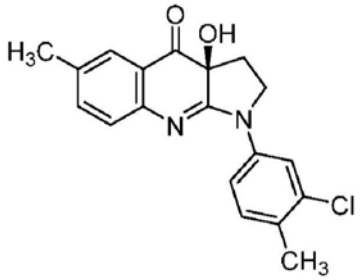
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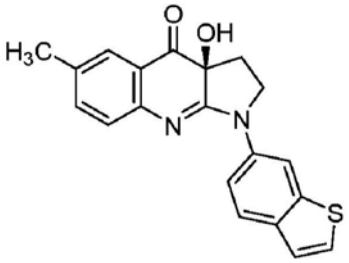
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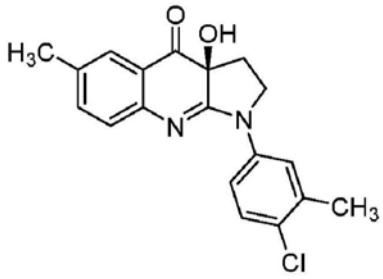
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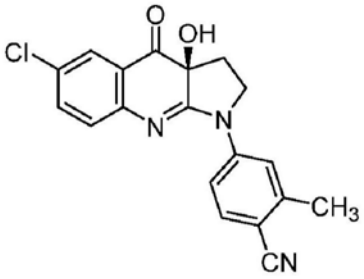
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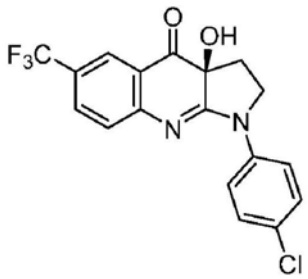
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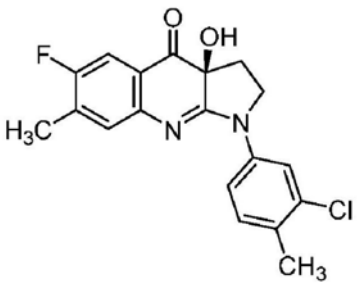
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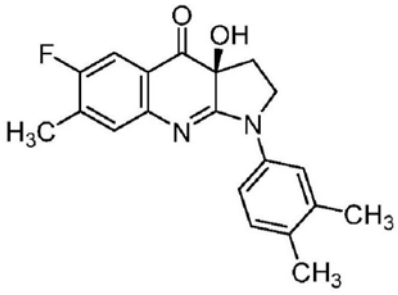
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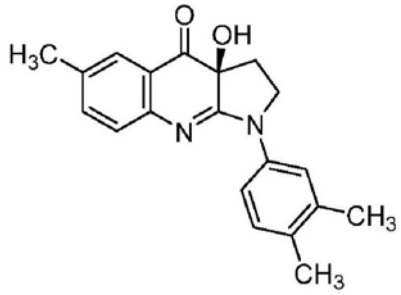
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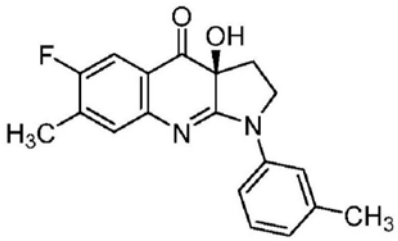
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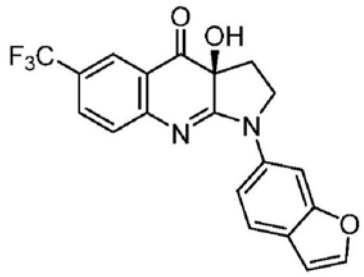
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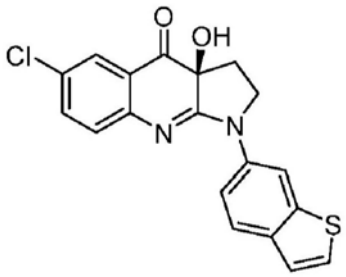
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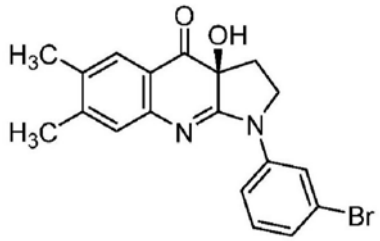
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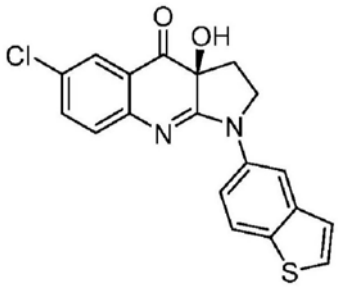
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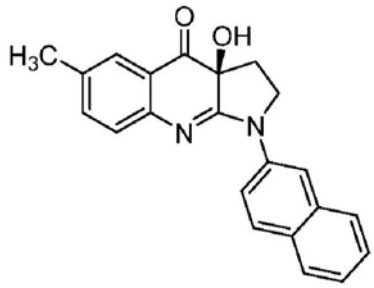
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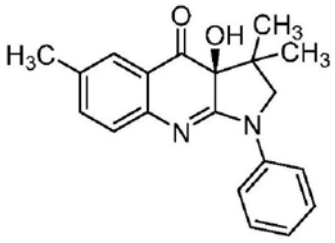
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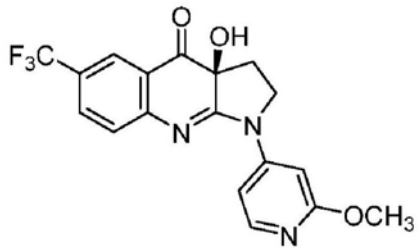
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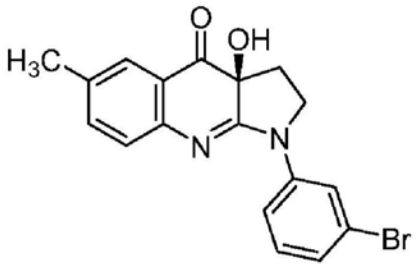
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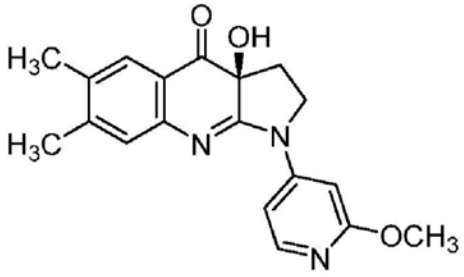
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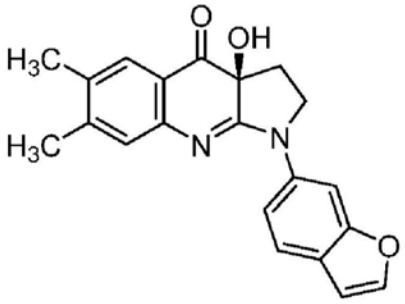
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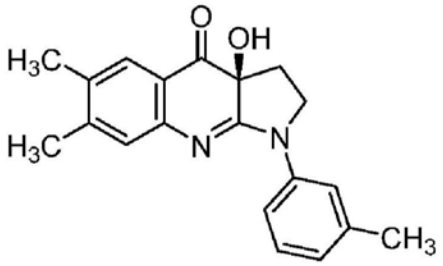
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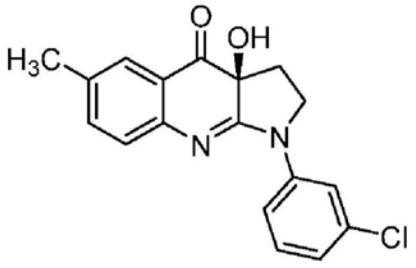
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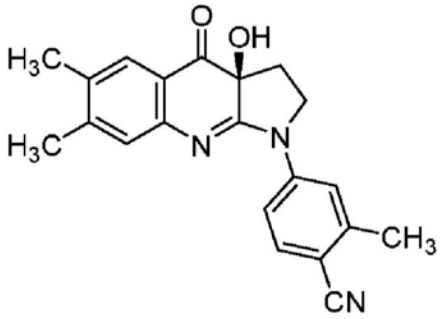
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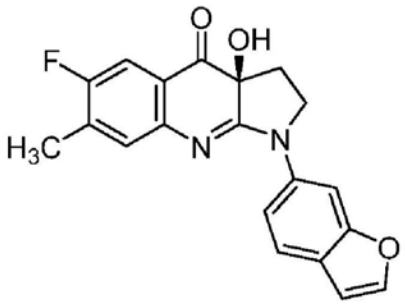
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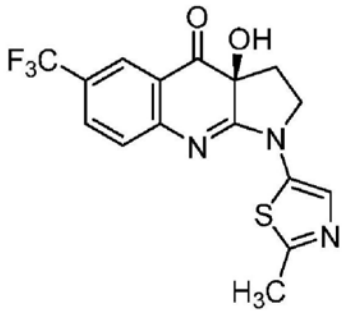
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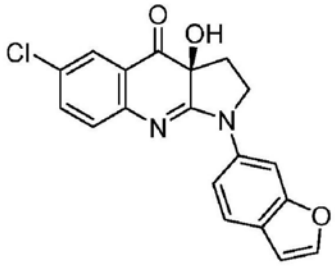
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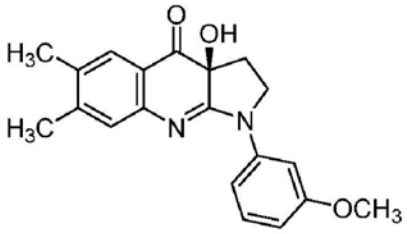
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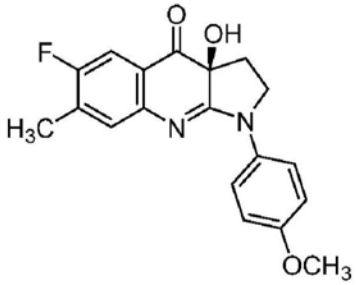
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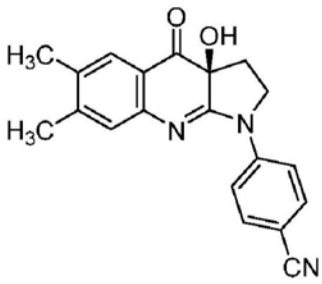
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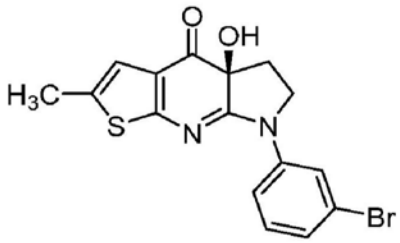
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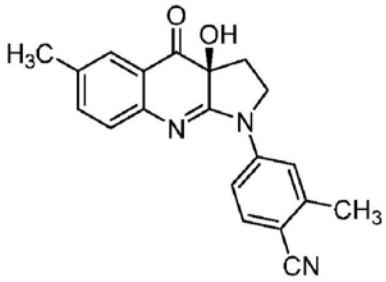
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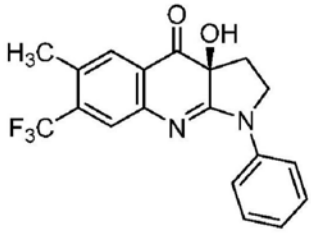
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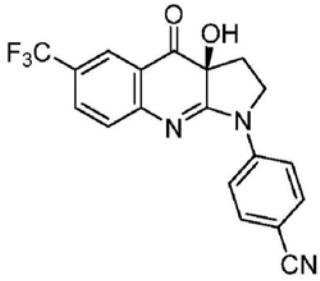
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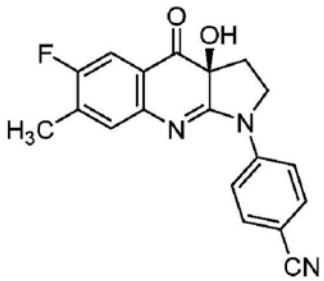
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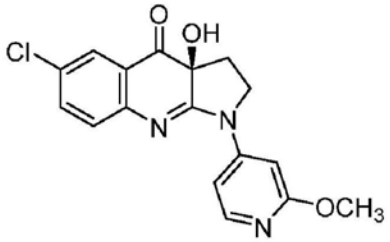
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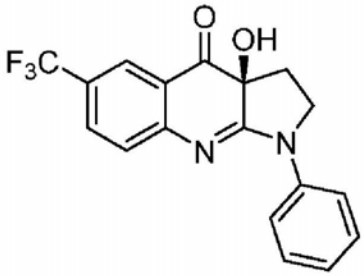
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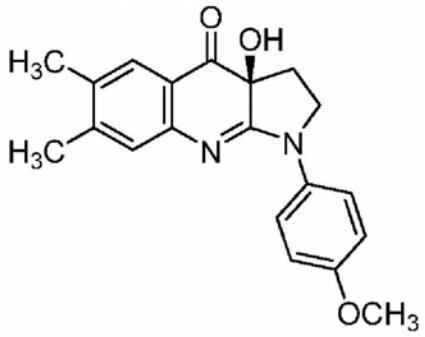
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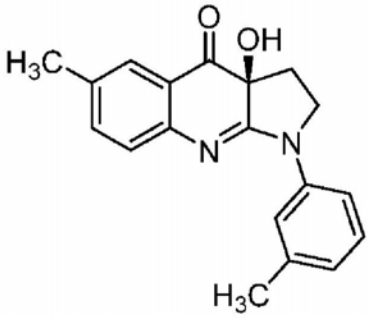
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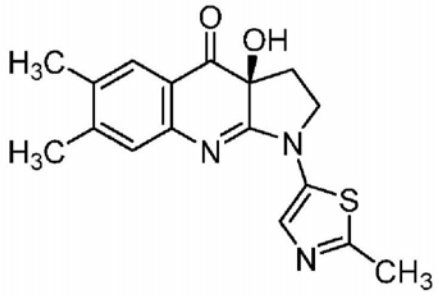
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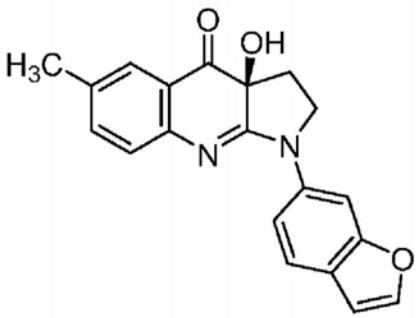
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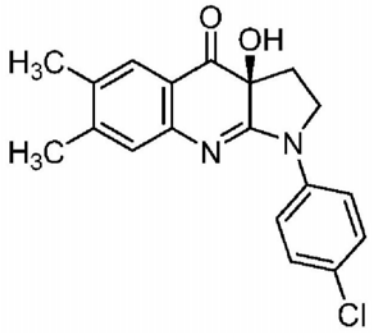
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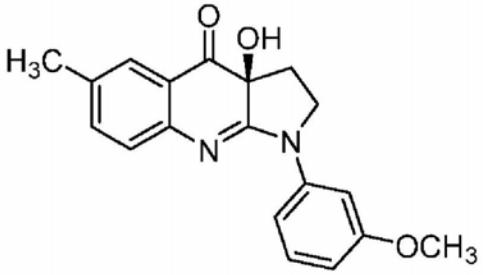
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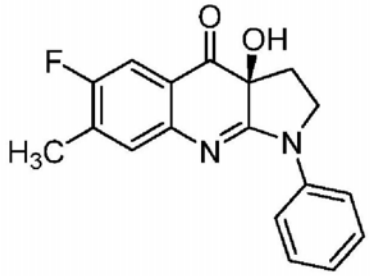
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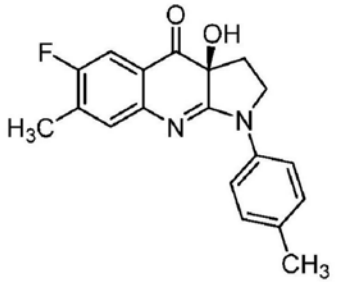
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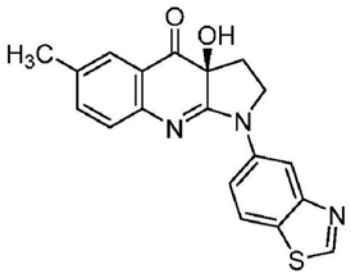
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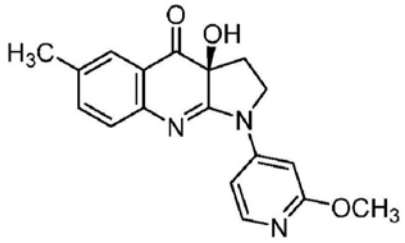
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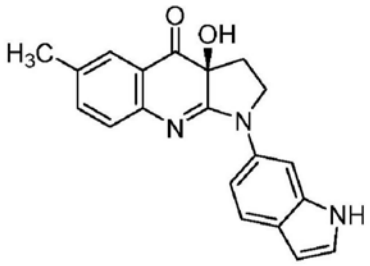
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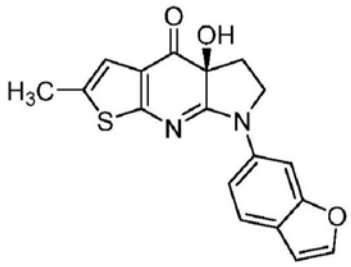
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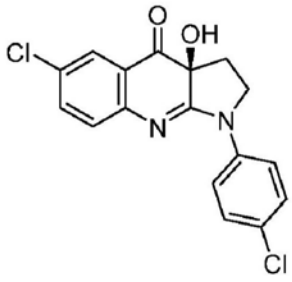
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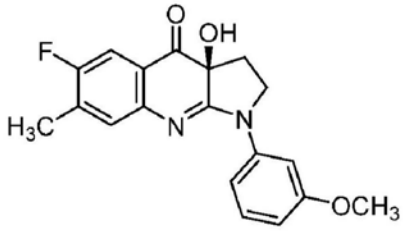
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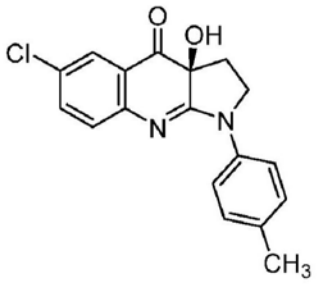
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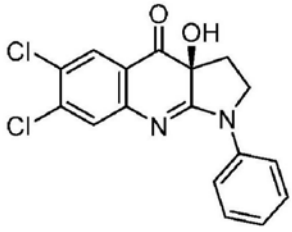
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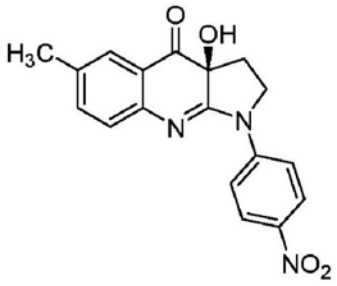
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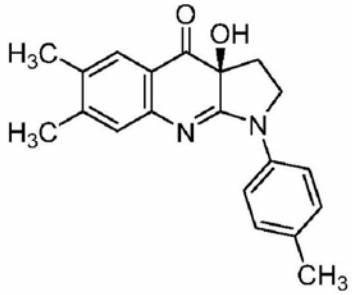
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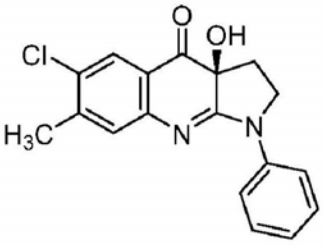
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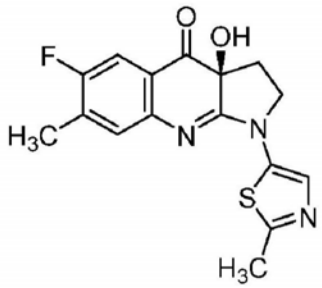
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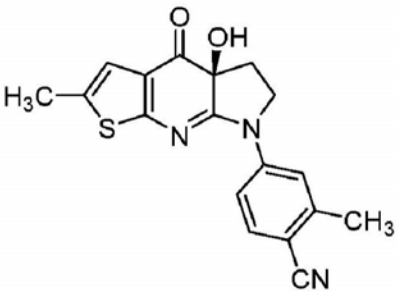
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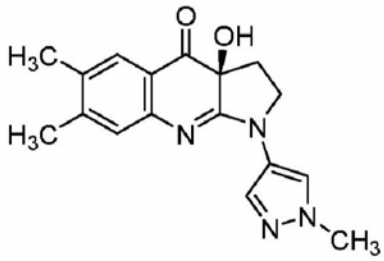
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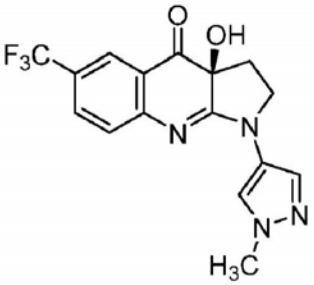
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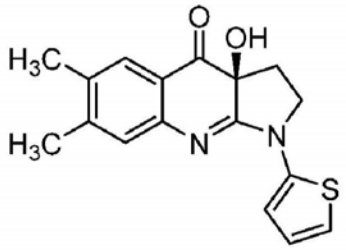
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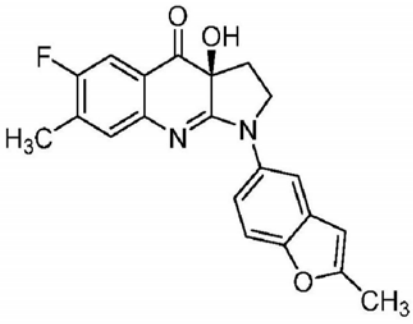
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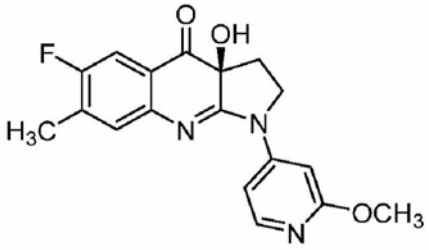
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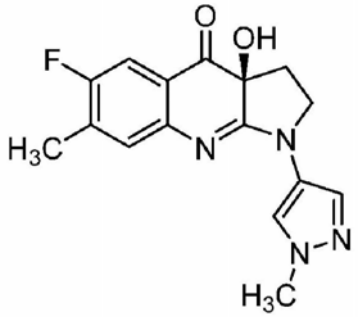
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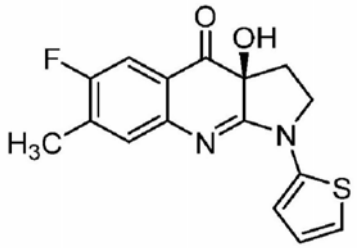
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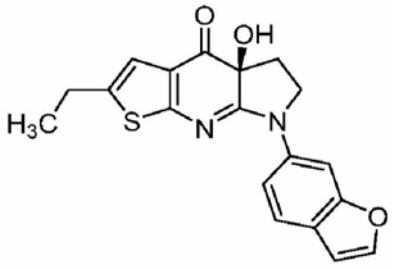
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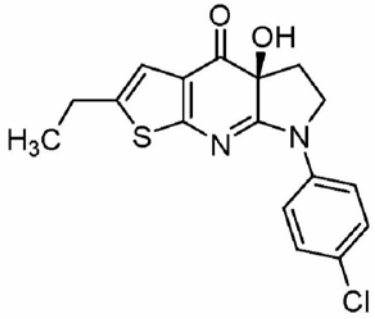
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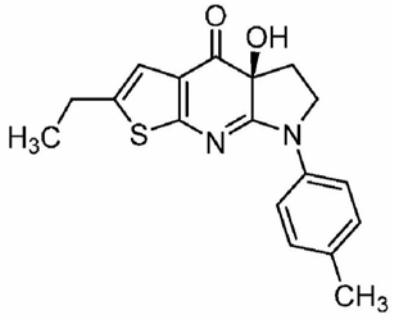
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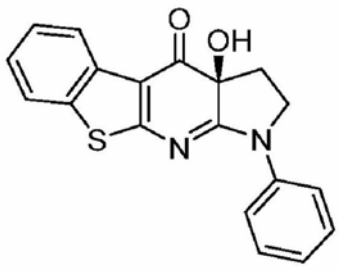
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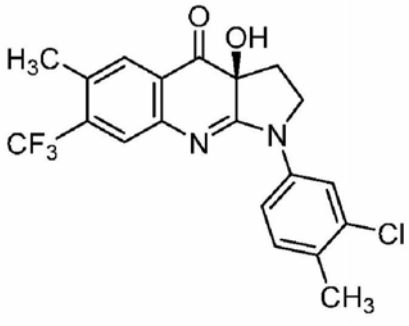
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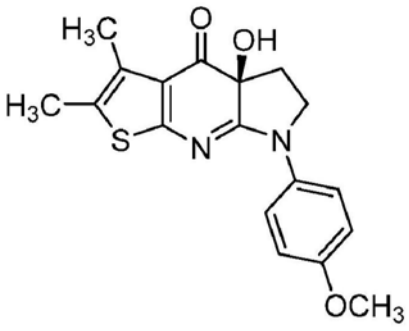
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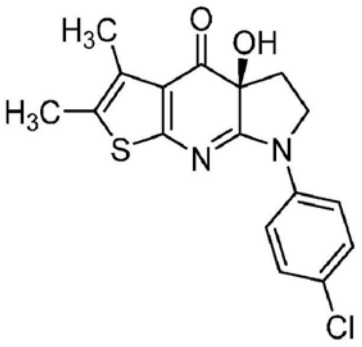
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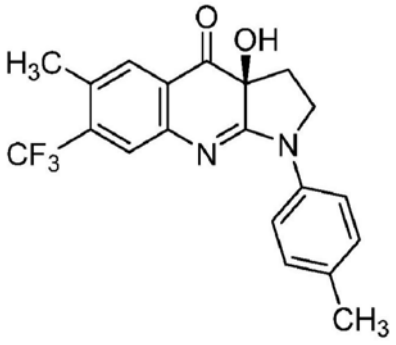
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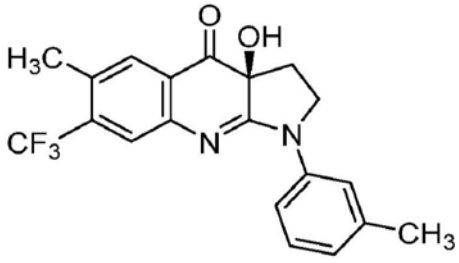
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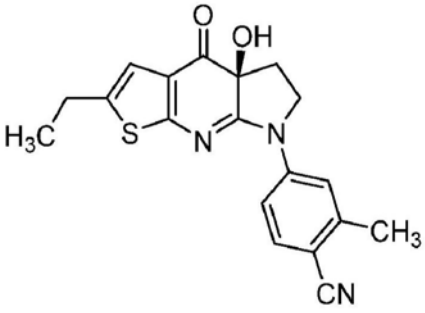
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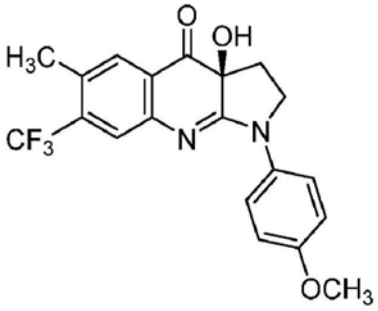
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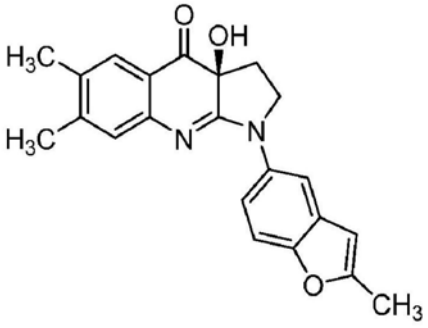
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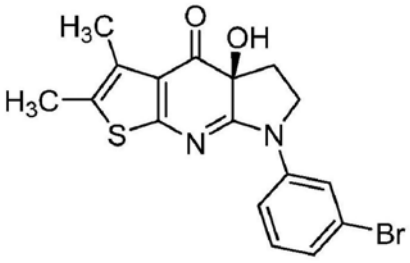
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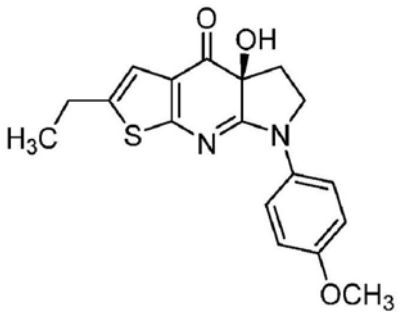
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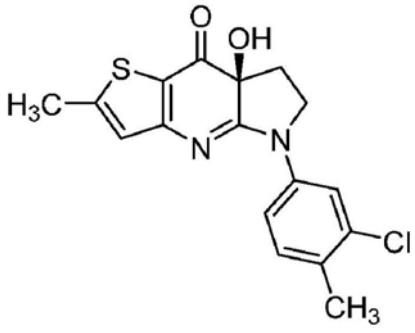
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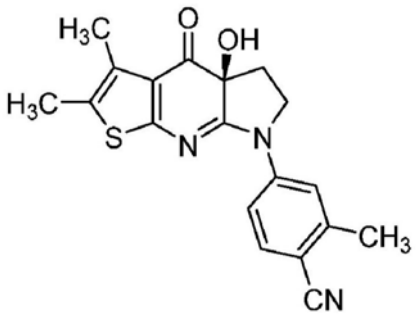
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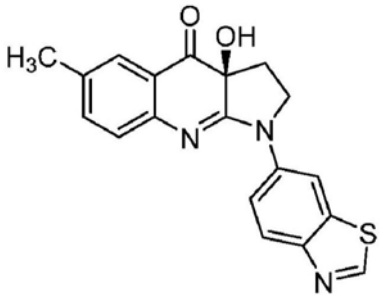
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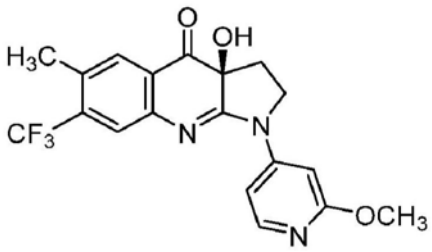
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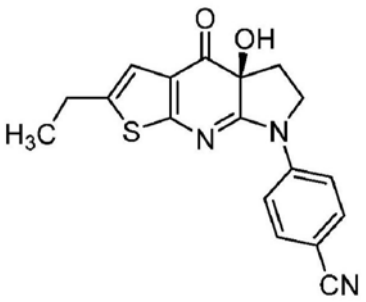
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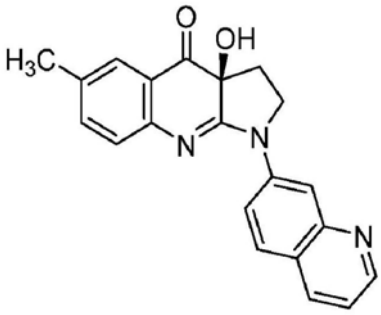
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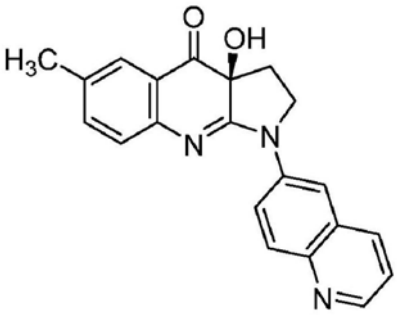
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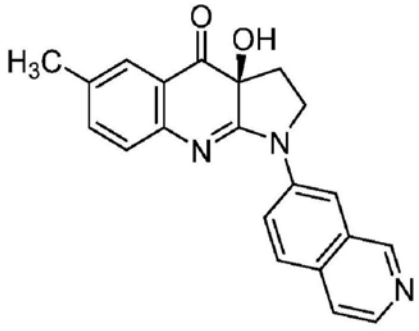
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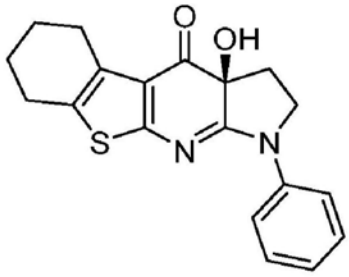
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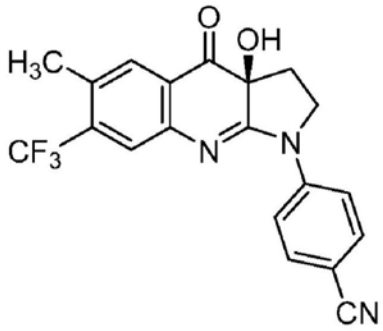
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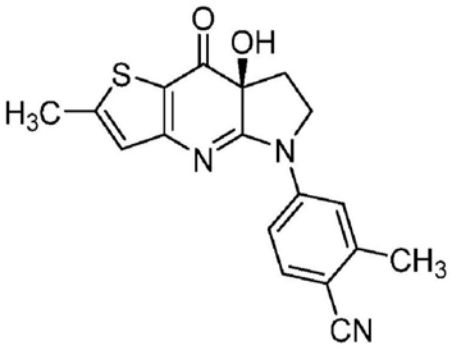
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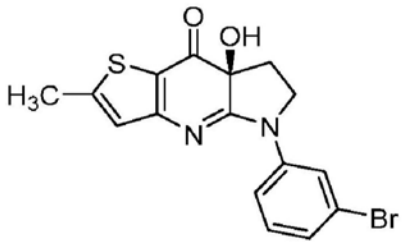
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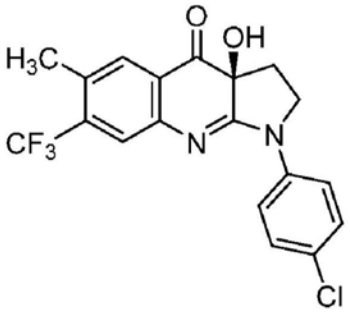
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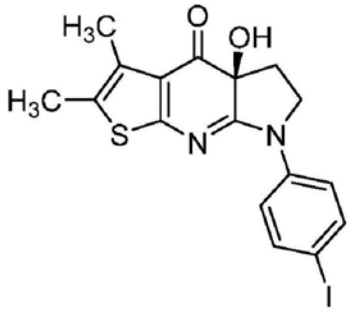
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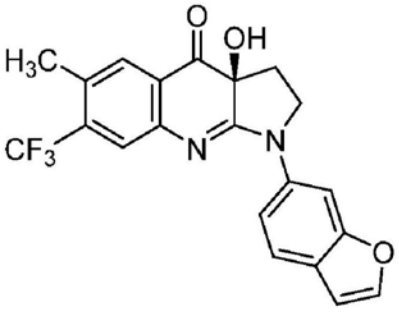
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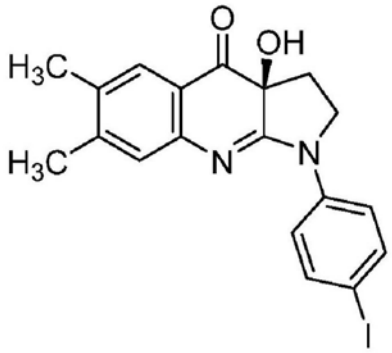
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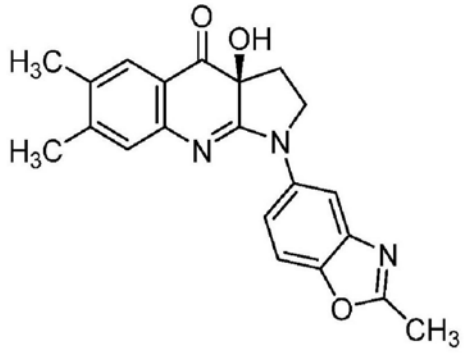
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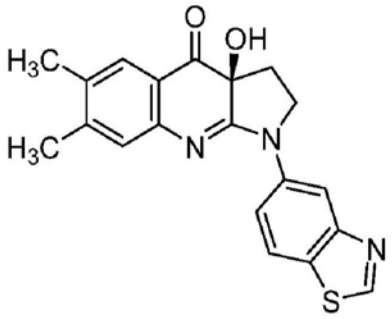
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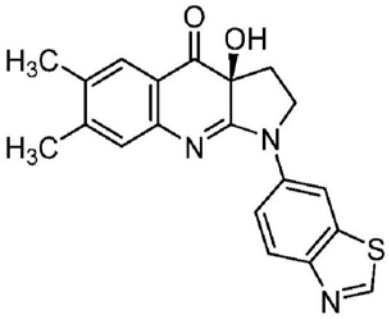
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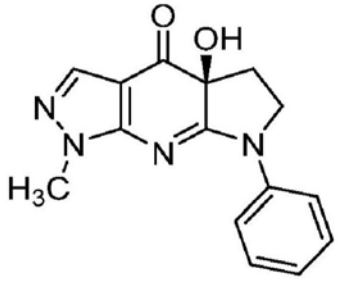
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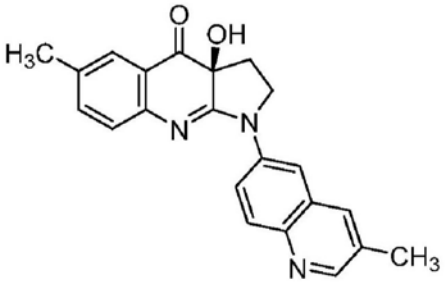
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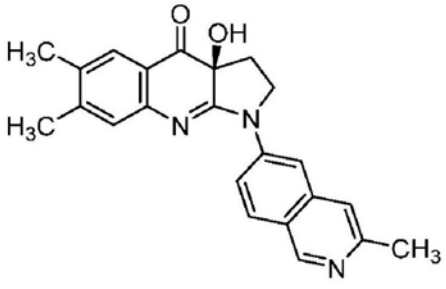
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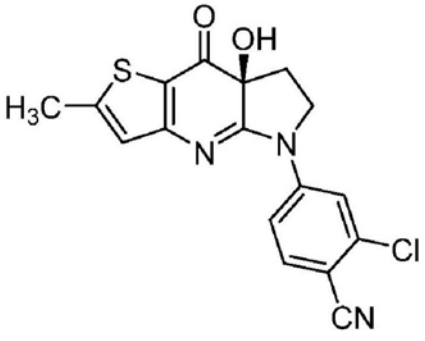
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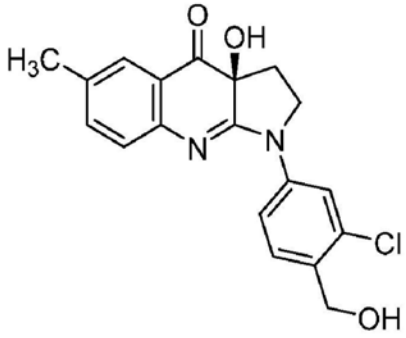
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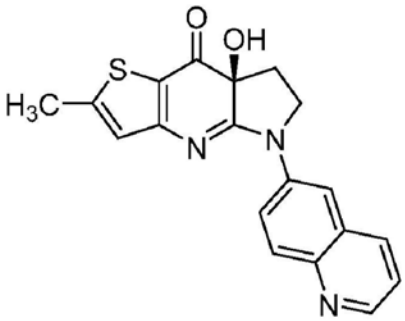
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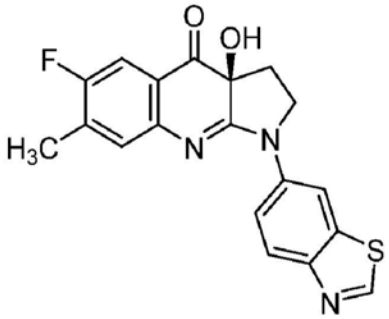
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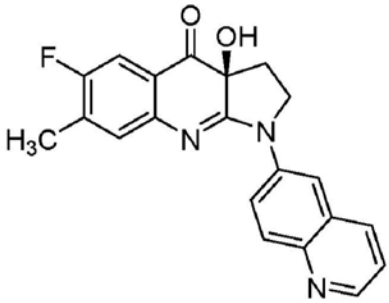
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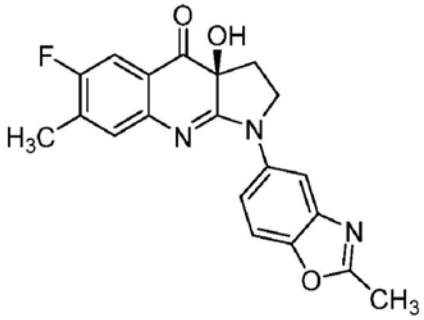
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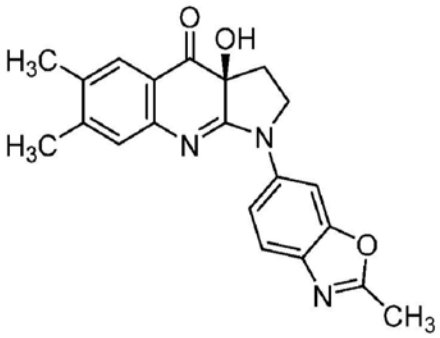
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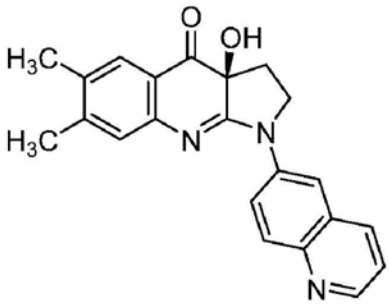
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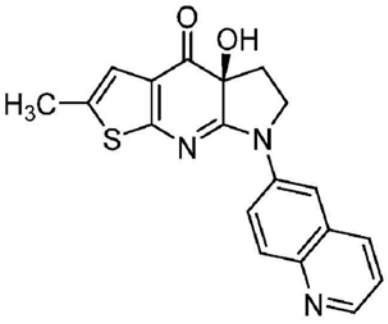
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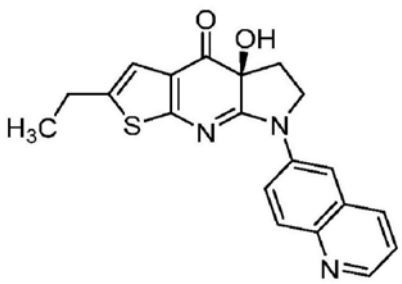
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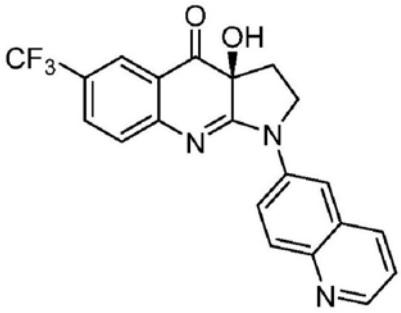
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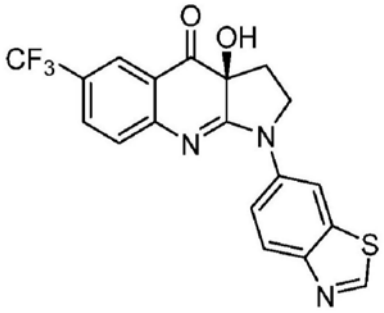
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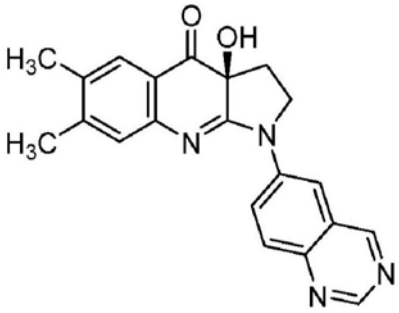
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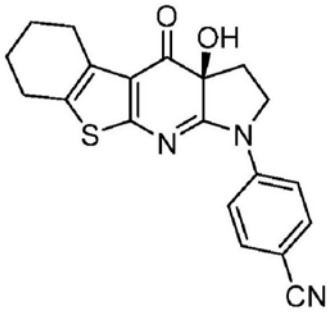
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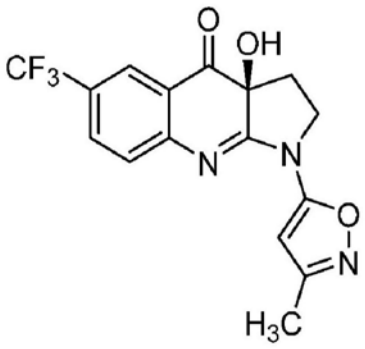
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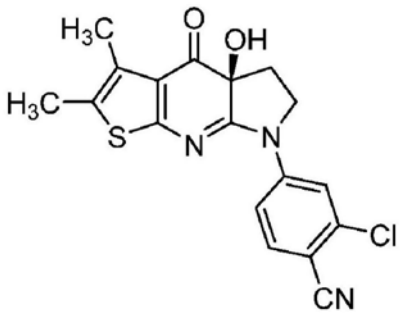
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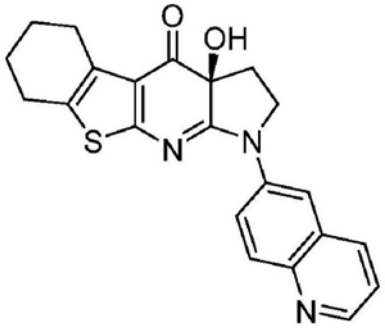
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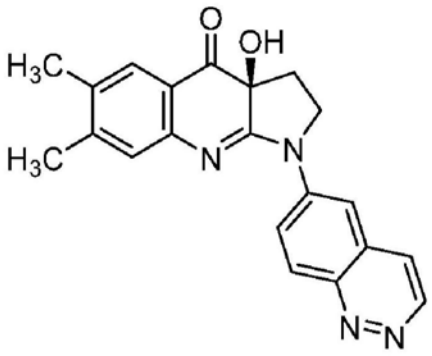
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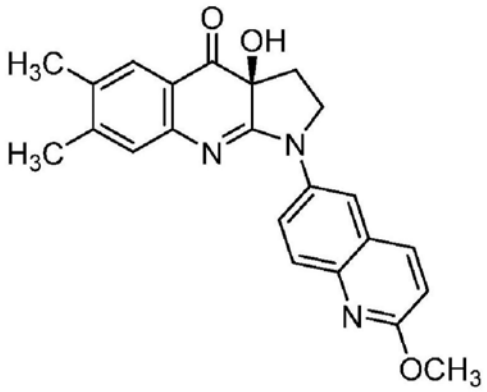
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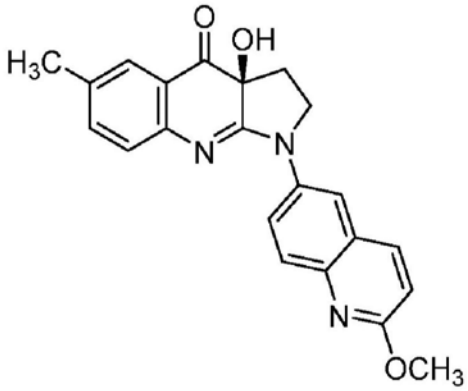
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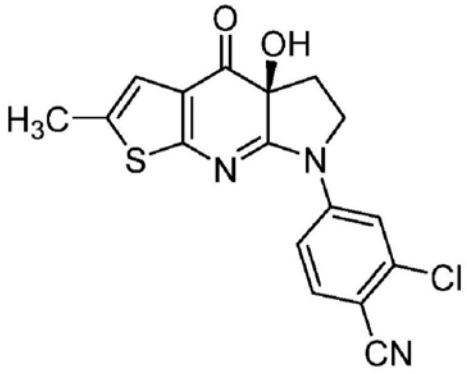
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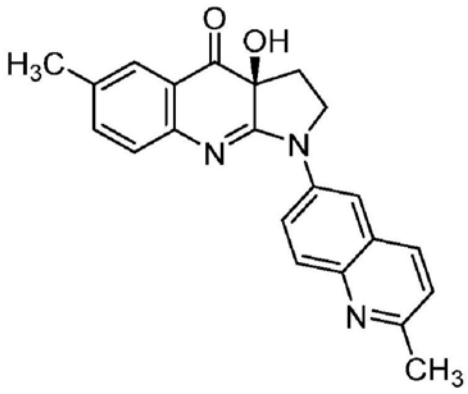
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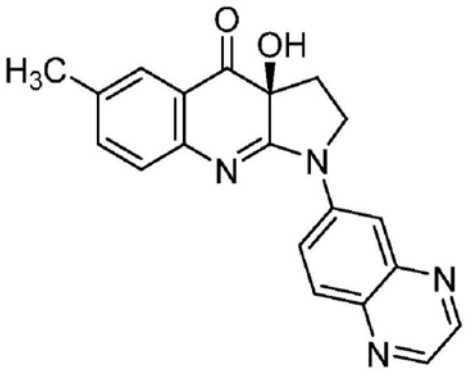
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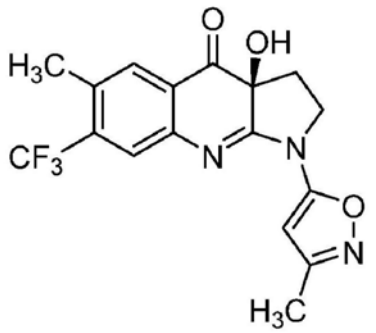
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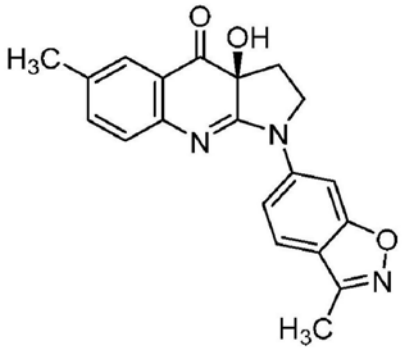
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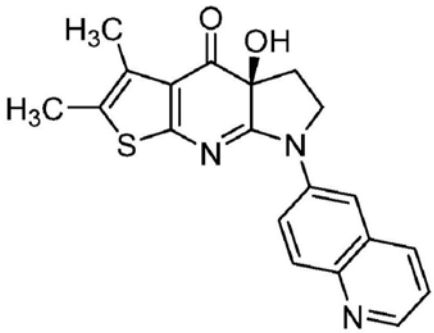
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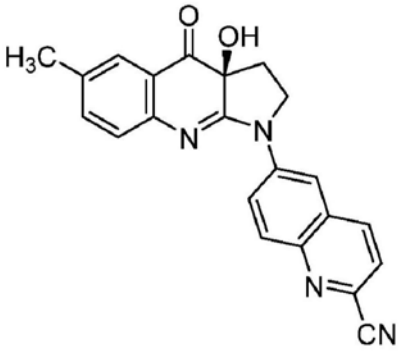
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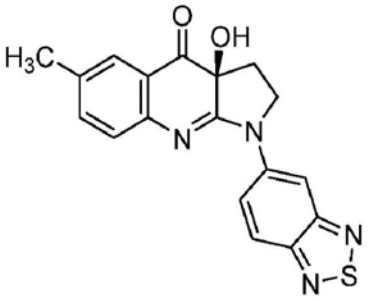
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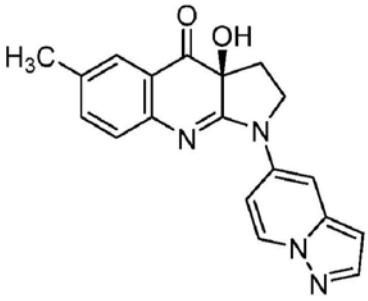
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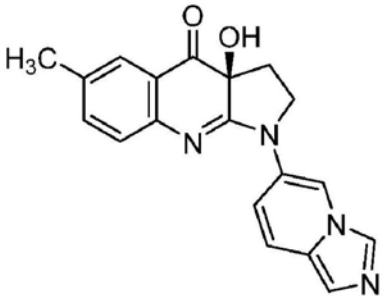
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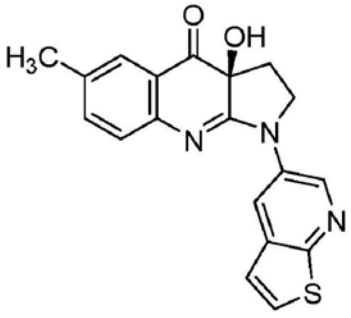
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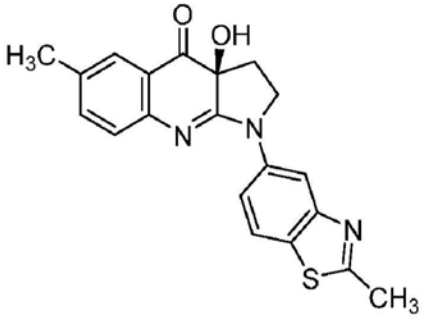
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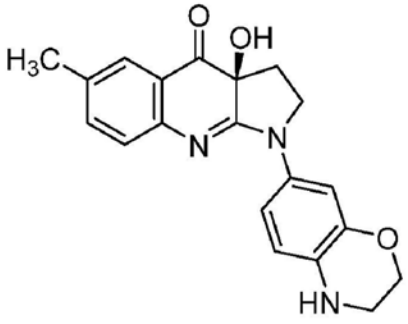
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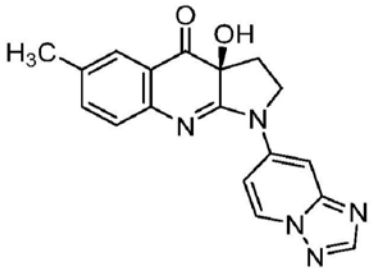
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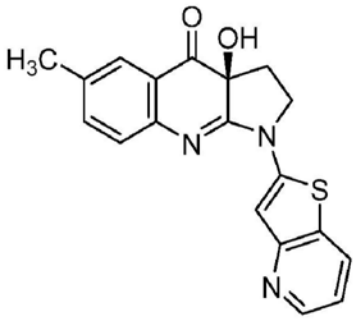
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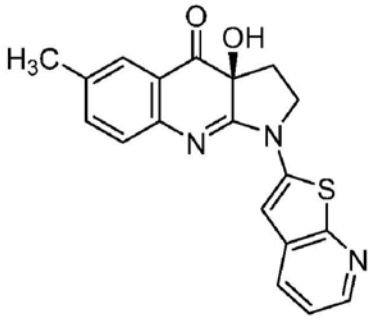
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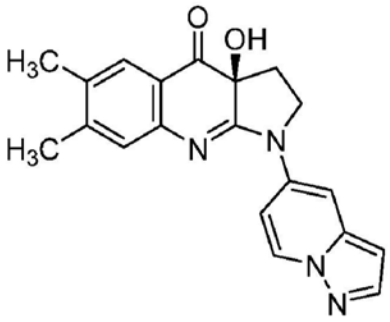
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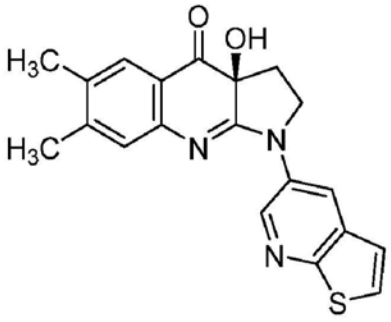
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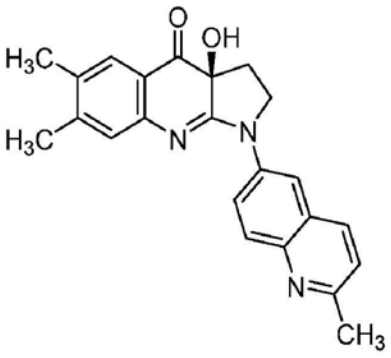
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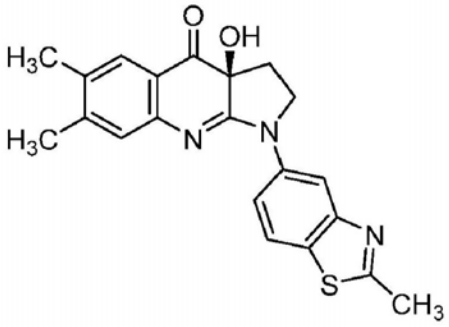
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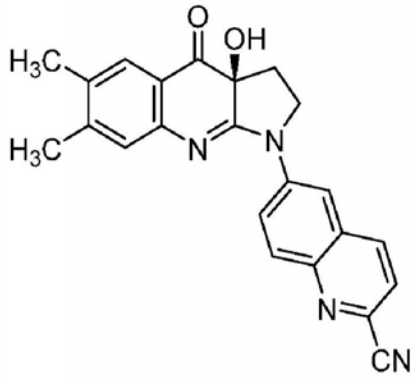
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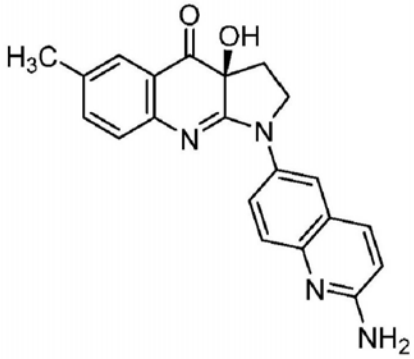
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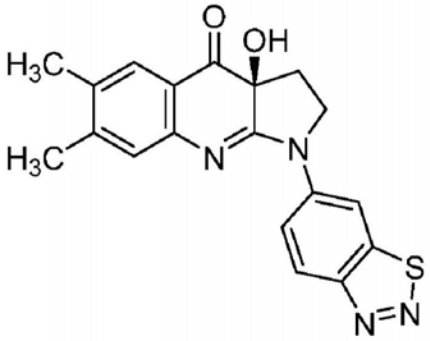
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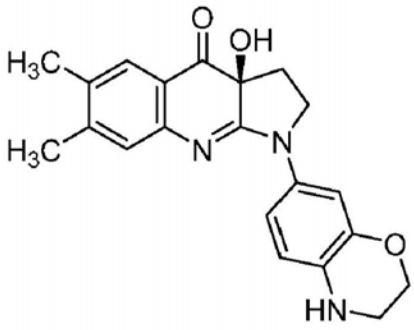
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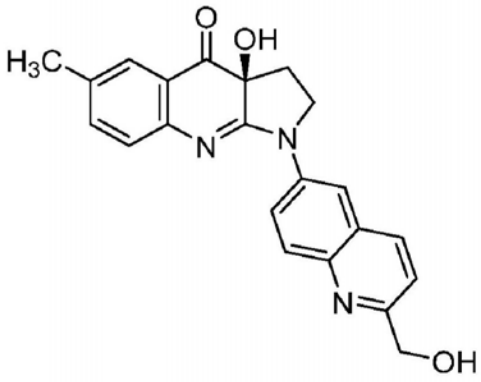
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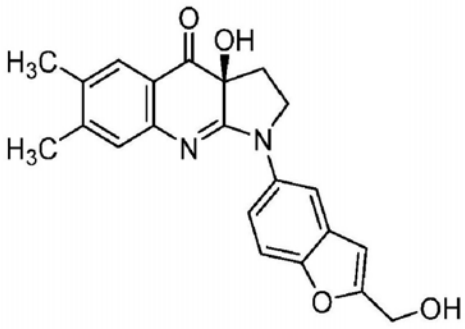
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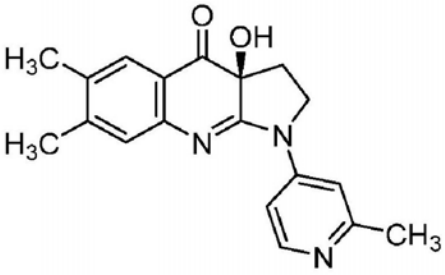


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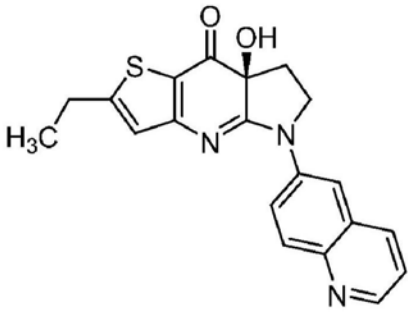


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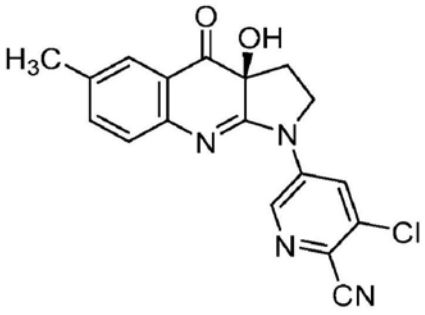




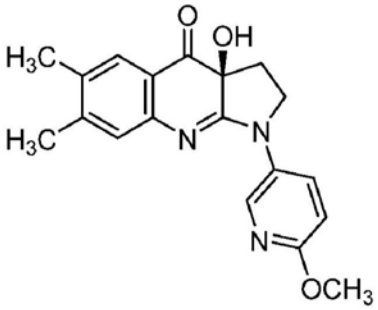
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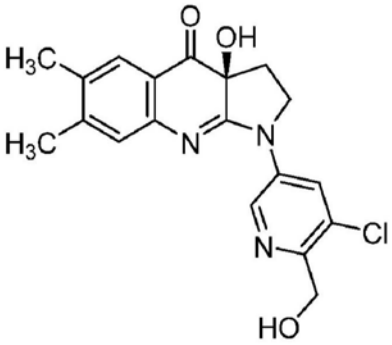
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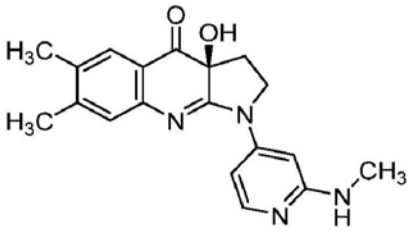
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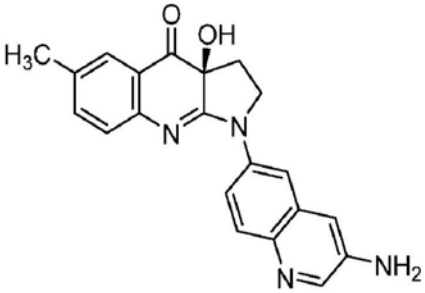
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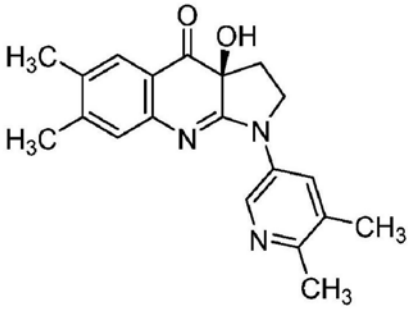
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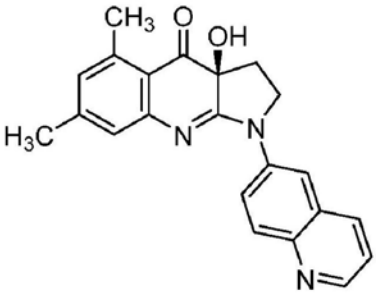
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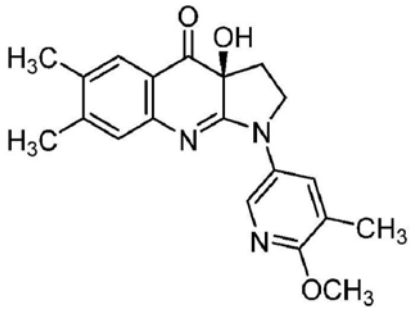
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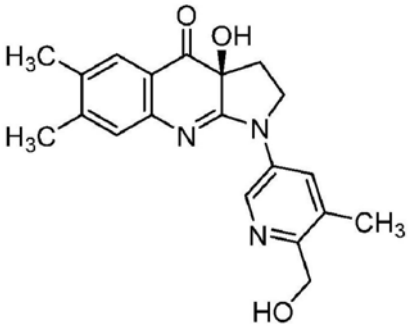
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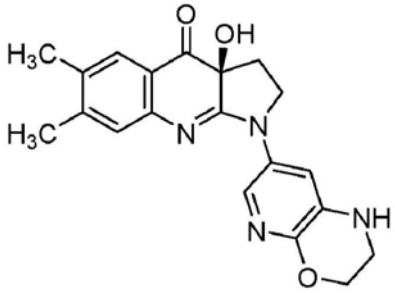
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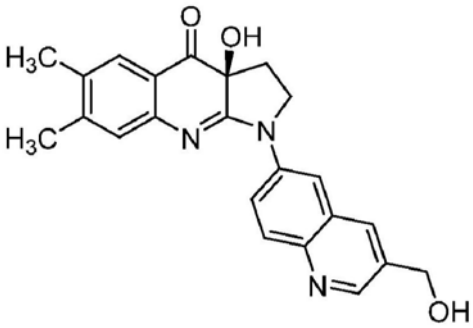
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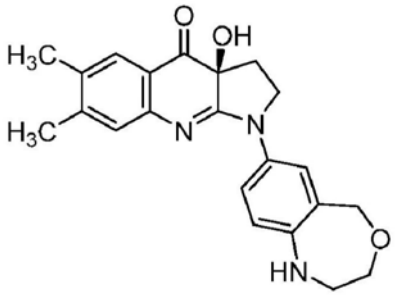
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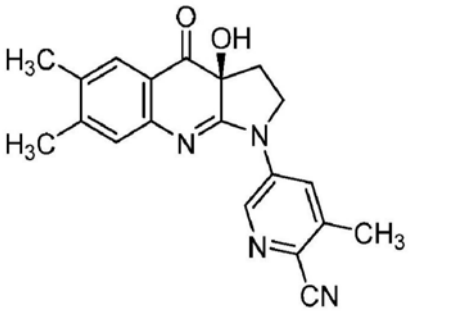
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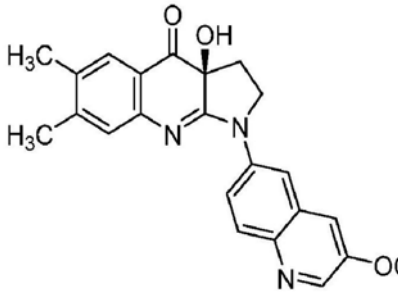
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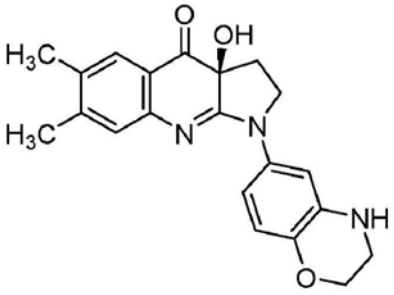
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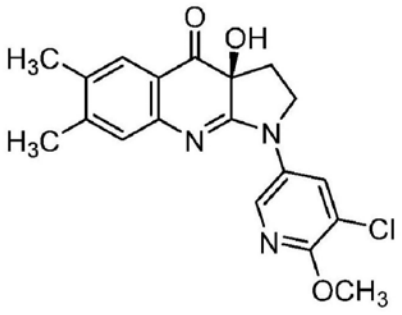


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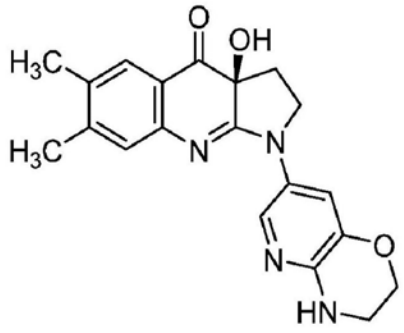
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BPN-0028790

