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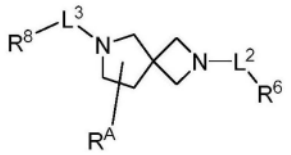
CDK2抑制剂及其使用方法

(57)摘要

本公开提供了化合物、其组合物以及将其用于抑制CDK2和治疗CDK2相关疾病和障碍的方法。

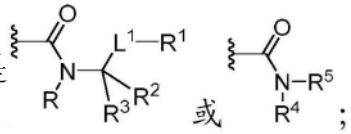
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1.一种化合物,其中所述化合物是式I的化合物:



I

或其药学上可接受的盐;其中:

R^A是;

L^1是共价键或饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链,其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-$NRS(O)_2$-、-$S(O)_2NR$-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

R^1是氢、任选取代的C_{1-6}脂族基团或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);

R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环或任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子);

R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);并且R^5是氢;或者R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了所述氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-$NRS(O)_2$-、-$S(O)_2NR$-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

R^6是任选取代的C_{1-6}脂族基团或选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有

1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中所述环状基团任选地用一个或多个R^7的实例取代;

R^7的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy;

L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^3的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-S(O)$_2$-、-C(S)-、-NRS(O)$_2$-、-S(O)$_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

R^8是选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中所述环状基团任选地用一个或多个R^9的实例取代;

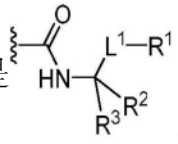
R^9的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy;

每个Cy独立地是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子);并且

每个R独立地是氢或任选取代的C_{1-6}脂族基团、任选取代的苯基、任选取代的3-7元饱和的或部分不饱和的碳环、任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)或任选取代的5-6元杂芳基环(含有1-4个独立地选自氮、氧和硫的杂原子);或

在所述相同氮上的两个R基团与介于它们之间的原子一起形成任选取代的4-7元饱和的、部分不饱和的或杂芳基环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

其中所述化合物不是6-(1-苄基-1H-吡唑-4-羰基)-N-(3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺。

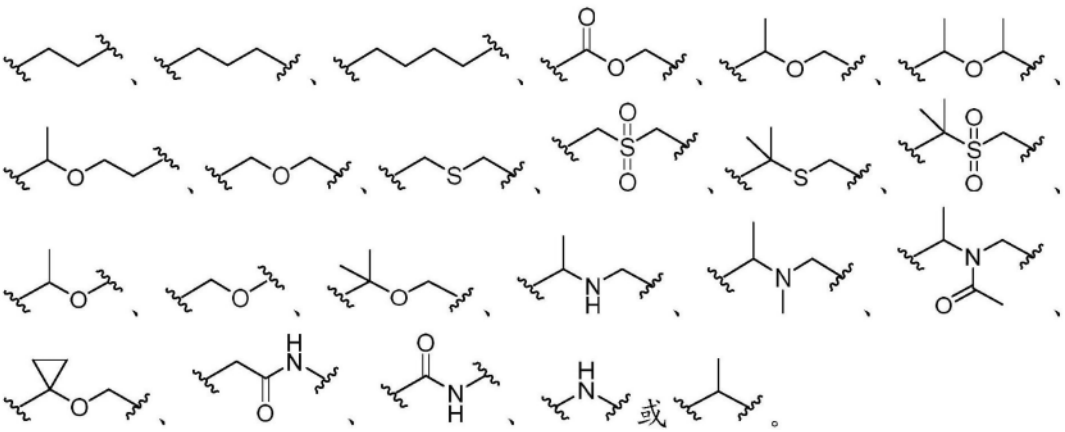
2.权利要求1所述的化合物,其中R^A是。

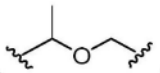
3.权利要求1-2任一项所述的化合物,其中L^1是共价键。

4.权利要求1-2任一项所述的化合物,其中L^1是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链,其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-S(O)$_2$-、-C(S)-、-NRS(O)$_2$-、-S(O)$_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。

5.权利要求1-2任一项所述的化合物,其中L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-S-、-C(O)O-、-C(O)-、-$S(O)_2$-或-NRC(O)-替代。

6.权利要求1-2任一项所述的化合物,其中L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。

7.权利要求1-2任一项所述的化合物,其中L^1是共价键、、或。

8.权利要求1-2任一项所述的化合物,其中L^1是。

9.权利要求1-8任一项所述的化合物,其中R^1是氢。

10.权利要求1-8任一项所述的化合物,其中R^1是任选取代的C_{1-6}脂族基团。

11.权利要求1-8任一项所述的化合物,其中R^1是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。

12.权利要求1-8任一项所述的化合物,其中R^1是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。

13.权利要求1-8任一项所述的化合物,其中R^1是选自以下的任选取代的环状基团:苯基、环己基、环戊基、环丁基、环丙基、环庚基、噁唑基、吡啶基、哒嗪基、1,3,4-噁二唑基、1,2,3-三唑基、吡唑基和四氢吡喃基。

14.权利要求1-8任一项所述的化合物,其中R^1是任选取代的环己基。

15.权利要求1-8任一项所述的化合物,其中R^1是任选取代的苯基。

16.权利要求1-15任一项所述的化合物,其中R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢。

17.权利要求1-15任一项所述的化合物,其中R^2是氢、甲基、-CH_2OR、-CH_2OCH_2R、-C(O)OR

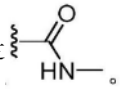
或-C(O)NR_2。

18.权利要求1-15任一项所述的化合物,其中R^2是-C(O)NR_2。

19.权利要求1-15任一项所述的化合物,其中R^2是-C(O)NR_2,其中所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

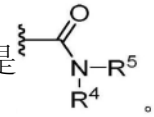
20.权利要求1-15任一项所述的化合物,其中R^2是-C(O)NR_2,其中所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环,其选自哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

21.权利要求1-15任一项所述的化合物,其中R^3是氢并且R^2是氢或表A的取代基。

22.权利要求1-15任一项所述的化合物,其中R^3是氢并且R^2是。

23.权利要求1-15任一项所述的化合物,其中R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环、或任选取代的3-7元饱和的或者部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。

24.权利要求1-15任一项所述的化合物,其中R^2和R^3与介于其间的碳原子一起形成任选取代的氧杂环丁烷基、环丙基、环丁基、环戊基、四氢吡喃基、哌啶基、哌嗪基、吗啉基、吡咯烷基或1,4-氧氮杂环庚基。

25.权利要求1所述的化合物,其中R^A是。

26.权利要求25所述的化合物,其中R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),并且R^5为氢。

27.权利要求25-26任一项所述的化合物,其中R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。

28.权利要求25-26任一项所述的化合物,其中R^4是选自以下的任选取代的环状基团:苯基、哌啶基、四氢吡喃基、1,4-氧氮杂环庚基、噁唑基、环丁基、环戊基或吡咯烷基。

29.权利要求25所述的化合物,其中R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了所述氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

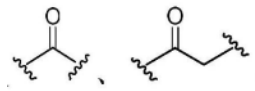
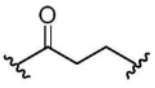
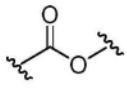
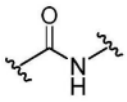
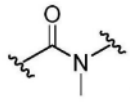
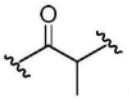
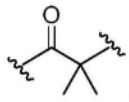
30.权利要求25所述的化合物,其中R^4和R^5与介于其间的氮原子一起形成选自以下的任选取代的环状基团:哌啶基、哌嗪基、吗啉基和吡咯烷基。

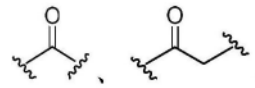
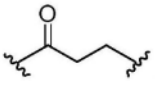
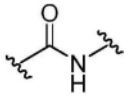
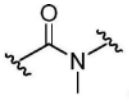
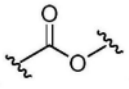
31.权利要求25、29和30任一项所述的化合物,其中通过R^4和R^5与介于其间的氮原子一起形成的所述环状基团被选自-C_{1-6}亚烷基-苯基、-O-C_{1-6}亚烷基-苯基、-C_{1-6}亚烷基-环已基

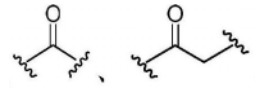
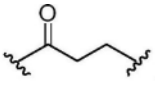
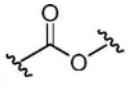
和-O-C_{1-6}亚烷基-环己基的基团取代。

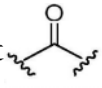
32.权利要求1所述的化合物,其中所述R^A是表A的取代基。

33.权利要求1-32任一项所述的化合物,其中L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-C(O)O-、-C(O)-或-C(O)NR-替代。

34.权利要求1-32任一项所述的化合物,其中L^2是、、、、、、、或。

35.权利要求1-32任一项所述的化合物,其中L^2是、、、、或。

36.权利要求1-32任一项所述的化合物,其中L^2是、、或。

37.权利要求1-32任一项所述的化合物,其中L^2是。

38.权利要求1-37任一项所述的化合物,其中R^6是任选取代的C_{1-6}脂族基团。

39.权利要求1-37任一项所述的化合物,其中R^6是任选地被一个或多个R^7的实例取代的苯基。

40.权利要求1-37任一项所述的化合物,其中R^6是任选地被一个或多个R^7的实例取代的3-8元饱和的或部分不饱和的单环碳环。

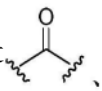
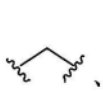
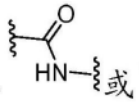
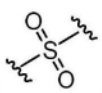
41.权利要求1-37任一项所述的化合物,其中R^6是任选地被一个或多个R^7的实例取代的环丙基基团。

42.权利要求1-37、39、40和41任一项所述的化合物,其中R^7的每个实例独立地是-F、甲基、乙基、异丙基、异丁基、-CN、任选取代的苯基、任选取代的苄基、$-CF_3$、$-CH_2OH$、$-CH_2OCH_3$、$-CH_2CH_2OCH_3$,$-CH_2CH_2F$、环丙基或$-CH_2-$(环丙基)。

43.权利要求1-32任一项所述的化合物,其中$-L^2-R^6$是表B的取代基。

44.权利要求1-43任一项所述的化合物,其中L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^3的0-2个亚甲基单元独立地被$-S(O)_2-$、-C(O)NR-或-C(O)-替代。

45.权利要求1-43任一项所述的化合物,其中L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}亚烷基链,其中L^3的0-2个亚甲基单元独立地被-C(O)O-或-C(O)-替代。

46.权利要求1-43任一项所述的化合物,其中L^3是、、或。

47.权利要求1-43任一项所述的化合物,其中L^3是。

48.权利要求1-47任一项所述的化合物,其中R^8是选自以下的环状基团:3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中所述环状基团任选地被一个或多个R^9的实例取代。

49.权利要求1-47任一项所述的化合物,其中R^8是选自以下的环状基团:吡唑基、噁唑基、噻唑基、吡咯烷基、四氢吡喃基、吡啶基、咪唑基、吲哚基、1,2,4-三唑基、1,2,4-噻二唑基、哌啶基和吲唑基,其中所述环状基团任选地被一个或多个R^9的实例取代。

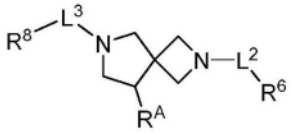
50.权利要求1-47任一项所述的化合物,其中R^8是任选地被一个或多个R^9的实例取代的吡唑基或噻唑基基团。

51.权利要求1-50任一项所述的化合物,其中R^9的每个实例独立地是卤素、任选取代的C_{1-6}脂族基团、任选取代的C_{1-6}脂族-Cy基团或Cy。

52.权利要求1-50任一项所述的化合物,其中R^9的每个实例独立地是任选取代的C_{1-6}脂族-Cy基团,其中所述Cy是选自以下的任选取代的基团:苯基、环己基、吡啶基、哌啶基、环丙基或四氢吡喃基。

53.权利要求1-44任一项所述的化合物,其中-L^3-R^8是表C的取代基。

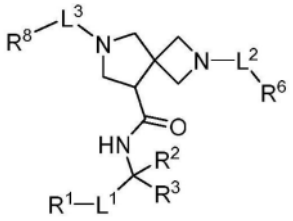
54.权利要求1所述的化合物,其中所述式I的化合物是式II的化合物:



II

或其药学上可接受的盐。

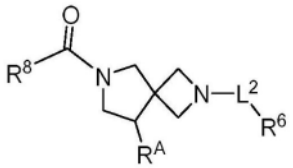
55.权利要求1所述的化合物,其中所述式I的化合物是式IIIa的化合物:



IIIa

或其药学上可接受的盐。

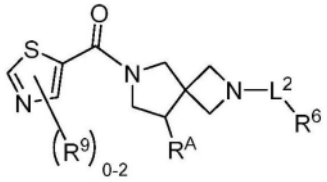
56.权利要求1所述的化合物,其中所述式I的化合物是式IVa的化合物:



IVa

或其药学上可接受的盐。

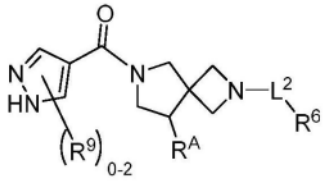
57.权利要求1所述的化合物,其中所述式I的化合物是式IVb的化合物:



IVb

或其药学上可接受的盐。

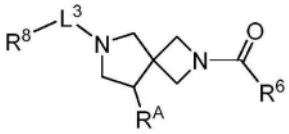
58.权利要求1所述的化合物,其中所述式I的化合物是式IVc的化合物:



IVc

或其药学上可接受的盐。

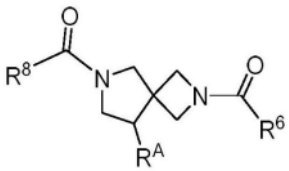
59.权利要求1所述的化合物,其中所述式I的化合物是式Va的化合物:



Va

或其药学上可接受的盐。

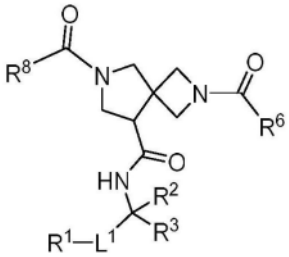
60.权利要求1所述的化合物,其中所述式I的化合物是式Vb的化合物:



Vb

或其药学上可接受的盐。

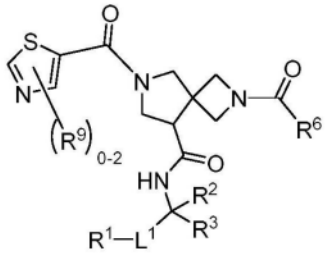
61.权利要求1所述的化合物,其中所述式I的化合物是式VIa的化合物:



VIa

或其药学上可接受的盐。

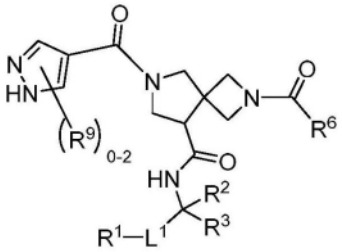
62.权利要求1所述的化合物,其中所述式I的化合物是式VIb的化合物:



VIb

或其药学上可接受的盐。

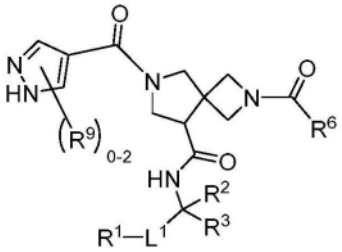
63.权利要求1所述的化合物,其中所述式I的化合物是式VIc的化合物:



VIc

或其药学上可接受的盐。

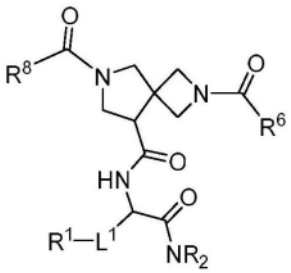
64.权利要求1所述的化合物,其中所述式I的化合物是式VIc的化合物:



VIc

或其药学上可接受的盐。

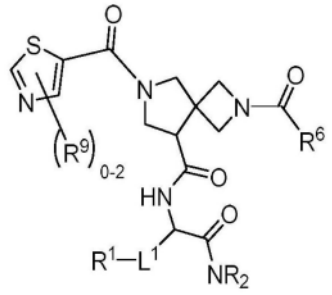
65.权利要求1所述的化合物,其中所述式I的化合物是式VIIa的化合物:



VIIa

或其药学上可接受的盐。

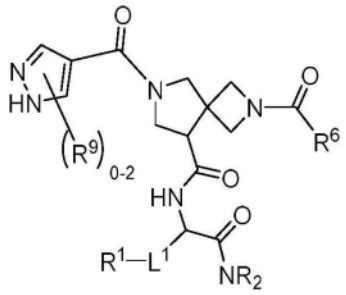
66.权利要求1所述的化合物,其中所述式I的化合物是式VIIb的化合物:



VIIb

或其药学上可接受的盐。

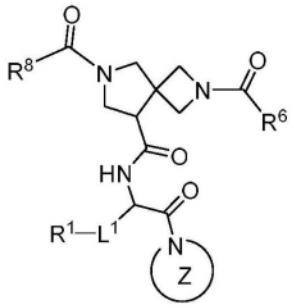
67.权利要求1所述的化合物,其中所述式I的化合物是式VIIc的化合物:



VIIc

或其药学上可接受的盐。

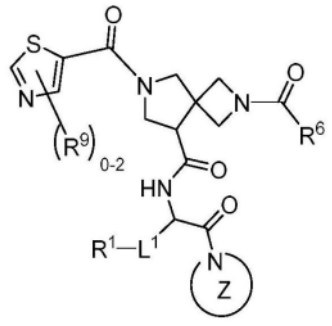
68.权利要求1所述的化合物,其中所述式I的化合物是式VIIIa的化合物:



VIIIa

或其药学上可接受的盐,其中环状部分Z由两个R基团形成,所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

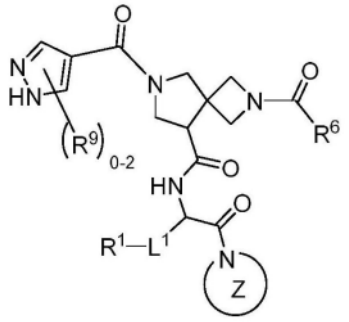
69.权利要求1所述的化合物,其中所述式I的化合物是式VIIIb的化合物:



VIIIb

或其药学上可接受的盐,其中环状部分Z由两个R基团形成,所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

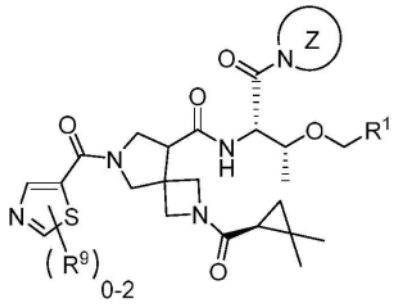
70.权利要求1所述的化合物,其中所述式I的化合物是式VIIIc的化合物:



VIIIc

或其药学上可接受的盐,其中环状部分Z由两个R基团形成,所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

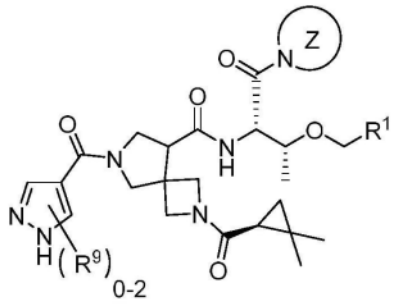
71.权利要求1所述的化合物,其中所述式I的化合物是式IXb*的化合物:



IXb*

或其药学上可接受的盐,其中环状部分Z由两个R基团形成,所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

72.权利要求1所述的化合物,其中所述式I的化合物是式IXc*的化合物:



IXc*

或其药学上可接受的盐,其中环状部分Z由两个R基团形成,所述两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了所述氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。

73.表1的化合物,或其药学上可接受的盐。

74.一种药学上可接受的组合物,其包含权利要求1-73任一项的化合物和药学上可接受的载体、赋形剂、媒介物、佐剂或稀释剂。

75.权利要求74所述的药学上可接受的组合物,其进一步包含额外的治疗剂。

76.抑制细胞周期蛋白依赖性激酶(CDK)活性的方法,其包含使权利要求1-73任一项的化合物与所述CDK接触。

77.在患者中治疗与CDK2活性相关的疾病或障碍的方法,其包含向所述有需要的患者施用权利要求1-73任一项的化合物或权利要求74-75任一项的药物组合物。

78.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍选自癌症、骨髓增生性障碍、自身免疫性障碍、炎症性障碍、病毒感染和纤维化障碍。

79.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是癌症。

80.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是癌症,其选自乳腺癌、卵巢癌、膀胱癌、子宫癌、前列腺癌、肺癌、食道癌、头颈癌、结直肠癌、肾癌、肝癌、胰腺癌、胃癌、黑色素瘤和甲状腺癌。

81.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是肝纤维化。

82.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是库欣病。

83.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是多囊肾病。

84.权利要求77所述的方法,其中所述与CDK2活性相关的疾病或障碍是阿尔茨海默氏病。

85.降低雄性生育能力的方法,包含向所述有需要的患者施用权利要求1-73中任一项的化合物或权利要求74-75中任一项的药物组合物。

CDK2抑制剂及其使用方法

发明领域

[0001] 本公开一般涉及抑制细胞周期蛋白依赖性激酶2(CDK2)的化学化合物及其在抑制CDK2活性中的用途。本公开还提供了包含本文公开的化合物的药学上可接受的组合物,以及在与CDK2活性有关的各种障碍的治疗中使用所述化合物和组合物的方法。

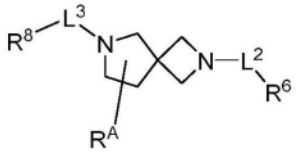
背景技术

[0002] 细胞周期失调(包括细胞生长失控、细胞分化受损和凋亡异常)已有表明是由细胞周期蛋白依赖性激酶(CDK)的过度活性引起的。CDK是重要的丝氨酸/苏氨酸蛋白激酶,其与特定的细胞周期蛋白搭配物结合时会变得活跃。CDK有多种亚型,每种亚型在细胞周期中都有不同的作用,在每个期都具有不同的活性水平。CDK1,CDK2,CDK4和CDK6已被发现是特别重要的亚型,其中一种或多种亚型的过度活性可能导致细胞周期失调和多种癌症的发展。细胞周期的S期负责DNA复制,是可能发生异常DNA复制的阶段。CDK2/细胞周期蛋白E复合物是细胞周期从G1期过渡到S期所必需的,CDK2/周期蛋白A复合物是细胞周期从S期过渡到G2期所必需。因此,CDK2/细胞周期蛋白E和/或CDK2/周期蛋白A复合物的选择性抑制可以阻止异常DNA复制,并可用于治疗某些癌症。

[0003] 因此,需要开发能够抑制CDK2/细胞周期蛋白复合物活性的化合物及其药物组合物,以预防和治疗CDK2相关疾病或障碍。

发明内容

[0004] 本公开至少部分基于结合和抑制细胞周期蛋白依赖性激酶2(CDK2)和/或CDK2/细胞周期蛋白复合物的化合物的识别以及使用其以治疗与CDK2活性相关的疾病的方法。本文公开了根据式I的化合物或其药学上可接受的盐:

[0005] 

I

[0006] 其中每个变量如本文所定义和描述的。

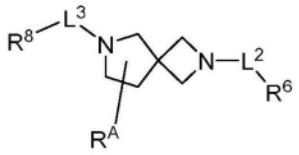
[0007] 本公开的化合物及其药学上可接受的组合物可用于治疗与CDK2活性相关的多种疾病、障碍或病症。这样的疾病、障碍或病症包括本文中描述的那些。

[0008] 某些实施方案的详细描述

[0009] 1.本公开的化合物的一般描述:

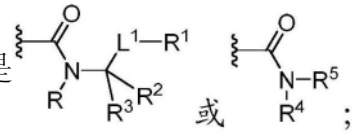
[0010] 本公开提供了能够抑制细胞周期蛋白依赖性激酶2(CDK2)和/或CDK2/细胞周期蛋白复合物的化合物。

[0011] 在一些实施方案中,本文提供是根据式I的化合物:

[0012] 

I

[0013] 或其药学上可接受的盐,其中:

[0014] R^A是;

[0015] L^1是共价键或饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链,其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS(O)$_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

[0016] R^1是氢、任选取代的C_{1-6}脂族基团或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);

[0017] R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环或任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子);

[0018] R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);并且R^5是氢;或者R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

[0019] L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS(O)$_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

[0020] R^6是任选取代的C_{1-6}脂族基团或选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳环杂环(含有1-5个独立地选

自氮、氧和硫的杂原子),其中该环状基团任选地用一个或多个R^7的实例取代;

[0021] R^7的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy;

[0022] L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^3的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-S(O)$_2$-、-C(S)-、-NRS(O)$_2$-、-S(O)$_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

[0023] R^8是选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中该环状基团任选地用一个或多个R^9的实例取代;

[0024] R^9的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy;

[0025] 每个Cy独立地是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子);并且

[0026] 每个R独立地是氢或任选取代的C_{1-6}脂族基团、任选取代的苯基、任选取代的3-7元饱和的或部分不饱和的碳环、任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)或任选取代的5-6元杂芳基环(含有1-4个独立地选自氮、氧和硫的杂原子);或

[0027] 在相同氮上的两个R基团与介于它们之间的原子一起形成任选取代的4-7元饱和的、部分不饱和的或杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

[0028] 其中所述化合物不是化合物X,其中化合物X在本文中定义。

[0029] CDK2的过度表达与细胞周期的异常调节有关。细胞周期蛋白E/CDK2复合物在G1/S过渡、组蛋白生物合成和中心体复制的调节中起着重要作用。通过细胞周期蛋白D/Cdk4/6和细胞周期蛋白E/Cdk2对视网膜母细胞瘤(Rb)的逐步磷酸化释放了G1转录因子、E2F,并促进了S期的进入。在S期早期,细胞周期蛋白A/CDK2的激活促进了内源性底物的磷酸化,从而允许DNA复制和E2F失活,以完成S期。(Asghar et al.,Nat.Rev.Drug.Discov.2015;14(2):130-146)。

[0030] 细胞周期蛋白E(CDK2的调节性细胞周期蛋白)在癌症中经常过度表达。细胞周期蛋白E扩增或过度表达长期与在乳腺癌中不好的结果相关。(Keyomarsi et al.,Cyclin E and survival in patients with breast cancer.N Engl JMed.(2002)347:1566-75)。细胞周期蛋白E2(CCNE2)的过度表达与在乳腺癌细胞中的内分泌抵抗有关,据报道,抑制CDK2可以在他莫昔芬耐药和CCNE2过度表达的细胞中恢复对他莫西芬或CDK4抑制剂的敏感性。

(Caldon et al.,Mol.Cancer Ther.(2012)11:1488-99;Herrera-Abreu et al.,Cancer Res.(2016)76:2301-2313)。据报道,细胞周期蛋白E的扩增也有助于在HER2+乳腺癌中的曲妥珠单抗的耐药。(Scaltriti et al.,Proc Natl Acad Sci.(2011)108:3761-6)。据报道,细胞周期蛋白E的过度表达也在基底样和三阴性乳腺癌(TNBC)以及炎症性乳腺癌中发挥作用。(Elsawaf&Sinn,Breast Care(2011)6:273-278;Alexander et al.,Oncotarget(2017)8:14897-14911.)。

[0031] 细胞周期蛋白E1(CCNE1)的扩增或过度表达也与在卵巢癌、胃癌、子宫内膜癌和其他癌症中的不好的结果有关。(Nakayama et al.,Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer,Cancer(2010)116:2621-34;Etemadmoghadam et al.,Clin Cancer Res(2013)19:5960-71;Au-Yeung et al.,Clin.Cancer Res.(2017)23:1862-1874;Ayhan et al.,Modern Pathology(2017)30:297-303;Ooi et al.,Hum Pathol.(2017)61:58-67;Noske et al.,Oncotarget(2017)8:14794-14805)。

[0032] 在本领域中仍然需要CDK抑制剂,尤其是选择性CDK2抑制剂,其可能有助于癌症或其他增殖性疾病或病症的治疗。特别是,CDK2抑制剂可在治疗CCNE1或CCNE2扩增的肿瘤中有用。

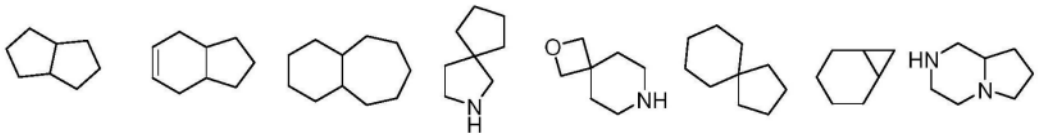
[0033] 2.化合物和定义:

[0034] 本公开的化合物包括本文一般描述的那些,并通过本文公开的类别、亚类和种类进一步说明。除非另有说明,如本文所用的以下定义应适用。就本公开而言,化学元素根据元素周期表(CAS版),化学和物理手册(101st Ed)进行识别。此外,有机化学的一般原则在“Organic Chemistry”,Thomas Sorrell,University Science Books,Sausalito:2005,以及“March's Advanced Organic Chemistry:Reactions Mechanisms and Structure”,8th Ed.,Ed.:Smith,M.B.,John Wiley&Sons,New York:2019中描述,其内容通过引用整体并入于此。

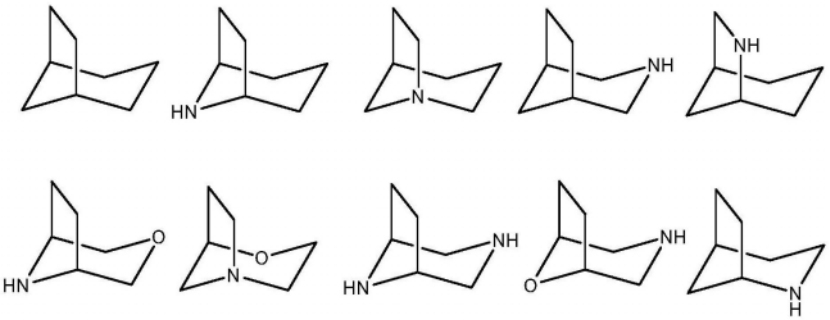
[0035] 本文使用的术语“脂族”或“脂族基团”指的是完全饱和的或含有一个或多个不饱和的单元的直链(即,非支链)或支链、取代或未取代的烃链,或者完全饱和的或含有一个或多个不饱和的单元的单环烃或双环烃,但其不是芳族(本文也称为“碳环”、“脂环族”或“环烷基”),其与分子的其余部分具有单一的连接点。除非另有规定,脂族基团包含1至6个脂族碳原子。在一些实施方案中,脂族基团包含1至5个脂族碳原子。在其它实施方案中,脂族基团包含1至4个脂族碳原子。在其它实施方案中,脂族基团包含1至3个脂族碳原子,并且在其它实施方案中,脂族基团包含1到2个脂族碳原子。在一些实施方案中,“脂环族”(或“碳环”或“环烷基”)指的是完全饱和的或包含一个或多个不饱和的单元但不是芳族的单环C_3-C_6烃,其与分子的其余部分具有单一的连接点。合适的脂族基团包括但不限于直链或支链、取代或未取代的烷基、烯基、炔基基团及其杂化物,例如(环烷基)烷基、(环烯基)烷基或(环烷基)烯基。

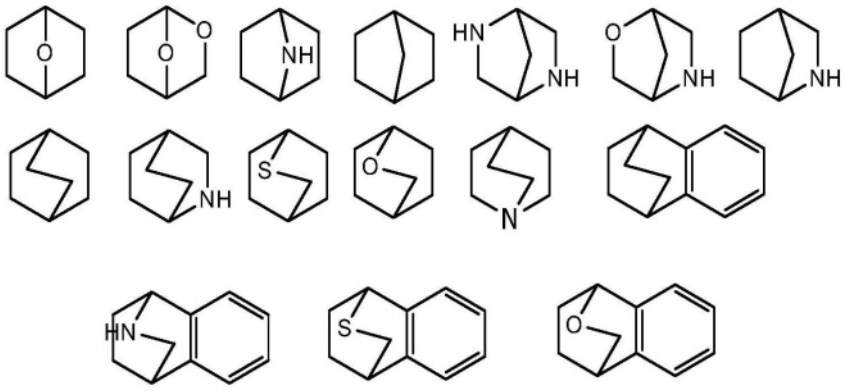
[0036] 如本文所用,术语“双环”或“双环体系”指的是在环体系的两个环之间具有一个或多个共同原子的任何双环体系(即碳环或杂环,饱和的或具有一个或多个不饱和的单元)。因此,该术语包括任何允许的环融合,例如邻位稠合的或螺环的。如本文所用,术语“杂双环”是“双环”的子集,其要求一个或多个杂原子存在于双环的一个或两个环中。这样的杂原

子可以存在于环连结处并且任选地被取代,并且可选自氮(包括N-氧化物)、氧、硫(包括氧化形式如砜类和磺酸盐)、磷(包括氧化形式如膦酸酯和磷酸酯)、硼等。在一些实施方案中,双环基团具有7-12个环成员和0-4个独立地选自氮、氧和硫的杂原子。如本文所用,术语"桥双环"指的是具有至少一个桥的任何双环体系(即碳环或杂环,饱和的或部分不饱和的)。如本文所用,"桥双环"环应理解为"双环"的子集,并落入"双环"范围内。根据IUPAC的定义,"桥"是连接两个桥头的无支链的原子链或原子或价键,其中"桥头"是与三个或更多骨架原子(不包括氢)结合的环体系的任何骨架原子。在一些实施方案中,桥双环基团具有7-12个环成员和0-4个独立地选自氮、氧和硫的杂原子。这样的桥双环基团在本领域中是众所周知的,并且包括下面列出的那些基团,其中每个基团在任何可取代的碳或氮原子处连接到分子的其余部分。除非另有规定,桥双环基团任选地被一个或多个如前所述的脂族基团取代基取代。此外或作为替代,桥双环基团的任何可取代的氮任选地被取代。示例性的双环包括:

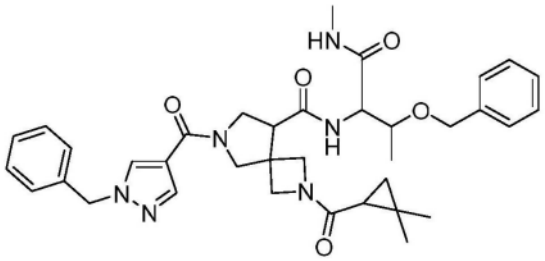
[0037] 

[0038] 被认为属于"双环"或"双环的环"的范围的示例性的桥双环包括:



[0039] 

[0040] 术语"化合物X"指的是6-(1-苄基-1H-吡唑-4-羰基)-N-(3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺。化合物X也可被描述为

[0041] 

[0042] 术语“低级烷基”指的是C_{1-4}直链或支链的烷基基团。示例性的低级烷基基团是甲基、乙基、丙基、异丙基、丁基、异丁基和叔丁基。

[0043] 术语“低级卤代烷基”指的是被一个或多个卤原子取代的C_{1-4}直链或支链的烷基基团。

[0044] 术语“杂原子”是指氧、硫、氮、磷或硅(包括氮、硫、磷或硅的任何氧化形式;任何碱性氮的季铵化形式;或在杂环中的氧、硫、氮、磷或硅原子)中的一个或多个。

[0045] 本文使用的术语“不饱和的”是指具有一个或多个不饱和的单元的部分。

[0046] 如本文所用,术语“二价C_{1-8}(或C_{1-6})饱和的或不饱和的、直链或支链烃链”指的是如本文所定义的直链或支链的二价亚烷基、亚烯基和亚炔基链。

[0047] 术语“亚烷基”指的是二价烷基基团。“亚烷基链”是多亚甲基基团(即-$(CH_2)_n$-),其中n是正整数,优选地为从1至6、从1至4、从1至3、从1至2或从2至3。取代的亚烷基链是其中一个或多个亚甲基氢原子被取代基取代的多亚甲基基团。合适的取代基包括下面描述的那些取代的脂族基团。

[0048] 术语“亚烯基”指的是二价烯基基团。取代的亚烯基链是含有至少一个双键的多亚甲基,其中一个或多个氢原子被取代基取代。合适的取代基包括下面描述的那些取代的脂族基团。

[0049] 术语“卤素”是指F、Cl、Br或I。

[0050] 术语“芳基”单独使用或作为较大部分如在“芳烷基”、“芳烷氧基”或“芳氧基烷基”中的一部分使用,其指的是总共具有4至14个环成员的单环或双环体系,其中在体系中至少有一个环是芳族,并且其中在体系中的每个环包含3至7个环成员。术语“芳基”可与术语“芳环”互换使用。在本公开的某些实施方案中,“芳基”指的是芳香环体系,其包括但不限于苯基、联苯基、萘基、蒽基等,其可带有一个或多个取代基。在本文所用术语“芳基”的范围内,还包括芳香环稠合至一个或多个非芳香环的基团,如茚基、邻苯二甲酰亚胺基、萘亚胺基(naphthimidyl)、菲啶基或四氢萘基等。

[0051] 术语“杂芳基”和“杂芳基-”单独使用或作为较大部分(例如“杂芳烷基”或“杂芳烷氧基”)的一部分使用,其是指具有5至10个环原子(优选地5、6或9个环原子)的基团;在环形阵列中共享6、10或14π电子;并且除碳原子外还具有1至5个杂原子。在“杂芳基”的上下文中的术语“杂原子”特别包括但不限于氮、氧或硫,并且包括氮或硫的任何氧化形式,以及碱性氮的任何季铵化形式。杂芳基基团包括不限于噻吩基、呋喃基、吡咯基、咪唑基、吡唑基、三唑基、四唑基、噁唑基、异噁唑基、噁二唑基、噻唑基、异噻唑基、噻二唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、中氮茚基、嘌呤基、萘啶基和蝶啶基。本文所用的术语“杂芳基”和“杂芳基-”还包括其中芳杂环稠合至一个或多个芳基、脂环族或杂环基环的基团,其中该基团或连接点位于芳杂环上。非限制性实例包括吲哚基、异吲哚基、苯并噻吩基、苯并呋喃基、二苯

并呋喃基、吲唑基、苯并咪唑基、苯并噻唑基、喹啉基、异喹啉基、噌啉基(cinnolinyl)、酞嗪基、喹唑啉基、喹喔啉基、4H-喹嗪基、咔唑基、吖啶基、吩嗪基、吩噻嗪基、吩噁嗪基、四氢喹啉基、四氢异喹啉基和吡啶并[2,3-b]-1,4-噁嗪-3(4H)-酮。杂芳基基团可以是单环或双环。杂芳基环可包含一个或多个氧代(=O)或硫代(=S)取代基。术语“杂芳基”可以与术语“杂芳基环”、“杂芳基基团”或“芳杂环”互换使用,任何该术语都包括任选被取代的环。术语“杂芳烷基”指的是被杂芳基取代的烷基基团,其中烷基和杂芳基部分独立地任选被取代。

[0052] 如本文所用,术语“杂环”、“杂环基”和“杂环基团”可互换使用,并且指的是饱和的或部分不饱和的稳定的5至7元单环或7至10元双环杂环部分,并且除碳原子外还含有一个或多个(优选地1至4个)杂原子(如上文所定义的)。当用于提及杂环的环原子时,术语“氮”包括取代的氮。作为实例,在饱和的或部分不饱和的环(含有0至3个选自氧、硫和氮的杂原子)中。

[0053] 杂环可以在产生稳定结构的任何杂原子或碳原子处连接至所提供的化合物,并且任何环原子可以任选被取代。此类饱和的或部分不饱和的杂环基团的实例包括不限于四氢呋喃基、四氢噻吩基吡咯烷基、哌啶基、吡咯啉基、四氢喹啉基、四氢异喹啉基、十氢喹啉基、噁唑烷基、哌嗪基、二噁烷基、二氧戊环基、二氮杂环庚三烯基、氧杂氮杂环庚三烯基(oxazepinyl)、硫氮杂环庚三烯基、吗啉基和奎宁环基。术语“杂环”、“杂环基”、“杂环基环”、“杂环基基团”、“杂环部分”和“杂环基团”在本文中可互换使用,并且还包括其中杂环基环稠合至一个或多个芳基、杂芳基或脂环族环的基团,例如二氢吲哚基、3H-吲哚基、苯并二氢吡喃基、菲啶基或四氢喹啉基。杂环基基团可以是单环或双环、桥双环或螺环。杂环可包含一个或多个氧代(=O)或硫代(=S)取代基。术语“杂环基烷基”指的是被杂环基取代的烷基基团,其中烷基和杂环基部分独立地任选被取代。

[0054] 如本文所用,术语“部分不饱和的”指的是包括至少一个双键或三键的环部分。术语“部分不饱和的”旨在包含具有多个不饱和的位点的环,但不旨在包括如本文定义的芳基或杂芳基部分。

[0055] 如本文所述,本公开的化合物可包含“取代的”部分。通常,术语“取代的”是指指定部分的一个或多个氢被合适的取代基替代。除非另有说明,“任选取代的”基团可以在该基团的一个或多个可取代位置具有合适的取代基,并且当任何给定结构中的一个以上位置被一个以上选自特定基团的取代基取代时,该取代基在每个位置上可以相同或不同。本公开所设想的取代基的组合优选地是导致形成稳定或化学上可行的那些化合物。本文所用的术语“稳定的”指的是当经受允许它们的生产、检测,以及在某些实施方案中,它们的回收、纯化和用于本文所公开的一个或多个目的的条件时基本上没有改变的化合物。

[0056] 在“任选取代的”基团的可取代碳原子上的合适的一价取代基独立地是卤素;-$(CH_2)_{0-6}R^o$;-$(CH_2)_{0-6}OR^o$;-O$(CH_2)_{0-6}R^o$,-O-$(CH_2)_{0-6}C(O)OR^o$;-$(CH_2)_{0-6}CH(OR^o)_2$;-$(CH_2)_{0-6}SR^o$;-$(CH_2)_{0-6}Ph$,其中Ph可以被R^o取代;-$(CH_2)_{0-46}O(CH_2)_{0-1}Ph$,其中Ph可以被$R^o$取代;-CH=CHPh,其中Ph可以被$R^o$取代;-$(CH_2)_{0-6}O(CH_2)_{0-1}$-吡啶基,该吡啶基可以被$R^o$取代;-$NO_2$;-CN;-$N_3$;-$(CH_2)_{0-6}N(R^o)_2$;-$(CH_2)_{0-6}N(R^o)C(O)R^o$;-$N(R^o)C(S)R^o$;-$(CH_2)_{0-6}N(R^o)C(O)NR^o_2$;-$N(R^o)C(S)NR^o_2$;-$(CH_2)_{0-6}N(R^o)C(O)OR^o$;-$N(R^o)N(R^o)C(O)R^o$;-$N(R^o)N(R^o)C(O)NR^o_2$;-$N(R^o)N(R^o)C(O)OR^o$;-$(CH_2)_{0-6}C(O)R^o$;-$C(S)R^o$;-$(CH_2)_{0-6}C(O)OR^o$;-$(CH_2)_{0-6}C(O)SR^o$;-$(CH_2)_{0-6}C(O)OSiR^o_3$;-$(CH_2)_{0-6}OC(O)R^o$;-OC(O)$(CH_2)_{0-6}SR^o$,-$(CH_2)_{0-6}SC(O)R^o$;-$(CH_2)_{0-6}C(O)NR^o_2$;-$C(S)NR^o_2$;-C(S)

SR^{o};-SC(S)SR^{o},-$(CH_2)_{0-6}OC(O)NR^{o}_2$;-C(O)N($OR^{o}$)$R^{o}$;-C(O)C(O)$R^{o}$;-$C(O)CH_2C(O)R^{o}$;-C($NOR^{o}$)$R^{o}$;-$(CH_2)_{0-6}SSR^{o}$;-$(CH_2)_{0-6}S(O)_2R^{o}$;-$(CH_2)_{0-6}S(O)_2OR^{o}$;-$(CH_2)_{0-6}OS(O)_2R^{o}$;-$S(O)_2NR^{o}_2$;-$(CH_2)_{0-6}S(O)R^{o}$;-N($R^{o}$)$S(O)_2NR^{o}_2$;-N($R^{o}$)$S(O)_2R^{o}$;-N($OR^{o}$)$R^{o}$;-C(NH)$NR^{o}_2$;-$P(O)_2R^{o}$;-$P(O)R^{o}_2$;-P(O)($OR^{o}$)$_2$;-OP(O)($R^{o}$)$OR^{o}$;-$OP(O)R^{o}_2$;-OP(O)($OR^{o}$)$_2$;$SiR^{o}_3$;-($C_{1-4}$直链或支链亚烷基)O-N($R^{o}$)$_2$;或-($C_{1-4}$直链或支链亚烷基)C(O)O-N($R^{o}$)$_2$,其中每个$R^{o}$可以如下文所定义被取代并且独立地是氢、$C_{1-6}$脂族、$-CH_2Ph$,$-O(CH_2)_{0-1}Ph$,$-CH_2-$(5至6元芳杂环)或3至6元饱和的、部分不饱和的或芳环(含有0至4个独立地选自氮、氧和硫的杂原子),或者,尽管有上述定义,两个独立出现的R^{o}与其介于其间的原子一起形成3至12元饱和的、部分不饱和的或芳基单环或双环(含有0至4个独立地选自氮、氧和硫的杂原子),其可以如下文所定义被取代。

[0057] 在R^{o}(或通过两个独立出现的R^{o}与其介于其间的原子一起形成的环)上合适的一价取代基独立地是卤素、$-(CH_2)_{0-2}R^{\bullet}$、-(卤代$R^{\bullet}$)、$-(CH_2)_{0-2}OH$、$-(CH_2)_{0-2}OR^{\bullet}$、$-(CH_2)_{0-2}CH(OR^{\bullet})_2$;-O(卤代$R^{\bullet}$)、-CN、$-N_3$、$-(CH_2)_{0-2}C(O)R^{\bullet}$、$-(CH_2)_{0-2}C(O)OH$、$-(CH_2)_{0-2}C(O)OR^{\bullet}$、$-(CH_2)_{0-2}SR^{\bullet}$、$-(CH_2)_{0-2}SH$、$-(CH_2)_{0-2}NH_2$、$-(CH_2)_{0-2}NHR^{\bullet}$、$-(CH_2)_{0-2}NR^{\bullet}_2$、$-NO_2$、$-SiR^{\bullet}_3$、$-OSiR^{\bullet}_3$、$-C(O)SR^{\bullet}$、-($C_{1-4}$直链或支链亚烷基)$C(O)OR^{\bullet}$或$-SSR^{\bullet}$,其中每个$R^{\bullet}$未被取代或其在“卤代”之前仅被一个或多个卤素取代,且独立地选自C_{1-4}脂族、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或5至6元饱和的、部分不饱和的或芳环(含有0至4个独立地选自氮、氧和硫的杂原子)。在R^{o}的饱和的碳原子上合适的二价取代基包括=O和=S。

[0058] 在“任选取代”基团的饱和的碳原子上的合适的二价取代基包括下述:=O、=S、=NNR^{*}_2、=NNHC(O)R^{*}、=NNHC(O)OR^{*}、=$NNHS(O)_2R^{*}$、=NR^{*}、=NOR^{*}、$-O(C(R^{*}_2))_{2-3}O-$或$-S(C(R^{*}_2))_{2-3}S-$,其中每个独立出现的R^{*}选自氢、C_{1-6}脂族,其可以如下定义被取代,以及是未取代的5至6元饱和的、部分不饱和的或芳基环(含有0至4个独立地选自氮、氧和硫的杂原子)。与“任选取代的”基团的相邻的可取代的碳结合的合适的二价取代基包括:$-O(CR^{*}_2)_{2-3}O-$,其中每个独立出现的R^{*}选自氢、C_{1-6}脂族其可如下定义被取代,以及是未取代的5至6元饱和的、部分不饱和的、或芳基环(含有0至4个独立地选自氮、氧和硫的杂原子)。

[0059] 在R^{*}的脂族基团上合适的取代基包括卤素,$R^{\bullet}$、-(卤代$R^{\bullet}$)、-OH、$-OR^{\bullet}$、-O(卤代$R^{\bullet}$)、-CN、-C(O)OH、$-C(O)OR^{\bullet}$、$-NH_2$、$-NHR^{\bullet}$、$-NR^{\bullet}_2$、或$-NO_2$,其中每个$R^{\bullet}$是未取代的或者其在“卤代”之前仅被一个或多个卤素取代,并且独立地是C_{1-4}脂族、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或5至6元饱和的、部分不饱和的或芳基环(含有0至4个独立地选自氮、氧和硫的杂原子)。

[0060] 在“任选取代的”基团的可取代氮上的合适取代基包括$-R^{\dagger}$、$-NR^{\dagger}_2$、$-C(O)R^{\dagger}$、$-C(O)OR^{\dagger}$、$-C(O)C(O)R^{\dagger}$、$-C(O)CH_2C(O)R^{\dagger}$、$-S(O)_2R^{\dagger}$、$-S(O)_2NR^{\dagger}_2$、$-C(S)NR^{\dagger}_2$、$-C(NH)NR^{\dagger}_2$或$-N(R^{\dagger})S(O)_2R^{\dagger}$;其中每个$R^{\dagger}$独立地是氢、$C_{1-6}$脂族其可如下定义被取代、未取代的-OPh或未取代的5-6元饱和的、部分不饱和的或芳基环(含有0至4个独立地选自氮、氧和硫的杂原子),或者,尽管有上述定义,两个独立出现的$R^{\dagger}$与介于它们之间的原子一起形成未取代的3至12元饱和的、部分不饱和的或芳基单环或双环(含有0至4个独立地选自氮、氧和硫的杂原子)。

[0062] 在$R^{\dagger}$的脂族基团上合适的取代基独立地是卤素,$-R^{\bullet}$、-(卤代$R^{\bullet}$)、-OH、$-OR^{\bullet}$、-O(卤素$R^{\bullet}$)、-CN、-C(O)OH、$-C(O)OR^{\bullet}$、$-NH_2$、$-NHR^{\bullet}$、$-NR^{\bullet}_2$或NO_2,其中每个$R^{\bullet}$是未取代的或其在“卤代”之前仅被一个或多个卤素取代,并且独立地是C_{1-4}脂族、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或5-6元饱

和的、部分不饱和的或芳基环(含有0至4个独立地选自氮、氧和硫的杂原子)。

[0063] 如本文所用,术语“所提供的化合物”或“本公开的化合物”指的是本文所述的任何属、亚属和/或种类。

[0064] 如本文所用,术语“药学上可接受的盐”指的是在合理的医学判断范围内,适合与人类和低等动物的组织接触使用而没有异常毒性、刺激性、过敏反应等,并且与合理的收益/风险比相称的盐。药学上可接受的盐在本领域中是众所周知的。例如,S.M.Berge等人在J.Pharmaceutical Sciences,1977,66,1-19中详细描述了药学上可接受的盐,其通过引用并入本文。本公开的化合物的药学上可接受的盐包括衍生自合适的无机和有机酸和碱的那些。药学上可接受的、无毒的酸加成盐的实例是氨基基团与无机酸例如盐酸、氢溴酸、磷酸、硫酸和高氯酸,或与有机酸例如乙酸、草酸、马来酸、酒石酸、柠檬酸、琥珀酸或丙二酸或通过使用在本领域中使用的其他方法例如离子交换形成的盐。其他药学上可接受的盐包括己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡萄糖酸盐、十二烷基硫酸盐、乙磺酸盐、甲酸盐、富马酸盐、葡庚糖酸盐、甘油磷酸盐、葡萄糖酸盐、半硫酸盐、庚酸盐、己酸盐、氢碘酸盐,2-羟基-乙磺酸盐,乳糖酸盐,乳酸盐,月桂酸盐,十二烷基硫酸盐,苹果酸盐,马来酸盐,丙二酸盐,甲磺酸盐,2-萘磺酸盐,烟酸盐,硝酸盐,油酸盐,草酸盐,棕榈酸盐,双羟萘酸盐,果胶酸盐,过硫酸盐,3-苯基丙酸盐、磷酸盐、三甲基乙酸盐、丙酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一烷酸盐、戊酸盐等。

[0065] 衍生自适当碱的盐包括碱金属、碱土金属、铵和$N^+(C_{1-4}$烷基$)_4$盐。代表性的碱金属或碱土金属盐包括钠、锂、钾、钙、镁等。当合适时,其他药学上可接受的盐包括无毒铵、季铵和使用抗衡离子(例如卤化物、氢氧化物、羧酸盐、硫酸盐、磷酸盐、硝酸盐、低级烷基磺酸盐和芳基磺酸盐)形成的胺阳离子。

[0066] 除非另有说明,本文所述的结构还意在包括该结构的所有异构(例如,对映体、非对映体和几何(或构象))形式;例如,每个不对称中心的R和S构型,Z和E双键异构体,以及Z和E构象异构体。因此,本发明化合物的单一立体化学异构体以及对映体、非对映体和几何(或构象)混合物都在本公开的范围内。除非另有说明,本公开的化合物的所有互变异构形式都在本公开的范围内。此外,除非另有说明,本文所描述的结构还意在包括仅在一个或多个同位素富集原子的存在中不同的化合物。例如,具有本结构的化合物,包括用氘或氚代替氢,或用^{13}C-或^{14}C-富集的碳代替碳,都在本公开的范围内。这些化合物是有用的,例如依照本公开用作分析工具、在生物测定中的探针或治疗剂。

[0067] 如本文所用,术语“抑制剂”定义为以可测量的亲和力结合和/或抑制CDK2的化合物。在某些实施方案中,当在适当的测定中测量时,抑制剂的IC_{50}和/或结合常数小于约50μM、小于约1μM、小于约500μM、小于约100μM、小于约10μM或小于约1μM。

[0068] 如本文所用,术语“患者”是指动物,优选地哺乳动物,并且最优选人类。

[0069] 术语“药学上可接受的载体、佐剂或媒介物”指的不会破坏与其配制的化合物的药理活性的无毒的载体、佐剂或媒介物。可用于本公开的组合物中的药学上可接受的载体、佐剂或媒介物包括但不限于离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白(例如人血清白蛋白)、缓冲物质例如磷酸盐、甘氨酸、山梨酸、山梨酸钾、饱和的植物脂肪酸的偏甘油酯混合物、水、盐或电解质,例如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐、胶体二氧

化硅、三硅酸镁、聚乙烯吡咯烷酮、纤维素基物质、聚乙二醇、羧甲基纤维素钠、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯-嵌段聚合物、聚乙二醇和羊毛脂。

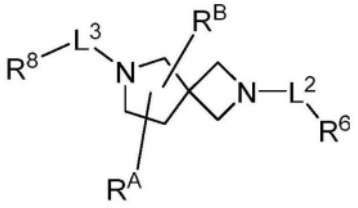
[0070] “药学上可接受的衍生物”是指本公开化合物的任何无毒盐、酯、酯的盐或其他衍生物,其在施用于接受者时能够直接地或间接地提供本公开化合物或其抑制或降解活性的代谢物或残留物。

[0071] 如本文所用,术语“其抑制活性的代谢物或残留物”是指其代谢物或残留物也是CDK2蛋白或其突变体的抑制剂。

[0072] 3.具体实施方案说明:

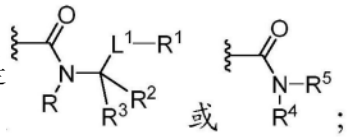
[0073] 在某些实施方案中,本公开提供了CDK2活性的抑制剂。

[0074] 在一些实施方案中,CDK2的抑制剂包括式IA的化合物:

[0075] 

IA

[0076] 或其药学上可接受的盐,其中:

[0077] R^A是;

[0078] R^B是氢、任选取代的C_{1-6}脂族基团、-OR、-NR_2或卤素;

[0079] L^1是共价键或饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链,其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

[0080] R^1是氢、任选取代的C_{1-6}脂族基团或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);

[0081] R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR、-C(O)NR_2、-$S(O)_2$R、-$S(O)_2NR_2$、-S(O)R、-P(O)R_2或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环、或任选取代的3-7元饱和的或部分

不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)；

[0082] R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)；并且R^5是氢;或者R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)；

[0083] L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代；

[0084] R^6是任选取代的C_{1-6}脂族基团、或选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中该环状基团任选地被一个或多个R^7的实例取代；

[0085] R^7的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2$R、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-C(O)R、-C(O)OR、-$C(O)NR_2$、-C(O)N(R)OR、-OC(O)R、-$OC(O)NR_2$、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)$S(O)_2NR_2$、-N(R)$S(O)_2$R、任选取代的C_{1-6}脂族基团、任选取代的C_{1-6}脂族-Cy基团或Cy；

[0086] L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^3的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代；

[0087] R^8是选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中该环基团任选地被一个或多个R^9的实例取代；

[0088] R^9的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-$S(O)_2$R、-$S(O)_2NR_2$、-S(O)R、-$S(O)NR_2$、-C(O)R、-C(O)OR、-$C(O)NR_2$、-C(O)N(R)OR、-OC(O)R、-$OC(O)NR_2$、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)$S(O)_2NR_2$、-N(R)$S(O)_2$R、任选取代的C_{1-6}脂族基团、任选取代的C_{1-6}脂族-Cy基团或Cy；

[0089] 每个Cy独立地是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)；并且

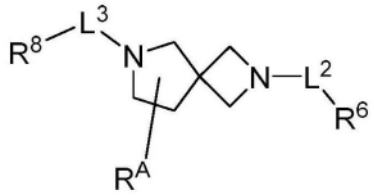
[0090] 每个R独立地是氢或任选取代的C_{1-6}脂族基团、任选取代的苯基、任选取代的3-7元

饱和的或部分不饱和的碳环、任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)或任选取代的5-6元杂芳基环(含有1-4个独立地选自氮、氧和硫的杂原子);或

[0091] 在同一氮上的两个R基团与介于它们之间的原子一起形成任选取代的4-7元饱和的、部分不饱和的或杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

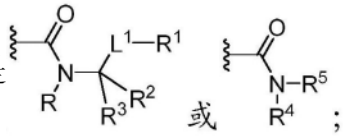
[0092] 其中该化合物不是化合物X,其中化合物X在本文中定义。

[0093] 在一些实施方案中,CDK2的抑制剂包括式I的化合物:

[0094] 

I

[0095] 或其药学上可接受的盐,其中:

[0096] R^A是;

[0097] L^1是共价键或饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链,其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS(O)$_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代;

[0098] R^1为氢、任选取代的C_{1-6}脂族基团或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);

[0099] R^2是氢、任选被取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环、或任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子);

[0100] R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);并且R^5是氢;或者R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)、或任选取代的杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子);

[0101] L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链，其中L^2的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代；

[0102] R^6是任选取代的C_{1-6}脂族基团或选自以下的环状基团：3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)，其中该环状基团任选地被一个或多个R^7的实例取代；

[0103] R^7的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy；

[0104] L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链，其中L^3的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-S(O)$_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代；

[0105] R^8是选自以下的环状基团：3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)，其中该环状基团任选地被一个或多个R^9的实例取代；

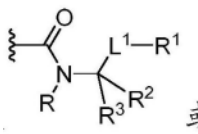
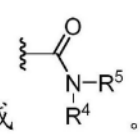
[0106] R^9的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy；

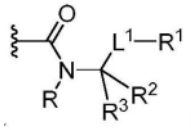
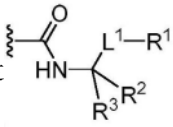
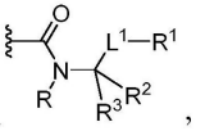
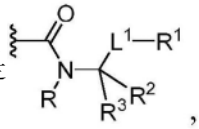
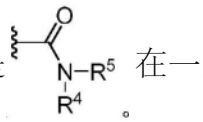
[0107] 每个Cy独立地是选自以下的任选取代的环状基团：3-8元饱和的或部分不饱和的单环碳环、苯基、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)；和

[0108] 每个R独立地是氢或任选取代的C_{1-6}脂族基团、任选取代的苯基、任选取代的3-7元饱和的或部分不饱和的碳环、任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、或任选取代的5-6元杂芳基环(含有1-4个独立地选自氮、氧和硫的杂原子)；或

[0109] 在同一氮上的两个R基团与介于它们之间的原子一起形成任选取代的4-7元饱和的、部分不饱和的或杂芳基环(除了氮之外，含有0-3个独立地选自氮、氧和硫的杂原子)；

[0110] 其中该化合物不是化合物X，其中化合物X在本文中定义。

[0111] 如上文一般定义，R^A是或。在一些实施方案中，R^A是

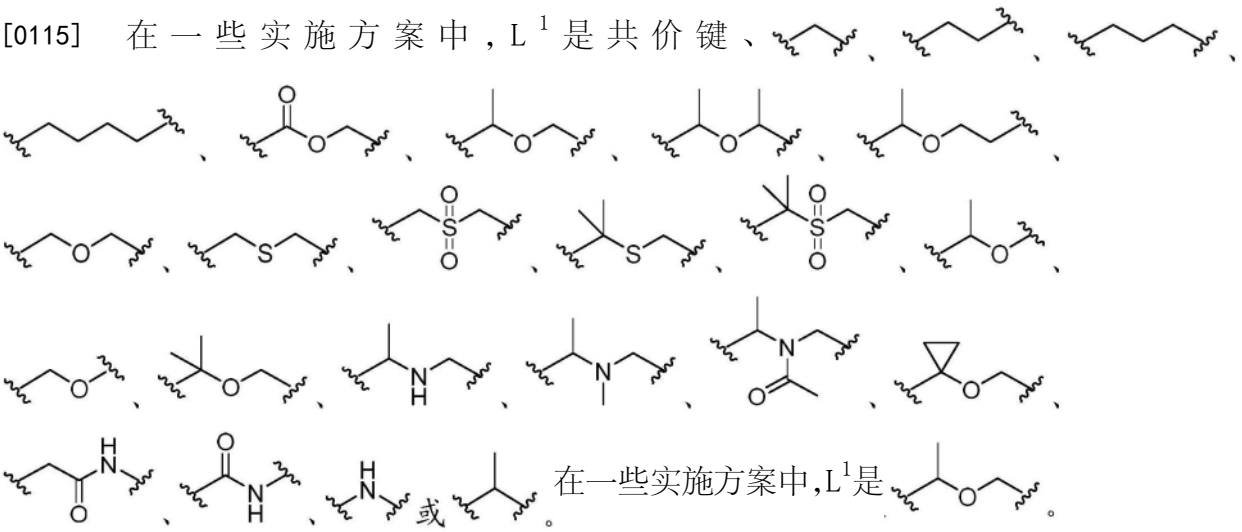
 在一些实施方案中，R^A是 在一些实施方案中，R^A是，其中所示的R基团是任选取代的C_{1-6}脂族基团。在一些实施方案中，R^A是 其中所示的R基团是任选取代的甲基基团。在一些实施方案中，R^A是 在一些实施方案中，R^A选自下表1的化合物中所描述的那些。

[0112] 如上文一般定义，R^B是氢、任选取代的C_{1-6}脂族基团、-OR、$-NR_2$或卤素。在一些实施方案中，R^B是氢。在一些实施方案中，R^B是任选取代的C_{1-6}脂族基团。在一些实施方案中，R^B是-OR。在一些实施方案中，R^B是$-NR_2$。在一些实施方案中，R^B是卤素。在一些实施方案中，R^B是甲基基团。在一些实施方案中，R^B是氟代基团。在一些实施方案中，R^B选自下表1的化合物中所描述的那些。

[0113] 如上文一般定义，L^1是共价键或饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链，其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、$-S(O)_2-$、-C(S)-、$-NRS(O)_2-$、$-S(O)_2NR-$、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。

[0114] 在一些实施方案中，L^1是共价键。在一些实施方案中，L^1是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-6}烃链，其中L^1的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、$-S(O)_2-$、-C(S)-、$-NRS(O)_2-$、$-S(O)_2NR-$、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。在一些实施方案中，L^1是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链，其中L的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、$-S(O)_2-$、-C(S)-、$-NRS(O)_2-$、$-S(O)_2NR-$、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。在一些实施方案中，L^1是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链。在一些实施方案中，L^1是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链，其中L^1的1或2个亚甲基单元被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、$-S(O)_2-$、-C(S)-、$-NRS(O)_2-$、$-S(O)_2NR-$、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。在一些实施方案中，L^1是饱和的、直链的或支链的、任选取代的二价C_{1-4}烃链。在一些实施方案中，L^1是部分不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链。在一些实施方案中，L^1是饱和的、直链的、任选取代的二价C_{1-4}烃链，其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、$-S(O)_2-$、-C(S)-、$-NRS(O)_2-$、$-S(O)_2NR-$、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。在一些实施方案中，L^1是任选取代的直链或支链C_{1-4}亚烷基链，其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-S-、-C(O)O-、-C(O)-、$-S(O)_2-$或-NRC(O)-替代。在一些实施方案中，L^1是任选取代的直链或支链C_{1-4}亚烷基链，其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-、-C(O)-或-NRC(O)-替代。在一些实施方案中，L^1是任选取代的直链或支链C_{1-4}亚烷基链，其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-

或-NRC(O)-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-S-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-$S(O)_2$-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-NR-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-C(O)O-替代。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-NRC(O)-替代。在一些实施方案中,L^1是未取代的直链C_{1-4}亚炔基。在一些实施方案中,L^1选自下表1的化合物中所描述的那些。

[0115] 在一些实施方案中,L^1是共价键、或。在一些实施方案中,L^1是。

[0116] 如上文一般定义,R^1是氢、任选取代的C_{1-6}脂族基团或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。

[0117] 在一些实施方案中,R^1是氢。在一些实施方案中,R^1是任选取代的C_{1-6}脂族基团。在一些实施方案中,R^1是甲基。在一些实施方案中,R^1是乙基。在一些实施方案中,R^1是异丙基。

[0118] 在一些实施方案中,R^1是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是任选取代的3-8元饱和的或部分不饱和的单环碳环。在一些实施方案中,R^1是任选取代的苯基。在一些实施方案中,R^1是任选取代的8-10元双环芳族

碳环。在一些实施方案中,R^1是任选取代的3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是任选取代的5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是任选取代的8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是选自以下的任选取代的环状基团:苯基、环己基、环戊基、环丁基、环丙基、环庚基、噁唑基、吡啶基、哒嗪基、1,3,4-噁二唑基、1,2,3-三唑基、吡唑基和四氢吡喃基。在一些实施方案中,R^1是任选取代的苯基。在一些实施方案中,R^1是任选取代的环己基。在一些实施方案中,R^1选自下表1的化合物中所描述的那些。

[0119] 在一些实施方案中,R^1是任选取代的7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是任选取代的7-12元饱和的或部分不饱和的双环碳环。在一些实施方案中,R^1是任选取代的7-12元桥双环碳环或任选取代的7-12元桥双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^1是任选取代的氧杂双环[2.2.2]辛基。在一些实施方案中,R^1为任选取代的双环[2.2.2]辛基。

[0120] 如上文一般定义,R^2为氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环或任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。

[0121] 或者,R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR、-C(O)NR_2、-S(O)$_2$R,-S(O)$_2$$NR_2$、-S(O)R、-P(O)$R_2$或选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子);并且R^3是氢;或R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环或任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。

[0122] 在一些实施方案中,R^2是氢、任选取代的C_{1-6}脂族基团、-C_{1-6}亚烷基-OR、-C_{1-3}亚烷基-O-C_{1-3}亚烷基-R、-C(O)OR或-C(O)NR_2;并且R^3是氢。在一些实施方案中,R^2是氢、甲基、-CH_2OR、-CH_2OCH_2R、-C(O)OR或-C(O)NR_2;并且R^3是氢。在一些实施方案中,R^2是氢。在一些实施方案中,R^2是任选取代的C_{1-6}脂族基团。在一些实施方案中,R^2是甲基。在一些实施方案中,R^2是-C_{1-6}亚烷基-OR。在一些实施方案中,R^2是-CH_2OR。在一些实施方案中,R^2是-CH_2OCH_2R。在一些实施方案中,R^2是-C(O)OR。在一些实施方案中,R^2是-C(O)NR_2。在一些实施方案中,R^2是-C(O)NR_2,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的、部分不饱和的或杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是-C(O)NR_2,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是-C(O)NR_2,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环,其选自哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

[0123] 在一些实施方案中R^2是-S(0)$_2$R,-S(0)$_2$$NR_2$、-S(0)R或-P(0)$R_2$。在一些实施方案中,$R^2$是-S(0)$_2$R。在一些实施方案中,$R^2$是-S(0)$_2$$NR_2$。在一些实施方案中,$R^2$是-S(0)R。在一些实施方案中,$R^2$是-P(0)$R_2$。在一些实施方案中,$R^2$是-S($O_2$)$CH_3$。在一些实施方案中,$R^2$是-P(0)($CH_3$)$_2$。

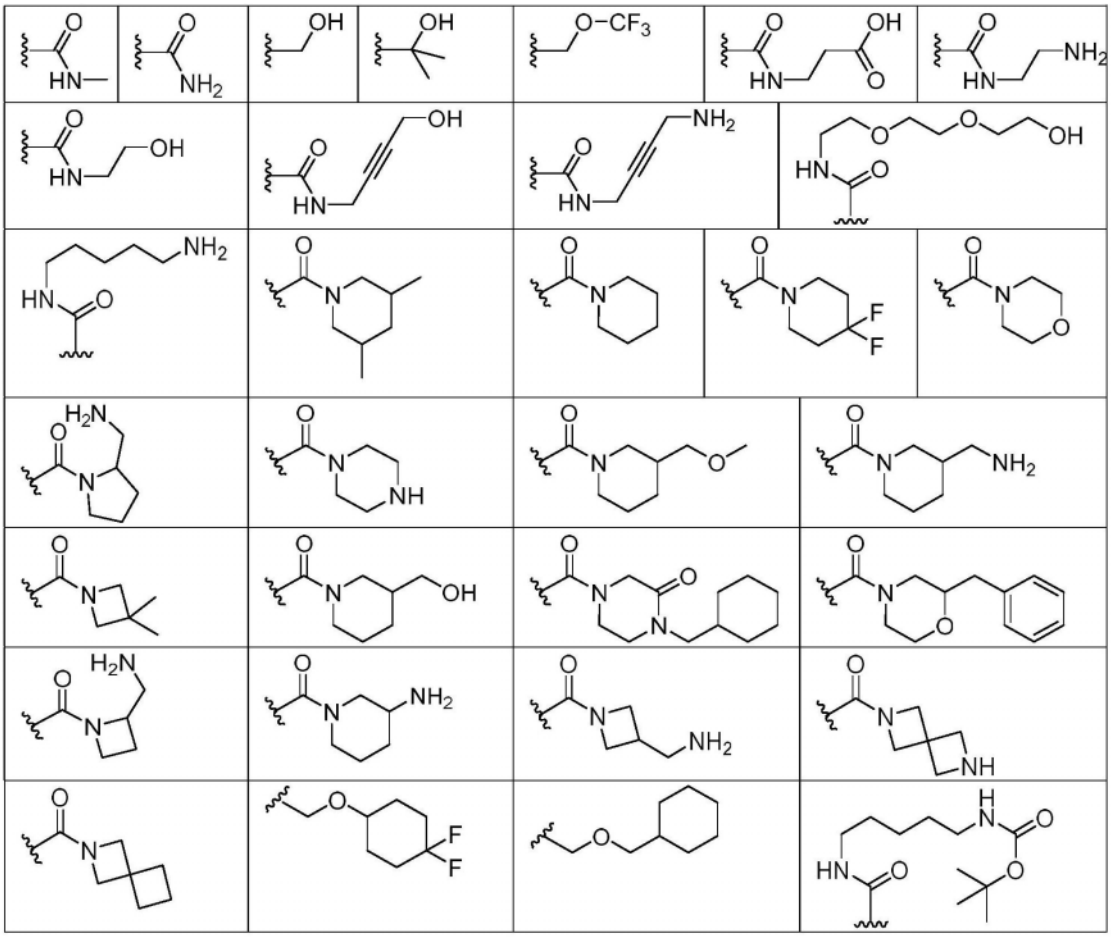
[0124] 在一些实施方案中,R^2是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是任选取代的3-8元饱和的或部分不饱和的单环碳环。在一些实施方案中,R^2是任选取代的苯基。在一些实施方案中,R^2是任选取代的8-10元双环芳族碳环。在一些实施方案中,R^2是任选取代的3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是任选取代的5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是任选取代的8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2是四氢呋喃基。在一些实施方案中,R^2是二噁烷基。在一些实施方案中,R^2是呋喃基。在一些实施方案中,R^2是噁二唑基。在一些实施方案中,R^2是噁唑基。

[0125] 在一些实施方案中,R^2选自下表1的化合物中所描述的那些。

[0126] 在一些实施方案中,R^3是氢并且R^2是氢或表R^2中的取代基:

[0127] 表R^2.示例性R^2取代基

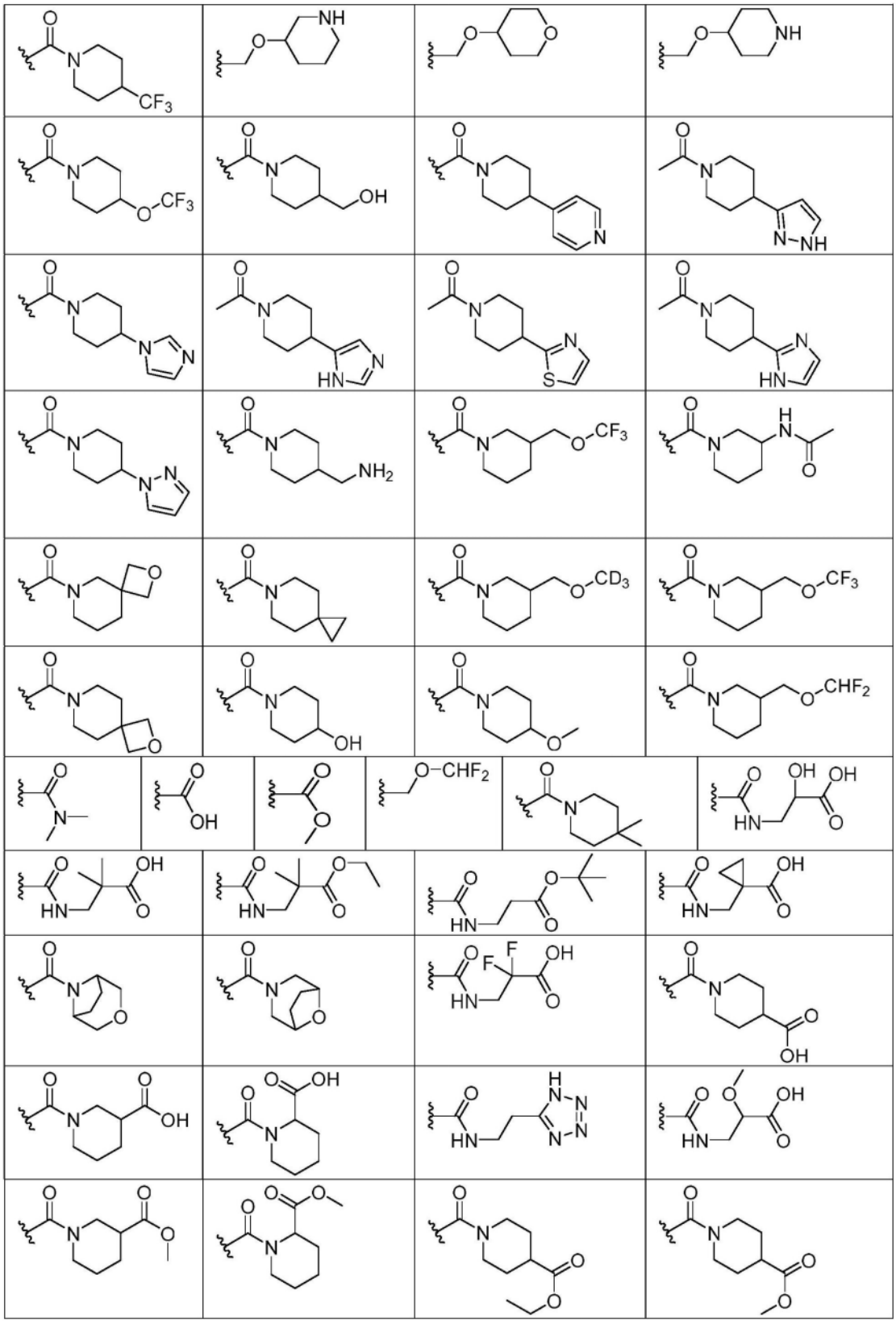
[0128]

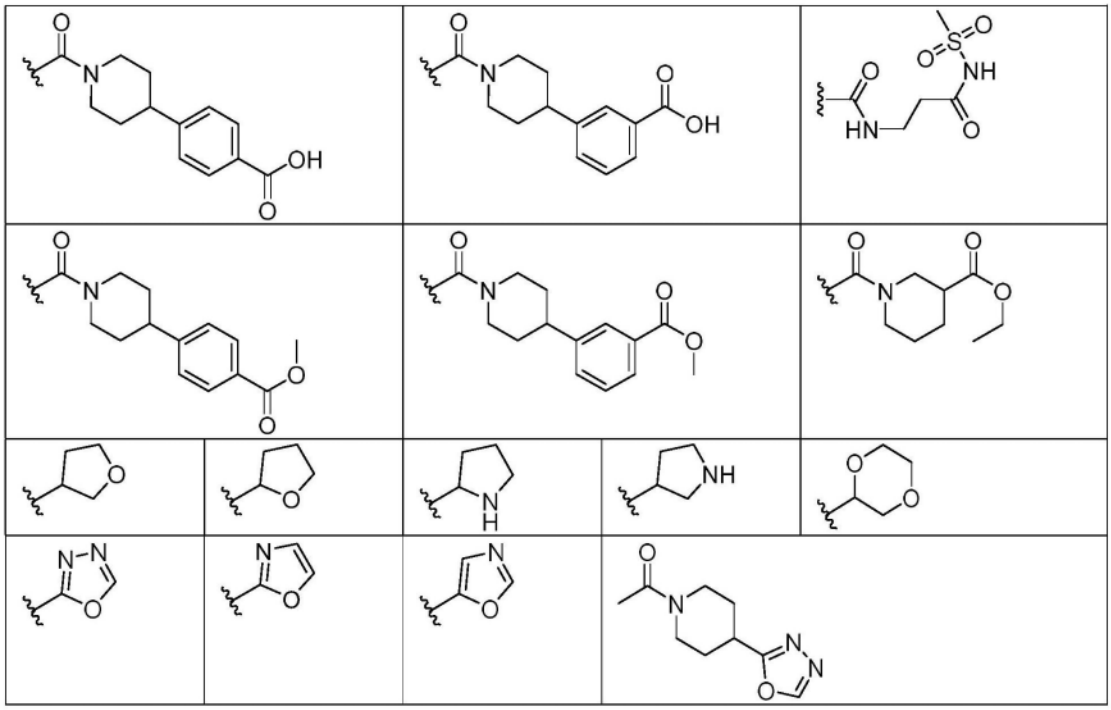


[0129] 在一些实施方案中,R^3是氢并且R^2是氢或表R^2-续中的取代基:

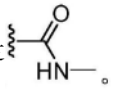
[0130] 表R^2-续.另外的示例性R^2取代基

[0131]



[0132] 

[0133] 在一些实施方案中,R^3是氢并且R^2是氢或在表R^2或表R^2-续中的取代基。

[0134] 在一些实施方案中,R^3是氢并且R^2是。

[0135] 在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环、或任选取代的3-7元饱和的或者部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的碳环。在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的碳环。在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的或部分不饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的3-7元饱和的杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^2和R^3与介于其间的碳原子一起形成任选取代的氧杂环丁烷基、环丙基、环丁基、环戊基、四氢吡喃基、哌啶基、哌嗪基、吗啉基、吡咯烷基或1,4-氧氮杂环庚基(1,4-oxazepanyl)。在一些实施方案中,R^2和R^3形成选自下表1的化合物中所描述的那些环状基团。

[0136] 如上文一般定义,R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),并且R^5是氢;或R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(含有0-3个独立地选自氮、氧和硫的杂原子)。

[0137] 在一些实施方案中,R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8

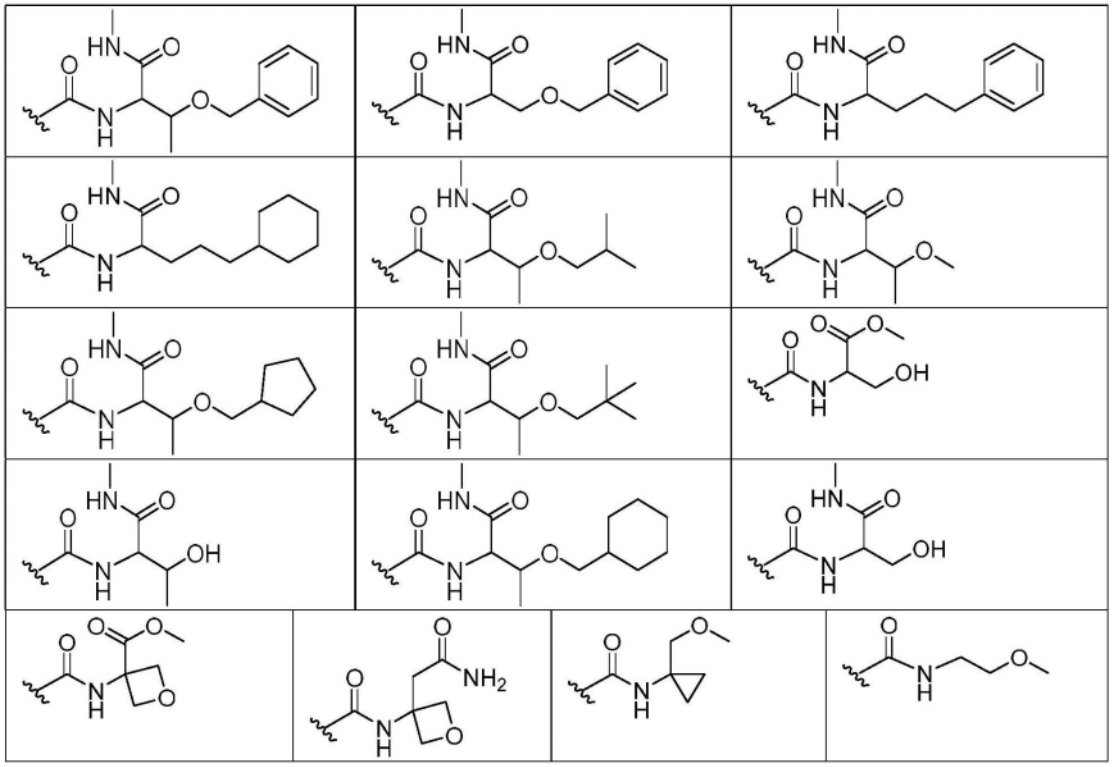
元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),并且R^5为氢。在一些实施方案中,R^4是选自以下的任选取代的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)和5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4是任选取代的3-8元饱和的或部分不饱和的单环碳环。在一些实施方案中,R^4是任选取代的7-12元饱和的或部分不饱和的双环碳环。在一些实施方案中,R^4是任选取代的苯基。在一些实施方案中,R^4是任选取代的8-10元双环芳族碳环。在一些实施方案中,R^4是任选取代的3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4是任选取代的5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4是选自以下的任选取代的环状基团:苯基、哌啶基、四氢吡喃基、1,4-氧氮杂环庚基、噁唑基、环丁基、环戊基或吡咯烷基。在一些实施方案中,R^4是选自下表1的化合物中所描述的那些。

[0138] 在一些实施方案中,R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)或任选取代的杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4和R^5与介于其间的氮原子一起形成任选取代的4-7元饱和的或部分不饱和的杂环(除了氮之外,含有0-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4和R^5与介于其间的氮原子一起形成任选取代的杂芳基环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^4和R^5与介于其间的氮原子一起形成选自以下的任选取代的环状基团:哌啶基、哌嗪基、吗啉基和吡咯烷基。在一些实施方案中,R^4和R^5与介于其间的氮原子一起形成取代的环状基团,其中该环状基团被选自-C_{1-6}亚烷基-苯基、-O-C_{1-6}亚烷基-苯基、-C_{1-6}亚烷基-环己基和-O-C_{1-6}亚烷基-环己基的基团取代。在一些实施方案中,R^4和R^5形成选自下表1的化合物中所描述的那些环状基团。

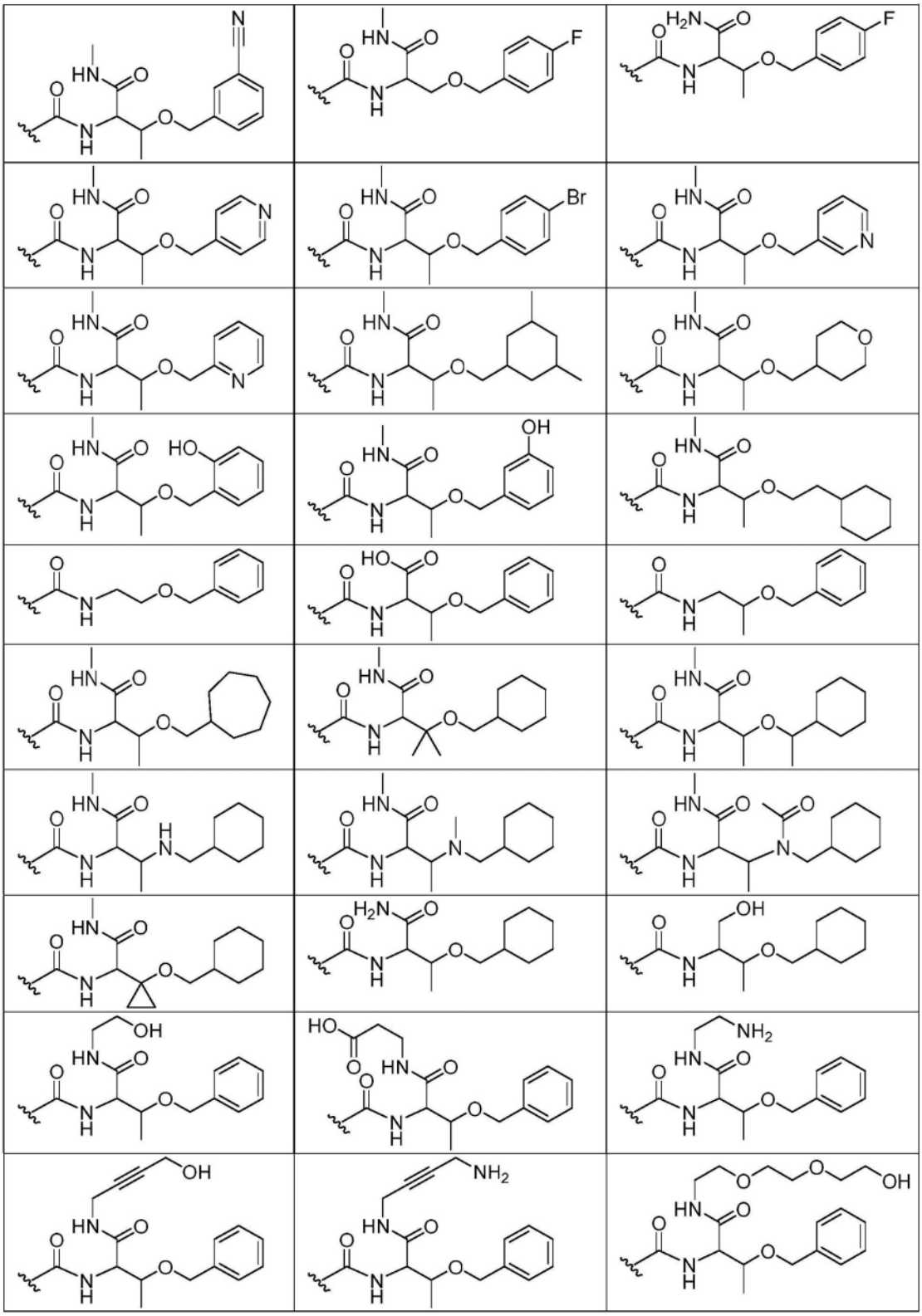
[0139] 在一些实施方案中,R^A是表A的取代基:

[0140] 表A:示例性R^A取代基

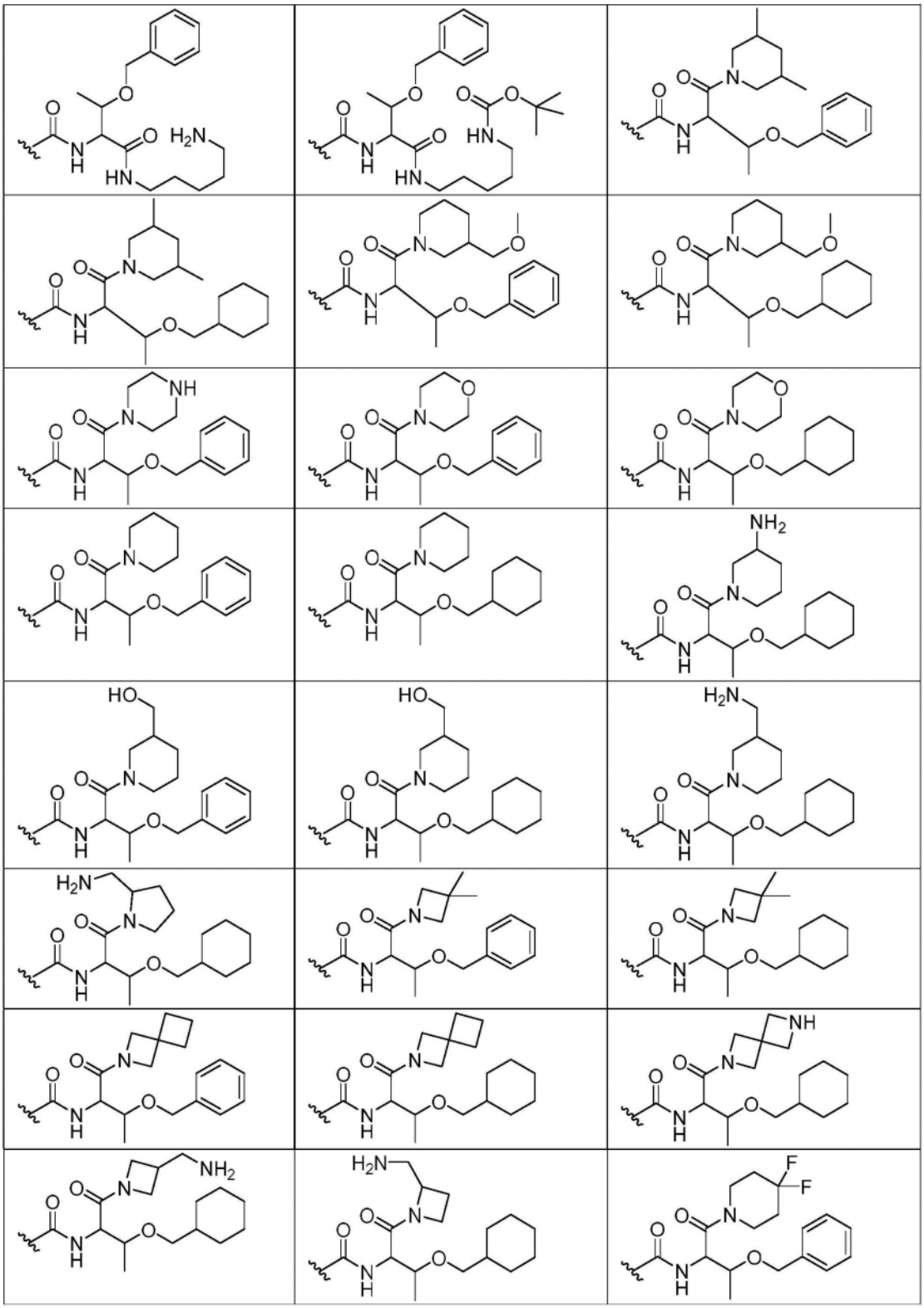
[0141]



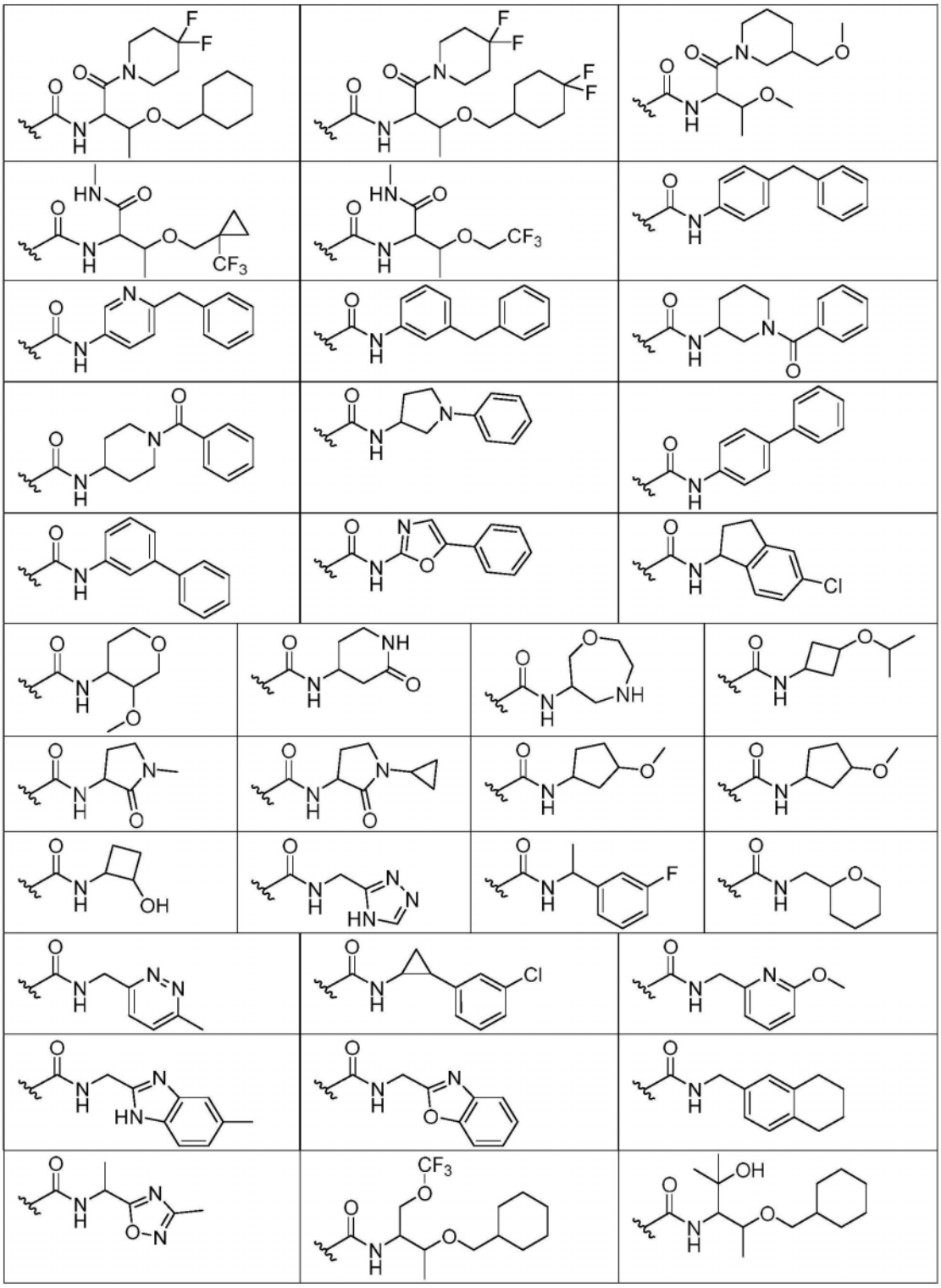
[0142]



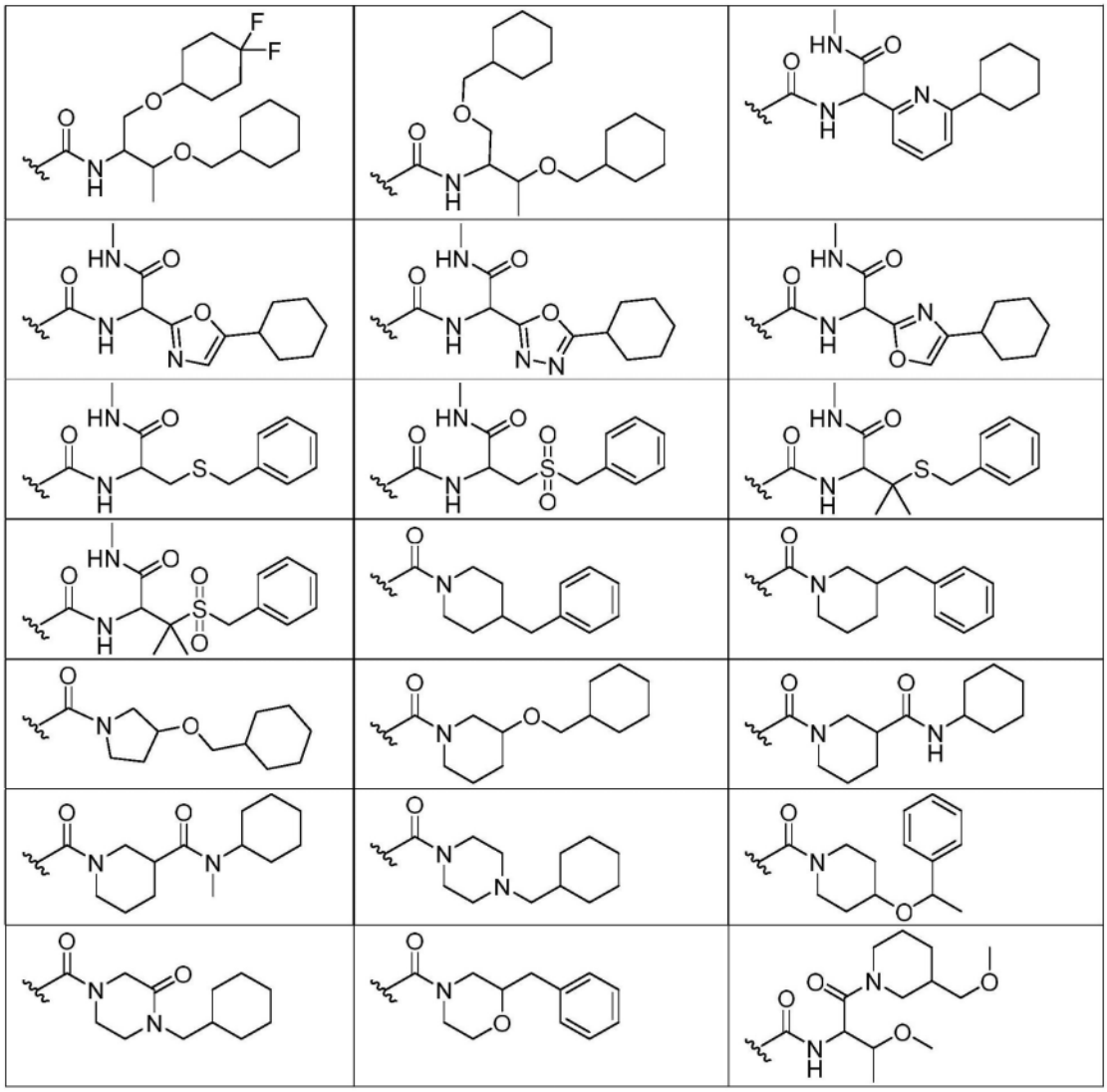
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[0144]



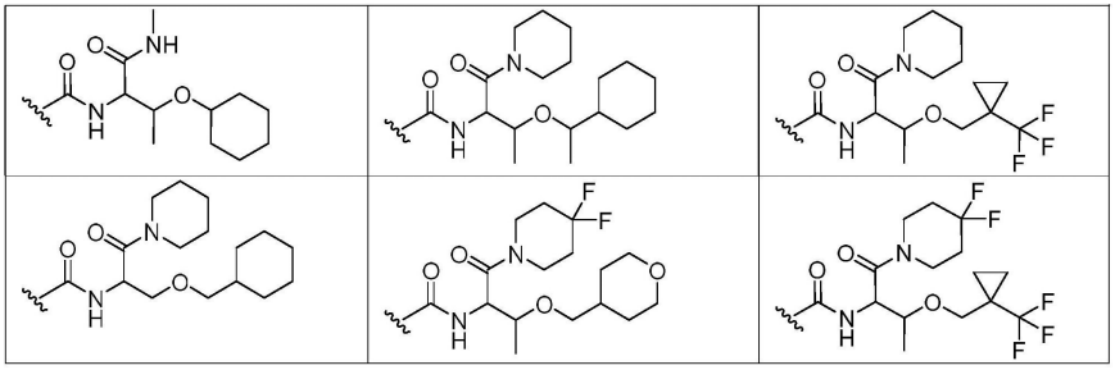
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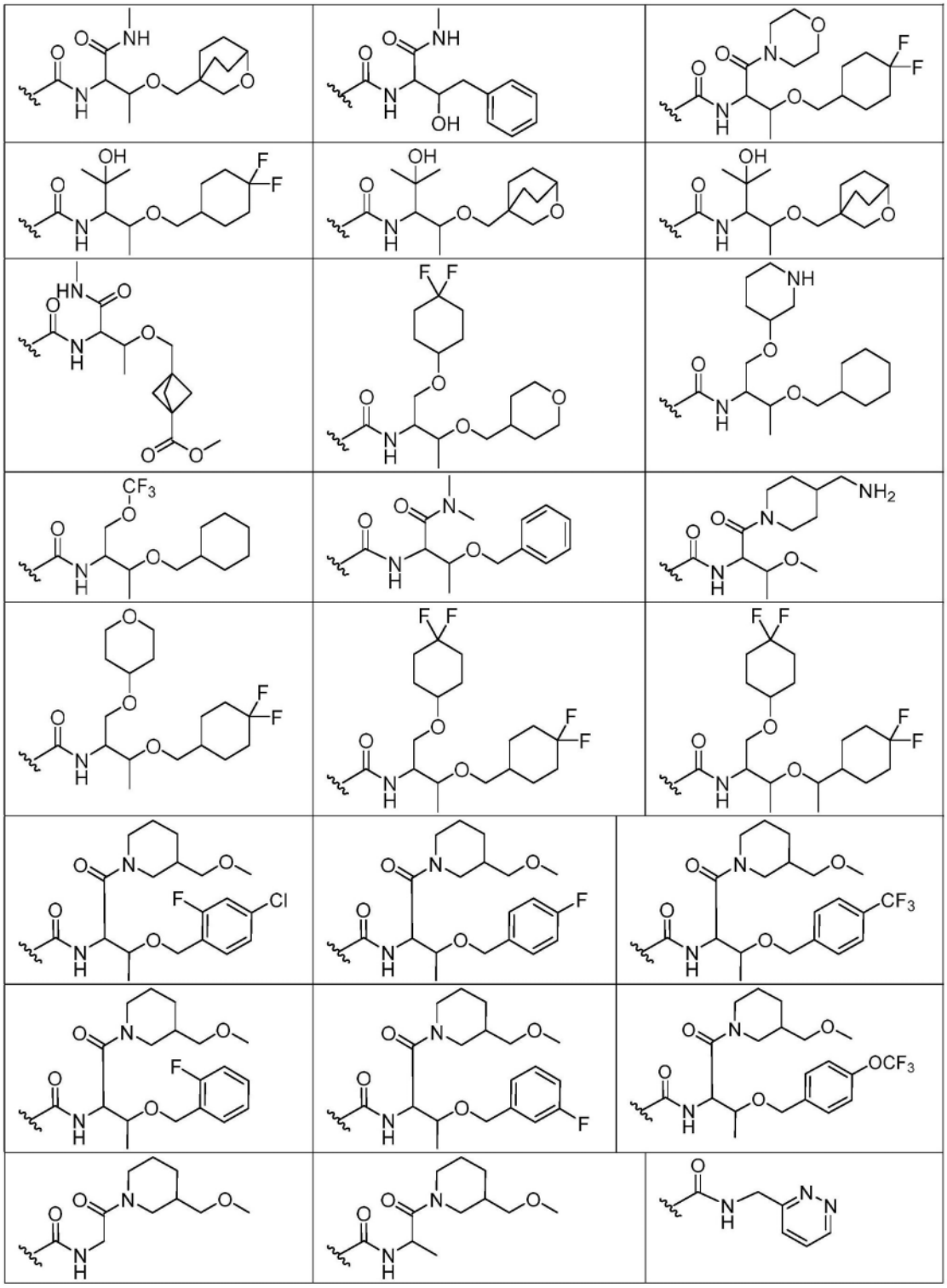
[0146] 在一些实施方案中,R^A是表A-续中的取代基:

[0147] 表A-续.另外的示例性RA取代基

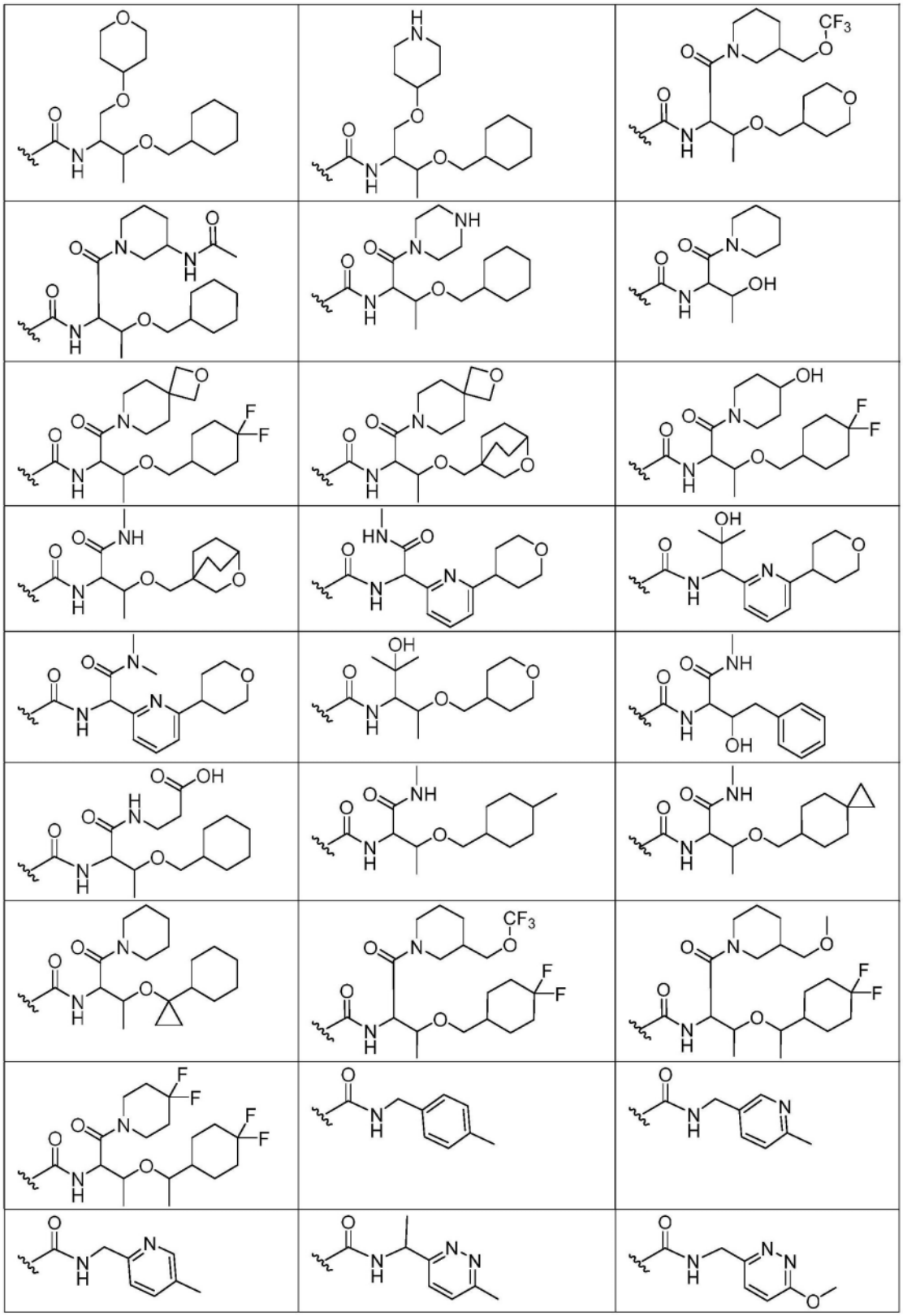
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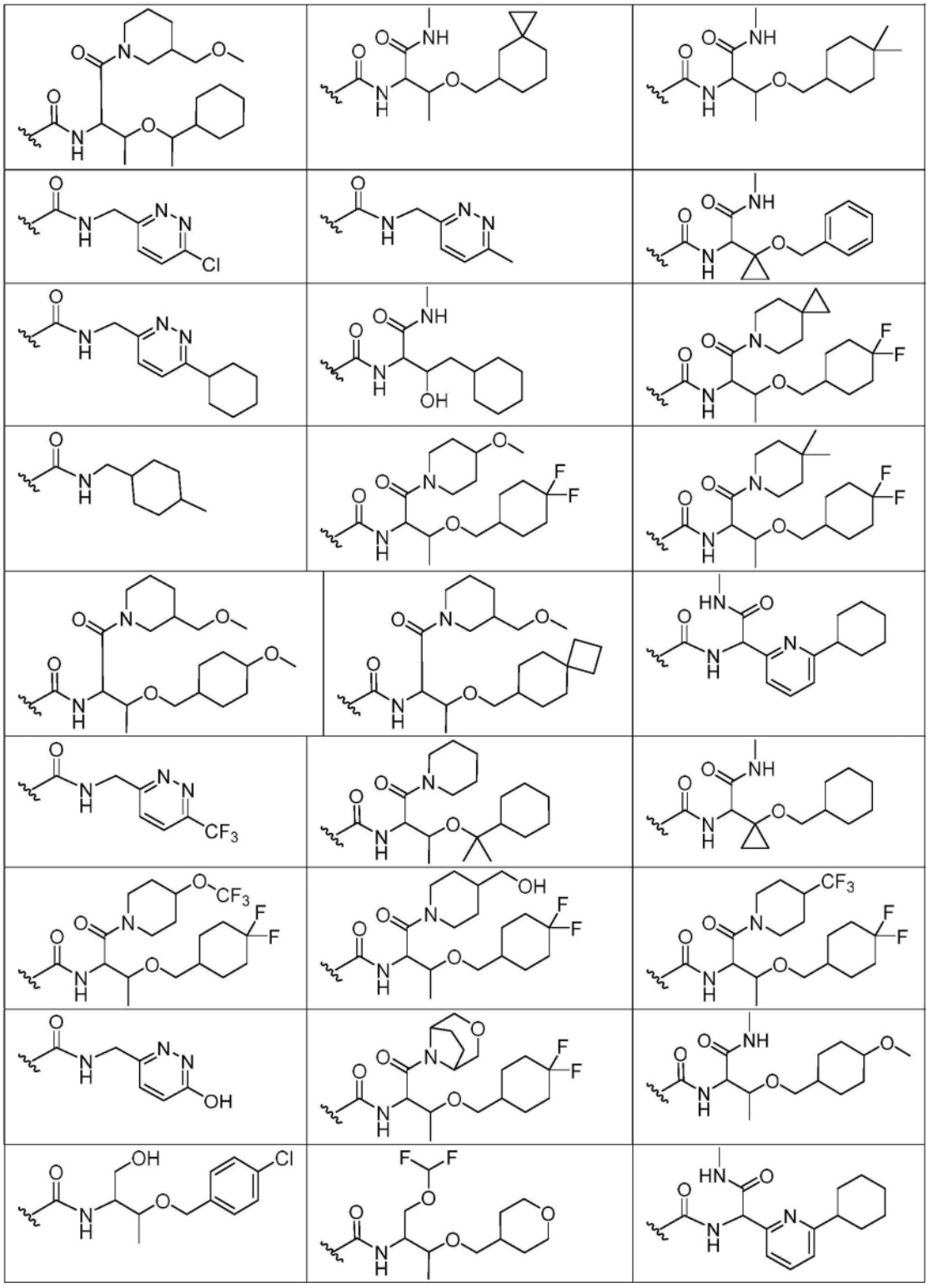
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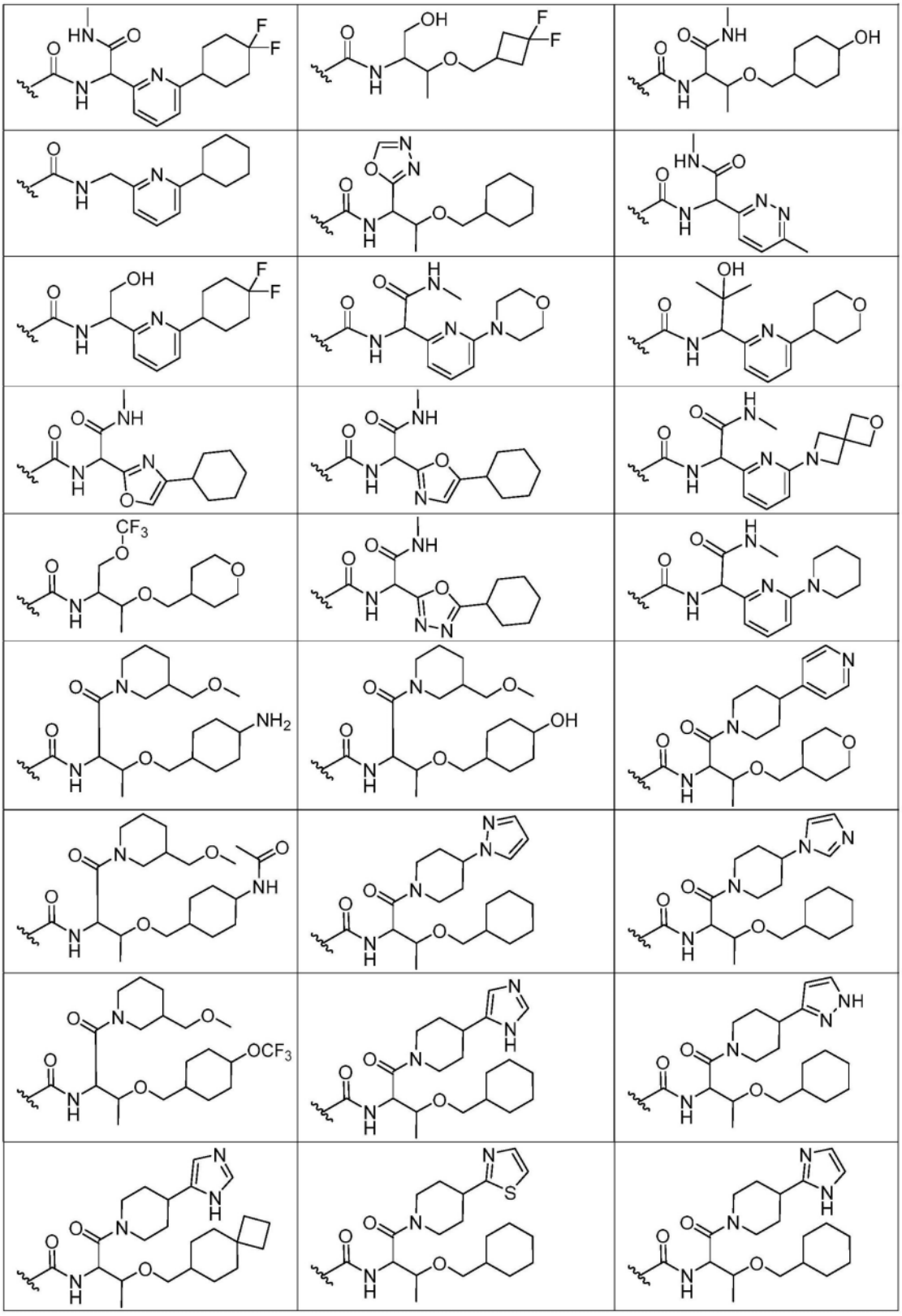
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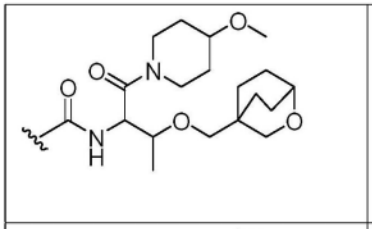
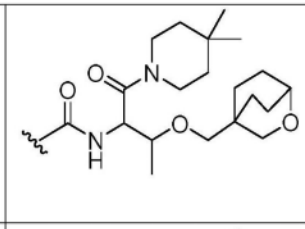
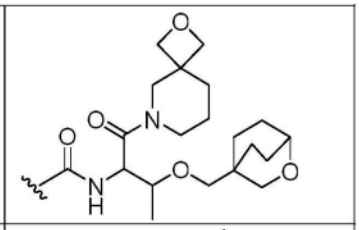
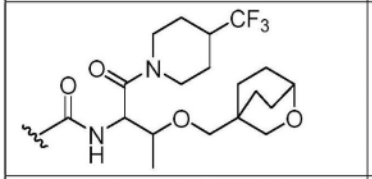
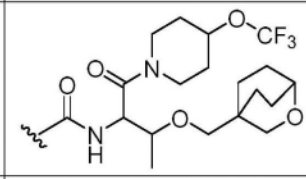
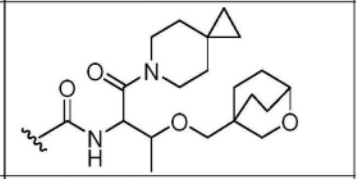
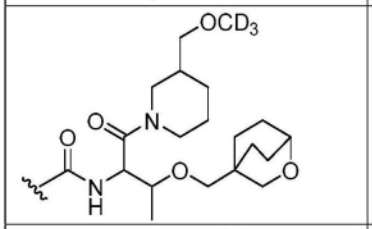
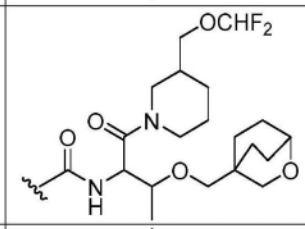
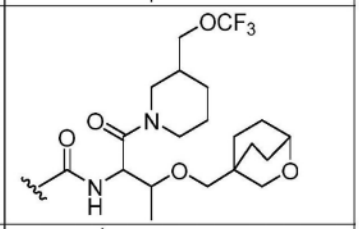
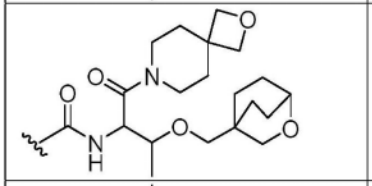
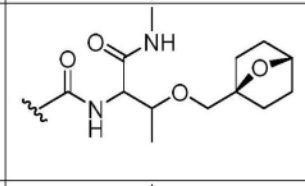
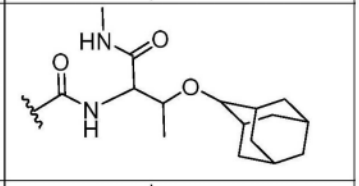
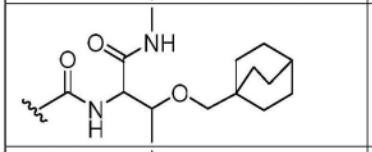
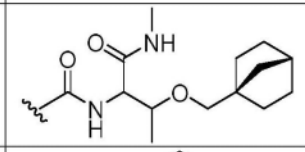
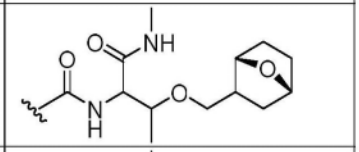
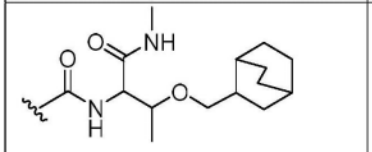
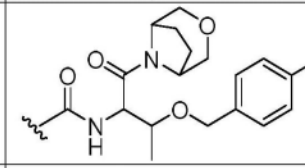
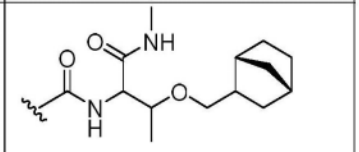
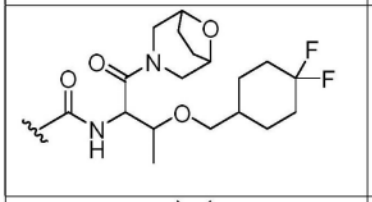
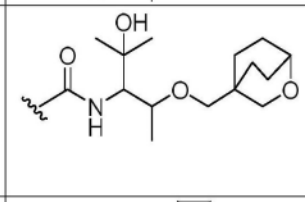
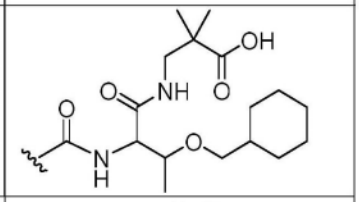
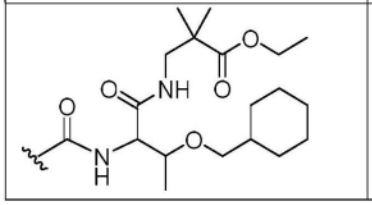
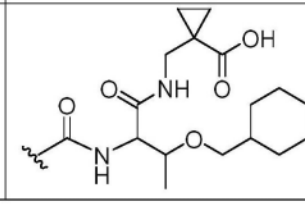
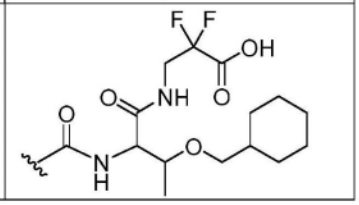
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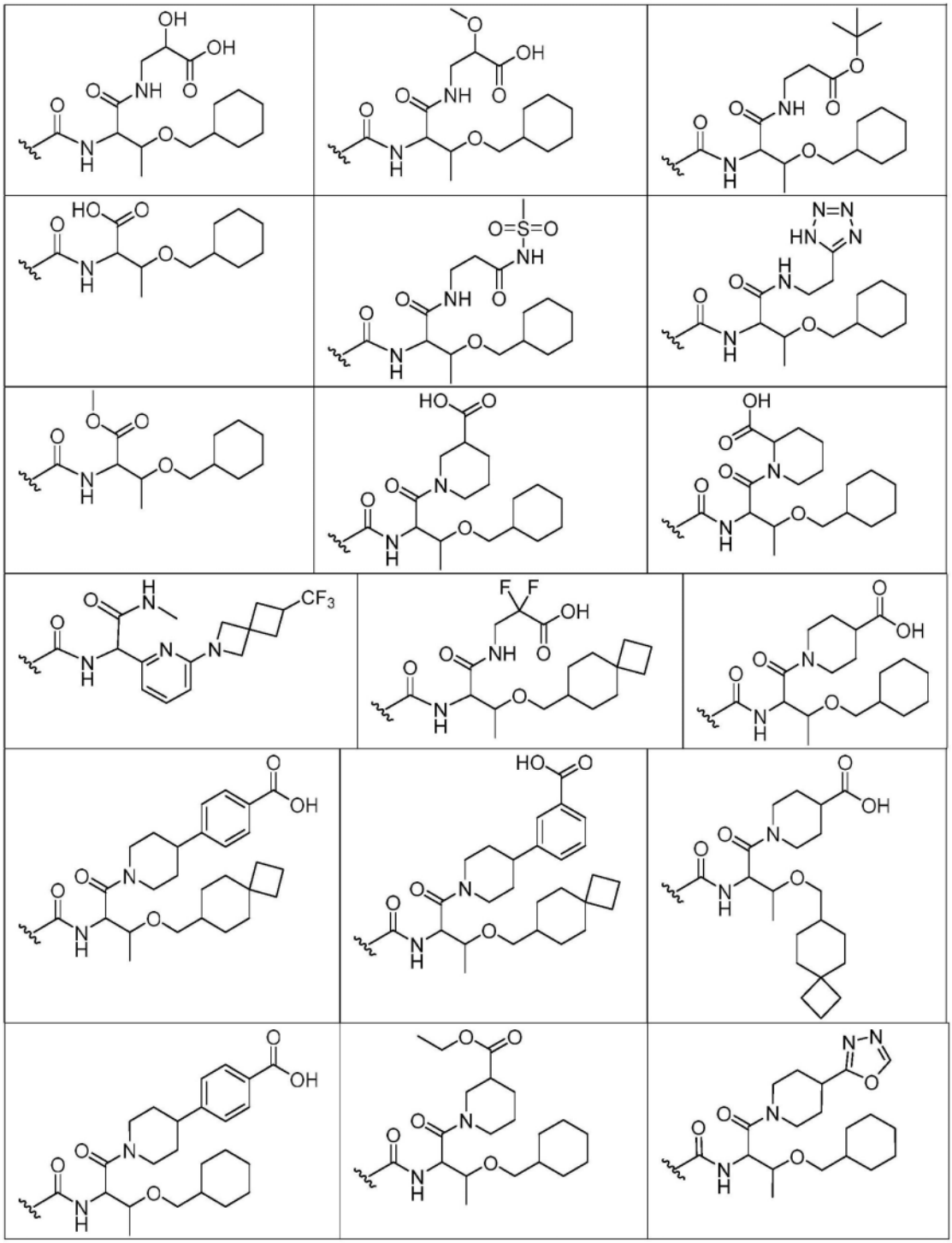
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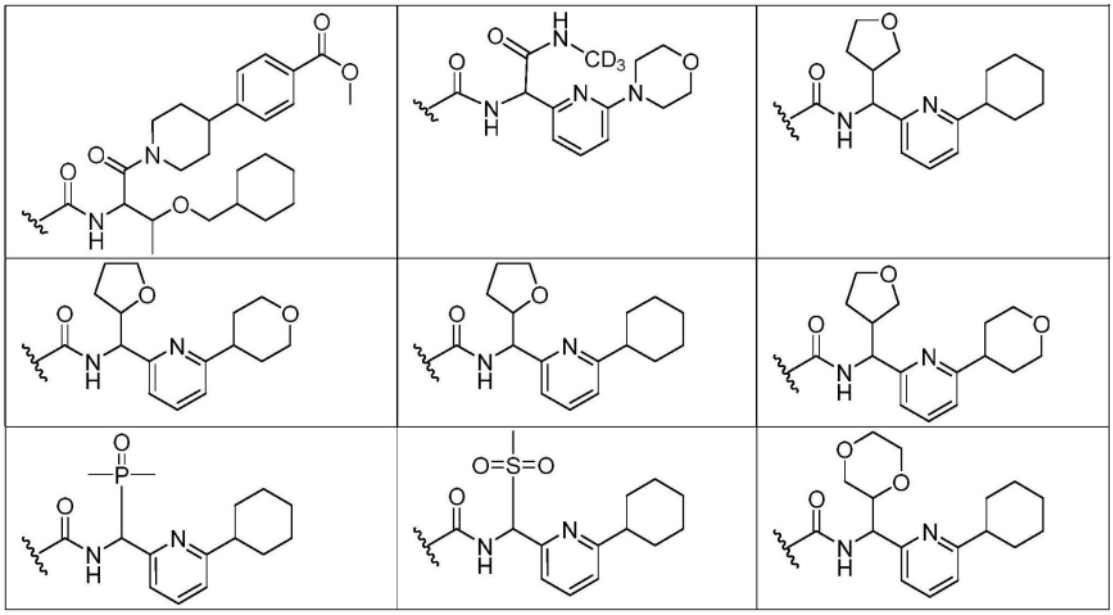


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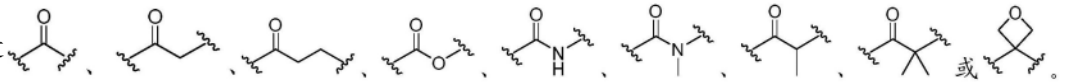
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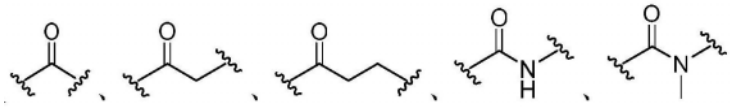
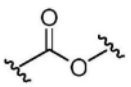


[0155] 

[0156] 在一些实施方案中,R^3是氢并且R^2是氢或在表A或表A-续中的取代基。

[0157] 如上文一般定义,L^2为饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS$(O)_2$-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。

[0158] 在一些实施方案中,L^2是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^2的0-2个亚甲基单元独立地被-C(O)O-、-C(O)-或-C(O)NR-替代。在一些实施方案中,L^2是C_{1-4}亚烷基链,其中L^2的1-2个亚甲基单元独立地被-C(O)O-、-C(O)-或-C(O)NR-替代。在一些实施方案中,L^2是C_{1-4}亚烷基链,其中L^2的1个亚甲基单元被-C(O)O-、-C(O)-或-C(O)NR-替代。在一些实施方案中,L^2是饱和的任选取代的二价C_{1-4}烃链。在一些实施方案中,L^2是在单个亚甲基单元上被两个取代基取代的饱和的二价C_{1-4}烃链,其与介于其间的碳原子一起形成3-7元碳环或杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,L^2是。

[0159] 在一些实施方案中,L^2是或。在一些实施方案中,L^2是。在一些实施方案中,L^2是。在一些实施方案中,L^2是选自下表1的化合物中所描述的那些。

[0160] 在一些实施方案中,L^2是饱和的、直链或支链的、任选取代的二价C_{1-4}烃链。在一些实施方案中,L^2是亚甲基。

[0161] 在一些实施方案中,L^2是-$S(O)_2$-。

[0162] 如上文一般定义,R^6是任选取代的C_{1-6}脂族基团或选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环

芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中该环状基团任选地被一个或多个R^7的实例取代。

[0163] 在一些实施方案中,R^6是任选取代的C_{1-6}脂族基团。在一些实施方案中,R^6是任选取代的甲基、乙基、异丙基或叔丁基基团。

[0164] 在一些实施方案中,R^6是选自以下的环状基团:3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子),其中该环状基团任选地被一个或多个R^7的实例取代。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的3-8元饱和的或部分不饱和的单环碳环。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的苯基。在一些实施方案中,R^6是选自以下的环状基团:环丙基、环丁基、环己基和苯基,其中该环状基团任选地被一个或多个R^7的实例取代。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的环丙基基团。在一些实施方案中,R^6是选自下表1的化合物中描述的那些。

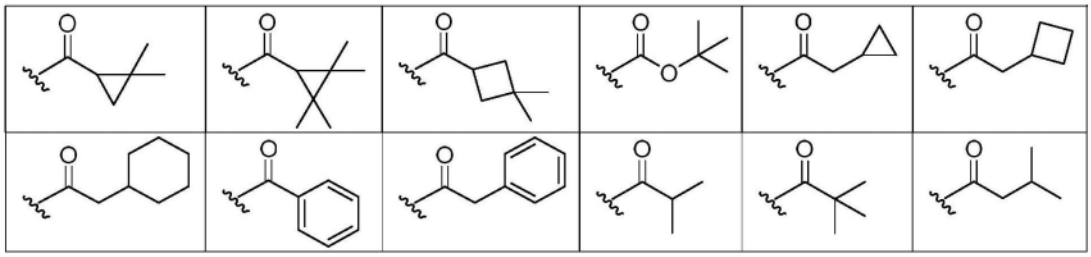
[0165] 在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的四氢呋喃基。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的四氢吡喃基。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的氧杂环丁烷。

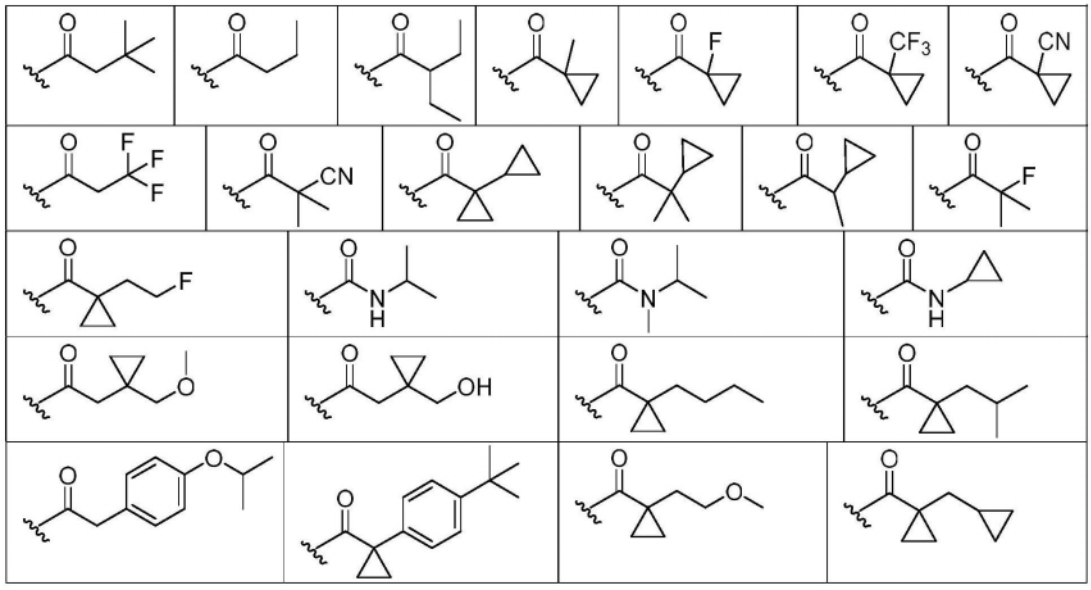
[0166] 在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的呋喃基。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的吡唑基。在一些实施方案中,R^6是任选地被一个或多个R^7的实例取代的噁唑基。

[0167] 如上文一般定义,R^7的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy。在一些实施方案中,$R^7$的每个实例独立地是卤素、-OR、-CN、任选取代的C_{1-6}脂族基团、任选取代的C_{1-6}脂族-Cy基团或Cy。在一些实施方案中,R^7的每个实例独立地是-F、甲基、乙基、异丙基、异丁基、-CN、任选取代的苯基、任选取代的苄基、-CF_3、-CH_2OH、-CH_2OCH_3、-$CH_2CH_2OCH_3$,-CH_2CH_2F、环丙基或-CH_2-(环丙基)。在一些实施方案中,R^7的每个实例独立地是C_{1-6}脂族基团。

[0168] 在一些实施方案中,-L^2-R^6是表B的取代基:

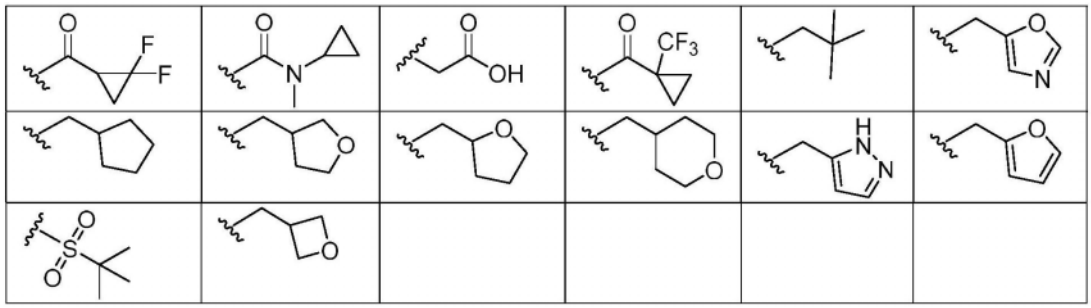
[0169] 表B:示例性-L^2-R^6取代基

[0170] 

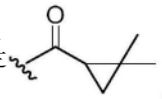
[0171] 

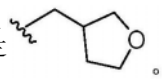
[0172] 在一些实施方案中,-L^2-R^6是表B-续的取代基:

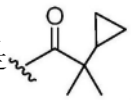
[0173] 表B-续.另外的示例性-L^2-R^6取代基

[0174] 

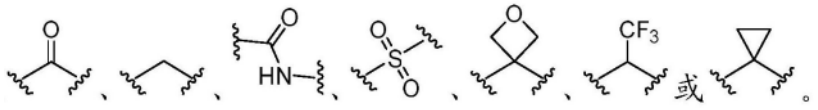
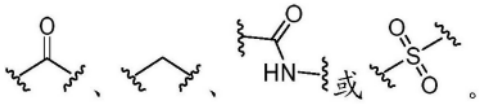
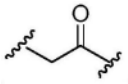
[0175] 在一些实施方案中,-L^2-R^6是表B或表B-续的取代基。

[0176] 在一些实施方案中、-L^2-R^6是。

[0177] 在一些实施方案中、-L^2-R^6是。

[0178] 在一些实施方案中、-L^2-R^6是。

[0179] 如上文一般定义,L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链,其中L^3的0-2个亚甲基单元独立地被-O-、-NR-、-S-、-OC(O)-、-C(O)O-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(S)-、-NRS(O)-、-$S(O)_2$NR-、-NRC(O)-、-C(O)NR-、-OC(O)NR-、-NRC(O)O-或-NRC(O)NR-替代。

[0180] 在一些实施方案中，L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}烃链，其中L^3的0-2个亚甲基单元独立地被-S(O)$_2$-、-C(O)NR-或-C(O)-替代。在一些实施方案中，L^3是C_{1-4}亚烷基链，其中L^3的1-2个亚甲基单元独立地被-S(O)$_2$-、-C(O)NR-或-C(O)-替代。在一些实施方案中，L^3是C_{1-4}亚烷基链，其中L^3的1个亚甲基单元被-S(O)$_2$-、-C(O)NR-或-C(O)-替代。在一些实施方案中，L^3是饱和的或不饱和的、直链或支链的、任选取代的二价C_{1-4}亚烷基链，其中L^3的0-2个亚甲基单元独立地被-C(O)O-或-C(O)-替代。在一些实施方案中，L^3是C_{1-4}亚烷基链，其中L^3的1-2个亚甲基单元独立地被-C(O)O-或-C(O)-替代。在一些实施方案中，L^3是C_{1-4}亚烷基链，其中L^3的1个亚甲基单元被-C(O)O-或-C(O)-替代。在一些实施方案中，L^3是饱和的任选取代的二价C_{1-4}烃链。在一些实施方案中，L^3是在单个亚甲基单元上被两个取代基取代的饱和的二价C_{1-4}烃链，其与介于其间的碳原子一起形成3-7元碳环或杂环（含有1-2个独立地选自氮、氧和硫的杂原子）。在一些实施方案中，L^3是在一些实施方案中，L^3是在一些实施方案中，L^3是。在一些实施方案中，L^3是。在一些实施方案中，L^3是选自下表1的化合物中所描述的那些。

[0181] 如上文一般定义，R^8是选自以下的环状基团：3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)，其中该环状基团任选地被一个或多个R^9的实例取代。

[0182] 在一些实施方案中，R^8是选自以下的环状基团：3-8元饱和的或部分不饱和的单环碳环、7-12元饱和的或部分不饱和的双环碳环、苯基、8-10元双环芳族碳环、3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、7-12元饱和的或部分不饱和的双环杂环(含有1-4个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)，其中该环状基团任选地被一个或多个R^9的实例取代。在一些实施方案中，R^8是选自以下的环状基团：3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)、5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)和8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)，其中该环状基团任选地被一个或多个R^9的实例取代。在一些实施方案中，R^8是任选地被一个或多个R^9的实例取代的3-8元饱和的或部分不饱和的单环杂环(含有1-2个独立地选自氮、氧和硫的杂原子)。在一些实施方案中，R^8是任选地被一个或多个R^9的实例的5-6元单环芳杂环(含有1-4个独立地选自氮、氧和硫的杂原子)。在一些实施方案中，R^8是任选地被一个或多个R^9的实例的8-10元双环芳杂环(含有1-5个独立地选自氮、氧和硫的杂原子)。在一些实施方案中，R^8是选自以下的环状基团：吡唑基、噁唑基、噻唑基、吡咯烷基、四氢吡喃基、吡啶基、咪唑基、吲哚基、1,2,4-三唑

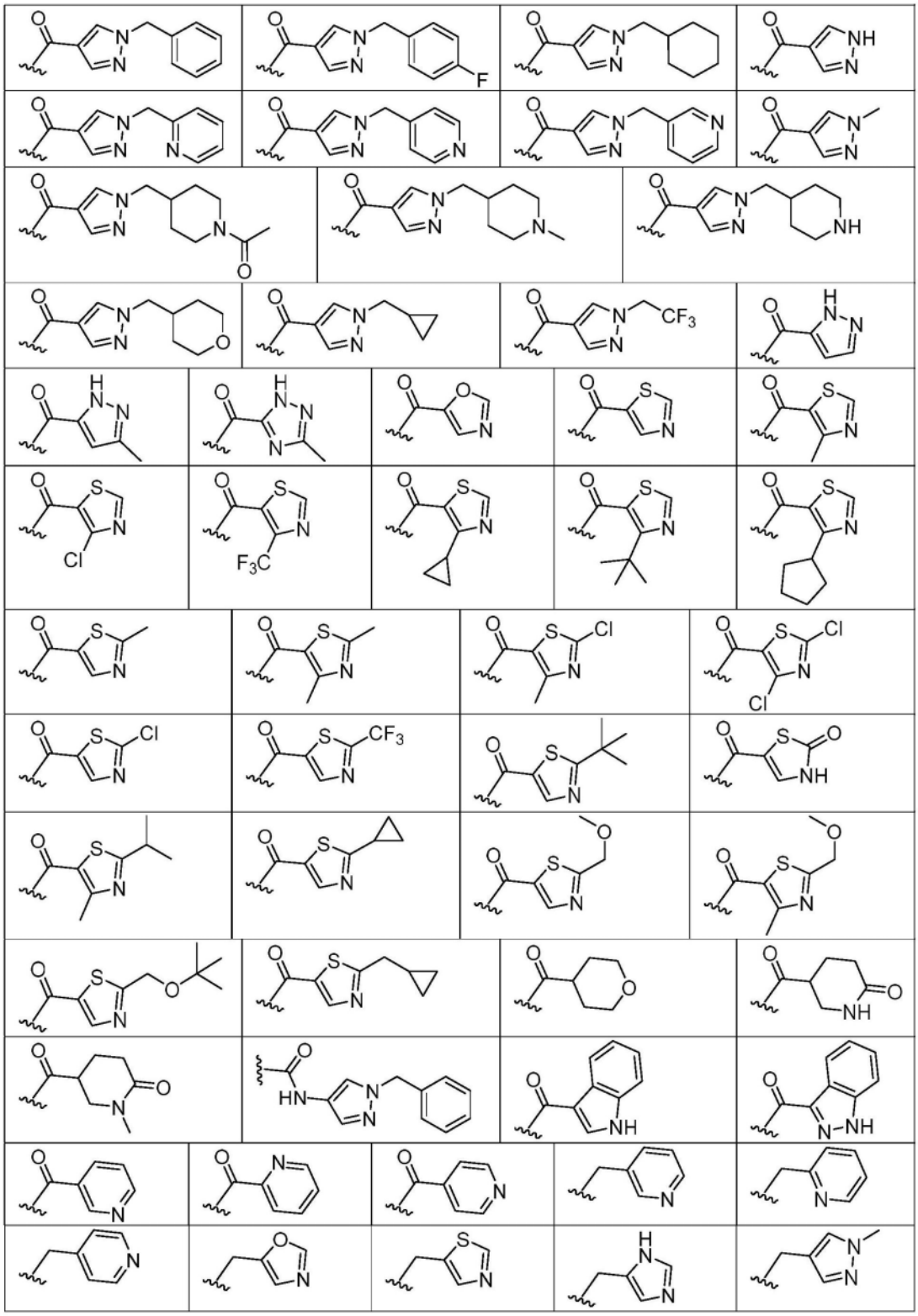
基、1,2,4-噻二唑基、哌啶基和吲唑基,其中该环状基团任选地被一个或多个R^9的实例取代。在一些实施方案中,R^8是任选地被一个或多个R^9的实例取代的吡唑基或噻唑基基团。在一些实施方案中,R^8是吡唑基或噻唑基基团。在一些实施方案中,R^8是选自下表1的化合物中所描述的那些。

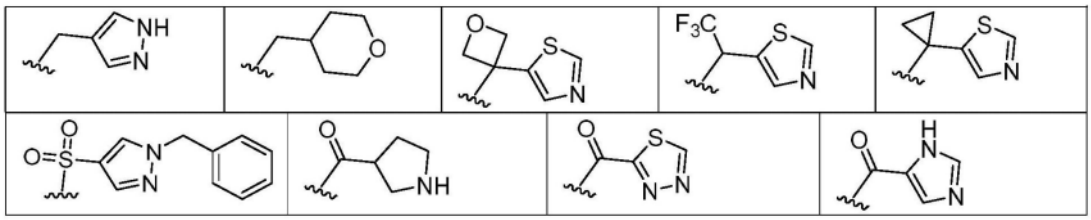
[0183] 如上文一般定义,R^9的每个实例独立地是卤素、-CN、-NO_2、-OR、-SR、-NR_2、-S(O)$_2$R、-S(O)$_2$$NR_2$、-S(O)R、-S(O)$NR_2$、-C(O)R、-C(O)OR、-C(O)$NR_2$、-C(O)N(R)OR、-OC(O)R、-OC(O)NR_2、-N(R)C(O)OR、-N(R)C(O)R、-N(R)C(O)NR_2、-N(R)C(NR)NR_2、-N(R)S(O)$_2$$NR_2$、-N(R)S(O)$_2$R、任选取代的$C_{1-6}$脂族基团、任选取代的$C_{1-6}$脂族-Cy基团或Cy。

[0184] 在一些实施方案中,R^9的每个实例独立地是卤素、任选取代的C_{1-6}脂族基团、任选取代的C_{1-6}脂族-Cy基团或Cy。在一些实施方案中,R^9的每个实例独立地是任选取代的C_{1-6}脂族-Cy基团,其中该Cy是选自以下的任选取代的基团:苯基、环己基、吡啶基、哌啶基、环丙基或四氢吡喃基。在一些实施方案中,R^9是苄基基团。在一些实施方案中,R^9的每个实例独立地是卤素或任选取代的C_{1-6}脂族基团。在一些实施方案中,R^9是选自下表1的化合物中所描述的那些。

[0185] 在一些实施方案中,-L^3-R^8是表C的取代基:

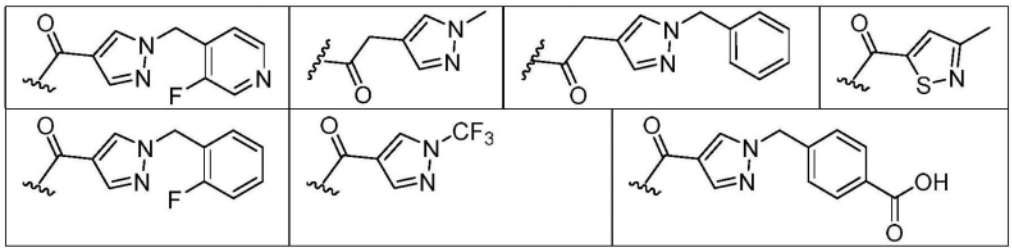
[0186] 表C:示例性-L^3-R^8取代基

[0187] 

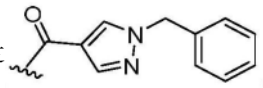
[0188] 

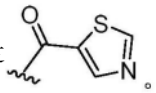
[0189] 在一些实施方案中,-L^3-R^8是表C-续的取代基:

[0190] 表C-续.另外的示例性-L^3-R^8取代基

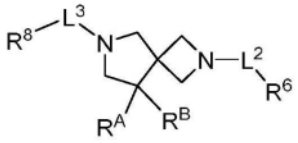
[0191] 

[0192] 在一些实施方案中,-L^3-R^8是表C或表C-续的取代基。

[0193] 在一些实施方案中,-L^3-R^8是。

[0194] 在一些实施方案中,-L^3-R^8是。

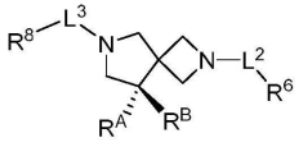
[0195] 在一些实施方案中,式IA的化合物是式IIA的化合物:

[0196] 

IIA

[0197] 或其药学上可接受的盐,其中R^A、R^B、L^2、R^6、L^3和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^A、R^B、L^2、R^6、L^3和R^8及其组成的基团各自如式IA中所定义和描述。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,-L^2-R^6是来自表B的取代基。在一些实施方案中,-L^3-R^8是来自表C的取代基。在一些实施方案中,R^A是来自表A的取代基并且-L^2-R^6是来自表B的取代基。在一些实施方案中,R^A是来自表A的取代基并且-L^3-R^8是来自表C的取代基。在一些实施方案中,-L^2-R^6是来自表B的取代基并且-L^3-R^8是来自表C的取代基。并且在一些实施方案中,R^A是来自表A的取代基,-L^2-R^6是来自表B的取代基并且-L^3-R^8是来自表C的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基。在一些实施方案中,-L^3-R^8是来自表C-续的取代基。在一些实施方案中,R^A是来自表A-续的取代基并且-L^2-R^6是来自表B-续的取代基。在一些实施方案中,R^A是来自表A-续的取代基并且-L^3-R^8是来自表C-续的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基并且-L^3-R^8是来自表C-续的取代基。并且在一些实施方案中,R^A是来自表A-续的取代基,-L^2-R^6是来自表B-续的取代基并且-L^3-R^8是来自于表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B或表B-续的取代基。在一些实施方案中,-L^3-R^8是来自表C或表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且-L^2-R^6是来自表B或表B-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且-L^3-R^8是来自表C或表C-续的取代基。在一些实施方案中,-L^2-R^6是来自表B或表B-续的取代基并且-L^3-R^8是来自表C或表C-续的取代基。并且在一些实施方案中,R^A是来自表A或表A-续的取代基,-L^2-R^6是来自表B或表B-续的取代基并且-L^3-R^8是来自于表C或表C-续的取代基。

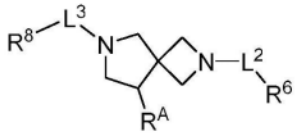
[0198] 在一些实施方案中,式IA的化合物是式IIB的化合物:

[0199] 

IIB

[0200] 或其药学上可接受的盐,其中R^A、R^B、L^2、R^6、L^3和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^A、R^B、L^2、R^6、L^3和R^8及其组成的基团各自如式IA中所定义和描述。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,$-L^2-R^6$是来自表B的取代基。在一些实施方案中,$-L^3-R^8$是来自表C的取代基。在一些实施方案中,R^A是来自表A的取代基并且$-L^2-R^6$是来自表B的取代基。在一些实施方案中,R^A是来自表A的取代基并且$-L^3-R^8$是来自表C的取代基。在一些实施方案中,$-L^2-R^6$是来自表B的取代基并且$-L^3-R^8$是来自表C的取代基。并且在一些实施方案中,R^A是表A的取代基,$-L^2-R^6$是来自表B的取代基并且$-L^3-R^8$是来自表C的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,$-L^2-R^6$是来自表B-续的取代基。在一些实施方案中,$-L^3-R^8$是来自表C-续的取代基。在一些实施方案中,R^A是来自表A-续的取代基并且$-L^2-R^6$是来自表B-续的取代基。在一些实施方案中,R^A是来自表A-续的取代基并且$-L^3-R^8$是来自表C-续的取代基。在一些实施方案中,$-L^2-R^6$是来自表B-续的取代基并且$-L^3-R^8$是来自表C-续的取代基。并且在一些实施方案中,R^A是来自表A-续的取代基,$-L^2-R^6$是来自表B-续的取代基并且$-L^3-R^8$是来自于表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基。在一些实施方案中,$-L^2-R^6$是来自表B或表B-续的取代基。在一些实施方案中,$-L^3-R^8$是来自表C或表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且$-L^2-R^6$是来自表B或表B-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且$-L^3-R^8$是来自表C或表C-续的取代基。在一些实施方案中,$-L^2-R^6$是来自表B或表B-续的取代基并且$-L^3-R^8$是来自表C或表C-续的取代基。并且在一些实施方案中,R^A是来自表A或表A-续的取代基,$-L^2-R^6$是来自表B或表B-续的取代基并且$-L^3-R^8$是来自于表C或表C-续的取代基。

[0201] 在一些实施方案中,式I或IA的化合物是式II的化合物:

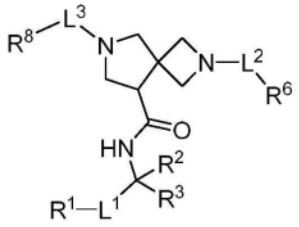
[0202] 

II

[0203] 或其药学上可接受的盐,其中R^A、L^2、R^6、L^3和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^A、L^2、R^6、L^3和R^8及其组成基团各自如式I中所定义和描述。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,$-L^2-R^6$是来自表B的取代基。在一些实施方案中,$-L^3-R^8$是来自表C的取代基。在一些实施方案中,R^A是来自表A的取代基并且$-L^2-R^6$是来自表B的取代基。在一些实施方案中,R^A是来自表A的取代基并且$-L^3-R^8$是来自表C的取代基。在一些实施方案中,$-L^2-R^6$是来自表B的取代基并且$-L^3-R^8$是来自表C的取代基。并且在一些实施方案中,R^A是来自表A的取代基,$-L^2-R^6$是来自表B的取代基并且$-L^3-R^8$是来自表C的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,$-L^2-R^6$是来自表B-续的取代基。在一些实施方案中,$-L^3-R^8$是来自表C-续的取代基。在一些实施方

案中,R^A是来自表A-续的取代基并且-L^2-R^6是来自表B-续的取代基。在一些实施方案中,R^A是来自表A-续的取代基并且-L^3-R^8是来自表C-续的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基并且-L^3-R^8是来自表C-续的取代基。并且在一些实施方案中,R^A是来自表A-续的取代基,-L^2-R^6是来自表B-续的取代基并且-L^3-R^8是来自于表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B或表B-续的取代基。在一些实施方案中,-L^3-R^8是来自表C或表C-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且-L^2-R^6是来自表B或表B-续的取代基。在一些实施方案中,R^A是来自表A或表A-续的取代基并且-L^3-R^8是来自表C或表C-续的取代基。在一些实施方案中,-L^2-R^6是来自表B或表B-续的取代基并且-L^3-R^8是来自表C或表C-续的取代基。并且在一些实施方案中,R^A是来自表A或表A-续的取代基,-L^2-R^6是来自表B或表B-续的取代基并且-L^3-R^8是来自表C或表C-续的取代基。

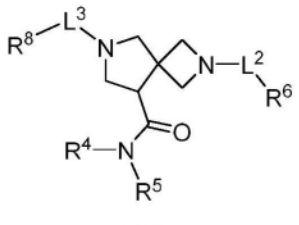
[0204] 在一些实施方案中,式I或IA的化合物是式IIIa的化合物:

[0205] 

IIIa

[0206] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^3、L^2、R^6、L^3和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,R^2是来自表R^2的取代基。在一些实施方案中,R^2是来自表R^2-续中的取代基。在一些实施方案中,R^2是-C(O)NR_2,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子),并且R^3是氢。在一些实施方案中,L^2是亚甲基。在一些实施方案中,L^3是亚甲基。在一些实施方案中,L^2和L^3都是亚甲基。在一些实施方案中,L^2是-C(O)-。在一些实施方案中,L^3是-C(O)-。在一些实施方案中,L^2和L^3都是-C(O)-。在一些实施方案中,-L^2-R^6是来自表B的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基。在一些实施方案中,-L^3-R^8是来自表C的取代基。在一些实施方案中,-L^3-R^8是来自表C的取代基。

[0207] 在一些实施方案中,式I或IA的化合物是式IIIb的化合物:

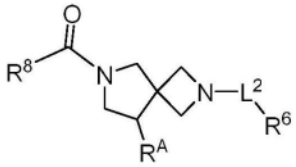
[0208] 

IIIb

[0209] 或其药学上可接受的盐,其中R^4、R^5、L^2、R^6、L^3和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,L^2是亚甲基。在一些实施方案中,L^3是亚甲基。在一些实施方案中,L^2和L^3都是亚甲基。在一些实施方案中,L^2是-C(O)-。在一些实施方案中,L^3是-C(O)-。在一些实施方案中,L^2和L^3都是-C(O)-。在一些实施方案中,-L^2-R^6是来自表B的取代基。在

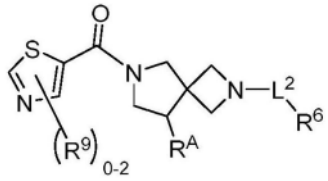
一些实施方案中,-L^2-R^6是来自表B-续的取代基。在一些实施方案中,-L^3-R^8是来自表C的取代基。在一些实施方案中,-L^3-R^8是来自表C的取代基。

[0210] 在一些实施方案中,式I或IA的化合物是式IVa的化合物:

[0211] 

IVa

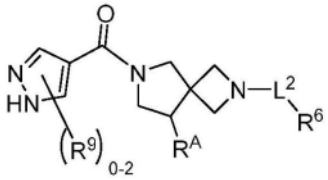
[0212] 或其药学上可接受的盐,其中R^A、L^2、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基。在一些实施方案中,式I的化合物是式IVb的化合物:

[0213] 

IVb

[0214] 或其药学上可接受的盐,其中R^A、L^2、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,噻唑基基团没有被R^9取代。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基。

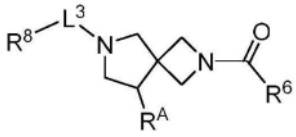
[0215] 在一些实施方案中,式I或IA的化合物是式IVc的化合物:

[0216] 

IVc

[0217] 或其药学上可接受的盐,其中R^A、L^2、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,-L^2-R^6是来自表B的取代基。在一些实施方案中,-L^2-R^6是来自表B-续的取代基。

[0218] 在一些实施方案中,式I或IA的化合物是式Va的化合物:

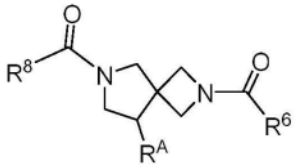
[0219] 

Va

[0220] 或其药学上可接受的盐,其中R^A、R^6、L^3和R^8及其组成的基团各自如本文所定义和

描述。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,R^A是来自表A-续的取代基。在一些实施方案中,$-L^3-R^8$是来自表C的取代基。在一些实施方案中,$-L^3-R^8$是来自表C-续的取代基。

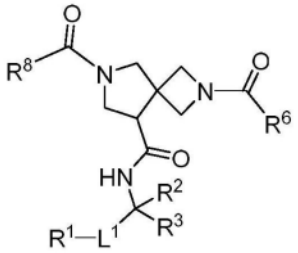
[0221] 在一些实施方案中,式I或IA的化合物是式Vb的化合物:

[0222] 

Vb

[0223] 或其药学上可接受的盐,其中R^A、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,R^A是来自表A的取代基。在一些实施方案中,R^A是来自表A-续的取代基。

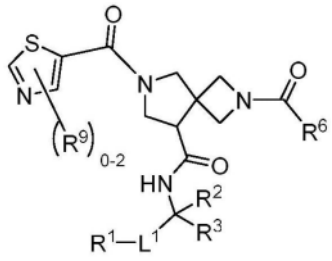
[0224] 在一些实施方案中,式I或IA的化合物是式VIa的化合物:

[0225] 

VIa

[0226] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^3、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,R^2是来自表R^2或表R^2-续的取代基。在一些实施方案中,R^2是$-C(O)NR_2$,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)并且R^3是氢。在一些实施方案中,R^6是任选取代的环丙基基团。

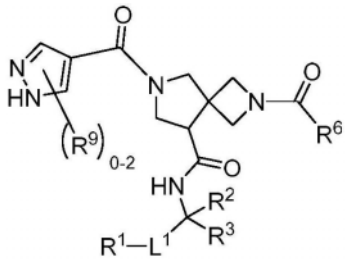
[0227] 在一些实施方案中,式I或IA的化合物是式VIb的化合物:

[0228] 

VIb

[0229] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^3、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^2是来自表R^2或表R^2-续的取代基。在一些实施方案中,R^2是$-C(O)NR_2$,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)并且R^3是氢。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,噻唑基基团没有被R^9取代。

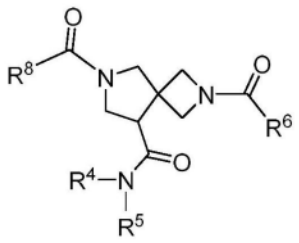
[0230] 在一些实施方案中,式I或IA的化合物是式VIc的化合物:

[0231] 

VIc

[0232] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^3、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^2是来自表R^2或表R^2-续的取代基。在一些实施方案中,R^2是-C(O)NR_2,其中两个R基团与介于其间的氮原子一起形成任选取代的4-7元饱和的环(除了氮之外,含有0-3个独立地选自氮、氧和硫的杂原子)并且R^3是氢。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。