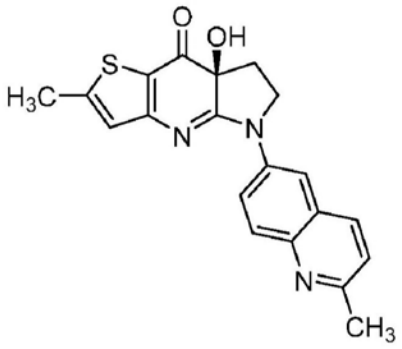




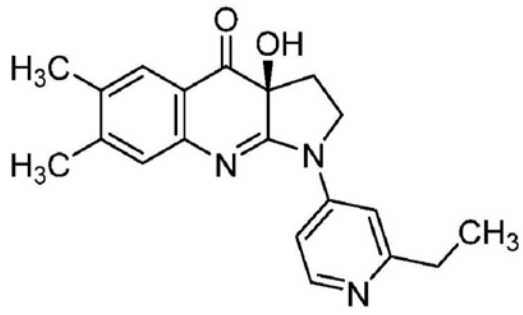
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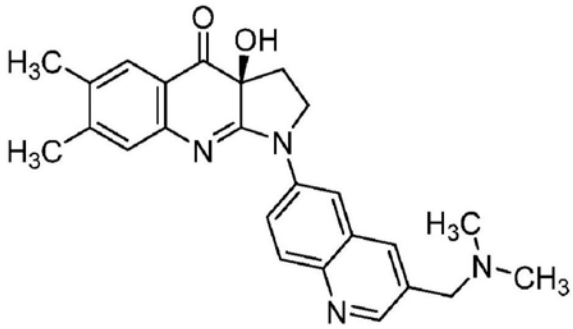
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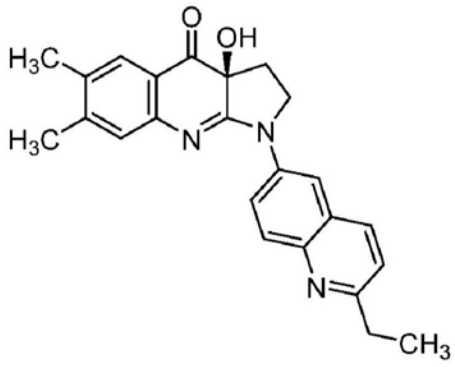
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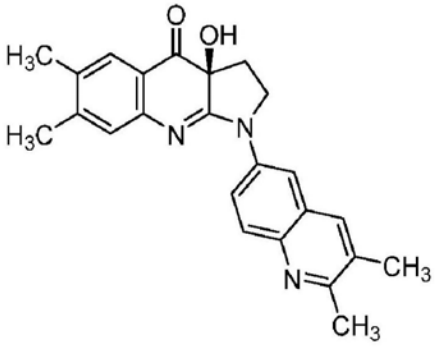
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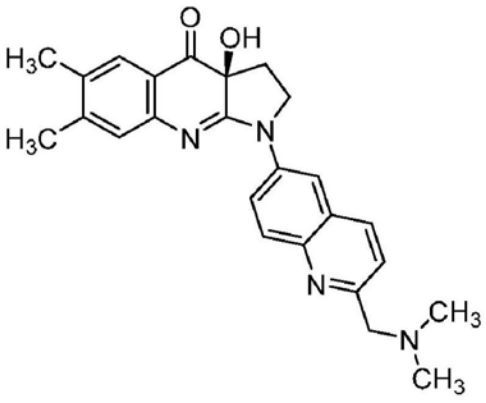


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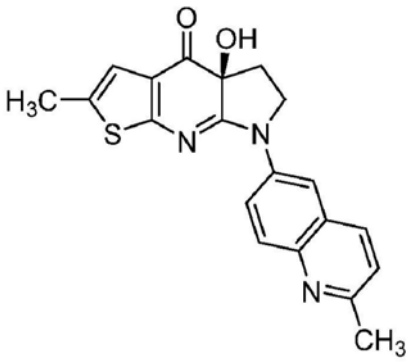


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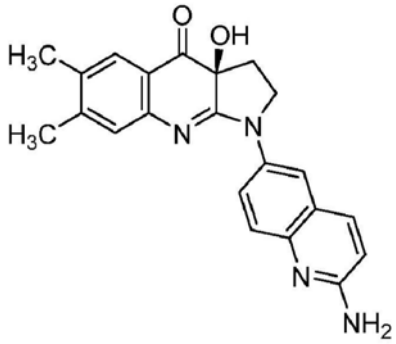




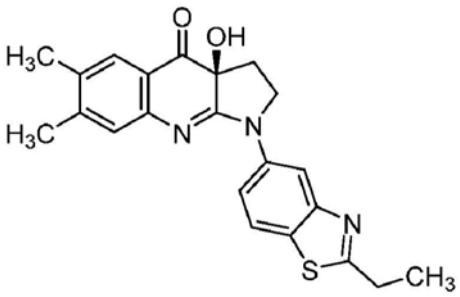
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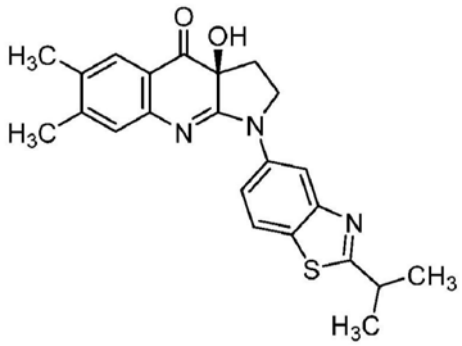
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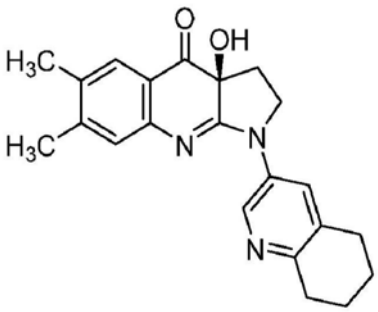
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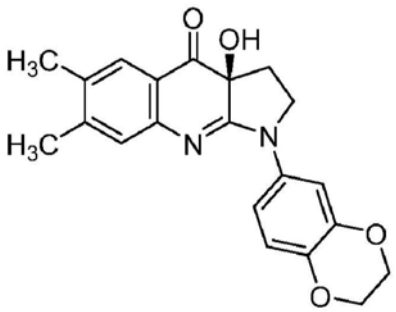
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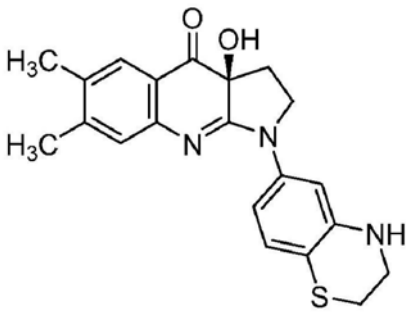
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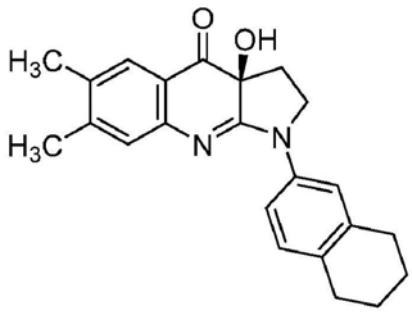
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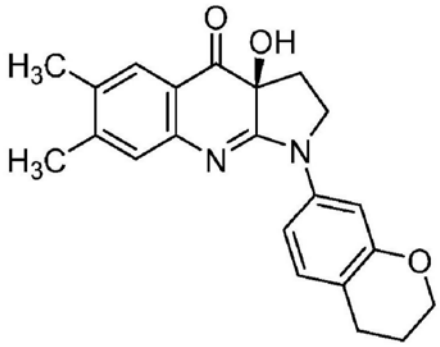
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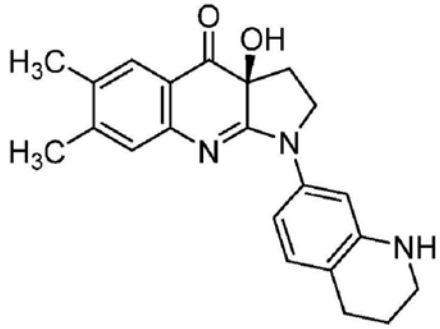
BPN-0028921



BPN-0028922



BPN-0028923



BPN-0028924

BPN-0028925

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用于物质使用复发的非肌肉肌球蛋白II抑制剂

[0001] 相关申请的交叉引用

[0002] 本专利申请要求2018年6月14日提交的美国临时专利申请No.62/685,158的优先权权益。该优先权申请的全部公开内容通过引用以其整体并出于所有目的并入本文。

[0003] 政府支持声明

[0004] 本发明是在美国国立卫生研究院(National Institutes of Health)授予的授权号为NS096833的政府资助下完成的。政府拥有本发明的某些权利。

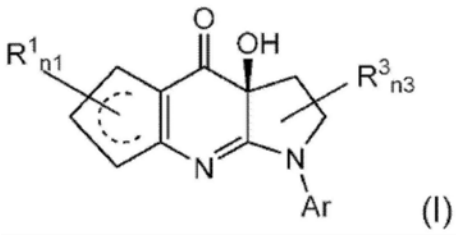
背景技术

[0005] 物质滥用病症是一种慢性复发性病症,没有复发,阻止了可对任何滥用药物进行的药物治疗。这是一个重大的治疗挑战,因为根深蒂固的药物寻求行为在停止药物使用后很长时间仍然持续。药物使用时,药物的中枢效应和外围效应与环境成分之间形成多种关联,范围可以从明显的(例如药物装备(drug paraphernalia))到更抽象的(例如音乐、雪景、口香糖)[1]。联系本身就变得非常有激发性,成为寻求药物的快速触发条件。由于联想记忆的持久性,也许最令人困扰的与药物相关的刺激保持其能够在成功康复和延长无药物时间后激发药物寻求行为的能力。

发明内容

[0006] 在多种实施方案中,本发明涉及可用于抑制非肌肉肌球蛋白II的化合物和方法,其可以相对于心肌球蛋白II而言是对非肌肉肌球蛋白II的选择性抑制。所述化合物是(S)-布雷他汀(“Blebb”)的类似物。

[0007] 在多种实施方案中,本发明可提供式(I)化合物或其可药用盐:

[0008] 

(I)

[0009] 其中

[0010] 带有R^1的环是5元、6元或7元芳基或杂芳基环系统,其包含0、1或2个选自S、O、N和NR^1的杂原子;其中所述环可以与芳基、杂芳基、环烷基或杂环基环稠合;其中R^1可以设置在多环系统的任何一个或更多个环上;

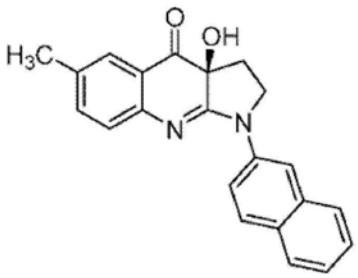
[0011] R^1在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、氰基、硝基或卤素;n1=0、1、2或3;

[0012] Ar是单环或双环芳基或杂芳基环系统,其中任何芳基或其杂芳基均可以被0、1、2或3个R^2取代;

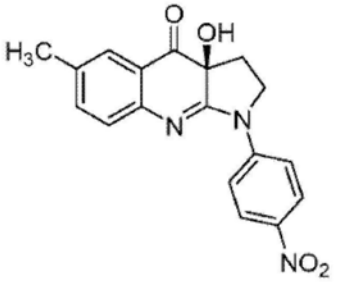
[0013] R^2在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、羟甲基、R_2NCH_2,其中R为H或烷基、氰基、硝基或卤素;

[0014] R^3在每次出现时独立地为(C1-C4)烷基、卤素或(C1-C4)卤代烷基;n3＝0、1、2、3或4;

[0015] 前提是所述化合物不是布雷他汀或任何下式的化合物:

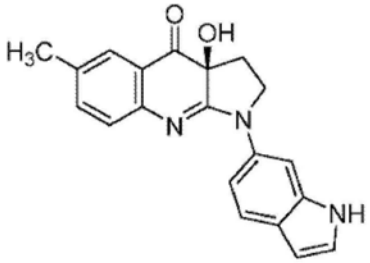


BPN-0025915



BPN-0025001

[0016]

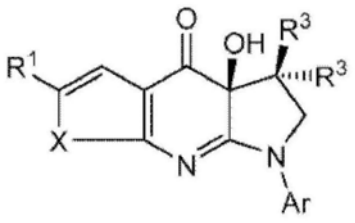


BPN-0026555。

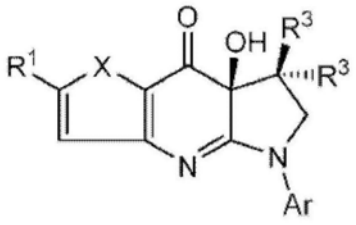
[0017] 例如,带有R^1的环可以是苯基、吡啶基或噻吩基。

[0018] 更具体地,式(I)化合物可以是式(IIa)或(IIb)化合物或者其可药用盐:

[0019]

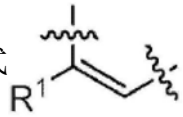


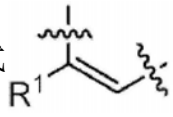
(IIa)



(IIb)

[0020] 其中

[0021] X是S,或者X是式  的基团,其中波浪线表示键合点;

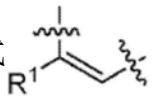
[0022] R^1在每次出现时独立地为H、(C1-C4)烷基、CF_3或卤素;前提是当X是式  的基团且Ar是未经取代的苯基时,至少一个R^1基团不为H或(C1-C4)烷基;

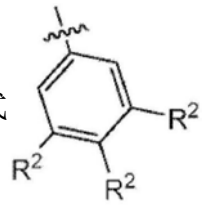
[0023] Ar是芳基或杂芳基,其中任何芳基或其杂芳基均可被0、1、2或3个R^2取代;

[0024] R^2在每次出现时独立地为卤素、氰基、硝基、CF_3、(C1-C4)烷基或(C1-C4)烷氧基;

[0025] R^3在每次出现时独立地为H或CH_3。

[0026] 例如,对于式(II)化合物,X可以是S。

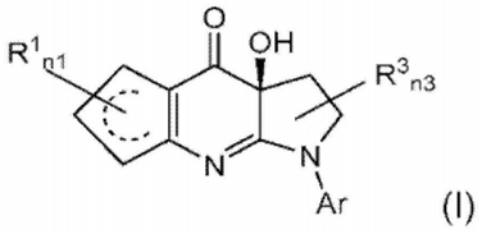
[0027] 在另一些实施方案中，对于式(II)化合物，X可以是式  的基团，其中波浪线表示键合点。在这些实施方案中，式(I)的至少一个R^1基团可以是甲基、卤素或CF_3。

[0028] 在式(I)的另一些实施方案中，Ar可以是式  的基团，其中波浪线表示键合点。

[0029] 在另一些实施方案中，Ar可以是吡唑基、噻吩基、异喹啉基、苯并噁唑基、喹唑啉基、异噁唑基、噌啉基、喹喔啉基、苯并异噁唑基、苯并噻二唑基、吡唑并吡啶基、咪唑并吡啶基、噻吩并吡啶基、二氢苯并噁嗪基、三唑并吡啶基、二氢吡啶并噁嗪基、四氢苯并氧氮杂䓬基、二氢苯并二氧杂芑基、二氢苯并噻嗪基、四氢喹啉基、四氢萘基或苯并二氢吡喃基环系统，其中的任一者均可以是未经取代的或者被1、2或3个R^2取代。

[0030] 在本发明的式(I)化合物的多种具体实施方案中，该化合物可以是表3中所示的除了布雷他汀本身和如上所述的由附带条件排除的三个化合物之外的任一化合物。

[0031] 在多种实施方案中，本发明可提供抑制非肌肉肌球蛋白II的方法，该方法包括使非肌肉肌球蛋白II与有效量或浓度的式(I)化合物或其可药用盐接触：

[0032] 

(I)

[0033] 其中

[0034] 带有R^1的环是5元、6元或7元芳基或杂芳基环系统，其包含0、1或2个选自S、O、N和NR^1的杂原子；其中所述环可与芳基、杂芳基、环烷基或杂环基环稠合；其中R^1可设置在多环系统的任何一个或更多个环上；

[0035] R^1在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、氰基、硝基或卤素；n1＝0、1、2或3；

[0036] Ar是单环或双环芳基或杂芳基环系统，其中任何芳基或其杂芳基均可被0、1、2或3个R^2取代；

[0037] R^2在每次出现时独立地为(C1-C4)烷基、(C1-C4)烷氧基、(C1-C4)烷氧基羰基、(C1-C4)卤代烷基、羟甲基、二烷基氨基甲基、氰基、硝基、或卤素；

[0038] R^3在每次出现时独立地为(C1-C4)烷基、卤素或(C1-C4)卤代烷基；n3＝0、1、2、3或4；

[0039] 前提是所述化合物不是布雷他汀。

[0040] 化合物BPN-0025915、BPN-0025001和BPN-0026555(参见表3)包括在可用于实施本发明方法的一个实施方案的化合物组中。

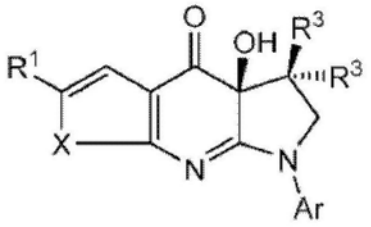
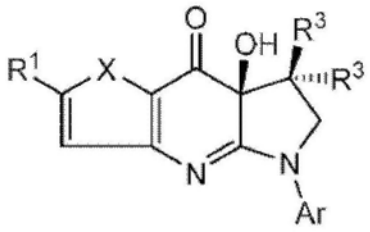
[0041] 在另一些实施方案中，本发明可提供治疗患者中的物质使用复发的方法，其包括

向该患者施用有效剂量的式(I)化合物。

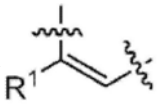
[0042] 在多种实施方案中,可用于实施本发明方法的化合物可包括:

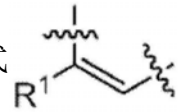
[0043] 式(I)化合物,其中带有R^1的环是苯基、吡啶基或噻吩基;

[0044] 为式(IIa)或(IIb)或者其可药用盐的式(I)化合物

[0045] 
(IIa)

(IIb)

[0046] 其中

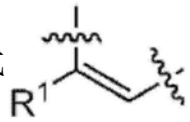
[0047] X是S,或者X是式  的基团,其中波浪线表示键合点;

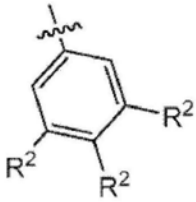
[0048] R^1在每次出现时独立地为H、(C1-C4)烷基、CF_3或卤素;前提是当X是式  的基团且Ar是未经取代的苯基时,至少一个R^1基团不为H或(C1-C4)烷基;

[0049] Ar是芳基或杂芳基,其中任何芳基或其杂芳基均可被0、1、2或3个R^2取代;

[0050] R^2在每次出现时独立地为卤素、氰基、硝基、CF_3、(C1-C4)烷基或(C1-C4)烷氧基;

[0051] R^3在每次出现时独立地为H或CH_3。

[0052] 在用于实施本发明方法的式(II)化合物的多种实施方案中,X可以是S;或X可以是式  的基团,其中波浪线表示键合点。在这些实施方案中,式(I)的至少一个R^1基团可以是甲基、卤素或CF_3。

[0053] 在可用于实施本发明方法的式(I)化合物的另一些实施方案中,Ar可以是式  的基团,其中波浪线表示键合点。

[0054] 在另一些实施方案中,Ar可以是吡唑基、噻吩基、异喹啉基、苯并噁唑基、喹唑啉基、异噁唑基、噌啉基、喹喔啉基、苯并异噁唑基、苯并噻二唑基、吡唑并吡啶基、咪唑并吡啶基、噻吩并吡啶基、二氢苯并噁嗪基、三唑并吡啶基、二氢吡啶并噁嗪基、四氢苯并氧氮杂䓬基、二氢苯并二氧杂芑基、二氢苯并噻嗪基、四氢喹啉基、四氢萘基或苯并二氢吡喃基环系统,其中的任一者均可以是未经取代的或者被1、2或3个R^2取代。

[0055] 为了实施本发明的方法,在多种实施方案中,式(I)化合物的一个具体实例可以是表3所示的除布雷他汀本身以外的任何化合物。

[0056] 在多种实施方案中,相对于来源于心肌的肌球蛋白II,该化合物在摩尔基础上可

更有效地抑制非肌肉肌球蛋白II。

[0057] 在另一方面中，本文描述的提供了包括调节肌球蛋白II ATP酶的治疗患者的疾病、病症或医学状况的方法，其中所述调节肌球蛋白II ATP酶包括以一定剂量以一定频率向患者施用式(I)或式(II)的至少一种化合物或者其可药用盐并持续一段时间，来为患者提供有益的作用。在多种实施方案中，所述疾病、病症或医学状况选自肾病[2]、癌症和转移，包括肝癌[3]、胰腺腺癌[4]、乳腺癌[5-6]、肺癌[7]、胶质母细胞瘤[8-11]、良性前列腺增生[12]、止血或血栓形成[13-15]、神经损伤[16](包括视网膜损伤[17])、肺纤维化[18]、肝纤维化[19]、关节纤维化[20]、伤口愈合[21-23]、脊髓损伤[24]、牙周炎[25]、青光眼[26-27]和免疫相关疾病(包括多发性硬化症)[28]。在某些实施方案中，所述疾病、病症或医学状况选自病毒感染(包括疱疹病毒[29-33])、高血压[34]、肺动脉高压[35]、慢性呼吸系统疾病[36]、心血管疾病[37]、勃起功能障碍[38]、血栓形成性疾病[13]、膀胱过度活动症[39]、心肌病[40]、痉挛[41-46]、骨骼肌病[47]和精神障碍(包括物质使用)[48]、焦虑性障碍(例如恐惧症)[49]和应激障碍(例如创伤后应激障碍)[50]。成瘾可包括滥用或成瘾于《精神障碍诊断与统计手册》(DSM)中归类为物质相关性或成瘾性病症的任何事物，所述事物例如但不限于可卡因、阿片类药物、安非他命[51-52]、乙醇、大麻(cannabis)/大麻药品(marijuana)、尼古丁以及活动(例如赌博)[53]。

附图说明

[0058] 图1(A、B、C)：通过杏仁核内施用(S)-布雷他汀(“Blebb”)(90ng/ul)引起的对METH(甲基苯丙胺)相关性记忆的持久破坏。

[0059] 图2A、2B、2C、2D：NMIIB的整合后丢失(post-consolidation loss)(A至B)产生对METH相关性记忆的持久破坏(C至D)。*P＜0.05。

[0060] 图3(A、B、C、D)：全身性NMII抑制选择性地靶向(A)METH相关性记忆的存储，(B)对听觉恐惧记忆没有影响。同样，与METH相关性记忆相关的脊柱密度降低(C)，但与恐惧记忆相关的脊柱密度则未降低(D)。

[0061] 图4：在小鼠中以10mg/kg IP给药后，布雷他汀的脑和血浆分布。

[0062] 图5：(S)-布雷他汀的结构和化合物编号方案。

[0063] 图6(A、B、C、D、E)：当隔天施用药物时，非肌肉肌球蛋白II抑制会破坏与多药物相关的记忆(A)实验设计示意图。(B)经载剂处理的小鼠在测试1中表现出显著的METH/NIC CPP，但在实验2中则没有。(C)经Blebb处理的小鼠在任一测试中均未显示出显著的METH/NIC CPP。(D)经载剂(Veh)处理的小鼠在测试1和2中显示出显著的METH/MOR CPP。(E)经Blebb处理的小鼠在任一测试中均未显示出显著的METH/MOR CPP。METH/NIC：Veh n＝10；METH/NIC：Blebb n＝10；METH/MOR：Veh n＝19；METH/MOR：Blebb n＝19；*p＜0.05，**p＜0.01，***p＜0.001。误差棒代表±s.e.m。

[0064] 图7：选定的布雷他汀类似物的心脏安全性表征：用IV药物输注的体内超声心动图评估。

具体实施方式

[0065] 记忆的物理存储位点是树突棘[54]。棘是在大多数前脑兴奋性突触中发现的小的、高度动态的突触后结构。在学习时，棘会经历对持久记忆的形成至关重要的结构和功能变

化[55-56]。这种脊柱可塑性的主力(workhorse)是肌动蛋白聚合反应,其是将肌动蛋白单体连接成复杂且分支化的丝(filament)(F-肌动蛋白)的过程[57-58]。在学习时破坏F-肌动蛋白的动力学阻止了长期记忆的形成[59-63]。然而,在突触刺激后,肌动蛋白迅速稳定,以使得在刺激的几分钟内,细胞骨架和相关性记忆就不会受到肌动蛋白解聚剂(例如拉春库林A(Latrunculin A,LatA))的破坏的影响[59,62-64]。与此形成鲜明对比的是,我们发现在支持基底外侧杏仁核复合体(BLC)(杏仁核(AMY)的一个子区域,脑的情绪记忆中心以及药物相关性记忆的枢纽(hub))中的METH相关性记忆的F-肌动蛋白,在学习之后很久仍然保持有动力。这揭示了病原性药物关联的出乎意料的弱点,为选择性地靶向METH相关性记忆的存储提供了一种机制[65]。

[0066] 重要地是,其他类型的记忆不会受到LatA的干扰,而一次饲养笼处理足以对记忆诱导的药物寻求产生立即且持久的破坏。因此,可有选择地操纵与药物相关的记忆而无需恢复[65]。

[0067] 鉴于这些结果,肌动蛋白解聚似乎是一个有希望的治疗靶标。然而,β-肌动蛋白(一种牵涉神经元可塑性的同种型[66-69])在体内普遍表达,并且对许多过程(例如细胞分裂和心脏功能)至关重要。因此,我们将我们的重点转向了非肌肉肌球蛋白II(NMII),其是突触肌动蛋白细胞骨架的一种直接调节剂。NMII是一种分子马达(molecular motor),我们证明它是突触肌动蛋白聚合和恐惧记忆的关键且时间受限的参与者[59,63]。布雷他汀的活性对映体(S)-布雷他汀是第一种也是直到最近唯一一种已知对非肌肉肌球蛋白II具有活性的抑制剂[70-73]。

[0068] 全文使用的术语布雷他汀和Blebb是指(S)-布雷他汀。本发明的布雷他汀类似物同样都是(S)-对映体。布雷他汀是市售(例如Tocris、Sigma)的,纯度>98%。使用布雷他汀,我们已经概括了所有LatA的发现,包括单一治疗在动物复发模型中足以阻止药物寻求持续至少一个月[52,74]。

[0069] 提议的发现和开发工作的依据基于过去几年中关于作为METH相关性记忆诱导的药物寻求靶标的NMII得到的一些关键发现[65,74]。

[0070] 在2013年,我们发表了一项发现,即肌动蛋白在AMY中的解聚以选择性且与恢复无关的方式破坏了METH相关性记忆的存储[65]。由于肌动蛋白解聚剂的临床潜力有限,因此我们转向了NMII,一种我们以前发现它是记忆、突触可塑性(长时程增强[LTP])和肌动蛋白在树突棘中聚合的关键调节因子的分子马达[59,63]。通过最近发表的研究中的一系列实验,我们详细介绍了NMII作为SUD复发的治疗靶标的潜力[52,74-76]。例如,通过单次BLC内或IP施用布雷他汀,我们已发现METH相关性记忆(条件性位置偏爱[CPP]测定)在成年和青春期的雄性和雌性小鼠和大鼠中被破坏(由于溶解度限制,非活性对映体用作BLC内药物递送下的对照或外消旋布雷他汀用于全身性药物递送下的对照)[52,65]。

[0071] 此外,布雷他汀阻止了情境诱导的METH寻求恢复(图1A;P<0.05至0.005),这是复发的金标准动物模型[52,74]。图1B示出了在情境A的自身给药训练期间,对METH的杠杆按压作用(lever pressing),以及在情境B中在除去METH的情况下,杠杆按压作用的随后消失。图1C示出了在第1天、第2天和第30天的无METH恢复期中,当动物返回到METH配对的环境时(情境A),杠杆按压。在单次BLC内施用布雷他汀或非活性对映体之后30分钟进行第1天的恢复测试。在第2天或第30天的恢复期之前未给予布雷他汀,表明单次施用布雷他汀会产生长期

持久的记忆破坏(至少一个月),而没有记忆的自发更新。

[0072] 已显示布雷他汀抑制所有类型的肌球蛋白II[77-79]。肌球蛋白II由轻链和重链构成,轻链在各个类别之间是可互换的,而重链则是每种肌球蛋白II同种型所独有的。重链包含肌动蛋白和ATP结合位点,以及移动肌动蛋白的力产生马达头(force generating motor head)。根据来自Miller实验室的RNA-Seq数据,成年小鼠的BLC中没有骨骼肌重链同种型表达。然而,心肌球蛋白II中的两种Myh7和Myh7b、平滑肌肌球蛋白II(Myh11)和所有三种非肌肉肌球蛋白重链同种型(Myh14、Myh10和Myh9),其中Myh10的表达最高,为数倍。在突触处发现所有六种肌球蛋白II。因此,我们采用了一种遗传方法对BLC中的MYH10进行了敏锐的局部敲低,发现其的训练后损失(图2A)足以破坏已建立的METH相关性记忆(图2B至C)[74]。有趣的是,尽管尚无蛋白质表达数据,但人AMY中的肌球蛋白II转录水平(Allen Brain Atlas)表明,从药物开发的角度来看,将NMII类作为一个整体来关注而不是仅关注NMIIB是明智的,因为NMIIA、B和C的mRNA均以相同水平表达。重要的是要注意,NMII是一类高度保守的基于肌动蛋白的分子马达。例如,小家鼠(M.musculus)Myh10与智人(H.sapiens)有99.1%的序列同源性。

[0073] 还研究了全身性NMII抑制以AMY内施用的方式选择性靶向METH相关性记忆的潜力。用IP施用Blebb的结果表明,它以足够高的浓度穿过血脑屏障以破坏METH相关性记忆(IP,10mg/kg[脑水平=90μM];图3A)。然而,这种作用仍然是选择性的,对恐惧记忆(图3B)或与食物奖励相关的记忆没有类似的即时作用[75]。IP施用布雷他汀也会破坏可卡因、尼古丁和甲氧麻黄酮的记忆再巩固,这是在治疗复发中具有另外的潜在治疗关联的结果[75-76]。此外,布雷他汀逆转了伴随METH相关性记忆的BLC脊柱密度增加(图3C),而不会改变与恐惧记忆相关的脊柱密度增加(图3D)[65,74]。

[0074] 患有物质使用病症的绝大多数个体是多药物使用者。例如,大多数METH使用者也吸烟。我们最近得到了一个与多药物使用直接相关的出乎意料的发现[76]。当同时或隔天用METH和自身不受Blebb影响的药物(尼古丁或吗啡)二者对动物进行处理时,尼古丁和吗啡记忆变得容易被Blebb直接破坏,类似于对单独METH记忆的作用(图6)。因此,当还形成METH关联时,先前不受影响的滥用药物的记忆变得容易受到NMII抑制的影响。重要的是,当用同时施用或在不同的日期分别施用的METH和其他滥用药物进行联合训练时,就会发生这种情况。我们目前正在将我们的分析扩大到其他常见滥用药物,包括其他阿片类药物,例如海洛因、酒精、可卡因和合成卡西酮。

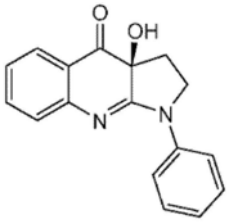
[0075] 除了在动物复发模型中的其效力外,Blebb的多种特性还使其成为药物化学的优异支架。其中最重要的是该分子的小尺寸,高脑渗透性,从血浆和脑中的迅速清除(短效作用已足够并减少了不必要的外周和中枢效应;图4)。此外,我们还在宽泛的啮齿动物行为组中观察到全身施用外消旋Blebb无作用[74]。

[0076] Blebb是在2000年代初期通过ATP酶测定在HTS活动中鉴定的[70],而且其很少的衍生物(图5)直到最近才成为唯一报道对NMII具有抑制活性的小分子。BDM(2,3-丁二酮肟)[80]一些N-苄基磺酰胺和羟基香豆素[81]抑制某些肌球蛋白II,但是它们对NMII没有活性和/或缺乏选择性,因此即使在体外研究中也不能用作可行的探针。自其发现以来,Blebb已被广泛用作体外探针。由于暴露在蓝光下会发生光灭活[73],因此开发了通过简单修饰制成的类似物(包括硝基衍生物)以建立光稳定性。[82-84]在下一部分中可找到对这些化合物的更多讨论。

[0077] Blebb是布雷他汀的(s)-构型(图5)。自发现以来,已经针对许多肌球蛋白ATP酶[70,73,77,85-88]并且在许多细胞/组织中[77,86-92]测定了其生物化学和细胞效力。据报道,多种肌球蛋白II中Blebb的生物化学IC_{50}值为1.8至9μM[77]。尚未报道基于细胞的测定中的特定IC_{50}值,但已显示Blebb在约900nM至90μM的宽浓度范围内均有效[79,86-87,93-94],表明Blebb具有细胞渗透性,与我们自己的数据一致。围绕Blebb的核芯结构进行了有限SAR[70],这可能是由于NMII抑制剂的治疗潜力仅在过去几年才实现。为了获得更具选择性的NMII抑制剂作为可行的药物候选物,需要对Blebb进行修饰和优化。

[0078] 如合成方案1至7(下文)中一般描述的那样,合成了当前类别的布雷他汀类似物,并将其在表1中进行体外表征。表1中列出的本发明化合物的化学结构示于下表3中。合成方案1是可用于制备具体实施例和通用结构权利要求中所述的结构的合成方法的概述,而合成方案2至7是某些具体实施例和通用结构权利要求中所述的结构的合成方法不同实施方案的实施例。

[0079] 表1列出了本发明化合物(布雷他汀类似物)的性质,其相对于心肌球蛋白II而言对非肌肉肌球蛋白II具有大于3.0的抑制选择性。如下所讨论的,相对于布雷他汀,对心肌球蛋白II具有明显更低的抑制活性(更高的Ki)化合物可表现出更低的心脏毒性。

[0080] 表1列出了选择性抑制化合物,其由Ki/EC50的该比例定义,其结构示于表3中,根据也在图中示出的具有相应的化学结构的独特化合物标识符。本发明的所有化合物具有与(S)-布雷他汀相同的绝对构型,并且基于母体环结构  (S)-3a-羟基-1-苯基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮。在本发明的某些类似物、化合物中,(S)-布雷他汀中的苯环可被取代,并且可被多种未经取代或经取代的杂芳基环替代。

[0081] 出于比较的目的,提供了顶部行的数据用于布雷他汀本身。布雷他汀的比率(CMMII/NMII)为0.789,表明母体化合物关于抑制心肌球蛋白II的Ki值低于非肌肉肌球蛋白II的EC50值,即该化合物对肌球蛋白II的心脏形式比其对肌球蛋白II的非肌肉形式具有更强效的抑制活性。本发明所有化合物或表1中所示的用于实施本发明方法的化合物在抑制心肌球蛋白II方面的Ki值相对于所述化合物在抑制非肌肉肌球蛋白方面的EC50值高至少三倍。

[0082] 表1的第一列提供了该化合物的独特数字标识符,其中每一个的结构均在表3中示出。表1的第二、第三和第四列提供了有关所示化合物光稳定性的数据。与布雷他汀相比,许多用于实施本发明方法的化合物表现出比布雷他汀明显更高的光稳定性。这些列(光稳定性)提供了在一定条件下在4小时和24小时光照后该化合物保持未降解的百分比值,与在相当条件下在黑暗中保持未降解的百分比相比较。已知布雷他汀在某种程度上是光不稳定的,并且光稳定性的改善在配制用于向经历治疗的患者施用的药物组合物中是有益的。

[0083] 表1的第五列提供了由所示化合物抑制非肌肉肌球蛋白II而确定的EC50值(μM)。这些数字如生物测定部分中所述的那样获得。第六和第七列给出了抑制心肌球蛋白II的Ki值(μM)以及相对于非肌肉肌球蛋白II的心肌肌球蛋白抑制比率。第八栏给出了骨骼肌肌球

蛋白II的抑制作用。对于标记为NMII选择性的化合物(“NMII-sel”),无法确定心肌球蛋白II的Ki值;该化合物没有相对于心肌球蛋白II的可检测的抑制特性。第九列示出了受试样品的手性纯度。

[0084] 表1.所选布雷他汀类似物的体外表征数据

[0085]

	光稳定性			NMII	CMMII	CMMII:NMII 比率	SKMMII	手性 HPLC 纯度
标识符	4 小时	24 小时	黑暗 (24小时)	EC50 (μM)	K_I (μM)	Ki/EC50	K_I (μM)	%
布雷他汀	82.9	9.3	>99	1.9	1.5	0.8	0.36	>99
BPN-0025044	90.3	12.1	>99	5.2	28.0	5.4	7.00	97.0
BPN-0025059	96.1	48.6	>99	5.1	120.0	23.5	22.00	>99
BPN-0025100	82.8	4.7	99.0	7.5	48.0	6.4	9.70	>99
BPN-0025110	6.6	2.6	>99	3.2	22.0	6.9	8.00	>99
BPN-0025240	93.0	28.6	94.7	10.2	400.0	39.2	35.00	>99
BPN-0025254	92.5	39.4	>99	4.6	n/a	NMII-sel	7.70	>99
BPN-0025903	39.8	7.5	98.3	6.4	n/a	NMII-sel	11.00	95.4
BPN-0025919	ND	ND	ND	3.9	18.0	4.6	1.80	91.7
BPN-0026282	64.0	7.0	>99	48.0	n/a	NMII-sel	n/a	87.5
BPN-0026283	39.4	10.8	92.0	3.5	n/a	NMII-sel	5.00	96.7
BPN-0026285	51.9	8.2	94.7	1.6	9.1	5.7	0.90	>99
BPN-0026324	98.5	90.4	>99	2.2	30.0	13.6	3.50	>99
BPN-0026325	89.0	14.0	97.8	5.3	n/a	NMII-sel	13.00	>99
BPN-0026387	85.2	18.0	93.5	2.5	13.0	5.2	1.20	98.2
BPN-0026393	97.9	75.0	>99	3.4	11.0	3.2	1.70	>99
BPN-0026394	>99	98.7	>99	3.8	n/a	NMII-sel	4.80	98.25
BPN-0026401	81.2	9.6	97.7	3.0	50.0	16.7	3.30	99.0

[0086]

BPN-0026404	ND	ND	ND	3.3	23.0	7.0	3.60	>99
BPN-0026413	94.3	82.2	97.3	36.0	110.0	3.1	33.00	49.5
BPN-0026457	98.6	77.1	>99	5.3	n/a	NMII-sel	15.00	96.5
BPN-0026495	80.9	15.9	93.4	6.6	n/a	NMII-sel	20.00	>99
BPN-0026496	41.7	3.5	97.9	2.6	83.0	31.9	15.00	>99
BPN-0026497	82.7	6.1	97.5	2.1	33.0	15.7	9.80	>99
BPN-0026499	97.7	84.9	>99	0.5	5.7	12.4	0.18	92.7
BPN-0026500	92.2	22.8	>99	2.4	n/a	NMII-sel	23.00	>99
BPN-0026533	87.7	6.4	91.7	33.0	n/a	NMII-sel	60.00	47.7
BPN-0026544	51.1	10.8	93.7	5.3	n/a	NMII-sel	4.80	93.0
BPN-0026545	89.4	5.1	>99	7.0	n/a	NMII-sel	12.00	92.1
BPN-0026546	81.2	12.5	93.5	8.9	n/a	NMII-sel	22.00	85.1
BPN-0026576	98.6	>99	>99	5.5	18.0	3.3	4.60	98.9
BPN-0026579	77.3	8.5	93.7	1.0	5.0	5.0	0.37	98.5
BPN-0026605	69.6	2.3	94.2	1.0	15.0	15.0	0.29	>99
BPN-0026606	85.9	4.1	95.5	5.9	n/a	NMII-sel	n/a	98.6
BPN-0026607	98.5	84.7	98.1	6.1	n/a	NMII-sel	5.80	96.1
BPN-0026608	86.7	<1	97.5	4.3	50.0	11.6	1.70	95.3
BPN-0026609	ND	ND	ND	1.5	5.5	3.7	0.43	98.5
BPN-0026618	92.3	17.2	96.6	4.8	18.0	3.8	5.90	>99
BPN-0026619	77.4	<1	91.0	1.6	36.0	22.5	2.50	99.0

[0087]

BPN-0026620	94.1	27.8	92.8	6.4	n/a	NMII-sel	16.00	>99
BPN-0026621	93.3	61.4	93.5	5.7	40.0	7.0	3.40	83.0
BPN-0026624	90.5	88.2	92.2	15.0	210.0	14.0	24.00	>99
BPN-0026638	87.9	71.9	91.6	1.7	12.0	7.1	0.37	94.3
BPN-0026639	89.8	49.5	>99	3.3	14.0	4.2	1.10	>99
BPN-0026640	71.1	17.8	96.8	2.0	8.0	4.0	0.53	89.6
BPN-0026643	64.0	<1	85.1	4.8	17.0	3.5	1.90	>99
BPN-0026648	94.3	84.3	97.7	4.7	56.0	11.9	4.50	91.3
BPN-0026650	80.5	5.5	>99	4.9	n/a	NMII-sel	4.30	>99
BPN-0026651	73.0	5.8	97.5	3.3	n/a	NMII-sel	3.90	96.3
BPN-0026659	72.1	17.9	91.1	2.6	9.0	3.5	0.93	93.2
BPN-0026660	87.4	7.6	93.8	8.2	n/a	NMII-sel	33.00	>99
BPN-0026661	95.5	65.4	98.2	2.4	53.0	22.1	2.20	89.4
BPN-0026662	85.4	7.5	>99	1.1	6.0	5.5	0.19	97.6
BPN-0026663	40.7	2.0	97.3	0.8	2.8	3.5	0.12	>99
BPN-0026664	30.3	<1	97.7	0.9	29.0	33.3	1.50	95.8
BPN-0026665	2.7	<1	97.4	0.6	4.2	6.7	0.14	>99
BPN-0026667	85.7	2.9	>99	1.2	6.2	5.2	0.33	98.6
BPN-0026669	87.8	11.2	>99	5.3	25.0	4.7	1.20	>99
BPN-0026693	34.1	1.7	>99	0.6	3.5	6.0	0.27	53.0
BPN-0026708	40.7	<1	>99	1.7	5.3	3.1	1.40	83.5

[0088]

BPN-0026709	98.7	93.0	98.2	1.2	30.6	25.5	1.30	95.7
BPN-0026710	6.6	<1	>99	1.7	5.2	3.1	0.95	92.2
BPN-0026726	76.3	24.1	95.4	6.0	n/a	NMII-sel	4.40	95.8
BPN-0026745	>99	94.2	>99	2.9	73.0	25.2	2.60	97.7
BPN-0026746	58.8	10.6	>99	4.5	17.0	3.8	3.60	98.3
BPN-0026748	88.2	22.4	>99	3.0	14.0	4.7	2.60	96.7
BPN-0026749	87.8	<5	>99	3.2	n/a	NMII-sel	23.00	>99
BPN-0026770	>99	92.9	>99	3.8	n/a	NMII-sel	1.50	>99
BPN-0026774	86.7	18.1	>99	2.6	8.9	3.4	1.10	>99
BPN-0026785	95.8	59.3	91.6	7.4	23.0	3.1	5.90	>99
BPN-0026786	87.8	66.6	96.0	11.0	n/a	NMII-sel	n/a	>99
BPN-0026813	82.0	<1	>99	0.5	1.6	3.1	0.11	>99
BPN-0026815	91.2	88.2	90.2	0.8	2.8	3.6	0.27	91.2
BPN-0026819	96.6	84.8	97.3	1.8	50.0	27.8	1.70	>99
BPN-0026847	99.0	91.8	>99	13.0	n/a	NMII-sel	n/a	>99
BPN-0026848	>99	98.7	>99	26.0	320.0	12.3	61.00	66.7
BPN-0026849	98.5	91.8	>99	1.0	16.0	16.0	0.77	>99
BPN-0026852	62.4	3.8	85.1	2.6	25.0	9.6	5.60	81.8
BPN-0026853	91.2	88.2	90.2	12.0	n/a	NMII-sel	n/a	98.9
BPN-0026881	70.9	1.8	>99	1.8	11.0	6.1	0.80	>99
BPN-0026882	98.8	96.8	>99	5.8	21.0	3.6	4.50	>99

[0089]

BPN-0026886	>99	98.5	>99	2.7	19.0	7.0	4.20	87.8
BPN-0027036	90.2	24.7	97.4	3.0	22.0	7.3	4.90	>99
BPN-0027037	>99	>99	>99	24.0	n/a	NMII-sel	18.00	69.1
BPN-0027038	>99	98.7	>99	2.7	17.0	6.3	0.61	>99
BPN-0027039	89.8	31.3	95.9	22.0	68.0	3.1	4.60	49.3
BPN-0027040	94.8	21.4	95.7	1.2	37.0	30.8	2.60	94.1
BPN-0027042	92.7	13.8	>99	6.7	n/a	NMII-sel	10.00	>99
BPN-0027043	97.7	72.3	>99	2.9	n/a	NMII-sel	15.00	89.1
BPN-0027071	>99	95.3	>99	10.0	n/a	NMII-sel	20.00	45.6
BPN-0027072	>99	>99	>99	10.0	31.0	3.1	5.00	96.3
BPN-0027074	95.8	93.4	94.5	21.0	77.0	3.7	16.00	>99
BPN-0027080	98.1	88.1	>99	3.0	n/a	NMII-sel	4.80	>99
BPN-0027081	97.0	46.3	96.9	1.1	9.0	8.2	0.29	89.8
BPN-0027108	>99	97.0	>99	2.8	n/a	NMII-sel	10.00	>99
BPN-0027109	82.5	29.4	>99	0.5	11.0	21.2	0.27	91.4
BPN-0027118	68.6	9.2	94.4	1.2	5.5	4.6	0.68	84.2
BPN-0027121	75.6	6.5	98.6	2.5	19.0	7.6	2.70	70.3
BPN-0027122	69.5	5.3	97.1	1.7	45.0	26.5	5.90	82.7
BPN-0027159	89.9	22.5	>99	14.0	n/a	NMII-sel	330.00	>99
BPN-0027160	95.5	73.0	>99	2.9	30.0	10.3	0.20	81.9
BPN-0027161	78.6	60.2	98.3	1.1	24.0	21.8	0.24	73.7

[0090]

BPN-0027162	98.5	95.9	>99	7.9	52.0	6.6	4.50	77.2
BPN-0027163	95.0	44.6	>99	4.2	21.0	5.0	5.90	92.4
BPN-0027181	>99	99.0	>99	2.7	91.0	33.7	3.10	97.5
BPN-0027196	94.9	7.1	>99	7.5	n/a	NMII-sel	12.00	75.2
BPN-0027197	>99	36.4	>99	2.5	n/a	NMII-sel	2.40	58.8
BPN-0027198	89.9	21.4	>99	2.9	10.5	3.6	0.88	72.8
BPN-0027213	46.3	1.0	85.0	2.9	33.0	11.4	0.45	79.2
BPN-0027215	73.2	9.2	97.3	0.4	n/a	NMII-sel	1.00	>99
BPN-0027216	97.2	85.0	>99	2.7	31.0	11.5	4.60	>99
BPN-0027217	97.9	76.0	>99	7.8	160.0	20.5	21.00	>99
BPN-0027218	90.0	4.4	95.5	6.9	n/a	NMII-sel	40.00	49.1
BPN-0027219	46.2	3.8	98.3	39.0	n/a	NMII-sel	n/a	50.0
BPN-0027228	>99	89.1	>99	28.0	300.0	10.7	4.60	70.8
BPN-0027236	>99	84.9	>99	5.9	N/A	NMII-sel	5.00	55.9
BPN-0027237	79.8	15.8	82.7	11.0	50.0	4.5	6.70	40.8
BPN-0027238	>99	>99	>99	4.1	n/a	NMII-sel	3.70	90.8
BPN-0027240	94.1	74.6	98.0	3.8	n/a	NMII-sel	n/a	82.3
BPN-0027241	91.6	87.0	97.4	13.0	100.0	7.7	7.20	54.2
BPN-0027250	45.8	2.7	70.1	1.0	n/a	NMII-sel	1.00	78.1
BPN-0027255	82.4	42.2	98.3	1.9	n/a	NMII-sel	0.80	71.5
BPN-0027257	97.0	78.0	97.4	5.9	40.0	6.8	4.20	96.7

[0091]

BPN-0027289	91.9	26.3	97.0	1.7	50.0	29.4	1.00	95.8
BPN-0027330	92.7	64.6	>99	10.0	80.0	8.0	4.20	>99
BPN-0027346	97.7	98.7	98.1	4.8	33.0	6.9	2.00	>99
BPN-0027374	96.9	86.4	>99	8.7	n/a	NMII-sel	0.82	68.8
BPN-0027376	90.4	2.8	97.0	5.9	46.0	7.8	6.70	89.5
BPN-0027393	95.2	83.9	97.5	5.2	30.0	5.8	3.50	96.3
BPN-0027394	92.2	57.2	98.7	4.1	14.0	3.4	1.10	>99
BPN-0027396	85.5	23.5	>99	1.8	9.5	5.3	1.10	74.1
BPN-0027406	75.7	1.6	>99	53.0	200.0	3.8	7.50	84.0
BPN-0027410	91.5	41.8	>99	3.4	25.0	7.4	1.60	96.8
BPN-0027411	81.8	6.4	98.8	6.3	51.0	8.1	1.10	74.7
BPN-0027412	90.8	67.7	95.5	5.8	21.0	3.6	2.70	>99
BPN-0027441	97.2	71.4	91.8	50.0	230.0	4.6	12.00	64.4
BPN-0027468	83.3	77.5	98.3	4.0	n/a	NMII-sel	1.20	62.6
BPN-0027469	58.8	44.3	>99	2.0	n/a	NMII-sel	0.68	90.6
BPN-0027488	49.4	20.0	96.4	0.8	n/a	NMII-sel	0.90	>99
BPN-0027489	76.1	8.5	>99	0.8	26.0	33.3	0.94	85.0
BPN-0027490	80.8	6.8	98.5	0.7	n/a	NMII-sel	0.41	97.0
BPN-0027491	54.0	6.7	97.1	2.3	24.0	10.4	0.68	84.9
BPN-0027492	95.1	66.9	>99	2.9	n/a	NMII-sel	2.60	89.5
BPN-0027494	63.5	<1.0	88.4	4.2	n/a	NMII-sel	4.70	无结果

[0092]

BPN-0028550	92.7	77.6	89.4	9.3	70.0	7.5	9.40	50.7
BPN-0028552	87.7	62.2	91.8	1.2	26.0	21.7	2.50	71.1
BPN-0028554	87.6	35.9	97.6	9.7	120.0	12.4	9.00	91.6
BPN-0028555	4.7	<1	93.6	0.8	4.6	6.1	1.50	64.2
BPN-0028616	93.2	71.0	89.4	15.0	200.0	13.3	11.00	50.8
BPN-0028625	84.4	84.6	81.8	5.3	300.0	56.6	8.90	46.3
BPN-0028646	>99	97.1	98.2	4.5	n/a	NMII-sel	1.30	>99
BPN-0028648	52.5	<1	98.4	1.3	4.4	3.4	0.26	82.7
BPN-0028649	96.7	73.1	98.4	4.2	30.0	7.1	2.70	62.9
BPN-0028650	88.7	62.6	93.4	9.1	40.0	4.4	12.00	70.0
BPN-0028652	86.2	22.8	98.5	8.3	80.0	9.6	1.30	>99
BPN-0028694	55.3	11.2	98.0	1.9	16.0	8.4	1.70	82.0
BPN-0028697	88.4	25.4	97.3	8.0	60.0	7.5	1.90	98.4
BPN-0028731	37.6	7.4	>99	5.2	40	7.7	2.2	81.1
BPN-0028733	82.1	14.8	96.6	8.7	27	3.1	6.8	74.8
BPN-0028734	76	<1	96.3	3	15	5.0	2.9	86.1
BPN-0028736	64	2	95.3	13	90	6.9	1.5	91.1
BPN-0028758	90.9	55.3	93.3	51	210	4.1	40	91
BPN-0028760	87.9	83	87.6	3.7	16	4.3	0.94	40.3
BPN-0028790	92.7	64	95.3	0.63	2.4	3.8	1	>99
BPN-0028820	80.9	62.7	94.2	7.2	N/A	NMII-sel	3	85.2

[0093]

BPN-0028821	89.8	29.1	98.5	0.96	12	12.5	0.77	84.1
BPN-0028863	98.8	94.7	99	2.6	N/A	NMII-sel	2.8	91.2
BPN-0028864	97.4	88.4	98.4	7	N/A	NMII-sel	12	65.4
BPN-0028866	77.8	2.9	97.8	10	N/A	NMII-sel	400	82.8
BPN-0028867	69.9	1	98.7	2.8	N/A	NMII-sel	1.3	88.2
BPN-0028868	46.7	43.3	98.9	0.76	24	31.6	0.23	88.5
BPN-0028897	82.8	5.4	98.4	9	300	33.3	110	52.4
BPN-0028898	93.4	58.1	96.4	3	95	31.7	1.9	>99
BPN-0028899	70.8	29.7	97.8	1.5	N/A	NMII-sel	3.8	86.1
BPN-0028918	54.2	7.8	>99	2	11	5.5	0.64	97.2
BPN-0028919	48.4	<1	98.5	2.8	N/A	NMII-sel	1.4	95.4
BPN-0028920	36.6	2.5	98.4	3.2	N/A	NMII-sel	3.9	97.5
BPN-0028921	2.8	3.1	97.2	0.75	8.4	11.2	1	95.9
BPN-0028922	86.1	27.7	94.8	1.1	9.7	8.8	0.77	95.3
BPN-0028923	77.5	1	98.1	3.5	30	8.6	6	>99
BPN-0028924	44.7	<1	97.7	1.7	20	11.8	2.6	88
BPN-0028925	85.9	24.7	93.7	0.8	5.8	7.3	0.7	99

[0094] 下表2和图7提供了概述两种不同的心脏安全性测定的数据。第一种(结果示于表2)评估了我们的化合物对心肌细胞收缩性的作用。随着心脏Ki的提高,收缩性作用急剧下降。然而,与成年心脏不同,此测定中使用的hiPS心肌细胞表达NMII,这很可能解释了在最高受试剂量下所见的残留的收缩性作用。因此,我们转向了体内超声心动图,该超声心动图评估了活体动物的收缩性(图7)。与我们对心肌细胞的研究结果相似,无论NMII效力如何,提高心脏Ki均可抵御在布雷他汀的情况下所观察到的显著的收缩性作用。因此,本发明的化合物和用于实施本发明方法的化合物可产生比布雷他汀更小的心脏毒性。

[0095] 表2:选定的布雷他汀类似物的心脏安全性表征I:

[0096] 评估hiPS来源的心肌细胞的跳动参数。

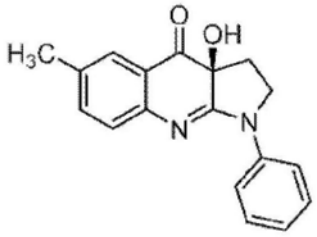
[0097]

化合物	NMII EC50	CMMII Ki	CMMII/NMII 比率	对收缩性的定性影响（例如，完全影响（Full）=完全抑制收缩）	15 分钟时 1 uM 下的幅度变化
布雷他汀	1.2 uM	0.67 uM	0.56	注意：基线 0.1 uM：无影响 0.3 uM：部分影响 1.0 uM：完全影响 3.0 uM：完全影响	-57.9± 12.8%
BPN-0025059	5.1 uM	47.2 uM	9.25	注意：效力降低，选择性、溶解度、光稳定性提高 0.1 uM 至 1.0 uM：无影响；3.0 uM：影响很小	+1.1± 0.1%
BPN-0025060	0.78 uM	0.48 uM	0.62	注意：效力提高，选择性略有提高，溶解度/光稳定性更差 类似于 Blebb	-81.8± 86.9%
BPN-0025100	7.5 uM	26.3 uM	3.51	注意：效力降低，但选择性和溶解度得到合理提高 0.1 uM 至 1.0 uM：无影响；3.0 uM：影响很小	-7.8±1.3%

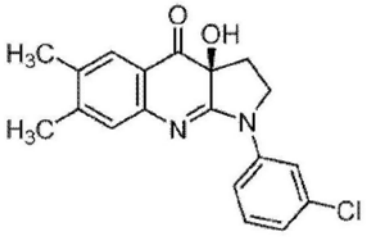
[0098]

BPN-0025002	2.6 uM	1.97 uM	0.76	注意：效力略有降低，但选择性略有提高 类似于 Blebb	-38.9± 2.4%
BPN-0025046	26.8 uM	1.74 uM	0.07	注意：效力降低和向心脏选择性的大转变 类似于 Blebb	-47.6± 5.2%
BPN-0025098	无 活性	无活性	N/A	注意：胞质分裂不活跃，溶解度提高（86 uM 与 Blebb = 9.3 uM） 在任何剂量下均无影响	+2.0±2.8%

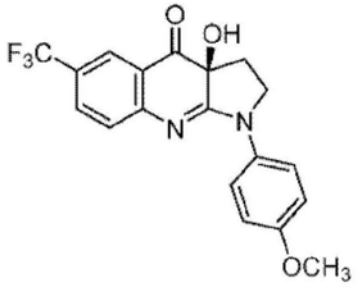
[0099] 表3:用于本发明方法的化合物的结构



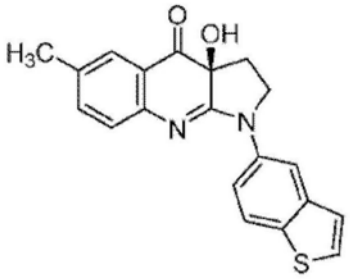
BPN-0024998 （布雷他汀，对照）



BPN-0026500

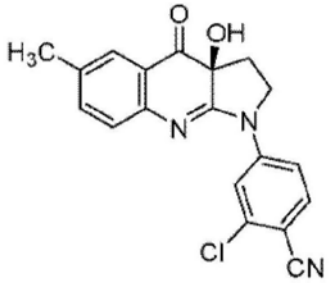


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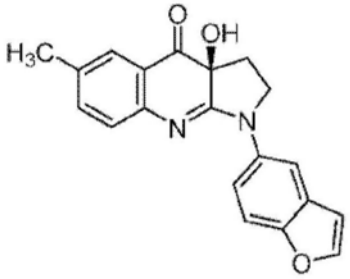


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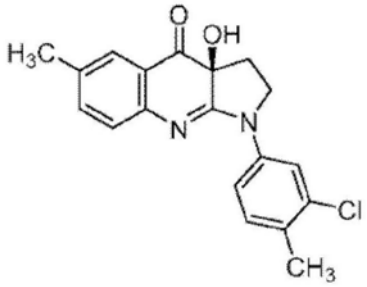
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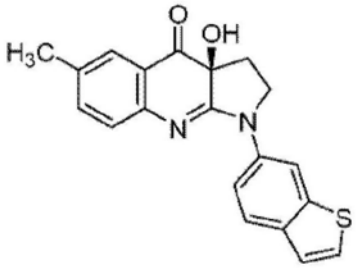
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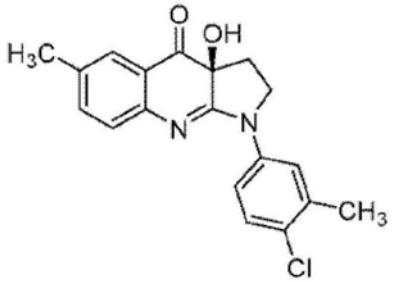
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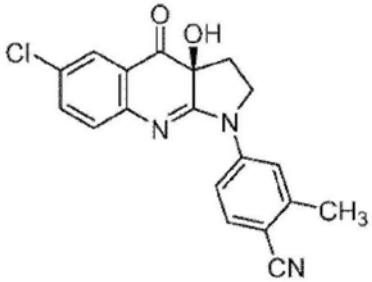
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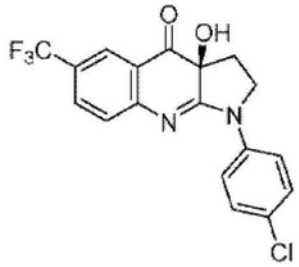
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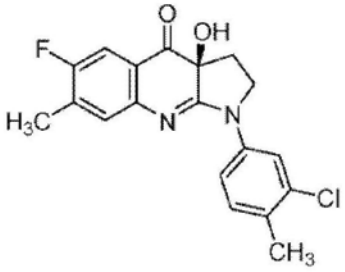
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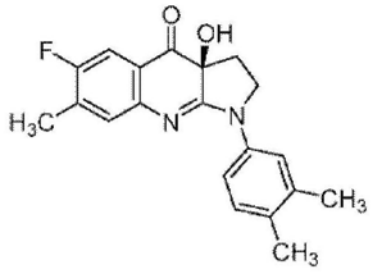
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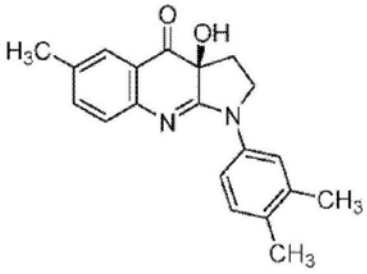
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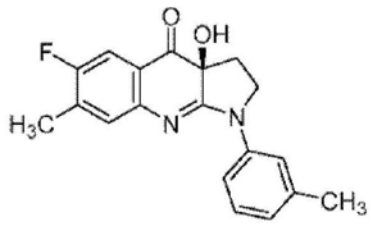


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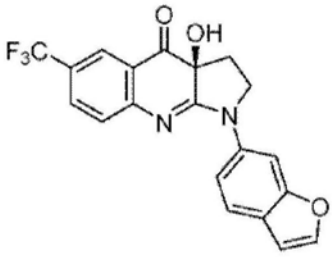


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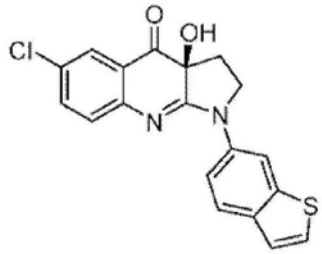
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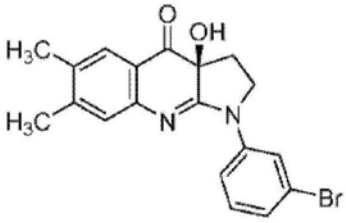
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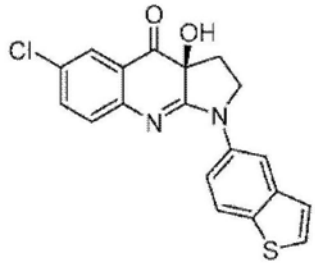
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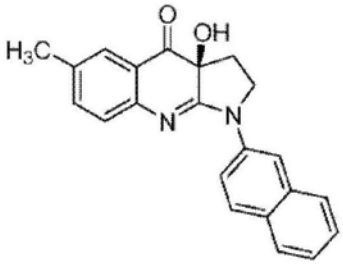
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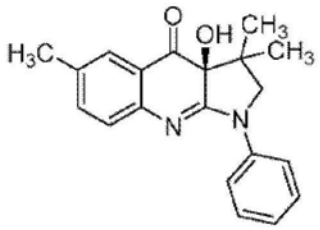
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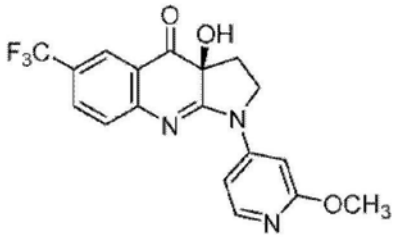
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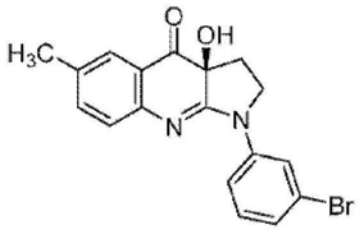
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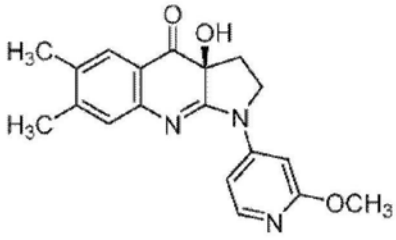
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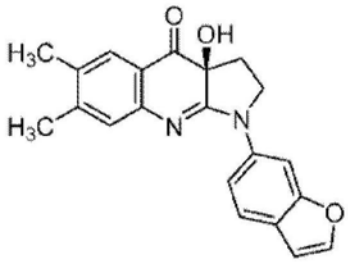


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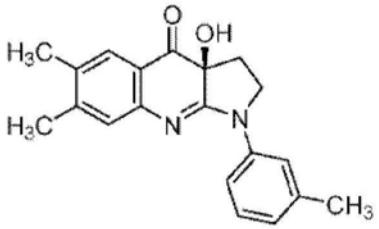


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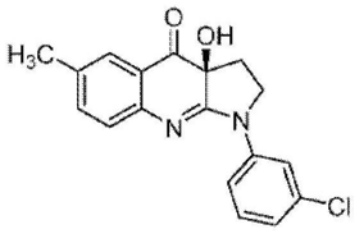
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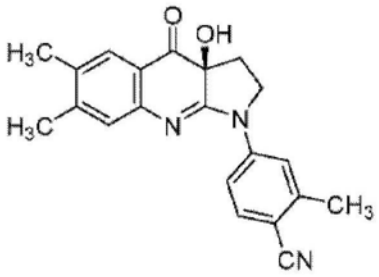
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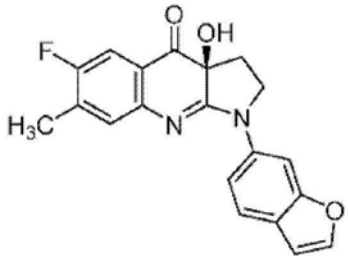
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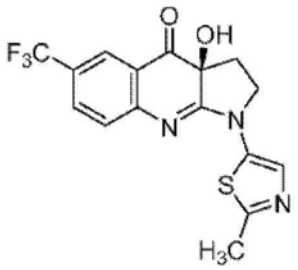
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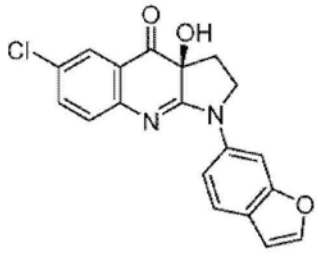
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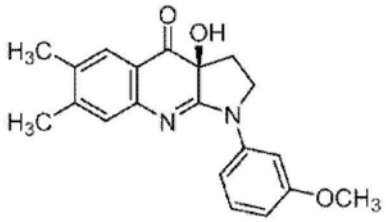
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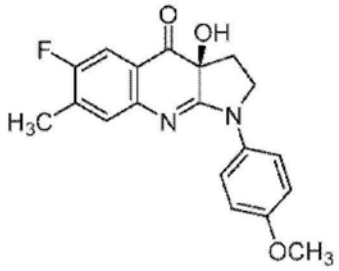
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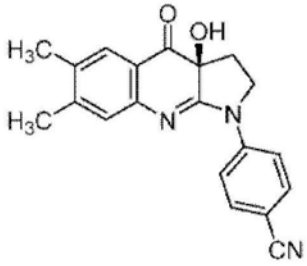
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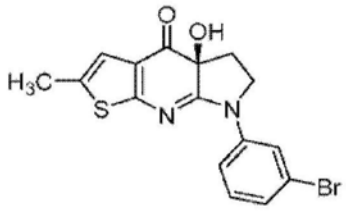


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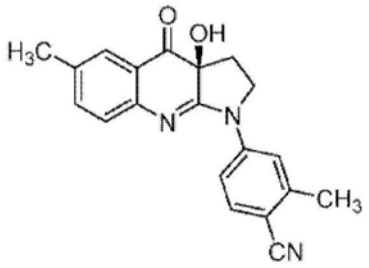


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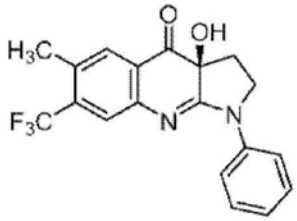
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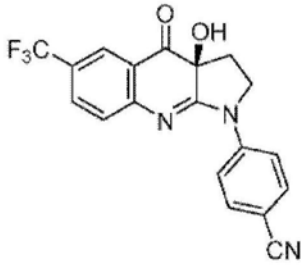
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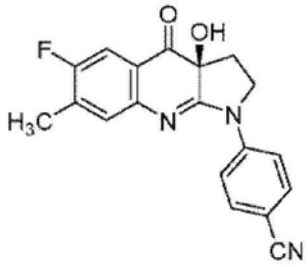
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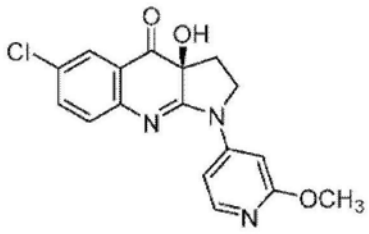
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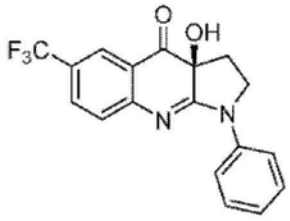


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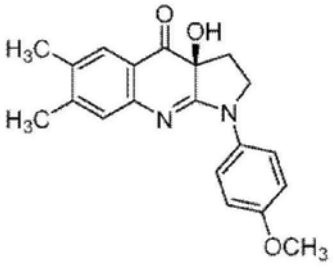