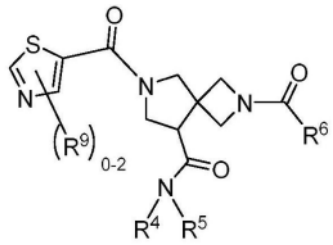
[0233] 在一些实施方案中,式I或IA的化合物是式VId的化合物:

[0234] 

VId

[0235] 或其药学上可接受的盐,其中R^4、R^5、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^6是任选取代的环丙基基团。

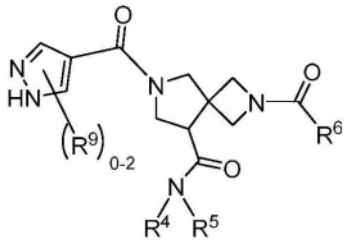
[0236] 在一些实施方案中,式I或IA的化合物是式VIe的化合物:

[0237] 

VIe

[0238] 或其药学上可接受的盐,其中R^4、R^5、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,噻唑基基团没有被R^9取代。

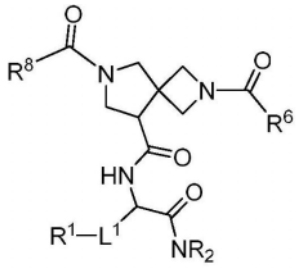
[0239] 在一些实施方案中,式I或IA的化合物是式VIf的化合物:

[0240] 

VIf

[0241] 或其药学上可接受的盐,其中R^4、R^5、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。

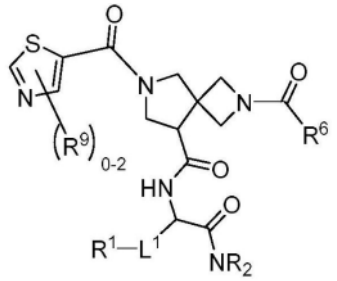
[0242] 在一些实施方案中,式I或IA的化合物是式VIIa的化合物:

[0243] 

VIIa

[0244] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。

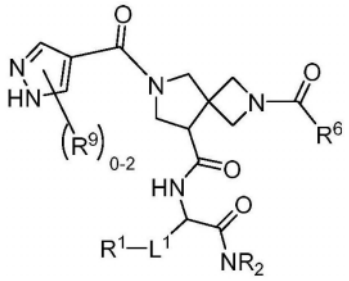
[0245] 在一些实施方案中,式I或IA的化合物是式VIIb的化合物:

[0246] 

VIIb

[0247] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,噻唑基基团没有被R^9取代。

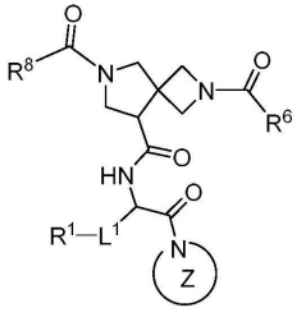
[0248] 在一些实施方案中,式I或IA的化合物是式VIIc的化合物:

[0249] 

VIIc

[0250] 或其药学上可接受的盐,其中L^1、R^1、R^2、R^6和R^9及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。

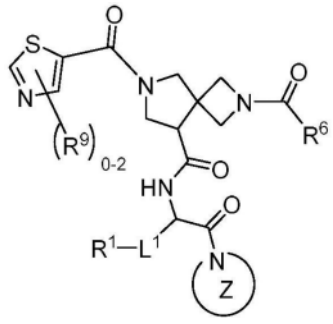
[0251] 在一些实施方案中,式I或IA的化合物是式VIIIa的化合物:

[0252] 

VIIIa

[0253] 或其药学上可接受的盐,其中L^1、R^1、R^6和R^8及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

[0254] 在一些实施方案中,式I或IA的化合物是式VIIIb的化合物:

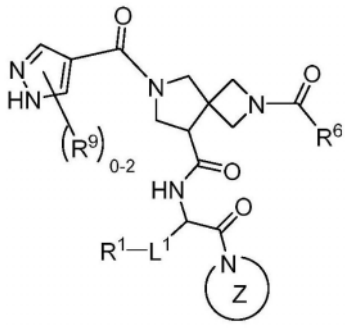
[0255] 

VIIIb

[0256] 或其药学上可接受的盐,其中L^1、R^1和R^9及其组成的基团各自如本文所定义和描

述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,噻唑基基团没有被R^9取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

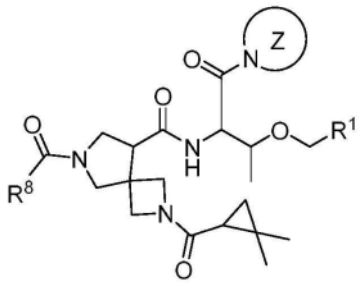
[0257] 在一些实施方案中,式I或IA的化合物是式VIIIc的化合物:

[0258] 

VIIIc

[0259] 或其药学上可接受的盐,其中L^1、R^1、R^6和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,L^1是任选取代的直链或支链C_{1-4}亚烷基链,其中L^1的1-2个亚甲基单元独立地被-O-、-NR-、-C(O)O-或-NRC(O)-替代。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

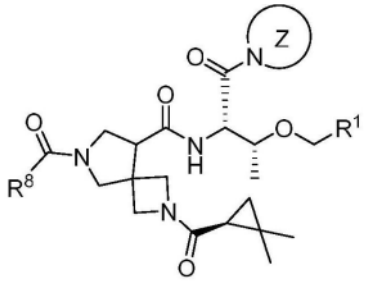
[0260] 在一些实施方案中,式I或IA的化合物是式IXa的化合物:

[0261] 

IXa

[0262] 或其药学上可接受的盐,其中R^1和R^8及其组成基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团,如本文所限定和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,Z是任选取代的环状基团,选自哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

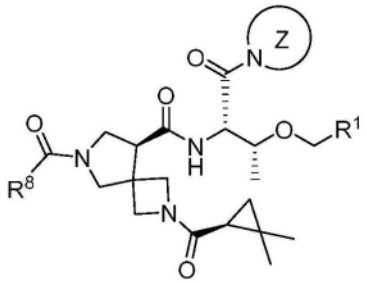
[0263] 在一些实施方案中,式I或IA的化合物是式IXa*的化合物:

[0264] 

IXa*

[0265] 或其药学上可接受的盐,其中R^1和R^8及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

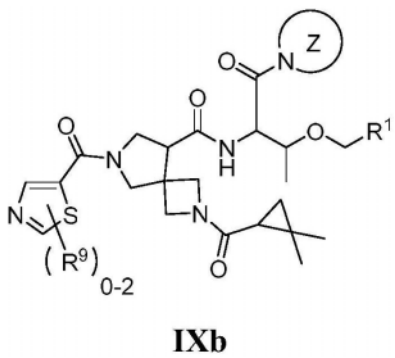
[0266] 在一些实施方案中,式I或IA的化合物是式IXa*的化合物:

[0267] 

IXa**

[0268] 或其药学上可接受的盐,其中R^1和R^8及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

[0269] 在一些实施方案中,式I或IA的化合物是式IXb的化合物:

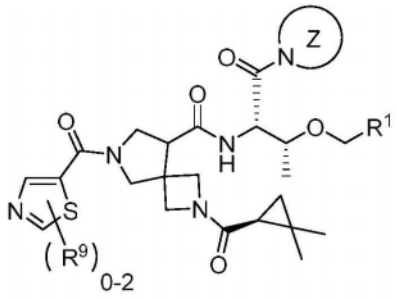
[0270] 

IXb

[0271] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,噻唑基基团没有被R^9取代。在一些实施方案中,噻唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯

烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

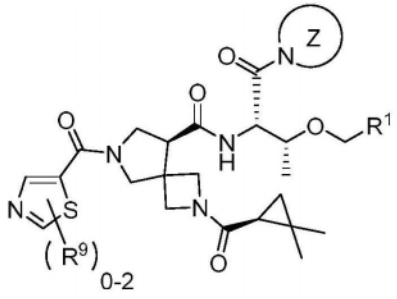
[0272] 在一些实施方案中,式I或IA的化合物是式IXb*的化合物:

[0273] 

IXb*

[0274] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,噻唑基基团没有被R^9取代。在一些实施方案中,噻唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

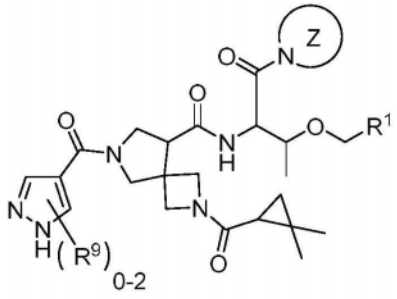
[0275] 在一些实施方案中,式I或IA的化合物是式IXb**的化合物:

[0276] 

IXb**

[0277] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,噻唑基基团没有被R^9取代。在一些实施方案中,噻唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

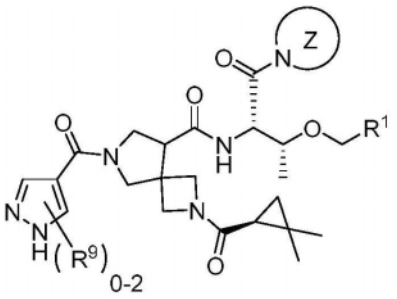
[0278] 在一些实施方案中,式I或IA的化合物是式IXc的化合物:

[0279] 

IXc

[0280] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

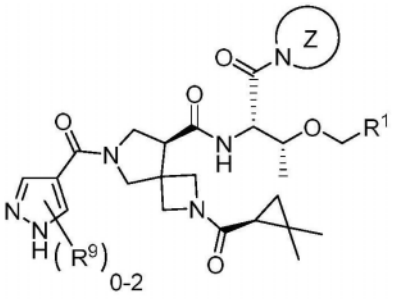
[0281] 在一些实施方案中,式I或IA的化合物是式IXc*的化合物:

[0282] 

IXc*

[0283] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

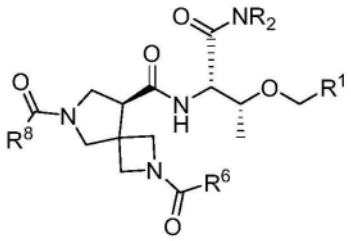
[0284] 在一些实施方案中,式I或IA的化合物是式IXc**的化合物:

[0285] 

IXc**

[0286] 或其药学上可接受的盐,其中R^1和R^9及其组成的基团各自如本文所定义和描述,并且环状部分Z是由两个R基团形成的任选取代的环状基团(如本文所定义和描述)。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环己基。在一些实施方案中,吡唑基基团没有被R^9取代。在一些实施方案中,吡唑基基团被一个R^9的实例(其是苄基基团)取代。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

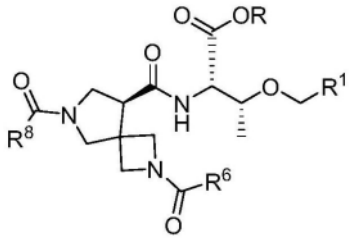
[0287] 在一些实施方案中,式I或IA的化合物是式Xa的化合物:

[0288] 

Xa

[0289] 或其药学上可接受的盐,其中R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。

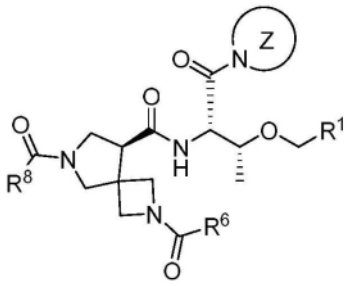
[0290] 在一些实施方案中,式I或IA的化合物是式Xb的化合物:

[0291] 

Xb

[0292] 或其药学上可接受的盐,其中R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。

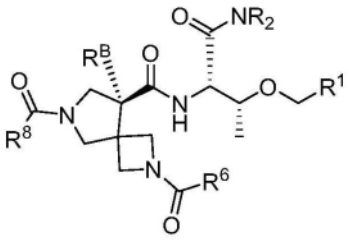
[0293] 在一些实施方案中,式I或IA的化合物是式Xc的化合物:

[0294] 

Xc

[0295] 或其药学上可接受的盐,其中Z、R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

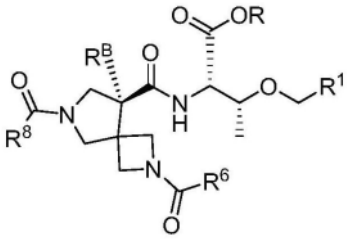
[0296] 在一些实施方案中,式IA的化合物是式XIa的化合物:

[0297] 

XIa

[0298] 或其药学上可接受的盐,其中R^B、R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。

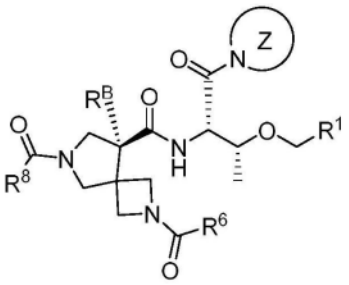
[0299] 在一些实施方案中,式IA的化合物是式XIb的化合物:

[0300] 

XIb

[0301] 或其药学上可接受的盐,其中R^B、R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。

[0302] 在一些实施方案中,式IA的化合物是式XIc的化合物:

[0303] 

XIc

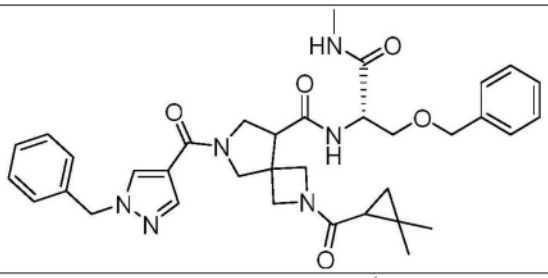
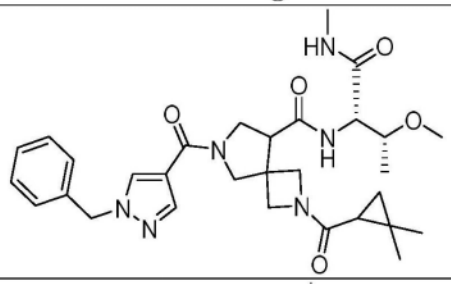
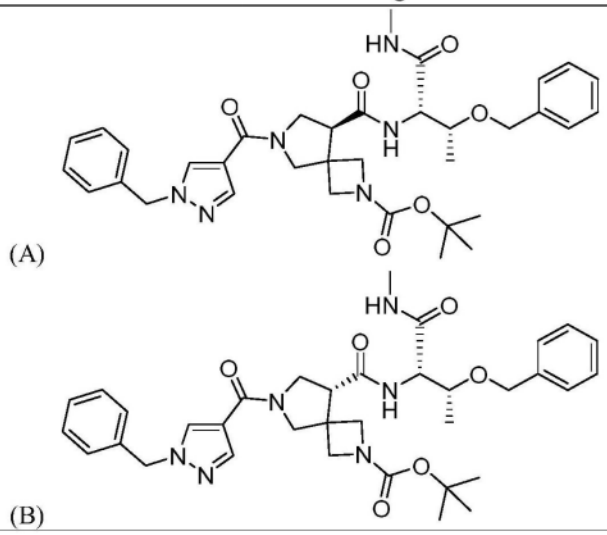
[0304] 或其药学上可接受的盐,其中Z、R^B、R^1、R^6和R^8及其组成的基团各自如本文所定义和描述。在一些实施方案中,R^1是苯基。在一些实施方案中,R^1是环已基。在一些实施方案中,R^6是任选取代的环丙基基团。在一些实施方案中,Z是选自以下的任选取代的环状基团:哌啶基、吗啉基、哌嗪基、氮杂环丁基、吡咯烷基、氮杂螺[3.3]庚基和二氮杂螺[3.3]庚基。

[0305] 在一些实施方案中,该化合物的至少一个氢原子是氘原子。在一些实施方案中,该化合物的至少一个C_1-C_6脂族基团被至少一个氘原子取代。在一些实施方案中,该化合物的至少一个C_1-C_6烷基基团被至少一个氘原子取代。在一些实施方案中,该化合物的至少一个C_1-C_6亚烷基基团被至少一个氘原子取代。在一些实施方案中,该化合物的至少一个二价C_{1-6}烃链基团被至少一个氘原子取代。在一些实施方案中,R^B是-CD_3。在一些实施方案中,R^2被一个或多个氘原子取代。在一些实施方案中,R^1被一个或多个氘原子取代。

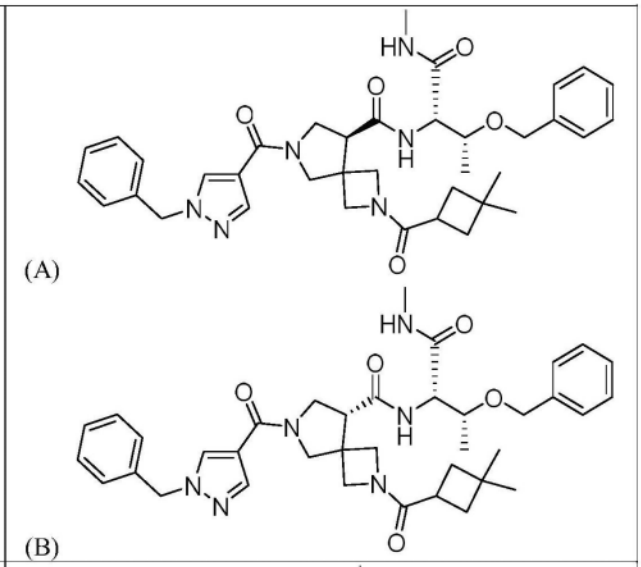
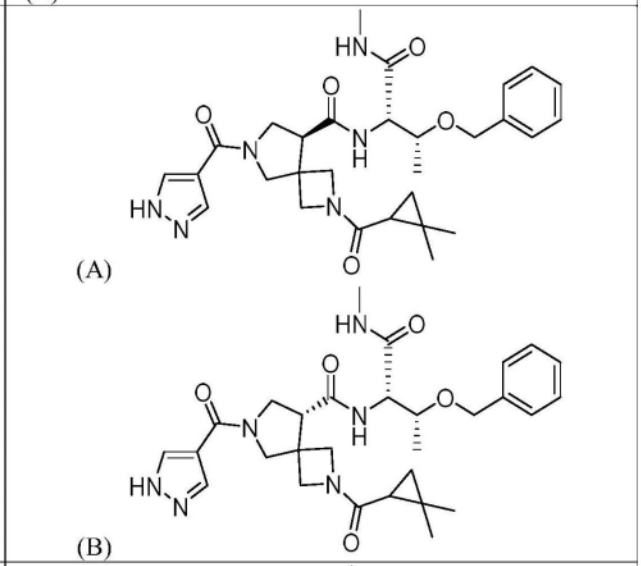
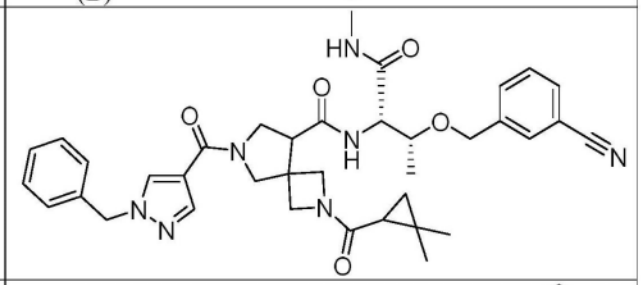
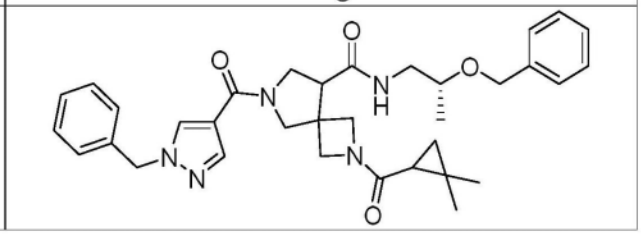
[0306] 本公开的示例性化合物列于下表1中。

[0307] 表1.示例性化合物

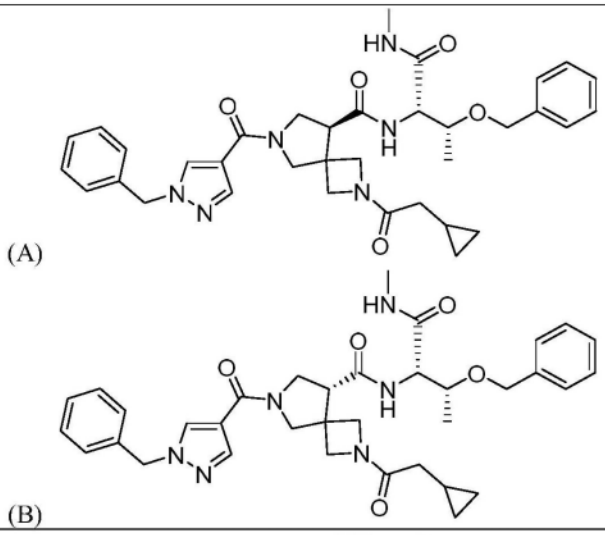
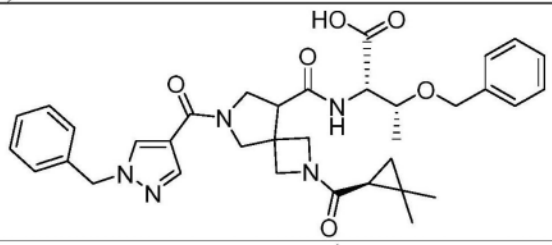
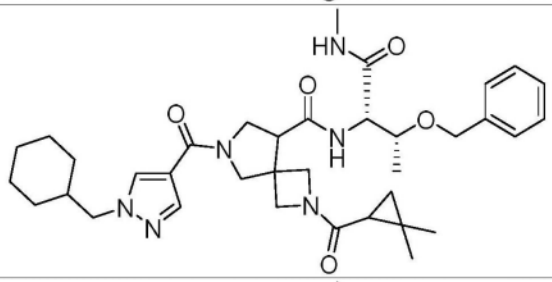
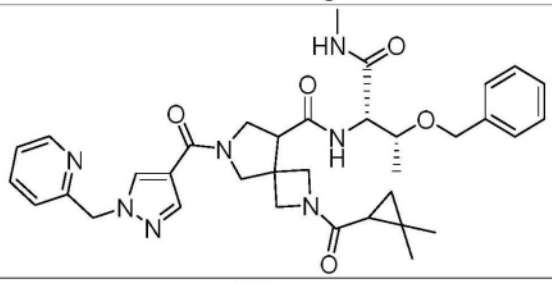
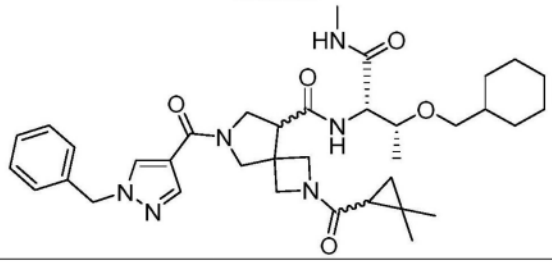
[0308]

化合物编号	结构
I-1	
I-2	
I-3	 (A) (B)

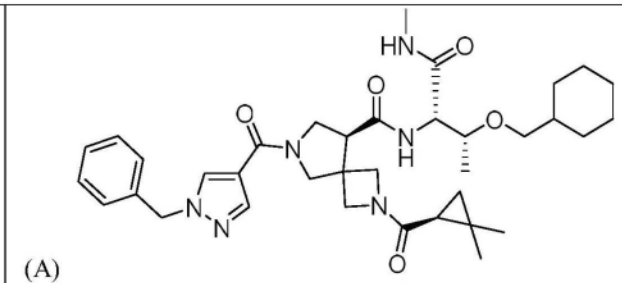
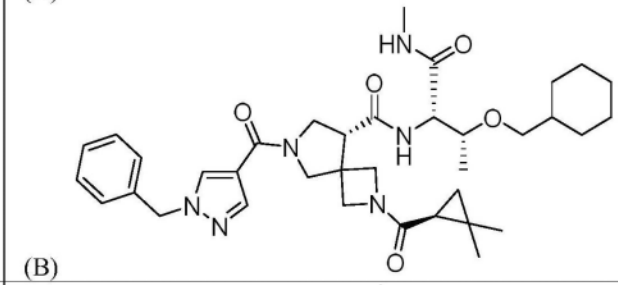
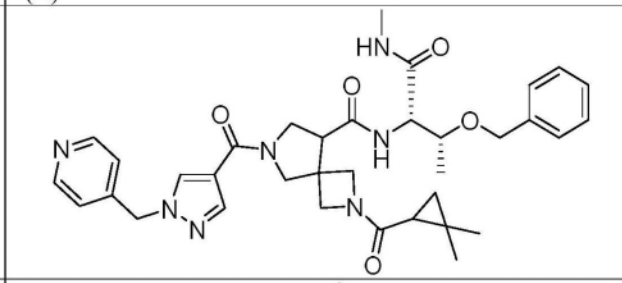
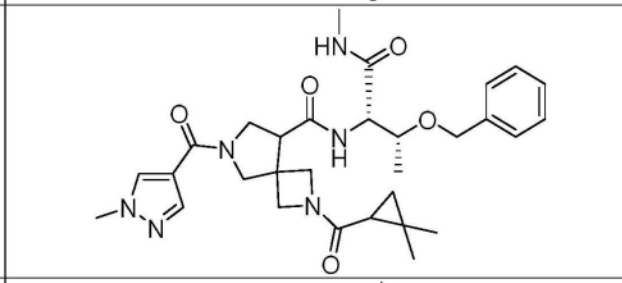
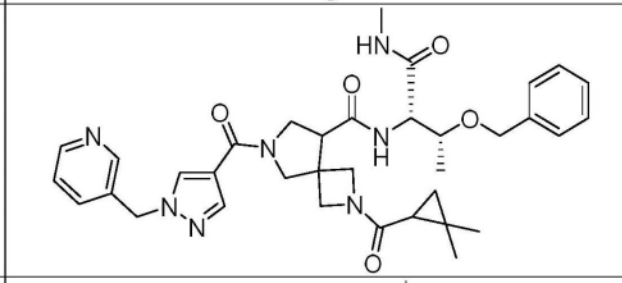
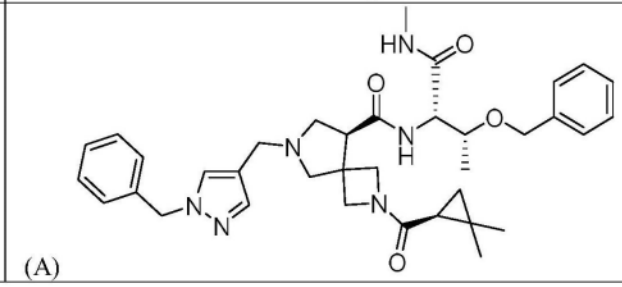
[0309]

I-4	 (A) (B)
I-5	 (A) (B)
I-6	
I-7	

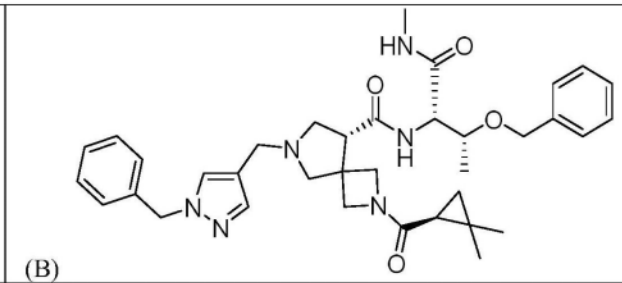
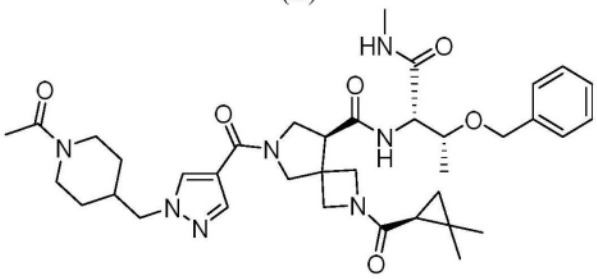
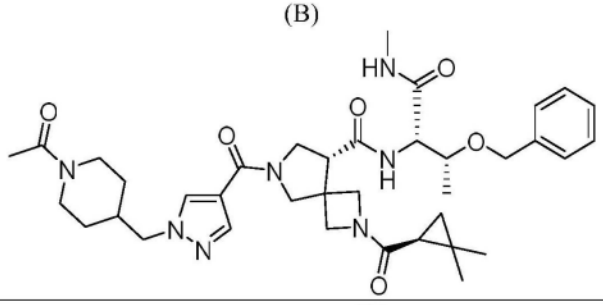
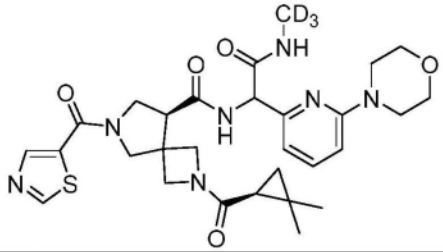
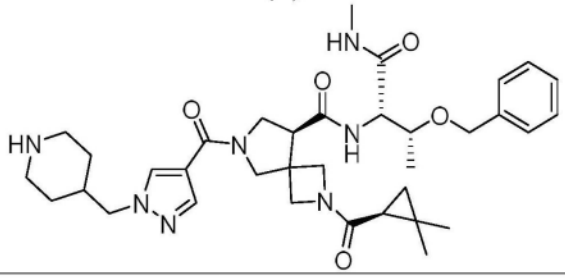
[0310]

I-8	 (A) (B)
I-9	
I-10	
I-11	
I-12	Mixture 

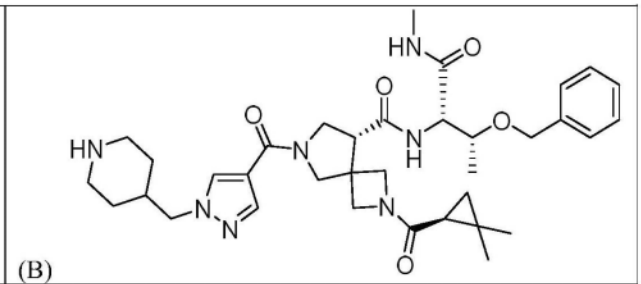
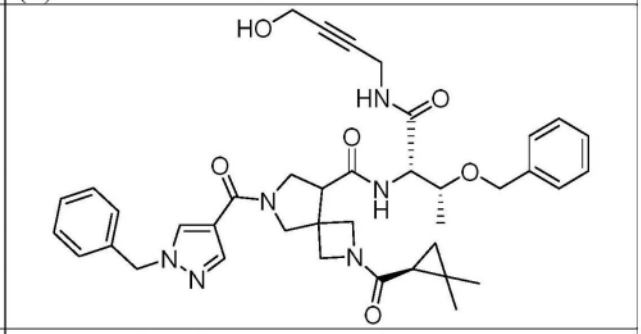
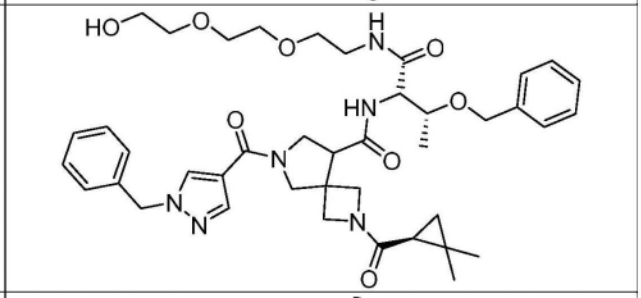
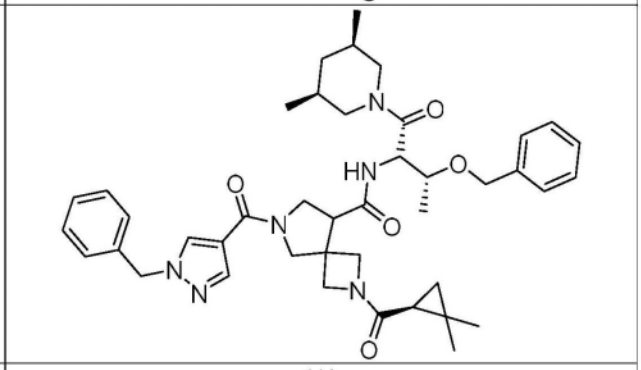
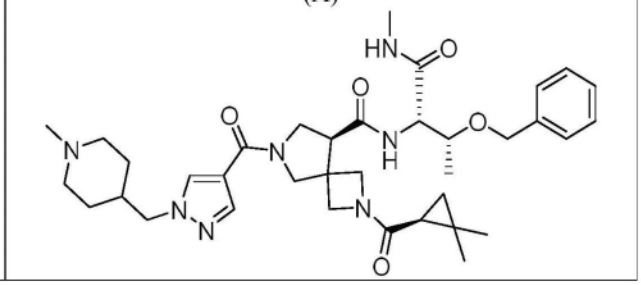
[0311]

	 (A)  (B)
I-13	
I-14	
I-15	
I-16	 (A)

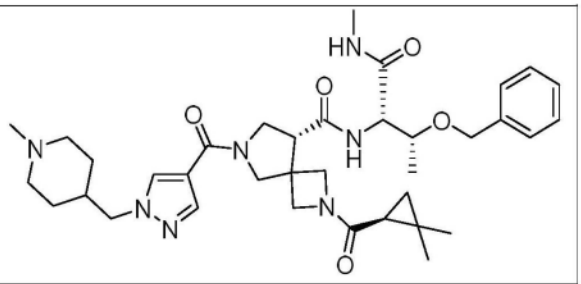
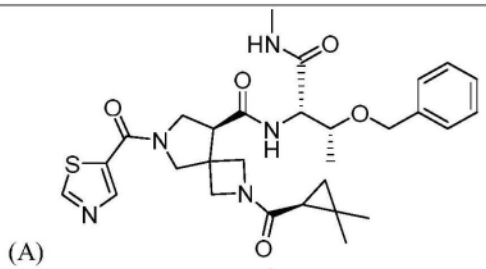
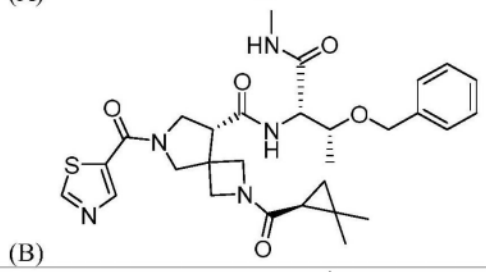
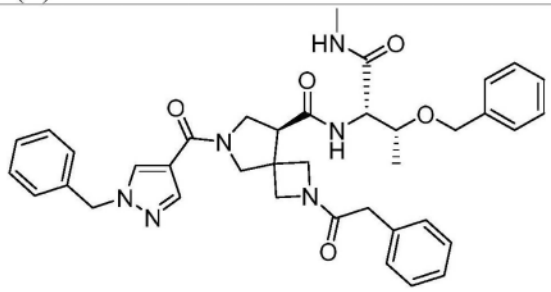
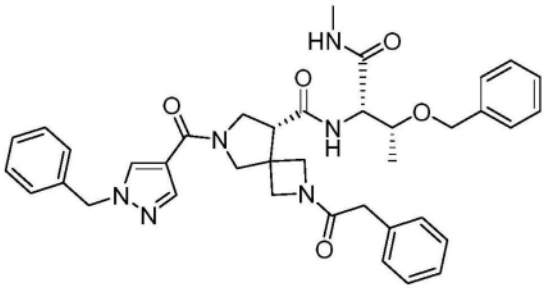
[0312]

	 (B)
I-17	(A)  (B) 
I-18	
I-19	(A) 

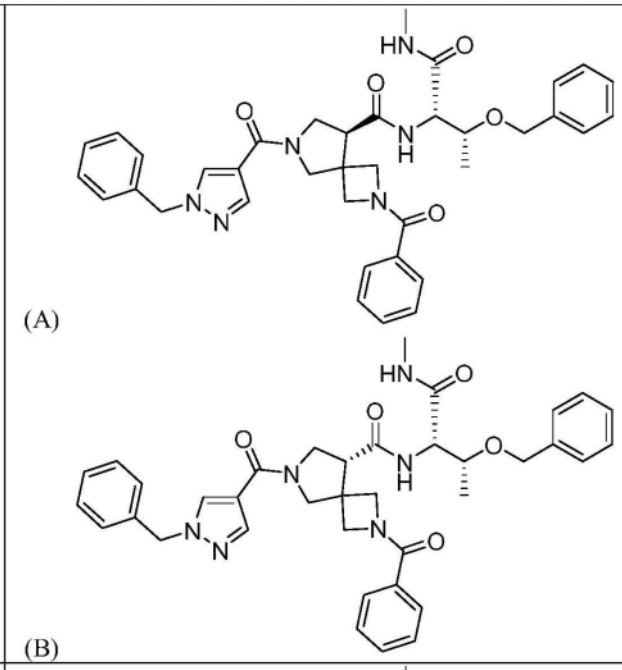
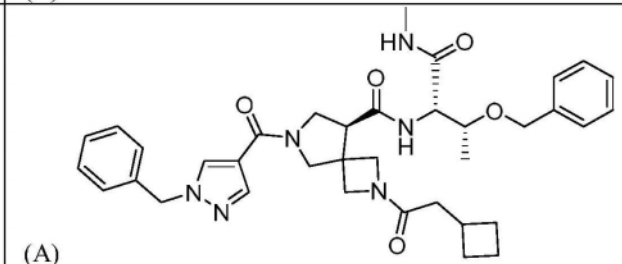
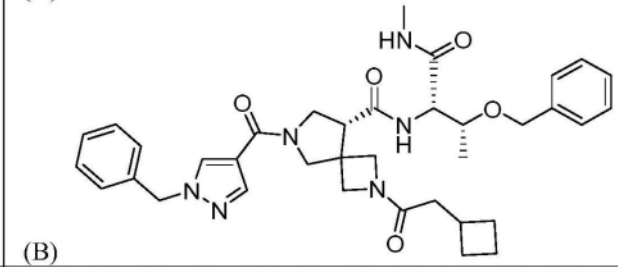
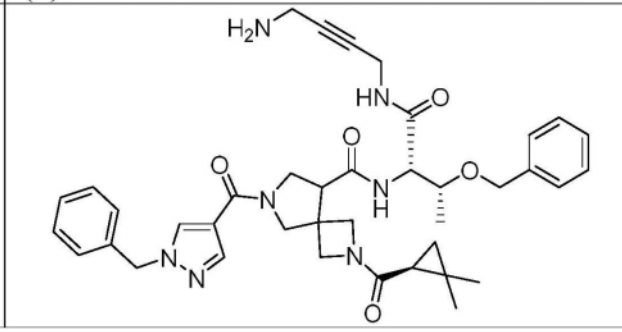
[0313]

	 (B)
I-20	
I-21	
I-22	
I-23	(A) 

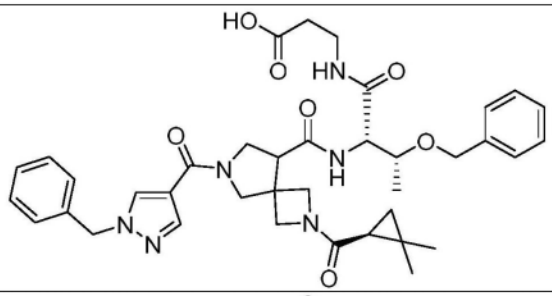
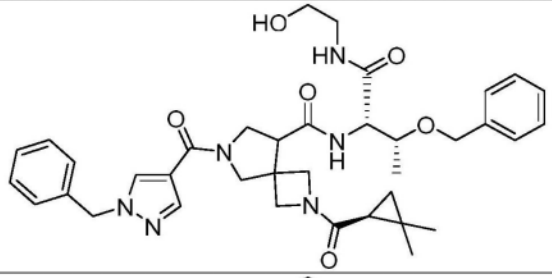
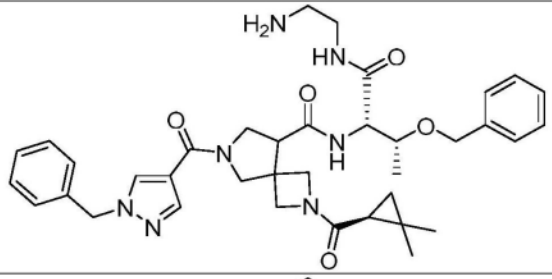
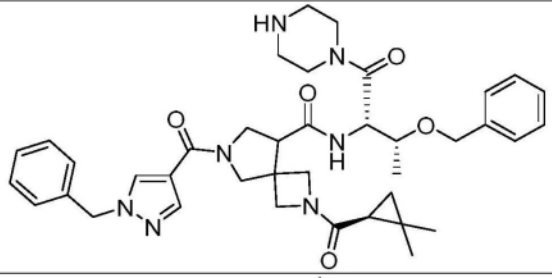
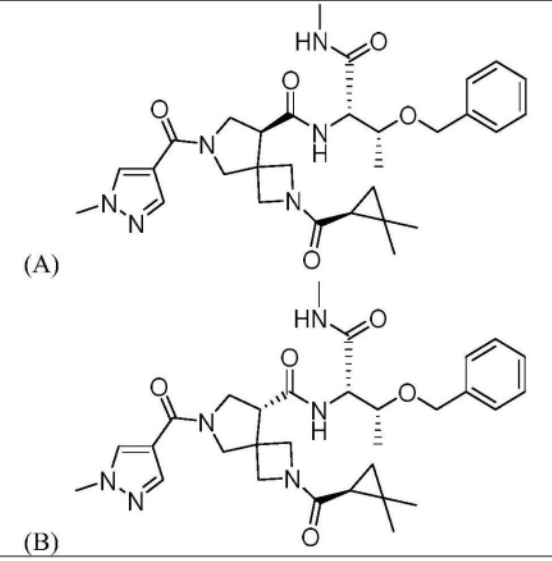
[0314]

	 (B)
I-24	 (A)  (B)
I-25	 (A)  (B)

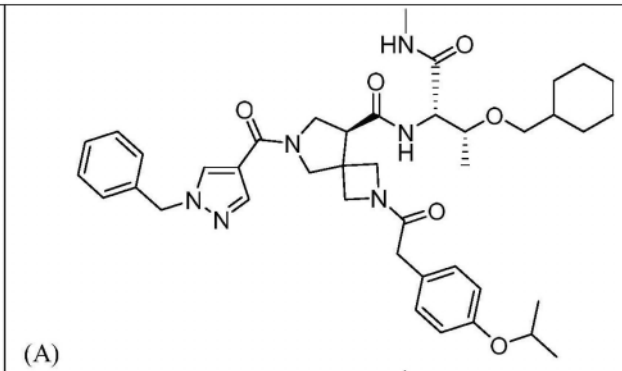
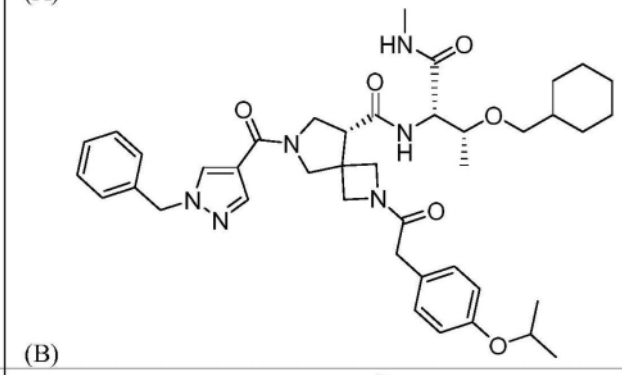
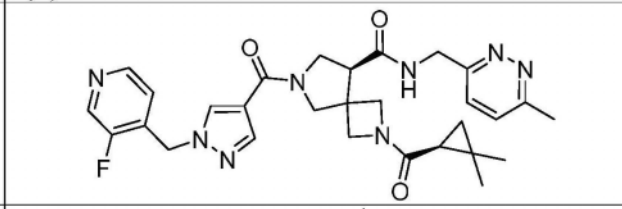
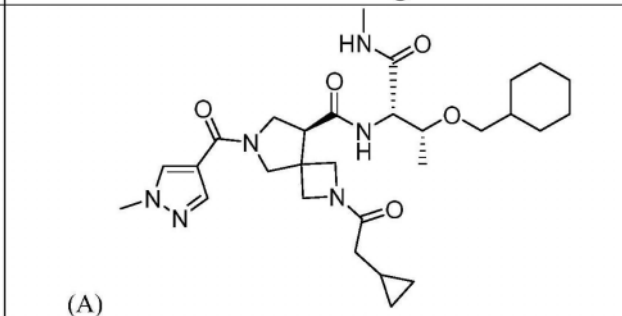
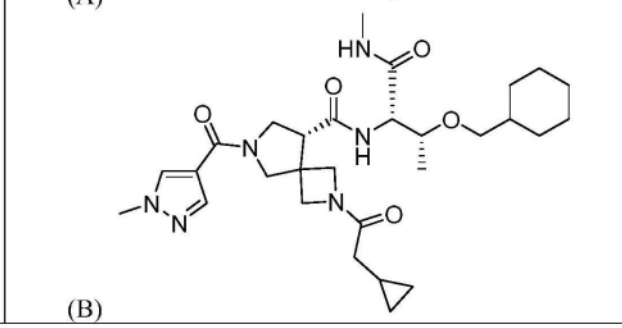
[0315]

I-26	 (A) (B)
I-27	 (A)  (B)
I-28	

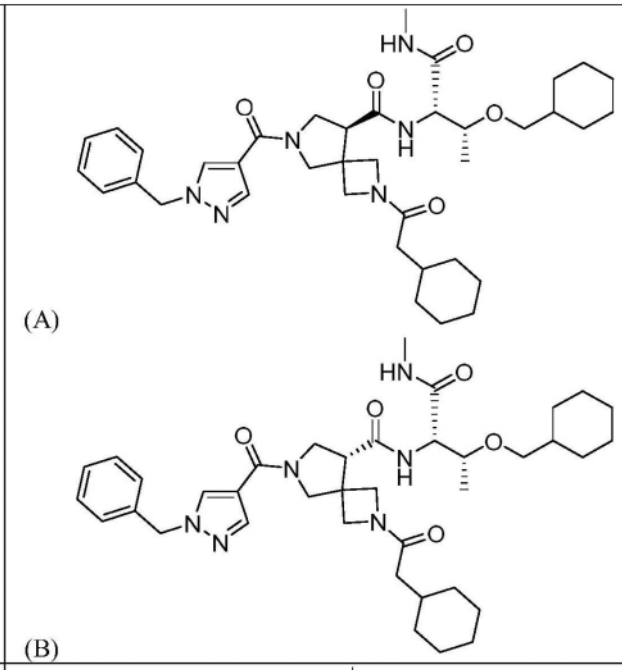
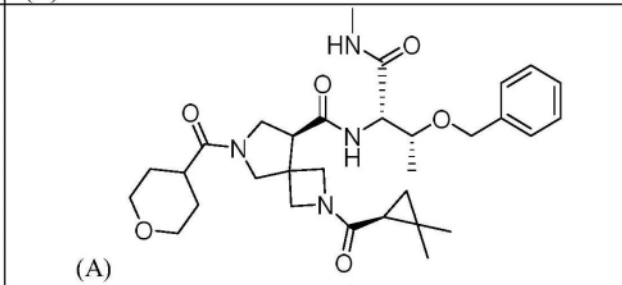
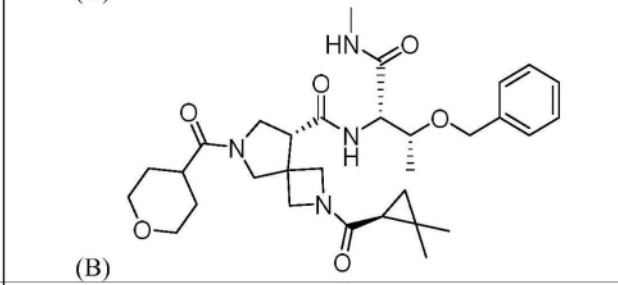
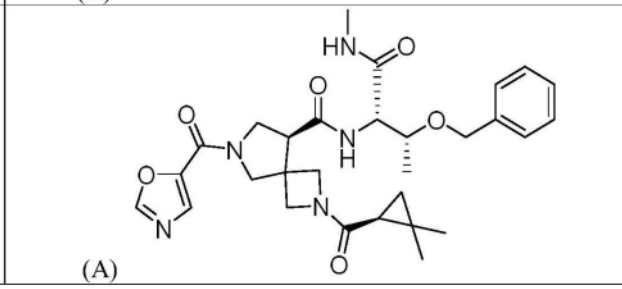
[0316]

I-29	
I-30	
I-31	
I-32	
I-33	 (A) (B)

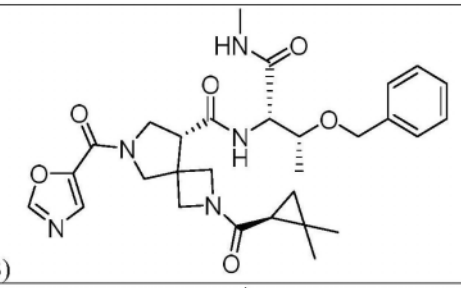
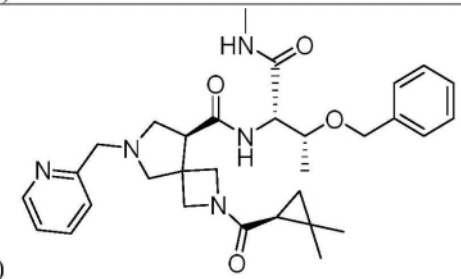
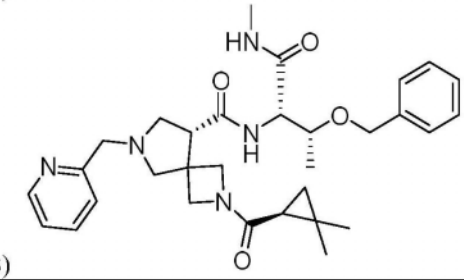
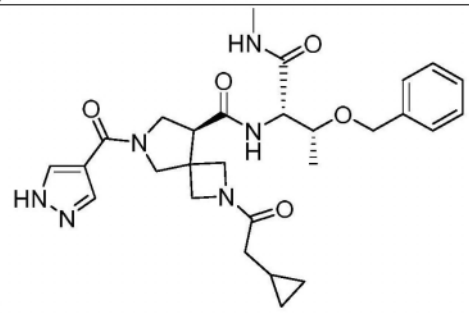
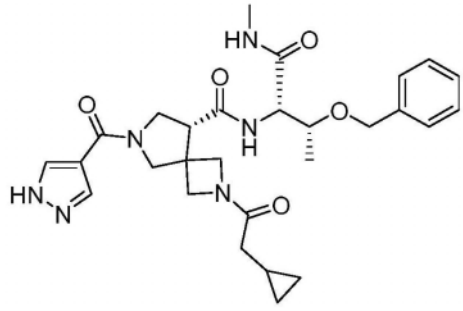
[0317]

I-34	 (A)  (B)
I-35	
I-36	 (A)  (B)

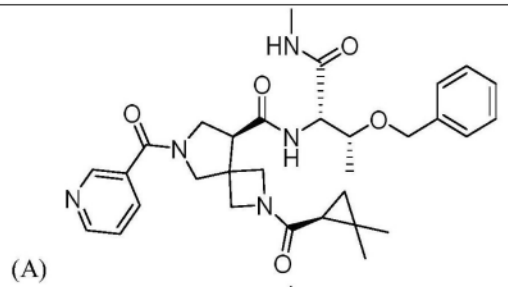
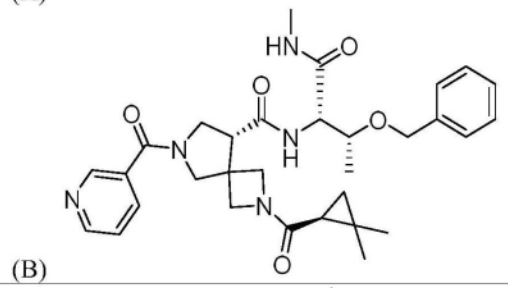
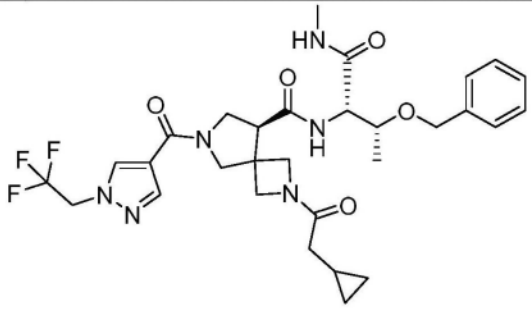
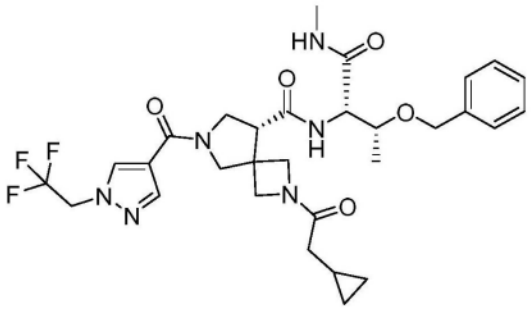
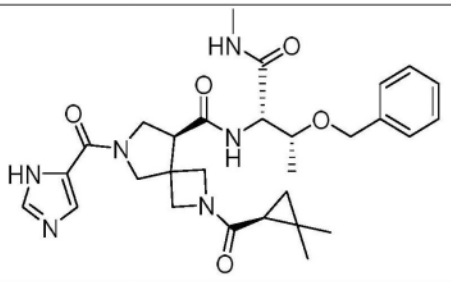
[0318]

I-37	 (A) (B)
I-38	 (A)  (B)
I-39	 (A)

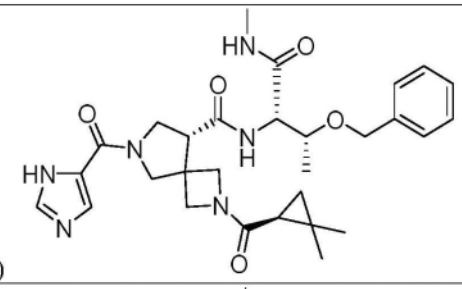
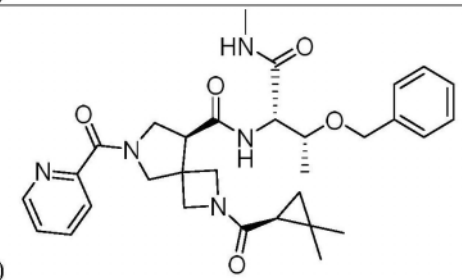
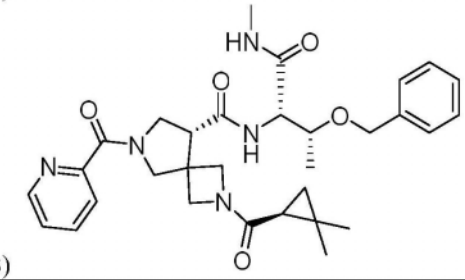
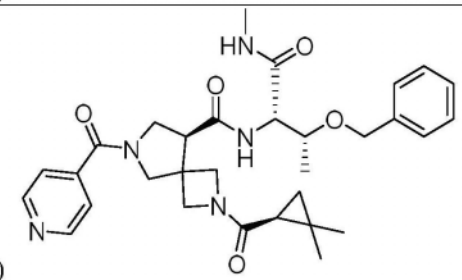
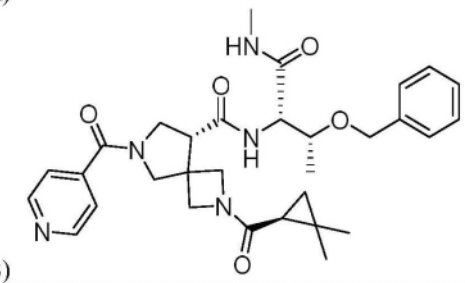
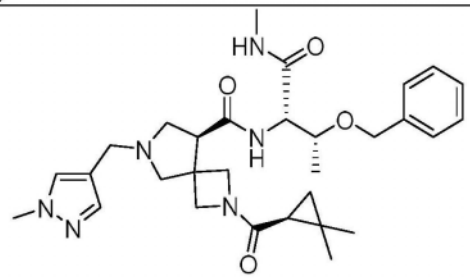
[0319]

	 (B)
I-40	 (A)  (B)
I-41	 (A)  (B)

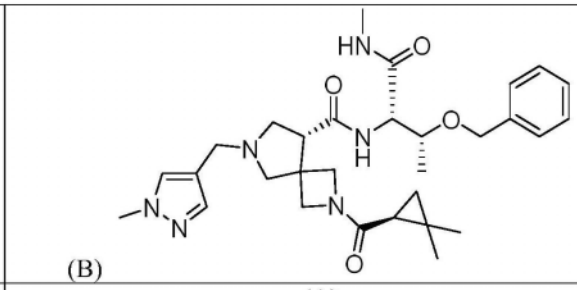
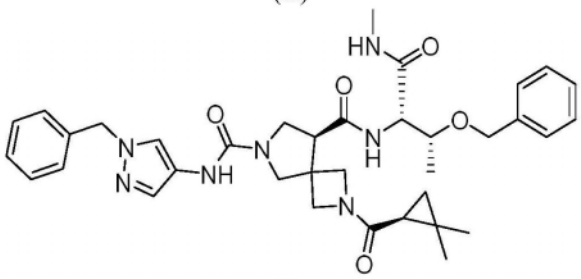
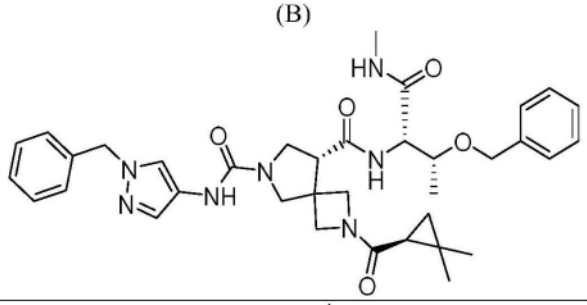
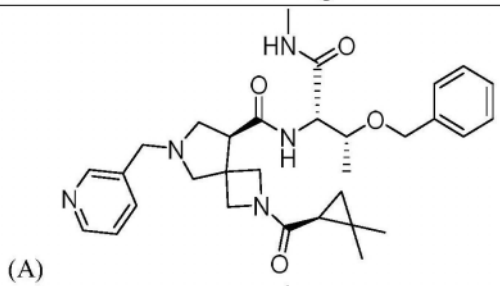
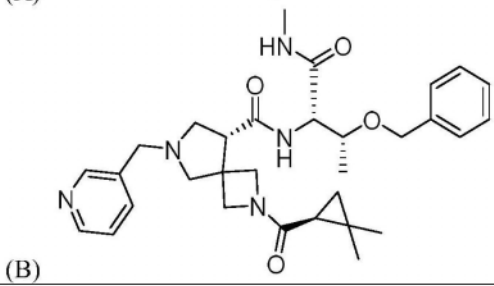
[0320]

I-42	 (A)  (B)
I-43	 (A)  (B)
I-44	 (A)

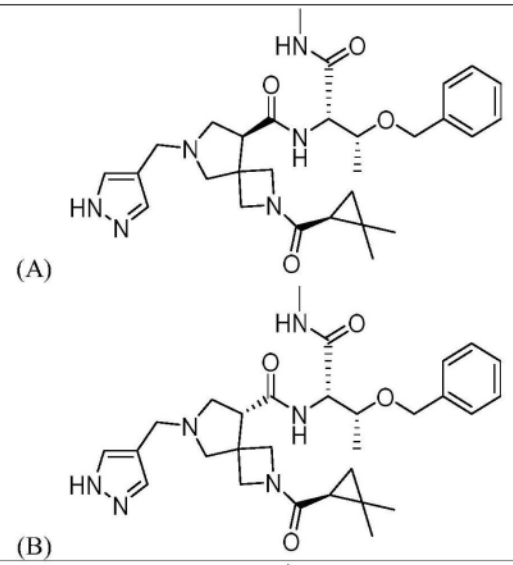
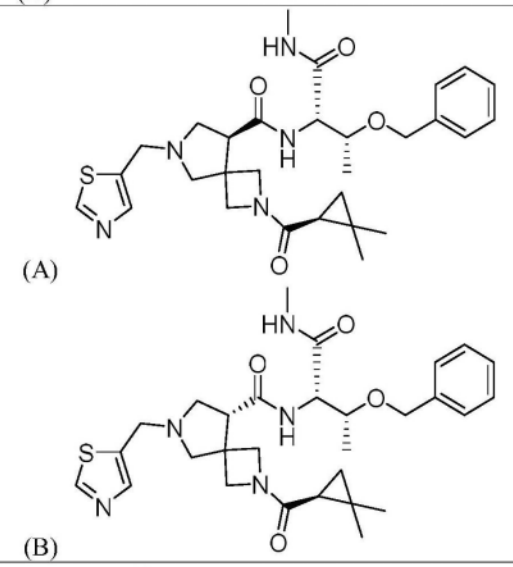
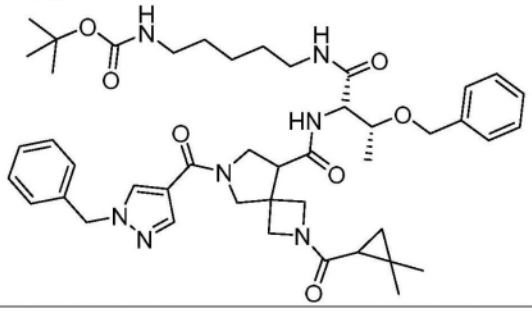
[0321]

	 (B)
I-45	 (A)  (B)
I-46	 (A)  (B)
I-47	 (A)

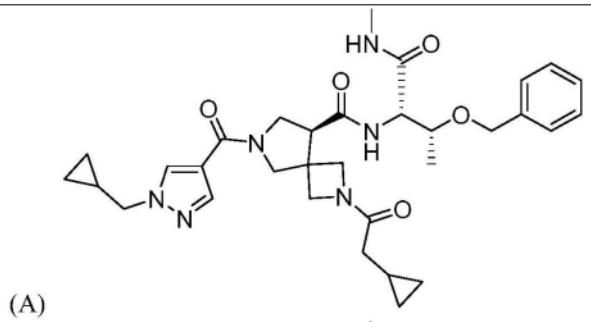
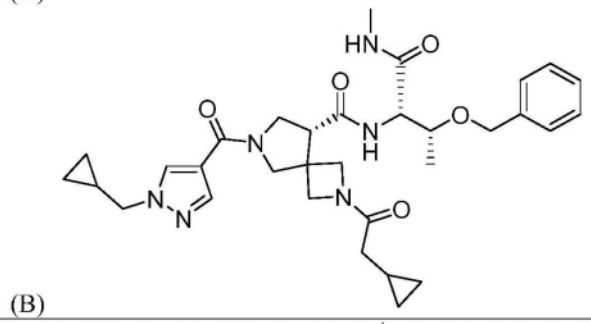
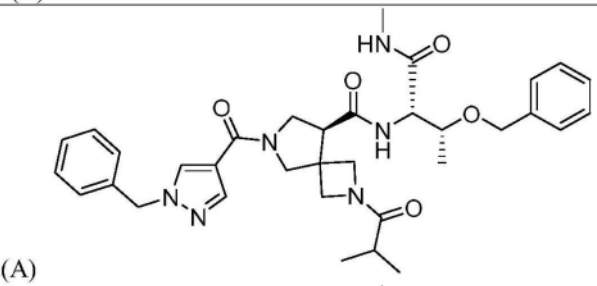
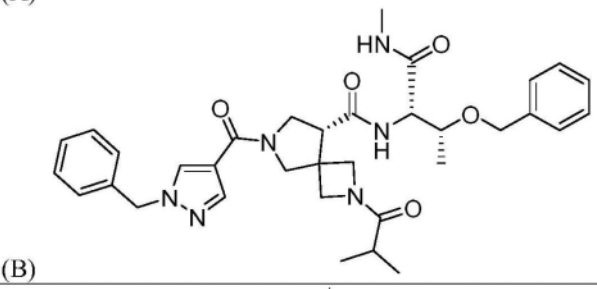
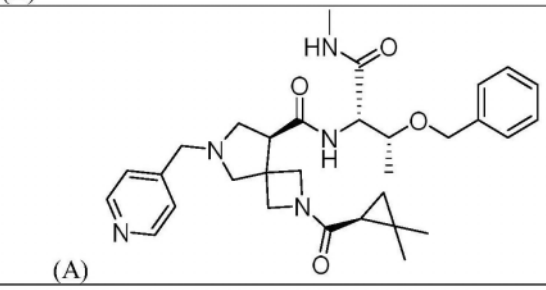
[0322]

	 (B)
I-48	(A)  (B) 
I-49	 (A)  (B)

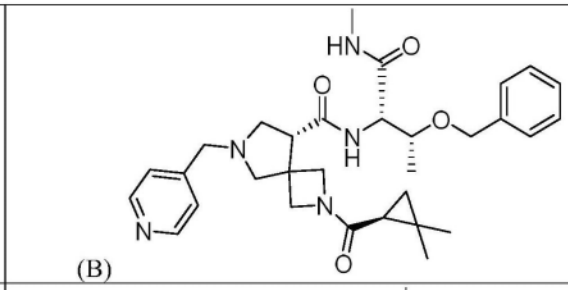
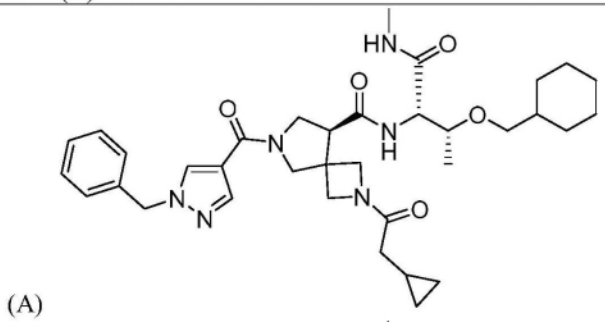
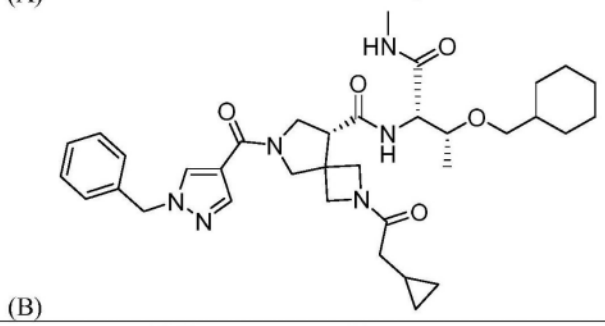
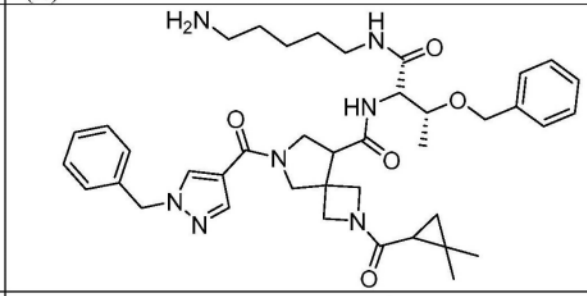
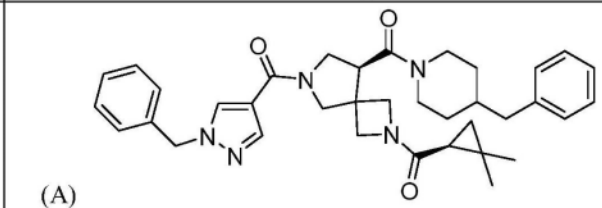
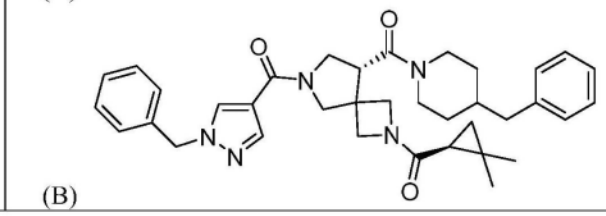
[0323]

I-50	 (A) (B)
I-51	 (A) (B)
I-52	

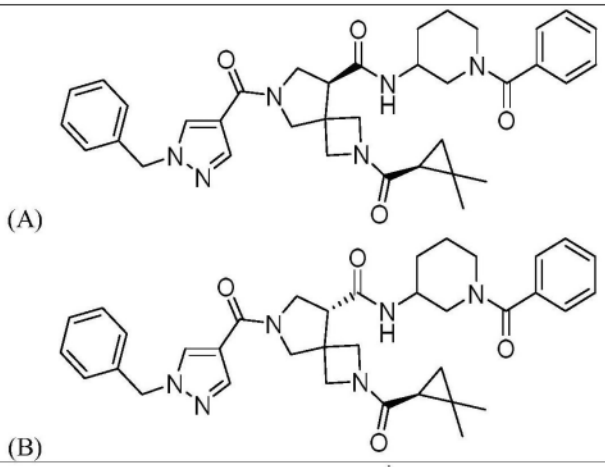
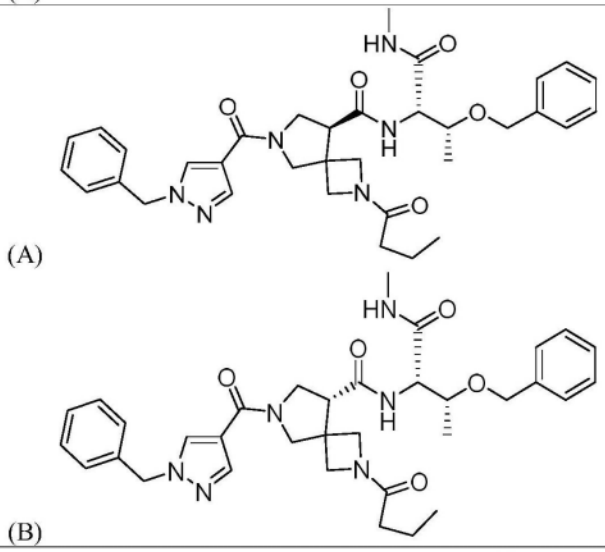
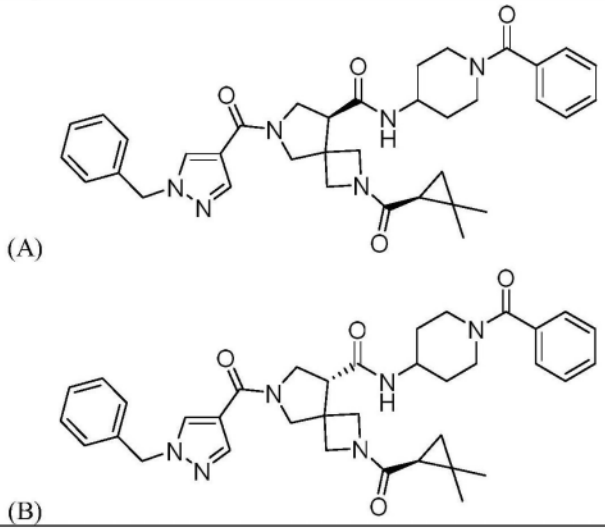
[0324]

I-53	 (A)  (B)
I-54	 (A)  (B)
I-55	 (A)

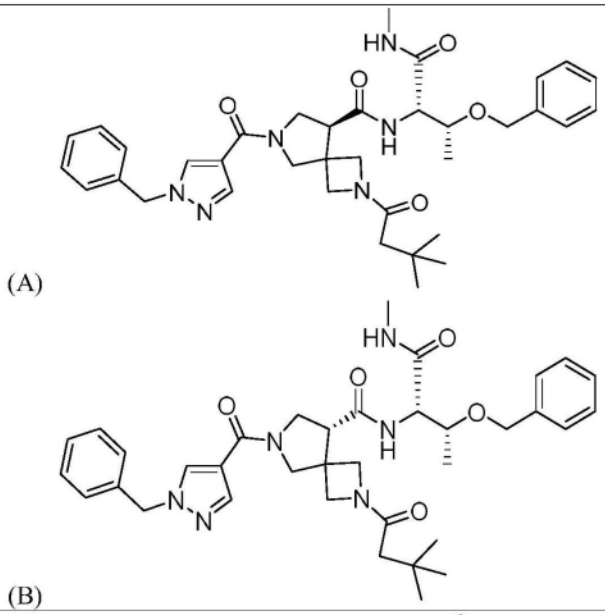
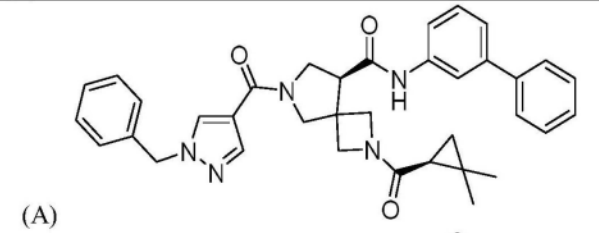
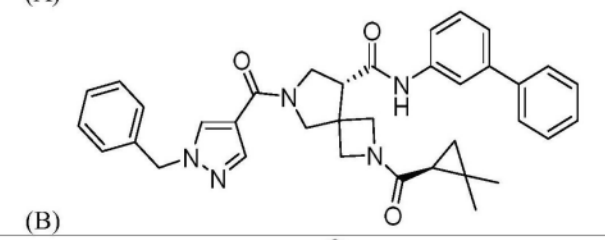
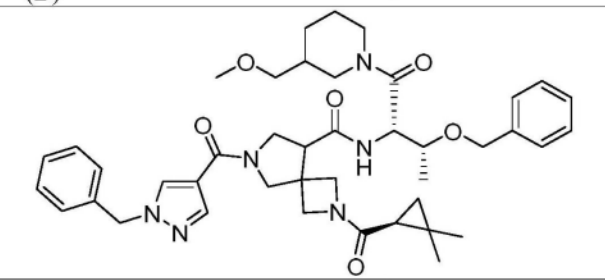
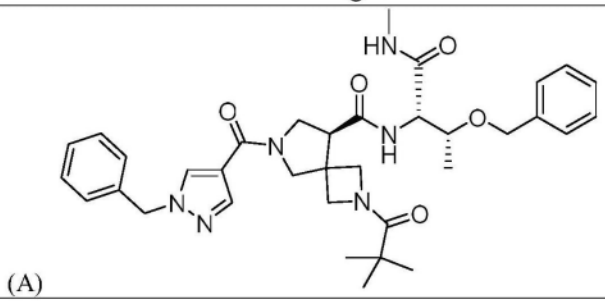
[0325]

	 (B)
I-56	 (A)  (B)
I-57	
I-58	 (A)  (B)

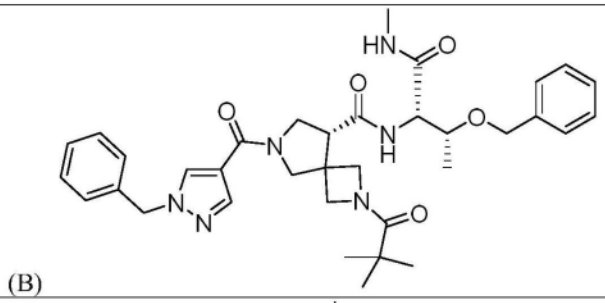
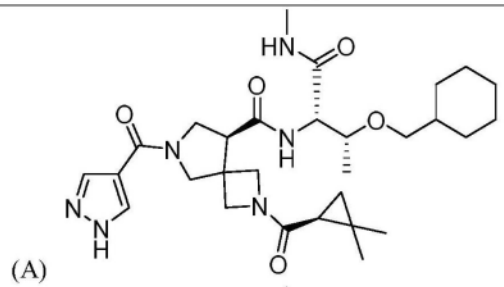
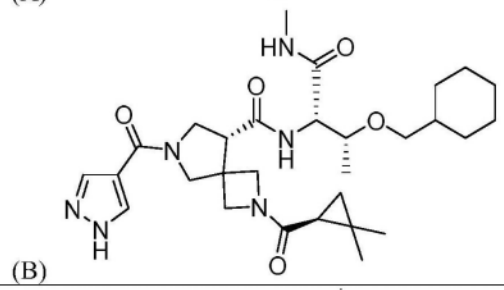
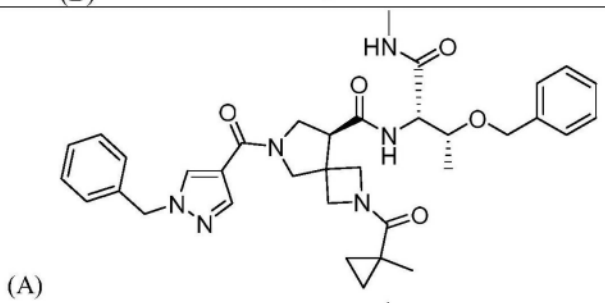
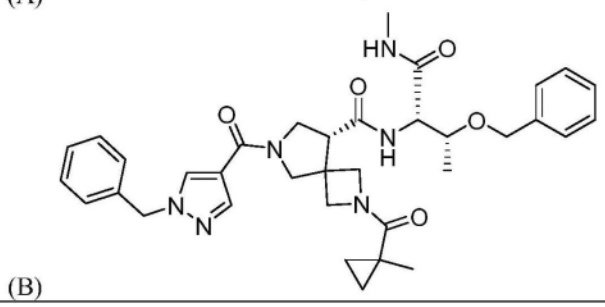
[0326]

I-59	 (A) (B)
I-60	 (A) (B)
I-61	 (A) (B)

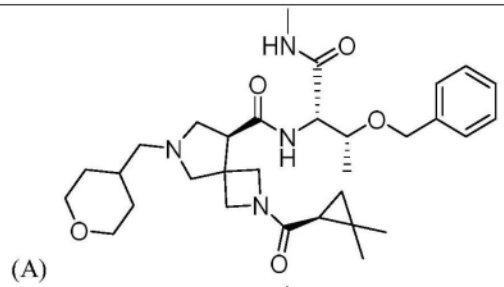
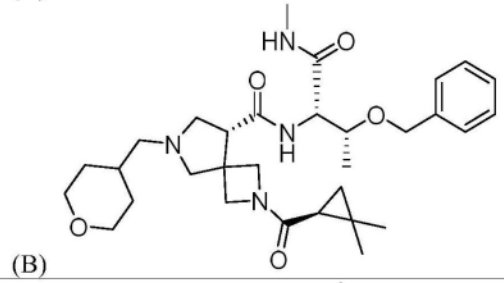
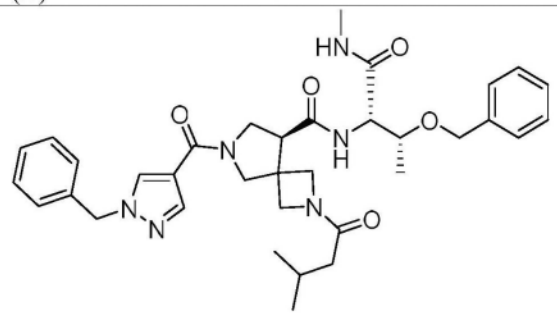
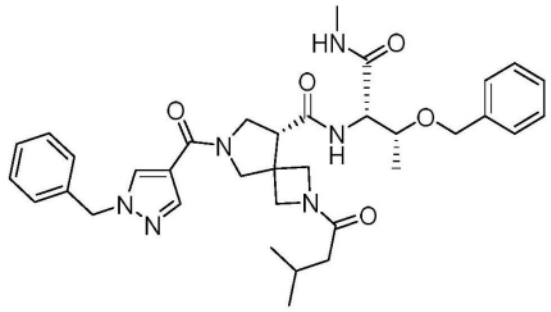
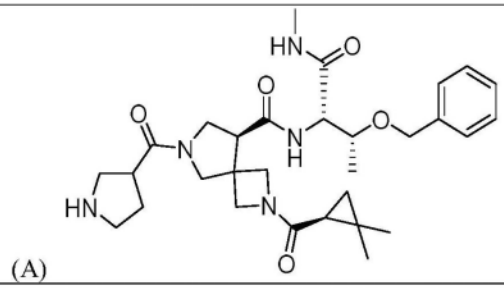
[0327]

I-62	 (A) (B)
I-63	 (A)  (B)
I-64	
I-65	 (A)

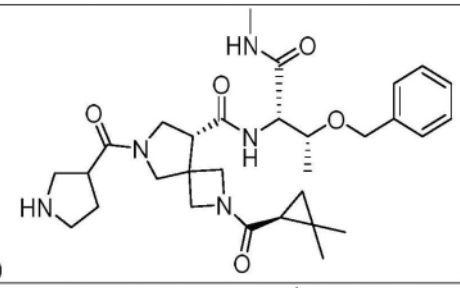
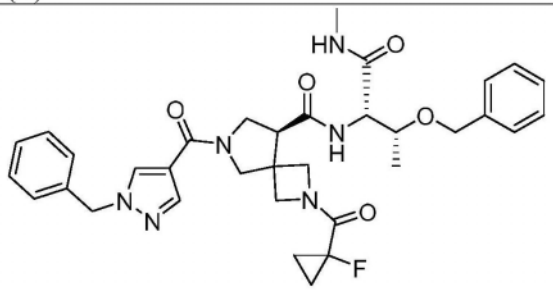
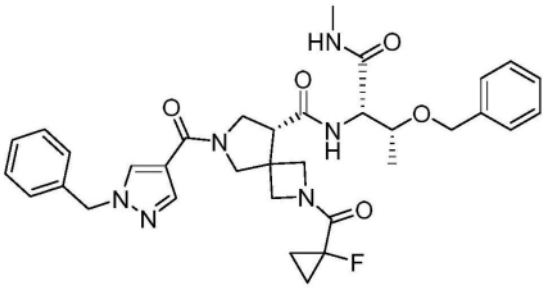
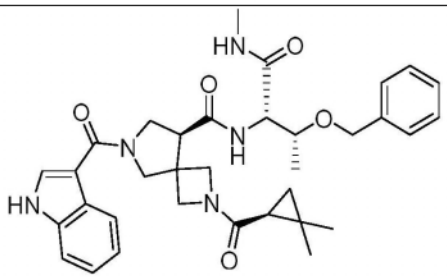
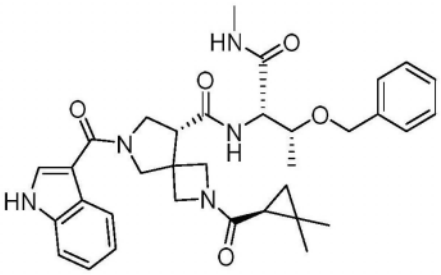
[0328]

	 (B)
I-66	 (A)  (B)
I-67	 (A)  (B)

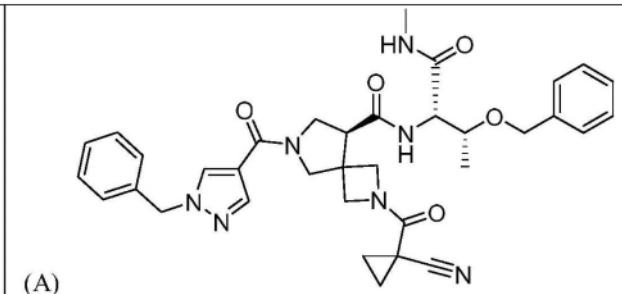
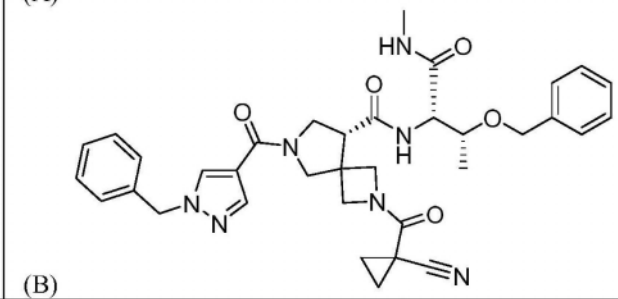
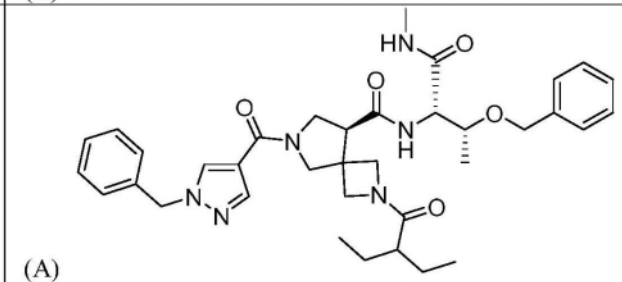
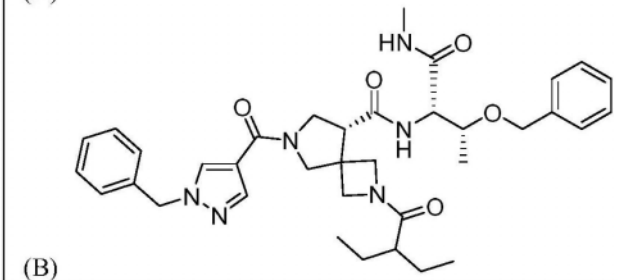
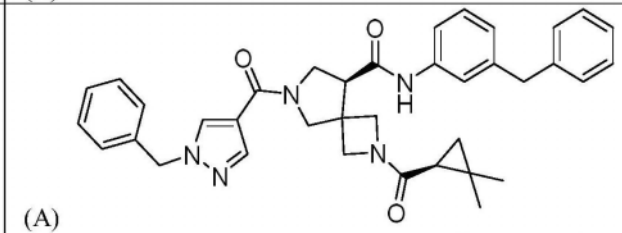
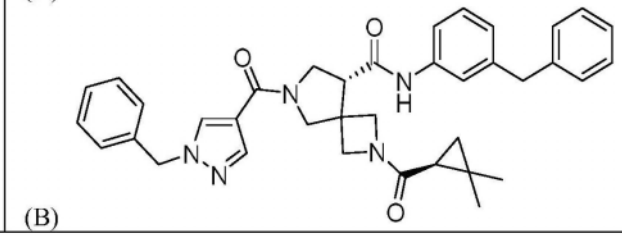
[0329]

I-68	 (A)  (B)
I-69	 (A)  (B)
I-70	 (A)

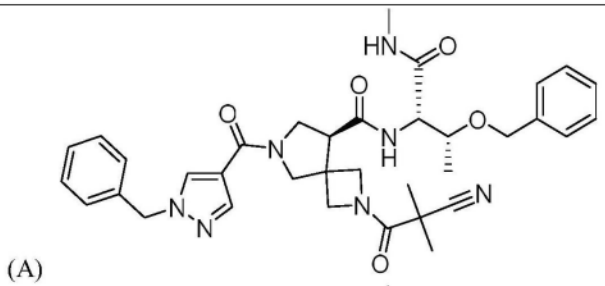
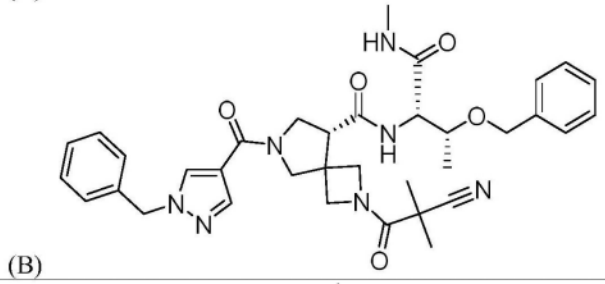
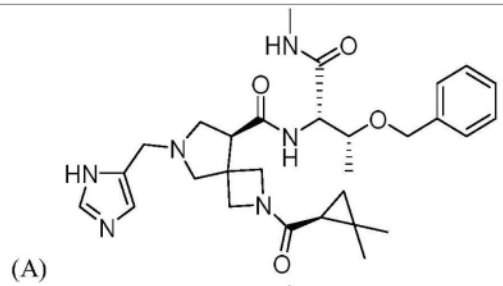
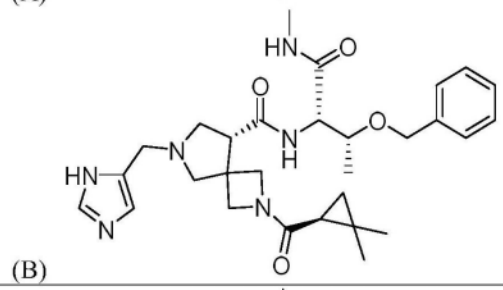
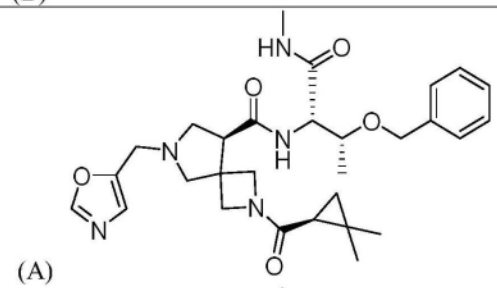
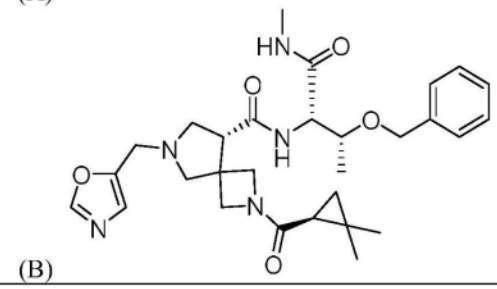
[0330]

	 (B)
I-71	 (A)  (B)
I-72	 (A)  (B)

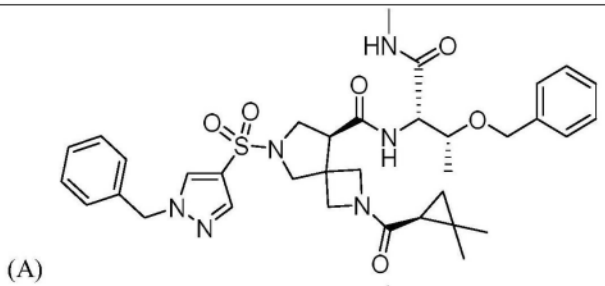
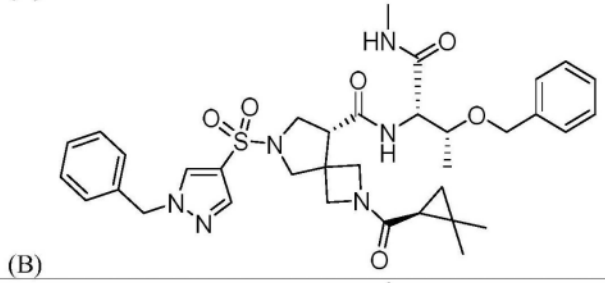
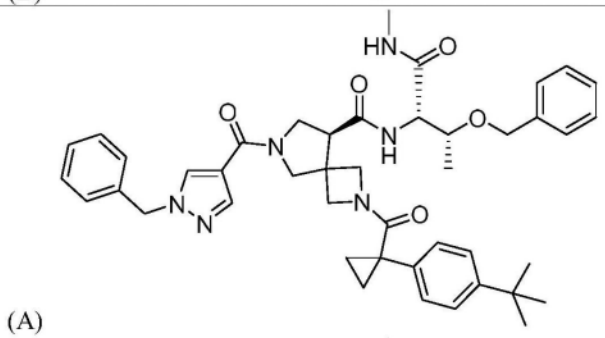
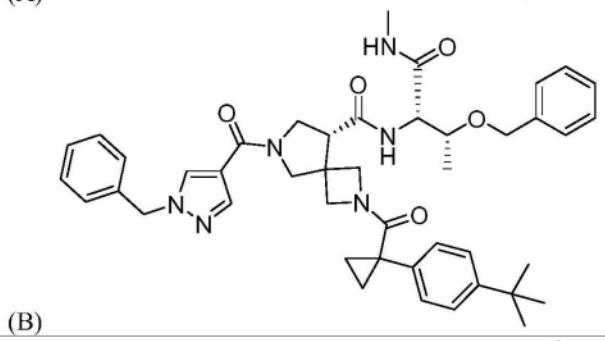
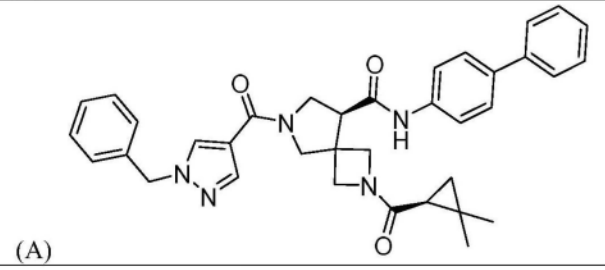
[0331]

I-73	 (A)  (B)
I-74	 (A)  (B)
I-75	 (A)  (B)

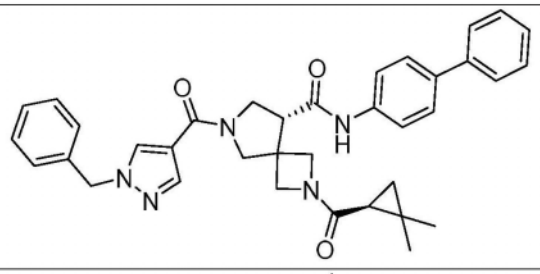
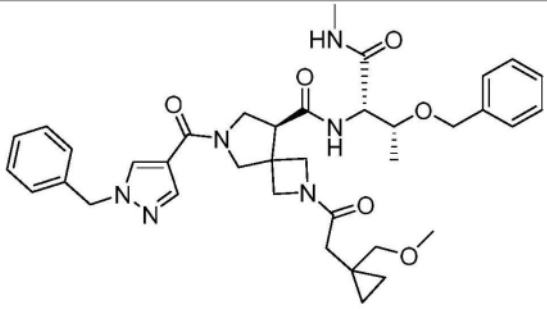
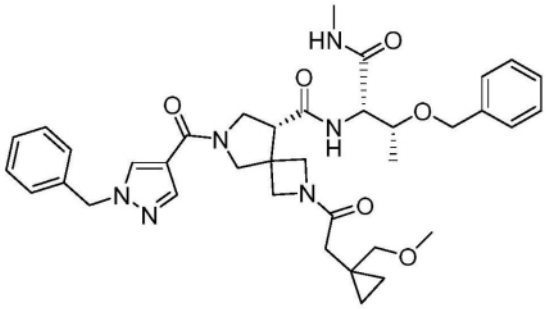
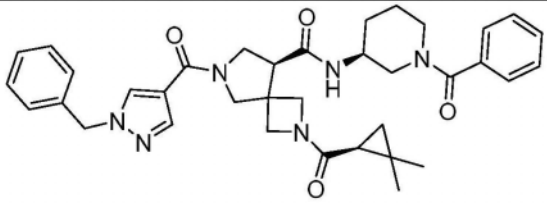
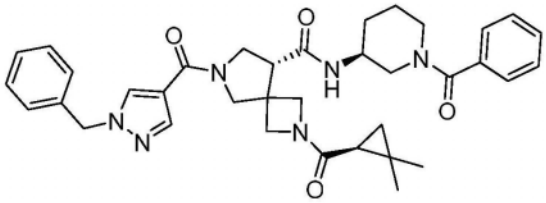
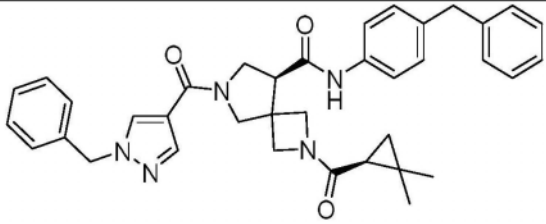
[0332]

I-76	 (A)  (B)
I-77	 (A)  (B)
I-78	 (A)  (B)

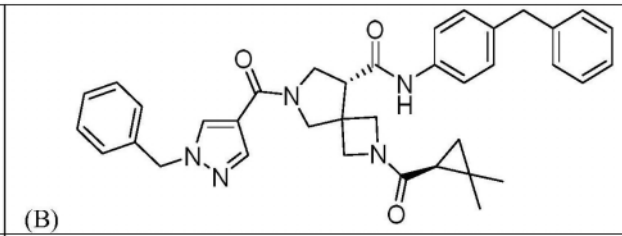
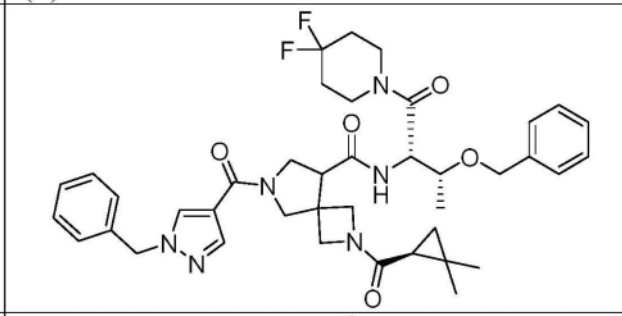
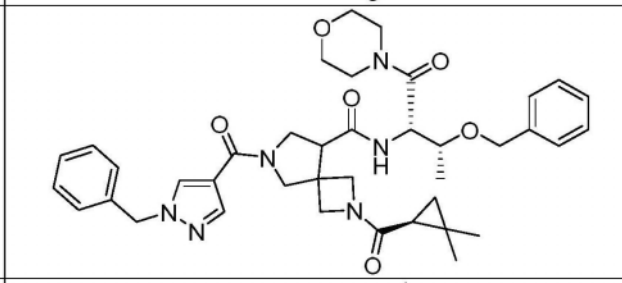
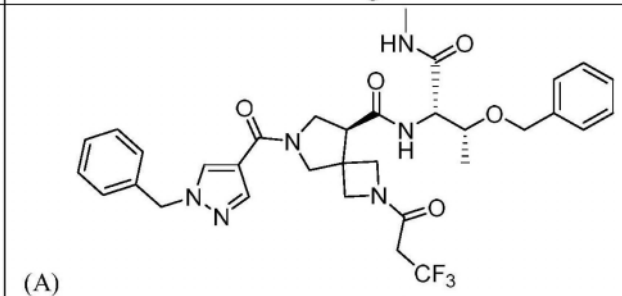
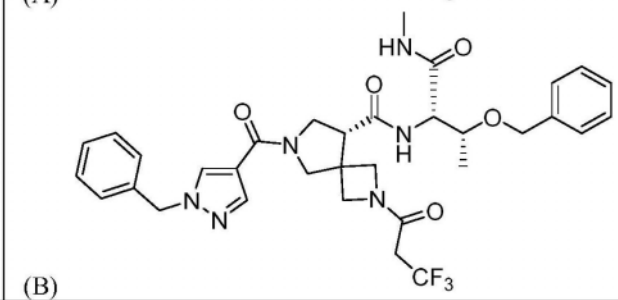
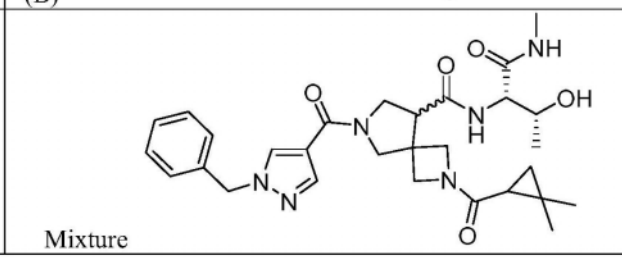
[0333]

I-79	 (A)  (B)
I-80	 (A)  (B)
I-81	 (A)

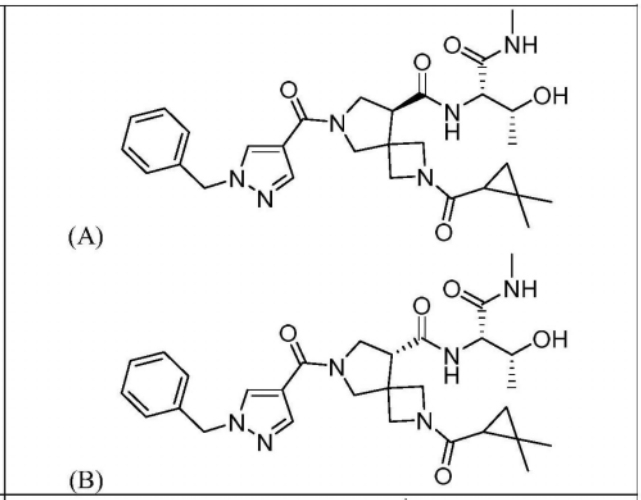
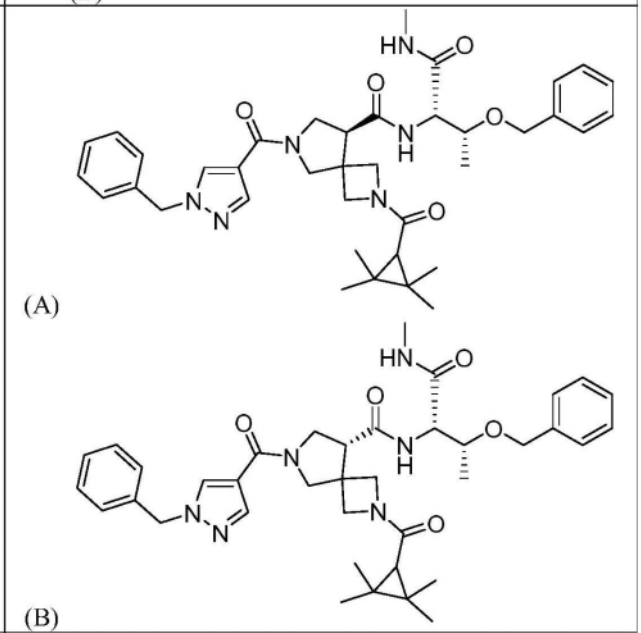
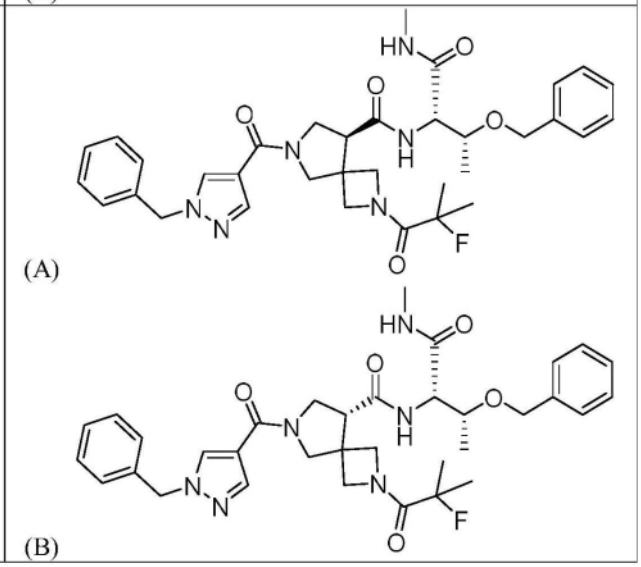
[0334]

	 (B)
I-82	 (A)  (B)
I-83	 (A)  (B)
I-84	 (A)

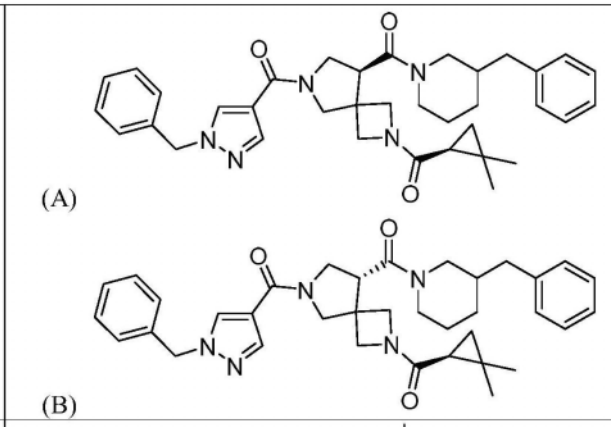
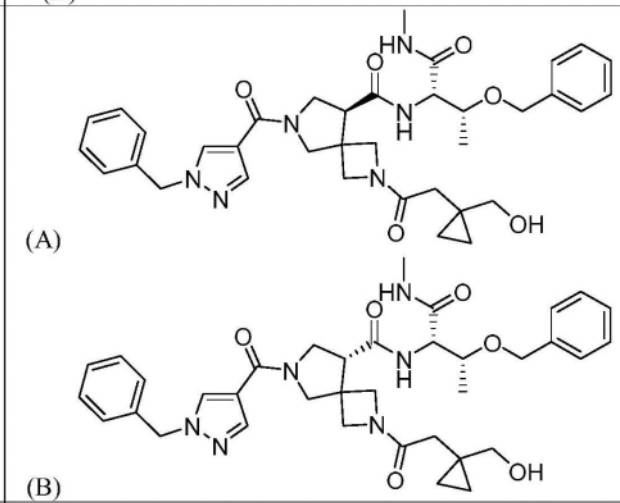
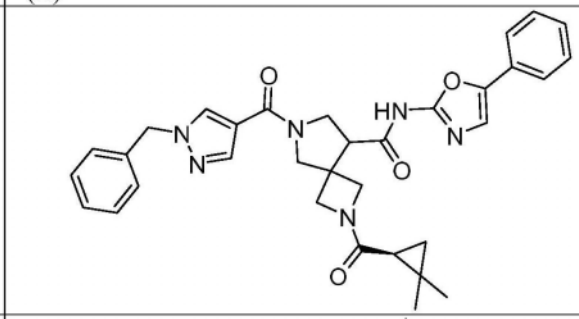
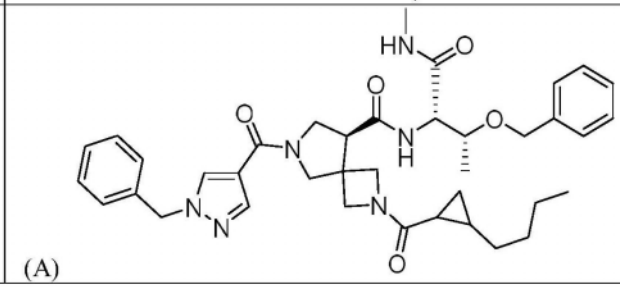
[0335]

	 (B)
I-85	
I-86	
I-87	 (A)  (B)
I-88	 Mixture

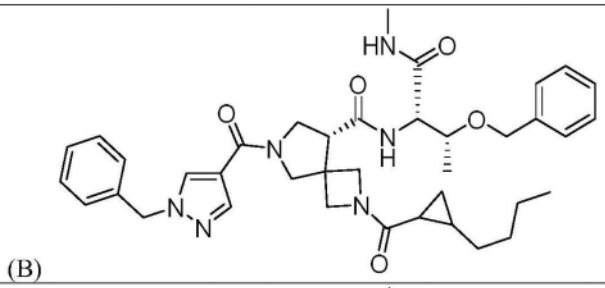
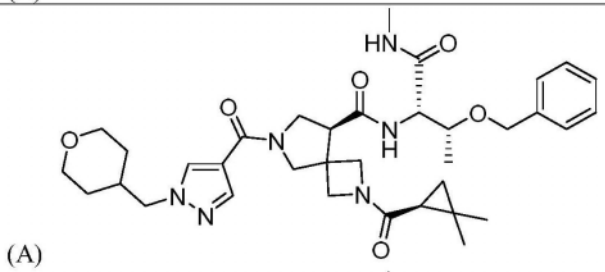
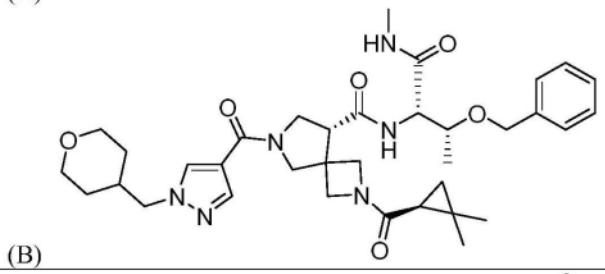
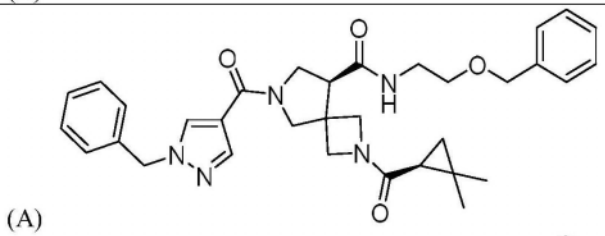
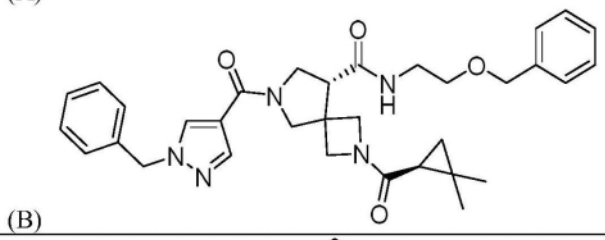
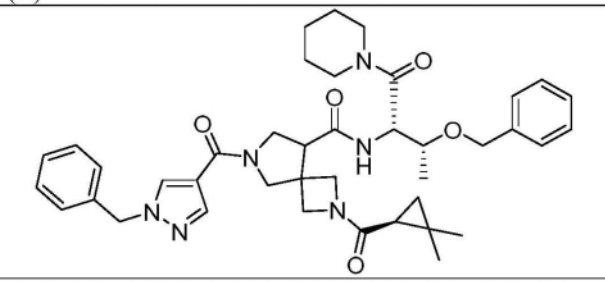
[0336]

	 (A) (B)
I-89	 (A) (B)
I-90	 (A) (B)

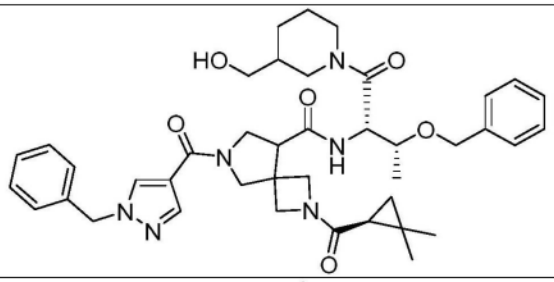
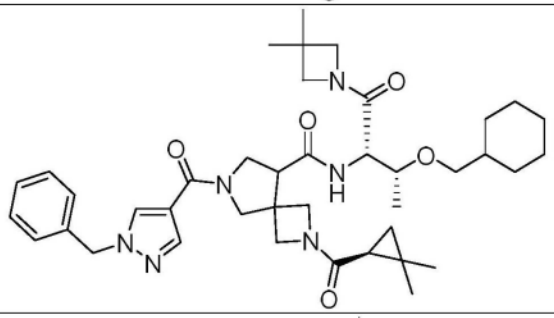
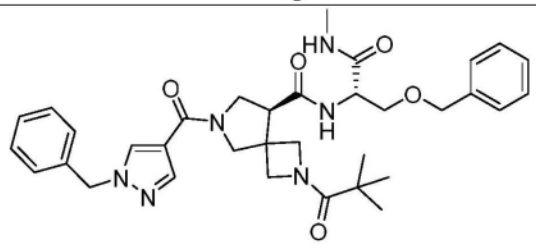
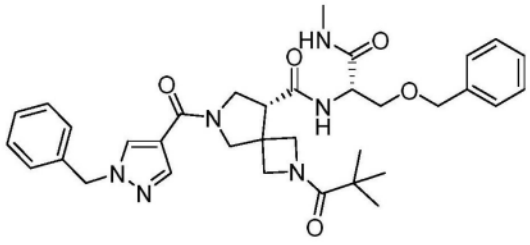
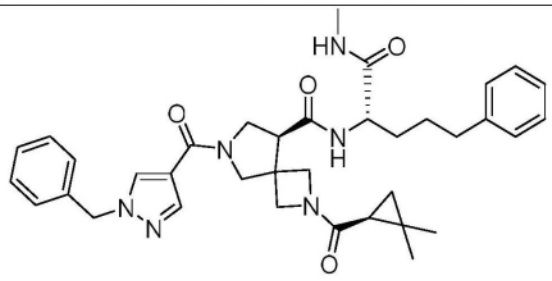
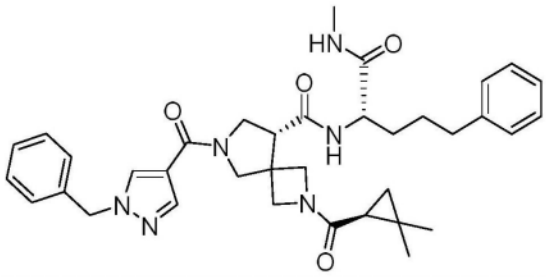
[0337]

I-91	 (A) (B)
I-92	 (A) (B)
I-93	
I-94	 (A)

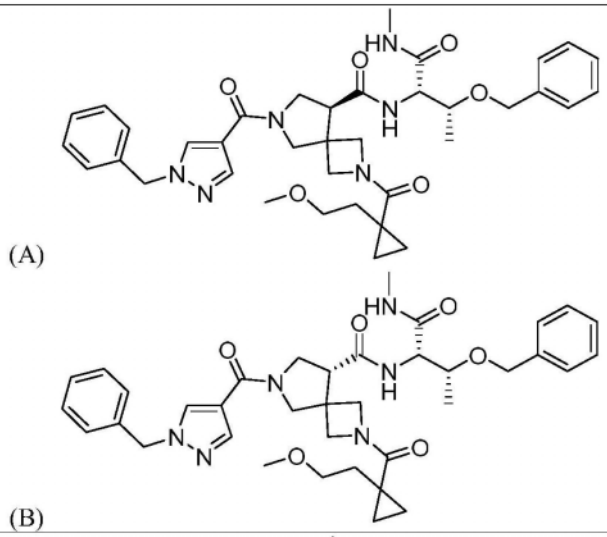
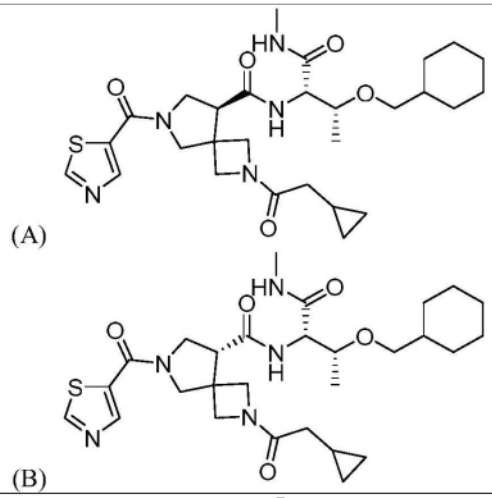
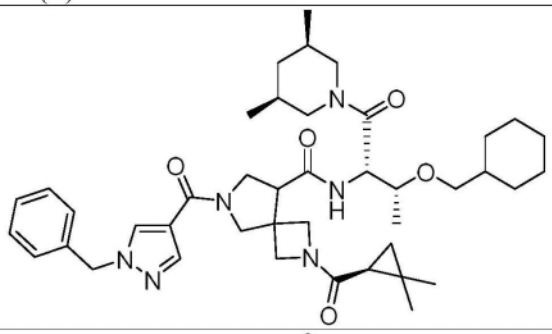
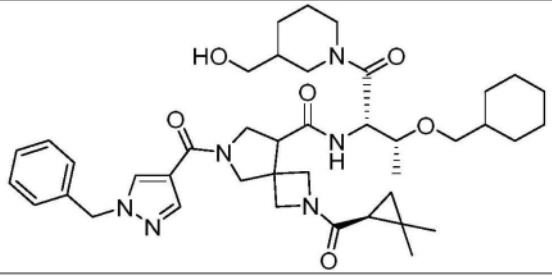
[0338]

	 (B)
I-95	 (A)  (B)
I-96	 (A)  (B)
I-97	

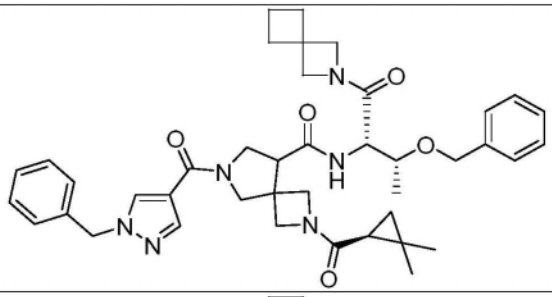
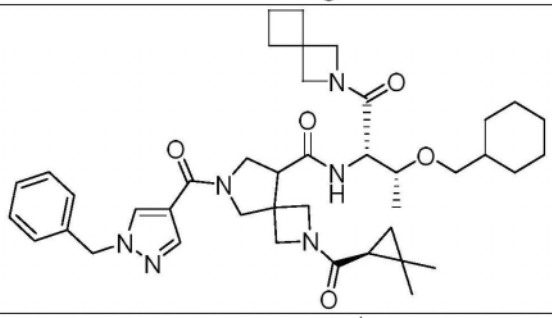
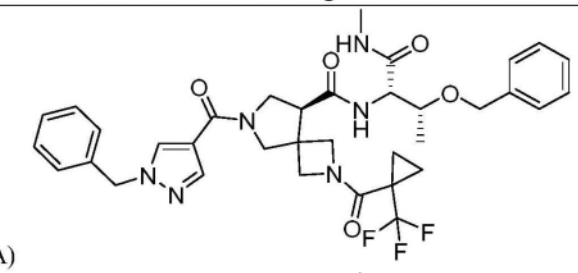
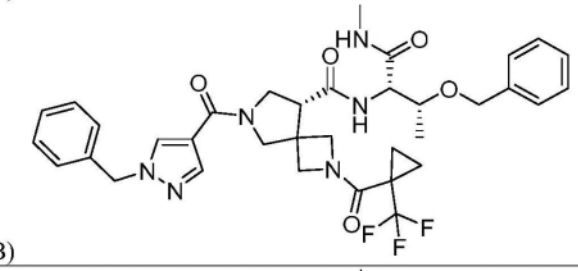
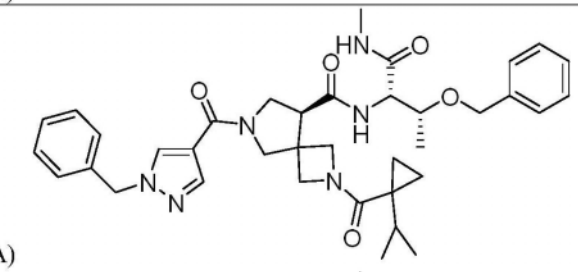
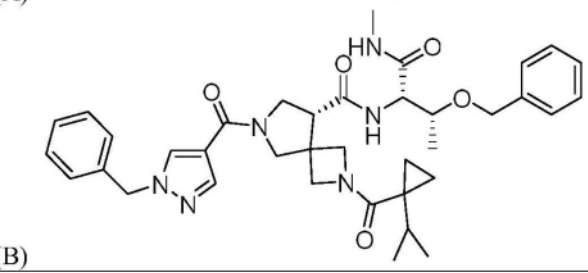
[0339]

I-98	
I-99	
I-100	 (A)  (B)
I-101	 (A)  (B)

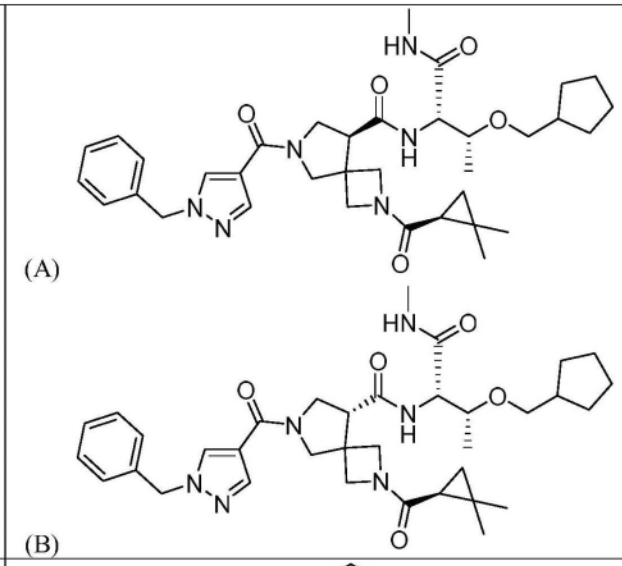
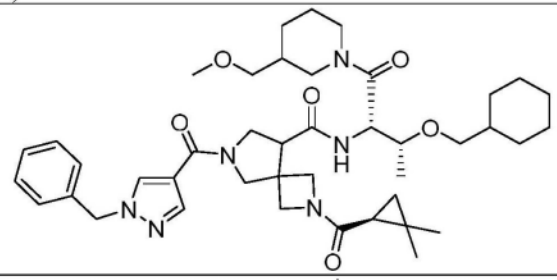
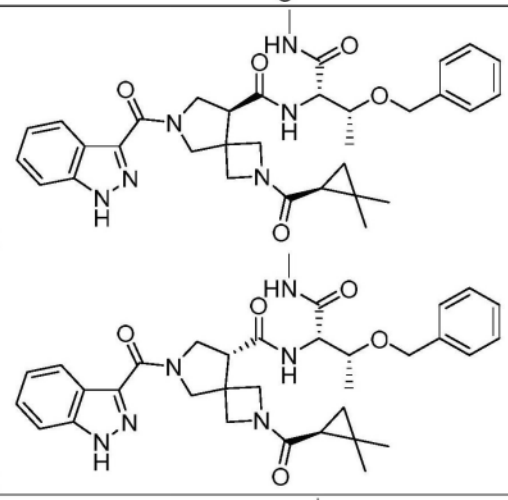
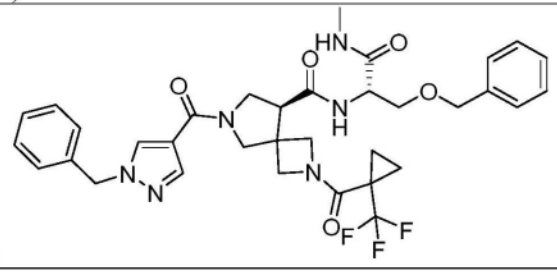
[0340]

I-102	 (A) (B)
I-103	 (A) (B)
I-104	
I-105	

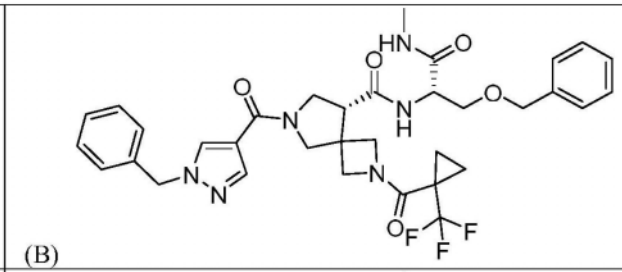
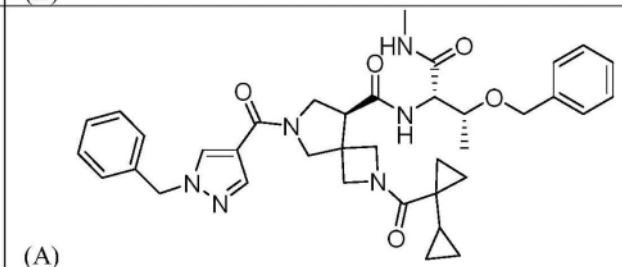
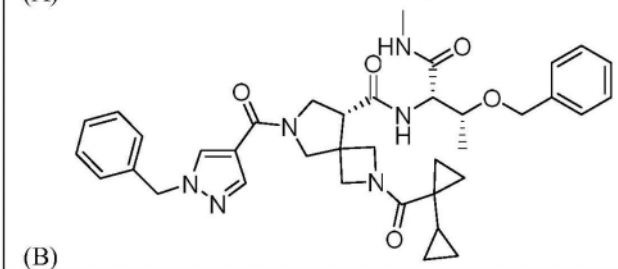
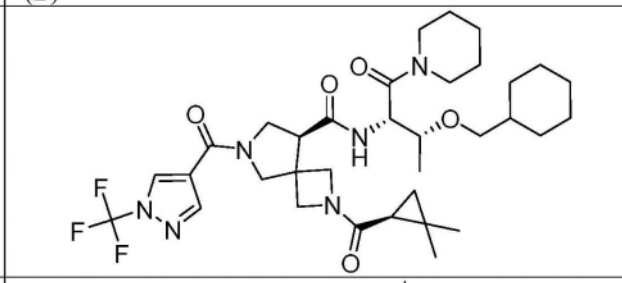
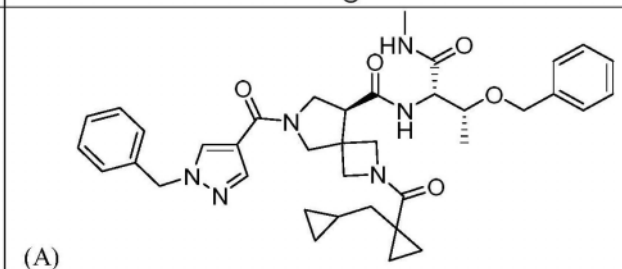
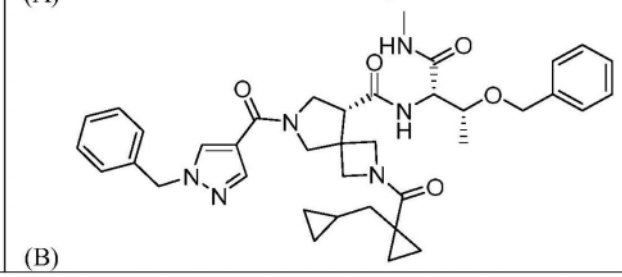
[0341]

I-106	
I-107	
I-108	 (A)  (B)
I-109	 (A)  (B)

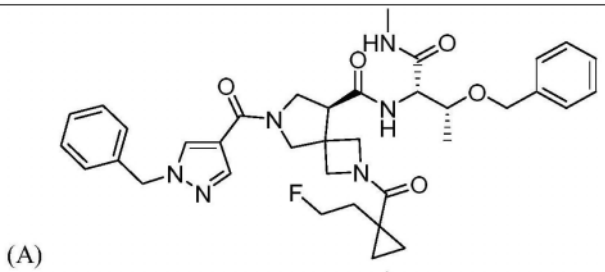
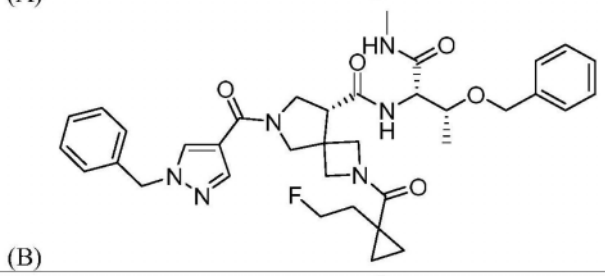
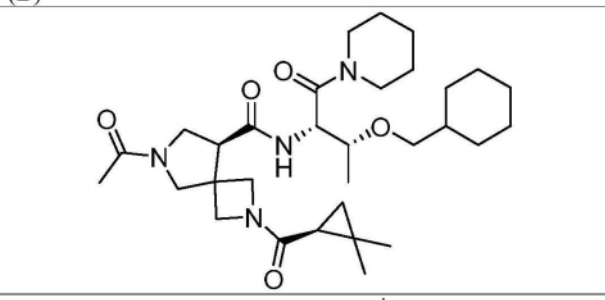
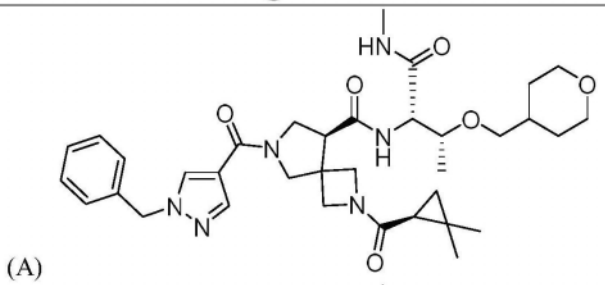
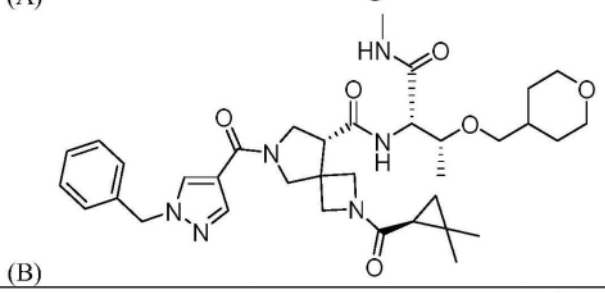
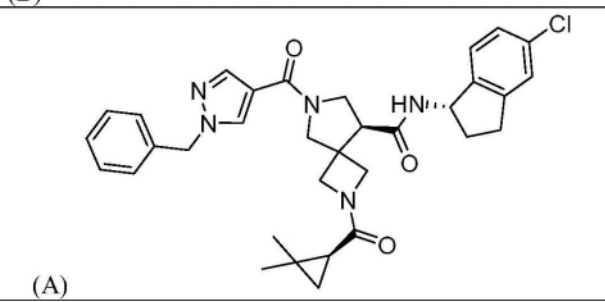
[0342]

I-110	 (A) (B)
I-111	
I-112	 (A) (B)
I-113	 (A)

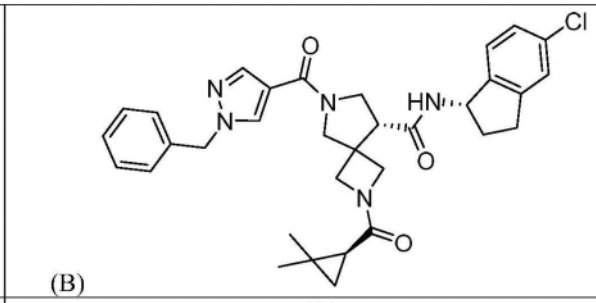
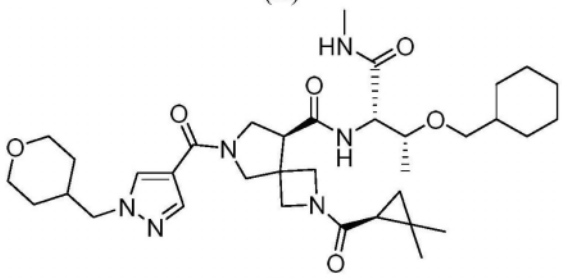
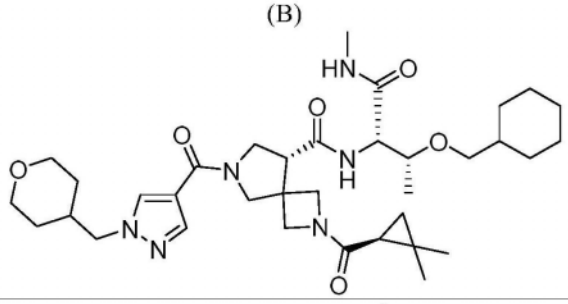
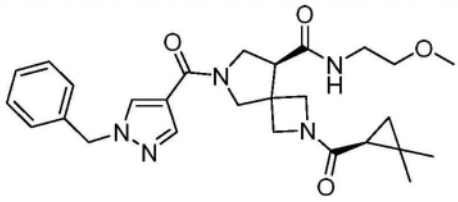
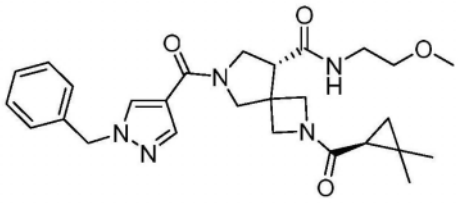
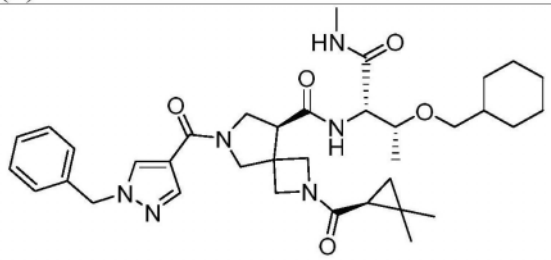
[0343]

	 (B)
I-114	 (A)  (B)
I-115	
I-116	 (A)  (B)

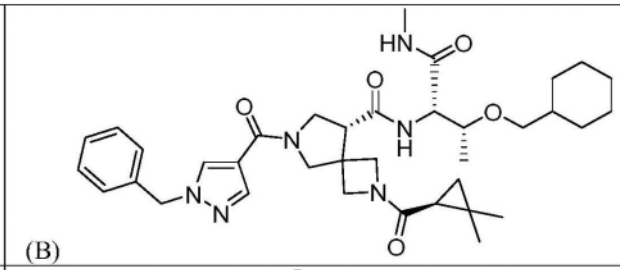
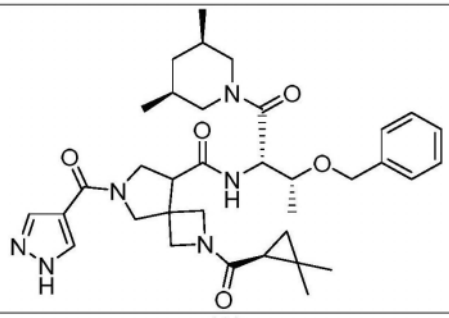
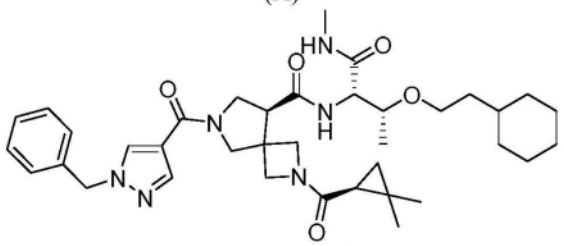
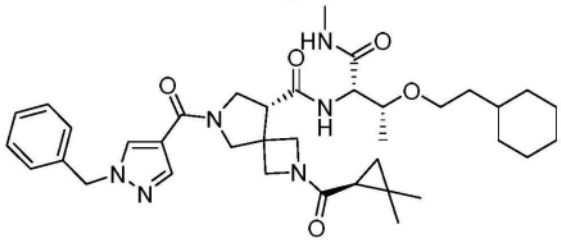
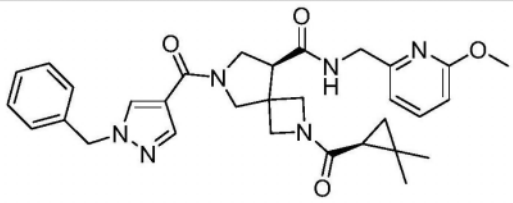
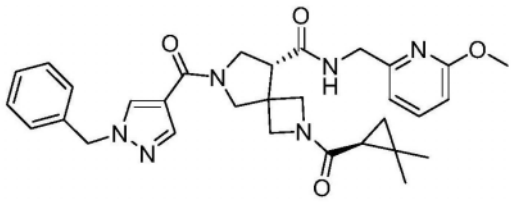
[0344]

I-117	 (A)  (B)
I-118	
I-119	 (A)  (B)
I-120	 (A)

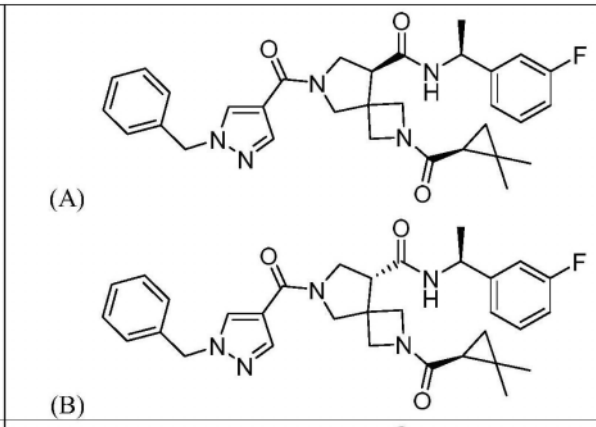
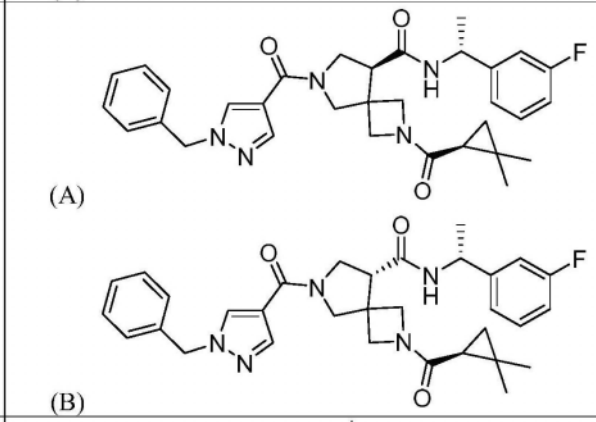
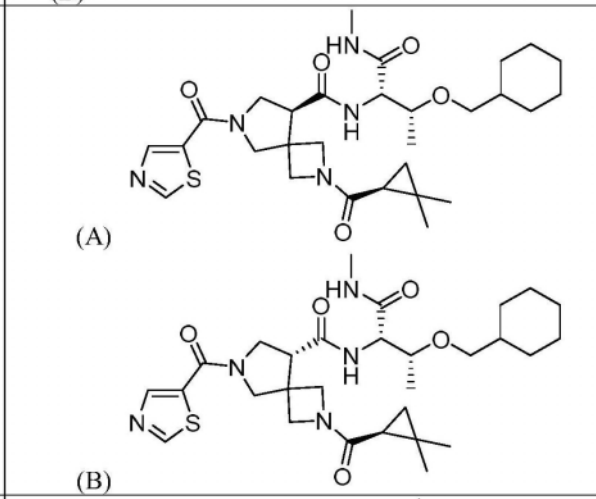
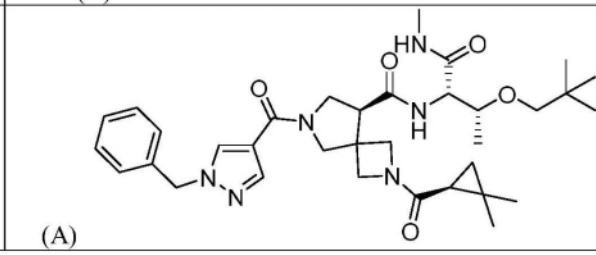
[0345]

	 (B)
I-121	(A)  (B) 
I-122	 (A)  (B)
I-123	 (A)

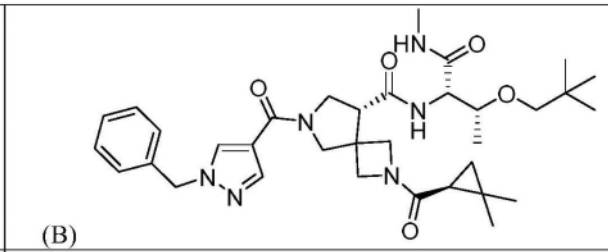
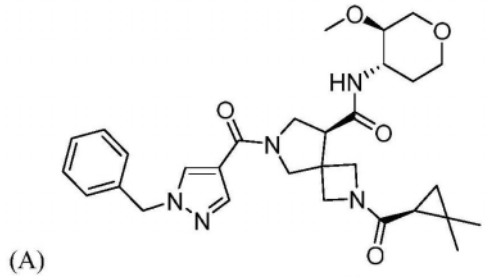
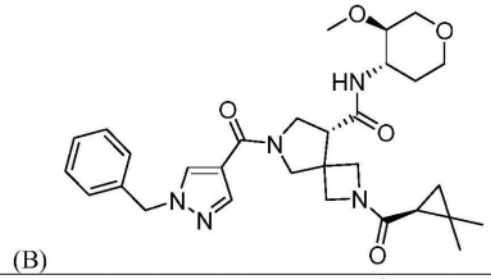
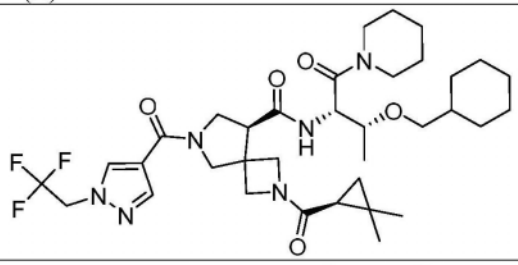
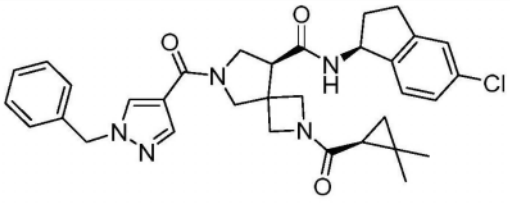
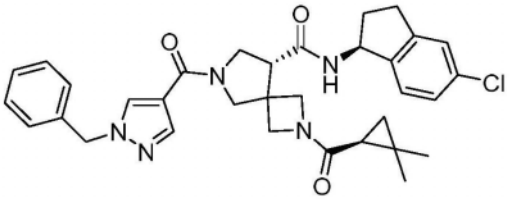
[0346]

	 (B)
I-124	 (A)
I-125	  (B)
I-126	 (A)  (B)

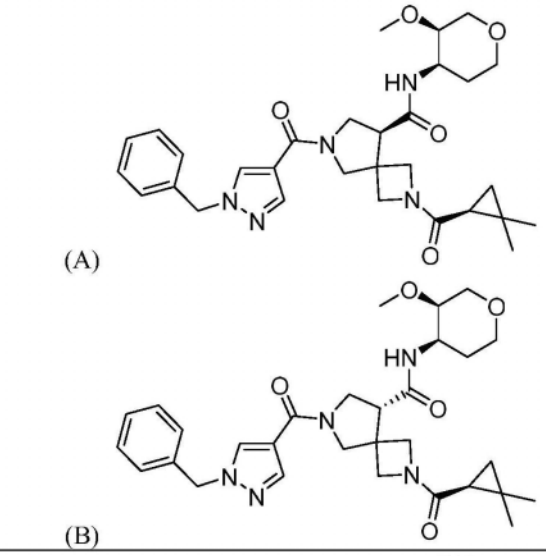
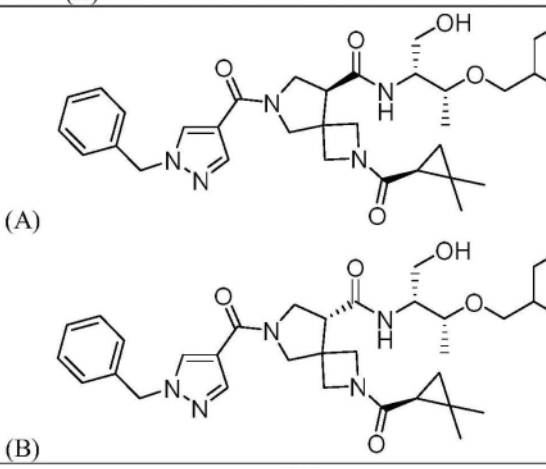
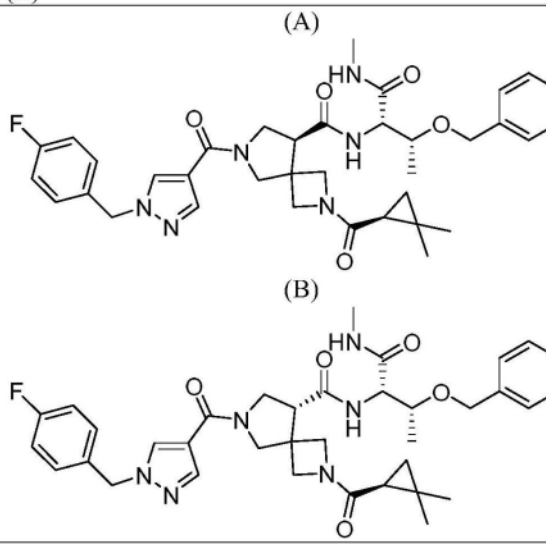
[0347]

I-127	 (A) (B)
I-128	 (A) (B)
I-129	 (A) (B)
I-130	 (A)

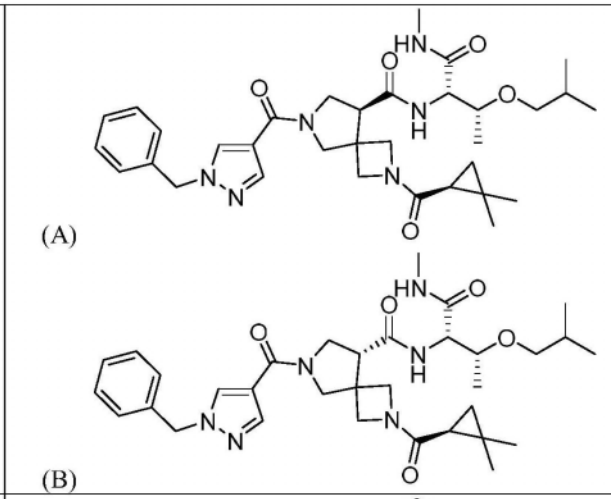
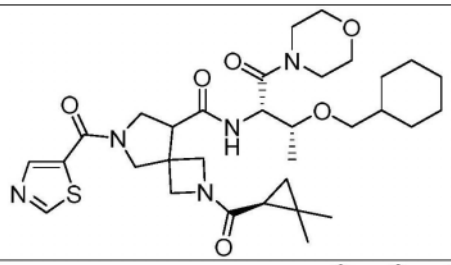
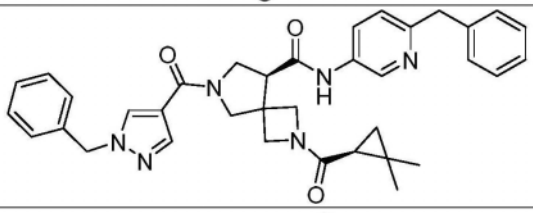
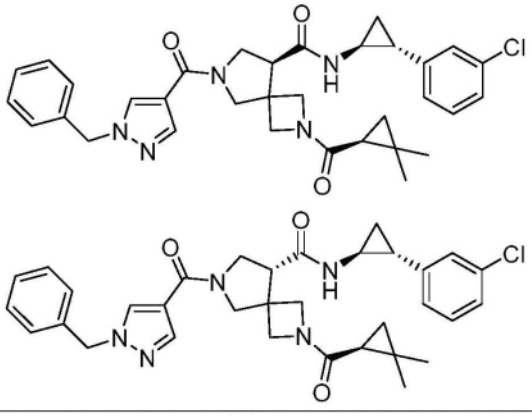
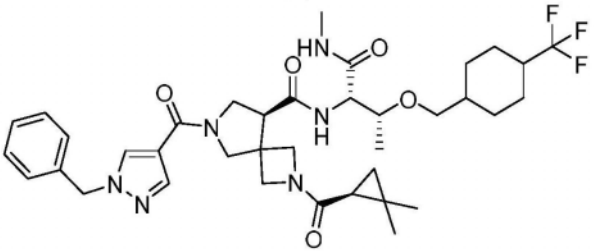
[0348]

	 (B)
I-131	 (A)  (B)
I-132	
I-133	 (A)  (B)

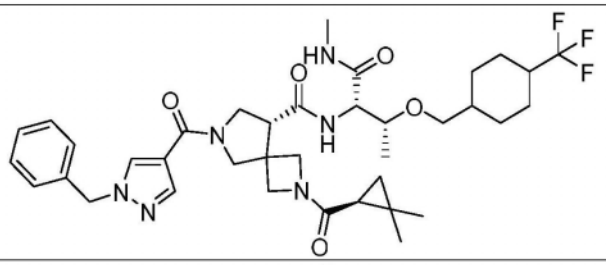
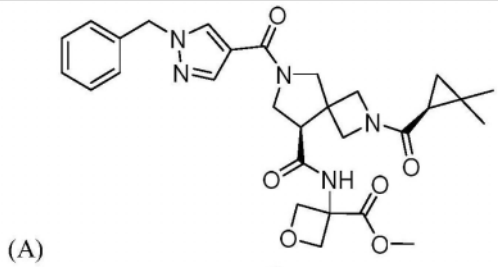
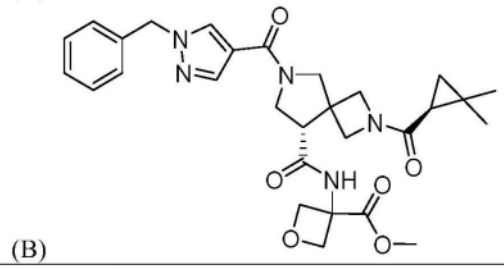
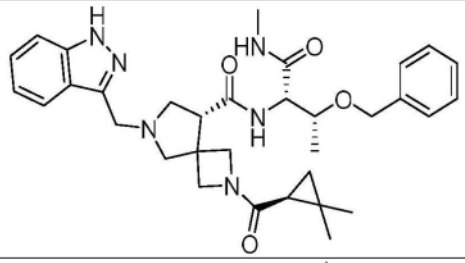
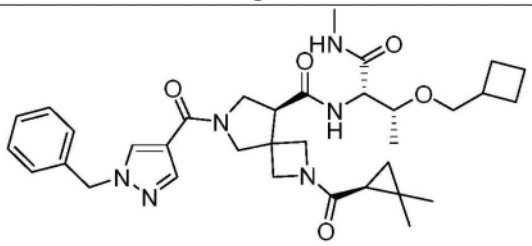
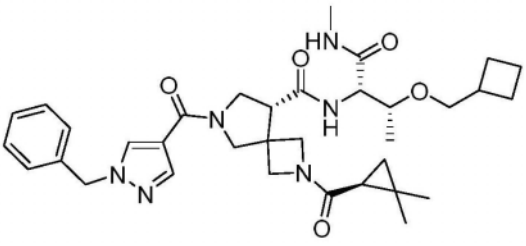
[0349]

I-134	
I-135	
I-136	

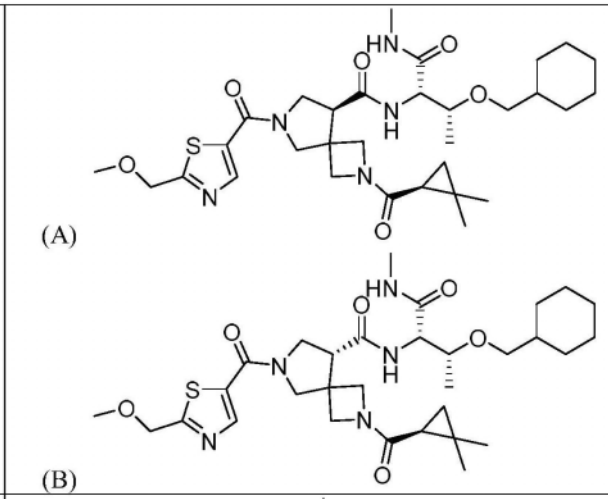
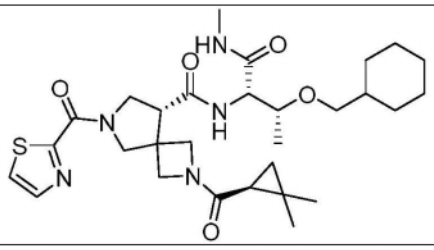
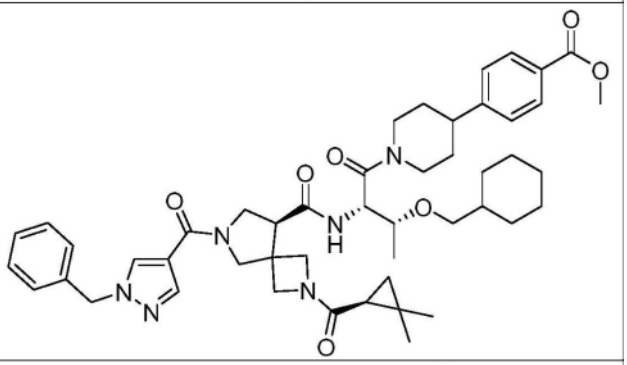
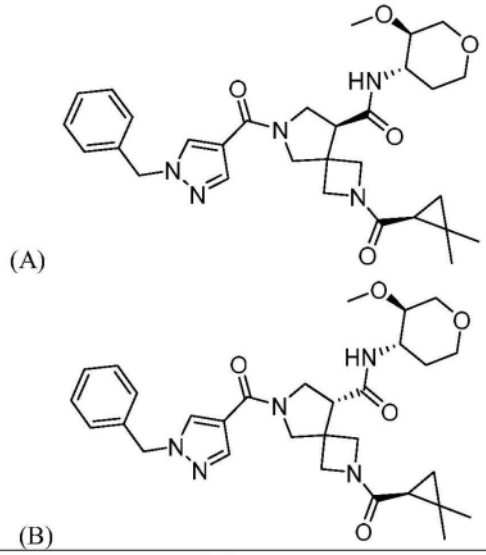
[0350]

I-137	 (A) (B)
I-138	
I-139	
I-140	 (A) (B)
I-141	(A)  (B)

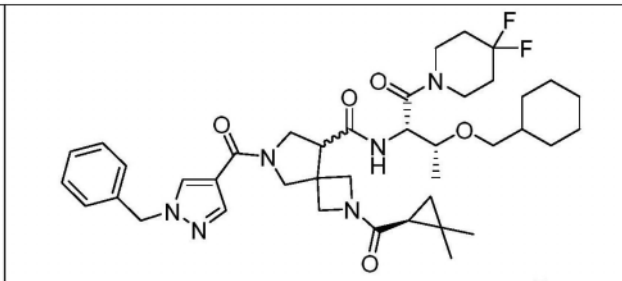
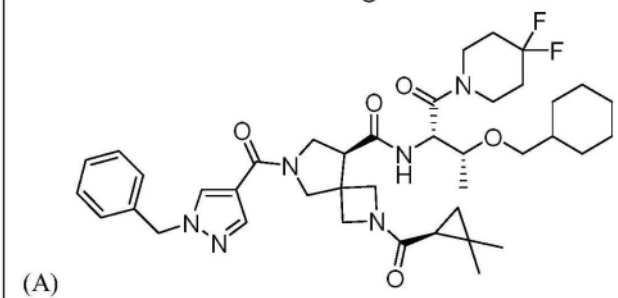
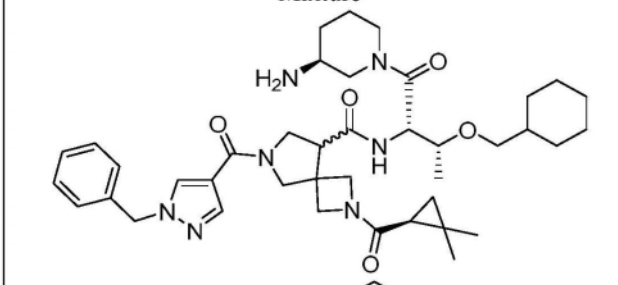
[0351]

	
I-142	 (A)  (B)
I-143	
I-144	 (A)  (B)

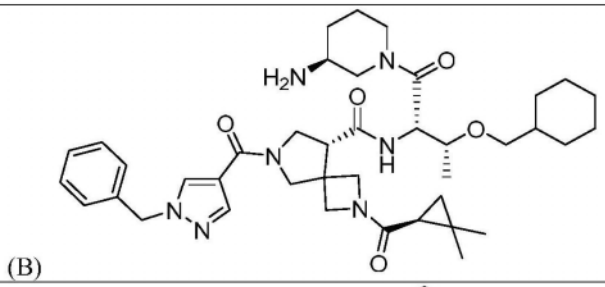
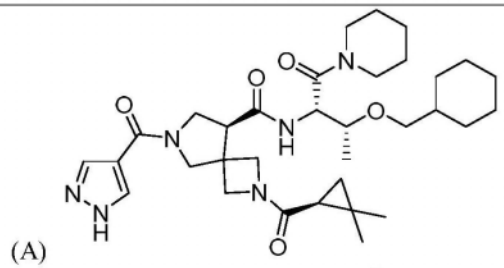
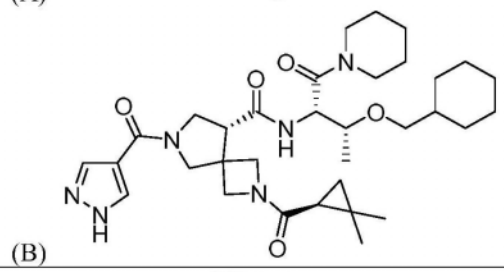
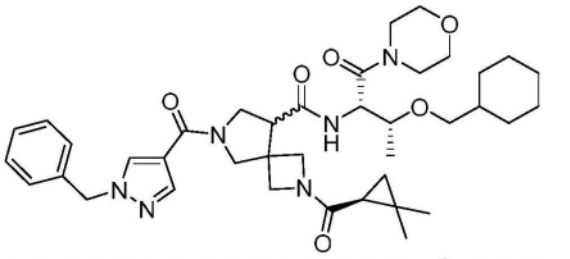
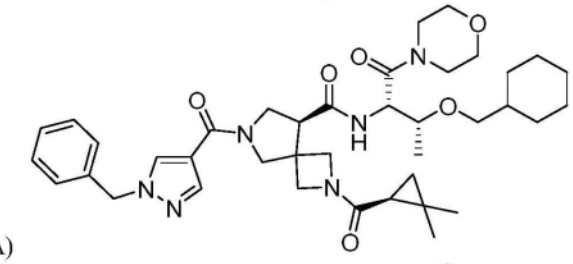
[0352]

I-145	 (A) (B)
I-146	
I-147	
I-148	 (A) (B)
I-149	Mixture

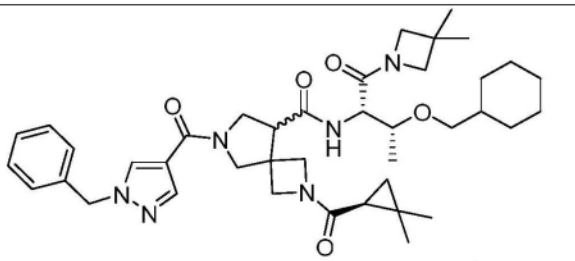
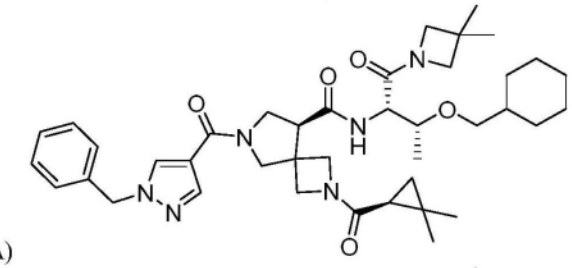
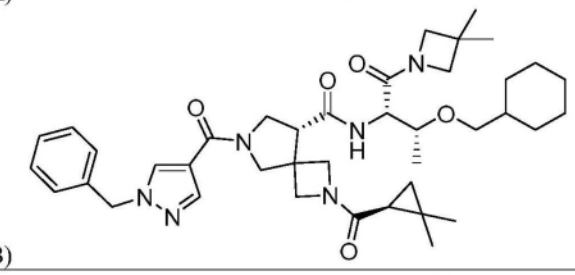
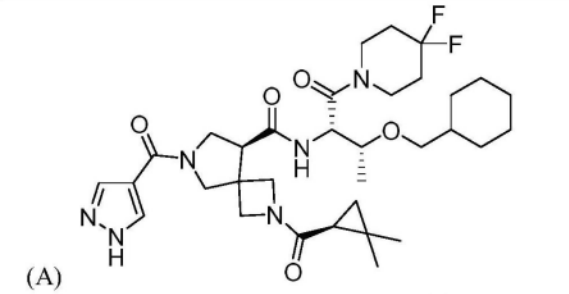
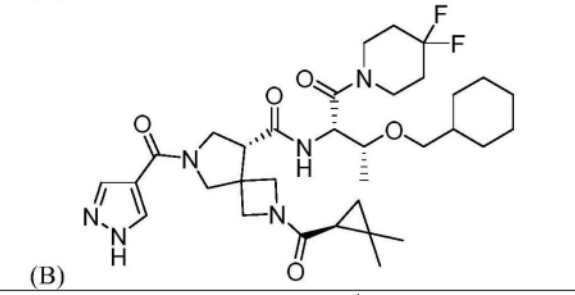
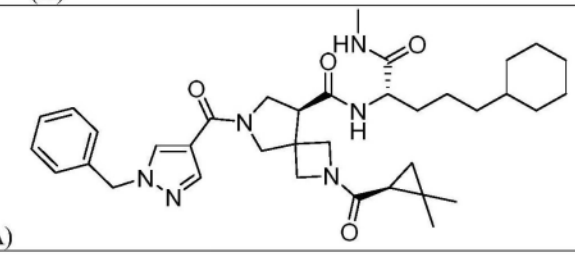
[0353]

	 (A)  (B)
I-150	Mixture  (A)

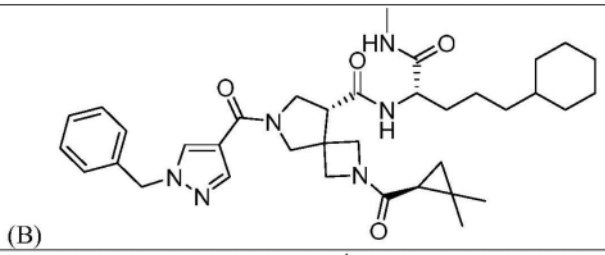
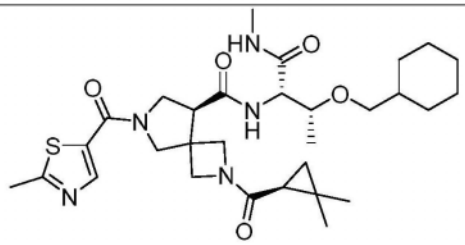
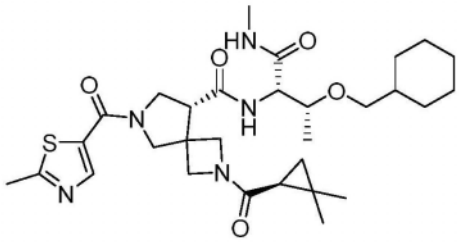
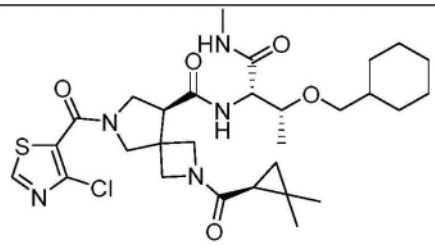
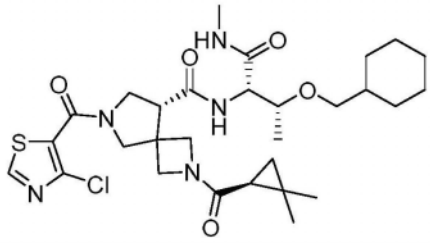
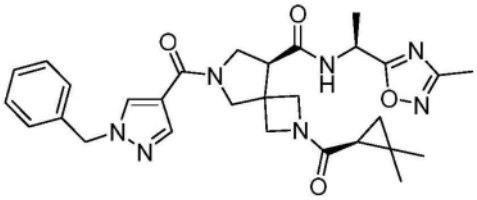
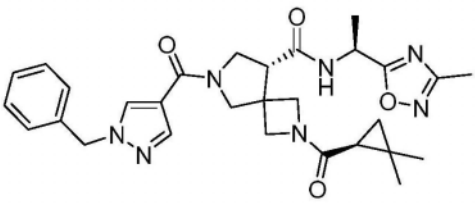
[0354]

	 (B)
I-151	 (A)  (B)
I-152	Mixture  (A)  (B)
I-153	Mixture

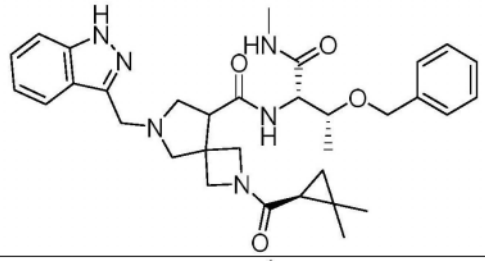
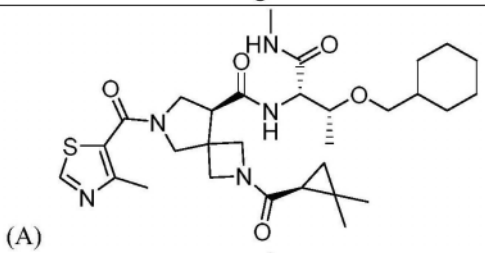
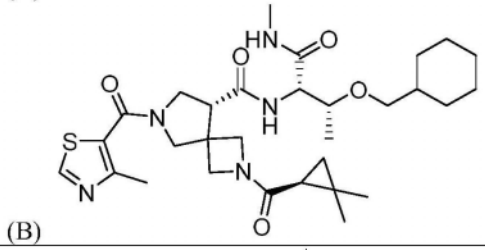
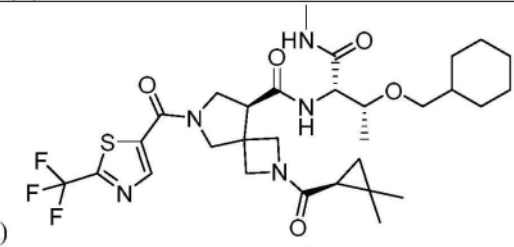
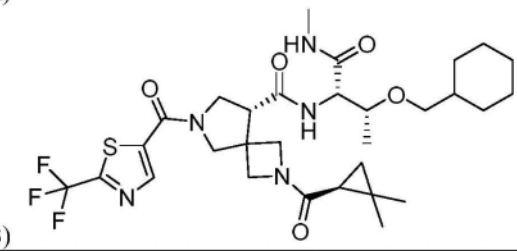
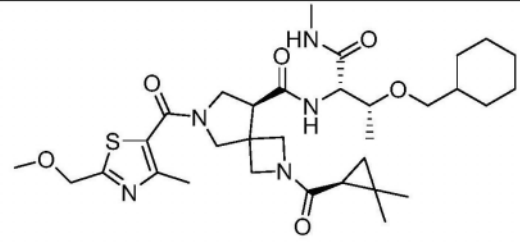
[0355]

	 (A)  (B) 
I-154	 (A)  (B)
I-155	 (A)

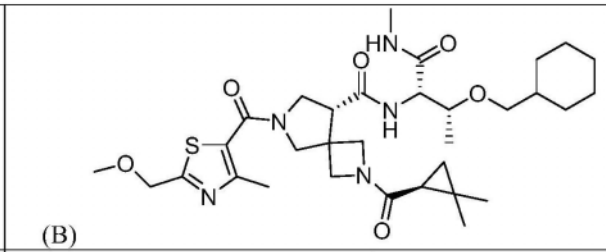
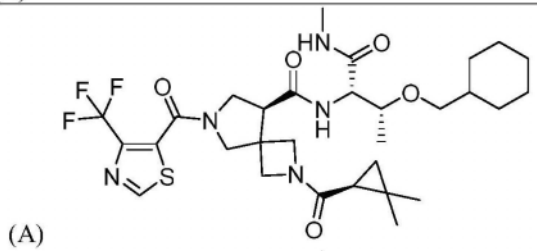
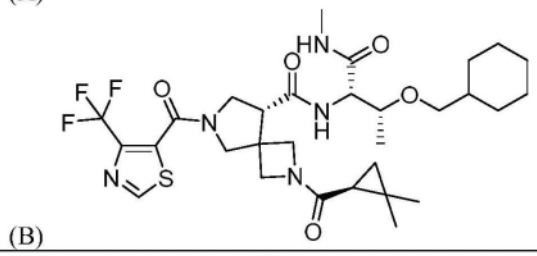
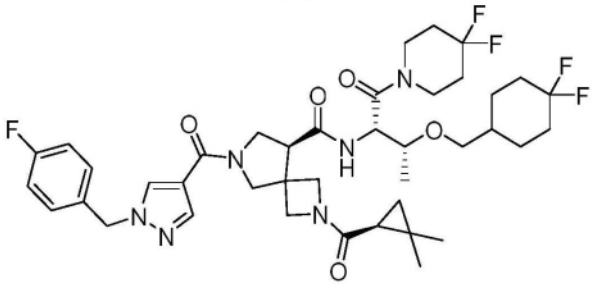
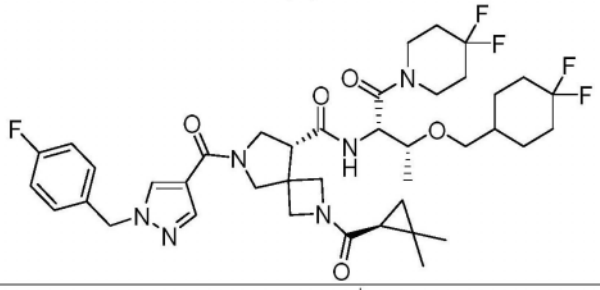
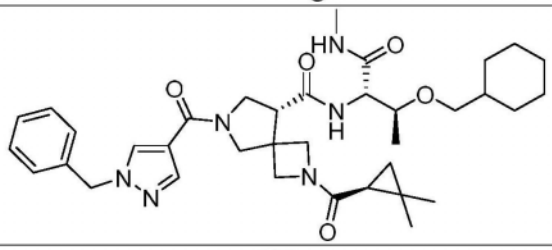
[0356]

	 (B)
I-156	 (A)  (B)
I-157	 (A)  (B)
I-158	 (A)  (B)

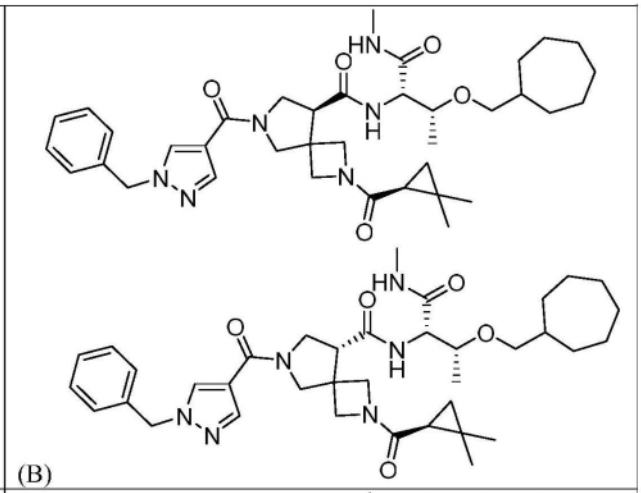
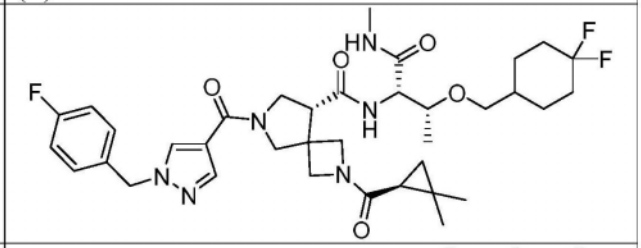
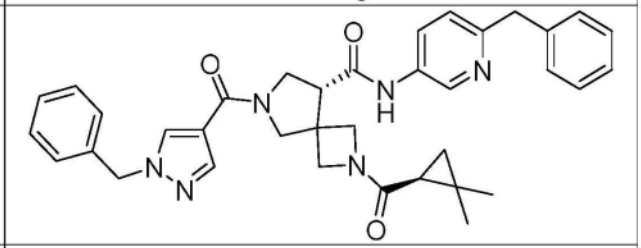
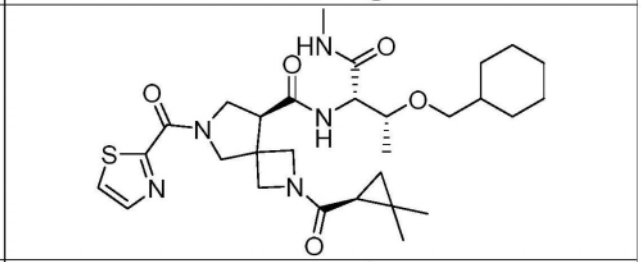
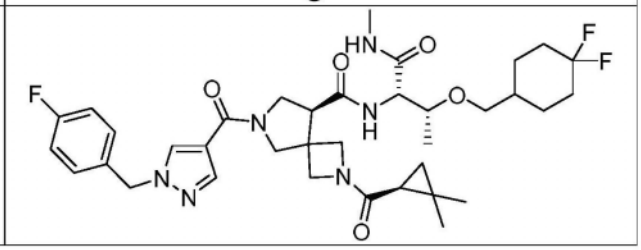
[0357]

I-159	
I-160	 (A)  (B)
I-161	 (A)  (B)
I-162	 (A)

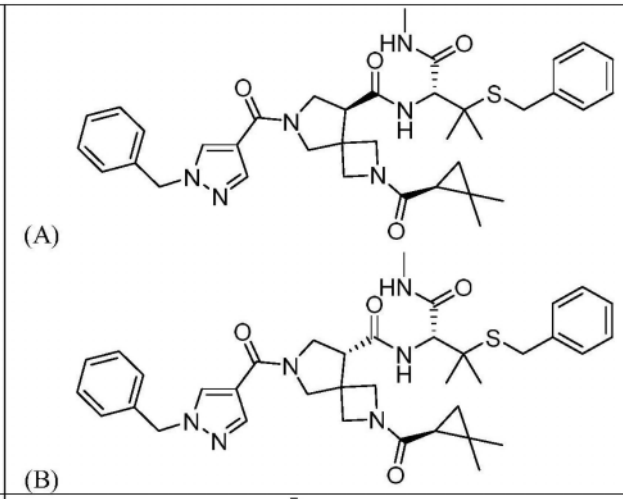
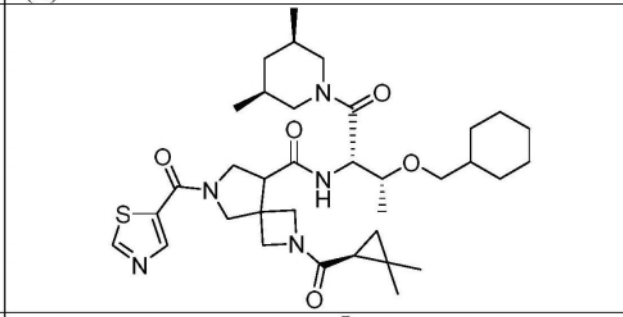
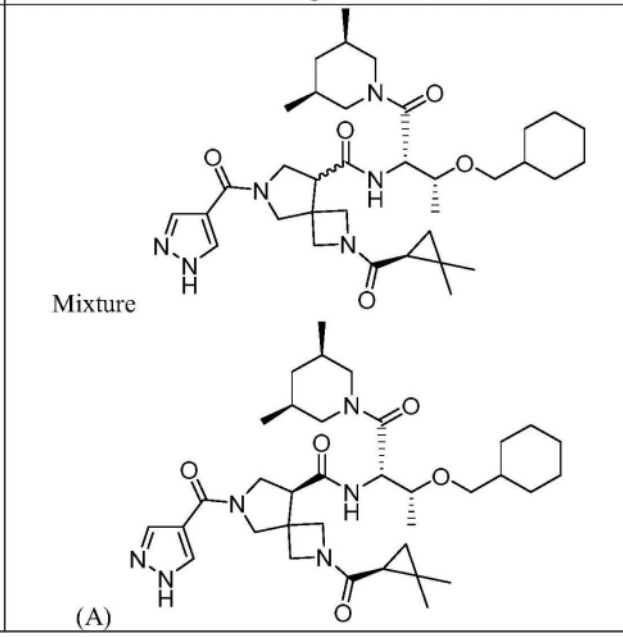
[0358]

	 (B)
I-163	 (A)  (B)
I-164	(A)  (B) 
I-165	
I-166	(A)

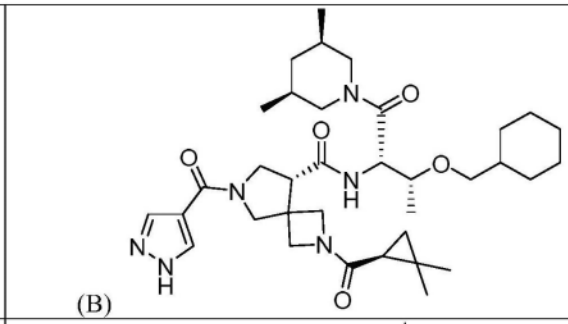
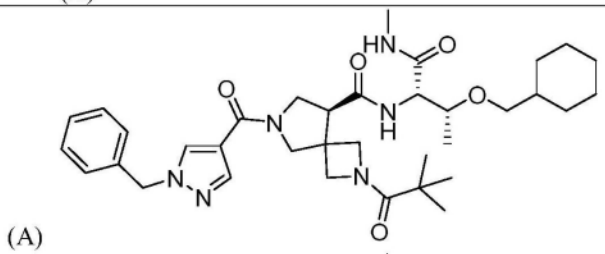
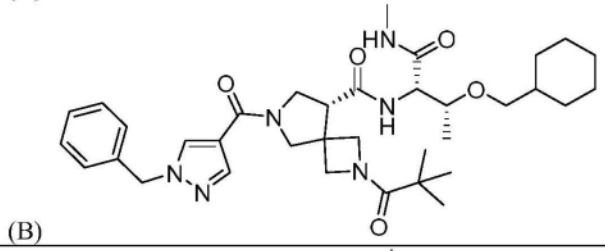
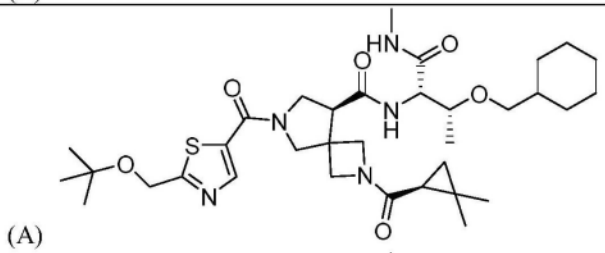
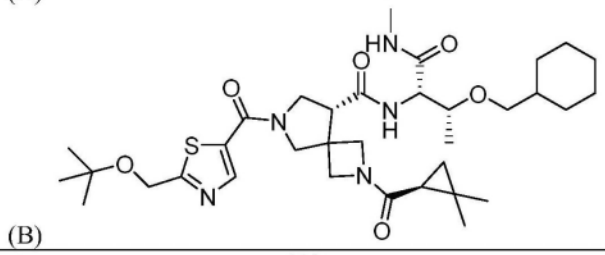
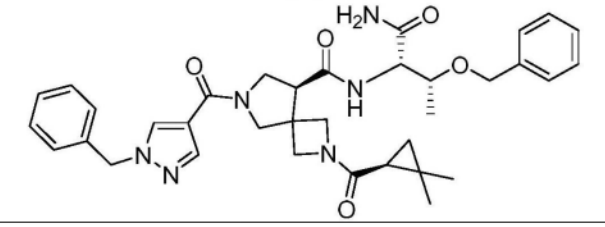
[0359]

	 (B)
I-167	
I-168	
I-169	
I-170	

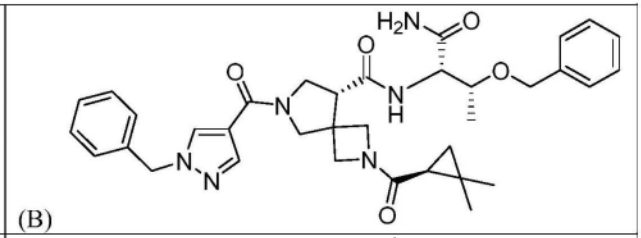
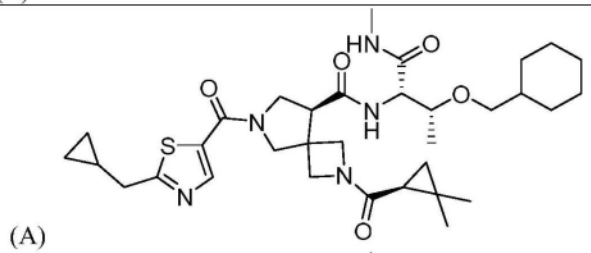
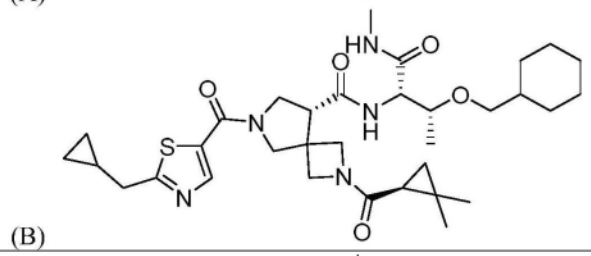
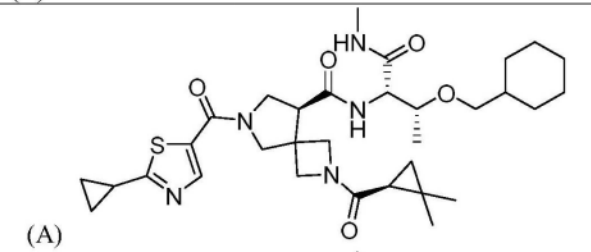
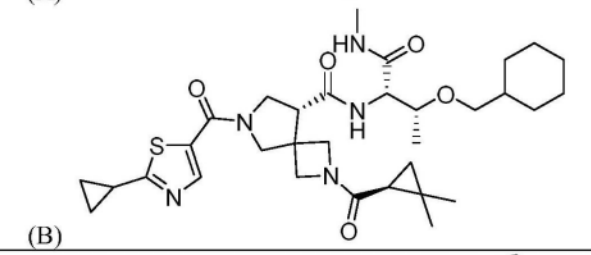
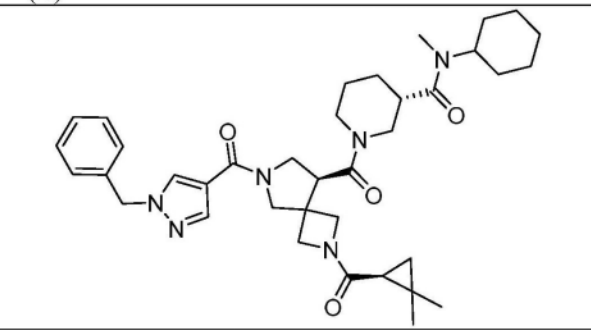
[0360]

I-171	 (A) (B)
I-172	
I-173	 Mixture (A)

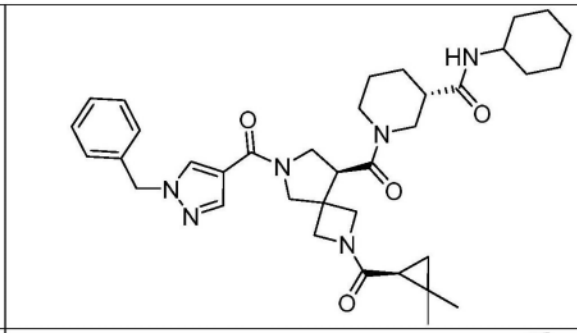
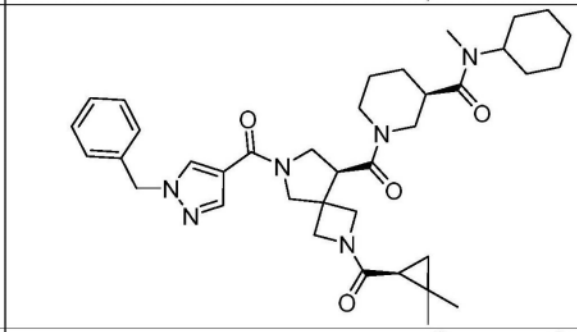
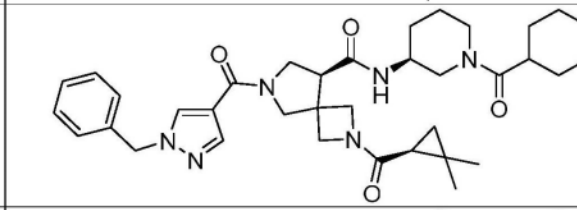
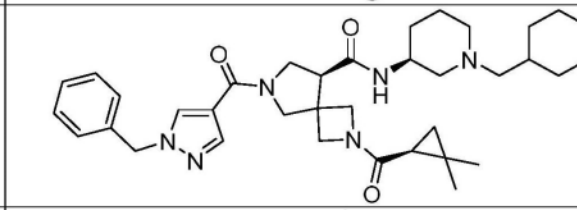
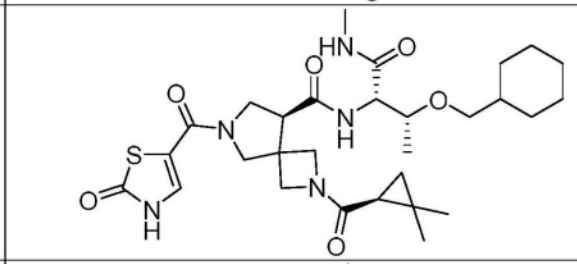
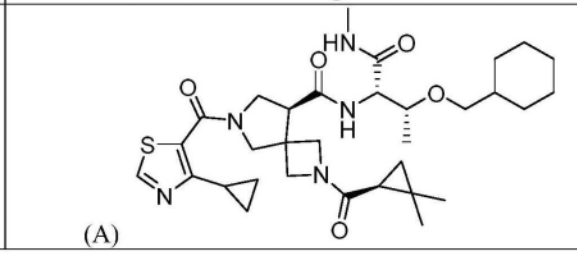
[0361]

	 (B)
I-174	 (A)  (B)
I-175	 (A)  (B)
I-176	(A) 

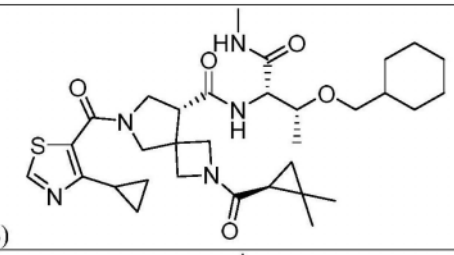
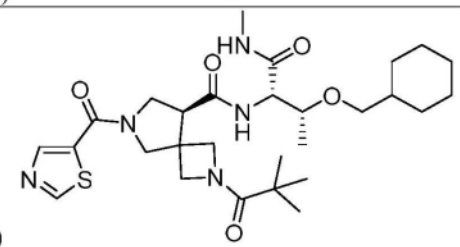
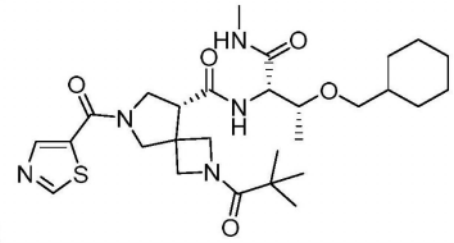
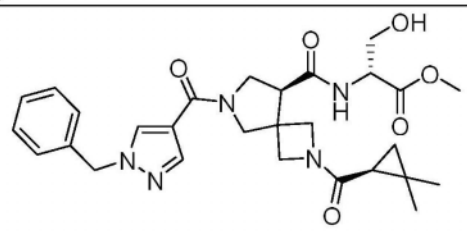
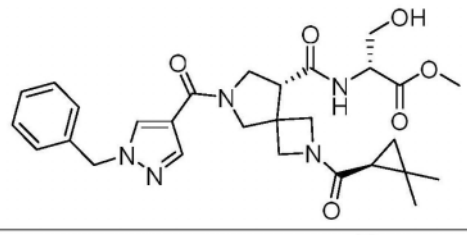
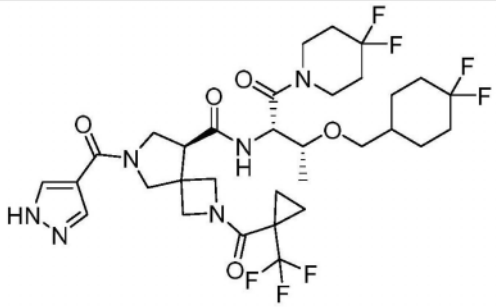
[0362]

	 (B)
I-177	 (A)  (B)
I-178	 (A)  (B)
I-179	

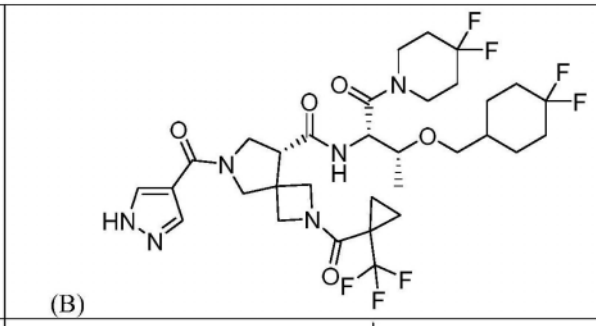
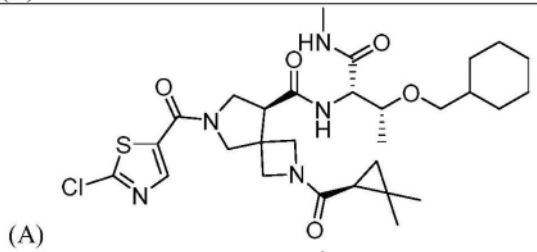
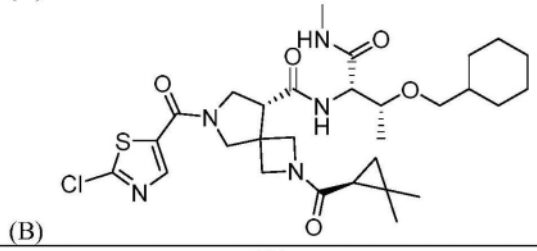
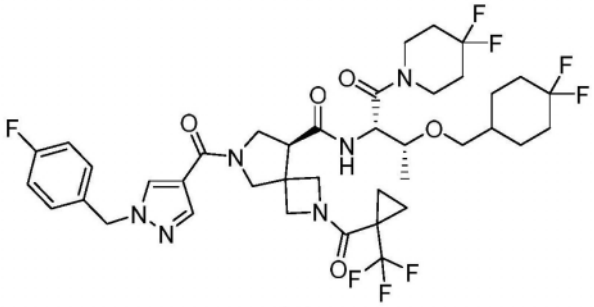
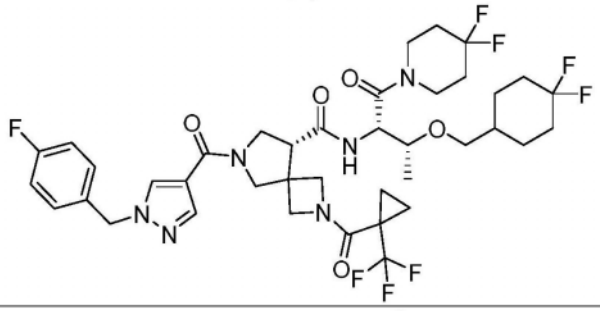
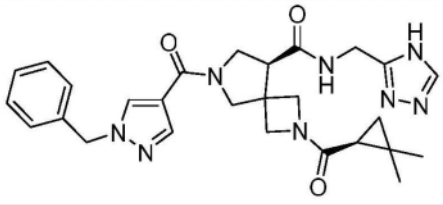
[0363]

I-180	
I-181	
I-182	
I-183	
I-184	
I-185	 (A)

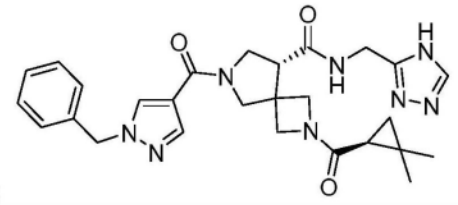
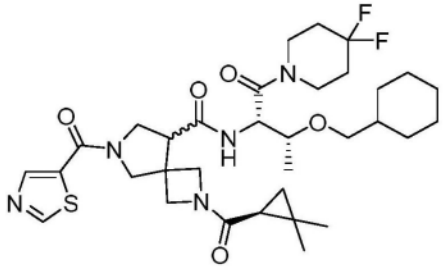
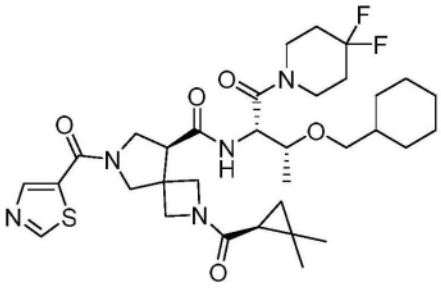
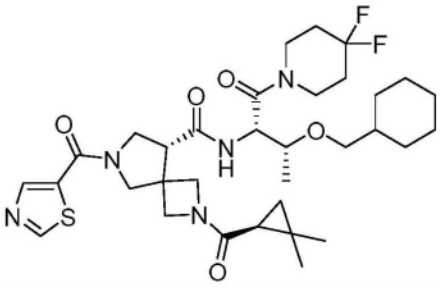
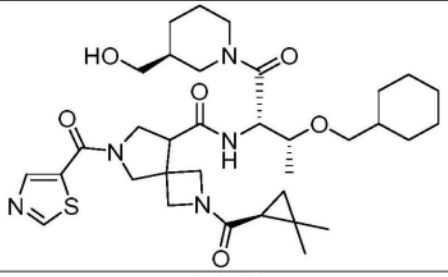
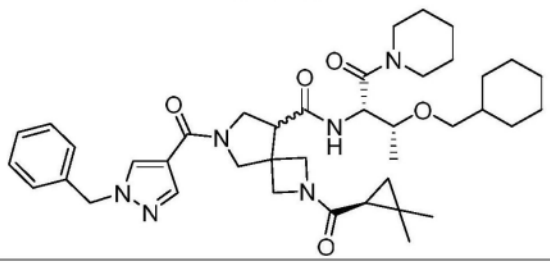
[0364]

	 (B)
I-186	 (A)  (B)
I-187	 (A)  (B)
I-188	 (A)

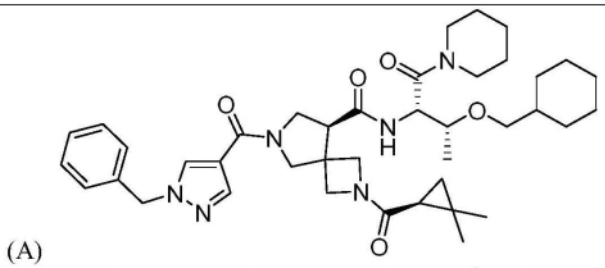
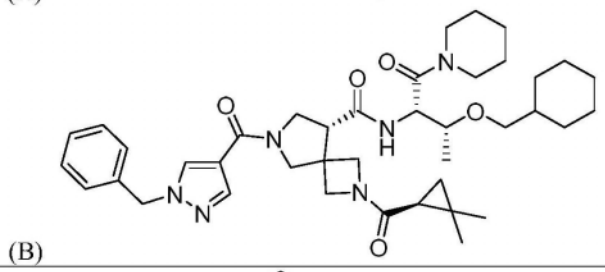
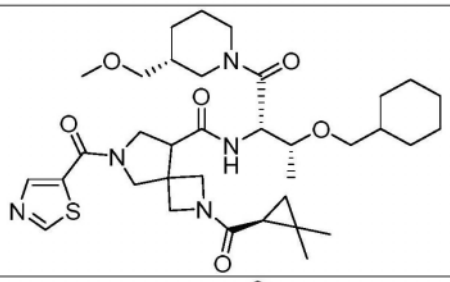
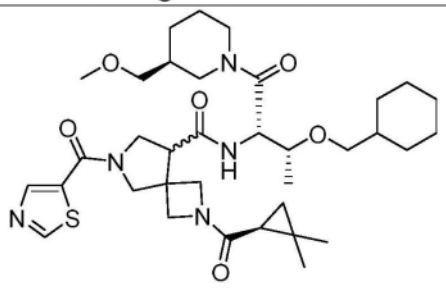
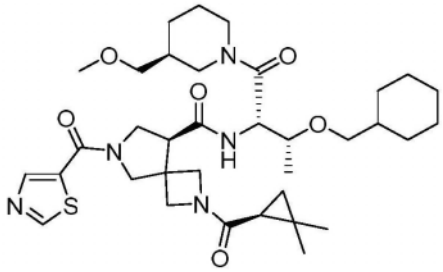
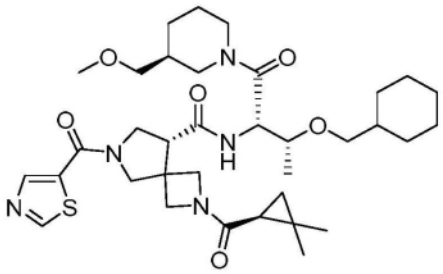
[0365]

	 (B)
I-189	 (A)  (B)
I-190	(A)  (B) 
I-191	 (A)

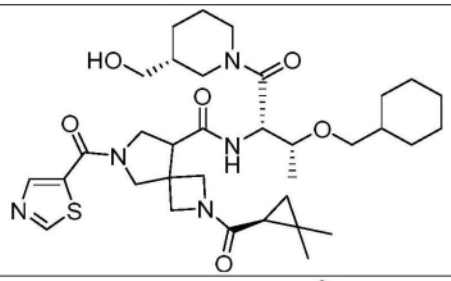
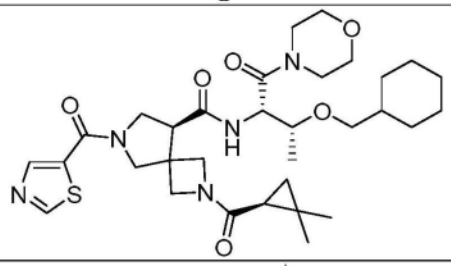
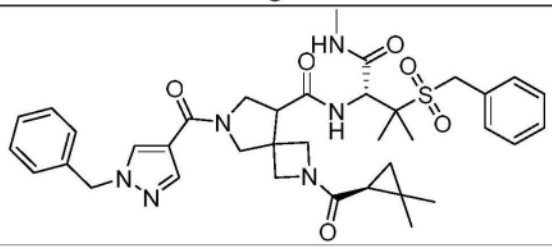
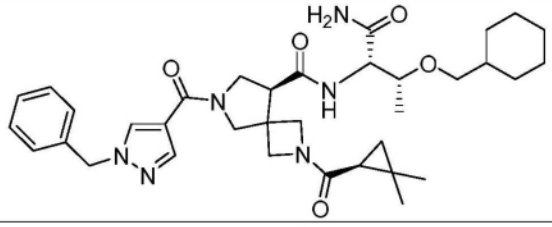
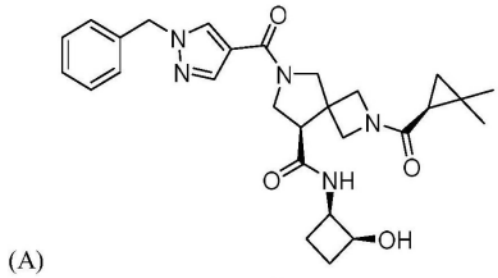
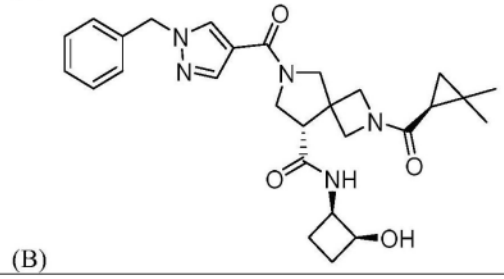
[0366]

	 (B)
I-192	 Mixture  (A)  (B)
I-193	
I-194	混合物 

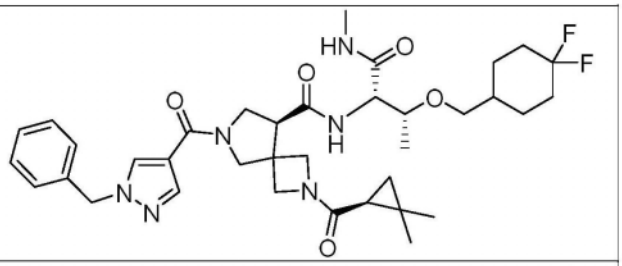
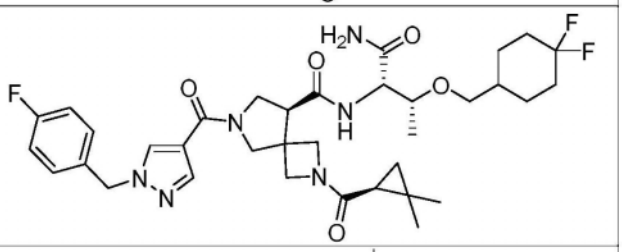
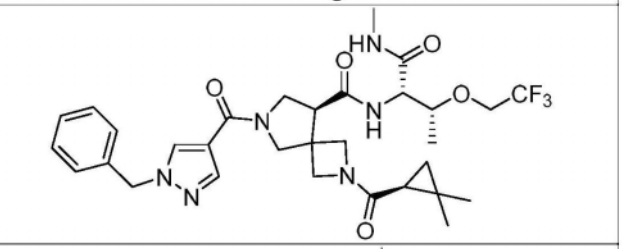
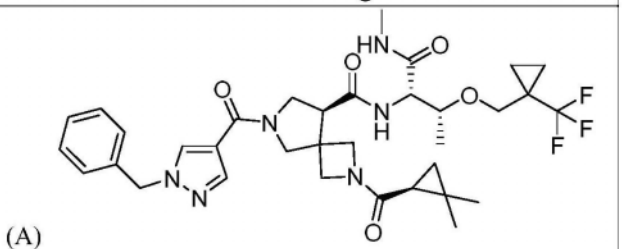
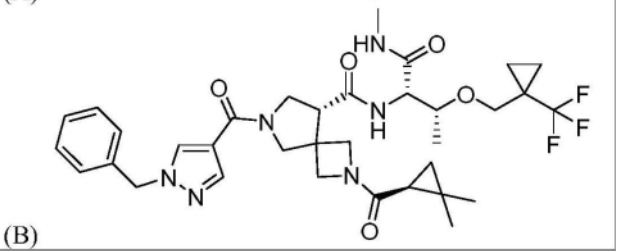
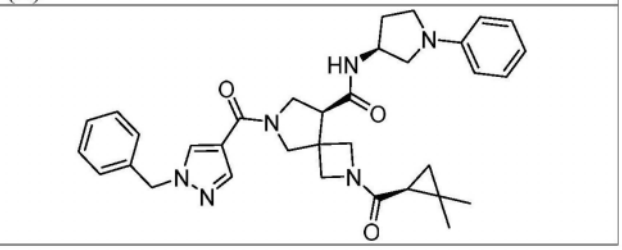
[0367]

	 (A)  (B)
I-195	
I-196	 混合物  (A)  (B)

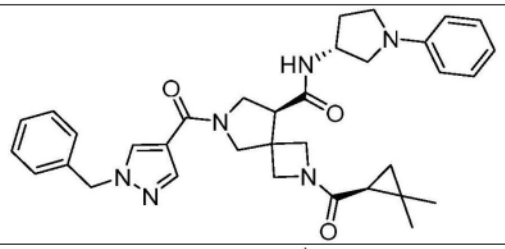
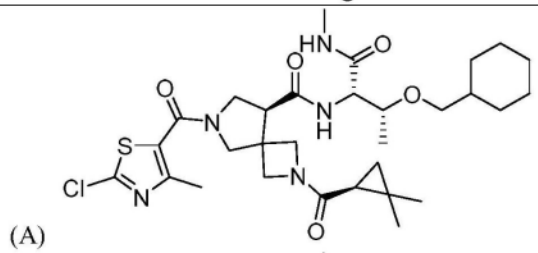
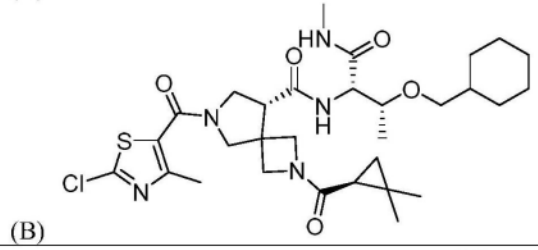
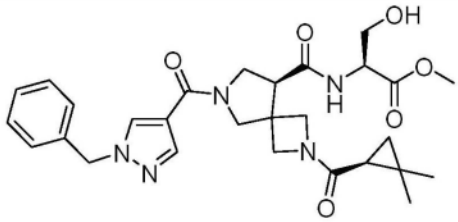
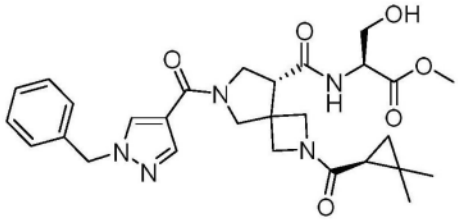
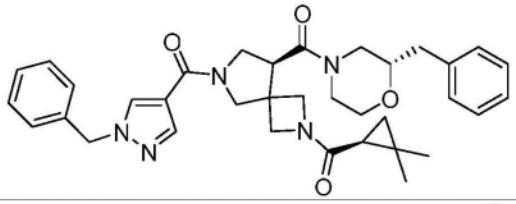
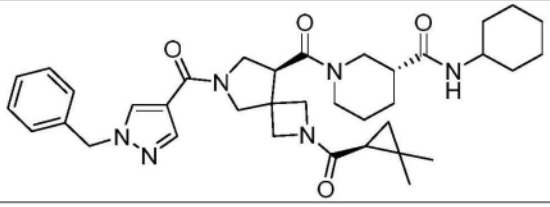
[0368]

I-197	
I-198	
I-199	
I-200	
I-201	 (A)  (B)

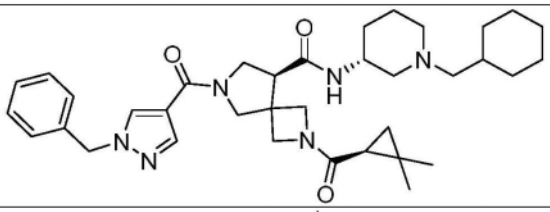
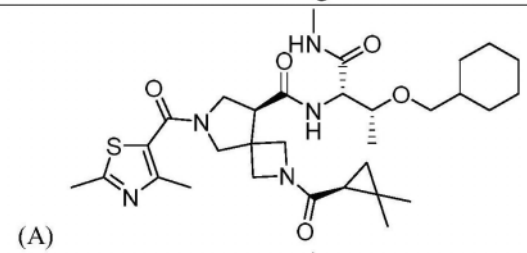
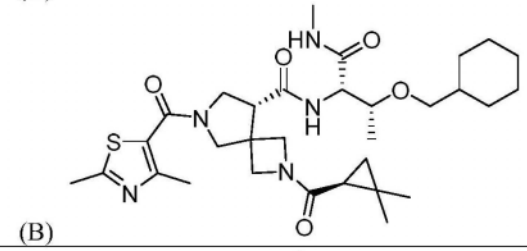
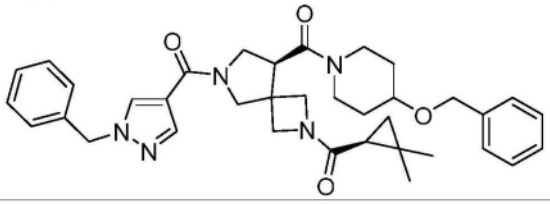
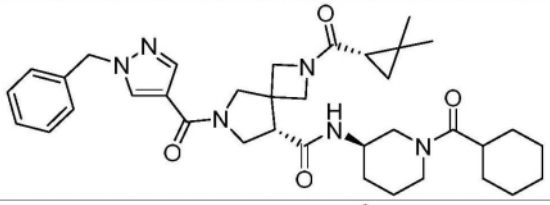
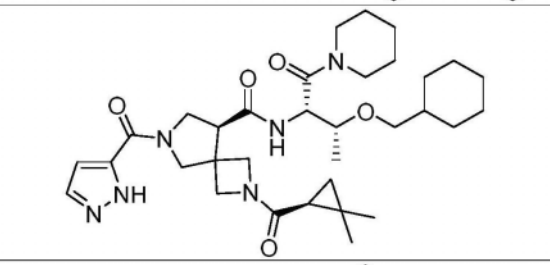
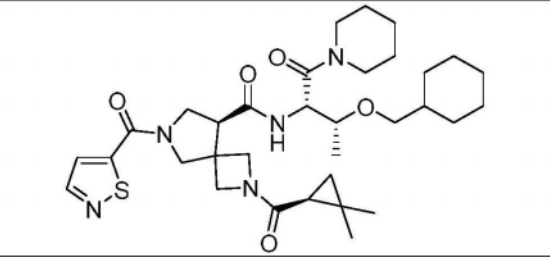
[0369]

I-202	
I-203	
I-204	
I-205	 (A)  (B)
I-206	

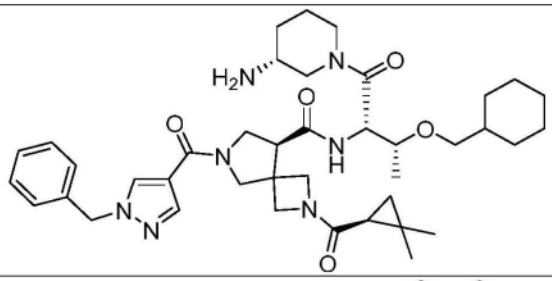
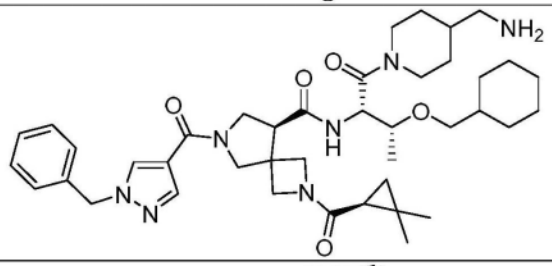
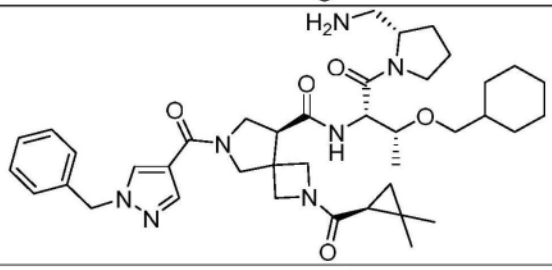
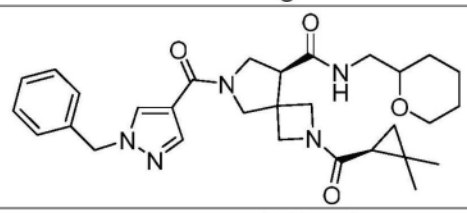
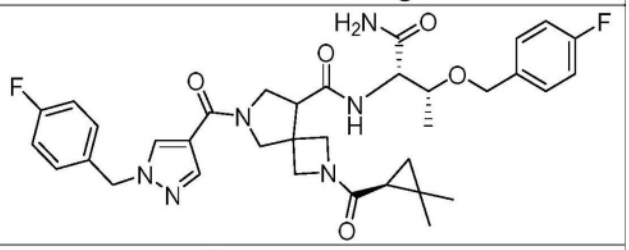
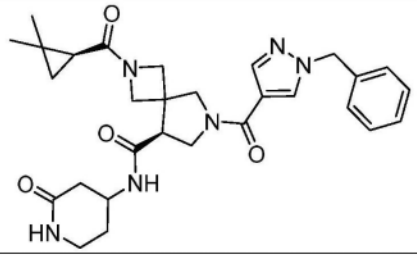
[0370]

I-207	
I-208	 (A)  (B)
I-209	 (A)  (B)
I-210	
I-211	

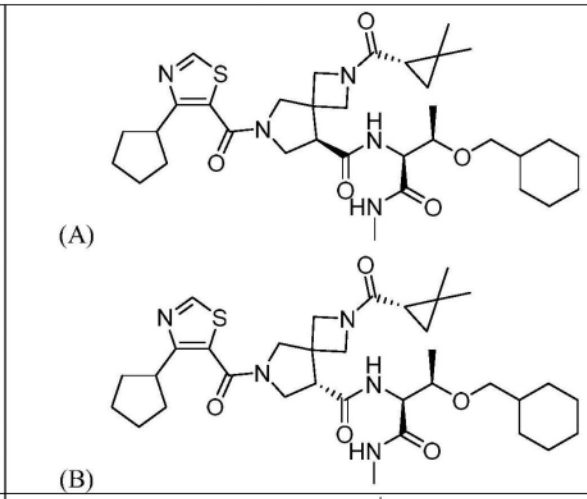
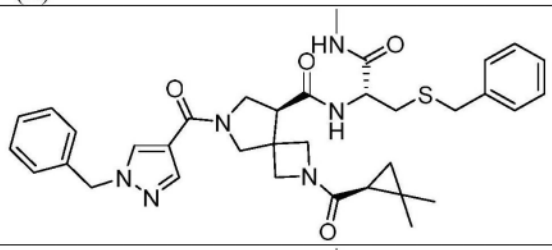
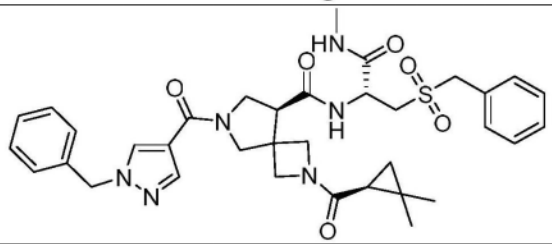
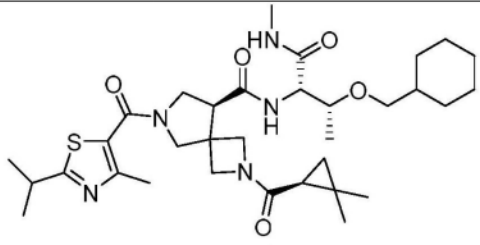
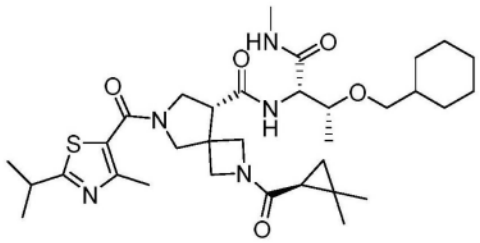
[0371]

I-212	
I-213	 (A)  (B)
I-214	
I-215	
I-216	
I-217	

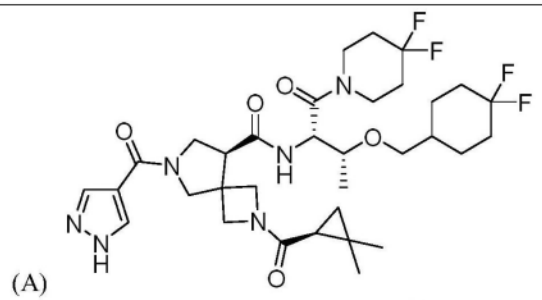
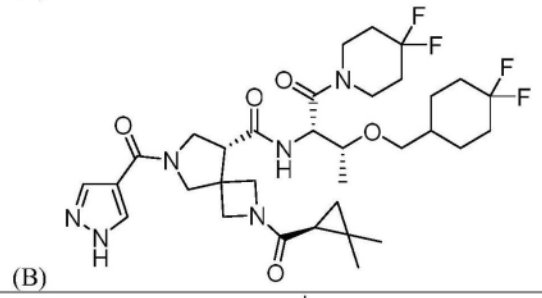
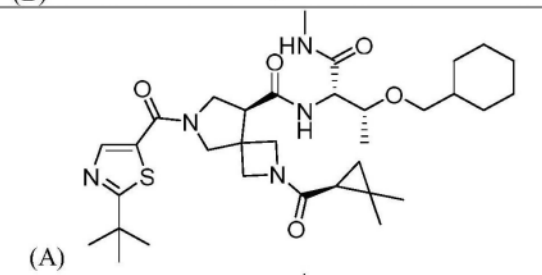
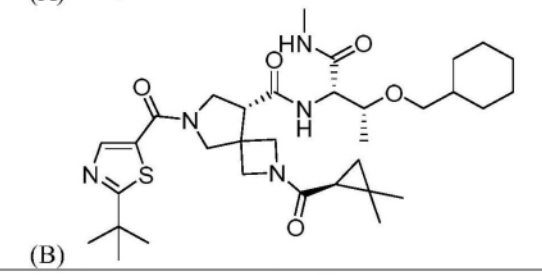
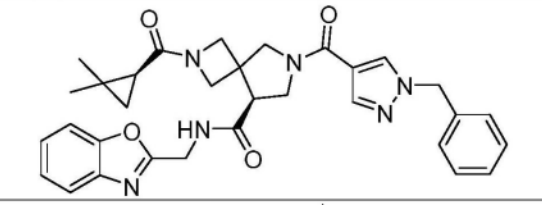
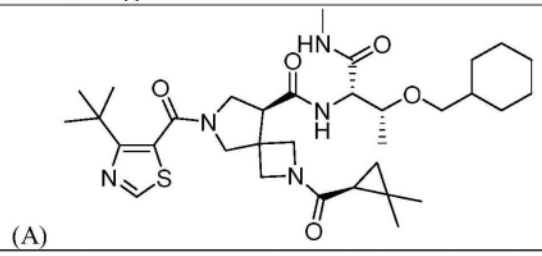
[0372]

I-218	
I-219	
I-220	
I-221	
I-222	
I-223	

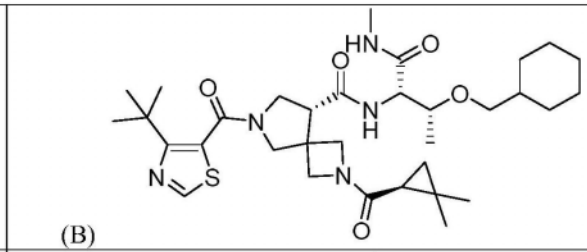
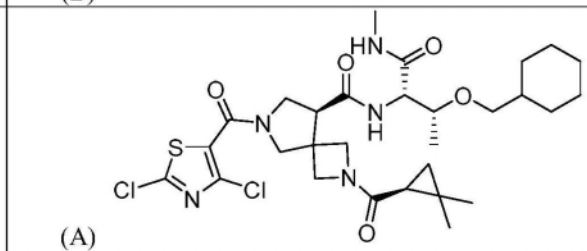
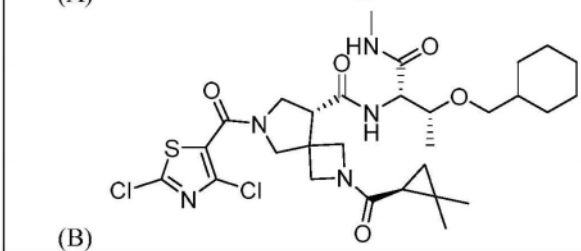
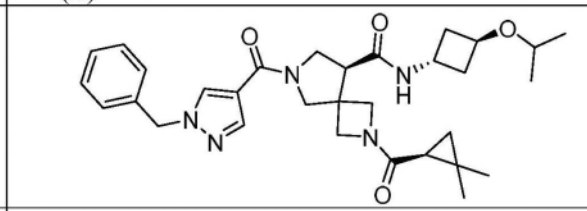
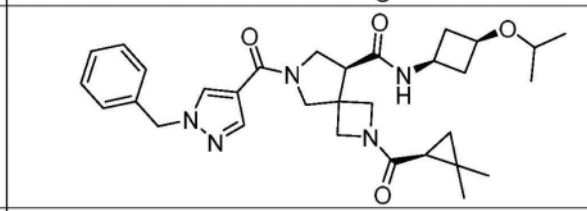
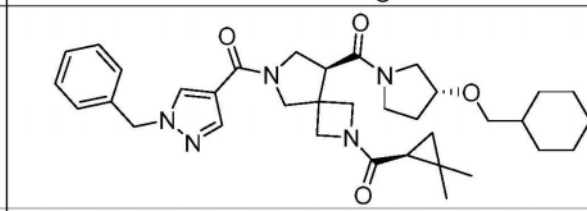
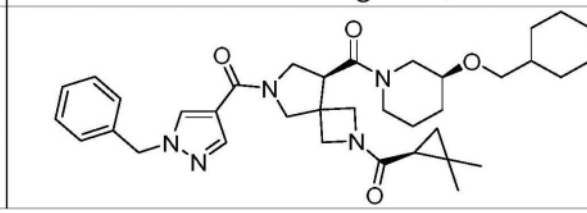
[0373]

I-224	 (A) (B)
I-225	
I-226	
I-227	 (A)  (B)

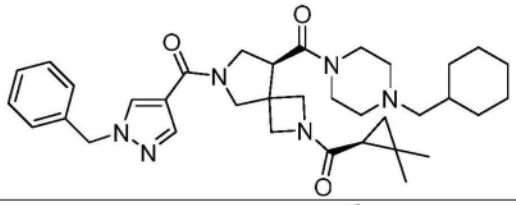
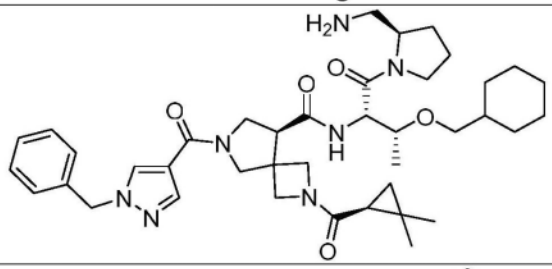
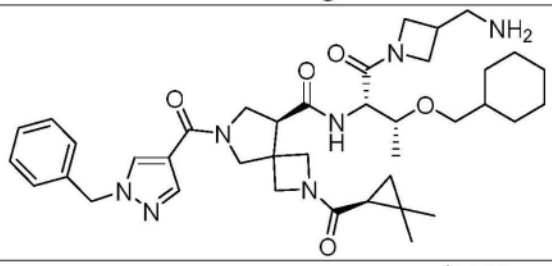
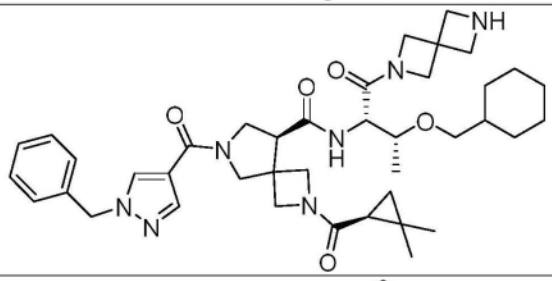
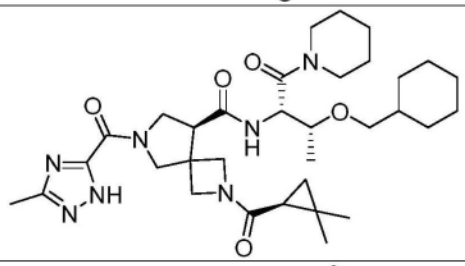
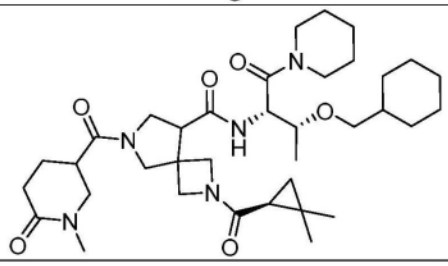
[0374]

I-228	 (A)  (B)
I-229	 (A)  (B)
I-230	
I-231	 (A)

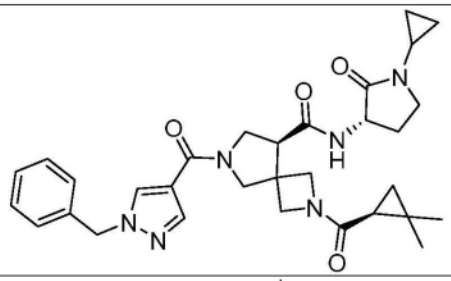
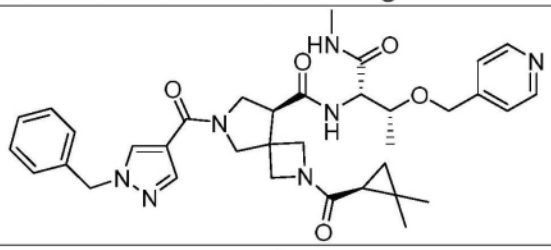
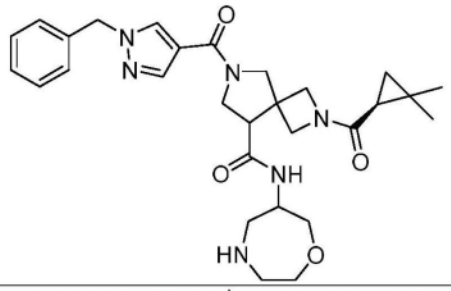
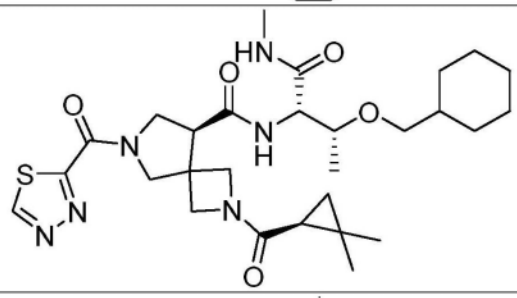
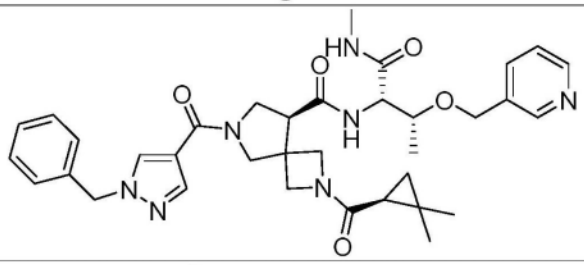
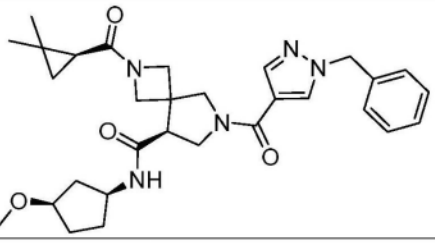
[0375]

	 (B)
I-232	 (A)  (B)
I-233	
I-234	
I-235	
I-236	

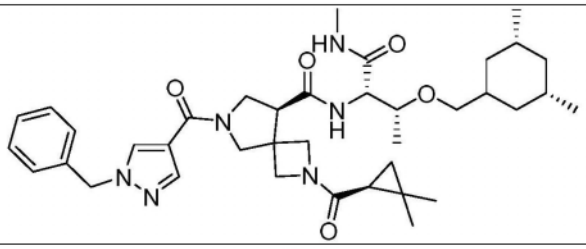
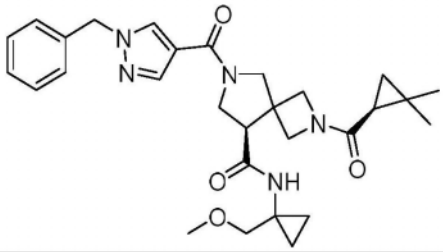
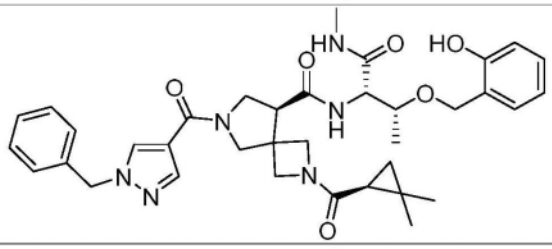
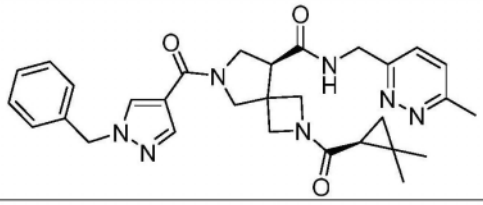
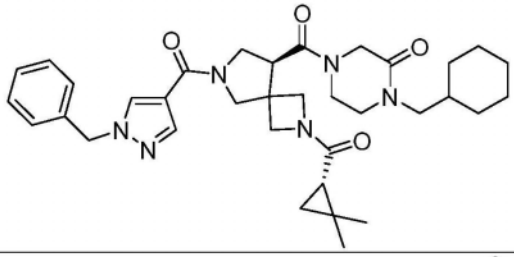
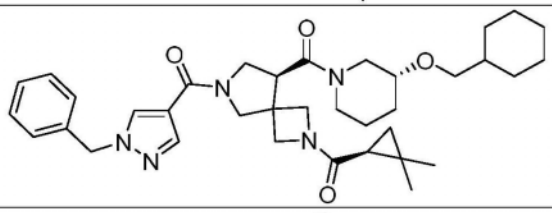
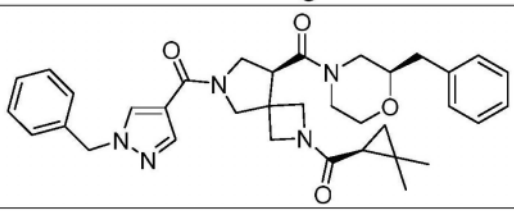
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I-238	
I-239	
I-240	
I-241	
I-242	

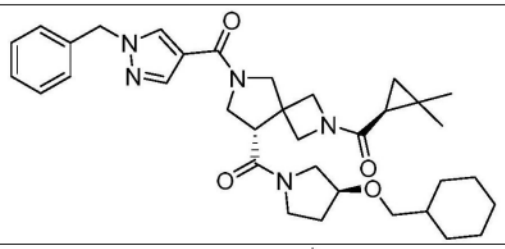
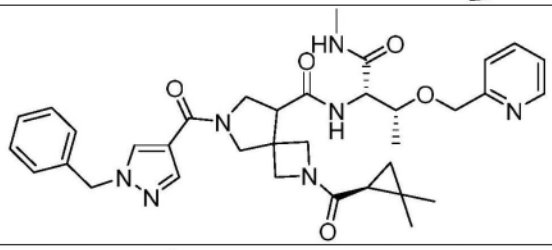
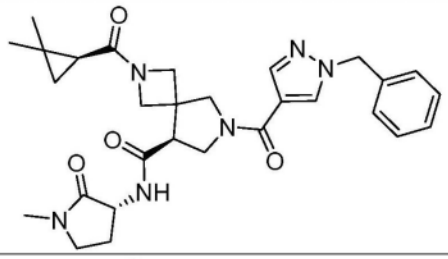
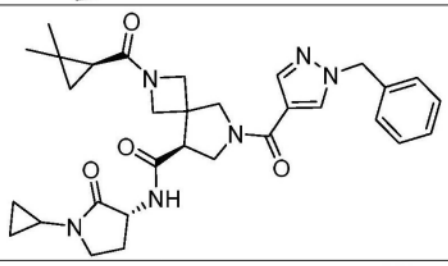
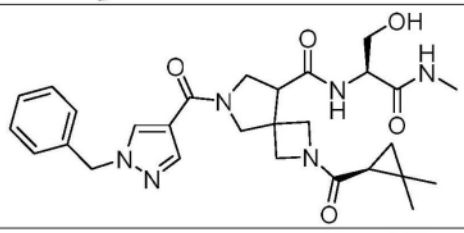
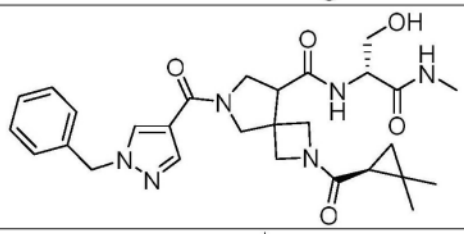
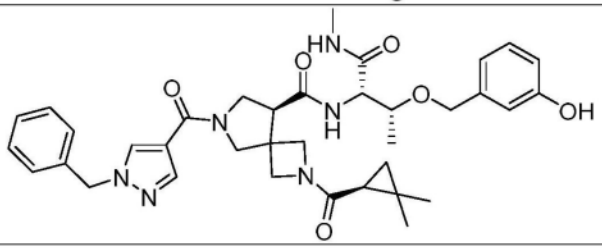
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I-244	
I-245	
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I-247	
I-248	

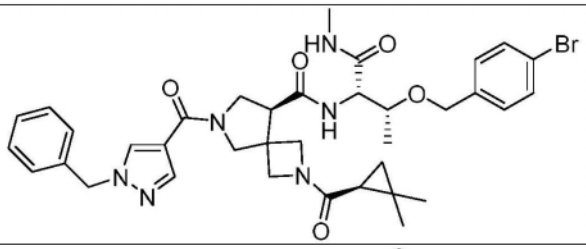
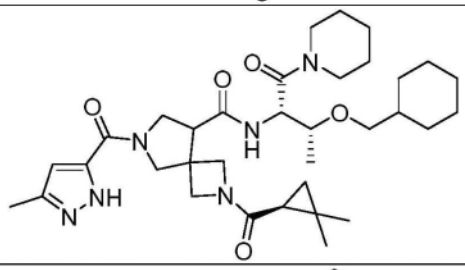
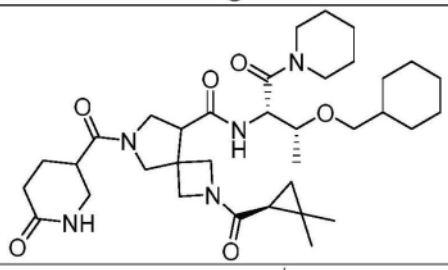
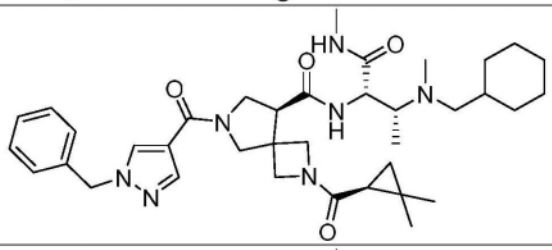
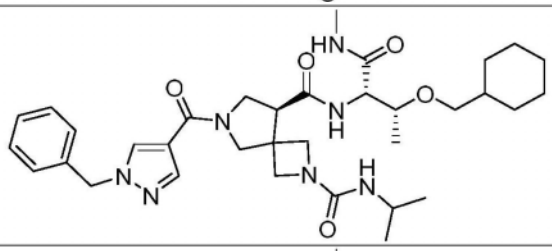
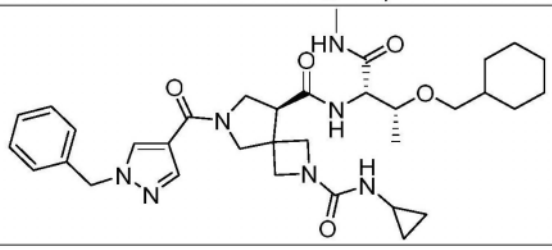
[0378]

I-249	
I-250	
I-251	
I-252	
I-253	
I-254	
I-255	

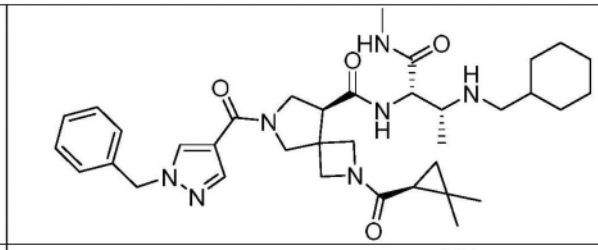
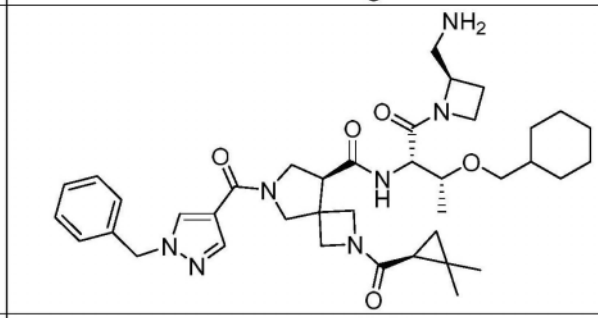
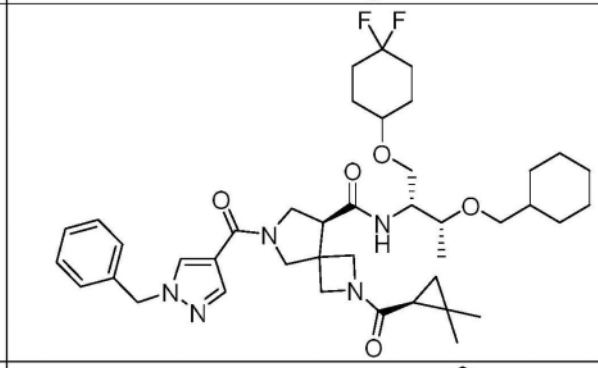
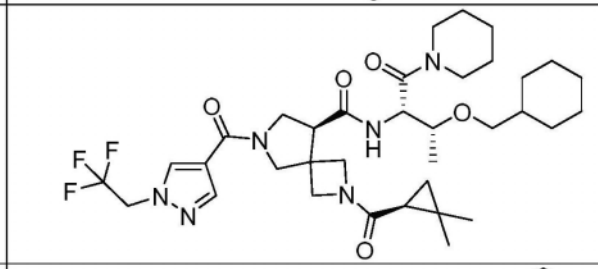
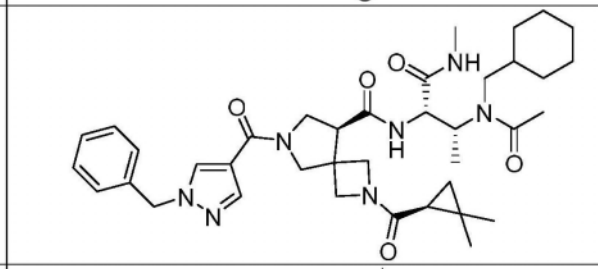
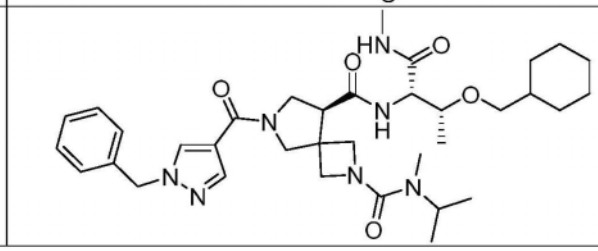
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I-257	
I-258	
I-259	
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I-261	
I-262	

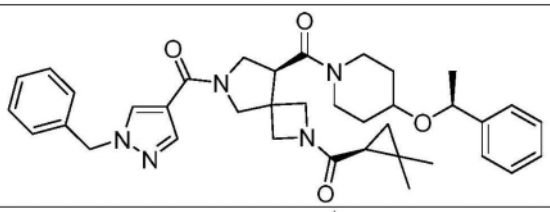
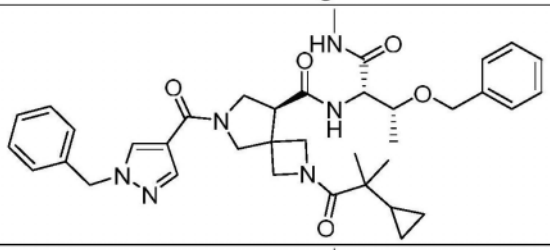
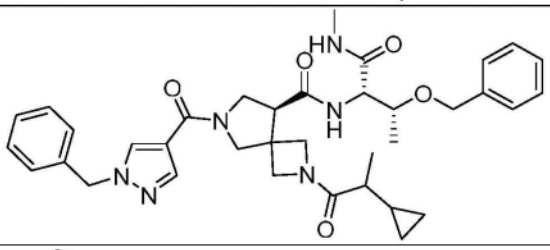
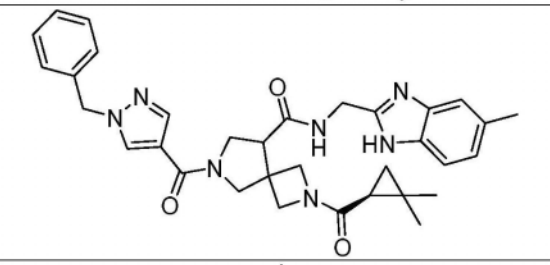
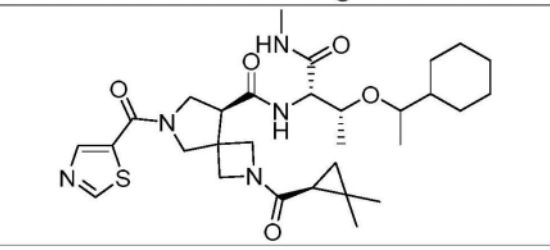
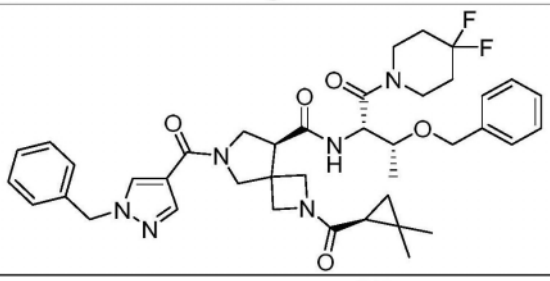
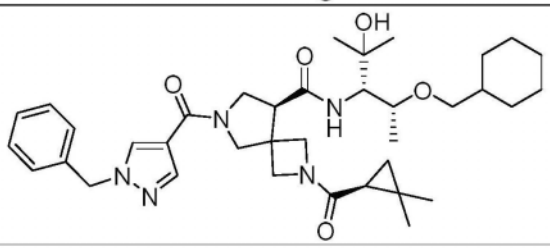
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I-263	
I-264	
I-265	
I-266	
I-267	
I-268	

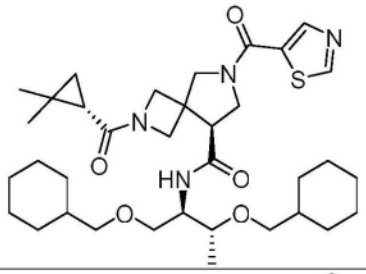
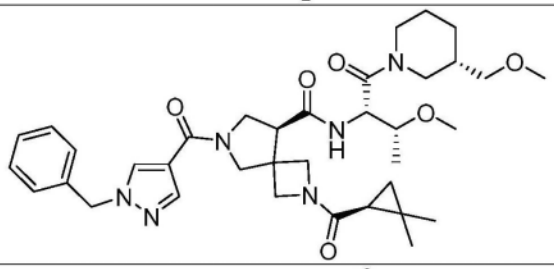
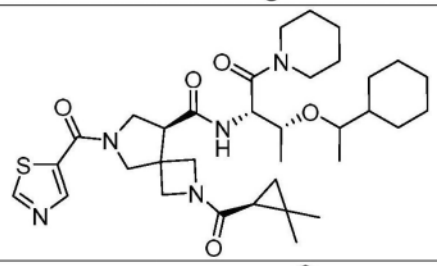
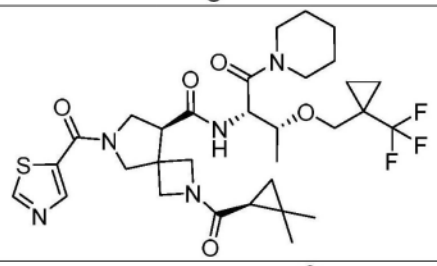
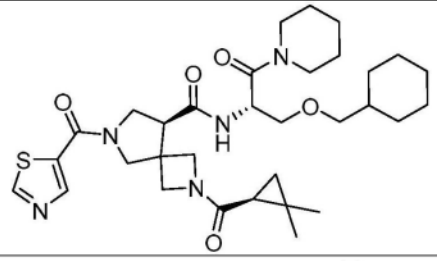
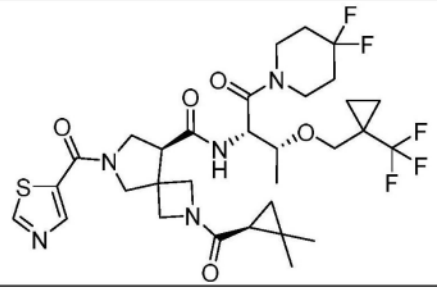
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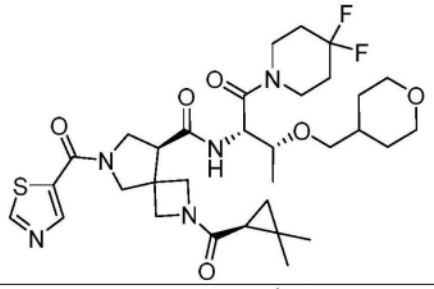
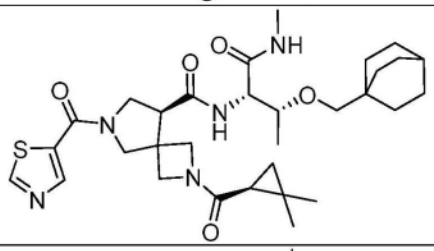
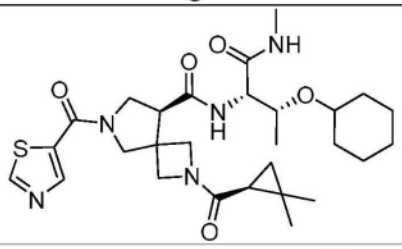
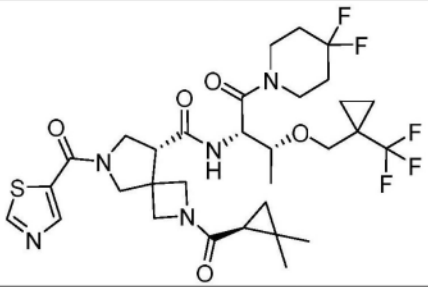
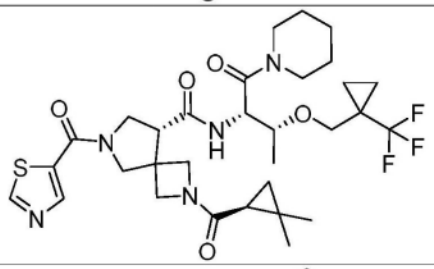
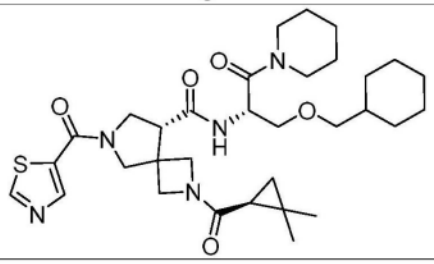
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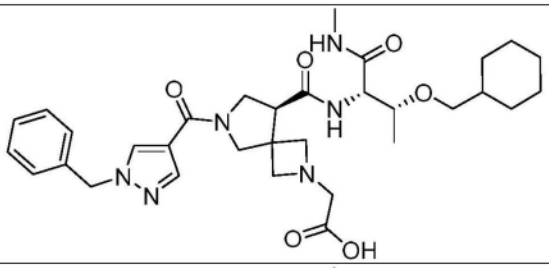
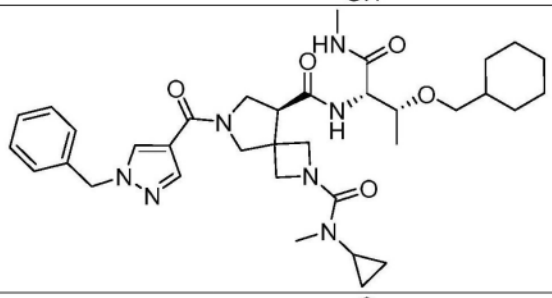
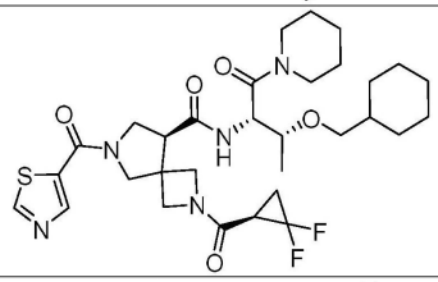
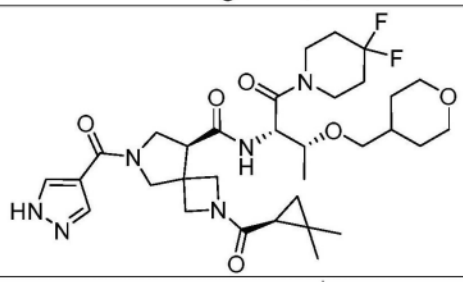
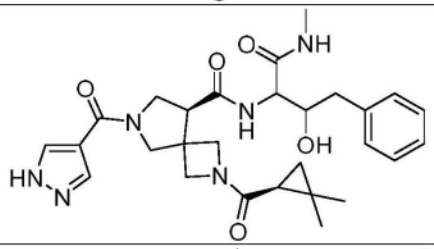
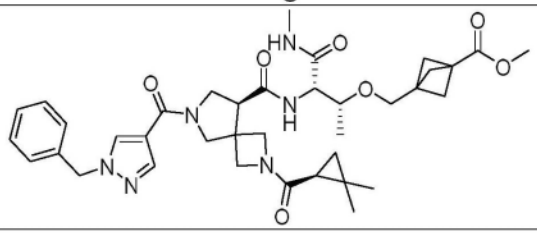
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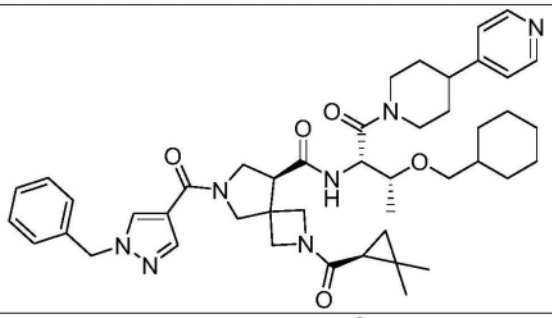
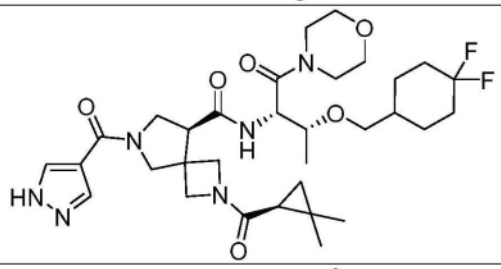
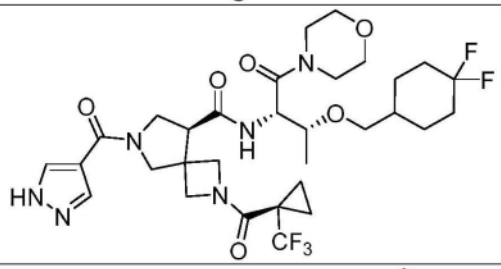
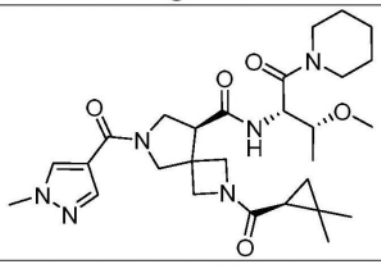
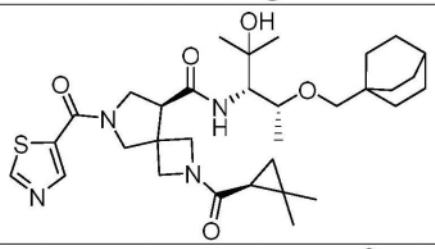
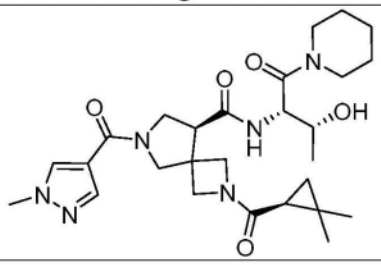
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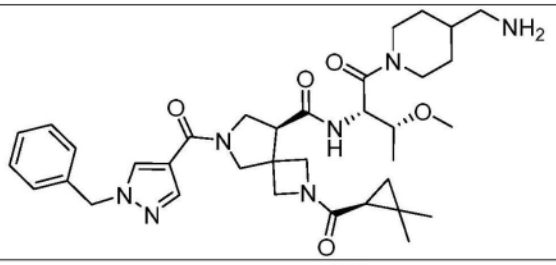
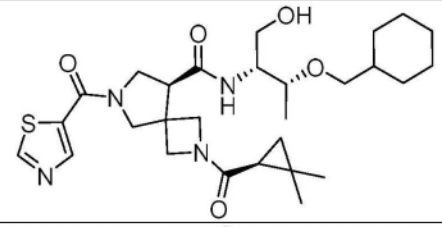
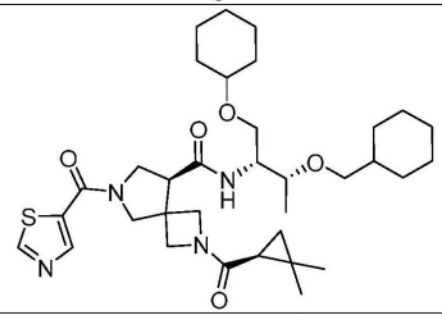
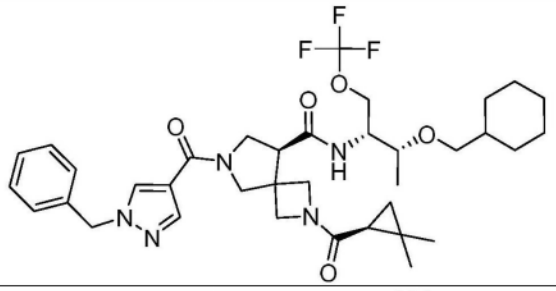
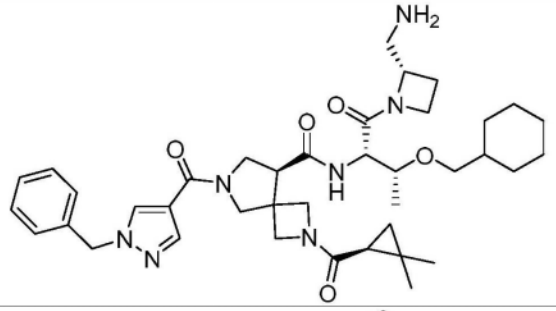
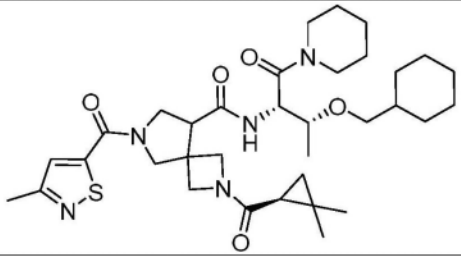
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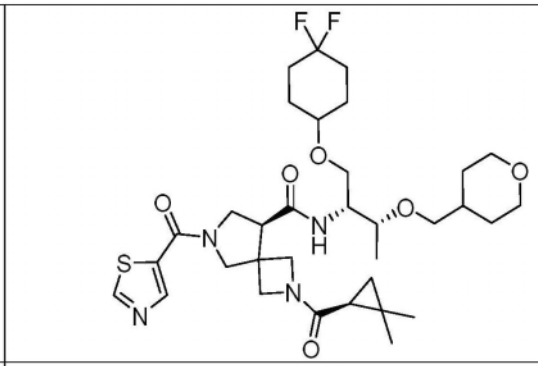
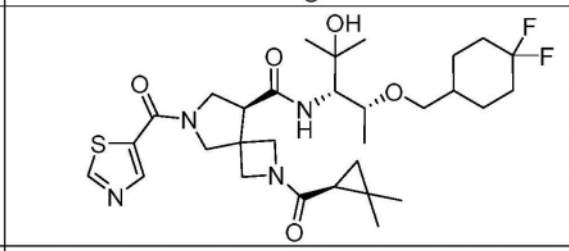
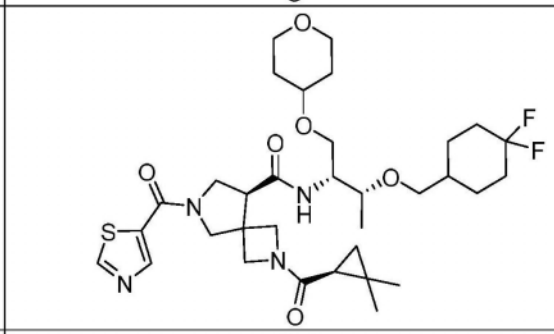
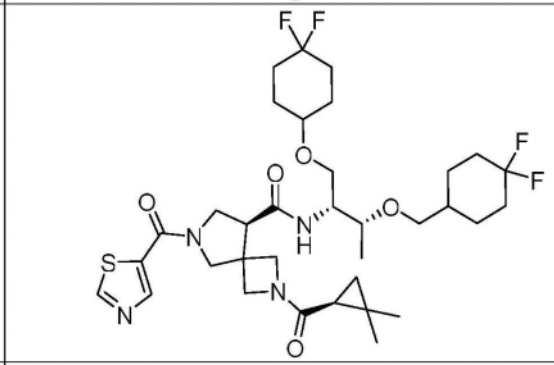
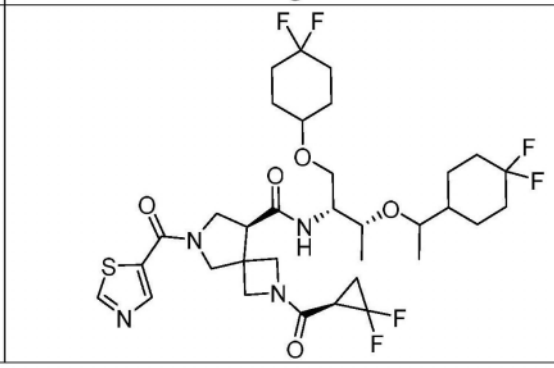
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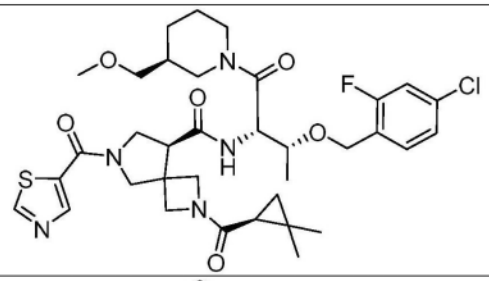
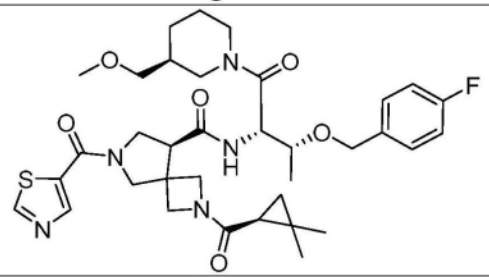
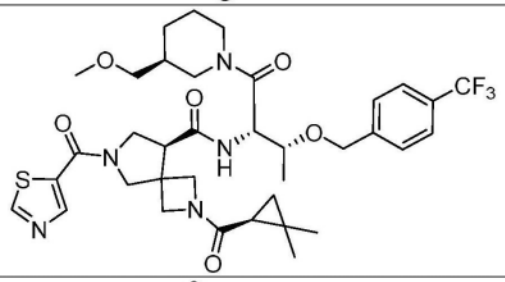
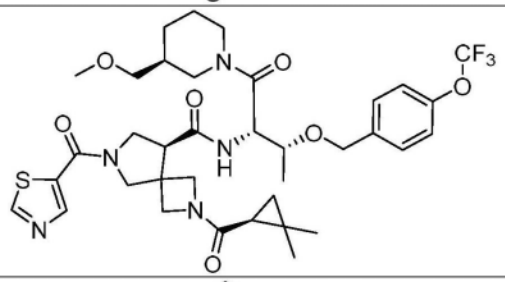
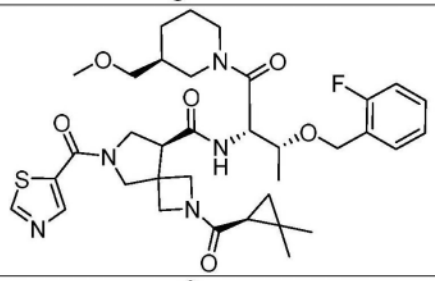
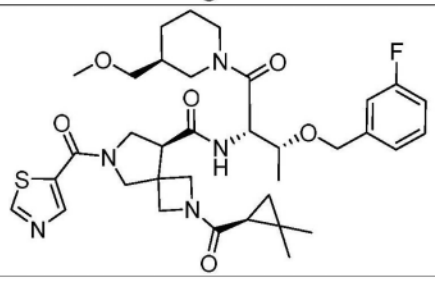
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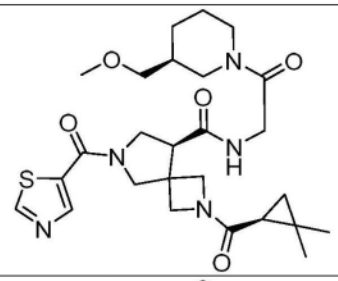
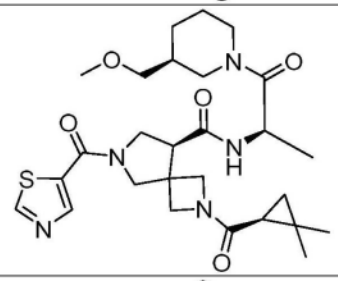
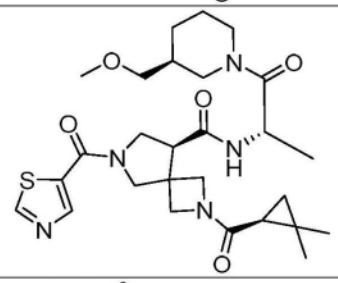
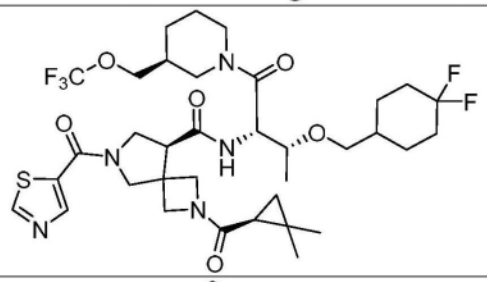
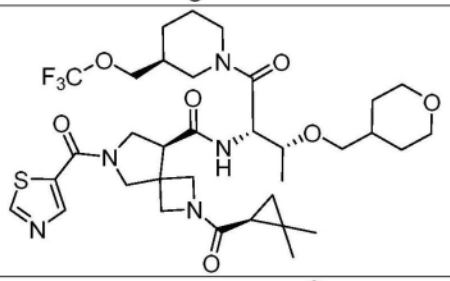
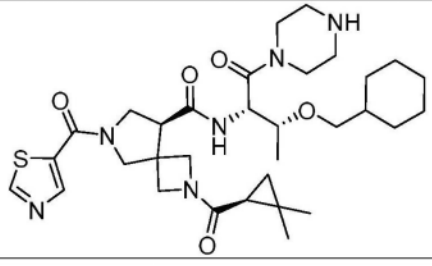
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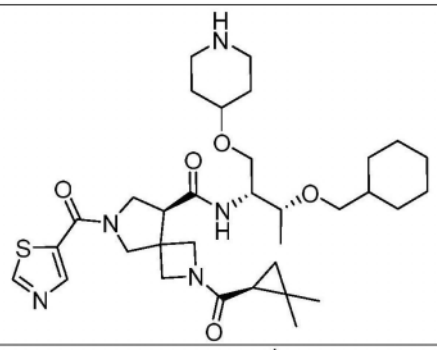
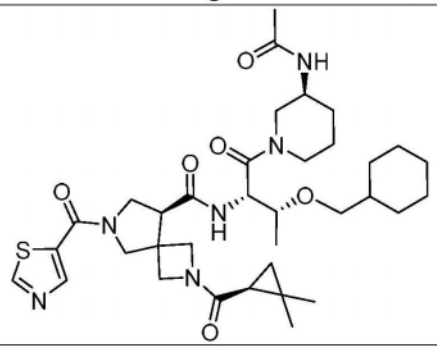
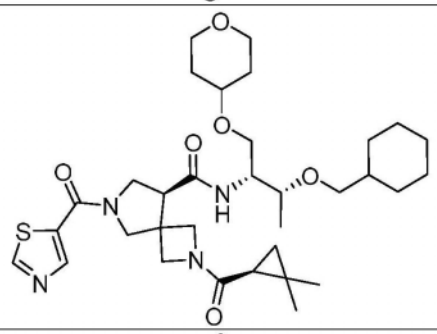
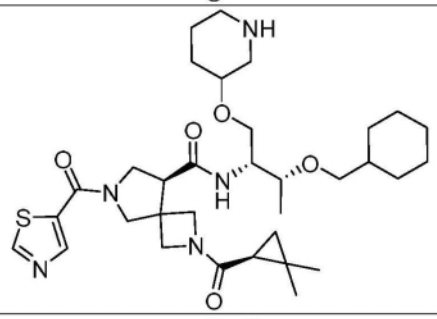
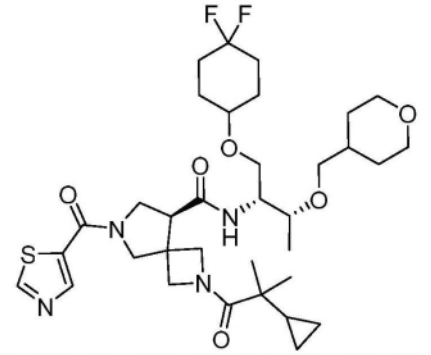
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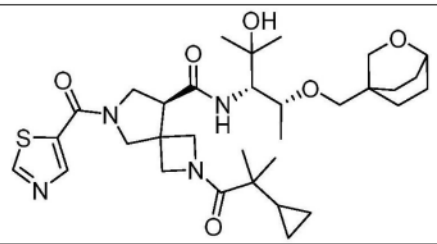
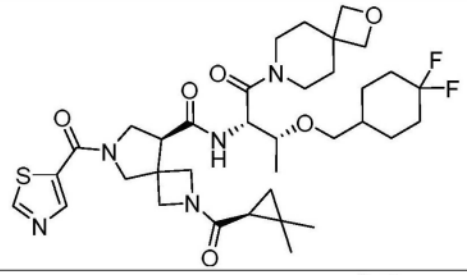
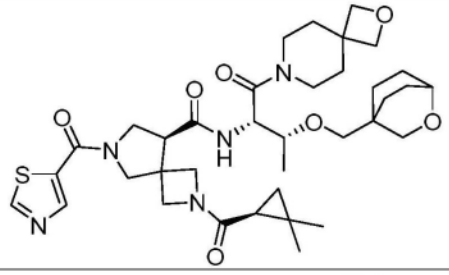
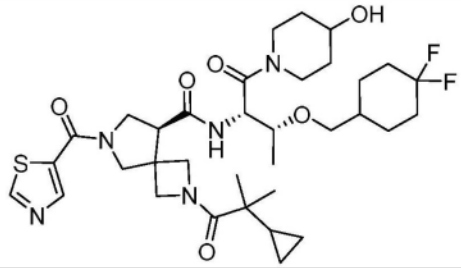
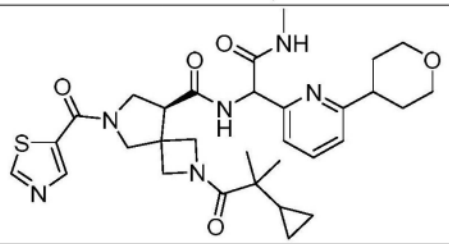
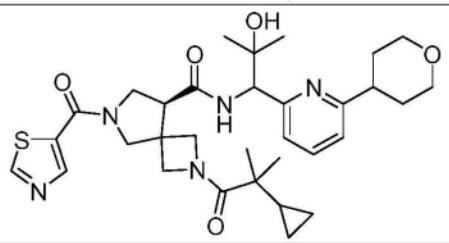
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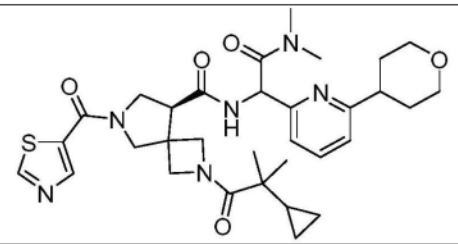
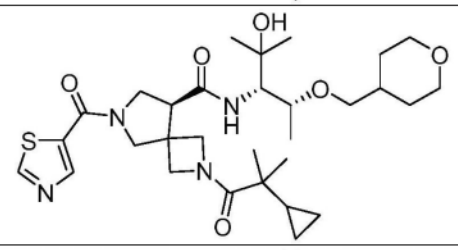
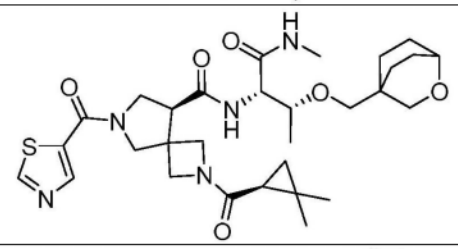
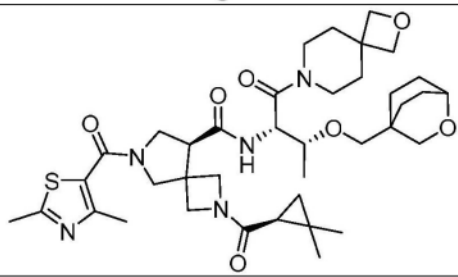
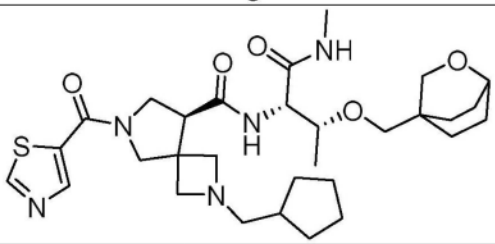
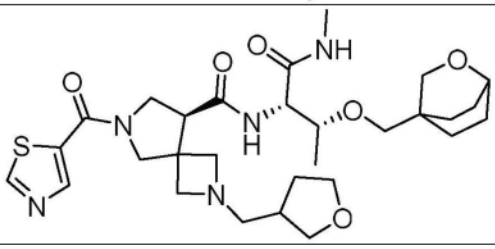
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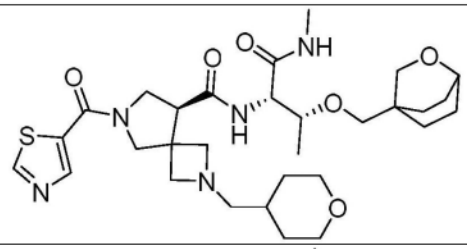
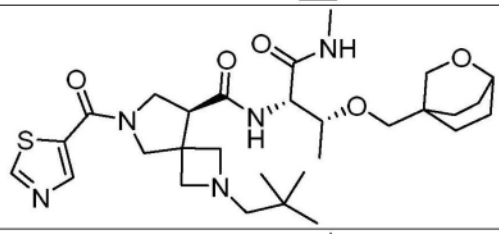
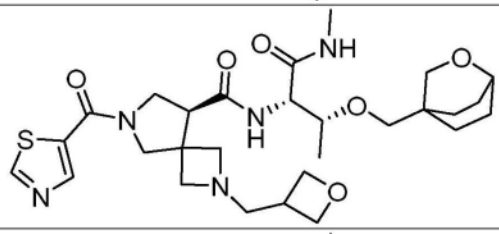
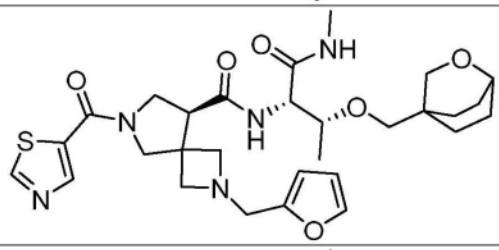
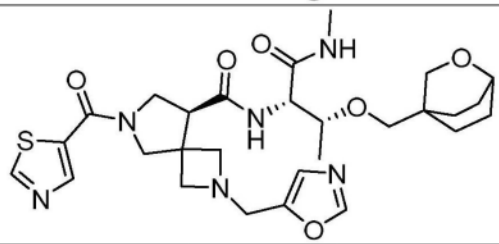
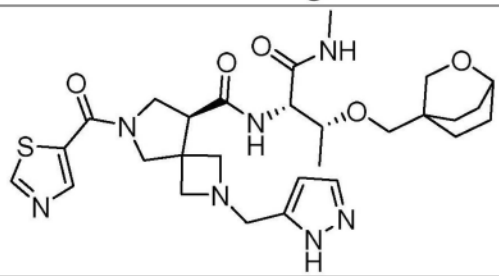
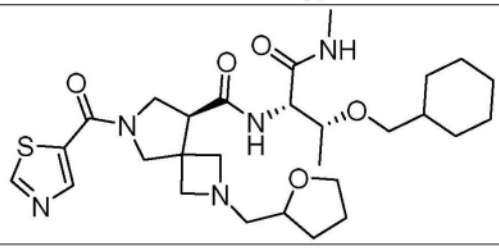
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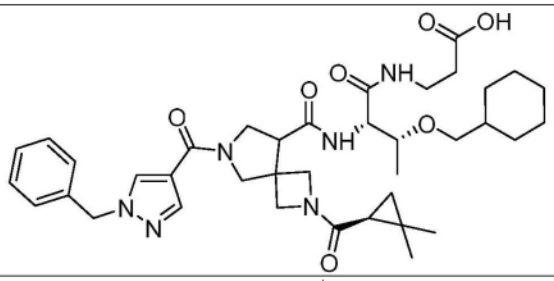
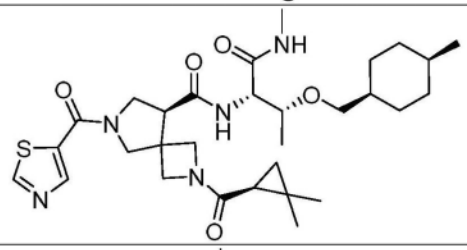
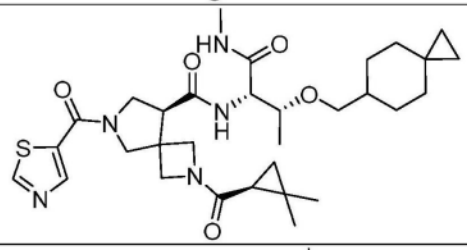
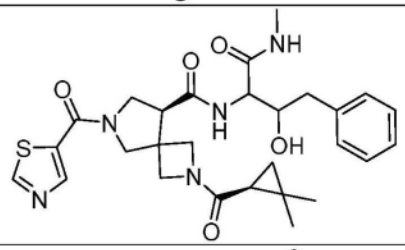
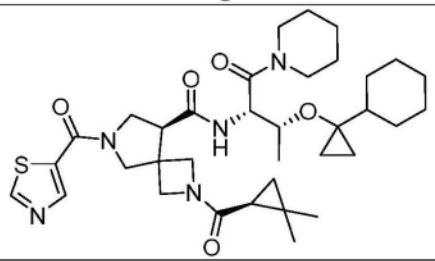
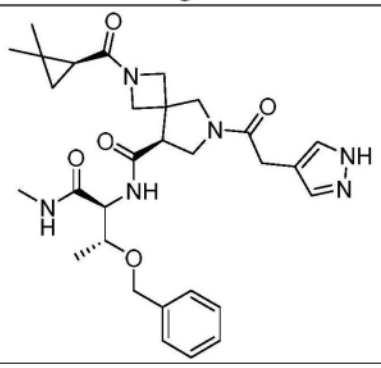
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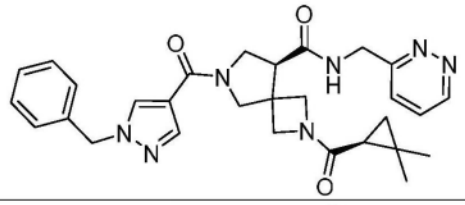
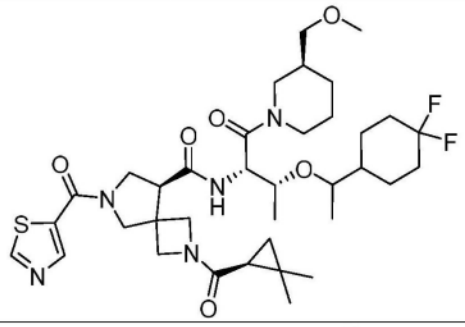
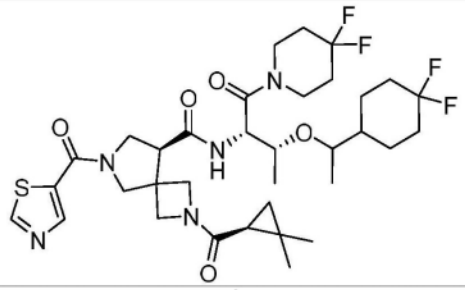
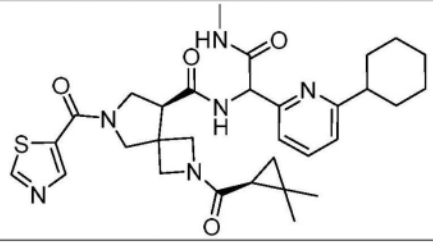
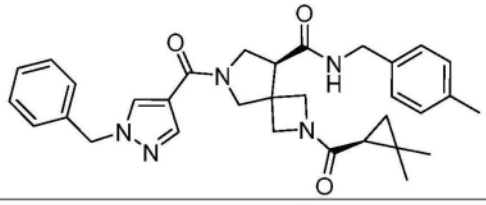
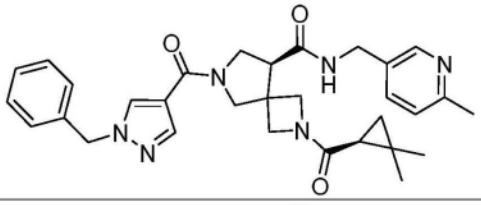
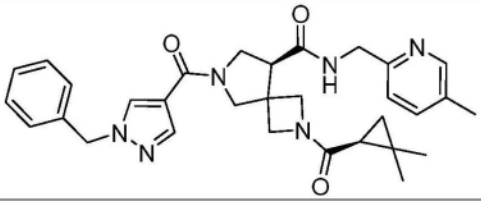
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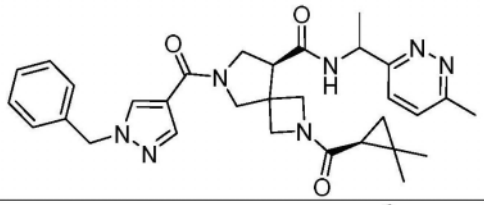
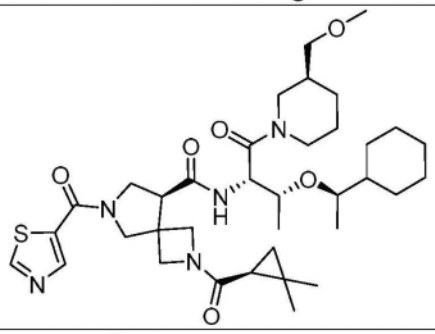
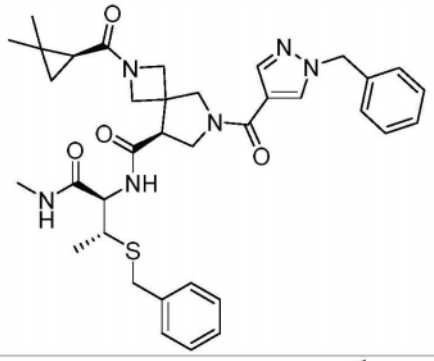
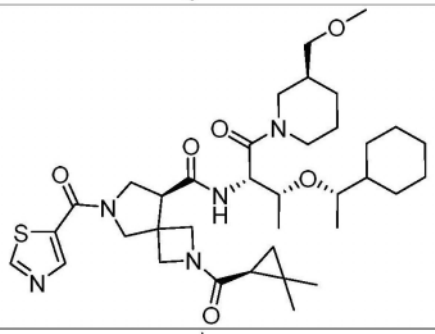
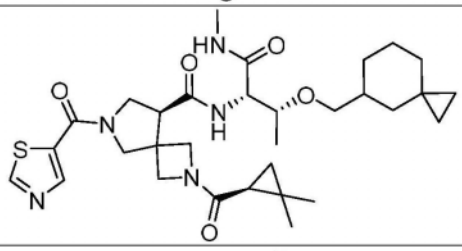
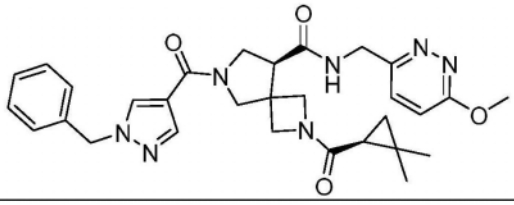
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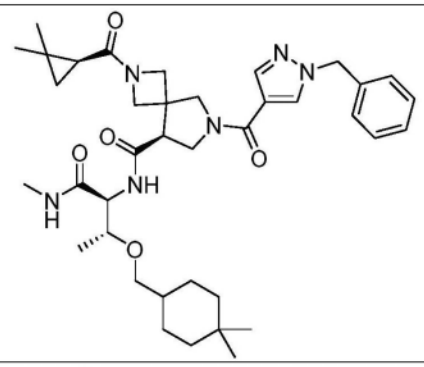
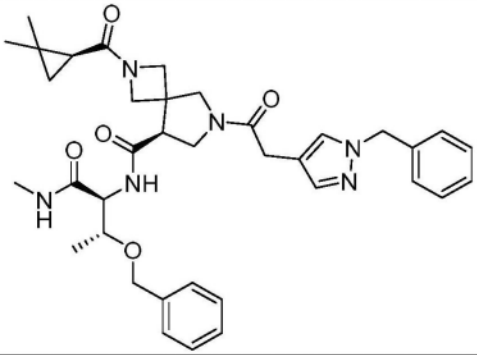
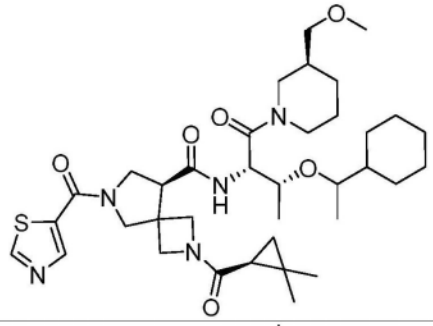
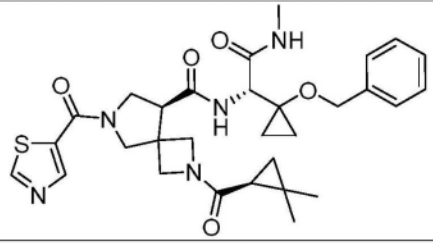
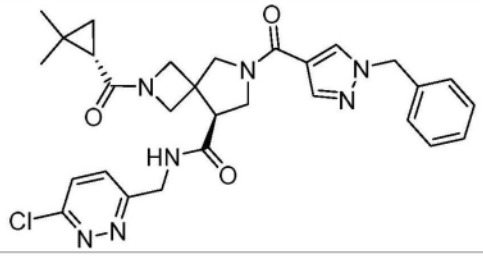
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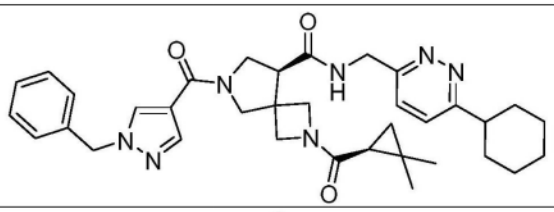
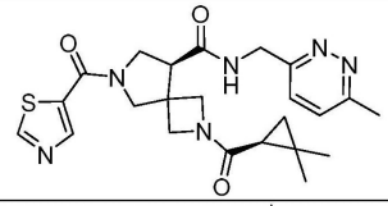
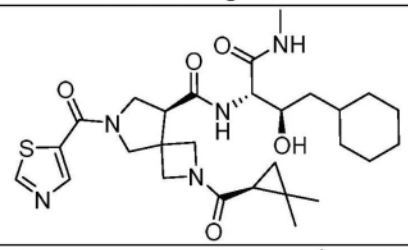
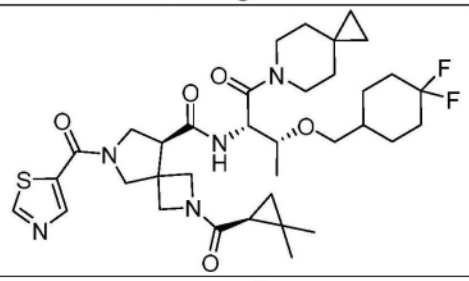
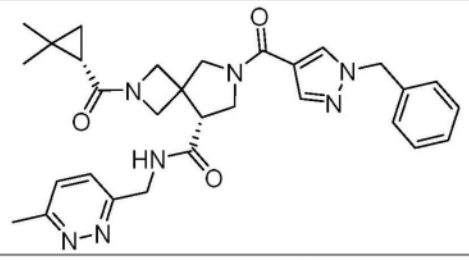
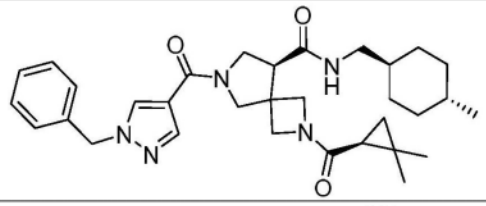
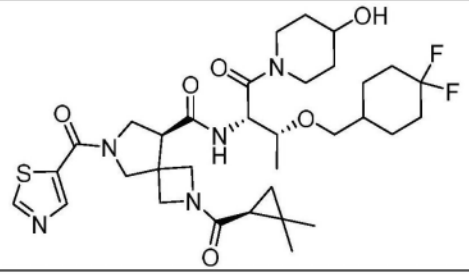
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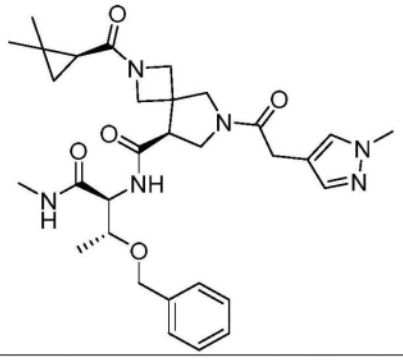
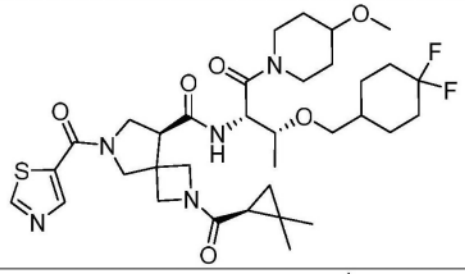
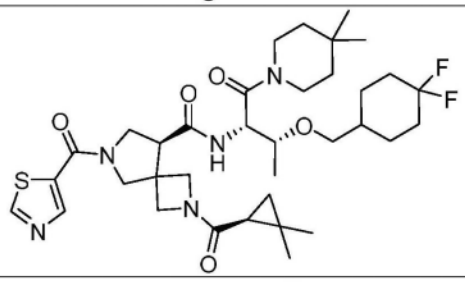
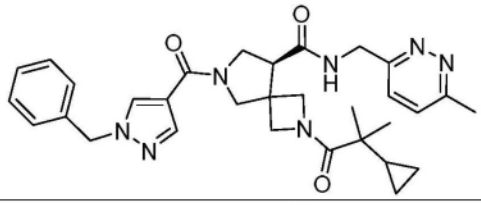
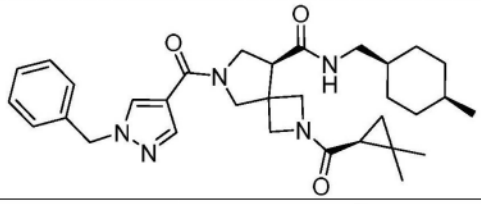
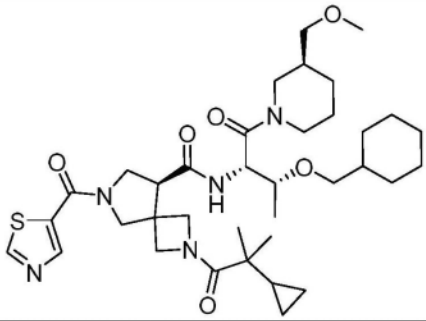
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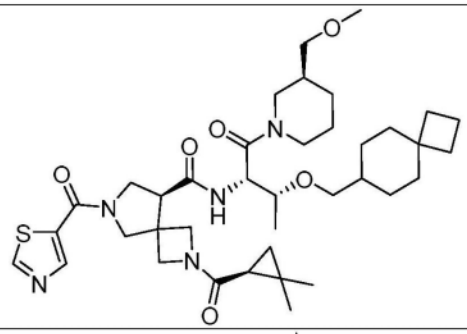
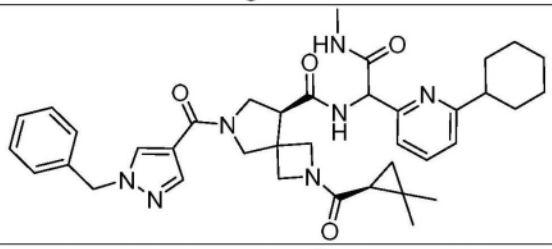
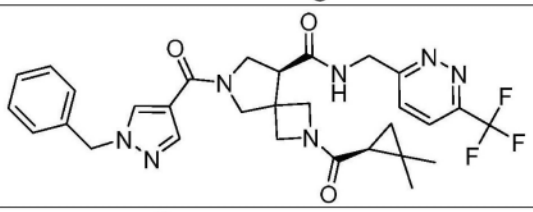
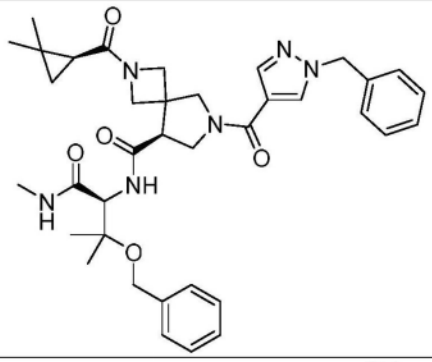
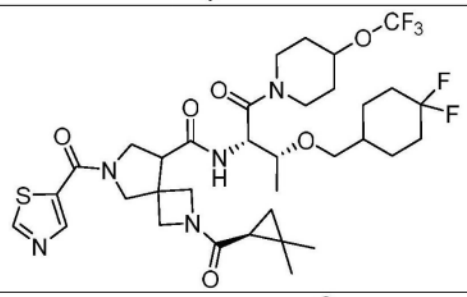
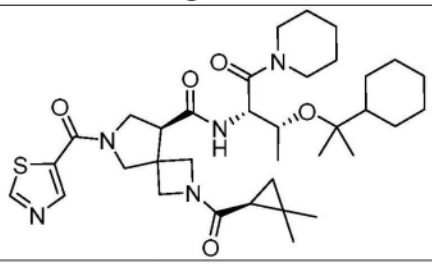
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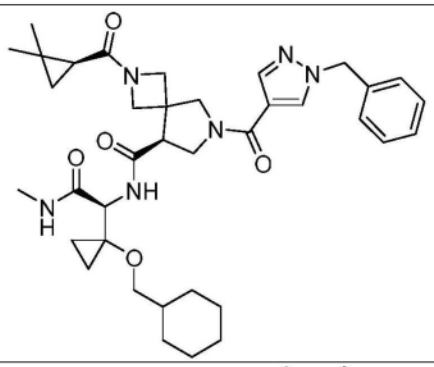
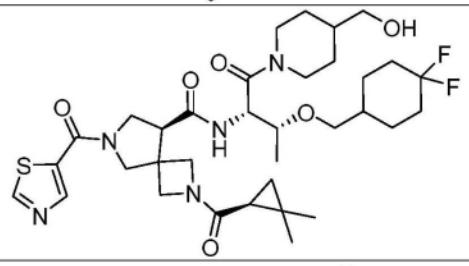
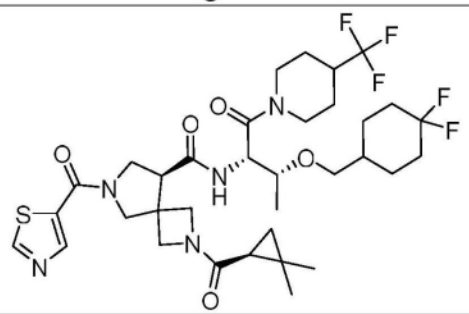
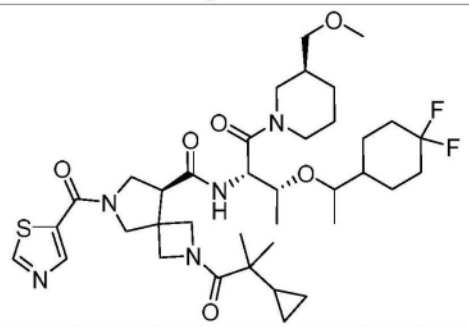
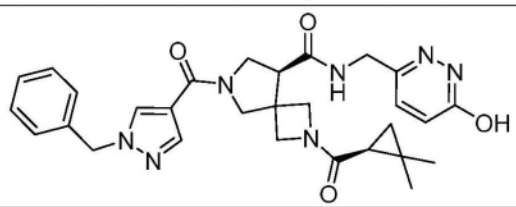
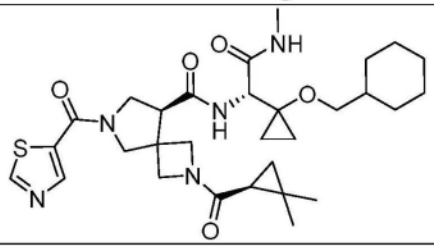
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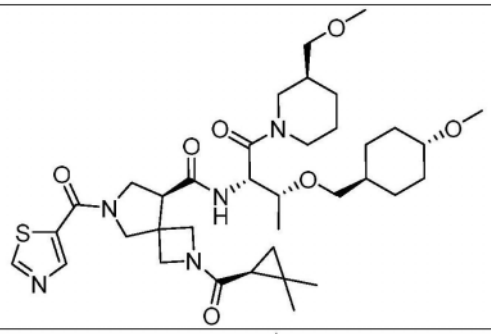
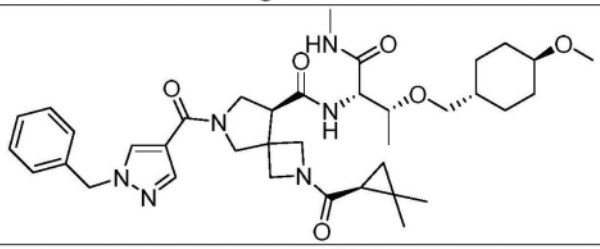
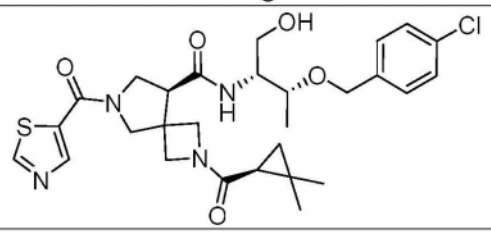
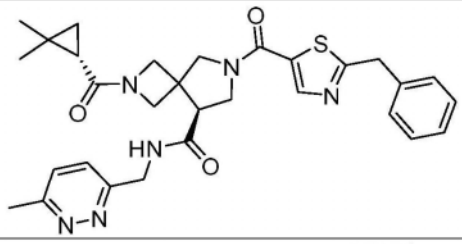
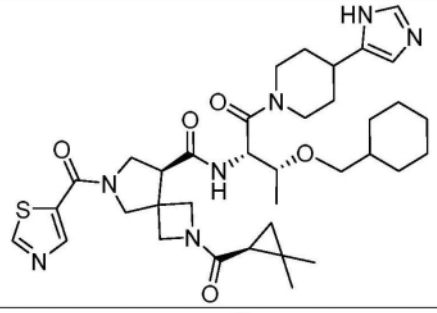
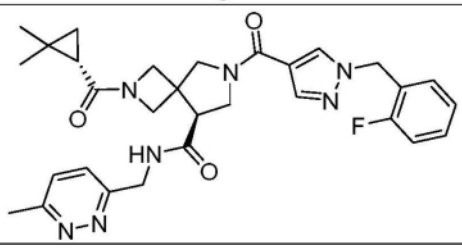
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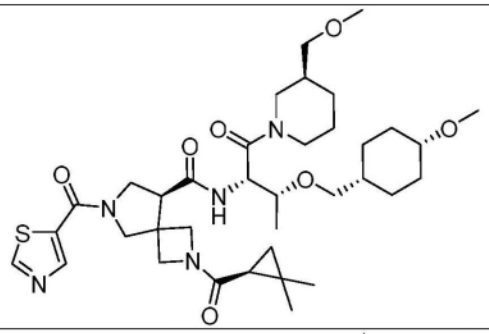
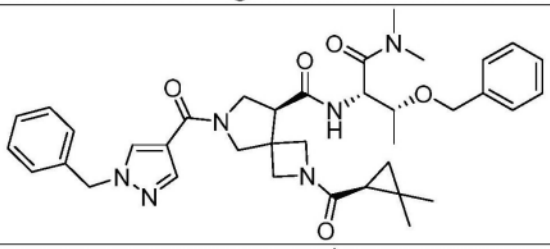
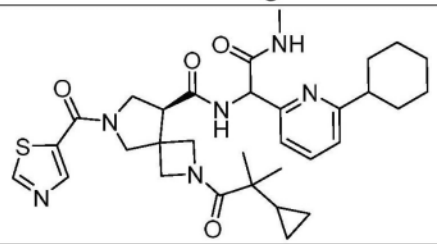
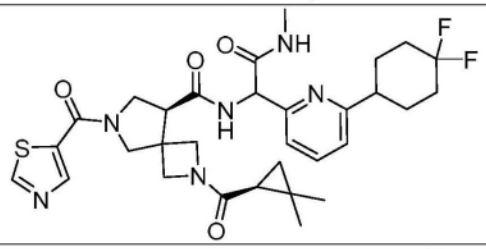
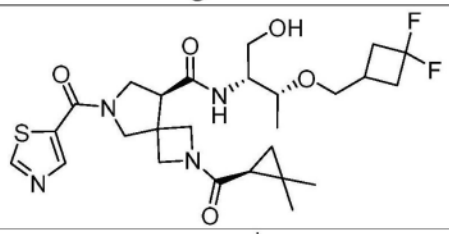
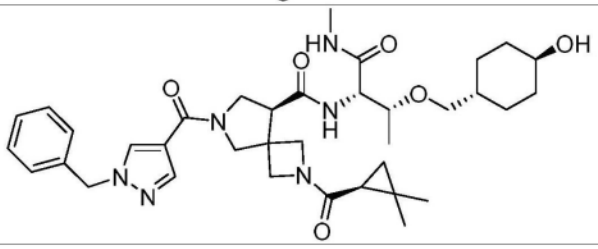
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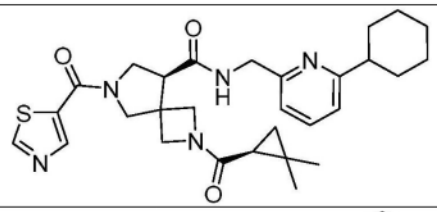
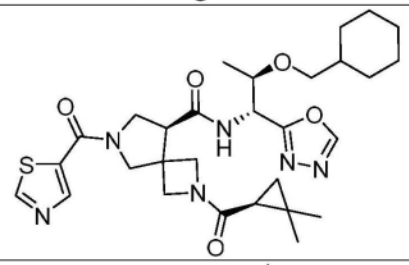
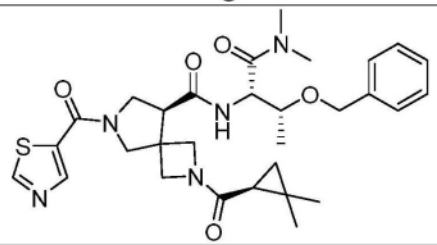
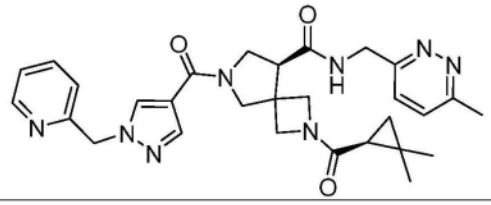
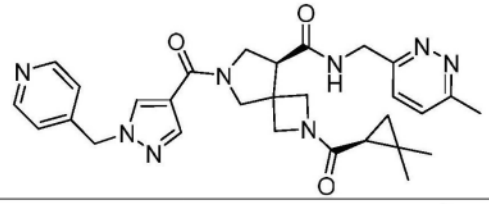
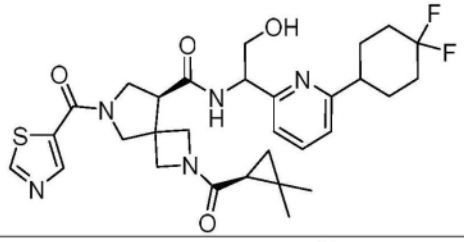
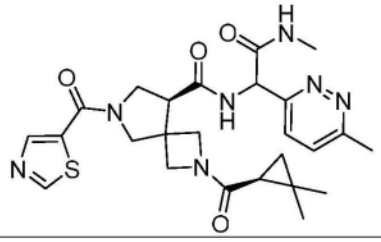
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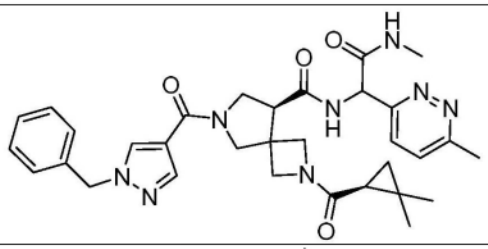
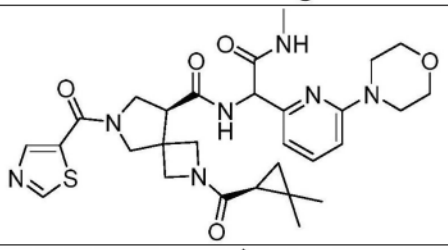
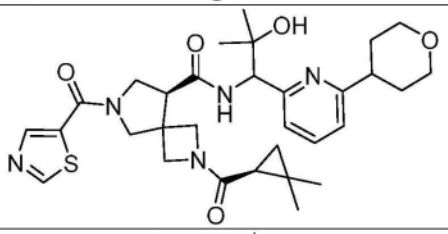
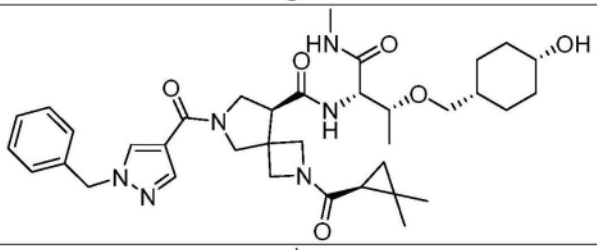
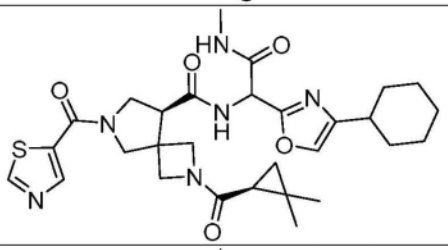
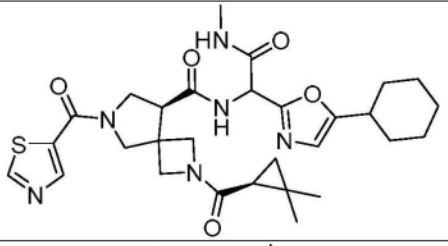
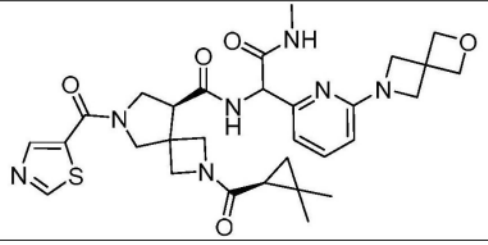
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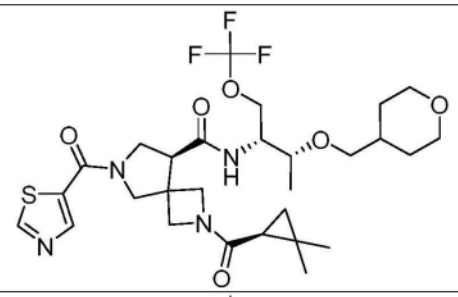
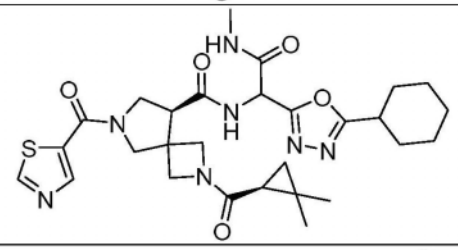
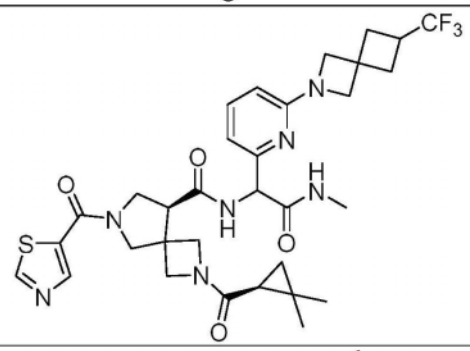
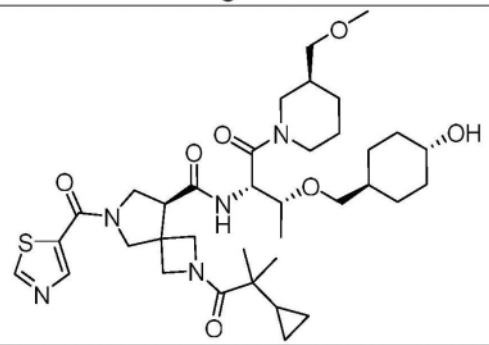
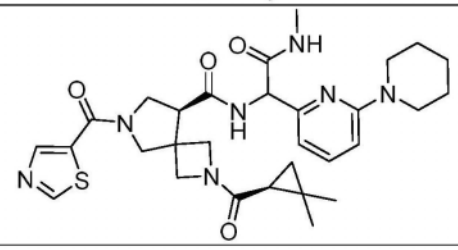
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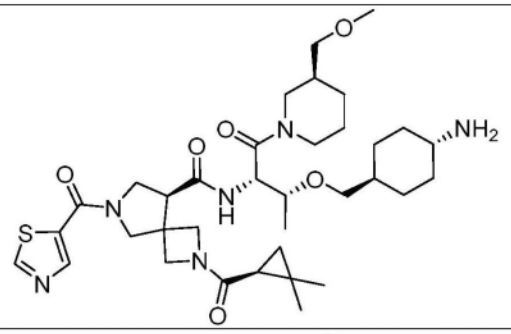
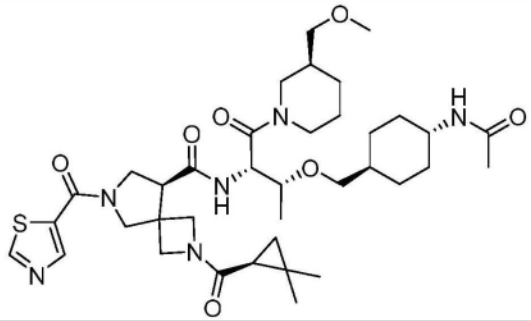
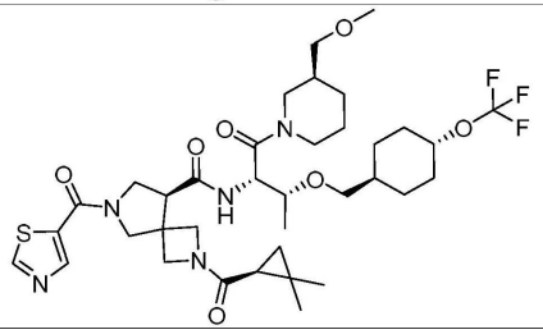
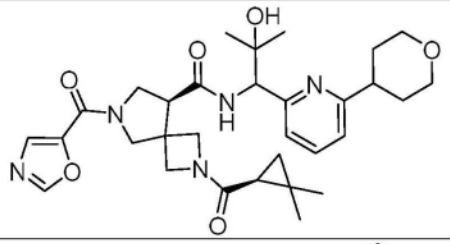
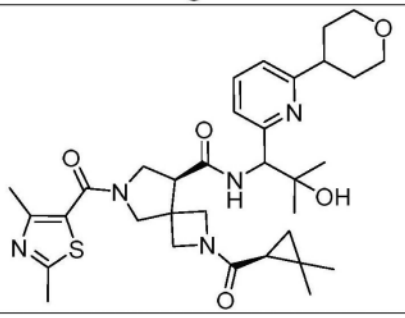
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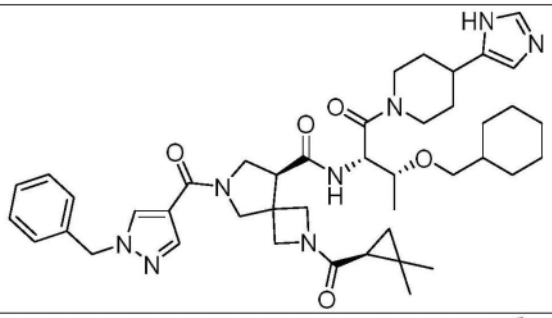
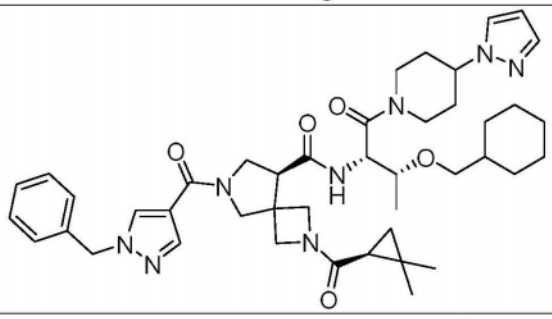
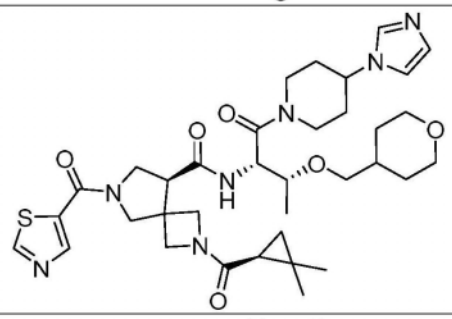
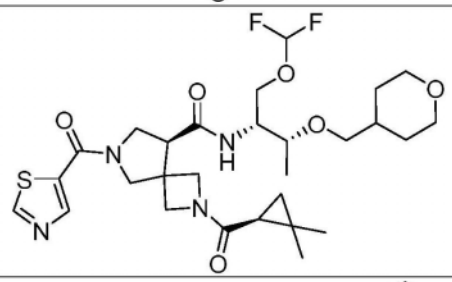
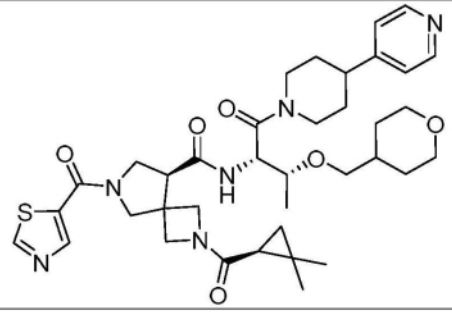
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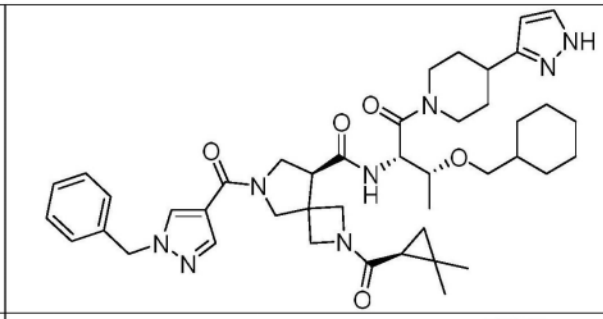
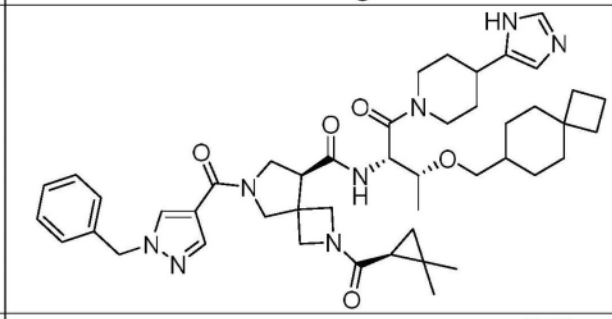
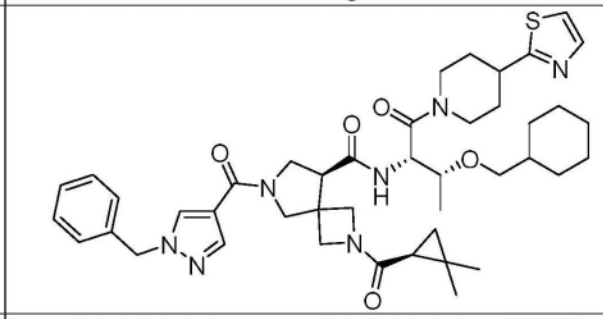
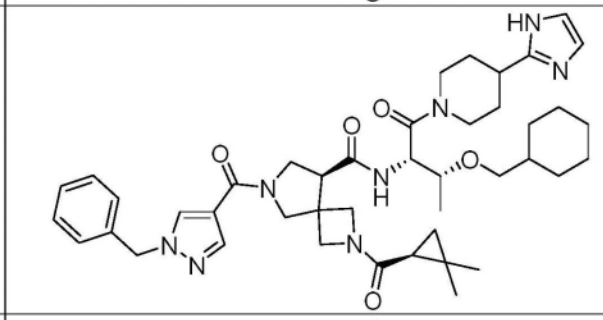
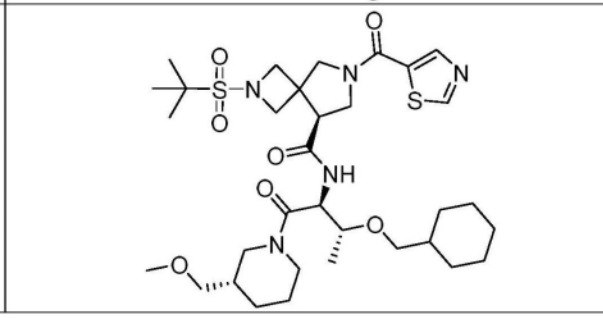
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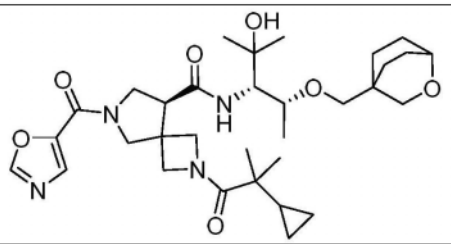
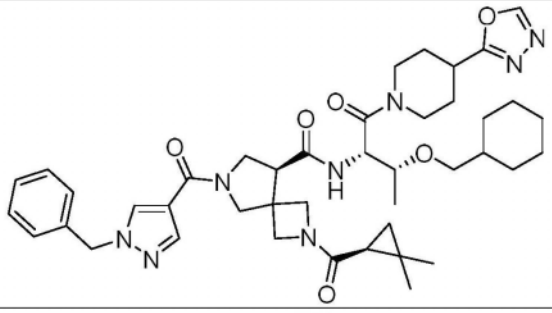
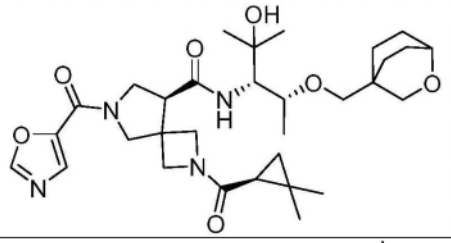
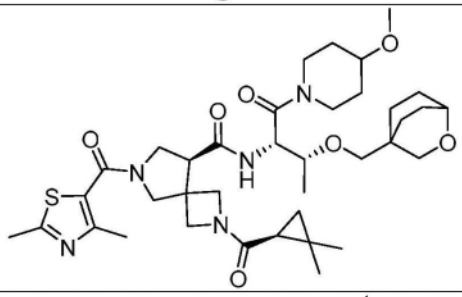
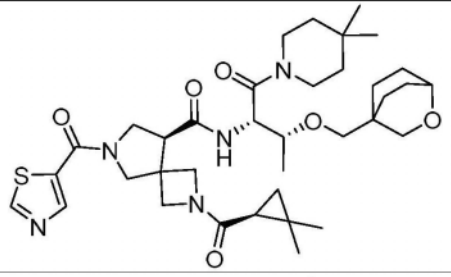
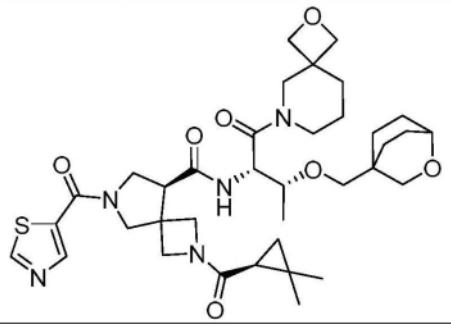
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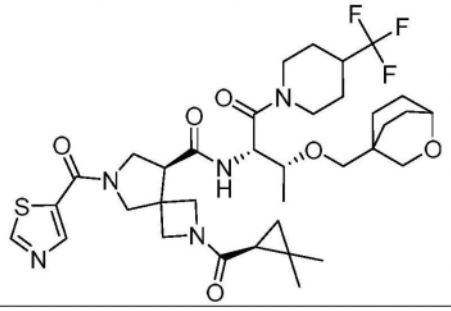
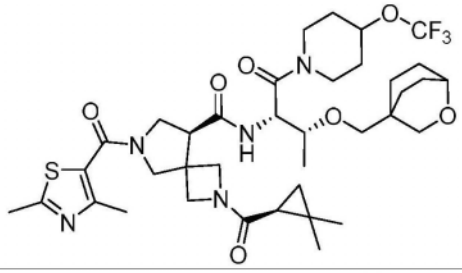
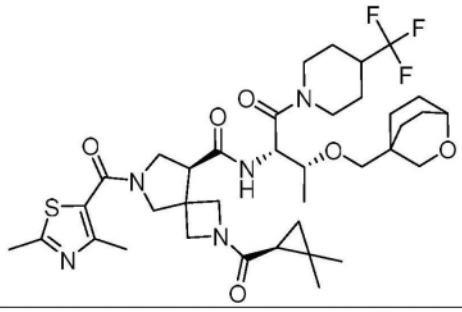
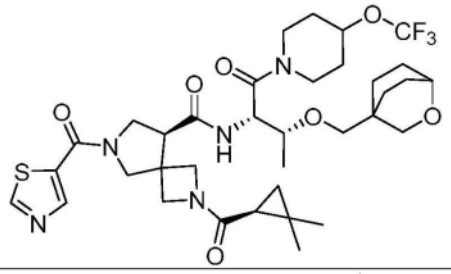
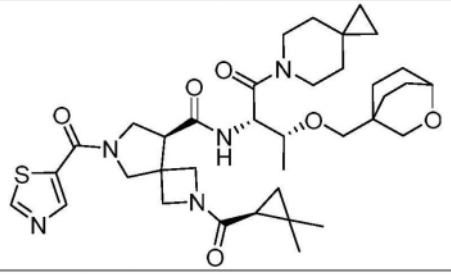
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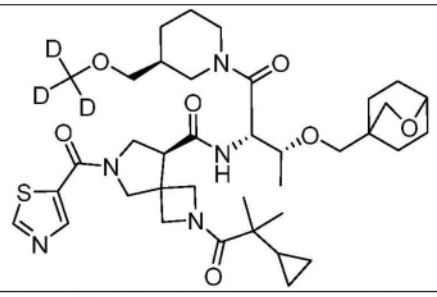
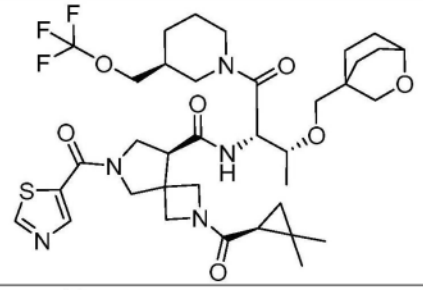
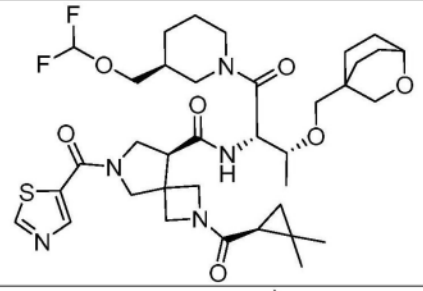
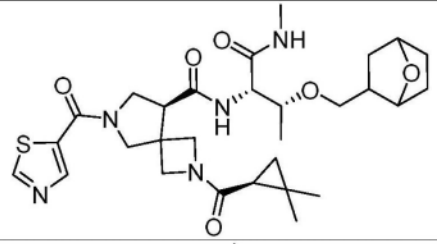
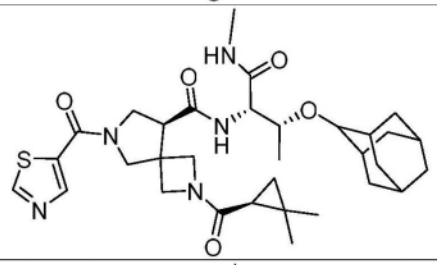
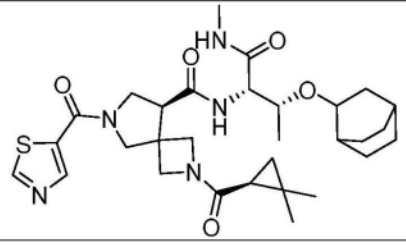
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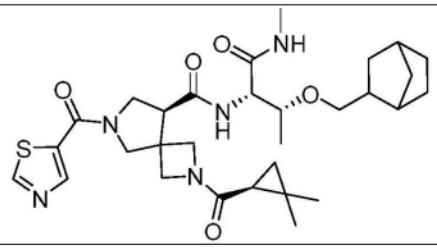
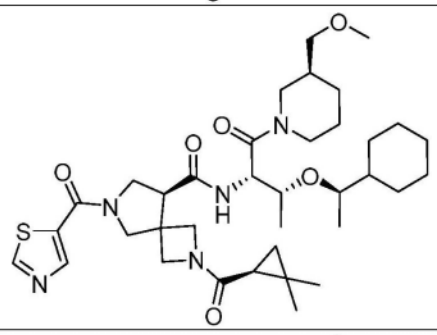
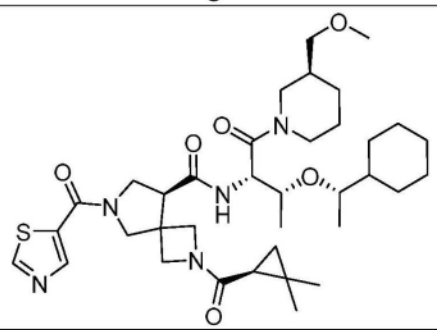
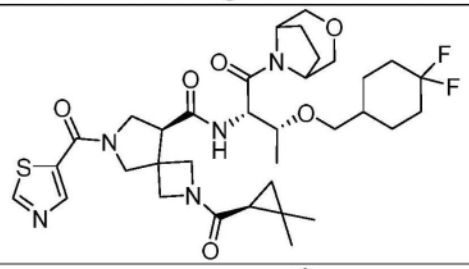
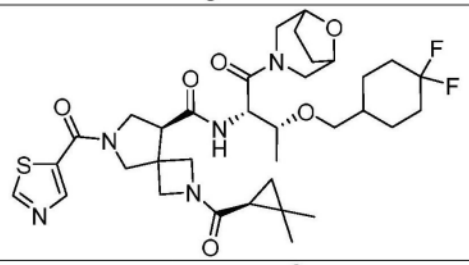
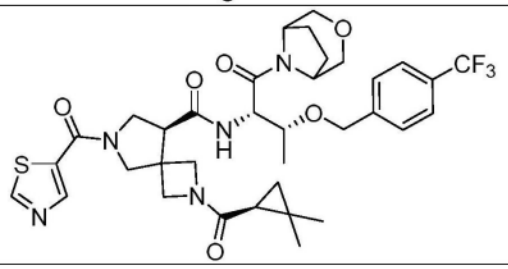
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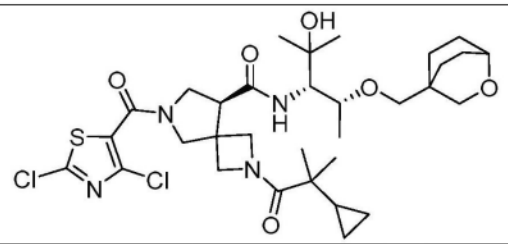
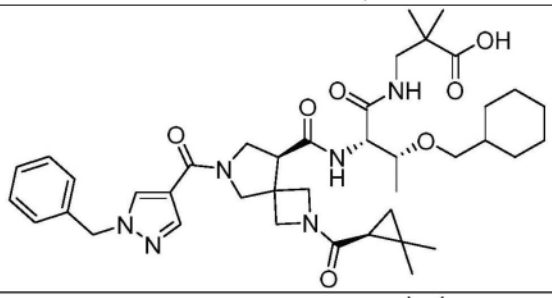
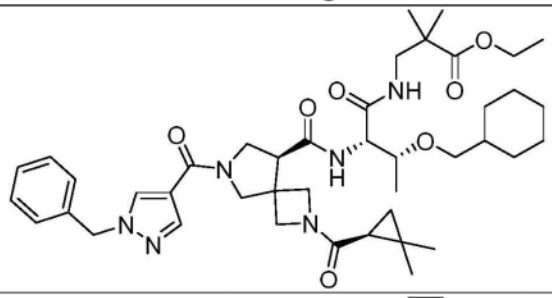
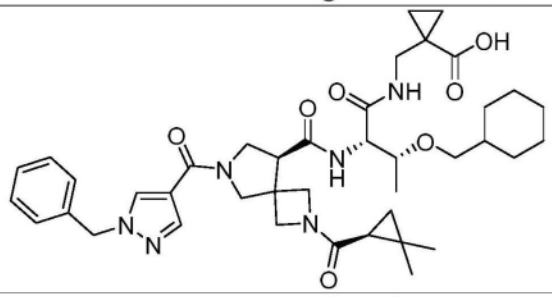
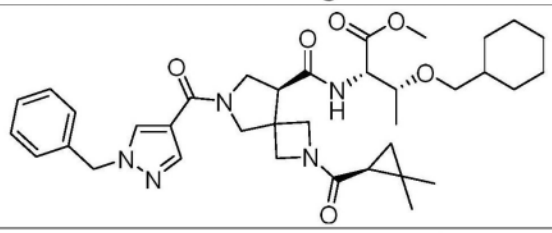
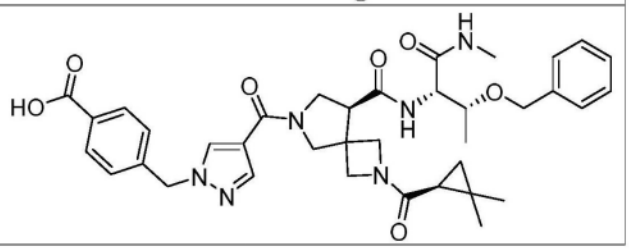
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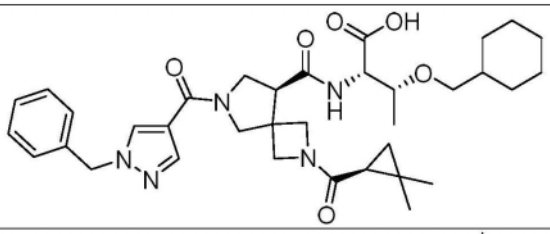
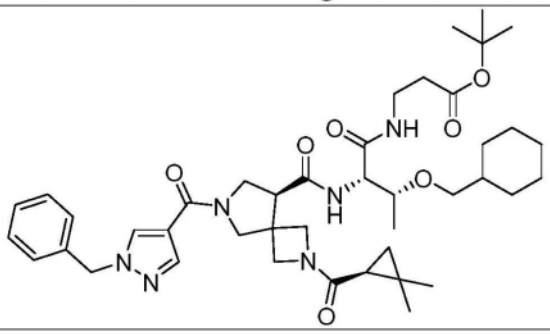
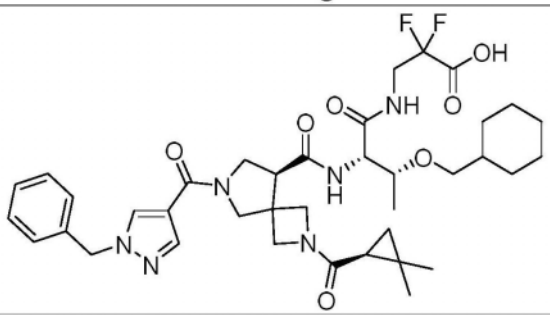
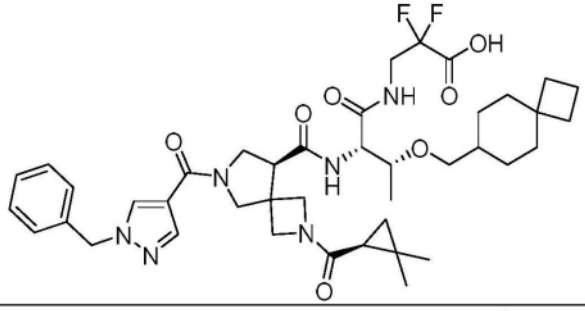
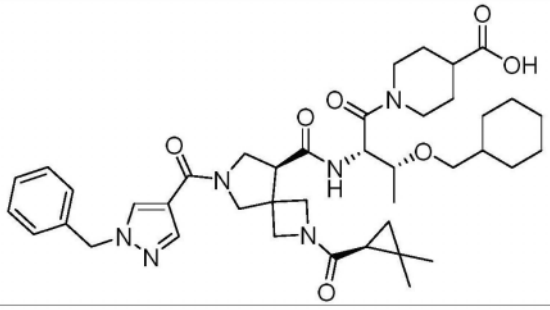
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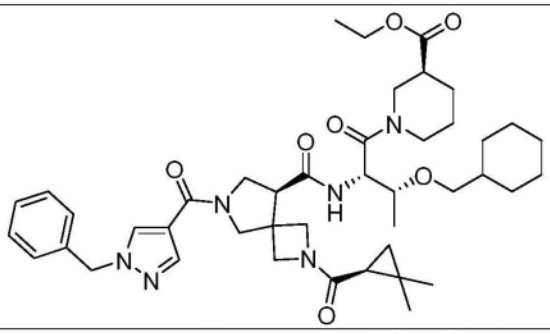
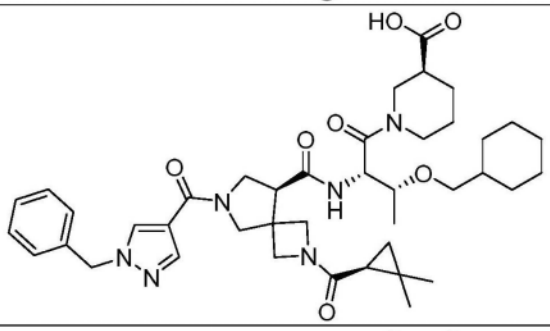
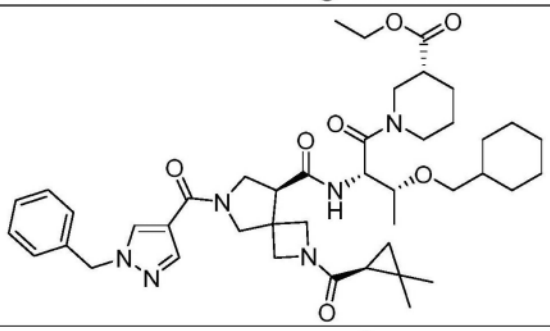
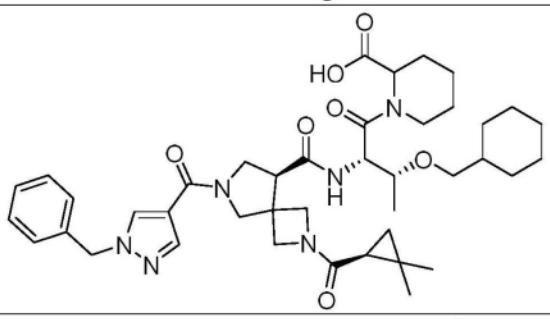
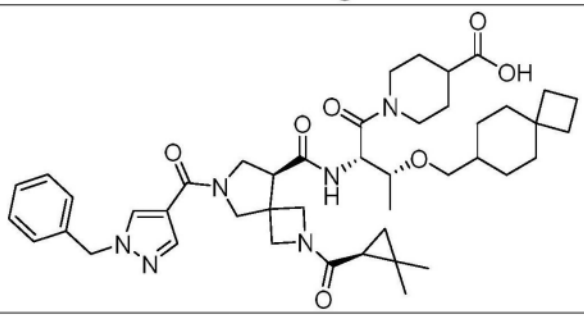
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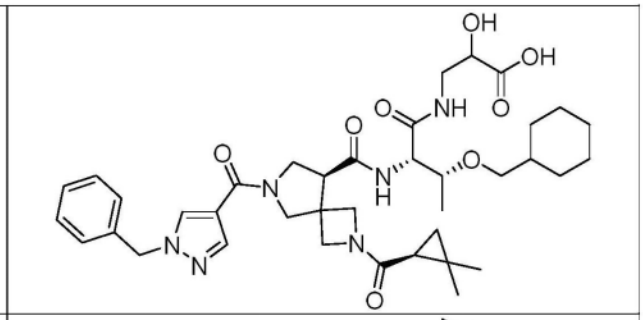
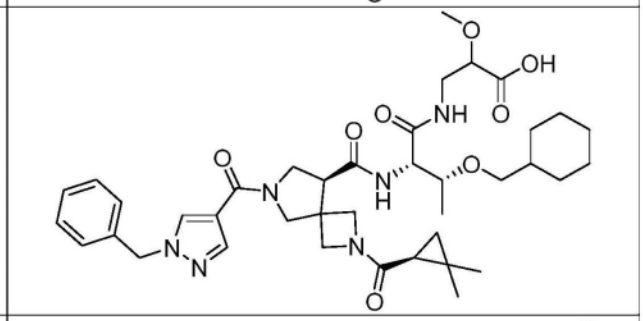
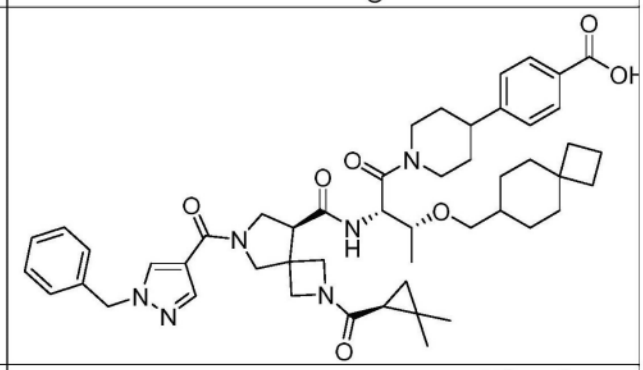
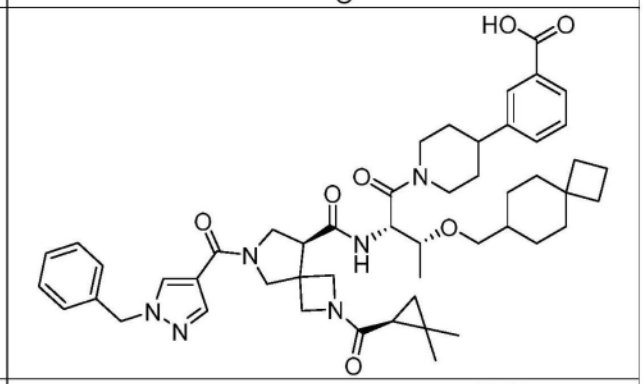
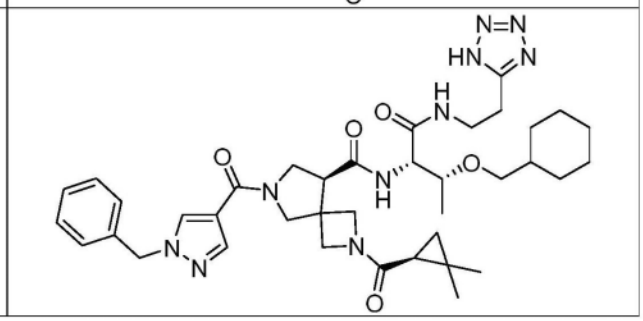
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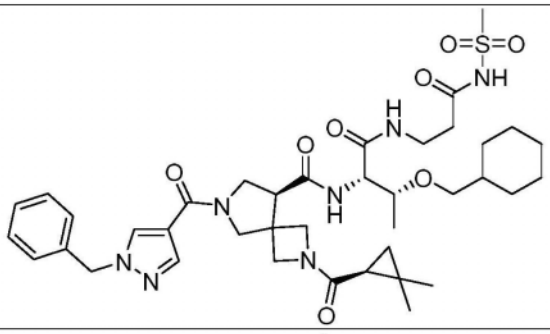
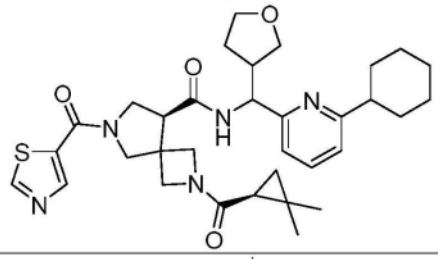
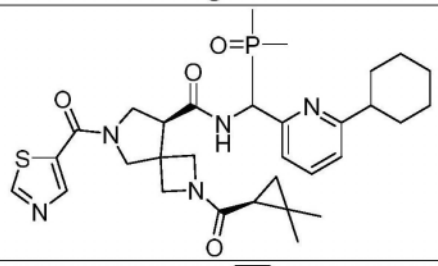
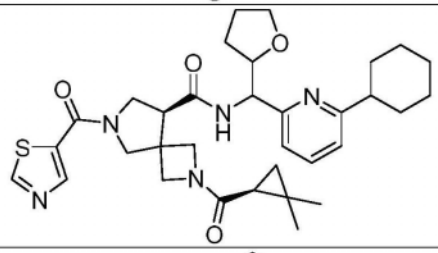
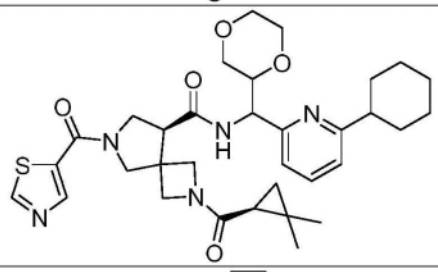
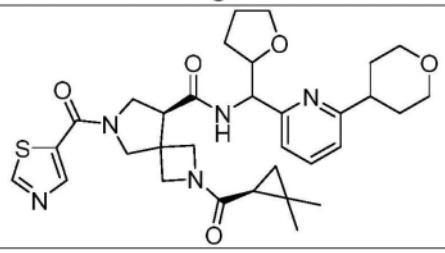
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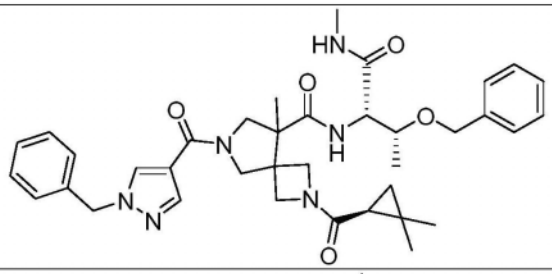
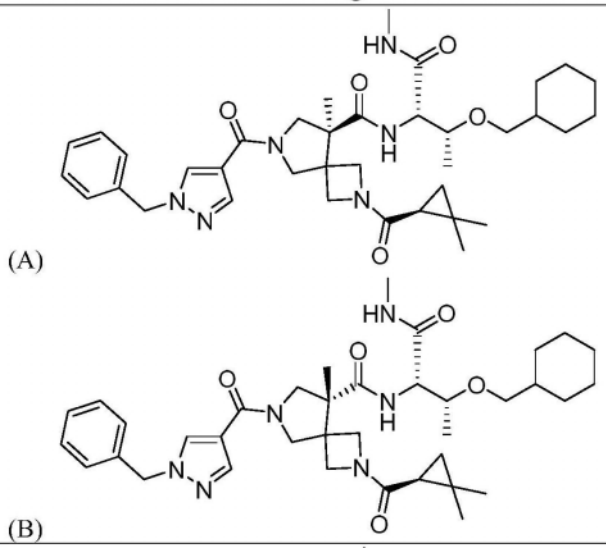
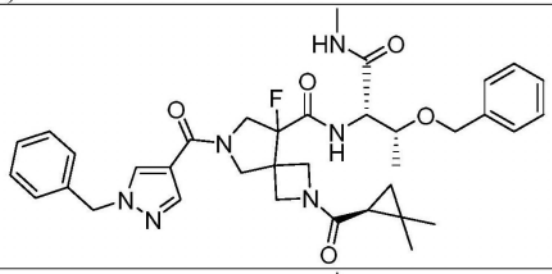
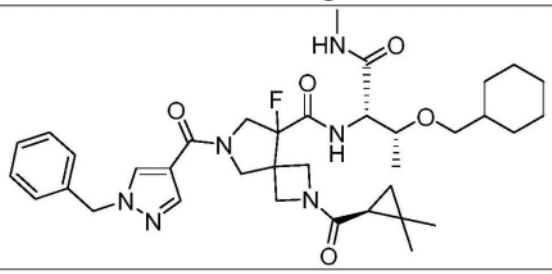
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[0421] 在一些实施方案中,本公开提供了上表1中列出的化合物或其药学上可接受的盐。在一些实施方案中,本公开提供了上表1中列出的化合物或其药学上可接受的盐,以及其任何对映体、非对映体或构象异构体。本公开涉及本文所示化合物的任何和所有对映体、非对映体和构象异构体。