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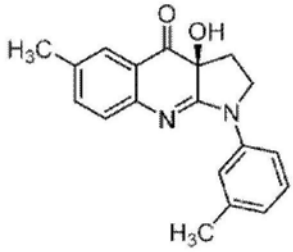
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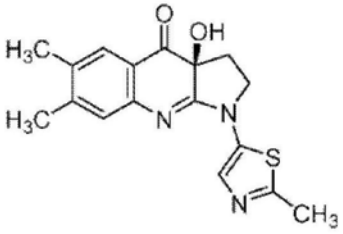
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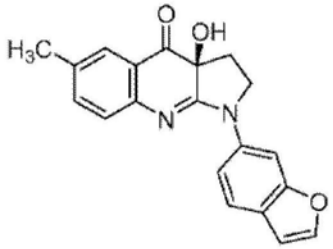
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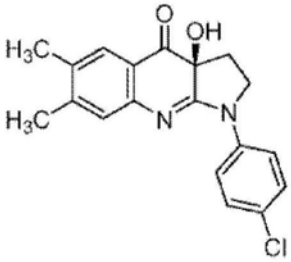
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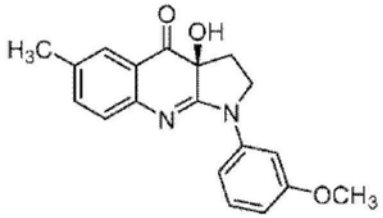
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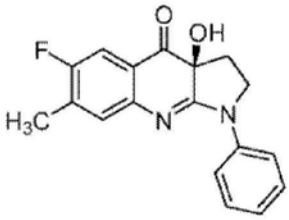
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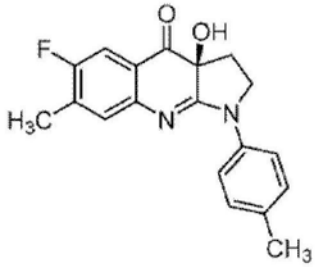
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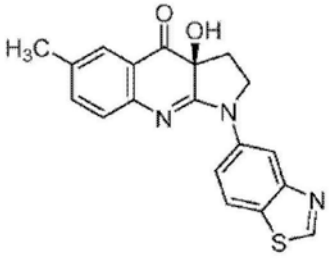
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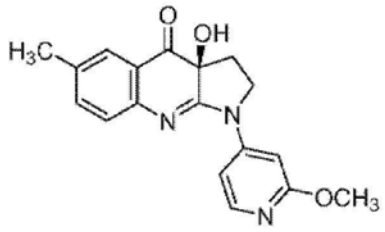
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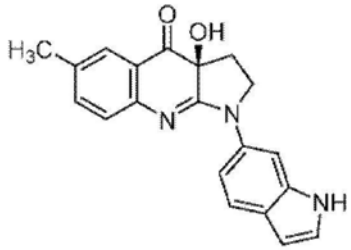
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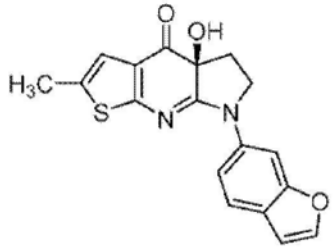
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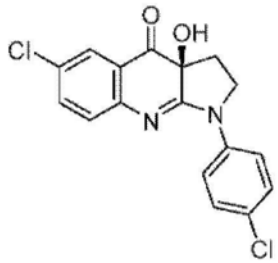
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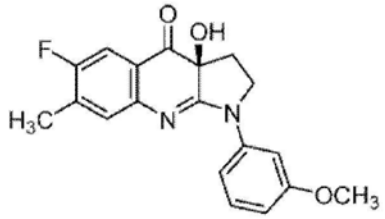


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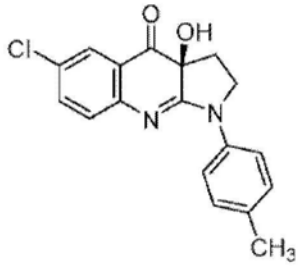


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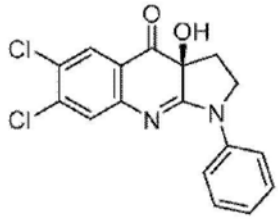
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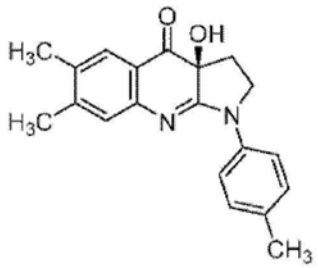
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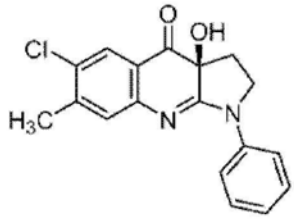
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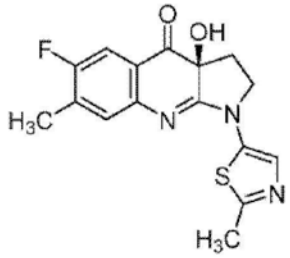
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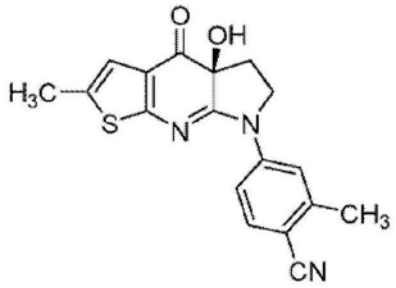
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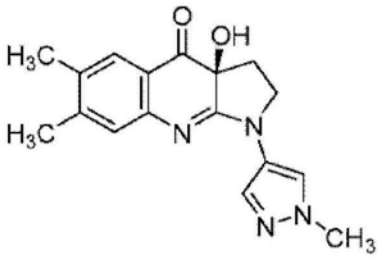
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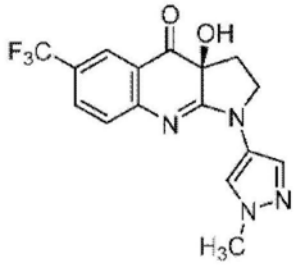
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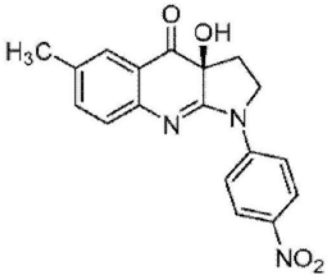
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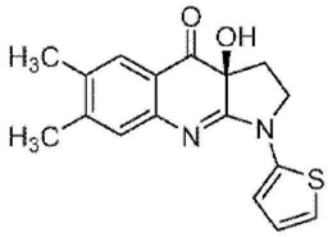


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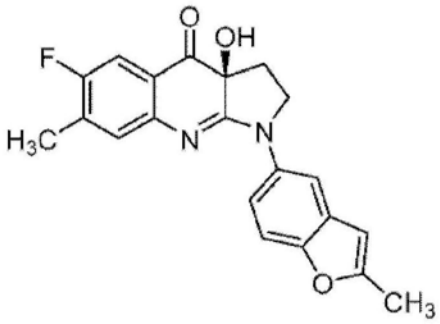


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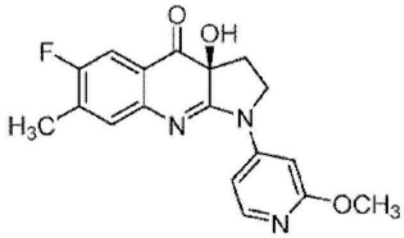
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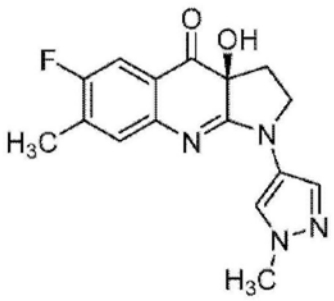
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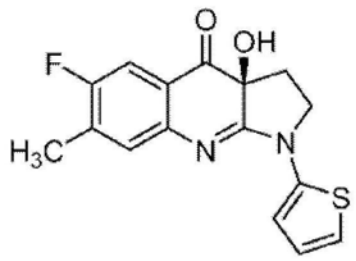
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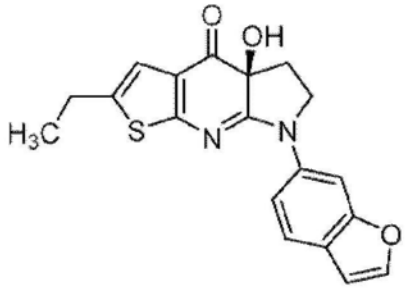
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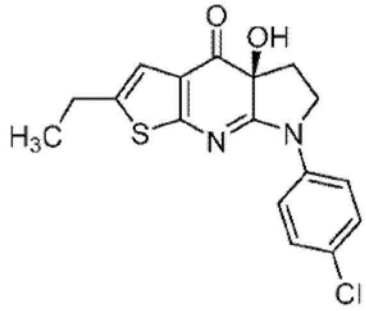
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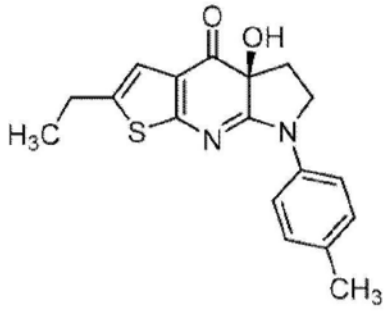
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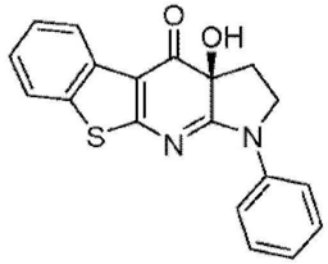


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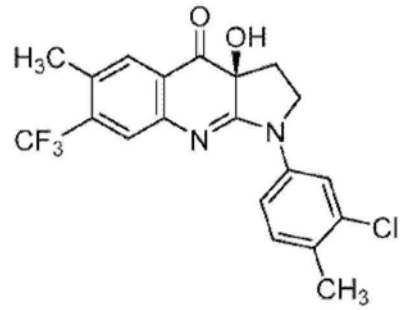


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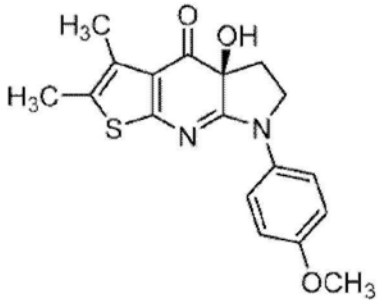
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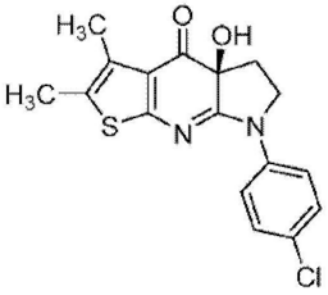
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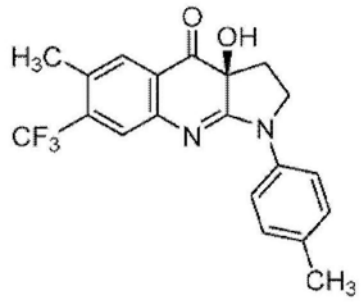
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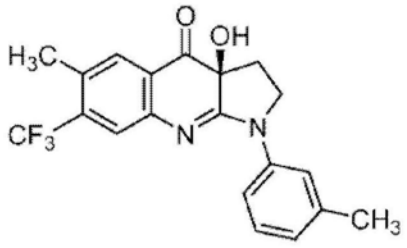
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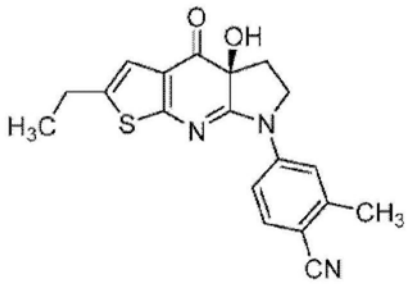
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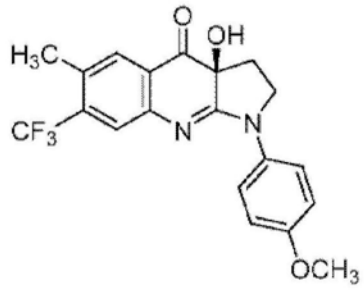
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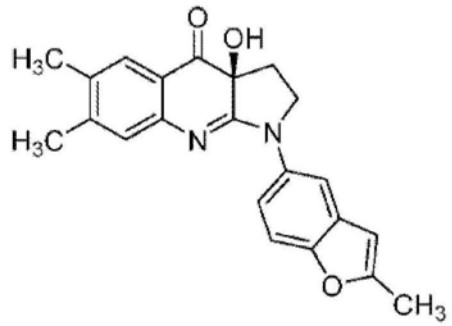


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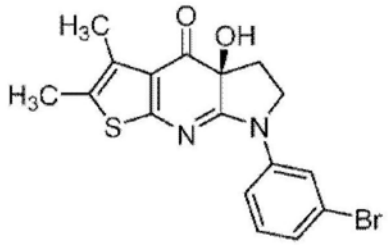


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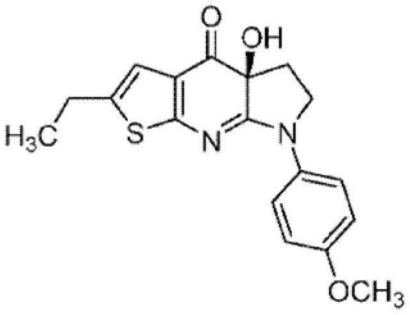
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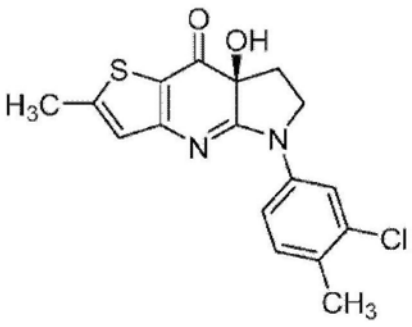
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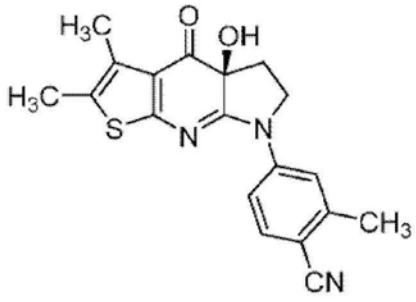
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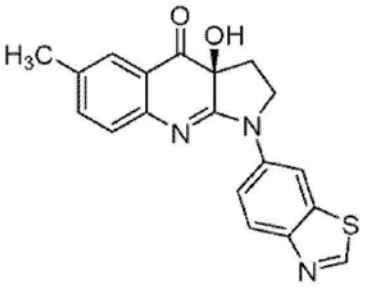
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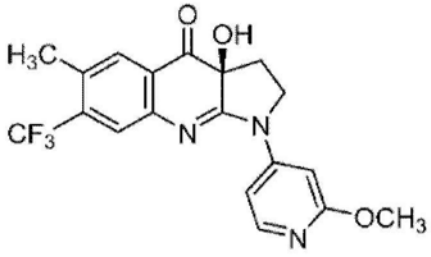
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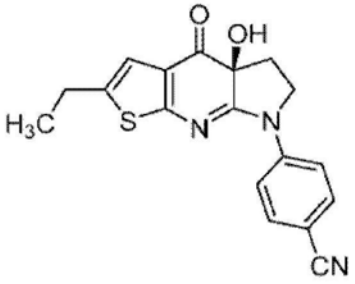
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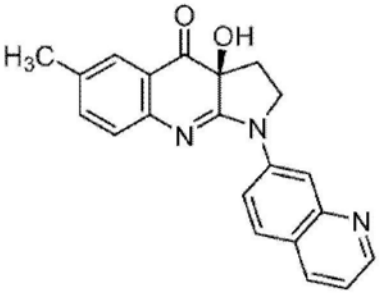


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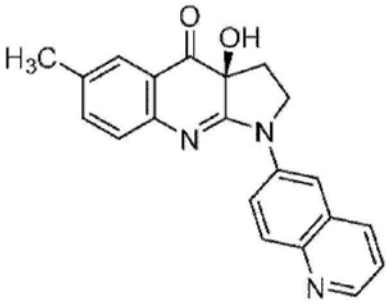


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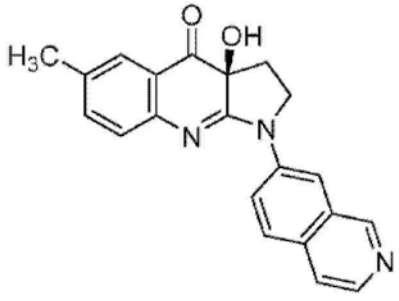
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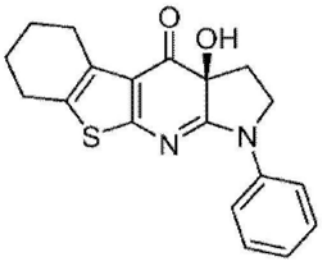
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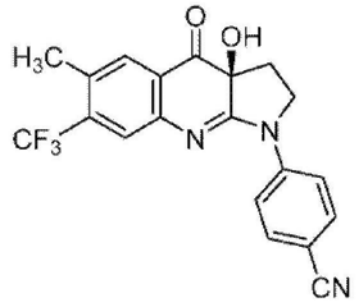
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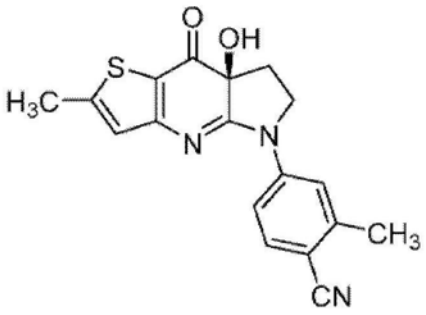
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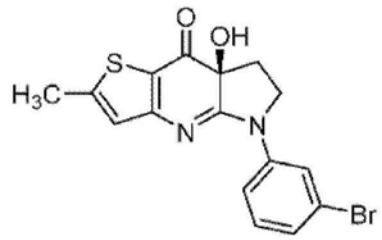
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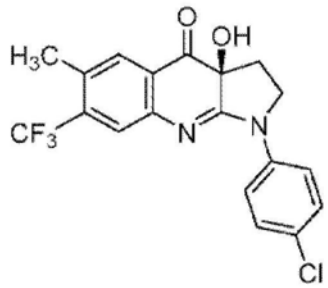
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BPN-0027072

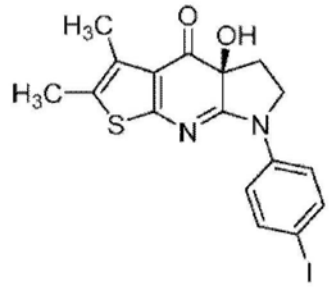


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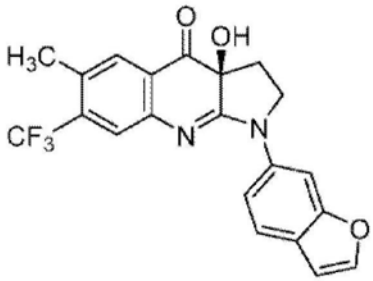


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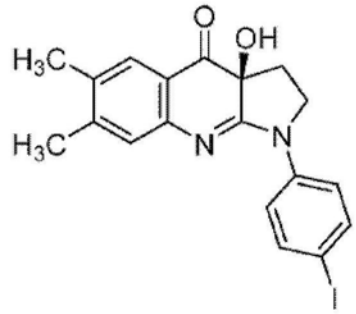
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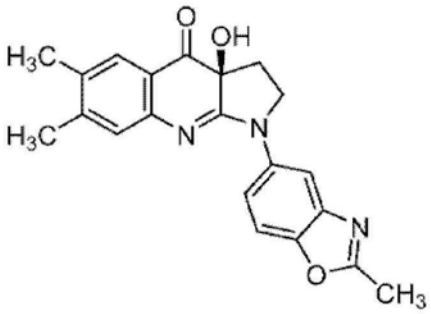
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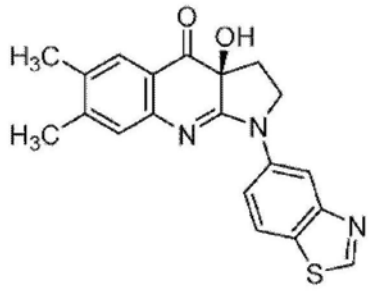
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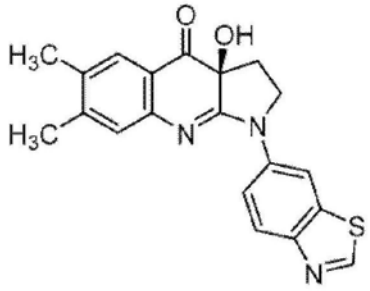
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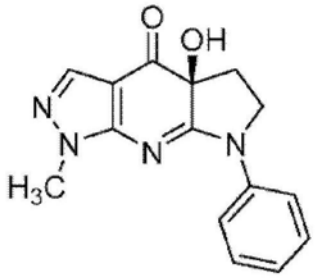
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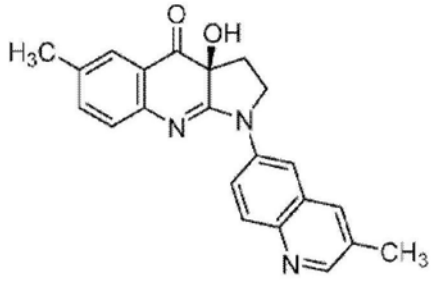
BPN-0027121



BPN-0027122

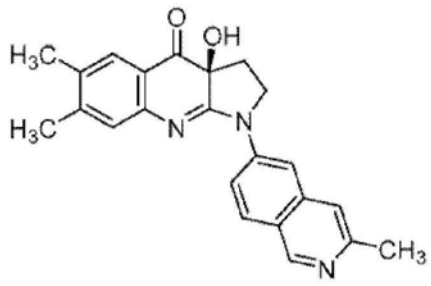


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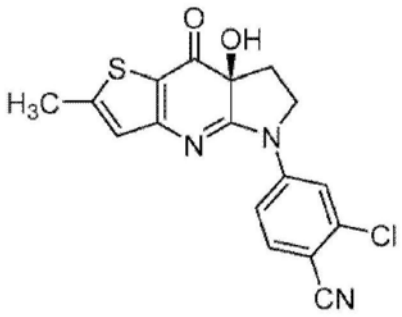


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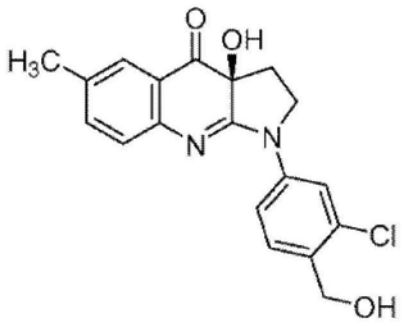
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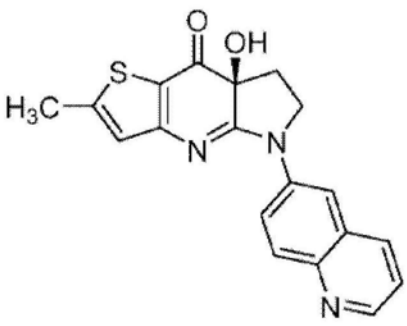
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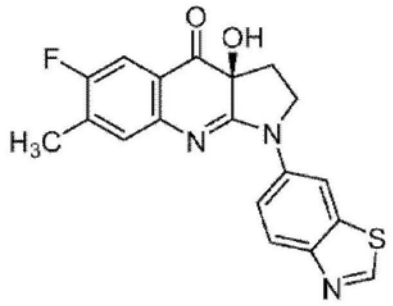
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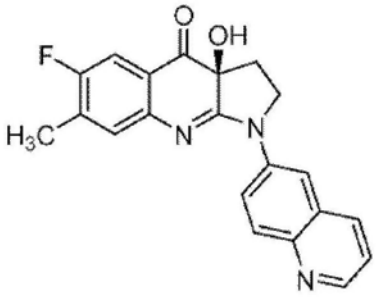
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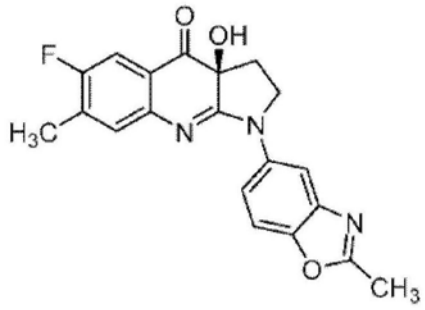
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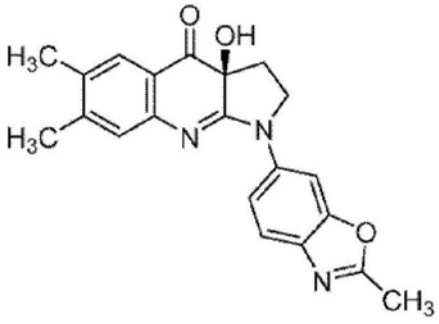
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BPN-0027197

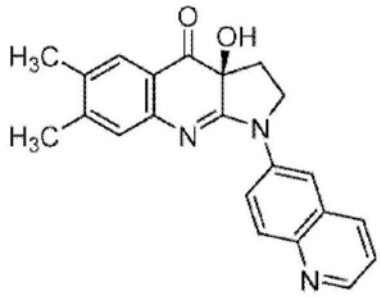


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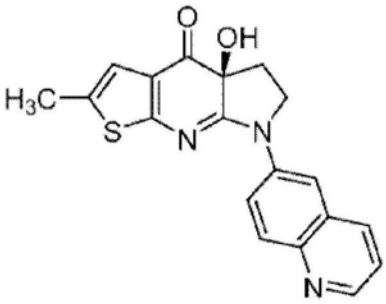


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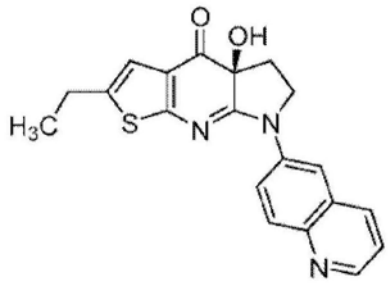
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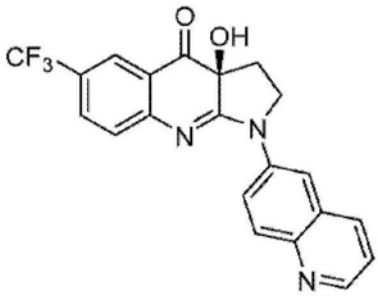
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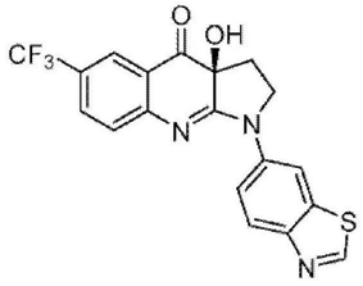
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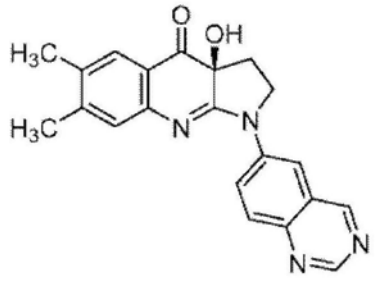
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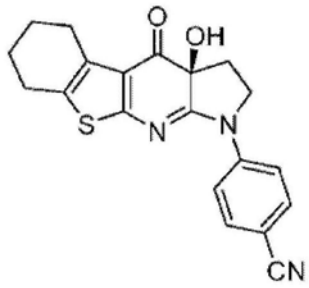
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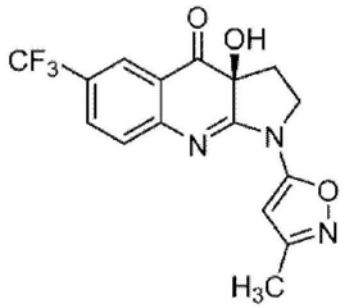
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BPN-0027228

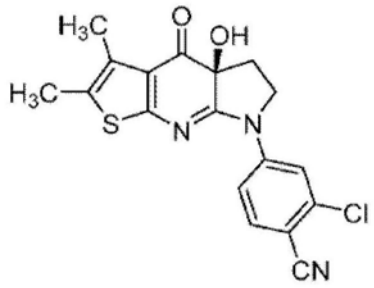


BPN-0027236

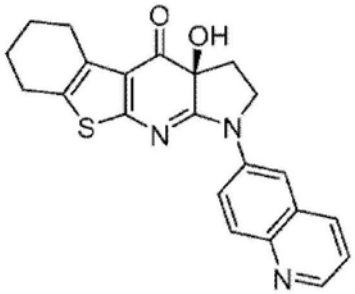


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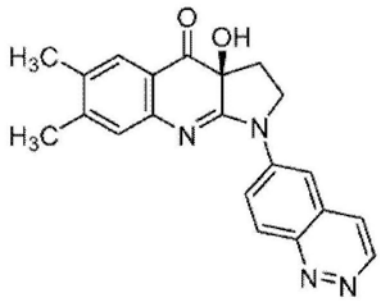
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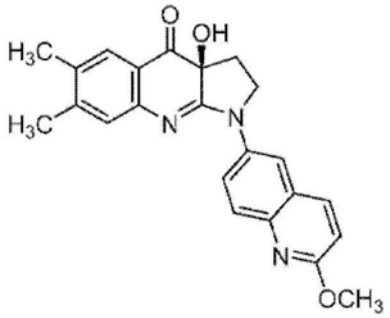
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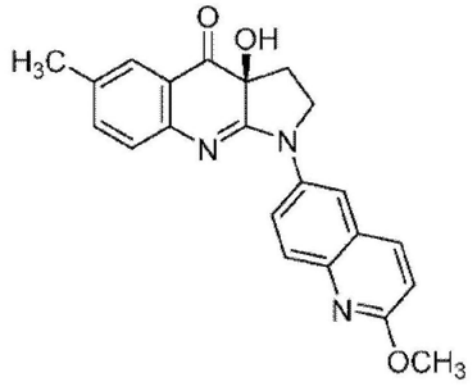
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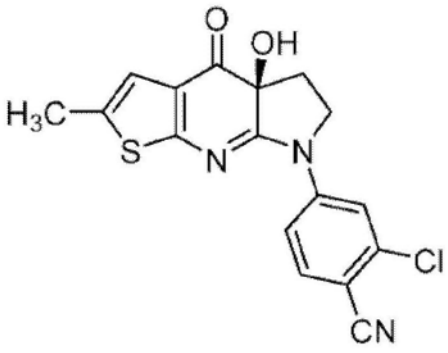
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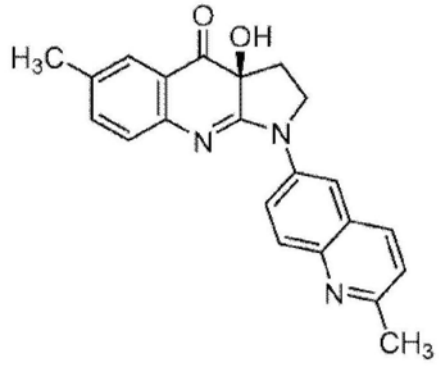


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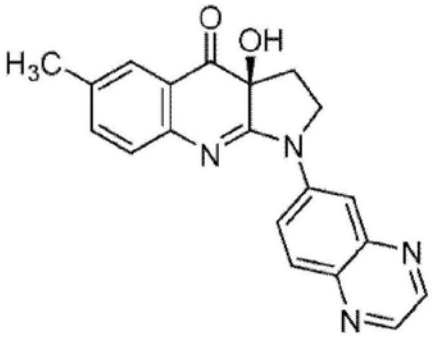


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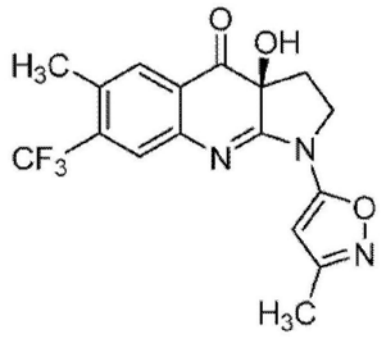
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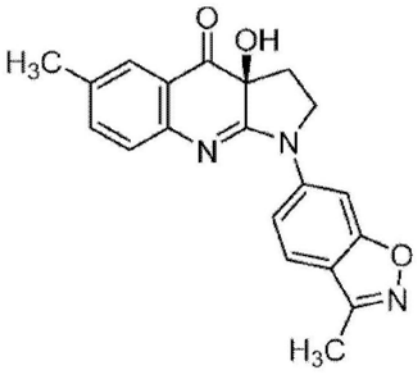
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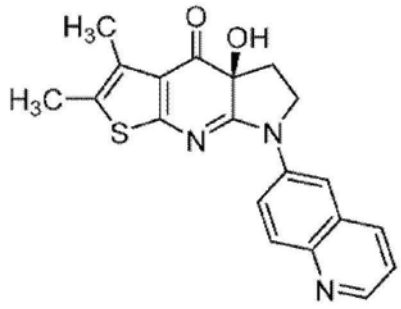
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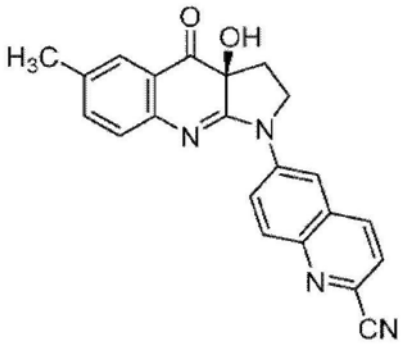
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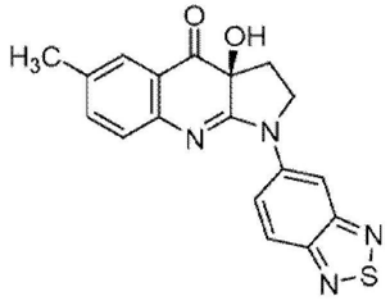
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BPN-0027376

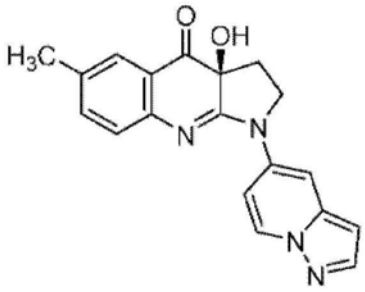


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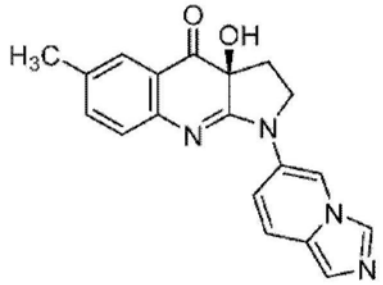


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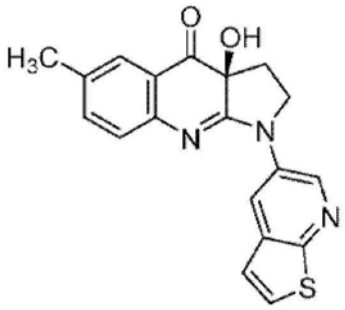
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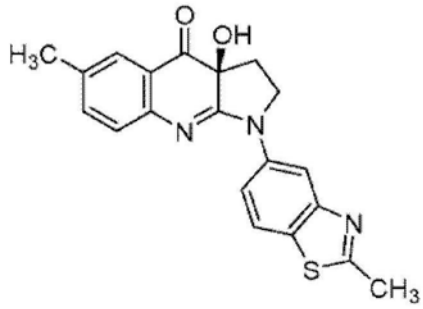
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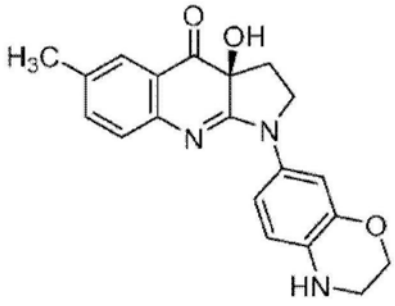
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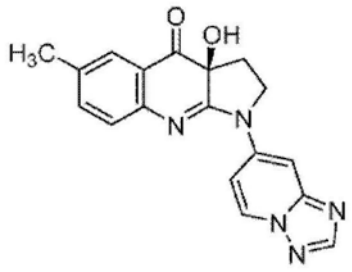
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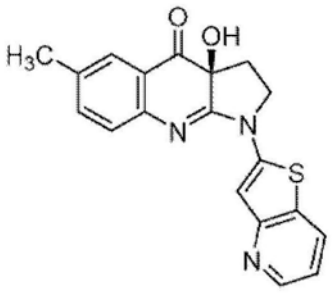
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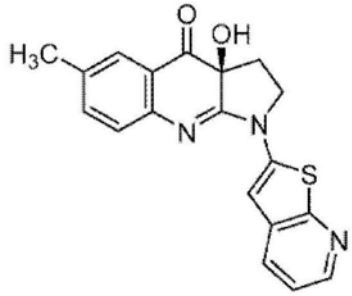
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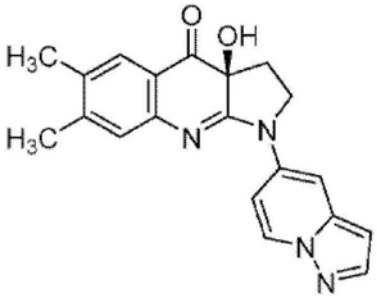
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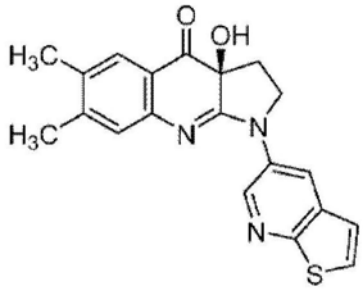


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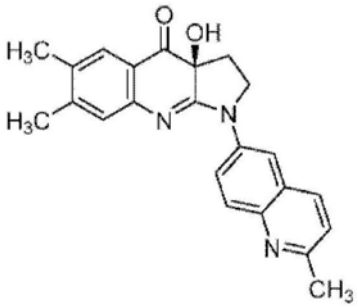


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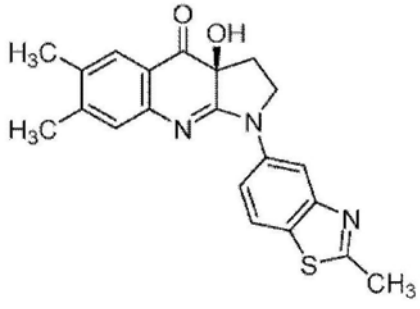
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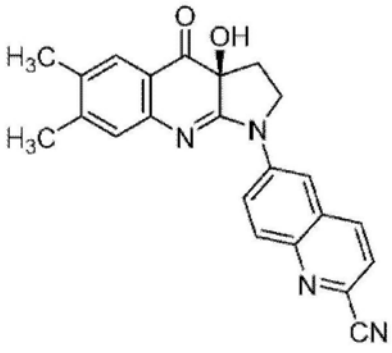
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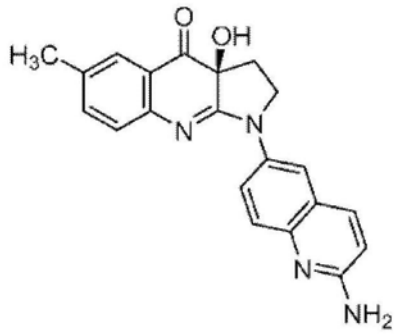
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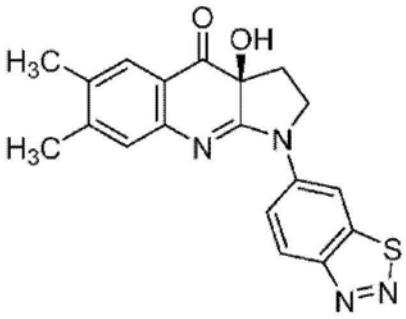
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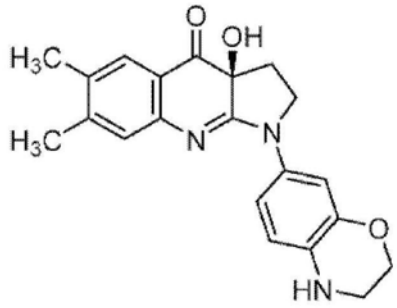
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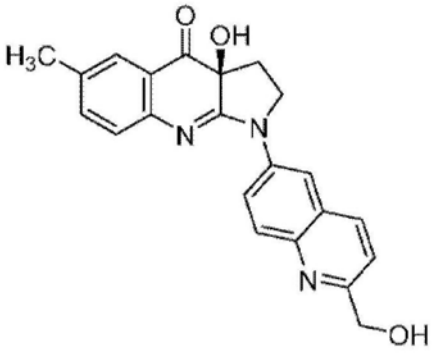
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BPN-0028550

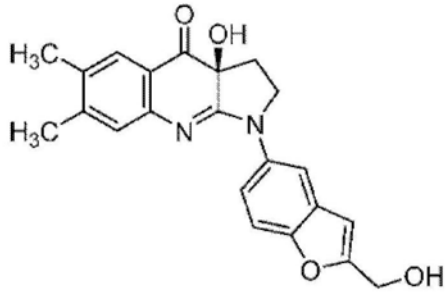


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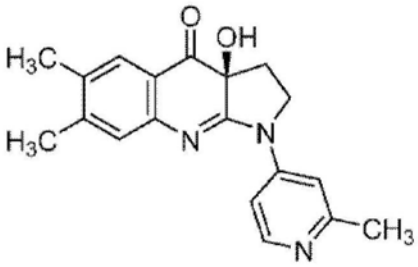


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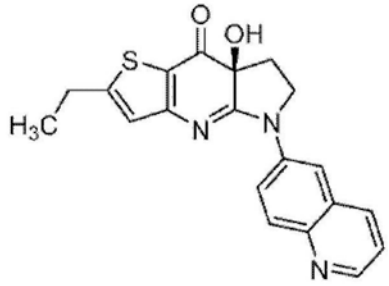
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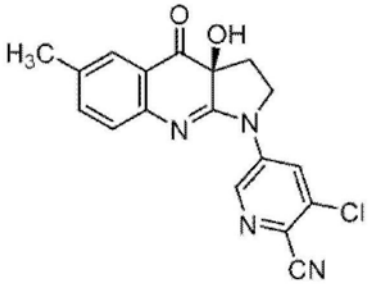
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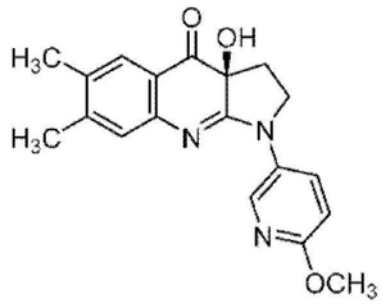
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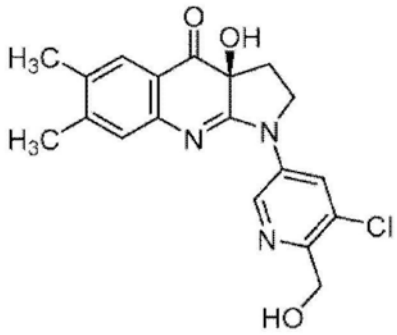
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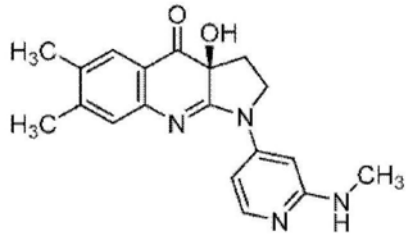
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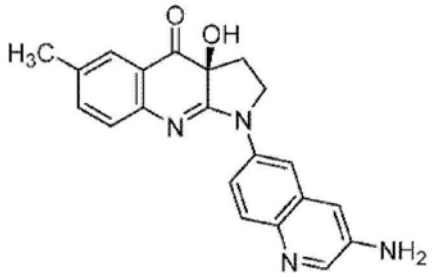
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BPN-0028649

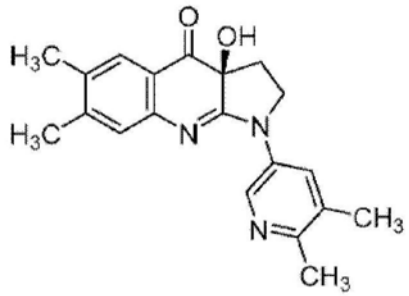


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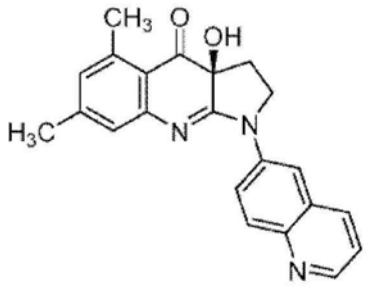


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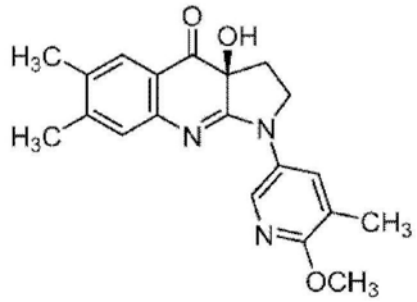
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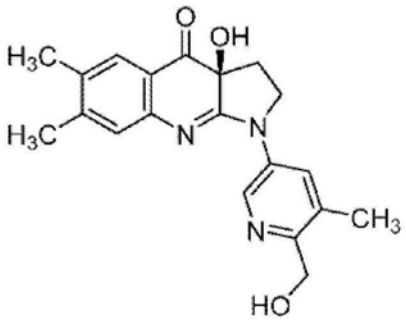
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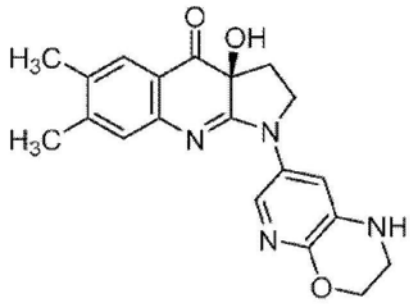
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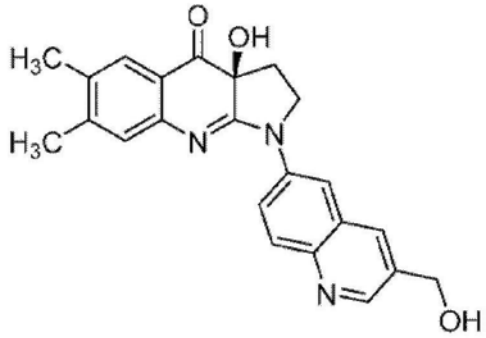
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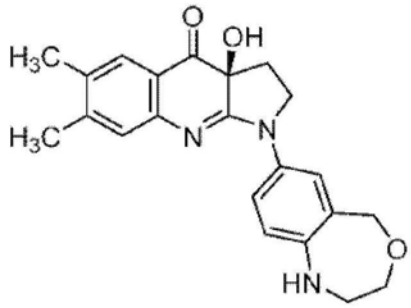
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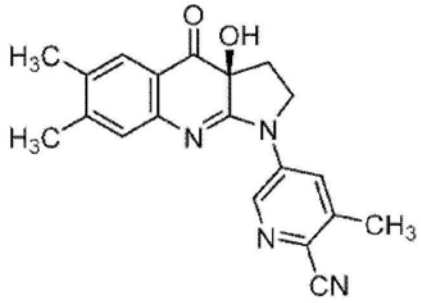
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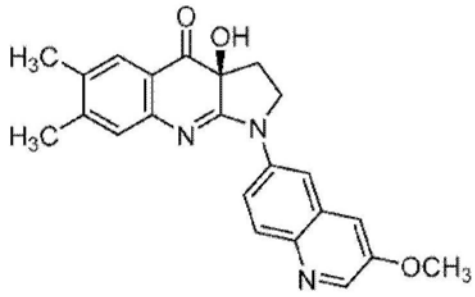


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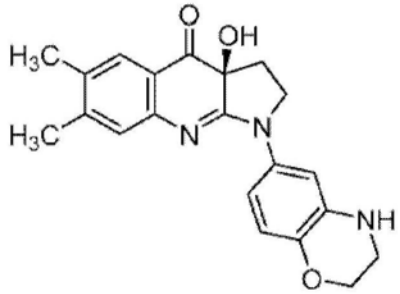


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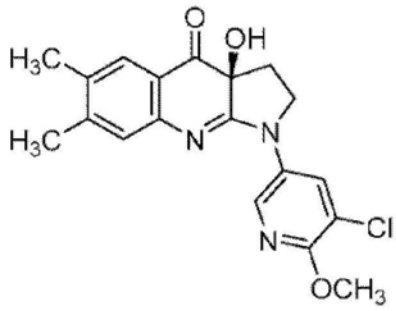
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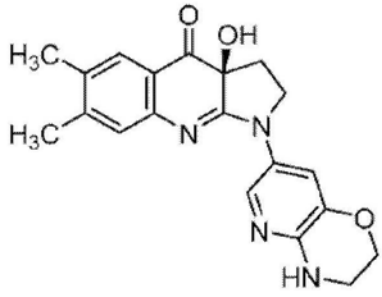
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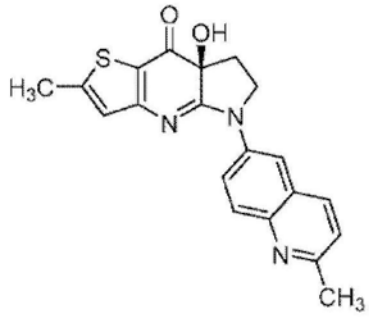
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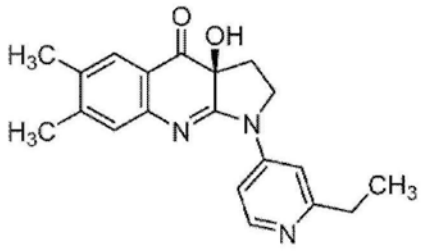
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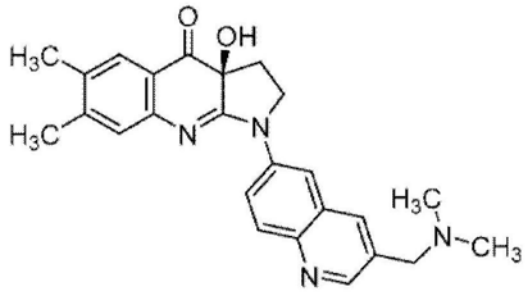
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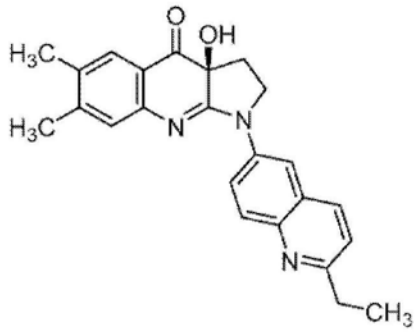
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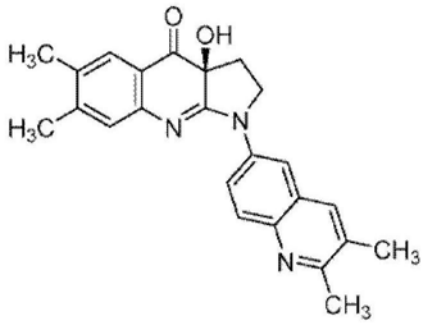


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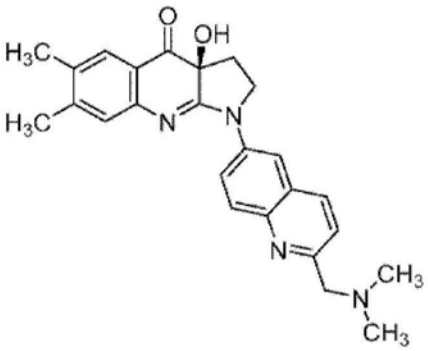


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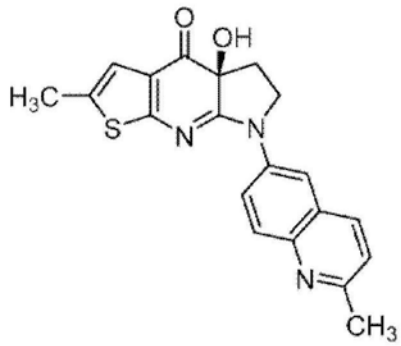
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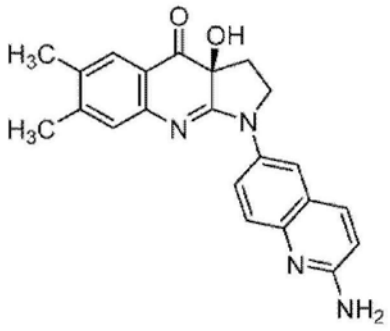
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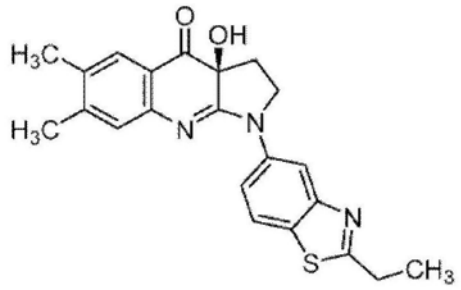
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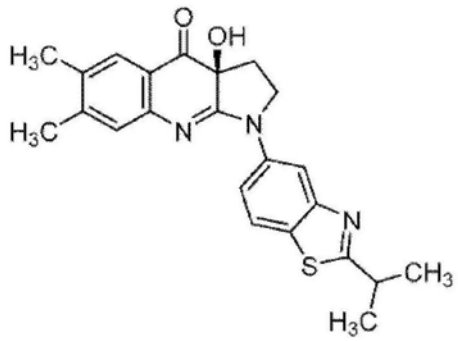
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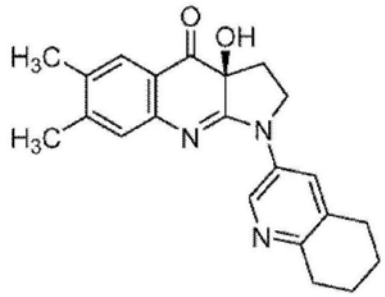
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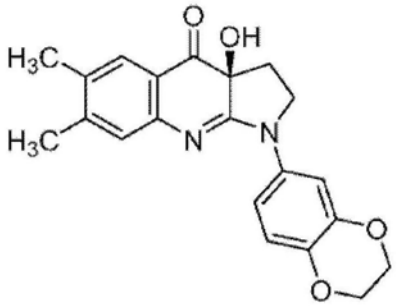


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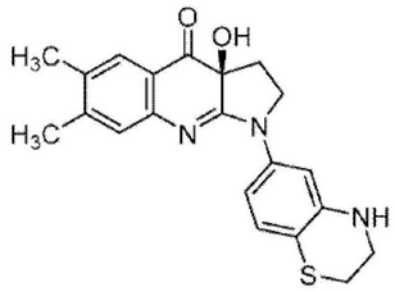


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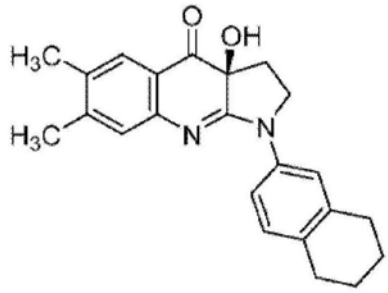
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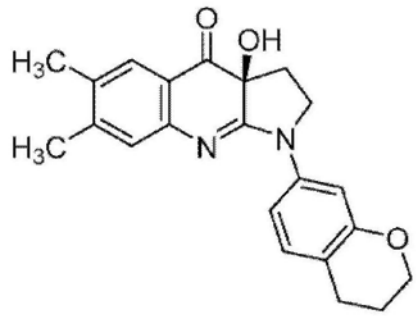
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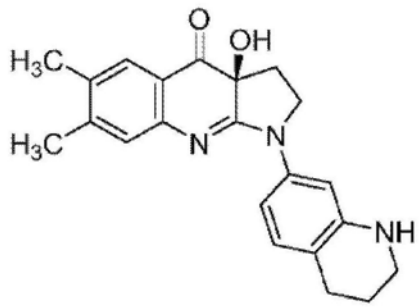
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[0122] 布雷他汀类似物生物测定方法

[0123] 1.测定心肌肌球蛋白II

[0124] 心肌肌球蛋白II肌动蛋白激活的ATP酶测定是一种生物化学测定。具体而言，它是

依赖于NADH荧光作为读数的NADH(烟酰胺腺嘌呤二核苷酸)偶联的ATP酶测定。心肌球蛋白是一种机械化学能换能器,其在其激活剂F-肌动蛋白存在的情况下水解ATP产生力。所得的ADP通过丙酮酸激酶(PK)再生为ATP,该丙酮酸激酶将一分子磷酸烯醇丙酮酸(PEP)并行转化为丙酮酸。随后,丙酮酸被乳酸脱氢酶(LDH)还原为乳酸,其转而将一分子的NADH氧化为NAD。

[0125] 因此,NADH浓度随时间的降低等于ATP水解速率。牛心肌球蛋白可从商业来源Cytoskeleton获得。PK、LDH、ATP、PEP和NADH从Sigma获得。F-肌动蛋白是从Rabbit Muscle Acetone Powder在内部(in house)制备的。该测定在384孔黑壁聚苯乙烯微孔板中于25℃进行,每孔总体积为20μl。用EnVision多模式读板器监测NADH荧光30分钟。荧光响应的斜率可通过简单的线性回归确定,其与反应速率成比例。最终测定条件为在含有10mM 3-(N-吗啉代)丙烷磺酸(pH=7.0)、2mM $MgCl_2$、0.15mM乙二醇-双(β-氨基乙基醚)-N,N,N',N'-四乙酸、0.1mg/mL牛血清白蛋白、0.5%(V/V)二甲基亚砜(DMSO)和1mM二硫苏糖醇的缓冲液中的300nM心肌球蛋白、10μM肌动蛋白、40U/ml LDH、200U/ml PK、220μM NADH、1mM PEP、1mM ATP。在测试化合物的抑制活性之前,在DMSO中制备从10mM化合物浓度开始的两倍稀释系列。随后,将100nl转移至含有肌球蛋白、LDH和PK混合物的测量板的每个孔中。通过添加包含ATP、PEP、NADH和肌动蛋白的混合物开始酶促反应。最终化合物的最高浓度为50uM。0.5%DMSO中的20μM对氨基布雷他汀作为阳性对照,而单独0.5%DMSO为阴性对照。反应速率通过使用所有板中包括的NADH稀释系列的荧光响应来确定,并绘制为抑制剂浓度的函数。所有测量均重复进行三次。通过将16点剂量响应数据拟合到对应于简单的一对一结合模型的二次方程式来确定抑制常数。在其溶解度或低于其溶解度时未显示出可观察到的抑制作用的小分子报道为无活性的。

[0126] 2.测定骨骼肌肌球蛋白II

[0127] 骨骼肌肌球蛋白II肌动蛋白激活的ATP酶测定以与心肌肌球蛋白II相同的那样进行,但以下情况除外:兔骨骼肌肌球蛋白获自Cytoskeleton,最终测定条件包含20nM骨骼肌肌球蛋白II。

[0128] 3.测定非肌肉肌球蛋白II

[0129] 胞质分裂是一种基于细胞的测定,用于评估非肌肉肌球蛋白II功能,使用COS7细胞进行。该测定在96孔板中运行,每孔铺有2,000个细胞。总孵育时间为48小时,其中用目的化合物处理24小时。在DMSO中制备两倍稀释系列的化合物溶液,随后用小分子进行处理。起始浓度基于化合物的溶解度确定。将化合物溶液在DMEM培养基中进一步稀释至2%的最终DMSO浓度(50倍稀释)。随后,将100μl稀释溶液转移至含有100μl细胞培养物的板的每个孔(实现1%最终DMSO浓度)。所有测量均重复进行三次。用细胞生存力染料二乙酸荧光素(6μM)、可透过细胞的Hoescht33342(10μM)和不可透过膜的碘化丙锭(4μM)对细胞染色,以分别标记所有细胞核和属于死细胞的细胞核。孵育10分钟后,用新鲜培养基替换染料溶液。INCell分析仪6000用于成像。目的信号是细胞核与细胞数目的比率,因为非肌肉肌球蛋白II的抑制作用阻止细胞出泡(blebbing),从而形成多核细胞。还测定了细胞毒性并以死细胞核与总细胞核的比率进行定量。在1%DMSO中的20μM对氨基布雷他汀用作阳性对照,仅1%DMSO是阴性对照。通过将6点剂量响应数据拟合到Hill方程来确定半最大有效浓度(EC_{50})。未显示出可观察到的抑制作用的小分子报道为无活性的。

[0130] 4.测定心脏安全性(测定1)

[0131] 使用ACEA×CELLigence RTCA Cardio仪器实时无标记地测量心肌细胞(CM)的自发收缩。所有测量均在细胞培养箱中于37℃下进行,从而使CM在生理条件下自发跳动。Cor.4U CM以3×104个细胞/孔接种在180ml/孔的维持培养基中。接种之前,进行背景阻抗测量(板加培养基)。CM的收缩涉及细胞形态和黏附的周期性调节,诱导了阻抗的δ变化。根据阻抗的周期性变化,可计算出跳动频率、幅度以及对跳动模式的影响。时间点"0"(基线)以1分钟间隔记录10次,持续20秒。此后,将化合物和对照(0.1%DMSO)添加至孔,并在30分钟之后测量效果。载剂对照是0.1%DMSO,阳性对照是100nM异丙肾上腺素。以0.1、0.3、1.0和3.0uM测试化合物。在孵育之后5、10、15、20和30分钟以及1、4、6、12和24小时时收集数据。

[0132] 5.测定心脏安全性(测定2)

[0133] 在使用前,使雄性Sprague-Dawley大鼠适应约1周。使用异氟烷轻轻麻醉大鼠,并放置静脉内导管用于给药目的。收集基线二维超声心动图(在乳头肌水平上为标准SAX B模式和M模式)。每只大鼠总共接受3次IV处理。首先施用载剂(10%DMSO,10%吐温80和80%水),随后在10分钟后进行两次后续输注,间隔10分钟。阳性对照布雷他汀的输注以0.5mg/kg IV递送。测试化合物的浓度取决于化合物和实验问题而变化。然而,如果可用的话,可基于血浆药代动力学和NMII效力来调整剂量。在每次处理开始时以及开始后1、5、10分钟收集标准SAX ECHO图像。计算包括缩短分数、射血分数、心率和心输出量的测量值。

[0134] 根据下面的合成方案1至7来制备本发明的化合物,并且本文中公开和要求保护的所有化合物可根据这些方案,结合合成有机化学家的普通技术和知识来制备,并通过下面进一步提供的特定实施例的详细过程进行举例说明。HPLC条件:

[0135] 方法A

[0136] 柱:Waters Symmetry 5μm C18(250×4.6mm)

[0137] 流动相A:含有0.1%v/v三氟乙酸的水

[0138] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0139] 检测:254nm

[0140] 方法A梯度

[0141]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	98.0	2.0
20.0	1.0	0.0	100.0
25.0	1.0	0.0	100.0

[0142] 方法B

[0143] 柱:YMC ODS-AQ C18120Å(150×4.6mm)

[0144] 流动相A:含有0.1%v/v三氟乙酸的水

[0145] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0146] 检测:254nm

[0147] 方法B梯度

[0148]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	98.0	2.0
15.0	1.0	0.0	100.0
19.0	1.0	0.0	100.0

[0149] 方法C

[0150] 柱:xBridge 3.5μm C18(150×4.6mm)

[0151] 流动相A:含有0.1%v/v三氟乙酸的水

[0152] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0153] 检测:254nm

[0154] 方法C梯度

[0155]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	95.0	5.0
20.0	1.0	0.0	100.0
25.0	1.0	0.0	100.0

[0156] 方法D

[0157] 柱:YMC ODS-AQ C18120Å(150×4.6mm)

[0158] 流动相A:含有0.1%v/v三氟乙酸的水

[0159] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0160] 检测:254nm

[0161] 方法D梯度

[0162]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	95.0	5.0
20.0	1.0	0.0	100.0
25.0	1.0	0.0	100.0

[0163] 方法E

[0164] 柱:YMC ODS-AQ C18120Å(150×4.6mm)

[0165] 流动相A:含有0.1%v/v三氟乙酸的水

[0166] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0167] 检测:254nm

[0168] 方法E梯度

[0169]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	100.0	0.0
5.0	1.0	100.0	0.0
15.0	1.0	0.0	100.0
18.0	1.0	0.0	100.0

[0170] 方法F

[0171] 柱:Waters Symmetry 5μm C18(250×4.6mm)

[0172] 流动相A:含有0.1%v/v三氟乙酸的水

[0173] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0174] 检测:290nm

[0175] 方法F梯度

[0176]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	95.0	5.0
20.0	1.0	0.0	100.0
25.0	1.0	0.0	100.0

[0177] UPLC条件:

[0178] 方法A

[0179] 柱:Acquity UPLC BEH 1.70μm C18(75×2.1mm)

[0180] 流动相A:含有0.1%v/v三氟乙酸的水

[0181] 流动相B:含有0.1%v/v三氟乙酸的乙腈

[0182] 检测:254nm

[0183] 方法A梯度

[0184]

时间（分）	流量（mL/分）	%A	%B
0.0	0.5	95.0	5.0
6.0	0.5	0.0	100.0
8.0	0.5	0.0	100.0

[0185] 手性HPLC条件:

[0186] 方法A

[0187] 柱:Chiralpak AD 5μm(250×4.6mm)

[0188] 流动相A:庚烷

[0189] 流动相B:异丙醇

[0190] 检测:254nm

[0191] 方法A梯度

[0192]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	90.0	10.0
5.0	1.0	90.0	10.0
20.0	1.0	50.0	50.0
35.0	1.0	50.0	50.0

[0193] 方法B

[0194] 柱:Chiralpak AD 5μm(250×4.6mm)

[0195] 流动相A:庚烷

[0196] 流动相B:异丙醇

[0197] 检测:290nm

[0198] 方法B梯度

[0199]

时间（分）	流量（mL/分）	%A	%B
0.0	1.0	90.0	10.0
5.0	1.0	90.0	10.0
20.0	1.0	50.0	50.0
35.0	1.0	50.0	50.0

[0200] 手性SFC条件:

[0201] 方法A

[0202] 柱:Chiralcel OJ-H 5μm(100×4.6mm)

[0203] 流动相A:CO_2

[0204] 流动相B:异丙醇

[0205] 检测:254nm

[0206] 方法A梯度

[0207]

时间（分）	流量（mL/分）	%A	%B
0.0	1.5	95.0	5.0
8.0	1.5	60.0	40.0

[0208] 方法B

[0209] 柱:Chiralcel OJ-H 5μm(100×4.6mm)

[0210] 流动相A:CO_2

[0211] 流动相B:甲醇

[0212] 检测:254nm

[0213] 方法B梯度

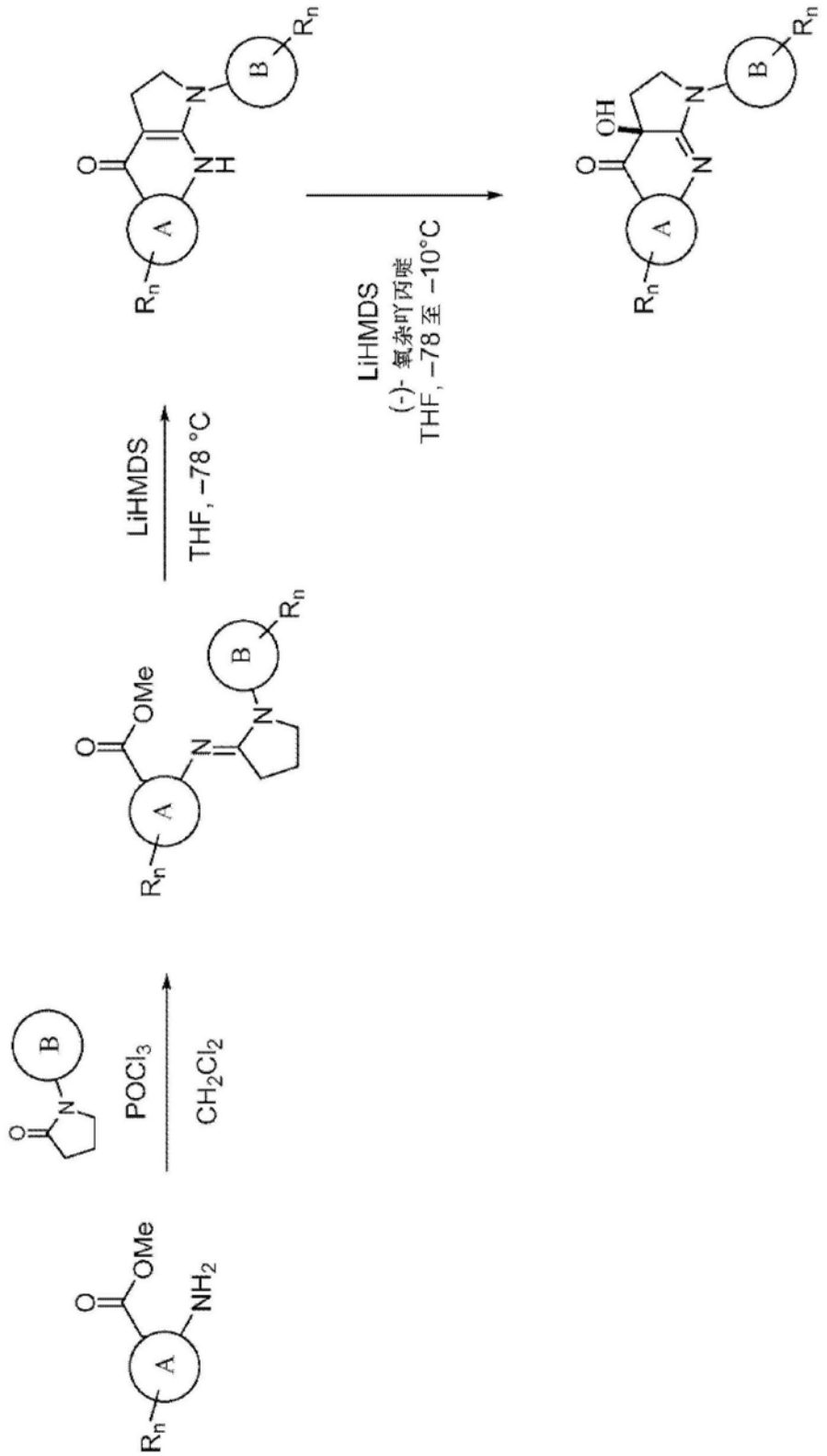
[0214]

时间（分）	流量（mL/分）	%A	%B
0.0	1.5	95.0	5.0
8.0	1.5	60.0	40.0

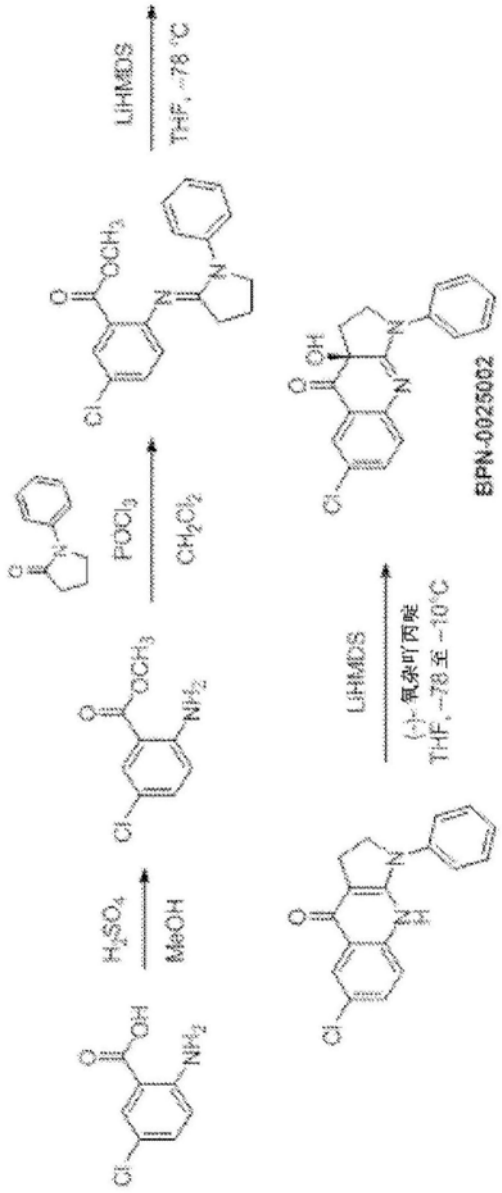
[0215] 合成方案

[0216] 方案1:化合物的合成方法

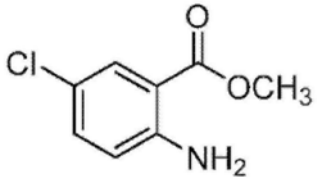
[0217]



[0218] 方案2:BPN-0025002

[0219] 

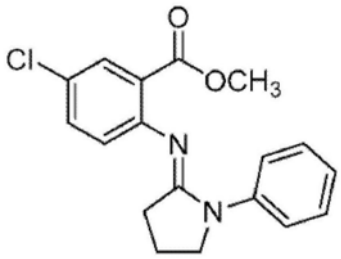
[0220] 2-氨基-5-氯苯甲酸甲酯的制备

[0221] 

[0222] 用浓硫酸(7.5mL)处理2-氨基-5-氯苯甲酸(5.00g,29.1mmol)在甲醇(75mL)中的溶液,并在氮气氛下在60℃下加热72小时。此时间之后,将反应混合物在减压下浓缩以除去挥发物。将所得剩余物用饱和碳酸氢钠水溶液(150mL)小心处理,并用乙酸乙酯(3×100mL)萃取。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为棕色固体的2-氨基-5-氯苯甲酸甲酯(5.10g,94%):

[0223] ^{1}H NMR(500MHz,DMSO-d_6)δ7.63(d,J=2.5Hz,1H),7.28(dd,J=8.5,2.5Hz,1H),6.81(d,J=8.5Hz,1H),6.77(br s,2H),3.80(s,3H).