[0422] 在一些实施方案中,本公开提供了药物组合物,其包含本公开的化合物或其药学可接受的盐,以及药学上可接受的载体、赋形剂、媒介物、佐剂或稀释剂。在一些实施方案中,本公开提供了药物组合物,其包含上表1中列出的化合物或其药学上可接受的盐,以及药学上可接受的载体、赋形剂、媒介物、佐剂或稀释剂。在一些实施方案中,该药物组合物进一步包含额外的治疗剂。

[0423] 在一些实施方案中,本公开提供了包含CDK2蛋白和本公开的化合物的复合物。

[0424] 在一些实施方案中,本公开提供了抑制细胞周期蛋白依赖性激酶(CDK)活性的方法。在一些实施方案中,该方法包含使本公开的化合物与CDK接触。在一些实施方案中,该化合物和CDK在体内接触。在一些实施方案中,该化合物和CDK在体外接触。在一些实施方案中,CDK选自CDK1、CDK2、CDK3、CDK4、CDK5、CDK6、CDK7、CDK8、CDK9、CDK10、CDK11、CDK12和CDK13。在一些实施方案中,该CDK是CDK2。在一些实施方案中,该CDK是CDK3。在一些实施方案中,该CDK是CDK4。在一些实施方案中,该CDK是CDK6。在一些实施方案中,该方法抑制CDK2和CDK3两者的活性。在一些实施方案中,该方法抑制CDK2以及CDK4和CDK6的一个或两个的活性。

[0425] 在一些实施方案中,本公开的化合物抑制选自CDK1、CDK2、CDK3、CDK4、CDK5、CDK6、CDK7、CDK8、CDK9、CDK10、CDK11、CDK12和CDK13的一种或多种CDK的活性。在一些实施方案中,本公开的化合物抑制CDK2。在一些实施方案中,本公开的化合物抑制CDK3。在一些实施方案中,本公开的化合物抑制CDK4。在一些实施方案中,本公开的化合物抑制CDK5。在一些实施方案中,本公开的化合物抑制CDK6。在一些实施方案中,本公开的化合物是CDK2/3抑制剂。在一些实施方案中,本公开的化合物是CDK2/4/6抑制剂。

[0426] 在一些实施方案中,本公开提供了相对于其他细胞周期蛋白依赖性激酶(CDK)选择性地抑制CDK2的化合物。在一些实施方案中,本公开的化合物相对于一种或多种其它选自CDK1、CDK3、CDK4、CDK5、CDK6、CDK7、CDK8、CDK9、CDK10、CDK11、CDK12和CDK13的CDK选择性地抑制CDK2。在一些实施方案中,本公开的化合物相对于CDK4选择性地抑制CDK2。在一些实施方案中,本公开的化合物相对于CDK6选择性地抑制CDK2。在一些实施方案中,本公开的化合物相对于CDK4和CDK6选择性地抑制CDK2。

[0427] 在一些实施方案中,本公开提供了相对于其它CDK复合物选择性地抑制CDK2/细胞周期蛋白E复合物的化合物。

[0428] 4.提供本发明化合物的一般方法

[0429] 本公开的化合物通常可通过本领域技术人员已知的类似化合物的合成和/或半合成方法以及通过本文实施例中详细描述的方法制备或分离。

[0430] 在下面的方案中,描述了特定的保护基团(“PG”)、离去基团(“LG”)或转化条件,本领域普通技术人员将理解,其他保护基团、离去基团和转化条件也是合适的并且是可考虑的。这种基团和转化在March’s Advanced Organic Chemistry:Reactions,Mechanisms,and Structure,M.B.Smith and J.March,5th Edition,John Wiley&Sons,2001,Comprehensive Organic Transformations,R.C.Larock,2nd Edition,John Wiley&Sons,1999,and Protecting Groups in Organic Synthesis,T.W.Greene and P.G.M.Wuts,3rd edition,John Wiley&Sons,1999中详细描述,其每一个通过引用整体并入本文。

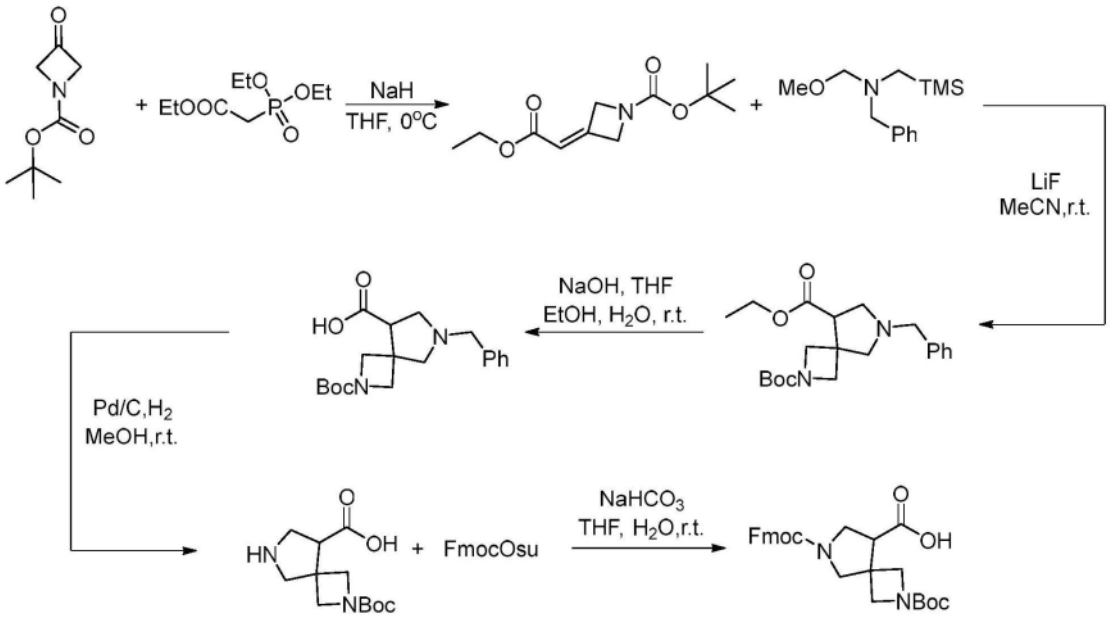
[0431] 如本文所用,短语“离去基团”(LG)包括但不限于卤素(例如氟化物、氯化物、溴化物、碘化物)、磺酸酯(例如甲磺酸酯、甲苯磺酸酯、苯磺酸酯、对溴苯磺酸酯、硝基苯磺酸酯(nosylate)、三氟甲磺酸酯)、重氮等。

[0432] 氨基保护基团在本领域中是众所周知的并且包括在Protecting Groups in Organic Synthesis,T.W.Greene and P.G.M.Wuts,3rd edition,John Wiley&Sons,1999中详细描述的那些,其通过引用整体并入本文。合适的氨基保护基团包括但不限于芳烷基胺类、氨基甲酸酯类、环状酰亚胺类、烯丙胺类、酰胺类等。此类基团的实例包括叔丁氧羰基

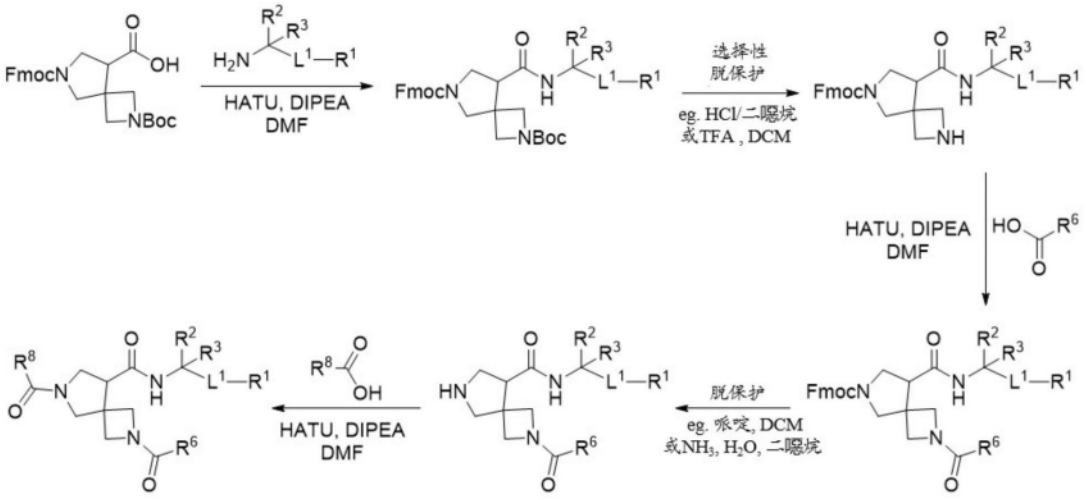
(BOC)、乙氧羰基、甲氧羰基、三氯乙氧羰基、烯丙氧羰基(Alloc)、苄氧羰基(CBZ)、烯丙基、邻苯二甲酰亚胺、苄基(Bn)、芴基甲基羰基(Fmoc)、甲酰基、乙酰基、氯乙酰基、二氯乙酰基、三氯乙酰基、苯乙酰基、三氟乙酰基、苯甲酰基等。

[0433] 本公开的化合物,包括式I的化合物和表1的化合物,通常可以根据下述方法制备。本领域普通技术人员可以根据需要使用公知常识对试剂和条件进行修改和替代,以得到本公开的化合物。

[0434] 方案1:螺环核心结构的合成

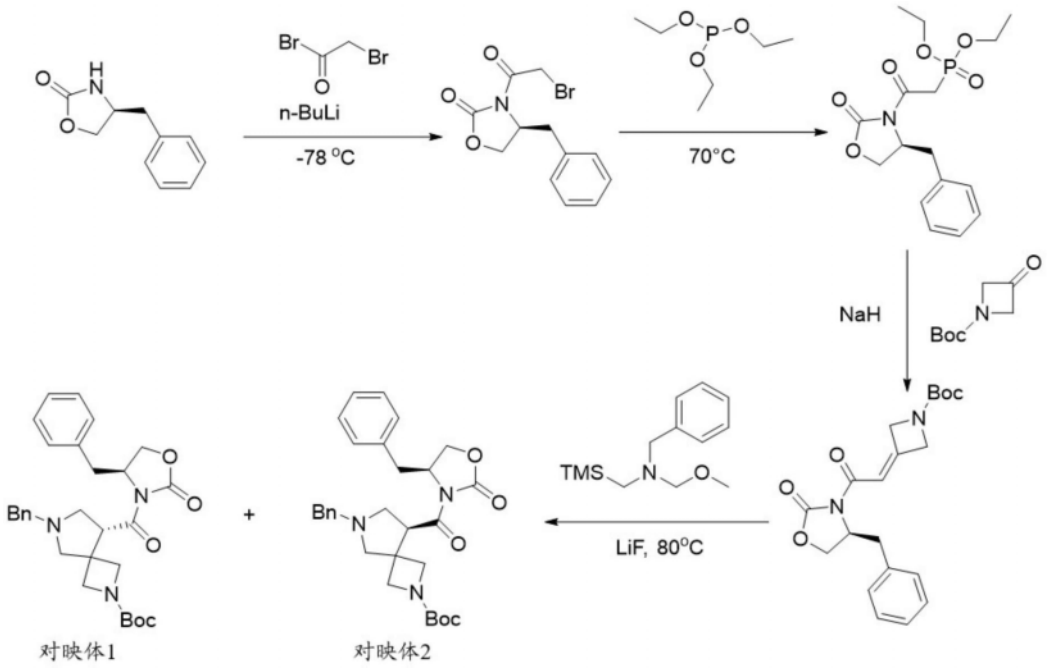
[0435] 

[0436] 方案2:螺环核心结构的外消旋官能化

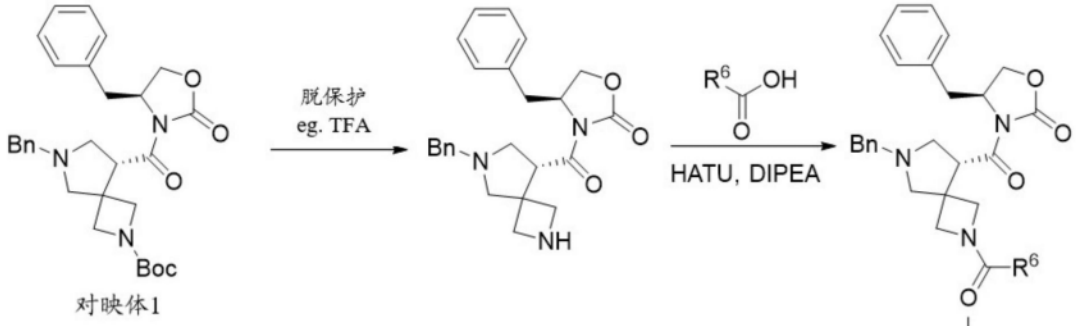
[0437] 

[0438] 方案3:通过使用噁唑烷酮助剂分离中间体合成单个对映体

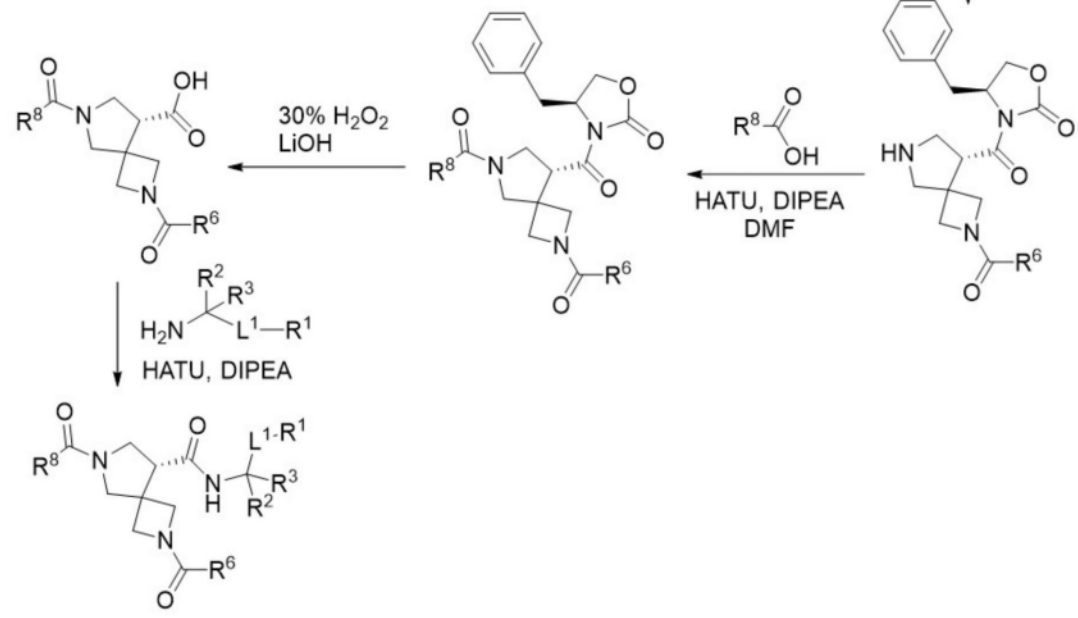
[0439]



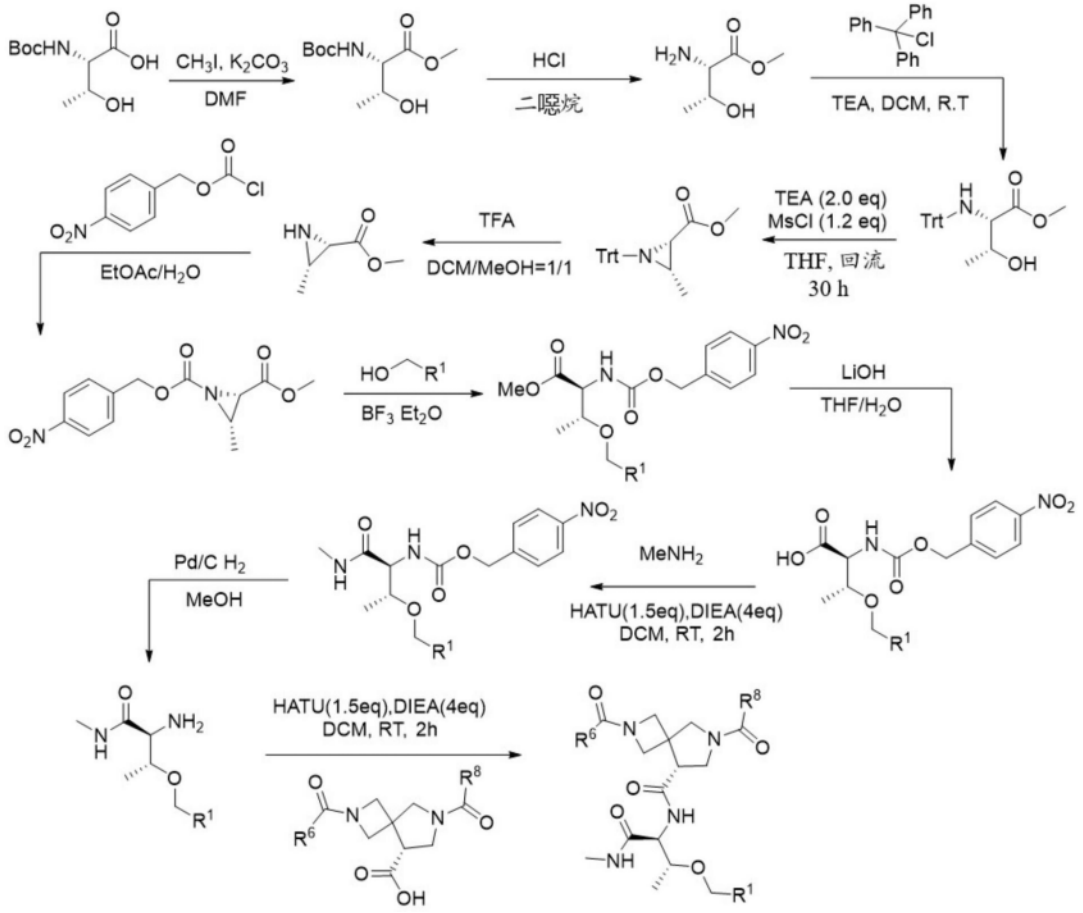
[0440] 方案4:从分离的中间体合成单个对映体



[0441]



[0442] 方案5:具有所需立体化学的苏氨酸衍生物R^A基团的化合物的合成

[0443] 

[0444] 5.用途、制剂和施用

[0445] 药学上可接受的组合物

[0446] 根据另一个实施方案,本公开提供了一种组合物,其包含本公开的化合物或其药学上可接受的衍生物和药学上可接受的载体、佐剂或媒介物。在本公开的组合物中的化合物的量使得其在生物样品或患者中有效的可测量地抑制CDK2蛋白或其突变体。在某些实施方案中,在本公开的组合物中的化合物的量使得其在生物样品或患者中有效的可测量地抑制CDK2蛋白或其突变体。在某些实施方案中,本公开的组合物被配制用于向有需要的患者施用这种组合物。在一些实施方案中,本公开的组合物被配制用于患者的口服施用。

[0447] 本公开的组合物可以口服、胃肠外、通过吸入喷雾、局部、直肠、鼻腔、经颊、阴道或通过植入的储存器施用。本文使用的术语“胃肠外”包括皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。优选地,该组合物是皮下、口服、腹膜内或静脉内施用。在一些实施方案中,该组合物是口服施用。在一些实施方案中,该组合物是腹膜内施用。在一些实施方案中,该组合物是静脉内施用。在一些实施方案中,该组合物是皮下施用。本公开的组合物的无菌注射形式可以是含水或含油的悬浮液。这些悬浮液可以根据本领域已知的技术使用合适的分散剂或润湿剂和悬浮剂配制。无菌注射制剂也可是在无毒的肠道外可接受的稀释剂或溶剂中的无菌注射溶液或悬浮液,例如在1,3-丁二醇中的溶液。在可接受的媒介物和溶剂之中可使用的是水、林格氏溶液和等渗氯化钠溶液。此外,通常使用无菌的、不挥发油作为溶剂或悬浮介质。

[0448] 为此,可以使用任何温和的不挥发油,包括合成的单甘油酯或二甘油酯。脂肪酸,

如油酸及其甘油酯衍生物可用于注射剂的制备,天然的药学上可接受的油,如橄榄油或蓖麻油,尤其是它们的聚氧乙烯化形式也是如此。这些油溶液或悬浮液还可含有长链醇稀释剂或分散剂,如羧甲基纤维素或类似的分散剂,其通常用于包括乳剂和悬浮剂的药学上可接受的剂型的配制。其他常用的表面活性剂,如吐温类、Spans和其他乳化剂或生物利用度增强剂,其常用于药学上可接受的固体、液体或其他剂型的制备,也可用于配制目的。

[0449] 本公开的药学上可接受的组合物可以以任何口服可接受的剂型口服施用,包括但不限于胶囊、片剂、含水的悬浮液或溶液。在口服使用片剂的情况下,常用的载体包括乳糖和玉米淀粉。通常还添加润滑剂,例如硬脂酸镁。对于以胶囊形式的口服施用,有用的稀释剂包括乳糖和干玉米淀粉。当需要口服使用含水的悬浮液时,将活性成分与乳化剂和悬浮剂相结合。如果需要,也可以添加某些甜味剂、调味剂或着色剂。

[0450] 或者,本公开的药学上可接受的组合物可以以用于直肠施用的栓剂的形式施用。这些可以通过将药剂与合适的无刺激性赋形剂混合来制备,该赋形剂在室温下为固体,但在直肠温度下为液体,并且因此将在直肠中融化以释放药物。这些材料包括可可脂、蜂蜡和聚乙二醇。

[0451] 本公开的药学上可接受的组合物也可以局部施用,特别是当治疗目标包括通过局部应用容易到达的区域或器官时,包括眼睛、皮肤或下肠道疾病。可以容易地为这些区域或器官中的每一个制备合适的局部制剂。

[0452] 下肠道的局部应用可以以直肠栓剂制剂(见上文)或以合适的灌肠制剂来实现。也可以使用局部透皮贴剂。

[0453] 对于局部应用,所提供的药学上可接受的组合物可以配制成合适的软膏,其含有悬浮或溶解在一种或多种载体中的活性成分。用于局部施用本公开化合物的载体包括但不限于矿物油、液体凡士林、白凡士林、丙二醇、聚氧乙烯、聚氧丙烯化合物、乳化蜡和水。或者,所提供的药学上可接受的组合物可以配制成合适的乳液或乳膏,其含有悬浮或溶解在一种或多种药学上可接受载体中的活性成分。合适的载体包括但不限于矿物油、山梨醇酐单硬脂酸酯、聚山梨醇酯60、十六烷基酯蜡、鲸蜡硬脂醇、2-辛基十二烷醇、苯甲醇和水。

[0454] 对于眼科用途,所提供的药学上可接受的组合物可以配制成在等渗、pH调节的无菌生理盐水中的微粉化悬浮液,或者优选地,配制成在含有或不含防腐剂(如苯扎氯铵)的等渗、pH调节的无菌生理盐水中的溶液。或者,对于眼科用途,药学上可接受的组合物可以配制成软膏(如凡士林)。

[0455] 本公开的药学上可接受的组合物也可以通过鼻气雾剂或吸入施用。这样的组合物是根据药物制剂领域中众所周知的技术制备的,并且可以使用苯甲醇或其他合适的防腐剂、增强生物利用度的吸收促进剂、碳氟化合物和/或其他常规增溶剂或分散剂制备成生理盐水溶液。

[0456] 最优选地,本公开的药学上可接受的组合物被配制用于口服施用。这种制剂可以与或不与食物一起施用。在一些实施方案中,本公开的药学上可接受的组合物不与食物一起施用。在其他实施方案中,本公开的药学上可接受的组合物与食物一起施用。

[0457] 可与载体材料组合以产生单一剂型的组合物的本公开的化合物的量将根据治疗的主体和特别的施用方式而变化。优选地,所提供的组合物应当配制成以便可以向接受这些组合物的患者施用在该化合物的0.01-100mg/kg体重/天之间的剂量。

[0458] 还应该理解,对于任何特定患者的具体剂量和治疗疗程将取决于多种因素,包括所使用的具体化合物的活性、年龄、体重、一般健康、性别、饮食、施用时间、排泄速率、药物组合,以及主治医生的判断和正在治疗的特定疾病的严重程度。本公开的化合物在组合物中的量也将取决于组合物中的具体化合物。

[0459] 化合物和药学上可接受的组合物的用途

[0460] 本文描述的化合物和组合物通常用于调节CDK2的活性。在一些实施方案中,本文描述的化合物和组合物是CDK2抑制剂。

[0461] 在一些实施方案中,本公开的化合物和组合物用于治疗与CDK2活性相关的疾病和障碍,包括但不限于癌症、骨髓增生性障碍、自身免疫性障碍、炎症性障碍、病毒感染、纤维化障碍和神经退行性障碍。

[0462] 在一些实施方案中,本公开提供了抑制CDK2活性的方法,该方法包含使本公开的化合物或其药学上可接受的盐与CDK2接触。在一些实施方案中,该接触发生在体外。在一些实施方案中,该接触发生在体内。

[0463] 在一些实施方案中,本公开提供了治疗、预防或减轻在患者中与CDK2活性相关的疾病或障碍的严重性的方法,其包括但不限于癌症、骨髓增生性障碍、自身免疫性障碍、炎症性障碍、纤维化障碍和神经退行性障碍,所述方法包含向有需要的患者施用本公开的化合物或其药学上可接受的盐,或包含有效量的本公开化合物或其药理学上可接受的盐的药物组合物。

[0464] 本公开进一步提供了本公开的化合物或其药学上可接受的盐、或包含有效量的本公开化合物或其药学上可接受的盐的药物组合物,其用于治疗与CDK2活性相关的疾病或障碍。

[0465] 本公开进一步提供了本公开的化合物或其药学上可接受的盐,或包含有效量的本公开化合物或其药学上可接受的盐的药物组合物,其用于制备用于治疗与CDK2活性相关的疾病或障碍的药物。

[0466] 在一些实施方案中,与CDK2活性相关的疾病或障碍是CDK2介导的疾病或障碍。在一些实施方案中,与CDK2活性相关的疾病或障碍是由CDK2过度活性引起的疾病或障碍。

[0467] 在一些实施方案中,与CDK2活性相关的疾病或障碍是癌症。

[0468] 在一些实施方案中,该癌症选自乳腺癌、卵巢癌、膀胱癌、子宫癌、前列腺癌、肺癌、食道癌、头颈癌、结直肠癌、肾癌、肝癌、胰腺癌、胃癌、黑色素瘤和甲状腺癌。

[0469] 在一些实施方案中,该癌症的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0470] 在一些实施方案中,该癌症是乳腺癌。在一些实施方案中,该乳腺癌是乳腺癌选自ER-阳性/HR-阳性乳腺癌、HER2-阴性乳腺癌、ER-阳性/HR-阳性乳腺癌、HER2阳性乳腺癌、三阴性乳腺癌(TNBC)、炎症性乳腺癌、内分泌耐药性乳腺癌、曲妥珠单抗耐药性乳腺癌、对CDK4/CDK6抑制有原发性或获得性耐药性的乳腺癌、晚期乳腺癌和转移性乳腺癌。在一些实施方案中乳腺癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0471] 在一些实施方案中,该癌症是卵巢癌。在一些实施方案中,该卵巢癌是高级别浆液性卵巢癌(HGSOC)。在一些实施方案中该卵巢癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0472] 在一些实施方案中,该癌症是膀胱癌。在一些实施方案中,该膀胱癌的特征在于

CCNE1和/或CCNE2的扩增或过度表达。

[0473] 在一些实施方案中,该癌症是子宫癌。在一些实施方案中,该子宫癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0474] 在一些实施方案中,该癌症是前列腺癌。在一些实施方案中,该前列腺癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0475] 在一些实施方案中,该癌症是肺癌。在一些实施方案中,该肺癌是肺癌选自非小细胞肺癌、小细胞肺癌、鳞状细胞癌、腺癌和间皮瘤。在一些实施方案中,该肺癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。在一些实施方案中,该肺癌是CCNE1扩增的鳞状细胞癌或CCNE1扩增的腺癌。

[0476] 在一些实施方案中,该癌症是头颈癌。在一些实施方案中,该头颈癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0477] 在一些实施方案中,该癌症是结直肠癌。在一些实施方案中,该结直肠癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0478] 在一些实施方案中,该癌症是肾癌。在一些实施方案中,该肾癌是肾细胞癌(RCC)。在一些实施方案中,该肾癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0479] 在一些实施方案中,该癌症是肝癌。在一些实施方案中,该肝癌是肝细胞癌(HCC)。在一些实施方案中,该肝癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0480] 在一些实施方案中,该癌症是胰腺癌。在一些实施方案中,该胰腺癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0481] 在一些实施方案中,该癌症是胃癌。在一些实施方案中,该胃癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0482] 在一些实施方案中,该癌症是黑色素瘤。在一些实施方案中,该黑色素瘤的特征在于CCNE1和/或CCNE2的扩增或过度表达。CDK2的表达受必需的黑素细胞转录因子MITF的调节。已发现CDK2耗尽抑制黑色素瘤的生长(Du et al.,Cancer Cell.2004Dec;6(6):565-576)

[0483] 在一些实施方案中,该癌症是甲状腺癌。在一些实施方案中,该甲状腺癌的特征在于CCNE1和/或CCNE2的扩增或过度表达。

[0484] 在一些实施方案中,与CDK2活性相关的疾病或障碍是骨髓增生性障碍。

[0485] 在一些实施方案中,与CDK2活性相关的疾病或障碍是神经退行性疾病或障碍。在一些实施方案中,该神经退行性疾病或障碍是阿尔茨海默氏病(AD)。据报道,在患有AD的受试者中的神经元细胞死亡之前发生了细胞周期事件。一种或多种CDKs的抑制可以抑制细胞周期事件并因此避免神经元细胞死亡(Yang et al.,J Neurosci.2003Apr 1;23(7):2557-2563)。

[0486] 在一些实施方案中,与CDK2活性相关的疾病或障碍是肝脏疾病。

[0487] 在一些实施方案中,与CDK2活性相关的疾病或障碍是肝纤维化。据报道,CCNE1敲除小鼠在暴露于促纤维化毒素CCl_4后不会出现肝纤维化,这表明肝纤维化可以通过施用CDK2抑制剂来治疗(Nevzorova,et al.,Hepatology.2012Sep;56(3):1140-1149.)

[0488] 在一些实施方案中,与CDK2活性相关的疾病或障碍是库欣病。垂体细胞周期蛋白E/E2F1信号传导是下丘脑-垂体-肾上腺轴潜在的神经内分泌调节的分子机制,并因此为垂

体ACTH依赖性皮质醇增多症(也称为库欣病)的CDK2抑制剂提供了亚细胞治疗靶点(Liu,et al.,J Clin Endocrinol Metab.2015Jul;100(7):2557-2564.)。

[0489] 在一些实施方案中,与CDK2活性相关的疾病或障碍是肾脏疾病。

[0490] 在一些实施方案中,与CDK2活性相关的疾病或障碍是多囊肾病。据报道,CDK2/CDK5抑制剂骨癌痛(roscovitine)在多囊肾病的小鼠模型中对囊性肾病产生有效抑制(Bukanov,et al.,Nature.2006Dec 14;444(7121):949-52)。

[0491] 在一些实施方案中,与CDK2活性相关的疾病或障碍是自身免疫性障碍。CDK2消融已被证明通过支持调节性T细胞的功能来促进免疫耐受(Chunder et al.,J Immunol.2012Dec 15;189(12):5659-66)。

[0492] 在一些实施方案中,与CDK2活性相关的疾病或障碍是炎症性障碍。细胞周期蛋白E消融已被证明可以减轻小鼠的肝炎,而p27敲除小鼠表现出肾脏炎症的恶化(Ehedego et al.,Oncogene.2018Jun;37(25):3329-3339.;Ophascharoensuk et al.,Nat Med.1998May;4(5):575-80.)。在一些实施方案中,炎症性障碍是肝炎。

[0493] 在一些实施方案中,本公开的化合物和组合物可用作雄性避孕药。基于雄性CDK2敲除小鼠不育的发现,CDK2抑制剂已被研究作为可能的雄性避孕药(Faber,et al.,Biol Reprod.2020Aug;103(2):357-367.)。在一些实施方案中,本公开提供了降低雄性生育能力的方法,包含向有需要的患者施用本公开的化合物或其药学上可接受的盐,或包含有效量的本公开化合物或其药理学上可接受的盐的药物组合物。

[0494] 在一些实施方案中,本公开的化合物和组合物可用于治疗与CDK5活性相关的疾病和障碍,包括但不限于癌症、骨髓增生性障碍、自身免疫性障碍、炎症性障碍、病毒感染、纤维化障碍和神经退行性障碍。在一些实施方案中,本公开的化合物和组合物可用于治疗与CDK5活性相关的神经退行性障碍。

[0495] 组合疗法

[0496] 依赖于待治疗的特定的病症或疾病,通常施用以治疗该病症的额外的治疗剂可以与本公开的化合物和组合物组合施用。如本文所用,通常施用于治疗特定疾病或病症的额外治疗剂被称为“适合于所治疗的疾病或病症”。

[0497] 在某些实施方案中,所提供的组合或其组合物与另一个治疗剂组合施用。

[0498] 在一些实施方案中,本公开提供了治疗公开的疾病或病症的方法,其包括向有需要的患者施用有效量的本文公开的化合物或其药学上可接受的盐,并同时或依次地共同施用有效量的一种或多种额外的治疗剂,例如本文描述的那些。在一些实施方案中,该方法包括共同施用一种额外的治疗剂。在一些实施方案中,该方法包括共同施用两种额外的治疗剂。在一些实施方案中,公开的化合物和额外的一种或多种治疗剂的组合协同作用。

[0499] 还可以与本公开的化合物组合的药剂的实例包括不限于:内分泌治疗剂、化疗剂和其他CDK抑制性化合物。

[0500] 在一些实施方案中,本公开提供了治疗公开的疾病或病症的方法,其包含向有需要的患者施用有效量的本文公开的化合物或其药学上可接受的盐,并同时或依次地共同施用有效量的内分泌治疗剂。

[0501] 在一些实施方案中,本公开提供了治疗公开的疾病或病症的方法,其包含向有需要的患者施用有效量的本文公开的化合物或其药学上可接受的盐,并同时或依次地共同施

用有效量的一种或多种额外的CDK抑制性化合物。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK4或CDK4/CDK6抑制剂。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK4、CDK6、CDK7或CDK4/CDK6抑制剂。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK4抑制剂。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK6抑制剂。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK7抑制剂。在一些实施方案中,一种或多种额外的CDK抑制性化合物是CDK4/CDK6抑制剂。

[0502] 在一些实施方案中,本公开提供了治疗公开的疾病或病症的方法,其包含向有需要的患者施用有效量的本文公开的化合物或其药学上可接受的盐,并同时或依次地共同施用有效量的化疗剂。在一些实施方案中,该化疗剂是紫杉烷。在一些实施方案中,该化疗剂是铂剂。在一些实施方案中,该化疗剂是曲妥珠单抗。

[0503] 如本文所用,术语“组合”、“结合”和相关术语指的是根据本公开同时或依次施用治疗剂。例如,本公开的组合可以与另一个治疗剂以单独的单位剂型同时或依次施用或者以单个单位剂型一起施用。

[0504] 在本公开的组合物中存在的额外的治疗剂的量将不超过在包含该治疗剂作为唯一活性剂的组合物中通常施用的量。优选地,在本公开的组合物中额外的治疗剂的量将在包含该药剂作为唯一治疗活性剂的组合物中通常存在的量的约50%至100%的范围内。

[0505] 作为多剂量方案的一部分,一种或多种其他治疗剂可以与本公开的化合物或组合物分开施用。或者,一种或多种其他治疗剂可以是单一剂型的一部分,在单一组合物中与本公开的化合物混合到一起。如果作为多剂量方案施用,一种或多种其他治疗剂和本公开的化合物或组合物可以同时、依次或在一段时间内彼此间隔施用,例如在1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、18、20、21、22、23或24小时内彼此间隔施用。在一些实施方案中,一种或多种其它治疗剂和本公开的化合物或组合物以多剂量方案在间隔大于24小时内施用。

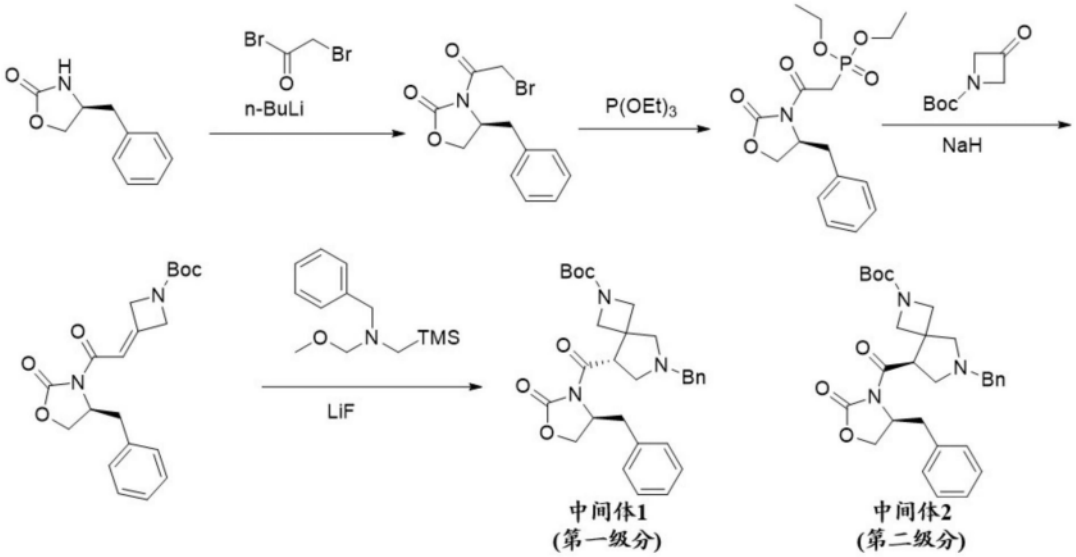
[0506] 在一个实施方案中,本公开提供了一种组合物,其包含提供的化合物或其药学上可接受的盐和一种或多种额外的治疗剂。该治疗剂可以与所提供的化合物或其药学上可接受的盐一起施用,或者可以在施用提供的化合物或其药学上可接受的盐之前或之后施用。合适的治疗剂在下面进一步详细描述。在某些实施方案中,所提供的化合物或其药学上可接受的盐可以在治疗剂之前至多5分钟、10分钟、15分钟、30分钟、1小时、2小时、3小时、4小时、5小时、6小时、7小时、8小时、9小时、10小时、11小时、12小时、13小时、14小时、15小时、16小时、17小时或18小时施用。在其它实施方案中,所提供的化合物或其药学上可接受的盐可在治疗剂之后至多5分钟、10分钟、15分钟、30分钟、1小时、2小时、3小时、4小时、5小时、6小时、7小时、8小时、9小时、10小时、11小时、12小时、13小时、14小时、15小时、16小时、17小时或18小时施用。

实施例

[0507] 如以下实施例描述,在某些示例性实施方案中,根据本文提供的一般步骤制备化合物。应当理解,尽管该一般方法描述了本公开的某些化合物的合成,但该一般方法和本领域普通技术人员已知的其他方法都可以应用于所有化合物以及这些化合物中的每种的亚类和种类(如本文所述)。

[0508] 实施例1:中间体的合成

[0509] 中间体1:(R)-6-苄基-8-((S)-4-苄基-2-氧代噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯和中间体2:(S)-6-苄基-8-((S)-4-苄基-2-氧代噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯

[0510] 

[0511] 步骤1:在-78℃在N_2气氛下向(S)-4-苄基噁唑烷-2-酮(40g,225mmol)在无水THF(400mL)中的溶液中逐滴添加n-BuLi(2.5M于已烷中,99mL,248mmol)。将反应混合物在-78℃搅拌0.5h,然后添加2-溴乙酰溴(21mL,237mmol)。将反应温热至室温并再搅拌2小时。将混合物用EtOAc(600mL)稀释,用水(200mL×2)洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=10:1-3:1),得到(S)-4-苄基-3-(2-溴乙酰基)噁唑烷-2-酮(50g,75%),其为黄色油状物。^1H NMR(400MHz,$CDCl_3$)δ7.38-7.26(m,3H),7.24-7.19(m,2H),4.70(ddt,J=9.6,7.8,3.2Hz,1H),4.61-4.48(m,2H),4.30-4.20(m,2H),3.33(dd,J=13.6,3.4Hz,1H),2.81(dd,J=13.4,9.6Hz,1H)。

[0512] 步骤2:将(S)-4-苄基-3-(2-溴乙酰基)噁唑烷-2-酮(100g,335mmol)在亚磷酸三乙酯(279g,1.68mol)中的混合物在50℃加热18小时。在70℃在真空下除去过量的亚磷酸三乙酯,得到(S)-(2-(4-苄基-2-氧代噁唑烷-3-基)-2-氧代乙基)膦酸二乙酯(110g粗品,92%),其为黄色油状物。LCMSm/z=356.0$[M+H]^+$;^1H NMR(400MHz,$CDCl_3$)δ7.37-7.16(m,5H),4.70(ddt,J=10.4,7.0,3.4Hz,1H),4.26-4.12(m,6H),3.88-3.71(m,2H),3.34(dd,J=13.4,3.4Hz,1H),2.75(dd,J=13.4,9.8Hz,1H),1.34(t,J=7.0Hz,6H)。

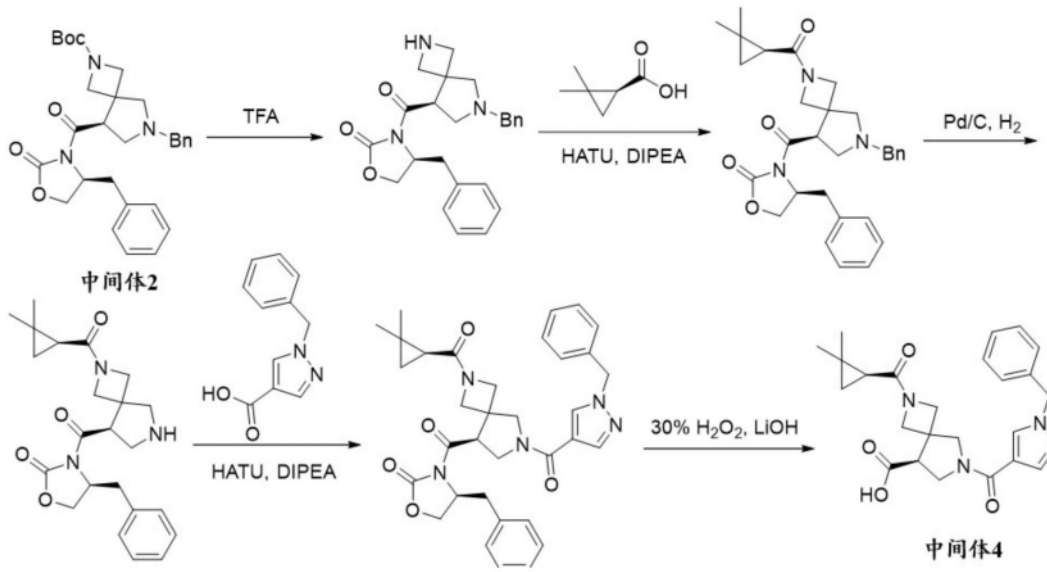
[0513] 步骤3:在0℃在N_2气氛下向(S)-(2-(4-苄基-2-氧代噁唑烷-3-基)-2-氧代乙基)膦酸二乙酯(30g,84mmol)在无水THF(300mL)中的溶液逐滴添加LiHMDS(1.0M于THF中,85mL,85mmol)。将反应混合物在0℃搅拌30分钟,然后添加3-氧代氮杂环丁烷-1-甲酸叔丁酯(21.68g,127mmol)。将反应温热至室温并再搅拌1h。将反应用EtOAc(1L)稀释并将有机层用饱和NH_4Cl(200mL)和水(200mL)洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=10:1),得到(S)-3-(2-(4-苄基-2-氧代噁唑烷-3-基)-2-氧代亚乙基)氮杂环丁烷-1-甲酸叔丁酯(17g,54%),其为黄色固体。LCMSm/z=373.1$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ7.35-7.29(m,2H),7.28-7.23(m,1H),7.22-7.17(m,2H),7.16-7.11(m,1H),4.85-4.60(m,5H),4.34(t,J=8.4Hz,1H),4.20(dd,J=8.8,

2.8Hz,1H),3.04(dd,J=13.4,3.2Hz,1H),2.94(dd,J=13.4,7.6Hz,1H),1.41(s,9H)。

[0514] 步骤4:将得到的(S)-3-(2-(4-苄基-2-氧代噁唑烷-3-基)-2-氧代亚乙基)氮杂环丁烷-1-甲酸叔丁酯(10g,26.85mmol)、N-苄基-1-甲氧基-N-((三甲基甲硅烷基)甲基)甲胺(8.29g,34.91mmol)和LiF(2.09g,80.55mmol)在乙腈(100mL)中的混合物在80℃加热16小时。冷却至室温后,将混合物用水(200mL)稀释,并用EtOAc(300mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到(R)-6-苄基-8-((S)-4-苄基-2-氧代噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体1)(5g,37%)作为第一洗脱异构体,其为黄色油状物。LCMSm/z=506.3$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.36-7.31(m,4H),7.30-7.23(m,4H),7.20-7.18(m,2H),4.66(d,J=7.2Hz,1H),4.33(t,J=8.4Hz,1H),4.23-4.20(m,1H),4.05(dd,J=8.0,5.2Hz,1H),3.90(d,J=9.0Hz,1H),3.75(s,1H),3.73-3.55(m,4H),3.19-3.09(m,1H),3.00-2.92(m,3H),2.74(d,J=8.8Hz,1H),2.45(dd,J=9.6,5.2Hz,1H),1.35(s,9H)。进一步洗脱提供了(S)-6-苄基-8-((S)-4-苄基-2-氧代噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体2)(5g,37%)。LCMSm/z=506.3$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.35--7.29(m,6H),7.28-7.22(m,4H),4.67--4.61(m,1H),4.30(t,J=8.4Hz,1H),4.23(dd,J=8.2,6.2Hz,1H),4.19--4.16(m,1H),3.90(br s,1H),3.83(d,J=9.2Hz,1H),3.68-3.66(m,2H),3.62(d,J=5.0Hz,2H),3.12-3.05(m,1H),3.02(d,J=8.8Hz,1H),2.97(d,J=9.0Hz,1H),2.86(dd,J=13.4,8.4Hz,1H),2.65(d,J=9.0Hz,1H),2.55(dd,J=9.4,6.2Hz,1H),1.36(s,9H)。

[0515] 中间体4:(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸

[0516]



[0517] 步骤1:向中间体2(6.2g,12.26mmol)在DCM(10mL)中的溶液添加TFA(5mL)。将反应混合物在室温搅拌2小时。在真空下除去溶剂,得到粗品(S)-4-苄基-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(5g,100%),其直接用于下一步。

[0518] 步骤2:向(S)-2,2-二甲基环丙烷-1-甲酸(1.55g,13.56mmol)在DCM(50mL)中的溶液添加HATU(7.03g,18.50mmol)。将混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(5g,12.33mmol)和DIPEA(6.37g,

49.32mmol)。将反应混合物在室温再搅拌4小时。将混合物用水(100mL)稀释,然后用DCM(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=3:1至DCM/EtOAc=3/1),得到(S)-4-苄基-3-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(5.2g,84%),其为黄色固体。LCMSm/z=502.3$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.53-7.36(m,5H),7.35-7.21(m,5H),4.67(ddt,J=8.2,5.6,2.6Hz,1H),4.58-4.46(m,1H),4.37-3.93(m,7H),3.89-3.79(m,1H),3.57-3.40(m,2H),3.10(dt,J=13.4,3.6Hz,1H),2.88(dd,J=13.4,8.4Hz,1H),1.35(dd,J=8.0,5.4Hz,1H),1.13-0.96(m,6H),0.86(q,J=4.4Hz,1H),0.70(ddd,J=14.8,8.0,3.6Hz,1H)。

[0519] 步骤3:向(S)-4-苄基-3-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(1.0g,1.99mmol)在EtOAc(8mL)中的溶液添加10%Pd/C(400mg)。将反应混合物在H_2气氛下搅拌24小时。转化约为50%。将混合物通过硅藻土过滤并浓缩。将残留物再溶于EtOAc(8mL)中,并添加另一批10%Pd/C(400mg)。将反应在H_2气氛下再搅拌24小时。将混合物过滤并浓缩,得到(S)-4-苄基-3-((S)-2-(S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(800mg,98%),其直接用于下一步。LCMSm/z=412.2$[M+H]^+$。

[0520] 步骤4:向1-苄基-1H-吡唑-4-甲酸(308mg,1.52mmol)在DMF(10mL)中的溶液添加HATU(790mg,2.08mmol)。将该混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(570mg,1.39mmol)和DIPEA(716mg,5.54mmol)。将反应混合物在室温再搅拌3小时。将混合物用水(100mL)稀释,用EtOAc(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH=30/1),得到(S)-4-苄基-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(410mg,50%),其为黄色固体。LCMSm/z=596.3$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.44-8.28(m,1H),7.88-7.76(m,1H),7.40-7.18(m,10H),5.36(d,J=4.4Hz,2H),4.70-4.60(m,1H),4.40-4.23(m,4H),4.21-4.01(m,3H),3.97-3.56(m,5H),3.18-2.84(m,3H),1.42-1.33(m,1H),1.28-1.21(m,5H),1.14-1.02(m,7H),0.86(d,J=7.2Hz,1H),0.69(d,J=6.4Hz,1H).

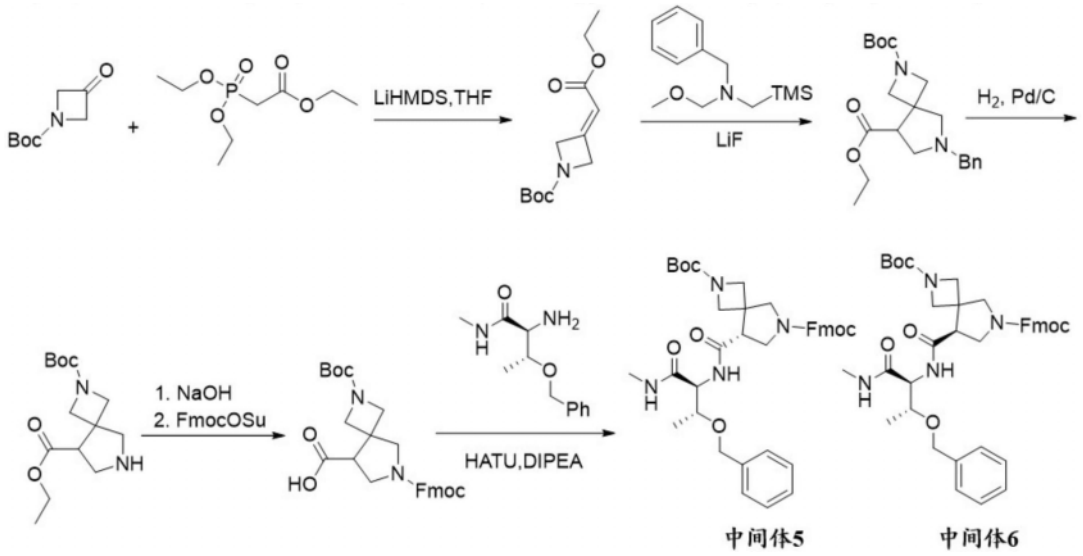
[0521] 步骤5:在0℃向(S)-4-苄基-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(410mg,0.69mmol)在THF/H_2O(16mL/2mL)中的溶液添加在H_2O(1mL)中的氢氧化锂一水合物(58mg,1.38mmol)和在H_2O(1mL)中的30%H_2O_2(0.18mL,1.72mmol)。将反应混合物在0℃搅拌1小时,然后用水(20mL)稀释并用EtOAc(30mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(60mL×3)萃取。合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(中间体4)(245mg,82%),其为黄色固体。LCMSm/z=437.0$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ12.69(s,1H),8.38-8.28(m,1H),7.88-7.79(m,1H),7.37-7.23(m,6H),5.36(s,2H),4.37-4.24(m,1H),4.17(s,1H),4.11-3.61(m,7H),1.42-1.32(m,1H),1.09(d,J=23.0Hz,6H),0.90-0.85(m,1H),0.72-0.64(m,1H).

[0522] 中间体3:(R)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸

[0523] 通过与中间体4相同的方法,从中间体1代替中间体2开始来制备中间体3。将中间体3(1.2g,40%)分离,其为白色固体,其无需纯化即可使用。LCMSm/z=437.2[M+H]$^+$.

[0524] 中间体5:(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-(叔丁基)酯和中间体6:(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-(叔丁基)酯

[0525]



[0526] 步骤1:在0℃在N_2气氛下向2-(二乙氧基磷酰基)乙酸乙酯(52g,0.23mol)在无水THF(200mL)中的溶液中逐滴添加LiHMDS(1.0M于THF中,234mL,0.23mol)。将反应混合物在0℃搅拌30分钟。添加3-氧代氮杂环丁烷-1-甲酸叔丁酯(20g,0.12mol)并将反应温热至室温并再搅拌1h。将混合物用EtOAc(1L)稀释,并将有机层用饱和NH_4Cl(200mL)和水(200mL)洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=10:1),得到3-(2-乙氧基-2-氧代亚乙基)氮杂环丁烷-1-甲酸叔丁酯(21g,75%),其为黄色固体。LCMSm/z=242.2[M+H]$^+$;^{1}H NMR(400MHz,氯仿-d)δ5.76(p,J=2.4Hz,1H),4.84-4.78(m,2H),4.61-4.55(m,2H),4.17(qd,J=7.2,0.8Hz,2H),1.45(s,9H),1.27(t,J=7.2,0.8Hz,3H).

[0527] 步骤2:将3-(2-乙氧基-2-氧代亚乙基)氮杂环丁烷-1-甲酸叔丁酯(17g,70.46mmol)、N-苄基-1-甲氧基-N-((三甲基硅烷基)甲基)甲胺(20g,84.55mmol)和LiF(5.48g,0.21mol)在乙腈(100mL)中的混合物在80℃加热16小时。冷却至室温后,将混合物用水(200mL)稀释,并用EtOAc(300mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到6-苄基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(20g,76%),其为黄色油状物。^{1}HNMR(400MHz,氯仿-d)δ7.31-7.26(m,3H),7.25-7.17(m,2H),4.20-4.10(m,2H),3.79(dd,J=12.6,8.8Hz,2H),3.69-3.63(m,2H),3.60(d,J=4.8Hz,2H),3.03-2.87(m,3H),2.76-2.64(m,2H),1.38(s,9H),1.24(t,J=7.2Hz,4H).

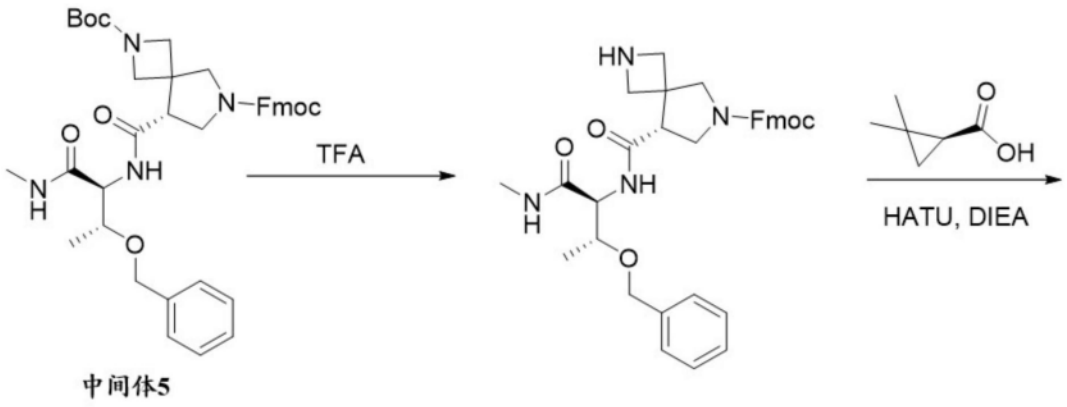
[0528] 步骤3:向6-苄基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯

(20g,53.41mmol)在EtOAc(120mL)中的溶液添加10％Pd/C(5g)。将反应混合物在H_2气氛下搅拌4天。将混合物通过硅藻土过滤并浓缩,得到2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(15g,100％),其直接用于下一步。

[0529] 步骤4和5:2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸向2-(叔丁基)8-乙基酯(15g,52.75mmol)在THF和H_2O(100mL/50mL)的混合物中的溶液添加NaOH(4.2g,0.1mol)。将反应混合物在室温搅拌5小时。添加FmocOSU(20g,59.29mmol)并将所得混合物再搅拌3小时,然后用水(50mL)稀释并用EtOAc(100mL)萃取。收集水层并用1M HCl酸化至pH～2,并用EtOAc(200mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH＝20/1),得到6-(((9H-芴-9-基)甲氧基)羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(10.5g,42％),其为白色固体。LCMSm/z＝479.3$[M+H]^+$;^{1}H NMR(400MHz,氯仿-d)δ7.77(dd,J＝7.6,3.6Hz,2H),7.58(d,J＝7.4Hz,2H),7.44-7.36(m,2H),7.36-7.28(m,2H),4.48-4.34(m,2H),4.23(t,J＝6.8Hz,1H),4.10(d,J＝9.4Hz,1H),3.99(t,J＝8.4Hz,1H),3.92-3.53(m,6H),3.18-3.07(m,1H),1.46(d,J＝6.6Hz,9H).

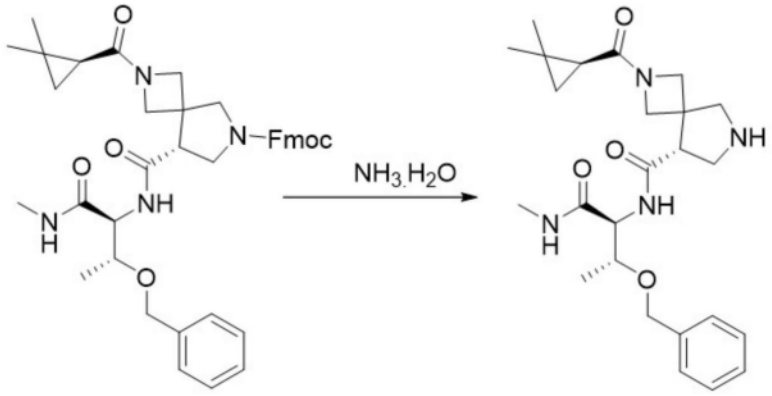
[0530] 步骤6:向6-(((9H-芴-9-基)甲氧基)羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(13g,27.20mmol)在DMF(100mL)中的溶液添加HATU(15.5g,40.80mmol)并将混合物在室温搅拌30分钟。添加(2S,3R)-2-氨基-3-(苄氧基)-N-甲基丁酰胺(7.2g,32.60mmol)和DIPEA(14g,0.11mol)并将该反应再搅拌3小时。将混合物用水(200mL)稀释,并用DCM(300mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc＝1:1),得到(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-(叔丁基)酯(中间体5)(6.8g,37％),其为白色固体。LCMSm/z＝683.2$[M+H]^+$;^{1}H NMR(400MHz,氯仿-d)δ7.77(d,J＝7.0Hz,2H),7.62-7.54(m,3H),7.45-7.28(m,11H),6.80(d,J＝6.2Hz,1H),6.48(s,1H),4.68-4.59(m,2H),4.56(dd,J＝6.0,3.2Hz,1H),4.40(t,J＝5.8Hz,2H),4.28-3.96(m,4H),3.91-3.78(m,5H),3.73-3.57(m,4H),2.99(t,J＝5.6Hz,1H),2.82(d,J＝4.8Hz,4H),1.45(d,J＝8.0Hz,12H),1.11(dd,J＝9.4,6.2Hz,4H)。进一步洗脱得到(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-(叔丁基)酯(中间体6)(7g,38％),其为白色固体。LCMSm/z＝683.3$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.30(s,1H),7.92-7.83(m,3H),7.69-7.62(m,2H),7.42(t,J＝7.4Hz,2H),7.35-7.25(m,7H),4.54(d,J＝12.0Hz,1H),4.44(d,J＝12.0Hz,1H),4.38-4.24(m,5H),4.02-3.83(m,3H),3.74-3.35(m,8H),2.61(t,J＝4.2Hz,3H),1.38-1.34(m,9H),1.10(d,J＝6.4Hz,3H).

[0531] 中间体7:(R)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺



中间体5

[0532]



中间体7

[0533] 步骤1:向中间体5(0.2g,0.29mmol)在DCM(1mL)中的溶液添加TFA(0.3mL)。将反应混合物在室温搅拌1小时。在真空下除去溶剂,得到(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲酯(170mg,100%),其直接用于下一步。LCMSm/z=583.3[M+H]$^+$。

[0534] 步骤2:向(S)-2,2-二甲基环丙烷-1-甲酸(37mg,0.32mmol)在DCM(2mL)中的溶液添加HATU(166mg,0.44mmol)。将混合物在室温搅拌30分钟。添加(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸酯(170mg,0.29mmol)和DIPEA(151mg,1.17mmol),并将反应混合物在室温再搅拌1h。将混合物用水(60mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=15:1),得到(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲酯(120mg,61%),其为白色固体。LCMSm/z=679.4[M+H]$^+$.^{1}H NMR(400MHz,DMSO-d_6)δ8.35(dd,J=8.0Hz,1H),7.99-7.85(m,3H),7.72-7.59(m,2H),7.54-7.19(m,9H),4.54(dd,J=12.2,4.2Hz,1H),4.46-4.38(m,1H),4.37-4.19(m,4H),4.13-4.02(m,1H),4.00-3.85(m,2H),3.82-3.68(m,1H),3.67-3.53(m,2H),3.50-3.39(m,3H),3.31(s,1H),2.61(dd,J=4.6,1.6Hz,3H),1.41-1.31(m,1H),1.15-1.03(m,9H),0.89-0.85(m,1H),0.74-0.65(m,1H).

[0535] 步骤3:向(R)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲酯(120mg,0.25mmol)在1,4-二噁烷(2mL)中的溶液添加25%氢氧化铵(2mL)。将反应混合物在50℃加热过夜,并在真空下除去溶剂。残留物用乙醚(10mL×2)研磨,得到(R)-N-

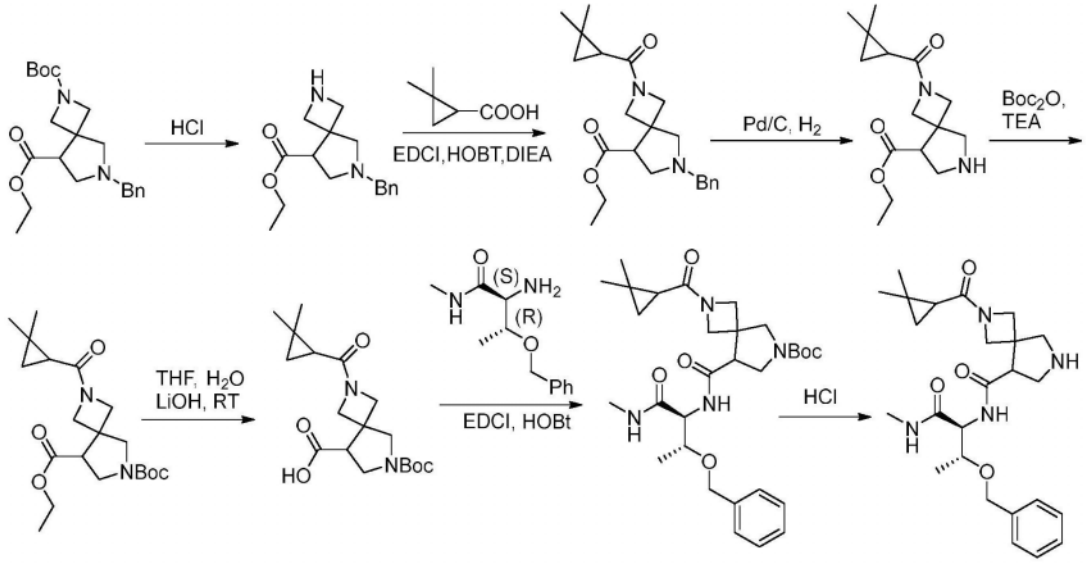
((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(中间体7)(70mg,88%),其为白色固体。LCMSm/z=457.3[M+H]$^+$。

[0536] 中间体8:(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺

[0537] 通过与中间体7相同的方法,从中间体6代替中间体5开始来制备中间体8。将中间体8(550mg,40%)分离,其为黄色固体。LCMSm/z=457.4[M+H]$^+$。

[0538] 中间体9:N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺

[0539]



[0540] 步骤1:向6-苄基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙酯(中间体5-步骤2)(2.0g,5.3mmol)在EtOH(2.0mL)中的溶液添加HCl/二噁烷(4M,10mL,40mmol)。将混合物在室温搅拌1h,然后在真空下除去溶剂,得到6-苄基-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯,其直接用于下一步。LCMSm/z=275.1[M+H]$^+$.

[0541] 步骤2:向2,2-二甲基环丙烷-1-甲酸(500mg,4.38mmol)在无水DMF(10mL)中的溶液添加EDCI(841mg,4.38mmol)、HOBt(591mg,4.38mmol)和DIPEA(2.0g,14.6mmol)并将混合物在室温搅拌1h。添加6-苄基-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(1.0g,3.65mmol)并将该反应再搅拌14h。将混合物用水(50mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=1:1),得到6-苄基-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(590mg,43%),其为无色油状物。LCMSm/z=371.1[M+H]$^+$;^{1}H NMR(400MHz,CD_3OD)δ7.53-7.02(m,5H),4.37-3.70(m,6H),3.67(s,2H),3.22-3.12(m,1H),3.02-2.77(m,4H),1.42-1.35(m,1H),1.32-1.23(m,3H),1.19-1.05(m,6H),1.04-0.97(m,1H),0.79-0.71(m,1H).

[0542] 步骤3:向6-苄基-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(50mg,0.135mmol)在MeOH(3.0mL)中的溶液添加10%Pd/C(35mg)。将该混合物在H_2气氛下搅拌过夜。将混合物通过硅藻土过滤并浓缩,得到2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯,其直接用于下一步。LCMSm/z=281.1[M+H]$^+$.

[0543] 步骤4:向2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(430mg,1.5mmol)在DCM(5mL)中的溶液添加(Boc)$_2$O(400mg,1.84mmol)和TEA(227mg,2.25mmol),并将混合物在室温搅拌4小时。在真空下除去溶剂并将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=3:1),得到2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6,8-二甲酸6-(叔丁基)8-乙酯(522mg,89%),其为无色油状物。LCMSm/z=381.2[M+H]$^+$.

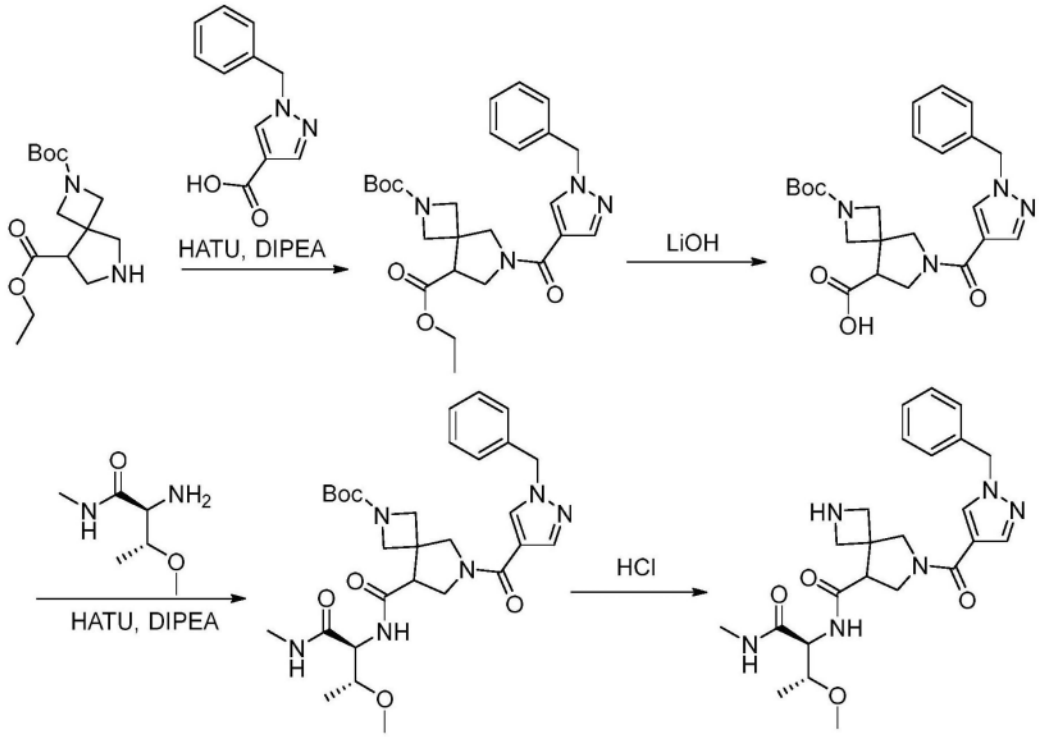
[0544] 步骤5:向2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-二甲酸6-(叔丁基)8-乙酯(522mg,1.37mmol)在THF和H_2O(4mL/1mL)的混合物中的溶液添加LiOH(247mg,4.12mmol)。将反应混合物在室温搅拌2h,然后用水(30mL)稀释并用EtOAc(50mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到6-(叔丁氧基羰基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(457mg,94%),其为白色固体,其直接用于下一步。LCMSm/z=353.2[M+H]$^+$.

[0545] 步骤6:向6-(叔丁氧基羰基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(100mg,0.284mmol)在无水DMA(2mL)中的溶液添加EDCI(82mg,0.426mmol)、HOBt(57.5mg,0.426mmol)和DIPEA(146mg,1.136mmol),并将混合物在室温搅拌1h。添加(2S,3R)-2-氨基-3-(苄氧基)-N-甲基丁酰胺(75.7mg,0.341mmol)并将该反应再搅拌14小时。将混合物用水(20mL)稀释并用EtOAc(60mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸叔丁酯(150mg,95%),其为白色固体。LCMSm/z=557.4[M+H]$^+$.

[0546] 步骤7:向8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸叔丁酯(556mg,1mmol)在二噁烷(4.0mL)中的溶液添加HCl在二噁烷(4M,3mL,12mmol)中的溶液。将混合物在室温搅拌1小时,然后在真空下除去溶剂,得到N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺,其为白色固体。LCMSm/z=457.2[M+H]$^+$。

[0547] 中间体10:6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺

[0548]



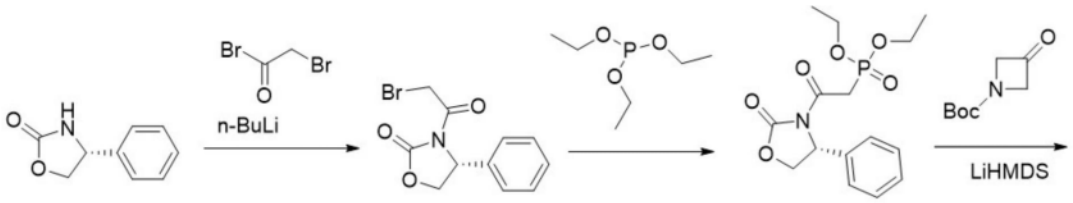
[0549] 步骤1:向1-苄基-1H-吡唑-4-甲酸(1.1g,5.6mmol)在无水DMF(10mL)中的溶液添加HATU(3.2g,8.4mmol)和DIEA(2.89g,22.4mmol),并将混合物在室温搅拌30分钟。添加2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(中间体5-步骤3)(1.9g,6.7mmol)并将反应搅拌4小时,然后用水(50mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到6-(1-苄基-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(2.9g,92%),其为白色固体。LCMSm/z=469.1$[M+H]^+$.

[0550] 步骤2:向6-(1-苄基-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(1.0g,2.1mmol)在THF和H_2O(8mL/2mL)的混合物中的溶液添加LiOH(0.15g,6.4mmol)。将反应混合物在室温搅拌2小时,然后用水(30mL)稀释并用醚(50mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到6-(1-苄基-1H-吡唑-4-羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(960mg,94%),其为白色固体,其直接用于下一步。^{1}HNMR(400MHz,DMSO-d_6)δ8.36(d,J=15.3Hz,1H),7.82(d,J=16.7Hz,1H),7.40-7.23(m,5H),5.35(s,2H),4.03-3.55(m,9H),2.85(s,1H),1.37(d,J=2.9Hz,9H).

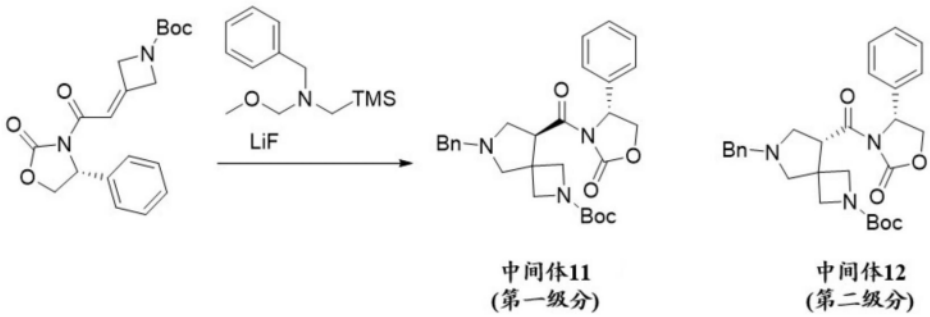
[0551] 步骤3:向6-(1-苄基-1H-吡唑-4-羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(200mg,0.46mmol)在无水DMF(5mL)中的溶液添加HATU(260mg,0.68mmol)和DIEA(234mg,1.81mmol),并将混合物在室温搅拌30分钟。添加(2S,3R)-2-氨基-3-甲氧基-N-甲基丁酰胺(80mg,0.55mmol)并将反应进一步搅拌4小时,然后用水(50mL)稀释,用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(118mg,46%),其为白色固体。LCMSm/z=569.3$[M+H]^+$.

[0552] 步骤4:向6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(130mg,0.23mmol)在二噁烷(2.0mL)中的溶液添加HCl在二噁烷(4M,2mL,8mmol)中的溶液。将该反应在室温搅拌1h,然后在真空下除去溶剂,得到6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(中间体10)(120mg),其为白色固体。

[0553] 中间体11:(S)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯和中间体12:(R)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯



[0554]



中间体11
(第一级分)

中间体12
(第二级分)

[0555] 步骤1:在-78℃在N_2气氛下向(R)-4-苯基噁唑烷-2-酮(10g,61mmol)在无水THF(100mL)中的溶液逐滴添加n-BuLi(2.5M于己烷中,27mL,67mmol)。将反应混合物在-78℃搅拌0.5小时,然后添加2-溴乙酰溴(5.6mL,64mmol)。将反应温热至室温并再搅拌2小时。将混合物用EtOAc(100mL)稀释,用饱和NH_4Cl(100mL)淬灭,用EtOAc(100mL×2)萃取,经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=10:1-3:1),得到(R)-3-(2-溴乙酰基)-4-苯基噁唑烷-2-酮(9g,52%),其为黄色油状物。^1H NMR(400MHz,DMSO-d6)δ7.42-7.37(m,2H),7.36-7.30(m,3H),5.52-5.46(m,1H),4.83-4.75(m,2H),4.56-4.50(m,1H),4.24-4.18(m,1H).

[0556] 步骤2:将(R)-3-(2-溴乙酰基)-4-苯基噁唑烷-2-酮(10g,35mmol)在亚磷酸三乙酯(29g,175mmol)中的混合物在50℃加热18h。在70℃在真空下将过量的亚磷酸三乙酯除去,得到(R)-(2-氧代-2-(2-氧代-4-苯基噁唑烷-3-基)乙基)膦酸二乙酯(12g粗品,99%),其为黄色油状物。LCMSm/z=342.1$[M+H]^+$;^1H NMR(400MHz,$CDCl_3$)δ7.41-7.29(m,5H),5.55-5.48(m,1H),4.78-4.70(m,1H),4.20-4.14(m,1H),4.03-3.96(m,5H),3.60-3.48(m,1H),1.27-1.15(m,8H).

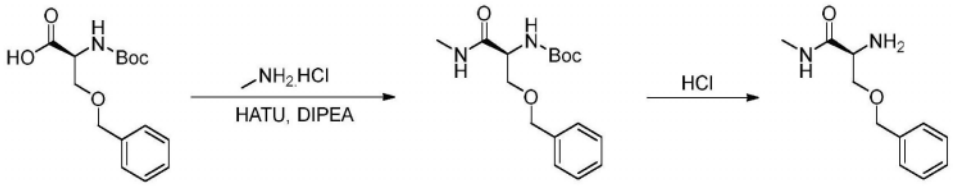
[0557] 步骤3:在0℃在N_2气氛下向(R)-(2-氧代-2-(2-氧代-4-苯基噁唑烷-3-基)乙基)膦酸二乙酯(10g,29mmol)在无水THF(100mL)中的溶液逐滴添加LiHMDS(1.0M于THF中,29mL,29mmol)。将反应混合物在0℃搅拌30分钟,然后添加3-氧代氮杂环丁烷-1-甲酸叔丁酯(21.68g,127mmol)。将该反应物温热至室温并搅拌1h。将该反应用EtOAc(200mL)稀释,并

用饱和NH_4Cl(100mL)洗涤有机层,经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=10:1),得到(R)-3-(2-氧代-2-(2-氧代-4-苯基噁唑烷-3-基)亚乙基)氮杂环丁烷-1-甲酸叔丁酯(10g,95%),其为黄色固体。LCMSm/z=492.0[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.41-7.36(m,2H),7.34-7.28(m,3H),7.20-7.15(m,1H),5.53-5.46(m,1H),4.79-4.73(m,1H),4.61(s,4H),4.21-4.14(m,1H),1.37(s,9H).

[0558] 步骤4:将(R)-3-(2-氧代-2-(2-氧代-4-苯基噁唑烷-3-基)亚乙基)氮杂环丁烷-1-甲酸叔丁酯(10g,27.90mmol)、N-苄基-1-甲氧基-N-((三甲基甲硅烷基)甲基)甲胺(8.61g,36.27mmol)和LiF(2.17g,83.71mmol)在乙腈(100mL)中的混合物在80℃加热16h。冷却至室温后,将混合物用水(100mL)稀释并用EtOAc(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=6:1),得到(S)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体11)(8g,58%)作为第一洗脱异构体,其为黄色固体。LCMSm/z=492[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.41-7.22(m,10H),5.49-5.43(m,1H),4.75-4.69(m,1H),4.23-4.11(m,2H),3.93-3.85(m,1H),3.79(s,1H),3.65-3.58(m,2H),3.56-3.51(m,2H),3.24-3.15(m,1H),2.94-2.87(m,1H),2.57-2.52(m,1H),2.35-2.27(m,1H),1.36(s,9H)。进一步洗脱得到了(R)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体12)(4g,29%)。LCMSm/z=492[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.37-7.24(m,10H),5.47-5.41(m,1H),4.76-4.69(m,1H),4.35-4.28(m,1H),4.21-4.14(m,1H),4.00-3.92(m,1H),3.66-3.60(m,1H),3.59-3.55(m,2H),3.36(s,2H),3.19-3.15(m,1H),3.06-2.98(m,1H),2.94-2.88(m,1H),2.55(s,1H),1.36(s,9H).

[0559] 另外的砌块化合物:

[0560] (S)-2-氨基-3-(苄氧基)-N-甲基丙酰胺

[0561] 

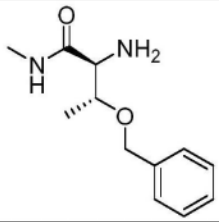
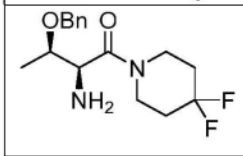
[0562] 步骤1:向O-苄基-N-(叔丁氧羰基)-L-丝氨酸(1g,3.38mmol)在DMF(10mL)中的溶液添加HATU(1.93g,5.07mmol),并将混合物在室温搅拌30分钟。添加甲胺盐酸盐(274mg,4.06mmol)和DIPEA(1.74g,13.52mmol)并将该反应再搅拌3h,然后用水(60mL)稀释并用DCM(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH=30/1),得到(S)-(3-(苄氧基)-1-(甲基氨基)-1-氧代丙-2-基)氨基甲酸叔丁酯(0.9g,87%),其为白色固体。LCMSm/z=309.10[M+H]$^+$;^{1}H NMR(400MHz,$CDCl_3$)δ7.39-7.25(m,5H),4.61-4.46(m,2H),3.91(dd,J=9.3,3.9Hz,1H),3.61-3.52(m,1H),2.83-2.79(m,4H),1.44(s,9H).

[0563] 步骤2:向(S)-(3-(苄氧基)-1-(甲基氨基)-1-氧代丙-2-基)氨基甲酸叔丁酯(0.9g,2.92mmol)在1,4-二噁烷(5mL)中的溶液添加HCl在二噁烷中的溶液(4M HCl/1,4二噁烷的溶液(9mL))。将反应混合物在室温搅拌3小时,然后在真空下除去溶剂,得到粗品(S)-2-氨基-3-(苄氧基)-N-甲基丙酰胺(607mg,100%),其无需纯化即可使用。LCMSm/z=

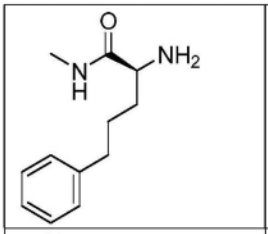
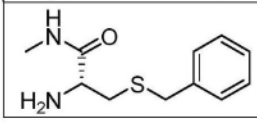
209.00[M+H]$^+$.

[0564] 根据(S)-2-氨基-3-(苄氧基)-N-甲基丙酰胺的步骤概述,使用合适的市售试剂合成以下化合物。

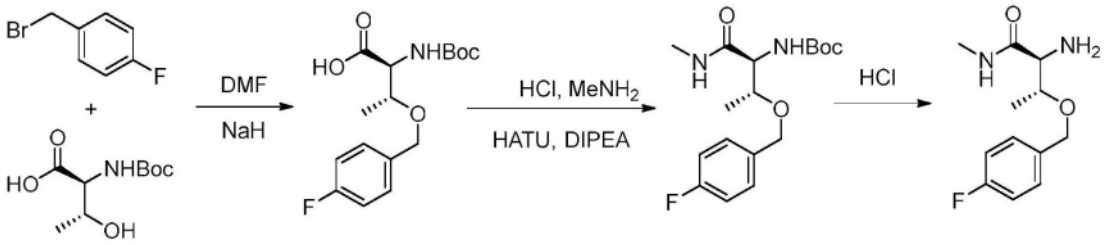
[0565]

化合物	表征
	LCMS*m/z* = 223.1 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (q, *J* = 4.6 Hz, 1H), 8.31 (d, *J* = 5.4 Hz, 2H), 7.37 – 7.26 (m, 5H), 4.59 – 4.47 (m, 2H), 3.90 – 3.77 (m, 2H), 2.65 (d, *J* = 4.6 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H).
	^{1}HNMR (400 MHz, CD_3OD): δ 7.31-7.37 (m, 5H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.49-4.53 (m, 2H), 3.90-3.92 (m, 1H), 3.83-3.86 (m, 1H), 3.60-3.63 (m, 1H), 3.46-3.52 (m, 1H), 3.39-3.42 (m, 1H), 1.81-1.95 (m, 4H), 1.36 (d, *J* = 6.4 Hz, 3H).

[0566]

	207.00 [M+H]$^+$
	225.1 [M+H]$^+$

[0567] (2S,3R)-2-氨基-3-((4-氟苄基)氧基)-N-甲基丁酰胺:

[0568] 

[0569] 步骤1:在0℃向(叔丁氧羰基)-L-苏氨酸(1g,4.60mmol)在无水DMF(5mL)中的溶液添加NaH(644mg,16.1mmol)。将混合物在0℃搅拌30分钟。添加1-(溴甲基)-4-氟苯(869mg,4.60mmol)并将所得反应混合物搅拌过夜,然后用水(30mL)稀释并用EtOAc(50mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过反相柱(65%乙腈/水)纯化,得到N-(叔丁氧羰基)-O-(4-氟苄基)-L-苏氨酸(400mg,27%),其为黄色油状物。LCMSm/z=350[M+Na]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.40-7.29(m,2H),7.21-7.10(m,2H),6.53(d,J=9.2Hz,1H),4.52(d,J=11.6Hz,1H),4.37(d,J=11.8Hz,1H),4.12-3.90(m,2H),1.39(s,9H),1.14(d,J=6.2Hz,3H).

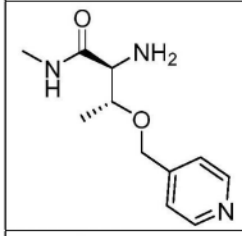
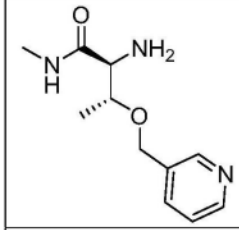
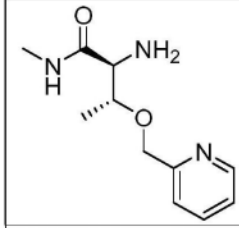
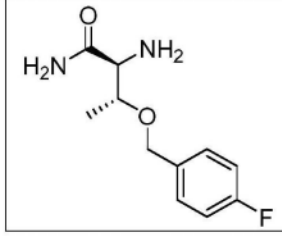
[0570] 步骤2:向N-(叔丁氧羰基)-O-(4-氟苄基)-L-苏氨酸(400mg,1.20mmol)在DMF(3mL)中的溶液添加HATU(684mg,1.80mmol),并将该混合物在室温搅拌30分钟。添加甲胺盐酸盐(97mg,1.40mmol)和DIPEA(619mg,4.80mmol)并将反应再搅拌6小时,然后用水(30mL)稀释并用DCM(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将

混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH＝50/1),得到(2S,3R)-3-((4-氟苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(320mg,77%),其为黄色固体。LCMSm/z＝341.2[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.82(d,J＝4.8Hz,1H),7.37-7.27(m,2H),7.19-7.09(m,2H),6.40(d,J＝9.2Hz,1H),4.49(d,J＝11.8Hz,1H),4.37(d,J＝11.8Hz,1H),4.02-3.95(m,1H),3.86-3.78(m,1H),2.59(d,J＝4.4Hz,3H),1.38(s,9H),1.07(d,J＝6.2Hz,3H).

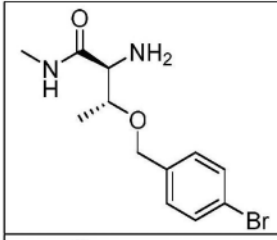
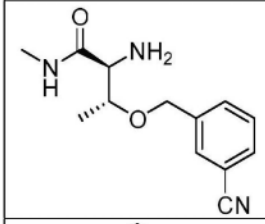
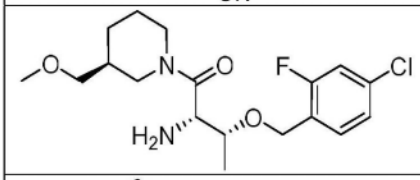
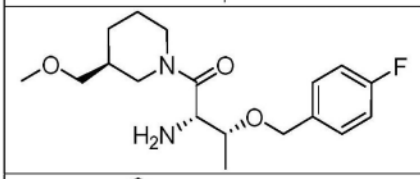
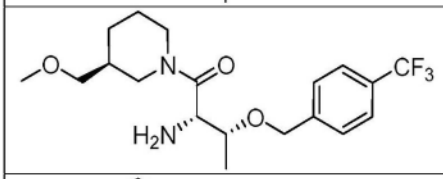
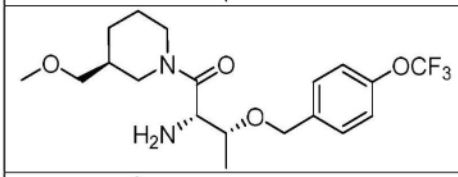
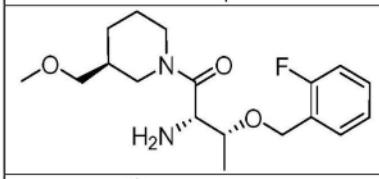
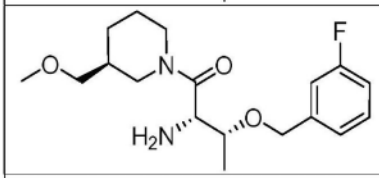
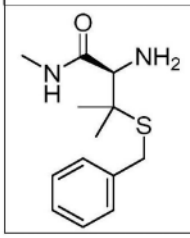
[0571] 步骤3:向(2S,3R)-3-((4-氟苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(200mg,0.60mmol)在1,4-二噁烷(2mL)中的溶液添加HCl在二噁烷中的溶液(4M HCl/1,4二噁烷溶液,3mL)。将反应混合物在室温搅拌2小时,然后在真空下除去溶剂,得到(2S,3R)-2-氨基-3-((4-氟苄基)氧基)-N-甲基丁酰胺(180mg,100%)。LCMSm/z＝241.00[M+H]$^+$。

[0572] 根据(2S,3R)-2-氨基-3-((4-氟苄基)氧基)-N-甲基丁酰胺的一般步骤概述,使用合适的市售试剂合成以下化合物。

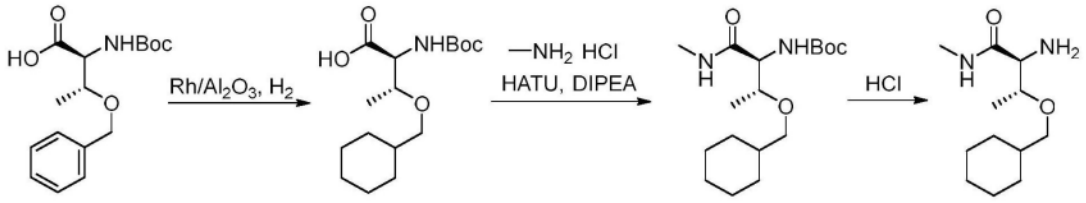
[0573]

化合物	表征
	224.1 [M+H]$^+$
	224.1 [M+H]$^+$
	224.1 [M+H]$^+$
	227.1 [M+H]$^+$

[0574]

	301.1 $[M+H]^+$
	248.0 $[M+H]^+$
	LCMS 未记录
	LCMS 未记录
	LCMS 未记录
	LCMS 未记录
	LCMS 未记录
	LCMS 未记录
	253.1 $[M+H]^+$

[0575] (2S,3R)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺：

[0576] 

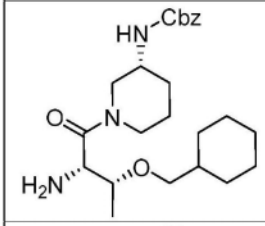
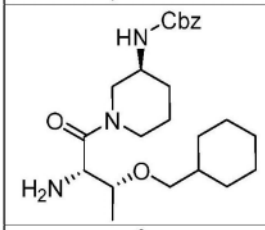
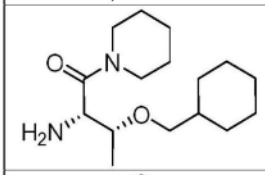
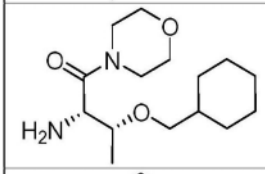
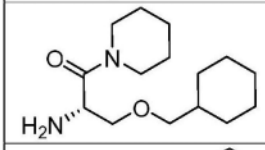
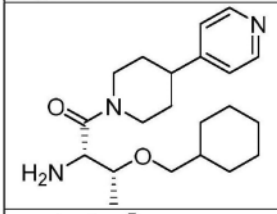
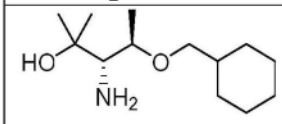
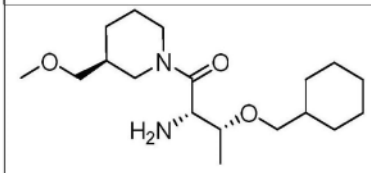
[0577] 步骤1:向O-苄基-N-(叔丁氧基羰基)-L-苏氨酸(5g,16.16mmol)在i-PrOH(30mL)中的溶液中添加在Al_2O_3上的铑(5%,1.25g)并将反应在H_2气氛下搅拌48h。通过硅藻土过滤除去催化剂并将滤液浓缩,得到N-(叔丁氧基羰基)-O-(环己基甲基)-L-苏氨酸(5g,98%),其为无色油状物。^{1}H NMR(400MHz,DMSO-d_6)δ6.20(d,J=9.2Hz,1H),3.99(dd,J=9.2,3.4Hz,1H),3.83-3.79(m,1H),3.25(dd,J=9.0,6.2Hz,1H),3.06(dd,J=9.0,6.6Hz,1H),1.69-1.62(m,3H),1.39(s,9H),1.20-1.03(m,10H),0.92-0.77(m,2H).

[0578] 步骤2:向N-(叔丁氧羰基)-O-(环己基甲基)-L-苏氨酸(5.4g,17.12mmol)、甲胺盐酸盐(1.39g,20.54mmol)和HATU(9.76g,25.68mmol)在DMF(25mL)中的溶液添加DIPEA(8.85g,68.48mmol)。将反应混合物在室温搅拌5h,然后用水(250mL)稀释。通过过滤收集形成的沉淀物,并用冷水(30mL×2)洗涤,得到(2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(3.8g,68%),其为白色固体。LCMSm/z=329.2[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.74(d,J=4.8Hz,1H),6.22(d,J=9.2Hz,1H),3.89(dd,J=9.2,4.4Hz,1H),3.64(dt,J=10.4,5.2Hz,1H),3.22(dd,J=9.2,6.4Hz,1H),3.06(dd,J=9.2,6.4Hz,1H),2.58(d,J=4.6Hz,3H),1.69-1.60(m,5H),1.38(s,9H),1.26-1.08(m,4H),1.00(d,J=6.2Hz,3H),0.90-0.79(m,2H).

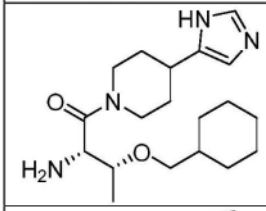
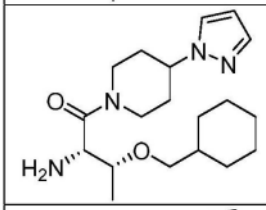
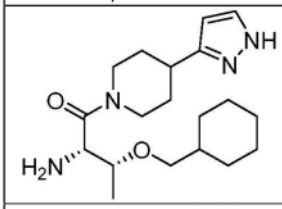
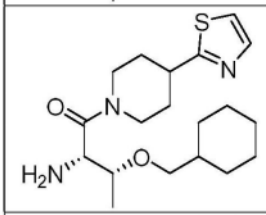
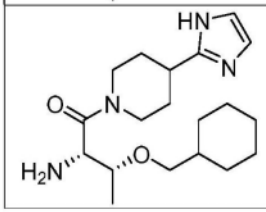
[0579] 步骤3:向(2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(3.8g,11.57mmol)在1,4-二噁烷(50mL)中的溶液添加HCl在1,4-二噁烷中的溶液(4M,15mL)。将反应混合物在室温搅拌3小时,在真空下除去溶剂,得到粗品(2S,3R)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺(3g,98%),其为白色固体。^{1}H NMR(400MHz,$CDCl_3$)δ8.28-8.10(m,4H),4.26(s,1H),4.02(s,1H),3.32(ddd,J=24.0,9.0,6.4Hz,2H),2.94(s,2H),2.82(d,J=3.4Hz,3H),1.73-1.62(m,6H),1.58-1.50(m,1H),1.32-1.10(m,7H),0.96-0.84(m,2H).

[0580] 根据(2S,3R)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺的步骤概述,使用合适的市售试剂合成以下化合物。

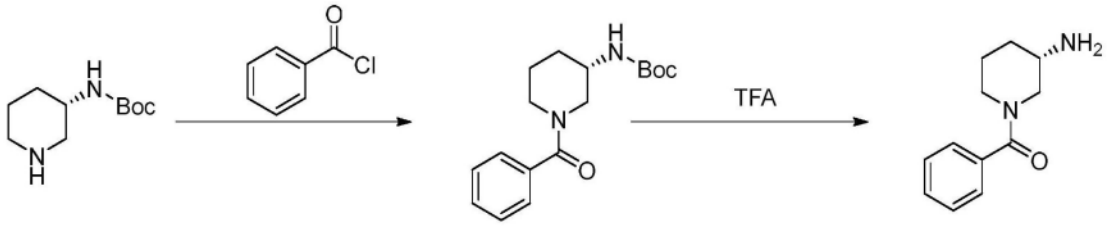
[0581]

化合物	表征
	432.2 $[M+H]^+$
	432.2 $[M+H]^+$
	283.2 $[M+H]^+$
	285.2 $[M+H]^+$
	269.2 $[M+H]^+$
	360.30 $[M+H]^+$
	230.2 $[M+H]^+$ *步骤 2：在 0 °C 用甲基溴化镁在四氢呋喃中代替甲胺盐酸盐、HATU、DMF 和 DIPEA
	327.3 $[M+H]^+$; ^1H NMR (400 MHz, 氯仿-d) δ 8.27 – 8.18 (m, 2H), 7.57 – 7.50 (m, 2H), 5.59 – 5.43 (m, 1H), 5.33 – 5.18 (m, 3H), 4.37 – 4.24 (m, 1H), 4.19 – 3.99 (m, 1H), 3.86 – 3.69 (m, 4H), 3.68 – 3.61 (m, 1H), 3.34 – 3.19 (m, 1H), 2.19 – 2.06 (m, 4H), 2.02 – 1.83 (m, 2H), 1.79 – 1.54 (m, 7H), 1.39 – 1.31 (m,

[0582]

	6H), 1.08 (d, J = 6.3 Hz, 1H), 0.98 (d, J = 6.1 Hz, 1H).
	349.2 $[M+H]^+$
	349.2 $[M+H]^+$
	349.2 $[M+H]^+$
	366.2 $[M+H]^+$
	349.2 $[M+H]^+$

[0583] (S)-(3-氨基哌啶-1-基)(苯基)甲酮:

[0584] 

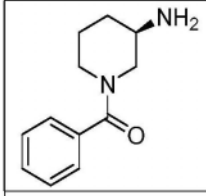
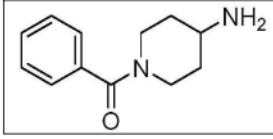
[0585] 步骤1:在0℃向(S)-哌啶-3-基氨基甲酸叔丁酯(1g,4.99mmol)在DCM(10mL)中的溶液添加TEA(1.5g,14.97mmol)和苯甲酰氯(1.05g,7.49mmol)。将所得混合物在室温搅拌30分钟,然后用水(50mL)稀释并用DCM(100mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到(S)-(1-苯甲酰基哌啶-3-基)氨基甲酸叔丁酯(1.5g,98%),其为黄色油状物,其直接用于下一步。LCMSm/z=305.5$[M+H]^+$.

[0586] 步骤2:向(S)-(1-苯甲酰基哌啶-3-基)氨基甲酸叔丁酯(1.5g,4.90mmol)在DCM(10mL)中的溶液添加TFA(3mL)。将反应混合物在室温搅拌1小时,然后在真空下除去溶剂,得到粗品(S)-(3-氨基哌啶-1-基)(苯基)甲酮(1.5g,100%)。LCMSm/z=205.2$[M+H]^+$.

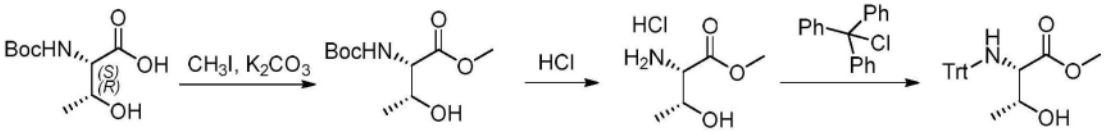
[0587] 根据(S)-(3-氨基哌啶-1-基)(苯基)甲酮的合成中的步骤概述,使用合适的市售

试剂合成以下化合物。

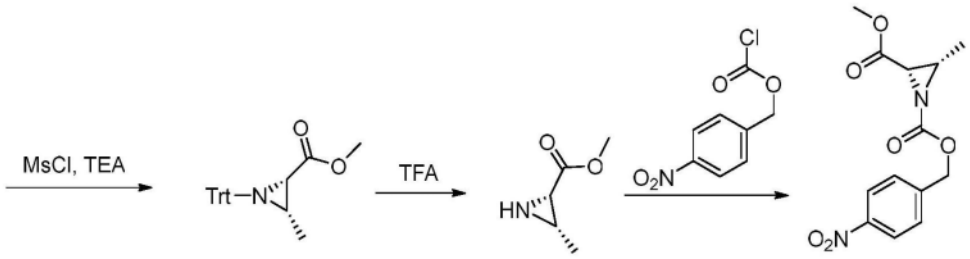
[0588]

化合物	表征
	205.2 $[M+H]^+$
	204.1$[M+H]^+$

[0589] (2S,3S)-3-甲基氮丙啶-1,2-二甲酸2-甲基1-(4-硝基苄基)酯:



[0590]



[0591] 步骤1:向(叔丁氧羰基)-L-苏氨酸(25.0g,0.11mol)在DMF(250mL)中的溶液添加K_2CO_3(23.0g,0.16mol)和CH_3I(19.4g,0.13mol)。将反应混合物在室温搅拌4小时,然后用水(300mL)稀释并用EtOAc(500mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=100:1-10:1),得到(叔丁氧羰基)-L-苏氨酸甲酯(20g,80%),其为黄色油状物。LCMSm/z=256.2$[M+Na]^+$;^1H NMR(400MHz,DMSO-d_6)δ6.53(d,J=8.8Hz,1H),4.78(d,J=7.2Hz,1H),4.01-3.96(m,1H),3.62(s,3H),1.38(s,9H),1.07(d,J=6.2Hz,3H).

[0592] 步骤2:将(叔丁氧羰基)-L-苏氨酸甲酯(20g,85.7mmol)在HCl在1,4-二噁烷(4M,250mL)中的溶液中的混合物在室温搅拌6h。在真空下除去溶剂,得到粗品L-苏氨酸甲酯盐酸盐(14.5g,100%),其直接用于下一步。LCMSm/z=134.2$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ8.52(s,3H),4.14-4.07(m,1H),3.90(d,J=3.8Hz,1H),3.73(s,3H),3.55(s,1H),1.20(d,J=6.6Hz,3H).

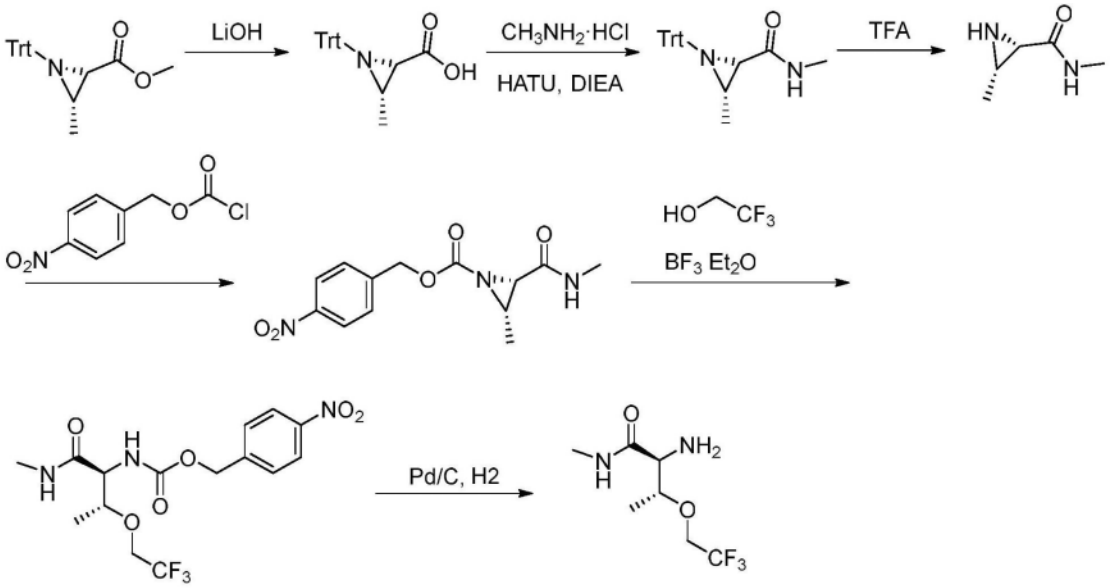
[0593] 步骤3:向L-苏氨酸甲酯盐酸盐(14.5g,85.5mmol)在DCM(300mL)中的溶液添加TEA(45g,0.44mol)和Trt-Cl(28.6g,102.6mmol)。将反应混合物在室温搅拌过夜,然后用水(200mL)稀释并用DCM(300mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=100:1-10:1),得到三苯甲基-L-苏氨酸甲酯(24g,75%),其为白色固体。^1H NMR(400MHz,DMSO-d_6)δ7.41(d,J=7.4Hz,7H),7.28(d,J=7.4Hz,7H),7.23-7.16(m,3H),5.05(d,J=4.8Hz,1H),3.98-3.87(m,1H),3.23-3.16(m,4H),3.02(s,3H),2.68(d,J=10.0Hz,1H),1.08(d,J=6.4Hz,3H).

[0594] 步骤4:向三苯甲基-L-苏氨酸甲酯(12g,32mmol)在THF(130mL)中的溶液添加TEA

(6.5g,64mmol)和MsCl(5.4g,38.4mmol)。将反应混合物在80℃加热30小时,然后冷却至室温,用水(100mL)稀释,并用EtOAc(250mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=100:1-20:1),得到(2S,3S)-3-甲基-1-三苯甲基氮丙啶-2-甲酸甲酯(8g,70%),其为白色固体。^1H NMR(400MHz,DMSO-d_6)δ7.45-7.38(m,6H),7.36-7.27(m,7H),7.29-7.21(m,4H),3.65(s,3H),1.71(d,J=6.6Hz,1H),1.61-1.50(m,1H),1.27(d,J=5.4Hz,3H).

[0595] 步骤5和6:向(2S,3S)-3-甲基-1-三苯甲基氮丙啶-2-甲酸甲酯(2g,5.6mmol)在DCM(20mL)和MeOH(1mL)的混合物中的溶液添加TFA(10mL)。将混合物在室温搅拌30分钟,然后用水(20mL)稀释并用Et_2O(30mL×2)萃取。使用固体$NaHCO_3$(LCMS:m/z=116.15[M+H]$^+$)将水层调节至pH~9。将水层与EtOAc(20mL)分配,并添加氯甲酸4-硝基苄酯(1.3g,5.6mmol)。将该混合物在室温搅拌过夜,然后用EtOAc(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=100:1-20:1),得到(2S,3S)-3-甲基氮丙啶-1,2-二甲酸2-甲基1-(4-硝基苄基)酯(500mg,31%),其为白色固体。LCMS:m/z=295.0[M+H]$^+$;^1H NMR(400MHz,DMSO-d_6)δ8.28-8.21(m,2H),7.68-7.61(m,2H),5.24(s,2H),3.70(s,3H),3.42(d,J=6.8Hz,1H),3.08-2.97(m,1H),1.21(d,J=5.6Hz,3H).

[0596] (2S,3R)-2-氨基-N-甲基-3-(2,2,2-三氟乙氧基)丁酰胺

[0597] 

[0598] 步骤1:向(2S,3S)-3-甲基-1-三苯甲基氮丙啶-2-甲酸甲酯(5g,13.4mmol)在THF(18mL)、MeOH(6mL)和水(6mL)的混合物中的溶液添加氢氧化锂一水合物(2g,46.9mmol)。将该反应在室温搅拌1h,用水(30mL)稀释,并用EtOAc(20mL)萃取。收集水层并用1M HCl酸化至pH~2,然后用EtOAc(20mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到(2S,3S)-3-甲基-1-三苯甲基氮丙啶-2-甲酸(2.9g,60%),其为黄色固体。LCMSm/z=342.05[M+H]$^+$.

[0599] 步骤2:向(2S,3S)-3-甲基-1-三苯甲基氮丙啶-2-甲酸(2.9g,8.4mmol)在DCM(16mL)中的溶液添加HATU(4.8g,33.8mmol),并将混合物在室温搅拌30分钟。然后添加甲胺盐酸盐(0.86g,12.7mmol)和DIPEA(4.36g,33.8mmol)并将反应混合物再搅拌2小时。然后添

加水(20mL)并将混合物用DCM(20mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1-2:1),得到(2S,3S)-N,3-二甲基-1-三苯甲基氮丙啶-2-甲酰胺(1.1g,36%),其为白色固体。^{1}H NMR(400MHz,DMSO-d_6)δ7.90(q,J=4.6Hz,1H),7.50-7.40(m,6H),7.35-7.21(m,9H),2.66(d,J=4.6Hz,3H),1.64(d,J=6.6Hz,1H),1.39-1.33(m,1H),1.23(d,J=5.6Hz,3H).

[0600] 步骤3和4:向(2S,3S)-N,3-二甲基-1-三苯甲基氮丙啶-2-甲酰胺(1.1g,3.1mmol)在DCM(3mL)和MeOH(3mL)的混合物中的溶液添加TFA(2mL)。将混合物在室温搅拌30分钟,然后用水(10mL)稀释并用Et_2O(10mL×2)萃取。用固体$NaHCO_3$将水层的pH调节至~9,并与EtOAc(10mL)分配。添加氯甲酸4-硝基苄酯(82mg,0.38mmol)并将混合物在室温搅拌过夜,然后用EtOAc(10mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=2:1-1:1),得到(2S,3S)-2-甲基-3-(甲基氨基甲酰基)氮丙啶-1-甲酸4-硝基苄酯(0.5g,45%),其为白色固体。LCMS:m/z=294.15[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.27-8.23(m,2H),7.92(d,J=4.8Hz,1H),7.68-7.64(m,2H),5.24(s,2H),3.17(d,J=6.8Hz,1H),2.94-2.88(m,1H),2.60(d,J=4.6Hz,3H),1.16(d,J=5.8Hz,3H).

[0601] 步骤5:在氮气气氛下向(2S,3S)-2-甲基-3-(甲基氨基甲酰基)氮丙啶-1-甲酸4-硝基苄酯(200mg,0.68mmol)和2,2,2-三氟乙-1-醇(200mg、2mmol)的混合物添加三氟化硼合乙醚(190mg,1.4mmol)。将反应混合物在室温搅拌4小时。将混合物通过反相柱纯化(42%ACN/水),得到((2S,3R)-1-(甲基氨基)-1-氧代-3-(2,2,2-三氟乙氧基)丁-2-基)氨基甲酸4-硝基苄酯(85mg,32%),其为黄色固体。LCMSm/z=394.15[M+H]$^+$.

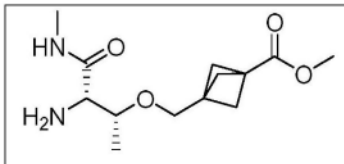
[0602] 步骤6:向((2S,3R)-1-(甲基氨基)-1-氧代-3-(2,2,2-三氟乙氧基)丁-2-基)氨基甲酸4-硝基苄酯(85mg,0.22mmol)在MeOH(10mL)中的溶液添加10%Pd/C(34mg)。将反应混合物在H_2气氛下搅拌3小时。通过硅藻土过滤除去催化剂并将滤液浓缩,得到(2S,3R)-2-氨基-N-甲基-3-(2,2,2三氟乙氧基)丁酰胺(42mg,90%),无需进一步纯化即可使用。LCMSm/z=215.1[M+H]$^+$.

[0603] 根据(2S,3R)-2-氨基-N-甲基-3-(2,2,2-三氟乙氧基)丁酰胺合成中的步骤概述,使用合适的市售试剂合成以下化合物。

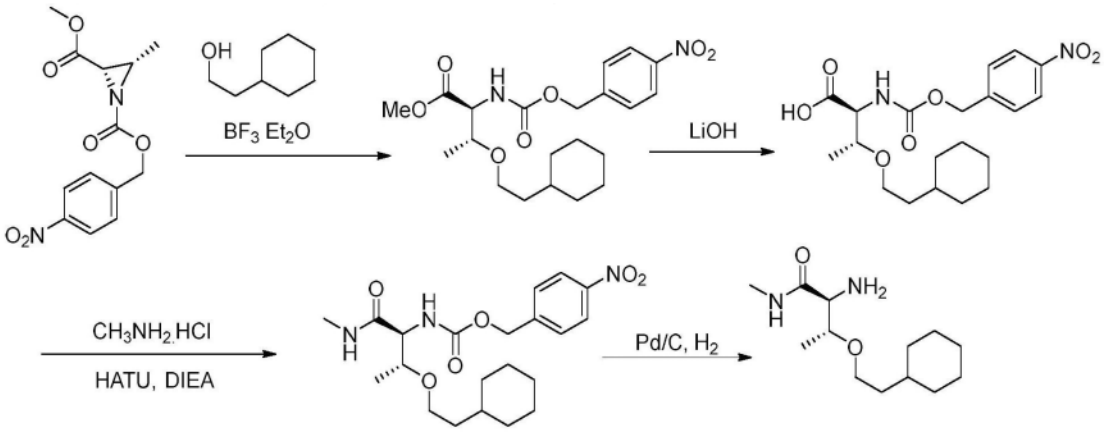
[0604]

化合物	LCMS

[0605]

	271.10 [M+H]$^+$

[0606] (2S,3R)-2-氨基-3-(2-环己基乙氧基)-N-甲基丁酰胺

[0607] 

[0608] 步骤1:在氮气气氛下向(2S,3S)-3-甲基氮丙啶-1,2-二甲酸2-甲基1-(4-硝基苄基)酯(500mg,1.70mmol)在甲苯(2mL)中的溶液添加2-环己基乙烷-1-醇(435mg,3.40mol)和三氟化硼合乙醚(0.2mL)。将反应混合物加热回流2小时,然后用水(30mL)稀释,用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到O-(2-环己基乙基)-N-(((4-硝基苄基)氧基)羰基)-L-苏氨酸甲酯(160mg,22%),其为黄色固体。LCMSm/z=423.15[M+H]$^+$.

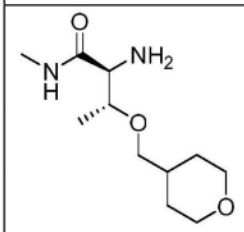
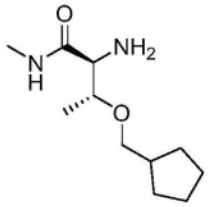
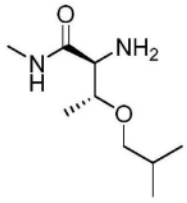
[0609] 步骤2:向O-(2-环己基乙基)-N-(((4-硝基苄基)氧基)羰基)-L-苏氨酸甲酯(150mg,0.36mmol)在THF(2mL)、MeOH(0.5mL)和水(0.5mL)的混合物中的溶液添加氢氧化锂一水合物(43mg,1.07mmol)。将反应在室温搅拌1h,然后用水(30mL)稀释并用EtOAc(60mL)萃取。收集水层并用1M HCl酸化至pH~2,然后用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到O-(2-环己基乙基)-N-(((4-硝基苄基)氧基)羰基)-L-苏氨酸(110mg,76%),其为白色固体。LCMSm/z=409.15[M+H]$^+$.

[0610] 步骤3:向O-(2-环己基乙基)-N-(((4-硝基苄基)氧基)羰基)-L-苏氨酸(110mg,0.27mmol)在DCM(2mL)中的溶液添加HATU(153mg,0.40mmol),并将混合物在室温搅拌30分钟。添加甲胺盐酸盐(27mg,0.40mmol)和DIPEA(138mg,1.08mmol)并将该反应再搅拌2小时。将混合物用水(20mL)稀释并用DCM(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过制备型TLC纯化(洗脱液:DCM/MeOH=30/1),得到((2S,3R)-3-(2-环己基乙氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸4-硝基苄酯(50mg,44%),其为白色固体。LCMSm/z=422.20[M+H]$^+$;^{1}HNMR(400MHz,氯仿-d)δ8.26-8.19(m,2H),7.55-7.48(m,2H),5.25-5.16(m,2H),4.27-4.16(m,1H),4.00-3.87(m,1H),2.86-2.83(m,3H),1.49-1.39(m,4H),1.34-1.30(m,3H),1.20-1.13(m,4H),1.10-1.04(m,3H),0.96-0.79(m,6H).

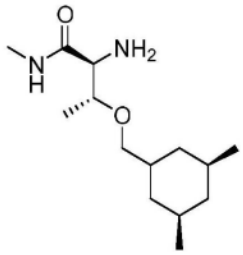
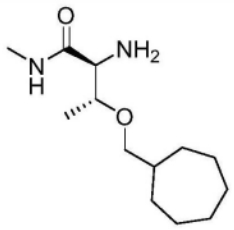
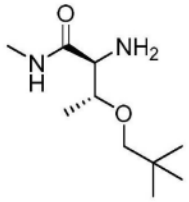
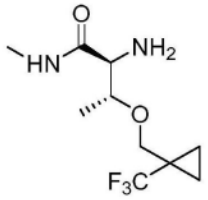
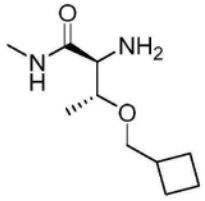
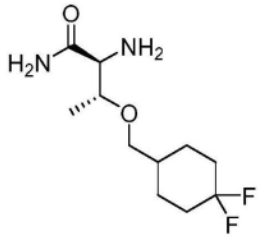
[0611] 步骤4:向((2S,3R)-3-(2-环己基乙氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸4-硝基苄酯(50mg,0.12mmol)在MeOH(2mL)中的溶液添加10%Pd/C(10mg)。将反应混合物在H_2气氛下搅拌3h。通过硅藻土过滤除去催化剂,并将滤液浓缩,得到(2S,3R)-2-氨基-3-(2-环己基乙氧基)-N-甲基丁酰胺(25mg,90%),其在无需纯化即可使用。LCMSm/z=243.15[M+H]$^+$.

[0612] 根据(2S,3R)-2-氨基-3-(2-环己基乙氧基)-N-甲基丁酰胺报道的一般步骤,使用合适的市售试剂合成以下化合物。

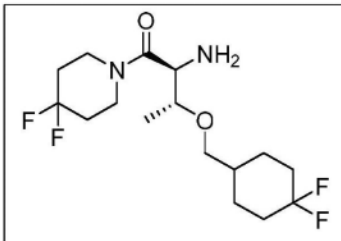
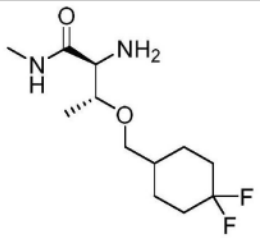
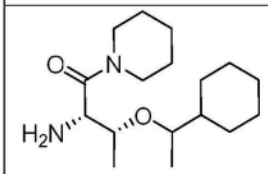
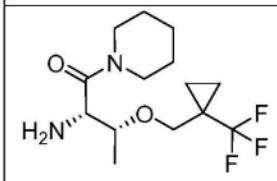
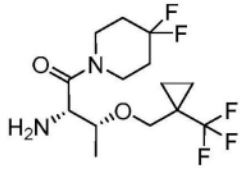
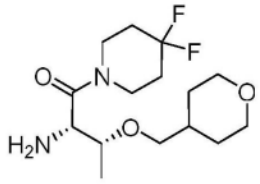
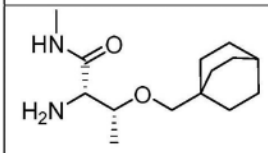
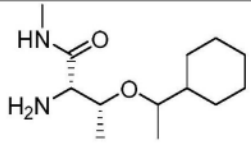
[0613]

化合物	表征
	231.1 $[M+H]^+$
	215.2 $[M+H]^+$
	189.10 $[M+H]^+$

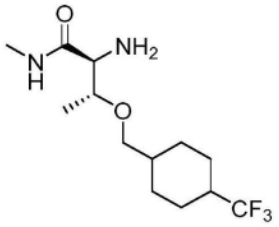
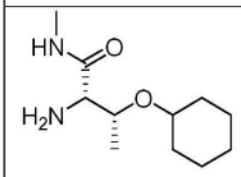
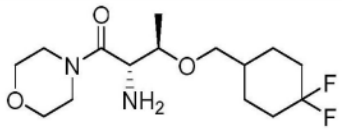
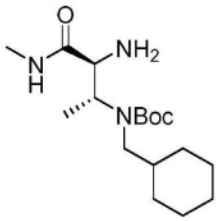
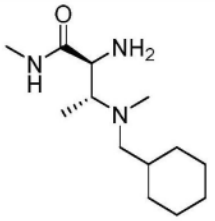
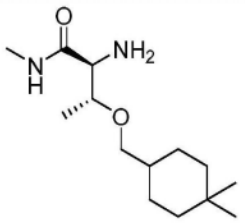
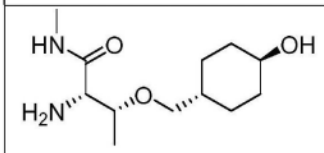
[0614]

	257.2 $[M+H]^+$
	243.3 $[M+H]^+$
	203.1 $[M+H]^+$
	255.1 $[M+H]^+$
	201.1 $[M+H]^+$
	251.2 $[M+H]^+$

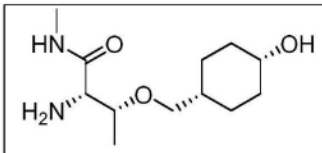
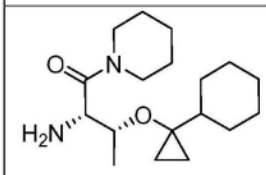
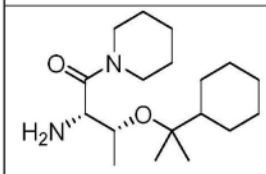
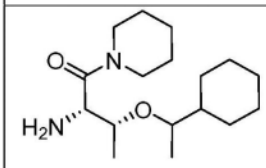
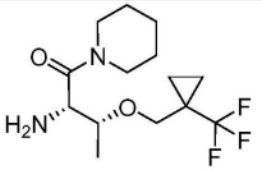
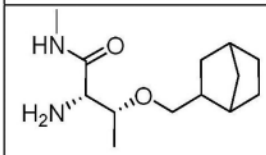
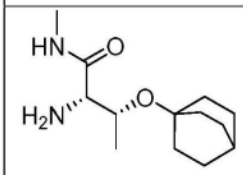
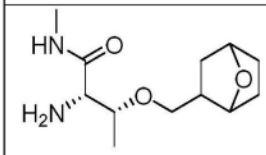
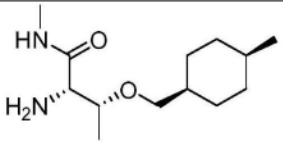
[0615]

	355.1 $[M+H]^+$
	265.2 $[M+H]^+$
	297.3 $[M+H]^+$
	309.1 $[M+H]^+$
	345.1 $[M+H]^+$
	321.2 $[M+H]^+$
	255.3 $[M+H]^+$
	243.3 $[M+H]^+$

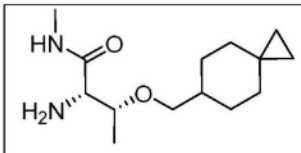
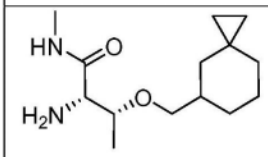
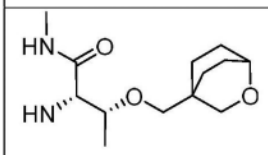
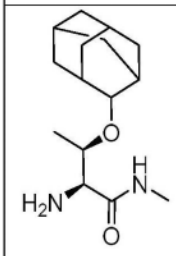
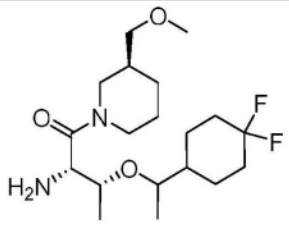
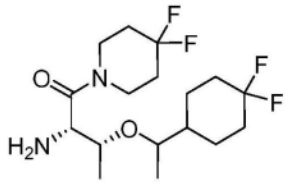
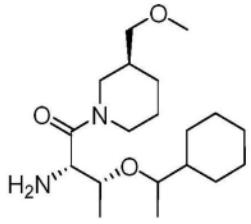
[0616]

	297.1[M+H]$^+$
	215.2 [M+H]$^+$
	LCMS 未记录// ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.61-3.73 (m, 9H), 3.43-3.52 (m, 2H), 3.20-3.24 (m, 1H), 2.07-2.14 (m, 2H), 1.78-1.84 (m, 2H), 1.66-1.76 (m, 2H), 1.25-1.36 (m, 3H), 1.11 (d, J = 6.4 Hz, 3H).
	328.2 [M+H]$^+$
	242.2 [M+H]$^+$
	m/z =257.1 [M+H]$^+$
	m/z = 245.2 [M+H]$^+$

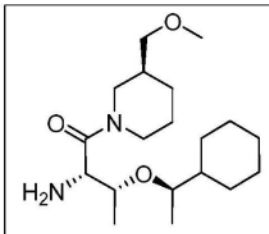
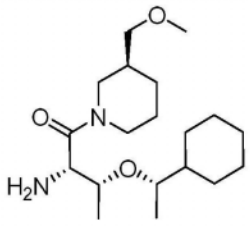
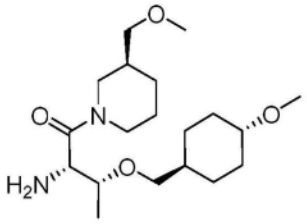
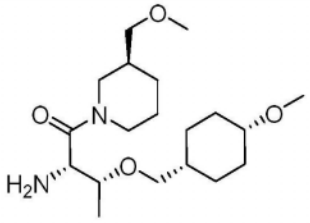
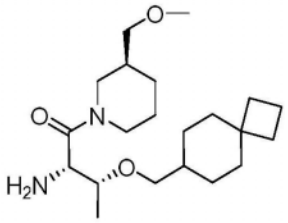
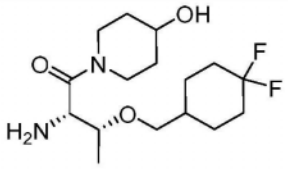
[0617]

	*m/z* = 245.2 $[M+H]^+$
	*m/z* = 309.2 $[M+H]^+$
	*m/z* = 311.3 $[M+H]^+$
	*m/z* = 297.3 $[M+H]^+$
	m/z = 309.1 $[M+H]^+$
	m/z =241.2 $[M+H]^+$
	m/z =241.3 $[M+H]^+$
	m/z =243.2 $[M+H]^+$
	m/z =243.3 $[M+H]^+$

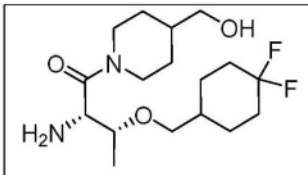
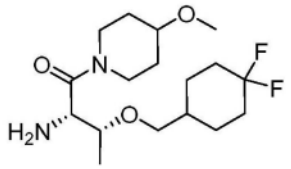
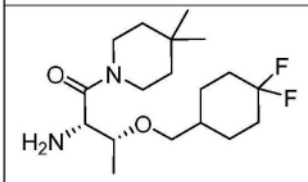
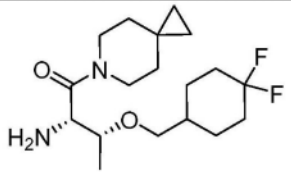
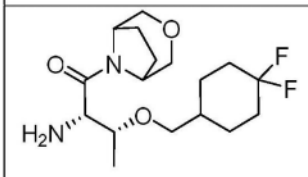
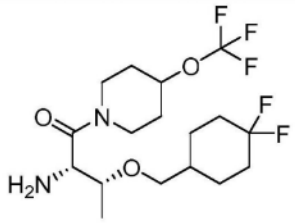
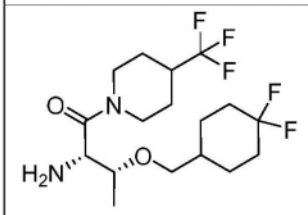
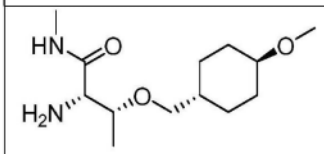
[0618]

	m/z = 255.2 [M+H]+
	m/z = 255.2 [M+H]+
	m/z = 257.3 [M+H]+
	m/z = 267.2 [M+H]+
	m/z = 377.2 [M+H]+
	m/z =369.1 [M+H]+
	m/z = 341.1 [M+H]+

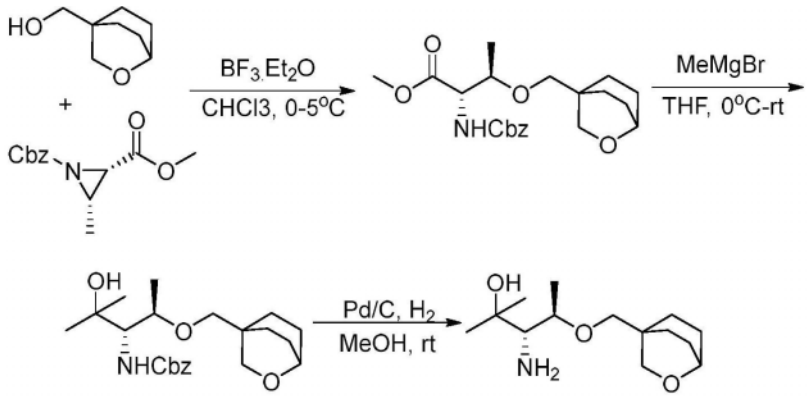
[0619]

	m/z = 341.2 $[M+H]^+$
	m/z = 341.2 $[M+H]^+$
	m/z =321.2 $[M+H]^+$
	m/z =357.4 $[M+H]^+$
	m/z = 357.4 $[M+H]^+$
	m/z = 367.4 $[M+H]^+$
	m/z = 335.2 $[M+H]^+$

[0620]

	m/z =349.2 $[M+H]^+$
	m/z = 349.2 $[M+H]^+$
	m/z =347.2 $[M+H]^+$
	m/z = 345.0 $[M+H]^+$
	m/z = 347.2 $[M+H]^+$
	*m/z* = 403.1 $[M+H]^+$
	m/z = 387.2 $[M+H]^+$
	m/z =259.2 $[M+H]^+$

[0621] (3S,4R)-4-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-3-氨基-2-甲基戊-2-醇

[0622] 

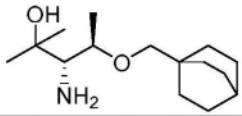
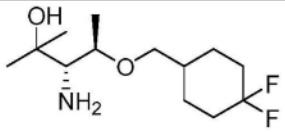
[0623] 步骤1:在0-5℃向2-氧杂双环[2.2.2]辛-4-基甲醇(0.500g,3.52mmol)和(2S,3S)-1-苄基-2-甲基3-甲基氮丙啶-1,2-二甲酸酯(0.876g,3.52mmol)在二氯甲烷(10mL)中的混合物添加三氟化硼合乙醚(100mg,0.70mmol)。将所得混合物在0℃搅拌1小时。在减压下将反应混合物浓缩以得到粗品残留物,其通过柱色谱法使用16%乙酸乙酯/己烷的梯度纯化,得到(2S,3R)-3-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-2-(((苄氧基)羰基)氨基)丁酸甲酯(0.376g,27%),其为无色油状物。MS:392.2[M+H]$^+$

[0624] 步骤2:在0-5℃向(2S,3R)-3-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-2-(((苄氧基)羰基)氨基)丁酸甲酯(0.376g,0.96mmol)在四氢呋喃(5mL)中的溶液添加甲基溴化镁(3M于醚中,1.6mL,4.81mmol)。将所得混合物在室温搅拌一小时。将反应混合物在0-5℃用水淬灭,并用乙酸乙酯(10mL x3)萃取。将合并的有机层用盐水(20mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过硅胶柱色谱法使用20%乙酸乙酯/己烷的梯度纯化,得到((3S,4R)-4-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-2-羟基-2-甲基戊-3-基)氨基甲酸苄酯(0.197g,14%),其为无色油状物。MS:392.1[M+H]$^+$

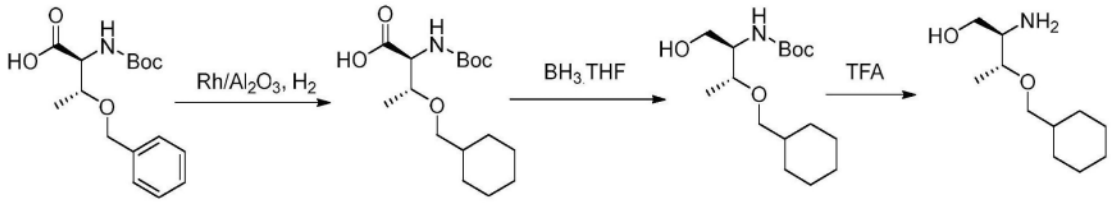
[0625] 步骤3:向((3S,4R)-4-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-2-羟基-2-甲基戊-3-基)氨基甲酸苄酯(0.197g,0.50mmol)在甲醇(10mL)中的溶液添加钯/碳(10%,0.060g)。将所得混合物在H_2气氛下在室温搅拌过夜。通过过滤除去钯/碳并用甲醇洗涤;将合并的有机溶液在减压下浓缩以得到粗品残留物,其通过硅胶柱色谱法使用10%甲醇/二氯甲烷的梯度纯化,得到(3S,4R)-4-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-3-氨基-2-甲基戊-2-醇(0.100g,77%),其为无色油状物。MS:258.1[M+H]$^+$

[0626] 根据(3S,4R)-4-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-3-氨基-2-甲基戊-2-醇报道的一般步骤,使用合适的市售试剂合成以下化合物。

[0627]

化合物	表征
	390.2 [M+H]$^+$
	LCMS 未记录// ^{1}HNMR (400 MHz, DMSO-d6): δ 12.40 (s, 1H), 8.25-8.26 (m, 1H), 7.86-7.91 (m, 1H), 7.55-7.60 (m, 1H), 7.48 (t, J = 2.0 Hz, 2H), 7.33 (t, J =12.0 Hz, 2H).

[0628] (2R,3R)-2-氨基-3-(环己基甲氧基)丁-1-醇

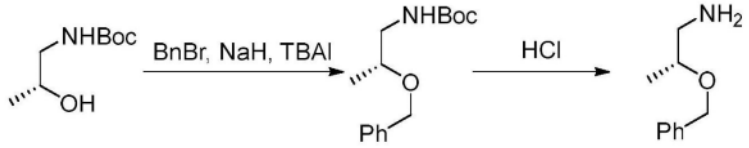
[0629] 

[0630] 步骤1:向O-苄基-N-(叔丁氧基羰基)-L-苏氨酸(600mg,1.94mmol)在异丙醇(5mL)中的溶液添加5%Rh/Al_2O_3(100mg)。将反应混合物在H_2气氛下搅拌16小时。通过硅藻土过滤除去催化剂并将滤液浓缩,得到粗品N-(叔丁氧基羰基)-O-(环己基甲基)-L-苏氨酸(400mg,65%),其为黄色油状物,其直接用于下一步。LCMSm/z=314.4[M-H]$^-$;^{1}H NMR(400MHz,氯仿-d)δ5.27(d,J=11.8Hz,1H),4.31(d,J=2.2Hz,1H),4.01(s,1H),3.36-3.27(m,1H),3.17-3.09(m,1H),1.68(s,3H),1.44(s,10H),1.18(s,7H),0.89(d,J=11.6Hz,2H).

[0631] 步骤2:在0℃向N-(叔丁氧羰基)-O-(环己基甲基)-L-苏氨酸(400mg,1.27mmol)在无水THF(4mL)中的溶液添加BH_3-THF(2M,1.58mL,3.17mmol)。将该混合物在室温搅拌3小时,然后通过添加MeOH(4mL)淬灭。在真空下除去溶剂,并将得到的固化残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=3:1),得到((2R,3R)-3-(环己基甲氧基)-1-羟基丁-2-基)氨基甲酸叔丁酯(200mg,52%),其为黄色油状物。LCMSm/z=302.4[M+H]$^+$;^{1}H NMR(400MHz,氯仿-d)δ5.08(d,J=7.6Hz,1H),3.81-3.54(m,4H),3.41-3.32(m,1H),3.11-3.02(m,1H),1.71(d,J=12.0Hz,7H),1.45(s,9H),1.25(d,J=6.0Hz,2H),1.16(d,J=6.2Hz,4H),0.97-0.85(m,2H).

[0632] 步骤3:向((2R,3R)-3-(环己基甲氧基)-1-羟基丁-2-基)氨基甲酸叔丁酯(200mg,0.66mmol)在DCM(5mL)中的溶液添加TFA(2mL)。将反应混合物在室温搅拌1h,然后在真空下除去溶剂,得到(2R,3R)-2-氨基-3-(环己基甲氧基)丁-1-醇(642mg,100%),其无需纯化即可使用。

[0633] (R)-2-(苄氧基)丙-1-胺

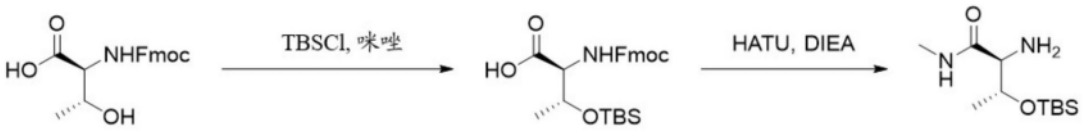
[0634] 

[0635] 步骤1:在0℃向(R)-(2-羟丙基)氨基甲酸叔丁酯(200mg,1.14mmol)在THF(5.0mL)中的溶液添加NaH(50mg,1.254mmol)和TBAI(84mg,0.228mmol),并将混合物在0℃搅拌30分钟。添加苄基溴(234mg,1.41mmol)并将反应在室温搅拌过夜。将反应混合物用水(50mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到(R)-(2-(苄氧基)丙基)氨基甲酸叔丁酯(300mg,98%),其为无色油状物。LCMSm/z=288.1[M+Na]$^+$.^{1}H NMR(400MHz,DMSO-d6)δ7.40-7.18(m,5H),6.82(t,J=5.6Hz,1H),4.58-4.37(m,2H),3.55-3.47(m,1H),3.09-2.91(m,2H),1.37(s,9H),1.07(d,J=6.4Hz,3H).

[0636] 步骤2:向(R)-(2-(苄氧基)丙基)氨基甲酸叔丁酯(300mg,1.13mmol)在二噁烷(2.0mL)中的溶液添加HCl在1,4-二噁烷(4M,2mL,8mmol)中的溶液。将混合物在室温搅拌1h,然后在真空下除去溶剂,得到(R)-2-(苄氧基)丙-1-胺(240mg),其为白色固体,其无需

纯化即可使用。LCMSm/z＝166.2[M+H]$^+$.

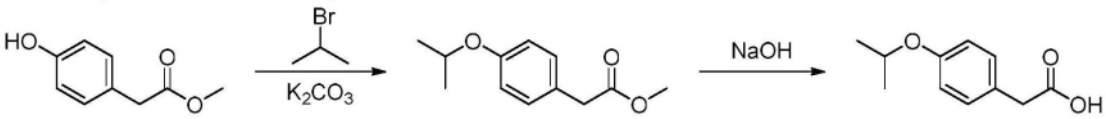
[0637] (2S,3R)-2-氨基-3-((叔丁基二甲基甲硅烷基)氧基)-N-甲基丁酰胺

[0638] 

[0639] 步骤1:向(((9H-芴-9-基)甲氧基)羰基)-L-苏氨酸(5g,14.60mmol)在无水DMF(50mL)中的溶液添加咪唑(2g,29.20mmol)和叔丁基二甲基氯硅烷(2.4g,16.06mmol)。将混合物在室温搅拌过夜,然后用水(100mL)稀释并用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH＝30:1)纯化,得到N-(((9H-芴-9-基)甲氧基)羰基)-O-(叔丁基二甲基甲硅烷基)-L-苏氨酸(480mg,18%),其为黄色油状物。进一步洗脱得到回收的起始材料(3g)。^{1}H NMR(400MHz,DMSO-d_6)δ12.80(s,1H),7.89(d,J＝7.6Hz,2H),7.75(t,J＝6.8Hz,2H),7.44-7.39(m,2H),7.35-7.28(m,2H),6.92(d,J＝9.4Hz,1H),4.34-4.22(m,4H),4.05(dd,J＝9.4,3.2Hz,1H),1.13(d,J＝6.2Hz,3H),0.85(s,9H),0.04(d,J＝11.8Hz,6H).

[0640] 步骤2:向N-(((9H-芴-9-基)甲氧基)羰基)-O-(叔丁基二甲基甲硅烷基)-L-苏氨酸(480mg,1.05mmol)在DMF(5mL)中的溶液添加HATU(440mg,1.16mmol),并将混合物在室温搅拌30分钟。添加甲胺盐酸盐(85mg,1.26mmol)和DIPEA(545mg,4.20mmol)并将反应再搅拌6h。将混合物用水(20mL)稀释,用EtOAc(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH＝60/1),得到(2S,3R)-2-氨基-3-((叔丁基二甲基甲硅烷基)氧基)-N-甲基丁酰胺(90mg,35%),其为白色固体。LCMSm/z＝247.25[M+H]$^+$.

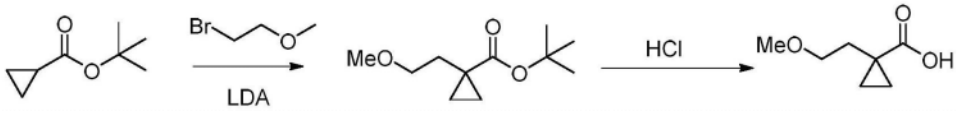
[0641] 2-(4-异丙氧基苯基)乙酸

[0642] 

[0643] 步骤1:向2-(4-羟基苯基)乙酸甲酯(1g,6.02mmol)在DMF(5mL)中的溶液添加2-溴丙烷(888mg,7.22mmol)和K_2CO_3(1.25g,9.03mmol)。将混合物在50℃加热过夜,然后冷却至室温,用水(60mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc＝20:1),得到2-(4-异丙氧基苯基)乙酸甲酯(820mg,61%),其为白色固体。LCMSm/z＝209.1[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.22-7.09(m,2H),6.88-6.80(m,2H),4.56(p,J＝6.0Hz,1H),3.60(s,3H),3.58(s,2H),1.24(d,J＝6.0Hz,6H).

[0644] 步骤2:向2-(4-异丙氧基苯基)乙酸甲酯(820mg,3.94mmol)在MeOH(2mL)和水(2mL)的混合物中的溶液添加NaOH(472mg,11.81mmol)。将混合物在50℃加热过夜,然后冷却至室温,用水(20mL)稀释并用EtOAc(30mL)萃取。收集水层并用1M HCl酸化至pH～2,并用EtOAc(60mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品2-(4-异丙氧基苯基)乙酸(730mg,96%),其为黄色固体,其无需纯化即可使用。LCMSm/z＝195.2[M+H]$^+$.

[0645] 1-(2-甲氧基乙基)环丙烷-1-甲酸

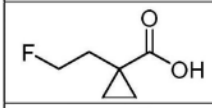
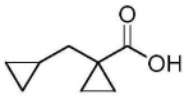
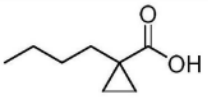
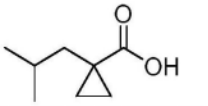
[0646] 

[0647] 步骤1:在-80℃在N_2下向LDA(2.1mL,2M于THF中)在无水THF(10mL)中的溶液逐滴添加环丙烷甲酸叔丁酯(500mg,3.50mmol)。将混合物在-80℃搅拌5.5h,然后将1-溴-2-甲氧基乙烷(1.5g,10.5mmol)在无水THF(2mL)中的溶液逐滴添加至反应混合物。将混合物温热至室温并再搅拌6小时。将反应用EtOAc(50mL)稀释,用盐水洗涤并将有机层经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=20:1),得到1-(2-甲氧基乙基)环丙烷-1-甲酸叔丁酯(200mg,28%),其为黄色油状物。^{1}H NMR(400MHz,氯仿-d)δ3.52(t,J=7.2Hz,2H),3.33(s,3H),1.79(t,J=7.2Hz,2H),1.43(s,9H),1.13(q,J=4.0Hz,2H),0.68(q,J=4.0Hz,2H).

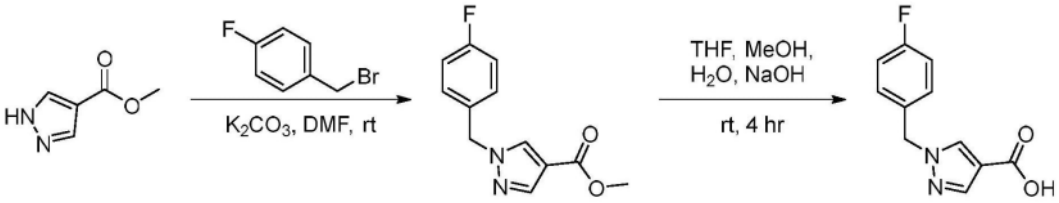
[0648] 步骤2:将1-(2-甲氧基乙基)环丙烷-1-甲酸叔丁酯(100mg,0.50mmol)在HCl在1,4-二噁烷(4M,3mL)中的溶液中的混合物在室温搅拌5小时。在真空下除去溶剂,得到1-(2-甲氧基乙基)环丙烷-1-甲酸,其为黄色油状物,其无需纯化即可使用。^{1}H NMR(400MHz,氯仿-d)δ3.59-3.52(m,2H),3.37(d,J=1.4Hz,3H),1.87-1.81(m,2H),1.13-1.02(m,4H).

[0649] 根据1-(2-甲氧基乙基)环丙烷-1-甲酸的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0650]

化合物	^{1}HNMR
	^{1}H NMR (400 MHz, 氯仿-*d*) δ 4.69 (t, *J* = 6.2 Hz, 1H), 4.57 (t, *J* = 6.2 Hz, 1H), 1.96 – 1.91 (m, 2H), 0.95 – 0.84 (m, 4H).
	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 1.46 – 1.42 (m, 2H), 1.07 – 1.03 (m, 1H), 1.02 – 0.99 (m, 2H), 0.77 – 0.73 (m, 2H), 0.38 – 0.32 (m, 2H), 0.07 – 0.02 (m, 2H).
	^{1}H NMR (400 MHz, 氯仿-*d*) δ 1.52 – 1.48 (m, 2H), 1.45 – 1.40 (m, 2H), 1.29 – 1.24 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.75 (q, *J* = 4.0 Hz, 2H).
	^{1}H NMR (400 MHz, DMSO-d_6) δ12.02 (s, 1H), 1.90 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.04 – 1.01 (m, 2H), 0.98 (t, *J* = 3.2 Hz, 2H), 0.86 (s, 3H), 0.85 (s, 3H), 0.68 – 0.62 (m, 2H).

[0651] 1-(4-氟苄基)-1H-吡唑-4-甲酸

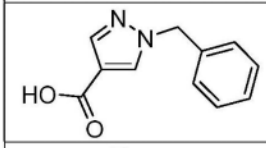
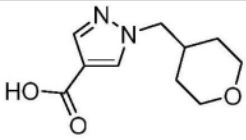
[0652] 

[0653] 步骤1:向1H-吡唑-4-甲酸甲酯(1g,7.90mmol)在DMF(10mL)中的溶液添加K_2CO_3(3.3g,23.70mmol)和1-(溴甲基)-4-氟苯(1.5g,7.90mol)。将该反应在室温搅拌过夜,然后用水(60mL)稀释并用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到1-(4-氟苄基)-1H-吡唑-4-甲酸甲酯(1.8g,97%),其为白色固体。LCMSm/z=235.0[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.48(s,1H),7.88(s,1H),7.37-7.30(m,2H),7.21-7.14(m,2H),5.35(s,2H),3.73(s,3H).

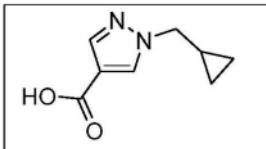
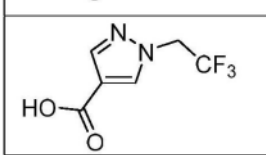
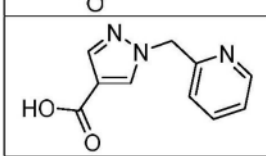
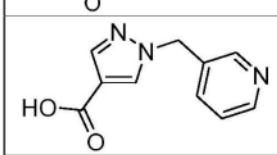
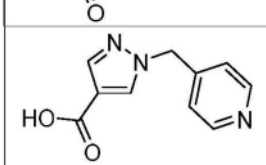
[0654] 步骤2:向1-(4-氟苄基)-1H-吡唑-4-甲酸甲酯(1g,4.30mmol)在THF(4mL)MeOH(1mL)和H_2O(1mL)的混合物中的溶液添加2M NaOH(2mL)。将混合物在室温搅拌4h,然后用水(50mL)稀释并用EtOAc(80mL)萃取。收集水层并用1M HCl酸化至pH～2,并用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到1-(4-氟苄基)-1H-吡唑-4-甲酸(870mg,93%),其为白色固体。LCMSm/z=221.0$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ12.34(s,1H),8.37(s,1H),7.81(d,J=1.8Hz,1H),7.38-7.30(m,2H),7.23-7.13(m,2H),5.34(s,2H).

[0655] 根据1-(4-氟苄基)-1H-吡唑-4-甲酸的一般步骤概述,使用合适的市售试剂合成以下化合物。

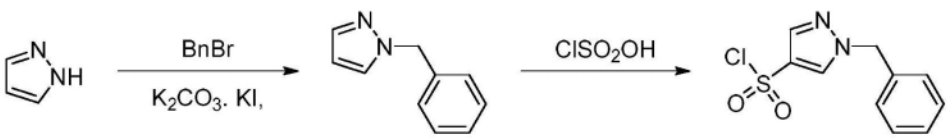
[0656]

砌块结构	^{1}HNMR	LCMS
	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.37 (s, 1H), 7.82 (s, 1H), 7.38 – 7.24 (m, 5H), 5.35 (s, 2H).	203.05 $[M+H]^+$
	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.22 (s, 1H), 7.79 (s, 1H), 4.03 (d, J = 7.2 Hz, 2H), 3.81 (ddd, J = 11.4, 4.4, 1.8 Hz, 2H), 3.23 (td, J = 11.8, 2.2 Hz, 2H), 2.13-1.98(m, 1H), 1.39-1.31 (m, 2H),1.28-1.14 (m, 2H).	211.2 $[M+H]^+$;

[0657]

	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 3.98 (d, J = 7.2 Hz, 2H), 1.25 (tt, J = 7.6, 4.8 Hz, 1H), 0.55 – 0.49 (m, 2H), 0.40 – 0.32 (m, 2H).	167.1 $[M+H]^+$
	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.92 (d, J = 0.6 Hz, 1H), 5.19 (q, J = 9.0 Hz, 2H).	195.2 $[M+H]^+$;
		204.0 $[M+H]^+$.
		204.0 $[M+H]^+$.
		204.0 $[M+H]^+$.

[0658] 1-苄基-1H-吡唑-4-磺酰氯:

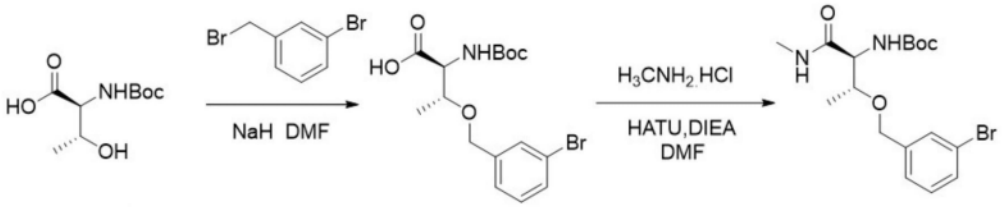
[0659] 

[0660] 步骤1:向1H-吡唑(1g,25.2mmol)在DMF(20mL)中的溶液添加K_2CO_3(3.4g,

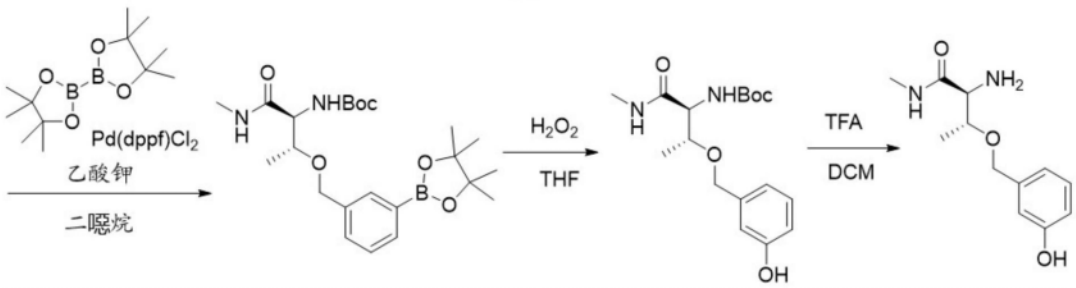
25.2mmol)、KI(140mg,0.086mmol)和(溴甲基)苯(2mL,16.8mmol)。将反应混合物在80℃加热过夜,然后用水(60mL)稀释并用DCM(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=15:1),得到1-苄基-1H-吡唑(1.4g,60%),其为黄色油状物。LCMSm/z=159.2$[M+H]^+$.

[0661] 步骤2:将1-苄基-1H-吡唑(200mg,1.26mmol)和氯磺酸(1mL)的混合物在110℃加热3h。将混合物冷却至室温,用DCM(50mL)稀释并用盐水洗涤。将有机层经Na_2SO_4干燥,过滤并浓缩,得到粗品1-苄基-1H-吡唑-4-磺酰氯(70mg,22%),其为黄色油状物,其无需纯化即可使用。LCMSm/z=257.1$[M+H]^+$.

[0662] (2S,3R)-2-氨基-3-((3-羟基苄基)氧基)-N-甲基丁酰胺



[0663]



[0664] 步骤1:在0℃向(叔丁氧羰基)-L-苏氨酸(3g,13.7mmol)在无水DMF(30mL)中的溶液添加NaH(1.9g,47.95mmol)。将反应混合物温热至室温并搅拌1h。然后添加1-溴-3-(溴甲基)苯(3.4g,13.7mmol)并将反应在rt搅拌过夜。将混合物用EtOAc(60mL)稀释,用水(100mL×2)洗涤,经Na_2SO_4干燥,过滤并浓缩,得到O-(3-溴苄基)-N-(叔丁氧羰基)-L-苏氨酸(1.6g,30%),其为黄色油状物。LCMSm/z=388.0$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ7.54-7.50(m,1H),7.47-7.44(m,1H),7.35-7.24(m,3H),4.64-4.53(m,2H),4.40(d,J=12.2Hz,1H),4.09(dd,J=9.1,3.8Hz,1H),1.41-1.38(m,9H),1.15(d,J=6.2Hz,3H).

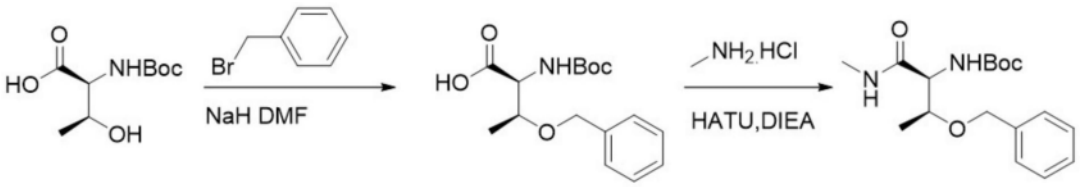
[0665] 步骤2:向O-(3-溴苄基)-N-(叔丁氧羰基)-L-苏氨酸(1.6g,4.13mmol)在DCM(20mL)中的溶液添加HATU(2.3g,6.19mmol),并将混合物在室温搅拌30分钟。添加甲胺盐酸盐(332mg,4.96mmol)和DIPEA(2.1g,16.5mmol)并将反应再搅拌3h。然后将反应混合物用水(60mL)稀释并用DCM(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过反相Biotage柱(C18,40g,ACN/H_2O=60%)纯化,得到(2S,3R)-3-((3-溴苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(750mg,45%),其为黄色油状物。LCMSm/z=400.0$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ7.84(d,J=4.8Hz,1H),7.51-7.43(m,2H),7.28(d,J=4.8Hz,2H),6.48(d,J=9.2Hz,1H),4.52(d,J=12.4Hz,1H),4.39(d,J=12.4Hz,1H),4.02-3.97(m,1H),3.88-3.79(m,1H),2.61(d,J=4.6Hz,3H),1.39(s,9H),1.08(d,J=6.2Hz,3H).

[0666] 步骤3:向(2S,3R)-3-((3-溴苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(750mg,1.87mmol)在二噁烷(10mL)中的溶液添加双(频那醇)二硼(950mg,

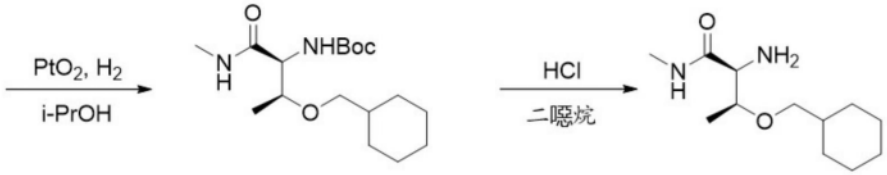
3.74mmol)、乙酸钾(550mg,5.61mmol)和Pd(dppf)Cl_2(82mg,0.11mmol)。然后将反应在80℃加热过夜。将反应冷却至室温,用水(20mL)稀释并用EtOAc(20mL)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过反相Biotage柱(C18,20g,ACN/H_2O=50%)纯化,得到((2S,3R)-1-(甲基氨基)-1-氧代-3-((3-(4,4,5,5-四甲基-1,3,2-二氧杂硼烷-2-基)苄基)氧基)丁-2-基)氨基甲酸叔丁酯(500mg,59%),其为黄色油状物。LCMSm/z=449.2$[M+H]^+$.

[0667] 步骤4:向((2S,3R)-1-(甲基氨基)-1-氧代-3-((3-(4,4,5,5-四甲基-1,3,2-二氧杂硼烷-2-基)苄基)氧基)丁-2-基)氨基甲酸叔丁酯(500mg,1.11mmol)在THF(10mL)中的溶液添加H_2O_2(506mg,4.46mmol),并将混合物在室温搅拌过夜。添加水(10mL)并将混合物用EtOAc(20mL)萃取。然后将合并的有机层分离,用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到((2S,3R)-3-((3-羟基苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(350mg,93%),其为黄色油状物。LCMSm/z=339.1$[M+H]^+$.

[0668] 步骤5:向((2S,3R)-3-((3-羟基苄基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(300mg,0.88mmol)在DCM(5mL)中的溶液添加TFA(1mL),并将反应混合物在室温搅拌1h。在真空下除去溶剂,得到(2S,3R)-2-氨基-3-((3-羟基苄基)氧基)-N-甲基丁酰胺(211mg,100%)。LCMSm/z=239.1$[M+H]^+$.(2S,3S)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺



[0669]



[0670] 步骤1:在0℃在N_2气氛下向(叔丁氧羰基)-L-别苏氨酸(800mg,3.65mmol)在DMF(8mL)中的溶液添加NaH(437mg,10.95mmol)。将反应混合物在0℃搅拌1小时,然后添加溴化苄(624mg,3.65mmol)。将反应温热至室温并搅拌过夜。将混合物用水(80mL)稀释并用EtOAc(80mL)萃取。然后将水层用1M HCl将酸化至pH~1,并用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到O-苄基-N-(叔丁氧羰基)-L-别苏氨酸(178mg,16%),其为黄色油状物。LCMSm/z=308.05$[M-H]^-$.

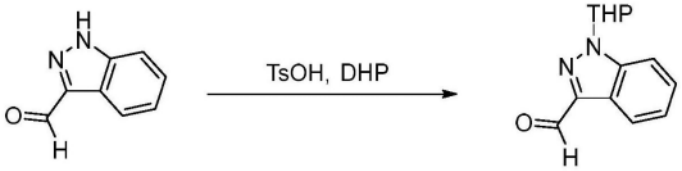
[0671] 步骤2:向O-苄基-N-(叔丁氧羰基)-L-别苏氨酸(200mg,0.65mmol)、甲胺盐酸盐(52mg,0.78mmol)和HATU(368mg,0.97mmol)在DMF(2mL)中的溶液添加DIEA(376mg,2.91mmol)。将混合物在室温搅拌2小时。将混合物用水(100mL)稀释并用EtOAc(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过RP-柱纯化,得到((2S,3S)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(143mg,69%),其为白色固体。LCMSm/z=323.10$[M+H]^+$.

[0672] 步骤3:向((2S,3S)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯

(155mg,0.48mmol)在AcOH(2mL)中的溶液添加PtO_2(65mg)。在H_2气氛下将反应在70℃加热过夜。通过硅藻土过滤除去催化剂,将滤液浓缩,得到((2S,3S)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(148mg,94%),其为白色固体。LCMSm/z=329.2[M+H]$^+$.

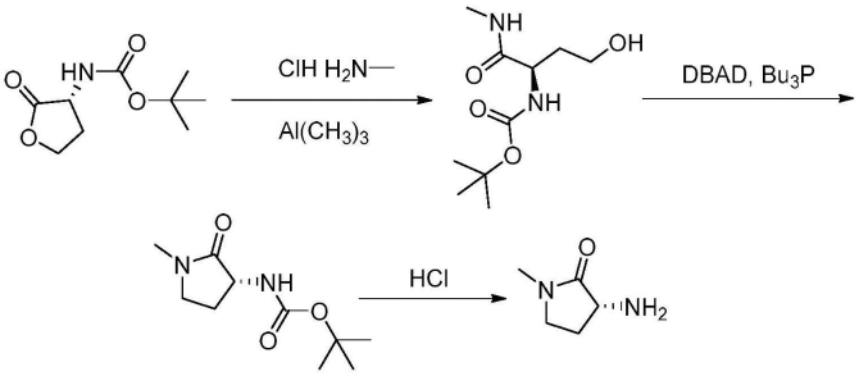
[0673] 步骤4:向((2S,3S)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(148mg,0.45mmol)在1,4-二噁烷(2mL)中的溶液添加HCl在1,4-二噁烷中的溶液(4M,2mL)。将混合物在室温搅拌1h。在真空下除去溶剂,得到(2S,3S)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺(87mg,85%),其为无色油状物。LCMSm/z=229.15[M+H]$^+$.

[0674] 1-(四氢-2H-吡喃-2-基)-1H-吲唑-3-甲醛

[0675] 

[0676] 向1H-吲唑-3-甲醛(200mg,1.37mmol)在MeCN(2mL)中的溶液添加TsOH(24mg,0.137mol)和3,4-二氢吡喃(230mg,2.74mmol)。在N_2下将该混合物在室温搅拌过夜。将混合物用水(30mL)稀释并用EtOAc(50mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到1-(四氢-2H-吡喃-2-基)-1H-吲唑-3-甲醛(220mg,70%),其为白色固体。LCMSm/z=230.9[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ11.07(s,1H),9.05-9.02(m,1H),8.80-8.78(m,1H),8.47-8.42(m,1H),8.32-8.28(m,1H),6.96-6.93(m,1H),4.81-4.63(m,2H),4.20(s,2H),3.35-3.26(m,1H),2.98-2.92(m,2H),2.72-2.61(m,1H).

[0677] (R)-3-氨基-1-甲基吡咯烷-2-酮

[0678] 

[0679] 步骤1:在0℃在氮气气氛下向甲胺盐酸盐(202mg,2.99mmol)在无水DCM(2mL)中的溶液添加三甲基铝(2.5mL,2mol/L于己烷中)。将混合物在0℃搅拌15分钟,然后添加(R)-(2-氧代四氢呋喃-3-基)氨基甲酸叔丁酯(500mg,2.49mmol)在无水DCM(5mL)中的溶液。将反应混合物温热至室温,然后搅拌过夜。添加水(30mL)并将混合物用DCM(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品(S)-(4-羟基-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(180mg,31%)。LCMSm/z=233.1[M+H]$^+$.

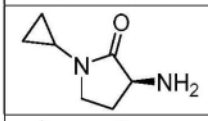
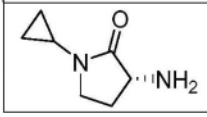
[0680] 步骤2:在0℃将偶氮二甲酸二叔丁酯(357mg,1.55mmol)和Bu_3P(783mg,3.88mmol)在无水THF(8mL)中的溶液搅拌30分钟。向其中添加(S)-(4-羟基-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酸叔丁酯(180mg,0.77mmol)在THF(2mL)中的溶液,并将所得混合物在60℃加

热过夜。然后将混合物用水(30mL)稀释,并用EtOAc(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过RP-柱纯化,得到(R)-(1-甲基-2-氧代吡咯烷-3-基)氨基甲酸叔丁酯(24mg,14%)。LCMSm/z=215.1[M+H]$^+$;^{1}H NMR(400MHz,$CDCl_3$)δ5.19-5.03(m,1H),4.20-4.08(m,1H),3.41-3.25(m,2H),2.93-2.85(m,3H),2.71-2.58(m,1H),1.96-1.81(m,1H),1.45(s,9H).

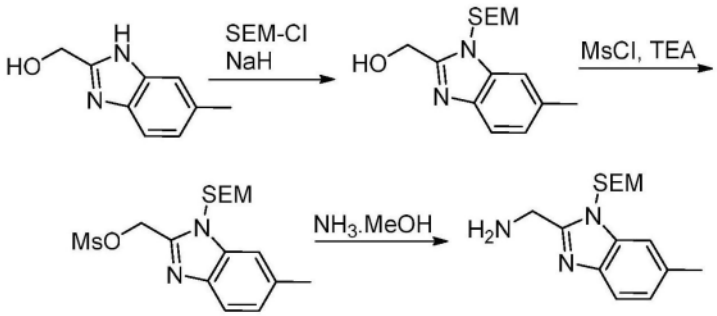
[0681] 步骤3:向(R)-(1-甲基-2-氧代吡咯烷-3-基)氨基甲酸叔丁酯(24mg,0.11mmol)在1,4-二噁烷(2mL)中的溶液添加HCl在二噁烷(4M,0.5mL)中的溶液。将反应混合物在室温搅拌2小时,然后在真空下除去溶剂,得到(R)-3-氨基-1-甲基吡咯烷-2-酮(13mg,100%)。LCMSm/z=115.0[M+H]$^+$.

[0682] 根据(R)-3-氨基-1-甲基吡咯烷-2-酮的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0683]

化合物	LCMS
	141.0 [M+H]$^+$
	141.0 [M+H]$^+$

[0684] (6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲胺

[0685] 

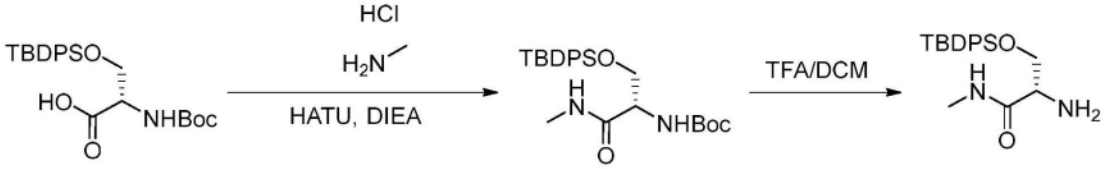
[0686] 步骤1:向(6-甲基-1H-苯并[d]咪唑-2-基)甲醇(2g,6.47mmol)在无水DMF(5mL)中的溶液添加60%的NaH(81mg,3.70mmol),并将混合物在室温搅拌30分钟。缓慢添加SEM-Cl(370mg,2.20mmol)并将混合物在室温再搅拌4小时。然后将反应用水(15mL)稀释并用EtOAc(30mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=1:1),得到(6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲醇(300mg,56%),其为黄色油状物。^{1}H NMR(400MHz,DMSO-d_6)δ7.48(dd,J=8.2,2.8Hz,1H),7.40(td,J=1.8,0.8Hz,1H),7.05(ddd,J=20.6,8.2,1.6Hz,1H),5.66-5.62(m,3H),4.72(dd,J=5.8,1.4Hz,2H),3.55-3.49(m,2H),2.41(d,J=10.2Hz,3H),0.83(dt,J=7.8,3.8Hz,2H),-0.09(d,J=1.6Hz,9H).

[0687] 步骤2:在0℃向(6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲醇(100mg,0.34mmol)和TEA(69mg,0.68mmol)在DCM(2mL)中的溶液添加MsCl(47mg,0.41mmol)。将反应混合物在室温搅拌1h。然后添加水(15mL)并将混合物用DCM(30mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品甲磺酸(6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲酯(80mg,63%),其

为棕色油状物。LCMSm/z＝371.20[M+H]$^+$.

[0688] 步骤3:将在密封管中的甲磺酸(6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲基酯(350mg,1.20mmol)和NH_3/MeOH(7M,4mL)的混合物在80℃加热4小时。将反应用水(20mL)稀释并用DCM(50mL×2)萃取,经Na_2SO_4干燥并浓缩。将残留物通过制备型TLC(洗脱液:石油醚:EtOAc＝1:1,然后DCM:MeOH＝20:1)纯化,得到(6-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-苯并[d]咪唑-2-基)甲胺(70mg,25%),其为灰色油状物。LCMSm/z＝292.10[M+H]$^+$.

[0689] (S)-2-氨基-3-((叔丁基二苯基甲硅烷基)氧基)-N-甲基丙酰胺

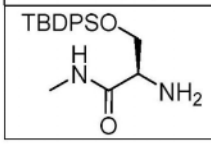
[0690] 

[0691] 步骤1:向N-(叔丁氧羰基)-O-(叔丁基二苯基甲硅烷基)-L-丝氨酸(200mg,0.45mmol)在DCM(2mL)中的溶液添加HATU(188mg,0.495mmol),并将反应混合物在室温搅拌30分钟。添加甲胺盐酸盐(36mg,0.54mmol)和DIPEA(233mg,1.8mmol)并将反应混合物再搅拌3h。然后在真空下除去溶剂并将残留物通过制备型TLC(洗脱液:DCM/MeOH＝20/1)纯化,得到(S)-(3-((叔丁基二苯基甲硅烷基)氧基)-1-(甲基氨基)-1-氧代丙-2-基)氨基甲酸叔丁酯(195mg,95%),其为白色固体。LCMSm/z＝457.2[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ7.95-7.93(m,1H),7.62-7.59(m,4H),7.47-7.40(m,6H),6.68(d,J＝8.8Hz,1H),4.20-4.15(m,1H),3.82-3.68(m,2H),2.6(d,J＝4.4Hz,3H),1.39(s,9H),0.96(s,9H).

[0692] 步骤2:向(S)-(3-((叔丁基二苯基甲硅烷基)氧基)-1-(甲基氨基)-1-氧代丙-2-基)氨基甲酸叔丁酯(125mg,0.274mmol)在DCM(3mL)中的溶液添加TFA(1mL)。将混合物在室温搅拌1小时,然后在真空下除去溶剂,得到(S)-2-氨基-3-((叔丁基二苯基甲硅烷基)氧基)-N-甲基丙酰胺(100mg,100%),其为黄色油状物。LCMSm/z＝357.3[M+H]$^+$.

[0693] 根据(S)-2-氨基-3-((叔丁基二苯基甲硅烷基)氧基)-N-甲基丙酰胺的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0694]

化合物	LCMS
	357.3 [M+H]$^+$

[0695] 1-(甲氧基甲基)环丙胺

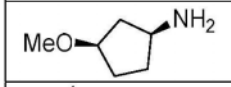
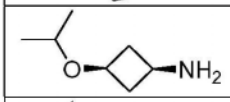
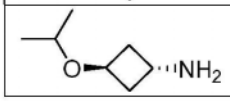
[0696] 

[0697] 步骤1:在密封管中将(1-(羟甲基)环丙基)氨基甲酸叔丁酯(500mg,2.67mmol)、AgO(1.24g,5.34mmol)、MeI(759mg,5.34mmol)和DCE(2mL)的混合物在60℃加热过夜。然后在真空下除去溶剂并将残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc＝20:1),得到(1-(甲氧基甲基)环丙基)氨基甲酸叔丁酯(200mg,37%),其为无色油状物。^{1}H NMR($CDCl_3$,400MHz)δ,5.04(1H,s),3.38(2H,s),3.36(3H,s),1.43(9H,s),0.81(2H,d,J＝4.8Hz),0.75(2H,d,J＝5.0Hz).

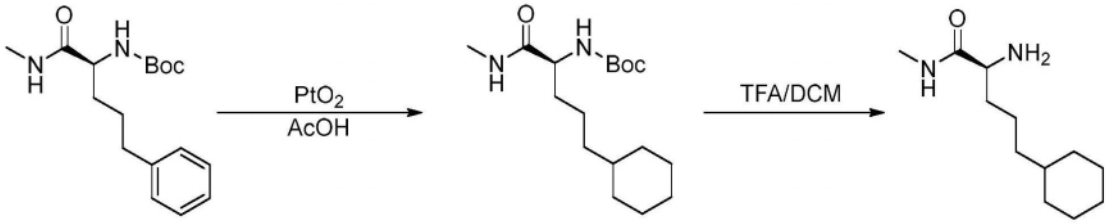
[0698] 步骤2:向(1-(甲氧基甲基)环丙基)氨基甲酸叔丁酯(100mg,0.50mmol)在DCM(2mL)中的溶液添加HCl在1,4-二噁烷(4M,1mL)中的溶液。将反应混合物在室温搅拌1h。然后在真空下除去溶剂,得到粗品1-(甲氧基甲基)环丙胺盐酸盐(68mg,100%),其为无色油状物。LCMSm/z=102.1[M+H]$^+$.

[0699] 根据1-(甲氧基甲基)环丙胺的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0700]

化合物	LCMS
	116.2 [M+H]$^+$
	130.2 [M+H]$^+$
	130.2 [M+H]$^+$

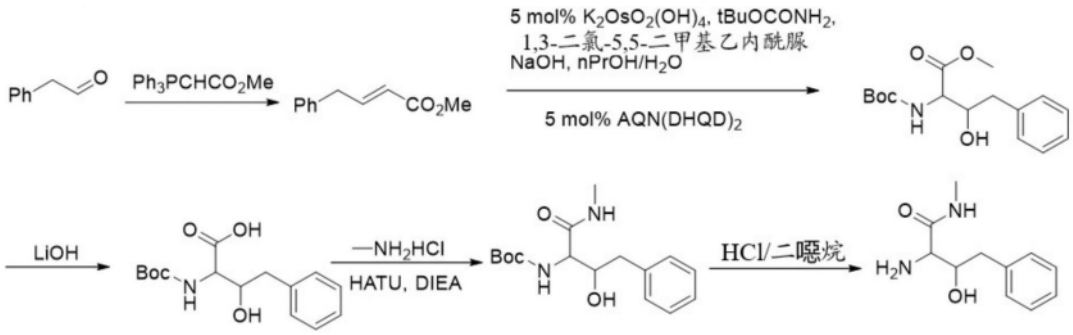
[0701] (S)-2-氨基-5-环己基-N-甲基戊酰胺

[0702] 

[0703] 步骤1:向(S)-(1-(甲基氨基)-1-氧代-5-苯基戊烷-2-基)氨基甲酸叔丁酯(350mg,1.14mmol)在AcOH(8mL)中的溶液添加PtO_2(50mg)。在压力容器中在4atm H_2下将反应在70℃加热过夜。通过硅藻土过滤除去催化剂并将滤液浓缩,得到粗品(S)-(5-环己基-1-(甲基氨基)-1-氧代戊烷-2-基)氨基甲酸叔丁酯(357mg,100%),其为黄色油状物。LCMSm/z=313.2[M+H]$^+$.

[0704] 步骤2:向(S)-(5-环己基-1-(甲基氨基)-1-氧代戊烷-2-基)氨基甲酸叔丁酯(70mg,0.224mmol)在DCM(4mL)中的溶液添加TFA(1mL)。将反应混合物在室温搅拌1h。在真空下除去溶剂,得到粗品(S)-2-氨基-5-环己基-N-甲基戊酰胺(48mg,100%)。LCMSm/z=213.2[M+H]$^+$.

[0705] (2S,3R)-2-氨基-3-羟基-N-甲基-4-苯基丁酰胺

[0706] 

[0707] 步骤1:在25℃向2-苯基乙醛(3.0g,24.97mmol)在甲苯(20mL)中的溶液添加Ph_3PCHCO_2Me(9.18mg,27.47mmol)。将反应混合物在90℃搅拌16h。将混合物浓缩,并将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=20:1),得到(E)-4-苯基丁-

2-烯酸甲酯(2.77g,62%),其为无色油状物。LCMSm/z=177.1[M+H]$^+$.

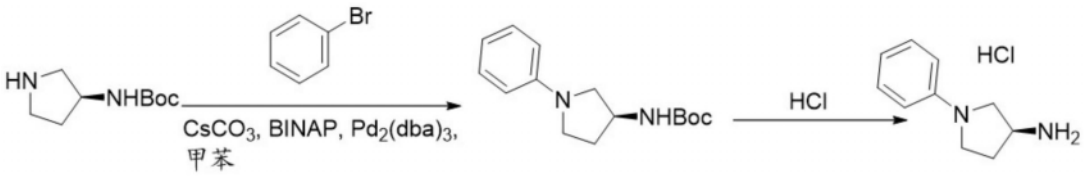
[0708] 步骤2:在室温向t-BuOCONH$_2$(1.99g,17.02mmol)在n-PrOH/H$_2$O(5mL/10mL)中的溶液添加NaOH(0.68g,17.02mmol)、1,3-二氯-5,5-二甲基乙内酰脲(2.24g,11.35mmol)、AQN(DHQD)$_2$(243mg,0.283mmol)和K$_2$OsO$_2$(OH)$_4$(104mg,0.283mmol)。将反应混合物在室温搅拌16h。将混合物用水(100mL)稀释并用EtOAc(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na$_2$SO$_4$干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=5:1),得到(2S,3R)-2-((叔丁氧羰基)氨基)-3-羟基-4-苯基丁酸甲酯(470mg,26%),其为黄色油状物。LCMSm/z=310.1[M+H]$^+$.^{1}H NMR(400MHz,CDCl$_3$)δ7.36-7.28(m,3H),7.26-7.20(m,2H),5.51-5.33(m,1H),4.44-4.26(m,2H),3.75(s,2H),3.70(s,1H),2.93-2.74(m,2H),1.61(s,2H),1.51-1.41(m,9H).

[0709] 步骤3:向(2S,3R)-2-((叔丁氧羰基)氨基)-3-羟基-4-苯基丁酸甲酯(0.1g,0.323mmol)在THF和水(2mL/1mL)的混合物中的溶液添加LiOH(0.024g,0.969mmol)。将反应混合物在室温搅拌2h,然后用水(10mL)稀释并用醚(20mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(10mL×3)萃取。将合并的有机层用盐水洗涤,经Na$_2$SO$_4$干燥,过滤并浓缩,得到(2S,3R)-2-((叔丁氧羰基)氨基)-3-羟基-4-苯基丁酸(90mg,94%),其为白色固体,其直接用于下一步。LCMSm/z=296.1[M+H]$^+$.

[0710] 步骤4:向(2S,3R)-2-((叔丁氧羰基)氨基)-3-羟基-4-苯基丁酸(90mg,0.304mmol)在DMF(1mL)中的溶液添加HATU(174mg,0.457mmol)。将混合物在室温搅拌30分钟。然后添加甲胺盐酸盐(31mg,0.457mmol)和DIPEA(158mg,1.22mmol),并将反应再搅拌3h。将混合物用水(20mL)稀释,用DCM(50mL×3)萃取,将合并的有机层用盐水洗涤,经Na$_2$SO$_4$干燥,过滤并浓缩。将残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=30:1),得到(2S,3R)-3-羟基-1-(甲基氨基)-1-氧代-4-苯基丁-2-基)氨基甲酸叔丁酯(65mg,69%),其为白色固体。LCMSm/z=309.1[M+H]$^+$.

[0711] 步骤5:向(2S,3R)-3-羟基-1-(甲基氨基)-1-氧代-4-苯基丁-2-基)氨基甲酸叔丁酯(65mg,0.210mmol)在1,4-二噁烷(1mL)中的溶液添加HCl在二噁烷(4M,2mL)中的溶液。将反应混合物在室温搅拌3h。在真空下除去溶剂,得到粗品(2S,3R)-2-氨基-3-羟基-N-甲基-4-苯基丁酰胺(60mg,100%),其无需纯化即可使用。LCMSm/z=209.1[M+H]$^+$.

[0712] (S)-1-苯基吡咯烷-3-胺HCl

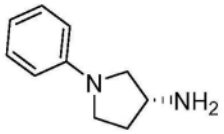
[0713] 

[0714] 步骤1:向(S)-吡咯烷-3-基氨基甲酸叔丁酯(300mg,1.61mmol)在甲苯(20mL)中的溶液添加溴苯(316.2mg,2.01mol)、Cs$_2$CO$_3$(787.3mg,2.42mmol)、BINAP(160.5mg,0.26mmol)和Pd$_2$(dba)$_3$(118.0mg,0.13mmol)。在N$_2$气氛下将反应混合物在110℃加热过夜。将反应混合物用水(30mL)稀释,并用EtOAc(3×50mL)萃取。将合并的有机层用盐水洗涤,经Na$_2$SO$_4$干燥,过滤并浓缩。将残留物通过制备型TLC(洗脱液:石油醚:EtOAc=3:1)纯化,得到(S)-1-苯基吡咯烷-3-胺(200mg,47%),其为白色固体。LCMSm/z=263.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d$_6$)δ7.18-7.15(m,1H),7.15-7.14(m,1H),7.14-7.11(m,1H),6.58(t,J=7.4,1.0Hz,1H),

6.50(s,1H),6.48(s,1H),4.18-4.06(m,1H),3.43(dd,J＝9.6,6.6Hz,1H),3.32-3.29(m,1H),3.24-3.15(m,1H),3.01(q,J＝9.6,5.2Hz,1H),2.20-2.09(m,1H),1.93-1.81(m,1H),1.39(s,9H).

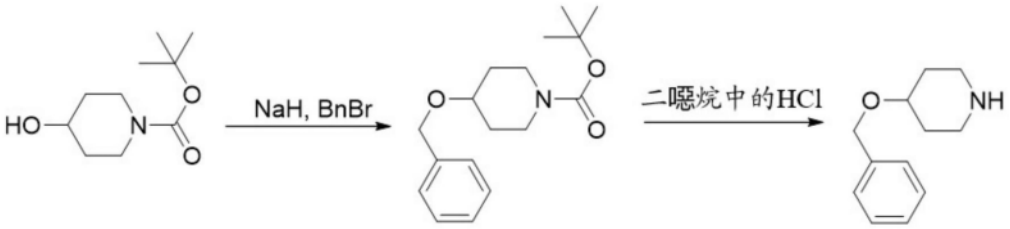
[0715] 步骤2:向(S)-(1-苯基吡咯烷-3-基)氨基甲酸叔丁酯(100mg,0.38mmol)在1,4-二噁烷(3mL)中的溶液添加HCl在1,4二噁烷(4M,4mL)中的溶液。将混合物在室温搅拌1h。在真空下除去溶剂,得到粗品(S)-1-苯基吡咯烷-3-胺(62mg,100%),其为白色固体。LCMSm/z＝163.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.45(s,3H),7.19(dd,2H),6.65(t,J＝7.2Hz,1H),6.56(d,J＝8.0Hz,2H),3.95-3.84(m,1H),3.56-3.42(m,2H),3.37-3.21(m,2H),2.37-2.24(m,1H),2.17-2.05(m,1H).

[0716] (R)-1-苯基吡咯烷-3-胺HCl

[0717] 

[0718] 根据(S)-1-苯基吡咯烷-3-胺步骤的概述,使用合适的市售试剂合成(R)-1-苯基吡咯烷-3-胺。LCMSm/z＝163.2[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.46(s,3H),7.23-7.16(m,2H),6.65(t,J＝7.2Hz,1H),6.56(d,J＝8.0Hz,2H),3.95-3.85(m,1H),3.56-3.41(m,2H),3.36-3.22(m,2H),2.37-2.23(m,1H),2.16-2.03(m,1H).

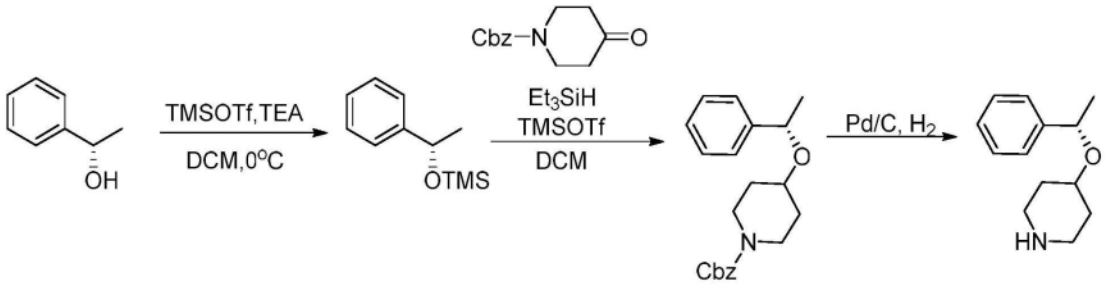
[0719] 4-(苄氧基)哌啶

[0720] 

[0721] 步骤1:在0℃向4-羟基哌啶-1-甲酸叔丁酯(500mg,2.5mmol)在THF(5mL)中的溶液添加苄基溴(547mg,3.2mmol)和60%氢化钠(120mg,3.0mmol)。将所得混合物温热至室温并搅拌3h。添加水并将水层用EtOAc萃取三次。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过硅胶柱色谱法(4%MeOH/DCM)纯化,得到4-(苄氧基)哌啶-1-甲酸叔丁酯(633mg,85%),其为无色油状物。^{1}H NMR(400MHz,DMSO-d_6)δ7.37-7.23(m,5H),4.51(s,2H),3.68-3.51(m,3H),3.10-2.98(m,2H),1.85-1.77(m,2H),1.45-1.35(m,11H).

[0722] 步骤2:将4-(苄氧基)哌啶-1-甲酸叔丁酯(100mg,0.34mmol)在HCl(4M二噁烷溶液,2mL)中的溶液搅拌1小时。除去溶剂,得到4-(苄氧基)哌啶(21mg,33%)。LCMSm/z＝192.1[M+H]$^+$.

[0723] (S)-4-(1-苯基乙氧基)哌啶

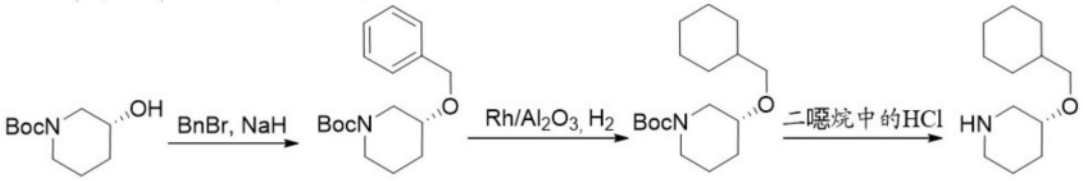
[0724] 

[0725] 步骤1:在0℃将TMSOTf(9.1g,40.9mmol)逐滴添加到(S)-1-苯基乙烷-1-醇(2.0g,16.4mmol)和TEA(8.3g,81.8mmol)在DCM(20.0mL)中的溶液。将所得溶液在2小时内温热至室温。然后添加水并用DCM萃取水相。将合并的有机层用水和盐水洗涤,并经Na_2SO_4干燥。除去溶剂,将残留物通过硅胶柱色谱法(10%EtOAc/PE)纯化,得到(S)-三甲基(1-苯基乙氧基)硅烷(2.4g,75%),其为无色油状物。^{1}HNMR(400MHz,CD_3OD)δ7.52-7.00(m,5H),4.95-4.80(m,1H),1.40(d,J=6.4Hz,3H),0.06(s,9H).

[0726] 步骤2:在-78℃向(S)-三甲基(1-苯基乙氧基)硅烷(150mg,0.77mmol)在DCM(3.0mL)中的溶液添加4-氧代哌啶-1-甲酸苄酯(180mg,0.77mmol)、三乙基硅烷(99mg,0.85mmol)和TMSOTf(86mg,0.39mmol)。然后将所得溶液温热至0℃并搅拌2小时。将反应混合物用1M H_3PO_4淬灭,添加水并用EtOAc萃取水相。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过制备型HPLC纯化,得到(S)-4-(1-苯基乙氧基)哌啶-1-甲酸酯(34mg,13%),其为黄色油状物。LCMSm/z=340.1$[M+H]^+$;^{1}HNMR(400MHz,CD_3OD)δ7.38-7.20(m,10H),5.09(s,2H),4.64(q,J=6.4Hz,1H),3.88-3.66(m,2H),3.49-3.39(m,1H),3.25-3.01(m,2H),1.92-1.80(m,1H),1.72-1.59(m,1H),1.59-1.40(m,2H),1.38(d,J=6.8Hz,3H).

[0727] 步骤3:向(S)-4-(1-苯基乙氧基)哌啶-1-甲酸酯(30mg,0.09mmol)在MeOH(2.0mL)中的溶液添加Pd/C(10%,15mg)。在H_2气氛下将所得混合物在室温搅拌4h。将反应混合物通过硅藻土过滤并将滤液减压浓缩,得到(S)-4-(1-苯基乙氧基)哌啶(18mg,定量)。LCMSm/z=206.2$[M+H]^+$.

[0728] (R)-3-(环己基甲氧基)哌啶

[0729] 

[0730] 步骤1:在0℃向(R)-3-羟基哌啶-1-甲酸叔丁酯(200mg,0.99mmol)在DMF(2mL)中的溶液添加NaH(79mg,1.99mmol),并将混合物搅拌30分钟。添加苄基溴(153mg,0.89mmol)并将反应温热至室温并搅拌过夜。添加水并用EtOAc萃取水层。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过硅胶柱色谱法(20%EtOAc/PE)纯化,得到(R)-3-(苄氧基)哌啶-1-甲酸叔丁酯(240mg,83%),其为白色固体。^{1}HNMR(400MHz,DMSO-d_6)δ7.38-7.25(m,5H),4.57-4.46(m,2H),3.37-3.06(m,4H),1.82-1.36(m,14H).

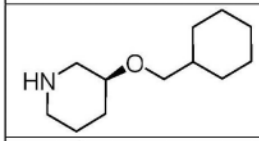
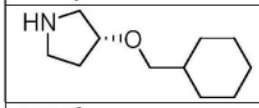
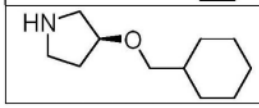
[0731] 步骤2:向(R)-3-(苄氧基)哌啶-1-甲酸叔丁酯(150mg,0.51mmol)在EtOAc(2mL)中的溶液添加Rh(在Al_2O_3上5%,15mg)。将该混合物在H_2气氛下搅拌过夜。将混合物过滤并在真空中浓缩滤液,得到(R)-3-(苄氧基)哌啶-1-甲酸叔丁酯(144mg,94%),其为白色固体。^{1}HNMR(400MHz,$CDCl_3$)δ3.67-3.52(m,2H),3.49-3.22(m,3H),3.18-2.80(m,2H),1.96-1.58(m,8H),1.55-1.33(m,13H),1.32-1.09(m,3H).

[0732] 步骤3:向(R)-3-(苄氧基)哌啶-1-甲酸叔丁酯(144mg,0.48mmol)在DCM(1mL)中的溶液添加HCl(4M二噁烷溶液,1mL)。混合物在室温搅拌3小时。然后真空除去溶剂,得到白色固体的(R)-3-(环己基甲氧基)哌啶(112mg,定量)。LCMSm/z=198.2$[M+H]^+$.

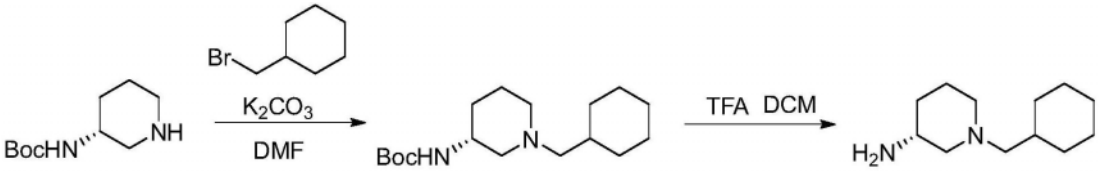
[0733] 根据(R)-3-(环己基甲氧基)哌啶的步骤概述,使用合适的市售试剂合成以下化合

物。

[0734]

化合物	LCMS
	198.2 $[M+H]^+$
	184.2 $[M+H]^+$
	184.2 $[M+H]^+$

[0735] (R)-1-(环己基甲基)哌啶-3-胺

[0736] 

[0737] 步骤1:向(R)-哌啶-3-基氨基甲酸叔丁酯(500mg,2.50mmol)在DMF(10.0mL)中的溶液添加(溴甲基)环己烷(451mg,2.56mmol)和K_2CO_3(690mg,5.00mmol)。将所得混合物在50℃加热4h。添加水并用EtOAc萃取水相三次。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过硅胶柱色谱法(30%EtOAc/PE)纯化,得到(R)-(1-(环己基甲基)哌啶-3-基)氨基甲酸叔丁酯(520mg,71%),其为无色油状物。^{1}HNMR(400MHz,CD_3OD)δ 3.64-3.45(m,1H),2.87-2.52(m,2H),2.18-2.08(m,2H),2.06-1.51(m,11H),1.47-1.41(m,9H),1.33-1.17(m,4H),0.96-0.83(m,2H).

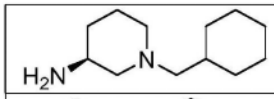
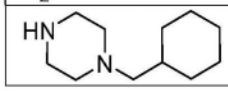
[0738] 步骤2:将(R)-(1-(环己基甲基)哌啶-3-基)氨基甲酸叔丁酯(35mg,0.12mmol)在HCl(4M二噁烷溶液,3mL)中的溶液在室温搅拌2h。除去溶剂,得到(R)-1-(环己基甲基)哌啶-3-胺(42mg,定量),其为无色油状物。

[0739] 根据(R)-1-(环己基甲基)哌啶-3-胺的步骤概述,使用合适的市售试剂合成以下化合物。

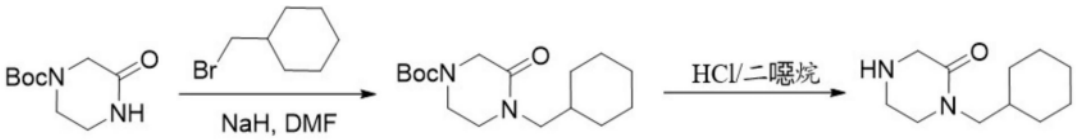
[0740]

化合物	LCMS

[0741]

	LCMS 未记录
	283.1 $[M+H]^+$

[0742] 1-(环己基甲基)哌嗪-2-酮

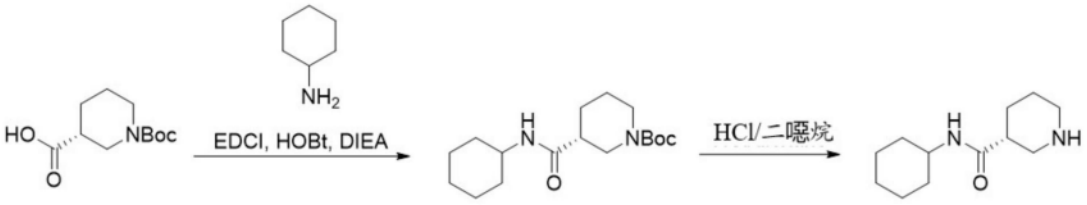
[0743] 

[0744] 步骤1:在0℃向3-氧代哌嗪-1-甲酸叔丁酯(500mg,2.5mmol)在DMF(5mL)中的溶液添加NaH(150mg,3.75mmol)。搅拌30分钟后,添加(溴甲基)环己烷(528mg,3.0mmol),并将溶液在40℃加热3小时。添加水并用EtOAc萃取水相三次。将合并的有机层用水、盐水洗涤并经

Na_2SO_4干燥。除去溶剂,得到4-(环己基甲基)-3-氧代哌嗪-1-甲酸叔丁酯(340mg,46%),其为白色固体。LCMSm/z=297.4[M+H]$^+$.

[0745] 步骤2:将4-(环己基甲基)-3-氧代哌嗪-1-甲酸叔丁酯(100mg,1.1mmol)在HCl(4M二噁烷溶液,3mL)中的溶液在室温搅拌4h。除去溶剂,得到1-(环己基甲基)哌嗪-2-酮(66mg,定量)。

[0746] (R)-N-环己基哌啶-3-甲酰胺

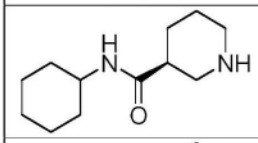
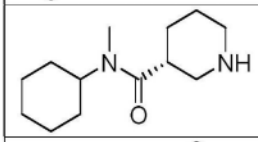
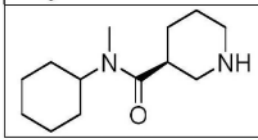
[0747] 

[0748] 步骤1:向(R)-1-(叔丁氧羰基)哌啶-3-甲酸(100mg,0.44mmol)在DMF(5mL)中的溶液添加环己胺(43mg,0.44mmol)、EDCI(88mg,0.66mmol)、HOBt(125mg,0.66mmol)和DIPEA(169mg,1.31mmol)。将所得混合物在室温搅拌过夜。添加水并用EtOAc萃取水相。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过硅胶柱色谱法(5%MeOH/DCM)纯化,得到(R)-3-(环己基氨基甲酰基)哌啶-1-甲酸叔丁酯(113mg,84%),其为白色固体。LCMSm/z=311.4[M+H]$^+$;^{1}HNMR(400MHz,$CDCl_3$)δ3.94-3.08(m,4H),2.29-2.17(m,1H),2.10-1.73(m,4H),1.73-1.65(m,2H),1.64-1.55(m,3H),1.46(s,9H),1.43-1.23(m,3H),1.21-1.02(m,3H).

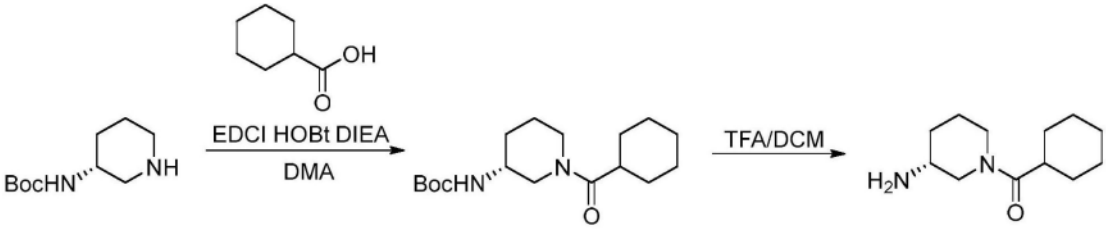
[0749] 步骤2:向(R)-3-(环己基氨基甲酰基)哌啶-1-甲酸叔丁酯(110mg,0.35mmol)在DCM(3mL)中的溶液添加HCl(4M二噁烷溶液,3mL)。将所得混合物在室温搅拌3h。除去溶剂,得到(R)-N-环己基哌啶-3-甲酰胺(90mg,定量)LCMSm/z=211.3[M+H]$^+$.

[0750] 根据(R)-N-环己基哌啶-3-甲酰胺的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0751]

化合物	LCMS
	211.1 [M+H]$^+$
	225.4 [M+H]$^+$
	225.1 [M+H]$^+$

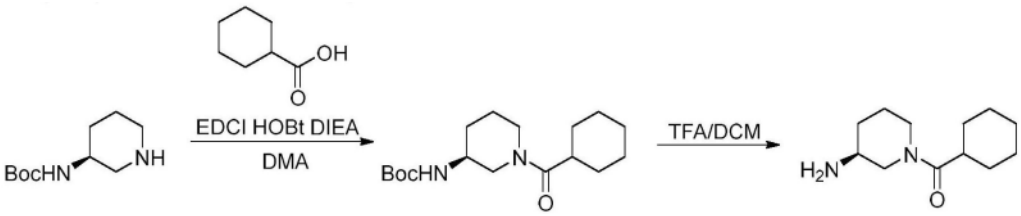
[0752] (R)-(3-氨基哌啶-1-基)(环己基)甲酮

[0753] 

[0754] 步骤1:向(R)-哌啶-3-基氨基甲酸叔丁酯(300mg,1.50mmol)在DMA(10mL)中的溶液添加环己烷甲酸(230mg,1.8mmol)、EDCI(432mg,2.3mmol),HOBt(304mg,2.3mol)和DIPEA(774mg,6.0mmol)。将所得混合物在室温搅拌过夜。添加水并将水相用EtOAc萃取三次。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将残留物通过硅胶柱色谱法(50%EtOAc/PE)纯化,得到(R)-(1-(环己烷羰基)哌啶-3-基)氨基甲酸叔丁酯(338mg,76%),其为白色固体。LCMSm/z=311.2$[M+H]^+$.

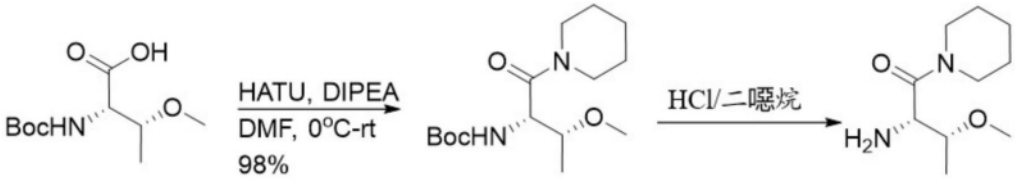
[0755] 步骤2:将(R)-(1-(环己烷羰基)哌啶-3-基)氨基甲酸叔丁酯(34mg,0.11mmol)在HCl(4M二噁烷溶液,3mL)中的溶液在室温搅拌2h。除去溶剂,得到(R)-(3-氨基哌啶-1-基)(环己基)甲酮(41mg,定量),其为淡黄色油状物。

[0756] (S)-(3-氨基哌啶-1-基)(环己基)甲酮

[0757] 

[0758] 使用与制备(R)-(3-氨基哌啶-1-基)(环己基)甲酮类似的步骤概述合成(S)-(3-氨基哌啶-1-基)(环己基)甲酮。LCMSm/z=211.2$[M+H]^+$.

[0759] (2S,3R)-2-氨基-3-甲氧基-1-(哌啶-1-基)丁-1-酮

[0760] 

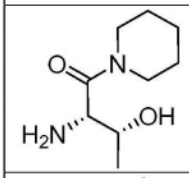
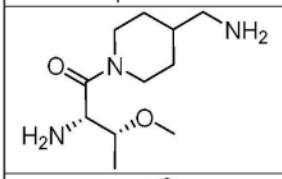
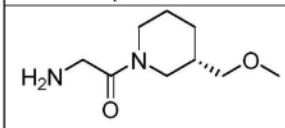
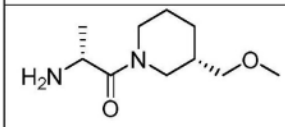
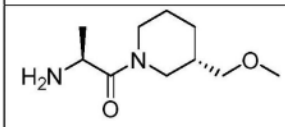
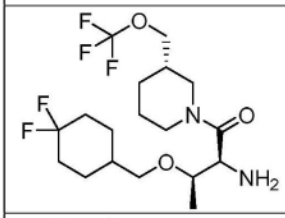
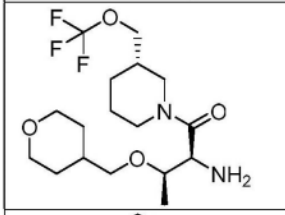
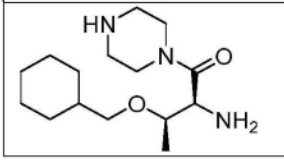
[0761] 步骤1:在0℃向(2S,3R)-2-((叔丁氧羰基)氨基)-3-甲氧基丁酸(500mg,2.15mmol)、哌啶(200mg,2.36mmol)和N,N-二异丙基乙胺(832mg,6.45mmol)在N,N-二甲基甲酰胺(3mL)中的溶液添加HATU(980mg,2.58mmol)。在N_2下将所得混合物在室温搅拌2h。将反应混合物倒入水(10mL)中并用乙酸乙酯(10mL x2)萃取。将合并的有机层用盐水(15mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩,得到粗品残留物,其通过柱色谱法使用20%乙酸乙酯/己烷的梯度纯化,得到(2S,3R)-3-甲氧基-1-氧代-1-(哌啶-1-基)丁-2-基)氨基甲酸叔丁酯(650mg,98%收率),其为无色油状物。^{1}HNMR(400MHz,DMSO-d6):δ6.51(d,J=8.6Hz,1H),4.35-4.41(m,1H),3.43-3.48(m,5H),3.23(s,3H),1.36-1.60(m,16H),1.02(d,J=6.2Hz,3H).

[0762] 步骤2:向(2S,3R)-3-甲氧基-1-氧代-1-(哌啶-1-基)丁-2-基)氨基甲酸叔丁酯(650mg,2.17mmol)在二氯甲烷(5mL)中的溶液添加氯化氢在二噁烷(4.0M,6mL)中的溶液;将所得混合物在室温搅拌3小时。将反应混合物在真空中浓缩,得到(2S,3R)-2-氨基-3-甲

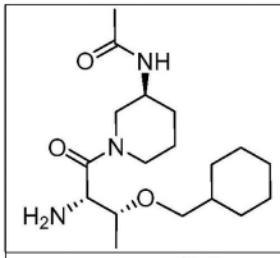
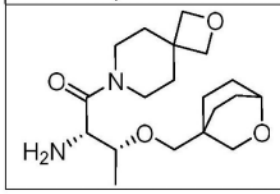
氧基-1-(哌啶-1-基)丁-1-酮(495mg,95%收率),其为浅黄色油状物。

[0763] 根据(2S,3R)-2-氨基-3-甲氧基-1-(哌啶-1-基)丁-1-酮的一般步骤概述,使用合适的市售试剂合成以下化合物。

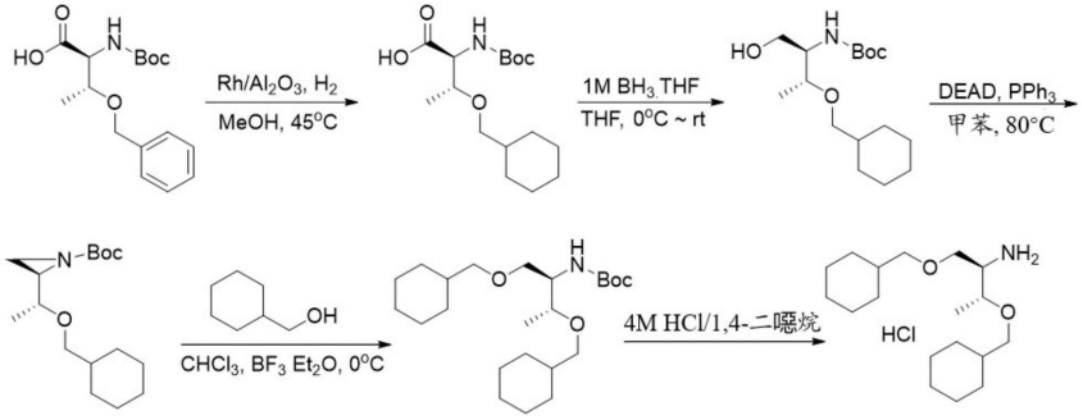
[0764]

化合物	表征
	LCMS 未记录
	LCMS 未记录 // ^{1}HNMR (400 MHz, $CDCl_3$): δ 4.64-4.67 (m, 2H), 4.04-4.08 (m, 1H), 3.65-3.66 (m, 1H), 3.38 (s, 3H), 3.00-3.05 (m, 3H), 2.54-2.62 (m, 1H), 1.69-1.77 (m, 6H), 1.44 (s, 9H), 1.09-1.23 (m, 5H).
	LCMS: m/z 287.1 $[M+H]^+$ // ^{1}HNMR (400 MHz, $CDCl_3$): δ 5.55 (s, 1H), 4.20-4.42 (m, 1H), 3.95-3.97 (m, 2H), 3.62 (q, J = 6.4Hz, 1H), 3.32 (s, 3H), 3.16-3.27 (m, 2H), 2.55-3.02 (m, 2H), 1.65-1.86 (m, 4H), 1.45 (s, 9H),1.30-1.33 (m, 1H).
	LCMS 未记录 // ^{1}H NMR (400 MHz, $CDCl_3$) δ5.70 (t, J = 10.2 Hz, 1H), 4.58-4.70 (m, 1H), 4.26-4.41 (m, 1H), 3.74-3.88 (m, 1H), 3.31 (s, 3H), 3.15-3.29 (m, 2H), 2.86-3.06 (m, 1H), 2.53-2.83 (m, 1H), 1.68-1.87 (m, 3H), 1.43 (s, 9H), 1.34-1.38 (m, 1H), 1.29 (t, J = 6.0 Hz, 4H).
	LCMS 未记录 // ^{1}HNMR (400 MHz, $CDCl_3$): δ 5.59-5.60 (m, 1H), 4.60-4.65 (m, 1H), 4.35-4.41 (m, 1H), 3.71-3.85 (m, 1H), 3.32 (s, 3H), 3.22-3.28 (m, 2H)3.05-3.11 (m, 0.5H), 2.84-2.90 (m, 0.5H), 2.57-2.72 (m, 1H), 1.79-1.83 (m, 2H), 1.44-1.48 (m, 11H), 1.28-1.30 (m, 4H).
	LCMS 未记录
	LCMS 未记录
	LCMS 未记录

[0765]

	LCMS 未记录
	353.1[M+H]$^+$

[0766] (2R,3R)-1,3-双(环己基甲氧基)丁-2-胺盐酸盐

[0767] 

[0768] 步骤1:将O-苄基-N-(叔丁氧羰基)-L-苏氨酸(4.4g,14.2mmol)和Rh/Al_2O_3(880mg,20%)在甲醇(50mL)中的混合物在45℃在氢气气氛(氢气球)下搅拌过夜。通过过滤除去催化剂,并用甲醇(20mL x2)洗涤。将合并的滤液在减压下浓缩,得到N-(叔丁氧基羰基)-O-(环己基甲基)-L-苏氨酸(4.6g,100%收率),其为无色油状物,其在下一步中使用而无需进一步纯化。LCMS:m/z 316.0[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$)δ4.31-4.39(m,1H),3.97-4.06(m,1H),3.36-3.43(m,1H),3.21-3.29(m,1H),1.52-1.74(m,5H),1.46(s,9H),1.10-1.29(m,7H),0.83-0.96(m,2H).

[0769] 步骤2:在0℃向N-(叔丁氧羰基)-O-(环己基甲基)-L-苏氨酸(4.9g,15.5mmol)在四氢呋喃(40mL)中的溶液逐滴添加硼烷-四氢呋喃络合物(1M,31.1mL)。将所得混合物在室温搅拌过夜。将反应混合物在0℃用甲醇淬灭,然后在减压下浓缩以得到粗品残留物,其通过柱色谱法使用15-25%乙酸乙酯/己烷的梯度纯化,得到((2R,3R)-3-(环己基甲氧基)-1-羟基丁-2-基)氨基甲酸叔丁酯(1.0g,22%收率),其为淡黄色油状物。LCMS:(ES$^+$):m/z 302.0[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$)δ5.00-5.15(m,1H),3.55-3.80(m,4H),3.34-3.41(m,1H),3.04-3.11(m,1H),2.74-2.85(m,1H),1.64-1.78(m,5H),1.45(s,9H),1.12-1.29(m,7H),0.85-0.99(m,2H).

[0770] 步骤3:在室温向叔丁基((2R,3R)-3-(环己基甲氧基)-1-羟基丁-2-基)(4.0g,13.3mmol)在无水甲苯(50mL)中的溶液添加三苯基膦(5.2g,19.9mmol);随后在0℃添加偶氮二甲酸二乙酯(3.1mL,19.9mmol)。在氮气气氛下将反应混合物在80℃搅拌过夜。将反应混合物在减压下浓缩以得到粗品残留物,其通过柱色谱法使用10-33%乙酸乙酯/己烷梯度

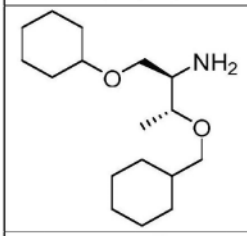
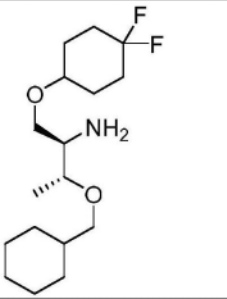
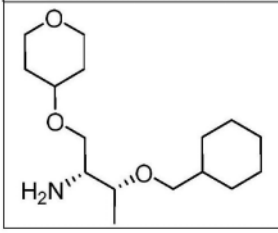
纯化,得到(R)-2-(((R)-1-(环己基甲氧基)乙基)氮丙啶-1-甲酸叔丁酯(1.8g,48%收率),其为无色油状物。LCMS:m/z 284.0[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$)δ3.54-3.60(m,1H),3.27-3.33(m,1H),3.13-3.21(m,1H),2.39-2.45(m,1H),2.24(d,J=6.8Hz,1H),1.93(d,J=3.6Hz,1H),1.63-1.83(m,5H),1.46(s,9H),1.12-1.32(m,7H),0.86-0.98(m,2H).

[0771] 步骤4:在0℃向(R)-2-((R)-1-(环己基甲氧基)乙基)氮丙啶-1-甲酸叔丁酯(400mg,1.4mmol)和环己基甲醇(209.5mg,1.8mmol)在二氯甲烷(8mL)中的混合物添加三氟化硼合乙醚(10.0mg,0.07mmol)。将所得混合物在0℃搅拌30分钟。将反应混合物用饱和碳酸氢钠水溶液在0℃淬灭,并用二氯甲烷(10mL x3)萃取。将合并的有机层用盐水洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用3%乙酸乙酯/己烷梯度纯化,得到((2R,3R)-1,3-双(环己基甲氧基)丁-2-基)氨基甲酸叔丁酯(360mg,收率64%).^{1}HNMR(400MHz,$CDCl_3$):δ4.78(d,J=9.2Hz,1H),3.60-3.73(m,2H),3.38(d,J=6.8Hz,2H),3.32-3.37(m,1H),3.17-3.26(m,2H),3.04-3.11(m,1H),1.62-1.80(m,10H),1.50-1.53(m,1H),1.44(s,9H),1.15-1.26(m,7H),1.12(d,J=6.4Hz,3H),0.85-0.97(m,4H).

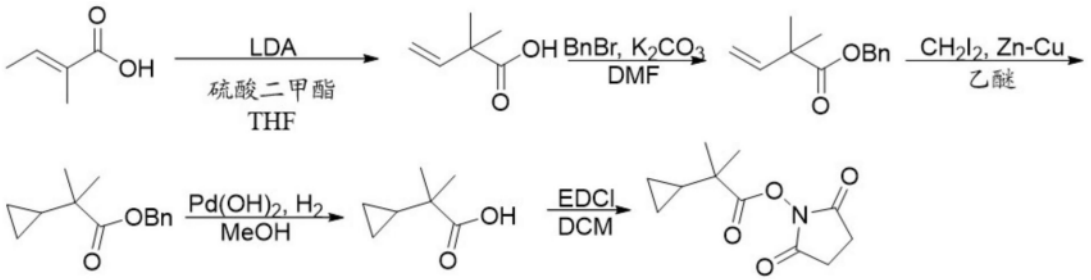
[0772] 步骤5:将(2R,3R)-1,3-双(环己基甲氧基)丁-2-基)氨基甲酸叔丁酯(68mg,0.17mmol)和在1,4-二噁烷(4M,1mL)中的氯化氢在二氯甲烷(2mL)中的混合物在室温搅拌1小时。在减压下除去挥发物以得到粗品(2R,3R)-1,3-双(环己基甲氧基)丁-2-胺盐酸盐(粗品75mg),其为白色固体。LCMS:m/z 298.4[M+H]$^+$.

[0773] 根据(2R,3R)-1,3-双(环己基甲氧基)丁-2-胺盐酸盐的一般步骤概述,使用合适的市售试剂合成以下化合物。

[0774]

化合物	LCMS
	LCMS 未记录
	320.4
	LCMS 未记录

[0775] 2-环丙基-2-甲基丙酸2,5-二氧代吡咯烷-1-基酯

[0776] 

[0777] 步骤1:在-70℃向LDA(2M,55mL,109.87mmol)在无水四氢呋喃(60mL)中的溶液缓慢逐滴添加(E)-2-甲基丁-2-烯酸(5.000g,49.94mmol)在四氢呋喃(20mL)中的溶液,并将所得混合物在0℃搅拌30分钟。将反应混合物再次冷却至-70℃,然后逐滴添加硫酸二甲酯(6.30g,49.94mmol)在无水四氢呋喃(20mL)中的溶液。将所得混合物在-70℃搅拌1h,然后温热至室温并搅拌1h。将反应混合物用水(100mL)淬灭,并用乙醚(100mL×3)洗涤以除去一些杂质。在0℃将水层用盐酸(3.0M)酸化,并用乙酸乙酯(100mL×3)萃取。将合并的有机层用盐水(100mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用50%乙酸乙酯/己烷的梯度纯化,得到2,2-二甲基丁-3-烯酸(3.500g,61%),其为无色油状物。

[0778] 步骤2:在N_2气氛下在室温向2,2-二甲基丁-3-烯酸(2.200g,19.27mmol)在无水N,N-二甲基甲酰胺(30mL)中的搅拌溶液中添加碳酸钾(5.300g,38.55mmol)。将所得混合物在室温搅拌5分钟,然后添加苄基溴(3.600g,21.20mmol),并将混合物在室温搅拌过夜。然后将反应混合物倒入水(50mL)中,并用乙酸乙酯(50mL×2)萃取。将合并的有机相用盐水(50mL×3)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用100%己烷的梯度纯化,得到2,2-二甲基丁-3-烯酸苄酯(1.200g,31%),其为无色油状物。MS[MH]$^+$205.0

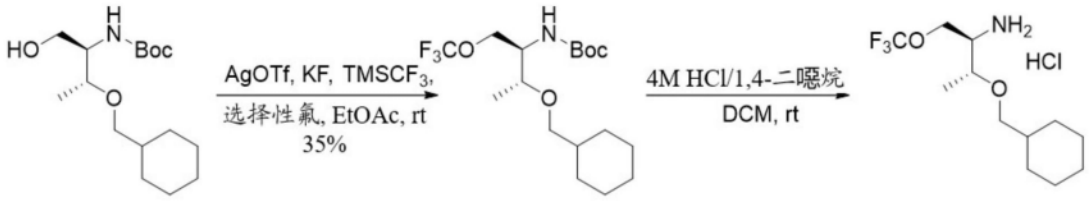
[0779] 步骤3:在室温在氩气气氛下向Zn-Cu合金(3g)在乙醚(20mL)中的悬浮液添加二碘甲烷(6.300g,23.50mmol),然后添加2,2-二甲基丁-3-烯酸酯(1.200g,5.87mmol)。在密封管中将所得混合物在60℃加热16小时。将反应混合物冷却至室温,并用乙酸乙酯(100mL)稀释。通过过滤去除固体,并用乙酸乙酯(20mL×2)洗涤滤饼。将合并的滤液用水(125mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用1%乙酸乙酯/己烷的梯度纯化,得到2-环丙基-2-甲基丙酸苄酯(0.950g,74%),其为无色油状物。MS[MH]$^+$219.0

[0780] 步骤4:向2-环丙基-2-甲基丙酸苄酯(950mg,4.36mmol)在甲醇(20mL)中的溶液添加Pd(OH)$_2$-C(100mg),并将混合物在氢气气氛下在室温搅拌过夜。通过过滤除去Pd(OH)$_2$-C,并用乙醇(10mL x2)洗涤。将合并的滤液在减压下浓缩,得到2-环丙基-2-甲基丙酸(0.540g,97%),其为无色油状物,其在下一步中使用无需进一步纯化。

[0781] 步骤5:在0℃向2-环丙基-2-甲基丙酸(0.540g,4.21mmol)和1-羟基吡咯烷-2,5-二酮(0.582g,5.06mmol)在二氯甲烷(10mL)中的溶液添加N-(3-二甲基氨基丙基)-N'-乙基碳二亚胺盐酸盐(0.969g,5.06mmol)。将所得混合物在室温搅拌过夜。然后将反应混合物倒入水(30mL)中,并用二氯甲烷(30mL×2)萃取。将合并的有机相用盐水(20mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用10%乙酸乙酯/己烷的梯度纯化,得到2-环丙基-2-甲基丙酸2,5-二氧代吡咯烷-1-基酯(730mg,收率77%),

其为无色油状物。

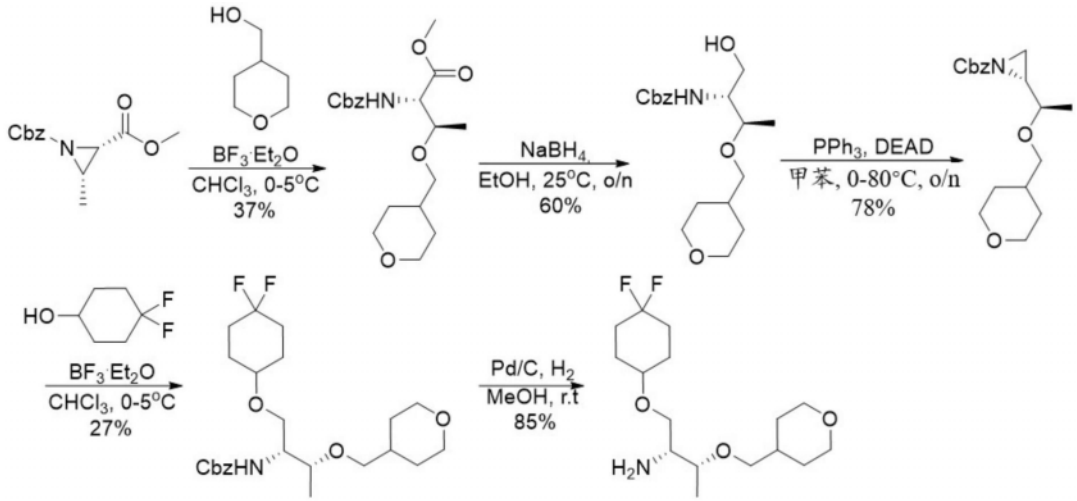
[0782] (2R,3R)-3-环己基甲氧基-1-(三氟甲氧基)丁烷-2-胺

[0783] 

[0784] 步骤1:在室温向((2R,3R)-3-(环己基甲氧基)-1-羟基丁-2-基)氨基甲酸叔丁酯(540mg,1.79mmol)、三氟甲磺酸银(921.2mg,3.59mmol)、氟化钾(312.0mg,5.37mmol)和选择性氟(selectfluour)(951.3mg,2.69mmol)在乙酸乙酯(10mL)中的混合物添加2-氟吡啶(348.6mg,3.59mmol)和(三氟甲基)三甲基硅烷(510.5mg,3.59mmol)。在氮气气氛下将所得混合物在室温搅拌过夜。将混合物通过短垫过滤并将滤饼用乙酸乙酯(8mL×2)洗涤;将合并的滤液在减压下浓缩以得到粗品残留物,其通过柱色谱法使用3.3%乙酸乙酯/已烷的梯度纯化,得到((2R,3R)-3-(环己基甲氧基)-1-(三氟甲氧基)丁-2-基)氨基甲酸叔丁酯(233mg,35%收率),其为无色油状物。LCMS:m/z 370.0[M+H]$^+$.^{1}HNMR(400MHz,$CDCl_3$):δ4.80(d,J=10.0Hz,1H),3.89-3.99(m,2H),3.74-3.85(m,1H),3.58-3.66(m,1H),3.34-3.41(m,1H),3.01-3.08(m,1H),1.64-1.78(m,5H),1.45(s,9H),1.10-1.26(m,7H),0.89-0.98(m,2H).

[0785] 步骤2:向((2R,3R)-3-(环己基甲氧基)-1-(三氟甲氧基)丁-2-基)氨基甲酸叔丁酯(100mg,0.27mmol)在二氯甲烷(2mL)中的溶液添加在1,4-二噁烷(4.0M,2mL)中的氯化氢。将所得混合物在室温搅拌1小时。将反应混合物在真空中浓缩,得到粗品(2R,3R)-3-(环己基甲氧基)-1-(三氟甲氧基)丁-2-胺。

[0786] (2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-胺

[0787] 

[0788] 步骤1:在0℃向(四氢-2H-吡喃-4-基)甲醇(500mg,4.304mmol)和(2S,3S)-3-甲基氮丙啶-1,2-二甲酸1-苄基2-甲基酯(1.07g,4.304mol)在氯仿(5mL)中的溶液逐滴添加三氟化硼合乙醚(611mg,4.3mmol);在氮气气氛下将所得混合物在0℃搅拌4小时。将反应混合物浓缩以得到粗品残留物,其通过柱色谱法使用25%乙酸乙酯/二氯甲烷的梯度纯化,得到(2S,3R)-2-(((苄氧基)羰基)氨基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁酸甲酯(585mg,37%收率),其为黄色油状物。LCMS:m/z 366.4[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$):δ7.31-7.38

(m,5H),5.42(d,J＝4.6Hz,1H),5.14(s,2H),4.33-4.36(m,1H),3.98-4.03(m,1H),3.92-3.95(m,2H),3.74(s,3H),3.31-3.39(m,3H),3.04-3.08(m,1H),1.63-1.74(m,2H),1.51-1.57(m,2H),1.22-1.24(m,1H),1.20(d,J＝3.2Hz,3H).

[0789] 步骤2:在0℃向(2S,3R)-2-(((苄氧基)羰基)氨基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁酸甲酯(250mg,0.684mmol)在乙醇(3mL)中的溶液添加硼氢化钠(78mg,2.052mmol);在氮气气氛下将所得混合物在25℃搅拌过夜。将反应混合物倒入水(6mL)中,并用二氯甲烷(8mLx4)萃取。将合并的有机层用盐水(8mL)洗涤,经无水硫酸钠干燥并浓缩以得到粗品残留物,其通过柱色谱法使用50％乙酸乙酯/二氯甲烷的梯度纯化,得到((2R,3R)-1-羟基-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-基)氨基甲酸苄酯(150mg,收率65％),其为无色油状物。LCMS:m/z 338.5[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$):δ7.33-7.38(m,5H),5.26(s,1H),5.12(s,2H),3.94-3.98(m,2H),3.69-3.77(m,4H),3.34-3.44(m,3H),3.14(t,J＝7.6Hz,1H),2.47(s,1H),1.77(s,1H),1.61(s,2H),1.31-1.38(m,2H),1.19(d,J＝3.0Hz,3H).

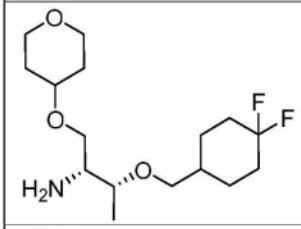
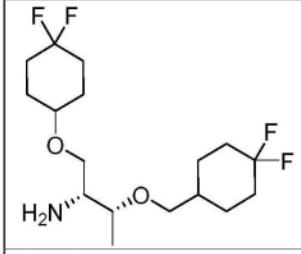
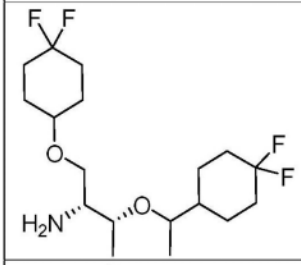
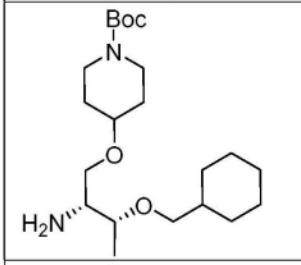
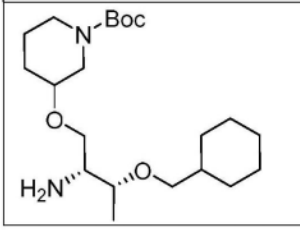
[0790] 步骤3:在0℃向((2R,3R)-1-羟基-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-基)氨基甲酸苄酯(150mg,0.445mmol)和三苯基膦(163mg,0.622mmol)在甲苯(2mL)中的溶液逐滴添加偶氮二甲酸二乙酯(108mg,0.6222mmol);在氮气气氛下将所得混合物在80℃搅拌过夜。将混合物浓缩以得到粗品残留物,其通过柱色谱法使用10％乙酸乙酯/二氯甲烷的梯度纯化,得到(R)-2-((R)-1-((四氢-2H-吡喃-4-基)甲氧基)乙基)氮丙啶-1-甲酸苄酯(130mg,收率78％),其为无色油状物。LCMS:m/z 320.2[M+H]$^+$.^{1}H NMR(400MHz,$CDCl_3$):δ7.31-7.35(m,5H),5.09-5.17(m,2H),3.89-3.94(m,2H),3.60-3.64(m,1H),3.29-3.38(m,3H),3.14-3.20(m,1H),3.49-3.54(m,1H),2.33(d,J＝3.4Hz,1H),2.02(d,J＝2.0Hz,1H),1.73-1.80(m,1H),1.62(s,1H),1.54(s,1H),1.28-1.33(m,2H),1.20(d,J＝3.2Hz,3H).

[0791] 步骤4:在0℃向(R)-2-((R)-1-((四氢-2H-吡喃-4-基)甲氧基)乙基)氮丙啶-1-甲酸苄酯(130mg,0.407mmol)和4,4-二氟环己醇(56mg,0.407％mmol)在氯仿(2mL)中的溶液逐滴添加三氟化硼合乙醚(29mg,0.204mmol);在氮气气氛下将所得混合物在0℃搅拌4小时。将反应混合物浓缩以得到粗品残留物,其通过柱色谱法使用17％乙酸乙酯/二氯甲烷的梯度纯化,得到((2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-基)氨基甲酸苄酯(50mg,27％收率),其为无色油状物。^{1}H NMR(400MHz,$CDCl_3$):δ7.32-7.37(m,5H),5.10(d,J＝2.4Hz,1H),3.94-3.98(m,2H),3.66-3.74(m,2H),3.34-3.48(m,7H),3.11(t,J＝7.8Hz,1H),1.92-2.02(m,2H),1.70-1.84(m,6H),1.59-1.65(m,2H),1.32-1.36(m,3H),1.16(d,J＝3.0Hz,3H).

[0792] 步骤5:向((2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-基)氨基甲酸苄酯(50mg,0.11mmol)在甲醇(10mL)中的溶液添加钯/碳(10％,5mg)。在氢气气氛(氢气球)下将得到的混合物在室温搅拌2小时。通过过滤除去钯/碳,并用甲醇(10mL x2)洗涤;将合并的有机溶液在减压下浓缩,得到(2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-胺(30mg粗品),其为白色固体。^{1}H NMR(400MHz,$CDCl_3$):δ3.95-3.98(m,2H),3.30-3.50(m,7H),3.12-3.16(m,1H),2.78-2.84(m,1H),1.97-2.09(m,2H),1.70-1.91(m,6H),1.64-1.67(m,2H),1.31-1.38(m,2H),1.20(t,J＝7.0Hz,1H),1.14(d,J＝3.0Hz,3H).

[0793] 根据(2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-胺的步骤概述,使用合适的市售试剂合成以下化合物。

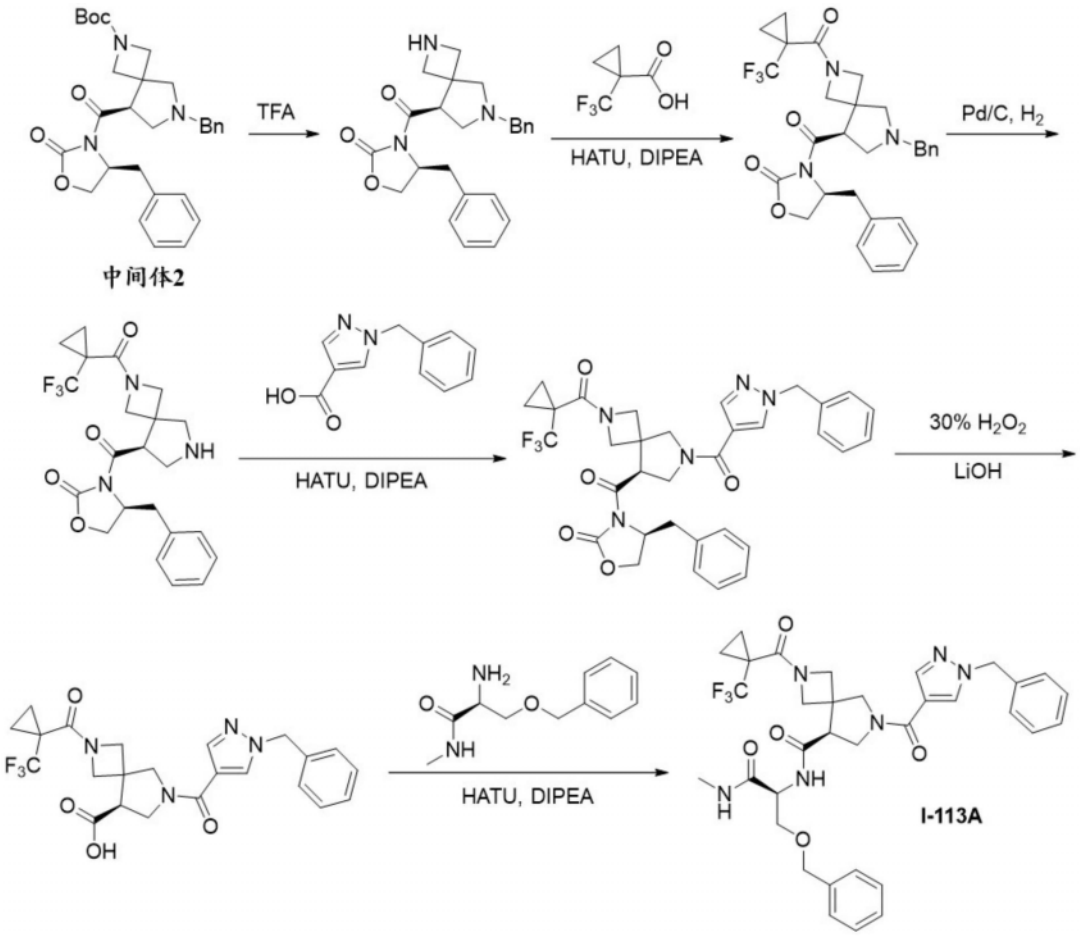
[0794]

化合物	表征
	LCMS 未记录
	LCMS 未记录
	^{1}HNMR (400 MHz, $CDCl_3$): δ 3.41-3.49 (m, 3H), 3.29-3.38 (m, 2H), 2.80-2.84 (m, 1H), 1.96-2.15 (m, 4H), 1.60-1.88 (m, 10H), 1.33-1.47 (m, 3H), 1.10-1.15 (m, 6H).
	^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69-3.80 (m, 5H), 3.55-3.59 (m, 1H), 3.35-3.39 (m, 1H), 3.18-3.27 (m, 2H), 3.09-3.15 (m, 2H), 1.84-1.85 (m, 3H), 1.65-1.76 (m, 7H), 1.45 (s, 9H), 1.13-1.24 (m, 5H), 0.86-0.94 (m, 3H).
	LCMS: m/z 385.5 $[M+H]^+$.

[0795] 实施例2:示例性化合物的合成

[0796] 方法1A,以I-113A的合成为例:

[0797]



[0798] 步骤1:向中间体2(0.4g,0.79mmol)在DCM(5mL)中的溶液添加TFA(1mL)并将反应混合物在室温搅拌1h。在真空下除去溶剂,得到(S)-4-苄基-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(320mg,100%),其直接用于下一步。LCMSm/z=406.1[M+H]$^+$.

[0799] 步骤2:向1-(三氟甲基)环丙烷-1-甲酸(146mg,0.95mmol)在DCM(5mL)中的溶液添加HATU(330mg,0.87mmol),并将混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(320mg,0.79mmol)和DIPEA(408mg,3.16mmol)并将反应在室温再搅拌2h。将混合物用水(60mL)稀释,并用DCM(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=3:1至DCM/EtOAc=3/1),得到(S)-4-苄基-3-((S)-6-苄基-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(0.4g,90%),其为黄色油状物。LCMSm/z=542.2[M+H]$^+$.

[0800] 步骤3:向(S)-4-苄基-3-((S)-6-苄基-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(367mg,0.68mmol)在EtOAc(8mL)中的溶液添加10%Pd/C(145mg)。将反应混合物在H_2气氛下搅拌24h。转化约为50%。将混合物通过硅藻土过滤并浓缩。将残留物再溶于EtOAc(8mL)中,并添加另一批10%Pd/C(145mg)。将反应在H_2气氛下再搅拌24h。将混合物过滤并浓缩,得到(S)-4-苄基-3-((S)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(305mg,100%),其直接用于下一步。LCMSm/z=452.1[M+H]$^+$;

[0801] 步骤4:向1-苄基-1H-吡唑-4-甲酸(54mg,0.27mmol)在DMF(2mL)中的溶液添加HATU(127mg,0.33mmol)。将混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(100mg,0.22mmol)和DIPEA(115mg,0.89mmol),将反应在室温再搅拌2小时。将混合物用水(100mL)稀释,并用EtOAc(150mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM/MeOH=30/1),得到(S)-4-苄基-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(70mg,50%),其为黄色油状物。LCMSm/z=636.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d6)δ8.46-8.28(m,1H),7.89-7.81(m,1H),7.37-7.08(m,10H),5.40-5.33(m,2H),4.68(s,1H),4.41-4.32(m,2H),4.27-4.10(m,4H),4.05-4.04(m,1H),3.87-3.68(m,3H),2.99-2.83(m,2H),1.16-1.15(m,3H).

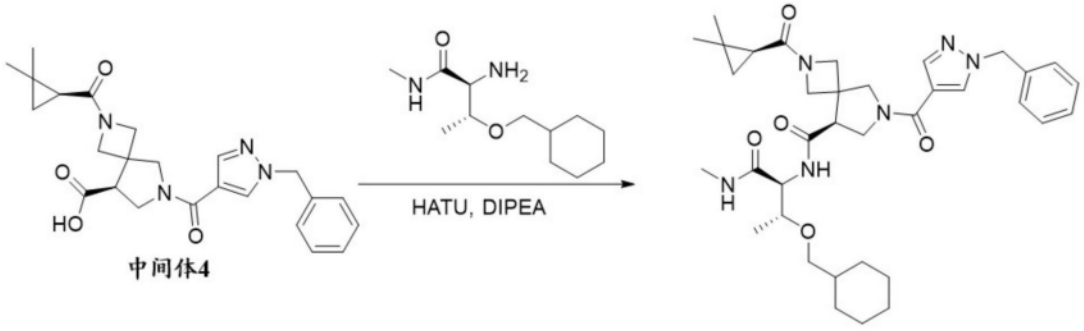
[0802] 步骤5:在0℃向(S)-4-苄基-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(100mg,0.16mmol)在THF和H_2O(6mL/0.5mL)的混合物中的溶液添加氢氧化锂一水合物(17mg,0.39mmol)在H_2O(0.5mL)中的溶液和30%H_2O_2(11mg,0.31mmol)在H_2O(0.5mL)中的溶液。将反应混合物在0℃搅拌2小时,然后用水(50mL)稀释并用EtOAc(80mL)萃取。收集水层并用1M HCl酸化至pH~2,然后用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(63mg,84%),其为白色固体,其直接用于下一步。LCMSm/z=477.1[M+H]$^+$.

[0803] 步骤6:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(63mg,0.13mmol)在DMF(2mL)中的溶液添加HATU(76mg,0.20mmol),并将反应在室温搅拌30分钟。添加(S)-2-氨基-3-(苄氧基)-N-甲基丙酰胺(33mg,0.16mmol)和DIPEA(69mg,0.53mmol)并将混合物在室温再搅拌2h。在真空下除去溶剂,将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((S)-3-(苄氧基)-1-(甲基氨基)-1-氧代丙-2-基)-2-(1-(三氟甲基)环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-113A)(26mg,30%),其为白色固体。LCMSm/z=667.4[M+H]$^+$;^{1}HNMR(400MHz,DMSO-d6)δ8.58(s,1H),8.35(d,J=8.0Hz,1H),8.04(s,1H),7.82(d,J=12.2Hz,1H),7.42-7.22(m,10H),5.36(s,2H),4.55(s,1H),4.46(s,2H),3.97-3.54(m,11H),2.59(dd,J=8.4,4.6Hz,3H),1.24(dd,J=13.4,6.8Hz,2H),1.18-1.10(m,2H).

[0804] 方法1B:以I-113B的合成为例:

[0805] 通过与方法1A类似的步骤,从中间体1代替中间体2开始来制备I-113B。

[0806] 方法2A:以I-123A的合成为例:

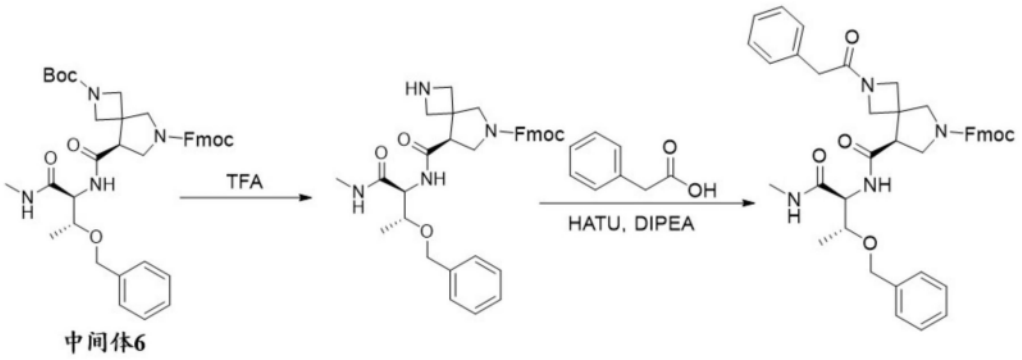
[0807] 

[0808] 向(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(中间体4)(1.10g,2.52mmol)在DCM(15mL)中的溶液添加HATU(1.44g,3.78mmol),并将反应混合物在室温搅拌30分钟。添加(2S,3R)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺(633mg,2.77mmol)和DIPEA(1.30g,10.08mmol)并将反应再搅拌3小时。在真空下除去溶剂,并将残留物通过反相柱(51%乙腈/水)纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-123A)(1.15g,72%),其为白色固体。LCMSm/z=647.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.41-8.31(m,1H),8.25-8.1(m,1H),7.88-7.68(m,2H),7.4-7.21(m,5H),5.35(s,2H),4.31-4.03(m,3H),4.03-3.58(m,7H),3.55-3.38(m,1H),3.26-3.16(m,1H),3.15-3.05(m,1H),2.63-2.55(m,3H),1.71-1.56(m,5H),1.50-1.26(m,2H),1.22-0.99(m,12H),0.91-0.75(m,3H),0.70-0.63(m,1H).

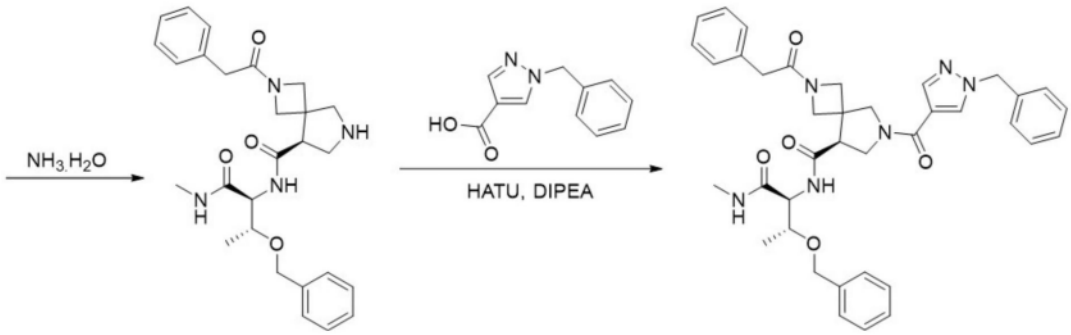
[0809] 方法2B:以I-123B的合成为例

[0810] 通过与方法2A类似的步骤,从中间体3代替中间体4开始来制备I-123B。

[0811] 方法3A:以I-25A的合成为例

[0812] 

中间体6



[0813] 步骤1:向中间体6(0.2g,0.3mmol)在DCM(5mL)中的溶液添加TFA(1mL)。将反应混合物在室温搅拌1h,然后在真空下除去溶剂,得到(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲酯(171mg,100%),其直接用于下一步。LCMSm/z=583.4[M+H]$^+$.

[0814] 步骤2:向2-苯基乙酸(44mg,0.32mmol)在DCM(5mL)中的溶液添加HATU(166mg,0.44mmol),并将混合物在室温搅拌30分钟。添加(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸酯(170mg,0.29mmol)和DIPEA(1.51mg,1.17mmol),并将反应再搅拌2h。将混合物用水(60mL)稀释,并用EtOAc

(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-(2-苯基乙酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸酯(150mg,73%),其为白色固体。LCMSm/z=701.4[m+H]+。

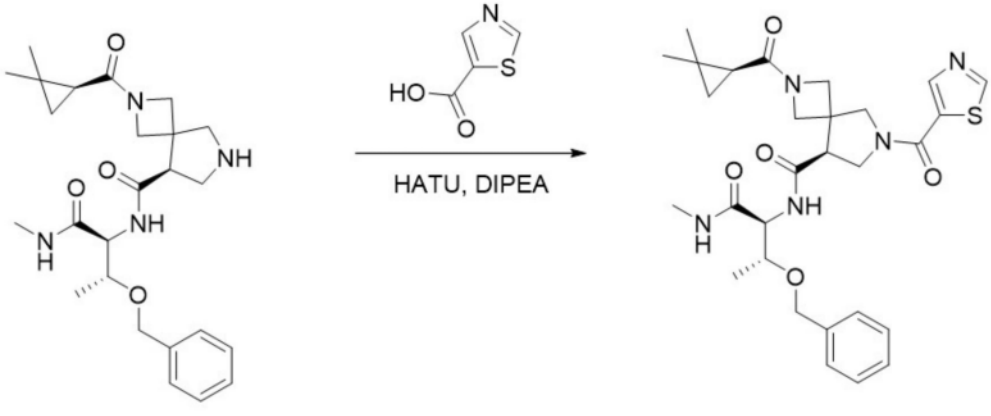
[0815] 步骤3:向(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-(2-苯基乙酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸酯(150mg,0.21mmol)在1,4-二噁烷(5mL)中的溶液添加25%氢氧化铵(5mL)。将反应混合物在50℃加热过夜。在真空下除去溶剂并将残留物用乙醚(20mL×2)研磨,得到(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-苯基乙酰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(40mg,30%),其为白色固体。LCMSm/z=479.2$[M+H]^+$.

[0816] 步骤4:向1-苄基-1H-吡唑-4-甲酸(16mg,0.08mmol)在DMF(1mL)中的溶液添加HATU(49mg,0.13mmol),并将混合物在室温搅拌30分钟。添加(S)-6-(1-苄基-1-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-苯基乙酰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(40mg,0.08mol)和DIPEA(41mg,0.32mmol),并将反应再搅拌2小时。将混合物用水(60mL)稀释,并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-苯基乙酰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-25A)(20mg,45%),其为白色固体。LCMSm/z=663.4$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.39-8.29(m,2H),7.82(d,J=12.0Hz,2H),7.38-7.23(m,13H),7.21-7.13(m,2H),5.35(s,2H),4.56-4.40(m,2H),4.38-4.10(m,2H),4.07-3.86(m,4H),3.82-3.69(m,2H),3.68-3.35(m,3H),3.30(d,J=2.0Hz,2H),2.64-2.56(m,3H),1.04(m,J=14.4,7.0Hz,3H).

[0817] 方法3B:以I-25B的合成为例

[0818] 通过与方法3A类似的步骤,从中间体5代替中间体6开始来制备I-25B。

[0819] 方法4A:以I-24A的合成为例

[0820] 

中间体8

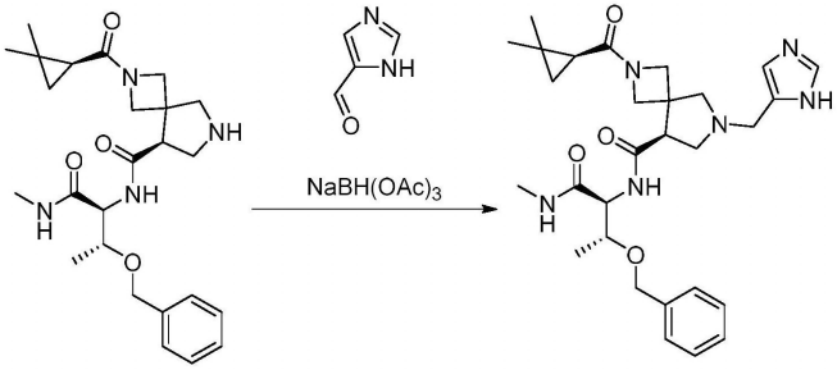
[0821] 向噻唑-5-甲酸(17mg,0.13mmol)在DMF(3mL)中的溶液添加HATU(65mg,0.16mmol)。将混合物在室温搅拌30分钟。添加中间体8(50mg,0.11mmol)和DIPEA(60mg,0.44mmol),并将反应混合物在室温再搅拌1h。将混合物用水(60mL)稀释,并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过制备型

HPLC纯化,得到(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-24A)(17mg,28%),其为白色固体。LCMSm/z=568.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ9.26(s,1H),8.45-8.35(m,2H),7.89(s,1H),7.40-7.20(m,5H),4.56-4.40(m,2H),4.39-4.16(m,2H),4.15-3.94(m,4H),3.93-3.70(m,3H),3.70-3.43(m,2H),2.62-2.58(m,3H),1.31-1.25(m,1H),1.10-1.02(m,9H),0.84(s,1H),0.64(s,1H).

[0822] 方法4B:以I-24B的合成为例

[0823] 通过与方法4A类似的步骤,从中间体7代替中间体8开始来制备I-24B。

[0824] 方法5A:以I-77A的合成为例

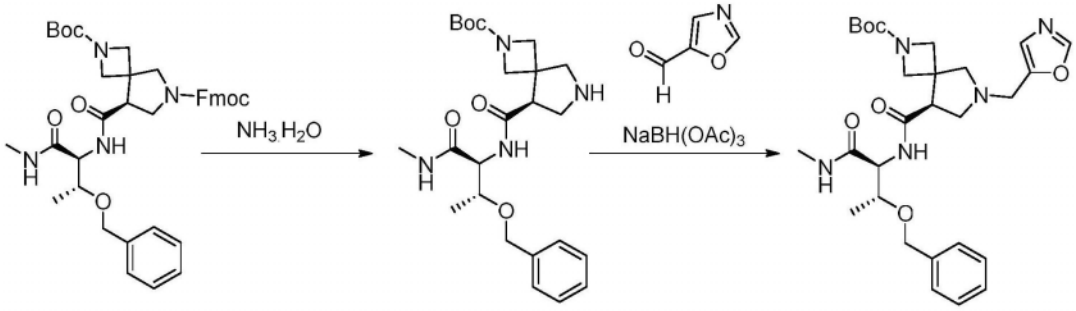
[0825] 

[0826] 向中间体8(80mg,0.17mmol)在DCE(2mL)中的溶液添加1H-咪唑-5-甲醛(18mg,0.18mmol)和NaBH(OAc)$_3$(148mg,0.70mmol),然后添加一滴AcOH。将所得混合物在室温搅拌过夜。在真空下除去溶剂,将残留物通过制备型HPLC纯化,得到(S)-6-((1H-咪唑-5-基)甲基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-77A)(35mg,37%),其为白色固体。LCMSm/z=537.4[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.23(dd,J=8.6Hz,1H),7.81(dd,J=13.2,5.6Hz,1H),7.60-7.54(m,1H),7.34-7.24(m,6H),6.90(s,1H),4.59-4.40(m,2H),4.40-4.24(m,2H),3.99-3.89(m,3H),3.74-3.63(m,1H),3.59-3.50(m,2H),3.28-3.20(m,1H),3.13-2.86(m,3H),2.67-2.57(m,5H),1.34-1.18(m,1H),1.14-1.02(m,6H),1.00(d,J=10.4Hz,3H),0.84-0.80(m,1H),0.65-0.60(m,1H).

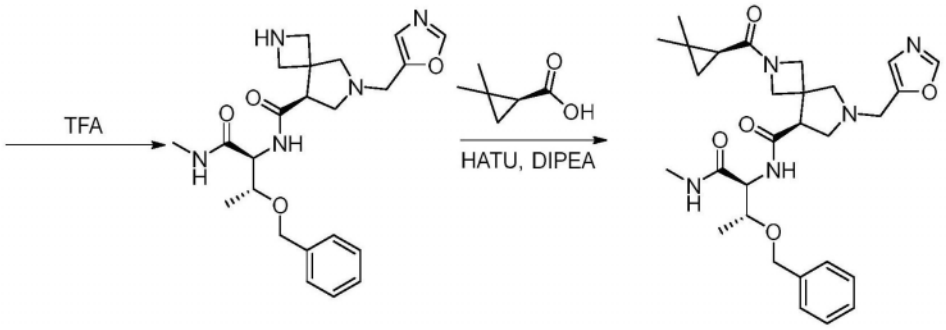
[0827] 方法5B:以I-77B的合成为例

[0828] 通过与方法5A类似的步骤,从中间体5代替中间体6开始来制备I-77B。

[0829] 方法6A:以I-78A的合成为例



[0830]



[0831] 步骤1:向中间体6(2.25g,3.30mmol)在1,4-二噁烷(14mL)中的溶液添加25%氢氧化铵(9mL)。将反应混合物在50℃加热过夜,然后在真空下除去溶剂。将残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=10:1),得到化合物(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(850mg,57%),其为黄色固体。LCMSm/z=461.2[M+H]$^+$.

[0832] 步骤2:向(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(100mg,0.22mmol)在DCE(2mL)中的溶液添加噁唑-5-甲醛(25mg,0.26mmol)、$NaBH(OAc)_3$(184mg,0.88mmol)和一滴AcOH。将所得混合物在室温搅拌过夜。将混合物用水(60mL)稀释,并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-6-(噁唑-5-基甲基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(95mg,81%),其为黄色固体。LCMSm/z=542.2[M+H]$^+$.

[0833] 步骤3:向(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-6-(噁唑-5-基甲基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸酯(95mg,0.18mmol)在DCM(2.5mL)中的溶液添加TFA(0.5mL)。将反应混合物在室温搅拌1h。在真空下除去溶剂,得到(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-6-(噁唑-5-基甲基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(77mg,100%),其直接用于下一步。LCMSm/z=442.1[M+H]$^+$.

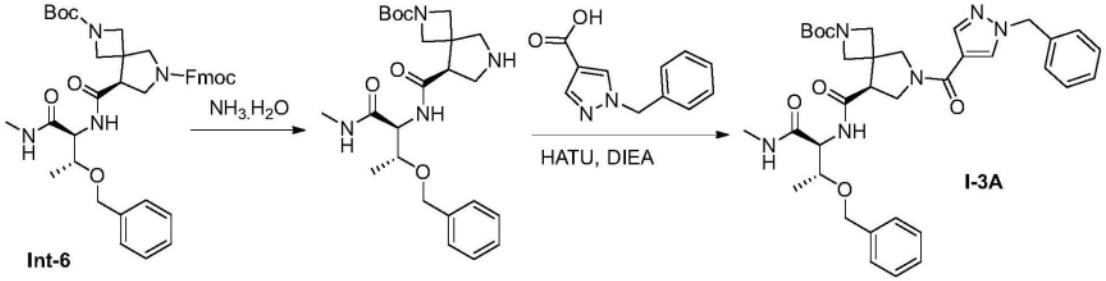
[0834] 步骤4:向(S)-2,2-二甲基环丙烷-1-甲酸(24mg,0.21mmol)在DCM(2mL)中的溶液添加HATU(100mg,0.26mmol),并将混合物在室温搅拌30分钟。添加(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-6-(噁唑-5-基甲基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(77mg,0.17mmol)和DIPEA(90mg,0.70mmol),并将反应混合物在室温再搅拌1h。将混合物用水(30mL)稀释,并用EtOAc(60mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将获得的残留物通过制备型HPLC纯化,得到(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噁唑-5-基甲

基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-78A)(12mg,13%),其为白色固体。LCMSm/z=538.2[M+H]$^+$;1H NMR(400MHz,DMSO-d_6)δ8.28(s,1H),8.26-8.18(m,1H),7.86-7.74(m,1H),7.34-7.24(m,5H),7.06(s,1H),4.54-4.48(m,1H),4.46-4.40(m,1H),4.36-4.30(m,1H),3.98-3.88(m,3H),3.74-3.62(m,3H),3.28-3.24(m,1H),3.00-2.88(m,2H),2.68-2.64(m,1H),2.62-2.54(m,4H),1.28(ddd,J=20.6,8.0,5.4Hz,1H),1.12-1.08(m,3H),1.06-0.98(m,6H),0.84-0.78(m,1H),0.66-0.58(m,1H).

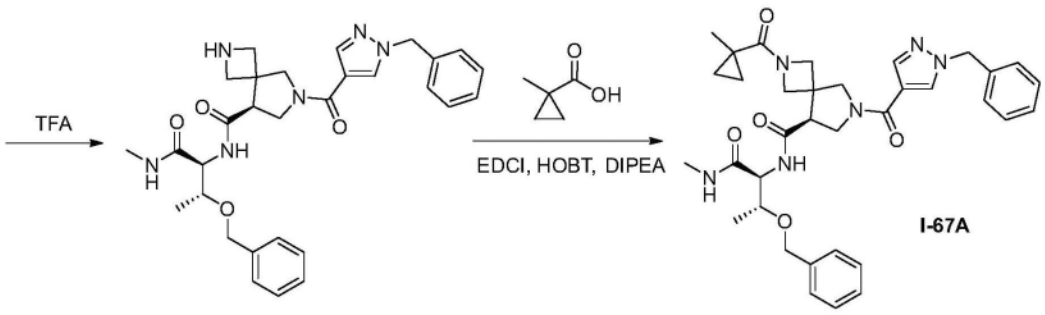
[0835] 方法6B:以I-78B的合成为例

[0836] 通过与方法6A类似的步骤,从中间体5代替中间体6开始来制备I-78B。

[0837] 方法7A:以通过I-3A合成I-67A为例



[0838]



[0839] 步骤1:向中间体6(2.25g,3.30mmol)在1,4-二噁烷(14mL)中的溶液添加25%氢氧化铵(9mL)。将反应混合物在50℃加热过夜,然后在真空下除去溶剂。将残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=10:1),得到化合物(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(850mg,57%),其为黄色固体。LCMSm/z=461.2[M+H]$^+$.

[0840] 步骤2:向1-苄基-1H-吡唑-4-甲酸(1.05g,5.21mmol)在DMF(20mL)中的溶液添加HATU(2.48g,6.50mmol),并将混合物在室温搅拌30分钟。添加(S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(参见方法6A)(2.0g,4.34mmol)和DIPEA(1.68g,13.02mmol),并将反应再搅拌3h。将混合物用水(80mL)稀释,并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(I-3A)(2.76g,99%),其为白色固体。LCMSm/z=645.5[M+H]$^+$;^{1}H NMR(400MHz,甲醇-d_4)δ8.19(d,J=16.6Hz,1H),7.90(d,J=9.8Hz,1H),7.30(dd,J=16.8,4.8Hz,10H),5.39-5.35(m,2H),4.62-4.43(m,3H),4.15-3.75(m,10H),2.73(d,J=10.4Hz,3H),1.41(s,9H),1.21(d,J=6.2Hz,3H).

[0841] 步骤3:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(苄氧基)-1-(甲基

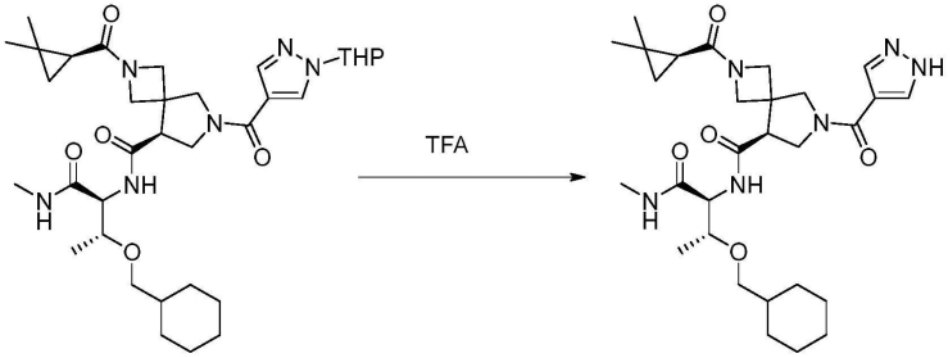
氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(70mg,0.11mmol)在DCM(2mL)中的溶液添加TFA(1mL)。将反应混合物在室温搅拌1h。在真空下除去溶剂,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(54mg,100%),其直接用于下一步。LCMSm/z=545.4[M+H]$^+$.

[0842] 步骤4:向1-甲基环丙烷-1-甲酸(11mg,0.11mmol)在DMA(1mL)中的溶液添加EDCI(27mg,0.14mmol)和HOBt(19mg,0.12mmol),并将混合物在室温搅拌30分钟。添加(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(60mg,0.09mmol)和DIPEA(48mg,0.37mmol)。将反应混合物在室温搅拌过夜,然后用水(60mL)稀释并用EtOAc(100mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(1-甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-67)(7mg,11%),其为白色固体。LCMSm/z=627.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.35(d,J=13.4Hz,2H),7.84-7.80(m,2H),7.38-7.23(m,10H),5.35(s,2H),4.53(d,J=12.0Hz,1H),4.47-4.29(m,3H),4.04-3.36(m,9H),2.60(dd,J=10.2,4.4Hz,3H),1.21-1.12(m,3H),1.08(t,J=5.4Hz,3H),0.87(s,2H),0.41(s,2H).

[0843] 方法7B:以通过I-3B合成I-67B为例

[0844] 通过与方法7A类似的步骤,从中间体5代替中间体6开始来制备I-3B和I-67B。

[0845] 方法8A:以I-66A的合成为例

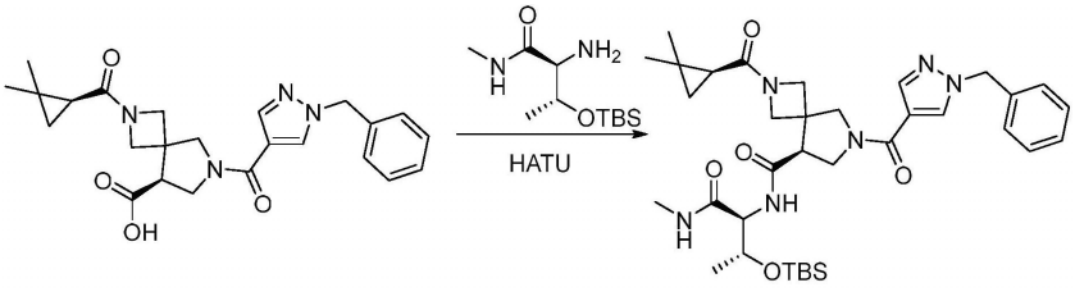
[0846] 

[0847] 向(8S)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(100mg,0.156mmol,根据方法1A由中间体2合成)在DCM(2mL)中的溶液添加TFA(1mL)。将反应混合物在室温搅拌1h。在真空下除去溶剂。将残留物通过制备型HPLC纯化,得到(S)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(30mg,35%),其为白色固体。LCMSm/z=557.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.17(dd,J=19.0,8.8Hz,1H),8.01(s,1H),7.82-7.67(m,1H),4.28-3.46(m,11H),3.25-3.21(m,1H),3.10(dd,J=9.4,6.4Hz,1H),2.60-2.56(m,3H),1.70-1.60(m,5H),1.44(s,1H),1.36-1.27(m,1H),1.19-1.12(m,3H),1.08(t,J=4.8Hz,3H),1.06-1.00(m,6H),0.88-0.78(m,3H),0.67(dd,J=8.0,4.0Hz,1H).

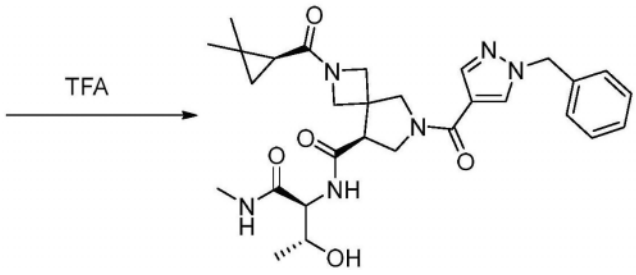
[0848] 方法8B:以I-66B的合成为例

[0849] 通过与方法8A类似的步骤,从中间体1代替中间体2开始来制备I-66B。

[0850] 方法9A:以I-88A的合成为例



[0851]



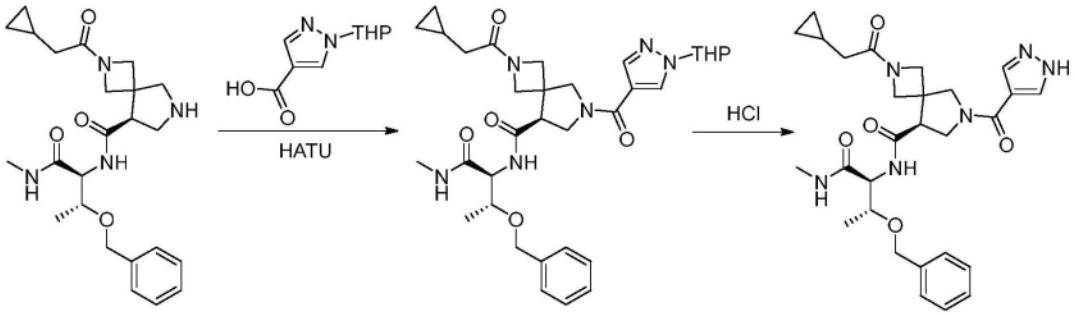
[0852] 步骤1:根据方法2A中的步骤概述,由中间体4合成(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺。LCMSm/z=665.5[M+H]$^+$.

[0853] 步骤2:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-((叔丁基二甲基甲硅烷基)氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(220mg,0.33mmol)在DCM(3mL)中的溶液添加TFA(2mL)。将反应混合物在室温搅拌过夜。在真空下除去溶剂,将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-N-((2S,3R)-3-羟基-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺,其为黄色固体。LCMSm/z=551.4[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d6)δ8.38-8.34(m,1H),8.19-8.13(m,1H),7.84-7.70(m,2H),7.37-7.25(m,5H),5.35(s,2H),4.26-4.13(m,2H),4.09-3.90(m,5H),3.78-3.73(m,4H),3.48-3.33(m,1H),2.61-2.56(m,2H),1.35-1.31(m,1H),1.12-1.01(m,9H),0.86-0.84(m,1H),0.69-0.64(m,1H).

[0854] 方法9B:以I-88B的合成为例

[0855] 通过与方法9A类似的步骤,从中间体3代替中间体4开始来制备I-88B。

[0856] 方法10A:以I-41A的合成为例

[0857] 

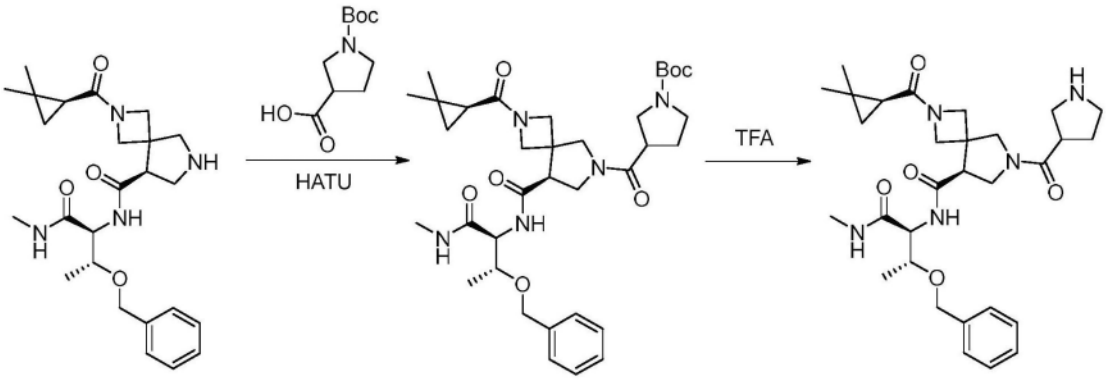
[0858] 步骤1:根据方法3A中的步骤概述,由中间体6合成(8S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-环丙基乙酰基)-6-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(30mg,27%),其为白色固体。LCMSm/z=621.4[M+H]$^+$.

[0859] 步骤2:将(8S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-环丙基乙酰基)-6-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(70mg,0.11mmol)在4M HCl/二噁烷(1mL)中的混合物在室温搅拌6h。在真空下除去溶剂。将残留物通过制备型HPLC纯化,得到(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2-环丙基乙酰基)-6-(1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺I-41A(16mg,36%),其为白色固体。LCMSm/z=537.4[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ13.22(s,1H),8.32(dd,J=23.6,9.0Hz,1H),7.84(s,2H),7.34-7.26(m,5H),4.55-4.40(m,2H),4.35(dd,J=8.6,3.4Hz,1H),4.20-3.38(m,10H),2.60(dd,J=11.2,4.4Hz,3H),1.88(dd,J=22.8,6.4Hz,2H),1.07(d,J=5.4Hz,3H),0.87(s,1H),0.40(s,2H),0.04(d,J=7.6Hz,2H).

[0860] 方法10B:以I-41B的合成为例

[0861] 通过与方法10A类似的步骤,从中间体5代替中间体6开始来制备I-41B。

[0862] 方法11A:以I-70A的合成为例

[0863] 

[0864] 步骤1:根据方法4A,由中间体8合成3-((S)-8-(((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6-羰基)吡咯烷-1-甲酸叔丁酯。LCMSm/z=654.3[M+H]$^+$.

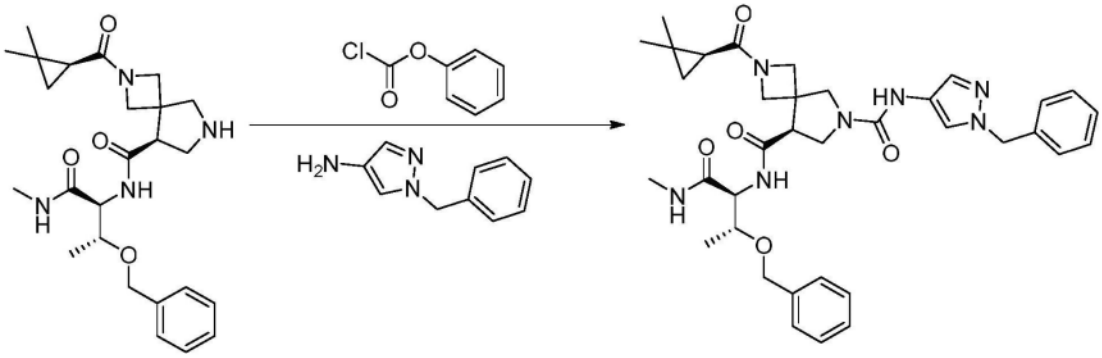
[0865] 步骤2:使用脱保护反应(类似于本文报道的中间体7,步骤1的条件)制备(8S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(吡咯烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-70A)。LCMSm/z=554.2[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.39-8.29(m,2H),7.92-7.82(m,1H),7.35-7.24(m,5H),

4.57-4.49(m,1H),4.47-4.40(m,1H),4.38-4.30(m,1H),4.23-4.11(m,1H),4.04-3.90(m,3H),3.84-3.74(m,2H),3.65-3.53(m,3H),3.47-3.39(m,2H),3.18-3.09(m,2H),3.01-2.93(m,2H),2.61(d,J=4.4Hz,3H),2.07-1.96(m,1H),1.91-1.78(m,1H),1.35-1.22(m,1H),1.11-1.00(m,9H),0.87-0.80(m,1H),0.68-0.60(m,1H).

[0866] 方法11B:以I-70B的合成为例

[0867] 通过与方法11A类似的步骤,从中间体7代替中间体8开始来制备I-70B。

[0868] 方法12A:以I-48A的合成为例

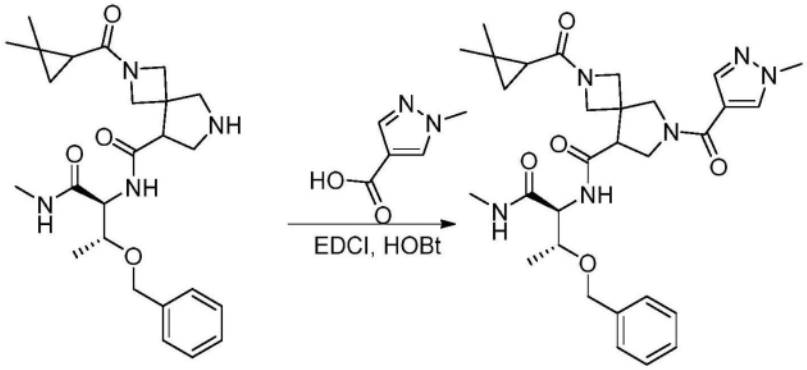
[0869] 

[0870] 在0℃向1-苄基-1H-吡唑-4-胺(34mg,0.164mmol)在无水THF(1mL)中的溶液添加TEA(66mg,0.657mmol)和氯甲酸苯酯(34mg、0.219mmol)。将反应混合物在0℃搅拌3h,然后用EtOAc(20mL)稀释并用盐水洗涤。有机层经Na_2SO_4干燥,过滤并浓缩,得到粗品(1-苄基-1H-吡唑-4-基)氨基甲酸苯酯,将其再溶解在干燥的DMF(1mL)中。将(S)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(中间体8)(50mg,0.110mmol)添加到混合物中,并在室温将反应搅拌过夜。将混合物用水(20mL)稀释,并用EtOAc(30mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过制备型TLC纯化(洗脱液:DCM:MeOH=20:1),得到(S)-N6-(1-苄基-1H-吡唑-4-基)-N8-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-6,8-二甲酰胺(I-48A):(5mg,7%),其为白色固体。LCMSm/z=656.1$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ8.31-8.25(m,2H),7.88-7.85(m,1H),7.75(s,1H),7.39(d,J=0.6Hz,1H),7.35-7.25(m,8H),7.19(s,1H),7.18(s,1H),5.23(s,2H),4.54-4.51(m,1H),4.44-4.37(m,1H),4.37-4.30(m,1H),4.23-4.14(m,1H),4.01-3.86(m,3H),3.71(dd,J=10.0,5.4Hz,1H),3.64-3.39(m,5H),2.61(d,J=4.6Hz,3H),1.36-1.25(m,1H),1.10-1.00(m,9H),0.84(t,J=4.6Hz,1H),0.66-0.58(m,1H).

[0871] 方法12B:以I-48B的合成为例

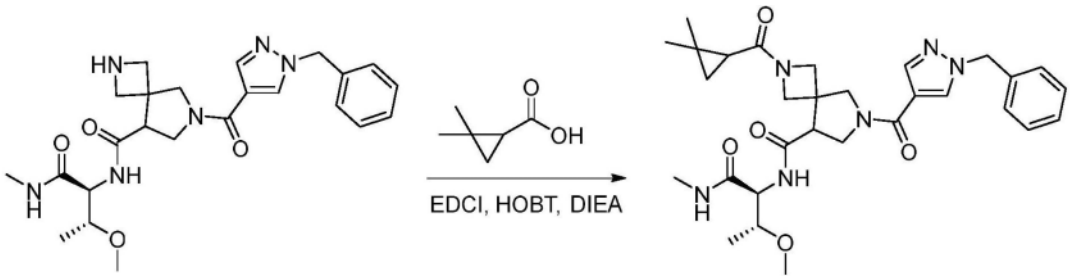
[0872] 通过与方法12A类似的步骤,从中间体7代替中间体8开始来制备I-48B。

[0873] 方法13:以I-14的合成为例

[0874] 

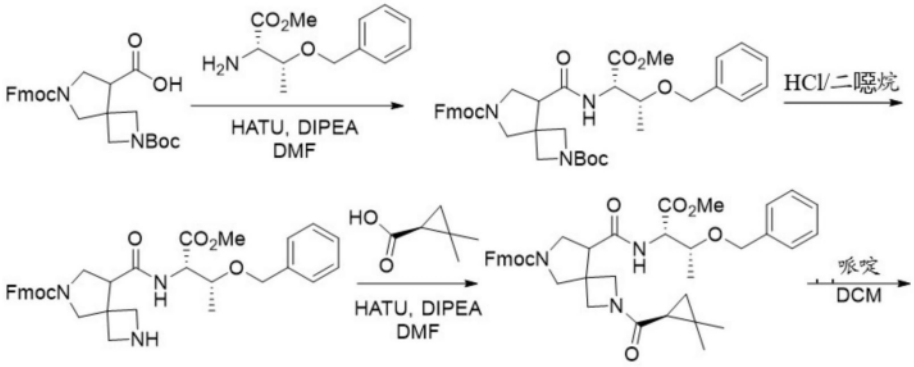
[0875] 向1-甲基-1H-吡唑-4-甲酸(18.4mg,0.146mmol)在无水DMA(2mL)中的溶液添加EDCI(35mg,0.184mmol)、HOBt(25mg,0.183mmol)和DIPEA(63mg,0.488mmol),并将混合物在室温搅拌1h。添加N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(中间体9)(60mg,0.122mmol),并将所得反应搅拌14h。将混合物用水(20mL)稀释,并用EtOAc(60mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将混合物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(2,2-二甲基环丙烷-1-羰基)-6-(1-甲基-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-14)(41mg,61%),其为白色固体。LCMSm/z=565.4[M+H]$^+$;^{1}H NMR(400MHz,甲醇-d_4)δ8.12-8.01(m,1H),7.90-7.80(m,1H),7.36-7.23(m,5H),4.65-3.83(m,15H),3.39(s,1H),2.74(s,3H),1.53-1.36(m,1H),1.24-1.09(m,9H),1.03(s,1H),0.77(s,1H).

[0876] 方法14:以I-2的合成为例

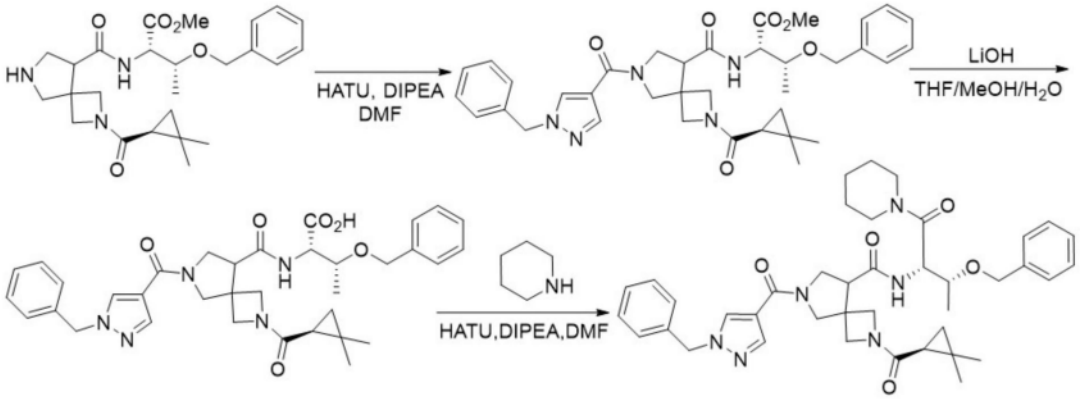
[0877] 

[0878] 向2,2-二甲基环丙烷-1-甲酸(15mg,0.127mmol)在无水DMF(1mL)中的溶液添加EDCI(20mg,0.104mmol)、HOBt(14mg,0.106mmol)和DIPEA(27mg,0.212mmol),并将混合物在室温搅拌1h。添加6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(中间体10)(50mg,0.106mmol),并将反应再搅拌4小时,然后用水(20mL)稀释并用EtOAc萃取(60mL×2)。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。通过制备型HPLC纯化混合物,得到6-(1-苄基-1H-吡唑-4-羰基)-2-(2,2-二甲基环丙烷-1-羰基)-N-((2S,3R)-3-甲氧基-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-2)(6.3mg,10%),其为白色固体。LCMSm/z=565.4[M+H]$^+$;^{1}H NMR(400MHz,甲醇-d_4)δ8.20(d,J=17.1Hz,1H),7.92(d,J=10.1Hz,1H),7.38-7.25(m,5H),5.37(s,2H),4.59-3.37(m,13H),2.78-2.70(m,3H),1.22-0.99(m,11H),0.82-0.73(m,1H).

[0879] 方法15:以通过I-9合成I-97的实例



[0880]



[0881] 步骤1:向6-(((9H-芴-9-基)甲氧基)羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(3.5g,7.31mmol)在N,N-二甲基甲酰胺(30mL)中的溶液添加(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(3.6g,9.5mmol)和N-乙基-N-异丙基丙-2-胺(2.8g,21.94mmol)。将所得混合物在室温搅拌30分钟,然后添加(2S,3R)-2-氨基-3-(苄氧基)丁酸甲酯盐酸盐(粗品)。将所得混合物在室温再搅拌2小时。将反应混合物倒入水(100mL)中,并用乙酸乙酯(50mL×3)萃取。将合并的有机层用盐水(50mL×3)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用30-50%乙酸乙酯/己烷的梯度纯化,得到8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-叔丁基酯(4.8g,96%收率),其为白色固体。^{1}HNMR(400MHz,$CDCl_3$):δ7.76(d,J=7.2Hz,2H),7.58-7.60(m,2H),7.30-7.40(m,7H),7.24-7.25(m,2H),6.34-6.38(m,1H),4.56-4.64(m,2H),4.34-4.40(m,3H),4.17-4.23(m,2H),4.03-4.09(m,1H),3.66-3.87(m,10H),2.98-3.03(m,1H),1.43-1.46(m,9H),1.26-1.28(m,3H).

[0882] 步骤2:将8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2,6-二甲酸6-((9H-芴-9-基)甲基)2-叔丁基酯(4.8g,7.02mmol)在二噁烷(4M,20mL)中的氯化氢溶液中的混合物在室温搅拌4小时。将反应混合物在真空中浓缩,得到粗品8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲酯盐酸盐,其用于下一步中无需进一步纯化。LCMS:m/z 585.0$[M+H]^+$.

[0883] 步骤3:向(S)-2,2-二甲基环丙烷-1-甲酸(801mg,7.02mmol)在N,N-二甲基甲酰胺(40mL)中的溶液添加(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(3.2g,8.42mol)和N-乙基-N-异丙基丙-2-胺(3.7mL,21.06mmol)。将所得混合物在室温搅

拌30min,然后添加8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲基酯盐酸盐(粗品,7.02mmol)。将所得混合物在室温再搅拌2小时。然后将反应混合物倒入水(100mL)中,并用乙酸乙酯(50mL×3)萃取。将合并的有机层用盐水(50mL×3)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用50%乙酸乙酯/己烷的梯度纯化,得到8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲基酯(2.99g,两步收率63%),其为白色固体。LCMS:680.2[M+H]$^+$.^{1}HNMR(400MHz,$CDCl_3$):δ7.76(d,J=7.6Hz,2H),7.58(d,J=7.2Hz,2H),7.30-7.40(m,7H),7.24-7.25(m,2H),6.41-6.54(m,1H),4.55-4.63(m,2H),4.08-4.45(m,7H),3.89-4.03(m,3H),3.63-3.77(m,6H),3.03-3.07(m,1H),1.14-1.23(m,11H),0.75-0.78(m,1H).

[0884] 步骤4:将8-(((2S,3R)-3-(苄氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-6-甲酸(9H-芴-9-基)甲基酯(2.99g,4.40mmol)和哌啶(2.0mL)在二氯甲烷(10mL)中的溶液在室温搅拌2小时。然后将反应混合物倒入水(50mL)中,并用乙酸乙酯(50mL×3)萃取。将合并的有机层用氯化铵(50mL×3)洗涤然后用盐水(50mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其使用10%甲醇/二氯甲烷的梯度进行柱色谱法纯化,得到(2S,3R)-3-(苄氧基)-2-(2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)丁酸甲酯(1.69g,84%收率),其为白色固体。LCMS:m/z 458.9[M+H]$^+$.^{1}HNMR(400MHz,DMSO-d_6):δ8.80-8.91(m,1H),8.30(br,2H),7.29-7.35(m,5H),4.51-4.57(m,2H),4.38-4.46(m,1H),4.02-4.23(m,3H),3.71-3.87(m,2H),3.46-3.55(m,3H),3.27-3.37(m,4H),1.03-1.32(m,10H),0.83-0.87(m,1H),0.66-0.72(m,1H).

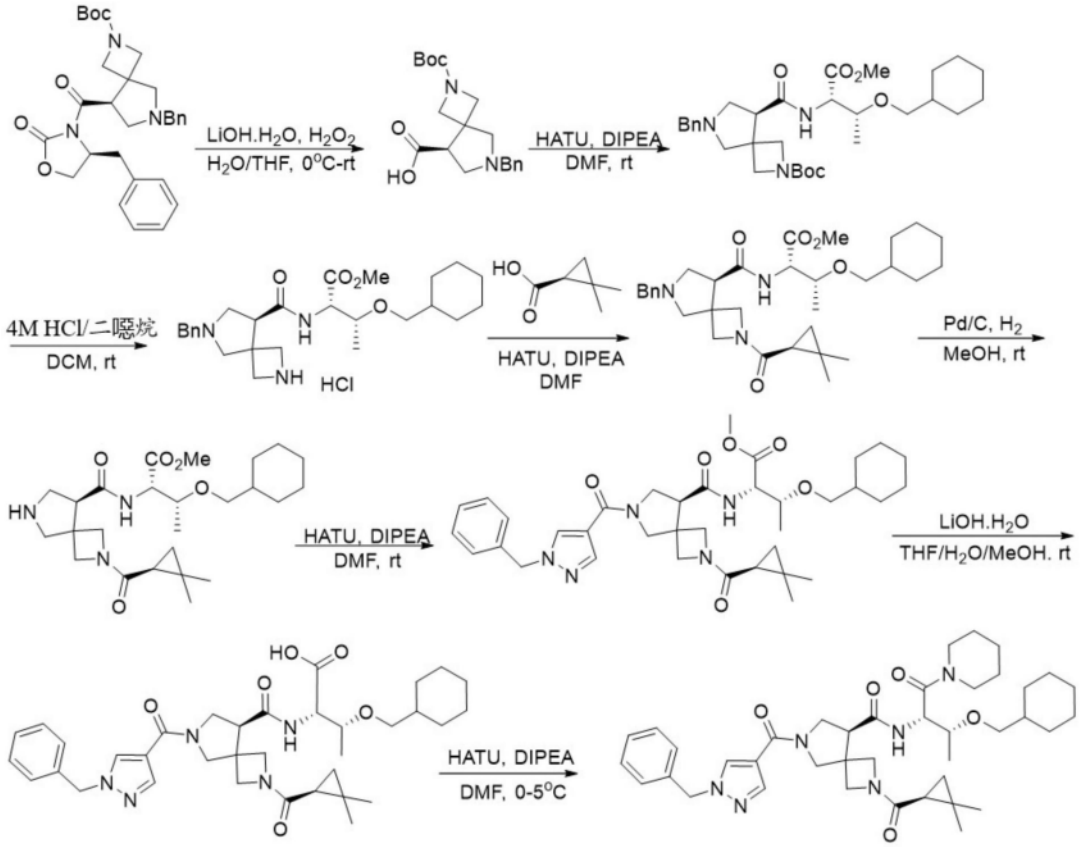
[0885] 步骤5:向1-苄基-1H-吡唑-4-甲酸(747mg,3.69mmol)在N,N-二甲基甲酰胺(35mL)中的溶液添加(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(1.7g,4.43mmol)和N-乙基-N-异丙基丙-2-胺(1.4g,11.08mmol)。将所得混合物在室温搅拌30分钟,然后添加(2S,3R)-3-(苄氧基)-2-(2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)丁酸甲酯(1.69g,3.69mmol)。将所得混合物在室温再搅拌4小时。然后将反应混合物倒入水中(50mL)并用乙酸乙酯(50mL×3)萃取。将合并的有机层用氯化铵(50mL×3)洗涤然后用盐水(50mL)洗涤,经无水硫酸钠干燥,在减压下浓缩以得到粗品残留物,其通过柱和色谱法使用10%甲醇/二氯甲烷的梯度纯化,得到(2S,3R)-2-(6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)-3-(苄氧基)丁酸甲酯(1.9g,80%收率),其为白色固体。LCMS:m/z 642.8[M+H]$^+$.^{1}HNMR(400MHz,CD_3OD):δ8.13-8.25(m,1H),7.92(d,J=8.0Hz,1H),7.27-7.34(m,10H),3.35-5.37(m,2H),4.59-4.64(m,2H),4.31-4.42(m,2H),3.78-4.25(m,8H),3.66(s,2H),3.60(d,J=6.0Hz,1H),3.38-3.48(m,1H),2.81(s,1H),1.30-1.44(m,2H),1.17-1.26(m,4H),1.10-1.15(m,4H),1.02-1.04(m,1H),0.74-0.79(m,1H).

[0886] 步骤6:向(2S,3R)-2-(6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)-3-(苄氧基)丁酸甲酯(300mg,0.47mmol)在四氢呋喃(6mL)-甲醇(3mL)-水(1.5mL)中的溶液添加氢氧化锂一水合物(20mg,0.47mmol,

1.0eq)。将所得混合物在0℃搅拌过夜。将反应混合物用盐酸(2.0N)酸化至pH 4-5,并用乙酸乙酯(20mL×3)萃取。将合并的有机相用盐水(10mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用10%甲醇/二氯甲烷的梯度纯化,得到(2S,3R)-2-(6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)-3-(苄氧基)丁酸(I-9)(240mg,收率82%),其为白色固体。LCMS:m/z 628.6[M+H]$^+$.^{1}HNMR(400MHz,CD_3OD):δ8.15-8.27(m,1H),7.93-7.95(m,1H),7.29-7.36(m,10H),5.38-5.40(m,2H),4.56-4.70(m,2H),4.20-4.51(m,4H),3.80-4.13(m,5H),3.40-3.50(m,1H),1.42-1.48(m,1H),1.32-1.37(m,1H),1.18-1.28(m,4H),1.11-1.18(m,4H),1.03-1.05(m,1H),0.75-0.79(m,1H).

[0887] 步骤7:在0℃向(2S,3R)-2-(6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)-3-(苄氧基)丁酸(25mg,0.04mmol)、哌啶(4.09mg,0.048mmol)和DIPEA(10.34mg,0.08mmol)在DMF(10mL)中的搅拌混合物添加HATU(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(22.8mg,0.06mmol)。将所得混合物在室温搅拌2h。将反应混合物在乙酸乙酯(30mL)和水(20mL)之间分配;收集有机层并用乙酸乙酯(10mL×2)萃取水层。将合并的有机层用盐水(30mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过预-TLC使用5%甲醇/二氯甲烷的梯度纯化,得到6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-氧代-1-(哌啶-1-基)丁-2-基)-2-((S)-2,2-二甲基环丙烷羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-97)(18mg,65%收率),其为白色固体。LCMS:m/z 695.5[M+H]$^+$.^{1}H NMR(400MHz,CD_3OD):δ8.14-8.23(m,1H),7.87-7.93(m,1H),7.17-7.42(m,10H),5.33-5.38(m,2H),4.93-4.98(m,1H),4.60-4.65(m,1H),4.50-4.56(m,1H),3.84-4.20(m,8H),3.43-3.58(m,4H),3.37(m,1H),2.19(t,J=7.6Hz,1H),2.02-2.03(m,1H),1.58-1.62(m,3H),1.43-1.53(m,4H),1.18(d,J=4.8Hz,2H),1.10-1.12(m,4H),1.02-1.04(m,1H),0.90(t,J=6.6Hz,2H),0.74-0.79(m,1H).

[0888] 方法16A:以I-194A的合成为例



[0889]

[0890] 步骤1:在0-5℃向(S)-6-苄基-8-((S)-4-苄基-2-氧代噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体2)(4.00g,7.92mmol)在四氢呋喃(30mL)中的溶液添加氢氧化锂一水合物(831mg,19.80mmol)和过氧化氢(30%H_2O溶液,1.8g,15.8mmol)在H_2O(2mL)中的溶液。将所得混合物在室温搅拌1h。将反应用亚硫酸钠水溶液(10mL)淬灭,并用乙酸乙酯(20mL×2)萃取。收集水层,用稀释的盐酸酸化至pH 4,并用IPA/DCM混合物(1:3,30mL x3)萃取。将合并的有机层用盐水(20mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩,得到粗品(S)-6-苄基-2-(叔丁氧羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(2.44g,89%收率),其为浅黄色固体。^{1}H NMR(400MHz,CDCl3)δ7.41-7.60(m,5H),4.24-4.46(m,2H),3.89-4.14(m,4H),3.40-3.82(m,5H),1.38(s,9H).

[0891] 步骤2:在0-5℃向(S)-6-苄基-2-(叔丁氧羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(2.74g,7.91mmol)、(2S,3R)-2-氨基-3-(环己基甲氧基)丁酸甲酯盐酸盐(1.99g,8.70mmol)和N-乙基-N-异丙基丙-2-胺(4.09g,31.64mmol)在N,N-二甲基甲酰胺(20mL)中的溶液添加2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(4.51g,11.86mmol)。将所得混合物在室温搅拌2小时。TLC显示反应完全。将反应混合物在乙酸乙酯(35mL)和水(30mL)之间分配。收集有机层、用饱和氯化铵水溶液(15mL)洗涤然后用盐水(15mL)洗涤、经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过硅胶快速色谱法使用25%乙酸乙酯加25%二氯甲烷/己烷的梯度纯化,得到(S)-6-苄基-8-(((2S,3R)-3-(环己基甲氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(3.30g,74%收率),其为白色固体。^{1}HNMR(400MHz,$CDCl_3$):δ7.40-7.48(m,5H),7.14(br,1H),4.37-4.50(m,3H),3.81-4.04(m,6H),3.73(s,3H),3.56-3.71(m,3H),3.31-3.34(m,1H),3.02-3.06(m,1H),1.55-1.68(m,5H),1.43-1.53(m,1H),1.33-1.39(m,9H),

1.06-1.22(m,6H),0.80-0.89(m,2H).

[0892] 步骤3:向(S)-6-苄基-8-(((2S,3R)-3-(环己基甲氧基)-1-甲氧基-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(3.30g,5.92mmol)在二氯甲烷(20mL)中的混合物中添加氯化氢的二噁烷溶液(4.0M,10mL)。将所得混合物在室温搅拌一小时。TLC显示反应完全。将反应混合物在真空中浓缩,得到粗品N-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸甲酯,其用于下一步中无需进一步纯化。

[0893] 步骤4:在0-5℃向(S)-2,2-二甲基环丙烷-1-甲酸(743mg,6.51mmol)、粗品N-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸甲酯(5.92mmol)和N-乙基-N-异丙基丙-2-胺(4mL,23.67mmol)在N,N-二甲基甲酰胺(20mL)中的溶液添加2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(2.70g,7.10mmol)。将所得混合物在室温搅拌2小时。TLC显示反应完全。将反应混合物在乙酸乙酯(35mL)和水(30mL)之间分配。收集有机层、用饱和氯化铵水溶液(15mL)洗涤然后用盐水(15mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用50%乙酸乙酯/己烷的梯度纯化,得到N-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸甲酯(2.00g,两步收率61%),其为黄色固体。^{1}HNMR(400MHz,$CDCl_3$):δ8.16(d,J=9.2Hz,1H),7.27-7.37(m,5H),4.56-4.59(m,1H),4.20-4.25(m,1H),3.88-4.09(m,4H),3.67-3.75(m,5H),3.29-3.41(m,2H),3.01-3.07(m,2H),2.92-2.96(m,1H),2.70-2.73(m,1H),2.61-2.65(m,1H),1.60-1.65(m,4H),1.07-1.22(m,15H),0.79-0.94(m,3H),0.67-0.72(m,1H).

[0894] 步骤5:向N-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸甲酯(2.00g,3.61mmol)在甲醇(70mL)中的溶液添加钯/碳(10%,400mg)。在H_2下将所得混合物在室温搅拌过夜。TLC显示反应完全。通过过滤除去钯/碳,并用甲醇洗涤;将合并的有机溶液在减压下浓缩以得到粗品残留物,其通过柱色谱法使用5-10%甲醇/二氯甲烷的梯度纯化,得到O-(环己基甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯(1.29g,77%收率),其为灰白色固体。^{1}HNMR(400MHz,DMSO-d_6):δ8.72(dd,J=8.8,20.4Hz,1H),4.51-4.55(m,1H),4.06-4.25(m,2H),3.86-3.96(m,2H),3.73-3.81(m,1H),3.65(s,3H),3.48-3.59(m,4H),3.24-3.32(m,4H),3.02-3.06(m,1H),1.60-1.69(m,4H),1.37-1.49(m,1H),1.04-1.34(m,13H),0.79-0.87(m,3H),0.68-0.71(m,1H).

[0895] 步骤6:在0-5℃向O-(环己基甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯(150mg,0.32mmol)、1-苄基-1H-吡唑-4-甲酸(79mg,0.39mmol)和N-乙基-N-异丙基丙-2-胺(125mg,0.97mmol)在N,N-二甲基甲酰胺(2mL)中的溶液添加(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(148mg,0.39mmol)。将所得混合物在室温搅拌2小时。TLC显示反应完全。将反应混合物在乙酸乙酯(25mL)和水(25mL)之间分配。收集有机层、用饱和氯化铵水溶液(15mL)洗涤然后用盐水(15mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过制备型TLC使用5%甲醇/二氯甲烷的梯度纯化,得到N-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-

苏氨酸甲酯(144mg,68%收率),其为无色油状物。LCMS:m/z 648.4[M+H]$^+$.^{1}HNMR(400MHz,CD_3OD):δ8.20-8.23(m,1H),7.92(d,J=10.0Hz,1H),7.28-7.37(m,5H),5.38(s,2H),4.57-4.60(m,1H),3.79-4.39(m,10H),3.67-3.73(m,3H),3.36-3.51(m,2H),3.05-3.11(m,1H),1.63-1.74(m,5H),1.45-1.52(m,1H),1.11-1.27(m,12H),1.03-1.05(m,1H),0.89-0.96(m,2H),0.75-0.79(m,1H).

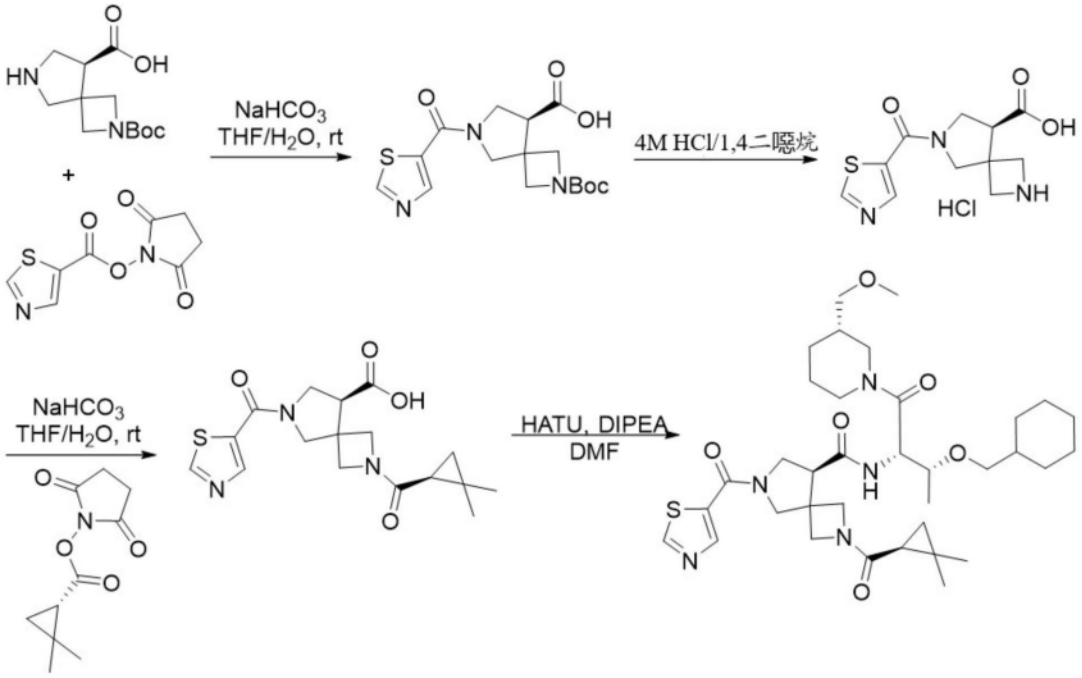
[0896] 步骤7:在0-5℃向N-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸甲酯(144mg,0.22mmol)在四氢呋喃(2mL)-甲醇(1mL)-水(1mL)中的溶液添加氢氧化锂一水合物(23mg,0.55mmol,2.5eq)。将所得混合物在0-5℃搅拌2小时。TLC显示反应完全。将反应混合物用盐酸(2.0N)酸化至pH 4-5,并用乙酸乙酯(10mL×2)萃取。将合并的有机层用盐水(10mL)洗涤、经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过制备型TLC使用10%甲醇/二氯甲烷的梯度纯化,得到N-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸(104mg,73%收率),其为白色固体。LCMS:m/z 634.4[M+H]$^+$.^{1}HNMR(400MHz,CD_3OD):δ8.22-8.25(m,1H),7.94(d,J=8.4Hz,1H),7.28-7.39(m,5H),5.40(s,2H),4.53-4.56(m,1H),3.81-4.43(m,10H),3.36-3.51(m,2H),3.14-3.19(m,1H),1.63-1.82(m,5H),1.49-1.59(m,1H),1.12-1.29(m,12H),1.04-1.08(m,1H),0.92-0.99(m,2H),0.77-0.80(m,1H).