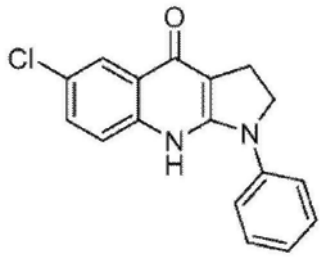
[0224] 5-氯-2-((1-苯基吡咯烷-2-亚基)氨基)苯甲酸甲酯的制备

[0225] 

[0226] 用氯氧化磷(0.60mL,0.99g,6.4mmol)处理1-苯基吡咯烷-2-酮(1.04g,6.45mmol)在二氯甲烷(13mL)中的溶液,并在氮气氛下在环境温度下搅拌持续3小时。将混合物用2-氨基-5-氯苯甲酸甲酯(1.00g,5.39mmol)在二氯甲烷(3mL)中的溶液处理,并在50℃下加热16小时。此时间之后,使反应混合物冷却至环境温度,用二氯甲烷(25mL)稀释,用饱和碳酸氢钠水溶液(2×25mL)和盐水(25mL)洗涤,经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,0至30%乙酸乙酯/二氯甲烷)纯化,以得到作为浅棕褐色油状物的5-氯-2-((1-苯基吡咯烷-2-亚基)氨基)苯甲酸甲酯(0.72g,41%):

[0227] ESI MS m/z 329$[C_{18}H_{17}ClN_2O_2+H]^+$.

[0228] 6-氯-1-苯基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4(9H)-酮的制备

[0229] 

[0230] 将5-氯-2-((1-苯基吡咯烷-2-亚基)氨基)苯甲酸甲酯(715mg,2.17mmol)在四氢呋喃(10mL)中的溶液在氮气氛下在干冰/丙酮浴中冷却,并用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(5.4mL,5.4mmol)逐滴处理。将混合物搅拌3.5小时,在此期间浴温升至约0℃。此时间之后,将混合物用冷却的饱和氯化铵水溶液(50mL)处理,并迅速搅拌1小时。通过过滤分离所得的固体,用水和乙酸乙酯洗涤,并在真空下干燥以得到作为浅橙色固体的6-氯-1-苯基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4(9H)-酮(435mg,67%):

[0231] ^1H NMR(500MHz,DMSO-d_6)δ10.77(s,1H),8.05(d,J=8.0Hz,2H),7.93(d,J=2.5Hz,1H),7.60(d,J=8.5Hz,1H),7.47(dd,J=8.5,2.5Hz,1H),7.39(表观t,J=7.5Hz,2H),7.02(表观t,J=7.5Hz,1H),4.11(t,J=8.0Hz,2H),3.19(t,J=8.0Hz,2H);ESI MS m/z 297$[C_{17}H_{13}ClN_2O+H]^+$.

[0232] (S)-6-氯-3a-羟基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0233] 

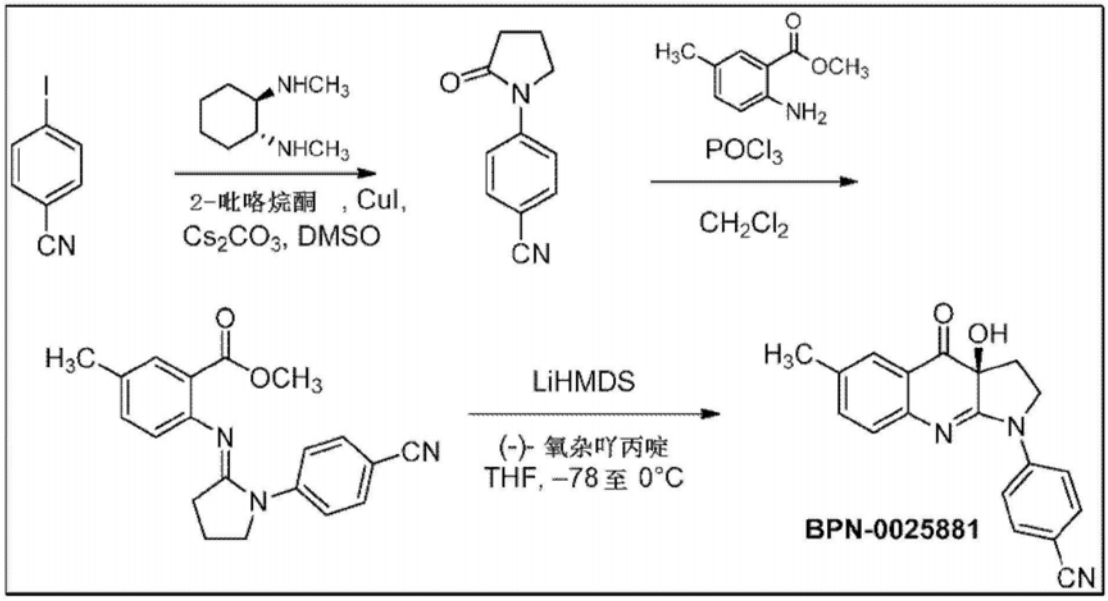
[0234] 将6-氯-1-苯基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4(9H)-酮(101mg,0.339mmol)在四氢呋喃(6mL)中的溶液在干冰/丙酮浴中冷却,并在氮气氛下用双(三甲基甲硅烷基)氨

基锂在四氢呋喃中的1.0M溶液(0.41mL,0.41mmol)处理。搅拌45分钟后,将混合物用(-)-(8,8-二氯樟脑基磺酰基)氧杂吖丙啶(245mg,0.821mmol)在四氢呋喃(3mL)中的溶液处理。将混合物搅拌2小时,同时浴温升至约0℃。用湿冰/盐水浴代替丙酮浴,并将混合物搅拌3小时。此时间之后,混合物用饱和碘化铵水溶液(6mL)处理,随后用饱和硫代硫酸钠水溶液(25ml)处理,并用乙酸乙酯(3×25mL)萃取。有机物用0.3M盐酸(3×25mL)萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约8,并用乙酸乙酯(4×25mL)萃取。有机物经硫酸钠干燥,过滤,并在减压下浓缩。粗制产物从热乙腈中重结晶,以得到作为黄色固体的(S)-6-氯-3a-羟基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮(37mg,35%):mp=199至200℃分解;

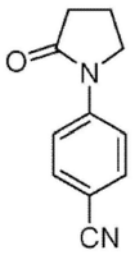
[0235] ^{1}H NMR(500MHz,DMSO-d_6)δ8.06(dd,J=7.5,1.0Hz,2H),7.64(d,J=2.5Hz,1H),7.56(dd,J=8.5,2.5Hz,1H),7.44(表观t,J=7.0Hz,2H),7.22(d,J=8.5Hz,1H),7.17(表观t,J=7.0Hz,1H),6.96(s,1H),4.14-4.08(m,1H),3.98(表观t,J=9.0Hz,1H),2.37-2.31(m,1H),2.26(dd,J=13.5,6.0Hz,1H);ESI MS m/z 313[$C_{17}H_{13}ClN_2O_2$+H]$^+$;

[0236] HPLC(方法A)>99%(AUC),t_R=11.17分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=11.17分钟。

[0237] 方案3:BPN-0025881

[0238] 

[0239] 4-(2-氧代吡咯烷-1-基)苄腈的制备

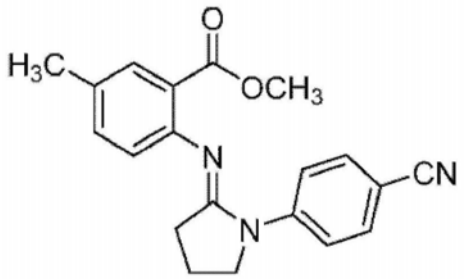
[0240] 

[0241] 用2-吡咯烷酮(331μL,4.36mmol)、碘化铜(83.0mg,0.436mmol)、碳酸铯(4.26g,13.1mmol)和N,N'-二甲基-(1R,2R)-1,2-环己二胺(137μL,0.872mmol)处理4-碘苄腈(1.00g,4.36mmol)在二甲基亚砜(10mL)中的溶液,并在110℃下在氮气氛下加热16小时。此

时间之后，使反应混合物冷却至环境温度，用水(50mL)稀释，并用乙酸乙酯(4×50mL)萃取。用水(4×10mL)洗涤合并的有机物，经硫酸钠干燥，过滤，并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶，0至100％乙酸乙酯/庚烷)纯化，以得到作为灰白色固体的4-(2-氧代吡咯烷-1-基)苄腈(514mg，63％)：

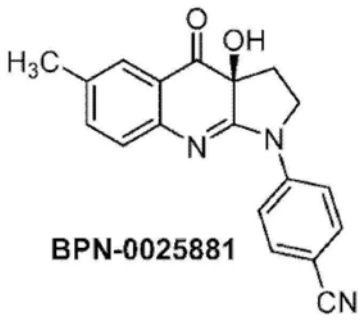
[0242] ^{1}H NMR(300MHz，DMSO-d_6)δ7.90-7.82(m，4H)，3.87(t，J＝7.2Hz，2H)，2.56(t，J＝3.9Hz，2H)，2.12-2.05(m，2H)．

[0243] 2-((1-(4-氰基苯基)吡咯烷-2-亚基)氨基)-5-甲基苯甲酸甲酯的制备

[0244] 

[0245] 用氯氧化磷(0.30mL，3.2mmol)处理4-(2-氧代吡咯烷-1-基)苄腈(400mg，2.14mmol)在二氯甲烷(9mL)中的溶液，并在氮气氛下在环境温度下搅拌持续16小时。将混合物用2-氨基-5-甲基苯甲酸甲酯(355mg，2.14mmol)在二氯甲烷(2mL)中的溶液处理，并在45℃下加热5天。此时间之后，使反应混合物冷却至环境温度，用饱和碳酸氢钠水溶液(15mL)淬灭，并用乙酸乙酯萃取。将有机物经硫酸钠干燥，过滤，并在减压下浓缩。将粗制剩余物溶于乙酸乙酯，并用0.3M盐酸(2×20mL)萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约11，并用乙酸乙酯(3×25mL)萃取。有机物经硫酸钠干燥，过滤，并在减压下浓缩，以得到作为黄色油状物的2-((1-(4-(氰基苯基)吡咯烷-2-亚基)氨基)-5-甲基苯甲酸甲酯(226mg，32％)，将其无需进一步纯化即可使用：ESI MS m/z 334[$C_{20}H_{19}N_3O_2$+H]$^{+}$．

[0246] (S)-4-(3a-羟基-6-甲基-4-氧代-2，3，3a，4-四氢-1H-吡咯并[2，3-b]喹啉-1-基)苄腈的制备

[0247] 

[0248] 将2-((1-(4-(氰基苯基)吡咯烷-2-亚基)氨基)-5-甲基苯甲酸甲酯(226mg，0.678mmol)在四氢呋喃(12mL)中的溶液在干冰/丙酮浴中在氮气氛下冷却，并用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(2.03mL，2.03mmol)处理。用湿冰/水浴代替丙酮浴，并将混合物搅拌3小时。搅拌3小时后，将混合物用(-)-(8，8-二氯樟脑基磺酰基)氧杂吖丙啶(505mg，1.70mmol)在四氢呋喃(8mL)中的溶液处理。将混合物在约0℃下搅拌2小时。此时间之后，将混合物顺序地用饱和碘化铵水溶液(0.7mL)、饱和硫代硫酸钠水溶液(2.3mL)和盐水(20mL)处理。将水层用乙酸乙酯(3×25mL)萃取。合并有机物，经硫酸钠干燥，过滤，并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶，0至100％乙酸乙酯/庚烷)纯

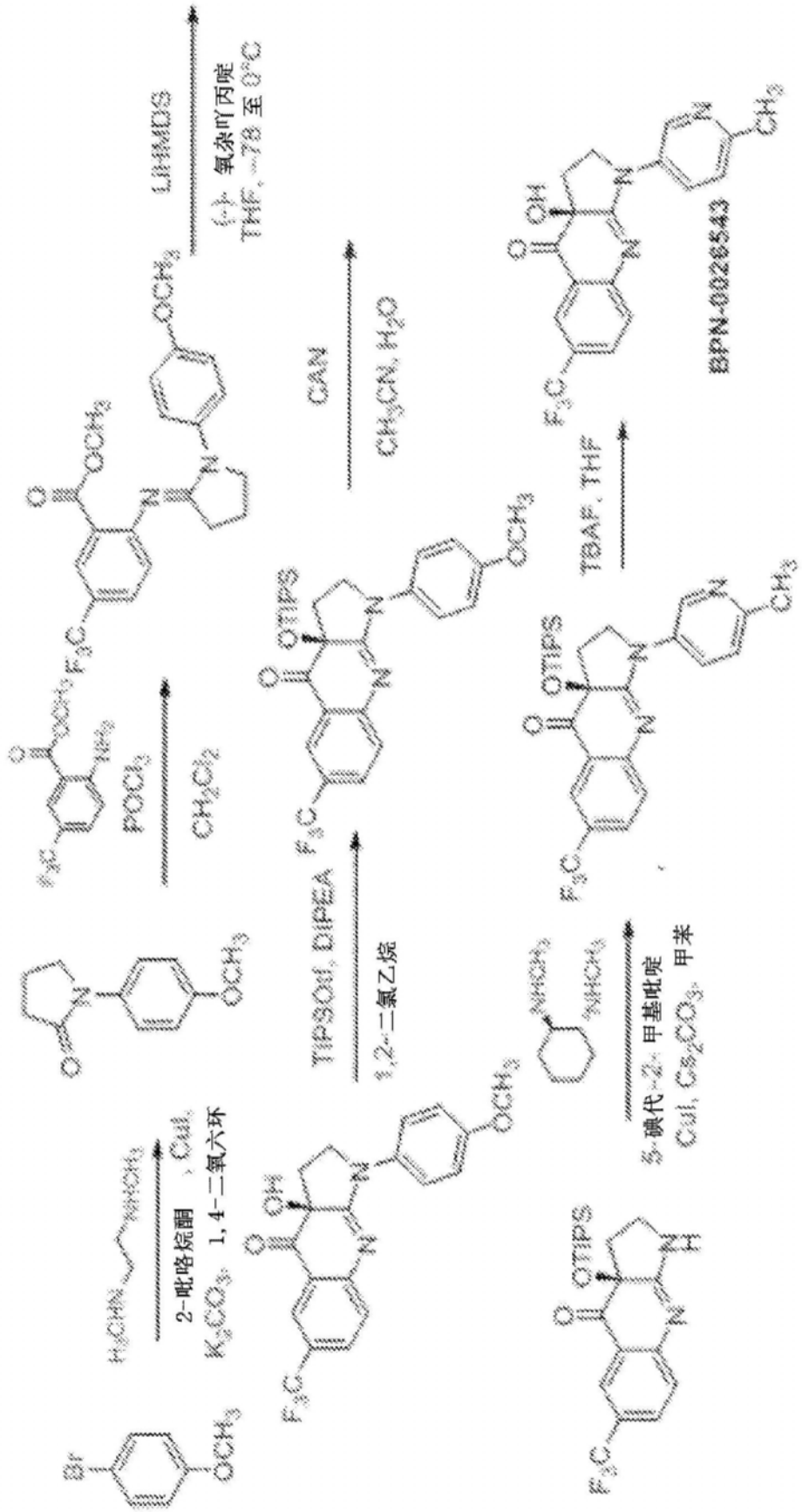
化,获得黄色胶状物,将其通过柱色谱法(硅胶,0至80%乙酸乙酯/庚烷)再纯化,并从热乙腈中重结晶,以得到作为黄色固体的(S)-4-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈(39mg,18%):mp=222至223℃;

[0249] ^{1}H NMR(500MHz,DMSO-d_6)δ8.32(dd,J=7.0,2.0Hz,2H),7.88(dd,J=7.0,2.0Hz,2H),7.57(表观d,J=2.0Hz,1H),7.42(dd,J=8.5,1.5Hz,1H),7.20(d,J=8Hz,1H),6.92(s,1H),4.06-4.02(m,2H),2.32(s,3H),2.29-2.27(m,2H);ESI MSm/z 318[$C_{19}H_{15}N_3O_2$+H]$^{+}$;

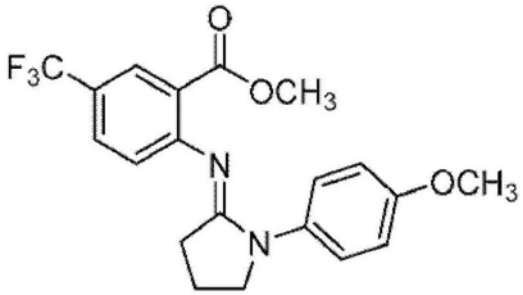
[0250] HPLC(方法B)>99%(AUC),t_R=9.48分钟。

[0251] 方案4:BPN-0026543

[0252]



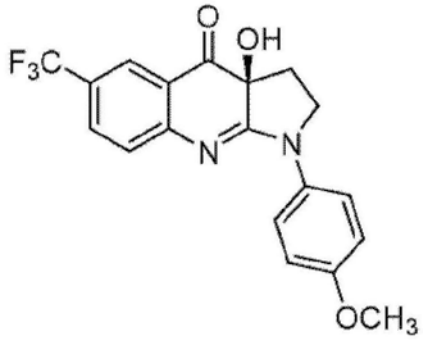
[0253] 2-((1-(4-甲氧基苯基)吡咯烷-2-亚基)氨基)-5-(三氟甲基)苯甲酸甲酯的制备

[0254] 

[0255] 用氯氧化磷(1.46mL,15.7mmol)处理1-(4-甲氧基苯基)吡咯烷-2-酮(2.00g,10.5mmol)在二氯甲烷(20mL)中的溶液,并在氮气氛下在环境温度下搅拌持续7小时。将混合物用2-氨基-5-(三氟甲基)苯甲酸甲酯(3.21g,14.6mmol)在二氯甲烷(20mL)中的溶液处理,并在45℃下加热2天。此时间之后,使反应混合物冷却至环境温度,用饱和碳酸氢钠水溶液(40mL)淬灭,并用乙酸乙酯萃取。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/庚烷)纯化,以得到作为透明胶状物的2-((1-(4-甲氧基苯基)吡咯烷-2-亚基)氨基)-5-(三氟甲基)苯甲酸甲酯(2.19g,53%):

[0256] ^{1}H NMR(500MHz,$CDCl_3$)δ8.10(s,1H),7.63(d,J=8.5Hz,2H),7.56(dd,J=8.5,1.5Hz,1H),6.90(d,J=8.5Hz,3H),3.88-3.85(m,5H),3.79(s,3H),2.47(t,J=7.5Hz,2H),2.11-2.05(m,2H).

[0257] (S)-3a-羟基-1-(4-甲氧基苯基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

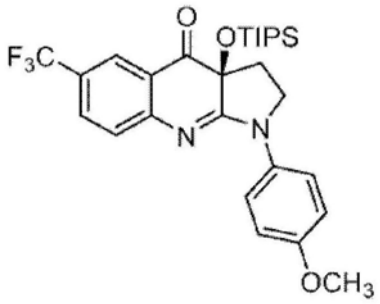
[0258] 

[0259] 将2-((1-(4-甲氧基苯基)吡咯烷-2-亚基)氨基)-5-(三氟甲基)苯甲酸甲酯(2.19g,5.59mmol)在四氢呋喃(35mL)中的溶液在氮气氛下在干冰/丙酮浴中冷却,并用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(16.8mL,16.8mmol)处理。用湿冰/水浴代替丙酮浴,并将混合物搅拌1小时。此时间之后,将混合物用(-)-(8,8-二氯樟脑基磺酰基)氧杂吖丙啶(4.17g,14.0mmol)在四氢呋喃(20mL)中的溶液处理。将混合物在约0℃下搅拌1小时。此时间之后,将混合物顺序地用饱和碘化铵水溶液(20mL)、饱和硫代硫酸钠水溶液(37mL)和盐水(50mL)处理。用乙酸乙酯(3×50mL)萃取水层。合并有机物,经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物在热乙腈中研磨,以得到作为黄棕色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(1.26g,60%):

[0260] ^{1}H NMR(500MHz,DMSO-d_6)δ7.93(dd,J=7.0,2.5Hz,2H),7.90(d,J=1.5Hz,1H),7.81(dd,J=8.5,2.5Hz,1H),7.29(d,J=8.0Hz,1H),7.03(dd,J=7.0,2.5Hz,2H),6.99(s,1H),4.16-4.12(m,1H),3.98-3.94(m,1H),3.79(s,3H),2.42-2.35(m,1H),2.28-2.25(m,

1H).

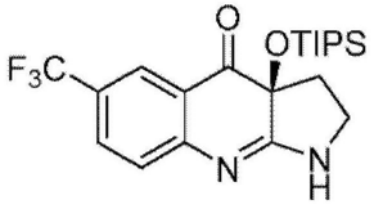
[0261] (S)-1-(4-甲氧基苯基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0262] 

[0263] 用N,N-二异丙基乙胺(1.35mL,7.76mmol)和三异丙基甲硅烷基三氟甲烷磺酸酯(1.56mL,5.82mmol)处理(S)-3a-羟基-1-(4-甲氧基苯基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(730mg,1.94mmol)在1,2-二氯乙烷(30mL)中的溶液并在90℃下在氮气氛下搅拌16小时。此时间之后,使反应混合物冷却至环境温度。混合物用冷的去离子水(17mL)处理,随后用饱和氯化铵水溶液(40mL)处理。用乙酸乙酯(3×50mL)萃取水层。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,0至60%乙酸乙酯/庚烷)纯化,以得到作为黄色固体的(S)-1-(4-甲氧基苯基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(870mg,84%):

[0264] ^{1}H NMR(500MHz,DMSO-d_6)δ7.93-7.88(m,3H),7.82(d,J=8.5Hz,1H),7.30(d,J=8.5Hz,1H),7.04(d,J=9.0Hz,2H),4.10-4.05(m,2H),3.79(s,3H),2.57-2.50(m,1H),2.33-2.30(m,1H),0.86-0.80(m,21H).

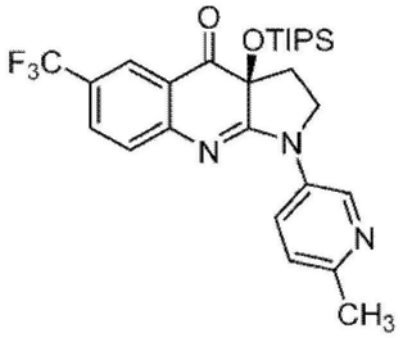
[0265] (S)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0266] 

[0267] 将(S)-1-(4-甲氧基苯基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(870mg,1.63mmol)在乙腈(24mL)中的溶液在氮气氛下在湿冰/水浴中冷却,并用硝酸铵铈(IV)(3.58g,6.53mmol)在去离子水(6mL)中的溶液逐滴处理,并在约0℃下搅拌2小时。将混合物用另外的硝酸铵铈(IV)(1.79g,3.27mmol)在去离子水(3mL)和乙腈(12mL)中的溶液处理,并在约0℃下搅拌3小时。此时间之后,将混合物用在去离子水(6mL)和乙腈(25mL)中的硫代硫酸钠五水合物(3.67g)处理,随后用饱和碳酸氢钠水溶液(50mL)处理以形成浆液状物。通过硅藻土过滤除去固体,并用乙酸乙酯清洗。滤液用乙酸乙酯(3×50mL)萃取。合并有机物,并用饱和碳酸氢钠、水和盐水洗涤。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/庚烷)纯化,以得到作为黄色固体的(S)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(358mg,52%):

[0268] ^{1}H NMR(300MHz,DMSO-d_6)δ7.84(s,1H),7.80(d,J=8.7Hz,1H),7.15(d,J=8.7Hz,1H),3.70(br s,2H),2.39-2.34(m,1H),2.17-2.16(m,1H),0.90-0.81(m,21H);未观察到NH质子。

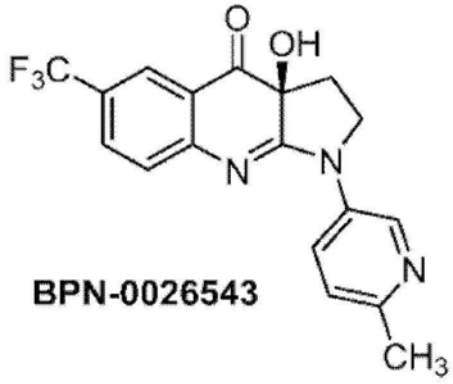
[0269] (S)-1-(6-甲基吡啶-3-基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0270] 

[0271] 用5-碘代-2-甲基吡啶(96mg,0.44mmol)、碘化铜(6.0mg,0.029mmol)、碳酸铯(286mg,0.879mmol)和N,N'-二甲基-(1R,2R)-1,2-环己二胺(9μL,0.06mmol)处理(S)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(125mg,0.293mmol)在甲苯(3mL)中的溶液,并在密封的小瓶中于105℃加热16小时。此时间之后,使反应混合物冷却至环境温度。通过过滤除去固体,并用乙酸乙酯洗涤。将滤液在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/庚烷)纯化,以得到作为黄色胶状物的(S)-1-(6-甲基吡啶-3-基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(143mg,94%):

[0272] ESI MS m/z 518[$C_{27}H_{34}F_3N_3O_2Si$+H]$^+$.

[0273] 提供(S)-3a-羟基-1-(6-甲基吡啶-3-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0274] 

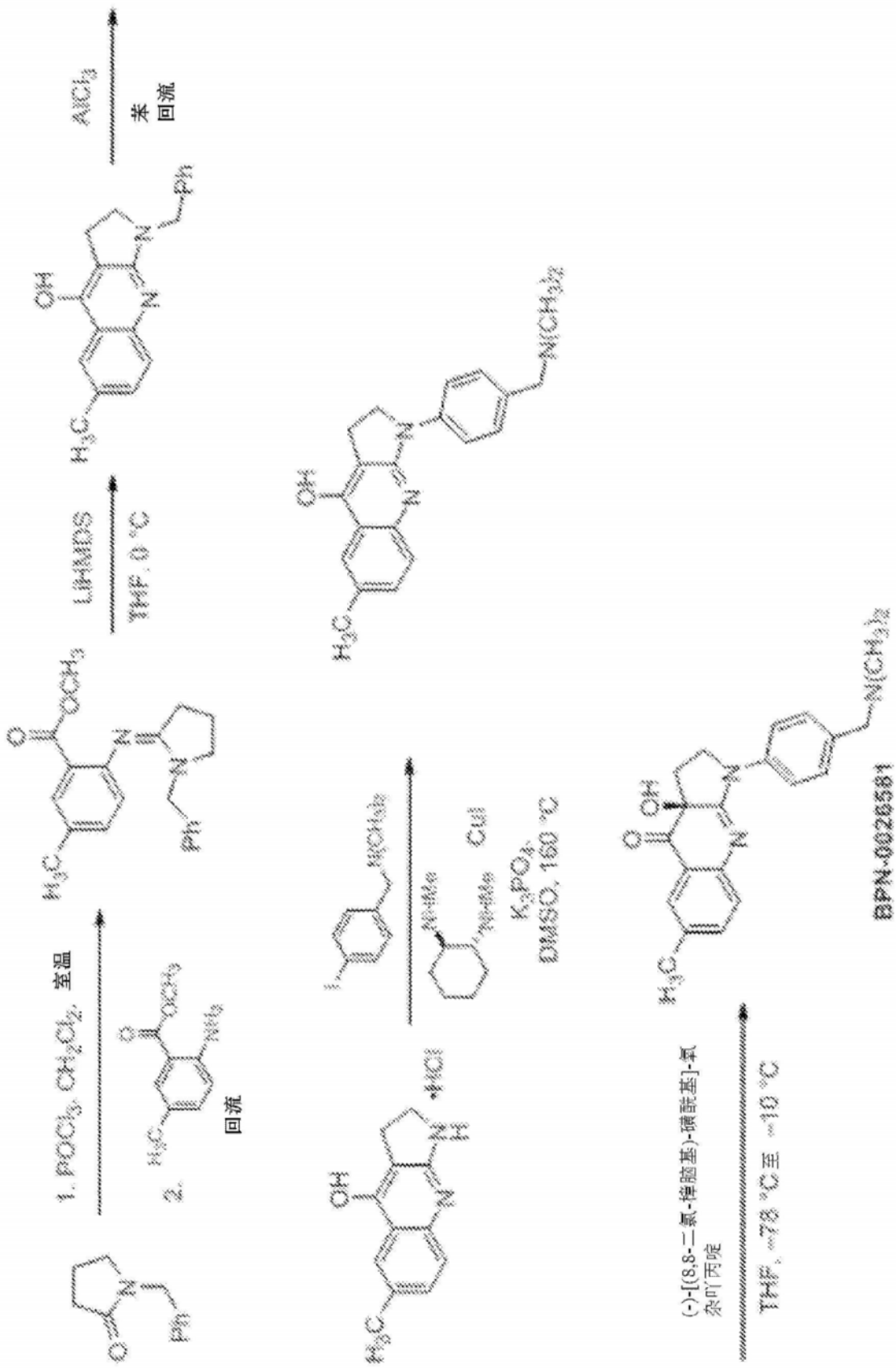
[0275] 用氟化四丁基铵在四氢呋喃中的1.0M溶液(0.829mL,0.829mmol)处理在氮气氛下的(S)-1-(6-甲基吡啶-3-基)-6-(三氟甲基)-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(143mg,0.276mmol)在四氢呋喃(5mL)中的溶液,并将混合物搅拌1小时。此时间之后,将混合物在减压下浓缩。通过柱色谱法(硅胶,0至20%甲醇/二氯甲烷)纯化粗制剩余物,以得到作为黄色固体的(S)-3a-羟基-1-(6-甲基吡啶-3-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(84mg,84%):mp=237至240℃分解;

[0276] ^{1}H NMR(300MHz,DMSO-d_6)δ9.09(d,J＝2.4Hz,1H),8.39(dd,J＝8.7,2.7Hz,1H),7.93(s,1H),7.87(d,J＝8.4Hz,1H),7.36(dd,J＝8.4,4.8Hz,2H),7.08(s,1H),4.19-4.12(m,1H),4.06-4.00(m,1H),2.32-2.27(m,2H),CH_3质子被溶剂所掩盖;ESI MS m/z 362 $[C_{18}H_{14}F_3N_3O_2+H]^+$;

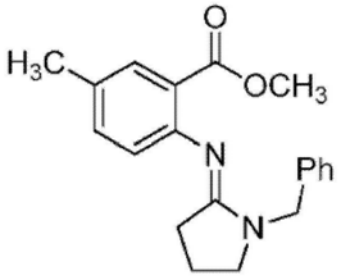
[0277] HPLC(方法C)＞99％(AUC),t_R＝12.49分钟;手性HPLC(Chiralpak AD,方法A)49.7％(AUC),t_R＝16.24分钟。

[0278] 方案5:BPN-0026581

[0279]

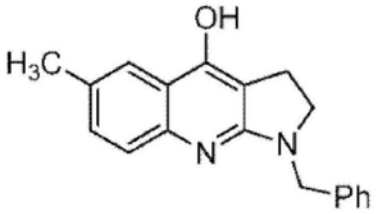


[0280] 2-((1-苄基吡咯烷-3-亚基)氨基)-5-甲基苯甲酸甲酯的制备

[0281] 

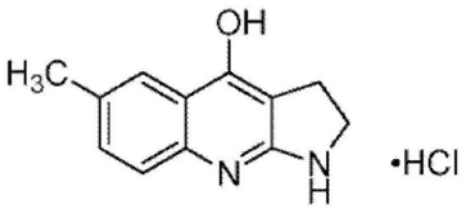
[0282] 用氯氧化磷(4.50mL,49.2mmol)处理1-苄基吡咯烷-2-酮(6.30g,35.9mmol)在二氯甲烷(200mL)中的溶液,并在氮气氛下在环境温度下搅拌4小时。将混合物用2-氨基-5-甲基苯甲酸甲酯(5.30g,32.1mmol)在二氯甲烷(20mL)中的溶液处理,并在回流下加热48小时。此时间之后,使反应混合物冷却至环境温度,并在减压下浓缩。将剩余物用乙酸乙酯稀释,用饱和碳酸氢钠水溶液洗涤,然后用水洗涤。用0.4M盐酸萃取有机层,并通过添加氢氧化钠将水性萃取物碱化至pH约12。将混合物用乙酸乙酯萃取,经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为浅黄色油状物的2-((1-苄基吡咯烷-3-亚基)氨基)-5-甲基苯甲酸甲酯(8.40g,81%):ESI MS m/z 323[$C_{20}H_{22}N_2O_2$+H]$^+$.

[0283] 1-苄基-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇的制备

[0284] 

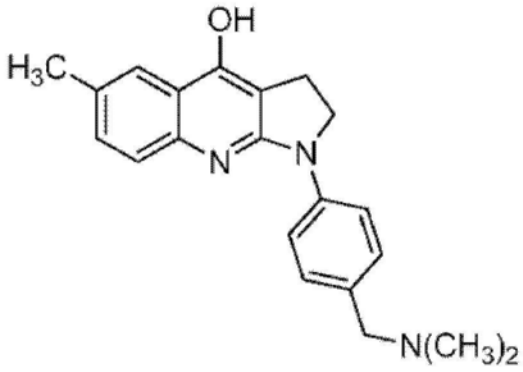
[0285] 用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(55mL,55mmol)逐滴处理在0℃下在氮气氛下的2-((1-苄基吡咯烷-3-亚基)氨基)-5-甲基苯甲酸甲酯(8.40g,26.1mmol)在四氢呋喃(200mL)中的溶液,并搅拌3小时。此时间之后,添加饱和氯化铵溶液(100mL),并将混合物搅拌30分钟。通过过滤收集沉淀物,用水和乙醚洗涤,并在高真空下干燥,以得到作为灰白色固体的1-苄基-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇(3.18g,42%):ESI MS m/z 291[$C_{19}H_{18}N_2O$+H]$^+$.

[0286] 6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇盐酸盐的制备

[0287] 

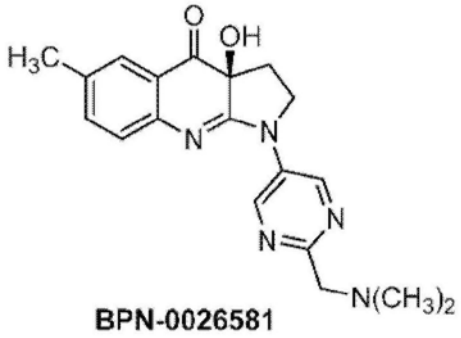
[0288] 将在苯(140mL)中的1-苄基-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇(6.30g,21.7mmol)和三氯化铝(12.8g,96.0mmol)的混合物在回流下搅拌3小时。此时间之后,将混合物冷却至室温,并倒入搅拌下的冰/水(250mL)中。将混合物搅拌15分钟,然后通过过滤收集沉淀物,用二乙醚洗涤并在高真空下干燥以得到6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇盐酸盐(5.1g,定量):ESI MS m/z 201[$C_{12}H_{12}N_2O$+H]$^+$.

[0289] 1-(4-((二甲基氨基)甲基)苯基)-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇的制备

[0290] 

[0291] 用1-(4-碘代苯基)-N,N-二甲基甲胺(460mg,1.77mmol)、碘化铜(40mg,0.21mmol)、磷酸三钾(650mg,3.06mmol)和反式-N,N'-二甲基-1,2-环己二胺(58mg,0.41mmol)处理6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇盐酸盐(260mg,1.10mmol)在二甲基亚砜(4mL)中的溶液。将所得混合物在160℃下在微波中加热4小时。此时间之后,将反应混合物通过硅藻土使用3/1的二氯甲烷/甲醇作为洗脱剂过滤。在减压下浓缩滤液,并将剩余物通过柱色谱法(硅胶,0至80%(二氯甲烷/甲醇/氢氧化铵80/18/2)、二氯甲烷)纯化,以得到1-(4-((二甲基氨基)甲基)苯基)-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇(200mg,54%):ESI MS m/z 334[$C_{21}H_{23}N_3O$+H]$^+$.

[0292] (S)-1-(4-((二甲基氨基)甲基)苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0293] 

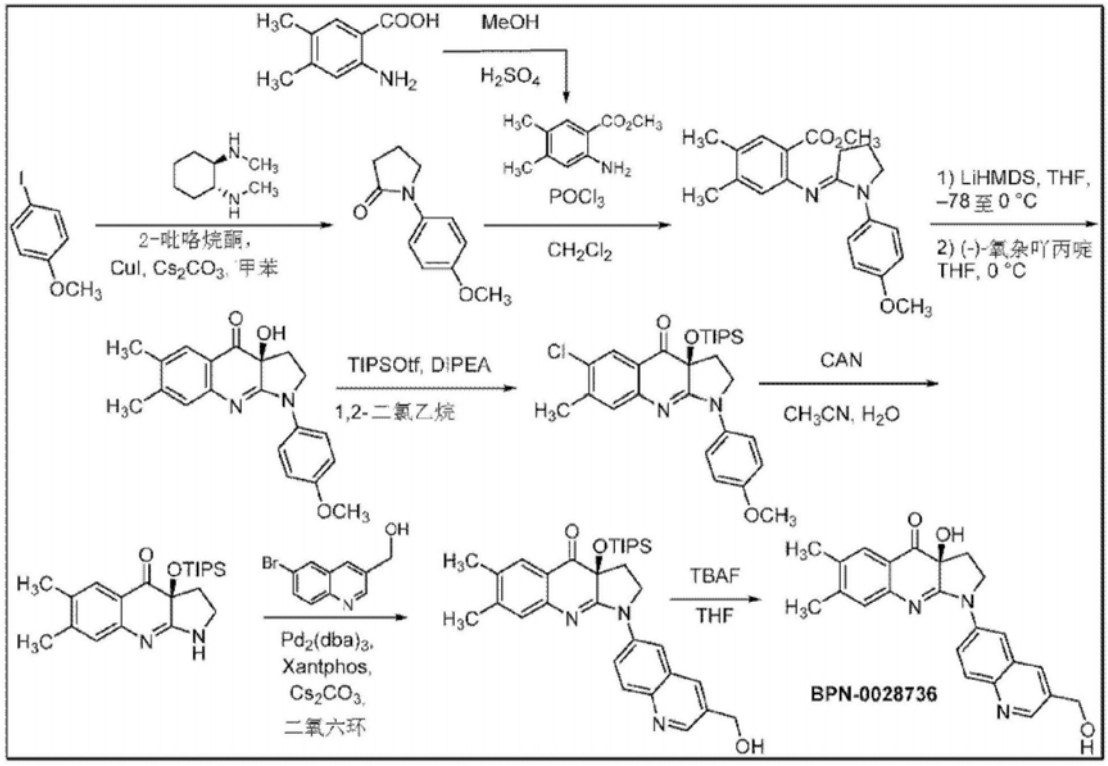
[0294] 用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(1.0mL,1.0mmol)逐滴处理-78℃下的1-(4-((二甲基氨基)甲基)苯基)-6-甲基-2,3-二氢-1H-吡咯并[2,3-b]喹啉-4-醇(200mg,0.60mmol)在四氢呋喃(8mL)中的溶液,随后一次添加(-)-(8,8-二氯樟脑基磺酰基)氧杂吖丙啶(600mg,2.01mmol)。搅拌混合物,同时使温度在2小时内升至-10℃。此时间之后,将混合物用饱和碘化铵水溶液(4mL)处理并搅拌20分钟。添加饱和硫代硫酸钠水溶液(10ml),并将混合物搅拌20分钟,然后用乙酸乙酯萃取。用0.8M盐酸萃取有机物,并通过添加氢氧化钠将水性萃取物碱化至pH约12。将混合物用乙酸乙酯萃取,经硫酸钠干燥,过滤,并在减压下浓缩。将剩余物从热乙腈中结晶,以得到作为黄色固体的(S)-1-(4-((二甲基氨基)甲基)苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮(26mg,12%):mp=194至195℃。

[0295] ^{1}H NMR(500MHz,DMSO-d_6)δ8.01(d,J=8.7Hz,1H),7.52(d,J=1.5Hz,1H),7.37(d,J=8.2,1.7Hz,1H),7.32(d,J=8.6Hz,1H),7.10(d,J=8.1Hz,1H),6.80(s,1H),4.08-4.02(m,1H),3.97-3.93(m,1H),3.37(s,2H),2.30(s,3H),2.27-2.23(m,2H),2.14(s,6H);;ESI

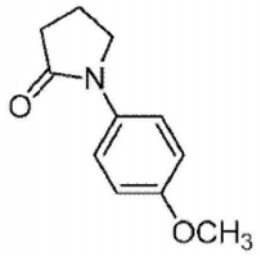
MS m/z 350[$C_{21}H_{23}N_3O_2$+H]$^+$;

[0296] HPLC(方法C)96.4%(AUC),t_R=9.73分钟;手性HPLC(Chiralpak AD,方法A)94.5%(AUC),t_R=15.86分钟。

[0297] 方案6:BPN-0028736

[0298] 

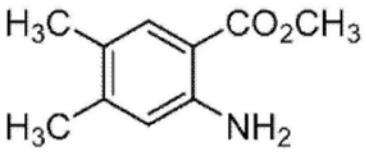
[0299] 1-(4-甲氧基苯基)吡咯烷-2-酮的制备

[0300] 

[0301] 用2-吡咯烷酮(3.8mL,4.3g,50mmol)、碘化铜(638mg,3.35mmol)、碳酸铯(26.1g,80.0mmol)和(1R,2R)-N^1,N^2-二甲基环己烷-1,2-二胺(1.1mL,0.99g,7.0mmol)处理1-碘代-4-甲氧基苯(8.00g,33.3mmol)在甲苯(50mL)中的溶液,并在氮气氛下于110℃加热持续22小时。此时间之后,使反应混合物冷却至环境温度,通过硅藻土过滤,并将滤液在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/庚烷)纯化,以得到作为白色固体的1-(4-甲氧基苯基)吡咯烷-2-酮(6.07g,95%):

[0302] ^{1}H NMR(300MHz,DMSO-d_6)δ7.54(d,J=9.3Hz,2H),6.93(d,J=9.0Hz,2H),3.78(t,J=7.2Hz,2H),3.74(s,3H),2.45(t,J=8.1Hz,2H),2.09-1.99(m,2H);ESI MS m/z 192[$C_{11}H_{13}NO_2$+H]$^+$.

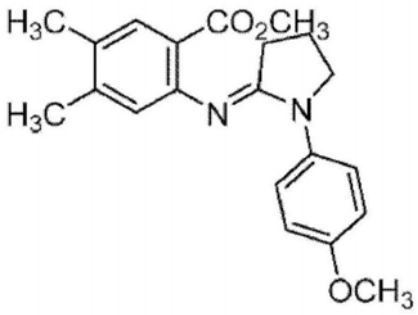
[0303] 2-氨基-4,5-二甲基苯甲酸甲酯的制备

[0304] 

[0305] 用浓硫酸(18mL)处理2-氨基-4,5-二甲基苯甲酸(10.00g,60.54mmol)在甲醇(180mL)中的溶液,并在氮气氛下在60℃下加热64.5小时。此时间之后,将反应混合物在减压下浓缩以除去挥发物。将所得剩余物用饱和碳酸氢钠水溶液(800mL)小心处理,并用乙酸乙酯(2×300mL)萃取。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为浅棕色固体的2-氨基-4,5-二甲基苯甲酸甲酯(10.14g,94%):

[0306] ^{1}H NMR(300MHz,DMSO-d_6)δ7.44(s,1H),6.56(s,1H),6.38(s,2H),3.75(s,3H),2.12(s,3H),2.07(s,3H);ESI MS m/z 180[$C_{10}H_{13}NO_2$+H]$^+$.

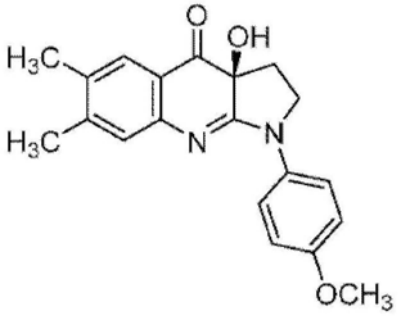
[0307] 2-((1-(4-甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯的制备

[0308] 

[0309] 用氯氧化磷(12mL,20g,130mmol)处理1-(4-甲氧基苯基)吡咯烷-2-酮(16.34g,85.45mmol)在1,2-二氯乙烷(100mL)中的溶液,并在环境温度下在氮气氛下搅拌5.25小时。将混合物用2-氨基-4,5-二甲基苯甲酸甲酯(15.36g,85.70mmol)在1,2-二氯乙烷(100mL)中的溶液处理,并在80℃下回流67小时。此时间之后,使反应混合物冷却至环境温度,并用碳酸氢钠(200mL)处理。分离有机层和水层,并将水层用乙酸乙酯洗涤。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩。将剩余物溶解在乙酸乙酯(200mL)中并用0.3M盐酸萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约11,并用乙酸乙酯萃取。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为棕色油状物的2-((1-(4-(甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯(25.93g,86%):

[0310] ^{1}H NMR(300MHz,DMSO-d_6)δ7.75-7.70(m,2H),7.51(s,1H),6.94-6.88(m,2H),6.58(s,1H),3.79(表观t,J=6.9Hz,2H),3.73-3.70(m,6H),234(表观t,J=7.8Hz,2H),2.19-2.18(m,6H),1.97-1.90(m,2H);ESI MS m/z 353[$C_{21}H_{24}N_2O_3$+H]$^+$.

[0311] (S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

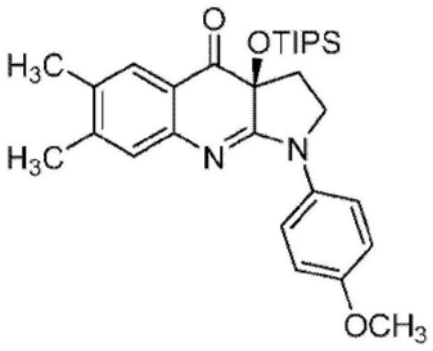
[0312] 

[0313] 将2-((1-(4-(甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯(1.87g,5.31mmol)在四氢呋喃(10mL)中的溶液在氮气氛下在干冰/丙酮浴中冷却,并用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(16mL,16mmol)逐滴处理。将混合物搅拌1小时,在此期间,浴温升至约0℃。1小时后,将混合物用(-)-(8,8-二氯樟脑基磺酰基)氧杂吖丙啶(3.17mg,10.6mmol)在四氢呋喃(10mL)中的溶液处理并搅拌1小时。此时间之后,将混合物用饱和碘化铵水溶液(6mL)处理,随后用饱和硫代硫酸钠水溶液(12ml)和盐水(40mL)处理。分离有机层和水层,并将水层用乙酸乙酯洗涤。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩。将剩余物溶于乙酸乙酯(25mL)中,并用0.3M盐酸(4×40mL)萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约8,并用乙酸乙酯(3×100mL)萃取。有机物经硫酸钠干燥,过滤,并在减压下浓缩。通过从热乙醇中重结晶来纯化粗制产物,以得到作为黄色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(422mg,24%):mp=199至200℃;

[0314] ^{1}H NMR(500MHz,DMSO-d_6)δ7.98-7.95(m,2H),7.46(s,1H),7.00-6.98(m,3H),6.72(s,1H),4.06-4.01(m,1H),3.91-3.88(m,1H),3.77(s,3H),2.25(s,3H),2.23-2.21(m,5H);ESI MS m/z 337[$C_{20}H_{20}N_2O_3$+H]$^+$;

[0315] HPLC(方法B)>99%(AUC),t_R=8.71分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=18.75分钟。

[0316] (S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

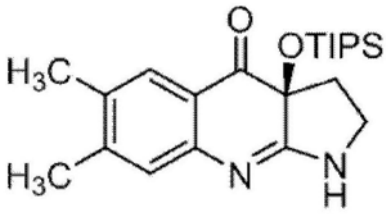
[0317] 

[0318] 用N,N-二异丙基乙胺(1.5mL,1.1g,8.6mmol)和三异丙基甲硅烷基三氟甲磺酸酯(1.8mL,2.0g,6.7mmol)处理(S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(725mg,2.16mmol)在1,2-二氯乙烷(25mL)中的溶液并在氮气氛下在80℃下搅拌21小时。此时间之后,使反应混合物冷却至环境温度。混合物用冷的去离子水(25mL)处理,随后用饱和氯化铵水溶液(25mL)处理,并分离有机层和水层。将水层

用乙酸乙酯(2×25mL)洗涤。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,5%至40%乙酸乙酯/庚烷)纯化,以得到作为黄色油状物的(S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(690mg,65%):

[0319] ^{1}H NMR(300MHz,DMSO-d_6)δ7.96(d,J=9.0Hz,2H),7.46(s,1H),7.02-6.99(m,3H),4.02-3.96(m,2H),3.77(s,3H),2.33-2.26(m,5H),2.20(s,3H),0.83-0.81(m,21H);ESI MS m/z 493[$C_{29}H_{40}N_2O_3Si$+H]$^+$.

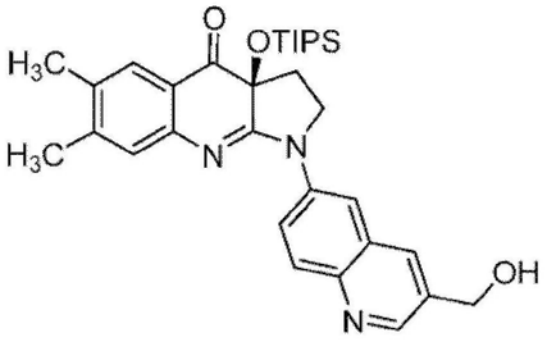
[0320] (S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0321] 

[0322] 将(S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(1.24g,2.52mmol)在乙腈(20mL)中的溶液在湿冰/水浴中冷却,并用硝酸铵铈(IV)(5.52g,10.1mmol)在去离子水(10mL)中的溶液逐滴处理,并在氮气氛下于约0℃搅拌30分钟。此时间之后,将混合物用硫代硫酸钠水溶液(15mL)和饱和碳酸氢钠水溶液(15mL)处理。将混合物通过硅藻土过滤,并将固体用乙酸乙酯洗涤。滤液用乙酸乙酯(2×100mL)萃取。合并的有机物用饱和碳酸氢钠、水和盐水洗涤。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,5%至100%乙酸乙酯/庚烷,0至20%甲醇/乙酸乙酯)纯化,以得到作为橙黄色固体的(S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(589mg,61%):

[0323] ^{1}H NMR(300MHz,DMSO-d_6)δ7.41(s,1H),6.77(s,1H),3.70-3.61(m,2H),2.21-2.16(m,8H),0.86-0.84(m,21H),未观察到NH质子;ESI MS m/z 387[$C_{22}H_{34}N_2O_2Si$+H]$^+$.

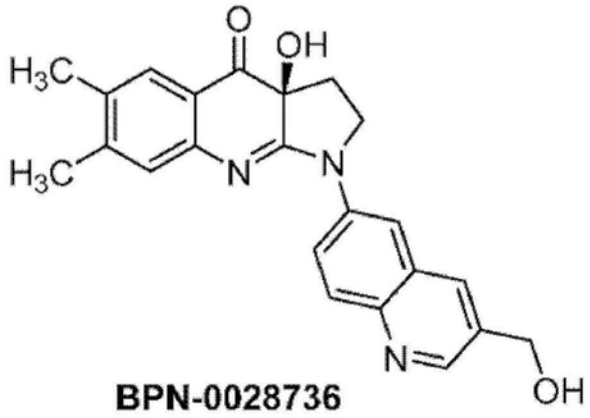
[0324] (S)-1-(3-(羟甲基)喹啉-6-基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0325] 

[0326] 将(S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(100mg,0.260mmol)、(6-溴喹啉-3-基)甲醇(105mg,0.440mmol)、4,5-双(二苯基膦基)-9,9-二甲基呫吨(xantphos)(90mg,0.16mmol)和碳酸铯(186mg,0.570mmol)在1,4-二氧六环(6mL)中的溶液用氩气脱气15分钟。添加三(二亚苄基丙酮)二钯(0)(25mg,

0.026mmol)，并将所得混合物在105℃下加热3小时。此时间之后，将反应混合物通过硅藻土使用二氯甲烷作为洗脱液过滤。在减压下浓缩滤液，并将剩余物通过柱色谱法(硅胶，0至100％乙酸乙酯/己烷)纯化，以得到(S)-1-(3-(羟甲基)喹啉-6-基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(43mg，30％)：ESI MS m/z 544[$C_{32}H_{41}N_3O_3Si$+H]$^+$.

[0327] (S)-3a-羟基-1-(3-(羟甲基)喹啉-6-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0328] 

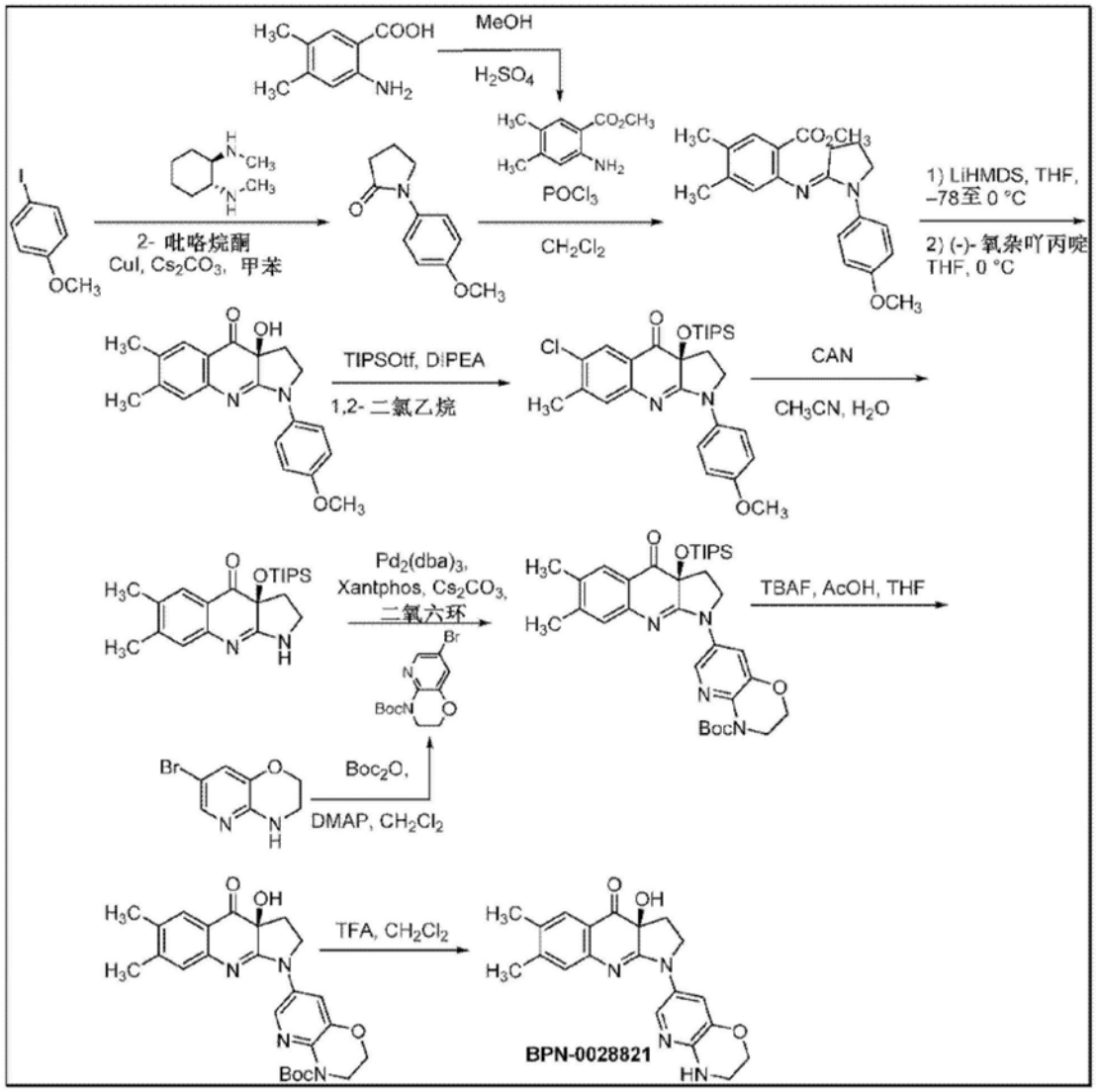
BPN-0028736

[0329] 用氟化四丁基铵在四氢呋喃中的1.0M溶液(0.10mL，0.10mmol)处理在氮气氛下的(S)-1-(3-(羟甲基)喹啉-6-基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(43mg，0.08mmol)在四氢呋喃(3mL)中的溶液，并将混合物搅拌4小时。此时间之后，将混合物在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶，0至20％甲醇/二氯甲烷)纯化，以得到作为黄色固体的(S)-3a-羟基-1-(3-(羟甲基)喹啉-6-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：

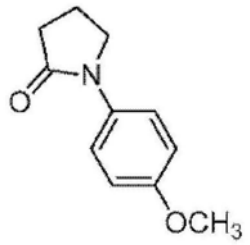
[0330] ^{1}H NMR(300MHz，DMSO-d_6)δ8.78(s，1H)，8.70(d，J＝9.6Hz，1H)，8.49(s，1H)，8.23(s，1H)，8.05(d，J＝9.0Hz，1H)，7.52(s，1H)，7.15(s，1H)，6.87(s，1H)，5.47(m，1H)，4.73(d，J＝4.2Hz，2H)4.19-4.13(m，2H)，2.31-2.24(m，8H)；ESI MS m/z 388[$C_{23}H_{21}N_3O_3$+H]$^+$；

[0331] UPLC(方法A)98.3％(AUC)，t_R＝10.24分钟；手性HPLC(Chiralpak AD，方法A)91.1％(AUC)，t_R＝19.45分钟。

[0332] 方案7：BPN-0028821

[0333] 

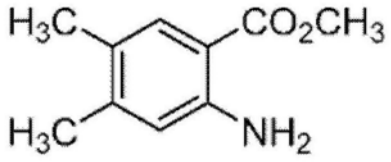
[0334] 1-(4-甲氧基苯基)吡咯烷-2-酮的制备

[0335] 

[0336] 用2-吡咯烷酮(3.8mL,4.3g,50mmol)、碘化铜(638mg,3.35mmol)、碳酸铯(26.1g,80.0mmol)和(1R,2R)-N^1,N^2-二甲基环己烷-1,2-二胺(1.1mL,0.99g,7.0mmol)处理1-碘代-4-甲氧基苯(8.00g,33.3mmol)在甲苯(50mL)中的溶液,并在氮气氛下在110℃下加热22小时。此时间之后,使反应混合物冷却至环境温度,通过硅藻土过滤,并将滤液在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/庚烷)纯化,以得到作为白色固体的1-(4-甲氧基苯基)吡咯烷-2-酮(6.07g,95%):

[0337] ^{1}H NMR(300MHz,DMSO-d_6)δ7.54(d,J=9.3Hz,2H),6.93(d,J=9.0Hz,2H),3.78(t,J=7.2Hz,2H),3.74(s,3H),2.45(t,J=8.1Hz,2H),2.09-1.99(m,2H);ESI MS m/z 192 $[C_{11}H_{13}NO_2+H]^+$.

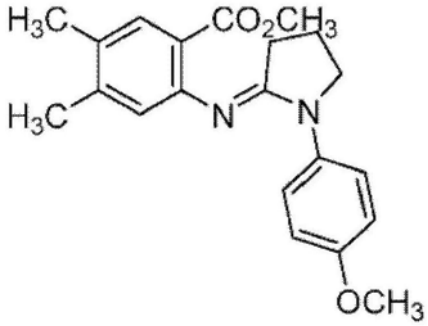
[0338] 2-氨基-4,5-二甲基苯甲酸甲酯的制备

[0339] 

[0340] 用浓硫酸(18mL)处理2-氨基-4,5-二甲基苯甲酸(10.00g,60.54mmol)在甲醇(180mL)中的溶液,并在氮气氛下在60℃下加热64.5小时。此时间之后,将反应混合物在减压下浓缩以除去挥发物。将所得剩余物用饱和碳酸氢钠水溶液(800mL)小心处理,并用乙酸乙酯(2×300mL)萃取。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为浅棕色固体的2-氨基-4,5-二甲基苯甲酸甲酯(10.14g,94%):

[0341] ^{1}H NMR(300MHz,DMSO-d_6)δ7.44(s,1H),6.56(s,1H),6.38(s,2H),3.75(s,3H),2.12(s,3H),2.07(s,3H);ESI MS m/z 180[$C_{10}H_{13}NO_2$+H]$^+$.

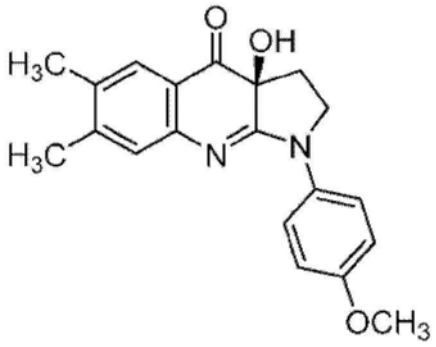
[0342] 2-((1-(4-甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯的制备

[0343] 

[0344] 用氯氧化磷(12.mL,20.g,130mmol)处理1-(4-甲氧基苯基)吡咯烷-2-酮(16.34g,85.45mmol)在1,2-二氯乙烷(100mL)中的溶液,并在环境温度下在氮气氛下搅拌5.25小时。将混合物用2-氨基-4,5-二甲基苯甲酸甲酯(15.36g,85.70mmol)在1,2-二氯乙烷(100mL)中的溶液处理,并在80℃下回流67小时。此时间之后,使反应混合物冷却至环境温度,并用饱和碳酸氢钠水溶液(200mL)处理。分离有机层和水层,并将水层用乙酸乙酯洗涤。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩。将剩余物溶于乙酸乙酯(200mL)中,并用0.3M盐酸萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约11,并用乙酸乙酯萃取。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩,以得到作为棕色油状物的2-((1-(4-(甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯(25.93g,86%):

[0345] ^{1}H NMR(300MHz,DMSO-d_6)δ7.75-7.70(m,2H),7.51(s,1H),6.94-6.88(m,2H),6.58(s,1H),3.79(表观t,J=6.9Hz,2H),3.73-3.70(m,6H),2.34(表观t,J=7.8Hz,2H),2.19-2.18(m,6H),1.97-1.90(m,2H);ESI MS m/z 353[$C_{21}H_{24}N_2O_3$+H]$^+$.

[0346] (S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

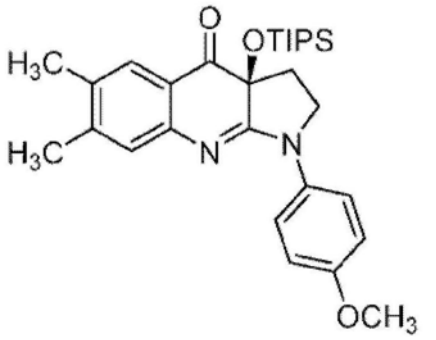
[0347] 

[0348] 将2-((1-(4-(甲氧基苯基)吡咯烷-2-亚基)氨基)-4,5-二甲基苯甲酸甲酯(1.87g,5.31mmol)在四氢呋喃(10mL)中的溶液在氮气氛下在干冰/丙酮浴中冷却,并用双(三甲基甲硅烷基)氨基锂在四氢呋喃中的1.0M溶液(16mL,16mmol)逐滴处理。将混合物搅拌1小时,在此期间,浴温升至约0℃。1小时后,用(-)-(8,8-二氯樟脑基磺酰基)氧杂吖丙啶(3.17mg,10.6mmol)在四氢呋喃(10mL)中的溶液处理混合物并搅拌1小时。此时间之后,将混合物用饱和碘化铵水溶液(6mL)处理,随后用饱和硫代硫酸钠水溶液(12ml)和盐水(40mL)处理。分离有机层和水层,并将水层用乙酸乙酯洗涤。合并的有机物经硫酸钠干燥,过滤,并在减压下浓缩。将剩余物溶于乙酸乙酯(25mL)中,并用0-3M盐酸(4×40mL)萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约8,并用乙酸乙酯(3×100mL)萃取。有机物经硫酸钠干燥,过滤,并在减压下浓缩。通过从热乙醇中重结晶来纯化粗制产物,以得到作为黄色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(422mg,24%):mp=199至200℃;

[0349] ^{1}H NMR(500MHz,DMSO-d_6)δ7.98-7.95(m,2H),7.46(s,1H),7.00-6.98(m,3H),6.72(s,1H),4.06-4.01(m,1H),3.91-3.88(m,1H),3.77(s,3H),2.25(s,3H),2.23-2.21(m,5H);ESI MS m/z 337[$C_{20}H_{20}N_2O_3$+H]$^{+}$;

[0350] HPLC(方法B)>99%(AUC),t_R=8.71分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=18.75分钟。

[0351] (S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

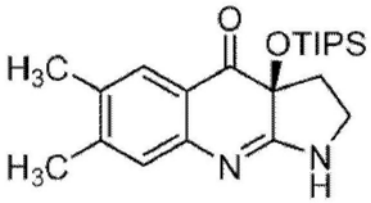
[0352] 

[0353] 用N,N-二异丙基乙胺(1.5mL,1.1g,8.6mmol)和三异丙基甲硅烷基三氟甲磺酸酯(1.8mL,2.0g,6.7mmol)处理(S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(725mg,2.16mmol)在1,2-二氯乙烷(25mL)中的溶液并在氮气氛下在80℃下搅拌21小时。此时间之后,使反应混合物冷却至环境温度。混合物用冷的去离子水(25mL)处理,随后用饱和氯化铵水溶液(25mL)处理,并分离有机层和水层。将水层

用乙酸乙酯(2×25mL)洗涤。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,5%至40%乙酸乙酯/庚烷)纯化,以得到作为黄色油状物的(S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(690mg,65%):

[0354] ^{1}H NMR(300MHz,DMSO-d_6)δ7.96(d,J=9.0Hz,2H),7.46(s,1H),7.02-6.99(m,3H),4.02-3.96(m,2H),3.77(s,3H),2.33-2.26(m,5H),2.20(s,3H),0.83-0.81(m,21H);ESI MS m/z 493[$C_{29}H_{40}N_2O_3Si$+H]$^+$.

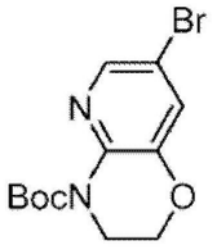
[0355] (S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0356] 

[0357] 将(S)-1-(4-甲氧基苯基)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(1.24g,2.52mmol)在乙腈(20mL)中的溶液在湿冰/水浴中冷却,并用硝酸铵铈(IV)(5.52g,10.1mmol)在去离子水(10mL)中的溶液逐滴处理,并在氮气氛下于约0℃下搅拌30分钟。此时间之后,将混合物用硫代硫酸钠水溶液(15mL)和饱和碳酸氢钠水溶液(15mL)处理。将混合物通过硅藻土过滤,并将固体用乙酸乙酯洗涤。滤液用乙酸乙酯(2×100mL)萃取。合并的有机物用饱和碳酸氢钠、水和盐水洗涤。有机物经硫酸钠干燥,过滤,并在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,5%至100%乙酸乙酯/庚烷,0至20%甲醇/乙酸乙酯)纯化,以得到作为橙黄色固体的(S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(589mg,61%):

[0358] ^{1}H NMR(300MHz,DMSO-d_6)δ7.41(s,1H),6.77(s,1H),3.70-3.61(m,2H),2.21-2.16(m,8H),0.86-0.84(m,21H),未观察到NH质子;ESI MS m/z 387[$C_{22}H_{34}N_2O_2Si$+H]$^+$.

[0359] 7-溴-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯的制备

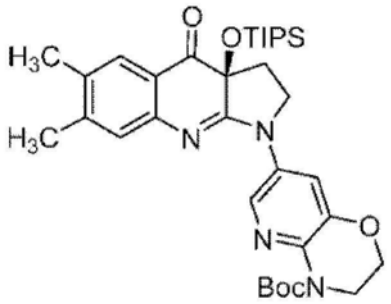
[0360] 

[0361] 将7-溴-3,4-二氢-2H-吡啶并[3,2-b][1,4]噁嗪(305mg,1.42mmol)和4-二甲基氨基吡啶(19mg,0.16mmol)在二氯甲烷(20mL)中的溶液在湿冰/水浴中冷却,并用2M二碳酸二叔丁酯在二氯甲烷中的溶液(0.78mL,1.6mmol)逐滴处理。10分钟后,将反应温热至室温并搅拌24小时。此时间之后,添加水(20mL),并分离有机层和水层。将有机物用盐水洗涤,经硫酸钠干燥,过滤,并在减压下浓缩,以提供作为粉红色固体的7-溴-2,3-二氢-4H-吡啶并[3,2-b][1,4]-噁嗪-4-羧酸叔丁酯(353mg,79%):

[0362] ^{1}H NMR(500MHz,DMSO-d_6)δ8.03(d,J=2.2Hz,1H),7.57(d,J=2.2Hz,1H),4.26-

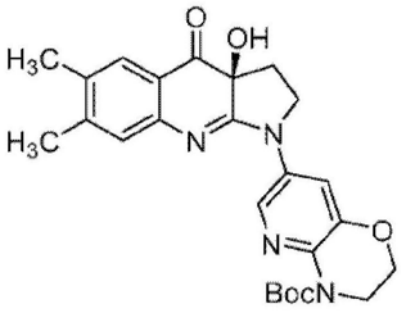
4.24(m,2H),3.84-3.82(m,2H),1.46(s,9H).

[0363] (S)-7-(6,7-二甲基-4-氧代-3a-((三异丙基甲硅烷基)氧基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯的制备

[0364] 

[0365] 将(S)-6,7-二甲基-3a-((三异丙基甲硅烷基)氧基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(202mg,0.522mmol)、7-溴-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯(250.mg,0.793mmol)和碳酸铯(172mg,0.578mmol)在1,4-二氧六环(10mL)中的溶液用氩气脱气10分钟。添加三(二亚苄基丙酮)二钯(0)(61mg,0.067mmol)和4,5-双(二苯基膦基)-9,9-二甲基呫吨(xantphos)(188mg,0.325mmol),并将所得混合物在90℃下在密封的小瓶中加热23.5小时。此时间之后,将反应混合物通过硅藻土使用乙酸乙酯作为洗脱液过滤。滤液在减压下浓缩,将剩余物通过柱色谱法(硅胶,12%至100%乙酸乙酯/己烷)纯化,以得到作为橙色固体的(S)-7-(6,7-二甲基-4-氧代-3a-((三异丙基甲硅烷基)氧基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯(133mg,41%):ESI MS m/z 621[$C_{34}H_{48}N_4O_5Si+H$]$^+$.

[0366] (S)-7-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯的制备

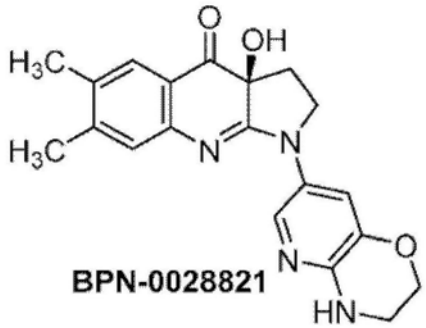
[0367] 

[0368] 用氟化四丁基铵在四氢呋喃中的1.0M溶液(0.64mL,0.64mmol)和乙酸(0.07mL,0.07g,1mmol)处理在氮气氛下的(S)-7-(6,7-二甲基-4-氧代-3a-((三异丙基甲硅烷基)氧基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯(133mg,0.214mmol)在四氢呋喃(5mL)中的溶液,并将混合物搅拌。17小时后,添加另外的氟化四丁基铵在四氢呋喃中的1.0M溶液(0.21mL,0.21mmol),并继续搅拌反应。12小时后,添加另外的氟化四丁基铵在四氢呋喃中的1.0M溶液(0.21mL,0.21mmol),并继续搅拌反应。4小时后,添加另外的氟化四丁基铵在四氢呋喃中的1.0M溶液(0.21mL,0.21mmol),并将反应继续搅拌3小时。此时间之后,将混合物在减压下浓缩。将粗制剩余物通过柱色谱法(硅胶,2至20%甲醇/二氯甲烷)纯化。将半粗制产物溶于乙酸乙酯(20mL)中,

并用0.3M盐酸萃取。用2.0M氢氧化钠水溶液将合并的酸层调节至pH约8，并用乙酸乙酯萃取。有机物经硫酸钠干燥，过滤，并在减压下浓缩，以得到(S)-7-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯与(S)-1-(3,4-二氢-2H-吡啶并[3,2-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的混合物(59mg)：

[0369] ESI MS m/z 465[$C_{25}H_{28}N_4O_5$+H]$^+$;ESI MS m/z 365[$C_{20}H_{20}N_4O_3$+H]$^+$.

[0370] (S)-1-(3,4-二氢-2H-吡啶并[3,2-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

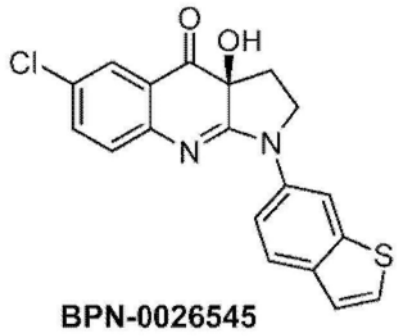
[0371] 

[0372] 将(S)-7-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2,3-二氢-4H-吡啶并[3,2-b][1,4]噁嗪-4-羧酸叔丁酯与(S)-1-(3,4-二氢-2H-吡啶并[3,2-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的混合物(59mg)溶于二氯甲烷(5mL)中，并用三氟乙酸(0.01mL,0.01g,0.1mmol)处理。将反应混合物在氮气氛下在室温搅拌3.5小时。此时间之后，将混合物用二氯甲烷(5mL)稀释，并用碳酸氢钠(10mL)处理。分离有机层和水层，有机层经硫酸钠干燥，过滤，并在减压下浓缩。将剩余物从热乙腈中结晶，以得到作为橙色固体的(S)-1-(3,4-二氢-2H-吡啶并[3,2-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮(34mg,74％)：

[0373] mp＝231-232℃;^{1}H NMR(500MHz,DMSO-d_6)δ8.03(d,J＝2.4Hz,1H),7.93(d,J＝2.2Hz,1H),7.45(s,1H),6.96(s,1H),6.70(s,1H),6.67(s,1H),4.15-4.13(m,2H),4.00-3.95(m,1H),3.87-3.83(m,1H),3.42-3.39(m,2H),2.25(s,3H),2.20-2.19(m,5H);ESI MS m/z 365[$C_{20}H_{20}N_4O_3$+H]$^+$;

[0374] UPLC(方法A)99.0％(AUC)，t_R＝2.66分钟;手性HPLC(Chiralpak AD,方法A)84.1％(AUC)，t_R＝20.76分钟。

[0375] (S)-1-(苯并[b]噻吩-6-基)-6-氯-3a-羟基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0376] 

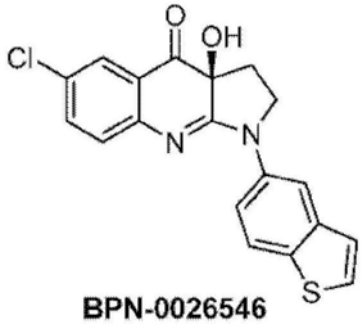
BPN-0026545

[0377] 根据合成方案3制备作为橙红色固体的(S)-1-(苯并[b]噻吩-6-基)-6-氯-3a-羟基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=221至229℃;

[0378] ^{1}H NMR(300MHz,DMSO-d_6)δ8.72(d,J=1.7,1H),8.15(dd,J=8.8,2.0Hz,1H),7.92(d,J=8.2Hz,1H),7.73(d,J=5.4Hz,1H),7.65(d,J=2.6,1H),7.58(dd,J=8.6,2.6Hz,1H),7.45(d,J=5.4Hz,1H),7.28(d,J=8.5Hz,1H),7.01(s,1H),4.22-4.04(m,2H),2.36-2.27(m,2H);ESI MS m/z 369[$C_{19}H_{13}ClN_2O_2S$+H]$^+$;

[0379] HPLC(方法C)>99%(AUC),t_R=13.20分钟;手性HPLC(Chiralpak AD,方法A)92.1%(AUC),t_R=17.57分钟。

[0380] (S)-1-(苯并[b]噻吩-5-基)-6-氯-3a-羟基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0381] 

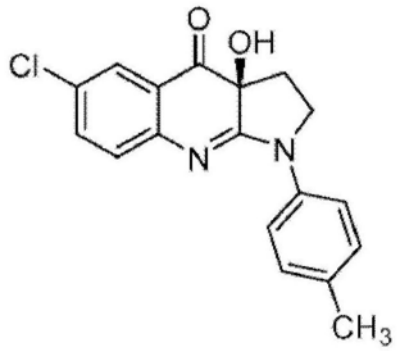
BPN-0026546

[0382] 根据合成方案3制备作为黄色固体的(S)-1-(苯并[b]噻吩-5-基)-6-氯-3a-羟基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=204至208℃;

[0383] ^{1}H NMR(300MHz,DMSO-d_6)δ8.16(d,J=2.1Hz,1H),8.15(d,J=2.0Hz,1H),8.05(d,J=8.9Hz,1H),7.82(d,J=5.4,1H),7.65(dd,J=2.5,2.6Hz,1H),7.58(d,J=3.7Hz,1H),7.50(d,J=5.4Hz,1H),7.25(d,J=8.6Hz,1H),7.01(s,1H),4.20-4.05(m,2H),2.50-2.27(m,2H);ESI MS m/z 369[$C_{19}H_{13}ClN_2O_2S$+H]$^+$;

[0384] HPLC(方法C)>99%(AUC),t_R=13.15分钟;手性HPLC(Chiralpak AD,方法A)85.1%(AUC),t_R=18.25分钟。

[0385] (S)-6-氯-3a-羟基-1-(对甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0386] 

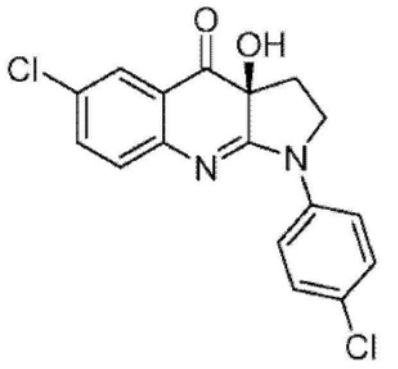
BPN-0026609

[0387] 根据合成方案2制备作为橙色固体的(S)-6-氯-3a-羟基-1-(对甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=217至220℃;

[0388] ^{1}H NMR(300MHz,DMSO-d_6)δ7.93(d,J=8.5Hz,2H),7.63(d,J=2.5Hz,1H),7.55(dd,J=3.7Hz,1H),7.22(m,3H),6.96(s,1H),4.02(m,2H),2.31(s,3H),2.27(m,2H);ESI MS m/z 327[$C_{18}H_{15}ClN_2O_2$+H]$^+$;

[0389] HPLC(方法C)97.0%(AUC),t_R=12.45分钟;手性HPLC(Chiralpak AD,方法A)98.5%(AUC),t_R=14.31分钟。

[0390] (S)-6-氯-1-(4-氯苯基)-3a-羟基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0391] 

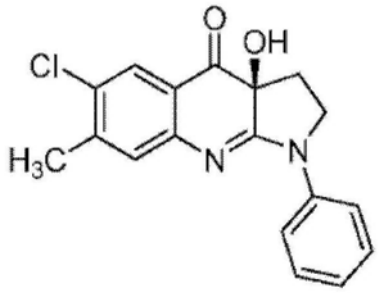
BPN-0026640

[0392] 根据合成方案2制备作为亮黄色固体的(S)-6-氯-1-(4-氯苯基)-3a-羟基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=212至216℃;

[0393] ^{1}H NMR(300MHz,DMSO-d_6)δ8.15-8.10(m,2H),7.65(d,J=2.6Hz,1H),7.59(dd,J=8.5,2.6Hz,1H),7.52-7.47(m,2H),7.24(d,J=8.5Hz,1H),7.00(s,1H),4.13-3.94(m,2H),2.37-2.22(m,2H);ESI MS m/z 347[$C_{17}H_{12}Cl_2N_2O_2$+H]$^+$;

[0394] HPLC(方法C)98.2%(AUC),t_R=13.45分钟;手性HPLC(Chiralpak AD,方法A)89.6%(AUC),t_R=19.74分钟。

[0395] (S)-6-氯-3a-羟基-7-甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0396] 

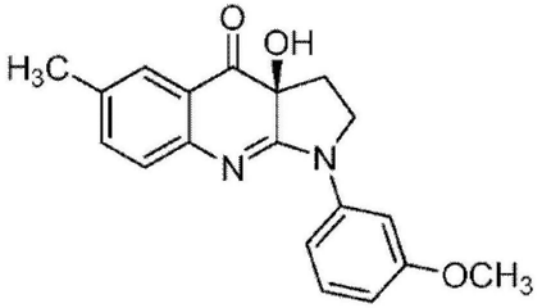
BPN-0026659

[0397] 根据合成方案2制备作为浅黄色固体的(S)-6-氯-3a-羟基-7-甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝219至223℃;

[0398] ^{1}H NMR(300MHz,DMSO-d_6)δ8.07(d,J＝8.0Hz,2H),7.63(s,1H),7.44(表观t,J＝7.9Hz,2H),7.24-7.15(m,2H),6.94(s,1H),4.14-3.94(m,2H),2.37-2.21(m,5H);ESI MS m/z 327[$C_{18}H_{15}ClN_2O_2$+H]$^+$;

[0399] HPLC(方法C)99.0%(AUC),t_R＝12.69分钟;手性HPLC(Chiralpak AD,方法A)93.2%(AUC),t_R＝18.38分钟。

[0400] (S)-3a-羟基-1-(3-甲氧基苯基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0401] 

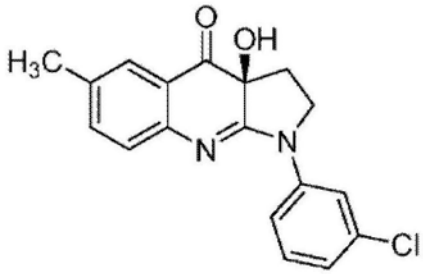
BPN-0025044

[0402] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(3-甲氧基苯基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝196至197℃;

[0403] ^{1}H NMR(500MHz,DMSO-d_6)δ7.99(表观t,J＝2.1Hz,1H),7.53(d,J＝1.2Hz,1H),7.48-7.46(m,1H),7.38(dd,J＝8.1,2.0Hz,1H),7.32(表观t,J＝8.2Hz,1H),7.12(d,J＝8.1Hz,1H),6.81(s,1H),6.73(dd,J＝8.2,2.2Hz,1H),4.06-4.01(m,1H),3.97-3.94(m,1H),3.80(s,3H),2.30(s,3H),2.26-2.24(m,2H);ESI MS m/z 323[$C_{19}H_{18}N_2O_3$+H]$^+$;

[0404] HPLC(方法C)＞99%(AUC),t_R＝12.05分钟;手性HPLC(Chiralpak AD,方法A)97.0%(AUC),t_R＝15.07分钟。

[0405] (S)-1-(3-氯苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

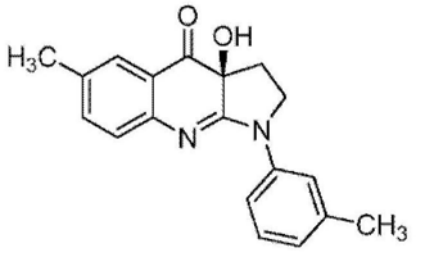
[0406] 

BPN-0025059

[0407] 根据合成方案2制备作为橙色固体的(S)-1-(3-氯苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝199至200℃;

[0408] ^{1}H NMR(500MHz,DMSO-d_6)δ839(表观t,J＝2.1Hz,1H),7.93(ddd,J＝8.4,2.2,0.7Hz,1H),7.55(d,J＝1.6Hz,1H),7.45(表观t,J＝8.2Hz,1H),7.41-7.39(m,1H),7.19(ddd,J＝7.9,1.9,0.6Hz,1H),7.15(d,J＝8.1Hz,1H),6.86(s,1H),4.07-3.96(m,2H),2.31-2.25(m,5H);ESI MS m/z 327[$C_{18}H_{15}ClN_2O_2$+H]$^+$;HPLC(方法C)＞99%(AUC),t_R＝12.18分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝14.59分钟。

[0409] (S)-3a-羟基-6-甲基-1-(间甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0410] 

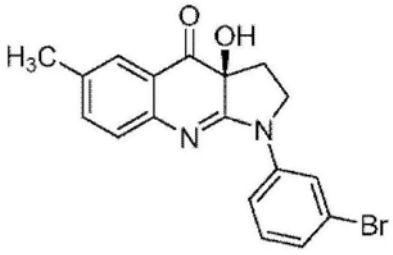
BPN-0025100

[0411] 根据合成方案3制备作为橙色固体的(S)-3a-羟基-6-甲基-1-(间甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝192至193℃;

[0412] ^{1}H NMR(500MHz,DMSO-d_6)δ7.94(dd,J＝8.2,2.0Hz,1H),7.84(s,1H),7.52(d,J＝2.0Hz,1H),7.38-7.36(m,1H),7.30(表观t,J＝7.9Hz,1H),7.11(d,J＝8.1Hz,1H),6.96(d,J＝75Hz,1H),6.79(s,1H),4.07-402(m,1H),3.96-3.93(m,1H),2.36(s,3H),2.30(s,3H),2.26-2.23(m,2H);ESI MS m/z 307[$C_{19}H_{18}N_2O_2$+H]$^+$;

[0413] HPLC(方法C)＞99%(AUC),t_R＝14.48分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝12.51分钟。

[0414] (S)-1-(3-溴苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0415] 

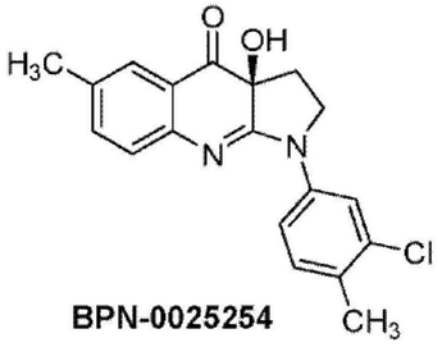
BPN-0025240

[0416] 根据合成方案3制备作为黄色固体的(S)-1-(3-溴苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝195至196℃;

[0417] ^{1}H NMR(500MHz,DMSO-d_6)δ8.53(表观t,J＝2.0Hz,1H),7.96(ddd,J＝8.3,2.2,0.9Hz,1H),7.55(d,J＝1.8Hz,1H),7.41-7.37(m,2H),7.32(ddd,J＝7.9,1.8,0.9Hz,1H),7.14(d,J＝8.1Hz,1H),6.87(s,1H),4.06-3.95(m,2H),2.31(s,3H),2.28-2.24(m,2H);ESI MS m/z 371[$C_{18}H_{15}BrN_2O_2$+H]$^+$;

[0418] HPLC(方法C)96.2%(AUC),t_R＝12.72分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝13.18分钟。

[0419] (S)-1-(3-氯-4-甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0420] 

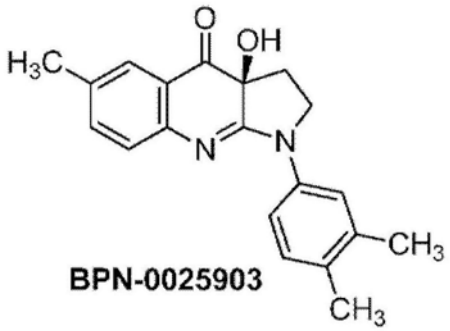
BPN-0025254

[0421] 根据合成方案3制备作为黄色固体的(S)-1-(3-氯-4-甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝213至214℃;

[0422] ^{1}H NMR(500MHz,DMSO-d_6)δ8.37(d,J＝2.4Hz,1H),7.82(dd,J＝8.4,2.3Hz,1H),7.54(d,J＝1.6Hz,1H),7.39(d,J＝8.3Hz,2H),7.12(d,J＝8.1Hz,1H),6.84(s,1H),4.05-3.93(m,2H),2.33-2.31(m,6H),2.27-2.22(m,2H);ESI MS m/z 341[$C_{19}H_{17}ClN_2O_2$+H]$^+$;

[0423] HPLC(方法C)＞99%(AUC),t_R＝2.30分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝14.28分钟。

[0424] (S)-1-(3,4-二甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

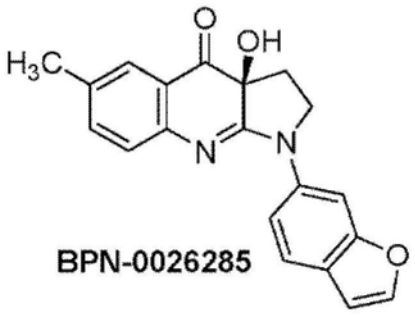
[0425] 

[0426] 根据合成方案3制备作为黄色固体的(S)-1-(3,4-二甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝197至199℃;

[0427] ^{1}H NMR(500MHz,DMSO-d_6)δ7.83(dd,J＝8.5,2.0Hz,1H),7.78(d,J＝1.5Hz,1H),7.51(d,J＝1.0Hz,1H),7.35(dd,J＝7.5,1.5Hz,1H),7.17(d,J＝8.5Hz,1H),7.09(d,J＝8.0Hz,1H),6.77(s,1H),4.05-4.00(m,1H),3.94-3.90(m,1H),2.29-2.22(m,11H);ESI MS m/z 321[$C_{20}H_{20}N_2O_2$+H]$^+$;

[0428] HPLC(方法F)98.4%(AUC),t_R＝14.99分钟;手性HPLC(Chiralpak AD,方法A)95.4%(AUC),t_R＝13.05分钟。

[0429] (S)-1-(苯并呋喃-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

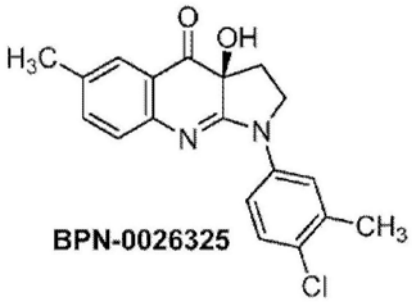
[0430] 

[0431] 根据合成方案3制备作为红橙色固体的(S)-1-(苯并呋喃-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝204至205℃;

[0432] ^{1}H NMR(500MHz,DMSO-d_6)δ8.54(s,1H),7.98(d,J＝2.5Hz,1H),7.88(dd,J＝8.5,2.0Hz,1H),7.68(d,J＝8.5Hz,1H),7.54(d,J＝1.5Hz,1H),7.38(dd,J＝8.5,2.0Hz,1H),7.15(d,J＝8.0Hz,1H),6.95(dd,J＝2.0,2.0Hz,1H),6.84(s,1H),4.16-4.11(m,1H),4.05-4.01(m,1H),2.33-2.25(m,5H);ESI MS m/z 333[$C_{20}H_{16}N_2O_3$+H]$^+$;

[0433] HPLC(方法C)＞99%(AUC),t_R＝12.24分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝17.78分钟。

[0434] (S)-1-(4-氯-3-甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0435] 

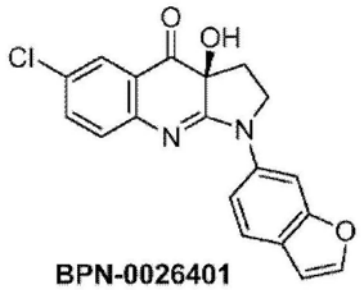
BPN-0026325

[0436] 根据合成方案3制备作为黄色固体的(S)-1-(4-氯-3-甲基苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=203至204℃;

[0437] ^{1}H NMR(500MHz,DMSO-d_6)δ8.06(dd,J=9.0,3.0Hz,1H),8.01(d,J=3.0Hz,1H),7.53(d,J=2.0Hz,1H),7.44(d,J=8.5Hz,1H),7.38(dd,J=8.5,2.0Hz,1H),7.14(d,J=8.0Hz,1H),6.83(s,1H),4.05-4.00(m,1H),3.97-3.93(m,1H),2.38(s,3H),2.31(s,3H),2.27-2.24(m,2H);ESIMS m/z 341[$C_{19}H_{17}ClN_2O_2$+H]$^+$;

[0438] HPLC(方法C)>99%(AUC),t_R=13.07分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.68分钟。

[0439] (S)-1-(苯并呋喃-6-基)-6-氯-3a-羟基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0440] 

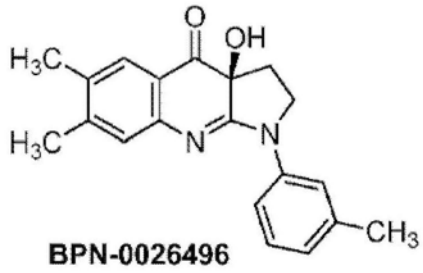
BPN-0026401

[0441] 根据合成方案3制备作为黄橙色固体的(S)-1-(苯并呋喃-6-基)-6-氯-3a-羟基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=209至211℃;

[0442] ^{1}H NMR(500MHz,DMSO-d_6)δ8.50(s,1H),8.00(d,J=2.0Hz,1H),7.87(dd,J=9.0,2.0Hz,1H),7.69(d,J=9.0Hz,1H),7.65(d,J=2.5Hz,1H),7.57(dd,J=8.5,2.5Hz,1H),7.26(d,J=8.5Hz,1H),6.98(s,1H),6.96(dd,J=2.5,1.0Hz,1H),4.20-4.16(m,1H),4.07-4.03(m,1H,2.38-2.34(m,1H),2.30-2.26(m,1H);ESI MS m/z 353[$C_{19}H_{13}ClN_2O_3$+H]$^+$;

[0443] HPLC(方法B)>99%(AUC),t_R=9.12分钟;手性HPLC(Chiralpak AD,方法A)99.0%(AUC),t_R=17.23分钟。

[0444] (S)-3a-羟基-6,7-二甲基-1-(间甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0445] 

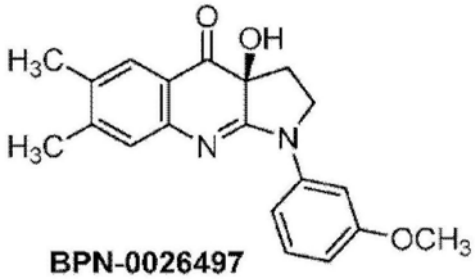
BPN-0026496

[0446] 根据合成方案3制备作为橙色固体的(S)-3a-羟基-6,7-二甲基-1-(间甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=196至198℃;

[0447] ^{1}H NMR(500MHz,DMSO-d_6)δ7.95(d,J=8.5Hz,1H),7.83(s,1H),7.48(s,1H),7.30(表观t,J=8.0Hz,1H),7.03(s,1H),6.96(d,J=7.5Hz,1H),6.74(s,1H),4.06-4.01(m,1H),3.95-3.92(m,1H),2.36(s,3H),2.27(s,3H),2.24-2.20(m,5H);ESI MS m/z 321 [$C_{20}H_{20}N_2O_2$+H]$^+$;

[0448] HPLC(方法C)>99%(AUC),t_R=12.62分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.47分钟。

[0449] (S)-3a-羟基-1-(3-甲氧基苯基)-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0450] 

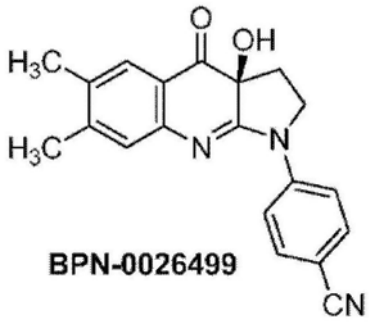
BPN-0026497

[0451] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(3-甲氧基苯基)-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=176至178℃;

[0452] ^{1}H NMR(500MHz,DMSO-d_6)δ7.97(表观t,J=2.0Hz,1H),7.48(dd,J=8.0,2.5Hz,2H),7.31(表观t,J=8.5Hz,1H),7.04(s,1H),6.76(s,1H),6.73(dd,J=8.0,2.0Hz,1H),4.05-4.00(m,1H),3.96-3.93(m,1H),3.80(s,3H),2.27(s,3H),2.24-2.21(m,5H);ESI MS m/z 337[$C_{20}H_{20}N_2O_3$+H]$^+$;

[0453] HPLC(方法C)>99%(AUC),t_R=12.41分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=16.05分钟。

[0454] (S)-4-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈的制备

[0455] 

BPN-0026499

[0456] 根据合成方案3制备作为黄棕色固体的(S)-4-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈:mp=229至231℃;

[0457] ^{1}H NMR(500MHz,DMSO-d_6)δ8.32(d,J=9.0Hz,2H),7.87(dd,J=7.5,2.0Hz,2H),7.52(s,1H),7.13(s,1H),6.86(s,1H),4.07-3.99(m,2H),2.29-2.24(m,8H);ESI MS m/z 332[$C_{20}H_{17}N_3O_2$+H]$^+$;

[0458] HPLC(方法C)>99%(AUC),t_R=12.60分钟;手性HPLC(Chiralpak AD,方法A)97.2%(AUC),tn=19.40分钟。

[0459] (S)-1-(3-氯苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0460] 

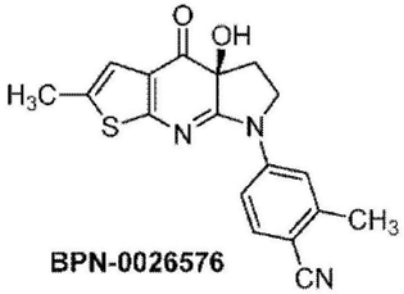
BPN-0026500

[0461] 根据合成方案3制备作为黄色固体的(S)-1-(3-氯苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=203至204℃;

[0462] ^{1}H NMR(500MHz,DMSO-d_6)δ8.40(表观t,J=2.0Hz,1H),7.92(d,J=7.5Hz,1H),7.50(s,1H),7.44(表观t,J=8.5Hz,1H),7.19(d,J=7.5Hz,1H),7.01(s,1H),6.80(s,1H),4.06-4.00(m,1H),3.97-3.95(m,1H),2.29(s,3H),2.25-2.23(m,5H);ESI MS m/z 341[$C_{19}H_{17}ClN_2O_2$+H]$^+$;

[0463] HPLC(方法C)>99%(AUC),t_R=12.89分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.96分钟。

[0464] (S)-4-(4a-羟基-2-甲基-4-氧代-5,6-二氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7(4aH)-基)-2-甲基苄腈的制备

[0465] 

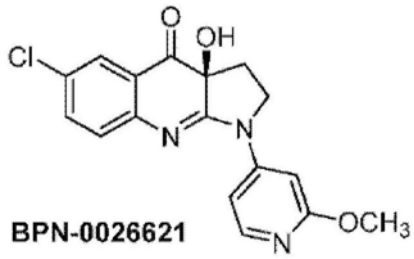
BPN-0026576

[0466] 根据合成方案3制备作为橙色固体的(S)-4-(4a-羟基-2-甲基-4-氧代-5,6-二氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7(4aH)-基)-2-甲基苄腈:mp=226至227℃;

[0467] ^{1}H NMR(500MHz,DMSO-d_6)δ8.17(dd,J=9.0,2.5Hz,1H),7.90(dd,J=2.0Hz,1H),7.83(d,J=9.0Hz,1H),6.97(s,1H),6.84(d,J=1.0Hz,1H),4.15-4.06(m,2H),2.52(s,3H),2.37(d,J=1.0,3H),2.25-2.21(m,2H);ESI MS m/z 338[$C_{18}H_{15}N_3O_2S$+H]$^+$;

[0468] HPLC(方法C)>99%(AUC),t_R=15.23分钟;手性HPLC(Chiralpak AD,方法A)98.9%(AUC),t_R=19.02分钟。

[0469] (S)-6-氯-3a-羟基-1-(2-甲氧基吡啶-4-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0470] 

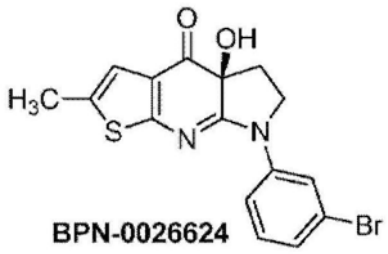
BPN-0026621

[0471] 根据合成方案6制备作为黄色固体的(S)-6-氯-3a-羟基-1-(2-甲氧基吡啶-4-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=230至231℃;

[0472] ^{1}H NMR(500MHz,DMSO-d_6)δ8.14(d,J=6.0Hz,1H),7.72(dd,J=6.0,2.0Hz,1H),7.68(d,J=3.0Hz,1H),7.63(dd,J=8.5,2.5Hz,1H),7.56(d,J=2.0Hz,1H),7.34(d,J=8.5Hz,1H),7.04(s,1H),4.02-4.00(m,2H),3.87(s,3H),2.39-2.32(m,1H),2.26-2.23(m,1H);ESI MS m/z 344[$C_{17}H_{14}ClN_3O_3$+H]$^+$;

[0473] HPLC(方法C)96.0%(AUC),t_R=13.01分钟;手性HPLC(Chiralpak AD,方法A)83.0%(AUC),t_R=14.71分钟。

[0474] (S)-7-(3-溴苯基)-4a-羟基-2-甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0475] 

BPN-0026624

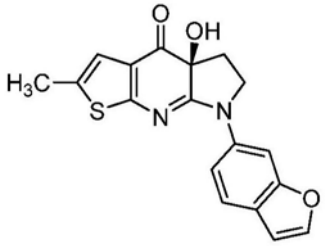
[0476] 根据合成方案3制备作为红橙色固体的(S)-7-(3-溴苯基)-4a-羟基-2-甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=236至238℃;

[0477] ^{1}H NMR(500MHz,DMSO-d_6)δ8.26(表观t,J=2.0Hz,1H),790(表观dt,J=8.0,1.5Hz,1H),7.43-7.37(m,2H),6.92(s,1H),6.81(d,J=1.0,1H),4.15-4.10(m,1H),4.05-4.01(m,1H),2.36(d,J=1.0,3H),2.22-2.19(m,2H);ESI MS m/z 377[$C_{16}H_{13}BrN_2O_2S$+H]$^+$;

[0478] HPLC(方法C)94.0%(AUC),t_R=16.31分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=16.36分钟。

[0479] (S)-7-(苯并呋喃-6-基)-4a-羟基-2-甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻

吩并[3,2-e]吡啶-4-酮的制备

[0480] 

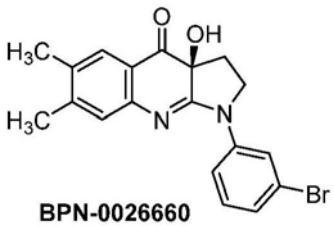
BPN-0026639

[0481] 根据合成方案3制备作为红色固体的(S)-7-(苯并呋喃-6-基)-4a-羟基-2-甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=247至248℃;

[0482] ^{1}H NMR(500MHz,DMSO-d_6)δ8.29(s,1H),8.02(d,J=2.5Hz,1H),7.81(dd,J=8.5,2.0Hz,1H),7.71(d,J=8.5Hz,1H),7.97(dd,J=2.0,1.0Hz,1H),6.90(s,1H),6.79(d,J=1.0,1H),4.25-4.20(m,1H),4.11-4.08(m,1H),2.35(d,J=1.0,3H),2.26-2.22(m,2H);ESI MS m/z 339[$C_{18}H_{14}N_2O_3S$+H]$^+$;

[0483] HPLC(方法B)>99%(AUC),t_R=10.20分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=22.00分钟。

[0484] (S)-1-(3-溴苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0485] 

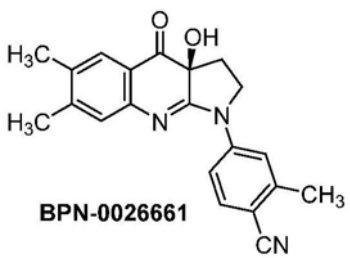
BPN-0026660

[0486] 根据合成方案3制备作为黄色固体的(S)-1-(3-溴苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=223至224℃;

[0487] ^{1}H NMR(500MHz,DMSO-d_6)δ8.52(表观t,J=2.0Hz,1H),7.96(ddd,J=8.3,2.2,1.0Hz,1H),7.50(s,1H),7.38(表观t,J=8.1Hz,1H),7.32(ddd,J=7.9,1.7,0.9Hz,1H),7.05(s,1H),6.81(s,1H),4.05-4.00(m,1H),3.98-3.94(m,1H),2.28(s,3H),2.25-2.23(m,5H);ESI MS m/z 385[$C_{19}H_{17}BrN_2O_2$+H]$^+$;

[0488] HPLC(方法C)93.1%(AUC),t_R=13.27分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=14.35分钟。

[0489] (S)-4-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈的制备

[0490] 

BPN-0026661

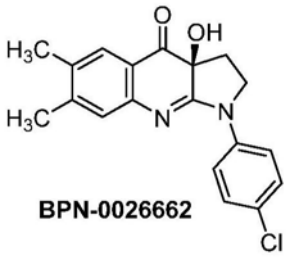
[0491] 根据合成方案3制备作为黄棕色固体的(S)-4-(3a-羟基-6,7-二甲基-4-氧代-2,

3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈:mp=240至241℃;

[0492] ^{1}H NMR(500MHz,DMSO-d_6)δ8.28(dd,J=8.8,2.2Hz,1H),8.10(d,J=1.9Hz,1H),7.79(d,J=8.7Hz,1H),7.52(s,1H),7.13(s,1H),7.85(s,1H),4.03-4.00(m,2H),2.53(s,3H),2.29(s,3H),2.27-2.24(m,5H);ESI MS m/z 346[$C_{21}H_{19}N_3O_2$+H]$^+$;

[0493] HPLC(方法C)98.6%(AUC),t_R=13.14分钟;手性HPLC(Chiralpak AD,方法A)88.1%(AUC),t_R=17.66分钟。

[0494] (S)-1-(4-氯苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0495] 

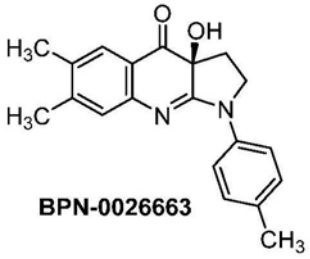
BPN-0026662

[0496] 根据合成方案3制备作为黄色固体的(S)-1-(4-氯苯基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=214至216℃;

[0497] ^{1}H NMR(500MHz,DMSO-d_6)δ8.15-8.12(m,2H),7.49-7.46(m,3H),7.06(s,1H),6.79(s,1H),4.05-4.02(m,1H),3.96-3.92(m,1H),2.27(s,3H),2.25-2.22(m,5H);ESI MS m/z 341[$C_{19}H_{17}ClN_2O_2$+H]$^+$;

[0498] HPLC(方法C)>99%(AUC),t_R=13.06分钟;手性HPLC(Chiralpak AD,方法A)97.6%(AUC),t_R=16.42分钟。

[0499] (S)-3a-羟基-6,7-二甲基-1-(对甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0500] 

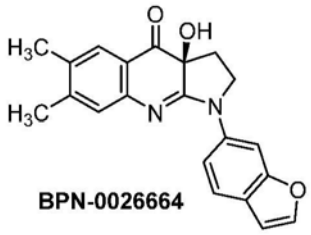
BPN-0026663

[0501] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(对甲苯基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=219至220℃;

[0502] ^{1}H NMR(500MHz,DMSO-d_6)δ7.96-3.94(m,2H),7.47(s,1H),7.22(d,J=8.3Hz,2H),7.02(s,1H),6.73(s,1H),4.05-4.00(m,1H),3.93-3.89(m,1H),2.31(s,3H),2.26(s,3H),2.24-2.21(m,5H);ESI MS m/z 321[$C_{20}H_{20}N_2O_2$+H]$^+$;

[0503] HPLC(方法B)>99%(AUC),t_R=8.97分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=15.61分钟。

[0504] (S)-1-(苯并呋喃-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0505] 

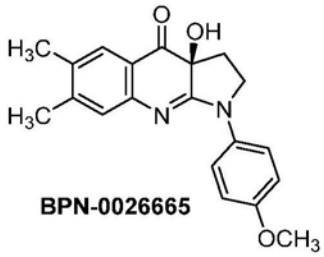
BPN-0026664

[0506] 根据合成方案3制备作为红色固体的(S)-1-(苯并呋喃-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝213至214℃;

[0507] ^{1}H NMR(500MHz,DMSO-d_6)δ8.56(s,1H),7.98(d,J＝2.2Hz,1H),7.88(dd,J＝8.6,2.0Hz,1H),7.67(d,J＝8.6Hz,1H),7.49(s,1H),7.09(s,1H),6.50(dd,J＝2.2,0.9Hz,1H),6.79(s,1H),4.15-4.10(m,1H),4.04-4.00(m,1H),2.28-2.25(m,5H),2.23(s,3H);ESI MS m/z 347[$C_{21}H_{18}N_2O_3$+H]$^+$;

[0508] HPLC(方法B)＞99%(AUC),t_R＝9.10分钟;手性HPLC(Chiralpak AD,方法A)95.8%(AUC),t_R＝19.08分钟。

[0509] (S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0510] 

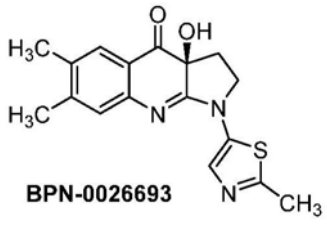
BPN-0026665

[0511] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝199至200℃;

[0512] ^{1}H NMR(500MHz,DMSO-d_6)δ7.98-7.95(m,2H),7.46(s,1H),7.00-6.98(m,3H),6.72(s,1H),4.06-4.01(m,1H),3.91-3.88(m,1H),3.77(s,3H),2.25(s,3H),2.23-2.21(m,5H);ESI MS m/z 337[$C_{20}H_{20}N_2O_3$+H]$^+$;

[0513] HPLC(方法B)＞99%(AUC),t_R＝8.71分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝18.75分钟。

[0514] (S)-3a-羟基-6,7-二甲基-1-(2-甲基噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0515] 

BPN-0026693

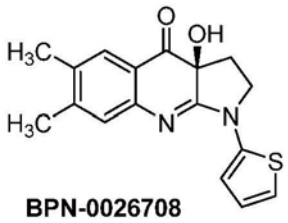
[0516] 根据合成方案6制备作为橙黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝234至235℃;

[0517] ^{1}H NMR(500MHz,DMSO-d_6)δ7.49(s,1H),7.44(s,1H),7.05(s,1H),6.87(s,1H),4.03-3.94(m,2H),2.60(s,3H),2.31-2.27(m,5H),2.22(s,3H);ESI MS m/z 328

$[C_{17}H_{17}N_3O_2S+H]^+$；

[0518] HPLC(方法C)＞99％(AUC)，t_R＝12.84分钟；手性HPLC(Chiralpak AD,方法A)53.0％(AUC)，t_R＝15.14分钟。

[0519] (S)-3a-羟基-6,7-甲基-1-(噻吩-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0520] 

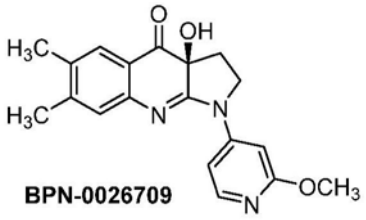
BPN-0026708

[0521] 根据合成方案4制备作为橙色固体的(S)-3a-羟基-6,7-二甲基-1-(噻吩-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：mp＝229至231℃；

[0522] ^{1}H NMR(500MHz,DMSO-d_e)δ7.49(s,1H)，7.14(dd,J＝5.5,1.4Hz,1H)，7.05(s,1H)，6.96(dd,J＝5.4,3.8Hz,1H)，6.83-6.82(m,2H)，4.07-3.97(m,2H)，2.37-2.35(m,2H)，2.28(s,3H)，2.22(s,3H)；ESI MS m/z 313$[C_{17}H_{16}N_2O_2S+H]^+$；

[0523] HPLC(方法B)＞99％(AUC)，t_R＝13.17分钟；手性HPLC(Chiralpak AD,方法A)83.5％(AUC)，t_R＝17.17分钟。

[0524] (S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0525] 

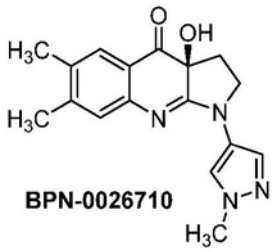
BPN-0026709

[0526] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮；mp＝218至220℃；

[0527] ^{1}H NMR(500MHz,DMSO-d_6)δ8.12(d,J＝5.9Hz,1H)，7.69(dd,J＝5.9,2.0Hz,1H)，7.59(d,J＝1.8Hz,1H)，7.52(s,1H)，7.14(s,1H)，6.86(s,1H)，3.97-3.94(m,2H)，3.87(s,3H)，2.30(s,3H)，2.26-2.23(m,5H)；ESI MS m/z 338$[C_{19}H_{19}N_3O_3+H]^+$；

[0528] HPLC(方法B)＞99％(AUC)，t_R＝9.04分钟；手性HPLC(Chiralpak AD,方法A)90.6％(AUC)，t_R＝15.27分钟。

[0529] (S)-3a-羟基-6,7-二甲基-1-(1-甲基-1H-吡唑-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0530] 

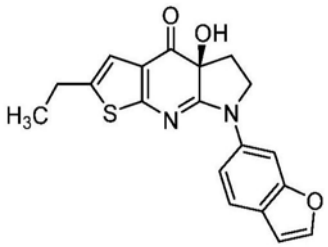
BPN-0026710

[0531] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(1-甲基-1H-吡唑-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝226至227℃;

[0532] ^{1}H NMR(500MHz,DMSO-d_6)δ7.25(s,1H),7.81(s,1H),7.44(s,1H),7.03(s,1H),6.69(s,1H),3.92-3.87(m,4H),3.81-3.78(m,1H),2.29-2.22(m,5H),2.20(s,3H);ESI MS m/z 311[$C_{17}H_{18}N_4O_2$+H]$^+$;

[0533] HPLC(方法B)＞99%(AUC),t_R＝7.50分钟;手性HPLC(Chiralpak AD,方法A)92.2%(AUC),t_R＝18.21分钟。

[0534] (S)-7-(苯并呋喃-6-基)-4a-羟基-2-乙基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0535] 

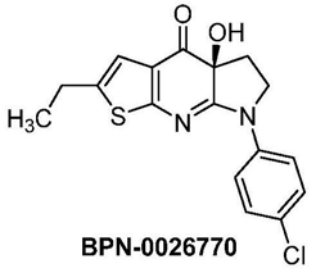
BPN-0026749

[0536] 根据合成方案3制备作为红橙色固体的(S)-7-(苯并呋喃-6-基)-4a-羟基-2.乙基-4a,5,6,7.四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝233至235℃;

[0537] ^{1}H NMR(500MHz,DMSO-d_6)δ8.30(s,1H),8.02(d,J＝2.2Hz,1H),7.81(dd,J＝8.6,1.9Hz,1H),7.71(d,J＝8.6Hz,1H),6.97(dd,J＝2.0,0.8Hz,1H),6.91(s,1H),6.82(s,1H),4.26-4.21(m,1H),4.11-4.08(m,1H),2.70(q,J＝7.5,2H),2.28-2.20(m,2H),1.22(t,J＝7.5Hz,3H);ESI MS m/z 353[$C_{19}H_{16}N_2O_3S$+H]$^+$;

[0538] HPLC(方法B)＞99%(AUC),t_R＝10.51分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝21.69分钟。

[0539] (S)-7-(4-氯苯基)-4a-羟基-2-乙基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0540] 

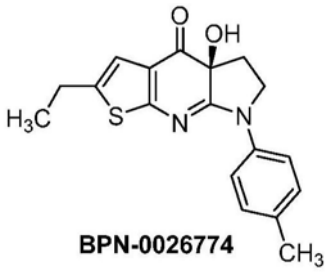
BPN-0026770

[0541] 根据合成方案3制备作为红橙色固体的(S)-7-(4-氯苯基)-4a-羟基-2-乙基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝235至236℃;

[0542] ^{1}H NMR(500MHz,DMSO-d_6)δ8.00-7.97(m,2H),7.53-7.50(m,2H),6.91(s,1H),6.82(表观t,J＝1.0Hz,1H),4.16-4.11(m,1H),4.03-4.00(m,1H),2.70(q,J＝7.4Hz,2H),2.23-2.20(m,2H),1.21(t,J＝7.5Hz,3H);ESI MS m/z 347[$C_{17}H_{15}ClN_2O_2S$+H]$^+$;

[0543] HPLC(方法B)＞99%(AUC),t_R＝11.20分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝18.88分钟。

[0544] (S)-2-乙基-4a-羟基-7-(对甲苯基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0545] 

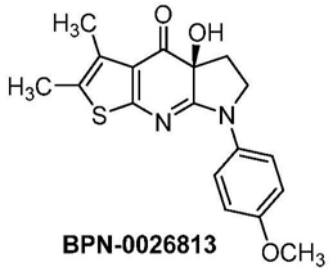
BPN-0026774

[0546] 根据合成方案3制备作为红色固体的(S)-2-乙基-4a-羟基-7-(对甲苯基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝248至249℃;

[0547] ^{1}H NMR(500MHz,DMSO-d_6)δ7.81-7.79(m,2H),7.26-7.24(m,2H),6.85(s,1H),6.79(表观t,J＝1.1Hz,1H),4.15-4.10(m,1H),4.01-3.98(m,1H),2.71-2.66(m,2H),2.31(s,3H),2.25-2.15(m,2H),2.21(t,J＝7.5Hz,3H);ESI MS m/z 327[$C_{18}H_{18}N_2O_2S$+H]$^+$;

[0548] HPLC(方法B)＞99%(AUC),t_R＝10.30分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝18.53分钟。

[0549] (S)-4a-羟基-7-(4-甲氧基苯基)-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0550] 

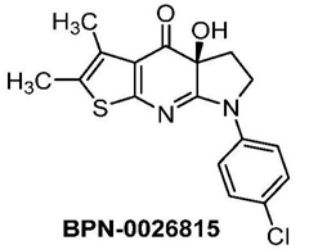
BPN-0026813

[0551] 根据合成方案3制备作为橙色固体的(S)-4a-羟基-7-(4-甲氧基苯基)-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝232至233℃;

[0552] ^{1}H NMR(500MHz,DMSO-d_6)δ7.83-7.81(m,2H),7.02-7.00(m,2H),6.80(s,1H),4.15-4.09(m,1H),3.99-3.95(m,1H),3.77(s,3H),2.20-2.17(m,8H);ESI MS m/z 343[$C_{18}H_{18}N_2O_3S$+H]$^+$;

[0553] HPLC(方法B)＞99%(AUC),t_R＝9.49分钟;手性HPLC(Chiralpak AD,方法A)85.2%(AUC),t_R＝18.94分钟。

[0554] (S)-7-(4-氯苯基)-4a-羟基-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0555] 

BPN-0026815

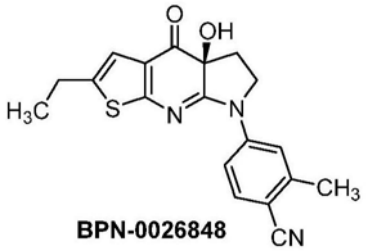
[0556] 根据合成方案3制备作为黄橙色固体的(S)-7-(4-氯苯基)-4a-羟基-2,3-二甲基-

4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝257至258℃;

[0557] ^{1}H NMR(500MHz,DMSO-d_6)δ7.99-7.98(m,2H),7.51-7.49(m,2H),6.88(s,1H),4.14-4.09(m,1H),4.03-4.00(m,1H),2.22-2.19(m,8H);ESI MS m/z 347[$C_{17}H_{15}ClN_2O_2S$+H]$^+$;

[0558] HPLC(方法B)＞99%(AUC),t_R＝11.17分钟;手性HPLC(Chiralpak AD,方法A)91.2%(AUC),t_R＝16.03分钟。

[0559] (S)-4-(2-乙基-4a-羟基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)-2-甲基苄腈的制备

[0560] 

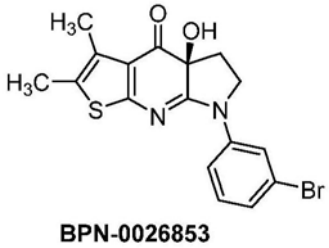
BPN-0026848

[0561] 根据合成方案3制备作为橙色固体的(S)-4-(2-乙基-4a-羟基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)-2-甲基苄腈:

[0562] ^{1}H NMR(500MHz,DMSO-d_6)δ8.16(dd,J＝8.6,2.2Hz,1H),7.91(d,J＝1.7Hz,1H),7.83(d,J＝8.7Hz,1H),6.98(s,1H),6.86(表观t,J＝1.0Hz,1H),4.13.-4.06(m,2H),2.74-2.70(m,2H),2.24-2.21(m,2H),1.22(t,J＝7.5Hz,3H),被溶剂峰掩盖的3H;ESI MS m/z 352[$C_{19}H_{17}N_3O_2S$+H]$^+$;

[0563] HPLC(方法B)＞99%(AUC),t_R＝11.33分钟;手性HPLC(Chiralpak AD,方法A)66.7%(AUC),t_R＝19.14分钟。

[0564] (S)-7-(3-溴苯基)-4a-羟基-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0565] 

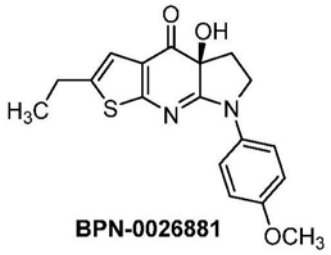
BPN-0026853

[0566] 根据合成方案3制备作为黄色固体的(S)-7-(3-溴苯基)-4a-羟基-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝259至260℃;

[0567] ^{1}H NMR(500MHz,DMSO-d_6)δ8.27(表观t,J＝1.9Hz,1H),7.90(ddd,J＝8.0,2.0,1.3Hz,1H),7.42-7.36(m,2H),6.90(s,1H),4.14-4.09(m,1H),4.04-4.01(m,1H),2.31-2.19(m,8H);ESI MS m/z 391[$C_{17}H_{15}BrN_2O_2S$+H]$^+$;

[0568] HPLC(方法C)90.9%(AUC),t_R＝18.45分钟;手性HPLC(Chiralpak AD,方法A)98.9%(AUC),t_R＝14.50分钟。

[0569] (S)-2-乙基-4a-羟基-7-(4-甲氧基苯基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0570] 

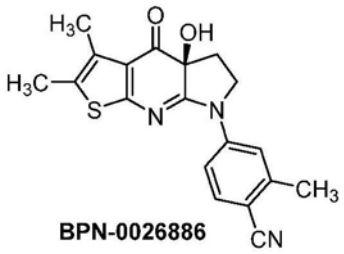
BPN-0026881

[0571] 根据合成方案3制备作为橙色固体的(S)-2-乙基-4a-羟基-7-(4-甲氧基苯基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp＝228至229℃;

[0572] ^{1}H NMR(500MHz,DMSO-d_6)δ7.83-7.80(m,2H),7.03-7.00(m,2H),6.83(s,1H),6.78(表观t,J＝1.2Hz,1H),4.16-4.11(m,1H),3.99-3.96(m,1H),3.77(s,3H),2.68(q,J＝7.4Hz,2H),2.25-2.15(m,2H),1.20(t,J＝7.5Hz,3H);ESI MS m/z 343[$C_{18}H_{18}N_2O_3S$+H]$^+$;

[0573] HPLC(方法B)＞99%(AUC),t_R＝10.28分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝22.29分钟。

[0574] (S)-4-(4a-羟基-2,3-二甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)-2-甲基苄腈的制备

[0575] 

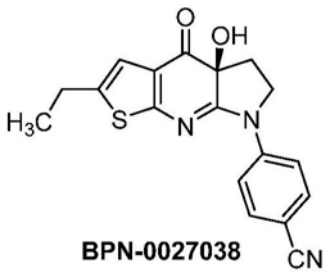
BPN-0026886

[0576] 根据合成方案3制备作为橙色固体的(S)-4-(4a-羟基-2,3-二甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)-2-甲基苄腈:mp＝245至246℃;

[0577] ^{1}H NMR(500MHz,DMSO-d_6)δ8.17(dd,J＝8.7,1.9Hz,1H),7.89(d,J＝1.9Hz,1H),7.82(d,J＝8.6Hz,1H),6.95(s,1H),4.14-4.05(m,2H),2.24-2.21(m,8H),被溶剂峰掩盖的3H;ESI MS m/z 352[$C_{19}H_{17}N_3O_2S$+H]$^+$;

[0578] HPLC(方法B)98.6%(AUC),t_R＝12.07分钟;手性HPLC(Chiralpak AD,方法A)87.8%(AUC),t_R＝17.22分钟。

[0579] (S)-4-(2-乙基-4a-羟基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈的制备

[0580] 

BPN-0027038

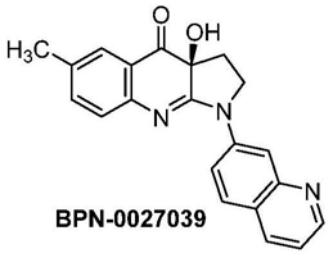
[0581] 根据合成方案3制备作为橙色固体的(S)-4-(2-乙基-4a-羟基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈:mp＝238至239℃;

[0582] ^{1}H NMR(500MHz,DMSO-d_6)δ8.19-8.17(m,2H),7.92-7.90(m,2H),6.99(s,1H),6.87

(表观t,J＝1.0Hz,1H),4.17-4.08(m,2H),2.75-2.70(m,2H),2.26-2.22(m,2H),1.22(t,J＝7.5Hz,3H);ESI MS m/z 338[$C_{18}H_{15}N_3O_2S$+H]$^+$;

[0583] HPLC(方法B)＞99%(AUC),t_R＝11.89分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝21.29分钟。

[0584] (S)-3a-羟基-6-甲基-1-(喹啉-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0585] 

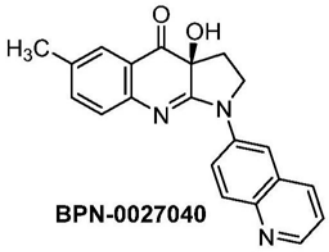
BPN-0027039

[0586] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(喹啉-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝242至243℃;

[0587] ^{1}H NMR(500MHz,DMSO-d_6)δ8.89(dd,J＝4.3,1.8Hz,1H),8.59(d,J＝2.2Hz,1H),8.56(dd,J＝9.0,2.3Hz,1H),8.33(dd,J＝8.2,1.1Hz,1H),8.02(d,J＝9.0Hz,1H),7.57(d,J＝1.5Hz,1H),7.46(dd,J＝8.2,4.2Hz,1H),7.42(dd,J＝8.2,1.9Hz,1H),7.21(d,J＝8.0Hz,1H),6.91(s,1H),4.23-4.14(m,2H),2.34-2.29(m,5H);ESI MS m/z 344[$C_{21}H_{17}N_3O_2$+H]$^+$;

[0588] HPLC(方法B)＞99%(AUC),t_R＝10.08分钟;手性HPLC(Chiralpak AD,方法A)49.3%(AUC),t_R＝21.31分钟。

[0589] (S)-3a-羟基-6-甲基-1-(喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0590] 

BPN-0027040

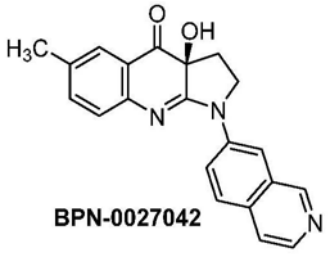
[0591] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝236至238℃;

[0592] ^{1}H NMR(500MHz,DMSO-d_6)δ8.83(dd,J＝4.2,1.7Hz,1H),8.77(dd,J＝9.3,2.6Hz,1H),8.47(d,J＝2.5Hz,1H),8.36(dd,J＝8.6,0.9Hz,1H),8.07(d,J＝9.3Hz,1H),7.56(d,J＝1.7Hz,1H),7.53(dd,J＝8.3,4.2Hz,1H),7.42(dd,J＝8.4,1.9Hz,1H),7.23(d,J＝8.0Hz,1H),6.91(s,1H),4.21-4.12(m,2H),2.34-2.30(m,5H);ESI MS m/z 344[$C_{21}H_{17}N_3O_2$+H]$^+$;

[0593] HPLC(方法B)＞99%(AUC),t_R＝6.83分钟;手性HPLC(Chiralpak AD,方法A)94.1%(AUC),t_R＝19.50分钟。

[0594] (S)-3a-羟基-1-(异喹啉-7-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹

啉-4-酮的制备

[0595] 

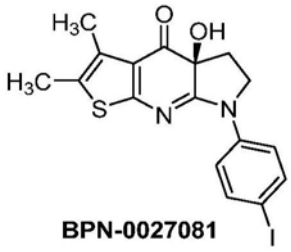
BPN-0027042

[0596] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-1-(异喹啉-7-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=217至218℃;

[0597] ^{1}H NMR(500MHz,DMSO-d_6)δ9.32(s,1H),8.77(dd,J=9.1,2.3Hz,1H),8.63(d,J=2.0Hz,1H),8.44(d,J=5.7Hz,1H),8.03(d,J=9.1Hz,1H),7.80(d,J=5.7Hz,1H),7.57(d,J=1.5Hz,1H),7.42(dd,J=8.2,1.9Hz,1H),7.24(d,J=8.1Hz,1H),6.91(s,1H),4.22-4.13(m,2H),2.34-2.31(m,5H);ESI MS m/z 344[$C_{21}H_{17}N_3O_2$+H]$^+$;

[0598] HPLC(方法B)>99%(AUC),t_R=9.72分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=20.95分钟。

[0599] (S)-4a-羟基-7-(4-碘苯基)-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0600] 

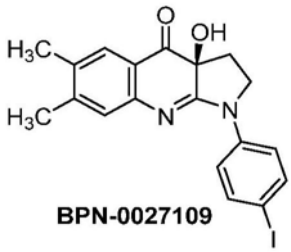
BPN-0027081

[0601] 根据合成方案3制备作为橙色固体的(S)-4a-羟基-7-(4-碘苯基)-2,3-二甲基-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=251至252℃;

[0602] ^{1}H NMR(500MHz,DMSO-d_6)δ7.78(s,4H),6.88(s,1H),4.12-4.07(m,1H),4.01-3.96(m,1H),2.22-2.18(m,8H);ESI MS m/z 439[$C_{17}H_{15}IN_2O_2S$+H]$^+$;

[0603] HPLC(方法B)>99%(AUC),t_R=11.15分钟;手性HPLC(Chiralpak AD,方法A)89.8%(AUC),t_R=17.96分钟。

[0604] (S)-3a-羟基-1-(4-碘苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0605] 