[0897] 步骤8:在0-5℃向N-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-O-(环己基甲基)-L-苏氨酸(796mg,1.26mmol)、哌啶(128mg,1.51mmol)和N-乙基-N-异丙基丙-2-胺(487mg,3.77mmol)在N,N-二甲基甲酰胺(7mL)中的溶液添加(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(573mg,1.51mmol)。将所得混合物在室温搅拌2小时。TLC显示反应完全。然后将反应混合物倒入水中并用乙酸乙酯萃取。将合并的有机相用盐水洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用3.3%甲醇/二氯甲烷的梯度纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-氧代-1-(哌啶-1-基)丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(850mg,收率82%),其为白色固体。LCMS:m/z 701.5[M+H]$^+$.^{1}HNMR(400MHz,CD_3OD):δ8.19-8.23(m,1H),7.92(d,J=12.0Hz,1H),7.26-7.36(m,5H),5.38(s,2H),4.91-4.94(m,1H),3.71-4.41(m,10H),3.50-3.60(m,4H),3.33-3.46(m,2H),3.17-3.22(m,1H),1.38-1.76(m,13H),1.10-1.24(m,11H),1.03-1.05(m,1H),0.87-0.97(m,2H),0.76-0.81(m,1H).

[0898] 方法16B:以I-194B的合成为例

[0899] 通过与方法16A类似的步骤,从中间体1代替中间体2开始来制备I-194B。

[0900] 方法17A:以I-196A的合成为例

[0901] 

[0902] 步骤1:向(S)-2-(叔丁氧羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(参见中间体6的合成)(2g,7.80mmol)在水(20mL)中的溶液添加$NaHCO_3$(1.3g,15.60mmol),然后逐滴添加噻唑-5-甲酸2,5-二氧代吡咯烷-1-基酯(1.7g,7.80mmol)在THF中的溶液,并将所得混合物在室温搅拌1小时。然后将反应混合物倒入水(5mL)中,并用乙酸乙酯(20mL×2)萃取以除去杂质。将水层用盐酸(2N)调节pH至3-4,并用10%甲醇/二氯甲烷(20mL×5)萃取。将合并的有机相经无水硫酸钠干燥,并在真空中浓缩,得到粗品(S)-2-(叔丁氧基羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(2.4g,收率84%),其用于下一步无需进一步纯化。LCMS:m/z 311.8[M-56]$^+$.^{1}HNMR(400MHz,$CDCl_3$):δ8.97(s,1H),8.27(d,J=3.6Hz,1H),4.12-4.18(m,3H),3.75-4.05(m,6H),3.22-3.27(m,1H),1.44(d,J=5.6Hz,9H).

[0903] 步骤2:向(S)-2-(叔丁氧基羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(2.4g,6.53mmol)在二氯甲烷(20mL)中的溶液添加氯化氢/二噁烷(4.0M,20mL)。将所得混合物在室温搅拌6小时。将反应混合物在真空中浓缩,得到粗品(S)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸,其用于下一步无需进一步纯化。LCMS:m/z 267.8[M+H]$^+$.

[0904] 步骤3:向(S)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(粗品)在水(20mL)中的溶液添加$NaHCO_3$(2.7g,32.66mmol),然后逐滴添加(S)-2,2-二甲基环丙烷甲酸2,5-二氧代吡咯烷-1-基酯(1.3g,6.53mmol)在THF中的溶液,并将所得混合物在室温搅拌1小时。然后将反应混合物倒入水(5mL)中,并用乙酸乙酯(20mL×2)萃取以除去杂质。用盐酸(2N)将水层的pH调节至3-4,并用10%甲醇/二氯甲烷(20mL×5)萃取。将合并的有机相经无水硫酸钠干燥,并在真空中浓缩,得到粗品(S)-2-((S)-2,2-二甲基环丙烷羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(1.6g,两步收率67%),其用于下一步无需进一步纯化。LCMS:m/z 364.0[M+H]$^+$.^{1}HNMR(400MHz,$CDCl_3$):δ8.96(s,1H),8.28(d,J=6.0Hz,1H),3.83-4.49(m,9H),3.26-3.31(m,1H),1.16-1.18(m,7H),0.81-0.84(m,1H).

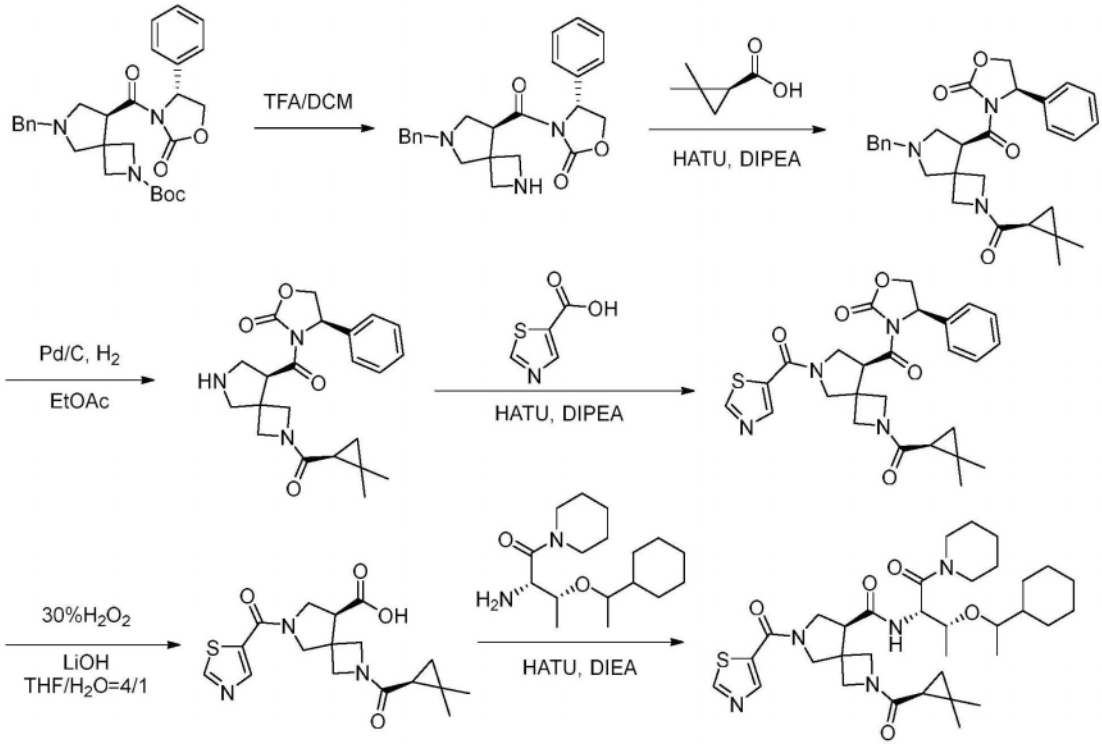
[0905] 步骤4:向粗品(S)-2-((S)-2,2-二甲基环丙烷羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(1.6g,4.35mmol)在N,N-二甲基甲酰胺(15mL)中的溶液添加(2S,

3R)-2-氨基-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)丁-1-酮盐酸盐(1.7g,4.79mmol)、N-乙基-N-异丙基丙-2-胺(2.3mL,13.06mmol)和(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(2.2g,5.66mmol)。将所得混合物在室温搅拌1小时。然后将反应混合物倒入水(30mL)中,并用乙酸乙酯(30mL×2)萃取。将合并的有机相用盐水(30mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用具有10%甲醇的50%乙酸乙酯/己烷的梯度纯化,得到(S)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-196A)(1.9g,收率64%),其为白色固体。LCMS:m/z 672.4[M+H]$^{+1}$HNMR(400MHz,CD_3OD):δ9.18(s,1H),8.39(d,J=13.2Hz,1H),4.95-4.99(m,1H),3.84-4.43(m,11H),3.71-3.76(m,1H),3.38-3.49(m,3H),3.20-3.28(m,5H),2.91-2.96(m,1H),2.64-2.72(m,1H),1.68-1.83(m,8H),1.41-1.53(m,3H),1.13-1.21(m,12H),1.05-1.08(m,1H),0.91-0.99(m,2H),0.79-0.84(m,1H).

[0906] 方法17B:以I-196B的合成为例

[0907] 通过与方法17A类似的步骤,从(R)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸开始制备I-196B。

[0908] 方法18:以I-284的合成为例

[0909] 

[0910] 步骤1:向(S)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体11)(1.1g,2.2mmol)在DCM(4mL)中的溶液添加TFA(2mL)。将反应混合物在室温搅拌2h。在真空下除去溶剂,得到粗品(R)-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)-4-苯基噁唑烷-2-酮(876mg,100%),其直接用于下一步。

[0911] 步骤2:向(S)-2,2-二甲基环丙烷-1-甲酸(274mg,2.4mmol)在DCM(10mL)中的溶液添加HATU(1.3g,3.3mmol)。将混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-6-苄基-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(876mg,2.2mmol)和DIPEA(1.1g,8.8mmol),

并将反应混合物在室温搅拌4h。将混合物用水(20mL)稀释,并用DCM(50mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将粗品通过柱色谱法在硅胶上纯化(洗脱液:石油醚:EtOAc=3:1至DCM/EtOAc=3:1),得到(R)-3-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-4-苯基噁唑烷-2-酮(900mg,82%),其为黄色固体。LCMSm/z=488.1$[M+H]^+$;^1H NMR(400MHz,DMSO-d6)δ7.44-7.24(m,10H),5.53-5.46(m,1H),4.78-4.71(m,1H),4.50-3.48(m,9H),3.21-2.53(m,3H),1.39-1.32(m,1H),1.28-1.22(m,2H),1.10(d,J=2.8Hz,3H),1.03(d,J=24.4Hz,3H),0.87-0.82(m,1H),0.71-0.64(m,1H).

[0912] 步骤3:向(S)-4-苄基-3-((S)-6-苄基-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(1.0g,2.1mmol)在EtOAc(8mL)中的溶液添加10%Pd/C(400mg)。将反应混合物在H_2气氛下搅拌24h。转化约为50%。将混合物通过硅藻土过滤并浓缩。将残留物再溶解在EtOAc(8mL)中,并添加另一批10%Pd/C(400mg)。将反应在H_2气氛下再搅拌24h。将混合物过滤并浓缩,得到(R)-3-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-4-苯基噁唑烷-2-酮(800mg,98%),其直接用于下一步。LCMSm/z=398.1$[M+H]^+$.

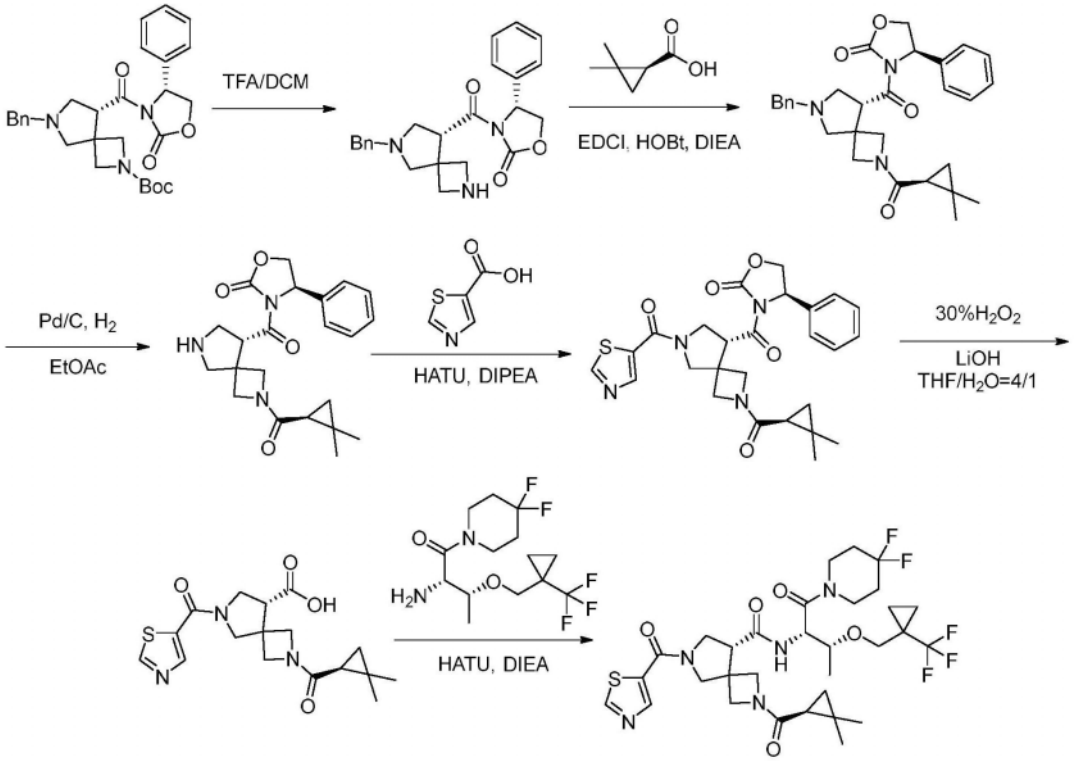
[0913] 步骤4:向1-苄基-1H-吡唑-4-甲酸(1.63g,12.6mmol)在DCM(50mL)中的溶液添加HATU(5.75g,15.1mmol),并将混合物在室温搅拌30分钟。添加(S)-4-苄基-3-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(5g,12.6mmol)和DIPEA(4.88g,37.8mmol),并将反应在室温再搅拌3h。将混合物用水(50mL)稀释,用DCM(150mL×2)萃取,并将合并的有机层用盐水洗涤,经Na_2SO_4干燥并过滤。除去溶剂,并将残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=30:1),得到(R)-3-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-4-苯基噁唑烷-2-酮(4.2g,66%),其为黄色固体。LCMSm/z=509.2$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ8.44-8.28(m,1H),7.88-7.76(m,1H),7.40-7.18(m,10H),5.36(d,J=4.4Hz,2H),4.70-4.60(m,1H),4.40-4.23(m,4H),4.21-4.01(m,3H),3.97-3.56(m,5H),3.18-2.84(m,3H),1.42-1.33(m,1H),1.28-1.21(m,5H),1.14-1.02(m,7H),0.86(d,J=7.2Hz,1H),0.69(d,J=6.4Hz,1H).

[0914] 步骤5:在0℃向(S)-4-苄基-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)噁唑烷-2-酮(1g,2mmol)在THF/H2O(8mL/1mL)的混合物中的溶液添加氢氧化锂一水合物(168mg,4mmol)在H_2O(0.5mL)中的溶液和30%H_2O_2(567mL,567mmol)在H_2O(0.5mL)中的溶液。将反应混合物在0℃搅拌1h,然后用水(20mL)稀释并用EtOAc(30mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(60mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品(S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(438mg,61%)其为黄色固体,其直接用于下一步。LCMSm/z=364.1$[M+H]^+$;^1H NMR(400MHz,DMSO-d6)δ9.26(s,1H),8.42-8.35(m,1H),4.37-3.70(m,9H),1.39-1.36(m,2H),1.15-1.01(m,6H),0.90-0.84(m,1H),0.73-0.64(m,1H).

[0915] 步骤6:向(S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(44mg,0.12mmol)在DCM(1mL)中的溶液添加HATU(42mg,0.11mmol),

并将混合物在室温搅拌30分钟。然后添加(2S,3R)-2-氨基-3-(1-环己基乙氧基)-1-(哌啶-1-基)丁-1-酮(30mg,0.10mmol)和DIPEA(39mg,0.30mmol),并将反应混合物在室温搅拌2h。将混合物用水(10mL)稀释,并用DCM(30mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥并过滤。除去溶剂并将粗品通过制备型HPLC纯化,得到(8S)-N-((2S,3R)-3-(1-环己基乙氧基)-1-氧代-1-(哌啶-1-基)丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-284)(16mg,25%),其为白色固体。LCMSm/z=642.5$[M+H]^+$;^1H NMR(400MHz,DMSO-d_6)δ9.25(s,1H),8.40-8.24(m,2H),4.83(s,1H),4.20-3.64(m,9H),3.53-3.45(m,5H),3.25-3.16(m,1H),1.66-1.29(m,13H),1.12-0.86(m,18H),0.67(s,1H).

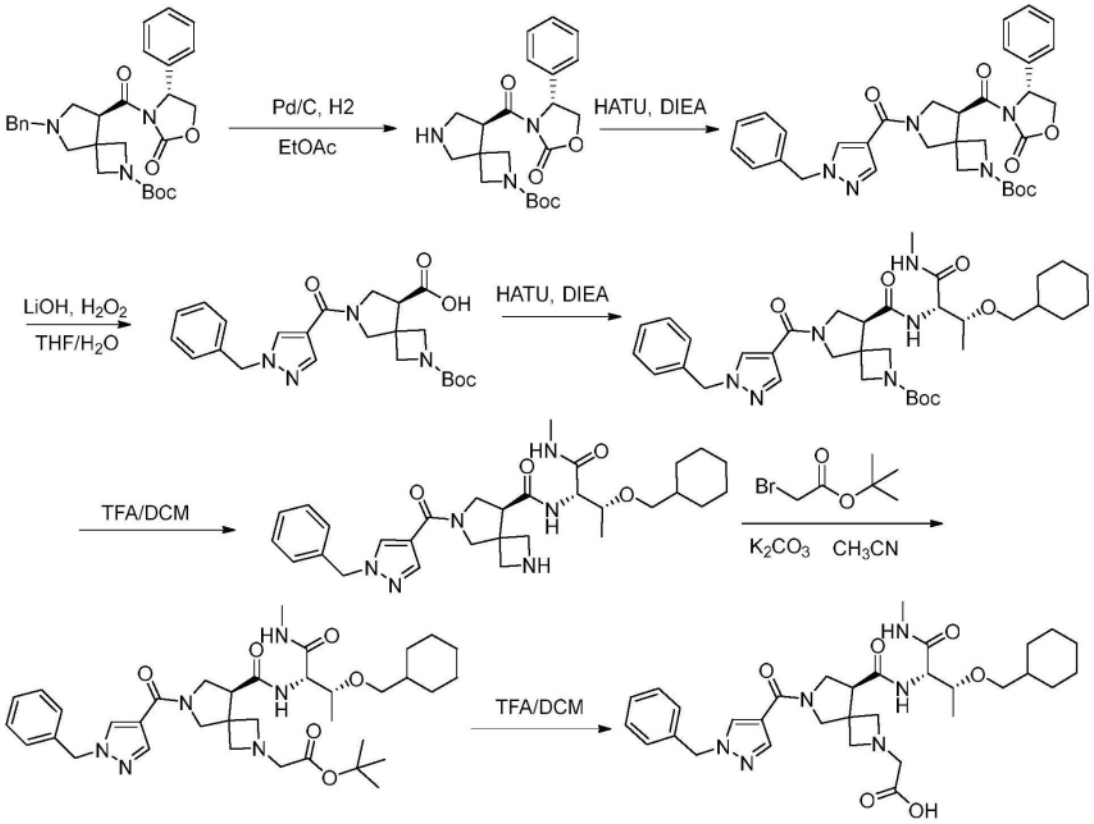
[0916] 方法19:以I-291的合成为例

[0917] 

[0918] 通过与方法18类似的步骤从中间体12开始制备I-291。

[0919] 方法20:以I-294的合成为例

[0920]



[0921] 步骤1:向(S)-6-苄基-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(中间体11)(1g,2.0mmol)的EtOAc(10mL)中的溶液添加10%Pd/C(300mg)。将反应混合物在H_2气氛下搅拌48h。将混合物过滤并浓缩,得到粗品(S)-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(800mg,100%),其直接用于下一步无需进一步纯化。LCMSm/z=402.2$[M+H]^+$.

[0922] 步骤2:向1-苄基-1H-吡唑-4-甲酸(2.2g,11.0mmol)在DCM(40mL)中的溶液添加HATU(4.79g,12.6mmol),并将混合物在室温搅拌30分钟。添加(S)-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(4.2g,10.5mmol)和DIPEA(2.03g,15.75mmol),并将反应在室温再搅拌2小时。将混合物用水(100mL)稀释,并用EtOAc(150mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=30:1),得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(4.7g,77%),其为黄色固体。LCMSm/z=586.3$[M+H]^+$.

[0923] 步骤3:在0℃向(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-((R)-2-氧代-4-苯基噁唑烷-3-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(100mg,0.17mmol)在THF和H_2O(3mL/0.25mL)的混合物中的溶液添加氢氧化锂一水合物(10mg,0.43mmol)在水(0.25mL)中的溶液和30%H_2O_2(12mg,0.34mmol)在水(0.25mL)中的溶液。将反应混合物在0℃搅拌1小时,然后用水(15mL)稀释并用EtOAc(30mL)萃取。收集水层并用1M HCl酸化至pH~2,并用EtOAc(80mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到粗品(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(50mg,66%),其为白色固体,其直接用于下一步。LCMSm/z=441.2$[M+H]^+$.

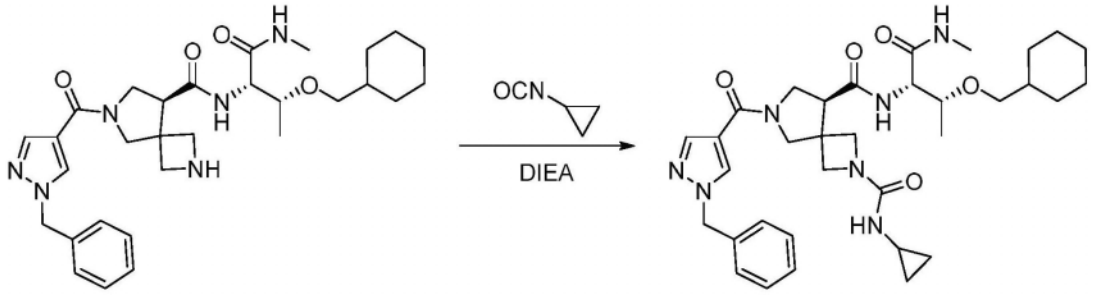
[0924] 步骤4:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(100mg,0.227mmol)在DCM(2mL)中的溶液添加HATU(103mg,0.272mmol),并将混合物在室温搅拌30分钟。添加(2S,3R)-2-氨基-3-(环己基甲氧基)-N-甲基丁酰胺盐酸盐(52mg,0.227mmol)和DIPEA(117mg、0.908mmol),并将反应在室温再搅拌2h。将混合物用水(30mL)稀释,并用EtOAc(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=30:1),得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(114mg,78%),其为黄色固体。LCMSm/z=651.4$[M+H]^+$.

[0925] 步骤5:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸酯(50mg,0.077mmol)在DCM(2mL)中的溶液添加TFA(1mL)。将反应混合物在室温搅拌1h。在真空下除去溶剂,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(42mg,100%),其直接用于下一步。LCMSm/z=551.3$[M+H]^+$.

[0926] 步骤6:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(85mg,1.54mmol)在CH_3CN(2mL)中的溶液添加2-溴乙酸叔丁酯(30mg,1.54mmol)和K_2CO_3(85mg,6.17mmol)。将混合物在室温搅拌过夜。将混合物用水(20mL)稀释,并用EtOAc(50mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过制备型TLC纯化(洗脱液:DCM/MeOH=30:1),得到2-((S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛-2-基)乙酸叔丁酯(25mg,24%),其为无色油状物。LCMSm/z=665.50$[M+H]^+$.

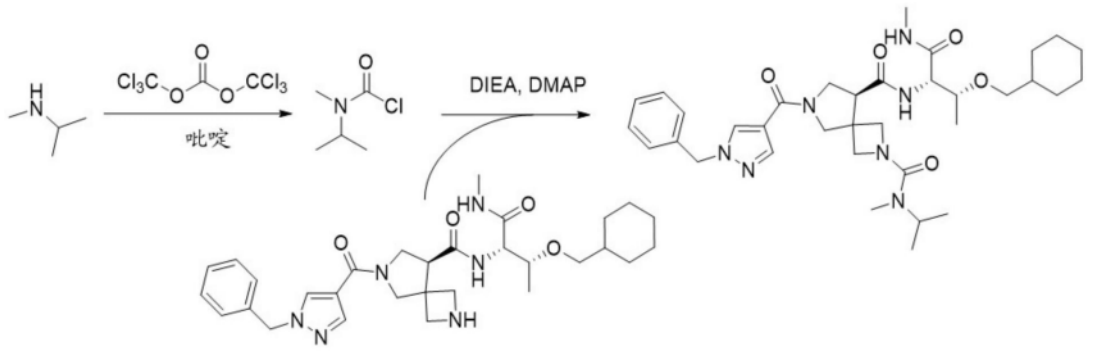
[0927] 步骤7:向2-((S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛-2-基)乙酸叔丁酯(25mg,0.37mmol)在DCM(0.6mL)中的溶液添加TFA(0.2mL)。将混合物在室温搅拌2h。在真空下除去溶剂。将残留物通过制备型HPLC纯化,得到2-((S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛-2-基)乙酸(I-294)(11mg,50%),其为白色固体。LCMSm/z=609.4$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d6)δ8.36-8.28(m,1H),8.15-8.06(m,1H),7.83-7.74(m,2H),7.38-7.23(m,5H),5.38-5.33(m,2H),4.27-4.20(m,1H),4.06-3.99(m,1H),3.92-3.44(m,11H),3.38-3.32(m,3H),3.26-3.21(m,1H),3.14-3.09(m,1H),2.60-2.55(m,3H),1.70-1.58(m,5H),1.49-1.38(m,1H),1.20-1.04(m,6H),0.89-0.79(m,2H).

[0928] 方法21:以I-268的合成为例

[0929] 

[0930] 向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(参见方法20-步骤5)(42mg,mmol)在THF(1mL)中的溶液添加异氰酸环丙酯(6mg,0.076mmol)和DIEA(29mg,0.229mmol)。将混合物在室温搅拌2h。在真空下除去溶剂,并将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N8-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-N2-环丙基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酰胺(25mg,51%),其为白色固体。LCMSm/z=634.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.38-8.33(m,1H),8.15-8.11(m,1H),7.83-7.70(m,2H),7.37-7.25(m,5H),6.43(d,J=3.2Hz,1H),5.35(s,2H),4.26-4.24(m,1H),3.98-3.71(m,6H),3.67-3.57(m,3H),3.55-3.45(m,1H),3.26-3.22(m,1H),3.12-3.08(m,1H),2.59-2.55(m,3H),2.42-2.39(m,1H),1.68-1.63(m,5H),1.45-1.43(m,1H),1.19-1.09(m,3H),1.04-1.01(m,3H),0.87-0.81(m,2H),0.54-0.51(m,2H),0.33-0.32(m,2H).

[0931] 方法22:以I-274的合成为例

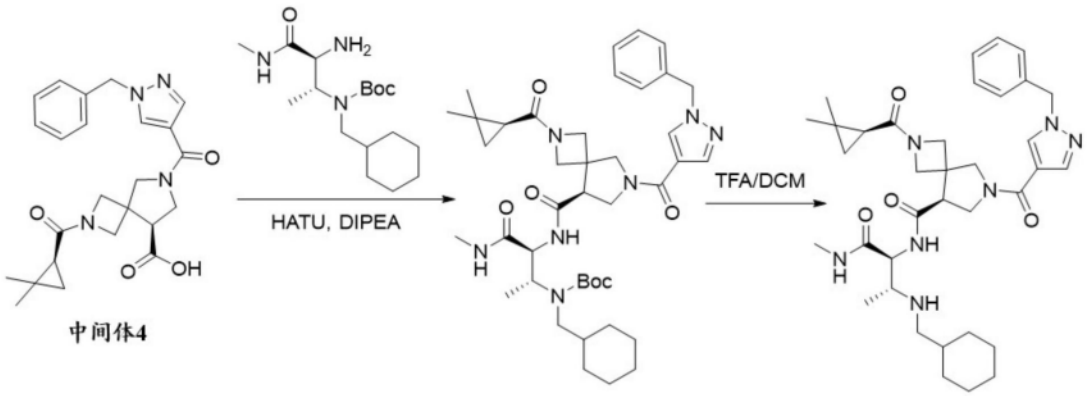
[0932] 

[0933] 步骤1:在0℃向N-甲基丙-2-胺(100mg,1.37mmol)和吡啶(215.2mg,2.72mmol)在无水THF(4mL)中的溶液添加三光气(202mg,0.68mmol)在无水THF(4mL)中的溶液。将反应混合物在室温搅拌3.5h。然后在真空下除去溶剂。将残留物用0.1N HCl(20mL)稀释,并用EtOAc(10mL×3)萃取。将合并的有机层经Na_2SO_4干燥,过滤并浓缩,得到粗品异丙基(甲基)氨基甲酰氯(110mg,59%),其直接用于下一步。^{1}H NMR(400MHz,DMSO-d_6)δ3.16(p,J=6.4Hz,1H),2.45(s,3H),1.22(d,J=6.4Hz,6H).

[0934] 步骤2:在0℃向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(参见方法20-步骤5)(50mg,0.09mmol)、DIEA(23.5mg,0.18mmol)和DMAP(1.0mg,0.009mmol)在无水DCM(0.5mL)中的溶液添加异丙基(甲基)氨基甲酰氯(18.3mg,0.136mmol)在无水DCM(0.5mL)中的溶液。将反应混合物在室温搅拌2h,然后在真空下除去溶剂。将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N8-((2S,3R)-3-(环己基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-N2-异丙基-N2-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酰胺(35mg,

43%)。LCMSm/z=650.50[M+1]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.35(d,J=21.4Hz,1H),8.14(t,J=7.0Hz,1H),7.81(d,J=16.4Hz,1H),7.75-7.66(m,1H),7.44-7.19(m,5H),5.35(d,J=2.2Hz,2H),4.27(dd,J=8.8,3.4Hz,1H),4.13-3.95(m,3H),3.94-3.87(m,1H),3.86-3.73(m,3H),3.73-3.63(m,2H),3.62-3.52(m,1H),3.49-3.34(m,1H),3.27-3.18(m,1H),3.10(dd,J=9.2,6.8Hz,1H),2.57(dd,J=13.8,3.4Hz,6H),1.63(q,J=13.8,12.6Hz,5H),1.42(d,J=10.2Hz,1H),1.21-1.08(m,3H),1.05-0.98(m,9H),0.84(t,J=11.8Hz,2H).

[0935] 方法23:以I-269的合成为例

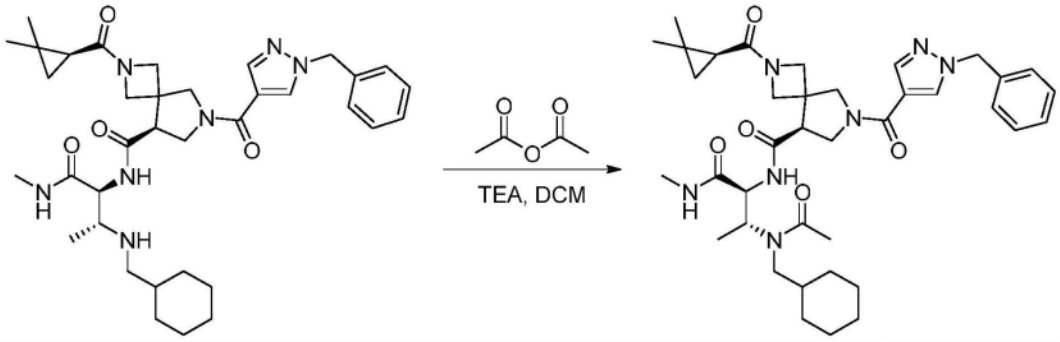
[0936] 

中间体4

[0937] 步骤1:根据方法2A中的步骤概述,使用合适的市售试剂和/或其他地方描述的中间体,从(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(中间体4)和((2R,3S)-3-氨基-4-(甲基氨基)-4-氧代丁-2-基)(环己基甲基)氨基甲酸叔丁酯合成(2R,3S)-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺)-4-(甲基氨基)-4-氧代丁-2-基)(环己基甲基)氨基甲酸叔丁酯。LCMSm/z=746.4[M+H]$^+$.

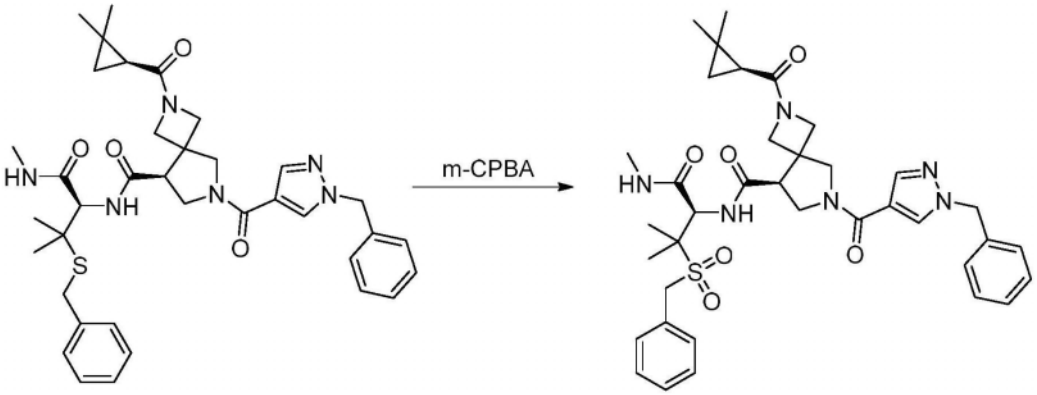
[0938] 步骤2:通过使用合适的市售试剂进行脱保护,从((2R,3S))-3-((S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰氨)-4-(甲基氨基)-4-氧代丁-2-基)(环己基甲基)氨基甲酸叔丁酯合成(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-((环己基甲基)氨基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-269)。LCMSm/z=646.5;^{1}H NMR(400MHz,DMSO-d_6)δ8.78-8.70(m,1H),8.41-8.31(m,3H),7.87-7.78(m,1H),7.40-7.23(m,5H),5.36(s,2H),4.81-4.72(m,1H),4.23-3.94(m,4H),3.86-3.63(m,4H),3.29-3.15(m,2H),2.95-2.75(m,2H),2.68-2.63(m,2H),2.60(d,J=4.6Hz,1H),1.82-1.56(m,6H),1.38-1.31(m,1H),1.24-1.12(m,6H),1.12-1.04(m,6H),1.01-0.92(m,2H),0.89-0.84(m,1H),0.74-0.65(m,1H).

[0939] 方法24:以I-273的合成为例

[0940] 

[0941] 向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-((环己基甲基)氨基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-269,方法23)(50mg,0.077mmol)在DCM(5mL)中的溶液添加TEA(16mg,0.154mmol)和乙酸酐(12mg,0.116mmol)。将反应混合物在室温搅拌2h。将混合物用水(20mL)稀释,并用DCM(50mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过制备型TLC纯化(洗脱液:DCM/MeOH=15/1,v/v),得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(N-(环己基甲基)乙酰胺)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-273)(20mg,40%),其为白色固体。LCMSm/z=688.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.70-8.50(m,1H),8.39-8.28(m,1H),8.16-8.07(m,1H),7.86-7.77(m,1H),7.38-7.22(m,5H),5.35(s,2H),4.72-4.43(m,1H),4.25-3.52(m,10H),3.26-3.10(m,1H),3.08-3.00(m,1H),2.64-2.53(m,3H),2.13(d,J=2.8Hz,1H),1.99-1.89(m,2H),1.72-1.53(m,6H),1.41-1.32(m,1H),1.24-1.22(m,1H),1.19-1.14(m,3H),1.12-1.02(m,8H),0.93-0.78(m,3H),0.71-0.63(m,1H).

[0942] 方法25:以I-199的合成为例

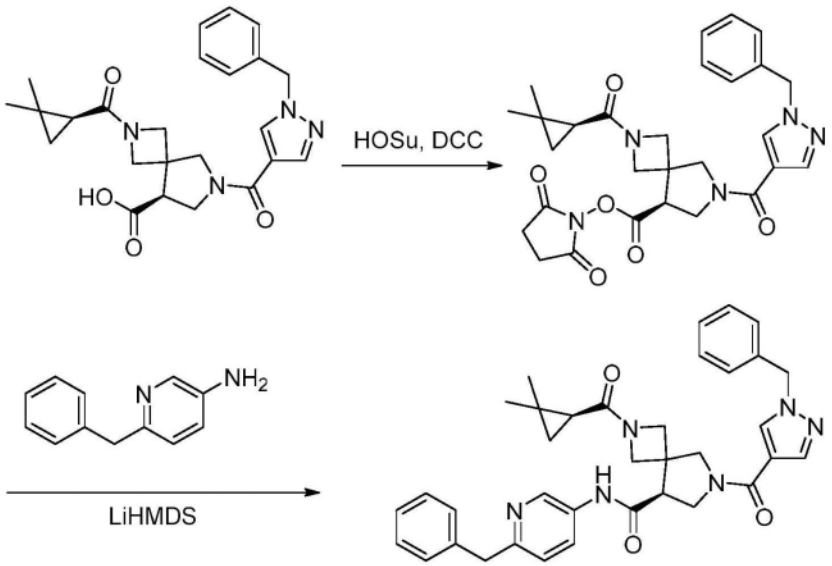
[0943] 

[0944] 在N_2下在0℃向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((R)-3-(苄硫基)-3-甲基-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-171A)(40mg,0.06mmol)在DCM(2mL)中的溶液添加m-CPBA(31mg,0.18mmol)。然后将反应混合物在室温搅拌8h。在真空下除去溶剂,并将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((R)-3-(苄基磺酰基)-3-甲基-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-199)(29mg,69%),其为白色固体。LCMSm/z=703.40[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.79(t,J=8.8Hz,1H),8.47-8.27(m,2H),7.82(dd,J=25.8,8.2Hz,1H),7.39-

7.07(m,10H),5.38-5.30(m,2H),5.20-5.11(m,1H),4.71(t,J＝12.8Hz,1H),4.20(dd,J＝42.4,10.8Hz,2H),4.11-4.00(m,2H),3.88(s,1H),3.78(m,3H),3.56(m,1H),3.46-3.33(m,1H),2.62(m,3H),1.48(d,J＝11.8Hz,3H),1.39(s,3H),1.35(t,J＝7.2Hz,1H),1.11(t,J＝6.0Hz,3H),1.05(t,J＝4.2Hz,3H),0.90-0.83(m,1H),0.72-0.65(m,1H).

[0945] 方法26A:以I-139的合成为例

[0946]



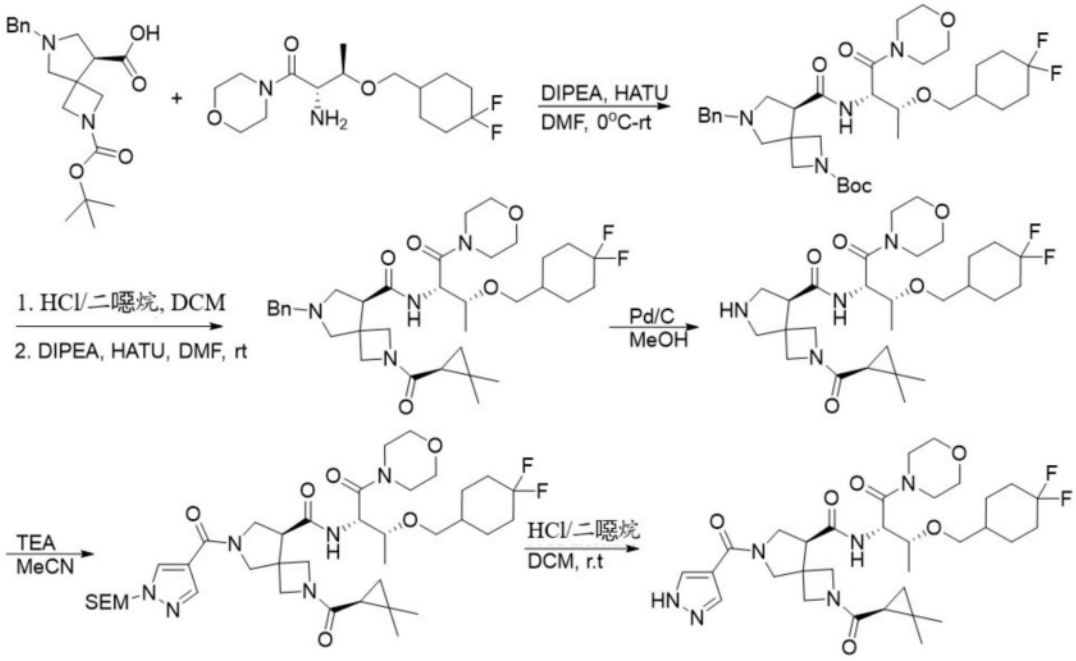
[0947] 步骤1:在0℃向(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(中间体4)(45mg,0.103mmol)在无水THF(1mL)中的溶液添加HOSu(18mg,0.155mmol)和DCC(25.5mg,0.124mmol)。在N_2气氛下将该混合物在室温搅拌过夜。将混合物通过硅藻土过滤,并将滤液在真空中浓缩,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸2,5-二氧代吡咯烷-1-基酯,其直接用于下一步。LCMSm/z＝534.1$[M+H]^+$.

[0948] 步骤2:向6-苄基吡啶-3-胺(19mg,0.103mmol)在无水THF(1mL)中的溶液添加LiHMDS(26mg,0.155mmol),并将反应混合物在室温搅拌0.5h。然后添加(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸2,5-二氧代吡咯烷-1-基酯(55mg,0.103mmol)在无水THF(1mL)中的溶液,并将所得混合物在室温搅拌6h。除去溶剂并将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-(6-苄基吡啶-3-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(3.4mg,5%),其为灰白色固体。LCMSm/z＝603.0$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.66-8.60(m,1H),8.26-8.18(m,2H),7.95-7.89(m,2H),7.36-7.19(m,10H),5.39-5.37(m,2H),4.44-4.14(m,3H),4.12-3.76(m,7H),3.48-3.35(m,1H),1.41-1.33(m,1H),1.20-1.13(m,2H),1.11-1.09(m,2H),1.01-0.96(m,1H),0.90-0.84(m,2H),0.77-0.71(m,1H).

[0949] 方法26B:以I-168的合成为例

[0950] 通过与方法26A类似的步骤,从中间体3代替中间体4开始来制备I-168。

[0951] 方法27:以I-301的合成为例

[0952] 

[0953] 步骤1:在0-5℃向(2S,3R)-2-氨基-3-((4,4-二氟环己基)甲氧基)-1-吗啉丁-1-酮(240mg,0.75mmol)、(S)-6-苄基-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(346mg,1.0mmol)和N-乙基-N-异丙基丙-2-胺(292.5mg,2.2mmol)在N,N-二甲基甲酰胺(8mL)中的溶液添加2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(427.8mg,1.13mmol)。将所得混合物在室温搅拌0.5小时。将反应混合物倒入水(30mL)中,并用乙酸乙酯(10mL×3)萃取。将合并的有机层用盐水(20mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用2%甲醇/二氯甲烷的梯度纯化,得到(S)-6-苄基-8-(((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(270mg,60%收率),其为浅黄色油状物。LCMS:m/z 649.6[M+H]$^+$.^{1}HNMR(400MHz,DMSO-d6):δ8.37(d,J=8.4Hz,1H),7.25-7.34(m,6H),4.80-4.84(m,1H),3.85-3.88(m,1H),3.46-3.73(m,15H),3.19-3.23(m,1H),3.12-3.15(m,1H),2.78-2.85(s,2H),2.59-2.61(m,1H),1.93-2.01(m,2H),1.70-1.84(m,4H),1.57-1.61(m,1H),1.34(s,9H),1.10-1.19(m,2H),1.06(d,J=5.6Hz,3H).

[0954] 步骤2:将(S)-6-苄基-8-(((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸酯(100mg,0.15mmol)在二噁烷(4.0M,2mL)-二氯甲烷(2mL)中的氯化氢中的混合物在室温搅拌1小时,之后在减压下蒸发挥发物。将残留物溶于N,N-二甲基甲酰胺(2mL)中,然后在0℃依次添加(S)-2,2-二甲基环丙烷-1-甲酸(16.4mg,0.14mmol)、N-乙基-N-异丙基丙烷-2-胺(77.6mg,0.6mmol)和HATU(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸)(68.4mg,0.18mmol)。使所得混合物温热至室温并搅拌30分钟。将所得混合物用水(10mL)稀释并用乙酸乙酯(5mLx3)萃取。将合并的有机相用盐水洗涤、经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过硅胶快速色谱法使用2.5%甲醇/二氯甲烷的梯度纯化,得到(S)-6-苄基-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(50mg,53%收率),其为白色固体。^{1}HNMR(400MHz,DMSO-d6):δ8.32-8.43(m,1H),7.25-7.33(m,6H),4.79-4.88(m,1H),4.20(d,J=

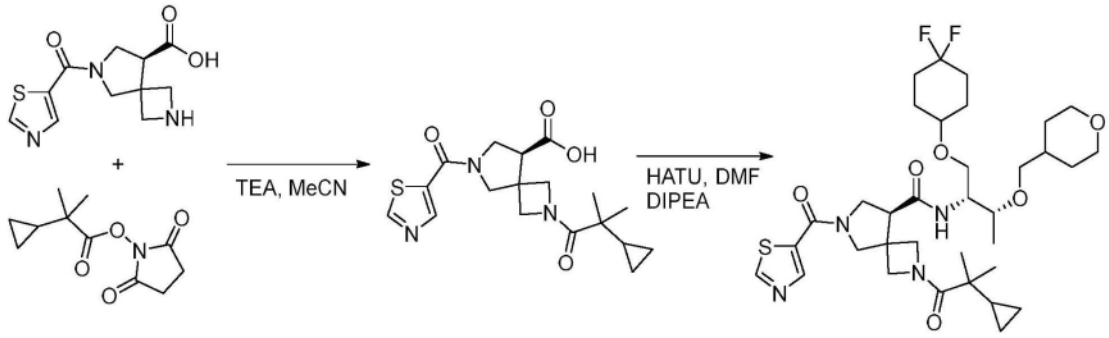
8.4Hz,,1H),3.85-3.98(m,2H),3.46-3.74(m,14H),3.12-3.24(m,3H),2.81-2.89(m,2H),2.59-2.68(m,1H),1.90-2.019(m,3H),1.67-1.80(m,4H),1.55-1.60(m,1H),1.30-1.35(m,1H),0.98-1.08(m,9H),0.80-0.84(m,1H),0.63-0.66(m,1H).LCMS:m/z 645.3[M+H]$^+$.

[0955] 步骤3:向(S)-6-苄基-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(50mg,0.078mmol)在甲醇(20mL)中的溶液添加钯/碳(10%,10mg)。在氢气气氛(氢气球)下将所得混合物在室温搅拌3小时。通过过滤除去钯/碳,并用甲醇(10mL x2)洗涤;将合并的有机溶液在减压下浓缩,得到(S)-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(40mg,93%收率),其为白色固体。^{1}HNMR(400MHz,DMSO-d6):δ8.30-8.53(m,1H),4.81-4.88(m,1H),4.16-4.21(m,1H),3.96-4.03(m,1H),3.41-3.87(m,12H),3.13-3.29(m,5H),2.87-3.10(m,2H),2.59-2.74(m,1H),1.90-2.02(m,2H),1.68-1.85(m,4H),1.54-1.64(m,1H),1.28-1.35(m,1H),1.04-1.12(m,10H),0.81-0.86(m,1H),0.64-0.69(m,1H).

[0956] 步骤4:在0℃向(S)-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(40mg,0.07mmol)和三乙胺(14.2mg,0.14mmol)在乙腈中的溶液添加1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑-4-甲酸2,5-二氧代吡咯烷-1-基酯(26.9mg,0.08mmol)。将所得混合物在室温搅拌3小时。然后将反应混合物浓缩以除去溶剂。将残留物用水(10mL)稀释,并用乙酸乙酯(10mLx3)萃取。将合并的有机相用盐水洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过制备型TLC使用7%甲醇/二氯甲烷的梯度纯化,得到(S)-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(26mg,46%收率),其为白色固体。LCMS:m/z 779.4[M+H]$^+$.

[0957] 步骤5:将(S)-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(28mg,0.028mmol)在二噁烷(4.0M,2mL)-二氯甲烷(2mL)中的氯化氢中的溶液在室温搅拌1小时。在减压下除去挥发物以得到粗品残留物,用碳酸钠水溶液将其pH调节至8-9,并用乙酸乙酯(10mL×3)萃取。将合并的有机层用盐水(20mL)洗涤,经硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过制备型TLC使用10%甲醇/二氯甲烷的梯度纯化,得到(S)-N-((2S,3R)-3-((4,4-二氟环己基)甲氧基)-1-吗啉-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(1H-吡唑-4-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-301)(14mg,60%收率),其为白色固体。LCMS:649.4[M+H]$^+$.^{1}HNMR(400MHz,DMSO-d6):δ13.20-13.25(m,1H),8.44-8.47(m,1H),8.17-8.20(m,1H),7.82-7.85(m,1H),4.81-4.89(m,1H),3.83-4.23(m,5H),3.42-3.81(m,11H),3.38-3.40(m,1H),3.28-3.30(s,1H),3.20-3.25(m,1H),1.94-2.03(m,2H),1.54-1.87(m,5H),1.23-1.45(m,4H),1.05-1.45(m,9H),0.84-0.88(m,1H),0.66-0.68(m,1H).

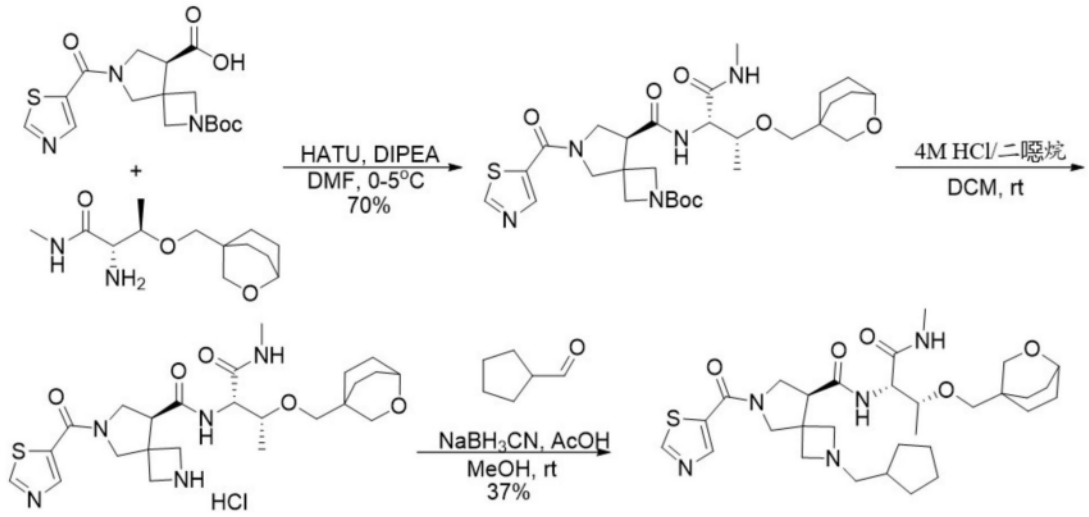
[0958] 方法28:以I-333的合成为例

[0959] 

[0960] 步骤1:向(S)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸盐酸盐(参见方法17A)(673mg,2.22mmol)在乙腈(10mL)中的搅拌溶液添加三乙胺(0.9mL,6.66mmol),然后缓慢添加2-环丙基-2-甲基丙酸2,5-二氧代吡咯烷-1-基酯(500mg,2.222mmol)在乙腈(5mL)中的溶液,并将所得混合物在室温搅拌1小时。然后将反应混合物倒入水(5mL)中,并用乙酸乙酯(10mL×2)萃取以除去一些杂质。用稀盐酸(2.0N)将水层的pH调节至3-4,并用10%甲醇/二氯甲烷(20mL×5)萃取。将合并的有机相经无水硫酸钠干燥,并在真空中浓缩,得到粗品(S)-2-(2-环丙基-2-甲基丙酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(0.400g,48%),其为白色固体,其用于下一步无需进一步纯化。MS[MH]$^+$378.3

[0961] 步骤2:向粗品(S)-2-(2-环丙基-2-甲基丙酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(0.050g,0.13mmol)在N,N-二甲基甲酰胺(1.5mL)中的溶液添加(2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-胺(0.043g,0.13mmol)、N-乙基-N-异丙基丙-2-胺(0.1mL,0.40mmol)和(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(0.060g,0.16mmol)。将所得混合物在室温搅拌1小时。然后将反应混合物倒入水(10mL)中,并用乙酸乙酯(10mL×2)萃取。将合并的有机相用盐水(10mL×2)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用10%甲醇/二氯甲烷的梯度纯化,得到(S)-2-(2-环丙基-2-甲基丙酰基)-N-((2R,3R)-1-((4,4-二氟环己基)氧基)-3-((四氢-2H-吡喃-4-基)甲氧基)丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-333)(0.028g,31%),其为白色固体。^{1}HNMR(400MHz,CD_3OD):δ9.06(s,1H),8.26(d,J=20.8Hz,1H),7.24-7.18(m,0.5H),4.60-4.38(m,2H),4.18-3.76(m,9H),3.58-3.25(m,8H),3.13-3.08(m,1H),1.92-1.55(m,10H),1.27-1.19(m,3H),1.02-0.91(m,10H),0.39-0.26(m,4H).MS[MH]$^+$681.7

[0962] 方法29:以I-344的合成为例

[0963] 

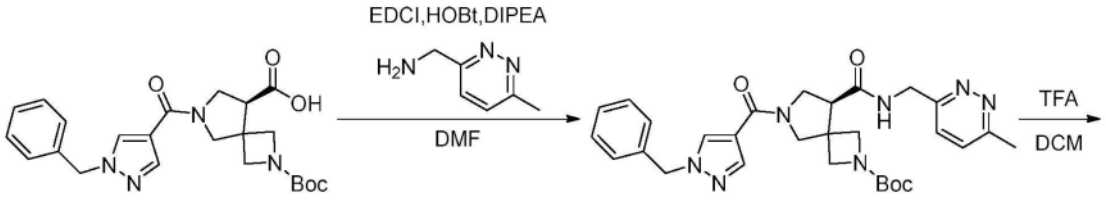
[0964] 步骤1:在0-5℃向(S)-2-(叔丁氧基羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(参见方法17A)(0.198g,0.54mmol)、(2S,3R)-3-(2-氧杂双环[2.2.2]辛烷-4-基甲氧基)-2-氨基-N-甲基丁酰胺(0.145g,0.57mmol)和N-乙基-N-异丙基丙-2-胺(0.140g,1.08mmol)在N,N-二甲基甲酰胺(2mL)中的溶液添加HATU(2-(7-氮杂-1H-苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐)(0.246g,0.65mmol),将所得混合物温热至室温并在室温搅拌1小时。将混合物倒入水(20mL)中,并用乙酸乙酯(15mL×2)萃取。收集有机层,用盐水(20mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过柱色谱法使用含有5%甲醇的50%乙酸乙酯/二氯甲烷的梯度纯化,得到(S)-8-(((2S,3R)-3-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛-2-甲酸叔丁酯(0.230g,70%),其为白色固体。^{1}HNMR(400MHz,$CDCl_3$):δ8.90(s,1H),8.24(s,1H),6.98-6.90(m,1H),6.48-6.37(m,1H),4.54-4.43(m,1H),4.11-3.81(m,10H),3.74-3.69(m,2H),3.29-3.24(m,2H),3.14-3.06(m,1H),2.87(d,J=4.8Hz,3H),2.09-1.99(m,2H),1.69-1.66(m,1H),1.63-1.58(m,2H),1.57-1.48(m,2H),1.43(s,9H),1.04(d,J=6.4Hz,3H).

[0965] 步骤2:向(S)-8-(((2S,3R)-3-(2-氧杂双环[2.2.2]辛-4-基甲基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)氨基甲酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛-2-甲酸叔丁酯(0.055g,0.09mmol)在二氯甲烷(3mL)中的混合物添加在1,4-二噁烷(4M,4,1mL)中的氯化氢,将所得混合物在室温搅拌30分钟。在减压下蒸发挥发物,得到粗品(S)-N-((2S,3R)-3-((2-氧杂双环[2.2.2]辛烷-4-基)甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺盐酸盐,其用于下一步中无需进一步纯化。

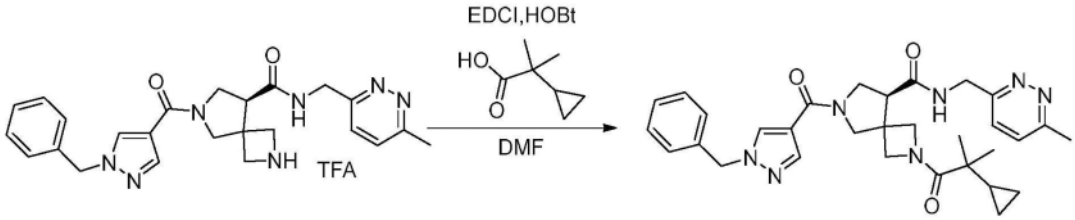
[0966] 步骤3:向(S)-N-((2S,3R)-3-(2-氧杂双环[2.2.2]辛-4-基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛-8-甲酰胺盐酸盐(0.09mmol)在甲醇(2mL)中的混合物中添加三乙胺(0.5mL)。将该混合物在室温搅拌10分钟。向所得混合物添加环戊烷甲醛(0.013g,0.14mmol)和乙酸(0.2mL),并将所得混合物在室温搅拌20分钟,然后添加氰基硼氢化钠(0.011g,0.18mmol)。将所得混合物在室温搅拌30分钟。将反应混合物倒入碳酸氢钠水溶液(10mL)中,并用二氯甲烷(10mL×2)萃取。将合并的有机层用盐水(10mL)洗涤,经无水硫酸钠干燥,并在减压下浓缩以得到粗品残留物,其通过制备型TLC使用10%甲醇/二氯甲烷的梯度纯化,得到(S)-N-((2S,3R)-3-(2-氧杂双环

[2.2.2]辛-4-基甲氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-(环戊基甲基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛-8-甲酰胺(I-344)(0.020g,37%),其为粉红色固体。^{1}HNMR(400MHz,CD_3OD):δ9.15(d,J=3.2Hz,1H),8.34(d,J=7.2Hz,1H),4.31(dd,J=3.2,8.8Hz,1H),4.12-4.02(m,2H),3.92-3.37(m,12H),3.27-3.25(m,1H),3.01-2.98(m,1H),2.74(d,J=14.8Hz,3H),2.64-2.57(m,2H),2.03-1.42(m,18H),1.19(d,J=6.4Hz,3H).MS:$[MH]^+$ 588.45.

[0967] 方法30:以I-387的合成为例



[0968]

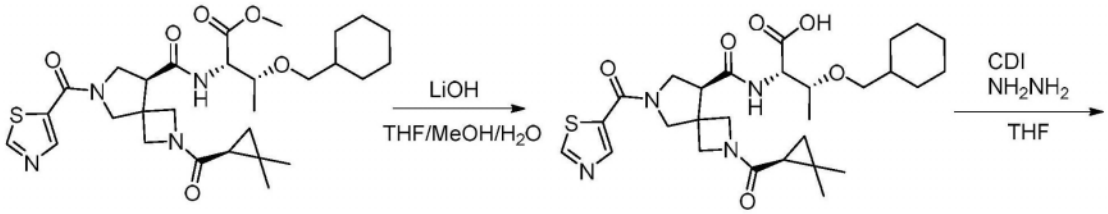


[0969] 步骤1:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(叔丁氧基羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(方法20-步骤3)(75mg,0.17mmol)在DMF(2.0mL)中的溶液添加(6-甲基哒嗪-3-基)甲胺(42mg,0.20mmol)、EDCI(49mg,0.26mmol)、HOBt(34.5mg,0.26mmol)和DIPEA(88mg,0.68mmol)。将所得混合物在室温搅拌14h,然后在真空下除去溶剂。将得到的残留物通过制备型TLC纯化(DCM:MeOH=12:1),得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((6-甲基哒嗪-3-基)甲基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸酯(25mg,26%),其为无色固体。LCMSm/z=546.1$[M+H]^+$.

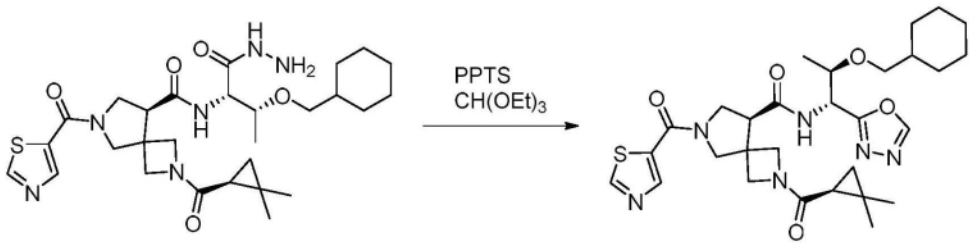
[0970] 步骤2:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-8-(((6-甲基哒嗪-3-基)甲基)氨基甲酰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸酯(25mg,0.046mmol)在DCM(3mL)中的溶液添加TFA(1mL)。将所得混合物搅拌2h,然后在减压下除去溶剂,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((6-甲基哒嗪-3-基)甲基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺2,2,2-三氟乙酸盐(30mg,定量),其直接用于下一步。

[0971] 步骤3:向(S)-6-(1-苄基-1H-吡唑-4-羰基)-N-((6-甲基哒嗪-3-基)甲基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺2,2,2-三氟乙酸盐(30mg,0.045mmol)在DMF(1.0mL)中的溶液添加2-环丙基-2-甲基丙酸(7mg,0.055mmol)、EDCI(13mg,0.068mmol)、HOBt(9mg,0.067mmol)和DIPEA(17.4mg,0.13mmol)。将所得混合物在室温搅拌14h,然后在真空下除去溶剂。将残留物通过制备型HPLC纯化,得到(S)-6-(1-苄基-1H-吡唑-4-羰基)-2-(2-环丙基-2-甲基丙酰基)-N-((6-甲基哒嗪-3-基)甲基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(11mg,44%),其为黄色固体。LCMSm/z=556.4$[M+H]^+$;^{1}H NMR(400MHz,甲醇-d_4)δ8.21(d,J=14.0Hz,1H),8.04-7.74(m,3H),7.40-7.20(m,5H),5.37(s,2H),4.76-3.72(m,9H),3.28-3.16(m,1H),2.76(s,3H),1.08-0.87(m,7H),0.52-0.21(m,4H).

[0972] 方法31:以I-415的合成为例



[0973]



[0974] 根据在方法18中的步骤概述,使用合适的市售试剂和/或其他地方描述的中间体,由中间体11合成O-(环己基甲基)-N-((S)-2-(((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯。LCMSm/z=575.3[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d6)δ9.25(s,1H),8.59-8.46(m,1H),8.41-8.34(m,1H),4.52(d,J=9.6Hz,1H),4.20-4.05(m,3H),3.96-3.55(m,11H),3.06(d,J=9.0Hz,1H),1.65(d,J=12.4Hz,6H),1.18-1.02(m,13H),0.85(s,3H),0.68(d,J=7.4Hz,1H).

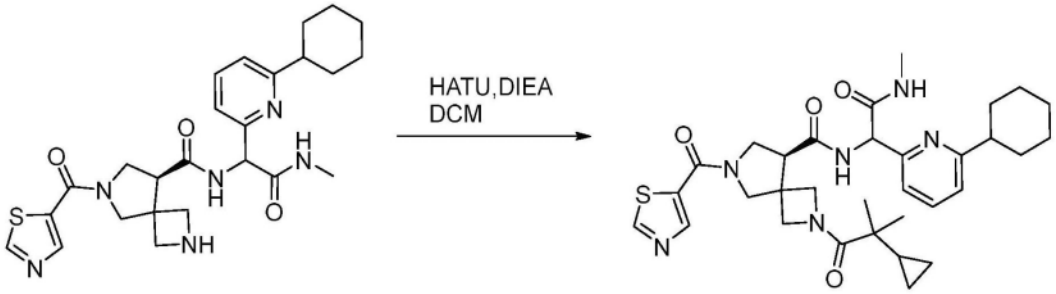
[0975] 步骤1:向O-(环己基甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯(800mg,1.39mmol)在THF和H_2O(8mL/2mL)的混合物中的溶液添加LiOH(67mg,2.78mmol)。将反应混合物在室温搅拌2h,然后用水(30mL)稀释并用醚(50mL)萃取。收集水层并用1M HCl酸化至pH 2,并用EtOAc(50mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩,得到O-(环己基甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸(500mg,64%),其为白色固体,其直接用于下一步。LCMSm/z=561.2[M+H]$^+$.

[0976] 步骤2:向O-(环己基甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸(500mg,0.89mmol)在THF(10mL)中的溶液添加CDI(180mg,1.07mmol)。将混合物在室温搅拌1h,然后添加NH_2NH_2(70mg,1.33mmol)。将反应混合物在室温搅拌过夜,然后将混合物用水(20mL)稀释并用EtOAc(30mL×2)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将残留物通过制备型TLC纯化(DCM/MeOH=10/1),得到(S)-N-((2S,3R)-3-(环己基甲氧基)-1-肼基-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(80mg,15%),其为白色固体。LCMSm/z=575.3[M+H]$^+$.

[0977] 步骤3:向(S)-N-((2S,3R)-3-(环己基甲氧基)-1-肼基-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(80mg,0.13mmol)在原甲酸三乙酯(10mL)中的溶液添加对甲苯磺酸(1mg)。在微波反应器中将混合物在150℃搅拌1小时。在减压下除去溶剂,并将得到的残留物通过制备型HPLC纯化,得到(S)-N-((1S,2R)-2-(环己基甲氧基)-1-(1,3,4-噁二唑-2-基)丙基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(8.7mg,10%),其为白色固体。LCMSm/z=585.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d6)δ9.23(d,J=18.4Hz,2H),

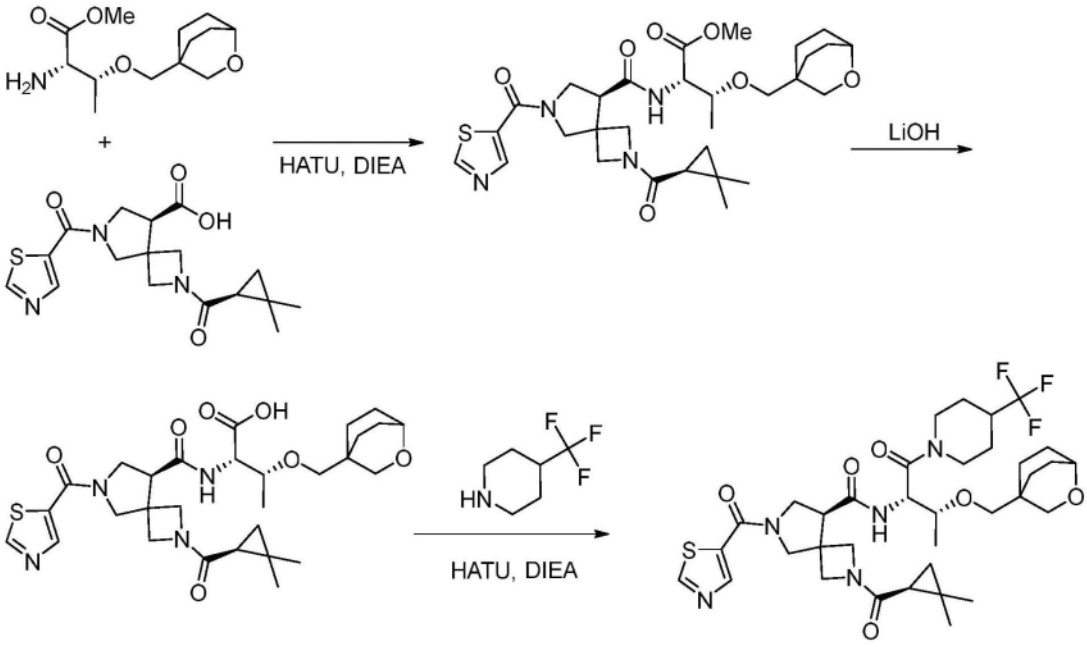
9.01-8.91(m,1H),8.37(d,J＝18.6Hz,1H),5.34(s,1H),4.25-4.00(m,4H),3.95-3.78(m,4H),3.70(s,1H),3.58-3.47(m,1H),3.06(s,1H),1.63-1.49(m,5H),1.39-1.35(m,1H),1.16-1.04(m,13H),0.86(d,J＝5.2Hz,1H),0.80-0.65(m,3H).

[0978] 方法32:以I-410的合成为例

[0979] 

[0980] 向2-环丙基-2-甲基丙酸(7mg,0.06mmol)在DCM(2mL)中的溶液添加HATU(23mg,0.06mmol),并将混合物在室温搅拌30分钟。添加(8S)-N-(1-(6-环己基吡啶-2-基)-2-(甲基氨基)-2-氧代乙基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(通过类似于方法20的方法制备)(29mg,0.06mmol)和DIPEA(23mg,0.06mmol),并将反应在室温再搅拌2小时。将混合物用水(10mL)稀释并用DCM(50mL)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过制备型HPLC纯化,得到(8S)-N-(1-(6-环己基吡啶-2-基)-2-(甲基氨基)-2-氧代乙基)-2-(2-环丙基-2-甲基丙酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(30mg,43%),其为白色固体。LCMSm/z＝512.2$[M+H]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ9.28-9.20(m,1H),9.08-8.76(m,1H),8.41-8.30(m,1H),8.21-8.09(m,1H),7.74-7.58(m,1H),7.30-7.11(m,2H),5.48(s,1H),4.65-4.16(m,2H),4.12-3.63(m,6H),3.59-3.44(m,1H),2.70-2.55(m,4H),1.89-1.68(m,5H),1.53-1.17(m,5H),1.04-0.71(m,7H),0.47-0.05(m,4H).

[0981] 方法33:以I-454的合成为例

[0982] 

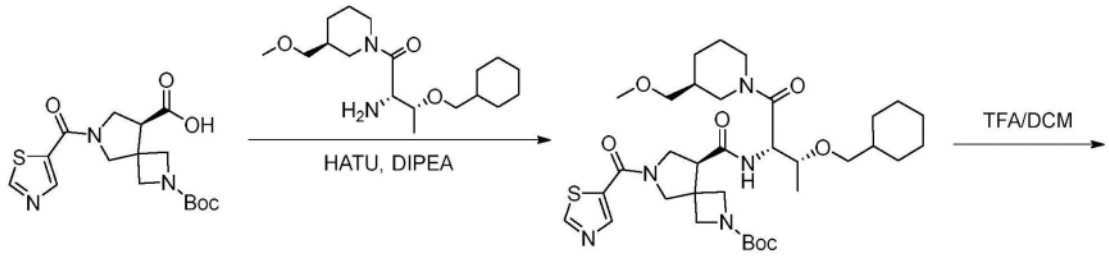
[0983] 步骤1:向(S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(参见方法17A)(835mg,2.3mmol)在DCM(6mL)中的溶液添加HATU

(874mg,2.3mol)和DIPEA(742mg,5.75mmol),并将混合物在室温搅拌30分钟。添加O-((2-氧杂双环[2.2.2]辛-4-基)甲基)-L-苏氨酸甲酯(600mg,2.3mmol),并将反应再搅拌2h。反应用水(30mL)淬灭,并用DCM(40mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过柱色谱法在硅胶上纯化(洗脱液:DCM:MeOH=50:1),得到O-((2-氧杂双环[2.2.2]辛烷-4-基)甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯(850mg,62%),其为黄色油状物。LCMSm/z=603.1[M+H]$^+$;^{1}H NMR(400MHz,$CDCl_3$)δ8.91(s,1H),8.27(s,1H),4.70-4.57(m,1H),4.40-3.96(m,10H),3.79-3.72(m,4H),3.65-3.58(m,1H),3.52-3.42(m,1H),3.23-3.09(m,2H),2.05-1.94(m,2H),1.58-1.51(m,4H),1.48-1.41(m,2H),1.19-1.11(m,12H),0.83-0.71(m,1H).

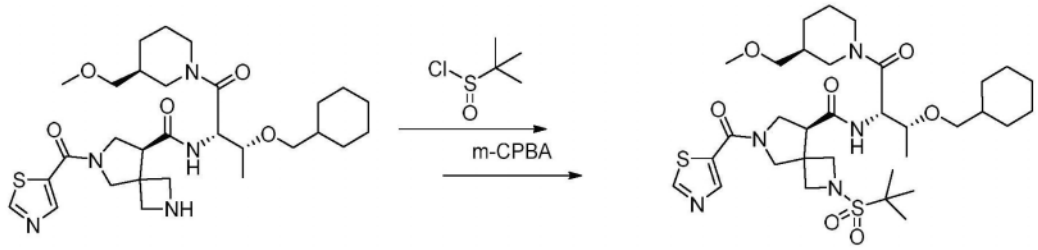
[0984] 步骤2:向O-((2-氧杂双环[2.2.2]辛烷-4-基)甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸甲酯(850mg,1.41mmol)在THF(8mL)、MeOH(2mL)和H_2O(2mL)的混合物中的溶液添加LiOH(97mg,4.23mmol)。将反应在室温搅拌4h,然后用水(50mL)稀释并用EtOAc(30mL×2)萃取。将水相用1M HCl酸化至pH 2,并用EtOAc(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥并浓缩,得到O-((2-氧杂双环[2.2.2]辛烷-4-基)甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸(600mg,72%),其为黄色油状物。LCMSm/z=589.2[M+H]$^+$.

[0985] 步骤3:向O-((2-氧杂双环[2.2.2]辛烷-4-基)甲基)-N-((S)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-羰基)-L-苏氨酸(50mg,0.085mmol)在DCM(2mL)中的溶液添加HATU(32mg,0.085mmol)和DIPEA(27mg,0.213mmol)。将混合物在室温搅拌30分钟,然后添加4-(三氟甲基)哌啶(14mg,0.094mmol)并将反应再搅拌2h。在减压下除去溶剂,将得到的残留物通过制备型HPLC纯化,得到(S)-N-((2S,3R)-3-((2-氧杂双环[2.2.2]辛烷-4-基)甲氧基)-1-氧代-1-(4-(三氟甲基)哌啶-1-基)丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(20mg,33%)。LCMSm/z=724.4[M+H]$^+$;^{1}H NMR(400MHz,CD_3OD)δ9.15(s,1H),8.37(m,1H),4.95(s,1H),4.58(m,1H),4.43-3.82(m,10H),3.72(m,3H),3.45(m,1H),3.27-3.13(m,2H),3.02(s,1H),2.69(s,1H),2.51(s,1H),1.96(m,4H),1.65(m,4H),1.57-1.36(m,5H),1.21-1.10(m,9H),1.05(s,1H),0.79(m,1H).

[0986] 方法34:以I-447的合成为例



[0987]



[0988] 步骤1:向(S)-2-(叔丁氧基羰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酸(参见方法17A)(200mg,0.54mmol)在DCM(5mL)中的溶液添加HATU(205mg,0.54mmol)和DIPEA(279mg,2.16mmol)。将混合物在室温搅拌30分钟,然后添加(2S,3R)-2-氨基-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)丁-1-酮(176mg,0.54mmol),并将反应再搅拌2h。将混合物用水(50mL)稀释,并用DCM(50mL×3)萃取。将合并的有机层用盐水洗涤,经Na_2SO_4干燥,过滤并浓缩。将得到的残留物通过制备型TLC纯化(洗脱液:DCM:MeOH=20:1),得到(S)-8-(((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)氨基甲酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(250mg,68%),其为黄色油状物。LCMSm/z=676.3$[M+H]^+$.

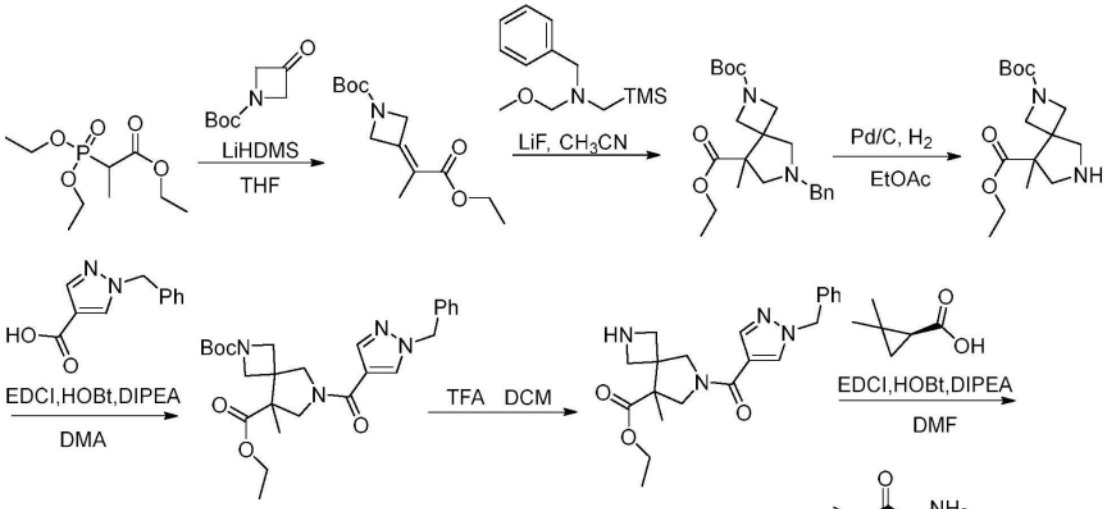
[0989] 步骤2:向(S)-8-(((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)氨基甲酰基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-2-甲酸叔丁酯(100mg,0.15mmol)在DCM(2mL)中的溶液添加TFA(0.5mL)。将反应搅拌1h,然后在真空下除去溶剂,得到(S)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(85mg,100%),其直接用于下一步。LCMSm/z=576.3$[M+H]^+$.

[0990] 步骤3:在0℃向(S)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(42mg,0.07mmol)和TEA(28mg,0.28mmol)在DCM(2mL)中的溶液添加2-甲基丙烷-2-亚磺酰氯(10mg,0.07mmol)。将反应混合物在室温搅拌2h,然后浓缩并将残留物通过制备型HPLC纯化,得到(8S)-2-(叔丁基亚磺酰基)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(15mg,31%),其为白色固体。LCMSm/z=680.5$[M+H]^+$;^1H NMR(400MHz,DMSO-d6)δ9.24(d,J=4.9Hz,1H),8.49-8.30(m,2H),4.84(s,1H),4.34-4.18(m,1H),4.12-3.32(m,12H),3.27-3.10(m,7H),3.07-2.74(m,1H),1.72-1.57(m,8H),1.50-1.39(m,1H),1.24-1.13(m,4H),1.10-1.00(m,13H),0.94-0.82(m,2H).

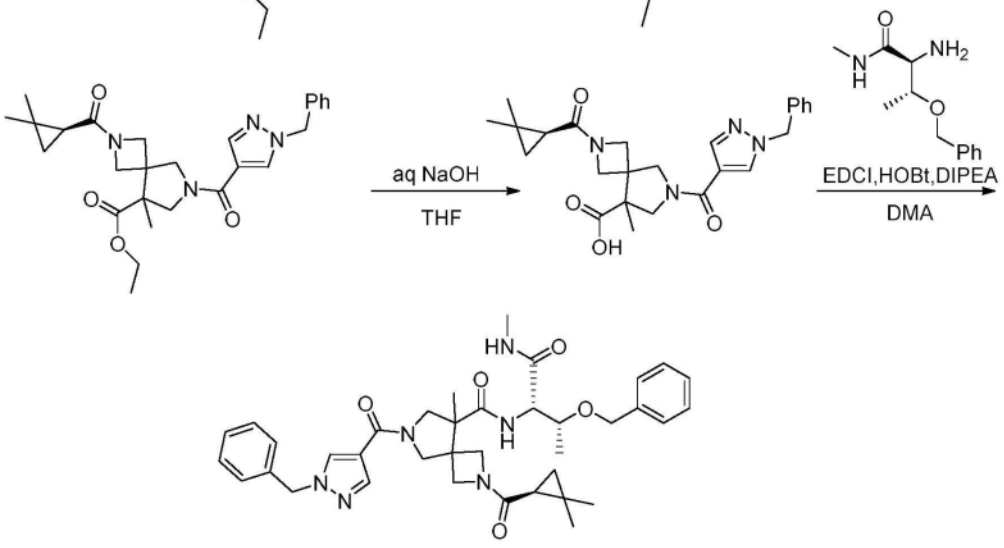
[0991] 步骤4:在0℃向(8S)-2-(叔丁基亚磺酰基)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(30mg,0.04mmol)在DCM(2mL)中的溶液添加m-CPBA(8mg,0.05mmol)。

将反应混合物在室温搅拌2h,然后除去溶剂并将残留物通过制备型HPLC纯化,得到(S)-2-(叔丁基磺酰基)-N-((2S,3R)-3-(环己基甲氧基)-1-((S)-3-(甲氧基甲基)哌啶-1-基)-1-氧代丁-2-基)-6-(噻唑-5-羰基)-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(16mg,52%),其为白色固体。LCMSm/z=696.5[M+H]$^+$;^{1}H NMR(400MHz,DMSO-d6)δ9.29-9.23(m,1H),8.57-8.47(m,1H),8.44-8.30(m,1H),4.86(s,1H),4.35-4.22(m,1H),4.17-3.36(m,12H),3.28-3.08(m,7H),3.06-2.74(m,1H),1.75-1.53(m,8H),1.52-1.32(m,2H),1.30-1.00(m,16H),0.92-0.79(m,2H).

[0992] 方法35:以I-498的合成为例



[0993]



[0994] 步骤1:在0℃将LiHMDS(1M于THF中,4.2mL,4.2mmol)逐滴添加到2-(二乙氧基磷酰基)丙酸乙酯(1.0g,4.2mmol)在THF(6mL)中的溶液。搅拌30分钟后,添加3-氧代氮杂环丁烷-1-甲酸叔丁酯(647mg,3.8mmol)在THF(5.0mL)中的溶液,并将所得溶液在室温搅拌1h。添加水并用EtOAc萃取水相。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将粗品通过硅胶柱色谱法(20%EtOAc/PE)纯化,得到3-(1-乙氧基-1-氧代丙-2-亚基)氮杂环丁烷-1-甲酸叔丁酯(552mg,52%),其为白色固体。LCMSm/z=256.2[M+H]$^+$;^{1}HNMR(400MHz,DMSO-d_6)δ4.60(s,2H),4.52(s,2H),4.10(q,J=7.2Hz,2H),1.67-1.65(m,3H),1.39(s,9H),1.21(t,J=7.1Hz,3H)

[0995] 步骤2:在室温向3-(1-乙氧基-1-氧代丙-2-亚基)氮杂环丁烷-1-甲酸叔丁酯(540mg,2.1mmol)和LiF(165mg,6.3mmol)在ACN(10.0mL)中的溶液中逐滴添加N-苄基-N-

(甲氧基甲基)-2-(三甲基甲硅烷基)乙烷-1-胺(603mg,2.5mmol)。然后将混合物加热回流过夜。将反应混合物冷却,添加水并用EtOAc萃取水相。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将粗品通过硅胶柱色谱法纯化(30%EtOAc/PE),得到6-苄基-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(378mg,44%)。LCMSm/z=389.2$[M+H]^+$.

[0996] 步骤3:向6-苄基-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(378mg,0.97mmol)在EtOAc(5.0mL)中的溶液添加Pd/C(10%,100mg)。在H_2气氛下将所得混合物在50℃搅拌5h。反应混合物通过硅藻土过滤,并将滤液在减压下浓缩,得到8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(234mg,88%)。

[0997] 步骤4:向8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(224mg,0.75mmol)在DMA(3.0mL)中的溶液添加1-苄基-1H-吡唑-4-甲酸(183mg,0.9mmol)、EDCI(216mg,1.1mmol)、HOBt(122mg,0.9mol)和DIPEA(292mg,2.3mmol)。将所得混合物在室温搅拌过夜。添加水并用EtOAc萃取水溶液。将合并的有机层用水、盐水洗涤并经Na_2SO_4干燥。除去溶剂并将粗品通过硅胶柱色谱法纯化(5%MeOH/DCM),得到6-(1-苄基-1H-吡唑-4-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(190mg,52%),其为白色固体。LCMSm/z=427.2$[M+H-56]^+$

[0998] 步骤5:向6-(1-苄基-1H-吡唑-4-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(190mg,1.93mmol)在DCM(10mL)中的溶液添加TFA(2mL)。将所得混合物搅拌2h,然后在减压下除去溶剂,得到6-(1-苄基-1H-吡唑-4-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(151mg,定量)。

[0999] 步骤6:使用与合成6-(1-苄基-1H-吡唑-4-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(方法35的步骤4)描述的类似的步骤制备,使用(S)-2,2-二甲基环丙烷-1-甲酸。LCMSm/z=479.4$[M+H]^+$.

[1000] 步骤7:向6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-8-甲酸乙酯(112mg,0.23mmol)在MeOH(1.0mL)中的溶液添加10%NaOH水溶液(4.0mL)。将所得混合物搅拌3h,然后在真空下除去溶剂。将得到的残留物用水稀释,并通过添加1M HCl将pH调节至~1。将水层用EtOAc萃取三次并将合并的有机层用水、盐水洗涤,经Na_2SO_4干燥并浓缩,得到6-(1-苄基-1H-吡唑-4-羰基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-8-甲酸(105mg,定量),其为灰白色固体。LCMSm/z=451.3$[M+H]^+$.

[1001] 步骤8:使用与合成6-(1-苄基-1H-吡唑-4-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-2,8-二甲酸2-(叔丁基)8-乙基酯(方法35的步骤4)描述的类似的步骤制备,通过制备型HPLC纯化后得到6-(1-苄基-1H-吡唑-4-羰基)-N-((2S,3R)-3-(苄氧基)-1-(甲基氨基)-1-氧代丁-2-基)-2-((S)-2,2-二甲基环丙烷-1-羰基)-8-甲基-2,6-二氮杂螺[3.4]辛烷-8-甲酰胺(I-498)。LCMSm/z=655.5$[M+H]^+$;^{1}HNMR(400MHz,CD_3OD)δ8.27-8.17(m,1H),7.96-7.93(m,1H),7.41-7.19(m,10H),5.35(d,J=11.3Hz,2H),4.70-3.58(m,13H),2.72(t,J=2.8Hz,3H),1.49-1.25(m,6H),1.22-1.15(m,4H),1.10-1.02(m,3H),0.78-0.73(m,1H).

[1002] 表2.示例性化合物的表征数据

[1003] 下表2包含表1化合物的表征数据。此外,表2公开了实施例2的方法,其最好地描述

了制备表1的每种化合物的步骤。合成表1化合物所需的合适的试剂、起始材料、条件和示例性合成方法的必要修改对本领域普通技术人员是显而易见的。除非另有规定,LCMS值显示为[M+H]+。

[1004]

化合物编号	方法	^{1}HNMR	LCMS
I-1	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.27 – 8.12 (m, 1H), 7.96 – 7.88 (m, 1H), 7.60 – 6.99 (m, 10H), 5.37 (s, 2H), 4.70 – 4.30 (m, 4H), 4.27 – 3.58 (m, 10H), 2.73 (s, 3H), 1.48 – 1.29 (m, 1H), 1.19 – 1.07 (m, 6H), 1.03 (s, 1H), 0.83 – 0.67 (m, 1H).	627.4
I-2	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.20 (d, J = 17.1 Hz, 1H), 7.92 (d, J = 10.1 Hz, 1H), 7.38 – 7.25 (m, 5H), 5.37 (s, 2H), 4.59 – 3.37 (m, 13H), 2.78 – 2.70 (m, 3H), 1.22 – 0.99 (m, 11H), 0.82 – 0.73 (m, 1H).	565.4
I-3A	7A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.19 (d, J = 16.6 Hz, 1H), 7.90 (d, J = 9.8 Hz, 1H), 7.30 (dd, J = 16.8, 4.8 Hz, 10H), 5.39 – 5.35 (m,	645.5

[1005]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 4.62 – 4.43 (m, 3H), 4.15 – 3.75 (m, 10H), 2.73 (d, J = 10.4 Hz, 3H), 1.41 (s, 9H), 1.21 (d, J = 6.2 Hz, 3H).	
I-3B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.27 (m, 2H), 7.92 – 7.76 (m, 2H), 7.39 – 7.20 (m, 10H), 5.75 (s, 1H), 5.34 (s, 2H), 4.59 – 4.27 (m, 3H), 4.07 – 3.36 (m, 11H), 2.61 (d, J = 4.4 Hz, 3H), 1.37 (s, 10H), 1.28 – 1.22 (m, 4H), 1.06 (dd, J = 20.2, 6.2 Hz, 3H).	645.5
I-4A	7A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 – 8.12 (m, 1H), 7.94 – 7.85 (m, 1H), 7.36 – 7.22 (m, 10H), 5.36 (s, 2H), 4.65 – 4.53 (m, 1H), 4.52 – 4.35 (m, 2H), 4.31 – 3.73 (m, 9H), 3.41 – 3.33 (m, 1H), 3.03 (ddt, J = 38.0, 17.0, 8.6 Hz, 1H), 2.79 – 2.68 (m, 3H), 2.07 – 1.75 (m, 4H), 1.24 – 1.13 (m, 6H), 1.09 – 1.03 (m, 3H).	655.5
I-4B	7B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 – 8.13 (m, 1H), 7.89 (d, J = 19.0 Hz, 1H), 7.37 – 7.20 (m, 10H), 5.35 (d, J = 4.8 Hz, 2H), 4.69 – 4.29 (m, 4H), 4.24 – 3.71 (m, 9H), 3.16 – 3.01 (m, 1H), 2.76 – 2.70 (m, 3H), 2.04 – 1.86 (m, 4H), 1.22 – 1.10 (m, 6H), 1.06 (s, 3H).	655.4
I-5	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.12 – 8.01 (m, 2H), 7.36 – 7.24 (m, 5H), 4.73 – 4.36 (m, 4H), 4.29 – 3.69 (m, 9H), 3.40 (s, 1H), 2.74 (dd, J = 7.0, 4.4 Hz, 3H), 1.52 – 1.33 (m, 1H), 1.25 – 1.09 (m, 9H), 1.03 (s, 1H), 0.77 (s, 1H).	550.3
I-6	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.27 – 8.12 (m, 1H), 7.90 (d, J = 22.2 Hz, 1H), 7.74 – 7.42 (m, 4H), 7.40 – 7.23 (m, 5H), 5.37 (s, 2H), 4.73 – 3.77 (m, 12H), 3.42 (s, 1H), 2.80 – 2.72 (m, 3H), 1.53 – 1.36 (m, 1H), 1.25 – 1.08 (m, 9H), 1.06 – 1.00 (m, 1H), 0.82 – 0.74 (m, 1H).	666.5
I-7	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.16 (d, J = 22.2 Hz, 1H), 7.90 (d, J = 14.6 Hz, 1H), 7.42 – 7.17 (m, 10H), 5.37 (s, 2H), 4.67 – 4.27 (m, 3H), 4.25 – 3.58 (m, 9H), 3.29 – 3.08 (m,	584.4

[1006]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 1.43 – 1.32 (m, 1H), 1.20 – 1.08 (m, 9H), 1.02 (s, 1H), 0.79 – 0.67 (m, 1H).	
I-8A	7A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.11 (m, 1H), 7.91 (s, 1H), 7.43 – 7.21 (m, 10H), 5.45 – 5.28 (m, 2H), 4.67 – 4.55 (m, 1H), 4.52 – 4.42 (m, 2H), 4.40 – 3.72 (m, 9H), 3.45 – 3.34 (m, 1H), 2.73 (s, 3H), 2.13 – 1.87 (m, 2H), 1.43 – 1.13 (m, 4H), 0.93 (s, 1H), 0.50 (s, 2H), 0.13 (s, 2H).	627.4
I-8B	7B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.32 – 8.12 (m, 1H), 7.89 (d, J = 18.8 Hz, 1H), 7.42 – 7.17 (m, 10H), 5.36 (s, 2H), 4.65 – 4.52 (m, 1H), 4.50 – 4.35 (m, 2H), 4.35 – 3.64 (m, 8H), 3.37 (s, 1H), 2.72 (s, 3H), 2.14 – 1.93 (m, 2H), 1.47 – 0.80 (m, 6H), 0.51 (s, 2H), 0.16 (s, 2H).	627.4
I-9	15	1HNMR (400 MHz, CD_3OD): δ 8.15-8.27 (m, 1H), 7.93-7.95 (m, 1H), 7.29-7.36 (m, 10H), 5.38-5.40 (m, 2H), 4.56-4.70 (m, 2H), 4.20-4.51 (m, 4H), 3.80-4.13 (m, 5H), 3.40-3.50 (m, 1H), 1.42-1.48 (m, 1H), 1.32-1.37 (m, 1H), 1.18-1.28 (m, 4H), 1.11-1.18 (m, 4H), 1.03-1.05 (m, 1H), 0.75-0.79 (m, 1H).	628.6
I-10	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.18 – 8.02 (m, 1H), 7.95 – 7.82 (m, 1H), 7.39 – 7.16 (m, 5H), 4.67 – 4.55 (m, 1H), 4.52 – 3.73 (m, 13H), 3.47 – 3.34 (m, 1H), 2.81 – 2.66 (m, 3H), 1.99 – 1.82 (m, 1H), 1.80 – 1.65 (m, 3H), 1.63 – 1.50 (m, 2H), 1.49 – 1.27 (m, 2H), 1.26 – 0.93 (m, 15H), 0.82 – 0.69 (m, 1H).	647.5
I-11	13	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.66 (s, 1H), 8.38 – 8.26 (m, 1H), 8.18 – 7.90 (m, 2H), 7.64 (s, 1H), 7.54 – 7.38 (m, 1H), 7.36 – 7.25 (m, 5H), 5.62 (s, 2H), 4.67 – 4.31 (m, 4H), 4.30 – 3.77 (m, 9H), 3.42 (s, 1H), 2.74 (t, J = 5.8 Hz, 3H), 1.43 – 1.34 (m, 1H), 1.27 – 1.10 (m, 9H), 1.07 – 0.96 (m, 1H), 0.84 – 0.68 (m, 1H).	642.4
I-12 混合物	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.25 – 8.16 (m, 1H), 7.95 – 7.88 (m, 1H), 7.38 – 7.24 (m,	647.5

[1007]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 4.56 – 3.76 (m, 10H), 3.48 – 3.33 (m, 2H), 3.22 – 3.10 (m, 1H), 2.77 – 2.69 (m, 3H), 1.79 – 1.62 (m, 6H), 1.57 – 1.38 (m, 2H), 1.37 – 1.08 (m, 14H), 1.07 – 1.00 (m, 2H), 0.91 (q, J = 11.8 Hz, 2H), 0.77 (dd, J = 7.6, 4.0 Hz, 1H).	
I-13	13	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.79 (s, 2H), 8.39 – 8.30 (m, 1H), 8.07 – 7.96 (m, 1H), 7.79 – 7.67 (m, 2H), 7.39 – 7.21 (m, 5H), 5.74 (d, J = 8.6 Hz, 2H), 4.65 – 4.29 (m, 4H), 4.26 – 3.79 (m, 8H), 3.61 (q, J = 7.0 Hz, 1H), 3.49 – 3.37 (m, 1H), 2.74 (t, J = 6.2 Hz, 3H), 1.24 – 1.17 (m, 5H), 1.16 – 1.11 (m, 4H), 1.07 – 1.00 (m, 1H), 0.83 – 0.72 (m, 1H).	642.4
I-14	13	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.12 – 8.01 (m, 1H), 7.90 – 7.80 (m, 1H), 7.36 – 7.23 (m, 5H), 4.65 – 3.83 (m, 15H), 3.39 (s, 1H), 2.74 (s, 3H), 1.53 – 1.36 (m, 1H), 1.24 – 1.09 (m, 9H), 1.03 (s, 1H), 0.77 (s, 1H).	565.4
I-15	13	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.79 (s, 2H), 8.44 – 8.26 (m, 2H), 8.02 – 7.93 (m, 2H), 7.37 – 7.22 (m, 5H), 5.64 (s, 2H), 4.66 – 4.56 (m, 1H), 4.51 – 3.77 (m, 11H), 3.42 (br s, 1H), 2.79 – 2.69 (m, 3H), 1.34 – 1.28 (m, 2H), 1.23 – 1.18 (m, 3H), 1.16 – 1.11 (m, 4H), 1.03 (br s, 1H), 0.83 – 0.68 (m, 1H).	642.4
I-16A	5A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 7.66 (d, J = 5.8 Hz, 1H), 7.51 (s, 1H), 7.34 – 7.18 (m, 10H), 5.28 (d, J = 3.3 Hz, 2H), 4.61 – 4.26 (m, 4H), 4.14 – 3.77 (m, 5H), 3.60 (s, 2H), 3.21 – 3.12 (m, 1H), 3.01 – 2.79 (m, 4H), 2.73 (s, 3H), 1.40 – 1.34 (m, 1H), 1.20 – 1.16 (m, 4H), 1.12 – 1.07 (m, 4H), 1.03 – 0.99 (m, 1H), 0.74 (dt, J = 7.8, 4.0 Hz, 1H).	627.4
I-16B	5B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 7.92 (s, 1H), 7.69 (s, 1H), 7.37 – 7.24 (m, 10H), 5.36 (s, 2H), 4.66 – 4.32 (m, 6H), 4.29 – 3.85 (m, 6H), 3.59 – 3.51 (m, 2H), 2.72 (s, 3H), 1.52 (t, J = 6.6 Hz, 1H), 1.39 – 1.28 (m, 1H), 1.26 – 1.15 (m, 7H), 1.12 (s, 3H), 1.06 – 1.01 (m, 1H), 0.80 (dd, J = 8.2, 4.2 Hz, 1H).	627.5

[1008]

化合物编号	方法	^{1}HNMR	LCMS
I-17A	4A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.13 (d, J = 11.0 Hz, 1H), 7.91 (d, J = 9.6 Hz, 1H), 7.39 – 7.21 (m, 5H), 4.61 (d, J = 11.8 Hz, 1H), 4.57 – 4.31 (m, 4H), 4.24 – 3.82 (m, 11H), 3.50 – 3.37 (m, 1H), 3.14 – 3.03 (m, 1H), 2.77 – 2.68 (m, 3H), 2.60 (t, J = 12.6 Hz, 1H), 2.19 (t, J = 7.6 Hz, 1H), 2.03 (q, J = 7.0, 6.4 Hz, 1H), 1.61 (s, 2H), 1.43 – 1.32 (m, 2H), 1.25 – 1.08 (m, 11H), 1.03 (t, J = 4.6 Hz, 1H), 0.77 (d, J = 9.6 Hz, 1H).	690.4
I-17B	4B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.12 (d, J = 25.6 Hz, 1H), 7.90 (d, J = 19.4 Hz, 1H), 7.36 – 7.23 (m, 5H), 4.64 – 4.41 (m, 5H), 4.27 – 4.07 (m, 5H), 4.04 – 3.87 (m, 6H), 3.84 – 3.75 (m, 1H), 3.46 – 3.36 (m, 1H), 3.07 (q, J = 11.2, 10.4 Hz, 1H), 2.74 (d, J = 2.0 Hz, 3H), 2.58 (q, J = 11.4, 11.0 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.08 (s, 3H), 1.60 (s, 2H), 1.51 – 1.41 (m, 1H), 1.22 – 1.18 (m, 5H), 1.16 – 1.11 (m, 5H), 1.06 – 1.02 (m, 1H), 0.81 – 0.75 (m, 1H).	690.4
I-18	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 2.6 Hz, 1H), 8.80 (t, J = 15.6 Hz, 1H), 8.41 – 8.32 (m, 1H), 8.08 – 7.98 (m, 1H), 7.51 (m, 1H), 6.72 (d, J = 8.8 Hz, 2H), 5.35 (d, J = 8.2 Hz, 1H), 4.15 (m, 4H), 3.96 – 3.74 (m, 3H), 3.72 – 3.53 (m, 6H), 3.46 (s, 4H), 1.40 – 1.21 (m, 1H), 1.13 – 1.00 (m, 5H), 0.90 (d, J = 5.0 Hz, 1H), 0.86 – 0.58 (m, 2H).	599.4
I-19A	11A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.16 – 8.10 (m, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.35 – 7.23 (m, 5H), 4.61 (d, J = 11.6 Hz, 1H), 4.52 – 4.31 (m, 3H), 4.24 – 3.81 (m, 11H), 3.48 – 3.35 (m, 1H), 3.04 (d, J = 12.4 Hz, 2H), 2.77 – 2.71 (m, 3H), 2.55 (t, J = 12.2 Hz, 2H), 2.09 – 1.98 (m, 1H), 1.55 (d, J = 13.2 Hz, 2H), 1.40 – 1.29 (m, 2H), 1.26 – 1.19 (m, 5H), 1.15 – 1.09 (m, 6H), 1.03 (t, J = 4.6 Hz, 1H), 0.77 (dd, J = 12.0, 5.4 Hz, 1H).	648.4
I-19B	11B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.17 – 8.08 (m, 1H), 7.93 – 7.86 (m, 1H), 7.41 – 7.20 (m,	648.5

[1009]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 4.67 – 4.36 (m, 4H), 4.30 – 4.12 (m, 3H), 4.10 – 3.79 (m, 9H), 3.46 – 3.37 (m, 1H), 3.06 – 3.00 (m, 2H), 2.74 (s, 3H), 2.59 – 2.50 (m, 2H), 2.04 (s, 1H), 1.60 – 1.47 (m, 3H), 1.23 – 1.17 (m, 6H), 1.15 – 1.12 (m, 4H), 1.07 – 1.02 (m, 1H), 0.83 – 0.74 (m, 1H).	
I-20	15	^{1}HNMR (400 MHz, CD_3OD): δ 8.13-8.03 (m, 1H), 7.83-7.78 (m, 1H), 7.24-7.18 (m, 10H), 8.28-8.26 (m, 2H), 4.52-4.34 (m, 3H), 4.10-3.75 (m, 12H), 3.37-3.29 (m, 1H), 1.27-1.19 (m, 2H), 1.11-0.93 (m, 9H), 0.80-0.64 (m, 2H).	695.9
I-21	15	^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.38-8.30 (m, 2H), 8.03-7.93 (m, 1H), 7.84-7.79 (m, 1H), 7.70-7.25 (m, 10H), 5.35-5.32 (m, 2H), 4.58-4.38 (m, 4H), 4.20-3.60 (m, 9H), 3.48-3.09 (m, 13H), 2.03-1.95 (m, 1H), 1.37-1.01 (m, 11H).	759.9
I-22	15	^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.68-8.31 (m, 3H), 7.84-7.78 (m, 1H), 7.37-7.25 (m, 10H), 5.35-5.31 (m, 2H), 5.00-4.85 (m, 1H), 4.54-3.58 (m, 14H), 2.02-1.95 (m, 2H), 1.10-1.03 (m, 10H), 0.87-0.82 (m, 6H), 0.72-0.65 (m, 5H).	723.8
I-23A	4A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.17 – 8.10 (m, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 7.36 – 7.22 (m, 5H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.51 – 4.31 (m, 3H), 4.24 – 3.80 (m, 10H), 3.49 – 3.34 (m, 1H), 2.87 (d, *J* = 11.6 Hz, 2H), 2.80 – 2.68 (m, 3H), 2.08 – 1.83 (m, 3H), 1.57 (d, *J* = 13.6 Hz, 2H), 1.40 – 1.28 (m, 5H), 1.25 – 1.18 (m, 3H), 1.15 – 1.08 (m, 6H), 1.03 (t, *J* = 4.6 Hz, 1H), 0.76 (dt, *J* = 12.6, 5.6 Hz, 1H).	662.5
I-23B	4B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.20 – 8.11 (m, 1H), 7.95 – 7.87 (m, 1H), 7.34 – 7.25 (m, 5H), 4.66 – 4.55 (m, 2H), 4.50 – 4.40 (m, 2H), 4.31 – 4.11 (m, 5H), 4.07 – 3.75 (m, 6H), 3.55 – 3.39 (m, 3H), 3.02 – 2.83 (m, 5H), 2.74 (s, 3H), 2.27 – 2.16 (m, 1H), 1.85 (s, 2H), 1.58 – 1.49 (m, 2H), 1.24 – 1.18 (m,	662.5

[1010]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 1.16 – 1.11 (m, 4H), 1.05 (s, 1H), 0.79 (s, 1H).	
I-24A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.45 – 8.35 (m, 2H), 7.89 (s, 1H), 7.40 – 7.20 (m, 5H), 4.56 – 4.40 (m, 2H), 4.39 – 4.16 (m, 2H), 4.15 – 3.94 (m, 4H), 3.93 – 3.70 (m, 3H), 3.70 – 3.43 (m, 2H), 2.62 – 2.58 (m, 3H), 1.31 – 1.25 (m, 1H), 1.10 – 1.02 (m, 9H), 0.84 (s, 1H), 0.64 (s, 1H).	568.3
I-24B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.44 – 8.31 (m, 2H), 7.96 – 7.84 (m, 1H), 7.35 – 7.23 (m, 5H), 4.58 – 4.30 (m, 3H), 4.21 – 4.00 (m, 3H), 3.94 – 3.62 (m, 5H), 3.57 – 3.44 (m, 1H), 3.30 (s, 1H), 2.61 (t, J = 2.6 Hz, 3H), 1.38 – 1.31 (m, 1H), 1.14 – 1.01 (m, 9H), 0.86 (s, 1H), 0.70 (dd, J = 8.6, 4.4 Hz, 1H).	568.4
I-25A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.29 (m, 2H), 7.82 (d, J = 12.0 Hz, 2H), 7.38 – 7.23 (m, 13H), 7.21 – 7.13 (m, 2H), 5.35 (s, 2H), 4.56 – 4.40 (m, 2H), 4.38 – 4.10 (m, 2H), 4.07 – 3.86 (m, 4H), 3.82 – 3.69 (m, 2H), 3.68 – 3.35 (m, 3H), 3.30 (d, J = 2.0 Hz, 2H), 2.64 – 2.56 (m, 3H), 1.04 (m, J = 14.4, 7.0 Hz, 3H).	663.4
I-25B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.30 (m, 2H), 7.92 – 7.78 (m, 2H), 7.36 – 7.26 (m, 11H), 7.22 (d, J = 7.2 Hz, 4H), 5.35 (s, 2H), 4.57 – 4.48 (m, 1H), 4.45 – 4.28 (m, 3H), 4.14 – 3.89 (m, 4H), 3.88 – 3.57 (m, 5H), 3.37 (s, 1H), 2.61 (dd, J = 11.0, 4.6 Hz, 3H), 1.11 – 1.02 (m, 3H).	663.2
I-26A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (q, J = 13.2, 12.4 Hz, 2H), 7.82 (d, J = 16.6 Hz, 2H), 7.62 (d, J = 7.4 Hz, 1H), 7.56 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.36 – 7.21 (m, 10H), 5.35 (s, 2H), 4.56 – 4.09 (m, 6H), 4.04 – 3.73 (m, 5H), 3.67 – 3.41 (m, 2H), 2.60 – 2.57 (m, 3H), 1.13 – 0.95 (m, 3H).	649.4
I-26B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.27 (m, 2H), 7.96 – 7.76 (m, 2H), 7.68 – 7.63 (m,	649.2

[1011]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 7.55 – 7.41 (m, 3H), 7.36 – 7.23 (m, 10H), 5.35 (s, 2H), 4.53 (t, J = 9.6 Hz, 1H), 4.48 – 4.36 (m, 2H), 4.33 – 4.20 (m, 3H), 4.10 – 3.79 (m, 5H), 3.77 – 3.41 (m, 3H), 2.64 – 2.51 (m, 3H), 1.12 – 0.99 (m, 3H).	
I-27A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 11.6 Hz, 2H), 7.89 – 7.80 (m, 2H), 7.37 – 7.25 (m, 10H), 5.35 (s, 2H), 4.53 (dd, J = 12.0, 4.8 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.36 (s, 1H), 4.07 – 3.83 (m, 5H), 3.80 – 3.57 (m, 3H), 3.37 (s, 1H), 3.30 (s, 1H), 2.60 (dd, J = 10.6, 4.4 Hz, 3H), 2.46 (d, J = 7.4 Hz, 1H), 2.18 – 1.90 (m, 4H), 1.81 – 1.70 (m, 2H), 1.62 – 1.52 (m, 2H), 1.08 (d, J = 6.2 Hz, 3H).	641.4
I-27B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.29 (m, 2H), 7.90 (d, J = 17.2 Hz, 1H), 7.81 (d, J = 15.6 Hz, 1H), 7.37 – 7.25 (m, 10H), 5.35 (s, 2H), 4.52 (t, J = 11.6 Hz, 1H), 4.46 – 4.21 (m, 2H), 4.13 – 3.52 (m, 8H), 3.50 – 3.37 (m, 1H), 2.60 (t, J = 4.4 Hz, 3H), 2.57 – 2.52 (m, 1H), 2.14 (t, J = 6.4 Hz, 2H), 2.01 (s, 2H), 1.78 (q, J = 8.2 Hz, 2H), 1.63 (t, J = 9.0 Hz, 2H), 1.12 – 0.99 (m, 3H).	641.4
I-28	15	^{1}HNMR (400 MHz, $CDCl_3$): δ 8.84-8.60 (m, 3H), 7.96-7.78 (m, 3H), 7.37-7.27 (m, 6H), 7.25-7.19 (m, 2H), 5.28 (s, 2H), 4.61-4.43 (m, 3H), 4.24-3.41 (m, 15H), 1.28-1.06 (m, 12H), 0.77-0.68 (m, 1H).	694.9
I-29	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.15-8.04 (m, 1H), 7.94-7.78 (m, 2H), 7.25-7.17 (m, 9H), 5.27 (d, J = 6.4 Hz, 2H), 4.52-4.23 (m, 4H), 4.11-3.69 (m, 8H), 3.41-3.27 (m, 3H), 2.42-2.38 (m, 2H), 1.21-1.19 (m, 2H), 1.12-0.98 (m, 8H), 0.95-0.91 (m, 1H),0.71-0.61 (m, 1H)	699.7
I-30	15	^{1}HNMR (400 MHz, CD_3OD): δ 8.15-8.04 (m, 1H), 7.83-7.78 (m, 1H), 7.45-7.03 (m, 10H), 5.28-5.23 (m, 2H), 4.53-4.34 (m, 3H), 4.33-4.16 (m, 1H), 4.14-3.63 (m, 8H), 3.50-3.45 (m, 2H), 3.36-3.25 (m, 1H), 2.13-1.91 (m, 1H), 1.52-1.29 (m, 1H), 1.19 (s, 2H),	671.9

[1012]

化合物编号	方法	^{1}HNMR	LCMS
		1.13-0.98 (m, 8H), 0.92 (s, 1H), 0.69-0.62 (m, 1H).	
I-31	15	^{1}H NMR (400 MHz, DMSO-d6) δ 8.38-8.33 (m, 2H), 7.96-7.79 (s, 2H), 7.37-7.26 (m, 9H), 5.35 (s, 2H), 4.56-4.36 (m, 3H), 4.24-3.89 (s, 5H), 3.81-3.40 (m, 5H), 3.14-3.05 (m, 2H), 2.59-2.55 (m, 1H), 2.08-1.96 (m, 1H), 1.23 (s, 3H), 1.11-1.01 (m, 7H), 0.86-0.81 (d, J = 6.8 Hz, 2H), 0.70-0.57 (m, 2H)	670.5
I-32	15	^{1}H NMR (400 MHz, CD_3OD) δ 8.23-8.16 (m, 1H), 7.93-7.88 (m, 1H), 7.37-7.28 (m, 10H), 5.38-5.37 (m, 2H), 5.00-4.92 (m, 1H), 4.65-4.44 (m, 3H), 4.39-4.24 (m, 1H), 4.22-3.81 (m, 8H), 3.60-3.48 (m, 4H), 2.91-2.70 (m, 4H), 1.37-1.33 (m, 1H), 1.24-1.10 (m, 9H), 1.03-1.02 (m, 1H), 0.79-0.74 (m, 1H).	696.9
I-33A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.26 (m, 1H), 8.17 (d, J = 13.4 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.35 – 7.26 (m, 5H), 4.55 – 4.40 (m, 2H), 4.35 (d, J = 8.4 Hz, 1H), 4.25 – 4.14 (m, 1H), 4.08 – 3.90 (m, 4H), 3.86 (s, 3H), 3.81 – 3.59 (m, 3H), 3.58 – 3.40 (m, 2H), 2.60 (dd, J = 9.0, 4.4 Hz, 3H), 1.34 – 1.25 (m, 1H), 1.12 – 1.03 (m, 8H), 1.01 (s, 1H), 0.84 (t, J = 4.6 Hz, 1H), 0.64 (q, J = 8.2, 5.8 Hz, 1H).	565.4
I-33B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.31 (m, 1H), 8.19 – 8.13 (m, 1H), 7.94 – 7.82 (m, 1H), 7.80 – 7.72 (m, 1H), 7.35 – 7.27 (m, 5H), 4.52 (t, J = 11.2 Hz, 1H), 4.46 – 4.29 (m, 2H), 4.17 – 3.94 (m, 3H), 3.94 – 3.56 (m, 8H), 3.54 – 3.39 (m, 1H), 3.30 (s, 1H), 2.61 (d, J = 4.4 Hz, 3H), 1.36 (t, J = 6.6 Hz, 1H), 1.15 – 1.02 (m, 9H), 0.89 – 0.82 (m, 1H), 0.71 – 0.65 (m, 1H).	565.2
I-34A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.28 (m, 2H), 7.82 (d, J = 12.0 Hz, 2H), 7.37 – 7.22 (m, 10H), 7.06 (dd, J = 15.2, 8.2 Hz, 2H), 6.85 – 6.75 (m, 2H), 5.35 (s, 2H), 4.54 – 4.41 (m, 3H), 4.36 – 4.32 (m, 1H), 4.27 – 4.05 (m, 1H), 4.05 – 3.84 (m, 4H), 3.83 – 3.68 (m, 2H), 3.68 – 3.58 (m, 2H), 3.41 –	721.4

[1013]

化合物编号	方法	^{1}HNMR	LCMS
		3.20 (m, 3H), 2.63 – 2.56 (m, 3H), 1.23 (d, *J* = 6.0 Hz, 6H), 1.05 (dd, *J* = 13.4, 6.4 Hz, 3H).	
I-34B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.29 (m, 2H), 7.92 – 7.77 (m, 2H), 7.35 – 7.25 (m, 10H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.85 – 6.79 (m, 2H), 5.35 (s, 2H), 4.60 – 4.47 (m, 2H), 4.45 – 4.31 (m, 2H), 4.21 – 3.33 (m, 12H), 2.61 (dd, *J* = 10.4, 4.6 Hz, 3H), 1.24 (dd, *J* = 6.0, 2.8 Hz, 6H), 1.12 – 1.02 (m, 3H).	721.2
I-35	1A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.50 – 8.47 (m, 1H), 8.37 – 8.29 (m, 2H), 8.00 – 7.94 (m, 1H), 7.71 – 7.61 (m, 2H), 7.16 – 7.10 (m, 1H), 5.57 (s, 2H), 4.81 – 4.58 (m, 2H), 4.45 – 4.28 (m, 1H), 4.27 – 4.16 (m, 2H), 4.14 – 3.98 (m, 3H), 3.97 – 3.84 (m, 2H), 3.30 – 3.22 (m, 1H), 2.71 – 2.66 (m, 3H), 1.43 – 1.32 (m, 1H), 1.21 – 1.11 (m, 4H), 1.10 – 1.07 (m, 2H), 1.05 – 1.01 (m, 1H), 0.80 – 0.73 (m, 1H).	561.5
I-36A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.26 (m, 1H), 8.19 – 8.12 (m, 1H), 7.89 – 7.73 (m, 2H), 7.35 – 7.24 (m, 5H), 4.56 – 4.40 (m, 2H), 4.35 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.21 – 3.88 (m, 5H), 3.85 (s, 3H), 3.78 – 3.38 (m, 5H), 2.60 (dd, *J* = 9.2, 4.4 Hz, 3H), 1.94 – 1.83 (m, 2H), 1.10 – 1.04 (m, 3H), 0.93 – 0.80 (m, 1H), 0.40 (t, *J* = 7.0 Hz, 2H), 0.08 – 0.01 (m, 2H).	551.4
I-36B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 – 8.29 (m, 1H), 8.22 – 8.09 (m, 1H), 7.93 – 7.72 (m, 2H), 7.35 – 7.26 (m, 5H), 4.52 (t, *J* = 10.6 Hz, 1H), 4.45 – 4.22 (m, 2H), 4.05 – 3.93 (m, 3H), 3.85 (d, *J* = 4.4 Hz, 5H), 3.76 – 3.36 (m, 5H), 2.62 – 2.58 (m, 3H), 1.96 (t, *J* = 7.4 Hz, 2H), 1.09 – 1.05 (m, 3H), 0.90 (d, *J* = 6.8 Hz, 1H), 0.46 – 0.38 (m, 2H), 0.09 (s, 2H).	551.2
I-37A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.28 (m, 2H), 7.88 – 7.77 (m, 2H), 7.38 – 7.23 (m, 10H), 5.35 (s, 2H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 9.0 Hz, 1H), 4.19 – 3.84 (m, 5H), 3.81 – 3.53 (m,	669.2

[1014]

化合物编号	方法	^{1}HNMR	LCMS
		3H), 3.52 – 3.35 (m, 1H), 3.30 (s, 1H), 2.60 (dd, *J* = 10.4, 4.4 Hz, 3H), 1.92 – 1.72 (m, 2H), 1.59 (s, 6H), 1.25 – 0.98 (m, 6H), 0.84 (d, *J* = 9.4 Hz, 2H).	
I-37B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.27 (m, 2H), 7.93 – 7.77 (m, 2H), 7.38 – 7.20 (m, 10H), 5.35 (s, 2H), 4.52 (t, *J* = 11.6 Hz, 1H), 4.46 – 4.20 (m, 2H), 4.11 – 3.79 (m, 5H), 3.77 – 3.51 (m, 3H), 3.49 – 3.38 (m, 1H), 2.60 (d, *J* = 4.4 Hz, 3H), 1.89 (s, 2H), 1.63 (s, 6H), 1.26 – 1.01 (m, 7H), 0.91 – 0.85 (m, 2H).	669.2
I-38A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 – 8.19 (m, 1H), 7.84 (dd, *J* = 11.0, 4.8 Hz, 1H), 7.35 – 7.25 (m, 5H), 4.56 – 4.39 (m, 2H), 4.38 – 4.32 (m, 1H), 4.23 – 4.10 (m, 1H), 4.05 – 3.33 (m, 13H), 2.66 (d, *J* = 11.1 Hz, 1H), 2.61 (d, *J* = 4.5 Hz, 3H), 1.57 – 1.52 (m, 4H), 1.36 – 1.20 (m, 1H), 1.11 – 1.00 (m, 9H), 0.83 (q, *J* = 4.6 Hz, 1H), 0.68 – 0.60 (m, 1H).	569.5
I-38B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.27 (m, 1H), 7.95 – 7.80 (m, 1H), 7.36 – 7.25 (m, 5H), 4.57 – 4.28 (m, 3H), 4.15 – 3.92 (m, 2H), 3.91 – 3.78 (m, 4H), 3.77 – 3.59 (m, 2H), 3.59 – 3.41 (m, 3H), 3.30 (s, 2H), 2.60 (d, *J* = 4.2 Hz, 3H), 1.54 (s, 4H), 1.37 – 1.34 (m, 1H), 1.11 (s, 3H), 1.10 – 1.02 (m, 6H), 0.86 (s, 1H), 0.69 (dt, *J* = 7.8, 4.2 Hz, 1H).	569.4
I-39A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 1.8 Hz, 1H), 8.41 – 8.33 (m, 1H), 7.88 – 7.78 (m, 2H), 7.35 – 7.25 (m, 5H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.34 (d, *J* = 8.6 Hz, 1H), 4.27 – 3.66 (m, 9H), 3.65 – 3.43 (m, 1H), 2.60 (dd, *J* = 7.4, 4.4 Hz, 3H), 1.32 – 1.23 (m, 1H), 1.11 – 1.02 (m, 9H), 0.84 (t, *J* = 4.6 Hz, 1H), 0.69 – 0.60 (m, 1H).	552.4
I-39B	4B	^{1}H NMR (400 MHz, DMSO-d6) δ 8.58 – 8.56 (m, 1H), 8.46 – 8.39 (m, 1H), 7.96 – 7.84 (m, 1H), 7.83 – 7.75 (m, 1H), 7.35 – 7.26 (m, 5H), 4.55 – 4.50 (m, 1H), 4.45 – 4.31 (m, 2H), 4.20 – 3.39 (m, 10H), 2.64 –	552.1

[1015]

化合物编号	方法	^{1}HNMR	LCMS
		2.59 (m, 3H), 1.38 – 1.32 (m, 1H), 1.13 – 1.05 (m, 9H), 0.87 (t, J = 5.0 Hz, 1H), 0.68 (dq, J = 7.8, 4.4, 3.6 Hz, 1H).	
I-40A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.47 (m, 1H), 8.26 – 8.19 (m, 1H), 8.17 (s, 1H), 7.84 – 7.72 (m, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.33 – 7.24 (m, 6H), 4.55 – 4.41 (m, 2H), 4.37 – 4.28 (m, 1H), 3.99 – 3.91 (m, 3H), 3.75 – 3.65 (m, 4H), 3.55 (d, J = 10.0 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.73 – 2.62 (m, 2H), 2.59 (d, J = 4.6 Hz, 3H), 1.34 – 1.26 (m, 1H), 1.13 – 0.99 (m, 9H), 0.85 – 0.79 (m, 1H), 0.65 – 0.60 (m, 1H).	548.4
I-40B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.45 (m, 1H), 8.27 (dd, J = 8.8, 4.8 Hz, 1H), 7.84 (dd, J = 22.8, 4.8 Hz, 1H), 7.73 (tdd, J = 7.6, 5.8, 1.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.32 – 7.22 (m, 6H), 4.52 (dd, J = 12.0, 1.6 Hz, 1H), 4.42 (dd, J = 12.0, 2.4 Hz, 1H), 4.35 (ddd, J = 13.8, 8.8, 4.4 Hz, 1H), 4.15 – 4.03 (m, 1H), 3.94 – 3.65 (m, 5H), 3.22 (q, J = 6.8 Hz, 1H), 3.06 – 2.90 (m, 2H), 2.73 – 2.65 (m, 1H), 2.64 – 2.56 (m, 4H), 1.33 (ddd, J = 23.8, 8.0, 5.4 Hz, 1H), 1.12 – 0.99 (m, 9H), 0.83 (dd, J = 5.4, 3.8 Hz, 1H), 0.65 (dd, J = 8.0, 3.8 Hz, 1H).	548.4
I-41A	10A	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 8.32 (dd, J = 23.6, 9.0 Hz, 1H), 7.84 (s, 2H), 7.34 – 7.26 (m, 5H), 4.55 – 4.40 (m, 2H), 4.35 (dd, J = 8.6, 3.4 Hz, 1H), 4.20 – 3.38 (m, 10H), 2.60 (dd, J = 11.2, 4.4 Hz, 3H), 1.88 (dd, J = 22.8, 6.4 Hz, 2H), 1.07 (d, J = 5.4 Hz, 3H), 0.87 (s, 1H), 0.40 (s, 2H), 0.04 (d, J = 7.6 Hz, 2H).	537.4
I-41B	10B	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 8.32 (t, J = 10.2 Hz, 1H), 8.23 – 8.00 (m, 1H), 7.97 – 7.76 (m, 2H), 7.35 – 7.24 (m, 5H), 4.52 (t, J = 12.2 Hz, 1H), 4.45 – 4.21 (m, 2H), 4.11 – 3.95 (m, 3H), 3.90 – 3.80 (m, 2H), 3.77 – 3.38 (m, 5H), 2.60 (d, J = 4.2 Hz, 3H), 2.00 – 1.92 (m, 2H), 1.10 – 1.03 (m,	537.1

[1016]

化合物编号	方法	^{1}HNMR	LCMS
		3H), 0.91 (s, 1H), 0.42 (t, J = 6.4 Hz, 2H), 0.09 (t, J = 6.0 Hz, 2H).	
I-42A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.66 (m, 2H), 8.43 – 8.24 (m, 1H), 7.99 – 7.70 (m, 1H), 7.52 – 7.44 (m, 1H), 7.35 – 7.22 (m, 5H), 4.52 (dd, J = 12.2, 6.0 Hz, 1H), 4.46 – 4.07 (m, 3H), 4.04 – 3.57 (m, 7H), 3.54 – 3.38 (m, 1H), 3.30 (s, 1H), 2.64 – 2.54 (m, 3H), 1.33 – 1.20 (m, 1H), 1.11 – 0.96 (m, 9H), 0.85 – 0.78 (m, 1H), 0.70 – 0.57 (m, 1H).	562.4
I-42B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 – 8.63 (m, 2H), 8.47 – 8.25 (m, 1H), 7.95 – 7.79 (m, 2H), 7.48 (dd, J = 7.6, 4.8 Hz, 1H), 7.37 – 7.16 (m, 5H), 4.59 – 4.30 (m, 3H), 4.28 – 4.00 (m, 1H), 3.98 – 3.63 (m, 6H), 3.60 – 3.34 (m, 2H), 3.31 (d, J = 4.8 Hz, 1H), 2.60 (dt, J = 7.4, 3.2 Hz, 3H), 1.41 – 1.22 (m, 1H), 1.16 – 1.01 (m, 7H), 1.00 – 0.92 (m, 2H), 0.90 – 0.80 (m, 1H), 0.72 – 0.61 (m, 1H).	562.2
I-43A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.28 (m, 2H), 7.93 (d, J = 12.8 Hz, 1H), 7.85 (d, J = 4.8 Hz, 1H), 7.36 – 7.23 (m, 5H), 5.18 (q, J = 9.0 Hz, 2H), 4.56 – 4.49 (m, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.35 (d, J = 8.6 Hz, 1H), 4.20 – 3.88 (m, 5H), 3.87 – 3.47 (m, 4H), 3.41 (dt, J = 12.6, 6.2 Hz, 1H), 2.60 (dd, J = 10.4, 4.5 Hz, 3H), 1.95 – 1.88 (m, 1H), 1.85 (dd, J = 6.9, 2.6 Hz, 1H), 1.12 – 1.04 (m, 3H), 0.87 (dt, J = 13.8, 6.6 Hz, 1H), 0.44 – 0.36 (m, 2H), 0.08 – 0.00 (m, 2H).	619.3
I-43B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.29 (m, 2H), 8.02 – 7.73 (m, 2H), 7.36 – 7.21 (m, 5H), 5.17 (q, J = 9.0 Hz, 2H), 4.52 (t, J = 11.2 Hz, 1H), 4.46 – 4.27 (m, 2H), 4.27 – 4.01 (m, 2H), 4.00 – 3.52 (m, 7H), 3.51 – 3.38 (m, 1H), 2.60 (dd, J = 4.6, 2.4 Hz, 3H), 1.96 (t, J = 7.4 Hz, 2H), 1.13 – 1.01 (m, 3H), 0.90 (d, J = 8.2 Hz, 1H), 0.43 (d, J = 7.8 Hz, 2H), 0.10 – 0.05 (m, 2H).	619.4
I-44A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.89 – 7.80 (m, 1H), 7.72 (s, 1H), 7.65	551.1

[1017]

化合物编号	方法	^{1}HNMR	LCMS
		(s, 1H), 7.41 – 7.26 (m, 5H), 4.53 (d, J = 12.2 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.39 – 4.09 (m, 3H), 4.07 – 3.36 (m, 8H), 2.60 (dd, J = 9.6, 4.4 Hz, 3H), 1.35 – 1.24 (m, 1H), 1.12 – 1.00 (m, 9H), 0.84 (br s, 1H), 0.63 (br s, 1H).	
I-44B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.32 (m, 1H), 7.92 – 7.86 (m, 1H), 7.75 – 7.68 (m, 1H), 7.64 (s, 1H), 7.35 – 7.27 (m, 5H), 4.58 – 4.26 (m, 4H), 4.25 – 4.05 (m, 2H), 4.04 – 3.84 (m, 2H), 3.84 – 3.77 (m, 2H), 3.65 (s, 2H), 2.61 (d, J = 4.0 Hz, 3H), 1.39 – 1.35 (m, 1H), 1.12 – 1.04 (m, 9H), 0.86 (br s, 1H), 0.68 (br s, 1H).	551.4
I-45A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 – 8.60 (m, 1H), 8.41 – 8.25 (m, 1H), 7.97 – 7.75 (m, 3H), 7.54 – 7.49 (m, 1H), 7.35 – 7.23 (m, 5H), 4.54 – 4.50 (m, 1H), 4.45 – 4.26 (m, 2H), 4.22 – 4.03 (m, 2H), 4.02 – 3.85 (m, 4H), 3.84 – 3.64 (m, 3H), 3.60 – 3.41 (m, 1H), 2.64 – 2.54 (m, 3H), 1.37 – 1.21 (m, 1H), 1.11 – 0.98 (m, 9H), 0.83 (dq, J = 12.6, 4.6, 4.0 Hz, 1H), 0.67 – 0.60 (m, 1H).	562.2
I-45B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 – 8.55 (m, 1H), 8.44 – 8.27 (m, 1H), 8.01 – 7.68 (m, 3H), 7.51 (ddd, J = 7.6, 4.6, 1.2 Hz, 1H), 7.40 – 7.16 (m, 5H), 4.59 – 4.11 (m, 4H), 4.10 – 3.53 (m, 8H), 3.49 – 3.38 (m, 1H), 2.60 (td, J = 5.2, 4.8, 2.6 Hz, 3H), 1.40 – 1.30 (m, 1H), 1.13 – 0.95 (m, 9H), 0.88 – 0.81 (m, 1H), 0.70 – 0.62 (m, 1H).	562.4
I-46A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 – 8.65 (m, 2H), 8.44 – 8.26 (m, 1H), 7.89 – 7.74 (m, 1H), 7.51 – 7.45 (m, 2H), 7.35 – 7.22 (m, 5H), 4.52 (dd, J = 12.2, 6.2 Hz, 1H), 4.45 – 4.25 (m, 2H), 4.23 – 4.07 (m, 1H), 4.03 – 3.81 (m, 3H), 3.78 – 3.37 (m, 6H), 2.63 (d, J = 4.6 Hz, 2H), 2.56 (dd, J = 4.6, 2.0 Hz, 1H), 1.35 – 1.19 (m, 1H), 1.11 – 0.96 (m, 9H), 0.87 – 0.77 (m, 1H), 0.69 – 0.56 (m, 1H).	562.1
I-46B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.65 (m, 2H), 8.45 – 8.25 (m, 1H), 7.94 – 7.79 (m,	562.2

[1018]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 7.46 – 7.43 (m, 2H), 7.36 – 7.18 (m, 5H), 4.58 – 4.19 (m, 4H), 4.14 – 4.01 (m, 1H), 3.97 – 3.81 (m, 2H), 3.80 – 3.75 (m, 1H), 3.73 – 3.65 (m, 3H), 3.62 – 3.46 (m, 1H), 3.40 – 3.35 (m, 1H), 2.62 – 2.58 (m, 3H), 1.39 – 1.27 (m, 1H), 1.13 – 0.94 (m, 9H), 0.85 (dt, *J* = 20.8, 4.8 Hz, 1H), 0.66 (ddt, *J* = 16.0, 8.0, 3.8 Hz, 1H).	
I-47A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (q, *J* = 8.4, 7.8 Hz, 1H), 8.15 (s, 1H), 7.86 – 7.77 (m, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.39 – 7.22 (m, 5H), 4.59 – 4.49 (m, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.37 – 4.24 (m, 1H), 3.99 – 3.89 (m, 3H), 3.79 (d, *J* = 5.8 Hz, 3H), 3.73 – 3.62 (m, 1H), 3.53 (dd, *J* = 15.4, 9.2 Hz, 2H), 3.25 (t, *J* = 7.6 Hz, 1H), 3.13 (dd, *J* = 14.2, 7.6 Hz, 1H), 3.00 – 2.91 (m, 2H), 2.71 – 2.54 (m, 5H), 1.28 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 1H), 1.12 – 0.96 (m, 8H), 0.85 – 0.79 (m, 1H), 0.66 – 0.60 (m, 1H).	551.40
I-47B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28-8.23 (m, 2H), 7.86-7.79 (m, 1H), 7.55 (d, 1H), 7.34-7.23 (m, 5H), 4.55-4.51 (m, 1H), 4.44-4.40 (m, 1H), 4.37-4.30 (m, 1H), 4.10-4.01 (m, 2H), 3.91-3.83 (m, 2H), 3.77 (d, 2H), 3.73-3.70 (m, 1H), 3.65-3.62 (m, 1H), 3.51-3.49 (m, 1H), 3.43-3.42(m, 2H), 3.16 (q, *J*=6.8 Hz, 1H), 2.95-2.83 (m, 2H), 2.61-2.58 (m, 3H), 2.54 (d, 1H), 1.36-1.27 (m, 1H), 1.1-1.0 (m, 9H), 0.84-0.82 (m, 1H), 0.66-0.63 (m, 1H).	551.2
I-48A	12A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.25 (m, 2H), 7.88 – 7.85 (m, 1H), 7.75 (s, 1H), 7.39 (d, *J* = 0.6 Hz, 1H), 7.35 – 7.25 (m, 8H), 7.19 (s, 1H), 7.18 (s, 1H), 5.23 (s, 2H), 4.54 – 4.51 (m, 1H), 4.44 – 4.37 (m, 1H), 4.37 – 4.30 (m, 1H), 4.23 – 4.14 (m, 1H), 4.01 – 3.86 (m, 3H), 3.71 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.64 – 3.39 (m, 5H), 2.61 (d, *J* = 4.6 Hz, 3H), 1.36 – 1.25 (m, 1H), 1.10 – 1.00 (m, 9H), 0.84 (t, *J* = 4.6 Hz, 1H), 0.66 – 0.58 (m, 1H).	656.1

[1019]

化合物编号	方法	^{1}HNMR	LCMS
I-48B	12B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 5.0 Hz, 1H), 7.91 – 7.84 (m, 1H), 7.74 (t, J = 0.8 Hz, 1H), 7.38 (s, 1H), 7.35 – 7.23 (m, 8H), 7.19 (d, J = 1.4 Hz, 1H), 7.19 – 7.15 (m, 1H), 5.23 (s, 2H), 4.56 – 4.49 (m, 1H), 4.47 – 4.38 (m, 1H), 4.37 – 4.30 (m, 1H), 4.12 – 4.05 (m, 1H), 4.01 – 3.69 (m, 3H), 3.66 – 3.35 (m, 6H), 2.61 (dd, J = 4.6, 1.8 Hz, 3H), 1.36 (ddd, J = 10.6, 7.8, 5.4 Hz, 1H), 1.14 – 1.04 (m, 9H), 0.86 (q, J = 4.8 Hz, 1H), 0.68 (td, J = 7.6, 3.8 Hz, 1H).	656.2
I-49A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.46 (dd, J = 4.8, 1.6 Hz, 1H), 8.25 – 8.19 (m, 1H), 7.86 – 7.77 (m, 1H), 7.73 (dt, J = 7.8, 2.0 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 4H), 4.52 (dd, J = 12.2, 5.2 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.34 (dt, J = 8.8, 3.6 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.94 – 3.91 (m, J = 13.8, 6.8 Hz, 2H), 3.75 – 3.65 (m, 1H), 3.63 (d, J = 3.2 Hz, 2H), 3.54 (d, J = 10.0 Hz, 1H), 3.30 – 3.20 (m, 1H), 2.89 (t, J = 9.4 Hz, 2H), 2.65 (dd, J = 9.0, 2.2 Hz, 1H), 2.59 (t, J = 4.2 Hz, 4H), 1.37 – 1.25 (m, 1H), 1.18 – 0.95 (m, 9H), 0.86 – 0.77 (m, 1H), 0.62 (dt, J = 8.4, 4.0 Hz, 1H).	548.4
I-49B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 2.4 Hz, 1H), 8.50 – 8.47 (m, 1H), 8.30 (dd, J = 9.0, 3.6 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.37 – 7.26 (m, 6H), 4.56 (d, J = 12.0 Hz, 1H), 4.44 (dd, J = 12.0, 2.8 Hz, 1H), 4.37 (ddd, J = 13.6, 8.8, 4.4 Hz, 1H), 4.17 – 4.10 (m, 1H), 3.97 – 3.86 (m, 1H), 3.79 (dd, J = 18.2, 9.4 Hz, 1H), 3.69 – 3.67 (m, 1H), 3.65 (s, 1H), 3.62 – 3.52 (m, 1H), 3.23 (q, J = 6.3 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.71 – 2.64 (m, 1H), 2.64 – 2.56 (m, 4H), 1.39 – 1.30 (m, 1H), 1.15 – 1.01 (m, 9H), 0.88 – 0.82 (m, 1H), 0.67 (dd, J = 8.0, 3.8 Hz, 1H).	548.4
I-50A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (t, J = 8.2 Hz, 1H), 8.18 (s, 1H), 7.79 (dd, J = 8.8,	537.4

[1020]

化合物编号	方法	^{1}HNMR	LCMS
		4.4 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.34 – 7.22 (m, 5H), 4.50 (d, *J* = 5.6 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.36 – 4.30 (m, 1H), 3.99 – 3.87 (m, 3H), 3.66 (dd, *J* = 20.5, 9.8 Hz, 1H), 3.57 – 3.40 (m, 3H), 3.25 – 3.20 (m, 1H), 2.93 – 2.83 (m, 2H), 2.64 – 2.52 (m, 5H), 1.33 – 1.23 (m, 1H), 1.13 – 0.97 (m, 9H), 0.84 – 0.78 (m, 1H), 0.66 – 0.59 (m, 1H).	
I-50B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28-8.25 (m, 1H), 7.87-7.78 (m, 1H), 7.48 (d, 2H), 7.33-7.23 (m, 5H), 4.54-4.51 (m, 1H), 4.44-4.40 (m, 1H), 4.37-4.30 (m, 1H), 4.10-4.01 (m, 1.5H), 3.91-3.81 (m, 1.5H), 3.77-3.62 (m, 2H), 3.51-3.43 (m, 4H), 3.16 (q, *J*=6.8 Hz, 1H), 2.94-2.83 (m, 2H), 2.61-2.58 (m, 3H), 1.36-1.27 (m, 1H), 1.1-1.0 (m, 9H), 0.84-0.82 (m, 1H), 0.65-0.62 (m, 1H).	537.2
I-51A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, *J* = 1.8 Hz, 1H), 8.26 – 8.15 (m, 1H), 7.84 – 7.76 (m, 2H), 7.35 – 7.23 (m, 5H), 4.52 (dd, *J* = 12.2, 5.6 Hz, 1H), 4.47 – 4.39 (m, 1H), 4.36 – 4.25 (m, 1H), 4.02 – 3.81 (m, 5H), 3.74 – 3.50 (m, 1H), 3.31 – 3.26 (m, 2H), 2.95 (p, *J* = 10.2, 9.4 Hz, 2H), 2.61 (dd, *J* = 14.6, 6.8 Hz, 5H), 1.29 (ddd, *J* = 14.2, 8.0, 5.4 Hz, 1H), 1.14 – 0.98 (m, 9H), 0.85 – 0.79 (m, 1H), 0.62 (ddd, *J* = 7.8, 6.0, 3.8 Hz, 1H).	554.4
I-51B	6B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, *J* = 1.4 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.84 (dd, *J* = 21.4, 4.6 Hz, 1H), 7.77 (s, 1H), 7.34 – 7.23 (m, 5H), 4.54 – 4.40 (m, 2H), 4.34 (ddd, *J* = 16.6, 8.9, 4.6 Hz, 1H), 4.15 – 3.99 (m, 1H), 3.93 – 3.81 (m, 4H), 3.78 – 3.73 (m, 1H), 3.64 – 3.48 (m, 1H), 3.27 – 3.19 (m, 1H), 3.07 – 2.87 (m, 2H), 2.68 – 2.52 (m, 5H), 1.33 (ddd, *J* = 23.2, 8.0, 5.4 Hz, 1H), 1.11 – 1.00 (m, 9H), 0.85 – 0.81 (m, 1H), 0.64 (dd, *J* = 8.0, 3.8 Hz, 1H).	554.4
I-52	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.24-8.14 (m, 1H), 7.97-7.87 (m, 2H), 7.51-7.06 (m, 10H), 5.37-5.33 (m, 2H), 4.63-4.30 (m, 4H), 4.08-3.78 (m, 8H), 3.46-3.35 (m, 1H), 3.20-	812.5

[1021]

化合物编号	方法	^{1}HNMR	LCMS
		3.15 (m, 2H), 3.01-2.95 (m, 2H), 1.50-1.41 (m, 13H), 1.38-1.25 (m, 4H), 1.25-1.09 (m, 8H), 1.06-1.00 (m, 1H), 0.82-0.70 (m, 1H)	
I-53A	3A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.28 (m, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.36 – 7.24 (m, 5H), 4.53 (dd, J = 12.2, 3.2 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.35 (dd, J = 8.8, 3.8 Hz, 1H), 4.20 – 3.84 (m, 8H), 3.80 – 3.37 (m, 4H), 2.60 (dd, J = 10.2, 4.4 Hz, 3H), 1.92 (dd, J = 7.0, 4.6 Hz, 1H), 1.86 (dd, J = 6.8, 2.4 Hz, 1H), 1.27 – 1.21 (m, 1H), 1.08 (p, J = 3.0 Hz, 3H), 0.86 (dq, J = 12.6, 6.6 Hz, 1H), 0.52 (d, J = 7.6 Hz, 2H), 0.42 – 0.36 (m, 4H), 0.08 – 0.01 (m, 2H).	591.2
I-53B	3B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (q, J = 11.4, 9.2 Hz, 1H), 8.24 – 8.16 (m, 1H), 7.93 – 7.75 (m, 2H), 7.35 – 7.24 (m, 5H), 4.52 (t, J = 11.4 Hz, 1H), 4.45 – 4.22 (m, 2H), 4.15 – 3.36 (m, 12H), 2.60 (d, J = 4.4 Hz, 3H), 1.96 (t, J = 7.6 Hz, 2H), 1.25 (d, J = 7.6 Hz, 1H), 1.10 – 1.03 (m, 3H), 0.91 (t, J = 6.2 Hz, 1H), 0.55 – 0.34 (m, 6H), 0.11 – 0.08 (m, 2H).	591.2
I-54A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.27 (m, 2H), 7.86 – 7.79 (m, 2H), 7.37 – 7.25 (m, 10H), 5.35 (s, 2H), 4.53 (dd, J = 12.2, 4.2 Hz, 1H), 4.45 – 4.32 (m, 2H), 4.25 – 4.06 (m, 2H), 4.00 – 3.85 (m, 4H), 3.81 – 3.60 (m, 3H), 3.57 – 3.40 (m, 1H), 2.63 – 2.57 (m, 3H), 2.40 – 2.22 (m, 1H), 1.09 – 1.04 (m, 3H), 0.98 – 0.86 (m, 6H).	615.1
I-54B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.27 (m, 2H), 7.92 – 7.78 (m, 2H), 7.37 – 7.26 (m, 10H), 5.35 (s, 2H), 4.52 (t, J = 11.4 Hz, 1H), 4.46 – 4.27 (m, 3H), 4.16 – 3.97 (m, 3H), 3.95 – 3.78 (m, 2H), 3.77 – 3.53 (m, 4H), 3.51 – 3.38 (m, 1H), 2.60 (d, J = 4.4 Hz, 3H), 2.40 (p, J = 6.6 Hz, 1H), 1.10 – 1.02 (m, 3H), 0.98 – 0.94 (m, 6H).	615.2
I-55A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 – 8.48 (m, 2H), 8.26 – 8.20 (m, 1H), 7.80 (dd, J =	548.5

[1022]

化合物编号	方法	^{1}HNMR	LCMS
		12.0, 4.8 Hz, 1H), 7.35 – 7.25 (m, 7H), 4.56 – 4.41 (m, 2H), 4.36 – 4.27 (m, 1H), 4.03 – 3.89 (m, 3H), 3.75 – 3.50 (m, 4H), 2.94 – 2.87 (m, 2H), 2.67 (t, J = 7.8 Hz, 1H), 2.59 (d, J = 4.6 Hz, 3H), 1.30 (ddd, J = 13.6, 8.0, 5.2 Hz, 1H), 1.13 – 0.99 (m, 9H), 0.82 (q, J = 5.2 Hz, 1H), 0.63 (dd, J = 8.0, 3.8 Hz, 1H).	
I-55B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 – 8.47 (m, 2H), 8.28 (dd, J = 9.0, 4.8 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.33 – 7.29 (m, 3H), 7.29 – 7.22 (m, 4H), 4.55 – 4.51 (m, 1H), 4.46 – 4.28 (m, 2H), 4.15 – 4.05 (m, 1H), 3.96 – 3.67 (m, 3H), 3.65 – 3.49 (m, 2H), 3.33 – 3.18 (m, 2H), 3.01 – 2.86 (m, 2H), 2.70 – 2.51 (m, 5H), 1.33 (ddd, J = 25.4, 8.0, 5.2 Hz, 1H), 1.13 – 0.97 (m, 9H), 0.83 (dd, J = 5.4, 3.8 Hz, 1H), 0.65 (dd, J = 8.0, 3.8 Hz, 1H).	548.2
I-56A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.31 (m, 1H), 8.26 – 8.12 (m, 1H), 7.86 – 7.70 (m, 2H), 7.38 – 7.23 (m, 5H), 5.35 (s, 2H), 4.30 – 4.24 (m, 1H), 4.22 – 4.04 (m, 1H), 4.04 – 3.79 (m, 4H), 3.79 – 3.52 (m, 4H), 3.52 – 3.35 (m, 1H), 3.26 – 3.19 (m, 1H), 3.14 – 3.06 (m, 1H), 2.61 – 2.54 (m, 3H), 1.98 – 1.89 (m, 2H), 1.70 – 1.56 (m, 5H), 1.43 (s, 1H), 1.26 – 1.06 (m, 3H), 1.04 – 0.98 (m, 3H), 0.95 – 0.77 (m, 3H), 0.47 – 0.39 (m, 2H), 0.12 – 0.04 (m, 2H).	633.3
I-56B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.29 (m, 1H), 8.28 – 8.10 (m, 1H), 7.93 – 7.70 (m, 2H), 7.38 – 7.21 (m, 5H), 5.35 (s, 2H), 4.31 – 4.21 (m, 1H), 4.11 – 3.84 (m, 3H), 3.83 – 3.51 (m, 4H), 3.50 – 3.37 (m, 1H), 3.27 – 2.62 (m, 3H), 2.61 – 2.53 (m, 3H), 1.99 – 1.90 (m, 2H), 1.71 – 1.50 (m, 6H), 1.50 – 1.30 (m, 1H), 1.17 – 1.07 (m, 3H), 1.02 – 0.78 (m, 6H), 0.46 – 0.39 (m, 2H), 0.12 – 0.05 (m, 2H).	633.55
I-57	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.25-8.14 (m, 1H), 7.93-7.87 (m, 1H), 7.57-7.03 (m, 10H), 5.38-5.34 (s, 2H), 4.64-4.32 (m, 4H),	712.5

[1023]

化合物编号	方法	^{1}HNMR	LCMS
		4.23-3.78 (m, 8H), 3.74-3.46 (m, 1H), 3.45-3.32 (m, 1H), 3.25-3.13 (m, 2H), 2.91-2.78 (m, 2H), 1.65-1.57 (m, 2H), 1.55-1.44 (m, 2H), 1.40-1.32 (m, 3H), 1.25-1.08 (m, 9H), 1.03-1.01 (m, 1H), 0.79-0.73 (m, 1H).	
I-58A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.29 (m, 1H), 7.87 – 7.76 (m, 1H), 7.39 – 7.23 (m, 7H), 7.18 (d, J = 7.6 Hz, 3H), 5.35 (d, J = 4.9 Hz, 2H), 4.34 (d, J = 12.5 Hz, 1H), 4.30 – 4.12 (m, 1H), 4.13 – 3.89 (m, 4H), 3.88 – 3.55 (m, 5H), 3.11 – 2.93 (m, 1H), 2.58 – 2.50 (m, 9H), 2.46 (s, 1H), 1.77 (s, 1H), 1.68 – 1.49 (m, 2H), 1.46 – 1.21 (m, 1H), 1.19 – 0.92 (m, 8H), 0.90 – 0.82 (m, 1H), 0.68 (dd, J = 12.1, 7.3 Hz, 1H).	593.34
I-58B	2B	^{1}H NMR (400 MHz, DMSO-d6) δ 8.43 – 8.28 (m, 1H), 7.88 – 7.77 (m, 1H), 7.38 – 7.19 (m, 8H), 7.19 – 7.13 (m, 2H), 5.35 (t, J = 5.2 Hz, 2H), 4.35 (d, 1H), 4.28 – 4.02 (m, 3H), 4.00 – 3.78 (m, 4H), 3.76 – 3.57 (m, 3H), 2.99 (d, 1H), 2.53 (s, 2H), 1.75 (s, 1H), 1.59 (d, J = 11.2 Hz, 2H), 1.46 – 1.34 (m, 1H), 1.13 (d, 4H), 1.07 – 0.98 (m, 3H), 0.86 (d, J = 12.1 Hz, 1H), 0.74 – 0.61 (m, 1H).	594.5
I-59A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.25 (m, 2H), 7.86 – 7.78 (m, 1H), 7.45 – 7.24 (m, 10H), 5.36 (s, 2H), 4.25 – 3.55 (m, 11H), 3.20 – 2.87 (m, 3H), 1.90 – 1.72 (m, 2H), 1.57 – 1.40 (m, 2H), 1.38 – 1.28 (m, 1H), 1.12 – 1.01 (m, 6H), 0.90 – 0.81 (m, 1H), 0.72 – 0.63 (m, 1H).	623.5
I-59B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.20 (m, 2H), 7.82 (d, J = 11.8 Hz, 1H), 7.45 – 7.24 (m, 10H), 5.35 (s, 2H), 4.32 – 3.55 (m, 11H), 3.10 (br s, 3H), 1.84 (s, 2H), 1.50 (s, 2H), 1.36 – 1.23 (m, 1H), 1.12 – 0.97 (m, 6H), 0.86 – 0.67 (m, 2H).	623.5
I-60A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, J = 24.8, 10.2 Hz, 2H), 7.83 (t, J = 10.6 Hz, 2H), 7.38 – 7.21 (m, 10H), 5.35 (s, 2H), 4.57 – 4.39 (m, 2H), 4.35 (d, J = 7.4 Hz, 1H), 4.18 – 3.40 (m, 10H), 2.60 (dd, J = 10.8, 4.6 Hz,	615.45

[1024]

化合物编号	方法	^{1}HNMR	LCMS
		3H), 1.90 (dh, J = 24.8, 8.0 Hz, 2H), 1.43 (dq, J = 11.4, 7.2 Hz, 2H), 1.08 (d, J = 6.0 Hz, 3H), 0.81 (dd, J = 8.6, 7.2 Hz, 3H).	
I-60B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.28 (m, 2H), 7.97 – 7.76 (m, 2H), 7.46 – 7.09 (m, 10H), 5.35 (s, 2H), 4.56 – 4.48 (m, 1H), 4.45 – 4.29 (m, 2H), 4.27 – 3.92 (m, 4H), 3.88 – 3.38 (m, 6H), 2.64 – 2.54 (m, 3H), 2.03 – 1.95 (m, 2H), 1.52 – 1.44 (m, 2H), 1.10 – 1.01 (m, 3H), 0.89 – 0.83 (m, 3H).	615.40
I-61A	2A	^{1}H NMR (DMSO, 400 MHz) δ 0.75 (2H, d, J=70.6 Hz), 0.97 – 1.47 (9H, m), 1.75 (2H, s), 3.01 – 3.18 (2H, m), 3.35 – 4.41 (11H, m), 5.35 (2H, s), 7.22 – 7.39 (7H, m), 7.44 (3H, dt, J=5.0, 2.4 Hz), 7.82 (1H, d, J=12.2 Hz), 8.22 – 8.38 (2H, m).	623.50
I-61B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.24 (m, 2H), 7.83 (d, J = 12.7 Hz, 1H), 7.45 – 7.23 (m, 10H), 5.35 (s, 2H), 4.28 – 3.54 (m, 11H), 3.15 – 3.02 (m, 2H), 1.96 – 1.62 (m, 2H), 1.43 – 0.98 (m, 10H), 0.93 – 0.60 (m, 2H).	623.45
I-62A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37-8.29 (m, 2H), 7.83-7.80 (m, 2H), 7.37-7.25 (m, 10H), 5.35 (d, 2H), 4.55-4.52 (m, 1H), 4.45-4.42 (m, 1H), 4.36-4.34 (m, 1H), 4.21-4.01 (m, 1.5H), 3.98-3.86 (m, 4H), 3.77-3.61 (m, 3H), 3.58-3.36 (m, 1.5H), 2.6 (dd, J=4.8 Hz, 3H), 1.93-1.80 (m, 2H), 1.09-1.07 (m, 3H), 0.95-0.91 (m, 9H).	643.2
I-62B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37-8.27 (m, 2H), 7.90-7.79 (m, 2H), 7.36-7.25 (m, 10H), 5.35 (s, 2H), 4.55-4.49 (m, 1H), 4.45-4.32 (m, 2H), 4.25-4.09 (m, 1H), 4.02-3.96 (m, 3H), 3.91-3.81 (m, 2H), 3.76-3.68 (m,2H), 3.65-3.53 (m, 1H), 3.46-3.37 (m, 1H), 2.60 (d, J=4.8 Hz, 1H), 1.94-1.86 (m, 2H), 1.09-1.02 (m, 3H), 0.97-0.96 (m, 9H).	643.2
I-63A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 – 10.37 (m, 1H), 8.43 – 8.36 (m, 1H), 7.99 – 7.91 (m, 1H), 7.89 – 7.82 (m, 1H), 7.63 – 7.51 (m, 3H), 7.50 – 7.25 (m, 10H), 5.38 –	588.1

[1025]

化合物编号	方法	^{1}HNMR	LCMS
		5.34 (m, 2H), 4.33 – 3.64 (m, 7H), 3.30 – 3.28 (m, 1H), 1.39 – 1.33 (m, 1H), 1.12 – 0.78 (m, 7H), 0.71 – 0.60 (m, 1H).	
I-63B	2B	^{1}H NMR (400 MHz, DMSO-d6) δ 10.39 (d, J = 12.6 Hz, 1H), 8.44 – 8.34 (m, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 15.2 Hz, 1H), 7.65 – 7.53 (m, 3H), 7.50 – 7.21 (m, 10H), 5.36 (s, 2H), 4.42 – 4.24 (m, 1H), 4.23 – 3.99 (m, 3H), 3.98 – 3.79 (m, 3H), 3.78 – 3.66 (m, 1H), 1.38 (tt, J = 34.0 Hz, 1H), 1.13 – 0.88 (m, 6H), 0.86 – 0.58 (m, 3H).	588.4
I-64	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.14-8.22 (m, 1H), 7.87-7.93 (m, 1H), 7.27-7.36 (m, 10H), 5.38 (s, 2H), 4.94-4.99 (m, 1H), 4.29-4.64 (m, 4H), 3.76-4.21 (m, 10H), 3.09-3.29 (m, 5H), 2.49-2.98 (m, 3H), 1.46-1.80 (m, 4H), 1.19-1.30 (m, 6H), 1.10-1.12 (m, 5H), 0.74-0.79 (m, 1H).	739.4
I-65A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 12.2 Hz, 2H), 7.82 (d, *J* = 16.0 Hz, 2H), 7.30 (m, 10H), 5.35 (s, 2H), 4.56 – 4.40 (m, 2H), 4.37 (dd, *J* = 8.6, 3.2 Hz, 1H), 4.23 (d, *J* = 45.8 Hz, 1H), 4.10 – 3.82 (m, 4H), 3.78 (m, 2H), 3.62 (m, 1H), 3.44 (m, 1H), 2.60 (dd, *J* = 10.0, 4.4 Hz, 3H), 1.39 – 1.16 (m, 1H), 1.05 (d, *J* = 15.4 Hz, 12H).	629.45
I-65B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, *J* = 21.8 Hz, 2H), 7.94 – 7.76 (m, 2H), 7.38 – 7.20 (m, 10H), 5.35 (d, *J* = 2.4 Hz, 2H), 4.58 – 4.20 (m, 5H), 4.03 – 3.78 (m, 4H), 3.73 – 3.41 (m, 4H), 2.59 (dd, *J* = 4.6, 2.1 Hz, 3H), 1.13 – 1.04 (m, 12H).	629.5
I-66A	8A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, *J* = 19.0, 8.8 Hz, 1H), 8.01 (s, 1H), 7.82 – 7.67 (m, 1H), 4.28 – 3.46 (m, 11H), 3.25 – 3.21 (m, 1H), 3.10 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.60 – 2.56 (m, 3H), 1.70 – 1.60 (m, 5H), 1.44 (s, 1H), 1.36 – 1.27 (m, 1H), 1.19 – 1.12 (m, 3H), 1.08 (t, *J* = 4.8 Hz, 3H), 1.06 – 1.00 (m, 6H), 0.88 – 0.78 (m, 3H), 0.67 (dd, *J* = 8.0, 4.0 Hz, 1H).	557.5

[1026]

化合物编号	方法	^{1}HNMR	LCMS
I-66B	8B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25-8.18 (m, 1H), 8.01-7.97 (m, 2H), 7.86-7.79 (m, 1H), 4.36-4.29 (m, 1H), 4.26-4.12 (m, 1H), 4.06-3.88 (m, 3H), 3.83-3.59 (m, 6H), 3.27-3.19 (m, 1H), 3.12-3.04 (m, 1H), 3.59 (t, *J*=4.8 Hz, 3H), 1.63-1.60 (m, 5H), 1.39-1.33 (m, 2H), 1.19-1.11 (m, 6H), 1.06-1.05 (m, 3H), 1.02-0.95 (m, 3H), 0.88-0.78 (m, 3H), 0.71-0.65 (m, 1H).	557.1
I-67A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 13.4 Hz, 2H), 7.84 – 7.80 (m, 2H), 7.38 – 7.23 (m, 10H), 5.35 (s, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.47 – 4.29 (m, 3H), 4.04 – 3.36 (m, 9H), 2.60 (dd, *J* = 10.2, 4.4 Hz, 3H), 1.21 – 1.12 (m, 3H), 1.08 (t, *J* = 5.4 Hz, 3H), 0.87 (s, 2H), 0.41 (s, 2H).	627.5
I-67B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.29 (m, 2H), 7.83 (t, *J* = 16.6 Hz, 2H), 7.37 – 7.23 (m, 11H), 5.35 (s, 2H), 4.57 – 4.26 (m, 4H), 4.03 – 3.38 (m, 9H), 2.60 (d, *J* = 4.6 Hz, 4H), 1.22 (s, 3H), 1.07 (dd, *J* = 17.6, 6.2 Hz, 4H), 0.90 (s, 2H), 0.45 (d, *J* = 2.6 Hz, 2H).	627.5
I-68A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (t, *J* = 8.2 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.35 – 7.22 (m, 5H), 4.55 – 4.48 (m, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.38 – 4.22 (m, 1H), 4.00 – 3.87 (m, 3H), 3.84 – 3.76 (m, 2H), 3.68 (dd, *J* = 23.5, 9.6 Hz, 1H), 3.54 (d, *J* = 10.0 Hz, 1H), 3.39 – 3.32 (m, 1H), 3.31 – 3.16 (m, 4H), 2.91 – 2.83 (m, 2H), 2.65 – 2.52 (m, 5H), 2.29 – 2.24 (m, 2H), 1.65 – 1.59 (m, 2H), 1.35 – 1.26 (m, 1H), 1.13 – 1.05 (m, 6H), 1.04 – 0.99 (m, 4H), 0.86 – 0.79 (m, 1H), 0.67 – 0.60 (m, 1H).	555.5
I-68B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.8 Hz, 1H), 8.14 (s, 1H), 7.82 (dd, *J* = 23.2, 4.8 Hz, 1H), 7.34 – 7.23 (m, 5H), 4.56 – 4.39 (m, 2H), 4.33 (m, 1H), 4.14 – 4.02 (m, 2H), 3.95 – 3.84 (m, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.59 (dd, *J* = 51.2, 9.6 Hz, 2H), 3.27 (q, *J* = 2.0 Hz, 1H), 3.23 (dt, *J* = 11.8, 2.4 Hz, 2H), 3.15 (q, *J* = 6.2 Hz,	555.50