BPN-0027109

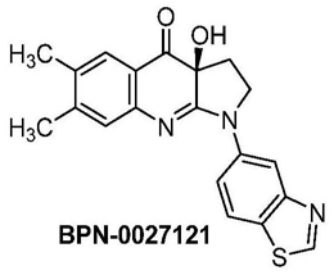
[0606] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(4-碘苯基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=240至241℃;

[0607] ^{1}H NMR(500MHz,DMSO-d_6)δ7.95-7.93(m,2H),7.75-7.73(m,2H),7.49(s,1H),7.05

(s,1H),6.79(s,1H),4.01-3.96(m,1H),3.94-3.89(m,1H),2.27(s,3H),2.25-2.22(m,5H);ESI MS m/z 433[$C_{19}H_{17}IN_2O_2$+H]$^+$;

[0608] HPLC(方法B)>99%(AUC),t_R=8.61分钟;手性HPLC(Chiralpak AD,方法A)91.4%(AUC),t_R=18.01分钟。

[0609] (S)-1-(苯并[d]噻唑-5-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0610] 

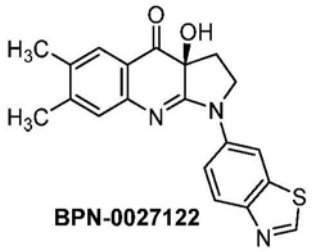
BPN-0027121

[0611] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d]噻唑-5-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0612] ^{1}H NMR(500MHz,DMSO-d_6)δ9.42(s,1H),8.85(d,J=2.1Hz,1H),8.28(dd,J=8.9,2.2Hz,1H),8.19(d,J=8.9Hz,1H),7.51(s,1H),7.10(s,1H),6.82(s,1H),4.19-4.14(m,1H),4.09-4.06(m,1H),2.30-2.28(m,5H),2.23(s,3H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0613] HPLC(方法B)95.3%(AUC),t_R=8.01分钟;手性HPLC(Chiralpak AD,方法A)70.3%(AUC),t_R=27.20分钟。

[0614] (S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0615] 

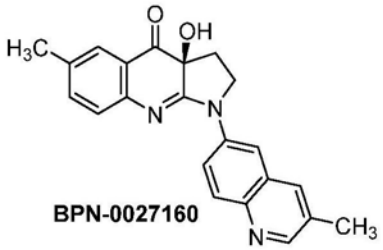
BPN-0027122

[0616] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0617] ^{1}H NMR(500MHz,DMSO-d_6)δ9.32(s,1H),8.90(d,J=2.3Hz,1H),8.35(dd,J=9.0,2.3Hz,1H),8.12(d,J=9.0Hz,1H),7.51(s,1H),7.13(s,1H),6.82(s,1H),4.17-4.12(m,1H),4.07-4.04(m,1H),2.30-2.29(m,5H),2.23(s,3H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0618] HPLC(方法B)97.5%(AUC),t_R=7.92分钟;手性HPLC(Chiralpak AD,方法A)83.3%(AUC),t_R=21.14分钟。

[0619] (S)-3a-羟基-6-甲基-1-(3-甲基喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

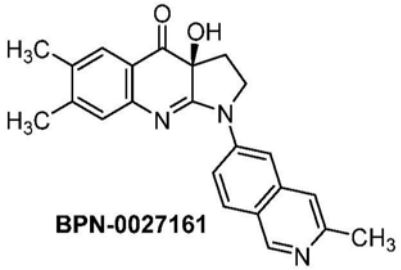
[0620] 

[0621] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(3-甲基喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=263至264℃;

[0622] ^{1}H NMR(500MHz,DMSO-d_6)δ8.69(d,J=2.1Hz,1H),8.63(dd,J=9.3,2.5Hz,1H),8.43(d,J=2.5Hz,1H),8.12(s,1H),8.01(d,J=9.3Hz,1H),7.56(d,J=1.6Hz,1H),7.41(dd,J=8.4,2.0Hz,1H),7.22(d,J=8.1Hz,1H),6.89(s,1H),4.20-4.10(m,2H),2.32-2.31(m,5H),被溶剂峰掩盖的3H;ESI MS m/z 358[$C_{22}H_{19}N_3O_2$+H]$^+$;

[0623] HPLC(方法C)97.1%(AUC),t_R=11.24分钟;手性HPLC(Chiralpak AD,方法A)81.9%(AUC),t_R=18.76分钟。

[0624] (S)-3a-羟基-6,7-二甲基-1-(3-甲基异喹啉-6-基)-1,2,3,3a.四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

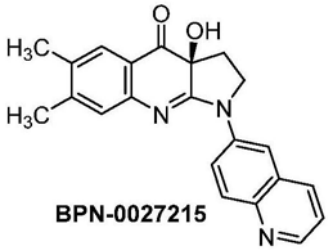
[0625] 

[0626] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(3-甲基异喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=265至267℃;

[0627] ^{1}H NMR(500MHz,DMSO-d_6)δ8.69(d,J=2.1Hz,1H),8.63(dd,J=9.3,2.6Hz,1H),8.43(d,J=2.5Hz,1H),8.12(s,1H),8.01(d,J=9.2Hz,1H),7.51(s,1H),7.14(s,1H),6.84(s,1H),4.19-4.09(m,2H),2.32-2.30(m,5H),2.24(s,3H),被溶剂峰掩盖的3H;ESI MS m/z 372[$C_{23}H_{21}N_3O_2$+H]$^+$;

[0628] HPLC(方法B)>99%(AUC),t_R=7.61分钟;手性HPLC(Chiralpak AD,方法A)73.7%(AUC),t_R=19.44分钟。

[0629] (S)-3a-羟基-6,7-二甲基-1-(喹啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0630] 

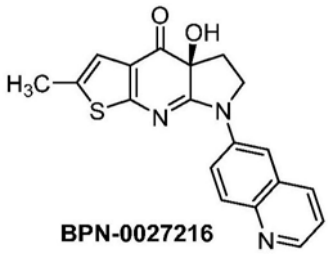
[0631] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(喹啉-6-基)-

1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=246至247℃;

[0632] ^{1}H NMR(500MHz,DMSO-d_6)δ8.83(dd,J=4.2,1.7Hz,1H),8.79(dd,J=9.3,2.6Hz,1H),8.45(d,J=2.5Hz,1H),8.36(d,J=7.6Hz,1H),8.06(d,J=9.3Hz,1H),7.54-7.52(m,2H),7.15(s,1H),6.85(s,1H),4.20-4.09(m,2H),2.33-2.30(m,5H),2.24(s,3H);ESI MS m/z 358[$C_{22}H_{19}N_3O_2$+H]$^+$;

[0633] HPLC(方法B)>97.9%(AUC),t_R=8.10分钟;手性HPLC(Chiralpak AD,方法A)61.1%(AUC),t_R=20.30分钟。

[0634] (S)-4a-羟基-2-甲基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0635] 

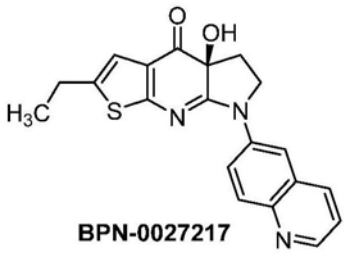
BPN-0027216

[0636] 根据合成方案3制备作为红橙色固体的(S)-4a-羟基-2-甲基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=242至243℃;

[0637] ^{1}H NMR(500MHz,DMSO-d_6)δ8.86(dd,J=4.2,1.6Hz,1H),8.60(dd,J=9.3,2.6Hz,1H),8.37(d,J=7.6Hz,1H),8.31(d,J=2.5Hz,1H),8.09(d,J=9.3Hz,1H),7.55(dd,J=8.3,4.2Hz,1H),6.97(s,1H),6.82(d,J=1.3Hz,1H),4.30-4.25(m,1H),4.21-4.18(m,1H),2.37-2.36(m,3H),2.30-2.27(m,2H);ESI MS m/z 350[$C_{19}H_{15}N_3O_2S$+H]$^+$;

[0638] HPLC(方法C)98.7%(AUC),t_R=11.45分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=21.33分钟。

[0639] (S)-2-乙基-4a-羟基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0640] 

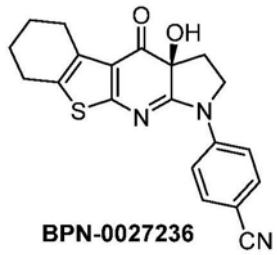
BPN-0027217

[0641] 根据合成方案3制备作为橙棕色固体的(S)-4a-羟基-2-甲基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=217至219℃:

[0642] ^{1}H NMR(500MHz,DMSO-d_6)δ8.86(dd,J=4.2,1.6Hz,1H),8.59(dd,J=9.3,2.6Hz,1H),8.37(d,J=8.5Hz,1H),8.32(d,J=2.4Hz,1H),8.09(d,J=9.3Hz,1H),7.55(dd,J=8.3,4.2Hz,1H),6.97(s,1H),6.85(s,1H),4.30-4.25(m,1H),4.21-4.18(m,1H),2.72(q,J=7.5Hz,2H),2.31-2.27(m,2H),2.23(t,J=7.5Hz,3H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0643] HPLC(方法C)>99%(AUC),t_R=12.26分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=20.87分钟。

[0644] (S)-4-(3a-羟基-4-氧代-2,3,3a,4,5,6,7,8-八氢-1H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-1-基)苄腈的制备

[0645] 

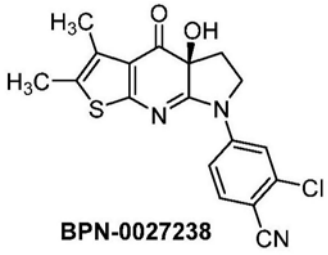
BPN-0027236

[0646] 根据合成方案3制备作为黄棕色固体的(S)-4-(3a-羟基-4-氧代-2,3,3a,4,5,6,7,8-八氢-1H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-1-基)苄腈:

[0647] ^{1}H NMR(500MHz,DMSO-d_6)δ8.18-8.16(m,2H),7.92-7.90(m,2H),6.96(s,1H),4.16-4.08(m,2H),2.24-2.21(m,3H),1.84-1.65(m,7H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0648] HPLC(方法B)95.4%(AUC),t_R=10.52分钟;手性HPLC(Chiralpak AD,方法A)55.9%(AUC),t_R=19.88分钟。

[0649] (S)-2-氯-4-(4a-羟基-2,3-二甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈的制备

[0650] 

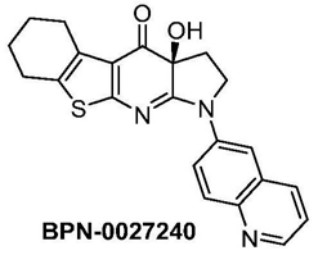
BPN-0027238

[0651] 根据合成方案3制备作为橙色固体的(S)-2-氯-4-(4a-羟基-2,3-二甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈;mp=275至276℃;

[0652] ^{1}H NMR(500MHz,DMSO-d_6)δ8.38(d,J=2.2Hz,1H),8.13(dd,J=8.8,2.2Hz,1H),8.02(d,J=8.8Hz,1H),7.01(s,1H),4.13-4.10(m,2H),2.26(s,3H),2.14-2.22(m,5H);ESI MS m/z 372[$C_{18}H_{14}ClN_3O_2S$+H]$^+$;

[0653] HPLC(方法B)96.7%(AUC),t_R=10.69分钟;手性HPLC(Chiralpak AD,方法A)90.8%(AUC),t_R=20.01分钟。

[0654] (S)-3a-羟基-1-(喹啉-6-基)-1,2,3,3a,5,6,7,8-八氢-4H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4-酮的制备

[0655] 

BPN-0027240

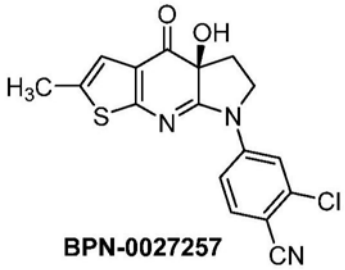
[0656] 根据合成方案3制备作为橙色固体的(S)-3a-羟基-1-(喹啉-6-基)-1,2,3,3a,5,6,7,8-八氢-4H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4-酮:mp=245至246℃;

[0657] ^{1}H NMR(500MHz,DMSO-d_6)δ8.86(dd,J=4.2,1.7Hz,1H),8.62(dd,J=9.3,2.6Hz,

1H),8.37(dd,J=8.3,1.1Hz,1H),8.30(d,J=2.6Hz,1H),8.09(d,J=9.2Hz,1H),7.54(dd,J=8.3,4.2Hz,1H),6.95(s,1H),4.29-4.24(m,1H),4.21-4.18(m,1H),2.65-2.57(m,4H),2.31-2.25(m,2H),1.79-1.70(m,4H);ESI MS m/z 390[$C_{22}H_{19}N_3O_2S$+H]$^+$;

[0658] HPLC(方法B)97.8%(AUC),t_R=9.06分钟;手性HPLC(Chiralpak AD,方法A)82.3%(AUC),t_R=19.47分钟。

[0659] (S)-2-氯-4-(4a-羟基-2-甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈的制备

[0660] 

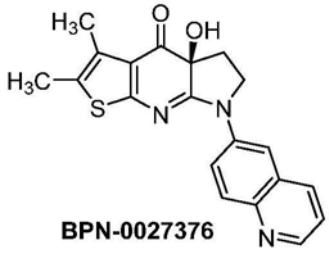
BPN-0027257

[0661] 根据合成方案3制备作为橙色固体的(S)-2-氯-4-(4a-羟基-2-甲基-4-氧代-4,4a,5,6-四氢-7H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-7-基)苄腈:

[0662] ^{1}H NMR(500MHz,DMSO-d_6)δ8.37(d,J=2.2Hz,1H),8.15(dd,J=8.8,2.2Hz,1H),8.02(d,J=8.8Hz,1H),7.03(s,1H),6.87(d,J=1.3Hz,1H),4.14-4.10(m,2H),2.38(d,J=1.2Hz,3H),2.25-2.22(m,2H);ESI MS m/z 358[$C_{17}H_{12}ClN_3O_2S$+H]$^+$;

[0663] HPLC(方法C)98.3%(AUC),t_R=16.02分钟;手性HPLC(Chiralpak AD,方法A)96.7%(AUC),t_R=20.06分钟。

[0664] (S)-4a-羟基-2,3-二甲基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

[0665] 

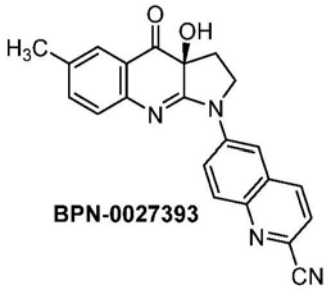
BPN-0027376

[0666] 根据合成方案3制备作为橙棕色固体的(S)-4a-羟基-2,3-二甲基-7-(喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶基-4-酮:mp=219至224℃

[0667] ^{1}H NMR(500MHz,DMSO-d_6)δ8.85(dd,J=4.1,1.6Hz,1H),8.61(dd,J=9.1,2.6Hz,1H),8.37(d,J=8.6Hz,1H),8.30(d,J=2.7Hz,1H),8.09(d,J=9.5Hz,1H),7.54(dd,J=8.3,4.2Hz,1H),6.94(s,1H),4.28-4.23(m,1H),4.21-4.18(m,1H),2.25-2.23(m,8H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0668] HPLC(方法C)95.8%(AUC),t_R=12.69分钟;手性HPLC(Chiralpak AD,方法A)89.5%(AUC),t_R=19.48分钟。

[0669] (S)-6-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)喹啉-2-甲腈的制备

[0670] 

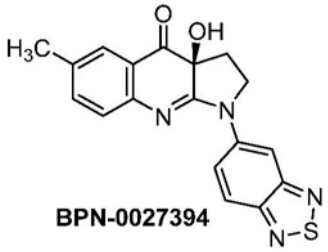
BPN-0027393

[0671] 根据合成方案6制备作为黄橙色固体的(S)-6-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)喹啉-2-甲腈:mp=271至273℃;

[0672] ^{1}H NMR(500MHz,DMSO-d_6)δ9.01(dd,J=9.4,2.5Hz,1H),8.64-8.60(m,2H),8.19(d,J=9.4Hz,1H),8.01(d,J=8.4Hz,1H),7.58(d,J=1.3Hz,1H),7.45(dd,J=8.0,2.1Hz,1H),7.29(d,J=8.0Hz,1H),6.96(s,1H),4.19-4.16(m,2H),2.35-2.31(m,5H);ESI MS m/z 369[$C_{22}H_{16}N_4O_2$+H]$^+$;

[0673] HPLC(方法C)99.0%(AUC),t_R=13.28分钟;手性HPLC(Chiralpak AD,方法A)96.3%(AUC),t_R=22.01分钟。

[0674] (S)-1-(苯并[c][1,2,5]噻二唑-5-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0675] 

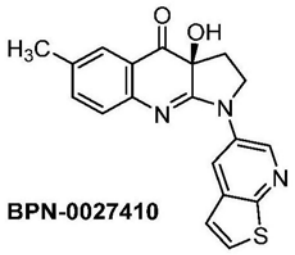
BPN-0027394

[0676] 根据合成方案6制备作为橙黄色固体的(S)-1-(苯并[c][1,2,5]噻二唑-5-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=231至232℃;

[0677] ^{1}H NMR(500MHz,DMSO-d_6)δ8.80(dd,J=9.7,2.2Hz,1H),8.60(d,J=2.1Hz,1H),8.13(d,J=9.6Hz,1H),7.58(d,J=1.7Hz,1H),7.43(dd,J=8.2,1.9Hz,1H),7.23(d,J=8.0Hz,1H),6.95(s,1H),4.23-4.13(m,2H),2.34-2.29(m,5H);ESI MS m/z 351[$C_{18}H_{14}N_4O_2S$+H]$^+$;

[0678] HPLC(方法C)98.8%(AUC),t_R=12.54分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=18.44分钟。

[0679] (S)-3a-羟基-6-甲基-1-(噻吩并[2,3-b]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0680] 

BPN-0027410

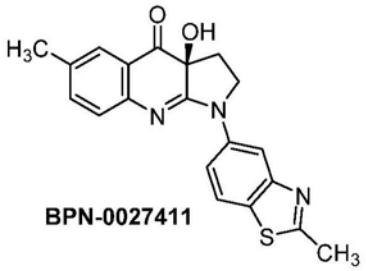
[0681] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(噻吩并[2,3-b]吡

啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝208至210℃;

[0682] ^{1}H NMR(500MHz,DMSO-d_6)δ9.33(d,J＝2.5Hz,1H),8.94(d,J＝2.5Hz,1H),7.93(d,J＝5.9Hz,1H),7.56(d,J＝1.7Hz,1H),7.50(d,J＝5.9Hz,1H),7.41(dd,J＝8.1,2.1Hz,1H),7.18(d,J＝8.1Hz,1H),6.91(s,1H),4.20-4.15(m,1H),4.09-4.06(m,1H),2.34-2.26(m,5H);ESI MS m/z 350[$C_{19}H_{15}N_3O_2S$+H]$^+$;

[0683] UPLC(方法A)97.9%(AUC),t_R＝2.96分钟;手性HPLC(Chiralpak AD,方法A)96.8%(AUC),t_R＝19.56分钟。

[0684] (S)-3a-羟基-6-甲基-1-(2-甲基苯并[d]噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0685] 

BPN-0027411

[0686] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(2-甲基苯并[d]噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝258至259℃;

[0687] ^{1}H NMR(500MHz,DMSO-d_6)δ8.71(d,J＝2.1Hz,1H),8.12(dd,J＝8.9,2.2Hz,1H),8.04(d,J＝8.8Hz,1H),7.55(d,J＝1.3Hz,1H),7.39(dd,J＝8.2,1.9Hz,1H),7.16(d,J＝8.1Hz,1H),6.87(s,1H),4.18-4.13(m,1H),4.06-4.03(m,1H),2.81(s,3H),2.31-2.26(m,5H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0688] UPLC(方法A)＞99%(AUC),t_R＝3.00分钟;手性HPLC(Chiralpak AD,方法A)74.7%(AUC),t_R＝21.78分钟。

[0689] (S)-1-(3,4-二氢-2H-苯并[b][1,4]噁嗪-7-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0690] 

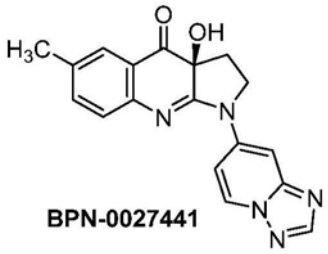
BPN-0027412

[0691] 根据合成方案4制备作为橙色固体的(S)-1-(3,4-二氢-2H-苯并[b¨[1,4]噁嗪-7-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝207至208℃;

[0692] ^{1}H NMR(500MHz,DMSO-d_6)δ7.53(d,J＝2.4Hz,1H),7.48(d,J＝1.6Hz,1H),7.32(dd,J＝8.1,2.0Hz,1H),7.21(dd,J＝8.7,2.5Hz,1H),7.02(d,J＝8.1Hz,1H),6.71(s,1H),6.58(d,J＝8.6Hz,1H),5.73(s,1H),4.15-4.13(m,2H),3.99-3.94(m,1H),3.85-3.81(m,1H),2.28(s,3H),2.21-2.18(m,2H),被溶剂峰掩盖的2H;ESI MS m/z 350[$C_{20}H_{19}N_3O_3$+H]$^+$;

[0693] UPLC(方法A)96.6%(AUC),t_R＝2.96分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝23.12分钟。

[0694] (S)-1-([1,2,4]三唑并[1,5-a]吡啶-7-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0695] 

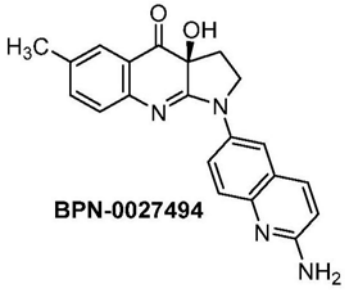
BPN-0027441

[0696] 根据合成方案6制备作为黄色固体的(S)-1-([1,2,4]三唑并[1,5-a]吡啶-7-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝260至261℃;

[0697] ^{1}H NMR(500MHz,DMSO-d_6)δ8.95(d,J＝7.7Hz,1H),8.43(s,1H),8.35(d,J＝2.2Hz,1H),8.29(dd,J＝7.6,2.4Hz,1H),7.59(d,J＝1.6Hz,1H),7.45(dd,J＝8.3,2.0Hz,1H),7.25(d,J＝8.0Hz,1H),6.97(s,1H),4.15-4.10(m,2H),2.35-2.27(m,5H);ESI MS m/z 334 $[C_{18}H_{15}N_5O_2+H]^+$;

[0698] UPLC(方法A)98.0%(AUC),t_R＝2.85分钟;手性HPLC(Chiralpak AD,方法A)64.4%(AUC),t_R＝20.26分钟。

[0699] (S)-1-(2-氨基喹啉-6-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0700] 

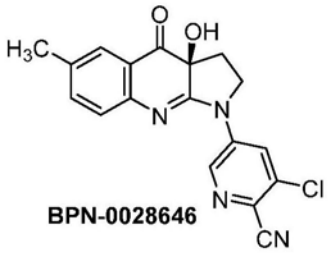
BPN-0027494

[0701] 根据合成方案6制备作为黄橙色固体的(S)-1-(2-氨基喹啉-6-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝261至262℃;

[0702] ^{1}H NMR(500MHz,DMSO-d_6)δ8.36(dd,J＝9.1,2.6Hz,1H),8.14(d,J＝2.5Hz,1H),7.90(d,J＝8.9Hz,1H),7.53(d,J＝2.0Hz,1H),7.49(d,J＝9.2Hz,1H),7.37(dd,J＝8.5,1.8Hz,1H),7.13(d,J＝8.1Hz,1H),6.82(s,1H),6.78(d,J＝8.9Hz,1H),6.38(s,2H),4.15-4.10(m,1H),4.04-4.01(m,1H),2.30-2.27(m,5H);ESI MS m/z 359$[C_{21}H_{18}N_4O_2+H]^+$;

[0703] UPLC(方法A)＞99%(AUC),t_R＝2.42分钟。

[0704] (S)-3-氯-5-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)吡啶腈的制备

[0705] 

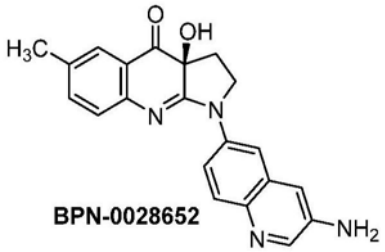
BPN-0028646

[0706] 根据合成方案6制备作为黄色固体的(S)-3-氯-5-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)吡啶腈:mp=243至245℃;

[0707] ^{1}H NMR(500MHz,DMSO-d_6)δ9.42(d,J=2.3Hz,1H),9.01(d,J=2.3Hz,1H),7.60(d,J=1.5Hz,1H),7.46(ddd,J=8.0,2.2,0.7Hz,1H),7.28(d,J=8.1Hz,1H),7.02(s,1H),4.14-4.04(m,2H),2.34-2.29(m,5H);ESI MS m/z 352[$C_{18}H_{13}ClN_4O_2$+H]$^+$;

[0708] UPLC(方法A)>99%(AUC),t_R=4.64分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=17.22分钟。

[0709] (S)-1-(3-氨基喹啉-6-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0710] 

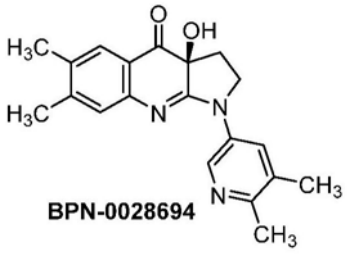
BPN-0028652

[0711] 根据合成方案6制备作为黄色固体的(S)-1-(3-氨基喹啉-6-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=243至244℃;

[0712] ^{1}H NMR(500MHz,DMSO-d_6)δ8.36(d,J=2.7Hz,1H),8.28(dd,J=9.2,2.5Hz,1H),8.08(d,J=2.5Hz,1H),7.79(d,J=9.2Hz,1H),7.55(d,J=1.8Hz,1H),7.39(dd,J=8.1,2.2Hz,1H),7.16(d,J=8.1Hz,1H),7.12(d,J=2.6Hz,1H),6.85(s,1H),5.66(s,2H),4.17-4.12(m,1H),4.09-4.05(m,1H),2.31-2.28(m,5H);ESI MS m/z 358[C_{21} $H_{18}N_4O_2$+H]$^+$;

[0713] UPLC(方法A)>99%(AUC),t_R=2.44分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=21.10分钟。

[0714] (S)-1-(5,6-二甲基吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0715] 

BPN-0028694

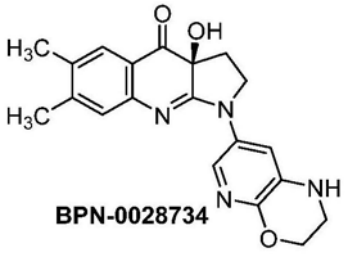
[0716] 根据合成方案6制备作为黄色固体的(S)-1-(5,6-二甲基吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=250至251℃;

[0717] ^{1}H NMR(500MHz,DMSO-d_6)δ8.96(d,J=2.5Hz,1H),8.23(d,J=2.3Hz,1H),7.48(s,1H),7.05(s,1H),6.79(s,1H),4.05-4.00(m,1H),3.99-3.93(m,1H),2.42(s,3H),2.30(s,3H),2.27-2.22(m,8H);ESI MS m/z 336[$C_{20}H_{21}N_3O_2$+H]$^+$;

[0718] UPLC(方法A)98.4%(AUC),t_R=3.01分钟;手性HPLC(Chiralpak AD,方法A)82.0%(AUC),t_R=15.59分钟。

[0719] (S)-1-(2,3-二氢-1H-吡啶并[2,3-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,

2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

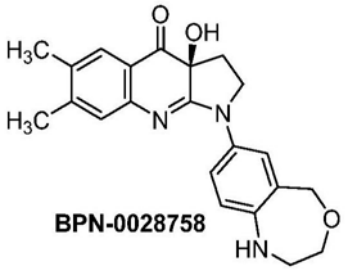
[0720] 

[0721] 根据合成方案4制备作为红橙色固体的(S)-1-(2,3-二氢-1H-吡啶并[2,3-b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=225至230℃;

[0722] ^{1}H NMR(500MHz,DMSO-d_6)δ7.86(d,J=2.4Hz,1H),7.82(d,J=2.4Hz,1H),7.46(s,1H),6.99(s,1H),6.73(s,1H),6.23(s,1H),4.25(t,J=4.5Hz,2H),3.98-3.94(m,1H),3.87-3.84(m,1H),2.26-2.21(m,10H);ESI MS m/z 365[$C_{20}H_{20}N_4O_3$+H]$^+$;

[0723] UPLC(方法A)98.3%(AUC),t_R=2.72分钟;手性HPLC(Chiralpak AD,方法A)86.1%(AUC),t_R=18.80分钟。

[0724] (S)-3a-羟基-6,7-二甲基-1-(1,2,3,5-四氢苯并[e][1,4]氧氮杂䓬-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

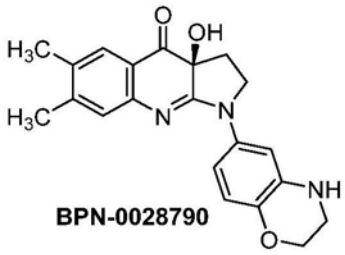
[0725] 

[0726] 根据合成方案4制备作为橙色固体的(S)-3a-羟基-6,7-二甲基-1-(1,2,3,5-四氢苯并[e][1,4]氧氮杂䓬-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0727] ^{1}H NMR(500MHz,DMSO-d_6)δ7.78(dd,J=8.6,2.6Hz,1H),7.74(d,J=2.6Hz,1H),7.45(s,1H),6.99(s,1H),6.93(d,J=8.6Hz,1H),6.68(s,1H),5.68(表观t,J=3.7Hz,1H),4.50(s,2H),4.02-3.97(m,1H),3.89-3.85(m,1H),3.72-3.70(m,2H),3.02-2.99(m,2H),2.25(s,3H),2.22-2.18(m,5H);ESI MS m/z 378[$C_{22}H_{23}N_3O_3$+H]$^+$;

[0728] UPLC(方法A)96.3%(AUC),t_R=2.97分钟;手性HPLC(Chiralpak AD,方法A)91.0%(AUC),t_R=23.89分钟。

[0729] (S)-1-(3,4-二氢-2H-苯并[b][1,4]噁嗪-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

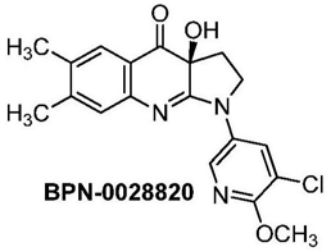
[0730] 

[0731] 根据合成方案4制备作为黄橙色固体的(S)-1-(3,4-二氢-2H-苯并[b][1,4]噁嗪-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=200至203℃;

[0732] ^{1}H NMR(500MHz,DMSO-d_6)δ7.44(s,1H),7.35(d,J=2.6Hz,1H),7.03(dd,J=8.7,2.7Hz,1H),6.97(s,1H),6.67-6.64(m,1H),5.88(s,1H),4.12-4.10(m,2H),3.98-3.93(m,1H),3.83-3.79(m,1H),2.25(s,3H),2.20-2.14(m,5H),被溶剂峰掩盖的3H;ESI MS m/z 364[$C_{21}H_{21}N_3O_3$+H]$^+$;

[0733] UPLC(方法A)>99%(AUC),t_R=3.14分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=20.43分钟。

[0734] (S)-1-(5-氯-6-甲氧基吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

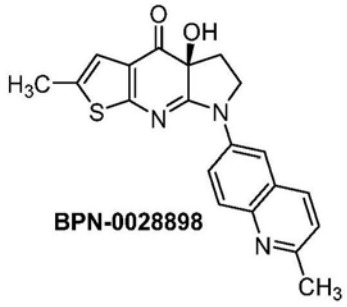
[0735] 

[0736] 根据合成方案6制备作为黄色固体的(S)-1-(5-氯-6-甲氧基吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0737] ^{1}H NMR(500MHz,DMSO-d_6)δ8.85(d,J=2.5Hz,1H),8.70(d,J=2.56Hz,1H),7.49(s,1H),7.05(s,1H),6.82(s,1H),4.05-4.02(m,1H),3.97-3.96(m,4H),2.27(s,3H),2.26-2.24(m,2H),2.22(s,3H);ESI MS m/z 372[$C_{19}H_{18}ClN_3O_3$+H]$^+$;

[0738] UPLC(方法A)98.2%(AUC),t_R=3.42分钟;手性HPLC(Chiralpak AD,方法A)85.2%(AUC),t_R=13.81分钟。

[0739] (S)-4a-羟基-2-甲基-7-(2-甲基喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮的制备

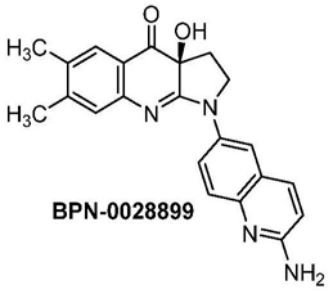
[0740] 

[0741] 根据合成方案3制备作为红色固体的(S)-4a-羟基-2-甲基-7-(2-甲基喹啉-6-基)-4a,5,6,7-四氢-4H-吡咯并[2,3-b]噻吩并[3,2-e]吡啶-4-酮:mp=247至249℃;

[0742] ^{1}H NMR(500MHz,DMSO-d_6)δ8.53(d,J=10.5Hz,1H),8.26-8.24(m,2H),7.99(d,J=9.5Hz,1H),7.43(d,J=9.1Hz,1H),6.95(s,1H),6.82(s,1H),4.27-4.24(m,1H),4;19-3.17(m,1H),2.66(s,3H),2.29-2.28(m,2H),被溶剂峰掩盖的3H;ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0743] UPLC(方法A)97.5%(AUC),t_R=2.80分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=18.84分钟。

[0744] (S)-1-(2-氨基喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0745] 

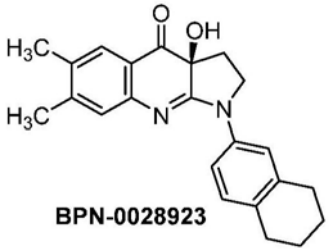
BPN-0028899

[0746] 根据合成方案6制备作为黄色固体的(S)-1-(2-氨基喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=282至283℃;

[0747] ^{1}H NMR(500MHz,DMSO-d_6)δ8.38(dd,J=9.1,2.5Hz,1H),8.13(d,J=2.5Hz,1H),7.91(d,J=9.1Hz,1H),7.50-7.48(m,2H),7.05(s,1H),6.79-6.76(m,2H),6.37(s,2H),4.15-4.09(m,1H),4.04-4.00(m,1H),2.27-2.25(m,5H),2.22(s,3H);ESI MS m/z 373 $[C_{22}H_{20}N_4O_2+H]^+$;

[0748] UPLC(方法A)>99%(AUC),t_R=2.58分钟;手性HPLC(Chiralpak AD,方法A)86.1%(AUC),t_R=23.54分钟。

[0749] (S)-3a-羟基-6,7-二甲基-1-(5,6,7,8-四氢萘-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0750] 

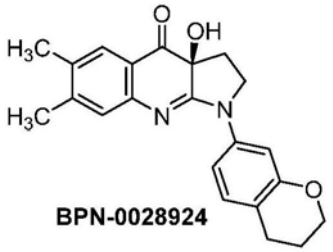
BPN-0028923

[0751] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(5,6,7,8-四氢萘-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=211至212℃;

[0752] ^{1}H NMR(500MHz,DMSO-d_6)δ7.84-7.82(m,1H),7.64-7.63(m,1H),7.46(s,1H),7.08(d,J=8.5Hz,1H),6.99(s,1H),6.71(s,1H),4.03-3.98(m,1H),3.91-3.88(m,1H),2.77-2.74(m,2H),2.72-2.69(m,2H),2.26(s,3H),2.22-2.19(m,5H),1.76-1.74(m,4H);ESI MS m/z 361 $[C_{23}H_{24}N_2O_2+H]^+$;

[0753] UPLC(方法A)96.8%(AUC),t_R=3.88分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.95分钟。

[0754] (S)-1-(色满-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

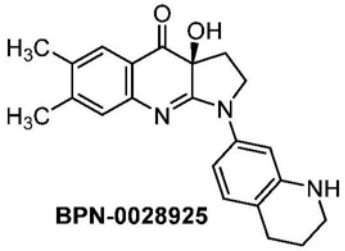
[0755] 

[0756] 根据合成方案6制备作为黄色固体的(S)-1-(色满-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=219至221℃;

[0757] ^{1}H NMR(500MHz,DMSO-d_6)δ7.63(d,J=2.3Hz,1H),7.47(s,1H),7.41(dd,J=8.4,2.3Hz,1H),7.07(d,J=8.4Hz,1H),7.02(s,1H),6.72(s,1H),4.15-4.13(m,2H),4.01-3.95(m,1H),3.90-3.87(m,1H),2.74-2.71(m,2H),2.27(s,3H),2.21-2.18(m,5H),1.95-1.90(m,2H);ESI MS m/z 363[$C_{22}H_{22}N_2O_3$+H]$^+$;

[0758] UPLC(方法A)>99%(AUC),t_R=3.46分钟;手性HPLC(Chiralpak AD,方法A)88.0%(AUC),t_R=19.01分钟。

[0759] (S)-3a-羟基-6,7-二甲基-1-(1,2,3,4-四氢喹啉-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0760] 

[0761] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(1,2,3,4-四氢喹啉-7-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=220至221℃;

[0762] ^{1}H NMR(500MHz,DMSO-d_6)δ7.45(s,1H),7.19(d,J=2.2Hz,1H),7.02(dd,J=8.2,2.3Hz,1H),6.99(s,1H),6.83(d,J=8.2Hz,1H),6.68(s,1H),5.73(s,1H),3.97-3.92(m,1H),3.83-3.80(m,1H),3.19-3.17(m,2H),2.65-2.63(m,2H),2.25(s,3H),2.20-2.16(m,5H),1.82-1.77(m,2H);ESI MS m/z 362[$C_{22}H_{23}N_3O_2$+H]$^+$;

[0763] UPLC(方法A)98.26%(AUC),t_R=3.07分钟;手性HPLC(Chiralpak AD,方法A)99.0%(AUC),t_R=20.30分钟。

[0764] (S)-3a-羟基-1-苯基-6-(三氟甲基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

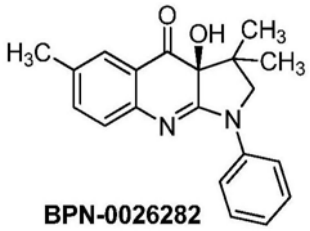
[0765] 

[0766] 根据合成方案2制备作为黄色固体的(S)-3a-羟基-1-苯基-6-(三氟甲基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=222至223℃;

[0767] ^{1}H NMR(500MHz,DMSO-d_6)δ8.06(dd,J＝8.5,1.0Hz,2H),7.93(d,J＝2.5Hz,1H),7.84(dd,J＝8.5,2.5Hz,1H),7.46(表观dt,J＝7.0,2.0Hz,2H),7.36(d,J＝8.5Hz,1H),7.21(表观t,J＝7.0Hz,1H),7.04(s,1H),4.20-4.14(m,1H),4.02(表观t,J＝9.0Hz,1H),2.43-2.36(m,1H),2.28(dd,J＝13.5,6.0Hz,1H);ESI MS m/z 347[$C_{18}H_{13}F_3N_2O_2$+H]$^+$;

[0768] 手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝10.74分钟。

[0769] (S)-3a-羟基-3,3,6-三甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0770] 

BPN-0026282

[0771] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-3,3,6-三甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝177至178℃;

[0772] ^{1}H NMR(500MHz,DMSO-d_6)δ8.03(dd,J＝8.5,1.0Hz,2H),7.56(d,J＝2.0Hz,1H),7.43-7.39(m,3H),7.15-7.12(m,2H),6.88(s,1H),3.85(d,J＝9.5Hz,1H),3.54(d,J＝9.5Hz,1H),2.30(s,3H),1.40(s,3H),1.00(s,3H);ESI MS m/z 321[$C_{20}H_{20}N_2O_2$+H]$^+$;

[0773] HPLC(方法C)＞99.0％(AUC),t_R＝13.15分钟;手性HPLC(Chiralpak AD,方法A)87.5％(AUC),t_R＝10.04分钟。

[0774] (S)-6-氟-3a-羟基-7-甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0775] 

BPN-0026387

[0776] 根据合成方案2制备作为橙色固体的(S)-6-氟-3a-羟基-7-甲基-1-苯基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝211至213℃;

[0777] ^{1}H NMR(500MHz,DMSO-d_6)δ8.07(dd,J＝8.5,1.0Hz,2H),7.43(表观dt,J＝7.5,2.0Hz,2H),7.36(d,J＝9.5Hz,1H),7.18-7.14(m,2H),6.87(s,1H),4.10-4.05(m,1H),3.98-2.95(m,1H),2.29-2.25(m,5H);ESI MS m/z 311[$C_{18}H_{15}FN_2O_2$+H]$^+$;

[0778] HPLC(方法C)95.0％(AUC),t_R＝11.66分钟;手性HPLC(Chiralpak AD,方法A)98.2％(AUC),t_R＝17.81分钟。

[0779] (S)-3a-羟基-1-苯基-3,3a,5,6,7,8-六氢-1H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4(2H)-酮的制备

[0780] 

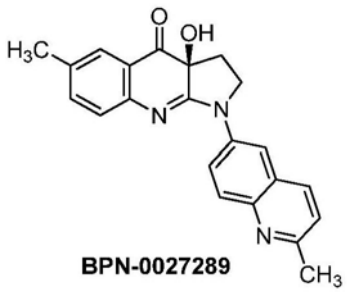
BPN-0027043

[0781] 根据合成方案2制备作为黄色固体的(S)-3a-羟基-1-苯基-3,3a,5,6,7,8-六氢-1H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4(2H)-酮:mp=259至261℃;

[0782] ^{1}H NMR(500MHz,DMSO-d_6)δ7.93(brd,J=7.5Hz,2H),7.45(br s,2H),7.19(br s,1H),6.85(s,1H),4.14(br s,1H),4.04-4.03(br m,1H),2.74-2.59(m,4H),2.21(br s,2H),1.76(br s,4H);ESI MS m/z 339[$C_{19}H_{18}N_2O_2S$+H]$^+$;

[0783] HPLC(方法C)>99%(AUC),t_R=15.91分钟;手性HPLC(Chiralpak AD,方法A)89.1%(AUC),t_R=18.50分钟。

[0784] (S)-3a-羟基-6-甲基-1-(2-甲基喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0785] 

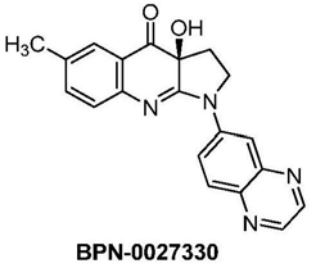
BPN-0027289

[0786] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(2-甲基喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=237至239℃分解;

[0787] ^{1}H NMR(500MHz,DMSO-d_6)δ8.70(dd,J=9.0,2.5Hz,1H),8.42(d,J=2.5Hz,1H),8.24(d,J=8.5Hz,1H),7.96(d,J=8.5Hz,1H),7.56(d,J=1.5Hz,1H),7.43-7.40(m,2H),7.21(d,J=8.0Hz,1H),6.89(s,1H),4.20-4.15(m,1H),4.13-4.09(m,1H),2.65(s,3H),2.37-2.30(m,5H);ESI MS m/z 358[$C_{22}H_{19}N_3O_2$+H]$^+$;

[0788] HPLC(方法C)97.3%(AUC),t_R=11.08分钟;手性HPLC(Chiralpak AD,方法A)95.8%(AUC),t_R=17.12分钟。

[0789] (S)-3a-羟基-6-甲基-1-(喹喔啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0790] 

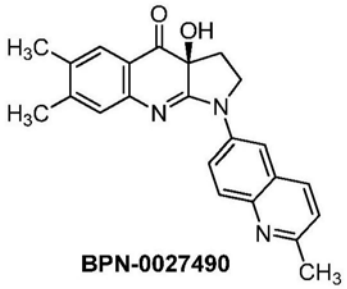
BPN-0027330

[0791] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(喹喔啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=151至153℃分解;

[0792] ^{1}H NMR(500MHz,DMSO-d_6)δ8.93(d,J＝1.5Hz,1H),8.86(d,J＝2.0Hz,1H),8.83(dd,J＝9.5,2.5Hz,1H),8.68(d,J＝2.5Hz,1H),8.14(d,J＝9.0Hz,1H),7.59(d,J＝2.0Hz,1H),7.44(dd,J＝8.5,2.0Hz,1H),7.24(d,J＝8.0Hz,1H),6.95(s,1H),4.24-4.17(m,2H),2.38-2.31(m,5H);ESI MS m/z 345[$C_{20}H_{16}N_4O_2$+H]$^+$;

[0793] HPLC(方法C)＞99%(AUC),t_R＝12.39分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝20.90分钟。

[0794] (S)-3a-羟基-6,7-二甲基-1-(2-甲基喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0795] 

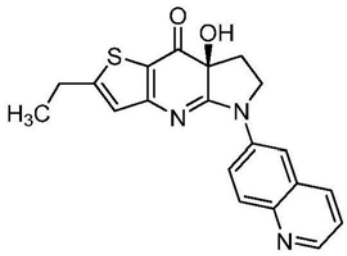
BPN-0027490

[0796] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝254至255℃分解;

[0797] ^{1}H NMR(500MHz,DMSO-d_6)δ8.73(dd,J＝15.5,4.0Hz,1H),8.40(d,J＝4.0Hz,1H),8.25(d,J＝14.0Hz,1H),7.96(d,J＝15.0Hz,1H),7.51(s,1H),7.42(d,J＝14.5Hz,1H),7.12(s,1H),6.86(s,1H),4.20-4.10(m,2H),2.65(s,3H),2.29-2.24(m,8H);ESI MS m/z 372[$C_{23}H_{21}N_3O_2$+H]$^+$;

[0798] UPLC(方法A)＞99%(AUC),t_R＝2.65分钟;手性HPLC(Chiralpak AD,方法A)97.0%(AUC),t_R＝16.10分钟。

[0799] (S)-2-乙基-7a-羟基-5-(喹啉-6-基)-7,7a-二氢-5H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8(6H)-酮的制备

[0800] 

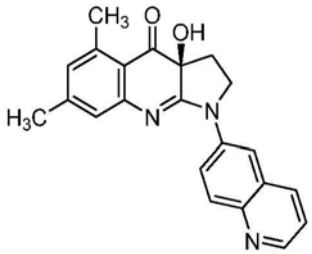
BPN-0028625

[0801] 根据合成方案3制备作为黄色固体的(S)-2-乙基-7a-羟基-5-(喹啉-6-基)-7,7a-二氢-5H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8(6H)-酮:

[0802] ^{1}H NMR(500MHz,DMSO-d_6)δ8.85(dd,J＝4.0,1.5Hz,1H),8.68(dd,J＝9.5,2.5Hz,1H),8.39(d,J＝2.5Hz,1H),8.36(d,J＝8.0Hz,1H),8.07(d,J＝9.0Hz,1H),7.55(dd,J＝8.0,4.0Hz,1H),6.97(s,1H),6.93(s,1H),4.27-4.24(m,1H),4.19-4.15(m,1H),2.85(q,J＝7.5Hz,2H),2.35-2.26(m,2H),1.28(t,J＝7.5Hz,3H);ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[0803] UPLC(方法A)92.2%(AUC),t_R＝2.85分钟;手性HPLC(Chiralpak AD,方法A)46.3%(AUC),t_R＝18.69分钟。

[0804] (S)-3a-羟基-5,7-二甲基-1-(喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0805] 

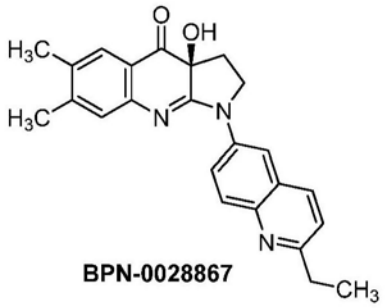
BPN-0028697

[0806] 根据合成方案3制备作为黄棕色固体的(S)-3a-羟基-5,7-二甲基-1-(喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=242至245℃分解;

[0807] ^{1}H NMR(500MHz,DMSO-d_6)δ8.83(dd,J=7.0,3.0Hz,1H),8.78(d,J=15.5,4.0Hz,1H),8.46(d,J=4.5Hz,1H),8.37(d,J=11.5Hz,1H),8.06(d,J=15.5Hz,1H),7.53(dd,J=13.5,7.0Hz,1H),7.02(s,1H),6.84(s,1H),6.78(s,1H),4.19-4.10(m,2H),2.38-2.22(m,5H),被溶剂掩盖的3个质子;ESI MS m/z 358[$C_{22}H_{19}N_3O_2$+H]$^+$;

[0808] UPLC(方法A)96.8%(AUC),t_R=2.76分钟;手性HPLC(Chiralpak AD,方法A)94.2%(AUC),t_R=16.59分钟。

[0809] (S)-1-(2-乙基喹啉-6-基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[0810] 

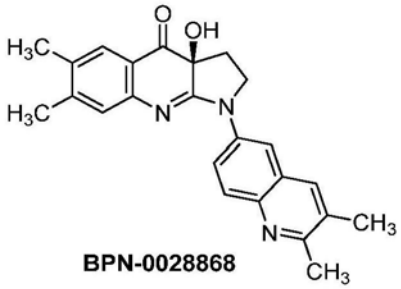
BPN-0028867

[0811] 根据合成方案6制备作为黄色固体的(S)-1-(2-乙基喹啉-6-基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=241至242℃;

[0812] ^{1}H NMR(500MHz,DMSO-d_6)δ8.73(dd,J=9.0,2.5Hz,1H),8.40(d,J=3.0Hz,1H),8.26(d,J=8.5Hz,1H),7.97(d,J=9.0Hz,1H),7.51(s,1H),7.45(d,J=8.5Hz,1H),7.14(s,1H),6.84(s,1H),4.19-4.08(m,2H),2.93(q,J=7.5Hz,2H),2.32-2.30(m,5H),2.24(s,3H),1.33(t,J=7.5Hz,3H);ESI MS m/z 386[$C_{24}H_{23}N_3O_2$+H]$^+$;

[0813] UPLC(方法A)99.0%(AUC),t_R=2.86分钟;手性HPLC(Chiralpak AD,方法A)88.2%(AUC),t_R=16.96分钟。

[0814] (S)-1-(2,3-二甲基喹啉-6-基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

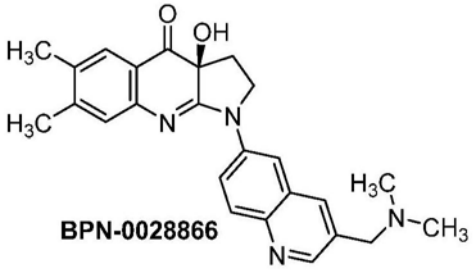
[0815] 

[0816] 根据合成方案6制备作为黄色固体的(S)-1-(2,3-二甲基喹啉-6-基)-3a-羟基-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=253至254℃;

[0817] ^{1}H NMR(500MHz,DMSO-d_6)δ8.57(dd,J=9.5,2.5Hz,1H),8.39(d,J=2.5Hz,1H),8.04(s,1H),7.92(d,J=9.5Hz,1H),7.51(s,1H),7.13(s,1H),6.82(s,1H),4.18-4.13(m,1H),4.11-4.07(m,1H),2.61(s,3H),2.44(s,3H),2.31-2.28(m,5H),2.24(s,3H);ESI MS m/z 386[$C_{24}H_{23}N_3O_2$+H]$^+$;

[0818] UPLC(方法A)>99%(AUC),t_R=2.78分钟;手性HPLC(Chiralpak AD,方法A)88.5%(AUC),t_R=17.13分钟。

[0819] (S)-1-(3-((二甲基氨基)甲基)喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

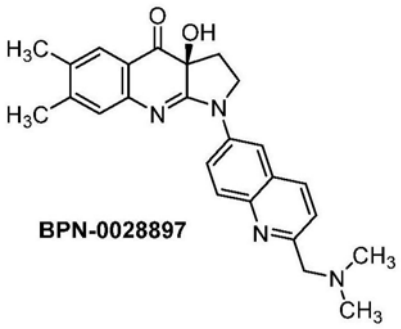
[0820] 

[0821] 根据合成方案6制备作为橙色固体的(S)-1-(3-((二甲基氨基)甲基)喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0822] ^{1}H NMR(300MHz,DMSO-d_6)δ8.76(dd,J=9.6,2.1Hz,1H),8.42(d,J=2.4Hz,1H),8.33-8.30(m,1H),8.01(d,J=9.3Hz,1H),7.61(d,J=8.7Hz,1H),7.51(s,1H),7.14(s,1H),6.86(s,1H),4.16-4.10(m,2H),3.68(s,2H),2.51-2.24(m,14H);ESI MS m/z 415[$C_{25}H_{26}N_4O_2$+H]$^+$;

[0823] UPLC(方法A)96.0%(AUC),t_R=2.64分钟;手性HPLC(Chiralpak AD,方法A)82.8%(AUC),t_R=17.32分钟。

[0824] (S)-1-(2-((二甲基氨基)甲基)喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

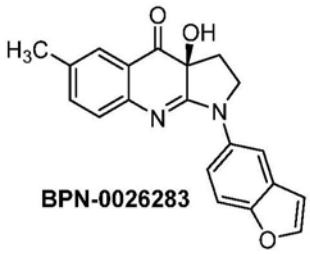
[0825] 

[0826] 根据合成方案6制备作为橙色固体的(S)-1-(3-((二甲基氨基)甲基)喹啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮;

[0827] ^{1}H NMR(300MHz,DMSO-d_6)δ8.76(dd,J=9.0,2.4Hz,1H),8.43-8.41(m,1H),8.33-8.30(m,1H),8.01(d,J=9.0Hz,1H),7.61(d,J=8.4Hz,1H),7.51(s,1H),7.14(s,1H),6.86(s,1H),4.16-4.10(m,2H),3.69(s,2H),2.35-2.23(m,14H);ESI MS m/z 415[$C_{25}H_{26}N_4O_2$+H]$^+$;

[0828] UPLC(方法A)98.8%(AUC),t_R=2.77分钟;手性HPLC(Chiralpak AD,方法A)52.4%(AUC),t_R=17.67分钟。

[0829] (S)-1-(苯并呋喃-5-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

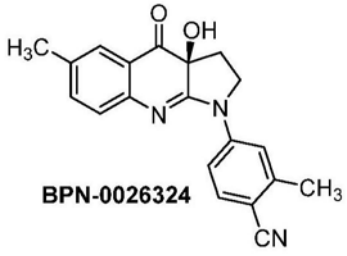
[0830] 

[0831] 根据合成方案3制备作为黄色固体的(S)-1-(苯并呋喃-5-基)-3a-羟基-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=213至214℃;

[0832] ^{1}H NMR(300MHz,DMSO-d_6)δ8.29(d,J=2.1Hz,1H),8.06(d,J=2.1Hz,1H),8.03(d,J=2.4Hz,1H),7.65(d,J=9.0Hz,1H),7.53(d,J=1.5Hz,1H),7.36(dd,J=8.4,1.5Hz,1H),7.10(d,J=8.4Hz,1H),7.02(dd,J=2.1,0.9Hz,1H),6.85(s,1H),4.19-4.10(m,1H),4.02-3.96(m,1H),2.30(s,3H),2.29-2.27(m,2H);ESI MS m/z 333[$C_{20}H_{16}N_2O_3$+H]$^+$;

[0833] HPLC(方法B)97.8%(AUC),t_R=9.42分钟;手性HPLC(Chiralpak AD,方法A)96.7%(AUC),t_R=17.19分钟。

[0834] (S)-4-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈的制备

[0835] 

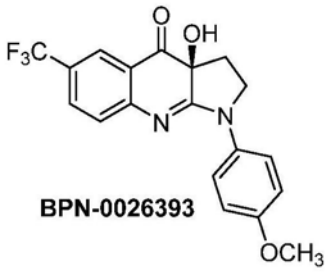
[0836] 根据合成方案3制备作为黄色固体的(S)-4-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-

四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈:mp=229至231℃;

[0837] ^{1}H NMR(500MHz,DMSO-d_6)δ8.27(dd,J=9.0,2.5Hz,1H),8.11(d,J=2.0Hz,1H),7.79(d,J=4.0Hz,1H),7.56(d,J=1.5Hz,1H),7.42(dd,J=8.0,1.5Hz,1H),7.21(d,J=8.0Hz,1H),6.90(s,1H),4.04-4.01(m,2H),2.53(s,3H),2.32(s,3H),2.28-2.26(m,2H);ESI MS m/z 332[$C_{20}H_{17}N_3O_2$+H]$^+$;

[0838] HPLC(方法B)98.4%(AUC),t_R=9.26分钟;手性HPLC(Chiralpak AD,方法A)98.9%(AUC),t_R=17.48分钟。

[0839] (S)-3a-羟基-1-(4-甲氧基苯基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0840] 

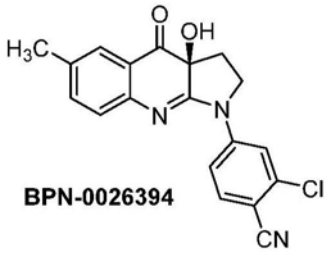
BPN-0026393

[0841] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=216至220℃;

[0842] ^{1}H NMR(500MHz,DMSO-d_6)δ7.93(dd,J=7.0,2.5Hz,2H),7.90(d,J=2.0Hz,1H),7.81(dd,J=8.5,2.5Hz,1H),7.29(d,J=8.0Hz,1H),7.03(dd,J=7.0,2.0Hz,2H),6.99(s,1H),4.17-4.12(m,1H),3.98-3.94(m,1H),3.79(s,3H),2.42-2.35(m,1H),2.28-2.25(m,1H);ESI MS m/z 377[$C_{19}H_{15}F_3N_2O_3$+H]$^+$;

[0843] HPLC(方法D)98.6%(AUC),t_R=9.55分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=14.30分钟。

[0844] (S)-2-氯-4-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈的制备

[0845] 

BPN-0026394

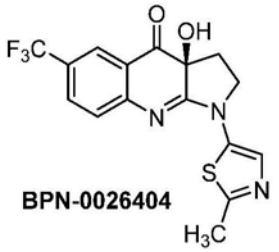
[0846] 根据合成方案4制备作为黄色固体的(S)-2-氯-4-(3a-羟基-6-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈:mp=215至220℃;

[0847] ^{1}H NMR(300MHz,DMSO-d_6)δ8.65(d,J=2.1Hz,1H),8.19(dd,J=9.0,2.1Hz,1H),8.01(d,J=9.0Hz,1H),7.58(s,1H),7.46(d,J=8.4Hz,1H),7.23(d,J=8.1Hz,1H),6.99(s,1H),4.05-4.02(m,2H),2.33(s,3H),2.27(表观s,2H);ESI MS m/z 352[$C_{19}H_{14}ClN_3O_2$+H]$^+$;

[0848] HPLC(方法B)>99%(AUC),t_R=10.49分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=18.14分钟。

[0849] (S)-3a-羟基-1-(2-甲基噻唑-5-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并

[2,3-b]喹啉-4-酮的制备

[0850] 

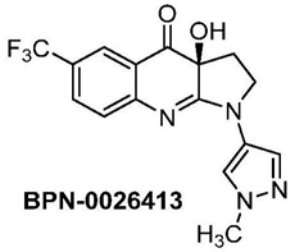
BPN-0026404

[0851] 根据合成方案4制备作为黄橙色固体的(S)-3a-羟基-1-(2-甲基噻唑-5-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=233至235℃:

[0852] ^{1}H NMR(500MHz,DMSO-d_6)δ7.93(d,J=2.5Hz,1H),7.88(dd,J=8.5,2.5Hz,1H),7.56(s,1H),7.39(d,J=8.0Hz,1H),7.11(s,1H),4.14-4.09(m,1H),4.07-4.03(m,1H),2.62(s,3H),2.56-2.52(m,1H),2.37-2.31(m,1H);ESI MS m/z 368[$C_{16}H_{12}F_3N_3O_2S$+H]$^+$;

[0853] HPLC(方法B)>99%(AUC),t_R=10.32分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.78分钟。

[0854] (S)-3a-羟基-1-(1-甲基-1H-吡唑-4-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0855] 

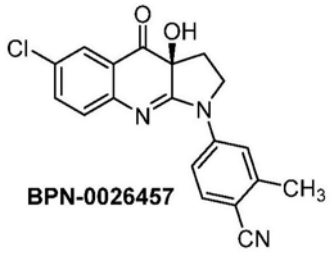
BPN-0026413

[0856] 根据合成方案4制备作为黄棕色固体的(S)-3a-羟基-1-(1-甲基-1H-吡唑-4-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0857] ^{1}H NMR(500MHz,DMSO-d_6)δ8.32(s,1H),7.90-7.89(m,2H),7.82(dd,J=8.5,2.0Hz,1H),7.37(d,J=8.5Hz,1H),6.96(s,1H),4.01-3.96(m,1H),3.91-3.87(m,4H),2.47-2.40(m,1H),2.30-2.26(m,1H);ESI MS m/z 351[$C_{16}H_{13}F_3N_4O_2$+H]$^+$;

[0858] 手性HPLC(Chiralpak AD,方法A)49.5%(AUC),t_R=15.24分钟。

[0859] (S)-4-(6-氯-3a-羟基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈的制备

[0860] 

BPN-0026457

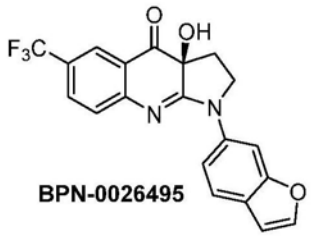
[0861] 根据合成方案3制备作为橙色固体的(S)-4-(6-氯-3a-羟基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈:mp=236至239℃;

[0862] ^{1}H NMR(500MHz,DMSO-d_6)δ8.24(dd,J=9.0,2.0Hz,1H),8.12(s,1H),7.81(d,J=9.0Hz,1H),7.68(d,J=3.0Hz,1H),7.62(dd,J=8.5,2.5Hz,1H),7.33(d,J=8.5Hz,1H),

7.03(s,1H),4.11-4.02(m,2H),2.53(s,3H),2.29-2.25(m,2H);ESI MS m/z 352 $[C_{19}H_{14}ClN_3O_2+H]^+$;

[0863] HPLC(方法D)＞99％(AUC),t_R＝10.20分钟;手性HPLC(Chiralpak AD,方法A)96.5％(AUC),t_R＝16.89分钟。

[0864] (S)-1-(苯并呋喃-6-基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0865] 

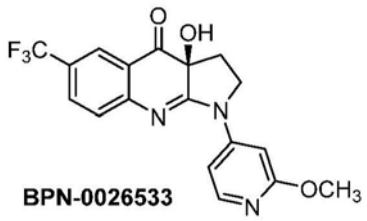
BPN-0026495

[0866] 根据合成方案3制备作为黄色固体的(S)-1-(苯并呋喃-6-基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝232至234℃;

[0867] ^{1}H NMR(300MHz,DMSO-d_6)δ8.49(s,1H),8.03(d,J＝2.1Hz,1H),7.94(s,1H),7.91-7.84(m,2H),7.72(d,J＝8.7Hz,1H),7.39(d,J＝8.4Hz,1H),7.08(s,1H),6.98(dd,J＝2.1,0.9Hz,1H),4.27-4.21(m,1H),4.11-4.05(m,1H),2.34-2.27(m,2H);ESI MS m/z 387 $[C_{20}H_{13}F_3N_2O_3+H]^+$;

[0868] HPLC(方法E)＞99％(AUC),t_R＝9.56分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝14.72分钟。

[0869] (S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0870] 

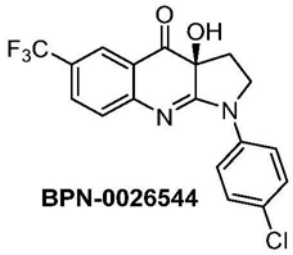
BPN-0026533

[0871] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0872] ^{1}H NMR(500MHz,DMSO-d_6)δ8.17(d,J＝6.0Hz,1H),7.96(s,1H),7.92(dd,J＝8.0,2.5Hz,1H),7.75(dd,J＝6.0,2.0Hz,1H),7.58(d,J＝2.0Hz,1H),7.49(d,J＝8.5Hz,1H),7.11(s,1H),4.08-4.05(m,2H),3.88(s,3H),2.44-2.37(m,1H),2.30-2.25(m,1H);ESI MS m/z 378$[C_{18}H_{14}F_3N_3O_3+H]^+$;

[0873] HPLC(方法B)93.3％(AUC),t_R＝9.81分钟;手性HPLC(Chiralpak AD,方法A)47.7％(AUC),t_R＝12.01分钟。

[0874] (S)-1-(4-氯苯基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0875] 

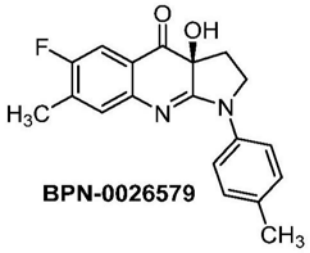
BPN-0026544

[0876] 根据合成方案3制备作为黄棕色固体的(S)-1-(4-氯苯基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=204至207℃;

[0877] ^{1}H NMR(500MHz,DMSO-d_6)δ8.12(dd,J=7.0,2.5Hz,2H),7.93(d,J=2.0Hz,1H),7.86(dd,J=8.5,2.5Hz,1H),7.52(dd,J=7.0,2.0Hz,2H),7.37(d,J=8.5Hz,1H),7.05(s,1H),4.17-4.12(m,1H),4.03-3.99(m,1H),2.46-2.39(m,1H),2.30-2.26(m,1H);ESI MS m/z 381[$C_{18}H_{12}ClF_3N_2O_2$+H]$^+$;

[0878] HPLC(方法B)97.9%(AUC),t_R=10.34分钟;手性HPLC(Chiralpak AD,方法A)93.0%(AUC),t_R=12.86分钟。

[0879] (S)-6-氟-3a-羟基-7-甲基-1-(对甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0880] 

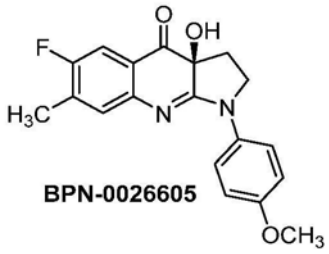
BPN-0026579

[0881] 根据合成方案3制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(对甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=217至220℃;

[0882] ^{1}H NMR(500MHz,DMSO-d_6)δ7.94(d,J=8.5Hz,2H),7.35(d,J=9.0Hz,1H),7.23(d,J=8.5Hz,2H),7.14(d,J=7.0Hz,1H),6.85(s,1H),4.08-4.03(m,1H),3.94-3.91(m,1H),2.31(s,3H),2.28(s,3H),2.26-2.24(m,2H);ESI MS m/z 325[$C_{19}H_{17}FN_2O_2$+H]$^+$;

[0883] HPLC(方法C)95.9%(AUC),t_R=12.90分钟;手性HPLC(Chiralpak AD,方法A)98.5%(AUC),t_R=13.82分钟。

[0884] (S)-6-氟-3a-羟基-1-(4-甲氧基苯基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0885] 

BPN-0026605

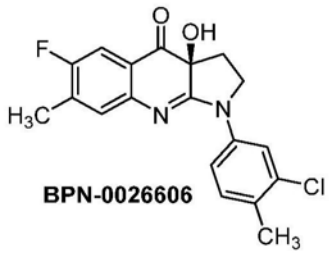
[0886] 根据合成方案3制备作为黄色固体的(S)-6-氟-3a-羟基-1-(4-甲氧基苯基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=220至222℃;

[0887] ^{1}H NMR(300MHz,DMSO-d_6)δ7.96(d,J=9.0Hz,2H),7.35(d,J=9.6Hz,1H),7.11(d,

J＝6.9Hz,1H),7.00(d,J＝9.0Hz,2H),6.85(s,1H),4.10-4.01(m,1H),3.93-3.88(m,1H),3.77(s,3H),2.27(s,3H),2.23(表观s,2H);ESI MS m/z 341[$C_{19}H_{17}FN_2O_3$+H]$^+$;