[1027]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 2.97 – 2.84 (m, 2H), 2.63 – 2.55 (m, 4H), 2.25 (dd, J = 7.0, 2.8 Hz, 2H), 1.60 (t, J = 15.2 Hz, 3H), 1.33 (m, 1H), 1.12 – 1.06 (m, 7H), 1.06 – 1.02 (m, 4H), 0.84 (dd, J = 5.4, 3.8 Hz, 1H), 0.65 (dd, J = 8.0, 3.8 Hz, 1H).	
I-69A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 10.4 Hz, 2H), 7.82 (d, J = 12.8 Hz, 2H), 7.39 – 7.23 (m, 10H), 5.35 (s, 2H), 4.53 (d, J = 12.2 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.17 – 3.83 (m, 5H), 3.80 – 3.60 (m, 3H), 3.56 – 3.38 (m, 2H), 2.60 (dd, J = 10.4, 4.4 Hz, 3H), 1.96 – 1.76 (m, 3H), 1.08 (d, J = 6.0 Hz, 3H), 0.86 – 0.80 (m, 6H).	629.45
I-69B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.27 (m, 2H), 7.95 – 7.78 (m, 2H), 7.38 – 7.22 (m, 10H), 5.35 (s, 2H), 4.56 – 4.48 (m, 1H), 4.45 – 4.21 (m, 2H), 4.12 – 3.79 (m, 5H), 3.76 – 3.52 (m, 3H), 3.49 – 3.36 (m, 1H), 2.60 (d, J = 4.4 Hz, 3H), 1.99 – 1.86 (m, 3H), 1.11 – 1.00 (m, 3H), 0.90 – 0.85 (m, 6H).	629.2
I-70A	11A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.29 (m, 2H), 7.92 – 7.82 (m, 1H), 7.35 – 7.24 (m, 5H), 4.57 – 4.49 (m, 1H), 4.47 – 4.40 (m, 1H), 4.38 – 4.30 (m, 1H), 4.23 – 4.11 (m, 1H), 4.04 – 3.90 (m, 3H), 3.84 – 3.74 (m, 2H), 3.65 – 3.53 (m, 3H), 3.47 – 3.39 (m, 2H), 3.18 – 3.09 (m, 2H), 3.01 – 2.93 (m, 2H), 2.61 (d, J = 4.4 Hz, 3H), 2.07 – 1.96 (m, 1H), 1.91 – 1.78 (m, 1H), 1.35 – 1.22 (m, 1H), 1.11 – 1.00 (m, 9H), 0.87 – 0.80 (m, 1H), 0.68 – 0.60 (m, 1H).	554.2
I-70B	11B	^{1}H NMR (400 MHz, DMSO-d_6) & 8.42-8.34 (m, 1H), 7.92-7.84 (m, 1H), 7.36-7.25 (m, 5H), 4.56-4.52 (m, 1H), 4.47-4.42 (m, 1H), 4.39-4.28 (m, 1H), 4.16-4.05 (m, 1H), 4.02-3.82 (m, 3H), 3.80-3.69 (m, 2H), 3.63-3.56 (m, 2H), 3.52-3.45 (m, 2H), 3.43-3.40 (m, 1H), 3.31-3.29 (m, 1H), 3.26-3.23 (m, 2H), 3.15-3.09 (m, 2H), 2.62-2.60 (m, 3H), 2.2-2.13 (m, 1H), 1.92-1.84 (m, 1H), 1.38-1.31	554.2

[1028]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 1H), 1.12-1.03 (m, 9H), 0.89-0.86 (m, 1H), 0.73-0.66 (m, 1H).	
I-71A	7A	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.42-8.32 (m, 2H), 7.84-7.80 (m, 2H), 7.37-7.24 (m, 10H), 5.35 (s, 2H), 4.55-4.42 (m, 3H), 4.38-4.20 (m, 2H), 4.13-3.97 (m, 3H), 3.91-3.88 (m, 1H), 3.83-3.67 (m, 2H), 3.63-3.58 (m, 1H), 3.56-3.46 (m, 1H), 2.62-2.58 (m, 3H), 1.25-1.15 (m, 4H), 1.11-1.06 (m, 3H).	631.1
I-71B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.29 (m, 2H), 7.88 – 7.77 (m, 2H), 7.39 – 7.20 (m, 10H), 5.35 (d, J = 3.2 Hz, 2H), 4.60 – 4.23 (m, 5H), 4.19 – 4.04 (m, 1H), 4.02 – 3.77 (m, 4H), 3.73 – 3.62 (m, 2H), 3.45 (s, 1H), 2.60 (d, J = 4.8 Hz, 3H), 1.31 – 1.15 (m, 4H), 1.10 – 1.03 (m, 3H).	631.4
I-72A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.39 – 8.28 (m, 1H), 8.11 – 8.01 (m, 1H), 7.91 – 7.75 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 – 7.23 (m, 5H), 7.19 – 7.04 (m, 2H), 4.53 (d, J = 12.2 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.29 – 4.14 (m, 1H), 4.10 – 3.86 (m, 5H), 3.79 – 3.65 (m, 2H), 3.54 – 3.41 (m, 1H), 3.30 (s, 1H), 2.60 (s, 3H), 1.37 – 1.18 (m, 2H), 1.12 – 1.08 (m, 3H), 1.07 – 1.03 (m, 3H), 1.01 (s, 2H), 0.87 – 0.79 (m, 1H), 0.67 – 0.58 (m, 1H).	600.4
I-72B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.34 (t, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.96 – 7.77 (m, 2H), 7.46 – 7.40 (m, 1H), 7.27 (s, 5H), 7.15 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.08 (tt, J = 7.0, 1.0 Hz, 1H), 4.51 (s, 1H), 4.44 – 4.33 (m, 2H), 4.18 – 3.65 (m, 9H), 3.45 (q, J = 6.2, 5.6 Hz, 1H), 2.61 (dd, J = 4.4, 2.8 Hz, 3H), 1.35 (dd, J = 7.8, 5.2 Hz, 1H), 1.11 – 1.05 (m, 9H), 0.86 (d, J = 4.8 Hz, 1H), 0.73 – 0.62 (m, 1H).	600.1
I-73A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 12.8 Hz, 2H), 7.83 (d, J = 15.6 Hz, 2H), 7.37 – 7.24 (m, 10H), 5.36 (d, J = 1.4 Hz, 2H), 4.68 – 4.34 (m, 5H), 4.11 – 3.44 (m,	638.45

[1029]

化合物编号	方法	^{1}HNMR	LCMS
		8H), 2.60 (dd, J = 10.6, 4.6 Hz, 3H), 1.50 (dd, J = 24.6, 7.0 Hz, 4H), 1.10 (d, J = 6.4 Hz, 3H).	
I-73B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.23 (m, 2H), 7.91 – 7.76 (m, 2H), 7.38 – 7.23 (m, 10H), 5.35 (d, J = 4.8 Hz, 2H), 4.66 – 4.48 (m, 2H), 4.47 – 4.30 (m, 3H), 4.17 – 4.05 (m, 1H), 4.00 – 3.39 (m, 7H), 2.60 (d, J = 4.6 Hz, 3H), 1.55 – 1.48 (m, 4H), 1.13 – 1.01 (m, 3H).	638.4
I-74A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.35 (m, 2H), 7.90 – 7.85 (m, 2H), 7.42 – 7.29 (m, 10H), 5.40 (s, 2H), 4.61 – 4.37 (m, 3H), 4.25 – 3.44 (m, 10H), 2.65 (dd, J = 10.7, 4.4 Hz, 3H), 2.11 – 1.93 (m, 1H), 1.46 – 1.27 (m, 4H), 1.14 (d, J = 6.2 Hz, 3H), 0.88 – 0.75 (m, 6H).	643.5
I-74B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.22 (m, 2H), 7.93 – 7.77 (m, 2H), 7.39 – 7.20 (m, 10H), 5.35 (s, 2H), 4.52 (t, J = 11.6 Hz, 1H), 4.46 – 4.31 (m, 2H), 4.30 – 3.42 (m, 9H), 3.41 – 3.34 (m, 1H), 2.63 – 2.57 (m, 3H), 2.08 – 1.97 (m, 1H), 1.49 – 1.37 (m, 2H), 1.35 – 1.21 (m, 2H), 1.11 – 1.00 (m, 3H), 0.83 – 0.75 (m, 6H).	643.5
I-75A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (d, J = 5.2 Hz, 1H), 8.42 – 8.34 (m, 1H), 7.88 – 7.8 (m, 1H), 7.49 – 7.40 (m, 2H), 7.39 – 7.14 (m, 11H), 6.95 (d, J = 7.6 Hz, 1H), 5.38 – 8.3 (m, 2H), 4.28 – 3.60 (m, 10H), 3.41 – 3.255 (m, 1H), 1.34 (q, J = 7.0 Hz, 1H), 1.12 – 1.02 (m, 4H), 0.96 – 0.77 (m, 3H), 0.68 – 0.60 (m, 1H).	602.4
I-75B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (d, J = 9.8 Hz, 1H), 8.41 – 8.32 (m, 1H), 7.84 (d, J = 16.6 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.38 – 7.14 (m, 11H), 6.95 (d, J = 7.2 Hz, 1H), 5.39 – 5.32 (m, 2H), 4.21 (d, J = 8.4 Hz, 1H), 4.18 – 4.07 (m, 1H), 4.07 – 3.94 (m, 2H), 3.92 – 3.79 (m, 4H), 3.78 – 3.62 (m, 2H), 1.43 – 1.31 (m, 1H), 1.13 – 1.01 (m, 5H), 0.91 –	602.5

[1030]

化合物编号	方法	^{1}HNMR	LCMS
		0.85 (m, 1H), 0.84 – 0.78 (m, 1H), 0.69 – 0.58 (m, 1H).	
I-76A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.31 (m, 2H), 7.89 – 7.80 (m, 2H), 7.38 – 7.23 (m, 10H), 5.35 (s, 2H), 4.64 – 3.38 (m, 12H), 3.31 – 3.29 (m, 1H), 2.64 – 2.56 (m, 3H), 1.49 – 1.39 (m, 6H), 1.12 – 1.04 (m, 3H).	640.2
I-76B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.30 (m, 2H), 7.93 – 7.77 (m, 2H), 7.38 – 7.22 (m, 10H), 5.35 (s, 2H), 4.64 – 4.31 (m, 5H), 4.20 – 3.40 (m, 8H), 2.60 (d, J = 4.4 Hz, 3H), 1.50 – 1.46 (m, 6H), 1.09 (d, J = 6.2 Hz, 2H), 1.05 (d, J = 5.8 Hz, 1H).	640.2
I-77A	5A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (dd, J = 8.6 Hz, 1H), 7.81 (dd, J = 13.2, 5.6 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.34 – 7.24 (m, 6H), 6.90 (s, 1H), 4.59 – 4.40 (m, 2H), 4.40 – 4.24 (m, 2H), 3.99 – 3.89 (m, 3H), 3.74 – 3.63 (m, 1H), 3.59 – 3.50 (m, 2H), 3.28 – 3.20 (m, 1H), 3.13 – 2.86 (m, 3H), 2.67 – 2.57 (m, 5H), 1.34 – 1.18 (m, 1H), 1.14 – 1.02 (m, 6H), 1.00 (d, J = 10.4 Hz, 3H), 0.84 – 0.80 (m, 1H), 0.65 – 0.60 (m, 1H).	537.4
I-77B	5B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (dd, J = 7.6 Hz, 1H), 8.18 (s, 1H), 7.87 – 7.80 (m, 1H), 7.55 (s, 1H), 7.31 – 7.25 (m, 5H), 6.89 (s, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.42 (dd, J = 12.0, 2.8 Hz, 1H), 4.34 (ddd, J = 13.8, 8.6, 4.4 Hz, 1H), 4.14 – 3.71 (m, 4H), 3.66 – 3.46 (m, 3H), 3.18 (d, J = 7.2 Hz, 1H), 3.05 – 2.86 (m, 2H), 2.69 – 2.53 (m, 5H), 1.32 (dt, J = 20.0, 7.0 Hz, 1H), 1.11 – 1.00 (m, 9H), 0.83 (t, J = 4.6 Hz, 1H), 0.64 (dd, J = 8.0, 3.6 Hz, 1H).	537.4
I-78A	6A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.26 – 8.18 (m, 1H), 7.86 – 7.74 (m, 1H), 7.34 – 7.24 (m, 5H), 7.06 (s, 1H), 4.54 – 4.48 (m, 1H), 4.46 – 4.40 (m, 1H), 4.36 – 4.30 (m, 1H), 3.98 – 3.88 (m, 3H), 3.74 – 3.62 (m, 3H), 3.28 – 3.24 (m, 1H), 3.00 – 2.88 (m, 2H), 2.68 – 2.64 (m, 1H), 2.62 – 2.54 (m, 4H), 1.28 (ddd, J = 20.6, 8.0, 5.4	538.2

[1031]

化合物编号	方法	^{1}HNMR	LCMS
		Hz, 1H), 1.12 – 1.08 (m, 3H), 1.06 – 0.98 (m, 6H), 0.84 – 0.78 (m, 1H), 0.66 – 0.58 (m, 1H).	
I-78B	6B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.13 (s, 1H), 7.83 (dd, J = 22.4, 4.6 Hz, 1H), 7.33 – 7.23 (m, 5H), 7.05 (s, 1H), 4.52 (dd, J = 12.0, 1.6 Hz, 1H), 4.42 (dd, J = 12.0, 3.0 Hz, 1H), 4.34 (ddd, J = 17.4, 8.8, 4.6 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.91 – 3.63 (m, 5H), 3.50 (d, J = 10.0 Hz, 1H), 3.24 – 3.20 (m, 1H), 2.98 (ddd, J = 21.8, 9.0, 5.0 Hz, 2H), 2.66 (dd, J = 13.6, 8.8 Hz, 1H), 2.59 (dd, J = 6.4, 4.6 Hz, 4H), 1.33 (ddd, J = 21.4, 8.0, 5.4 Hz, 1H), 1.10 – 1.01 (m, 9H), 0.83 (t, J = 4.6 Hz, 1H), 0.65 (dd, J = 8.2, 3.8 Hz, 1H).	538.5
I-79A		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (q, J = 9.2 Hz, 1H), 7.87 (t, J = 2.6 Hz, 1H), 7.85 – 7.47 (m, 5H), 7.38 (dd, J = 8.6, 2.0 Hz, 2H), 7.34 – 7.22 (m, 5H), 6.29 (dt, J = 10.0, 2.2 Hz, 1H), 5.47 (s, 2H), 4.51 – 4.34 (m, 2H), 4.24 (td, J = 8.6, 3.2 Hz, 1H), 4.13 – 3.87 (m, 2H), 3.81 – 3.65 (m, 2H), 3.54 – 3.35 (m, 6H), 2.60 (dd, J = 4.6, 1.6 Hz, 3H), 1.24 – 1.14 (m, 1H), 1.08 – 1.01 (m, 6H), 1.01 – 0.93 (m, 3H), 0.79 (d, J = 4.5 Hz, 1H), 0.66 – 0.55 (m, 1H).	677.45
I-79B		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 9.6 Hz, 1H), 7.90 – 7.62 (m, 4H), 7.58 – 7.48 (m, 1H), 7.39 – 7.25 (m, 6H), 6.36 – 6.27 (m, 1H), 5.49 (d, J = 2.4 Hz, 2H), 4.53 (d, J = 11.8 Hz, 1H), 4.42 (dd, J = 12.0, 4.8 Hz, 1H), 4.29 – 4.14 (m, 1H), 4.08 – 3.36 (m, 9H), 3.23 (d, J = 4.2 Hz, 1H), 2.59 (dd, J = 4.6, 2.0 Hz, 3H), 1.31 – 1.23 (m, 1H), 1.11 (t, J = 3.2 Hz, 3H), 1.08 – 1.00 (m, 6H), 0.84 (d, J = 4.6 Hz, 1H), 0.68 (dd, J = 8.0, 3.8 Hz, 1H).	677.40
I-80A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 – 8.20 (m, 2H), 7.90 – 7.73 (m, 2H), 7.37 – 7.22 (m, 12H), 7.15 (dd, J = 20.0, 7.8 Hz, 2H), 5.34 (d, J = 5.8 Hz, 2H), 4.58 – 4.23 (m, 3H), 4.15	745.5

[1032]

化合物编号	方法	^{1}HNMR	LCMS
		– 3.34 (m, 9H), 3.29 – 3.15 (m, 1H), 2.58 (dd, *J* = 10.2, 4.4 Hz, 3H), 1.22 (d, *J* = 8.4 Hz, 12H), 1.10 – 0.96 (m, 4H).	
I-80B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.19 (m, 2H), 7.95 – 7.74 (m, 2H), 7.28 (tdd, *J* = 27.4, 14.9, 8.1 Hz, 14H), 5.35 (d, *J* = 7.4 Hz, 2H), 4.53 (t, *J* = 11.9 Hz, 1H), 4.46 – 4.28 (m, 2H), 4.11 – 3.87 (m, 2H), 3.86 – 3.54 (m, 5H), 3.50 – 3.38 (m, 2H), 3.29 – 3.16 (m, 1H), 2.72 – 2.61 (m, 3H), 1.35 – 1.21 (m, 11H), 1.12 – 1.00 (m, 4H), 0.99 – 0.84 (m, 1H).	745.5
I-81A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (d, *J* = 4.6 Hz, 1H), 8.44 – 8.35 (m, 1H), 7.86 (d, *J* = 12.8 Hz, 1H), 7.69 (d, *J* = 4.6 Hz, 2H), 7.67 – 7.60 (m, 4H), 7.44 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.39 – 7.23 (m, 6H), 5.37 (s, 2H), 4.34 – 3.62 (m, 8H), 3.47 – 3.34 (m, 1H), 1.41 – 1.31 (m, 1H), 1.15 – 1.02 (m, 5H), 0.88 (s, 1H), 0.87 – 0.78 (m, 1H), 0.66 (s, 1H).	588.40
I-81B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (d, *J* = 10.8 Hz, 1H), 8.39 (d, *J* = 12.4 Hz, 1H), 7.86 (d, *J* = 14.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.32 (dt, *J* = 19.8, 9.2 Hz, 6H), 5.37 (s, 2H), 4.43 – 3.99 (m, 4H), 3.84 (m, 4H), 1.39 (m, 1H), 1.07 (d, *J* = 14.8 Hz, 6H), 0.92 (d, *J* = 7.6 Hz, 1H), 0.83 (s, 1H), 0.66 (s, 1H).	588.40
I-82A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.28 (m, 2H), 7.87 – 7.79 (m, 2H), 7.37 – 7.24 (m, 10H), 5.35 (s, 2H), 4.55 – 4.41 (m, 2H), 4.38 – 4.32 (m, 1H), 4.20 – 3.40 (m, 11H), 3.20 (d, *J* = 6.0 Hz, 1H), 3.16 (s, 2H), 3.15 – 3.12 (m, 1H), 2.60 (dd, *J* = 11.2, 4.6 Hz, 3H), 2.13 – 1.90 (m, 2H), 1.10 – 1.05 (m, 3H), 0.40 – 0.33 (m, 4H).	671.45
I-82B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 – 8.27 (m, 2H), 7.95 – 7.76 (m, 2H), 7.38 – 7.19 (m, 10H), 5.34 (s, 2H), 4.57 – 4.47 (m, 1H), 4.46 – 4.29 (m, 2H), 4.11 – 3.56 (m, 8H), 3.50 – 3.37 (m, 2H), 3.23 – 3.13 (m, 5H), 2.60 (d, *J*	671.2

[1033]

化合物编号	方法	^{1}HNMR	LCMS
		= 4.4 Hz, 3H), 2.19 – 1.98 (m, 2H), 1.12 – 0.99 (m, 3H), 0.48 – 0.32 (m, 4H).	
I-83A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 – 8.21 (m, 2H), 7.88 – 7.78 (m, 1H), 7.71 – 7.15 (m, 10H), 5.36 (s, 2H), 4.54 – 3.50 (m, 11H), 3.23 – 2.65 (m, 3H), 2.00 – 1.30 (m, 5H), 1.16 – 0.88 (m, 6H), 0.87 – 0.80 (m, 1H), 0.73 – 0.57 (m, 1H).	623.50
I-83B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 30.6 Hz, 2H), 7.82 (d, J = 13.4 Hz, 1H), 7.46 – 7.35 (m, 5H), 7.34 – 7.22 (m, 5H), 5.35 (s, 2H), 4.17 (m, 1H), 3.96 (m, 3H), 3.73 (m, 4H), 3.56 – 3.34 (m, 3H), 3.09 (m, 2H), 1.85 (m, 2H), 1.49 (m, 2H), 1.30 (m, 2H), 1.12 – 1.08 (m, 3H), 1.05 (m, 3H), 0.85 (s, 1H), 0.68 (d, J = 7.8 Hz, 1H).	623.45
I-84A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 – 10.21 (m, 1H), 8.42 – 8.36 (m, 1H), 7.88 – 7.81 (m, 1H), 7.53 – 7.46 (m, 2H), 7.39 – 7.23 (m, 7H), 7.22 – 7.14 (m, 5H), 5.38 – 5.34 (m, 2H), 4.28 – 3.63 (m, 10H), 1.39 – 1.30 (m, 1H), 1.12 – 1.08 (m, 1H), 1.06 – 1.02 (m, 3H), 0.91 – 0.87 (m, 1H), 0.86 – 0.76 (m, 2H), 0.69 – 0.60 (m, 1H).	602.1
I-84B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 – 10.18 (m, 1H), 8.42 – 8.33 (m, 1H), 7.88 – 7.80 (m, 1H), 7.54 – 7.47 (m, 2H), 7.37 – 7.24 (m, 7H), 7.21 – 7.13 (m, 5H), 5.38 – 5.33 (m, 2H), 4.39 – 3.90 (m, 4H), 3.88 – 3.62 (m, 4H), 3.33 (s, 3H), 1.43 – 1.29 (m, 1H), 1.12 – 0.99 (m, 5H), 0.89 – 0.76 (m, 2H), 0.68 – 0.60 (m, 1H).	602.2
I-85	15	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 3.2 Hz, 2H), 7.29-7.37 (m, 7.4H), 7.23 (m, 2.6H), 6.85 (d, J = 7.2 Hz, 1H), 5.31-5.36 (m, 2H), 4.98-5.02 (m, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.42-4.46 (m, 1H), 3.75-4.21 (m, 11H), 3.43-3.54 (m, 4H), 3.06 (m, 1H), 2.23 (t, J = 7.6 Hz, 0.5H), 1.99-2.05 (m, 1.5H), 1.13-1.22 (m, 10H), 0.88 (t, J = 6.6 Hz, 1H), 0.72-0.77 (m, 1H).	731.5

[1034]

化合物编号	方法	^{1}HNMR	LCMS
I-86	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.15-8.23 (m, 1H), 7.90 (t, *J* = 10.2 Hz, 1H), 7.26-7.36 (m, 10H), 5.33-5.38 (m, 2H), 4.90-4.97 (m, 1H), 4.42-4.66 (m, 3H), 4.04-4.22 (m, 3H), 3.84-4.00 (m, 5H), 3.35-3.53 (m, 8H), 2.19 (t, *J* = 7.6 Hz, 0.4H), 2.00-2.05 (m, 0.7H), 1.58-1.61 (m, 0.5H), 1.45-1.49 (m, 0.5H), 1.22-1.24 (m, 2H), 1.17-1.18 (m, 2H), 1.10-1.13 (m, 4H), 1.03 (m, 1H), 0.90 (t, *J* = 6.8 Hz, 1H), 0.74-0.79 (m, 1H).	697.5
I-87A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.30 (m, 2H), 7.83 – 7.75 (m, 2H), 7.38 – 7.22 (m, 10H), 5.35 (s, 2H), 4.56 – 3.44 (m, 12H), 3.30 (s, 3H), 2.60 (dd, *J* = 11.4, 4.2 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H).	655.4
I-87B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.28 (m, 2H), 7.95 – 7.75 (m, 2H), 7.37 – 7.23 (m, 10H), 5.35 (s, 2H), 4.59 – 4.35 (m, 2H), 4.33 – 4.20 (m, 1H), 4.17 – 3.99 (m, 2H), 3.98 – 3.84 (m, 2H), 3.84 – 3.67 (m, 2H), 3.65 – 3.58 (m, 1H), 3.51 – 3.34 (m, 2H), 3.30 – 3.22 (m, 1H), 2.60 (q, *J* = 3.8 Hz, 3H), 1.30 – 1.24 (m, 1H), 1.11 – 1.01 (m, 4H).	655.4
I-88 - 混合物	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.24 – 8.18 (m, 1H), 7.96 – 7.89 (m, 1H), 7.40 – 7.24 (m, 5H), 5.38 (s, 2H), 4.55 – 3.82 (m, 10H), 3.39 (s, 1H), 2.78 – 2.71 (m, 3H), 1.51 – 1.37 (m, 1H), 1.22 – 1.09 (m, 9H), 1.03 (s, 1H), 0.78 (s, 1H).	551.4
I-88A	9A	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.38-8.34 (m, 1H), 8.19-8.13 (m, 1H), 7.84-7.70 (m, 2H), 7.37-7.25 (m, 5H), 5.35 (s, 2H), 4.26-4.13 (m, 2H), 4.09-3.90 (m, 5H), 3.78-3.73 (m, 4H), 3.48-3.33 (m, 1H), 2.61-2.56 (m, 2H), 1.35-1.31 (m, 1H), 1.12-1.01 (m, 9H), 0.86-0.84 (m, 1H), 0.69-0.64 (m, 1H).	551.4
I-88B	9B	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.38-8.32 (m, 1H), 8.19-8.10 (m, 1H), 7.84-7.78 (m, 2H), 5.35 (s, 2H), 4.15-4.10 (m, 2H), 4.05-3.99 (m, 4H), 3.83-3.62 (m, 5H), 2.59 (t, *J*=4.8 Hz, 3H), 1.36-1.35 (m, 1H), 1.12-0.95	551.4

[1035]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 9H), 0.87-0.86 (m, 1H), 0.69-0.68 (m, 1H).	
I-89A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.27 (m, 2H), 7.88 – 7.80 (m, 2H), 7.43 – 7.19 (m, 10H), 5.35 (s, 2H), 4.56 – 4.50 (m, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.21 – 3.38 (m, 10H), 2.60 (dd, J = 10.6, 4.4 Hz, 3H), 1.17 – 1.04 (m, 15H), 0.92 – 0.86 (m, 1H).	669.5
I-89B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.26 (m, 2H), 7.96 – 7.75 (m, 2H), 7.45 – 7.12 (m, 10H), 5.35 (s, 2H), 4.52 (t, J = 11.6 Hz, 1H), 4.45 – 4.21 (m, 2H), 4.11 – 3.77 (m, 5H), 3.77 – 3.46 (m, 4H), 3.43 – 3.39 (m, 1H), 2.61 (t, J = 3.6 Hz, 3H), 1.18 – 0.92 (m, 16H).	669.5
I-90A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.31 (m, 2H), 7.88 – 7.78 (m, 2H), 7.38 – 7.23 (m, 10H), 5.35 (s, 2H), 4.57 – 4.40 (m, 2H), 4.39 – 3.42 (m, 11H), 2.60 (dd, J = 10.6, 4.4 Hz, 3H), 1.52 – 1.35 (m, 6H), 1.10 – 1.05 (m, 3H).	633.5
I-90B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.28 (m, 2H), 7.92 – 7.78 (m, 2H), 7.37 – 7.22 (m, 10H), 5.35 (s, 2H), 4.55 – 3.38 (m, 13H), 2.61 – 2.58 (m, 3H), 1.47 (d, J = 22.0 Hz, 6H), 1.11 – 1.01 (m, 3H).	633.45
I-91A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.30 (m, 1H), 7.86 – 7.76 (m, 1H), 7.39 – 7.10 (m, 10H), 5.34 – 5.23 (m, 2H), 4.35 – 3.49 (m, 11H), 3.20 – 2.59 (m, 2H), 2.43 – 2.33 (m, 1H), 1.79 – 1.31 (m, 4H), 1.31 – 0.98 (m, 9H), 0.90 – 0.63 (m, 2H).	594.5
I-91B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.28 (m, 1H), 7.87 – 7.75 (m, 1H), 7.38 – 7.09 (m, 10H), 5.35 (s, 2H), 4.29 – 3.90 (m, 5H), 3.87 – 3.49 (m, 6H), 3.17 – 2.94 (m, 1H), 2.90 – 2.63 (m, 1H), 2.44 – 2.35 (m, 1H), 1.80 – 1.51 (m, 3H), 1.49 – 1.28 (m, 2H), 1.27 – 1.15 (m, 2H), 1.14 – 1.00 (m, 6H), 0.90 – 0.80 (m, 1H), 0.71 – 0.62 (m, 1H).	594.45

[1036]

化合物编号	方法	^{1}HNMR	LCMS
I-92A	7A	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.37-8.29 (m, 2H), 7.86-7.80 (m, 2H), 7.37-7.24 (m, 10H), 5.35 (s, 2H), 4.61-4.59 (m, 1H), 4.55-4.42 (m, 2H), 4.37-4.34 (m, 1H), 4.19-3.86 (m, 6H), 3.79-3.63 (m, 3H), 3.58-3.4 (m, 1H), 3.28-3.16 (m, 2H), 2.60 (dd, *J*=4.8 Hz, 3H), 2.24-2.12 (m, 1H), 2.04-1.91 (m, 1H), 1.09-1.06 (m, 3H), 0.36-0.29 (m, 4H).	657.1
I-92B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.30 (m, 2H), 7.96 – 7.79 (m, 2H), 7.45 – 7.18 (m, 10H), 5.37 (s, 2H), 4.71 – 4.61 (m, 1H), 4.54 (t, *J* = 11.7 Hz, 1H), 4.47 – 4.25 (m, 2H), 4.15 – 3.98 (m, 3H), 3.96 – 3.40 (m, 7H), 3.28 (d, *J* = 11.2 Hz, 2H), 2.63 (d, *J* = 4.5 Hz, 3H), 2.28 – 2.04 (m, 2H), 1.17 – 0.99 (m, 3H), 0.45 – 0.29 (m, 4H).	657.5
I-93	2B	^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 – 8.34 (m, 1H), 7.88 – 7.78 (m, 1H), 7.64 – 7.52 (m, 2H), 7.48 – 7.17 (m, 10H), 5.38 – 5.28 (m, 2H), 4.38 – 3.58 (m, 10H), 1.12 – 0.92 (m, 7H), 0.84 (s, 1H), 0.70 – 0.58 (m, 1H).	579.1
I-94A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.28 (m, 2H), 7.88 – 7.77 (m, 2H), 7.38 – 7.22 (m, 10H), 5.35 (s, 2H), 4.55 – 4.35 (m, 3H), 4.02 – 3.37 (m, 10H), 2.60 (dd, *J* = 10.6, 4.6 Hz, 3H), 1.28 (d, *J* = 44.0 Hz, 6H), 1.08 (t, *J* = 5.4 Hz, 3H), 0.81 (dq, *J* = 13.2, 6.4, 6.0 Hz, 5H), 0.41 (s, 2H).	669.50
I-94B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.21 (m, 2H), 7.88 – 7.77 (m, 2H), 7.39 – 7.13 (m, 10H), 5.35 (d, *J* = 3.2 Hz, 2H), 4.56 – 4.35 (m, 3H), 4.33 – 3.44 (m, 10H), 2.60 (d, *J* = 4.6 Hz, 3H), 1.49 – 1.31 (m, 2H), 1.26 (t, *J* = 6.4 Hz, 4H), 1.06 (dd, *J* = 17.6, 6.2 Hz, 3H), 0.87 – 0.81 (d, *J* = 8.6 Hz, 5H), 0.49 – 0.39 (m, 2H).	669.5
I-95A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.27 (m, 1H), 8.20 (d, *J* = 11.6 Hz, 1H), 7.90 – 7.75 (m, 2H), 7.36 – 7.23 (m, 5H), 4.56 – 4.5 (m, 1H), 4.47 – 4.4(m, 1H), 4.38 – 4.31(m, 1H), 4.27 – 4.21(m, 1H), 4.08 – 3.39 (m,	649.2

[1037]

化合物编号	方法	^{1}HNMR	LCMS
		13H), 3.24 (t, J = 11.6 Hz, 2H), 2.65 – 2.56 (m, 3H), 2.07 (s, 1H), 1.41 – 1.17 (m, 5H), 1.11 – 1.01 (m, 9H), 0.84 (t, J = 4.6 Hz, 1H), 0.68 – 0.61 (m, 1H).	
I-95B	4B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.18 – 8.07 (m, 1H), 7.94 – 7.85 (m, 1H), 7.37 – 7.22 (m, 5H), 4.61 – 4.56 (m, 1H), 4.49 – 4.40 (m, 2H), 4.29 – 4.12 (m, 3H), 4.05 (dt, J = 22.2, 7.2 Hz, 4H), 3.96 – 3.86 (m, 5H), 3.85 – 3.75 (m, 1H), 3.43 – 3.34 (m, 3H), 2.74 (s, 3H), 2.21 – 2.11 (m, 1H), 1.53 – 1.42 (m, 3H), 1.40 – 1.29 (m, 3H), 1.21 – 1.17 (m, 4H), 1.15 – 1.11 (m, 4H), 1.07 – 1.02 (m, 1H), 0.81 – 0.75 (m, 1H).	649.5
I-96A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.32 (m, 2H), 7.88 – 7.77 (m, 1H), 7.40 – 7.21 (m, 10H), 5.35 (d, J = 2.6 Hz, 2H), 4.50 – 4.42 (m, 2H), 4.23 – 4.02 (m, 2H), 4.00 – 3.41 (m, 8H), 3.31 – 3.04 (m, 3H), 1.39 – 1.22 (m, 1H), 1.11 – 0.97 (m, 6H), 0.87 – 0.82 (m, 1H), 0.69 – 0.59 (m, 1H).	570.4
I-96B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 – 8.32 (m, 2H), 7.87 – 7.79 (m, 1H), 7.41 – 7.22 (m, 10H), 5.38 – 5.33 (m, 2H), 4.52 – 4.40 (m, 2H), 4.33 – 3.54 (m, 8H), 3.51 – 3.35 (m, 3H), 3.29 – 3.05 (m, 2H), 1.40 – 1.21 (m, 1H), 1.11 – 1.02 (m, 6H), 0.90 – 0.81 (m, 1H), 0.71 – 0.59 (m, 1H).	570.1
I-97	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.14-8.23 (m, 1H), 7.87-7.93 (m, 1H), 7.17-7.42 (m, 10H), 5.33-5.38 (m, 2H), 4.93-4.98 (m, 1H), 4.60-4.65 (m, 1H), 4.50-4.56 (m, 1H), 3.84-4.20 (m, 8H), 3.43-3.58 (m, 4H), 3.37 (m, 1H), 2.19 (t, J = 7.6 Hz, 1H), 2.02-2.03 (m, 1H), 1.58-1.62 (m, 3H), 1.43-1.53 (m, 4H), 1.18 (d, J = 4.8 Hz, 2H), 1.10-1.12 (m, 4H), 1.02-1.04 (m, 1H), 0.90 (t, J = 6.6 Hz, 2H), 0.74-0.79 (m, 1H).	695.5
I-98	15	^{1}H NMR (400 MHz, CD_3OD): δ 8.15-8.23 (m, 1H), 7.87-7.93 (m, 1H), 7.19-7.36 (m, 10H), 5.33-5.38 (m, 2H), 4.95-5.02 (m, 1H), 4.30-4.65 (m, 5H), 3.81-4.21 (m, 10H), 3.35-	725.5

[1038]

化合物编号	方法	^{1}HNMR	LCMS
		4.43 (m, 2H), 2.41-2.98 (m, 5H), 2.19 (t, *J* = 7.4 Hz, 0.4H), 2.00-2.05 (m, 0.7 H), 1.60-1.78 (m, 3H), 1.18 (d, *J* = 5.2 Hz, 2H), 1.10-1.12 (m, 4H), 1.01-1.04 (m, 1H), 0.90 (t, *J* = 6.8 Hz, 1H), 0.73-0.79 (m, 1H).	
I-99	15	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.83 (m, 2H), 7.24-7.38 (m, 10H), 6.70-6.77 (m, 1H),4.62 (d, *J* = 12.0 Hz, 1H), 4.50-4.57 (m, 1H), 4.454.48 (m, 1H), 3.60-4.20 (m, 14H), 3.05 (s, 1H),1.99-2.03 (m, 1H), 1.12-1.24 (m, 16H), 0.85-0.90 (m, 1H), 0.72-0.75 (m, 1H).	695.5
I-100A	1A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.59-8.53 (m, 1H), 8.35 (d, *J*=11.6 Hz, 1H), 8.03-8.02 (m, 1H), 7.84-7.80 (m, 1H), 7.37-7.25 (m, 10H), 5.35 (s, 2H), 4.55-4.42 (m, 4H), 4.28-3.87 (m, 4H), 3.78-3.62 (m, 3H), 3.56-3.54 (m, 2H), 3.26-3.25 (m, 1H), 2.60-2.57 (m, 3H), 1.07-1.02 (m, 9H).	615.2
I-100B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 – 8.47 (m, 1H), 8.35 (d, 1H), 8.07 – 7.90 (m, 1H), 7.83 – 7.79 (m, 1H), 7.38 – 7.20 (m, 10H), 5.35 (d, *J* = 4.2 Hz, 2H), 4.54 – 4.43 (m, 3H), 4.32 – 4.20 (m, 1H), 4.01 – 3.76 (m, 3H), 3.76 – 3.65 (m, 2H), 3.63 – 3.53 (m, 3H), 3.30 – 3.26 (m, 1H), 2.59 (d, *J* = 4.4 Hz, 3H), 1.09 (s, 9H).	615.2
I-101A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 – 8.41 (m, 1H), 8.38 – 8.35 (m, 1H), 7.95 (t, 1H), 7.86 – 7.79 (m, 1H), 7.41 – 7.07 (m, 10H), 5.39 – 5.32 (m, 2H), 4.28 – 3.80 (m, 6H), 3.80 – 3.57 (m, 3H), 3.27 – 3.21 (m, 1H), 2.58 – 2.52 (m, 5H), 1.67 – 1.47 (m, 4H), 1.35 – 1.22 (m, 1H), 1.10 – 1.07 (m, 1H), 1.06 – 1.00 (m, 5H), 0.88 – 0.82 (m, 1H), 0.67 – 0.60 (m, 1H).	625.2
I-101B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.30 (m, 2H), 8.01 – 7.78 (m, 2H), 7.38 – 7.08 (m, 10H), 5.35 (s, 2H), 4.38 – 4.10 (m, 2H), 4.09 – 3.85 (m, 3H), 3.85 – 3.53 (m, 4H), 3.27 – 3.21 (m, 1H), 2.61 – 2.51 (m, 5H), 1.73 – 1.40 (m, 4H), 1.34 (dd, *J* = 7.6, 5.6 Hz, 1H),	625.2

[1039]

化合物编号	方法	^{1}HNMR	LCMS
		1.14 – 1.03 (m, 6H), 0.85 (q, *J* = 4.8 Hz, 1H), 0.72 – 0.62 (m, 1H).	
I-102A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 11.4 Hz, 2H), 7.89 – 7.76 (m, 2H), 7.38 – 7.20 (m, 10H), 5.35 (s, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.46 – 4.33 (m, 2H), 4.21 – 3.42 (m, 10H), 3.16 (d, *J* = 18.8 Hz, 3H), 2.60 (dd, *J* = 10.8, 4.6 Hz, 3H), 1.70 – 1.53 (m, 2H), 1.07 (t, *J* = 5.6 Hz, 3H), 0.78 (s, 2H), 0.49 (s, 2H).	671.45
I-102B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.26 (m, 2H), 7.96 – 7.7 (m, 2H), 7.39 – 7.20 (m, 10H), 5.35 (s, 2H), 4.52 (t, *J* = 12.0 Hz, 1H), 4.46 – 4.30 (m, 2H), 4.24 – 3.37 (m, 10H), 3.30 (s, 2H), 3.18 (d, *J* = 18.0 Hz, 3H), 2.60 (d, *J* = 4.4 Hz, 3H), 1.76 – 1.56 (m, 2H), 1.06 (dd, *J* = 18.6, 6.2 Hz, 3H), 0.87 – 0.77 (m, 2H), 0.53 (s, 2H).	671.5
I-103A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.38-8.34 (m, 1H), 8.23 (dd, *J*=8.4 Hz, 1H), 7.80-7.73 (m, 1H), 4.28-4.21 (m, 1H), 4.18-3.96 (m, 4H), 3.93-3.86 (m, 1H), 3.82-3.71 (m, 3H), 3.70-3.60 (m, 1H), 3.52-3.42 (m, 1H), 3.25-3.20 (m, 1H), 3.12-3.07 (m, 1H), 2.59 (d, *J*=4.4 Hz, 2H), 2.57-2.55 (m, 1H), 1.98-1.92 (m, 2H), 1.68-1.63 (m, 5H), 1.44-1.42 (m, 1H), 1.19-1.09 (m, 3H), 1.03-1.00 (m, 3H), 0.91-0.81 (m, 3H), 0.43-0.40 (m, 2H), 0.10-0.05 (m, 2H).	560.1
I-103B	1B	^{1}H NMR (DMSO, 400 MHz) δ 0.06 – 0.12 (2H, m), 0.40 – 0.46 (2H, m), 0.77 – 0.98 (4H, m), 1.02 (2H, d, *J*=6.2 Hz), 1.08 – 1.21 (3H, m), 1.41 (1H, s), 1.61 (5H, d, *J*=12.4 Hz), 1.93 – 2.01 (2H, m), 2.59 (3H, s), 3.09 (1H, m), 3.19 – 3.27 (1H, m), 3.46 (1H, m), 3.61 – 3.89 (5H, m), 3.94 – 4.17 (4H, m), 4.20 – 4.33 (1H, m), 7.77 – 7.89 (1H, m), 8.20 – 8.31 (1H, m), 8.33 – 8.39 (1H, m), 9.25 (1H, s).	560.40
I-104	15	^{1}H NMR (400 MHz, CD3OD): δ 8.08-8.16 (m, 1H), 7.80-7.83(d, *J* = 13.2 Hz, 1H), 7.19-7.27 (m, 5H), 5.28 (s, 2H), 4.79-4.86 (m, 1H), 3.50-4.49 (m, 13H), 3.21-3.32 (m, 2H),	729.5

[1040]

化合物编号	方法	^{1}HNMR	LCMS
		3.04-3.10 (m, 1H), 2.45-2.55 (m, 1H), 1.93-2.03 (m, 1H), 1.74-1.78 (m, 1H), 1.55-1.66 (m, 6H), 1.30-1.41(m, 3H), 1.00-1.07(m, 10H), 0.67-0.83(m, 11H).	
I-105	15	^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, J =14.8 Hz, 1H), 7.92 (d, J =12.0 Hz, 1H), 7.28-7.37 (m, 5H), 5.38 (s, 2H), 4.91-4.99 (m, 1H), 3.70-4.41 (m, 12H), 3.35-3.51 (m, 3H), 3.11-3.24 (m, 2H), 2.84-3.04 (m, 1H), 2.52-2.70 (m, 1H), 1.55-1.88 (m, 9H), 1.04-1.29 (m, 13H), 1.03-1.05 (m, 1H), 0.88-0.97 (m, 3H), 0.76-0.80 (m, 1H).	731.5
I-106	15	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.23 (m, 1H), 7.88-7.93 (m, 1H), 7.27-7.36 (m, 10H), 5.33-5.38 (m, 2H), 4.28-4.66 (m, 4H), 3.76-4.23 (m, 12H), 3.35-3.37 (m, 1H), 2.02-2.21 (m, 5H), 1.78-1.82 (m, 2H), 1.29-1.30 (m, 6H), 1.18-1.24 (m, 4H), 1.09-1.15 (m, 4H), 1.01-1.04 (m, 1H), 0.88-0.91 (m, 1H), 0.76-0.79 (m, 1H).	707.5
I-107	15	^{1}H NMR (400 MHz, CD_3OD) δ 8.17-8.25 (m, 2H), 7.89-7.93 (m, 1H), 7.28-7.36 (m, 5H), 5.38 (s, 2H), 4.50-4.56 (m, 1H), 3.70-4.43 (m, 15H), 3.31-3.36 (m, 1H), 3.17-3.23 (m, 1H), 2.11-2.25 (m, 4H), 1.82-1.89 (m, 2H), 1.65-1.77 (m, 5H), 1.02-1.20 (m, 13H), 0.86-0.97 (m, 2H), 0.76-0.80 (m, 1H).	713.5
I-108A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 15.0 Hz, 2H), 7.41 – 7.23 (m, 10H), 5.35 (s, 2H), 4.53 (d, J = 12.2 Hz, 1H), 4.50 – 4.26 (m, 3H), 3.92 (m, 4H), 3.77 (m, 2H), 3.62 – 3.38 (m, 2H), 3.30 (s, 1H), 2.60 (dd, J = 10.8, 4.5 Hz, 3H), 1.21 – 1.05 (m, 7H).	681.4
I-108B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36-8.31 (m, 2H), 7.88-7.79 (m, 2H), 7.37-7.23 (m, 10H), 5.35-5.34 (m, 2H), 4.52 (t, J=12 Hz, 1H), 4.44-4.34 (m, 3H), 4.12-3.96 (m, 3H), 3.90-3.85 (m, 2H), 3.79-3.62 (m, 3H), 3.49-3.40 (m, 1H), 2.61-2.59 (m, 3H), 1.28-1.04 (m, 7H).	681.4

[1041]

化合物编号	方法	^{1}HNMR	LCMS
I-109A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 11.0 Hz, 2H), 7.83 (d, J = 16.0 Hz, 2H), 7.38 – 7.23 (m, 10H), 5.36 (s, 2H), 4.56 – 4.41 (m, 2H), 4.39 – 3.37 (m, 11H), 3.30 (s, 1H), 2.60 (dd, J = 10.4, 4.4 Hz, 3H), 1.63 (s, 1H), 1.24 (s, 1H), 1.09 (d, J = 5.6 Hz, 3H), 1.00 – 0.92 (m, 1H), 0.84 (s, 8H), 0.40 (s, 2H).	669.45
I-109B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 22.6 Hz, 2H), 7.82 (d, J = 20.0 Hz, 1H), 7.39 – 7.21 (m, 10H), 5.35 (d, J = 3.8 Hz, 2H), 4.52 (t, J = 11.6 Hz, 1H), 4.44 – 3.44 (m, 12H), 2.60 (d, J = 4.4 Hz, 3H), 1.66 (s, 1H), 1.38 – 1.23 (m, 2H), 1.06 (dd, J = 16.6, 6.2 Hz, 3H), 0.86 (d, J = 6.2 Hz, 8H), 0.43 (s, 2H).	669.45
I-110A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.4 Hz, 1H), 8.25 – 8.13 (m, 1H), 7.86 – 7.69 (m, 2H), 7.38 – 7.24 (m, 5H), 5.35 (s, 2H), 4.31 – 3.53 (m, 11H), 3.29 (d, J = 7.4 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.58 (dd, J = 10.0, 4.4 Hz, 3H), 2.08 – 1.98 (m, 1H), 1.63 – 1.29 (m, 7H), 1.17 – 1.00 (m, 11H), 0.85 (d, J = 4.4 Hz, 1H), 0.67 (d, J = 8.0 Hz, 1H).	633.4
I-110B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.18 (m, 2H), 7.82 (d, J = 17.8 Hz, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.38 – 3.49 (m, 11H), 3.33 – 3.26 (m, 1H), 3.15 (d, J = 7.4 Hz, 1H), 2.59 (t, J = 5.0 Hz, 3H), 1.99 (m, 1H), 1.63 – 1.33 (m, 7H), 1.16 – 0.94 (m, 11H), 0.91 – 0.81 (m, 1H), 0.68 (m, 1H).	633.5
I-111	15	^{1}H NMR (400 MHz, CD_3OD) δ 8.18-8.24 (m, 1H), 7.92 (d, J =12.0 Hz, 1H), 7.28-7.37 (m, 5H), 5.38 (s, 2H), 4.88-4.96 (m, 1H), 3.64-4.56 (m, 13H), 3.33-3.39 (m, 2H), 3.13-3.28 (m, 4H), 2.44-3.05 (m, 3H), 1.61-1.85 (m, 8H), 1.45-1.56 (m, 2H), 1.01-1.22 (m, 13H), 0.83-0.97 (m, 3H), 0.74-0.79 (m, 1H).	745.5
I-112A	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.59-13.56 (m, 1H), 8.39-8.31 (m, 1H), 8.25-8.16 (m, 1H), 7.93-7.80 (m, 1H), 7.65-7.61 (m, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.36-7.21 (m,	601.5

[1042]

化合物编号	方法	^{1}HNMR	LCMS
		6H), 4.56-4.51 (m, 1H), 4.46-4.41 (m, 1H), 4.38-4.29 (m, 2H), 4.26-4.05 (m, 3H), 4.03-3.92 (m, 2H), 3.90-3.78 (m, 2H), 3.75-3.62 (m, 1H), 3.57-3.45 (m, 1H), 2.63-2.57 (m, 3H), 1.37-1.23 (m, 1H), 1.18-1.01 (m, 9H), 0.85-0.83 (m, 1H), 0.67-0.61(m, 1H).	
I-112B	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 8.40-8.34 (m, 1H), 8.16 (d, J=8.4 Hz, 1H), 7.93-7.84 (m, 1H), 7.63-7.60 (m, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.35-7.20 (m, 6H), 4.57-4.30 (m, 4H), 4.25-4.20 (m, 1H), 4.16-4.13 (m, 1H), 4.10-4.02 (m, 1H), 3.99-3.86 (m, 2H), 3.83-3.64 (m, 3H), 3.54-3.45 (m, 1H), 2.63-2.60 (m, 3H), 1.41-1.34 (m, 1H), 1.14-1.06 (m, 7H), 1.04-0.98 (m, 2H), 0.89-0.83 (m, 1H), 0.72-0.63 (m, 1H).	601.5
I-113A	1A	^{1}H NMR (400 MHz, DMSO-$d6$) δ 8.58 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.82 (d, J = 12.2 Hz, 1H), 7.42 – 7.22 (m, 10H), 5.36 (s, 2H), 4.55 (s, 1H), 4.46 (s, 2H), 3.97 – 3.54 (m, 11H), 2.59 (dd, J = 8.4, 4.6 Hz, 3H), 1.24 (dd, J = 13.4, 6.8 Hz, 2H), 1.18 – 1.10 (m, 2H).	667.4
I-113B	1B	^{1}H NMR (400 MHz, DMSO-$d6$) δ 8.51 – 8.49 (m, 1H), 8.36 – 8.32 (m, 1H), 8.00 – 7.99 (m, 1H), 7.84 – 7.80 (m, 1H), 7.37 – 7.24 (m, 10H), 5.35 – 5.34 (m, 2H), 4.48 – 4.45 (m, 3H), 4.04 – 3.91 (m, 2H), 3.79 – 3.71 (m, 2H), 3.60 – 3.56 (m, 3H), 3.38 – 3.36 (m, 1H), 3.29 – 3.27 (m, 2H), 2.60 (d, J=4.4 Hz, 3H), 2.51 (s, 1H), 1.27 – 1.23 (m, 2H), 1.17 – 1.14 (m, 2H).	667.4
I-114A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.6 Hz, 2H), 7.83 (d, J = 16.6 Hz, 2H), 7.36 – 7.24 (m, 10H), 5.36 (s, 2H), 4.57 – 4.47 (m, 2H), 4.46 – 4.34 (m, 3H), 4.03 – 3.40 (m, 8H), 2.63 – 2.57 (m, 3H), 1.31 – 1.16 (m, 1H), 1.11 – 1.04 (m, 3H), 0.75 (s, 2H), 0.34 (s, 4H), 0.02 (s, 2H).	653.45
I-114B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.29 (m, 2H), 7.96 – 7.75 (m, 2H), 7.38 – 7.21 (m, 10H), 5.35 (d, J = 3.2 Hz, 2H), 4.52 (t, J =	653.45

[1043]

化合物编号	方法	^{1}HNMR	LCMS
		11.6 Hz, 1H), 4.46 – 4.30 (m, 3H), 4.09 – 3.95 (m, 2H), 3.93 – 3.41 (m, 7H), 2.63 – 2.57 (m, 3H), 1.33 – 1.24 (m, 1H), 1.07 (dd, *J* = 17.2, 6.2 Hz, 3H), 0.85 – 0.72 (m, 2H), 0.44 – 0.34 (m, 4H), 0.12 – 0.01 (m, 2H).	
I-115	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.90 (m, 1H), 8.41 – 8.35 (m, 1H), 8.26 – 8.24 (m, 1H), 4.88 – 4.86 (m, 1H), 4.21 – 4.02 (m, 3H), 3.98 – 3.83 (m, 2H), 3.79 – 3.69 (m, 2H), 3.61 – 3.40 (m, 7H), 3.26 – 3.16 (m, 2H), 1.66 – 1.58 (m, 7H), 1.46 – 1.30 (m, 6H), 1.17 – 1.09 (m, 6H), 1.07 – 1.03 (m, 6H), 0.87 – 0.84 (m, 3H), 0.69 – 0.66 (m, 1H).	679.4
I-116A	7A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 – 8.18 (m, 1H), 7.94 – 7.89 (m, 1H), 7.38 – 7.24 (m, 10H), 5.40 – 5.36 (m, 2H), 4.64 – 4.58 (m, 1H), 4.50 – 4.41 (m, 2H), 4.34 – 4.31 (m, 1H), 4.20 – 3.94 (m, 6H), 3.87 – 3.83 (m, 1H), 3.61 – 3.58 (m, 2H), 2.73 (d, *J* = 11.2 Hz, 3H), 1.46 – 1.37 (m, 2H), 1.22 – 1.15 (m, 4H), 0.93 – 0.71 (m, 4H), 0.48 – 0.37 (m, 2H), 0.11 – 0.05 (m, 2H).	667.45
I-116B	7B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.27 (m, 2H), 7.94 – 7.77 (m, 2H), 7.39 – 7.17 (m, 10H), 5.35 (s, 2H), 4.57 – 4.47 (m, 1H), 4.46 – 4.34 (m, 2H), 4.29 – 3.58 (m, 8H), 3.50 – 3.33 (m, 2H), 2.60 (d, *J* = 4.6 Hz, 3H), 1.47 – 1.29 (m, 2H), 1.13 – 1.00 (m, 3H), 0.80 (s, 2H), 0.74 – 0.61 (m, 1H), 0.54 (s, 2H), 0.40 – 0.28 (m, 2H), 0.08 – -0.01 (m, 2H).	667.4
I-117A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 9.8 Hz, 2H), 7.85 – 7.79 (m, 2H), 7.37 – 7.32 (m, 3H), 7.31 – 7.24 (m, 7H), 5.35 (s, 2H), 4.55 – 4.34 (m, 6H), 3.99 – 3.44 (m, 9H), 2.62 – 2.58 (m, 3H), 1.86 – 1.72 (m, 2H), 1.09 – 1.05 (m, 3H), 0.84 (s, 2H), 0.55 (s, 2H).	659.45
I-117B	7B	^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.83 (s, 2H), 7.42 – 7.27 (m, 10H), 5.31 (s, 2H), 4.69 – 4.42 (m, 5H), 4.35 – 3.76 (m, 9H), 3.10 (s,	659.45

[1044]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 2.89 – 2.78 (m, 3H), 1.96 – 1.83 (m, 2H), 1.16 – 0.93 (m, 5H), 0.64 (s, 2H).	
I-118	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 – 8.28 (m, 1H), 4.90 – 4.82 (m, 1H), 4.21 – 4.12 (m, 1H), 4.09 – 3.95 (m, 1H), 3.93 – 3.66 (m, 3H), 3.63 – 3.48 (m, 5H), 3.46 – 3.35 (m, 4H), 3.27 – 3.21 (m, 1H), 3.17 – 3.13 (m, 1H), 1.94 – 1.91 (m, 3H), 1.69 – 1.58 (m, 7H), 1.47 – 1.37 (m, 5H), 1.36 – 1.26 (m, 1H), 1.20 – 1.08 (m, 6H), 1.06 – 1.02 (m, 6H), 0.89 – 0.83 (m, 3H), 0.70 – 0.66 (m, 1H).	559.4
I-119A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.2 Hz, 1H), 8.26 – 8.16 (m, 1H), 7.82 (d, J = 15.6 Hz, 2H), 7.39 – 7.23 (m, 5H), 5.35 (s, 2H), 4.29 – 3.57 (m, 14H), 3.25 – 3.14 (m, 2H), 2.61 – 2.55 (m, 3H), 1.69 (s, 1H), 1.53 (d, J = 12.8 Hz, 2H), 1.32 (d, J = 19.8 Hz, 1H), 1.18 – 0.99 (m, 12H), 0.85 (s, 1H), 0.68 (d, J = 8.0 Hz, 1H).	649.45
I-119B	2B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.29 – 8.14 (m, 1H), 7.98 – 7.88 (m, 1H), 7.40 – 7.24 (m, 5H), 4.65 – 4.49 (m, 1H), 4.46 – 4.34 (m, 1H), 4.27 – 3.81 (m, 10H), 3.48 – 3.33 (m, 4H), 3.20 (ddd, J = 14.6, 9.2, 6.6 Hz, 1H), 2.74 (s, 3H), 1.86 – 1.69 (m, 1H), 1.60 (t, J = 16.0 Hz, 2H), 1.52 – 1.35 (m, 1H), 1.33 – 1.09 (m, 11H), 1.04 (q, J = 5.8, 4.8 Hz, 2H), 0.83 – 0.73 (m, 1H).	649.5
I-120A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (dd, J = 18.8, 8.0 Hz, 1H), 8.44 – 8.31 (m, 1H), 7.85 (d, J = 10.2 Hz, 1H), 7.43 – 7.08 (m, 8H), 5.36 (s, 2H), 5.31 – 5.2 (m, 1H), 4.27 – 3.59 (m, 8H), 3.24 – 3.03 (m, 1H), 2.99 – 2.75 (m, 2H), 2.44 – 2.31 (s, 1H), 1.98 – 1.73 (m, 1H), 1.41 – 1.28 (m, 1H), 1.15 – 1.03 (m, 6H), 0.86 (s, 1H), 0.67 (dd, J = 8.4, 4.2 Hz, 1H).	586.0
I-120B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (q, J = 9.8, 8.8 Hz, 1H), 8.42 – 8.34 (m, 1H), 7.84 (d, J = 14.6 Hz, 1H), 7.43 – 7.08 (m, 8H), 5.36 (s, 2H), 5.28 (dq, J = 16.4, 7.8 Hz, 1H),	586.3

[1045]

化合物编号	方法	^{1}HNMR	LCMS
		4.35 (t, J = 10.4 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.94 (d, J = 10.4 Hz, 1H), 3.83 (d, J = 17.2 Hz, 2H), 3.64 (d, J = 14.2 Hz, 2H), 3.19 – 3.04 (m, 1H), 2.98 – 2.77 (m, 2H), 2.41 (s, 1H), 1.86 (dq, J = 17.2, 8.9 Hz, 1H), 1.35 (d, J = 18.4 Hz, 1H), 1.14 – 1.03 (m, 6H), 0.86 (d, J = 6.4 Hz, 1H), 0.71 (dd, J = 8.6, 4.2 Hz, 1H).	
I-121A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.13 (m, 2H), 7.84 – 7.70 (m, 2H), 4.31 – 4.11 (m, 2H), 4.10 – 3.99 (m, 3H), 3.99 – 3.38 (m, 10H), 3.30 – 3.18 (m, 3H), 3.15 – 3.06 (m, 1H), 2.64 – 2.54 (m, 3H), 2.14 – 1.99 (m, 1H), 1.71 – 1.56 (m, 5H), 1.49 – 0.98 (m, 18H), 0.91 – 0.77 (m, 3H), 0.71 – 0.62 (m, 1H).	655.1
I-121B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 – 8.16 (m, 2H), 7.88 – 7.77 (m, 2H), 4.39 – 3.95 (m, 7H), 3.91 – 3.46 (m, 8H), 3.27 – 3.19 (m, 3H), 3.12 – 3.05 (m, 1H), 2.59 (t, J = 4.8 Hz, 3H), 2.12 – 2.01 (m, 1H), 1.62 (s, 5H), 1.44 – 1.33 (m, 4H), 1.27 – 1.17 (m, 3H), 1.14 – 0.99 (m, 10H), 0.95 (d, J = 6.6 Hz, 1H), 0.89 – 0.78 (m, 3H), 0.69 (td, J = 7.8, 4.0 Hz, 1H).	655.5
I-122A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.30 (m, 2H), 7.85 – 7.80 (m, 1H), 7.38 – 7.23 (m, 5H), 5.35 (s, 2H), 4.25 – 3.54 (m, 9H), 3.28 – 3.01 (m, 6H), 1.40 – 1.29 (m, 1H), 1.15 – 1.01 (m, 6H), 0.89 – 0.82 (m, 1H), 0.71 – 0.64 (m, 1H).	494.35
I-122B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.31 (m, 2H), 7.86 – 7.79 (m, 1H), 7.40 – 7.22 (m, 5H), 5.35 (s, 2H), 4.32 – 3.59 (m, 9H), 3.30 (s, 1H), 3.26 – 3.21 (m, 3H), 3.21 – 3.05 (m, 2H), 1.40 – 1.30 (m, 1H), 1.14 – 1.02 (m, 6H), 0.85 (s, 1H), 0.71 – 0.63 (m, 1H).	494.0
I-123 - 混合物	14	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.25 – 8.16 (m, 1H), 7.95 – 7.88 (m, 1H), 7.38 – 7.24 (m, 5H), 4.56 – 3.76 (m, 10H), 3.48 – 3.33 (m, 2H), 3.22 – 3.10 (m, 1H), 2.77 – 2.69 (m, 3H), 1.79 – 1.62 (m, 6H), 1.57 – 1.38 (m, 2H), 1.37 – 1.08 (m, 14H), 1.07 – 1.00 (m,	647.5

[1046]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 0.91 (q, J = 11.8 Hz, 2H), 0.77 (dd, J = 7.6, 4.0 Hz, 1H).	
I-123A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.31 (m, 1H), 8.25 – 8.1 (m, 1H), 7.88 – 7.68 (m, 2H), 7.4 – 7.21 (m, 5H), 5.35 (s, 2H), 4.31 – 4.03 (m, 3H), 4.03 – 3.58 (m, 7H), 3.55 – 3.38 (m, 1H), 3.26 – 3.16 (m, 1H), 3.15 – 3.05 (m, 1H), 2.63 – 2.55 (m, 3H), 1.71 – 1.56 (m, 5H), 1.50 – 1.26 (m, 2H), 1.22 – 0.99 (m, 12H), 0.91 – 0.75 (m, 3H), 0.70 – 0.63 (m, 1H).	647.5
I-123B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.16 (m, 2H), 7.88 – 7.68 (m, 2H), 7.38 – 7.20 (m, 5H), 5.35 (s, 2H), 4.39 – 4.19 (m, 2H), 4.13 (t, J = 8.4 Hz, 1H), 4.04 – 3.99 (m, 2H), 3.78 – 3.60 (m, 5H), 3.48 – 3.40 (m, 1H), 3.27 – 3.19 (m, 1H), 3.10 – 3.06 (m, 1H), 2.61 – 2.57 (m, 3H), 1.62 (br s, 6H), 1.43 – 1.33 (m, 2H), 1.11 (s, 5H), 1.07 – 1.05 (m, 3H), 1.02 – 0.99 (m, 2H), 0.96 (t, J = 6.4 Hz, 1H), 0.87 – 0.78 (m, 3H), 0.71 – 0.66 (m, 1H).	647.5
I-125	15	^{1}H NMR (400 MHz, CD_3OD): δ 7.91-7.97 (m, 2H), 7.18-7.22 (m, 5H), 4.88-4.93 (m, 1H), 4.32-4.57 (m, 4H), 3.71-4.17 (m, 10H), 3.27 (m, 1H), 2.25-2.43 (m, 2H), 1.89-1.99 (m, 1H), 1.58-1.72 (m, 1H), 1.19-1.23 (m, 1H), 1.08-1.16 (m, 5H), 1.02 (d, J = 9.6 Hz, 3H), 0.92-0.95 (m, 1H), 0.78-0.81 (m, 4H), 0.58-0.69 (m, 4H).	633.5
I-125A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.14 (m, 2H), 7.87 – 7.67 (m, 2H), 7.37 – 7.24 (m, 5H), 5.35 (s, 2H), 4.29 – 4.10 (m, 2H), 4.08 – 3.40 (m, 11H), 2.61 – 2.55 (m, 3H), 1.68 – 1.58 (m, 5H), 1.38 – 1.27 (m, 4H), 1.20 – 1.12 (m, 2H), 1.13 – 1.01 (m, 10H), 0.89 – 0.79 (m, 3H), 0.70 – 0.62 (m, 1H).	661.50
I-125B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.13 (m, 2H), 7.85 – 7.73 (m, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.39 – 4.13 (m, 2H), 4.12 – 3.39 (m, 11H), 2.63 – 2.57 (m, 3H), 1.61 (s, 5H), 1.39 – 1.27 (m, 4H), 1.14 – 0.93 (m,	661.65

[1047]

化合物编号	方法	^{1}HNMR	LCMS
		12H), 0.89 – 0.79 (m, 3H), 0.73 – 0.64 (m, 1H).	
I-126A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (t, J = 6.2 Hz, 1H), 8.37 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 10.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.38 – 7.24 (m, 5H), 6.84 (q, J = 8.0, 7.4 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 5.35 (s, 2H), 4.43 – 4.07 (m, 4H), 4.02 – 3.63 (m, 9H), 3.28 – 3.15 (m, 1H), 1.38 – 1.28 (m, 1H), 1.13 – 0.96 (m, 6H), 0.86 (d, J = 9.2 Hz, 1H), 0.67 (td, J = 8.2, 3.6 Hz, 1H).	557.40
I-126B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 – 8.72 (m, 1H), 8.36 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 11.3 Hz, 1H), 7.67 – 7.53 (m, 1H), 7.39 – 7.23 (m, 5H), 6.89 – 6.78 (m, 1H), 6.67 (d, J = 6.8 Hz, 1H), 5.35 (s, 2H), 4.40 (dd, J = 16.2, 6.0 Hz, 1H), 4.28 – 4.08 (m, 2H), 4.00 (d, J = 24.0 Hz, 3H), 3.83 (d, J = 9.3 Hz, 5H), 3.75 – 3.62 (m, 2H), 3.27 – 3.16 (m, 1H), 1.39 – 1.34 (m, 1H), 1.31 – 1.27 (m, 1H), 1.13 – 1.08 (m, 3H), 1.07 – 1.02 (m, 3H), 0.88 – 0.83 (m, 1H), 0.71 – 0.63 (m, 1H).	557.4
I-127A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 – 8.65 (m, 1H), 8.39 – 8.30 (m, 1H), 7.81 (d, J = 14.4 Hz, 1H), 7.41 – 7.00 (m, 9H), 5.34 (d, J = 5.6 Hz, 2H), 5.01 – 4.91 (m, 1H), 4.30 – 3.84 (m, 5H), 3.83 – 3.65 (m, 2H), 3.67 – 3.57 (m, 1H), 3.21 – 3.05 (m, 1H), 1.40 – 1.30 (m, 4H), 1.14 – 1.03 (m, 7H), 0.90 – 0.84 (m, 1H), 0.73 – 0.64 (m, 1H).	558.35
I-127B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 – 8.64 (m, 1H), 8.38 – 8.33 (m, 1H), 7.84 – 7.79 (m, 1H), 7.36 – 6.99 (m, 9H), 5.36 – 5.33 (m, 2H), 4.96 – 4.89 (m, 1H), 4.16 – 3.96 (m, 2H), 3.95 – 3.84 (m, 2H), 3.84 – 3.67 (m, 3H), 3.64 (s, 1H), 3.23 – 3.10 (m, 1H), 1.39 – 1.34 (m, 3H), 1.12 – 0.80 (m, 8H), 0.65 (d, J = 8.0 Hz, 1H).	558.4
I-128A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (m, 1H), 8.37 (s, 1H), 7.83 (d, J = 5.8 Hz, 1H), 7.39 – 7.22 (m, 6H), 7.15 (t, J = 7.9 Hz, 2H),	558.4

[1048]

化合物编号	方法	^{1}HNMR	LCMS
		7.04 (t, J = 8.7 Hz, 1H), 5.35 (s, 2H), 5.02 – 4.88 (m, 1H), 4.23 – 3.59 (m, 8H), 3.26 – 3.07 (m, 1H), 1.37 (d, J = 7.4 Hz, 3H), 1.26 (m, 1H), 1.12 – 0.90 (m, 6H), 0.82 (m, 1H), 0.70 – 0.60 (m, 1H).	
I-128B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75-8.69 (m, 1H), 8.36-8.32 (m, 1H), 7.83-7.79 (m, 1H), 7.37-7.23 (m, 6H), 7.16-7.12 (m, 2H), 8.75-8.69 (m, 1H), 7.37-7.23 (m, 6H), 7.16-7.12 (m, 2H), 7.07-7.05 (m, 1H), 5.35-5.34 (m, 2H), 4.97-4.93 (m, 1H), 4.34-4.18 (m, 1H), 4.13-3.96 (m, 2H), 3.93-3.89 (m, 1H), 3.83-3.74 (m, 2H), 3.71-3.61 (m, 2H), 3.21-3.13 (m, 1H), 1.38-1.35 (m, 4H), 1.12-1.02 (m, 6H), 0.86-0.85 (m, 1H), 0.71-0.68 (m, 1H).	558.4
I-129A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 – 9.22 (m, 1H), 8.42 – 8.32 (m, 1H), 8.27 – 8.18 (m, 1H), 7.81 – 7.68 (m, 1H), 4.29 – 4.05 (m, 4H), 4.03 – 3.77 (m, 4H), 3.77 – 3.44 (m, 3H), 3.26 – 3.19 (m, 1H), 3.14 – 3.06 (m, 1H), 2.61 – 2.54 (m, 3H), 1.70 – 1.58 (m, 5H), 1.48 – 1.38 (m, 1H), 1.37 – 1.27 (m, 1H), 1.26 – 1.11 (m, 4H), 1.10 – 1.06 (m, 3H), 1.05 – 0.99 (m, 5H), 0.90 – 0.77 (m, 3H), 0.71 – 0.64 (m, 1H).	574.4
I-129B	1B	^{1}H NMR (DMSO, 400 MHz) δ 0.68 (1H, m), 0.77 – 0.89 (3H, m), 0.96 (1H, t, J=5.8 Hz), 1.02 (2H, d, J=6.2 Hz), 1.06 (3H, d, J=6.0 Hz), 1.08 – 1.23 (6H, m), 1.34 (2H, m), 1.56 – 1.68 (5H, m), 2.59 (3H, t, J=4.8 Hz), 3.04 – 3.12 (1H, m), 3.17 – 3.29 (2H, m), 3.42 – 3.52 (1H, m), 3.63 – 3.87 (5H, m), 3.98 – 4.27 (4H, m), 4.29 – 4.41 (1H, m), 7.77 – 7.89 (1H, m), 8.24 – 8.41 (2H, m), 9.25 (1H, s).	574.40
I-130A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.32 (m, 1H), 8.14 – 8.04 (m, 1H), 7.87 – 7.79 (m, 1H), 7.79 – 7.69 (m, 1H), 7.39 – 7.22 (m, 5H), 5.36 (s, 2H), 4.33 – 3.59 (m, 11H), 3.15 – 3.08 (m, 1H), 3.00 – 2.90 (m, 1H), 2.61 – 2.55 (m, 3H), 1.37 – 1.20 (m, 2H), 1.12 –	621.45

[1049]

化合物编号	方法	^{1}HNMR	LCMS
		1.01 (m, 9H), 0.85 – 0.81 (m, 9H), 0.69 – 0.65 (m, 1H).	
I-130B	2B	^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 – 8.12 (m, 2H), 7.90 – 7.70 (m, 2H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 4.37 – 4.25 (m, 1H), 4.17 – 3.55 (m, 9H), 3.51 – 3.37 (m, 1H), 3.15 – 3.06 (m, 1H), 2.99 – 2.89 (m, 1H), 2.62 – 2.55 (m, 3H), 1.40 – 1.31 (m, 1H), 1.14 – 1.09 (m, 3H), 1.07 – 1.01 (m, 5H), 1.00 – 0.96 (m, 1H), 0.89 – 0.85 (m, 1H), 0.85 – 0.80 (m, 6H), 0.80 – 0.77 (m, 3H), 0.72 – 0.64 (m, 1H).	621.1
I-131A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.24 (m, 2H), 7.87 – 7.81 (m, 1H), 7.39 – 7.23 (m, 5H), 5.36 (s, 2H), 4.26 – 3.56 (m, 12H), 3.31 – 3.27 (m, 4H), 3.09 – 3.04 (m, 2H), 1.84 – 1.73 (m, 1H), 1.44 – 1.30 (m, 2H), 1.13 – 1.03 (m, 6H), 0.89 – 0.82 (m, 1H), 0.71 – 0.65 (m, 1H).	550.4
I-131B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.25 (m, 2H), 7.87 – 7.79 (m, 1H), 7.40 – 7.22 (m, 5H), 5.35 (s, 2H), 4.34 – 3.58 (m, 12H), 3.30 (s, 2H), 3.25 – 3.22 (m, 1H), 3.18 – 2.99 (m, 3H), 1.78 (s, 1H), 1.48 – 1.29 (m, 2H), 1.14 – 1.03 (m, 6H), 0.88 – 0.81 (m, 1H), 0.73 – 0.64 (m, 1H).	550.0
I-132	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 – 8.40 (m, 1H), 8.36 – 8.33 (m, 1H), 7.96 – 7.91 (m, 1H), 5.17 (q, J=9.2 Hz, 2H), 4.88 – 4.85 (m, 1H), 4.24 – 3.94 (m, 4H), 3.89 – 3.82 (m, 1H), 3.77 – 3.67 (m, 2H), 3.61 – 3.58 (m, 2H), 3.51 – 3.40 (m, 5H), 3.25 – 3.22 (m, 1H), 3.17 – 3.13 (m, 1H), 1.69 – 1.58 (m, 6H), 1.44 – 1.23 (m, 7H), 1.19 – 1.09 (m, 6H), 1.06 – 1.03 (m, 6H), 0.86 – 0.85 (m, 1H), 0.69 – 0.67 (m, 1H).	693.3
I-133A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 – 8.62 (m, 1H), 8.42 – 8.35 (m, 1H), 7.88 – 7.80 (m, 1H), 7.41 – 7.22 (m, 6H), 7.21 – 7.06 (m,	586.35

[1050]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 5.36 (s, 2H), 5.33 – 5.26 (m, 1H), 4.29 – 3.75 (m, 7H), 3.69 – 3.63 (m, 1H), 3.23 – 3.01 (m, 1H), 2.99 – 2.90 (m, 1H), 2.88 – 2.77 (m, 1H), 2.46 – 2.39 (m, 1H), 1.90 – 1.75 (m, 1H), 1.41 – 1.21 (m, 1H), 1.11 – 0.99 (m, 6H), 0.90 – 0.83 (m, 1H), 0.71 – 0.64 (m, 1H).	
I-133B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 – 8.60 (m, 1H), 8.41 – 8.36 (m, 1H), 7.88 – 7.81 (m, 1H), 7.38 – 7.14 (m, 8H), 5.36 (s, 2H), 5.27 – 5.20 (m, 1H), 4.35 – 4.02 (m, 3H), 3.99 – 3.80 (m, 3H), 3.78 – 3.64 (m, 2H), 3.21 – 3.04 (m, 1H), 2.97 – 2.75 (m, 2H), 2.46 – 2.31 (m, 1H), 1.87 – 1.76 (m, 1H), 1.39 – 1.33 (m, 1H), 1.14 – 1.09 (m, 3H), 1.07 – 1.04 (m, 3H), 0.88 – 0.83 (m, 1H), 0.73 – 0.66 (m, 1H).	586.30
I-134A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38-8.36 (m, 1H), 8.27-8.16(m, 1H), 7.84-7.81 (m, 1H), 7.37-7.27 (m, 5H), 5.35 (s, 2H), 4.26-4.15 (m, 1H), 4.12-3.86 (m, 6H), 3.77-3.71 (m, 3H), 3.66-3.61 (m, 1H), 3.43-3.38 (m, 1H), 3.31-3.21 (m, 6H), 1.75-1.73 (m, 1H), 1.46-1.44 (m, 1H), 1.35-1.30 (m, 1H), 1.12-1.02 (m, 6H), 0.86-0.84 (m, 1H), 0.70-0.65 (m, 1H).	550.4
I-134B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37-8.35 (m, 1H), 8.30-8.17 (m, 1H), 7.84-7.81 (m, 1H), 7.35-7.25 (m, 5H), 5.35 (s, 2H), 4.36-4.16 (m, 1H), 4.08-3.83 (m, 6H), 3.80-3.57 (m, 5H), 3.28-3.20 (m, 6H), 1.76-1.74 (m, 1H), 1.46-1.44 (m, 1H), 1.38-1.24 (m, 1H), 1.11-1.05 (m, 6H), 0.86-0.83 (m, 1H), 0.70-0.68 (m, 1H).	550.3
I-135A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 11.0 Hz, 1H), 7.93 – 7.79 (m, 2H), 7.40 – 7.22 (m, 5H), 5.35 (s, 2H), 4.69 – 4.54 (m, 1H), 4.32 – 3.92 (m, 4H), 3.89 – 3.68 (m, 4H), 3.66 – 3.38 (m, 4H), 3.28 – 3.22 (m, 1H), 3.16 – 3.08 (m, 1H), 1.78 – 1.58 (m, 5H), 1.48 (s, 1H), 1.32 (d, J = 30.6 Hz, 1H), 1.24 – 1.12 (m, 3H), 1.11 – 1.02 (m, 6H),	620.5

[1051]

化合物编号	方法	^{1}HNMR	LCMS
		1.01 – 0.94 (m, 3H), 0.92 – 0.81 (m, 3H), 0.72 – 0.61 (m, 1H).	
I-135B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 12.4 Hz, 1H), 7.91 – 7.74 (m, 2H), 7.41 – 7.20 (m, 5H), 5.35 (s, 2H), 4.62 (dd, J = 10.4, 5.4 Hz, 1H), 4.35 (t, J = 8.2 Hz, 1H), 4.10 – 3.90 (m, 3H), 3.85 – 3.70 (m, 4H), 3.65 – 3.38 (m, 4H), 3.29 – 3.23 (m, 1H), 3.10 (t, J = 8.2 Hz, 1H), 1.71 – 1.63 (m, 5H), 1.46 (s, 1H), 1.35 (s, 1H), 1.25 – 1.14 (m, 3H), 1.13 – 1.09 (m, 5H), 1.05 (d, J = 3.4 Hz, 2H), 1.01 – 0.92 (m, 3H), 0.86 (s, 2H), 0.68 (s, 1H).	620.5
I-136A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.27 (m, 2H), 7.9 – 7.78 (m, 2H), 7.39 – 7.28 (m, 4H), 7.16 (q, J = 9.4 Hz, 4H), 5.34 (s, 2H), 4.56 – 4.30 (m, 3H), 4.26 – 4.12 (m, 1H), 4.09 – 3.59 (m, 8H), 3.56 – 3.38 (m, 1H), 2.64 – 2.55 (m, 3H), 1.35 – 1.21 (m, 1H), 1.15 – 0.99 (m, 9H), 0.84 (t, J = 4.8 Hz, 1H), 0.69 – 0.56 (m, 1H).	677.5
I-136B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.30 (m, 2H), 7.94 – 7.77 (m, 2H), 7.37 – 7.26 (m, 4H), 7.21 – 7.09 (m, 4H), 5.34 (s, 2H), 4.50 (t, J = 13.0 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.13 (t, J = 8.2 Hz, 1H), 4.08 – 3.91 (m, 3H), 3.90 – 3.76 (m, 2H), 3.75 – 3.64 (m, 2H), 3.63 – 3.57 (m, 1H), 3.53 – 3.39 (m, 1H), 2.62 – 2.58 (m, 3H), 1.39 – 1.32 (m, 1H), 1.13 – 1.00 (m, 9H), 0.89 – 0.83 (m, 1H), 0.73 – 0.64 (m, 1H).	677.45
I-137A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.6 Hz, 1H), 8.25 – 8.15 (m, 1H), 7.82 (d, J = 15.4 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.40 – 7.21 (m, 5H), 5.35 (s, 2H), 4.29 – 4.02 (m, 3H), 4.00 – 3.56 (m, 7H), 3.53 – 3.39 (m, 1H), 3.22 – 3.15 (m, 1H), 3.11 – 3.03 (m, 1H), 2.61 – 2.55 (m, 3H), 1.71 (dt, J = 13.4, 6.6 Hz, 1H), 1.38 – 1.27 (m, 1H), 1.13 – 1.01 (m, 9H), 0.88 – 0.84 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H), 0.69 – 0.64 (m, 1H).	607.45
I-137B	2B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.25 – 8.16 (m, 1H), 7.91 (d, J = 16.8 Hz, 1H), 7.38 –	607.45

[1052]

化合物编号	方法	^{1}HNMR	LCMS
		7.25 (m, 5H), 5.38 (s, 2H), 4.58 (s, 1H), 4.37 (q, J = 4.8 Hz, 1H), 4.27 – 3.77 (m, 9H), 3.47 – 3.37 (m, 1H), 3.14 – 3.08 (m, 1H), 2.75 (s, 3H), 1.77 (dq, J = 12.8, 6.2 Hz, 1H), 1.52 – 1.39 (m, 1H), 1.19 – 1.11 (m, 8H), 1.04 (d, J = 6.7 Hz, 2H), 0.87 (ddd, J = 11.2, 5.4, 2.4 Hz, 6H), 0.79 (dd, J = 8.0, 4.2 Hz, 1H).	
I-138	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.4 Hz, 1H), 4.89-4.95 (m, 1H), 4.22-4.40 (m, 3H), 3.87-4.18 (m, 6H), 3.55-3.75 (m, 10H), 3.33-3.38 (m, 1H), 3.19-3.24 (m, 1H), 1.66-1.76 (m, 5H), 1.49-1.55 (m, 1H), 1.11-1.22 (m, 12H), 0.90-0.90 (m, 3H), 0.76-0.82 (m, 1H).	630.4
I-139	26A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 – 8.60 (m, 1H), 8.26 – 8.18 (m, 2H), 7.95 – 7.89 (m, 2H), 7.36 – 7.19 (m, 10H), 5.39 – 5.37 (m, 2H), 4.44 – 4.14 (m, 3H), 4.12 – 3.76 (m, 7H), 3.48 – 3.35 (m, 1H), 1.41 – 1.33 (m, 1H), 1.20 – 1.13 (m, 2H), 1.11 – 1.09 (m, 2H), 1.01 – 0.96 (m, 1H), 0.90 – 0.84 (m, 2H), 0.77 – 0.71 (m, 1H).	603.0
I-140A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 – 8.55 (m, 1H), 8.36 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 11.8 Hz, 1H), 7.40 – 7.14 (m, 8H), 7.10 – 7.03 (m, 1H), 5.35 (s, 2H), 4.27 – 3.60 (m, 8H), 3.15 – 2.96 (m, 1H), 2.83 (s, 1H), 1.93 (d, J = 43.0 Hz, 1H), 1.41 – 1.31 (m, 1H), 1.28 – 1.15 (m, 2H), 1.14 – 1.02 (m, 5H), 0.97 (d, J = 9.8 Hz, 1H), 0.90 – 0.82 (m, 1H), 0.73 – 0.63 (m, 1H).	586.3
I-140B	2B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.17 (m, 1H), 7.92 (d, J = 10.6 Hz, 1H), 7.39 – 7.12 (m, 8H), 7.09 – 7.02 (m, 1H), 5.37 (s, 2H), 4.51 – 3.78 (m, 8H), 3.19 – 3.07 (m, 1H), 2.93 – 2.82 (m, 1H), 2.10 – 1.90 (m, 1H), 1.47 – 1.37 (m, 1H), 1.28 – 1.04 (m, 9H), 0.78 (td, J = 8.4, 4.0 Hz, 1H).	586.3
I-141A	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.28 – 8.15 (m, 1H), 7.92 (d, J = 10.0 Hz, 1H), 7.47 – 7.16 (m, 5H), 5.38 (s, 2H), 4.58 (s, 1H), 4.43 – 4.30 (m, 2H), 4.26 – 4.15 (m, 2H), 4.08 –	715.5

[1053]

化合物编号	方法	^{1}HNMR	LCMS
		3.98 (m, 3H), 3.92 – 3.80 (m, 2H), 3.57 – 3.41 (m, 2H), 2.77 – 2.72 (m, 3H), 2.18 (d, *J* = 11.6 Hz, 1H), 1.88 (s, 1H), 1.67 (d, *J* = 11.8 Hz, 4H), 1.55 – 1.50 (m, 3H), 1.45 – 1.38 (m, 1H), 1.37 – 1.32 (m, 1H), 1.30 (d, *J* = 7.6 Hz, 1H), 1.21 – 1.17 (m, 3H), 1.16 (d, *J* = 4.2 Hz, 3H), 1.13 (d, *J* = 5.4 Hz, 1H), 1.11 (s, 2H), 1.03 (d, *J* = 5.2 Hz, 1H), 0.77 (dd, *J* = 8.0, 4.2 Hz, 1H).	
I-141B	2B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.29 – 8.14 (m, 1H), 7.91 (d, *J* = 17.0 Hz, 1H), 7.41 – 7.22 (m, 5H), 5.38 (s, 2H), 4.64 – 4.51 (m, 1H), 4.43 – 4.34 (m, 1H), 4.27 – 4.07 (m, 3H), 3.99 – 3.85 (m, 4H), 3.84 – 3.74 (m, 1H), 3.55 – 3.40 (m, 2H), 2.74 (d, *J* = 2.8 Hz, 3H), 2.14 (s, 1H), 1.86 (s, 1H), 1.66 (d, *J* = 10.0 Hz, 3H), 1.50 (dd, *J* = 8.0, 5.4 Hz, 4H), 1.30 (d, *J* = 10.6 Hz, 1H), 1.21 – 1.13 (m, 6H), 1.12 (d, *J* = 4.8 Hz, 2H), 1.08 – 1.02 (m, 2H), 0.79 (dd, *J* = 7.8, 4.2 Hz, 1H).	715.5
I-142A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (d, *J* = 3.8 Hz, 1H), 8.36 (d, *J* = 12.0 Hz, 1H), 7.83 (d, *J* = 10.8 Hz, 1H), 7.47 – 7.13 (m, 5H), 5.35 (s, 2H), 4.91 – 4.78 (m, 2H), 4.58 – 4.45 (m, 2H), 4.35 – 3.94 (m, 4H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.78 (dd, *J* = 15.0, 8.8 Hz, 2H), 3.65 (dd, *J* = 15.6, 5.8 Hz, 4H), 3.25 – 3.11 (m, 1H), 1.44 – 1.29 (m, 1H), 1.13 – 1.08 (m, 3H), 1.06 (d, *J* = 11.2 Hz, 3H), 0.86 (s, 1H), 0.69 (dd, *J* = 8.0, 3.8 Hz, 1H).	550.3
I-142B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (d, *J* = 16.4 Hz, 1H), 8.33 (d, *J* = 12.0 Hz, 1H), 7.79 (d, *J* = 12.0 Hz, 1H), 7.40 – 7.20 (m, 5H), 5.32 (s, 2H), 4.89 – 4.78 (m, 2H), 4.50 (dd, *J* = 11.8, 5.4 Hz, 2H), 4.30 (d, *J* = 9.4 Hz, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 4.02 – 3.86 (m, 4H), 3.79 – 3.67 (m, 2H), 3.64 – 3.58 (m, 4H), 3.14 (d, *J* = 5.4 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 1H), 1.08 (t, *J* = 2.4 Hz, 3H), 1.03 (d, *J* = 7.8 Hz, 3H), 0.83 (s, 1H), 0.66 (s, 1H).	550.3

[1054]

化合物编号	方法	^{1}HNMR	LCMS
I-143	4B	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.50 (s, 1H), 10.61 (s, 0.5H), 8.72 – 8.68 (m, 1H), 7.94 – 7.92 (m, 2H), 7.61 (d, J=8.4 Hz, 1H), 7.44 (t, J=7.2 Hz, 1H), 7.33 – 7.22 (m, 5.5H), 4.87 – 4.72 (m, 2H), 4.56 – 4.53 (m, 1H), 4.46 – 4.42 (m, 1H), 4.36 – 4.34 (m, 1H), 4.25 – 4.08 (m, 1H), 4.00 – 3.85 (m, 4H), 3.70 – 3.65 (m, 5H), 2.60 – 2.59 (m, 3H), 1.31 – 1.23 (m, 1H), 1.11 – 1.03 (m, 9H), 0.86 – 0.84 (m, 1H), 0.70 – 0.68 (m, 7H).	587
I-144A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.4 Hz, 1H), 8.27 – 8.15 (m, 1H), 7.86 – 7.70 (m, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.29 – 3.62 (m, 10H), 3.51 – 3.37 (m, 2H), 3.29 (s, 1H), 2.62 – 2.55 (m, 3H), 2.46 – 2.38 (m, 1H), 1.98 – 1.88 (m, 2H), 1.84 – 1.76 (m, 2H), 1.70 – 1.59 (m, 2H), 1.38 – 1.26 (m, 1H), 1.12 – 1.01 (m, 9H), 0.88 – 0.83 (m, 1H), 0.70 – 0.64 (m, 1H).	619.45
I-144B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 – 8.27 (m, 1H), 8.21 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 17.8 Hz, 2H), 7.36 – 7.21 (m, 5H), 5.33 (s, 2H), 4.38 – 3.74 (m, 12H), 3.28 – 3.23 (m, 1H), 2.60 – 2.56 (m, 3H), 2.42 – 2.31 (m, 1H), 1.95 – 1.82 (m, 2H), 1.80 – 1.70 (m, 2H), 1.66 – 1.53 (m, 2H), 1.38 – 1.31 (m, 1H), 1.12 – 0.95 (m, 9H), 0.89 – 0.81 (m, 1H), 0.72 – 0.64 (m, 1H).	619.4
I-145A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 – 8.16 (m, 2H), 7.83 – 7.66 (m, 1H), 4.72 (s, 2H), 4.29 – 3.64 (m, 11H), 3.62 – 3.46 (m, 1H), 3.32 (s, 4H), 3.26 – 3.19 (m, 1H), 3.14 – 3.07 (m, 1H), 2.58 (dd, J = 11.4, 4.4 Hz, 3H), 1.71 – 1.58 (m, 5H), 1.49 – 1.26 (m, 2H), 1.20 – 1.00 (m, 12H), 0.89 – 0.75 (m, 3H), 0.69 – 0.63 (m, 1H).	618.0
I-145B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.16 (m, 2H), 7.91 – 7.77 (m, 1H), 4.71 (d, J = 2.0 Hz, 2H), 4.39 – 4.29 (m, 1H), 4.25 (dd, J = 8.8, 4.4 Hz, 1H), 4.21 – 4.10 (m, 1H), 4.03 (m, 2H), 3.75 (m, 5H), 3.54 – 3.44 (m, 1H), 3.42 (d, J = 1.6 Hz, 3H), 3.29 – 3.18 (m, 2H),	618.5

[1055]

化合物编号	方法	^{1}HNMR	LCMS
		3.09 (dt, *J* = 9.6, 6.8 Hz, 1H), 2.59 (t, *J* = 4.8 Hz, 3H), 1.61 (d, *J* = 13.0 Hz, 5H), 1.34 (m, 2H), 1.17 (m, 2H), 1.13 – 1.11 (m, 3H), 1.08 – 1.05 (m, 3H), 1.04 – 1.00 (m, 2H), 0.96 (t, *J* = 5.4 Hz, 1H), 0.86 (d, J = 9.6 Hz, 2H), 0.80 (m, 1H), 0.68 (m, 1H).	
I-146	1B	^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (q, J = 16.0, 9.0 Hz, 1H), 8.06 – 8.00 (m, 2H), 7.91 – 7.77 (m, 1H), 4.51 – 4.33 (m, 1H), 4.30 – 3.98 (m, 4H), 3.92 – 3.59 (m, 5H), 3.53 – 3.39 (m, 1H), 3.28 – 3.20 (m, 1H), 3.13 – 3.02 (m, 1H), 2.61 – 2.57 (m, 3H), 1.68 – 1.55 (m, 5H), 1.45 – 1.33 (m, 2H), 1.28 – 1.10 (m, 6H), 1.07 – 1.04 (m, 3H), 1.02 (dd, J = 6.4, 2.4 Hz, 2H), 0.97 (t, J = 5.8 Hz, 1H), 0.90 – 0.78 (m, 3H), 0.71 – 0.65 (m, 1H).	574.4
I-147	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 – 8.30 (m, 2H), 7.93 – 7.78 (m, 3H), 7.39 – 7.22 (m, 7H), 5.35 (s, 2H), 4.97 – 4.88 (m, 1H), 4.60 – 4.49 (m, 1H), 4.22 – 3.91 (m, 5H), 3.83 (s, 3H), 3.76 – 3.59 (m, 4H), 3.28 – 3.09 (m, 4H), 2.95 – 2.84 (m, 1H), 2.64 – 2.54 (m, 4H), 2.46 – 2.41 (m, 1H), 1.90 – 1.81 (m, 1H), 1.70 – 1.56 (m, 5H), 1.50 – 1.29 (m, 3H), 1.12 – 1.04 (m, 10H), 0.90 – 0.81 (m, 3H), 0.71 – 0.64 (m, 1H).	835.4
I-148A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.27 (m, 2H), 7.83 (d, *J* = 11.8 Hz, 1H), 7.44 – 7.18 (m, 5H), 5.36 (s, 2H), 4.28 – 4.12 (m, 1H), 4.10 – 4.05 (m, 1H), 4.05 – 3.81 (m, 4H), 3.80 – 3.67 (m, 4H), 3.63 (t, *J* = 5.2 Hz, 1H), 3.31 – 3.28 (m, 3H), 3.24 (d, *J* = 2.8 Hz, 1H), 3.16 – 2.98 (m, 3H), 1.77 (d, *J* = 13.0 Hz, 1H), 1.45 – 1.28 (m, 2H), 1.14 – 1.08 (m, 3H), 1.07 – 1.01 (m, 3H), 0.85 (dd, *J* = 5.4, 3.6 Hz, 1H), 0.72 – 0.62 (m, 1H).	550.4
I-148B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.18 (m, 2H), 7.83 (d, *J* = 13.0 Hz, 1H), 7.38 – 7.23 (m, 5H), 5.35 (s, 2H), 4.37 – 3.55 (m, 12H), 3.30 – 3.25 (m, 3H), 3.18 – 3.01 (m, 3H), 1.82 – 1.73 (m, 1H), 1.46 – 1.27 (m,	550.4

[1056]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 1.14 – 1.02 (m, 6H), 0.88 – 0.83 (m, 1H), 0.71 – 0.65 (m, 1H).	
I-149 –混合物	15	^{1}H NMR (400 MHz, CD_3CD) δ 8.17-8.23 (m, 2H), 7.95 (d, *J* = 12.4 Hz, 1H), 7.27-7.36 (m, 5H), 5.37 (s, 2H), 4.30-4.40 (m, 1H), 3.92-4.25 (m, 6H), 3.66-3.87 (m, 18H), 3.54-3.60 (m, 1H), 3.30-3.46 (m, 2H), 3.18-3.23 (m, 1H), 1.88-2.12 (m, 4H), 1.65-1.75 (m, 4H), 1.39-1.55 (m, 2H), 1.24-1.33 (m, 3H), 1.10-1.18 (m, 9H), 1.02-1.04 (m, 1H), 0.86-0.92 (m, 2H), 0.72-0.80 (m, 1H).	737.5
I-149A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.21–8.26 (m, 1H), 7.94 (d, *J* = 12.8 Hz, 1H), 7.29-7.39 (m, 5H), 5.40 (s, 2H), 4.95-4.98 (m, 1H), 4.53-4.56 (m, 0.6H), 3.72-4.29 (m, 11.3H), 3.38-3.41 (m, 2H), 3.18-3.24 (m, 1H), 1.97-2.07 (m, 4H), 1.40-1.73 (m, 7H), 1.12-1.31 (m, 13H), 1.06 (s, 1H), 0.92-0.96 (m, 2H), 0.78-0.81 (m, 1H).	737.5
I-149B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 8.18-8.23 (m, 1H), 7.92 (d, *J* = 12.8 Hz, 1H), 7.26-7.37 (m, 5H), 5.36-5.38 (m, 2H), 4.95-4.99 (m, 1H), 3.55-4.40 (m, 15H), 3.33-3.38 (m, 1H), 3.19-3.24 (m, 1H), 1.86-2.05 (m, 4H), 1.65-1.77 (m, 5H), 1.03-1.25 (m, 14H), 0.91-0.97 (m, 2H), 0.76-0.80 (m, 1H).	737.4
I-150 - 混合物	15	^{1}HNMR (400 MHz, MeOD):δ 8.46-8.49 (m, 1H), 8.20–8.25 (m, 1H), 7.92–7.95 (m, 1H), 7.31-7.37 (m, 5H), 5.40 (s, 2H), 3.59-4.64 (m, 13H), 3.37-3.40 (m, 2H), 3.20-3.24 (m, 1H), 2.48-2.91 (m, 3H), 2.10-2.19 (m, 1H), 1.92-2.02 (m, 1H), 1.13-1.89 (m, 21H), 1.04-1.08 (m, 1H), 0.90-1.00 (m, 2H), 0.79-0.83 (m, 1H). 分离为 HCl 盐	717.1
I-150A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.21-8.26 (m, 1H), 7.92-7.95 (m, 1H), 7.29-7.39 (m, 5H), 5.40 (s, 2H), 4.90-4.94 (m, 1H), 3.67-4.39 (m, 12H), 3.36-3.66 (m, 4H), 3.18-3.28 (m, 2H), 2.08-2.16 (m, 1H), 1.85-1.99 (m, 1H), 1.50-1.80 (m, 9H), 1.13-1.27 (m, 12H), 0.94-1.00 (m, 2H), 0.78-0.81 (m, 1H).	717.1

[1057]

化合物编号	方法	^{1}HNMR	LCMS
I-150B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 8.21-8.26 (m, 1H), 7.92-7.95 (m, 1H), 7.29-7.39 (m, 5H), 5.40 (s, 2H), 4.90-4.94 (m, 1H), 3.67-4.39 (m, 12H), 3.36-3.66 (m, 4H), 3.18-3.28 (m, 2H), 2.08-2.16 (m, 1H), 1.85-1.99 (m, 1H), 1.50-1.80 (m, 9H), 1.13-1.27 (m, 12H), 0.94-1.00 (m, 2H), 0.78-0.81 (m, 1H).	717.1
I-151A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.16-8.20 (m, 1H), 7.96-7.99 (m, 1H), 4.93-4.97 (m, 1H), 4.54-4.58 (m, 1H), 3.71-4.29 (m, 9H), 3.57-3.64 (m, 4H), 3.35-3.42 (m, 2H), 3.15-3.23 (m, 1H), 1.42-1.72 (m, 12H), 1.03-1.31 (m, 13H), 0.90-0.97 (m, 2H), 0.76-0.81 (m, 1H).	611.5
I-151B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 7.93-8.28 (m, 2H), 4.93-4.95 (m, 2H), 3.74-4.56 (m, 9H), 3.45-3.64 (m, 4H), 3.35-3.44 (m, 2H), 3.17-3.25 (m, 1H), 1.37-1.76 (m, 12H), 1.11-1.35 (m, 12H), 1.00-1.05(m, 1H), 0.89-0.97 (m, 2H), 0.75-0.85 (m, 1H).	611.4
I-152 - 混合物	15	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 2H), 7.33-7.39 (m, 3H), 7.21-7.25 (m, 1H), 6.81-6.91 (m, 1H), 5.31 (s, 2H), 4.91-4.96 (m, 1H), 3.45-4.22 (m, 18H), 3.29-3.33 (m, 1H), 3.15-3.20 (m, 1H), 3.02-3.07 (m, 1H), 1.67-1.74 (m, 6H), 1.44-1.51 (m, 1H), 1.07-1.22 (m, 12H), 0.86-0.92 (m, 2H), 0.72-0.76 (m, 1H).	703.5
I-152A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.21-8.26 (m, 1H), 7.94 (d, J = 13.6 Hz, 1H), 7.31-7.39 (m, 5H), 5.40 (s, 2H), 4.89-4.93 (m, 1H), 4.53-4.57 (m, 0.6H), 3.62-4.29 (m, 15.4H), 3.37-3.42 (m, 2H), 3.18-3.24 (m, 1H), 1.71-1.77 (m, 5H), 1.13-1.50 (m, 15H), 1.04-1.06 (m, 1H), 0.91-0.96 (m, 2H), 0.80 (dd, J = 8.2, 4.2 Hz, 1H).	703.5
I-152B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 8.21 (d, J = 18.4 Hz, 1H), 7.92 (d, J = 12.8 Hz, 1H), 7.28-7.35 (m, 5H), 5.38 (s, 2H), 4.90-4.93 (m, 1H), 3.60-4.37 (m, 18H), 3.33-3.45 (m, 2H), 3.18-3.25 (m, 1H), 1.64-1.78 (m, 5H),	703.4

[1058]

化合物编号	方法	^{1}HNMR	LCMS
		1.47-1.57 (m, 1H), 1.04-1.24 (m, 13H), 0.89-0.94 (m, 2H), 0.74-0.82 (m, 1H).	
I-153 - 混合物	15	^{1}H NMR (400 MHz, CD_3CD) δ 8.19-8.24 (m, 2H), 7.89-7.95 (m, 1H), 7.28-7.36 (m, 5H), 5.37 (s, 2H), 4.34-4.57 (m, 2H), 3.91-4.25 (m, 8H), 3.66-3.77 (m, 4H), 3.54-3.62 (m, 1H), 3.31-3.42 (m, 2H), 3.18-3.23 (m, 1H), 1.67-1.76 (m, 4H), 1.48-1.56 (m, 4H), 1.24-1.30 (m, 9H), 1.10-1.18 (m, 10H), 1.02-1.04 (m, 1H), 0.86-0.94 (m, 2H), 0.76-0.80 (m, 1H).	701.5
I-153A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.20-8.26 (m, 1H), 7.94 (d, J = 15.2 Hz, 1H), 7.31-7.39 (m, 5H), 5.40 (s, 2H), 4.39-4.58 (m, 2H), 3.62-4.26 (m, 13H), 3.36-3.43 (m, 2H), 3.20-3.26 (m, 1H), 1.69-1.76 (m, 5H), 1.13-1.53 (m, 20H), 1.04-1.08 (m, 1H), 0.94-0.98 (m, 2H), 0.80 (dd, J = 8.0, 4.2 Hz, 1H).	701.5
I-153B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 8.19-8.23 (m, 1H), 7.92 (d, J = 12.0 Hz, 1H), 7.27-7.37 (m, 5H), 5.38 (s, 2H), 3.59-4.46 (m, 16H), 3.35-3.37 (m, 1H), 3.22-3.26 (m, 1H), 1.49-1.80 (m, 7H), 1.10-1.26 (m, 16H), 1.03-1.05 (m, 1H), 0.89-0.97 (m, 3H), 0.76-0.80 (m, 1H).	701.4
I-154A	16A	^{1}HNMR (400 MHz, DMSO-d6): δ 13.22 (brs, 1H), 8.49-5.57 (m, 1H), 8.14-8.19 (m, 1H), 7.80-7.84 (m, 1H), 4.85-4.87 (m, 1H), 3.89-4.28 (m, 4H), 3.59-3.79 (m, 7H), 3.35-3.48 (m, 1H), 3.24-3.29 (m, 1H), 3.13-3.17 (m, 1H), 1.86-2.02 (m, 4H), 1.59-1.68 (m, 4H), 1.32-1.47 (m, 2H), 1.21-1.31 (m, 3H), 1.02-1.15 (m, 10H), 0.80-0.87 (m, 5H), 0.66-0.68 (m, 1H).	647.4
I-154B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 7.95-8.16 (m, 2H), 5.00 (s, 1H), 3.50-4.39 (m, 12H), 3.35-3.48 (m, 2H), 3.20 (s, 1H), 1.84-2.19 (m, 4H), 1.37-1.80 (m, 7H), 0.78-1.25 (m, 15H).	647.4
I-155A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 – 8.33 (m, 2H), 7.94 – 7.87 (m, 1H), 7.82 (d, J = 13.6 Hz, 1H), 7.38 – 7.23 (m, 5H), 5.35 (s,	631.5

[1059]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 4.26 – 4.09 (m, 2H), 4.08 – 4.01 (m, 1H), 3.99 – 3.88 (m, 2H), 3.86 – 3.56 (m, 4H), 3.29 – 3.13 (m, 1H), 2.59 – 2.54 (m, 3H), 1.70 – 1.56 (m, 6H), 1.49 – 1.39 (m, 1H), 1.37 – 1.26 (m, 2H), 1.22 – 1.08 (m, 10H), 1.06 – 1.02 (m, 3H), 0.89 – 0.77 (m, 3H), 0.66 (dd, J = 7.8, 3.8 Hz, 1H).	
I-155B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.31 (m, 2H), 7.98 – 7.76 (m, 2H), 7.39 – 7.29 (m, 3H), 7.28 – 7.23 (m, 2H), 5.35 (s, 2H), 4.38 – 4.10 (m, 2H), 4.09 – 3.88 (m, 3H), 3.85 – 3.54 (m, 4H), 3.31 – 3.19 (m, 1H), 2.57 (t, J = 4.8 Hz, 3H), 1.74 – 1.63 (m, 1H), 1.62 – 1.52 (m, 5H), 1.51 – 1.43 (m, 1H), 1.35 (t, J = 6.8 Hz, 1H), 1.25 – 1.09 (m, 10H), 1.08 – 1.01 (m, 4H), 0.91 – 0.74 (m, 3H), 0.73 – 0.60 (m, 1H).	631.5
I-156A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 – 8.16 (m, 1H), 8.14 – 8.04 (m, 1H), 7.84 – 7.68 (m, 1H), 4.29 – 4.04 (m, 4H), 4.00 – 3.60 (m, 6H), 3.57 – 3.42 (m, 1H), 3.26 – 3.19 (m, 1H), 3.14 – 3.06 (m, 1H), 2.67 (s, 3H), 2.62 – 2.54 (m, 3H), 1.72 – 1.57 (m, 5H), 1.50 – 1.27 (m, 2H), 1.20 – 1.00 (m, 12H), 0.89 – 0.77 (m, 3H), 0.70 – 0.62 (m, 1H).	588.0
I-156B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41-8.25 (m, 1H), 8.11-8.06 (m, 1H), 7.88-7.81 (m, 1H), 4.37-4.30 (m, 1H), 4.26-4.16 (m, 1H), 4.12-4.03 (m, 2H), 4.01-3.97 (m, 1H), 3.86-3.63 (m, 5H), 3.50-3.42 (m, 1H), 3.27-3.19 (m, 2H), 3.12-3.04 (m, 1H), 2.66 (s, 3H), 2.59 (t, J=4.8 Hz, 3H), 1.63-1.60 (m, 5H), 1.38-1.32 (m, 2H), 1.12-1.11 (m, 4H), 1.06-1.05 (m, 3H), 1.02-0.95 (m, 3H), 0.88-0.66 (m, 5H).	588.4
I-157A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 – 9.22 (m, 1H), 8.28 – 8.16 (m, 1H), 7.86 – 7.68 (m, 1H), 4.29 – 3.99 (m, 3H), 3.97 – 3.77 (m, 3H), 3.73 – 3.45 (m, 5H), 3.26 – 3.19 (m, 1H), 3.14 – 3.05 (m, 1H), 2.62 – 2.54 (m, 3H), 1.70 – 1.57 (m, 5H), 1.49 – 1.26 (m,	608.9

[1060]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 1.19 – 0.98 (m, 12H), 0.90 – 0.77 (m, 3H), 0.70 – 0.61 (m, 1H).	
I-157B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.41 – 8.15 (m, 1H), 7.91 – 7.73 (m, 1H), 4.39 – 4.18 (m, 2H), 4.16 – 4.02 (m, 1H), 4.01 – 3.90 (m, 1H), 3.88 – 3.77 (m, 2H), 3.76 – 3.64 (m, 3H), 3.62 – 3.55 (m, 1H), 3.50 – 3.42 (m, 1H), 3.29 – 3.19 (m, 1H), 3.15 – 3.02 (m, 1H), 2.61 – 2.56 (m, 3H), 1.71 – 1.55 (m, 5H), 1.49 – 1.37 (m, 1H), 1.36 – 1.25 (m, 1H), 1.21 – 1.09 (m, 5H), 1.08 – 1.03 (m, 4H), 1.03 – 0.98 (m, 2H), 0.96 – 0.91 (m, 1H), 0.90 – 0.74 (m, 3H), 0.72 – 0.62 (m, 1H).	608.4
I-158A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 – 9.01 (m, 1H), 8.42 – 8.32 (m, 1H), 7.83 (d, J = 11.4 Hz, 1H), 7.39 – 7.21 (m, 5H), 5.35 (s, 2H), 5.23 – 5.09 (m, 1H), 4.27 – 4.04 (m, 2H), 4.03 – 3.92 (m, 2H), 3.92 – 3.76 (m, 2H), 3.75 – 3.58 (m, 2H), 3.23 – 3.07 (m, 1H), 2.35 – 2.25 (m, 3H), 1.52 – 1.43 (m, 3H), 1.41 – 1.30 (m, 1H), 1.14 – 1.08 (m, 3H), 1.08 – 1.00 (m, 3H), 0.86 (s, 1H), 0.72 – 0.65 (m, 1H).	546.4
I-158B	2B	^{1} H NMR (400 MHz, DMSO-d_6) δ 9.14 – 9.02 (m, 1H), 8.41 – 8.33 (m, 1H), 7.86 – 7.79 (m, 1H), 7.38 – 7.23 (m, 5H), 5.35 (s, 2H), 5.20 – 5.08 (m, 1H), 4.38 – 4.13 (m, 1H), 4.10 – 3.61 (m, 7H), 3.27 – 3.13 (m, 1H), 2.34 – 2.26 (m, 3H), 1.53 – 1.45 (m, 3H), 1.39 – 1.27 (m, 1H), 1.14 – 1.02 (m, 6H), 0.89 – 0.83 (m, 1H), 0.73 – 0.65 (m, 1H).	546.4
I-159	4A	^{1}H NMR (400 MHz, DMSO-d_6) & 13.52 (s, 1H), 10.67 (s, 1H), 8.70 – 8.64 (m, 1H), 7.96 – 7.88 (m, 2H), 7.62 – 7.60 (m, 1H), 7.46 – 7.42 (m, 1H), 7.34 – 7.22 (m, 5H), 4.89 – 4.73 (m, 2H), 4.55 – 4.51 (m, 1H), 4.44 – 4.41 (m, 1H), 4.34 – 4.25 (m, 1H), 4.14 – 4.06 (m, 1H), 4.03 – 3.82 (m, 4H), 3.74 – 3.64 (m, 5H), 2.62 – 2.61 (m, 3H), 1.27 –	587

[1061]

化合物编号	方法	^{1}HNMR	LCMS
		1.23 (m, 1H), 1.16 – 1.02 (m, 9H), 0.85 – 0.82 (m, 1H), 0.69 – 0.66 (m, 1H).	
I-160A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 – 9.08 (m, 1H), 8.28 – 8.12 (m, 1H), 7.84 – 7.66 (m, 1H), 4.29 – 3.48 (m, 11H), 3.26 – 3.19 (m, 1H), 3.13 – 3.06 (m, 1H), 2.62 – 2.53 (m, 3H), 2.44 – 2.40 (m, 3H), 1.70 – 1.57 (m, 5H), 1.48 – 1.25 (m, 2H), 1.20 – 0.98 (m, 12H), 0.89 – 0.77 (m, 3H), 0.70 – 0.62 (m, 1H).	588.4
I-160B	1B	^{1}H NMR (400 MHz, DMSO-d6) δ 9.09 (s, 1H), 8.41 – 8.17 (m, 1H), 7.92 – 7.75 (m, 1H), 4.38 – 3.42 (m, 11H), 3.25 – 3.01 (m, 2H), 2.59 (t, J = 4.8 Hz, 3H), 2.41 (s, 3H), 1.61 (d, J = 22.0 Hz, 5H), 1.46 – 1.27 (m, 2H), 1.16 – 1.00 (m, 10H), 0.96 – 0.61 (m, 6H).	588.5
I-161A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.62 – 8.50 (m, 1H), 8.33 – 8.18 (m, 1H), 7.83 – 7.67 (m, 1H), 4.29 – 3.68 (m, 10H), 3.62 – 3.46 (m, 1H), 3.26 – 3.20 (m, 1H), 3.14 – 3.06 (m, 1H), 2.63 – 2.55 (m, 3H), 1.71 – 1.55 (m, 5H), 1.49 – 1.38 (m, 1H), 1.36 – 1.27 (m, 1H), 1.21 – 1.00 (m, 12H), 0.89 – 0.77 (m, 3H), 0.70 – 0.64 (m, 1H).	642.0
I-161B	1B	1H NMR (400 MHz, DMSO-d6) & 8.58 – 8.54 (m, 1H), 8.36 – 8.28 (m, 1H), 7.88 – 7.79 (m, 1H), 4.38 – 4.30 (m, 1H), 4.27 – 4.21 (m, 1H), 4.19 – 4.13 (m, 1H), 4.11 – 4.09 (m, 1H), 4.06 – 4.00 (m, 1H), 3.86 – 3.78 (m, 2H), 3.76 – 3.61 (m, 3H), 3.53 – 3.48 (m, 1H), 2.61 – 2.58 (m, 3H), 1.62 – 1.59 (m, 5H), 1.42 – 1.31 (m, 2H), 1.15 – 1.09 (m, 6H), 1.07 – 1.05 (m, 3H), 1.03 – 1.01 (m, 2H), 0.98 – 0.95 (m, 1H), 0.87 – 0.81 (m, 3H), 0.72 – 0.66 (m, 1H).	641.9
I-162A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 – 8.11 (m, 1H), 7.86 – 7.65 (m, 1H), 4.68 (s, 2H), 4.28 – 3.40 (m, 14H), 3.26 – 3.19 (m, 1H), 3.13 – 3.06 (m, 1H), 2.59 (s, 3H), 2.38 (s, 3H), 1.70 – 1.57 (m, 5H), 1.49 – 1.27 (m,	632.5

[1062]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 1.23 – 0.98 (m, 12H), 0.89 – 0.76 (m, 3H), 0.70 – 0.61 (m, 1H).	
I-162B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 – 8.19 (m, 1H), 7.90 – 7.77 (m, 1H), 4.67 (s, 2H), 4.31 (m, 2H), 4.15 – 3.89 (m, 2H), 3.78 – 3.39 (m, 10H), 3.24 (m, 1H), 3.08 (m, 1H), 2.59 (t, J = 4.8 Hz, 3H), 2.37 (d, J = 3.2 Hz, 3H), 1.47 (m, 8H), 1.10 (d, J = 9.6 Hz, 5H), 1.05 (s, 2H), 1.02 – 0.92 (m, 3H), 0.76 (m, 5H).	632.5
I-163A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 – 9.31 (m, 1H), 8.27 – 8.12 (m, 1H), 7.85 – 7.64 (m, 1H), 4.29 – 4.08 (m, 2H), 4.00 – 3.36 (m, 9H), 3.26 – 3.19 (m, 1H), 3.13 – 3.05 (m, 1H), 2.62 – 2.53 (m, 3H), 1.70 – 1.57 (m, 5H), 1.48 – 1.25 (m, 2H), 1.21 – 0.98 (m, 12H), 0.89 – 0.77 (m, 3H), 0.71 – 0.62 (m, 1H).	642.9
I-163B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (d, J = 3.0 Hz, 1H), 8.37 – 8.17 (m, 1H), 7.90 – 7.74 (m, 1H), 4.37 – 3.82 (m, 4H), 3.82 – 3.69 (m, 2H), 3.66 – 3.42 (m, 4H), 3.30 – 3.19 (m, 2H), 3.15 – 3.01 (m, 1H), 2.61 – 2.55 (m, 3H), 1.70 – 1.51 (m, 5H), 1.49 – 1.26 (m, 2H), 1.24 – 1.08 (m, 5H), 1.07 – 1.01 (m, 5H), 0.99 (s, 1H), 0.95 (d, J = 6.2 Hz, 1H), 0.89 – 0.72 (m, 3H), 0.67 (dq, J = 8.6, 4.2 Hz, 1H).	642.4
I-164A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 8.4 Hz, 1H), 8.40 – 8.32 (m, 1H), 7.82 (dd, J = 15.4, 3.2 Hz, 1H), 7.33 (dd, J = 8.8, 5.2 Hz, 2H), 7.23 – 7.13 (m, 2H), 5.34 (s, 2H), 4.95 – 4.86 (m, 1H), 4.25 – 3.81 (m, 5H), 3.80 – 3.44 (m, 9H), 3.42 – 3.33 (m, 1H), 3.27 – 3.20 (m, 1H), 2.04 – 1.53 (m, 11H), 1.39 – 1.27 (m, 1H), 1.20 – 1.03 (m, 11H), 0.85 (s, 1H), 0.68 (dd, J = 8.0, 3.6 Hz, 1H).	791.5
I-164B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.48 (m, 1H), 8.40 – 8.31 (m, 1H), 7.85 – 7.78 (m, 1H), 7.32 (dd, J = 8.6, 5.2 Hz, 2H), 7.17 (t, J = 8.6 Hz, 2H), 5.34 (s, 2H), 4.89 – 4.82 (m, 1H), 4.30 – 3.40 (m, 15H), 3.24 – 3.17 (m,	791.5

[1063]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 2.08 – 1.83 (m, 7H), 1.79 – 1.65 (m, 4H), 1.61 – 1.51 (m, 1H), 1.38 – 1.26 (m, 1H), 1.12 – 1.03 (m, 10H), 0.88 – 0.82 (m, 1H), 0.70 – 0.64 (m, 1H).	
I-165	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.23 (m, 2H), 8.03 – 7.89 (m, 1H), 7.86 – 7.74 (m, 1H), 7.37 – 7.21 (m, 5H), 5.35 (s, 2H), 4.51 – 4.41 (m, 1H), 4.16 – 3.91 (m, 3H), 3.81 – 3.52 (m, 5H), 3.44 – 3.37 (m, 1H), 3.30 – 3.29 (m, 1H), 3.21 – 3.08 (m, 2H), 2.60 – 2.55 (m, 3H), 1.66 – 1.48 (m, 5H), 1.38 – 1.30 (m, 2H), 1.24 – 1.22 (m, 1H), 1.12 – 0.99 (m, 11H), 0.88 – 0.78 (m, 3H), 0.71 – 0.64 (m, 1H).	647.1
I-166A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 15.0 Hz, 1H), 8.25 – 8.13 (m, 1H), 7.86 – 7.70 (m, 2H), 7.39 – 7.24 (m, 5H), 5.35 (s, 2H), 4.30 – 3.51 (m, 11H), 3.23 – 3.16 (m, 1H), 3.11 – 3.04 (m, 1H), 2.62 – 2.55 (m, 3H), 1.70 – 1.33 (m, 12H), 1.11 – 1.00 (m, 11H), 0.88 – 0.82 (m, 1H), 0.70 – 0.63 (m, 1H)	661.6
I-166B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.30 (m, 1H), 8.28 – 8.19 (m, 1H), 7.89 – 7.75 (m, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.40 – 3.44 (m, 11H), 3.26 – 3.16 (m, 1H), 3.10 – 3.02 (m, 1H), 2.62 – 2.55 (m, 3H), 1.65 – 1.31 (m, 12H), 1.12 – 0.94 (m, 11H), 0.89 – 0.83 (m, 1H), 0.72 – 0.64 (m, 1H).	661.5
I-167	1B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.17 (m, 1H), 7.95 – 7.87 (m, 1H), 7.33 (tt, J = 5.8, 3.2 Hz, 2H), 7.11 – 7.05 (m, 2H), 5.36 (d, J = 2.6 Hz, 2H), 4.56 (dd, J = 10.2, 6.6 Hz, 1H), 4.40 – 4.35 (m, 1H), 4.26 – 4.08 (m, 3H), 4.00 – 3.80 (m, 5H), 3.45 – 3.37 (m, 2H), 3.25 – 3.17 (m, 1H), 2.75 (d, J = 2.8 Hz, 3H), 2.00 (s, 2H), 1.83 – 1.73 (m, 3H), 1.69 – 1.57 (m, 2H), 1.51 – 1.37 (m, 1H), 1.24 – 1.10 (m, 10H), 1.05 (t, J = 5.6 Hz, 2H), 0.82 – 0.74 (m, 1H).	701.5
I-168	26b	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 – 10.54 (m, 1H), 8.62 – 8.59 (m, 1H), 8.47 –	603.0

[1064]

化合物编号	方法	^{1}HNMR	LCMS
		8.36 (m, 1H), 8.23 – 8.22 (m, 1H), 7.90 – 7.82 (m, 2H), 7.36 – 7.18 (m, 10H), 5.36 – 5.35 (m, 2H), 4.36 – 3.73 (m, 7H), 3.52 – 3.50 (m, 4H), 1.76 – 1.58 (m, 2H), 1.35 – 1.27 (m, 2H), 1.11 – 1.08 (m, 2H), 0.86 – 0.75 (m, 2H), 0.64 – 0.63 (m, 1H).	
I-169	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 – 8.18 (m, 1H), 8.07 – 8.02 (m, 2H), 7.82 – 7.71 (m, 1H), 4.44 – 4.35 (m, 1H), 4.28 – 4.08 (m, 4H), 3.97 – 3.89 (m, 1H), 3.88 – 3.69 (m, 4H), 3.58 – 3.45 (m, 1H), 3.26 – 3.20 (m, 1H), 3.13 – 3.06 (m, 1H), 2.62 – 2.56 (m, 3H), 1.71 – 1.57 (m, 5H), 1.49 – 1.21 (m, 3H), 1.17 – 1.11 (m, 3H), 1.10 – 1.06 (m, 3H), 1.05 – 1.01 (m, 5H), 0.89 – 0.79 (m, 3H), 0.69 – 0.64 (m, 1H).	574.3
I-170	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 13.4 Hz, 1H), 8.28 – 8.18 (m, 1H), 7.86 – 7.72 (m, 2H), 7.36 – 7.30 (m, 2H), 7.18 (t, J = 8.8 Hz, 2H), 5.34 (s, 2H), 4.35 – 4.02 (m, 4H), 3.99 – 3.61 (m, 7H), 3.51 – 3.39 (m, 1H), 3.18 (dd, J = 9.4, 6.2 Hz, 1H), 2.60 – 2.55 (m, 3H), 2.02 – 1.93 (m, 2H), 1.86 – 1.65 (m, 5H), 1.59 (s, 1H), 1.37 – 1.27 (m, 1H), 1.12 – 1.02 (m, 10H), 0.88 – 0.82 (m, 1H), 0.70 – 0.64 (m, 1H).	701.5
I-171A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (m, 1H), 8.44 – 8.18 (m, 2H), 7.89 – 7.76 (m, 1H), 7.38 – 7.03 (m, 10H), 5.36 (d, J = 6.8 Hz, 2H), 4.73 – 4.64 (m, 1H), 4.20 – 4.01 (m, 3H), 3.95 – 3.80 (m, 3H), 3.79 – 3.69 (m, 3H), 3.66 – 3.38 (m, 2H), 2.61 (dd, J = 7.2, 4.4 Hz, 3H), 1.38 (d, J = 9.4 Hz, 3H), 1.34 (dd, J = 8.0, 3.2 Hz, 1H), 1.25 (d, J = 11.8 Hz, 3H), 1.11 (t, J = 5.8 Hz, 3H), 1.04 (d, J = 5.2 Hz, 3H), 0.86 (s, 1H), 0.68 (m, 1H).	671.4
I-171B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 – 8.45 (m, 1H), 8.38 (d, J = 6.6 Hz, 1H), 8.30 (dd, J = 12.0, 4.8 Hz, 1H), 7.89 – 7.80 (m, 1H), 7.44 – 7.13 (m, 10H), 5.36 (d, J = 5.2 Hz, 2H), 4.81 – 4.66 (m, 1H), 4.44 (dd, J = 23.4, 8.6 Hz, 1H), 4.15 – 4.00 (m, 2H), 3.97 – 3.82	671.5

[1065]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 3H), 3.80 – 3.67 (m, 3H), 3.65 – 3.48 (m, 2H), 2.61 (dd, J = 8.8, 4.2 Hz, 3H), 1.38 (d, J = 8.4 Hz, 3H), 1.27 (d, J = 3.0 Hz, 3H), 1.08 – 1.04 (m, 2H), 0.98 – 0.88 (m, 4H), 0.82 (d, J = 6.4 Hz, 1H), 0.67 (d, J = 14.6 Hz, 1H), 0.37 – 0.26 (m, 1H).	
I-172	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.37 (d, J = 14.4 Hz, 1H), 4.89-4.95 (m, 1H), 3.62-4.50 (m, 12H), 3.33-3.47 (m, 2H), 3.16-3.24 (m, 1H), 2.50-2.63 (m, 1H), 2.01-2.14 (m, 1H), 1.62-1.76 (m, 6H), 1.38-1.61 (m, 4H), 1.04-1.22 (m, 12H), 0.88-0.95 (m, 8H), 0.72-0.82 (m, 2H).	656.4
I-173 - 混合物	15	^{1}HNMR (400 MHz, CD_3OD): δ 8.01-8.21 (m, 1H), 7.91-8.00 (m, 1H), 4.91-4.97 (m, 1H), 4.43-4.52 (m, 2H), 3.83-4.21 (m, 9H), 3.64-3.73 (m, 1H), 3.34-3.38 (m, 2H), 3.12-3.20 (m, 1H), 2.52-2.67 (m, 1H), 2.06-2.14 (m, 1H), 1.81-1.87 (m, 1H), 1.66-1.69 (m, 5H), 1.41-1.52 (m, 3H), 1.03-1.24 (m, 11H), 0.89-0.95 (m, 8H), 0.81-0.85 (m, 1H), 0.76-0.78 (m, 1H).	639.7
I-173A	15	^{1}HNMR (400 MHz, CD_3OD): δ 8.01-8.21 (m, 1H), 7.91-8.00 (m, 1H), 4.91-4.97 (m, 1H), 4.43-4.52 (m, 2H), 3.83-4.21 (m, 9H), 3.64-3.73 (m, 1H), 3.34-3.38 (m, 2H), 3.12-3.20 (m, 1H), 2.52-2.67 (m, 1H), 2.06-2.14 (m, 1H), 1.81-1.87 (m, 1H), 1.66-1.69 (m, 5H), 1.41-1.52 (m, 3H), 1.03-1.24 (m, 11H), 0.89-0.95 (m, 8H), 0.81-0.85 (m, 1H), 0.76-0.78 (m, 1H).	639.7
I-173B	15	^{1}HNMR (400 MHz, CD_3OD): δ 8.01-8.21 (m, 1H), 7.91-8.00 (m, 1H), 4.91-4.97 (m, 1H), 4.43-4.52 (m, 2H), 3.83-4.21 (m, 9H), 3.64-3.73 (m, 1H), 3.34-3.38 (m, 2H), 3.12-3.20 (m, 1H), 2.52-2.67 (m, 1H), 2.06-2.14 (m, 1H), 1.81-1.87 (m, 1H), 1.66-1.69 (m, 5H), 1.41-1.52 (m, 3H), 1.03-1.24 (m, 11H), 0.89-0.95 (m, 8H), 0.81-0.85 (m, 1H), 0.76-0.78 (m, 1H).	639.7
I-174A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 14.0 Hz, 1H), 8.21 (s, 1H), 7.82 (d, J =	635.5

[1066]

化合物编号	方法	^{1}HNMR	LCMS
		17.2 Hz, 1H), 7.76 (s, 1H), 7.45 – 7.19 (m, 5H), 5.36 (s, 2H), 4.28 (dd, *J* = 8.8, 3.4 Hz, 2H), 3.95 (d, *J* = 39.6 Hz, 3H), 3.84 – 3.70 (m, 3H), 3.62 (s, 1H), 3.48 (s, 1H), 3.40 (d, *J* = 6.4 Hz, 1H), 3.22 (t, *J* = 8.4 Hz, 1H), 3.10 (t, *J* = 8.0 Hz, 1H), 2.58 (dd, *J* = 9.8, 4.4 Hz, 3H), 1.65 (s, 5H), 1.43 (s, 1H), 1.20 – 1.05 (m, 12H), 1.01 (s, 3H), 0.84 (t, *J* = 11.8 Hz, 2H).	
I-174B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 18.4 Hz, 1H), 8.22 (s, 1H), 7.81 (d, *J* = 17.6 Hz, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.32 – 3.53 (m, 10H), 3.30 – 3.29 (m, 1H), 3.26 – 3.19 (m, 1H), 3.08 (s, 1H), 2.61 – 2.55 (m, 3H), 1.68 – 1.56 (m, 5H), 1.45 – 1.35 (m, 1H), 1.16 – 1.05 (m, 12H), 1.03 – 0.95 (m, 3H), 0.89 – 0.76 (m, 2H).	635.4
I-175A	1A	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.27 – 8.15 (m, 2H), 7.82 – 7.67 (m, 1H), 4.70 (s, 2H), 4.30 – 4.17 (m, 2H), 4.15 – 3.95 (m, 3H), 3.92 – 3.64 (m, 5H), 3.58 – 3.44 (m, 1H), 3.26 – 3.19 (m, 1H), 3.15 – 3.06 (m, 1H), 2.61 – 2.55 (m, 3H), 1.70 – 1.59 (m, 5H), 1.48 – 1.40 (m, 1H), 1.35 – 1.27 (m, 1H), 1.24 (s, 9H), 1.19 – 1.01 (m, 12H), 0.88 – 0.78 (m, 3H), 0.71 – 0.64 (m, 1H).	660.0
I-175B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.24 (m, 1H), 8.20 – 8.14 (m, 1H), 7.88 – 7.81 (m, 1H), 4.70 (s, 2H), 4.36 – 4.30 (m, 1H), 4.26 – 4.17 (m, 1H), 4.13 – 3.98 (m, 3H), 3.83 – 3.72 (m, 3H), 3.68 – 3.63 (m, 2H), 3.45 – 3.43 (m, 1H), 3.27 – 3.19 (m, 1H), 3.12 – 3.08 (m, 1H), 2.59 (t, J=4.8 Hz, 3H), 1.62 – 1.59 (m, 5H), 1.40 – 1.32 (m, 2H), 1.24 (s, 9H), 1.12 – 1.05 (m, 9H), 1.02 – 0.95 (m, 3H), 0.87 – 0.78 (m, 3H), 0.71 – 0.68 (m, 1H).	660.0
I-176A	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.23 (m, 2H), 7.85 – 7.81 (m, 1H), 7.40 – 7.19 (m, 12H), 5.35 (s, 2H), 4.56 – 4.53 (m, 1H), 4.48 – 4.45 (m, 1H), 4.38 – 4.35 (m, 1H), 4.26 – 4.15 (m, 1H), 4.09 – 3.96 (m, 3H), 3.94 –	627.0

[1067]

化合物编号	方法	^{1}HNMR	LCMS
		3.81 (m, 2H), 3.77 – 3.59 (m, 3H), 3.55 – 3.35 (m, 1H), 1.34 – 1.25 (m, 1H), 1.11 – 1.01 (m, 9H), 0.84 – 0.82 (m, 1H), 0.66 – 0.61 (m, 1H).	
I-176B	2B	^{1}H NMR (400 MHz, DMSO-d_6) & 8.47 – 8.38 (m, 1H), 8.32 – 8.29 (m, 1H), 7.84 – 7.80 (m, 1H), 7.42 – 7.14 (m, 12H), 5.35 (s, 2H), 4.57 – 4.33 (m, 4H), 4.14 – 4.12 (m, 1H), 4.02 – 3.96 (m, 3H), 3.76 – 3.61 (m, 4H), 3.45 – 3.43 (m, 1H), 1.36 – 1.33 (m, 1H), 1.15 – 1.06 (m, 9H), 0.87 – 0.86 (m, 1H), 0.68 – 0.66 (m, 1H).	627.0
I-177A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 – 8.17 (m, 1H), 8.17 – 8.09 (m, 1H), 7.82 – 7.68 (m, 1H), 4.28 – 4.19 (m, 2H), 4.15 – 3.62 (m, 9H), 3.58 – 3.43 (m, 1H), 3.25 – 3.20 (m, 1H), 3.14 – 3.06 (m, 1H), 2.88 (d, J = 7.2 Hz, 2H), 2.61 – 2.55 (m, 3H), 1.69 – 1.59 (m, 5H), 1.50 – 1.28 (m, 2H), 1.18 – 1.01 (m, 13H), 0.88 – 0.79 (m, 3H), 0.70 – 0.64 (m, 1H), 0.61 – 0.55 (m, 2H), 0.31 (q, J = 5.2 Hz, 2H).	628.4
I-177B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.24 (m, 1H), 8.16 – 8.10 (m, 1H), 7.88 – 7.81 (m, 1H), 4.36 – 4.32 (m, 1H), 4.27 – 4.17 (m, 1H), 4.14 – 3.98 (m, 3H), 3.80 – 3.63 (m, 5H), 3.50 – 3.43 (m, 1H), 3.27 – 3.19 (m, 1H), 3.12 – 3.06 (m, 1H), 2.88 (d, J=7.2 Hz, 2H), 2.59 (t, J=4.8 Hz, 3H), 1.63 – 1.59 (m, 5H), 1.36 – 1.33 (m, 2H), 1.12 – 1.05 (m, 10H), 1.03 – 0.95 (m, 3H), 0.87 – 0.78 (m, 3H), 0.71 – 0.68 (m, 1H), 0.60 – 0.55 (m, 2H), 0.31 – 0.30 (m, 1H).	628.0
I-178A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, J = 20.2, 8.6 Hz, 1H), 8.03 (d, J = 16.4 Hz, 1H), 7.84 – 7.62 (m, 1H), 4.30 – 4.06 (m, 3H), 4.05 – 3.88 (m, 2H), 3.87 – 3.53 (m, 5H), 3.52 – 3.38 (m, 1H), 3.23 (dd, J = 9.4, 6.6 Hz, 1H), 3.10 (dd, J = 9.4, 6.4 Hz, 1H), 2.58 (t, J = 6.4 Hz, 3H), 2.48 – 2.39 (m, 1H), 1.64 (d, J = 11.8 Hz, 5H), 1.43 (s, 1H), 1.35 – 1.23 (m, 1H), 1.21 – 1.13 (dt, J = 8.1, 3.5 Hz,	614.5

[1068]

化合物编号	方法	^{1}HNMR	LCMS
		4H), 1.10 (d, J = 15.8 Hz, 4H), 1.07 – 0.94 (m, 8H), 0.83 (d, J = 14.0 Hz, 3H), 0.71 – 0.63 (m, 1H).	
I-178B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 – 8.22 (m, 1H), 8.08 – 7.98 (m, 1H), 7.90 – 7.76 (m, 1H), 4.36 – 4.15 (m, 2H), 4.12 – 3.95 (m, 3H), 3.85 – 3.74 (m, 2H), 3.69 – 3.60 (m, 2H), 3.53 – 3.40 (m, 1H), 3.30 – 3.19 (m, 2H), 3.14 – 3.03 (m, 1H), 2.59 (t, J = 4.8 Hz, 3H), 2.46 – 2.39 (m, 1H), 1.67 – 1.55 (m, 5H), 1.46 – 1.32 (m, 2H), 1.20 – 1.14 (m, 3H), 1.13 – 1.03 (m, 8H), 1.03 – 0.95 (m, 5H), 0.90 – 0.77 (m, 3H), 0.73 – 0.64 (m, 1H).	614.5
I-179	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.29 – 8.15 (m, 1H), 7.97 – 7.88 (m, 1H), 7.39 – 7.22 (m, 5H), 5.39 –5.35 (m, 2H), 4.49 – 3.37 (m, 13H), 3.28 – 2.57 (m, 6H), 1.93 – 1.53 (m, 9H), 1.51 – 1.31 (m, 5H), 1.19 – 1.01 (m, 8H), 0.74 – 0.80 (m, 1H).	643.5
I-180	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.29 – 8.16 (m, 1H), 7.97 – 7.87 (m, 1H), 7.39 – 7.23 (m, 5H), 5.39 – 5.36 (m, 2H), 4.49 – 3.86 (m, 9H), 3.84 – 3.39 (m, 3H), 3.27 – 2.34 (m, 2H), 2.32 – 1.44 (m, 10H), 1.43 – 1.01 (m, 14H), 0.82 – 0.74 (m, 1H)	629.5
I-181	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.15 (m, 1H), 7.96 – 7.86 (m, 1H), 7.38 – 7.23 (m, 5H), 5.38 – 5.35 (m, 2H), 4.51 – 3.71 (m, 12H), 3.00 – 2.65 (m, 5H), 1.94 – 1.25 (m, 15H), 1.20 – 1.07 (m, 7H), 1.06 – 1.00 (m, 1H), 0.82 – 0.72 (m, 1H)	643.5
I-182	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.32 – 8.17 (m, 1H), 7.97 – 7.88 (m, 1H), 7.53 – 7.14 (m, 5H), 5.38 (s, 2H), 4.44 – 3.64 (m, 11H), 3.24 – 2.92 (m, 2H), 2.68 – 2.53 (m, 1H), 2.05 – 0.99 (m, 23H), 0.82 – 0.73 (m, 1H).	629.5
I-183	2A	^{1}HNMR (400 MHz, DMSO-d_6) δ 9.54 – 9.35 (m, 0.5H), 8.60 – 8.43 (m, 0.5 H), 8.42 – 8.33 (m, 1H), 7.87 – 7.79 (m, 1H), 7.41 – 7.23 (m, 5H), 5.36 (s, 2H), 4.30 – 4.06 (m, 3H), 4.04 – 3.60 (m, 6H), 3.48 – 3.38 (m, 1H), 3.24 –	615.6

[1069]

化合物编号	方法	^{1}HNMR	LCMS
		2.60 (m, 5H) ,1.84 – 1.58 (m, 9H), 1.40 – 1.22 (m, 6H), 1.14 – 0.63 (m, 14H).	
I-184	1A	^{1}H NMR (400 MHz, 甲醇-d4) δ 7.44 (s, 1H), 4.59 (s, 1H), 4.42 – 4.31 (m, 2H), 4.23 – 3.81 (m, 8H), 3.38 – 3.35 (m, 1H), 3.18 – 3.13 (m, 1H), 2.75 (s, 3H), 1.71 (m, 5H), 1.52 (s, 1H), 1.43 – 1.37 (m, 1H), 1.30 – 1.21 (m, 4H), 1.18 – 1.11 (m, 8H), 1.06 – 1.01 (m, 1H), 0.92 (d, *J* = 11.8 Hz, 2H), 0.78 (dd, *J* = 8.0, 4.2 Hz, 1H).	590.3
I-185A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.27 – 8.15 (m, 1H), 7.84 – 7.68 (m, 1H), 4.28 – 3.61 (m, 11H), 3.25 – 3.20 (m, 1H), 3.09 (t, *J* = 8.0 Hz, 1H), 2.62 – 2.54 (m, 3H), 2.24 – 2.17 (m, 1H), 1.71 – 1.57 (m, 5H), 1.47 – 1.39 (m, 1H), 1.37 – 1.26 (m, 1H), 1.17 – 0.92 (m, 15H), 0.88 – 0.80 (m, 3H), 0.70 – 0.63 (m, 1H).	614.4
I-185B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.34 – 8.17 (m, 1H), 7.90 – 7.76 (m, 1H), 4.38 – 3.47 (m, 11H), 3.27 – 3.19 (m, 1H), 3.14 – 3.01 (m, 1H), 2.61 – 2.56 (m, 3H), 2.23 – 2.14 (m, 1H), 1.74 – 1.24 (m, 8H), 1.16 – 0.85 (m, 18H), 0.71 – 0.63 (m, 1H).	614.5
I-186A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.36 (d, *J* = 20.2 Hz, 1H), 8.24 (s, 1H), 7.76 (s, 1H), 4.64 – 4.16 (m, 3H), 4.13 – 3.93 (m, 2H), 3.90 – 3.73 (m, 3H), 3.67 (d, *J* = 5.8 Hz, 1H), 3.55 – 3.41 (m, 1H), 3.29 (s, 1H), 3.22 (t, *J* = 8.0 Hz, 1H), 3.10 (dd, *J* = 9.6, 6.2 Hz, 1H), 2.58 (dd, *J* = 12.4, 4.4 Hz, 3H), 1.64 (d, *J* = 10.8 Hz, 5H), 1.43 (s, 1H), 1.28 – 1.12 (m, 3H), 1.08 (s, 9H), 1.01 (s, 3H), 0.84 (t, *J* = 12.0 Hz, 2H).	562.4
I-186B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40 – 8.20 (m, 2H), 7.82 (d, *J* = 41.8 Hz, 1H), 4.38 – 3.36 (m, 11H), 3.28 – 3.19 (m, 1H), 3.13 – 3.03 (m, 1H), 2.58 (d, *J* = 4.4 Hz, 3H), 1.60 (d, *J* = 13.6 Hz, 5H), 1.48 – 1.33 (m, 1H), 1.19 – 1.06 (m, 12H), 0.99 (dd, *J* = 21.0, 6.2 Hz, 3H), 0.90 – 0.73 (m, 2H).	562.6

[1070]

化合物编号	方法	^{1}HNMR	LCMS
I-187A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 – 8.66 (m, 1H), 8.39 – 8.35 (m, 1H), 7.84 – 7.81 (m, 1H), 7.37 – 7.25 (m, 5H), 5.35 (s, 2H), 5.11 (s, 1H), 4.41 – 4.34 (m, 1H), 4.29 – 4.14 (m, 1H), 4.11 – 4.01 (m, 2H), 3.93 – 3.88 (m, 1H), 3.79 – 3.71 (m, 3H), 3.65 – 3.54 (m, 5H), 3.44 – 3.43 (m, 1H), 3.29 – 3.26 (m, 1H), 1.36 – 1.32 (m, 1H), 1.12 – 1.05 (m, 6H), 0.86 – 0.84 (m, 1H), 0.70 – 0.66 (m, 1H).	538.0
I-187B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 – 8.62 (m, 1H), 8.38 – 8.35 (m, 1H), 7.84 – 7.81 (m, 1H), 7.37 – 7.25 (m, 5H), 5.35 (s, 2H), 5.14 – 5.07 (m, 1H), 4.39 – 4.35 (m, 1H), 4.31 – 4.14 (m, 1H), 4.11 – 3.82 (m, 4H), 3.78 – 3.69 (m, 3H), 3.63 – 3.62 (m, 3H), 3.58 – 3.57 (m, 1H), 3.38 – 3.35 (m, 1H), 3.30 – 3.28 (m, 1H), 1.37 – 1.34 (m, 1H), 1.11 – 1.05 (m, 6H), 0.87 – 0.85 (m, 1H), 0.70 – 0.67 (m, 1H).	538.0
I-188A	1A+8A	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 8.53-7.84 (m, 3H), 4.91 (s, 1H), 4.37-4.17 (m, 2H), 4.05-3.87 (m, 3H), 3.73-3.45 (m, 9H), 3.26-3.22 (m, 2H), 2.03-1.59 (m, 13H), 1.15-1.12 (m, 4H), 1.05 (d, J=6.0 Hz, 3H).	722.9
I-188B	1B+8B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 14.6 Hz, 2H), 4.85 (s, 1H), 4.21 (m, 2H), 3.98 (m, 3H), 3.73 – 3.60 (m, 7H), 3.37 – 3.31 (m, 2H), 3.23 – 3.17 (m, 1H), 1.95 (s, 6H), 1.73 (m, 4H), 1.27 – 1.03 (m, 10H).	723.4
I-189A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 – 8.11 (m, 2H), 7.81 – 7.67 (m, 1H), 4.48 – 4.23 (m, 1H), 4.22 – 3.85 (m, 5H), 3.84 – 3.44 (m, 5H), 3.25 – 3.20 (m, 1H), 3.13 – 3.07 (m, 1H), 2.62 – 2.55 (m, 3H), 1.73 – 1.54 (m, 5H), 1.45 – 1.25 (m, 2H), 1.20 – 0.98 (m, 12H), 0.90 – 0.76 (m, 3H), 0.71 – 0.63 (m, 1H).	608.4
I-189B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 – 8.24 (m, 1H), 8.20 – 8.11 (m, 1H), 7.89 – 7.78 (m,	608.4

[1071]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 4.38 – 4.29 (m, 1H), 4.26 – 4.00 (m, 4H), 3.83 – 3.61 (m, 5H), 3.54 – 3.43 (m, 1H), 3.27 – 3.19 (m, 1H), 3.12 – 3.05 (m, 1H), 2.61 – 2.58 (m, 3H), 1.67 – 1.58 (m, 5H), 1.41 – 1.31 (m, 2H), 1.15 – 1.05 (m, 9H), 1.03 – 0.97 (m, 3H), 0.89 – 0.79 (m, 3H), 0.73 – 0.66 (m, 1H).	
I-190A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.33 (m, 2H), 7.83 – 7.79 (m, 1H), 7.34 – 7.30 (m, 2H), 7.20 – 7.15 (m, 2H), 5.34 – 5.33 (m, 2H), 4.92 – 4.84 (m, 1H), 4.37 – 3.85 (m, 6H), 3.74 – 3.46 (m, 8H), 3.37 – 3.33 (m, 1H), 3.26 – 3.23 (m, 1H), 1.99 – 1.59 (m, 12H), 1.16 – 1.12 (m, 5H), 1.05 (d, J = 6.4 Hz, 3H).	828.9 $[M-H]^-$
I-190B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 12.8 Hz, 1H), 7.81 (d, J = 17.0 Hz, 1H), 7.32 (dd, J = 8.4, 5.6 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 5.33 (d, J = 5.0 Hz, 2H), 4.84 (s, 1H), 4.43 – 4.12 (m, 2H), 3.95 (dd, J = 24.2, 14.0 Hz, 3H), 3.79 – 3.59 (m, 7H), 3.52 (s, 1H), 3.44 (q, J = 7.0 Hz, 2H), 3.21 (dd, J = 9.2, 6.8 Hz, 1H), 1.95 (s, 5H), 1.70 (s, 3H), 1.55 (s, 1H), 1.25 (d, J = 7.6 Hz, 2H), 1.20 – 1.10 (m, 4H), 1.06 (t, J = 7.0, 4H).	831.5
I-191A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.40 – 8.33 (m, 1H), 7.86 – 7.80 (m, 1H), 7.38 – 7.23 (m, 5H), 5.37 – 5.34 (m, 2H), 4.39 – 4.31 (m, 1H), 4.24 – 4.15 (m, 1H), 4.11 – 3.57 (m, 8H), 3.30 – 3.29 (m, 1H), 3.25 – 3.09 (m, 1H), 1.38 – 1.30 (m, 1H), 1.12 – 1.08 (m, 3H), 1.06 – 1.01 (m, 3H), 0.88 – 0.81 (m, 1H), 0.71 – 0.65 (m, 1H).	517.3
I-191B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.39 – 8.31 (m, 1H), 7.86 – 7.80 (m, 1H), 7.38 – 7.23 (m, 5H), 5.37 – 5.33 (m, 2H), 4.42 – 4.34 (m, 2H), 4.17 – 3.90 (m, 4H), 3.84 – 3.59 (m, 5H), 1.38 – 1.32 (m, 1H), 1.13 – 1.02 (m, 6H), 0.88 – 0.83 (m, 1H), 0.72 – 0.64 (m, 1H).	517.4

[1072]

化合物编号	方法	^{1}HNMR	LCMS
I-192 –混合物	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.8 Hz, 1H), 4.96-5.01 (m, 1H), 3.57-4.40 (m, 14H), 3.34-3.48 (m, 2H), 3.16-3.25 (m, 1H), 1.88-2.00 (m, 2H), 1.62-1.76 (m, 5H), 1.47-1.58 (m, 1H), 1.41-1.46 (m, 1H), 1.02-1.24 (m, 14H), 0.90-0.97 (m, 2H), 0.75-0.81 (m, 1H).	664.4
I-192A	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.8 Hz, 1H), 4.96-5.01 (m, 1H), 3.57-4.40 (m, 14H), 3.34-3.48 (m, 2H), 3.16-3.25 (m, 1H), 1.88-2.00 (m, 2H), 1.62-1.76 (m, 5H), 1.47-1.58 (m, 1H), 1.41-1.46 (m, 1H), 1.02-1.24 (m, 14H), 0.90-0.97 (m, 2H), 0.75-0.81 (m, 1H).	664.4
I-192B	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.8 Hz, 1H), 4.96-5.01 (m, 1H), 3.57-4.40 (m, 14H), 3.34-3.48 (m, 2H), 3.16-3.25 (m, 1H), 1.88-2.00 (m, 2H), 1.62-1.76 (m, 5H), 1.47-1.58 (m, 1H), 1.41-1.46 (m, 1H), 1.02-1.24 (m, 14H), 0.90-0.97 (m, 2H), 0.75-0.81 (m, 1H).	664.4
I-193	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.39 (d, J = 12.0 Hz, 1H), 4.96-5.05 (m, 2H), 4.60 (s, 1H), 3.74-4.43 (m, 10H), 3.41-3.49 (m, 3H), 3.16-3.24 (m, 2H), 2.90-2.97 (m, 1H), 2.60-2.72 (m, 1H), 1.55-1.85 (m, 9H), 1.41-1.47 (m, 2H), 1.07-1.26 (m, 12H), 0.85-0.99 (m, 3H), 0.77-0.81 (m, 1H).	658.4
I-194 –混合物	15	^{1}H NMR (400 MHz, CD_3OD) δ 8.19-8.24 (m, 1H), 7.90-7.93 (m, 1H), 7.28-7.37 (m, 5H), 5.38 (s, 2H), 4.91-4.94 (m, 1H), 3.70-4.41 (m, 10H), 3.48-3.62 (m, 4H), 3.33-3.41 (m, 2H), 3.12-3.22 (m, 1H), 1.45-1.76 (m, 13H), 1.01-1.19 (m, 11H), 0.86-0.97 (m, 3H), 0.76-0.79 (m, 1H).	701.5
I-194A	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.19-8.23 (m, 1H), 7.92 (d, J = 12.0 Hz, 1H), 7.26-7.36 (m, 5H), 5.38 (s, 2H), 4.91-4.94 (m, 1H), 3.71-4.41 (m, 10H), 3.50-3.60 (m, 4H), 3.33-3.46 (m, 2H), 3.17-3.22 (m, 1H), 1.38-1.76 (m, 13H), 1.10-1.24 (m, 11H), 1.03-1.05 (m, 1H), 0.87-0.97 (m, 2H), 0.76-0.81 (m, 1H).	701.5

[1073]

化合物编号	方法	^{1}HNMR	LCMS
I-194B	16B	^{1}HNMR (400 MHz, CD_3OD): δ 8.19-8.23 (m, 1H), 7.92 (d, J = 12.4 Hz, 1H), 7.26-7.36 (m, 5H), 5.37 (s, 2H), 4.91-4.94 (m, 1H), 3.71-4.41 (m, 10H), 3.50-3.60 (m, 4H), 3.33-3.46 (m, 2H), 3.17-3.22 (m, 1H), 1.46-1.76 (m, 13H), 1.03-1.21 (m, 12H), 0.89-0.97 (m, 2H), 0.75-0.80 (m, 1H).	701.4
I-195	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.37 (d, J = 12.5 Hz, 1H), 4.92-4.97 (m, 1H), 3.86-4.41 (m, 9H), 3.69-3.76 (m, 2H), 3.40-3.48 (m, 1H), 3.23 (dd, J = 14.9, 7.4 Hz, 3H), 2.93-3.08 (m, 1H), 2.60 (dd, J = 24.9, 12.1 Hz, 1H), 1.66-1.80 (m, 6H), 1.31-1.52 (m, 12H), 1.10-1.27 (m, 11H), 1.04 (s, 1H), 0.92 (dd, J = 24.0, 11.6 Hz, 2H), 0.76-0.79 (m, 1H).	672.4
I-196 - 混合物	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.37 (d, J = 12.8 Hz, 1H), 4.91-4.96 (m, 2H), 4.23-4.40 (m, 4H), 3.99-4.17 (m, 4H), 3.84-3.97 (m, 3H), 3.70-3.78 (m, 1H), 3.35-3.46 (m, 2H), 3.18-3.27 (m, 4H), 2.88-2.96 (m, 1H), 2.61-2.71 (m, 1H), 1.66-1.81 (m, 8H), 1.36-1.53 (m, 4H), 1.10-1.24 (m, 12H), 1.04-1.07 (m, 1H), 0.89-0.97 (m, 2H), 0.76-0.81 (m, 1H).	672.4
I-196A	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.39 (d, J = 13.2 Hz, 1H), 4.95-4.99 (m, 1H), 3.84-4.43 (m, 11H), 3.71-3.76 (m, 1H), 3.38-3.49 (m, 3H), 3.20-3.28 (m, 5H), 2.91-2.96 (m, 1H), 2.64-2.72 (m, 1H), 1.68-1.83 (m, 8H), 1.41-1.53 (m, 3H), 1.13-1.21 (m, 12H), 1.05-1.08 (m, 1H), 0.91-0.99 (m, 2H), 0.79-0.84 (m, 1H).	672.4
I-196B	17B	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.35-8.40 (m, 1H), 4.94-5.00 (m, 1H), 3.69-4.58 (m, 13H), 3.39-3.42 (m, 3H), 3.11-3.28 (m, 5H), 2.92-2.99 (m, 1H), 2.54-2.76 (m, 1H), 1.69-1.83 (m, 9H), 1.40-1.54 (m, 3H), 1.11-1.19 (m, 11H), 1.03-1.05 (m, 1H), 0.88-0.94 (m, 2H), 0.77-0.79 (m, 1H).	672.3
I-197	15	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.4 Hz, 1H), 4.91-5.00 (m, 1H),	658.4

[1074]

化合物编号	方法	^{1}HNMR	LCMS
		3.75-4.41 (m, 12H), 3.34-3.51 (m, 4H), 3.13-3.24 (m, 2H), 2.87-3.04 (m, 1H), 1.66-1.81 (m, 7H), 1.35-1.41 (m, 3H), 1.00-1.24 (m, 14H), 0.91-0.97 (m, 2H), 0.75-0.81 (m, 1H).	
I-198	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.4 Hz, 1H), 4.89-4.95 (m, 1H), 4.22-4.40 (m, 3H), 3.87-4.18 (m, 6H), 3.55-3.75 (m, 10H), 3.33-3.38 (m, 1H), 3.19-3.24 (m, 1H), 1.66-1.76 (m, 5H), 1.49-1.55 (m, 1H), 1.11-1.22 (m, 12H), 0.90-0.90 (m, 3H), 0.76-0.82 (m, 1H).	630.4
I-199	25	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (t, J = 8.8 Hz, 1H), 8.47 – 8.27 (m, 2H), 7.82 (dd, J = 25.8, 8.2 Hz, 1H), 7.39 – 7.07 (m, 10H), 5.38 – 5.30 (m, 2H), 5.20 – 5.11 (m, 1H), 4.71 (t, J = 12.8 Hz, 1H), 4.20 (dd, J = 42.4, 10.8 Hz, 2H), 4.11 – 4.00 (m, 2H), 3.88 (s, 1H), 3.78 (m, 3H), 3.56 (m, 1H), 3.46 – 3.33 (m, 1H), 2.62 (m, 3H), 1.48 (d, J = 11.8 Hz, 3H), 1.39 (s, 3H), 1.35 (t, J = 7.2 Hz, 1H), 1.11 (t, J = 6.0 Hz, 3H), 1.05 (t, J = 4.2 Hz, 3H), 0.90 – 0.83 (m, 1H), 0.72 – 0.65 (m, 1H).	703.40
I-200	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 15.0 Hz, 1H), 8.20 – 8.08 (m, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.39 – 7.11 (m, 7H), 5.35 (s, 2H), 4.33 – 4.12 (m, 2H), 4.10 – 3.77 (m, 6H), 3.73 – 3.46 (m, 3H), 3.26 – 3.21 (m, 1H), 3.18 – 3.12 (m, 1H), 1.73 – 1.59 (m, 5H), 1.51 – 1.39 (m, 1H), 1.37 – 1.26 (m, 1H), 1.22 – 1.08 (m, 6H), 1.07 – 1.01 (m, 6H), 0.90 – 0.80 (m, 3H), 0.70 – 0.63 (m, 1H).	633.0
I-201A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.32 (m, 1H), 8.28 – 8.17 (m, 1H), 7.86 – 7.78 (m, 1H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 5.23 – 5.09 (m, 1H), 4.26 – 4.12 (m, 3H), 4.10 – 3.83 (m, 4H), 3.80 – 3.57 (m, 3H), 3.29 – 3.18 (m, 1H), 2.07 – 1.90 (m, 2H), 1.83 – 1.72 (m, 2H), 1.39 – 1.31 (m, 1H), 1.12 – 1.01 (m, 6H), 0.88 – 0.81 (m, 1H), 0.71 – 0.62 (m, 1H).	506.0

[1075]

化合物编号	方法	^{1}HNMR	LCMS
I-201B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.33 (m, 1H), 8.32 – 8.16 (m, 1H), 7.86 – 7.79 (m, 1H), 7.40 – 7.21 (m, 5H), 5.37 – 5.33 (m, 2H), 5.22 – 5.05 (m, 1H), 4.48 – 4.41 (m, 1H), 4.26 – 4.17 (m, 2H), 4.16 – 3.93 (m, 3H), 3.91 – 3.81 (m, 1H), 3.80 – 3.69 (m, 2H), 3.68 – 3.53 (m, 2H), 3.26 – 3.17 (m, 1H), 2.08 – 1.94 (m, 2H), 1.86 – 1.72 (m, 2H), 1.41 – 1.33 (m, 1H), 1.12 – 1.04 (m, 6H), 0.89 – 0.82 (m, 1H), 0.71 – 0.64 (m, 1H).	506.0
I-202	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.20 (d, J = 16.0 Hz, 1H), 7.91 (d, J = 10.2 Hz, 1H), 7.37 – 7.23 (m, 5H), 5.37 (s, 2H), 4.41 – 4.28 (m, 2H), 4.20 – 3.79 (m, 8H), 3.47 – 3.38 (m, 2H), 3.26 – 3.18 (m, 1H), 2.73 (d, J = 8.4 Hz, 3H), 2.02 – 1.95 (m, 2H), 1.85 – 1.74 (m, 3H), 1.70 – 1.58 (m, 2H), 1.43 – 1.33 (m, 1H), 1.29 – 1.21 (m, 2H), 1.18 – 1.13 (m, 6H), 1.09 (s, 2H), 1.06 – 1.00 (m, 1H), 0.80 – 0.74 (m, 1H).	683.5
I-203	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 13.8 Hz, 1H), 8.24 – 8.11 (m, 1H), 7.82 (d, J = 15.8 Hz, 1H), 7.38 – 7.25 (m, 3H), 7.18 (t, J = 8.8 Hz, 3H), 5.34 (s, 2H), 4.30 (s, 1H), 4.25 – 3.37 (m, 11H), 3.21 (t, J = 8.0 Hz, 1H), 2.03 – 1.91 (m, 2H), 1.83 – 1.58 (m, 5H), 1.38 – 1.26 (m, 1H), 1.17 – 1.02 (m, 11H), 0.88 – 0.82 (m, 1H), 0.70 – 0.63 (m, 1H).	687.4
I-204	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.33 (m, 2H), 7.94 – 7.78 (m, 2H), 7.40 – 7.21 (m, 5H), 5.35 (s, 2H), 4.34 (q, J = 4.8 Hz, 1H), 4.19 (m, 1H), 4.04 (m, 6H), 3.88 (dd, J = 16.8, 7.6 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.52 – 3.35 (m, 1H), 2.59 (dd, J = 8.8, 4.2 Hz, 3H), 1.37 – 1.27 (m, 1H), 1.08 (m, 9H), 0.85 (m, 1H), 0.67 (dd, J = 8.0, 3.6 Hz, 1H).	633.4
I-205A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 15.4 Hz, 1H), 8.26 – 8.16 (m, 1H), 7.87 – 7.73 (m, 2H), 7.40 – 7.21 (m, 5H), 5.36 (s,	673.4