[0888] HPLC(方法B)＞99％(AUC),t_R＝8.57分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝16.69分钟。

[0889] (S)-1-(3-氯-4-甲基苯基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0890] 

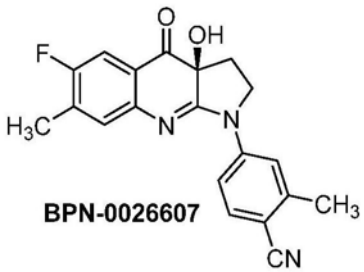
BPN-0026606

[0891] 根据合成方案3制备作为黄色固体的(S)-1-(3-氯-4-甲基苯基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝213至215℃;

[0892] ^{1}H NMR(300MHz,DMSO-d_6)δ8.37(d,J＝2.4Hz,1H),7.81(dd,J＝8.4,2.4Hz,1H),7.39(dd,J＝8.1,2.4Hz,2H),7.18(d,J＝7.2Hz,1H),6.92(s,1H),4.09-3.92(m,2H),2.33(s,3H),2.30(s,3H),2.27-2.24(m,2H);ESI MS m/z 359[$C_{19}H_{16}ClFN_2O_2$+H]$^+$;

[0893] HPLC(方法B)＞99％(AUC),t_R＝9.59分钟;手性HPLC(Chiralpak AD,方法A)98.6％(AUC),t_R＝12.35分钟。

[0894] (S)-4-(6-氟-3a-羟基-7-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈的制备

[0895] 

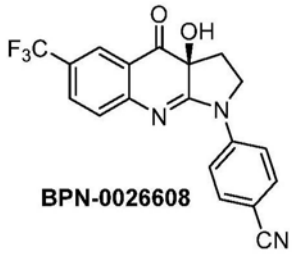
BPN-0026607

[0896] 根据合成方案3制备作为黄色固体的(S)-4-(6-氟-3a-羟基-7-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-2-甲基苄腈:mp＝229至231℃;

[0897] ^{1}H NMR(300MHz,DMSO-d_6)δ8.25(dd,J＝8.4,1.8Hz,1H),8.11(d,J＝2.1Hz,1H),7.80(d,J＝8.7Hz,1H),7.41(d,J＝9.3Hz,1H),7.28(d,J＝6.9Hz,1H),6.97(s,1H),4.07-4.02(m,2H),2.53(s,3H),2.31(s,3H),2.27(表观s,2H);ESI MS m/z 350[$C_{20}H_{16}FN_3O_2$+H]$^+$;

[0898] HPLC(方法B)97.8％(AUC),t_R＝9.58分钟;手性HPLC(Chiralpak AD,方法A)96.1％(AUC),t_R＝16.29分钟。

[0899] (S)-4-(3a-羟基-4-氧代-6-(三氟甲基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈的制备

[0900] 

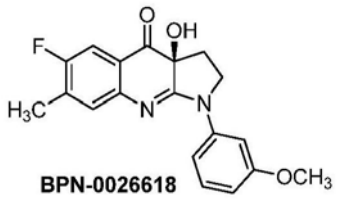
BPN-0026608

[0901] 根据合成方案3制备作为黄色固体的(S)-4-(3a-羟基-4-氧代-6-(三氟甲基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈:mp=233至235℃;

[0902] ^{1}H NMR(500MHz,DMSO-d_6)δ8.33(dd,J=7.0,2.0Hz,2H),7.96(d,J=2.0Hz,1H),7.93-7.90(m,3H),7.46(d,J=8.5Hz,1H),7.12(s,1H),4.18-4.13(m,1H),4.10-4.06(m,1H),2.44-2.39(m,1H),2.32-2.28(m,1H);ESI MS m/z 372[$C_{19}H_{12}F_3N_3O_2$+H]$^+$;

[0903] HPLC(方法B)>99%(AUC),t_R=10.66分钟;手性HPLC(Chiralpak AD,方法A)95.3%(AUC),t_R=16.42分钟。

[0904] (S)-6-氟-3a-羟基-1-(3-甲氧基苯基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0905] 

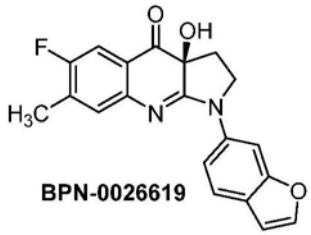
BPN-0026618

[0906] 根据合成方案3制备作为黄色固体的(S)-6-氟-3a-羟基-1-(3-甲氧基苯基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=182至183℃;

[0907] ^{1}H NMR(500MHz,DMSO-d_6)δ7.96(t,J=2.0Hz,1H),7.47(dd,J=8.0,1.5Hz,1H),7.37(d,J=9.0Hz,1H),7.32(t,J=8.0Hz,1H),7.18(d,J=6.5Hz,1H),6.87(s,1H),6.74(dd,J=8.0,2.0Hz,1H),4.08-4.03(m,1H),3.98-3.95(m,1H),3.80(s,3H),2.29(s,3H),2.28-2.24(m,2H);ESI MS m/z 341[$C_{19}H_{17}FN_2O_3$+H]$^+$;

[0908] HPLC(方法B)>99%(AUC),t_R=8.53分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=14.78分钟。

[0909] (S)-1-(苯并呋喃-6-基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0910] 

BPN-0026619

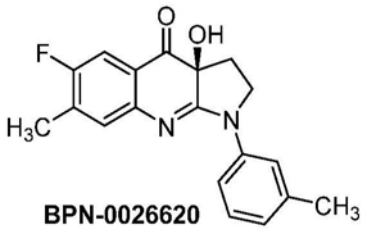
[0911] 根据合成方案3制备作为棕橙色固体的(S)-1-(苯并呋喃-6-基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=211至214℃;

[0912] ^{1}H NMR(500MHz,DMSO-d_6)δ8.54(s,1H),7.99(d,J=2.0Hz,1H),7.87(dd,J=8.5,2.0Hz,1H),7.68(d,J=8.5Hz,1H),7.38(d,J=9.0Hz,1H),7.22(d,J=6.5Hz,1H),6.95

(dd,J＝2.0,1.0Hz,1H),6.90(s,1H),4.18-4.13(m,1H),4.05-4.02(m,1H),2.30-2.26(m,5H);ESI MS m/z 351[C20H$_{15}$FN$_2$O$_3$+H]$^+$;

[0913] HPLC(方法B)＞99％(AUC),t_R＝8.89分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝17.52分钟。

[0914] (S)-6-氟-3a-羟基-7-甲基-1-(间甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0915] 

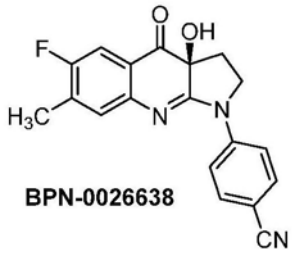
BPN-0026620

[0916] 根据合成方案3制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(间甲苯基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝201至203℃;

[0917] ^{1}H NMR(500MHz,DMSO-d$_6$)δ7.92(d,J＝6.0Hz,1H),7.83(s,1H),7.36(d,J＝9.0Hz,1H),7.30(t,J＝8.0Hz,1H),7.16(d,J＝6.5Hz,1H),6.98(d,J＝7.0Hz,1H),6.86(s,1H),4.08-4.03(m,1H),3.97-3.93(m,1H),2.36(s,3H),2.28(表观d,J＝1.0Hz,3H),2.27-2.24(m,2H);ESI MS m/z 325[C$_{19}$H$_{17}$FN$_2$O$_2$+H]$^+$;

[0918] HPLC(方法B)＞99％(AUC),t_R＝8.80分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝12.23分钟。

[0919] (S)-4-(6-氟-3a-羟基-7-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈的制备

[0920] 

BPN-0026638

[0921] 根据合成方案4制备作为黄色固体的(S)-4-(6-氟-3a-羟基-7-甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈:

[0922] ^{1}H NMR(500MHz,DMSO-d$_6$)δ8.31(d,J＝9.0Hz,2H),7.88(d,J＝9.0Hz,2H),7.42(d,J＝9.0Hz,1H),7.27(d,J＝6.5Hz,1H),6.98(宽处s,1H),4.07-4.03(m,2H),2.31-2.27(m,5H);ESI MS m/z 336[C$_{19}$H$_{14}$FN$_3$O$_2$+H]$^+$;

[0923] HPLC(方法B)＞99％(AUC),t_R＝8.24分钟;手性SFC(Chiralcel OJ-H,方法B)＞99％(AUC),t_R＝5.29分钟。

[0924] (S)-6,7-二氯-3a-羟基-1-苯基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0925] 

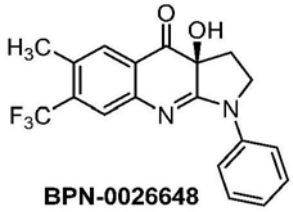
BPN-0026643

[0926] 根据合成方案3制备作为黄色固体的(S)-6,7-二氯-3a-羟基-1-苯基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=202至204℃;

[0927] ^{1}H NMR(300MHz,DMSO-d_6)δ8.05(dd,J=8.7,1.2Hz,2H),7.81(s,1H),7.47-7.42(m,3H),7.20(t,J=7.5Hz,1H),7.04(s,1H),4.18-4.10(m,1H),4.02-3.96(m,1H),2.42-2.32(m,1H),2.28-2.22(m,1H);ESI MS m/z 347[$C_{17}H_{12}Cl_2N_2O_2$+H]$^+$;

[0928] HPLC(方法B)97.4%(AUC),t_R=9.10分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=12.93分钟。

[0929] (S)-3a-羟基-6-甲基-1-苯基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0930] 

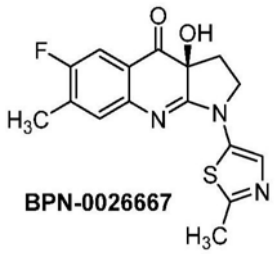
BPN-0026648

[0931] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6-甲基-1-苯基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=205至209℃;

[0932] ^{1}H NMR(300MHz,DMSO-d_6)δ8.08(d,J=7.8Hz,2H),7.73(s,1H),7.48-7.43(m,3H),7.18(t,J=7.5Hz,1H),6.99(s,1H),4.13-4.08(m,1H),4.03-3.96(m,1H),2.43(s,3H),2.38-2.29(m,2H);ESI MS m/z 361[$C_{19}H_{15}F_3N_2O_2$+H]$^+$;

[0933] HPLC(方法B)98.3%(AUC),t_R=9.29分钟;手性SFC(Chiralcel OJ,方法A)91.3%(AUC),t_R=4.16分钟。

[0934] (S)-6-氟-3a-羟基-7-甲基-1-(2-甲基噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0935] 

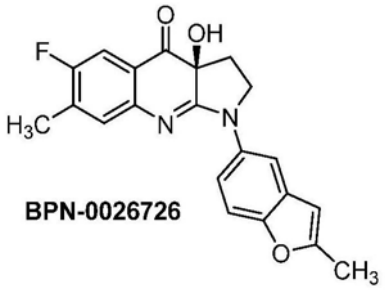
BPN-0026667

[0936] 根据合成方案4制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(2-甲基噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0937] ^{1}H NMR(500MHz,DMSO-d_6)δ7.47(s,1H),7.38(d,J=9.0Hz,1H),7.18(d,J=6.5Hz,1H),6.97(s,1H),4.07-3.92(m,2H),2.60(s,3H),2.44-2.41(m,1H),2.31-2.28(m,4H);ESI MS m/z 332[$C_{16}H_{14}FN_3O_2S$+H]$^+$;

[0938] HPLC(方法B)＞99％(AUC)，t_R＝9.16分钟；手性HPLC(Chiralpak AD，方法A)98.6％(AUC)，t_R＝13.72分钟。

[0939] (S)-6-氟-3a-羟基-7-甲基-1-(2-甲基苯并呋喃-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0940] 

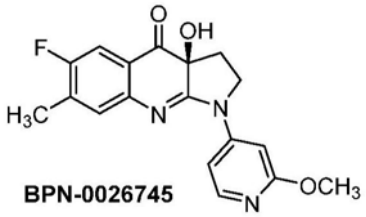
BPN-0026726

[0941] 根据合成方案4制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(2-甲基苯并呋喃-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：mp＝203至205℃；

[0942] ^{1}H NMR(500MHz，DMSO-d_6)δ8.12(d，J＝2.5Hz，1H)，7.91(dd，J＝9.0，2.5Hz，1H)，7.52(d，J＝9.0Hz，1H)，7.36(d，J＝9.5Hz，1H)，7.13(d，J＝7.0Hz，1H)，6.86(s，1H)，6.62(s，1H)，4.17-4.12(m，1H)，3.99-3.95(m，1H)，2.46(表观d，J＝1.0Hz，3H)，2.28-2.26(m，5H)；ESI MS m/z 365[$C_{21}H_{17}FN_2O_3$+H]$^+$；

[0943] HPLC(方法B)＞99％(AUC)，t_R＝9.12分钟；手性HPLC(Chiralpak AD，方法A)95.8％(AUC)，t_R＝15.34分钟。

[0944] (S)-6-氟-3a-羟基-1-(2-甲氧基吡啶-4-基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0945] 

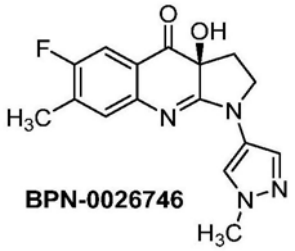
BPN-0026745

[0946] 根据合成方案4制备作为黄色固体的(S)-6-氟-3a-羟基-1-(2-甲氧基吡啶-4-基)-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：mp＝211至215℃；

[0947] ^{1}H NMR(500MHz，DMSO-d_6)δ8.13(d，J＝6.0Hz，1H)，7.68(dd，J＝6.0，2.0Hz，1H)，7.59(d，J＝2.0Hz，1H)，7.41(d，J＝9.0Hz，1H)，7.29(d，J＝7.0Hz，1H)，6.96(s，1H)，4.00-3.97(m，2H)，3.87(s，3H)，2.36(s，3H)，2.31-2.23(m，2H)；ESI MS m/z 342[$C_{18}H_{16}FN_3O_3$+H]$^+$；

[0948] HPLC(方法B)＞99％(AUC)，t_R＝8.95分钟；手性HPLC(Chiralpak AD，方法A)97.7％(AUC)，t_R＝14.01分钟。

[0949] (S)-6-氟-3a-羟基-7-甲基-1-(1-甲基-1H-吡唑-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0950] 

BPN-0026746

[0951] 根据合成方案4制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(1-甲基-1H-吡唑-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=234至238℃;

[0952] ^{1}H NMR(500MHz,DMSO-d_6)δ8.25(s,1H),7.83(s,1H),7.32(d,J=9.5Hz,1H),7.15(d,J=7.0Hz,1H),6.80(s,1H),3.92-3.91(m,1H),3.87(s,3H),3.83-3.81(m,1H),2.36-2.35(m,1H),2.31(s,3H),2.28-2.25(m,1H);ESI MS m/z 315[$C_{16}H_{15}FN_4O_2$+H]$^+$;

[0953] HPLC(方法B)>99%(AUC),t_R=7.31分钟;手性HPLC(Chiralpak AD,方法A)98.3%(AUC),t_R=16.79分钟。

[0954] (S)-6-氟-3a-羟基-7-甲基-1-(噻吩-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0955] 

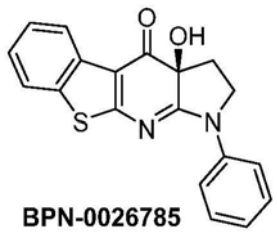
BPN-0026748

[0956] 根据合成方案4制备作为红橙色固体的(S)-6-氟-3a-羟基-7-甲基-1-(噻吩-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=210至215℃;

[0957] ^{1}H NMR(500MHz,DMSO-d_6)δ7.37(d,J=9.5Hz,1H),7.18-7.15(m,2H),6.96(dd,J=5.5,4.0Hz,1H),6.94(s,1H),6.85(dd,J=4.0,1.5Hz,1H),4.09-3.99(m,2H),2.44-2.37(m,1H),2.30-2.27(m,4H);ESI MS m/z 317[$C_{16}H_{13}FN_2O_2S$+H]$^+$;

[0958] HPLC(方法B)>99%(AUC),t_R=8.89分钟;手性HPLC(Chiralpak AD,方法A)96.7%(AUC),t_R=15.19分钟。

[0959] (S)-3a-羟基-1-苯基-1,2,3,3a-四氢-4H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4-酮的制备

[0960] 

BPN-0026785

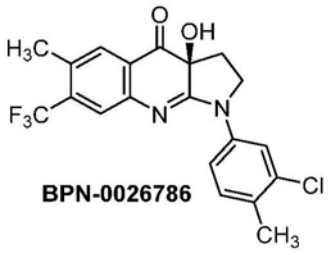
[0961] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-苯基-1,2,3,3a-四氢-4H-苯并[4,5]噻吩并[2,3-b]吡咯并[3,2-e]吡啶-4-酮:mp=247至248℃;

[0962] ^{1}H NMR(500MHz,DMSO-d_6)δ8.19(d,J=7.5Hz,1H),7.96(dd,J=8.5,7.5Hz,2H),7.84(d,J=7.5Hz,1H),7.52-7.49(m,2H),7.42-7.39(m,1H),7.29-7.25(m,2H),7.06(s,1H),4.30-4.25(m,1H),4.12(表观t,J=7.5Hz,1H),2.36-2.30(m,2H);ESI MS m/z 335

$[C_{19}H_{14}N_2O_2S+H]^+$；

[0963] HPLC(方法B)＞99％(AUC)，t_R＝10.70分钟；手性HPLC(Chiralpak AD，方法A)＞99％(AUC)，t_R＝21.14分钟。

[0964] (S)-1-(3-氯-4-甲基苯基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0965] 

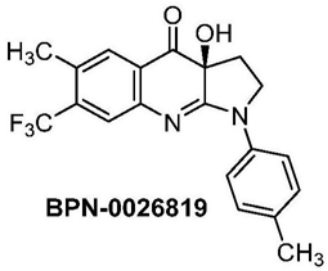
BPN-0026786

[0966] 根据合成方案3制备作为橙色固体的(S)-1-(3-氯-4-甲基苯基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：mp＝212至217℃；

[0967] ^{1}H NMR(300MHz，DMSO-d_6)δ8.28(d，J＝2.4Hz，1H)，7.89(dd，J＝8.4，2.1Hz，1H)，7.74(s，1H)，7.41(t，J＝4.8Hz，2H)，7.01(s，1H)，4.13-3.95(m，2H)，2.44(s，3H)，2.34(s，3H)，2.28-2.26(m，2H)；ESI MS m/z 409$[C_{20}H_{16}ClF_3N_2O_2+H]^+$；

[0968] HPLC(方法B)＞99％(AUC)，t_R＝10.44分钟；手性HPLC(Chiralpak AD，方法A)＞99％(AUC)，t_R＝9.82分钟。

[0969] (S)-3a-羟基-6-甲基-1-(对甲苯基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0970] 

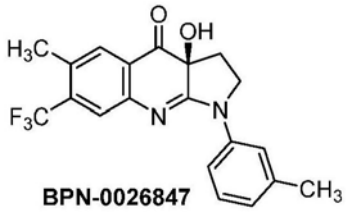
BPN-0026819

[0971] 根据合成方案3制备作为橙黄色固体的(S)-3a-羟基-6-甲基-1-(对甲苯基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮；mp＝202至205℃；

[0972] ^{1}H NMR(500MHz，DMSO-d_6)δ7.93(d，J＝8.5Hz，2H)，7.71(s，1H)，7.39(s，1H)，7,25(d，J＝8.5Hz，2H)，6.94(s，1H)，4,12-4.07(m，1H)，3.96(表观t，J＝7.5Hz，1H)2.42(s，3H)，2.36-2.34(m，1H)，2.32(s，3H)，2.27-2.23(m，1H)；ESI MS m/z 375$[C_{20}H_{17}F_3N_2O_2+H]^+$；

[0973] HPLC(方法C)＞99％(AUC)，t_R＝14.19分钟；手性HPLC(Chiralpak AD，方法A)＞99％(AUC)，t_R＝10.94分钟。

[0974] (S)-3a-羟基-6-甲基-1-(间甲苯基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0975] 

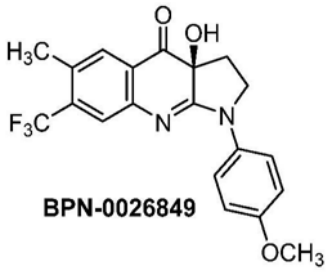
BPN-0026847

[0976] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(间甲苯基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=181至185℃;

[0977] ^{1}H NMR(300MHz,DMSO-d_6)δ7.95(d,J=8.4Hz,1H),7.80(s,1H),7.73(s,1H),7.42(s,1H),7.33(t,J=7.8Hz,1H),7.00(d,J=7.5Hz,1H),6.98(s,1H),4.15-4.06(m,1H),3.98(表观t,J=9.0Hz,1H),2.43(s,3H),2.37(s,3H),2.30-2.22(m,2H);ESI MS m/z 375 $[C_{20}H_{17}F_3N_2O_2+H]^+$;

[0978] HPLC(方法B)>99%(AUC),t_R=9.63分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=9.40分钟。

[0979] (S)-3a-羟基-1-(4-甲氧基苯基)-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0980] 

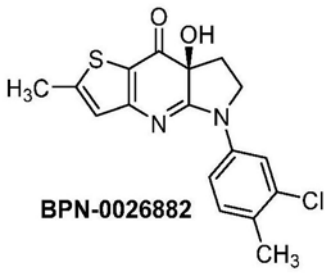
BPN-0026849

[0981] 根据合成方案3制备作为黄色固体的(S)-3a-羟基-1-(4-甲氧基苯基)-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=185至188℃;

[0982] ^{1}H NMR(500MHz,DMSO-d_6)δ7.95(dd,J=7.0,2.5Hz,2H),7.70(s,1H),7.36(s,1H),7.01(dd,J=7.0,2.0Hz,2H),6.93(s,1H),4.10-4.08(m,1H),3.94(表观t,J=9.0Hz,1H),3.78(s,3H),2.42(s,3H),2.36-2.33(m,1H),2.27-2.23(m,1H);ESI MS m/z 391 $[C_{20}H_{17}F_3N_2O_3+H]^+$;

[0983] HPLC(方法B)>99%(AUC),t_R=9.83分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=13.62分钟。

[0984] (S)-5-(3-氯-4-甲基苯基)-7a-羟基-2-甲基-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮的制备

[0985] 

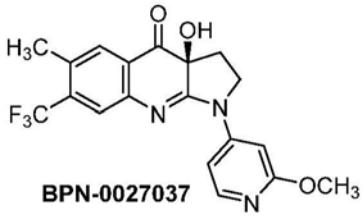
BPN-0026882

[0986] 根据合成方案3制备作为黄色固体的(S)-5-(3-氯-4-甲基苯基)-7a-羟基-2-甲基-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮:mp=210至212℃;

[0987] ^{1}H NMR(500MHz,DMSO-d_6)δ8.25(表观d,J＝2.0Hz,1H),7.75(dd,J＝8.0,2.0Hz,1H),7.40(d,J＝8.5Hz,1H),6.90(s,1H),6.84(s,1H),4.11-4.09(m,1H),3.99(表观t,J＝9.5Hz,1H),2.33(s,3H),2.24-2.18(m,2H),被溶剂峰掩盖的3H;ESI MS m/z 347[$C_{17}H_{15}ClN_2O_2S$+H]$^+$;

[0988] HPLC(方法B)＞99％(AUC),t_R＝9.74分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝16.62分钟。

[0989] (S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[0990] 

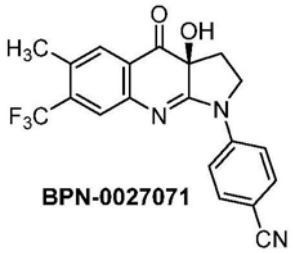
BPN-0027037

[0991] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[0992] ^{1}H NMR(500MHz,DMSO-d_6)δ8.15(d,J＝6.0Hz,1H),7.80-7.77(m,2H),7.53-7.51(m,2H),7.05(s,1H),4.03-4.01(m,2H),3.87(s,3H),2.46(s,3H),2.28-2.23(m,2H);ESI MS m/z 392[$C_{19}H_{16}F_3N_3O_3$+H]$^+$;

[0993] HPLC(方法B)＞99％(AUC),t_R＝11.12分钟;手性HPLC(Chiralpak AD,方法A)69.1％(AUC),t_R＝11.35分钟。

[0994] (S)-4-(3a-羟基-6-甲基-4-氧代-7-(三氟甲基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈的制备

[0995] 

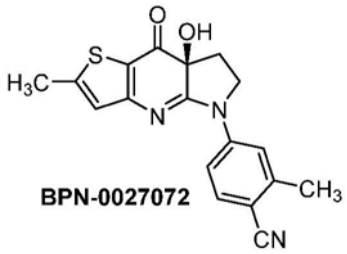
BPN-0027071

[0996] 根据合成方案6制备作为黄色固体的(S)-4-(3a-羟基-6-甲基-4-氧代-7-(三氟甲基)-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)苄腈:mp＝225至228℃;

[0997] ^{1}H NMR(500MHz,DMSO-d_6)δ8.33(d,J＝9.0Hz,2H),7.89(d,J＝9.0Hz,2H),7.77(s,1H),7.53(s,1H),7.05(s,1H),4.11-4.06(m,2H),2.45(s,3H),2.43-2.38(m,1H),2.30-2.27(m,1H);ESI MS m/z 386[$C_{20}H_{14}F_3N_3O_2$+H]$^+$;

[0998] HPLC(方法C)＞99％(AUC),t_R＝15.95分钟;手性HPLC(Chiralpak AD,方法A)45.6％(AUC),t_R＝16.30分钟。

[0999] (S)-4-(7a-羟基-2-甲基-8-氧代-6,7,7a,8-四氢-5H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-5-基)-2-甲基苄腈的制备

[1000] 

BPN-0027072

[1001] 根据合成方案3制备作为黄棕色固体的(S)-4-(7a-羟基-2-甲基-8-氧代-6,7,7a,8-四氢-5H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-5-基)-2-甲基苄腈:mp=223至224℃;

[1002] ^{1}H NMR(500MHz,DMSO-d_6)δ8.19(dd,J=8.5,2.5Hz,1H),8.02(d,J=2.0Hz,1H),7.81(d,J=8.5Hz,1H),6.97(s,1H),6.90(表观d,J=1.0Hz,1H),4.12-4.05(m,2H),2.52(s,3H),2.49(s,3H),2.27-2.22(m,2H);ESI MS m/z 338[$C_{18}H_{15}N_3O_2S$+H]$^+$;

[1003] HPLC(方法B)>99%(AUC),t_R=8.67分钟;手性HPLC(Chiralpak AD,方法A)96.3%(AUC),t_R=19.63分钟。

[1004] (S)-5-(3-溴苯基)-7a-羟基-2-甲基-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮的制备

[1005] 

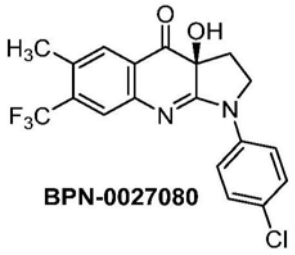
BPN-0027074

[1006] 根据合成方案3制备作为黄橙色固体的(S)-5-(3-溴苯基)-7a-羟基-2-甲基-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮:mp=193至197℃;

[1007] ^{1}H NMR(300MHz,DMSO-d_6)δ8.42(s,1H),7.90(dd,J=7.2,4.8Hz,1H),7.43-7.38(m,2H),6.94(s,1H),6.90(表观d,J=0.9Hz,1H),4.16-3.98(m,2H),2.27-2.14(m,2H),被溶剂峰掩盖的3H;ESI MS m/z 377[$C_{16}H_{13}BrN_2O_2S$+H]$^+$;

[1008] HPLC(方法B)97.4%(AUC),t_R=8.27分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=16.25分钟。

[1009] (S)-1-(4-氯苯基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1010] 

BPN-0027080

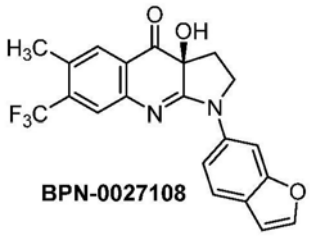
[1011] 根据合成方案3制备作为黄色固体的(S)-1-(4-氯苯基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=223至226℃;

[1012] ^{1}H NMR(500MHz,DMSO-d_6)δ8.13(表观dt,J=9.0,3.5Hz,2H),7.34(s,1H),7.50(表观dt,J=9.0,3.5Hz,2H),7.44(s,1H),6.99(s,1H),4.11-4.07(m,1H),3.99(表观t,J=9.5Hz,1H),2.43(s,3H),2.40-2.34(m,1H),2.28-2.24(m,1H);ESI MS m/z 395

$[C_{19}H_{14}ClF_3N_2O_2+H]^+$;

[1013] HPLC(方法C)＞99％(AUC),t_R＝15.90分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝12.18分钟。

[1014] (S)-1-(苯并呋喃-6-基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1015] 

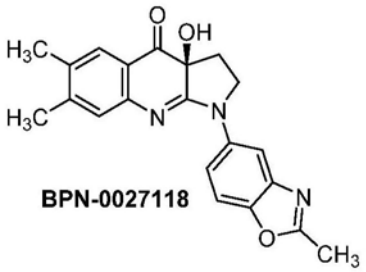
BPN-0027108

[1016] 根据合成方案3制备作为亮橙色固体的(S)-1-(苯并呋喃-6-基)-3a-羟基-6-甲基-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝206至209℃;

[1017] ^{1}H NMR(500MHz,DMSO-d_6)δ8.47(s,1H),8.01(d,J＝2.5Hz,1H),7.92(dd,J＝8.5,2.0Hz,1H),7.74(s,1H),7.70(d,J＝8.5Hz,1H),7.45(s,1H),6.99(s,1H),6.97(表观dd,J＝2.0,1.0Hz,1H),4.22-4.17(m,1H),4.06(表观t,J＝9.0Hz,1H),2.43(s,3H),2.41-2.38(m,1H),2.30-2.27(m,1H);ESI MS m/z 401$[C_{21}H_{15}F_3N_2O_3+H]^+$;

[1018] HPLC(方法B)＞99％(AUC),t_R＝8.96分钟;手性HPLC(Chiralpak AD,方法A)＞99％(AUC),t_R＝14.11分钟。

[1019] (S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噁唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1020] 

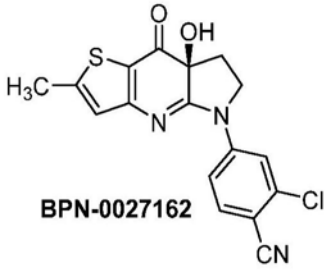
BPN-0027118

[1021] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噁唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1022] ^{1}H NMR(500MHz,DMSO-d_6)δ8.44(表观d,J＝2.0Hz,1H),8.01(dd,J＝9.0,2.5Hz,1H),7.68(d,J＝9.0Hz,1H),7.49(s,1H),7.05(s,1H),6.78(s,1H),4.16-4.11(m,1H),4.05-3.98(m,1H),2.62(s,3H),2.27-2.26(m,5H),2.22(s,3H);ESI MS m/z 362$[C_{21}H_{19}N_3O_3+H]^+$;

[1023] HPLC(方法B)＞99％(AUC),t_R＝7.83分钟;手性HPLC(Chiralpak AD,方法A)84.2％(AUC),t_R＝23.32分钟。

[1024] (S)-2-氯-4-(7a-羟基-2-甲基-8-氧代-6,7,7a,8-四氢-5H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-5-基)苄腈的制备

[1025] 

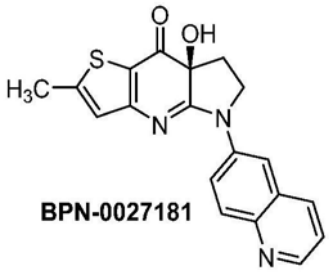
BPN-0027162

[1026] 根据合成方案3制备作为黄色固体的(S)-2-氯-4-(7a-羟基-2-甲基-8-氧代-6,7,7a,8-四氢-5H-吡咯并[2,3。b]噻吩并[2,3-e]吡啶-5-基)苄腈:mp=247至250℃;

[1027] ^{1}H NMR(500MHz,DMSO-d_6)δ8.55(表观d,J=2.0Hz,1H),8.13(dd,J=9.0,2.0Hz,1H),8.01(d,J=9.0Hz,1H),7.04(s,1H),6.95(表观d,J=1.0Hz,1H),4.14-4.08(m,2H),2.52(s,3H),2.29-2.19(m,2H);ESI MS m/z 358[$C_{17}H_{12}ClN_3O_2S$+H]$^+$;

[1028] HPLC(方法B)>99%(AUC),t_R=9.82分钟;手性HPLC(Chiralpak AD,方法A)77.2%(AUC),t_R=20.56分钟。

[1029] (S)-7a-羟基-2-甲基-5-(喹啉-6-基)-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮的制备

[1030] 

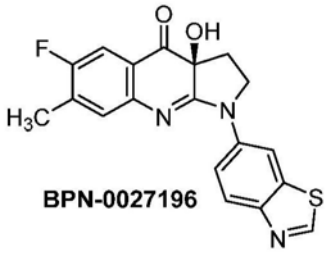
BPN-0027181

[1031] 根据合成方案3制备作为黄色固体的(S)-7a-羟基-2-甲基-5-(喹啉-6-基)-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮:mp=247至249℃;

[1032] ^{1}H NMR(500MHz,DMSO-d_6)δ8.86(dd,J=4.5,2.0Hz,1H),8.67(dd,J=9.0,2.5Hz,1H),8.38(d,J=2.0Hz,1H),8.36(d,J=7.0Hz,1H),8.07(d,J=9.5Hz,1H),7.55(dd,J=8.0,4.0Hz,1H),6.97(s,1H),6.88(表观d,J=0.5Hz,1H),4.29-4.24(m,1H),4.17(表观t,J=7.5Hz,1H),2.52(s,3H),2.32-2.27(m,2H);ESI MS m/z 350[$C_{19}H_{15}N_3O_2S$+H]$^+$;

[1033] HPLC(方法B)>99%(AUC),t_R=7.18分钟;手性HPLC(Chiralpak AD,方法A)97.5%(AUC),t_R=21.48分钟。

[1034] (S)-1-(苯并[d]噻唑-6-基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1035] 

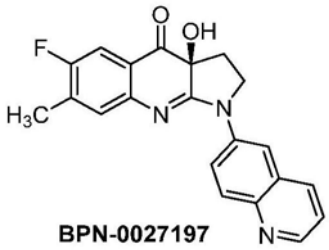
BPN-0027196

[1036] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d]噻唑-6-基)-6-氟-3a-羟基-7-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=130至133℃;

[1037] ^{1}H NMR(500MHz,DMSO-d_6)δ9.33(s,1H),8.90(d,J=2.5Hz,1H),8.32(dd,J=9.0,2.0Hz,1H),8.12(d,J=9.0Hz,1H),7.39(d,J=9.0Hz,1H),7.26(d,J=6.5Hz,1H),6.93(s,1H),4.20-4.14(m,1H),4.07(表观t,J=8.0Hz,1H),2.34-2.27(m,5H);ESI MS m/z 368 $[C_{19}H_{14}FN_3O_2S+H]^+$;

[1038] HPLC(方法C)>99%(AUC),t_R=12.76分钟;手性HPLC(Chiralpak AD,方法A)75.2%(AUC),t_R=20.73分钟。

[1039] (S)-6-氟-3a-羟基-7-甲基-1-(喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1040] 

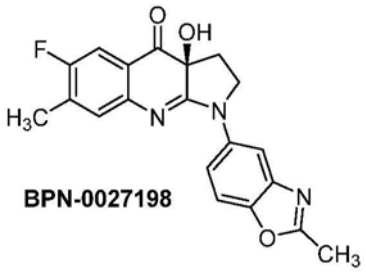
BPN-0027197

[1041] 根据合成方案6制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(喹啉-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:

[1042] ^{1}H NMR(500MHz,DMSO-d_6)δ8.84(dd,J=4.5,2.0Hz,1H),8.76(dd,J=9.0,2.5Hz,1H),8.46(d,J=2.5Hz,1H),8.37(d,J=8.5Hz,1H),8.06(d,J=9.0Hz,1H),7.54(dd,J=8.5,4.5Hz,1H),7.41(d,J=9.5Hz,1H),7.28(d,J=6.5Hz,1H),6.96(s,1H),4.21-4.14(m,2H),2.37-2.31(m,5H);ESI MS m/z 362$[C_{21}H_{16}FN_3O_2+H]^+$;

[1043] HPLC(方法C)>99%(AUC),t_R=12.21分钟;手性HPLC(Chiralpak AD,方法A)58.8%(AUC),t_R=19.16分钟。

[1044] (S)-6-氟-3a-羟基-7-甲基-1-(2-甲基苯并[d]噁唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1045] 

BPN-0027198

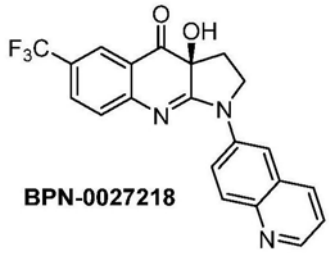
[1046] 根据合成方案4制备作为黄色固体的(S)-6-氟-3a-羟基-7-甲基-1-(2-甲基苯并[d]噁唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1047] ^{1}H NMR(500MHz,DMSO-d_6)δ8.42(d,J=2.0Hz,1H),7.99(dd,J=9.0,2.0Hz,1H),7.69(d,J=9.0Hz,1H),7.37(d,J=9.0Hz,1H),7.18(d,J=7.5Hz,1H),6.89(s,1H),4.16-4.13(m,1H),4.01(表观t,J=7.5Hz,1H),2.63(s,3H),2.31-2.26(m,5H);ESI MS m/z 366 $[C_{20}H_{16}FN_aO_3+H]^+$;

[1048] HPLC(方法C)>99%(AUC),t_R=12.02分钟;手性HPLC(Chiralpak AD,方法A)72.8%(AUC),t_R=20.60分钟。

[1049] (S)-3a-羟基-1-(喹啉-6-基)-6-(三氟甲基)-1,2,3,3a.四氢-4H-吡咯并[2,3-b]

喹啉-4-酮的制备

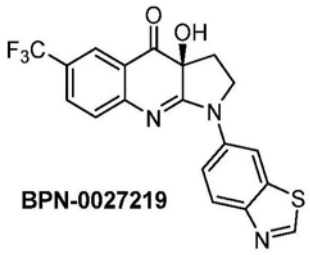
[1050] 

[1051] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(喹啉-6-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=258至260℃;

[1052] ^{1}H NMR(300MHz,DMSO-d_6)δ8.87(dd,J=3.9,2.4Hz,1H),8.73(dd,J=9.0,2.7Hz,1H),8.51(s,1H),8.41(d,J=6.9Hz,1H),8.10(d,J=9.3Hz,1H),7.96(s,1H),7.91(d,J=8.4Hz,1H),7.56(dd,J=8.4,4.5Hz,1H),7.47(d,J=8.7Hz,1H),7.13(s,1H),4.30-4.16(m,2H),2.74-2.63(m,1H),2.17-1.98(m,1H);ESI MS m/z 398[$C_{21}H_{14}F_3N_3O_2$+H]$^+$;

[1053] HPLC(方法C)>99%(AUC),t_R=13.48分钟;手性HPLC(Chiralpak AD,方法A)49.1%(AUC),t_R=16.74分钟。

[1054] (S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

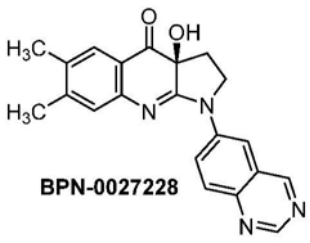
[1055] 

[1056] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮;

[1057] ^{1}H NMR(500MHz,DMSO-d_6)δ9.37(s,1H),8.87(d,J=2.5Hz,1H),8.32(dd,J=9.0,2.5Hz,1H),8.15(d,J=9.0Hz,1H),7.94(d,J=2.0Hz,1H),7.87(dd,J=8.5,2.5Hz,1H),7.44(d,J=8.5Hz,1H),7.09(s,1H),4.28-4.23(m,1H),4.12(表观t,J=9.5Hz,1H),2.34-2.31(m,2H);ESI MS m/z 404[$C_{19}H_{12}F_3N_3O_2S$+H]$^+$;

[1058] HPLC(方法C)>99%(AUC),t_R=13.22分钟;手性HPLC(Chiralpak AD,方法A)50.0%(AUC),t_R=16.78分钟。

[1059] (S)-3a-羟基-6,7-甲基-1-(喹唑啉-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1060] 

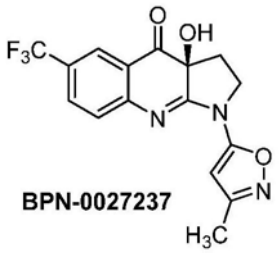
[1061] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(喹唑啉-6-

基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=275至276℃;

[1062] ^{1}H NMR(500MHz,DMSO-d_6)δ9.61(s,1H),9.23(s,1H),9.04(dd,J=9.0,2.5Hz,1H),8.65(d,J=2.5Hz,1H),8.08(d,J=9.5Hz,1H),7.53(s,1H),7.19(s,1H),6.89(s,1H),4.23-4.13(m,2H),2.34-2.32(m,2H),2.31(s,3H),2.25(s,3H);ESI MS m/z 359[$C_{21}H_{18}N_4O_2$+H]$^+$;

[1063] HPLC(方法C)>99%(AUC),t_R=11.18分钟;手性HPLC(Chiralpak AD,方法A)70.8%(AUC),t_R=20.49分钟。

[1064] (S)-3a-羟基-1-(3-甲基异噁唑-5-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

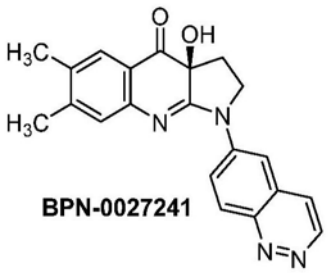
[1065] 

[1066] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(3-甲基异噁唑-5-基)-6-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1067] ^{1}H NMR(500MHz,DMSO-d_6)δ7.97-7.94(m,2H),7.52(d,J=8.0Hz,1H),7.18(s,1H),7.00(s,1H),4.17-4.07(m,2H),2.32-2.29(m,2H),2.27(s,3H);ESI MS m/z 352[$C_{16}H_{12}F_3N_3O_3$+H]$^+$;

[1068] HPLC(方法F)98.2%(AUC),t_R=15.70分钟;手性HPLC(Chiralpak AD,方法B)59.1%(AUC),t_R=12.14分钟。

[1069] (S)-1-(噌啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

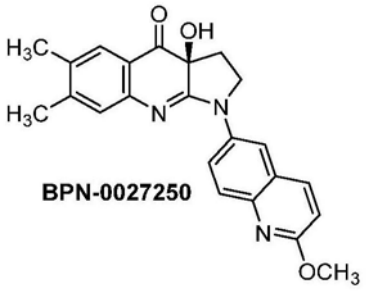
[1070] 

[1071] 根据合成方案6制备作为黄色固体的(S)-1-(噌啉-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=274至276℃;

[1072] ^{1}H NMR(500MHz,DMSO-d_6)δ9.28(d,J=6.0Hz,1H),9.03(dd,J=9.5,2.5Hz,1H),8.49(dd,J=5.0,2.5Hz,2H),8.17(d,J=6.0Hz,1H),7.55(s,1H),7.22(s,1H),6.92(s,1H),4.19-4.16(m,2H),2.36-2.32(m,5H),2.26(s,3H);ESI MS m/z 359[$C_{21}H_{18}N_4O_2$+H]$^+$;

[1073] HPLC(方法C)>99%(AUC),t_R=12.43分钟;手性HPLC(Chiralpak AD,方法A)54.2%(AUC),t_R=16.90分钟。

[1074] (S)-3a-羟基-1-(2-甲氧基喹啉-6-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1075] 

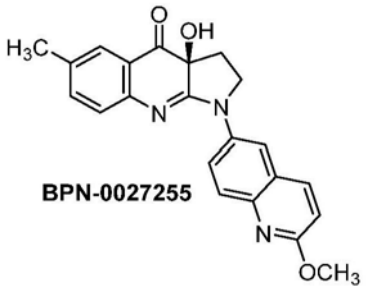
BPN-0027250

[1076] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基喹啉-6-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=233至237℃;

[1077] ^{1}H NMR(500MHz,DMSO-d_6)δ8.65(dd,J=9.5,2.5Hz,1H),8.38(d,J=2.5Hz,1H),8.25(d,J=9.0Hz,1H),7.83(d,J=9.5Hz,1H),7.50(s,1H),7.11(s,1H),7.04(d,J=9.0Hz,1H),6.81(s,1H),4.18-4.13(m,1H),4.09-4.04(m,1H),3.99(s,3H),2.31-2.29(m,5H),2.23(s,3H);ESI MS m/z 388[$C_{23}H_{21}N_3O_3$+H]$^+$;

[1078] HPLC(方法C)95.9%(AUC),t_R=14.47分钟;手性HPLC(Chiralpak AD,方法A)78.1%(AUC),t_R=18.25分钟。

[1079] (S)-3a-羟基-1-(2-甲氧基喹啉-6-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1080] 

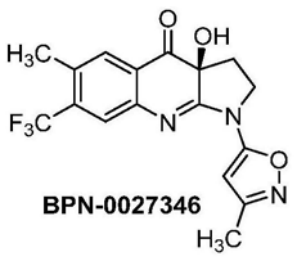
BPN-0027255

[1081] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基喹啉-6-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=230至234℃;

[1082] ^{1}H NMR(500MHz,DMSO-d_6)δ8.62(dd,J=9.0,2.5Hz,1H),8.40(d,J=2.5Hz,1H),8.25(d,J=8.5Hz,1H),7.83(d,J=9.0Hz,1H),7.55(d,J=1.5Hz,1H),7.40(dd,J=8.5,2.5Hz,1H),7.19(d,J=8.0Hz,1H),7.04(d,J=9.0Hz,1H),6.87(s,1H),4.19-4.14(m,1H),4.10-4.07(m,1H),3.99(s,3H),2.32-2.30(m,5H);ESI MS m/z 374[$C_{22}H_{19}N_3O_3$+H]$^+$;

[1083] HPLC(方法C)>99%(AUC),t_R=13.28分钟;手性HPLC(Chiralpak AD,方法A)71.5%(AUC),t_R=17.22分钟。

[1084] (S)-3a-羟基-6-甲基-1-(3-甲基异噁唑-5-基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1085] 

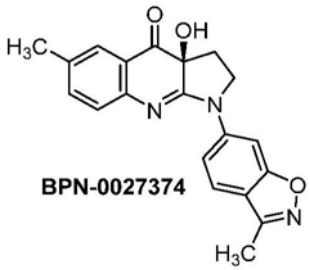
BPN-0027346

[1086] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(3-甲基异噁唑-5-基)-7-(三氟甲基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1087] ^{1}H NMR(500MHz,DMSO-d_6)δ7.78(s,1H),7.59(s,1H),7.12(s,1H),6.69(s,1H),4.15-4.11(m,1H),4.09-4.03(m,1H),2.46(s,3H),2.30-2.28(m,2H),2.26(s,3H);ESI MS m/z 366[$C_{17}H_{14}F_3N_3O_3$+H]$^+$;

[1088] HPLC(方法C)98.3%(AUC),t_R=18.85分钟;手性HPLC(Chiralpak AD,方法A)49.5%(AUC),t_R=15.32分钟。

[1089] (S)-3a-羟基-6-甲基-1-(3-甲基苯并[d]异噁唑-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1090] 

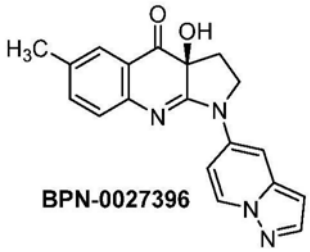
BPN-0027374

[1091] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(3-甲基苯并[d]异噁唑-6-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=249至251℃;

[1092] ^{1}H NMR(500MHz,DMSO-d_6)δ8.62(d,J=1.5Hz,1H),8.08(dd,J=9.0,2.0Hz,1H),7.86(d,J=9.0Hz,1H),7.57(d,J=1.5Hz,1H),7.42(dd,J=8.0,1.5Hz,1H),7.23(d,J=8.0Hz,1H),6.91(s,1H),4.17-4.02(m,2H),2.55(s,3H),2.33(s,3H),2.31-2.29(m,2H);ESI MS m/z 348[$C_{20}H_{17}N_3O_3$+H]$^+$;

[1093] HPLC(方法C)>99%(AUC),t_R=12.92分钟;手性HPLC(Chiralpak AD,方法A)68.8%(AUC),t_R=19.68分钟。

[1094] (S)-3a-羟基-6-甲基-1-(吡唑并[1,5-a]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1095] 

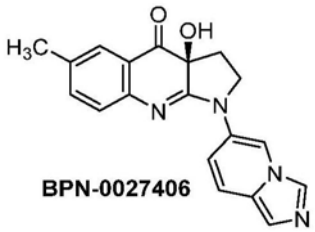
BPN-0027396

[1096] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(吡唑并[1,5-a]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=242至243℃;

[1097] ^{1}H NMR(500MHz,DMSO-d_6)δ8.69(d,J=8.0Hz,1H),8.16(d,J=2.5Hz,1H),8.00(dd,J=8.0,2.5Hz,1H),7.96(d,J=2.0Hz,1H),7.56(d,J=2.0Hz,1H),7.42(dd,J=8.5,2.0Hz,1H),7.21(d,J=8.0Hz,1H),6.91(s,1H),6.56(dd,J=2.0,0.5Hz,1H),4.18-4.13(m,1H),4.09-4.05(m,2H),2.36(s,3H),2.30-2.28(m,2H);ESI MS m/z 333[$C_{19}H_{16}N_4O_2$+H]$^+$;

[1098] UPLC(方法A)95.5%(AUC),t_R=2.80分钟;手性HPLC(Chiralpak AD,方法A)74.1%(AUC),t_R=21.26分钟。

[1099] (S)-3a-羟基-1-(咪唑并[1,5-a]吡啶-6-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

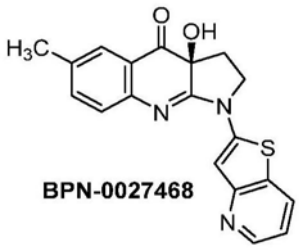
[1100] 

[1101] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(咪唑并[1,5-a]吡啶-6-基)-6-甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=215至219℃分解;

[1102] ^{1}H NMR(500MHz,DMSO-d_6)δ9.26(s,1H),8.45(s,1H),7.62(d,J=10.0Hz,1H),7.54-7.50(m,2H),7.40(d,J=8.0Hz,1H),7.37(s,1H),7.18(d,J=8.0Hz,1H),6.87(s,1H),4.08-4.02(m,1H),3.96(表观t,J=8.0Hz,1H),2.31(s,3H),2.28-2.25(m,2H);ESI MS m/z 333[$C_{19}H_{16}N_4O_2$+H]$^+$;

[1103] UPLC(方法A)>99%(AUC),t_R=2.40分钟;手性HPLC(Chiralpak AD,方法A)84.0%(AUC),t_R=20.09分钟。

[1104] (S)-3a-羟基-6-甲基-1-(噻吩并[3,2-b]吡啶-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

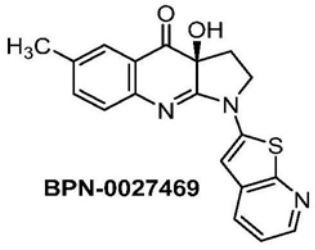
[1105] 

[1106] 根据合成方案6制备作为橙色固体的(S)-3a-羟基-6-甲基-1-(噻吩并[3,2-b]吡啶-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=260至262℃;

[1107] ^{1}H NMR(300MHz,DMSO-d_6)δ8.57(d,J=3.3Hz,1H),8.36(d,J=7.5Hz,1H),7.58(s,1H),7.45(d,J=7.8Hz,1H),7.25-7.20(m,2H),7.16(s,1H),7.05(s,1H),4.17-4.15(m,2H),2.38-2.28(m,5H);ESI MS m/z 350[$C_{19}H_{15}N_3O_2S$+H]$^+$;

[1108] UPLC(方法A)>99%(AUC),t_R=3.30分钟;手性HPLC(Chiralpak AD,方法A)62.6%(AUC),t_R=17.28分钟。

[1109] (S)-3a-羟基-6-甲基-1-(噻吩并[2,3-b]吡啶-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1110] 

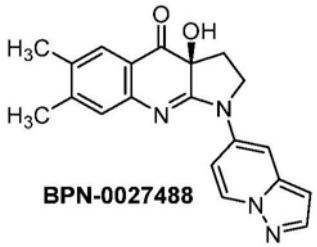
[1111] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6-甲基-1-(噻吩并[2,3-b]吡

啶-2-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=255至257℃;

[1112] ^{1}H NMR(300MHz,DMSO-d_6)δ8.42(dd,J=4.5,1.5Hz,1H),8.08(dd,J=8.1,1.5Hz,1H),7.57(s,1H),7.45(d,J=7.8Hz,1H),7.39(dd,J=7.8,4.5Hz,1H),7.25(d,J=7.8Hz,1H),7.02(d,J=7.8Hz,2H),4.14-4.06(m,2H),2.36-2.33(m,5H);ESI MS m/z 350 $[C_{19}H_{15}N_3O_2S+H]^+$;

[1113] UPLC(方法A)>99%(AUC),t_R=3.71分钟;手性HPLC(Chiralpak AD,方法A)61.0%(AUC),t_R=19.64分钟。

[1114] (S)-3a-羟基-6,7-二甲基-1-(吡唑并[1,5-a]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1115] 

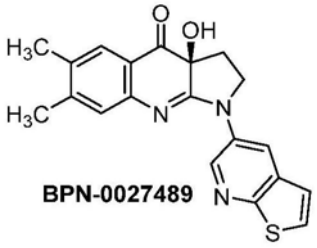
BPN-0027488

[1116] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(吡唑并[1,5-a]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=261至264℃;

[1117] ^{1}H NMR(300MHz,DMSO-d_6)δ8.70(d,J=7.8Hz,1H),8.17(d,J=2.1Hz,1H),8.01(dd,J=7.5,2.1Hz,1H),7.97(d,J=2.1Hz,1H),7.52(s,1H),7.13(s,1H),6.88(s,1H),6.56(d,J=2.1Hz,1H),4.08-3.99(m,2H),2.29(s,3H),2.26(表观s,2H),2.24(s,3H);ESI MS m/z 347$[C_{20}H_{18}N_4O_2+H]^+$;

[1118] UPLC(方法A)98.7%(AUC),t_R=3.02分钟;手性HPLC(Chiralpak AD,方法A)67.3%(AUC),t_R=18.70分钟。

[1119] (S)-3a-羟基-6,7-二甲基-1-(噻吩并[2,3-b]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1120] 

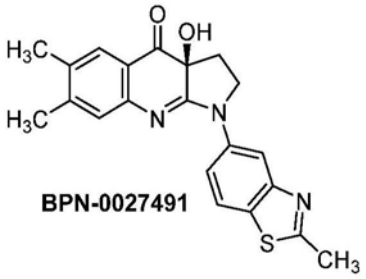
BPN-0027489

[1121] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(噻吩并[2,3-b]吡啶-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=237至241℃;

[1122] ^{1}H NMR(300MHz,DMSO-d_6)δ9.32(d,J=2.1Hz,1H),8.97(d,J=2.1Hz,1H),7.94(d,J=6.0Hz,1H),7.50(d,J=5.7Hz,2H),7.11(s,1H),6.88(s,1H),4.21-4.07(m,2H),2.32-2.28(m,5H),2.23(s,3H);ESI MS m/z 364$[C_{20}H_{17}N_3O_2S+H]^+$;

[1123] UPLC(方法A)>99%(AUC),t_R=3.16分钟;手性HPLC(Chiralpak AD,方法A)85.0%(AUC),t_R=18.22分钟。

[1124] (S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

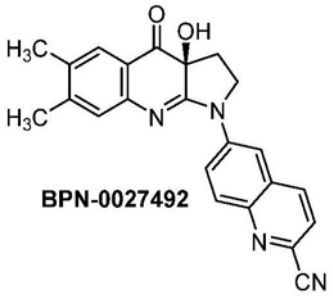
[1125] 

[1126] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噻唑-5-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=233至235℃;

[1127] ^{1}H NMR(300MHz,DMSO-d_6)δ8.75(d,J=2.1Hz,1H),8.12(dd,J=9.0,2.1Hz,1H),8.04(d,J=9.0Hz,1H),7.50(s,1H),7.10(s,1H),6.83(s,1H),4.19-4.02(m,2H),2.82(s,3H),2.29(表观s,5H),2.23(s,3H);ESI MS m/z 378[$C_{21}H_{19}N_3O_2S$+H]$^+$;

[1128] UPLC(方法A)96.9%(AUC),t_R=3.19分钟;手性HPLC(Chiralpak AD,方法A)84.9%(AUC),t_R=21.69分钟。

[1129] (S)-6-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)喹啉-2-甲腈的制备

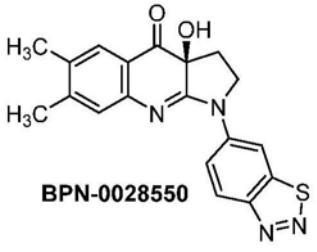
[1130] 

[1131] 根据合成方案6制备作为黄橙色固体的(S)-6-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)喹啉-2-甲腈:mp=272至274℃;

[1132] ^{1}H NMR(300MHz,DMSO-d_6)δ9.04(dd,J=9.6,2.4Hz,1H),8.63(d,J=8.4Hz,1H),8.58(d,J=2.4Hz,1H),8.19(d,J=9.3Hz,1H),8.02(d,J=8.7Hz,1H),7.54(s,1H),7.21(s,1H),6.93(s,1H),4.18-4.14(m,2H),2.33-2.31(m,5H),2.25(s,3H);ESI MS m/z 383[$C_{23}H_{18}N_4O_2$+H]$^+$;

[1133] UPLC(方法A)>99%(AUC),t_R=3.46分钟;手性HPLC(Chiralpak AD,方法A)89.5%(AUC),t_R=21.66分钟。

[1134] (S)-1-(苯并[d][1,2,3]噻二唑-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1135] 

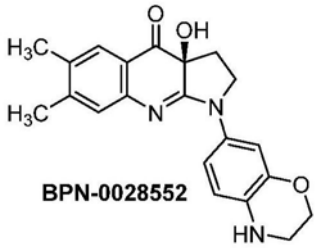
[1136] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d][1,2,3]噻二唑-6-基)-3a-

羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：

[1137] ^{1}H NMR(300MHz,DMSO-d_6)δ9.10(d,J＝1.8Hz,1H),8.74-8.64(m,2H),7.54(s,1H),7.22(s,1H),6.93(s,1H),4.18-4.13(m,2H),2.31(表观s,5H),2.25(s,3H);ESI MS m/z 365[$C_{19}H_{16}N_4O_2S$+H]$^+$;

[1138] UPLC(方法A)96.2%(AUC),t_R＝3.36分钟;手性HPLC(Chiralpak AD,方法A)50.7%(AUC),t_R＝18.41分钟。

[1139] (S)-1-(3,4-二氢-2H-苯并[b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1140] 

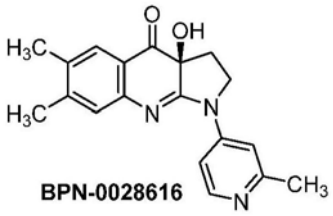
BPN-0028552

[1141] 根据合成方案4制备作为红橙色固体的(S)-1-(3,4-二氢-2H-苯并[b][1,4]噁嗪-7-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮：

[1142] ^{1}H NMR(300MHz,DMSO-d_6)δ7.57(d,J＝2.4Hz,1H),7.44(s,1H),7.21(dd,J＝8.4,2.7Hz,1H),6.96(s,1H),6.62(s,1H),6.58(d,J＝8.7Hz,1H),5.73(s,1H),4.14-4.13(m,2H),3.99-3.79(m,2H),3.30(表观s,2H),2.26(s,3H),2.25-2.20(m,5H);ESI MS m/z 364[$C_{21}H_{21}N_3O_3$+H]$^+$;

[1143] UPLC(方法A)96.7%(AUC),t_R＝3.16分钟;手性HPLC(Chiralpak AD,方法A)71.1%(AUC),t_R＝23.14分钟。

[1144] (S)-3a-羟基-6,7-二甲基-1-(2-甲基吡啶-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1145] 

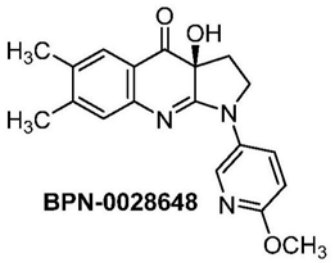
BPN-0028616

[1146] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基吡啶-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝265至267℃;

[1147] ^{1}H NMR(300MHz,DMSO-d_6)δ8.38(d,J＝6.0Hz,1H),8.03(dd,J＝6.0,2.4Hz,1H),7.85(d,J＝2.1Hz,1H),7.52(s,1H),7.16(s,1H),6.87(s,1H),4.04-3.94(m,2H),2.30(s,3H),2.28-2.24(m,1H),2.21(表观s,4H),被溶剂峰掩盖的3H;ESI MS m/z 322[$C_{19}H_{19}N_3O_2$+H]$^+$;UPLC

[1148] (方法A)95.1%(AUC),t_R＝3.17分钟;手性HPLC(Chiralpak AD,方法A)50.8%(AUC),t_R＝14.81分钟。

[1149] (S)-3a-羟基-1-(6-甲氧基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

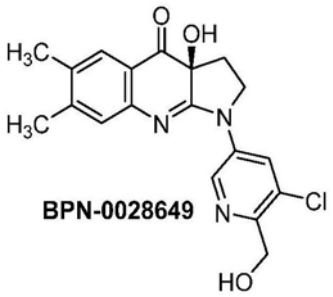
[1150] 

[1151] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(6-甲氧基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=213至216℃;

[1152] ^{1}H NMR(300MHz,DMSO-d_6)δ8.74(d,J=3.0Hz,1H),8.53(dd,J=9.0,2.7Hz,1H),7.48(s,1H),7.02(s,1H),6.91(d,J=9.3Hz,1H),6.80(s,1H),4.09-3.91(m,2H),3.87(s,3H),2.28-2.26(m,5H),2.21(s,3H);ESI MS m/z 338[$C_{19}H_{19}N_3O_3$+H]$^+$;

[1153] UPLC(方法A)>99%(AUC),t_R=2.97分钟;手性HPLC(Chiralpak AD,方法A)82.7%(AUC),t_R=15.44分钟。

[1154] (S)-1-(5-氯-6-(羟甲基)吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

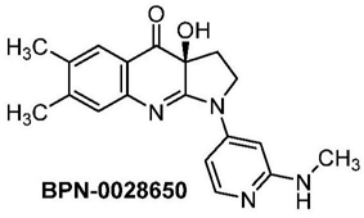
[1155] 

[1156] 根据合成方案6制备作为黄色固体的(S)-1-(5-氯-6-(羟甲基)吡啶-3-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=242至245℃;

[1157] ^{1}H NMR(300MHz,DMSO-d_6)δ9.10(d,J=2.1Hz,1H),8.83(d,J=2.4Hz,1H),7.52(s,1H),7.10(s,1H),6.89(s,1H),5.24(t,J=6.0Hz,1H),4.64(表观t,J=5.7Hz,2H),4.12-4.03(m,2H),2.30-2.27(m,5H),2.23(s,3H);ESI MS m/z 372[$C_{19}H_{18}ClN_3O_3$+H]$^+$;

[1158] UPLC(方法A)>99%(AUC),t_R=2.98分钟;手性HPLC(Chiralpak AD,方法A)62.9%(AUC),t_R=17.17分钟。

[1159] (S)-3a-羟基-6,7-二甲基-1-(2-(甲基氨基)吡啶-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1160] 

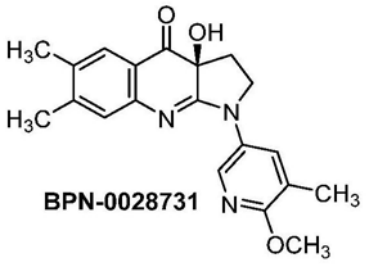
[1161] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-(甲基氨基)吡啶-4-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1162] ^{1}H NMR(300MHz,DMSO-d_6)δ7.93(d,J=6.0Hz,1H),7.51(s,1H),7.29(s,1H),7.22

(d,J＝5.7Hz,1H),7.11(s,1H),6.83(s,1H),6.61-6.40(m,1H),3.92(表观t,J＝6.0Hz,2H),2.79(d,J＝4.8Hz,3H),2.29(s,3H),2.24-2.18(m,5H);ESI MS m/z 337[$C_{19}H_{20}N_4O_2$+H]$^+$;

[1163] UPLC(方法A)95.5%(AUC),t_R＝3.22分钟;手性HPLC(Chiralpak AD,方法A)70.0%(AUC),t_R＝18.22分钟。

[1164] (S)-3a-羟基-1-(6-甲氧基-5-甲基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1165] 

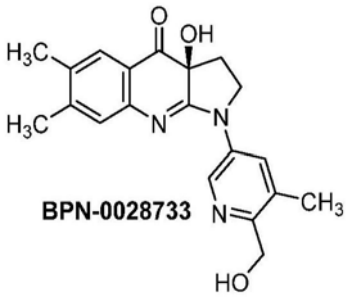
BPN-0028731

[1166] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(6-甲氧基-5-甲基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝195至199℃;

[1167] ^{1}H NMR(300MHz,DMSO-d_6)δ8.65(d,J＝2.4Hz,1H),8.29(s,1H),7.47(s,1H),7.03(s,1H),6.78(s,1H),4.07-3.93(m,2H),3.89(s,3H),2.26(表观s,5H),2.21(s,6H);ESI MS m/z 352[$C_{20}H_{21}N_3O_3$+H]$^+$;

[1168] UPLC(方法A)＞99%(AUC),t_R＝3.26分钟;手性HPLC(Chiralpak AD,方法A)81.1%(AUC),t_R＝13.45分钟。

[1169] (S)-3a-羟基-1-(6-(羟甲基)-5-甲基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1170] 

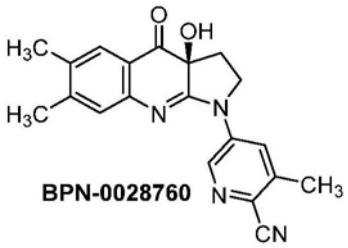
BPN-0028733

[1171] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(6-(羟甲基)-5-甲基吡啶-3-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝218至222℃;

[1172] ^{1}H NMR(300MHz.DMSO-d_6)δ9.07(d,J＝2.7Hz,1H),8.28(s,1H),7.50(s,1H),7.07(s,1H),6.83(s,1H),5.02(t,J＝5.4Hz,1H),4.57(d,J＝5.4Hz,2H),4.09-3.98(m,2H),2.39(s,3H),2.28(表观s,5H),2.23(s,3H);ESI MS m/z 352[$C_{20}H_{21}N_3O_3$+H]$^+$;

[1173] UPLC(方法A)98.3%(AUC),t_R＝2.89分钟;手性HPLC(Chiralpak AD,方法A)74.8%(AUC),t_R＝18.63分钟。

[1174] (S)-5-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-3-甲基吡啶腈的制备

[1175] 

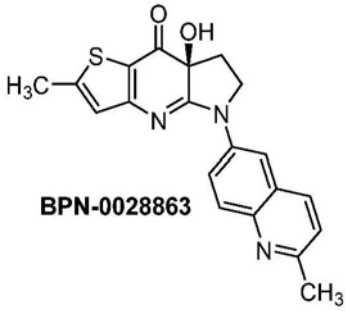
BPN-0028760

[1176] 根据合成方案6制备作为黄色固体的(S)-5-(3a-羟基-6,7-二甲基-4-氧代-2,3,3a,4-四氢-1H-吡咯并[2,3-b]喹啉-1-基)-3-甲基吡啶腈:mp=249至253℃;

[1177] ^{1}H NMR(300MHz,DMSO-d_6)δ9.41(d,J=2.4Hz,1H),8.58(d,J=2.1Hz,1H),7.54(s,1H),7.19(s,1H),6.94(s,1H),4.05(表观t,J=6.3Hz,2H),2.34(s,3H),2.30-2.27(m,5H),2.25(s,3H);ESI MS m/z 347[$C_{20}H_{18}N_4O_2$+H]$^+$;

[1178] UPLC(方法A)95.0%(AUC),t_R=3.91分钟;手性HPLC(Chiralpak AD,方法A)40.3%(AUC),t_R=17.33分钟。

[1179] (S)-7a-羟基-2-甲基-5-(2-甲基喹啉-6-基)-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮的制备

[1180] 

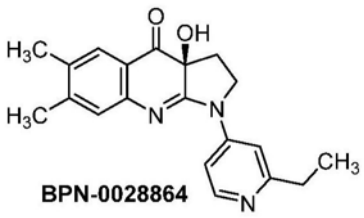
BPN-0028863

[1181] 根据合成方案3制备作为橙色固体的(S)-7a-羟基-2-甲基-5-(2-甲基喹啉-6-基)-5,6,7,7a-四氢-8H-吡咯并[2,3-b]噻吩并[2,3-e]吡啶-8-酮:mp=244至247℃;

[1182] ^{1}H NMR(300MHz,DMSO-d_6)δ8.61(dd,J=9.3,2.7Hz,1H),8.33(d,J=2.7Hz,1H),8.24(d,J=8.4Hz,1H),7.97(d,J=9.3Hz,1H),7.44(d,J=8.4Hz,1H),6.97(s,1H),6.88(d,J=1.2Hz,1H),4.29-4.12(m,2H),2.66(s,3H),2.36-2.25(m,2H),被溶剂峰掩盖的3H;ESI MS m/z 364[$C_{20}H_{17}N_3O_2S$+H]$^+$;

[1183] UPLC(方法A)98.8%(AUC),t_R=2.47分钟;手性HPLC(Chiralpak AD,方法A)91.2%(AUC),t_R=19.24分钟。

[1184] (S)-1-(2-乙基吡啶-4-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1185] 

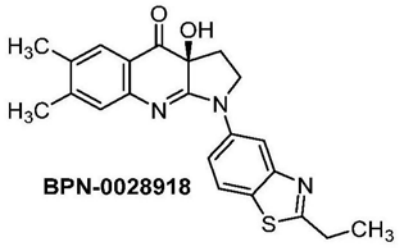
BPN-0028864

[1186] 根据合成方案6制备作为黄色固体的(S)-1-(2-乙基吡啶-4-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=269至270℃;

[1187] ^{1}H NMR(300MHz,DMSO-d_6)δ8.41(d,J＝5.7Hz,1H),7.99(dd,J＝5.7,2.4Hz,1H),7.91(d,J＝1.8Hz,1H),7.52(s,1H),7.15(s,1H),6.87(s,1H),4.04-3.95(m,2H),2.76(q,J＝7.5Hz,2H),2.30(s,3H),2.28-2.24(m,5H),1.26(t,J＝7.5Hz,3H);ESI MS m/z 336 $[C_{20}H_{21}N_3O_2+H]^+$;

[1188] UPLC(方法A)＞99％(AUC),t_R＝3.31分钟;手性HPLC(Chiralpak AD,方法A)65.4％(AUC),t_R＝13.92分钟。

[1189] (S)-1-(2-乙基苯并[d]噻唑-5-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1190] 

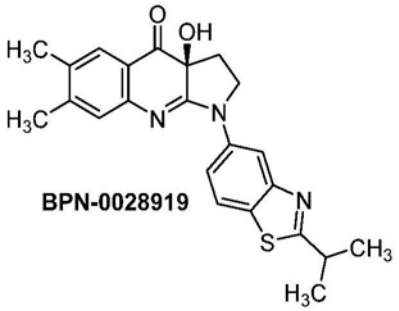
BPN-0028918

[1191] 根据合成方案6制备作为黄色固体的(S)-1-(2-乙基苯并[d]噻唑-5-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp＝232至235℃;

[1192] ^{1}H NMR(300MHz,DMSO-d_6)δ8.73(d,J＝2.1Hz,1H),8.16(dd,J＝9.0,2.4Hz,1H),8.06(d,J＝8.7Hz,1H),7.50(s,1H),7.10(s,1H),6.83(s,1H),4.19-4.02(m,2H),3.15(q,J＝7.2Hz,2H),2.29(m,5H),2.23(s,3H),1.40(t,J＝7.5Hz,3H);ESI MS m/z 392 $[C_{22}H_{21}N_3O_2S+H]^+$;

[1193] UPLC(方法A)＞99％(AUC),t_R＝3.45分钟;手性HPLC(Chiralpak AD,方法A)97.2％(AUC),t_R＝22.48分钟。

[1194] (S)-3a-羟基-1-(2-异丙基苯并[d]噻唑-5-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

[1195] 

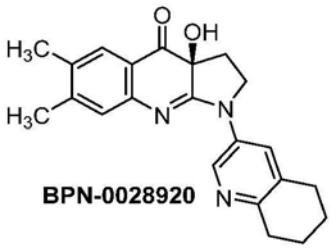
BPN-0028919

[1196] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(2-异丙基苯并[d]噻唑-5-基)-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1197] ^{1}H NMR(300MHz,DMSO-d_6)δ8.71(d,J＝2.1Hz,1H),8.20(dd,J＝8.7,2.1Hz,1H),8.07(d,J＝8.7Hz,1H),7.50(s,1H),7.10(s,1H),6.83(s,1H),4.16-4.02(m,2H),3.50-3.38(m,1H),2.29(m,5H),2.23(s,3H),1.44(s,3H),1.42(s,3H);ESI MS m/z 406 $[C_{23}H_{23}N_3O_2S+H]^+$;

[1198] UPLC(方法A)＞99％(AUC),t_R＝3.72分钟;手性HPLC(Chiralpak AD,方法A)95.4％(AUC),t_R＝20.82分钟。

[1199] (S)-3a-羟基-6,7-二甲基-1-(5,6,7,8-四氢喹啉-3-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

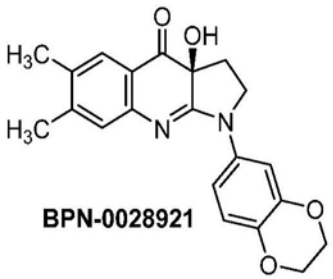
[1200] 

[1201] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(5,6,7,8-四氢喹啉-3-基)-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=243至248℃;

[1202] ^{1}H NMR(300MHz,DMSO-d_6)δ9.00(d,J=2.7Hz,1H),8.13(d,J=2.4Hz,1H),7.49(s,1H),7.03(s,1H),6.81(s,1H),4.06-3.91(m,2H),2.82-2.78(m,4H),2.33(s,5H),2.22(s,3H),1.84-1.76(m,4H);ESI MS m/z 362[$C_{22}H_{23}N_3O_2$+H]$^+$;

[1203] UPLC(方法A)>99%(AUC),t_R=3.23分钟;手性HPLC(Chiralpak AD,方法A)97.5%(AUC),t_R=15.36分钟。

[1204] (S)-1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

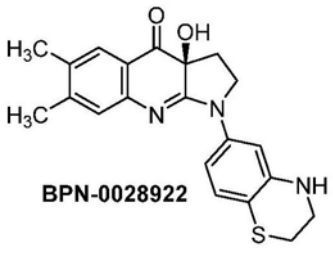
[1205] 

[1206] 根据合成方案6制备作为黄橙色固体的(S)-1-(2,3-二氢苯并[b][1,4]二噁英-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:mp=213至217℃;

[1207] ^{1}H NMR(300MHz,DMSO-d_6)δ7.80(d,J=2.7Hz,1H),7.46(s,1H),7.39(dd,J=9.0,2.7Hz,1H),7.00(s,1H),6.89(d,J=9.0Hz,1H),6.74(s,1H),4.27-4.26(m,4H),4.00-3.85(m,2H),2.28(s,5H),2.21(s,3H);ESI MS m/z 365[$C_{21}H_{20}N_2O_4$+H]$^+$;

[1208] UPLC(方法A)>99%(AUC),t_R=3.26分钟;手性HPLC(Chiralpak AD,方法A)95.9%(AUC),t_R=22.57分钟。

[1209] (S)-1-(3,4-二氢-2H-苯并[b][1,4]噻嗪-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮的制备

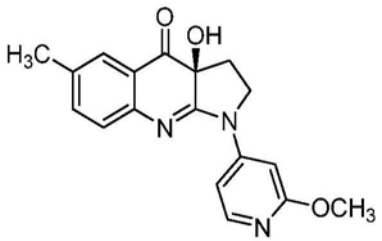
[1210] 

[1211] 根据合成方案6制备作为橙色固体的(S)-1-(3,4-二氢-2H-苯并[b][1,4]噻嗪-6-基)-3a-羟基-6,7-二甲基-1,2,3,3a-四氢-4H-吡咯并[2,3-b]喹啉-4-酮:

[1212] ^{1}H NMR(300MHz,DMSO-d_6)δ7.46(s,1H),7.36(d,J=2.4Hz,1H),7.12(dd,J=8.4,2.1Hz,1H),7.02(s,1H),6.86(d,J=8.4Hz,1H),6.72(s,1H),6.18(s,1H),3.95-3.82(m,2H),3.53-3.46(m,2H),2.99-2.96(m,2H),2.27(s,3H),2.21(s,5H);ESI MS m/z 380 $[C_{21}H_{21}N_3O_2S+H]^+$;

[1213] UPLC(方法A)98.5%(AUC),t_R=3.50分钟;手性HPLC(Chiralpak AD,方法A)95.3%(AUC),t_R=22.99分钟。

[1214] (S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1215] 

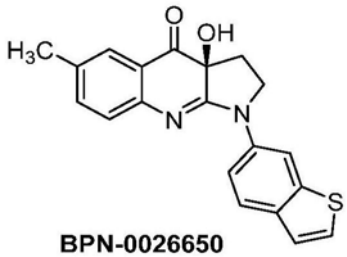
BPN-0025919

[1216] 根据合成方案4制备作为黄色固体的(S)-3a-羟基-1-(2-甲氧基吡啶-4-基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=229至230℃;

[1217] ^{1}H NMR(500MHz,$CDCl_3$)δ8.14(d,J=6.0Hz,1H),7.70(d,J=1.6Hz,1H),7.62(dd,J=6.0,1.9Hz,1H),7.42-7.39(m,2H),7.30(d,J=8.1Hz,1H),4.13-4.08(m,1H),3.98-3.92(m,4H),2.50(dd,J=14.0,5.9Hz,1H),2.36-2.27(m,4H),OH质子丢失;ESI MS m/z 324 $[C_{18}H_{17}N_3O_3+H]^+$;

[1218] HPLC(方法C)95.0%(AUC),t_R=12.46分钟;手性HPLC(Chiralpak AD,方法A)48.1%(AUC),t_R=15.26分钟。

[1219] (S)-1-(苯并[b]噻吩-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1220] 

BPN-0026650

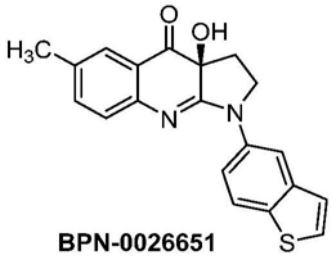
[1221] 根据合成方案5制备作为黄色固体的(S)-1-(苯并[b]噻吩-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=217至218℃;

[1222] ^{1}H NMR(500MHz,DMSO-d_6)δ8.74(d,J=1.9Hz,1H),8.16(dd,J=8.8,2.1Hz,1H),7.91(d,J=8.8Hz,1H),7.70(d,J=5.5Hz,1H),7.54(d,J=1.3Hz,1H),7.44-7.43(m,1H),7.39-7.37(m,1H),7.17(d,J=8.0Hz,1H),6.85(s,1H),4.17-4.12(m,1H),4.07-4.03(m,1H),2.31-2.28(m,5H);ESI MS m/z 349$[C_{20}H_{16}N_2O_2S+H]^+$;

[1223] HPLC(方法C)>99%(AUC),t_R=12.99分钟;手性HPLC(Chiralpak AD,方法A)>

99％(AUC)，t_R＝17.48分钟。

[1224] (S)-1-(苯并[b]噻吩-5-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1225] 

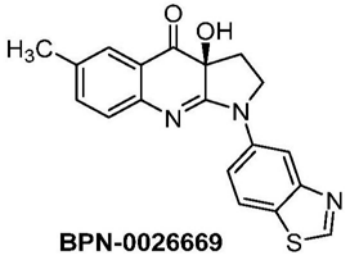
BPN-0026651

[1226] 根据合成方案5制备作为橙色固体的(S)-1-(苯并[b]噻吩-5-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝215至216℃；

[1227] ^{1}H NMR(500MHz,DMSO-d6)δ8.50(d,J＝2.1Hz,1H),8.20(dd,J＝8.9,2.1Hz,1H),8.03(d,J＝8.9Hz,1H),7.80(d,J＝5.4Hz,1H),7.54(d,J＝1.5Hz,1H),7.49(d,J＝5.4Hz,1H),7.38(d,J＝8.1,1.8Hz,1H),7.14(d,J＝8.1Hz,1H),6.85(s,1H),4.18-4.12(m,1H),4.05-4.02(m,1H),2.32-2.29(m,5H)；ESI MS m/z 349$[C_{20}H_{16}N_2O_2S+H]^+$；

[1228] HPLC(方法C)＞99％(AUC)，t_R＝13.35分钟；手性HPLC(Chiralpak AD,方法A)96.3％(AUC)，t_R＝21.69分钟。

[1229] (S)-1-(苯并[d]噻唑-5-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1230] 

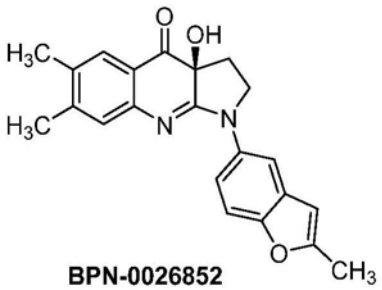
BPN-0026669

[1231] 根据合成方案4制备作为橙黄色固体的(S)-1-(苯并[d]噻唑-5-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝224至225℃；

[1232] ^{1}H NMR(500MHz,DMSO-d6)δ9.42(s,1H),8.83(d,J＝2.1Hz,1H),8.28(dd,J＝8.9,2.2Hz,1H),8.19(d,J＝8.9Hz,1H),7.55(d,J＝1.6Hz,1H),7.41-7.39(m,1H),7.17(d,J＝8.1Hz,1H),6.89(s,1H),4.20-4.15(m,1H),4.10-4.06(m,1H),2.34-2.27(m,5H)；ESI MS m/z 350$[C_{19}H_{15}N_3O_2S+H]^+$；

[1233] HPLC(方法C)＞99％(AUC)，t_R＝11.40分钟；手性HPLC(Chiralpak AD,方法A)＞99％(AUC)，t_R＝26.92分钟。

[1234] (S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并呋喃-5-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1235] 

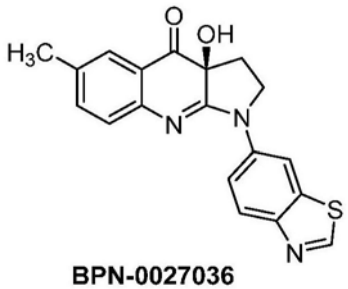
BPN-0026852

[1236] 根据合成方案5制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并呋喃-5-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=191至192℃;

[1237] ^{1}H NMR(500MHz,DMSO-d6)δ8.14(d,J=2.3Hz,1H),7.94(dd,J=9.0,2.3Hz,1H),7.52(d,J=9.0Hz,1H),7.47(s,1H),7.01(s,1H),6.74(s,1H),6.62(表观t,J=0.9Hz,1H),4.14-4.09(m,1H),3.98-3.94(m,1H),2.46(d,J=0.8Hz,3H),2.26-2.25(m,5H),2.21(s,3H);ESI MS m/z 361[$C_{22}H_{20}N_2O_3$+H]$^+$;

[1238] HPLC(方法A)96.6%(AUC),t_R=13.64分钟;手性HPLC(Chiralpak AD,方法A)81.8%(AUC),t_R=17.48分钟。

[1239] (S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1240] 

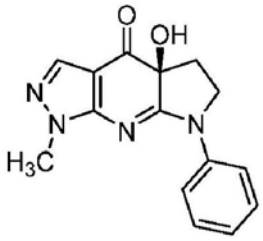
BPN-0027036

[1241] 根据合成方案6制备作为黄色固体的(S)-1-(苯并[d]噻唑-6-基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=225至226℃;

[1242] ^{1}H NMR(500MHz,DMSO-d6)δ9.32(s,1H),8.88(d,J=2.2Hz,1H),8.35(dd,J=9.0,2.3Hz,1H),8.12(d,J=9.0Hz,1H),7.55(d,J=1.7Hz,1H),7.40(dd,J=8.2,2.1Hz,1H),7.20(d,J=8.1Hz,1H),6.88(s,1H),4.18-4.13(m,1H),4.08-4.04(m,1H),2.33-2.29(m,5H);ESI MS m/z 350[$C_{19}H_{15}N_3O_2S$+H]$^+$;

[1243] HPLC(方法C)97.0%(AUC),t_R=11.57分钟;手性HPLC(Chiralpak AD,方法A)>99%(AUC),t_R=23.11分钟。

[1244] (S)-4a-羟基-1-甲基-7-苯基-4a,5,6,7-四氢吡唑并[3,4-b]吡咯并[3,2-e]吡啶-4(1H)-酮的制备

[1245] 

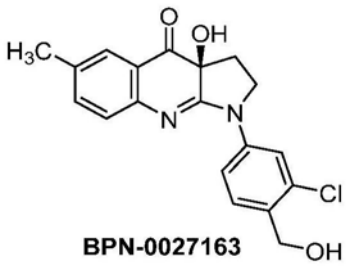
BPN-0027159

[1246] 根据合成方案2制备作为黄色固体的(S)-4a-羟基-1-甲基-7-苯基-4a,5,6,7-四氢吡唑并[3,4-b]吡咯并[3,2-e]吡啶-4(1H)-酮:mp＝244至245℃;

[1247] ^{1}H NMR(500MHz,DMSO-d6)δ8.01(d,J＝7.9Hz,2H),7.72(s,1H),7.49-7.46(m,2H),7.23(表观t,J＝7.4Hz,1H),6.84(s,1H),4.22-4.17(m,1H),4.07-4.04(m,1H),3.73(s,3H),2.26-2.14(m,2H);ESI MS m/z 283[$C_{15}H_{14}N_4O_2$+H]$^+$;

[1248] HPLC(方法C)＞99%(AUC),t_R＝12.99分钟;手性HPLC(Chiralpak AD,方法A)＞99%(AUC),t_R＝22.19分钟。

[1249] (S)-1-(3-氯-4-(羟甲基)苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1250] 

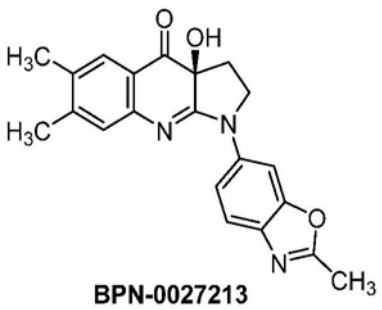
BPN-0027163

[1251] 根据合成方案6制备作为黄色固体的(S)-1-(3-氯-4-(羟甲基)苯基)-3a-羟基-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp＝199至200℃;

[1252] ^{1}H NMR(500MHz,DMSO-d6)δ8.40(d,J＝2.3Hz,1H),7.88(dd,J＝8.6,2.3Hz,1H),7.56-7.54(m,2H),7.40-7.38(m,1H),7.13(d,J＝8.1Hz,1H),6.85(s,1H),5.34(表观t,J＝5.6Hz,1H),4.56(d,J＝5.6Hz,2H),4.06-4.01(m,1H),3.99-3.95(m,1H),2.31(s,3H),2.29-2.24(m,2H);ESI MS m/z 357[$C_{19}H_{17}ClN_2O_3$+H]$^+$;

[1253] HPLC(方法C)98.9%(AUC),t_R＝11.91分钟;手性HPLC(Chiralpak AD,方法A)92.4%(AUC),t_R＝20.92分钟。

[1254] (S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噁唑-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1255] 

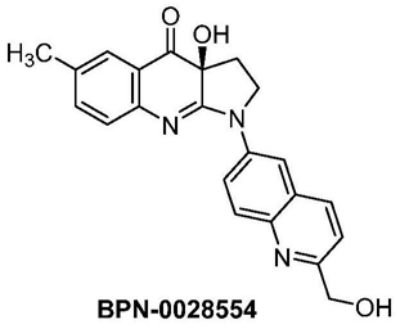
BPN-0027213

[1256] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-6,7-二甲基-1-(2-甲基苯并[d]噁唑-6-基)-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=205至209℃;

[1257] ^{1}H NMR(500MHz,DMSO-d6)δ8.66(d,J=2.0Hz,1H),7.90(dd,J=8.8,2.1Hz,1H),7.67(d,J=8.7Hz,1H),7.50(s,1H),7.09(s,1H),6.80(s,1H),4.14-4.09(m,1H),4.04-3.99(m,1H),2.62(s,3H),2.28-2.25(m,5H),2.23(s,3H);ESI MS m/z 362[$C_{21}H_{19}N_3O_3$+H]$^+$;

[1258] HPLC(方法C)90.8%(AUC),t_R=12.58分钟;手性HPLC(Chiralpak AD,方法A)79.2%(AUC),t_R=18.93分钟。

[1259] (S)-3a-羟基-1-(2-(羟甲基)喹啉-6-基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1260] 

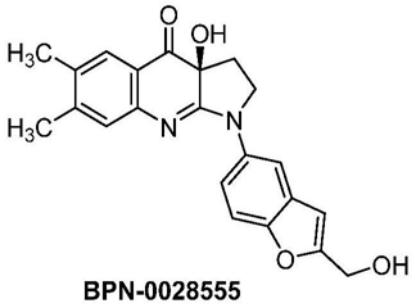
BPN-0028554

[1261] 根据合成方案6制备作为黄色固体的(S)-3a-羟基-1-(2-(羟甲基)喹啉-6-基)-6-甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=223至224℃;

[1262] ^{1}H NMR(300MHz,DMSO-d6)δ8.75(dd,J=9.3,2.6Hz,1H),8.46(d,J=2.4Hz,1H),8.36(d,J=8.5Hz,1H),8.00(d,J=9.3Hz,1H),7.66(d,J=8.5Hz,1H),7.56(d,J=2.1Hz,1H),7.43-7.40(m,1H),7.22(d,J=8.1Hz,1H),6.91(s,1H),),5.55(表观t,J=5.9Hz,1H),4.72(d,J=5.9Hz,2H),4.19-4.12(m,2H),2.36-2.27(m,5H);ESI MS m/z 374[$C_{22}H_{19}N_3O_3$+H]$^+$;

[1263] UPLC(方法A)97.9%(AUC),t_R=2.47分钟;手性HPLC(Chiralpak AD,方法A)91.6%(AUC),t_R=19.66分钟。

[1264] (S)-3a-羟基-1-(2-(羟甲基)苯并呋喃-5-基)-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮的制备

[1265] 

BPN-0028555

[1266] 根据合成方案6制备作为黄橙色固体的(S)-3a-羟基-1-(2-(羟甲基)苯并呋喃-5-基)-6,7-二甲基-3,3a-二氢-1H-吡咯并[2,3-b]喹啉-4(2H)-酮:mp=210至211℃;

[1267] ^{1}H NMR(300MHz,DMSO-d6)δ8.21(d,J=2.2Hz,1H),8.03(dd,J=9.0,2.3Hz,1H),7.58(d,J=9.0Hz,1H),7.48(s,1H),7.03(s,1H),6.80(d,J=0.7Hz,1H),6.78(s,1H),5.52-5.48(m,1H),4.58(d,J=5.7Hz,2H),4.17-4.09(m,1H),4.00-3.94(m,1H),2.26-2.22

(m,8H);ESI MS m/z 377[$C_{22}H_{20}N_2O_4$+H]$^+$;

[1268] UPLC(方法A)97.4%(AUC),t_R=3.05分钟;手性HPLC(Chiralpak AD,方法A)64.2%(AUC),t_R=24.05分钟。

[1269] 本文中提及的所有专利和出版物均以如同每个单独的出版物均明确地和单独地表明通过引用整体并入的相同程度通过引用并入本文。

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[1365] 本文中提及的所有专利和出版物均以如同每个单独的出版物均明确地和单独地

表明通过引用整体并入的相同程度通过引用并入本文。

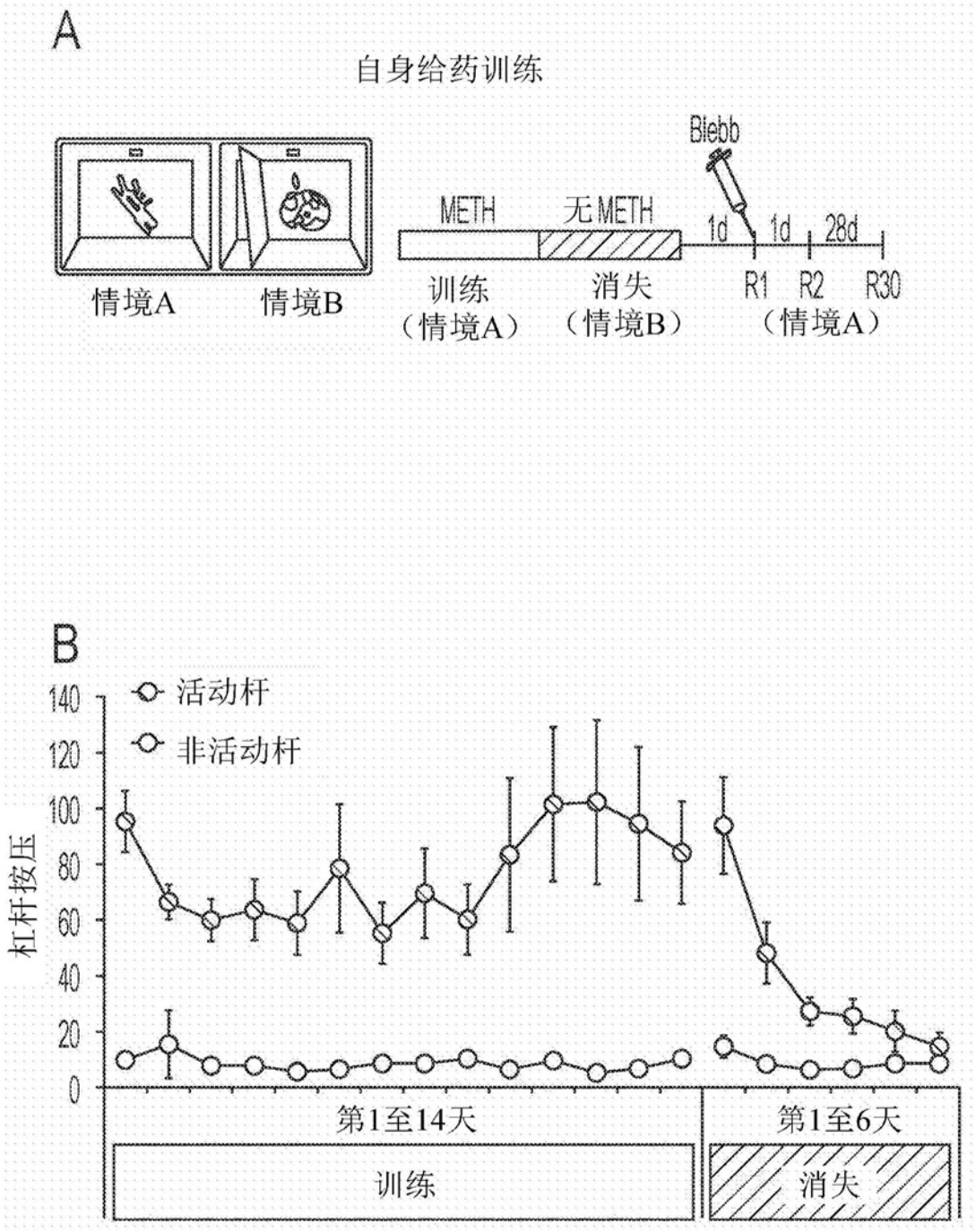

A
自身给药训练
Biebb
METH
无METH
1d
1d
28d
情境A
情境B
训练
（情境A）
消失
（情境B）
R1
R2
R30
（情境A）
B
活动杆
非活动杆
杠杆按压
140
120
100
80
60
40
20
0
第1至14天
第1至6天
训练
消失

图1

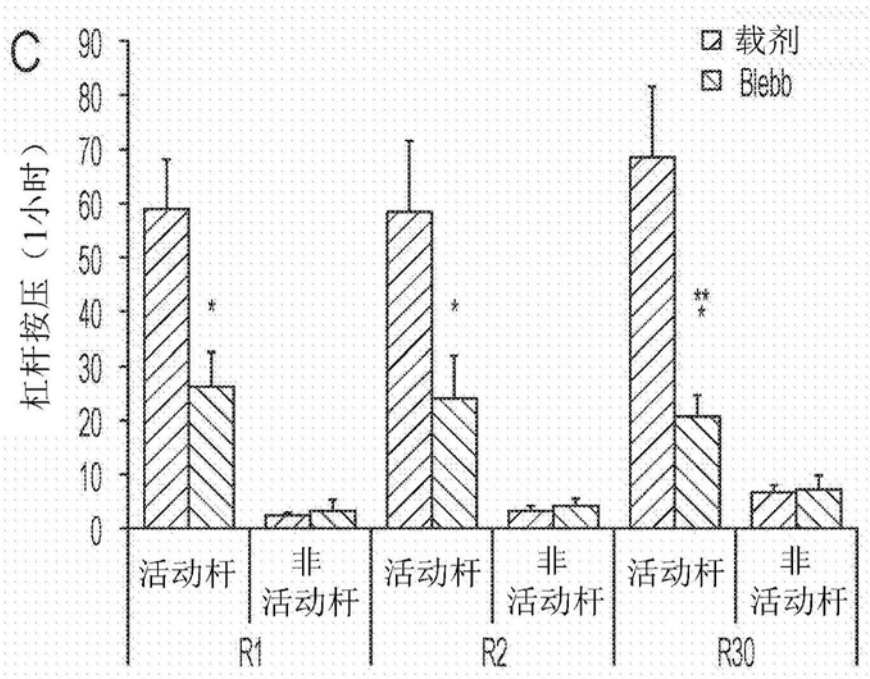

C
杠杆按压（1小时）
载剂
Blebb
活动杆
非活动杆
R1
R2
R30

图1(续)

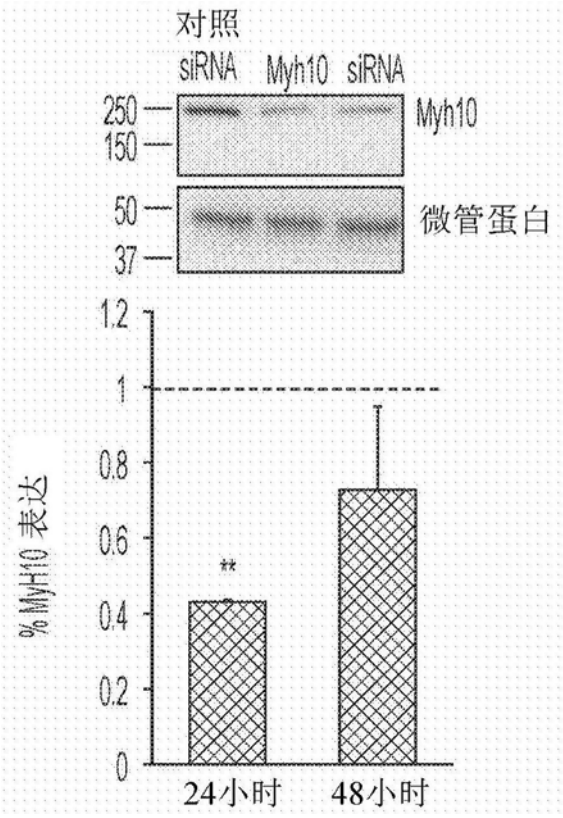

对照
siRNA
Myh10
siRNA
Myh10
微管蛋白
% Myh10 表达
24小时
48小时

图2A

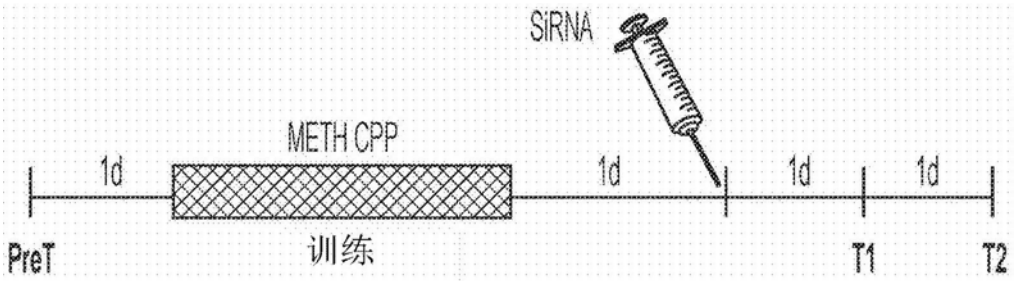

SiRNA
METH CPP
1d
1d
1d
1d
PreT
训练
T1
T2

图2B

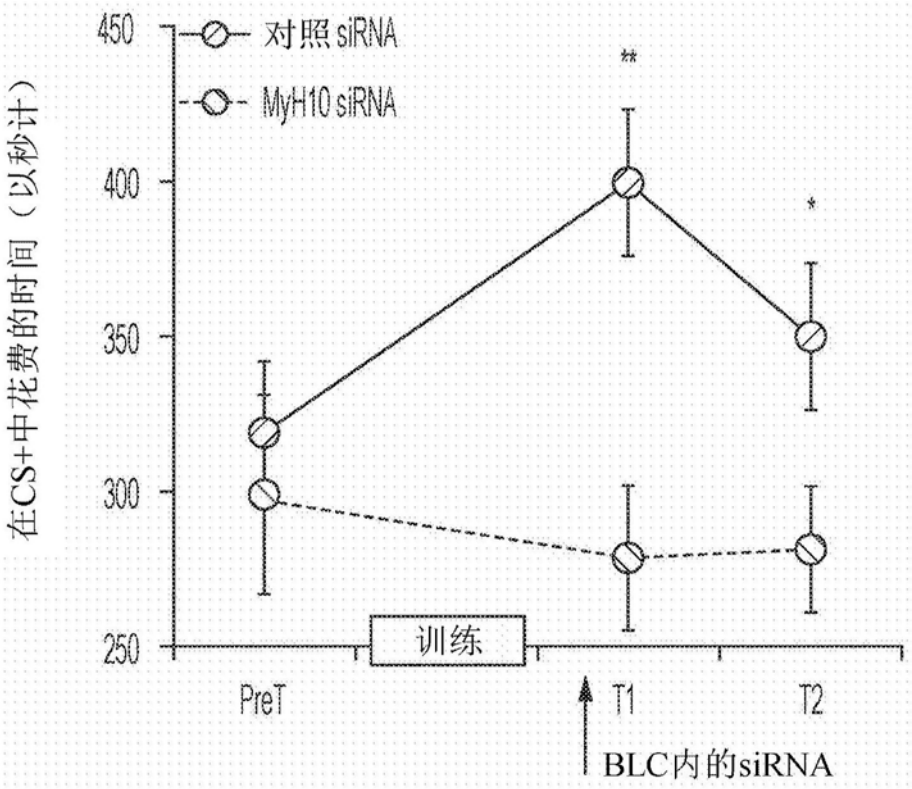

450
400
350
300
250
对照 siRNA
MyH10 siRNA
在CS+中花费的时间（以秒计）
**
*
训练
PreT
T1
T2
BLC内的siRNA

图2C

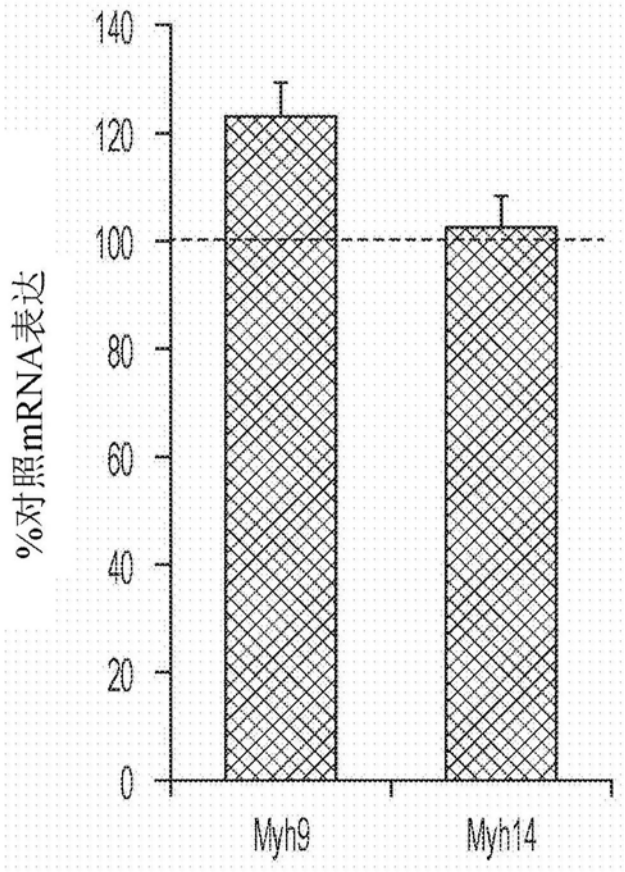


图2D

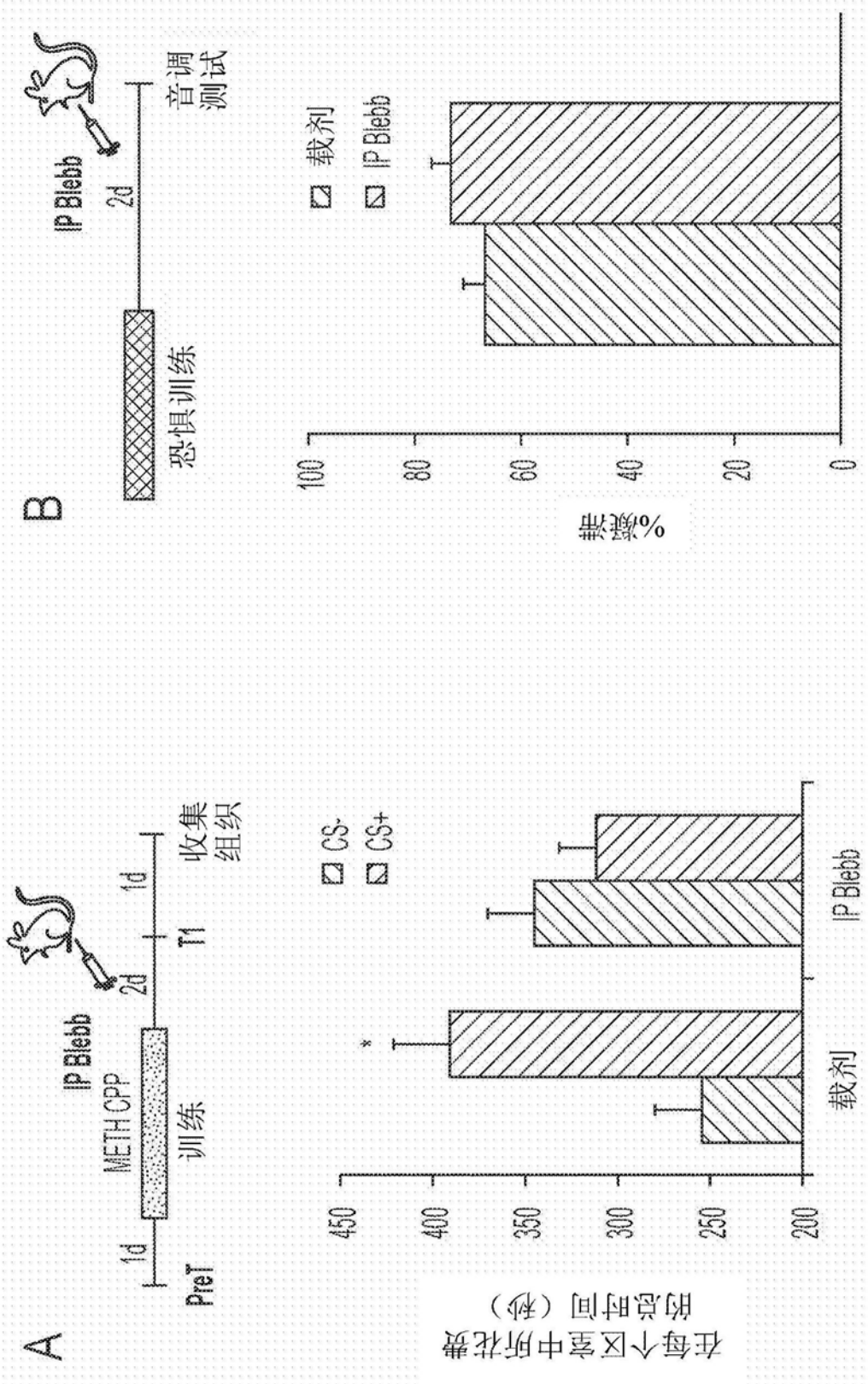

A
PreT
1d
训练
METH CPP
IP Blebb
2d
T1
1d
收集
组织
CS-
CS+
*
在每个区室中所花费
的总时间（秒）
450
400
350
300
250
200
载剂
IP Blebb
B
恐惧训练
IP Blebb
2d
音调
测试
载剂
IP Blebb
100
80
60
40
20
0
%凝滞

图3

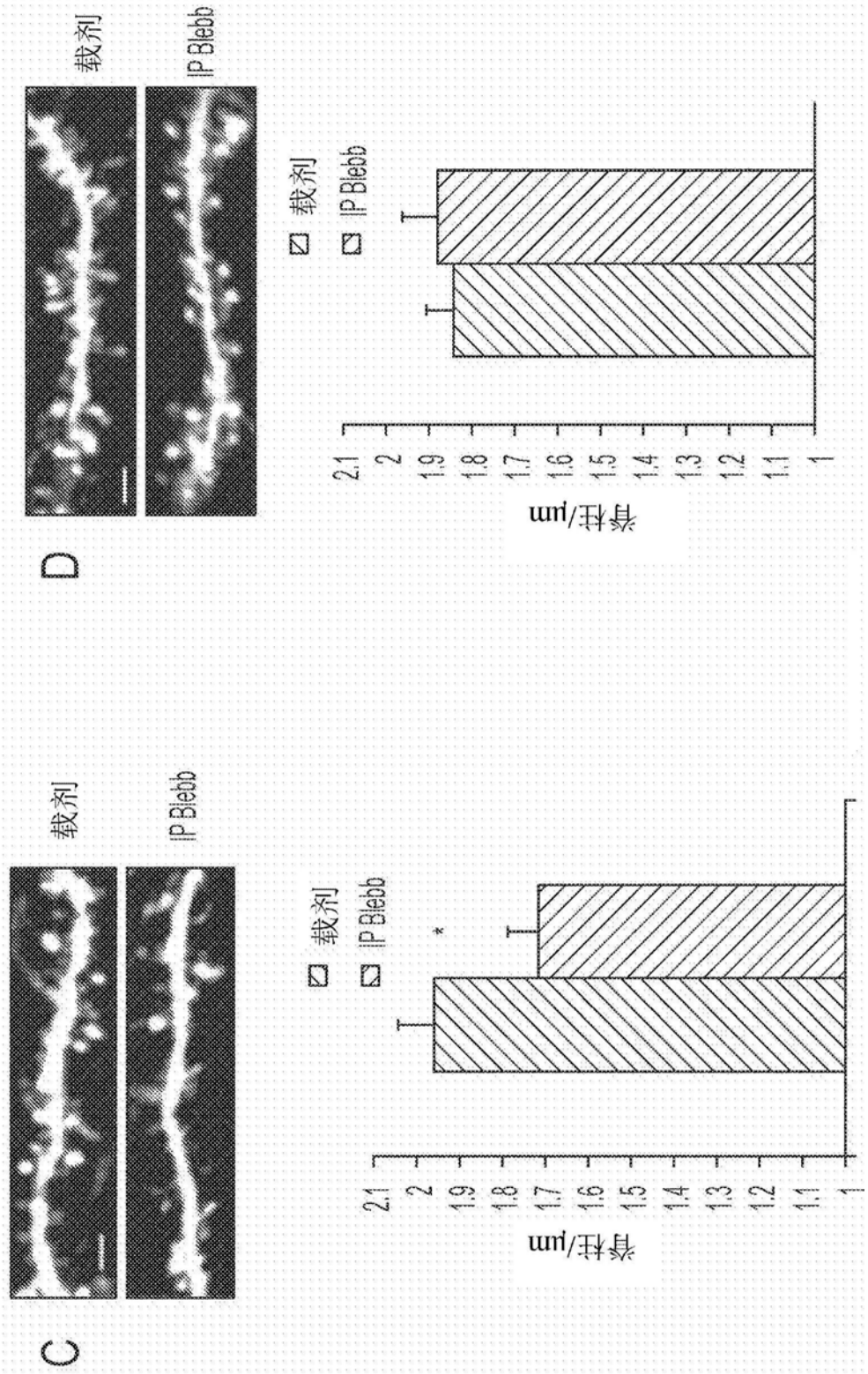

C
载剂
IP Blebb
载剂
IP Blebb
*
骨柱/μm
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
D
载剂
IP Blebb
载剂
IP Blebb
骨柱/μm
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1

图3(续)

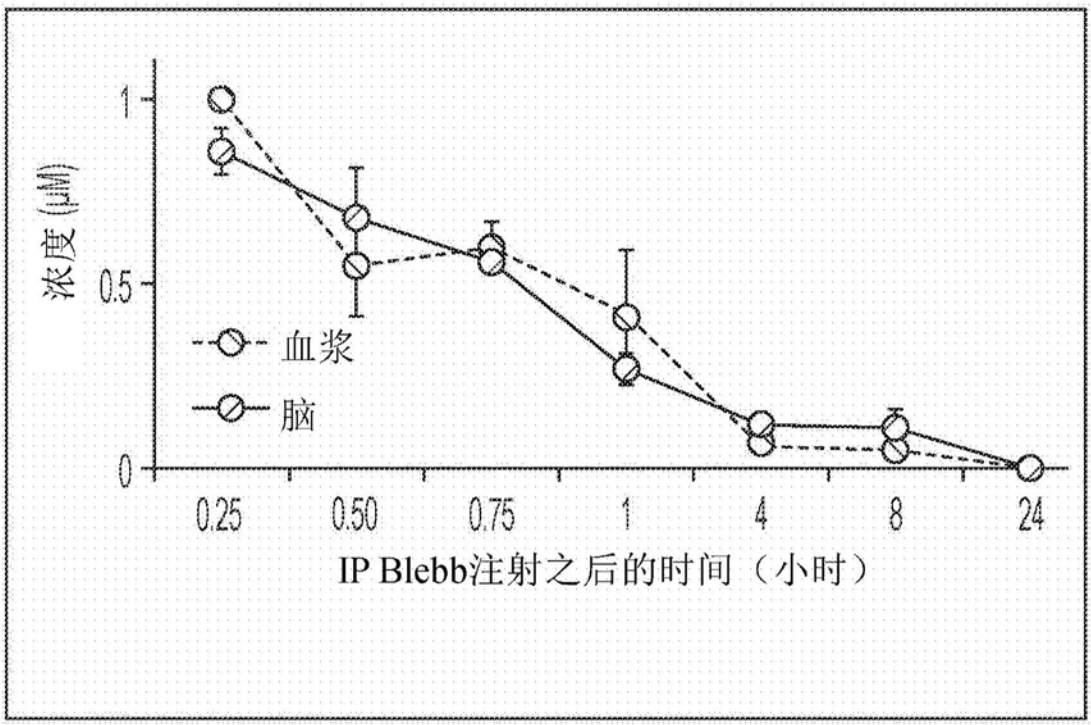

浓度 (μM)
1
0.5
0
血浆
脑
0.25
0.50
0.75
1
4
8
24
IP Blebb注射之后的时间（小时）

图4

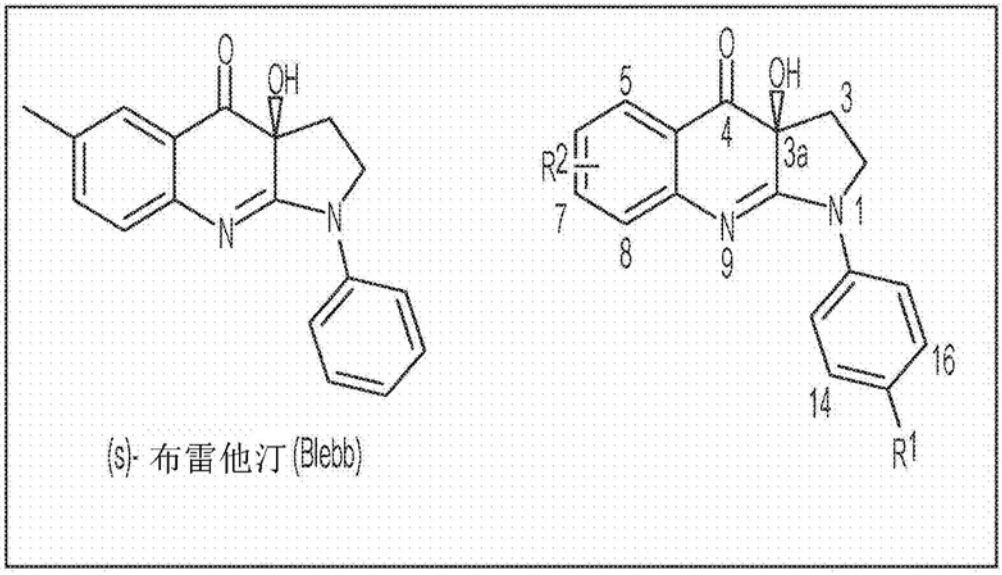

O
OH
N
N
(s)- 布雷他汀 (Blebb)
5
4
3
3a
R2
7
8
9
N
1
16
14
R1

图5

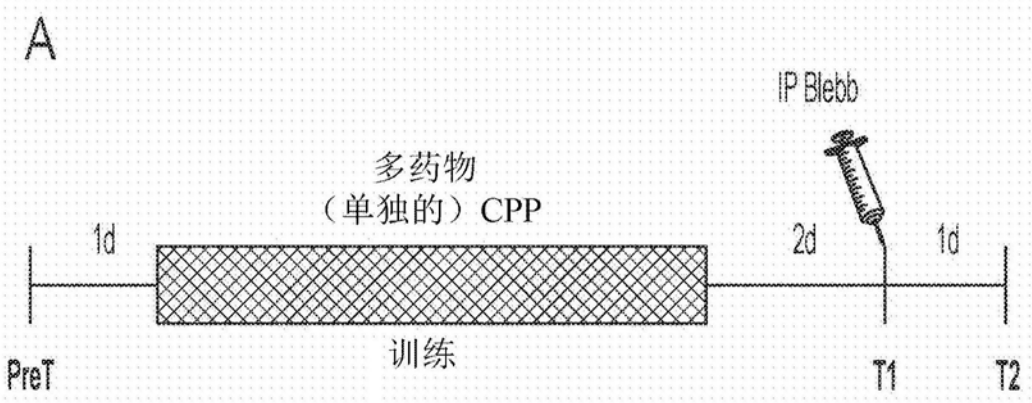


图6

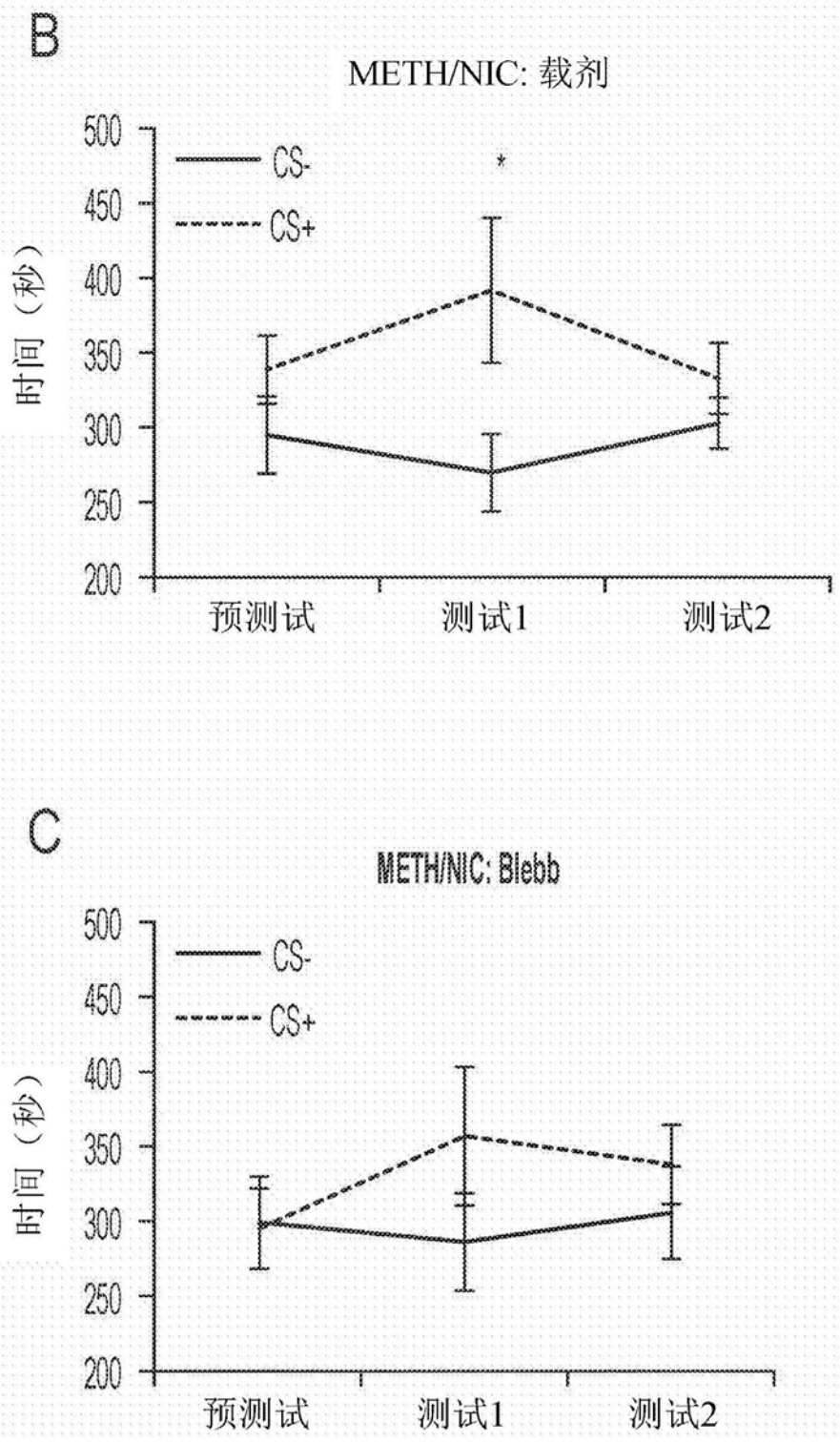

B
METH/NIC: 载剂
500
450
400
350
300
250
200
时间（秒）
CS-
CS+
*
预测试
测试1
测试2
C
METH/NIC: Blebb
500
450
400
350
300
250
200
时间（秒）
CS-
CS+
预测试
测试1
测试2

图6(续)

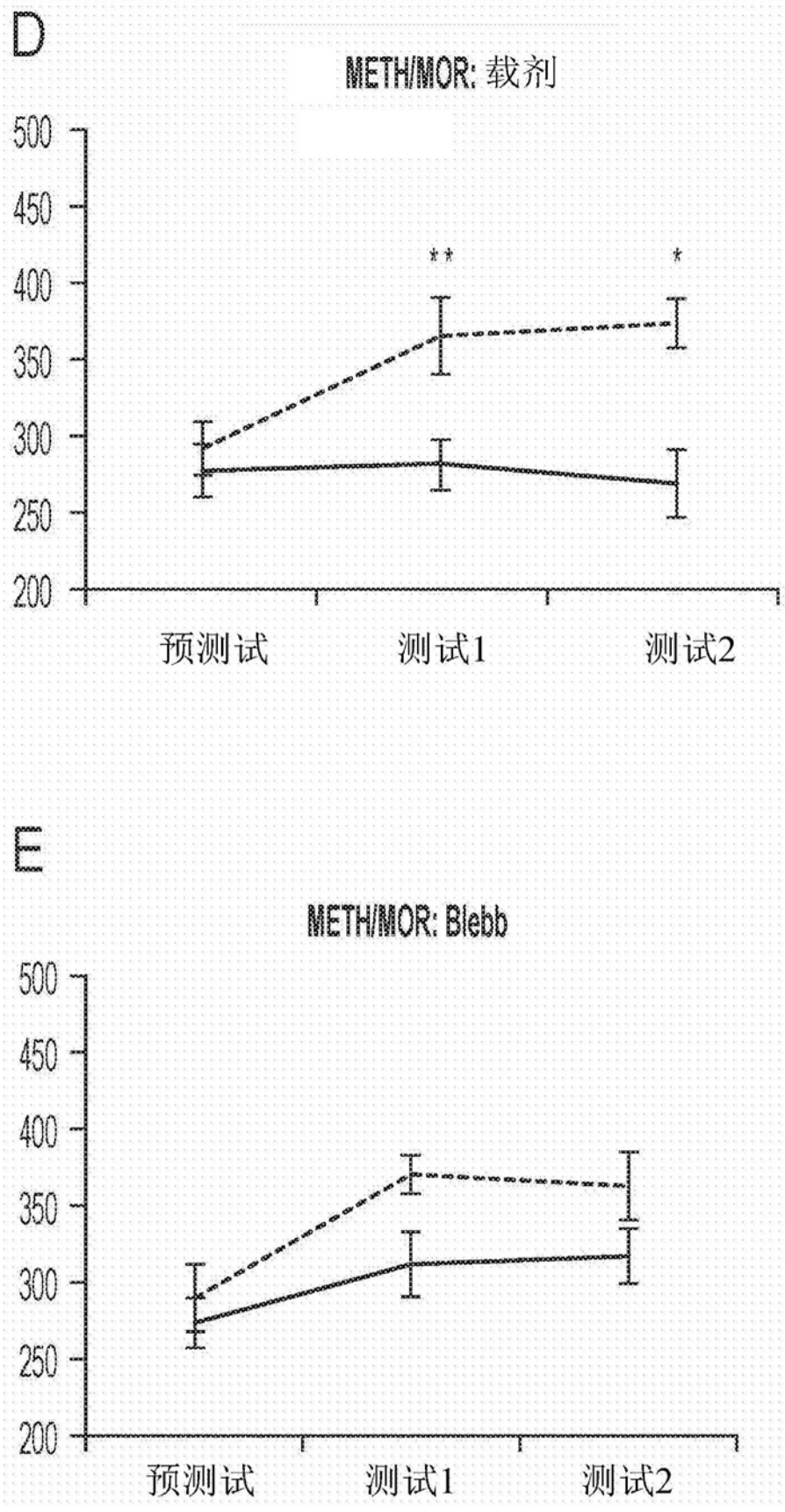

D
METH/MOR: 载剂
500
450
400
350
300
250
200
**
*
预测试
测试1
测试2
E
METH/MOR: Blebb
500
450
400
350
300
250
200
预测试
测试1
测试2

图6(续)

标识符	NMII (EC50 uM)	CMII (Ki uM)
布雷他汀	1.90	1.50
BPN-0026496	2.60	83.0
BPN-0026499	0.43	6.30

图7

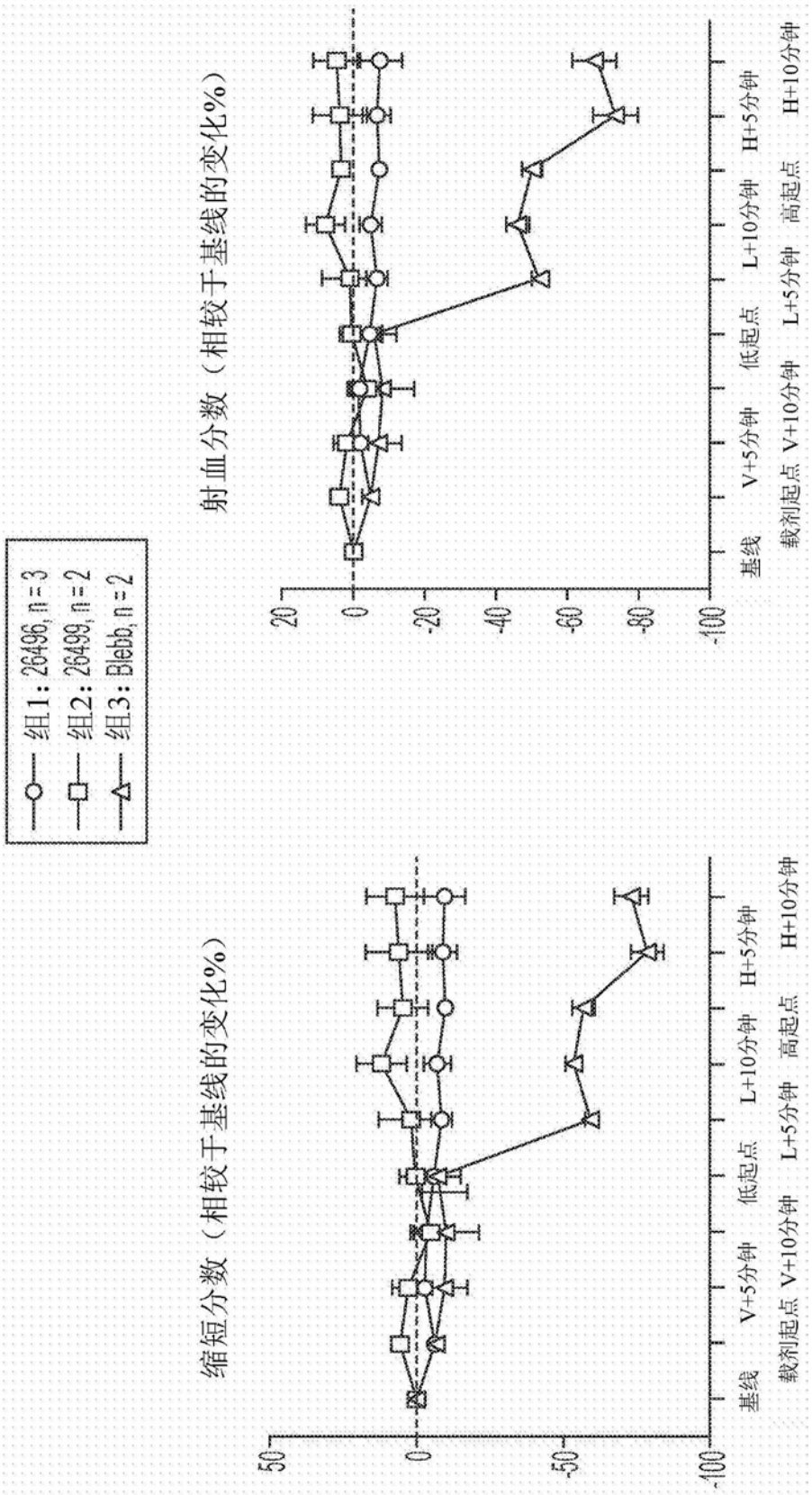

组1：26496, n=3
组2：26499, n=2
组3：Blebb, n=2
射血分数（相较于基线的变化%）
20
0
-20
-40
-60
-80
-100
基线
V+5分钟
低起点
L+10分钟
H+5分钟
载剂起点
V+10分钟
L+5分钟
高起点
H+10分钟
缩短分数（相较于基线的变化%）
50
0
-50
-100
基线
V+5分钟
低起点
L+10分钟
H+5分钟
载剂起点
V+10分钟
L+5分钟
高起点
H+10分钟

图7(续)

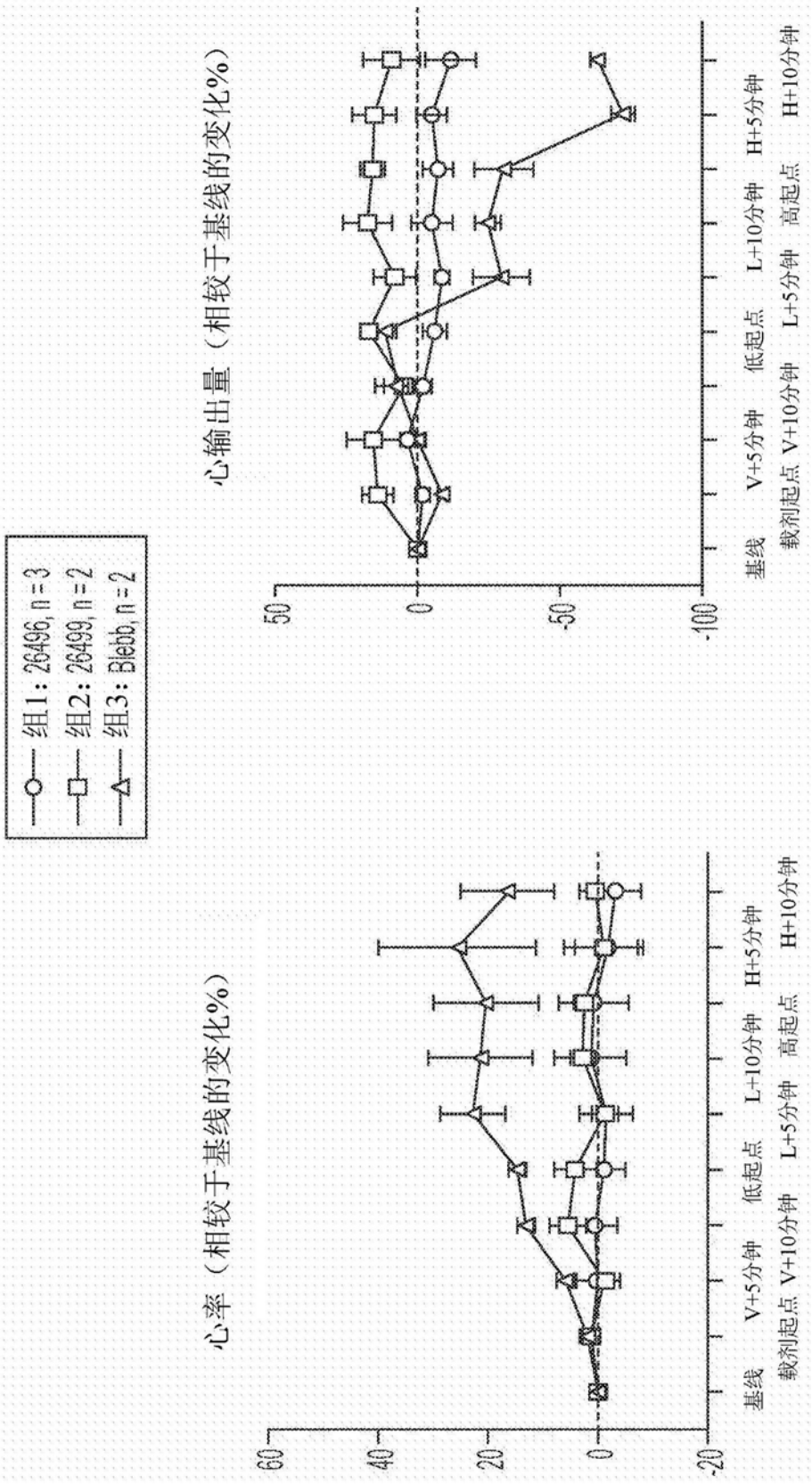

组1：26496, n = 3
组2：26499, n = 2
组3：Blebb, n = 2
心输出量（相较于基线的变化%）
50
0
-50
-100
基线
V+5分钟
低起点
L+10分钟
H+5分钟
载剂起点
V+10分钟
L+5分钟
高起点
H+10分钟
心率（相较于基线的变化%）
60
40
20
0
-20
基线
V+5分钟
低起点
L+10分钟
H+5分钟
载剂起点
V+10分钟
L+5分钟
高起点
H+10分钟

图7(续)