[1076]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 4.33 – 4.26 (m, 1H), 4.23 – 4.04 (m, 2H), 4.01 – 3.59 (m, 8H), 3.54 – 3.36 (m, 2H), 2.62 – 2.55 (m, 3H), 1.37 – 1.24 (m, 1H), 1.12 – 1.02 (m, 9H), 0.93 – 0.81 (m, 5H), 0.70 – 0.63 (m, 1H).	
I-205B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.20 (m, 2H), 7.91 – 7.76 (m, 2H), 7.41 – 7.19 (m, 5H), 5.35 (s, 2H), 4.37 – 4.12 (m, 2H), 4.09 – 3.90 (m, 3H), 3.84 – 3.57 (m, 6H), 3.52 – 3.35 (m, 2H), 2.59 (t, J = 5.2 Hz, 3H), 1.40 – 1.31 (m, 1H), 1.13 – 1.08 (m, 3H), 1.07 – 0.97 (m, 6H), 0.92 – 0.77 (m, 5H), 0.73 – 0.63 (m, 1H).	673.0
I-206	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (dt, J = 18.4, 6.6 Hz, 1H), 8.41 – 8.33 (m, 1H), 7.83 (d, J = 14.2 Hz, 1H), 7.41 – 7.21 (m, 5H), 7.16 (t, J = 8.4, 7.0 Hz, 2H), 6.60 (t, J = 7.2 Hz, 1H), 6.56 – 6.50 (m, 2H), 5.35 (d, J = 3.6 Hz, 2H), 4.42 (s, 1H), 4.24 – 3.59 (m, 8H), 3.52 – 3.44 (m, 1H), 3.36 (d, J = 8.0 Hz, 1H), 3.29 – 3.16 (m, 1H), 3.16 – 3.01 (m, 2H), 2.22 – 2.11 (m, 1H), 1.91 – 1.80 (m, 1H), 1.41 – 1.28 (m, 1H), 1.14 – 1.03 (m, 6H), 0.89 – 0.83 (m, 1H), 0.73 – 0.65 (m, 1H).	581.5
I-207	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 – 8.50 (m, 1H), 8.43 – 8.32 (m, 1H), 7.83 (d, J = 11.8 Hz, 1H), 7.38 – 7.24 (m, 5H), 7.19 – 7.12 (m, 2H), 6.60 (t, J = 7.0 Hz, 1H), 6.51 (t, J = 8.2 Hz, 2H), 5.36 (s, 2H), 4.49 – 4.36 (m, 1H), 4.22 – 3.45 (m, 9H), 3.43 – 3.35 (m, 1H), 3.29 – 3.21 (m, 1H), 3.21 – 3.07 (m, 1H), 3.07 – 2.99 (m, 1H), 2.26 – 2.12 (m, 1H), 1.98 – 1.83 (m, 1H), 1.40 – 1.20 (m, 1H), 1.13 – 1.00 (m, 6H), 0.90 – 0.80 (m, 1H), 0.72 – 0.61 (m, 1H).	581.5
I-208A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 – 8.14 (m, 1H), 7.83 – 7.67 (m, 1H), 4.29 – 4.01 (m, 3H), 3.98 – 3.77 (m, 3H), 3.75 – 3.58 (m, 4H), 3.52 – 3.42 (m, 1H), 3.26 – 3.19 (m, 1H), 3.12 – 3.06 (m, 1H), 2.62 – 2.54 (m, 3H), 2.38 – 2.34 (m, 3H), 1.70 – 1.58 (m,	622.4

[1077]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 1.48 – 1.38 (m, 1H), 1.36 – 1.26 (m, 1H), 1.25 – 0.97 (m, 13H), 0.87 – 0.81 (m, 2H), 0.70 – 0.63 (m, 1H).	
I-208B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 – 8.17 (m, 1H), 7.91 – 7.77 (m, 1H), 4.37 – 3.90 (m, 4H), 3.84 – 3.70 (m, 3H), 3.66 – 3.58 (m, 2H), 3.53 – 3.40 (m, 1H), 3.30 – 3.19 (m, 2H), 3.14 – 3.03 (m, 1H), 2.59 (t, J = 4.7 Hz, 3H), 2.39 – 2.31 (m, 3H), 1.69 – 1.56 (m, 5H), 1.46 – 1.32 (m, 2H), 1.21 – 1.08 (m, 6H), 1.07 – 1.04 (m, 2H), 1.04 – 0.93 (m, 4H), 0.89 – 0.76 (m, 3H), 0.72 – 0.64 (m, 1H).	622.4
I-209A	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 – 8.55 (m, 1H), 8.37 (d, J = 10.2 Hz, 1H), 7.83 (d, J = 11.4 Hz, 1H), 7.44 – 7.20 (m, 5H), 5.35 (s, 2H), 5.10 (q, J = 6.0 Hz, 1H), 4.38 (s, 1H), 4.24 – 4.05 (m, 2H), 4.04 – 3.82 (m, 3H), 3.80 – 3.67 (m, 3H), 3.61 (d, J = 18.4 Hz, 5H), 3.30 (s, 1H), 1.34 (d, J = 7.6 Hz, 1H), 1.12 – 1.08 (m, 3H), 1.07 – 1.02 (m, 3H), 0.85 (s, 1H), 0.67 (s, 1H).	538.4
I-209B	2B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.61 (m, 1H), 8.41 – 8.31 (m, 1H), 7.88 – 7.76 (m, 1H), 7.46 – 7.14 (m, 5H), 5.35 (s, 2H), 5.15 (s, 1H), 4.46 – 4.32 (m, 1H), 4.20 – 3.99 (m, 2H), 3.98 – 3.84 (m, 2H), 3.83 – 3.59 (m, 8H), 3.40 (s, 1H), 3.30 (s, 1H), 1.42 – 1.29 (m, 1H), 1.15 – 1.10 (m, 3H), 1.09 – 1.04 (m, 3H), 0.92 – 0.81 (m, 1H), 0.75 – 0.61 (m, 1H).	538.4
I-210	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.25 – 8.11 (m, 1H), 7.96 – 7.79 (m, 1H), 7.36 – 7.15 (m, 10H), 5.39 – 5.35(m, 2H), 4.39 – 4.16 (m, 3H), 4.14 – 3.69 (m, 9H), 3.69 – 3.36 (m, 2H), 3.28 – 2.49 (m, 4H), 1.46 – 1.31 (m, 1H), 1.19 – 1.00 (m, 7H), 0.80 – 0.72 (m, 1H).	596.4
I-211	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.29 – 8.17 (m, 1H), 7.97 – 7.89 (m, 1H), 7.41 – 7.25 (m, 5H), 5.41 – 5.38 (m, 2H), 4.46 – 3.55 (m, 12H), 3.52 – 3.37 (m, 1H), 3.28 – 2.85 (m,	629.5

[1078]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 2.49 – 2.18 (m, 1H), 2.02 – 1.75 (m, 6H), 1.66 – 1.51 (m, 2H), 1.48 – 1.29 (m, 4H), 1.27 – 1.03 (m, 11H), 0.85 – 0.74 (m, 1H)	
I-212	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.28 – 8.16 (m, 1H), 7.97 – 7.87 (m, 1H), 7.41 – 7.17 (m, 5H), 5.43 – 5.33 (m, 2H), 4.45 – 3.73 (m, 9H), 3.66 – 3.44 (m, 2H), 3.26 – 2.56 (m, 5H), 2.13 – 1.98 (m, 2H), 1.95 – 1.70 (m, 7H), 1.68 – 1.34 (m, 4H), 1.27 – 1.10 (m, 7H), 1.08 – 0.76 (m, 4H).	615.5
I-213A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.12 (m, 1H), 7.84 – 7.65 (m, 1H), 4.27 – 3.99 (m, 3H), 3.97 – 3.50 (m, 8H), 3.26 – 3.19 (m, 1H), 3.13 – 3.06 (m, 1H), 2.64 – 2.61 (m, 3H), 2.60 – 2.54 (m, 3H), 2.34 (s, 3H), 1.68 – 1.57 (m, 5H), 1.47 – 1.38 (m, 1H), 1.36 – 1.26 (m, 1H), 1.21 – 0.98 (m, 13H), 0.86 – 0.81 (m, 2H), 0.69 – 0.63 (m, 1H).	602.4
I-213B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.91 – 7.74 (m, 1H), 4.40 – 3.87 (m, 4H), 3.81 – 3.57 (m, 6H), 3.44 (s, 1H), 3.24 (s, 1H), 3.08 (s, 1H), 2.61 (s, 3H), 2.59 (t, J = 4.6 Hz, 3H), 2.33 (d, J = 3.6 Hz, 3H), 1.63 (s, 5H), 1.33 (s, 2H), 1.08 (d, J = 24.4 Hz, 12H), 0.85 (s, 3H), 0.68 (s, 1H).	602.4
I-214	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.26 – 8.15 (m, 1H), 7.95 – 7.87 (m, 1H), 7.40 – 7.19 (m, 10H), 5.40 – 5.34 (m, 2H), 4.62 – 4.55 (m, 2H), 4.39 – 4.20 (m, 2H), 4.16 – 3.71 (m, 10H), 3.51 – 3.35 (m, 2H), 2.05 – 1.54 (m, 5H), 1.46 – 1.27 (m, 3H), 1.21 – 1.00 (m, 6H), 0.82 – 0.74 (m, 1H)	610.5
I-215	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.16 (m, 1H), 7.98 – 7.85 (m, 1H), 7.48 – 7.17 (m, 5H), 5.43 – 5.30 (m, 2H), 4.41 – 3.67 (m, 11H), 3.22 – 2.57 (m, 4H), 2.10 – 1.52 (m, 9H), 1.49 – 0.99 (m, 14H), 0.84 – 0.74 (m, 1H).	629.5
I-216	27	^{1}HNMR (400 MHz, CD_3OD):δ 7.68-7.78 (m, 1H), 6.75-6.78 (m, 1H), 5.51 (d, J = 12.2 Hz, 0.5H), 4.91-4.96 (m, 1H), 3.86-4.64 (m, 9H),	611.3

[1079]

化合物编号	方法	^{1}HNMR	LCMS
		3.71-3.75 (m, 1H), 3.55-3.56 (m, 4H), 3.32-3.41 (m, 2H), 3.17-3.23 (m, 1H), 1.51-1.76 (m, 11H), 1.37-1.47 (m, 1H), 1.11-1.28 (m, 12H), 1.01-1.07 (m, 1H), 0.91-0.97 (m, 2H), 0.74-0.81 (m, 1H).	
I-217	27	^{1}HNMR (400 MHz, CD_3OD): δ 8.55-8.56 (m, 1H), 7.72-7.75 (m, 1H), 4.91-4.95 (m, 1H), 3.70-4.41 (m, 10H), 3.33-3.56 (m, 6H), 3.17-3.23 (m, 1H), 1.50-1.76 (m, 11H), 1.11-1.45 (m, 13H), 1.02-1.07 (m, 1H), 0.89-0.97 (m, 2H), 0.76-0.80 (m, 1H).	628.4
I-218	16A	^{1}HNMR (400 MHz, $CDCl_3$): δ 8.45-8.71 (m, 2H), 7.84-7.93 (m, 2H), 7.30-7.33 (m, 5H), 5.30-5.35 (m, 2H), 4.79-4.98 (m, 1H), 3.79-4.48 (m, 9H), 3.49-3.64 (m, 2H), 2.81-3.25 (m, 10H), 1.93-2.26 (m, 2H), 1.54-1.75 (m, 5H), 1.44-1.47 (m, 1H), 1.02-1.32 (m, 15H), 0.76-0.88 (m, 1H).	716.6
I-219	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.22 (d, J = 22.0 Hz, 1H), 7.92 (d, J = 14.0 Hz, 1H), 7.27-7.37 (m, 5H), 5.38 (s, 2H), 4.91-4.95 (m, 1H), 4.47-4.60 (m, 1H), 3.63-4.39 (m, 12H), 3.33-3.41 (m, 1H), 3.12-3.24 (m, 2H), 2.80-2.88 (m, 2H), 2.64-2.71 (m, 1H), 1.83-1.98 (m, 2H), 1.62-1.80 (m, 6H), 1.47-1.56 (m, 1H), 1.01-1.24 (m, 16H), 0.90-0.97 (m, 2H), 0.75-0.81 (m, 1H).	731.0
I-220	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.20-8.25 (m, 1H), 7.89-7.93 (m, 1H), 7.24-7.37 (m, 5H), 5.38 (s, 2H), 4.68-4.71 (m, 1H), 3.72-4.38 (m, 12H), 3.60-3.68 (m, 1H), 3.50-3.43 (m, 2H), 3.22-3.26 (m, 1H), 3.08-3.13 (m, 1H), 2.95-3.02 (m, 1H), 1.90-2.21 (m, 4H), 1.67-1.84 (m, 6H), 1.50-1.60 (m, 1H), 1.37-1.44 (m, 1H), 1.11-1.26 (m, 12H), 1.02-1.06 (m, 1H), 0.94-1.00 (m, 2H), 0.76-0.81 (m, 1H).	717.1
I-221	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.25 (m, 2H), 7.87 – 7.79 (m, 1H), 7.37 – 7.25 (m, 5H), 5.37 – 5.34 (m, 2H), 4.25 – 3.52 (m, 10H), 3.26 – 2.89 (m, 4H), 1.74 (s, 1H), 1.56	534.4

[1080]

化合物编号	方法	^{1}HNMR	LCMS
		– 1.22 (m, 6H), 1.12 – 1.04 (m, 6H), 0.88 – 0.82 (m, 1H), 0.70 – 0.65 (m, 1H).	
I-222	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.32 (m, 1H), 8.14 – 8.04 (m, 1H), 7.87 – 7.79 (m, 1H), 7.79 – 7.69 (m, 1H), 7.39 – 7.22 (m, 5H), 5.36 (s, 2H), 4.33 – 3.59 (m, 11H), 3.15 – 3.08 (m, 1H), 3.00 – 2.90 (m, 1H), 2.61 – 2.55 (m, 3H), 1.37 – 1.20 (m, 2H), 1.12 – 1.01 (m, 9H), 0.85 – 0.81 (m, 9H), 0.69 – 0.65 (m, 1H).	662.45
I-223	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.31 (m, 2H), 7.83 (d, J = 12.4 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.39 – 7.21 (m, 5H), 5.35 (s, 2H), 4.23 – 3.56 (m, 9H), 3.21 – 3.00 (m, 3H), 2.46 – 2.33 (m, 1H), 2.12 – 1.98 (m, 1H), 1.82 (s, 1H), 1.60 (s, 1H), 1.39 – 1.29 (m, 1H), 1.13 – 1.01 (m, 6H), 0.89 – 0.82 (m, 1H), 0.72 – 0.64 (m, 1H).	533.4
I-224A	1A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.00 (s, 1H), 4.40 – 4.26 (m, 2H), 4.16 – 3.76 (m, 6H), 3.68 (s, 1H), 3.49 – 3.39 (m, 1H), 3.39 – 3.32 (m, 2H), 3.20 – 3.11 (m, 1H), 2.74 (d, J = 19.6 Hz, 3H), 2.03 (d, J = 5.2 Hz, 2H), 1.90 – 1.65 (m, 11H), 1.51 (s, 1H), 1.38 (s, 1H), 1.30 – 1.02 (m, 14H), 0.97 – 0.87 (m, 2H), 0.78 (s, 1H).	642.5
I-224B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.35 – 8.16 (m, 1H), 7.84 (d, J = 26.8 Hz, 1H), 4.37 – 3.43 (m, 10H), 3.30 – 3.21 (m, 2H), 3.14 – 3.01 (m, 1H), 2.62 – 2.55 (m, 3H), 1.98 – 1.81 (m, 2H), 1.78 – 1.30 (m, 13H), 1.17 – 0.62 (m, 17H).	642.4
I-225	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 – 8.56 (m, 1H), 8.41 – 8.33 (m, 1H), 8.12 (t, J = 5.2 Hz, 1H), 7.87 – 7.79 (m, 1H), 7.37 – 7.22 (m, 10H), 5.36 (d, J = 3.8 Hz, 2H), 4.54 – 4.44 (m, 1H), 4.32 – 4.19 (m, 1H), 4.10 – 4.00 (m, 2H), 3.94 – 3.83 (m, 1H), 3.80 – 3.57 (m, 6H), 3.27 (d, J = 12.0 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.79 – 2.70 (m, 1H), 2.62 – 2.57 (m, 3H), 1.33 – 1.24 (m, 1H), 1.12 – 1.00 (m,	643.4

[1081]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 0.97 (s, 1H), 0.87 – 0.80 (m, 1H), 0.67 – 0.60 (m, 1H).	
I-226	25，从I-225开始	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.15 (m, 1H), 7.92 (d, J = 13.4 Hz, 1H), 7.49 – 7.24 (m, 10H), 5.37 (d, J = 6.2 Hz, 2H), 5.04 – 4.93 (m, 1H), 4.62 – 4.51 (m, 1H), 4.49 – 4.44 (m, 2H), 4.26 – 3.73 (m, 8H), 3.70 – 3.60 (m, 1H), 3.26 – 3.17 (m, 1H), 2.72 (d, J = 15.8 Hz, 3H), 1.44 – 1.28 (m, 2H), 1.15 – 1.10 (m, 2H), 1.09 – 1.07 (m, 3H), 1.03 – 0.97 (m, 1H), 0.76 – 0.63 (m, 1H).	675.40
I-227A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 – 8.13 (m, 1H), 7.75 (s, 1H), 4.26 – 3.42 (m, 11H), 3.28 – 3.19 (m, 2H), 3.13 – 3.06 (m, 1H), 2.62 – 2.54 (m, 3H), 2.36 (s, 3H), 1.69 – 1.56 (m, 5H), 1.49 – 1.27 (m, 8H), 1.19 – 1.00 (m, 12H), 0.89 – 0.75 (m, 3H), 0.70 – 0.62 (m, 1H).	630.5
I-227B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.93 – 7.74 (m, 1H), 4.39 – 3.88 (m, 4H), 3.78 – 3.60 (m, 5H), 3.54 – 3.35 (m, 2H), 3.28 – 3.19 (m, 2H), 3.14 – 3.03 (m, 1H), 2.62 – 2.56 (m, 3H), 2.40 – 2.30 (m, 3H), 1.62 (s, 5H), 1.40 – 1.28 (m, 8H), 1.20 – 0.95 (m, 12H), 0.85 (s, 3H), 0.71 – 0.63 (m, 1H).	630.0
I-228A	1A+8A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.50 – 8.40 (m, 1H), 8.09 – 7.92 (m, 2H), 4.96 – 4.86 (m, 1H), 4.22 – 3.83 (m, 6H), 3.78 – 3.47 (m, 9H), 3.40 – 3.32 (m, 1H), 3.27 – 3.20 (m, 1H), 2.02 – 1.70 (m, 10H), 1.66 – 1.56 (m, 1H), 1.39 – 1.24 (m, 1H), 1.19 – 1.04 (m, 11H), 0.89 – 0.82 (m, 1H), 0.71 – 0.65 (m, 1H).	683.5
I-228B	1B+8B	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 8.55 (dt, J = 25.4, 9.6 Hz, 1H), 8.17 (d, J = 18.2 Hz, 1H), 7.83 (d, J = 14.2 Hz, 1H), 4.87 (t, J = 7.2 Hz, 1H), 4.30 – 4.11 (m, 1H), 4.10 – 3.90 (m, 3H), 3.84 – 3.56 (m, 9H), 3.47 – 3.33 (m, 2H), 3.20 (q, J = 9.4, 8.8 Hz, 1H), 2.06 – 1.86 (m, 6H), 1.81 – 1.65 (m, 4H), 1.54 (dd, J = 13.8, 3.4 Hz, 1H), 1.39 –	683.0

[1082]

化合物编号	方法	^{1}HNMR	LCMS
		1.26 (m, 1H), 1.15 – 1.01 (m, 11H), 0.89 – 0.82 (m, 1H), 0.67 (dd, J = 8.0, 4.0 Hz, 1H)	
I-229A	1A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.27 – 8.17 (m, 1H), 8.16 – 8.10 (m, 1H), 7.82 – 7.68 (m, 1H), 4.29 – 4.04 (m, 4H), 4.00 – 3.63 (m, 6H), 3.58 – 3.43 (m, 1H), 3.26 – 3.19 (m, 1H), 3.13 – 3.07 (m, 1H), 2.61 – 2.55 (m, 3H), 1.71 – 1.60 (m, 5H), 1.48 – 1.36 (m, 11H), 1.16 – 1.00 (m, 12H), 0.89 – 0.77 (m, 3H), 0.70 – 0.64 (m, 1H).	630.5
I-229B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 – 8.23 (m, 1H), 8.16 – 8.08 (m, 1H), 7.90 – 7.76 (m, 1H), 4.36 – 3.44 (m, 11H), 3.27 – 3.18 (m, 1H), 3.12 – 3.03 (m, 1H), 2.59 (t, J = 4.8 Hz, 3H), 1.68 – 1.56 (m, 5H), 1.41 – 1.32 (m, 11H), 1.15 – 0.94 (m, 12H), 0.89 – 0.77 (m, 3H), 0.73 – 0.64 (m, 1H).	630.4
I-230	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 – 9.04 (m, 1H), 8.40 – 8.33 (m, 1H), 7.86 – 7.81 (m, 1H), 7.71 – 7.62 (m, 2H), 7.42 – 7.21 (m, 7H), 5.35 (s, 2H), 4.76 – 4.50 (m, 2H), 4.38 – 4.23 (m, 1H), 4.20 – 3.88 (m, 4H), 3.87 – 3.63 (m, 3H), 3.31 – 3.18 (m, 1H), 1.37 – 1.32 (m, 1H), 1.13 – 0.98 (m, 6H), 0.87 – 0.83 (m, 1H), 0.69 – 0.64 (m, 1H).	567.4
I-231A	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 – 9.03 (m, 1H), 8.25 – 8.09 (m, 1H), 7.83 – 7.68 (m, 1H), 4.31 – 3.93 (m, 3H), 3.92 – 3.73 (m, 3H), 3.71 – 3.49 (m, 3H), 3.47 – 3.35 (m, 2H), 3.26 – 3.19 (m, 1H), 3.13 – 3.04 (m, 1H), 2.61 – 2.54 (m, 3H), 1.71 – 1.55 (m, 5H), 1.49 – 1.36 (m, 1H), 1.34 – 1.26 (m, 10H), 1.18 – 0.98 (m, 12H), 0.89 – 0.77 (m, 3H), 0.71 – 0.62 (m, 1H).	630.4
I-231B	1B	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 4.8 Hz, 1H), 8.32 – 8.17 (m, 1H), 7.90 – 7.79 (m, 1H), 4.34 – 4.16 (m, 2H), 4.11 – 4.01 (m, 1H), 3.91 (t, J = 9.4 Hz, 1H), 3.83 – 3.74 (m, 2H), 3.67 (m, 1H), 3.59 (m, 2H), 3.49 – 3.46 (m, 1H), 3.30 – 3.18 (m, 2H), 3.12 – 3.02 (m, 1H), 2.58 (td, J = 4.5, 2.2 Hz, 3H), 1.60 (d, J = 31.2 Hz, 6H), 1.30 (dd, J =	630.4

[1083]

化合物编号	方法	^{1}HNMR	LCMS
		6.8, 3.6 Hz, 12H), 1.11 (d, J = 4.2 Hz, 3H), 1.06 (dd, J = 6.2, 2.8 Hz, 4H), 1.02 (dd, J = 6.4, 2.0 Hz, 2H), 0.99 – 0.96 (m, 2H), 0.84 (d, J = 10.7 Hz, 2H), 0.70 – 0.65 (m, 1H).	
I-232A	1A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 4.43 – 3.79 (m, 9H), 3.50 – 3.33 (m, 2H), 3.19 – 3.12 (m, 1H), 2.78 – 2.71 (m, 3H), 1.78 – 1.65 (m, 5H), 1.57 – 1.47 (m, 1H), 1.37 – 1.13 (m, 11H), 1.11 (s, 2H), 1.08 – 1.00 (m, 1H), 0.97 – 0.85 (m, 2H), 0.81 – 0.74 (m, 1H).	642.3
I-232B	1B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 4.60 – 4.51 (m, 1H), 4.41 – 4.34 (m, 1H), 4.29 – 3.69 (m, 9H), 3.50 – 3.34 (m, 3H), 3.20 – 3.12 (m, 1H), 2.75 (s, 3H), 1.78 – 1.65 (m, 5H), 1.56 – 1.43 (m, 2H), 1.33 – 1.05 (m, 15H), 0.98 – 0.87 (m, 2H), 0.81 – 0.75 (m, 1H).	642.3
I-233	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.55 (m, 1H), 8.46 – 8.37 (m, 1H), 7.87 (d, J = 12.6 Hz, 1H), 7.43 – 7.25 (m, 5H), 5.40 (s, 2H), 4.27 – 4.10 (m, 4H), 4.10 – 3.87 (m, 3H), 3.85 – 3.71 (m, 2H), 3.67 – 3.62 (m, 1H), 3.54 (q, J = 6.2 Hz, 1H), 3.17 – 3.01 (m, 1H), 2.22 – 2.08 (m, 4H), 1.42 – 1.35 (m, 1H), 1.17 – 1.09 (m, 6H), 1.09 – 1.06 (m, 6H), 0.91 – 0.86 (m, 1H), 0.74 – 0.68 (m, 1H).	548.3
I-234	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 – 8.42 (m, 1H), 8.37 (d, J = 6.6 Hz, 1H), 7.83 (d, J = 11.2 Hz, 1H), 7.39 – 7.24 (m, 5H), 5.36 (s, 2H), 4.22 – 3.97 (m, 3H), 3.94 – 3.84 (m, 2H), 3.81 – 3.66 (m, 4H), 3.62 – 3.49 (m, 2H), 3.12 – 2.94 (m, 1H), 2.60 – 2.52 (m, 2H), 1.82 – 1.68 (m, 2H), 1.38 – 1.31 (m, 1H), 1.13 – 1.05 (m, 6H), 1.05 – 1.02 (m, 6H), 0.87 – 0.84 (m, 1H), 0.71 – 0.63 (m, 1H).	548.3
I-235	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.28 – 8.15 (m, 1H), 7.96 – 7.86 (m, 1H), 7.38 – 7.28 (m, 5H), 5.40 – 5.33 (m, 2H), 4.36 – 3.37 (m, 13H), 3.29 – 3.20 (m, 1H), 2.19 – 1.90 (m, 2H), 1.80 – 1.61 (m, 5H), 1.58 – 0.85 (m, 16H), 0.82 – 0.72 (m, 1H).	602.5

[1084]

化合物编号	方法	^{1}HNMR	LCMS
I-236	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.15 (m, 1H), 7.96 – 7.86 (m, 1H), 7.39 – 7.22 (m, 5H), 5.38 – 5.36 (m, 2H), 4.39 – 4.21 (m, 2H), 4.17 – 3.72 (m, 8H), 3.66 – 3.47 (m, 2H), 3.25 – 3.17 (m, 1H), 2.10 – 0.76 (m, 27H).	616.5
I-237	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.31 – 8.14 (m, 1H), 7.97 – 7.86 (m, 1H), 7.38 – 7.23 (m, 5H), 5.38 (s, 2H), 4.37 – 4.22 (m, 2H), 4.18 – 3.48 (m, 11H), 2.57 – 2.16 (m, 6H), 1.91 – 1.62 (m, 5H), 1.60 – 1.37 (m, 2H), 1.33 – 1.23 (m, 3H), 1.18 – 0.77 (m, 10H)	601.5
I-238	16A	^{1}HNMR (400 MHz, DMSO-d_6): δ 8.10-8.14 (m, 1H), 7.80-7.84 (m, 1H), 7.19-7.27 (m, 5H), 5.28 (s, 2H), 4.53-4.60 (m, 1H), 3.99-4.27 (m, 5H), 3.69-3.91 (m, 7H), 3.54-3.59 (m, 1H), 3.25-3.30 (m, 2H), 3.12-3.15 (m, 1H), 2.81-2.92 (m, 2H), 1.73-2.00 (m, 5H), 1.56-1.63 (m, 5H), 1.29-1.43 (m, 2H), 1.01-1.11 (m, 10H), 0.95 (s, 1H), 0.82-0.85 (m, 2H), 0.67-0.69 (m, 1H).	716.9
I-239	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.09-8.14 (m, 1H), 7.80-7.84 (m, 1H), 7.17-7.27 (m, 5H), 5.28 (s, 2H), 3.57-4.46 (m, 16H), 3.23-3.27 (m, 1H), 3.12-3.21 (m, 1H), 2.98-3.03 (m, 2H), 2.73-2.82 (m, 1H), 1.57-1.70 (m, 5H), 1.39-1.52 (m, 2H), 1.13-1.16 (m, 2H), 1.01-1.09 (m, 10H), 0.93-0.95 (m, 1H), 0.80-0.90 (m, 3H), 0.65-0.70 (m, 1H).	702.9
I-240	16A	^{1}HNMR (400 MHz, DMSO-d_6): δ 8.12 (d, J = 17.6 Hz, 1H), 7.82 (d, J = 13.6 Hz, 1H), 7.19-7.27 (m, 5H), 5.28 (s, 2H), 4.42-4.44 (m, 1H), 4.28-4.35 (m, 2H), 3.63-4.25 (m, 16H), 3.25-3.33 (m, 2H), 3.10-3.15 (m, 1H), 1.56-1.65 (m, 5H), 1.27-1.45 (m, 3H), 1.13-1.19 (m, 6H), 1.00-1.02 (m, 3H), 0.80-0.94 (m, 5H), 0.68-0.69 (m, 1H).	714.9
I-241	16A	^{1}HNMR (400 MHz, CD_3OD): δ 4.93-4.99 (m, 1H), 3.85-4.59 (m, 9H), 3.73-3.77 (m, 1H), 3.52-3.64 (m, 4H), 3.35-3.46 (m, 2H), 3.20-3.25 (m, 1H), 2.49 (d, J = 6.6 Hz, 3H), 1.54-1.79 (m, 11H), 1.39-1.48 (m, 1H), 1.14-	626.4

[1085]

化合物编号	方法	^{1}HNMR	LCMS
		1.31 (m, 12H), 1.05-1.09 (m, 1H), 0.94-0.99 (m, 2H), 0.78-0.82 (m, 1H).	
I-242	15	^{1}HNMR (400 MHz, CD_3OD): δ 4.94-4.97 (m, 1H), 3.50-4.38 (m, 15H), 3.37-3.47 (m, 2H), 3.21-3.24 (m, 1H), 3.09-3.15 (m, 1H), 2.97 (s, 3H), 2.42-2.47 (m, 2H), 1.92-2.07 (m, 2H), 1.52-1.79 (m, 11H), 1.15-1.45 (m, 14H), 1.05-1.09 (m, 1H), 0.94-0.99 (m, 2H), 0.78-0.83 (m, 1H).	656.4
I-243	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (m, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 10.2 Hz, 1H), 7.39 – 7.24 (m, 5H), 5.36 (s, 2H), 4.36 (m, 1H), 4.24 – 4.13 (m, 1H), 4.12 – 3.87 (m, 4H), 3.87 – 3.65 (m, 3H), 3.64 (m, 1H), 3.27 – 3.10 (m, 3H), 2.70 – 2.64 (m, 1H), 2.23 (m, 1H), 1.66 (p, J = 10.8 Hz, 1H), 1.37 – 1.29 (m, 1H), 1.11 – 1.02 (m, 6H), 0.84 (d, J = 4.6 Hz, 1H), 0.69 – 0.63 (m, 4H).	559.40
I-244	2A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 – 8.48 (m, 2H), 8.43 – 8.34 (m, 2H), 7.94 – 7.79 (m, 2H), 7.39 – 7.21 (m, 7H), 5.36 (s, 2H), 4.63 – 4.45 (m, 2H), 4.41 – 4.34 (m, 1H), 4.28 – 4.14 (m, 1H), 4.10 – 3.50 (m, 9H), 2.65 – 2.56 (m, 3H), 1.34 – 1.20 (m, 1H), 1.13 – 0.99 (m, 9H), 0.86 – 0.80 (m, 1H), 0.67 – 0.57 (m, 1H).	642.3
I-245	23	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.28 (m, 2H), 8.21 (s, 1H), 7.82 (d, J = 12.4 Hz, 1H), 7.45 – 7.18 (m, 5H), 5.35 (s, 2H), 4.16 (d, J = 8.8 Hz, 1H), 4.13 – 4.03 (m, 2H), 3.99 (d, J = 9.6 Hz, 2H), 3.87 (t, J = 11.8 Hz, 2H), 3.79 – 3.74 (m, 2H), 3.66 – 3.54 (m, 4H), 3.29 – 3.07 (m, 2H), 2.99 (s, 1H), 2.81 (s, 2H), 1.41 – 1.26 (m, 1H), 1.14 – 1.08 (m, 3H), 1.05 (d, J = 8.6 Hz, 3H), 0.85 (d, J = 5.2 Hz, 1H), 0.74 – 0.62 (m, 1H).	535.3
I-246	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.30 – 8.19 (m, 1H), 7.82 – 7.72 (m, 1H), 4.44 – 4.07 (m, 5H), 3.99 – 3.69 (m, 5H), 3.62 – 3.48 (m, 1H), 3.26 – 3.20 (m, 1H), 3.15 – 3.07 (m, 1H), 2.62 – 2.55 (m, 3H), 1.73 – 1.57 (m, 5H), 1.50 – 1.39 (m,	575.4

[1086]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 1.37 – 1.25 (m, 1H), 1.21 – 1.07 (m, 7H), 1.06 – 1.01 (m, 5H), 0.91 – 0.78 (m, 3H), 0.72 – 0.64 (m, 1H).	
I-247	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, J = 7.6 Hz, 2H), 8.43 – 8.33 (m, 2H), 7.93 – 7.80 (m, 3H), 7.56 – 7.50 (m, 1H), 7.39 – 7.22 (m, 5H), 5.36 (s, 2H), 4.67 – 4.59 (m, 1H), 4.54 – 4.47 (m, 1H), 4.41 – 4.34 (m, 1H), 4.15 – 3.56 (m, 10H), 2.62 – 2.56 (m, 3H), 1.25 (q, J = 6.4 Hz, 1H), 1.13 – 0.98 (m, 9H), 0.83 (t, J = 4.6 Hz, 1H), 0.69 – 0.59 (m, 1H).	642.4
I-248	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.33 (m, 1H), 8.29 – 8.19 (m, 1H), 7.86 – 7.79 (m, 1H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 4.23 – 4.00 (m, 3H), 3.99 – 3.83 (m, 3H), 3.80 – 3.69 (m, 3H), 3.65 – 3.57 (m, 1H), 3.19 – 3.14 (m, 3H), 3.13 – 2.99 (m, 1H), 2.21 – 2.11 (m, 1H), 1.85 – 1.74 (m, 1H), 1.72 – 1.61 (m, 2H), 1.50 – 1.38 (m, 2H), 1.36 – 1.21 (m, 1H), 1.13 – 1.01 (m, 6H), 0.88 – 0.80 (m, 1H), 0.71 – 0.61 (m, 1H).	534.4
I-249	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.8 Hz, 1H), 8.24 – 8.13 (m, 1H), 7.86 – 7.70 (m, 2H), 7.37 – 7.24 (m, 5H), 5.35 (s, 2H), 4.30 – 3.60 (m, 11H), 3.26 – 3.20 (m, 1H), 3.13 – 3.05 (m, 1H), 2.61 – 2.56 (m, 3H), 1.67 – 1.56 (m, 3H), 1.40 – 1.29 (m, 3H), 1.12 – 0.99 (m, 10H), 0.85 (d, J = 6.4 Hz, 7H), 0.70 – 0.63 (m, 1H), 0.50 – 0.37 (m, 3H).	675.6
I-250	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 – 8.53 (m, 1H), 8.39 – 8.34 (m, 1H), 7.87 – 7.78 (m, 1H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.20 – 3.58 (m, 8H), 3.37 – 3.29 (m, 2H), 3.23 (dd, J = 10.6, 3.6 Hz, 3H), 3.11 – 2.94 (m, 1H), 1.38 – 1.25 (m, 1H), 1.13 – 1.04 (m, 6H), 0.88 – 0.82 (m, 1H), 0.71 – 0.57 (m, 5H).	520.4
I-251	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.41 – 8.26 (m, 2H), 7.89 – 7.77 (m, 2H), 7.38 – 7.29 (m, 3H), 7.28 – 7.21 (m, 3H), 7.10 – 7.04 (m, 1H), 6.85 – 6.71 (m, 2H), 5.36 (s, 2H), 4.52 – 4.35 (m, 3H), 4.29 –	657.4

[1087]

化合物编号	方法	^{1}HNMR	LCMS
		3.87 (m, 6H), 3.78 – 3.47 (m, 4H), 2.63 – 2.57 (m, 3H), 1.35 – 1.21 (m, 1H), 1.12 – 1.07 (m, 3H), 1.07 – 1.02 (m, 6H), 0.86 – 0.81 (m, 1H), 0.68 – 0.59 (m, 1H).	
I-252	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, J = 5.4 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 10.6 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.68 – 4.43 (m, 2H), 4.27 – 4.13 (m, 1H), 4.08 (dd, J = 17.4, 8.6 Hz, 1H), 3.98 (d, J = 8.0 Hz, 1H), 3.96 – 3.76 (m, 3H), 3.75 – 3.68 (m, 1H), 3.66 (d, J = 5.8 Hz, 1H), 3.25 – 3.13 (m, 1H), 2.58 (d, J = 2.4 Hz, 3H), 1.38 – 1.24 (m, 1H), 1.12 – 0.96 (m, 6H), 0.84 (d, J = 5.6 Hz, 1H), 0.70 – 0.61 (m, 1H).	542.4
I-253	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.16 (m, 1H), 7.96 – 7.87 (m, 1H), 7.39 – 7.24 (m, 5H), 5.40 – 5.35 (m, 2H), 4.40 – 3.79 (m, 13H), 3.56 – 3.36 (m, 2H), 3.30 – 3.20 (m, 2H), 1.80 – 1.60 (m, 6H), 1.50 – 1.35 (m, 1H), 1.33 – 0.90 (m, 13H), 0.83 – 0.72 (m, 1H)	615.4
I-254	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.28 – 8.15 (m, 1H), 7.97 – 7.86 (m, 1H), 7.40 – 7.21 (m, 5H), 5.40 – 5.36 (m, 2H), 4.43 – 4.22 (m, 2H), 4.16 – 3.38 (m, 11H), 3.28 – 2.98 (m, 2H), 2.10 – 1.51 (m, 9H), 1.48 – 1.22 (m, 6H), 1.18 – 1.09 (m, 7H), 1.07 – 0.96 (m, 3H).	616.5
I-255	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.28 – 8.15 (m, 1H), 7.97 – 7.89 (m, 1H), 7.38 – 7.20 (m, 10H), 5.39 – 5.33 (m, 2H), 4.44 – 3.34 (m, 15H), 2.94 – 2.54 (m, 3H), 1.46 – 1.31 (m, 1H), 1.22 – 1.03 (m, 7H), 0.80 – 0.77 (m, 1H).	596.4
I-256	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.29 – 8.16 (m, 1H), 7.97 – 7.87 (m, 1H), 7.40 – 7.24 (m, 5H), 5.40 – 5.35 (m, 2H), 4.38 – 4.23 (m, 2H), 4.18 – 3.35 (m, 12H), 3.30 – 3.21 (m, 2H), 2.22 – 1.96 (m, 2H), 1.81 – 1.63 (m, 5H), 1.60 – 0.87 (m, 15H), 0.83 – 0.73 (m, 1H).	602.5

[1088]

化合物编号	方法	^{1}HNMR	LCMS
I-257	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 0.63 (1H, s), 0.82 (1H, s), 0.99 (1H, s), 1.03 – 1.08 (4H, m), 1.09 – 1.15 (3H, m), 1.24 – 1.33 (2H, m), 2.57 – 2.65 (3H, m), 3.63 – 3.86 (7H, m), 4.17 – 4.23 (2H, m), 4.40 (2H, s), 4.68 (2H, d, *J*=20.4 Hz), 5.36 (2H, s), 7.23 – 7.40 (5H, m), 7.58 (2H, d, *J*=41.0 Hz), 7.81 (1H, d), 8.07 (2H, s), 8.32 – 8.40 (1H, m), 8.42 – 8.56 (1H, m), 8.65 (1H, s).	642.5
I-258	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.52 (m, 1H), 8.42 – 8.34 (m, 1H), 7.87 – 7.80 (m, 1H), 7.39 – 7.23 (m, 5H), 5.35 (s, 2H), 4.41 – 3.82 (m, 6H), 3.80 – 3.58 (m, 3H), 3.32 – 3.08 (m, 3H), 2.74 (d, *J* = 1.8 Hz, 3H), 2.34 – 2.22 (m, 1H), 1.83 – 1.68 (m, 1H), 1.41 – 1.30 (m, 1H), 1.14 – 1.03 (m, 6H), 0.88 – 0.83 (m, 1H), 0.70 – 0.65 (m, 1H).	533.4
I-259	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.50 (m, 1H), 8.41 – 8.33 (m, 1H), 7.87 – 7.80 (m, 1H), 7.39 – 7.22 (m, 5H), 5.38 – 5.33 (m, 2H), 4.45 – 3.70 (m, 8H), 3.66 – 3.57 (m, 1H), 3.23 – 3.05 (m, 3H), 2.69 – 2.62 (m, 1H), 2.29 – 2.16 (m, 1H), 1.78 – 1.65 (m, 1H), 1.42 – 1.31 (m, 1H), 1.15 – 1.01 (m, 6H), 0.91 – 0.82 (m, 1H), 0.73 – 0.60 (m, 5H).	559.4
I-260	23	^{1}H NMR (400 MHz, DMSO-d_6) & 8.37 – 8.3 (m, 2H), 7.84 – 7.81 (m, 2H), 7.37 – 7.25 (m, 5H), 5.35 (s, 2H), 4.94 – 4.88 (m, 1H), 4.26 – 3.53 (m, 12H), 2.59 – 2.56 (m, 3H), 1.35 – 1.31 (m, 3H), 1.11 – 1.04 (m, 6H), 0.86 – 0.84 (m, 1H), 0.69 – 0.64 (m, 1H).	537.4
I-261	23	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.25 (m, 2H), 7.84 – 7.81 (m, 2H), 7.37 – 7.25 (m, 5H), 5.35 (s, 2H), 4.91 – 4.88 (m, 1H), 4.26 – 3.55 (m, 12H), 2.59 – 2.57 (m, 3H), 1.35 – 1.34 (m, 1H), 1.11 – 1.04 (m, 6H), 0.86 – 0.84 (m, 1H), 0.69 – 0.66 (m, 1H).	537.4
I-262	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (d, *J* = 5.0 Hz, 1H), 8.41 – 8.26 (m, 2H), 7.82 (d, *J* = 15.0 Hz, 2H), 7.39 – 7.24 (m, 5H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.61 (m, 3H), 5.35 (s,	657.5

[1089]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 4.46 – 3.60 (m, 13H), 2.64 – 2.56 (m, 3H), 1.36 – 1.22 (m, 1H), 1.10 – 0.99 (m, 9H), 0.85 (d, *J* = 5.0 Hz, 1H), 0.68 – 0.61 (m, 1H).	
I-263	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.29 (m, 2H), 7.88 – 7.78 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.22 (m, 7H), 5.36 (s, 2H), 4.50 (d, *J* = 12.6 Hz, 1H), 4.44 – 4.31 (m, 2H), 4.26 – 4.11 (m, 1H), 4.06 (t, *J* = 9.6 Hz, 1H), 3.98 – 3.40 (m, 8H), 2.59 (dd, *J* = 10.4, 4.6 Hz, 3H), 1.35 – 1.20 (m, 1H), 1.10 – 0.99 (m, 9H), 0.87 – 0.81 (m, 1H), 0.67 – 0.59 (m, 1H).	719.3
I-264	15	^{1}HNMR (400 MHz, CD_3OD):δ 6.49 (d, *J* = 5.6 Hz, 1H), 4.93-4.99 (m, 1H), 3.86-4.59 (m, 9H), 3.73-3.77 (m, 1H), 3.50-3.64 (m, 4H), 3.35-3.39 (m, 2H), 3.19-3.25 (m, 1H), 2.34 (d, *J* = 5.0 Hz, 3H), 1.51-1.78 (m, 11H), 1.39-1.46 (m, 1H), 1.13-1.35 (m, 12H), 1.04-1.09 (m, 1H), 0.93-0.10 (m, 2H), 0.77-0.82 (m, 1H).	625.4
I-265	15	^{1}HNMR (400 MHz, CD_3OD): δ 4.94-4.96 (m, 1H), 3.35-4.39 (m, 17H), 3.20-3.24 (m, 1H), 2.98-3.05 (m, 1H), 2.42-2.45 (m, 2H), 1.90-2.10 (m, 2H), 1.52-1.78 (m, 11H), 1.14-1.46 (m, 14H), 1.05-1.09 (m, 1H), 0.93-0.99 (m, 2H), 0.78-0.83 (m, 1H).	642.5
I-266	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.32 (m, 1H), 8.18 – 8.01 (m, 2H), 7.87 – 7.77 (m, 1H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 4.28 – 3.94 (m, 5H), 3.90 – 3.71 (m, 3H), 3.62 – 3.56 (m, 1H), 2.82 – 2.73 (m, 1H), 2.58 – 2.53 (m, 4H), 2.19 – 2.05 (m, 5H), 1.81 – 1.69 (m, 2H), 1.67 – 1.58 (m, 3H), 1.39 – 1.33 (m, 2H), 1.29 – 1.21 (m, 4H), 1.11 – 1.03 (m, 6H), 0.87 – 0.84 (m, 1H), 0.82 – 0.77 (m, 4H), 0.71 – 0.64 (m, 1H).	660.6
I-267	21	^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.36 (d, *J* = 22.0 Hz, 1H), 8.13 (t, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.41 – 7.22 (m, 5H), 6.03 (d, *J* = 7.8 Hz, 1H),	636.5

[1090]

化合物编号	方法	^{1}HNMR	LCMS
		5.35 (s, 2H), 4.25 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.00 – 3.75 (m, 5H), 3.73 – 3.52 (m, 5H), 3.49 – 3.36 (m, 1H), 3.24 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.10 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.57 (dd, *J* = 11.6, 4.6 Hz, 3H), 1.70 – 1.58 (m, 5H), 1.49 – 1.37 (m, 1H), 1.21 – 1.10 (m, 3H), 1.06 – 0.98 (m, 9H), 0.84 (dd, *J* = 13.8, 9.6 Hz, 2H).	
I-268	21	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38-8.33 (m, 1H), 8.15 – 8.11 (m, 1H), 7.83 – 7.70 (m, 2H), 7.37 – 7.25 (m, 5H), 6.43 (d, J=3.2 Hz, 1H), 5.35 (s, 2H), 4.26 – 4.24 (m, 1H), 3.98 – 3.71 (m, 6H), 3.67 – 3.57 (m, 3H), 3.55 – 3.45 (m, 1H), 3.26 – 3.22 (m, 1H), 3.12 – 3.08 (m, 1H), 2.59 – 2.55 (m, 3H), 2.42 – 2.39 (m, 1H), 1.68 – 1.63 (m, 5H), 1.45 – 1.43 (m, 1H), 1.19 – 1.09 (m, 3H), 1.04 – 1.01 (m, 3H), 0.87 – 0.81 (m, 2H), 0.54 – 0.51 (m, 2H), 0.33 – 0.32 (m, 2H).	634.3
I-269	23	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 – 7.24 (m, 10H), 5.47 – 5.41 (m, 1H), 4.76 – 4.69 (m, 1H), 4.35 – 4.28 (m, 1H), 4.21 – 4.14 (m, 1H), 4.00 – 3.92 (m, 1H), 3.66 – 3.60 (m, 1H), 3.59 – 3.55 (m, 2H), 3.36 (s, 2H), 3.19 – 3.15 (m, 1H), 3.06 – 2.98 (m, 1H), 2.94 – 2.88 (m, 1H), 2.55 (s, 1H), 1.36 (s, 9H).	492
I-270	16A	^{1}HNMR (400 MHz, DMSO-*d*6): δ 8.44-8.51 (m, 1H), 8.37-8.39 (m, 1H), 8.05 (br, 2H), 7.81-7.85 (m, 1H), 7.26-7.37 (m, 5H), 5.36 (s, 2H), 4.48-4.56 (m, 1H), 4.34-4.41 (m, 1H), 4.05-4.21 (m, 4H), 3.85-3.98 (m, 2H), 3.48-3.81 (m, 5H), 3.36-3.42 (m, 1H), 3.05-3.26 (m, 5H), 2.30-2.39 (m, 1H), 2.05-2.14 (m, 1H), 1.59-1.74 (m, 5H), 1.44-1.53 (m, 1H), 1.28-1.36 (m, 1H), 1.14-1.25 (m, 3H), 1.05-1.09 (m, 8H), 0.86-0.93 (m, 3H), 0.66-0.69 (m, 1H).	702.9
I-271	2A	^{1}HNMR (400 MHz, CD_3OD): δ 8.16-8.25 (m, 1H), 7.88-7.95 (m, 1H), 7.25-7.38 (m, 5H), 5.35-5.41 (m, 2H), 3.78-4.41 (m, 10H), 3.35-3.68 (m, 6H), 3.11-3.18 (m, 1H), 1.91-2.03 (m, 2H), 1.66-1.83 (m, 10H), 1.08-1.45	738.4

[1091]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 14H), 1.01-1.06 (m, 1H), 0.91-1.00 (m, 2H), 0.74-0.81 (m, 1H).	
I-272	25	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (t, J = 8.8 Hz, 1H), 8.47 – 8.27 (m, 2H), 7.82 (dd, J = 25.8, 8.2 Hz, 1H), 7.39 – 7.07 (m, 10H), 5.38 – 5.30 (m, 2H), 5.20 – 5.11 (m, 1H), 4.71 (t, J = 12.8 Hz, 1H), 4.20 (dd, J = 42.4, 10.8 Hz, 2H), 4.11 – 4.00 (m, 2H), 3.88 (s, 1H), 3.78 (m, 3H), 3.56 (m, 1H), 3.46 – 3.33 (m, 1H), 2.62 (m, 3H), 1.48 (d, J = 11.8 Hz, 3H), 1.39 (s, 3H), 1.35 (t, J = 7.2 Hz, 1H), 1.11 (t, J = 6.0 Hz, 3H), 1.05 (t, J = 4.2 Hz, 3H), 0.90 – 0.83 (m, 1H), 0.72 – 0.65 (m, 1H).	703.40
I-273	23+24	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 – 8.50 (m, 1H), 8.39 – 8.28 (m, 1H), 8.16 – 8.07 (m, 1H), 7.86 – 7.77 (m, 1H), 7.38 – 7.22 (m, 5H), 5.35 (s, 2H), 4.72 – 4.43 (m, 1H), 4.25 – 3.52 (m, 10H), 3.26 – 3.10 (m, 1H), 3.08 – 3.00 (m, 1H), 2.64 – 2.53 (m, 3H), 2.13 (d, J = 2.8 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.72 – 1.53 (m, 6H), 1.41 – 1.32 (m, 1H), 1.24 – 1.22 (m, 1H), 1.19 – 1.14 (m, 3H), 1.12 – 1.02 (m, 8H), 0.93 – 0.78 (m, 3H), 0.71 – 0.63 (m, 1H).	688.5
I-274	22	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 21.4 Hz, 1H), 8.14 (t, J = 7.0 Hz, 1H), 7.81 (d, J = 16.4 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.44 – 7.19 (m, 5H), 5.35 (d, J = 2.2 Hz, 2H), 4.27 (dd, J = 8.8, 3.4 Hz, 1H), 4.13 – 3.95 (m, 3H), 3.94 – 3.87 (m, 1H), 3.86 – 3.73 (m, 3H), 3.73 – 3.63 (m, 2H), 3.62 – 3.52 (m, 1H), 3.49 – 3.34 (m, 1H), 3.27 – 3.18 (m, 1H), 3.10 (dd, J = 9.2, 6.8 Hz, 1H), 2.57 (dd, J = 13.8, 3.4 Hz, 6H), 1.63 (q, J = 13.8, 12.6 Hz, 5H), 1.42 (d, J = 10.2 Hz, 1H), 1.21 – 1.08 (m, 3H), 1.05 – 0.98 (m, 9H), 0.84 (t, J = 11.8 Hz, 2H).	650.50
I-275	2A	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.11 (m, 1H), 7.95 – 7.84 (m, 1H), 7.37 – 7.22 (m, 10H), 5.40 – 5.33 (m, 2H), 4.67 – 3.75 (m, 12H), 2.04 – 1.52 (m, 4H), 1.43 – 1.32 (m,	624.5

[1092]

化合物编号	方法	^{1}HNMR	LCMS
		6H), 1.22 – 1.00 (m, 8H), 0.93 – 0.72 (m, 3H).	
I-276	7A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 11.8 Hz, 2H), 7.82 (d, J = 15.4 Hz, 2H), 7.38 – 7.23 (m, 10H), 5.35 (s, 2H), 4.52 (d, J = 12.0 Hz, 1H), 4.46 – 4.29 (m, 3H), 4.26 – 3.59 (m, 8H), 3.49 (m, 1H), 2.60 (m, 3H), 1.07 (s, 3H), 0.88 (s, 7H), 0.27 (d, J = 34.4 Hz, 4H).	655.4
I-277	7A	^{1} H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.31 (m, 2H), 7.87 – 7.78 (m, 2H), 7.37 – 7.24 (m, 10H), 5.35 (s, 2H), 4.56 – 4.49 (m, 1H), 4.46 – 4.40 (m, 1H), 4.38 – 4.32 (m, 1H), 4.22 – 4.08 (m, 1H), 4.06 – 3.87 (m, 5H), 3.79 – 3.60 (m, 3H), 3.53 – 3.36 (m, 1H), 2.64 – 2.56 (m, 3H), 1.68 – 1.49 (m, 1H), 1.12 – 1.04 (m, 3H), 1.03 – 0.93 (m, 3H), 0.88 – 0.73 (m, 1H), 0.41 – 0.28 (m, 2H), 0.18 – -0.01 (m, 2H).	641.4
I-278	23	^{1}H NMR (DMSO, 400 MHz) δ 9.05 (1H, s), 8.35 (1H, m) , 7.83 (1H, d, J=7.8 Hz) , 7.57 (1H, m), 7.48 (1H, m) , 7.21 – 7.37 (6H, m) , 5.35 (2H, s) , 4.62 (2H, m) , 3.70 – 4.24 (9H, m) , 2.45 (3H, d, J=3.4 Hz) , 1.34 (1H, d, J=6.6 Hz) , 1.11 (2H, m) , 1.04 (3H, d, J=2.4 Hz) , 1.00 (1H, s) , 0.84 (1H, d, J=5.0 Hz), 0.66 (1H, dd, J=7.8, 3.8 Hz).	580.4
I-279	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 9.22 (m, 1H), 8.40 – 8.35 (m, 1H), 8.10 – 8.00 (m, 1H), 7.76 – 7.72 (m, 1H), 4.29 – 4.10 (m, 4H), 3.99 – 3.70 (m, 6H), 3.62 – 3.47 (m, 1H), 3.24 – 3.10 (m, 1H), 2.61 – 2.55 (m, 3H), 1.66 – 1.58 (m, 5H), 1.36 – 1.24 (m, 2H), 1.12 – 0.98 (m, 13H), 0.95 – 0.86 (m, 5H), 0.68 – 0.66 (m, 1H).	588.3
I-280	2A	^{1}HNMR (400 MHz, CD_3OD): δ 8.24 (d, J = 16.8 Hz, 1H), 7.93 (d, J = 12.0 Hz, 1H), 7.28-7.38 (m, 10H), 5.39 (d, J = 2.4 Hz, 2H), 4.99-5.03 (m, 1H), 4.64-4.68 (m, 1H), 4.48-4.52 (m, 1H), 4.33-4.40 (m, 1H), 4.13-4.24 (m, 2H), 3.96-4.10 (m, 3H), 3.75-3.92 (m, 4H), 3.65-3.66 (m, 1H), 3.36-3.53 (m, 3H),	731.4

[1093]

化合物编号	方法	^{1}HNMR	LCMS
		1.78-1.94 (m, 4H), 1.26-1.27 (m, 3H), 1.12-1.18 (m, 6H), 1.04-1.07 (m, 1H), 0.77-0.80 (m, 1H).	
I-281	2A	^{1}HNMR (400 MHz, CD_3OD): δ 8.19-8.26 (m, 1H), 7.90-7.95 (m, 1H), 7.23-7.39 (m, 5H), 5.36-5.41 (m, 2H), 3.78-4.44 (m, 11H), 3.39-3.49 (m, 2H), 3.13-3.18 (m, 1H), 1.66-1.85 (m, 5H), 1.51-1.61 (m, 1H), 1.35-1.46 (m, 1H), 0.98-1.29 (m, 20H), 0.75-0.81 (m, 1H).	648.4
I-282	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.17 (s, 1H), 8.34-8.41 (m, 1H), 3.84-4.41 (m, 9H), 3.33-3.64 (m, 5H), 3.13-3.28 (m, 3H), 1.64-1.86 (m, 9H), 1.49-1.61 (m, 2H), 0.87-1.42 (m, 21H), 0.75-0.81 (m, 1H).	643.4
I-283	2A	^{1}H NMR (400 MHz, *DMSO*) d ppm 1.33-1.43 (m, 1H), 0.63-0.72 (m, 1H), 1.59-1.77 (m, 2H), 0.82-0.89 (m, 1H), 1.00-1.11 (m, 6H), 1.25 (dd, J = 12.00, 6.40 Hz, 9H), 3.31 (s, 3H), 3.08-3.26 (m, 7H), 3.49-4.33 (m, 11H), 4.76-4.88 (m, 1H), 5.36 (s, 1H), 8.48-8.61 (m, 1H), 8.33-8.43 (m, 1H), 7.25-7.36 (m, 3H), 7.78-7.89 (m, 1H)	663.7
I-284	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40 – 8.24 (m, 2H), 4.83 (s, 1H), 4.20 – 3.64 (m, 9H), 3.53 – 3.45 (m, 5H), 3.25 – 3.16 (m, 1H), 1.66 – 1.29 (m, 13H), 1.12 – 0.86 (m, 18H), 0.67 (s, 1H).	642.5
I-285	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.51 – 8.32 (m, 2H), 4.91 – 4.82 (m, 1H), 4.26 – 4.06 (m, 3H), 4.05 – 3.71 (m, 4H), 3.69 – 3.59 (m, 3H), 3.58 – 3.37 (m, 6H), 1.61 – 1.29 (m, 7H), 1.13 – 1.03 (m, 9H), 0.96 – 0.80 (m, 5H), 0.72 – 0.64 (m, 1H).	654.3
I-286	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 – 9.24 (m, 1H), 8.70 – 8.56 (m, 1H), 8.40 – 8.34 (m, 1H), 5.01 – 4.92 (m, 1H), 4.22 – 3.91 (m, 4H), 3.90 – 3.71 (m, 3H), 3.69 – 3.62 (m, 1H), 3.59 – 3.35 (m, 7H), 3.26 – 3.13 (m, 2H), 1.68 – 1.53 (m, 7H), 1.51 – 1.36 (m, 5H), 1.35 – 1.28 (m, 1H), 1.20 – 1.04 (m,	614.4

[1094]

化合物编号	方法	^{1}HNMR	LCMS
		9H), 0.91 – 0.80 (m, 3H), 0.71 – 0.66 (m, 1H).	
I-287	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.49 (dt, J = 22.0, 8.2 Hz, 1H), 8.37 (dd, J = 19.6, 3.8 Hz, 1H), 4.96 (m, 1H), 4.25 – 4.06 (m, 3H), 4.01 – 3.72 (m, 4H), 3.69 – 3.40 (m, 9H), 1.98 (m, 4H), 1.40 – 1.25 (m, 1H), 1.12 – 1.03 (m, 9H), 0.94 – 0.82 (m, 5H), 0.67 (d, J = 7.6 Hz, 1H).	690.3
I-288	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.53 – 8.44 (m, 1H), 8.41 – 8.33 (m, 1H), 4.92 (s, 1H), 4.23 – 4.06 (m, 3H), 4.03 – 3.93 (m, 1H), 3.86 – 3.75 (m, 4H), 3.69 – 3.48 (m, 7H), 3.47 – 3.39 (m, 1H), 3.30 – 3.17 (m, 4H), 1.94 (s, 4H), 1.70 (s, 1H), 1.60 – 1.50 (m, 2H), 1.38 – 1.27 (m, 1H), 1.18 – 1.04 (m, 11H), 0.88 – 0.83 (m, 1H), 0.72 – 0.64 (m, 1H).	666.3
I-289	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40 – 8.35 (m, 1H), 8.11 – 8.05 (m, 1H), 7.76 – 7.67 (m, 1H), 4.27 – 4.07 (m, 4H), 4.02 – 3.66 (m, 6H), 3.58 – 3.45 (m, 1H), 3.03 (d, J=8.8 Hz, 1H), 2.87 (d, J=8.8 Hz, 1H), 2.60 – 2.56 (m, 3H), 1.51 – 1.46 (m, 7H), 1.32 – 1.28 (m, 7H), 1.12 – 0.99 (m, 9H), 0.87 – 0.86 (m, 1H), 0.68 – 0.66 (m, 1H) .	600.4
I-290	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.44 – 8.30 (m, 1H), 8.19 – 8.05 (m, 1H), 7.79 – 7.64 (m, 1H), 4.30 – 4.16 (m, 2H), 4.15 – 4.06 (m, 2H), 4.03 – 3.93 (m, 2H), 3.92 – 3.73 (m, 3H), 3.68 (dd, J = 13.0, 6.4 Hz, 1H), 3.57 (s, 2H), 3.27 (s, 1H), 2.58 (dd, J = 13.0, 4.6 Hz, 3H), 1.73 (s, 2H), 1.64 (d, J = 9.6 Hz, 2H), 1.43 (d, J = 7.8 Hz, 1H), 1.38 – 1.28 (m, 1H), 1.22 (d, J = 8.4 Hz, 2H), 1.18 – 1.14 (m, 2H), 1.12 (s, 1H), 1.08 (dd, J = 6.4, 4.2 Hz, 3H), 1.03 (d, J = 8.2 Hz, 5H), 0.86 (t, J = 5.0 Hz, 1H), 0.72 – 0.63 (m, 1H).	560.4
I-291	19	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.68 – 8.51 (m, 1H), 8.41 – 8.32 (m, 1H), 4.94 – 4.85 (m, 1H), 4.27 – 4.01 (m,	690.35

[1095]

化合物编号	方法	^{1}HNMR	LCMS
		3H), 3.89 – 3.39 (m, 13H), 2.05 – 1.84 (m, 4H), 1.38 – 1.25 (m, 1H), 1.11 – 1.03 (m, 9H), 0.93 – 0.77 (m, 5H), 0.70 – 0.65 (m, 1H).	
I-292	19	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.66 – 8.49 (m, 1H), 8.42 – 8.32 (m, 1H), 4.89 – 4.78 (m, 1H), 4.31 – 4.15 (m, 1H), 4.08 – 4.00 (m, 2H), 3.93 – 3.75 (m, 3H), 3.71 – 3.64 (m, 3H), 3.59 – 3.37 (m, 7H), 1.62 – 1.53 (m, 2H), 1.49 – 1.38 (m, 4H), 1.30 – 1.22 (m, 1H), 1.14 – 1.09 (m, 3H), 1.07 – 1.01 (m, 6H), 0.91 (s, 1H), 0.88 – 0.81 (m, 3H), 0.80 – 0.74 (m, 1H), 0.71 – 0.64 (m, 1H).	654.4
I-293	19	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.70 – 8.55 (m, 1H), 8.36 (dd, J = 23.6, 2.0 Hz, 1H), 4.96 (s, 1H), 4.32 – 3.90 (m, 4H), 3.88 – 3.70 (m, 3H), 3.67 (d, J = 5.8 Hz, 1H), 3.60 – 3.33 (m, 7H), 3.24 – 3.10 (m, 2H), 1.59 (d, J = 11.2 Hz, 7H), 1.45 (d, J = 28.0 Hz, 5H), 1.35 – 1.26 (m, 1H), 1.17 – 1.03 (m, 9H), 0.85 (d, J = 10.0 Hz, 3H), 0.68 (dd, J = 8.6, 3.8 Hz, 1H).	614.4
I-294	20	^{1}H NMR (400 MHz, DMSO-d6) δ 8.36 – 8.28 (m, 1H), 8.15 – 8.06 (m, 1H), 7.83 – 7.74 (m, 2H), 7.38 – 7.23 (m, 5H), 5.38 – 5.33 (m, 2H), 4.27 – 4.20 (m, 1H), 4.06 – 3.99 (m, 1H), 3.92 – 3.44 (m, 11H), 3.38 – 3.32 (m, 3H), 3.26 – 3.21 (m, 1H), 3.14 – 3.09 (m, 1H), 2.60 – 2.55 (m, 3H), 1.70 – 1.58 (m, 5H), 1.49 – 1.38 (m, 1H), 1.20 – 1.04 (m, 6H), 0.89 – 0.79 (m, 2H).	609.4
I-295	22	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 20.2 Hz, 1H), 8.16 (dd, J = 9.0, 3.8 Hz, 1H), 7.88 – 7.64 (m, 2H), 7.41 – 7.18 (m, 5H), 5.35 (d, J = 4.2 Hz, 2H), 4.27 (dd, J = 8.6, 3.4 Hz, 1H), 4.08 (dd, J = 19.6, 8.4 Hz, 1H), 4.01 – 3.91 (m, 2H), 3.88 – 3.68 (m, 5H), 3.63 – 3.54 (m, 1H), 3.46 (t, J = 6.0 Hz, 2H), 3.23 (t, J = 7.6 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.71 (d, J = 2.4 Hz, 3H), 2.58 (dd, J = 10.8, 4.6 Hz, 3H), 1.64 (q, J = 13.6, 12.4 Hz,	648.5

[1096]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 1.49 – 1.38 (m, 1H), 1.24 – 1.08 (m, 3H), 1.03 (dd, *J* = 6.4, 3.2 Hz, 3H), 0.83 (q, *J* = 12.4 Hz, 2H), 0.69 (t, *J* = 6.4 Hz, 2H), 0.64 – 0.55 (m, 2H).	
I-296	1A	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.51 – 8.29 (m, 2H), 4.84 (m, 1H), 4.30 – 4.14 (m, 2H), 4.12 – 3.92 (m, 2H), 3.89 – 3.74 (m, 2H), 3.68 – 3.36 (m, 7H), 3.23 (d, *J* = 6.8 Hz, 1H), 3.15 (m, 1H), 2.60 (m, 1H), 1.93 – 1.80 (m, 2H), 1.63 (q, *J* = 15.8, 14.6 Hz, 7H), 1.45 (s, 5H), 1.23 – 1.08 (m, 3H), 1.02 (s, 3H), 0.86 (t, *J* = 12.0 Hz, 2H).	636.3
I-297	1A+8A	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (s, 1H), 8.43 (s, 1H), 8.17 (s, 1H), 7.84 (s, 1H), 4.96 – 4.89 (m, 1H), 4.21 – 3.35 (m, 18H), 3.27 – 3.22 (m, 2H), 2.06 – 1.87 (m, 4H), 1.76 – 1.65 (m, 1H), 1.54 (d, *J* = 13.2 Hz, 2H), 1.38 – 1.27 (m, 1H), 1.16 – 1.02 (m, 11H), 0.86 (s, 1H), 0.71 – 0.65 (m, 1H).	649.45
I-298A	1A+8A	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.64 – 8.56 (m, 1H), 8.29 – 7.73 (m, 2H), 7.62 (s, 1H), 7.36 – 7.13 (m, 5H), 5.11 (s, 1H), 4.90 – 4.79 (m, 1H), 4.36 – 4.20 (m, 1H), 4.16 – 3.67 (m, 7H), 3.62 – 3.52 (m, 1H), 3.41 (s, 1H), 2.54 (s, 3H), 2.21 – 2.04 (m, 2H), 1.39 (s, 1H), 1.16 – 1.02 (m, 6H), 0.87 (s, 1H), 0.73 – 0.65 (m, 1H).	537.3
I-299	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.32 (m, 1H), 8.25 – 8.13 (m, 1H), 7.88 – 7.72 (m, 2H), 7.38 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 5.35 (s, 2H), 4.31 – 4.02 (m, 4H), 4.00 – 3.94 (m, 1H), 3.92 – 3.83 (m, 2H), 3.81 – 3.69 (m, 2H), 3.68 – 3.62 (m, 1H), 3.58 (s, 3H), 3.47 – 3.35 (m, 3H), 2.64 – 2.56 (m, 3H), 1.90 – 1.87 (m, 5H), 1.38 – 1.25 (m, 1H), 1.14 – 1.00 (m, 10H), 0.89 – 0.82 (m, 1H), 0.71 – 0.63 (m, 1H).	689.3
I-300	1A	^{1}HNMR (400 MHz, CD_3OD): δ 8.48-8.39 (m, 2H), 8.24-8.16 (m, 1H), 7.94-7.88 (m, 1H), 7.37-7.26 (m, 7H), 5.37 (s, 2H), 5.02-4.95 (m, 1H), 4.76-4.58 (m, 1H), 4.38-3.73 (m, 10H), 3.45-3.36 (m, 1H), 3.28-3.16 (m,	778.45

[1097]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 2.96-2.86 (m, 1H), 2.83-2.73 (m, 1H), 2.04-1.86 (m, 2H), 1.81-1.35 (m, 10H), 1.25-1.10 (m, 12H), 1.07-1.02 (m, 1H), 0.99-0.90 (m, 2H), 0.80-0.74 (m, 1H).	
I-301	27	^{1}HNMR (400 MHz, DMSO-*d*6): δ 13.20-13.25 (m, 1H), 8.44-8.47 (m, 1H), 8.17-8.20 (m, 1H), 7.82-7.85 (m, 1H), 4.81-4.89 (m, 1H), 3.83-4.23 (m, 5H), 3.42-3.81 (m, 11H), 3.38-3.40 (m, 1H), 3.28-3.30 (s, 1H), 3.20-3.25 (m, 1H), 1.94-2.03 (m, 2H), 1.54-1.87 (m, 5H), 1.23-1.45 (m, 4H), 1.05-1.45 (m, 9H), 0.84-0.88 (m, 1H), 0.66-0.68 (m, 1H).	649.4
I-302	27	^{1}HNMR (400 MHz, DMSO-*d*6): δ 13.22 (br, 1H), 8.43-8.47 (m, 1H), 8.09-8.23 (m, 1H), 7.75-7.93 (m, 1H), 4.86 (br, 1H), 4.11-4.42 (m, 2H), 3.67-4.09 (m, 5H), 3.41-3.64 (m, 10H), 3.36-3.68 (m, 1H), 3.21-3.25 (m, 1H), 1.94-2.01 (m, 2H), 1.67-1.86 (m, 4H), 1.56-1.64 (m, 10H), 1.04-1.24 (m, 1H)	689.3
I-303	27	^{1}HNMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.90 (d, *J* = 10.6 Hz, 1H), 3.48-4.52 (m, 17H), 3.33-3.38 (m, 4H), 1.53 -1.74 (m, 6H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.11-1.17 (m, 8H), 1.06 (d, *J* = 4.4 Hz, 1H), 0.77-0.84 (m, 1H).	543.6
I-304	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.35-8.40 (m, 1H), 3.82-4.45 (m, 11H), 3.47-3.56 (m, 1H), 3.18-3.20 (m, 1H), 2.92-2.96 (m, 1H), 1.57-1.60 (m, 7H), 1.43-1.45 (m, 6H), 1.25-1.28 (m, 3H), 1.14-1.20 (m, 5H), 1.03-1.11 (m, 8H), 0.76-0.81 (m, 1H).	601.5
I-305	27	^{1}H NMR (400 MHz, *CDCl$_3$*) d 0.73-0.80 (m, 1H), 1.16 (dd, *J* = 11.44, 7.00 Hz, 9H), 1.45 (d, *J* = 6.6 Hz, 2H), 1.56 (dd, *J* = 12.2, 6.8 Hz, 5H), 1.62-1.69 (m, 2H), 3.08-3.14 (m, 1H), 3.52 (s, 5H), 3.95 (s, 6H), 4.04- 4.15 (m, 3H), 4.22-4.30 (m, 1H), 4.81-4.94 (m, 1H), 7.82 (d, *J* = 21.2 Hz, 2H)	529.5
I-306	2A	^{1}HNMR (400 MHz, DMSO-*d*6): δ 8.52-8.61 (m, 1H), 8.37-8.40 (m, 1H), 7.69-7.85 (m, 4H), 7.26-7.37 (m, 4H), 5.36 (s, 2H), 4.83-4.85 (m, 1H), 4.33-4.39 (m, 1H), 4.17-4.24 (m, 1H), 3.97-4.10 (m, 3H), 3.86-3.90 (m,	648.9

[1098]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 3.67-3.80 (m, 2H), 3.40-3.62 (m, 3H), 3.24-3.26 (m, 3H),2.91-3.10 (m, 2H), 2.57-2.72 (m, 3H), 1.66-1.88 (m, 3H), 1.30-1.38 (m, 1H), 1.23 (s, 1H), 0.93-1.15 (m, 10H), 0.85-0.86 (m, 1H), 0.65-0.70 (m, 1H).	
I-307	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 12.0Hz, 1H), 3.82-4.45 (m, 9H), 3.55-3.72 (m, 3H), 3.32-3.42 (m, 2H), 3.13-3.20 (m, 1H), 1.64-1.85 (m, 5H), 1.49-1.60 (m, 1H), 1.36-1.46 (m, 1H), 1.03-1.32 (m, 13H), 0.92-1.12 (m, 2H), 0.74-0.81 (m, 1H).	547.5
I-308	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.34-8.39 (m, 1H), 3.82-4.39 (m, 10H), 3.33-3.65 (m, 6H), 3.12-3.17 (m, 1H), 1.67-1.88 (m, 11H), 1.50-1.60 (m, 2H), 1.09-1.26 (m, 16H), 0.92-0.98 (m, 2H), 0.75-0.80 (m, 1H).	629.5
I-309	2A	^{1}HNMR (400 MHz, CD_3OD): δ 8.21 (dd, J = 3.6, 20.0 Hz, 1H), 7.90-7.93 (m, 1H), 7.25-7.37 (m, 5H), 5.37-5.38 (m, 2H), 3.80-4.40 (m, 12H), 3.61-3.66 (m, 1H), 3.25-3.42 (m, 2H), 3.11-3.15 (m, 1H), 1.65-1.82 (m, 5H), 1.50-1.60 (m, 1H), 1.35-1.46 (m, 1H), 1.18-1.26 (m, 3H), 1.10-1.16 (m, 8H), 0.94-1.07 (m, 3H), 0.75-0.80 (m, 1H).	688.4
I-310	16A	^{1}HNMR (400 MHz, CD_3OD): δ 8.19-8.24 (m, 1H), 7.90-7.94 (m, 1H), 7.27-7.37 (m, 5H), 5.38 (s, 2H), 4.55-4.66 (m, 1H), 3.75-4.44 (m, 13H), 3.34-3.45 (m, 2H), 3.15-3.25 (m, 3H), 2.40-2.50 (m, 1H), 2.08-2.16 (m, 1H), 1.48-1.79 (m, 7H), 1.11-1.23 (m, 11H), 0.95-1.05 (m, 3H), 0.76-0.79 (m, 1H).	703.1
I-311	27	^{1}HNMR (400 MHz, CD_3OD): δ 7.50-7.55 (m, 1H), 4.90-4.95 (m, 1H), 3.71-4.40 (m, 10H), 3.34-3.56 (m, 6H), 3.16-3.22 (m, 1H), 2.51 (d, J = 5.4 Hz, 3H), 1.53-1.76 (m, 11H), 1.10-1.29 (m, 13H), 1.02-1.07 (m, 1H), 0.90-0.97 (m, 2H), 0.75-0.81 (m, 1H).	642.3
I-312	17A	^{1}H NMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 3.80-4.40 (m, 12H), 3.37-3.70 (m, 8H), 3.20-3.23 (m, 1H), 1.94-2.05 (m, 2H), 1.66-1.86 (m, 9H), 1.40-1.47	667.8

[1099]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 1H), 1.11-1.19 (m, 9H), 1.02-1.06 (m, 1H), 0.90 (t, J = 6.6 Hz, 1H), 0.77-0.79 (m, 1H).	
I-313	17A	^{1}HNMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 6.33-6.39 (m, 1H), 4.08-4.51 (m, 4H), 3.89-4.07 (m, 5H), 3.75-3.85 (m, 1H), 3.44-3.53 (m, 2H), 3.08-3.19 (m, 2H), 1.99-2.12 (m, 2H), 1.65-1.78 (m, 5H), 1.30-1.34 (m, 6H), 1.10-1.22 (m, 12H), 0.75-0.78 (m, 1H).	611.2
I-314	17A	^{1}HNMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.27 (s, 1H), 5.89-5.91 (m, 1H), 3.88-4.37 (m, 11H), 3.75-3.76 (m, 1H), 3.40-3.54 (m, 6H), 3.14-3.22 (m, 1H), 2.99-3.07 (m, 1H), 2.06-2.19 (m, 2H), 1.72-1.91 (m, 6H), 1.46-1.64 (s, 4H), 1.14-1.15 (m, 8H), 1.25 (s, 4H), 0.74-0.78 (m, 1H). LC_MS: m/z 667.3 $[M+H]^+$.	667.3
I-315	17A	^{1}HNMR (400 MHz, DMSO-*d*6): δ 8.92 (s, 1H), 8.25-8.28 (m, 1H), 5.86-5.93 (m, 1H), 3.84-4.44 (m, 9H), 3.70-3.77 (m, 1H), 3.40-3.53 (m, 4H), 3.11-3.20 (m, 1H), 2.98-3.08 (m, 1H), 1.94-2.17 (m, 4H), 1.72-1.87 (m, 8H), 1.63-1.67 (m, 1H), 1.13-1.36 (m, 15H), 00.73-0.80 (m, 1H).	701.2
I-316	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.34-8.39 (m, 1H), 3.81-4.47 (m, 9H), 3.70-3.80 (m, 1H), 3.59-3.67 (m, 1H), 3.34-3.57 (m, 4H), 2.49-2.62 (m, 1H), 1.64-2.10 (m, 16H), 1.29-1.56 (m, 4H), 1.09-1.13 (m, 6H).	723.2
I-317	17A	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.34-8.37 (m, 1H), 7.43-7.46 (m, 1H), 7.17-7.22 (m, 2H), 4.98-4.99 (m, 1H), 4.64-4.67 (m, 1H), 4.52-4.56 (m, 1H), 3.88-4.39 (m, 12H), 3.44-3.48 (m, 1H), 3.12-3.28 (m, 5H), 2.78-2.81 (m, 1H), 2.59-2.62 (m, 1H), 1.67-1.77 (m, 3H), 1.32-1.35 (m, 2H), 1.22-1.28 (m, 5H), 1.09-1.13 (m, 5H), 0.98-1.03 (m, 1H), 0.70-0.76 (m, 1H).	718.2
I-318	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 10.0 Hz, 1H), 7.32-7.40 (m, 2H), 7.07-7.09 (m, 2H), 4.95-5.00 (m, 1H), 4.58-	684.3

[1100]

化合物编号	方法	^{1}HNMR	LCMS
		4.63 (m, 1H), 3.82-4.50 (m, 12H), 3.36-3.48 (m, 1H), 3.08-3.29 (m, 5H), 2.71-2.88 (m, 1H), 2.57-2.65 (m, 1H), 1.60-1.80 (m, 3H), 1.21-1.41 (m, 7H), 1.10-1.14 (m, 5H), 1.01-1.06 (m, 1H), 0.73-0.80 (m, 1H).	
I-319	17A	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.37 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 3.4 Hz, 2H), 7.54 (d, J = 3.4 Hz, 2H), 4.98-5.02 (m, 1H), 4.69-4.74 (m, 1H), 4.58-4.61 (m, 1H), 4.32-4.40 (m, 2H), 4.18-4.30 (m, 2H), 4.15 (d, J = 5.2 Hz, 1H), 3.77-4.08 (m, 7H), 3.40-3.49 (m, 1H), 3.13-3.28 (m, 5H), 3.73-3.83 (m, 1H), 2.60-2.63 (m, 1H), 1.68 (t, J = 9.6 Hz, 3H), 1.33-1.40 (m, 2H),1.20-1.31 (m, 6H), 1.08 (d, J = 3.0 Hz, 3H), 1.02 (t, J = 3.8 Hz, 1H).	734.3
I-320	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 10.0 Hz, 1H), 7.44-7.46 (m, 2H), 7.24-7.26 (m, 2H), 4.95-5.01 (m, 1H), 4.63-4.68 (m, 1H), 4.49-4.55 (m, 1H), 3.81-4.40 (m, 12H), 3.38-3.48 (m, 1H), 3.13-3.28 (m, 5H), 2.58-2.85 (m, 2H), 1.58-1.82 (m, 3H), 1.22-1.29 (m, 5H), 1.09-1.15 (m, 6H), 1.00-1.04 (m, 1H), 0.71-0.78 (m, 1H).	750.7
I-321	17A	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.34-8.37 (m, 1H), 7.42-7.46 (m, 1H), 7.29-7.35 (m, 1H), 7.14-7.18 (m, 1H), 7.05-7.09 (m, 1H), 4.96-4.99 (m, 1H), 4.66-4.69 (m, 1H), 4.56-4.60 (m, 1H), 3.81-4.41 (m, 11H), 3.41-3.48 (m, 1H), 3.07-3.27 (m, 5H), 2.75-2.81 (m, 1H), 2.59-2.65 (m, 1H), 1.64-1.76 (m, 3H), 1.28-1.36 (m, 2H), 1.21-1.26 (m, 4H), 1.12-1.19 (m, 5H), 1.02-1.06 (m, 1H), 0.70-0.75 (m, 1H).	684.7
I-322	17A	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.36 (d, J = 4.2 Hz, 1H), 7.31-7.37 (m, 1H), 7.11-7.13 (m, 2H), 6.96-7.05 (m, 1H), 4.96-5.01 (m, 1H), 4.64 (d, J = 6.2 Hz, 1H), 4.48-4.54 (m, 1H), 4.31-4.41 (m, 2H), 4.18-4.28 (m, 2H), 4.01-4.16 (m, 3H), 3.73-3.99 (m, 5H), 3.38-3.49 (m, 1H), 3.26 (d, J = 3.4 Hz, 3H), 3.20-3.23 (m, 1H), 3.10-3.17 (m, 1H),	684.7

[1101]

化合物编号	方法	^{1}HNMR	LCMS
		2.73-2.83 (m, 1H), 2.59-2.69 (m, 1H), 1.65-1.77 (m, 3H), 1.24-1.41 (m, 5H), 1.09-1.13 (m, 6H), 1.00-1.04 (m, 1H), 0.71-0.79 (m, 1H).	
I-323	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, J = 7.6 Hz, 1H), 4.40-4.54 (m, 1H), 4.15-4.36 (m, 4H), 3.99-4.09 (m, 4H), 3.82-3.89 (m, 3H), 3.72-3.76 (m, 1H), 3.33-3.34 (m, 2H), 2.95-3.12 (m, 2H), 2.00-2.22 (m, 1H), 1.68-1.88 (m, 3H), 1.40-1.46 (m, 2H), 1.09-1.19 (m, 7H), 1.03-1.04 (m, 1H), 0.88-0.92 (m, 2H), 0.76-0.78 (m, 1H).	532.1
I-324	17A	^{1}H NMR (400 MHz, CD_3OD) δ9.15 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 4.91 (s, 1H), 4.32-4.54 (m, 2H), 3.83-4.25 (m, 9H), 3.48-3.74 (m, 1H), 3.33 (s,2H), 2.85-3.25 (m, 4H), 2.56-2.62 (m, 1H), 1.60-1.82(m, 4H), 1.38-1.45 (m, 3H), 1.02-1.19 (m, 8H), 0.77 (s, 1H).	546.4
I-325	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.52-8.61 (m, 1H), 8.39-8.40 (m, 1H), 3.83-4.36 (m, 9H), 3.14-3.25 (m, 6H), 2.71-2.96 (m, 2H), 1.74-2.05 (m, 3H), 1.33-1.44 (m, 7H), 1.15-1.21 (m, 2H), 1.03-1.06 (m, 1H), 0.80-0.93 (m, 3H).	546.4
I-326	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.36 (d, J = 14.0 Hz, 1H), 4.93-4.97 (m, 1H), 3.74-4.48 (m, 13H), 3.42-3.47 (m, 2H), 3.25-3.29 (m, 2H), 2.94-3.09 (m, 1H), 2.64-2.84 (m, 1H), 2.00-2.02 (m, 2H), 1.64-1.85 (m, 8H), 1.40-1.44 (m, 2H), 1.12-1.29 (m, 11H), 1.03-1.05 (m, 1H), 0.78-0.79 (m, 2H).	762.3
I-327	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.36 (d, J = 14.0 Hz, 1H), 4.92-4.96 (m, 1H), 3.90-4.44 (m, 14H), 3.70-3.75 (m, 1H), 3.39-3.48 (m, 4H), 3.22-3.25 (m, 1.5 H), 2.96-3.03 (m, 0.5H), 2.76-2.83 (m, 0.5H), 2.62-2.67 (m, 0.5H), 1.80-1.99 (m, 4H), 1.62-1.65 (m, 2H), 1.40-1.46 (m, 2H), 1.26-1.31 (m, 3H), 1.11-1.19 (m, 8H), 1.03-1.05 (m, 1H), 0.77-0.79 (m, 1H).	728.6

[1102]

化合物编号	方法	^{1}HNMR	LCMS
I-328	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.39 (d, J = 12.0 Hz, 1H), 6.97-7.38 (m ,1H), 4.94-4.98 (m, 1H), 3.36-4.48 (m, 8H), 3.58-5.76 (m, 5H), 3.21-3.23 (m, 1H), 2.78-2.87 (m, 4H), 1.69-1.78 (m, 5H), 1.42-1.56 (m, 2H), 1.26-1.33 (m, 4H), 1.15-1.26 (m, 9H), 0.93-1.06 (m, 4H), 0.76-0.83 (m, 1H).	629.8
I-329	17A	^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (s, 1H), 8.34-8.40 (m, 1H), 3.84-4.40 (m, 10H), 3.64-3.66 (m, 3H), 3.54 (t, J = 8.6 Hz, 3H), 3.35-3.42 (m, 2H), 3.22-3.25 (m, 2H), 3.12-3.16 (m, 1H), 3.04-3.08 (m, 2H), 1.94-1.98 (m, 2H), 1.67-1.83 (m, 7H), 1.56 (s, 1H), 1.38-1.45 (m, 1H), 1.23-1.29 (m, 3H), 1.11-1.17 (m, 8H), 0.93-1.05 (m, 3H), 0.77-0.79 (m, 1H)	630.7
I-330	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.35-8.39 (m, 1H), 4.91-4.99 (m, 1H), 3.68-4.40 (m, 13H), 3.34-3.46 (m, 2H), 3.11-3.27 (m, 2H), 2.75-3.05 (m, 1H), 1.85-1.97 (m, 5H), 1.65-1.76 (m, 6H), 1.48-1.62 (m, 3H), 1.13-1.24 (m, 11H), 1.02-1.07 (m, 1H), 0.89-0.98 (m, 2H), 0.74-0.81 (m, 1H).	685.4
I-331	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.34-8.39 (m, 1H), 3.81-4.40 (m, 11H), 3.58-3.68 (m, 2H), 3.38-3.53 (m, 5H), 3.13-3.18 (m, 1H), 1.67-1.90 (m, 7H), 1.35-1.60 (m, 5H), 1.09-1.26 (m, 12H), 0.95-1.06 (m, 3H), 0.77-0.82 (m, 1H).	631.3
I-332	17A	^{1}HNMR (400 MHz, CDCl3): δ 8.90 (s, 1H), 8.25-8.27(m, 2H), 4.23-4.45 (m, 3H), 4.02-4.13 (m, 3H), 3.77-3.97 (m, 4H), 2.87-3.70 (m, 11H), 1.92-2.23 (m, 3H), 1.65-1.70 (m, 5H), 1.40-1.57 (m, 5H), 1.08-1.25 (m, 9H), 0.87-0.91 (m, 3H), 0.67-0.76 (m, 1H).	630.8
I-333	28	^{1}HNMR (400 MHz, CD_3OD): δ 9.06 (s, 1H), 8.26 (d, J = 20.8 Hz, 1H), 7.24-7.18 (m, 0.5H), 4.60-4.38 (m, 2H), 4.18-3.76 (m, 9H), 3.58-3.25 (m, 8H), 3.13-3.08 (m, 1H), 1.92-1.55 (m, 10H), 1.27-1.19 (m, 3H), 1.02-0.91 (m, 10H), 0.39-0.26 (m, 4H).	681.7

[1103]

化合物编号	方法	^{1}HNMR	LCMS
I-334	28	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.40 (d, *J*=18.4 Hz, 1H), 4.75-4.50 (m, 2H), 4.32-3.82 (m, 8H), 3.77 (s, 3H), 3.54-3.47 (m, 1H), 3.29-3.27 (m, 1H), 3.05-3.01 (m, 1H), 2.06-2.00 (m, 2H), 1.72-1.57 (m, 6H), 1.27-1.02- (m, 17H), 0.48-0.38 (m, 4H).	617.6
I-335	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.39 (d, *J* = 16.0 Hz, 1H), 4.98-4.96 (m, 1H), 4.51-4.45 (m, 4H), 4.30-3.86 (m, 8H), 3.75-3.59 (m, 8H), 3.28-3.24 (m, 1H), 2.04-1.61 (m, 12H), 1.47-1.38 (m, 1H), 1.19-1.13 (m, 8H), 1.06-1.05 (m, 1H), 0.94-0.90 (m, 2H), 0.81-0.79 (m, 1H).	706.7
I-336	17A	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (s, 1H), 8.37 (d, *J* = 16.0 Hz, 1H), 4.95-4.90 (m, 1H), 4.50-3.82 (m, 13H), 3.76-3.70 (m, 5H), 3.50-3.36 (m, 3H), 3.23 (d, *J* = 7.2 Hz, 1H), 3.04-2.98 (m, 1H), 1.98-1.82 (m, 5H), 1.68-1.62 (m, 3H), 1.52-1.44 (m, 2H), 1.37 (d, *J* = 6.4 Hz, 6H), 1.20-1.11 (m, 8H), 0.82-0.75 (m, 1H).	698.7
I-337	28	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.37 (d, *J* = 7.4 Hz, 1H), 4.97-4.94 (m, 1H), 4.71-4.44 (m, 2H), 4.08-3.75 (m, 10H), 3.45-3.34 (m, 3H), 3.26-3.23 (m, 2H), 3.13-3.07 (m, 1H), 2.05-1.99 (m, 2H), 1.92-1.39 (m, 10H), 1.23 (s, 1H), 1.17 (t, *J* = 5.6 Hz, 3H), 1.02 (d, *J* = 4.4 Hz, 7H), 0.48-0.43 (m, 2H), 0.36-0.35 (m, 2H).	694.6
I-338	28	^{1}HNMR (400 MHz, CD_3OD): δ 9.18 (s, 1H), 8.41-8.35 (m, 1H), 7.75(d, *J* = 7.6 Hz, 1H), 7.35-7.26 (m, 1H), 5.61-5.57 (m 1H), 4.64-4.44 (m, 2H), 4.25-3.94 (m, 7H), 3.66-3.45 (m, 3H), 3.05-2.98 (m, 3H), 2.76-2.75 (m, 3H), 1.97-1.84 (m, 3H), 1.40-1.32 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 2H), 0.95-0.90 (m, 4H), 0.52 (s, 1H), 0.40-0.24 (m, 3H).	609.5
I-339	28	^{1}HNMR (400 MHz, CD_3OD): δ 9.15-9.12 (m, 1H), 8.35-8.19 (m, 2H), 7.77-7.68 (m, 2H), 5.10 (s, 2H), 4.50-3.42 (m, 13H), 3.22 (s, 1H), 1.91 (s, 4H), 1.31-0.78 (m, 13H), 0.48-0.20 (m, 4H).	610.5

[1104]

化合物编号	方法	^{1}HNMR	LCMS
I-340	28	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (s, 1H), 8.38-8.32 (m, 1H), 7.77-7.69 (m, 1H), 7.31-7.21 (m, 2H), 6.08 (s, 1H), 4.55-3.76 (m, 11H), 3.56 (t, *J* = 11.0 Hz, 2H), 3.45-3.39 (m, 1H), 3.09-3.06 (m, 3H), 3.00-2.93 (m, 4H), 1.90-1.80 (m, 4H), 1.37 (d, *J* = 6.6 Hz, 1H), 1.04 (d, *J* = 7.7 Hz, 3H), 0.96-0.88 (m, 4H), 0.48-0.30 (m, 4H).	623.6
I-341	28	^{1}HNMR (400 MHz, DMSO-*d*6): δ 9.15 (s, 1H), 8.37 (d, *J* = 17.6 Hz, 1H), 7.87-7.79 (m, 1H), 4.76-4.46 (m, 2H), 4.31-3.82 (m, 10H), 3.48-3.38 (m, 4H), 3.23-3.17 (m, 1H), 1.87-1.78 (m, 1H), 1.70-1.67 (m, 2H), 1.38-1.00 (m, 18H), 0.48-0.36 (m, 4H).	591.6
I-342	17A	^{1}HNMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 4.40-3.88 (m, 11H), 3.74-3.68 (m, 3H), 3.27-3.23 (m, 1H), 3.01-2.96 (m, 1H), 2.75 (d, *J* = 11.6 Hz, 3H), 2.02-1.92 (m, 2H), 1.71-1.59 (m, 4H), 1.53-1.44 (m, 2H), 1.37 (d, *J* = 6.4 Hz, 3H), 1.19-1.11 (m, 8H), 1.06-1.01 (m, 1H), 0.80-0.75 (m, 1H).	602.25
I-343	17A	^{1}HNMR (400 MHz, CD_3OD): δ 4.97-4.92 (m, 1H), 4.50-4.45 (m, 4H), 4.34-3.40 (m, 17H), 3.21 (d, *J* = 9.2 Hz, 1H), 3.02-3.00 (m, 1H), 2.68 (s, 3H), 2.42 (s, 3H), 1.96-1.85 (m, 6H), 1.67-1.62 (m, 4H), 1.50-1.38 (m, 3H), 1.17-1.03 (m, 10H), 0.78-0.77 (m, 1H).	726.6
I-344	29	^{1}HNMR (400 MHz, CD_3OD): δ 9.15 (d, *J* = 3.2 Hz, 1H), 8.34 (d, *J* = 7.2 Hz, 1H), 4.31 (dd, *J* = 3.2, 8.8 Hz, 1H), 4.12-4.02 (m, 2H), 3.92-3.37 (m, 12H), 3.27-3.25 (m, 1H), 3.01-2.98 (m, 1H), 2.74 (d, *J* = 14.8 Hz, 3H), 2.64-2.57 (m, 2H), 2.03-1.42 (m, 18H), 1.19 (d, *J* = 6.4 Hz, 3H).	588.45
I-345	29	^{1}H NMR (400 MHz, CD_3OD) δ9.15 (d, *J* = 1.8 Hz, 1H), 8.34 (d, *J* = 4.0 Hz, 1H), 4.33-4.30 (m, 1H), 4.08-4.03 (m, 2H), 3.94-3.72 (m, 10H), 3.56-3.35 (m, 6H), 3.28-3.25 (m, 1H), 3.01-2.98 (m, 1H), 2.74 (d, *J* = 7.2 Hz, 3H), 2.66-2.60 (m, 2H). 2.32-2.25 (m, 1H),	590.45

[1105]

化合物编号	方法	^{1}HNMR	LCMS
		2.07-1.95 (m, 3H), 1.69-1.49 (m, 8H), 1.19 (d, J = 3.0 Hz, 3H).	
I-346	29	^{1}HNMR (400 MHz, CD_3OD): δ 9.06 (s, 1H), 8.25 (d, J = 6.4 Hz, 1H), 4.23-4.21 (m, 1H), 4.01-3.94 (m, 2H), 3.83-3.78 (m, 5H), 3.64-3.54 (m, 4H), 3.45-3.29 (m, 6H), 3.16 (d, J = 9.6 Hz, 1H), 2.90 (d, J = 9.2 Hz, 1H), 2.64 (d, J = 14.4 Hz, 3H), 2.55-2.48 (m, 2H), 1.92-1.85 (m, 2H), 1.59-1.54 (m, 7H), 1.42-1.36 (m, 2H), 1.16 (s, 1H), 1.09 (d, J = 6.0 Hz, 3H).	604.85
I-347	29	^{1}H NMR (400 MHz, CD_3OD) δ9.05 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 4.8 Hz, 1H), 4.24-4.21 (m, 1H), 4.04-3.93 (m, 2H), 3.83-3.62 (m, 7H), 3.47-3.25 (m, 4H), 3.18-3.15 (m, 1H), 2.91-2.88 (m, 1H), 2.65 (d, J = 7.2 Hz, 3H), 2.41-2.36 (m, 2H). 1.92-1.85 (m, 2H), 1.59-1.53 (m, 4H), 1.42-1.39 (m, 2H), 1.09 (d, J = 3.2 Hz, 3H) , 0.84-0.81 (m, 9H).	576.40
I-348	29	^{1}H NMR (400 MHz, CD_3OD) δ9.05 (d, J = 2.0 Hz, 1H), 8.24 (d, J = 4.2 Hz, 1H), 4.69-4.64 (m, 2H), 4.34-4.29 (m, 2H), 4.22-4.19 (m, 1H), 3.97-3.62 (m, 8H), 3.37-3.25 (m, 3H), 3.18-3.16 (m, 3H), 2.98-2.89 (m, 2H), 2.79-2.74 (m, 2H). 2.64 (d, J = 7.4 Hz, 1H), 1.92-1.83 (m, 2H), 1.60-1.54 (m, 4H), 1.45-1.42 (m, 6H), 1.08 (d, J = 3.0 Hz, 3H).	576.45
I-349	29	^{1}HNMR (400 MHz, CD_3OD): δ 9.04 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.37-7.35 (m, 1H), 6.27-6.25 (m,1H), 6.20-6.16 (m, 1H), 4.19-4.15 (m, 1H), 3.94-3.90 (m, 2H), 3.82-3.73 (m, 2H), 3.68-3.57 (m, 6H), 3.41-3.30 (m, 4H), 3.17-3.14 (m,2H), 2.89-2.86 (m, 1H), 2.63 (d, J = 16.4 Hz, 3H), 1.91-1.85 (m, 2H), 1.59-1.53 (m, 4H), 1.41-1.38 (m, 2H), 1.07-1.04 (m, 3H).	586.85
I-350	29	^{1}H NMR (400 MHz, CD_3OD) δ 9.17 (d, J = 4.4 Hz, 1H), 8.36 (d, J = 10.0 Hz, 1H), 8.21 (d, J = 6.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H),4. 32-4. 28 (m, 1H), 4.08-4.04 (m, 2H), 3.93-3.86 (m, 2H), 3.83-3.73 (m, 6H), 3.52-3.25 (m, 7H), 3.01-2.97 (m, 1H), 2.76 (d, J =	587.40

[1106]

化合物编号	方法	^{1}HNMR	LCMS
		15.6 Hz, 3H),1.95-2.04 (m, 2H), 1.64-1.72 (m, 4H), 1.45-1.54 (m, 2H), 1.15-1.18 (m, 3H).	
I-351	29	^{1}HNMR (400 MHz, CD_3OD): δ 9.16 (d, J = 5.6 Hz, 1H), 8.36 (d, J = 10.4 Hz, 1H), 7.6 (s, 1H), 6.29 (d, J = 9.6 Hz, 1H), 4.32-4.29 (m,1H), 4.08-4.04 (m, 2H), 3.93-3.88 (m, 2H), 3.83-3.73 (m, 6H), 3.50-3.37 (m, 5H), 3.28-3.25 (m, 1H), 3.01-2.97 (m, 1H), 2.75 (d, J = 16.0 Hz, 3H), 1.99-1.97 (m, 2H), 1.70-1.65 (m, 4H), 1.52-1.49 (m, 2H), 1.18-1.16 (m, 3H).	586.45
I-352	29	^{1}HNMR (400 MHz, CD3OD): δ 9.18(s, 1H), 8.37 (s, 1H), 4.36 (s, 1H), 4.19-3.76 (m, 12H), 3.57-3.50(m, 1H), 3.39 (t, J = 8.4 Hz, 1H), 3.20 (t, J = 8.4 Hz ,1H), 3.04-3.01(m, 2H), 2.75 (d, J = 13.6 Hz, 3H), 2.09-2.07(m, 2H), 1.94-1.92(m, 2H), 1.77-1.68 (m, 5H), 1.58-1.54 (m, 2H), 1.31-1.19 (m, 6H),0.95-0.93 (m, 2H).	562.6
I-353	16A	^{1}H NMR (400 MHz, CD_3OD): δ 8.22 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 6.4 Hz, 1H), 7.42-7.23 (m, 5H), 5.38 (s, 2H), 4.45-4.31 (m, 5.83 Hz, 2H), 4.22-3.80 (m, 8H), 3.52-3.33 (m, 4H), 3.23-3.12 (m, 1H), 2.53-2.49 (m, 2H), 1.76-1.66 (m, 5H), 1.53 (s, 1H), 1.44-1.32 (m, 2H), 1.27-1.19 (m, 3H), 1.06-1.01 (m, 1H), 1.11 (s, 2H), 1.15 (d, J = 7.2 Hz, 6H), 0.97-0.90 (m, 2H), 0.78-0.75 (m, 1H).	705.10
I-354	18	^{1}H NMR (400 MHz, DMSO-d_6) & 9.25 (s, 1H), 8.40-8.35 (m, 1H), 8.27-8.19 (m, 1H), 7.79-7.69 (m, 1H), 4.28-4.19 (m, 2H), 4.13-3.93 (m, 3H), 3.90-3.69 (m, 5H), 3.46-3.34 (m, 2H), 3.23-3.19 (m, 1H), 2.60-2.55 (m, 3H), 1.61-1.59 (m, 2H), 1.38-1.29 (m, 7H), 1.18-1.16 (m, 2H), 1.12-1.04 (m, 10H), 0.87 (d, J=6.8 Hz, 3H), 0.68-0.66 (m, 1H).	588.4
I-355	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.37 (d, J = 17.8 Hz, 1H), 8.24 (m, 1H), 7.82 – 7.68 (m, 1H), 4.23 (m, 2H), 4.14 – 4.07 (m, 2H), 4.01 – 3.67 (m, 6H), 3.58 – 3.46 (m, 1H), 3.29 – 3.25 (m, 1H), 3.16 (t, J	600.4

[1107]

化合物编号	方法	^{1}HNMR	LCMS
		= 7.8 Hz, 1H), 2.58 (dd, *J* = 13.0, 4.4 Hz, 3H), 1.63 (m, 4H), 1.48 (s, 1H), 1.37 – 1.28 (m, 1H), 1.13 – 0.98 (m, 11H), 0.85 (d, *J* = 11.0 Hz, 3H), 0.67 (s, 1H), 0.26 – 0.20 (m, 2H), 0.14 (m, 2H).	
I-356	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.44 – 8.26 (m, 2H), 7.78 – 7.64 (m, 1H), 7.30 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 5.22 – 5.17 (m, 1H), 4.38 – 4.26 (m, 1H), 4.26 – 4.04 (m, 5H), 4.01 – 3.69 (m, 4H), 3.62 – 3.47 (m, 1H), 2.68 – 2.53 (m, 5H), 1.38 – 1.29 (m, 1H), 1.13 – 1.02 (m, 3H), 0.94 – 0.88 (m, 3H), 0.84 – 0.78 (m, 1H), 0.67 – 0.56 (m, 1H).	554.3
I-357	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.41 – 8.24 (m, 2H), 4.83 – 4.72 (m, 1H), 4.20 – 4.05 (m, 3H), 4.01 – 3.92 (m, 1H), 3.89 – 3.75 (m, 4H), 3.64 (s, 1H), 3.43 (s, 5H), 1.70 – 1.56 (m, 8H), 1.49 – 1.39 (m, 4H), 1.20 – 1.16 (m, 1H), 1.12 – 1.03 (m, 11H), 0.88 – 0.65 (m, 5H), 0.58 (s, 2H), 0.49 – 0.41 (m, 2H).	654.4
I-358	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34-8.25 (m, 1H), 7.86-7.82 (m, 1H), 7.46-7.44 (m, 1H), 7.34-7.26 (m, 5H), 4.54-4.32 (m, 3H), 4.23-4.10 (m, 1H), 4.00-3.78 (m, 4H), 3.75-3.42 (m, 7H), 2.61 (t, *J*=3.6 Hz, 3H), 1.31-1.21 (m, 1H), 1.10-1.00 (m, 9H), 0.85-0.83 (m, 1H), 0.67-0.64 (m, 1H).	565.4
I-359	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.09 (s, 1H), 8.19 (s, 1H), 7.92 (d, J = 9.5 Hz, 1H), 7.76 – 7.59 (m, 2H), 7.45 – 7.19 (m, 5H), 5.38 (s, 2H), 4.80 – 4.61 (m, 2H), 4.47 – 3.76 (m, 8H), 1.41 (s, 1H), 1.36 – 1.33 (m, 1H), 1.15 (s, 3H), 1.08 (s, 3H), 1.03 (d, J = 4.7 Hz, 1H), 0.89 (d, J = 7.5 Hz, 1H), 0.79 – 0.73 (m, 1H).	528.3
I-360	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.44 – 8.29 (m, 2H), 4.84 (s, 1H), 4.41 – 3.59 (m, 11H), 3.28 – 3.10 (m, 6H), 3.08 – 2.78 (m, 1H), 1.98 (s, 2H), 1.85 – 1.51 (m, 7H), 1.42 – 1.14 (m, 5H), 1.12 – 0.97 (m, 13H), 0.86 (s, 1H), 0.68 (s, 1H).	722.3

化合物编号	方法	^{1}HNMR	LCMS
I-361	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.47 – 8.33 (m, 2H), 4.97 – 4.86 (m, 1H), 4.24 – 3.37 (m, 15H), 2.04 – 1.64 (m, 10H), 1.49 – 1.33 (m, 1H), 1.32 – 1.16 (m, 2H), 1.14 – 0.99 (m, 13H), 0.89 – 0.83 (m, 1H), 0.73 – 0.64 (m, 1H).	714.1
I-362	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (t, J = 3.6 Hz, 1H), 8.95 – 8.79 (m, 1H), 8.41 – 8.31 (m, 1H), 8.21 – 8.05 (m, 1H), 7.72 – 7.57 (m, 1H), 7.29 – 7.20 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 5.56 – 5.41 (m, 1H), 4.30 – 3.96 (m, 4H), 3.94 – 3.64 (m, 4H), 3.61 – 3.46 (m, 1H), 2.72 – 2.63 (m, 1H), 2.59 (dd, J = 8.5, 4.2 Hz, 3H), 1.91 – 1.76 (m, 4H), 1.70 (d, J = 12.6 Hz, 1H), 1.55 – 1.43 (m, 2H), 1.38 (t, J = 11.9 Hz, 2H), 1.32 – 1.18 (m, 2H), 1.14 – 1.07 (m, 3H), 1.06 – 0.99 (m, 2H), 0.92 – 0.73 (m, 2H), 0.70 – 0.58 (m, 1H).	593.4
I-363	2A	^{1}HNMR (400 MHz, 甲醇-d_4) δ 8.25 – 8.17 (m, 1H), 7.92 (d, J = 13.2 Hz, 1H), 7.38 – 7.24 (m, 5H), 7.19 – 7.09 (m, 4H), 5.37 (s, 2H), 4.49 – 3.81 (m, 10H), 3.25 – 3.07 (m, 1H), 2.29 (s, 3H), 1.48 – 1.20 (m, 2H), 1.17 – 1.02 (m, 7H), 0.79 – 0.73 (m, 1H).	540.3
I-364	2A	^{1}HNMR (400 MHz, 甲醇-d_4) δ 8.39 – 8.34 (m, 1H), 8.25 – 8.16 (m, 1H), 7.94 – 7.88(m, 1H), 7.70 – 7.61 (m, 1H), 7.38 – 7.20 (m, 6H), 5.38 (s, 2H), 4.49 – 4.33 (m, 2H), 4.33 – 3.77 (m, 8H), 3.25 – 3.09 (m, 1H), 2.50 (s, 3H), 1.46 – 1.31 (m, 2H), 1.20 – 1.10 (m, 4H), 1.09 – 0.99 (m, 3H), 0.93 – 0.83 (m, 1H).	541.3
I-365	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.31 (d, J = 8.9 Hz, 1H), 8.21 (d, J = 14.3 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.60 (s, 1H), 7.31 (d, J = 18.0 Hz, 6H), 5.38 (s, 2H), 4.61 – 3.77 (m, 10H), 2.32 (s, 3H), 1.41 (s, 2H), 1.19 – 1.01 (m, 8H), 0.77 (s, 1H).	541.3
I-366	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.23 – 8.14 (m, 1H), 7.93-7.86 (m, 1H), 7.63 – 7.47 (m,	556.3

[1108]

[1109]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 7.39 – 7.22 (m, 5H), 5.36 (s, 2H), 5.27 – 5.17 (m, 1H), 4.48 – 3.73 (m, 8H), 3.28 – 3.14 (m, 1H), 2.65 (s, 3H), 1.59 – 1.51 (m, 3H), 1.42 – 1.25 (m, 1H), 1.20 – 0.93 (m, 7H), 0.83 – 0.70 (m, 1H).	
I-367	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.41 – 8.31 (m, 2H), 4.86 (s, 1H), 4.22 – 3.71 (m, 10H), 3.70 – 3.60 (m, 3H), 3.23 – 3.11 (m, 7H), 1.83 – 1.53 (m, 11H), 1.14 – 0.95 (m, 17H), 0.87 (s, 2H), 0.67 (s, 1H).	686.4
I-368	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.21 (d, J = 17.2 Hz, 1H), 7.92 (d, J = 12.8 Hz, 1H), 7.29 (m, 10H), 5.38 (d, J = 4.8 Hz, 2H), 4.74 – 4.33 (m, 3H), 4.21 – 3.77 (m, 9H), 3.12 (d, J = 8.8 Hz, 1H), 2.74 (d, J = 10.6 Hz, 3H), 1.51 – 1.00 (m, 13H), 0.73 (d, J = 8.0 Hz, 1H).	657.3
I-369	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 13.8Hz, 1H), 4.92 (s, 2H), 4.46 – 3.79 (m, 12H), 3.48 (s, 1H), 3.27 – 2.58 (m, 6H), 1.71 (m, 8H), 1.39 (s, 3H), 1.20 – 0.95 (m, 19H), 0.78 (s, 1H).	686.4
I-370	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.44 – 8.32 (m, 1H), 8.27 – 8.14 (m, 1H), 7.80 – 7.63 (m, 1H), 4.32 – 4.06 (m, 4H), 4.03 – 3.61 (m, 6H), 3.58 – 3.44 (m, 1H), 3.24 (dd, J = 14.8, 7.0 Hz, 1H), 3.13 (dt, J = 15.8, 7.8 Hz, 1H), 2.57 (dd, J = 13.0, 4.4 Hz, 3H), 1.75 – 1.49 (m, 4H), 1.31 (p, J = 13.0, 12.4 Hz, 3H), 1.13 – 0.99 (m, 9H), 0.95 – 0.81 (m, 4H), 0.75 – 0.56 (m, 1H), 0.27 – 0.10 (m, 4H).	600.4
I-371	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.24 – 8.18 (m, 1H), 7.92 (d, J = 9.3 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.38 – 7.24 (m, 5H), 7.17-7.09 (m, 1H), 5.38 (s, 2H), 4.71 – 4.49 (m, 2H), 4.42 – 4.09 (m, 3H), 4.06 (s, 3H), 4.04 – 3.81 (m, 4H), 1.43 – 1.32 (m, 3H), 1.18 – 1.13 (m, 3H), 1.13 – 1.07 (m, 3H), 1.04 – 1.01 (m, 1H), 0.79 – 0.73 (m, 1H).	558.3
I-372	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.25 – 8.10 (m, 2H), 7.92 (d, J = 9.9 Hz, 1H), 7.32 (dq, J	675.5

[1110]

化合物编号	方法	^{1}HNMR	LCMS
		= 15.1, 5.9, 4.6 Hz, 5H), 5.38 (s, 2H), 4.50 – 4.27 (m, 2H), 4.25 – 4.11 (m, 2H), 4.10 – 4.00 (m, 2H), 3.95 (dd, *J* = 12.8, 7.4 Hz, 2H), 3.90 – 3.77 (m, 2H), 3.47 – 3.34 (m, 2H), 3.21 (dd, *J* = 9.2, 6.3 Hz, 1H), 2.74 (d, *J* = 8.6 Hz, 3H), 1.57 (d, *J* = 11.2 Hz, 2H), 1.47 – 1.28 (m, 5H), 1.18 (d, *J* = 4.3 Hz, 3H), 1.15 (d, *J* = 7.3 Hz, 6H), 1.10 (s, 3H), 1.07 – 1.01 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 6H), 0.77 (dd, *J* = 8.0, 4.2 Hz, 1H).	
I-373	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33-8.24 (m, 1H), 7.86-7.81 (m, 1H), 7.66-7.65 (m, 1H), 7.34-7.19 (m, 11H), 5.27 (s, 2H), 4.54-4.33 (m, 3H), 4.21-4.11 (m, 1H), 4.00-3.59 (m, 7H), 3.53-3.36 (m, 4H), 2.62-2.60 (m, 3H), 1.32-1.20 (m, 1H), 1.12-1.00 (m, 9H), 0.85-0.83 (m, 1H), 0.67-0.60 (m, 1H).	655.4
I-374	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40-8.31 (m, 2H), 4.87 (s, 1H), 4.26-3.65 (m, 13H), 3.22-3.13 (m, 7H), 1.78-1.59 (m, 9H), 1.31-1.09 (m, 9H), 1.07-0.96 (m, 10H), 0.87-0.86 (m, 2H), 0.68-0.66 (m, 1H).	686.5
I-375	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.70 – 8.59 (m, 1H), 8.41 – 8.33 (m, 1H), 8.19 – 8.07 (m, 1H), 7.35 – 7.21 (m, 5H), 4.82 – 4.67 (m, 1H), 4.61 – 4.44 (m, 2H), 4.27 – 4.17 (m, 1H), 4.13 – 3.91 (m, 3H), 3.88 – 3.62 (m, 4H), 3.59 – 3.41 (m, 1H), 2.65 – 2.57 (m, 3H), 1.27 – 1.18 (m, 1H), 1.08 – 0.96 (m, 6H), 0.93 – 0.74 (m, 4H), 0.70 – 0.55 (m, 2H).	580.2
I-376	2A	^{1}H NMR (400 MHz, 甲醇-d_4)δ 8.21 (d, J = 13.7 Hz, 1H), 7.91 (d, J = 9.6 Hz, 1H), 7.69 (m, J = 26.0, 8.6, 4.5 Hz, 2H), 7.41 – 7.22 (m, 5H), 5.37 (s, 2H), 4.79 – 4.58 (m, 2H), 4.44 – 3.81 (m, 9H), 1.47 – 1.27 (m, 3H), 1.20 – 1.13 (m, 4H), 1.08 (s, 3H), 0.76 (m, J = 8.0, 4.3 Hz, 1H).	562.2
I-377	2A	^{1}HNMR (400 MHz, 甲醇-d_4) δ 8.21 (d, J = 12.0 Hz, 1H), 8.18 – 7.95 (m, 2H), 7.91 (d, J = 9.4 Hz, 1H), 7.37 – 7.24 (m, 5H), 5.37 (s, 2H), 4.83 – 4.61 (m, 2H), 4.44 – 3.73 (m,	610.4

[1111]

化合物编号	方法	^{1}HNMR	LCMS
		8H), 3.40 – 3.33 (m, 1H), 3.11 – 2.97 (m, 1H), 2.05 – 1.88 (m, 4H), 1.85 – 1.78 (m, 1H), 1.70 – 1.32 (m, 7H), 1.20 – 1.10 (m, 5H), 1.08 – 0.99 (m, 2H).	
I-378	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.16 (s, 1H), 8.37 (d, J = 9.8 Hz, 1H), 7.62 – 7.47 (m, 2H), 4.78 – 4.57 (m, 2H), 4.40 (m 1H), 4.32 – 4.19 (m, 2H), 4.19 – 4.00 (m, 3H), 4.01 – 3.80 (m, 3H), 2.66 (m, 3H), 1.47 – 1.26 (m, 2H), 1.19 – 1.01 (m, 7H), 0.76 (m, 1H).	469.2
I-379	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.42 – 8.33 (m, 1H), 8.21 – 8.12 (m, 1H), 7.77 – 7.63 (m, 1H), 4.90 – 4.81 (m, 1H), 4.27 – 3.61 (m, 10H), 3.56 – 3.40 (m, 1H), 2.62 – 2.53 (m, 3H), 1.75 – 1.51 (m, 5H), 1.41 – 1.24 (m, 3H), 1.22 – 0.99 (m, 10H), 0.95 – 0.75 (m, 3H), 0.72 – 0.65 (m, 1H).	560.2
I-380	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.49-8.35 (m, 2H), 4.87 (s, 1H), 4.22-3.95 (m, 4H), 3.86-3.75 (m, 3H), 3.65-3.42 (m, 8H), 3.23-3.19 (m, 1H), 1.97-1.95 (m, 2H), 1.76-1.69 (m, 4H), 1.30-1.24 (m, 5H), 1.12-1.04 (m, 12H), 0.87-0.85 (m, 1H), 0.68-0.66 (m, 1H), 0.31 (s, 4H).	690.3
I-381	2B	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.16 (m, 1H), 7.96 – 7.87 (m, 1H), 7.55 (t, J = 8.8 Hz, 2H), 7.39 – 7.23 (m, 5H), 5.38 (s, 2H), 4.77 – 4.46 (m, 2H), 4.32 – 3.77 (m, 8H), 3.26 (q, J = 5.3 Hz, 1H), 2.65 (s, 3H), 1.44 – 1.37 (m, 1H), 1.19 – 1.02 (m, 7H), 0.82 – 0.72 (m, 1H).	542.3
I-382	2A	^{1}H NMR (400 MHz, 甲醇-D4) δ 8.25 – 8.15 (m, 1H), 7.92 (d, J = 13.2 Hz, 1H), 7.49 – 7.19 (m, 5H), 5.38 (s, 2H), 4.39 – 3.76 (m, 8H), 3.24 – 2.89 (m, 3H), 1.82-1.64 (m, 4H), 1.46 – 1.36 (m, 2H), 1.22 – 1.08 (m, 6H), 1.06 – 0.87 (m, 9H), 0.81-0.73 (m, 1H).	546.3
I-383	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.46 – 8.33 (m, 2H), 4.86 (d, J = 5.2 Hz, 1H), 4.73 (d, J = 17.9 Hz, 1H), 4.25 – 3.59	680.4

[1112]

化合物编号	方法	^{1}HNMR	LCMS
		(m, 13H), 3.47 (d, J = 33.1 Hz, 1H), 3.22 (s, 2H), 3.05 (s, 7H), 1.97 (s, 2H), 1.73 (s, 7H), 1.31 (s, 2H), 1.18 – 1.02 (m, 12H), 0.85 (s, 1H), 0.68 (s, 1H).	
I-384	4A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33-8.24 (m, 1H), 7.87-7.81 (m, 1H), 7.53-7.51 (m, 1H), 7.35-7.24 (m, 5H), 4.54-4.51 (m, 1H), 4.45-4.41 (m, 1H), 4.38-3.83 (m, 6H), 3.79-3.78 (m, 3H), 3.74-3.35 (m, 7H), 2.62-2.60 (m, 3H), 1.35-1.28 (m, 1H), 1.10-1.00 (m, 9H), 0.85-0.83 (m, 1H), 0.67-0.60 (m, 1H).	579.3
I-385	18	H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.48 – 8.33 (m, 2H), 4.92 – 4.83 (m, 1H), 4.25 – 3.93 (m, 4H), 3.92 – 3.69 (m, 5H), 3.67 – 3.58 (m, 2H), 3.44 – 3.37 (m, 2H), 3.31 – 3.18 (m, 6H), 3.18 – 3.08 (m, 1H), 2.03 – 1.92 (m, 2H), 1.85 – 1.68 (m, 6H), 1.66 – 1.56 (m, 1H), 1.41 – 1.23 (m, 3H), 1.15 – 1.02 (m, 11H), 0.88 – 0.83 (m, 1H), 0.70 – 0.64 (m, 1H).	694.3
I-386	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.48 – 8.33 (m, 2H), 4.91 – 4.82 (m, 1H), 4.25 – 3.71 (m, 7H), 3.68 – 3.59 (m, 2H), 3.54 – 3.38 (m, 5H), 3.38 – 3.32 (m, 1H), 3.26 – 3.18 (m, 1H), 2.04 – 1.90 (m, 2H), 1.85 – 1.54 (m, 5H), 1.36 – 1.04 (m, 16H), 0.96 – 0.83 (m, 7H), 0.71 – 0.65 (m, 1H).	692.3
I-387	30	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.21 (d, J = 14.0 Hz, 1H), 8.04-7.74 (m, 3H), 7.40-7.20 (m, 5H), 5.37 (s, 2H), 4.76 – 3.72 (m, 9H), 3.28-3.16 (m, 1H), 2.76 (s, 3H), 1.08 – 0.87 (m, 7H), 0.52-0.21 (m, 4H).	556.4
I-388	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.27 – 8.11 (m, 1H), 7.91 (d, J = 13.2 Hz, 1H), 7.44 – 7.19 (m, 5H), 5.37 (d, J = 2.8 Hz, 2H), 4.42 – 4.02 (m, 4H), 4.02 – 3.74 (m, 4H), 3.27 – 3.00 (m, 3H), 1.78– 1.58 (m, 2H), 1.55 – 1.26 (m, 8H), 1.19– 1.16 (m, 2H), 1.16–1.07 (m, 4H), 1.06 – 1.00 (m, 1H), 0.99 – 0.82 (m, 4H), 0.81 – 0.75 (m, 1H).	546.4

[1113]

化合物编号	方法	^{1}HNMR	LCMS
I-389	20	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 13.8 Hz, 1H), 4.96 – 3.61 (m, 13H), 3.41 – 2.55 (m, 5H), 2.39 – 1.35 (m, 12H), 1.26 – 0.88 (m, 18H), 0.65 – 0.09 (m, 5H).	686.5
I-390	18	1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40-8.34 (m, 2H), 4.87 (s, 1H), 4.14-4.09 (m, 3H), 3.88-3.78 (m, 5H), 3.65-3.56 (m, 4H), 3.20-3.15 (m, 9H), 1.81-1.77 (m, 3H), 1.70-1.63 (m, 7H), 1.54-1.51 (m, 3H), 1.36-1.29 (m, 3H), 1.24-1.09 (m, 8H), 1.06-1.04 (m, 4H), 0.87-0.86 (m, 3H), 0.68-0.67 (m, 1H).	712.6
I-391	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.09 (m, 1H), 7.95 – 7.86 (m, 1H), 7.81 – 7.63 (m, 1H), 7.39 – 7.17 (m, 7H), 5.60 – 5.31 (m, 2H), 4.54 – 4.11 (m, 3H), 4.08 – 3.78 (m, 5H), 3.55 – 3.34 (m, 1H), 2.81 – 2.65 (m, 4H), 1.90 (dd, J = 28.4, 12.8 Hz, 4H), 1.76 (d, J = 12.6 Hz, 1H), 1.56 (q, J = 12.2, 11.8 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.39 – 1.24 (m, 2H), 1.22 – 1.03 (m, 6H), 1.01 – 0.89 (m, 1H), 0.81 – 0.66 (m, 1H).	666.5
I-392	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.28 – 8.16 (m, 1H), 8.08– 8.01 (m, 1H), 7.95 – 7.81 (m, 2H), 7.43 – 7.24 (m, 5H), 5.37 (s, 2H), 4.92–4.85 (m, 1H), 4.82 – 4.72 (m, 1H), 4.50 – 4.31 (m, 1H), 4.26 – 3.75 (m, 7H), 3.38 – 3.32 (m, 1H), 1.47– 1.35 (m, 1H), 1.19 – 1.00 (m, 7H), 0.79– 0.72 (m, 1H). ^{19}F NMR (376 MHz, 甲醇-d_4) δ -68.47.	596.4
I-393	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 – 8.31 (m, 2H), 8.01 (m, 1H), 7.85 – 7.79 (m, 1H), 7.29 (m,10H), 5.35 (d, J = 7.2 Hz, 2H), 4.69 – 4.58 (m, 1H), 4.46 (s, 2H), 4.23 – 4.11 (m, 1H), 4.05 – 3.91 (m, 2H), 3.90 – 3.74 (m, 2H), 3.73 – 3.62 (m, 2H), 3.61 – 3.42 (m, 2H), 2.62 – 2.55 (m, 3H), 1.25 (t, J = 7.6 Hz, 6H), 1.18 (m, 1H), 1.10 – 0.99 (m, 6H), 0.83 (q, J = 4.6 Hz, 1H), 0.63 (m, 1H).	655.4

[1114]

化合物编号	方法	^{1}HNMR	LCMS
I-394	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.51 – 8.41 (m, 1H), 8.41 – 8.33 (m, 1H), 4.94 – 4.84 (m, 1H), 4.73 – 4.63 (m, 1H), 4.26 – 3.36 (m, 14H), 3.27 – 3.18 (m, 2H), 2.03 – 1.86 (m, 4H), 1.82 – 1.67 (m, 4H), 1.66 – 1.49 (m, 3H), 1.41 – 1.25 (m, 1H), 1.17 – 1.02 (m, 11H), 0.90 – 0.82 (m, 1H), 0.73 – 0.64 (m, 1H).	748.2
I-395	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40-8.34 (m, 1H), 8.22-8.16 (m, 1H), 4.87-4.74 (m, 1H), 4.32-4.18 (m, 1H), 4.14-3.92 (m, 3H), 3.89-3.65 (m, 5H), 1.77-1.69 (m, 4H), 1.62-1.26 (m, 9H), 1.12-1.00 (m, 18H), 0.94-0.84 (m, 3H), 0.67-0.64 (m, 1H).	656.4
I-396	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.39 (m, 1H), 8.39 – 8.32 (m, 1H), 8.05 – 7.97 (m, 1H), 7.87 – 7.78 (m, 1H), 7.42 – 7.20 (m, 5H), 5.35 (s, 2H), 4.67 – 4.58 (m, 1H), 4.29 – 4.14 (m, 1H), 4.11 – 3.79 (m, 4H), 3.78 – 3.68 (m, 2H), 3.62 – 3.55 (m, 1H), 3.53 – 3.39 (m, 1H), 3.27 – 3.21 (m, 2H), 2.60 – 2.54 (m, 3H), 1.66 – 1.56 (m, 5H), 1.38 – 1.28 (m, 2H), 1.16 – 1.03 (m, 9H), 0.89 – 0.76 (m, 4H), 0.71 – 0.54 (m, 4H).	659.3
I-397	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.47 – 8.32 (m, 2H), 4.87 (s, 1H), 4.51 – 4.30 (m, 2H), 4.25 – 3.39 (m, 12H), 3.22 (m, 3H), 3.07 – 2.92 (m, 1H), 1.97 (s, 2H), 1.83 – 1.56 (m, 8H), 1.39 – 1.25 (m, 1H), 1.19 – 1.02 (m, 12H), 0.92 (s, 1H), 0.85 (s, 1H), 0.67 (d, J = 4.2 Hz, 1H).	694.4
I-398	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.54 – 8.30 (m, 2H), 4.89 (ddd, J = 13.4, 8.3, 4.4 Hz, 1H), 4.47 (s, 1H), 4.27 – 3.71 (m, 8H), 3.64 (s, 2H), 3.48 (dt, J = 34.2, 5.7 Hz, 1H), 3.22 (dd, 1H), 3.09 (dd, J = 15.3 Hz, 1H), 2.61 (s, 2H), 2.04 – 1.70 (m, 8H), 1.60 (s, 1H), 1.32 (ddd, J = 22.3, 8.5, 5.0 Hz, 2H), 1.25 – 1.12 (m, 3H), 1.11 – 1.00 (m, 9H), 0.85 (p, J = 4.2 Hz, 1H), 0.68 (dq, J = 7.1, 3.3 Hz, 1H).	732.3

[1115]

化合物编号	方法	^{1}HNMR	LCMS
I-399	20	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 16.6 Hz, 1H), 5.04 – 4.89 (m, 1H), 4.78 – 3.72 (m, 12H), 3.42 – 3.33 (m, 1H), 3.24 – 2.84 (m, 2H), 2.70 – 2.61 (m, 1H), 2.10 – 1.92 (m, 3H), 1.85 – 1.61 (m, 7H), 1.51 – 0.97 (m, 21H), 0.49 – 0.48 (m, 2H), 0.41 – 0.35 (m, 2H).	736.6
I-400	2A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.26 – 8.17 (m, 1H), 7.92 (d, J = 11.2 Hz, 1H), 7.49 – 7.22 (m, 6H), 6.93 (t, J = 8.5 Hz, 1H), 5.38 (s, 2H), 4.55 – 3.75 (m, 11H), 3.29 – 3.15 (m, 1H), 1.46 – 1.27 (m, 2H), 1.19 – 1.10 (m, 5H), 1.06 (s, 2H), 0.78 (dd, J = 8.0, 4.4 Hz, 1H).	544.2
I-401	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.54 – 8.43 (m, 1H), 8.42 – 8.33 (m, 1H), 8.06 – 7.96 (m, 1H), 4.69 – 4.56 (m, 1H), 4.30 – 4.15 (m, 1H), 4.13 – 3.93 (m, 3H), 3.88 – 3.62 (m, 4H), 3.54 – 3.40 (m, 1H), 3.28 – 3.19 (m, 2H), 2.62 – 2.53 (m, 3H), 1.66 – 1.55 (m, 5H), 1.38 – 1.28 (m, 2H), 1.17 – 1.03 (m, 9H), 0.90 – 0.77 (m, 4H), 0.71 – 0.54 (m, 4H).	586.2
I-402	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.45 – 8.16 (m, 2H), 4.87 (s, 1H), 4.33 – 4.04 (m, 4H), 4.00 – 3.61 (m, 6H), 3.54 (d, J = 24.3 Hz, 2H), 3.31 (s, 11H), 3.10 – 2.93 (m, 2H), 1.97 (d, 2H), 1.78 – 1.55 (m, 5H), 1.46 – 1.33 (m, 2H), 1.28 – 1.14 (m, 2H), 1.10 (d, J = 11.4 Hz, 4H), 1.06 – 0.99 (m, 7H), 0.93 – 0.82 (m, 3H), 0.67 (t, J = 5.6 Hz, 1H).	702.4
I-403	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, 1H), 8.19 (dd, J = 18.3, 8.8 Hz, 1H), 7.86 – 7.69 (m, 2H), 7.39 – 7.20 (m, 5H), 5.35 (s, 2H), 4.34 – 4.12 (m, 2H), 4.10 – 3.82 (m, 4H), 3.79 – 3.49 (m, 4H), 3.46 – 3.36 (m, 1H), 3.21 (s, 4H), 3.10 (t, J = 7.8 Hz, 1H), 3.05 – 2.96 (m, 1H), 2.58 (dd, J = 9.4 Hz, 3H), 1.96 (d, J = 12.4 Hz, 2H), 1.72 (d, J = 13.1 Hz, 2H), 1.45 – 1.27 (m, 2H), 1.12 – 1.06 (m, 4H), 1.02 (d, J = 6.6 Hz, 7H), 0.93 –	677.4

[1116]

化合物编号	方法	^{1}HNMR	LCMS
		0.87 (m, 1H), 0.86 – 0.78 (m, 2H), 0.70 – 0.62 (m, 1H).	
I-404	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.38 (d, J = 17.8 Hz, 1H), 8.07 – 7.96 (m, 1H), 7.40 (d, J = 3.2 Hz, 4H), 4.70 (s, 1H), 4.60 – 4.41 (m, 2H), 4.19 – 4.04 (m, 3H), 3.98 – 3.64 (m, 7H), 3.55 – 3.39 (m, 2H), 3.17 (s, 1H), 1.35 – 1.18 (m, 1H), 1.09 – 0.99 (m, 9H), 0.84 (d, J = 4.9 Hz, 1H), 0.69 – 0.57 (m, 1H).	575.4
I-405	1A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.19 – 7.97 (m, 3H), 7.37 – 7.19 (m, 5H), 4.82 – 4.60 (m , 2H), 4.40 – 3.82 (m, 10H), 3.37 (s, 1H), 2.84 – 2.73 (m, 3H), 1.44 – 1.34 (m, 1H), 1.17 – 0.99 (m, 7H), 0.80 – 0.73 (m, 1H).	559.4
I-406	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.37 (m, 2H), 7.12 (d, J = 22.2 Hz, 1H), 4.92 (s, 1H), 4.41 (m, 1H), 4.11 (dd, J = 20.4, 10.8 Hz, 4H), 3.80 (m, 2H), 3.65 (m, 3H), 3.37 – 3.16 (m, 5H), 2.88 (m, 1H), 2.74 (m, 1H), 1.95 (m, 2H), 1.65 (m, 5H), 1.39 (d, J = 34.6 Hz, 4H), 1.07 (t, J = 9.8 Hz, 12H), 0.86 (s, 3H), 0.68 (m, 1H).	694.4
I-407	1A	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.50 – 8.47 (m, 1H), 8.37 – 8.29 (m, 2H), 8.00 – 7.94 (m, 1H), 7.71 – 7.61 (m, 2H), 7.16 – 7.10 (m, 1H), 5.57 (s, 2H), 4.81 – 4.58 (m, 2H), 4.45 – 4.28 (m, 1H), 4.27 – 4.16 (m, 2H), 4.14 – 3.98 (m, 3H), 3.97 – 3.84 (m, 2H), 3.30 – 3.22 (m, 1H), 2.71 – 2.66 (m, 3H), 1.43 – 1.32 (m, 1H), 1.21 – 1.11 (m, 4H), 1.10 – 1.07 (m, 2H), 1.05 – 1.01 (m, 1H), 0.80 – 0.73 (m, 1H).	561.5
I-408	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40-8.34 (m, 2H), 4.87 (s, 1H), 4.27-3.77 (m, 10H), 3.73-3.34 (m, 5H), 3.20-3.17 (m, 9H), 3.02-3.00 (m, 1H), 1.75-1.72 (m, 4H), 1.39-1.29 (m, 7H), 1.24-1.19 (m, 4H), 1.12-1.04 (m, 9H), 0.87-0.86 (m, 1H), 0.69-0.67 (m, 1H).	702.5
I-409	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 – 8.42 (m, 1H), 8.36 (d, J = 10.8 Hz, 1H), 7.82 (d, J	655.4

[1117]

化合物编号	方法	^{1}HNMR	LCMS
		= 13.6 Hz, 1H), 7.38 – 7.23 (m, 10H), 5.38 – 5.33 (m, 2H), 4.91 (m, 1H), 4.58 – 4.45 (m, 2H), 4.25 – 4.12 (m, 1H), 4.05 – 3.96 (m, 2H), 3.87 (s, 1H), 3.76 (m, 3H), 3.63 – 3.54 (m, 1H), 3.53 – 3.32 (m, 2H), 2.96 (d, *J* = 4.4 Hz, 3H), 2.81 (d, *J* = 9.6 Hz, 3H), 1.27 (m, 1H), 1.12 – 1.01 (m, 9H), 0.84 (m, 1H), 0.63 (s, 1H).	
I-410	32	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 – 9.20 (m, 1H), 9.08 – 8.76 (m, 1H), 8.41 – 8.30 (m, 1H), 8.21 – 8.09 (m, 1H), 7.74 – 7.58 (m, 1H), 7.30 – 7.11 (m, 2H), 5.48 (s, 1H), 4.65 – 4.16 (m, 2H), 4.12 – 3.63 (m, 6H), 3.59 – 3.44 (m, 1H), 2.70 – 2.55 (m, 4H), 1.89 – 1.68 (m, 5H), 1.53 – 1.17 (m, 5H), 1.04 – 0.71 (m, 7H), 0.47 – 0.05 (m, 4H).	512.2
I-411	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 4.4 Hz, 1H), 9.02 – 8.83 (m, 1H), 8.41 – 8.31 (m, 1H), 8.27 – 8.13 (m, 1H), 7.78 – 7.63 (m, 1H), 7.33 – 7.18 (m, 2H), 5.56 – 5.47 (m, 1H), 4.28 – 3.98 (m, 4H), 3.94 – 3.62 (m, 4H), 3.57 – 3.39 (m, 1H), 3.00 – 2.79 (m, 1H), 2.59 (s, 3H), 2.15 – 1.88 (m, 6H), 1.83 – 1.71 (m, 2H), 1.40 – 1.23 (m, 1H), 1.15 – 1.00 (m, 5H), 0.91 – 0.76 (m, 2H), 0.71 – 0.57 (m, 1H).	629.3
I-412	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.43 – 8.33 (m, 1H), 8.01 – 7.89 (m, 1H), 4.65 (s, 1H), 4.26 – 3.60 (m, 11H), 3.55 – 3.45 (m, 2H), 3.43 – 3.37 (m, 2H), 2.68 – 2.55 (m, 2H), 2.42 – 2.27 (m, 3H), 1.41 – 1.25 (m, 1H), 1.14 – 0.99 (m, 9H), 0.89 – 0.82 (m, 1H), 0.72 – 0.64 (m, 1H).	555.4
I-413	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 14.6 Hz, 1H), 8.15 (dd, J = 20.4 Hz, 1H), 7.82 (d, J = 15.8 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.39 – 7.23 (m, 5H), 5.35 (s, 2H), 4.44 (d, 1H), 4.32 – 4.13 (m, 2H), 4.08 (dd, J = 12.3 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.84 – 3.61 (m, 4H), 3.56 – 3.37 (m, 1H), 3.31 – 3.25 (m, 2H), 3.21 (t, J = 8.0 Hz, 1H), 3.10 (t, J = 7.7 Hz, 1H), 2.62 – 2.54 (m, 3H), 1.79 (d,	663.6

[1118]

化合物编号	方法	^{1}HNMR	LCMS
		J = 12.3 Hz, 2H), 1.67 (d, J = 12.6 Hz, 2H), 1.38 – 1.27 (m, 2H), 1.14 – 1.00 (m, 11H), 0.90 – 0.79 (m, 3H), 0.66 (t, 1H).	
I-414	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.16 (s, 1H), 8.37 (d, *J* = 10.1 Hz, 1H), 7.68 (q, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.60 – 4.42 (m, 2H), 4.40 – 4.22 (m, 2H), 4.22 – 4.09 (m, 2H), 4.12 – 3.84 (m, 4H), 3.42 – 3.30 (m, 4H), 2.69 (d, *J* = 10.3 Hz, 1H), 1.87 (t, *J* = 14.8 Hz, 4H), 1.77 (d, *J* = 12.8 Hz, 1H), 1.61 – 1.49 (m, 2H), 1.44 (d, *J* = 11.9 Hz, 2H), 1.39 – 1.27 (m, 2H), 1.17 (d, *J* = 13.9 Hz, 4H), 1.13 – 1.00 (m, 4H), 0.77 (d, 1H).	536.4
I-415	31	^{1}H NMR (400 MHz, DMSO-d6) δ 9.23 (d, *J* = 18.4 Hz, 2H), 9.01 – 8.91 (m, 1H), 8.37 (d, *J* = 18.6 Hz, 1H), 5.34 (s, 1H), 4.25 – 4.00 (m, 4H), 3.95 – 3.78 (m, 4H), 3.70 (s, 1H), 3.58 – 3.47 (m, 1H), 3.06 (s, 1H), 1.63 – 1.49 (m, 5H), 1.39 – 1.35 (m, 1H), 1.16 – 1.04 (m, 13H), 0.86 (d, *J* = 5.2 Hz, 1H), 0.80 – 0.65 (m, 3H).	585.5
I-416	18	HNMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.57 – 8.45 (m, 1H), 8.41 – 8.34 (m, 1H), 7.37 – 7.24 (m, 5H), 4.96 – 4.87 (m, 1H), 4.58 – 4.44 (m, 2H), 4.23 – 3.95 (m, 4H), 3.92 – 3.63 (m, 5H), 3.56 – 3.41 (m, 1H), 2.99 – 2.93 (m, 3H), 2.84 – 2.77 (m, 3H), 1.31 – 1.22 (m, 1H), 1.13 – 1.01 (m, 9H), 0.87 – 0.81 (m, 1H), 0.68 – 0.61 (m, 1H).	582.4
I-417	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 – 8.93 (m, 1H), 8.56 – 8.51 (m, 1H), 8.41 – 8.36 (m, 1H), 7.89 – 7.82 (m, 1H), 7.81 – 7.75 (m, 1H), 7.52 – 7.40 (m, 2H), 7.34 – 7.29 (m, 1H), 7.13 – 7.08 (m, 1H), 5.47 (s, 2H), 4.66 – 4.45 (m, 2H), 4.21 – 3.67 (m, 8H), 3.25 – 3.14 (m, 1H), 2.58 (s, 3H), 1.36 – 1.27 (m, 1H), 1.24 – 1.16 (m, 1H), 1.11 – 1.03 (m, 4H), 1.00 – 0.98 (m, 1H), 0.88 – 0.82 (m, 1H), 0.69 – 0.64 (m, 1H).	543.3
I-418	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 – 8.91 (m, 1H), 8.58 – 8.51 (m, 2H), 8.45 – 8.40 (m, 1H), 7.92 – 7.85 (m, 1H), 7.52 – 7.40 (m,	543.2

[1119]

化合物编号	方法	^{1}HNMR	LCMS
		2H), 7.19 – 7.12 (m, 2H), 5.43 (s, 2H), 4.67 – 4.44 (m, 2H), 4.27 – 4.14 (m, 1H), 4.13 – 4.04 (m, 1H), 4.04 – 3.98 (m, 1H), 3.95 – 3.84 (m, 2H), 3.82 – 3.64 (m, 3H), 3.28 – 3.12 (m, 1H), 2.60 – 2.56 (m, 3H), 1.31 – 1.23 (m, 1H), 1.12 – 0.98 (m, 6H), 0.88 – 0.81 (m, 1H), 0.70 – 0.63 (m, 1H).	
I-419	18	^{1}H NMR (400 MHz, DMSO-d6) δ9.25 – 9.24 (m, 1H), 8.71 – 8.65 (m, 1H), 8.39 – 8.34 (m, 1H), 7.70 – 7.59 (m, 1H), 7.20 – 7.13 (m, 2H), 4.91 – 4.89 (m, 1H), 4.28 – 3.65 (m, 11H), 2.88 – 2.82 (m, 1H), 2.10 – 1.77 (m, 9H), 1.38 – 1.27 (m, 1H), 1.13 – 1.00 (m, 6H), 0.87 – 0.85 (m, 1H), 0.70 – 0.67 (m, 1H).	602.5
I-420	18	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (d, J = 4.3 Hz, 1H), 8.40 – 8.28 (m, 1H), 8.03 (dddd, J = 45.9, 31.7, 10.6, 6.9 Hz, 2H), 4.50 – 3.81 (m, 9H), 3.56 – 3.38 (m, 1H), 2.77 (td, J = 11.2, 9.5, 7.0 Hz, 6H), 1.41 (ddd, J = 34.3, 10.8, 6.3 Hz, 1H), 1.21 – 1.07 (m, 6H), 1.07 – 0.99 (m, 1H), 0.93 (dd, J = 23.1, 5.0 Hz, 1H), 0.82 – 0.69 (m, 1H).	526.4
I-421	2A	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 – 8.16 (m, 1H), 7.93 – 7.86 (m, 1H), 7.74 – 7.49 (m, 2H), 7.32 (ddt, J = 19.9, 14.7, 7.0 Hz, 5H), 5.85 – 5.72 (m, 1H), 5.37 (d, J = 5.8 Hz, 2H), 4.56 – 3.81 (m, 8H), 3.41 (dtd, J = 17.7, 12.4, 6.3 Hz, 1H), 2.78 – 2.70 (m, 3H), 2.67 (d, J = 2.5 Hz, 3H), 1.50 – 1.30 (m, 1H), 1.21 – 0.90 (m, 7H), 0.75 (ddd, J = 25.6, 8.2, 4.2 Hz, 1H).	599.4
I-422	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 – 9.16 (m, 1H), 8.86 – 8.72 (m, 1H), 8.40 – 8.34 (m, 1H), 8.11 – 8.01 (m, 1H), 7.56 – 7.45 (m, 1H), 6.75 – 6.69 (m, 2H), 5.38 – 5.33 (m, 1H), 4.26 – 3.96 (m, 5H), 3.71 – 3.66 (m, 6H), 3.49 – 3.42 (m, 5H), 2.61 – 2.57 (m, 3H), 1.36 – 1.22 (m, 1H), 1.15 – 0.99 (m, 7H), 0.91 – 0.80 (m, 2H), 0.71 – 0.59 (m, 1H).	596.5

[1120]

化合物编号	方法	^{1}HNMR	LCMS
I-423	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 – 9.20 (m, 1H), 8.54 (q, J = 11.2, 10.2 Hz, 1H), 8.41 – 8.27 (m, 1H), 7.66 (dq, J = 15.4, 7.6 Hz, 1H), 7.26 – 7.13 (m, 2H), 5.08 – 4.97 (m, 1H), 4.92 – 4.81 (m, 1H), 4.31 – 4.08 (m, 2H), 4.07 – 3.91 (m, 4H), 3.90 – 3.69 (m, 3H), 3.67 – 3.49 (m, 2H), 3.48 – 3.40 (m, 2H), 2.92 (d, J = 5.6 Hz, 1H), 1.83 – 1.67 (m, 4H), 1.39 – 1.24 (m, 1H), 1.14 – 0.91 (m, 12H), 0.89 – 0.81 (m, 1H), 0.67 (td, J = 25.2, 24.2, 16.4 Hz, 1H).	596.3
I-424	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 14.4 Hz, 1H), 8.24 – 8.13 (m, 1H), 7.86 – 7.70 (m, 2H), 7.39 – 7.23 (m, 5H), 5.35 (s, 2H), 4.31 – 4.13 (m, 3H), 4.10 – 4.03 (m, 1H), 4.00 – 3.87 (m, 2H), 3.84 – 3.69 (m, 4H), 3.67 – 3.35 (m, 3H), 3.28 – 3.23 (m, 1H), 3.18 – 3.09 (m, 1H), 2.62 – 2.55 (m, 3H), 1.56 – 1.45 (m, 3H), 1.41 – 1.27 (m, 7H), 1.13 – 1.07 (m, 3H), 1.06 – 1.01 (m, 6H), 0.90 – 0.81 (m, 1H), 0.72 – 0.62 (m, 1H).	663.6
I-425	18	1H NMR (400 MHz, CD_3OD) δ 9.21 (s, 1H), 8.39 (s, 1H), 7.63 – 7.50 (m, 1H), 4.54 – 3.79 (m, 8H), 3.43 (m, 1H), 2.78 (m, 3H), 2.55 – 2.40 (m, 1H), 2.06 – 1.89 (m, 2H), 1.84 – 1.67 (m, 3H), 1.39 (m, 6H), 1.21 – 0.99 (m, 7H), 0.81 – 0.72 (m, 1H).	583.4
I-426	18	1H NMR (400 MHz, CD3OD) δ 9.15 (s, 1H), 8.39 – 8.34 (m, 1H), 6.79 – 6.70 (m, 1H), 4.59 – 3.83 (m, 9H), 3.50 – 3.35 (m, 1H), 2.81 – 2.78 (m, 3H), 2.70 (s, 1H), 2.00 (s, 2H), 1.79 (s, 2H), 1.74 – 1.67 (m, 1H), 1.47 – 1.35 (m, 5H), 1.21 – 1.03 (m, 7H), 0.77 (s, 1H).	583.5
I-427	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 – 9.21 (m, 1H), 8.83 – 8.67 (m, 1H), 8.42 – 8.32 (m, 1H), 8.05 (s, 1H), 7.54 – 7.40 (m, 1H), 6.74 – 6.62 (m, 1H), 6.32 – 6.19 (m, 1H), 5.37 – 5.24 (m, 1H), 4.75 – 4.66 (m, 4H), 4.28 – 4.15 (m, 1H), 4.14 – 4.04 (m, 6H), 4.03 – 3.41 (m, 6H), 2.62 – 2.55 (m, 3H), 1.38 –	608.3

[1121]

化合物编号	方法	^{1}HNMR	LCMS
		1.24 (m, 1H), 1.14 – 1.00 (m, 5H), 0.92 – 0.76 (m, 2H), 0.72 – 0.58 (m, 1H).	
I-428	18	^{1}HNMR (400 MHz, DMSO-d_6) δ 9.26 – 9.23 (m, 1H), 8.41 – 8.34 (m, 1H), 8.33 – 8.24 (m, 1H), 4.22 – 3.99 (m, 7H), 3.89 – 3.77 (m, 5H), 3.71 – 3.65 (m, 1H), 3.60 – 3.54 (m, 1H), 3.40 – 3.33 (m, 2H), 3.29 – 3.24 (m, 2H), 3.18 – 3.12 (m, 1H), 1.79 – 1.69 (m, 1H), 1.62 – 1.54 (m, 2H), 1.35 – 1.17 (m, 3H), 1.13 – 1.03 (m, 9H), 0.89 – 0.83 (m, 1H), 0.71 – 0.65 (m, 1H).	617.4
I-429	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.16 (s, 1H), 8.42 – 8.31 (m, 1H), 4.54 – 4.12 (m, 4H), 4.10 – 3.84 (m, 4H), 3.50 – 3.36 (m, 1H), 3.02 – 2.88 (m, 1H), 2.83 – 2.75 (m, 3H), 2.06 (s, 2H), 1.89 – 1.52 (m, 5H), 1.51 – 1.25 (m, 5H), 1.21 – 1.02 (m, 7H), 0.78 (s, 1H).	584.4
I-430	18	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (dd, J = 5.3, 2.6 Hz, 1H), 8.41 – 8.31 (m, 1H), 7.48 (t, J = 7.7 Hz, 1H), 6.72 (t, J = 7.0 Hz, 1H), 6.30 (dd, J = 8.8, 5.6 Hz, 1H), 5.43 – 5.36 (m, 1H), 4.56 – 3.82 (m, 13H), 3.61 – 3.41 (m, 1H), 3.06 – 2.93 (m, 1H), 2.74 (dd, J = 6.4, 3.4 Hz, 3H), 2.54 – 2.46 (m, 2H), 2.38 (dd, J = 13.2, 7.2 Hz, 2H), 1.37 – 1.30 (m, 2H), 1.22 – 1.14 (m, 3H), 1.11 – 1.05 (m, 2H), 0.97 (d, J = 8.6 Hz, 2H), 0.81 – 0.67 (m, 1H).	674.4
I-431	32	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 13.8 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.75 – 4.23 (m, 4H), 4.18 – 3.83 (m, 7H), 3.73 (s, 1H), 3.51 – 3.33 (m, 4H), 3.28 – 3.10 (m, 4H), 2.91 (s, 1H), 2.74 – 2.57 (m, 1H), 1.93 (d, 2H), 1.84 – 1.69 (m, 5H), 1.45 (s, 1H), 1.38 – 1.29 (m, 2H), 1.22 (d, J = 12.3 Hz, 2H), 1.16 (t, 3H), 1.03 (d, J = 7.8 Hz, 8H), 0.99 – 0.93 (m, 1H), 0.47 (t, 2H), 0.37 (s, 2H).	702.6
I-432	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.16 (s, 1H), 8.38 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 6.75 – 6.58 (m, 2H), 5.50 – 5.28 (m, 1H), 4.56 – 4.28 (m, 1H), 4.22 – 4.05 (m, 3H), 4.02 –	594.4

[1122]

化合物编号	方法	^{1}HNMR	LCMS
		3.86 (m, 3H), 3.64 – 3.35 (m, 6H), 2.74 (d, *J* = 6.3 Hz, 3H), 1.69 – 1.58 (m, 6H), 1.32 (d, *J* = 17.3 Hz, 2H), 1.20 (s, 1H), 1.16 (d, *J* = 6.3 Hz, 2H), 1.08 (t, *J* = 7.0 Hz, 2H), 0.98 (s, 1H), 0.81 – 0.66 (m, 1H).	
I-433	18	^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.38 (d, *J* = 28.1 Hz, 4H), 4.90 (s, 1H), 4.28 (s, 3H), 4.07 (s, 5H), 3.80 (s, 4H), 3.65 (s, 2H), 3.59 (s, 3H), 3.46 (s, 2H), 3.05 (s, 1H), 2.78 (s, 2H), 1.88 (s, 2H), 1.72 (s, 4H), 1.37 (d, *J* = 25.1 Hz, 3H), 1.20 (s, 4H), 1.12 (s, 1H), 1.09 (s, 2H), 1.05 (s, 4H), 0.93 (s, 1H), 0.89 (s, 1H), 0.86 (s, 1H), 0.68 (s, 1H).	687.4
I-434	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.48 – 8.31 (m, 2H), 7.69 – 7.61 (m, 1H), 4.88 (s, 1H), 4.35 – 4.07 (m, 4H), 4.02 – 3.73 (m, 5H), 3.70 – 3.49 (m, 3H), 3.48 – 3.36 (m, 2H), 3.22 – 3.16 (m, 5H), 3.04 – 2.78 (m, 1H), 1.83 – 1.54 (m, 11H), 1.48 – 1.16 (m, 5H), 1.13 – 1.02 (m, 11H), 0.98 – 0.82 (m, 3H), 0.71 – 0.63 (m, 1H).	729.4
I-435	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.43 – 8.32 (m, 2H), 4.86 (s, 1H), 4.31 – 4.02 (m, 7H), 3.90 – 3.73 (m, 4H), 3.62 (d, *J* = 24.8 Hz, 3H), 3.46 – 3.39 (m, 1H), 3.23 – 3.14 (m, 7H), 1.99 (d, *J* = 12.4 Hz, 2H), 1.79 – 1.67 (m, 4H), 1.48 – 1.37 (m, 4H), 1.26 – 1.18 (m, 2H), 1.11 – 1.00 (m, 12H), 0.90 – 0.82 (m, 1H), 0.72 – 0.64 (m, 1H).	756.5
I-436	18	^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 (d, *J* = 18.8 Hz, 2H), 7.77 (d, *J* = 26.5 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.24 – 7.13 (m, 2H), 5.07 – 4.97 (m, 1H), 4.91 – 4.82 (m, 1H), 4.31 – 4.08 (m, 2H), 4.07 – 4.01 (m, 1H), 3.99 – 3.90 (m, 3H), 3.89 – 3.80 (m, 1H), 3.77 – 3.71 (m, 1H), 3.69 – 3.40 (m, 5H), 2.99 – 2.85 (m, 1H), 1.80 – 1.72 (m, 4H), 1.41 – 1.31 (m, 1H), 1.23 – 1.14 (m, 1H), 1.13 – 1.09 (m, 4H), 1.07 – 1.04 (m, 4H), 1.02 – 0.93 (m, 2H), 0.90 – 0.73 (m, 2H), 0.72 – 0.57 (m, 1H).	580.3

[1123]

化合物编号	方法	^{1}HNMR	LCMS
I-437	32	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (1H, s), 7.60 – 7.73 (1H, m), 7.16 (2H, m), 5.03 (1H, d, *J*=5.6 Hz), 4.87 (1H, d, *J*=6.6 Hz), 3.88 – 4.27 (5H, m), 3.62 – 3.71 (2H, m), 3.75 (1H, s), 3.40 – 3.48 (3H, m), 2.97 (2H, m), 2.62 (3H, d, *J*=2.8 Hz), 2.30 – 2.36 (2H, m), 2.23 (1H, s), 1.72 (5H, m), 1.34 (1H, s), 1.10 (4H, s), 1.04 (5H, d, *J*=9.0 Hz), 0.94 (1H, s), 0.86 (1H, s), 0.80 (1H, s), 0.56 – 0.72 (1H, m).	624.4
I-438	2A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 – 8.10 (m, 3H), 7.86 – 7.77 (m, 1H), 7.40 – 7.03 (m, 6H), 5.35 (s, 2H), 4.99 – 4.86 (m, 1H), 4.48 – 4.33 (m, 1H), 4.25 – 3.48 (m, 12H), 3.21 – 3.13 (m, 2H), 2.96 – 2.70 (m, 2H), 2.07 – 1.85 (m, 2H), 1.71 – 1.56 (m, 5H), 1.52 – 1.27 (m, 4H), 1.19 – 1.03 (m, 12H), 0.92 – 0.79 (m, 3H), 0.71 – 0.65 (m, 1H).	767.5
I-439	2A	^{1} H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.32 (m, 2H), 7.86 – 7.79 (m, 1H), 7.75 – 7.72 (m, 1H), 7.46 – 7.39 (m, 1H), 7.37 – 7.23 (m, 5H), 6.25 – 6.19 (m, 1H), 5.37 – 5.33 (m, 2H), 4.99 – 4.89 (m, 1H), 4.50 – 4.40 (m, 2H), 4.22 – 3.48 (m, 12H), 3.24 – 3.15 (m, 2H), 2.85 – 2.73 (m, 1H), 2.08 – 1.99 (m, 2H), 1.88 – 1.54 (m, 8H), 1.48 – 1.28 (m, 2H), 1.14 – 1.01 (m, 11H), 0.92 – 0.79 (m, 3H), 0.70 – 0.64 (m, 1H).	767.6
I-440	18 + 15 的步骤 7	^{1}H NMR (400 MHz, 甲醇-d4) δ 9.16 (s, 1H), 8.37 (d, *J* = 10.4 Hz, 1H), 8.21 (s, 1H), 7.34 (s, 1H), 7.13 (d, *J* = 14.4 Hz, 1H), 5.01 – 4.89 (m, 2H), 4.78 – 4.43 (m, 3H), 4.42 – 4.29 (m, 2H), 4.27 – 3.97 (m, 5H), 3.95 – 3.75 (m, 4H), 3.51 – 3.33 (m, 5H), 2.90 – 2.76 (m, 1H), 2.31 – 1.95 (m, 3H), 1.93 – 1.75 (m, 2H), 1.69 – 1.59 (m, 2H), 1.48 – 1.10 (m, 13H), 1.08 – 1.02 (m, 1H), 0.83 – 0.76 (m, 1H).	696.4
I-441	18	^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.41 – 8.33 (m, 1H), 6.61 – 6.14 (m, 1H), 4.40 – 3.85 (m, 13H), 3.73 – 3.62 (m, 1H),	599.3

[1124]

化合物编号	方法	^{1}HNMR	LCMS
		3.49 – 3.34 (m, 4H), 3.26 – 3.18 (m, 1H), 1.90 – 1.79 (m, 1H), 1.74 – 1.62 (m, 2H), 1.46 – 1.28 (m, 3H), 1.20 – 1.10 (m, 9H), 1.09 – 1.00 (m, 1H), 0.83 – 0.75 (m, 1H).	
I-442	18 + 15 的步骤 7	^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.82 (s, 2H), 8.56 – 8.31 (m, 2H), 7.93 (d, *J* = 5.6 Hz, 2H), 4.94 (s, 1H), 4.57 (s, 1H), 4.26 – 3.90 (m, 7H), 3.83 – 3.78 (m, 3H), 3.54 – 3.43 (m, 1H), 3.37 – 3.06 (m, 7H), 2.69 (d, *J* = 13.6 Hz, 1H), 2.01 – 1.83 (m, 2H), 1.71 (s, 1H), 1.55 (d, *J* = 13.4 Hz, 4H), 1.39 – 1.26 (m, 1H), 1.21 – 0.99 (m, 12H), 0.86 (d, *J* = 5.6 Hz, 1H), 0.73 – 0.64 (m, 1H).	707.5
I-443	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, *J* = 13.0 Hz, 2H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.47 (m, 1H), 7.36 – 7.21 (m, 5H), 6.02 (s, 1H), 5.35 (s, 2H), 4.91 (m, 1H), 4.39 (m, 1H), 4.18 (d, *J* = 7.6 Hz, 1H), 4.11 – 3.81 (m, 5H), 3.77 – 3.43 (m, 5H), 3.17 (d, *J* = 8.6 Hz, 3H), 2.89 (m, 1H), 2.73 (m, 1H), 1.92 (m, 2H), 1.65 (m, 6H), 1.50 – 1.28 (m, 4H), 1.15 – 1.04 (m, 11H), 0.86 (s, 3H), 0.71 – 0.64 (m, 1H).	767.6
I-444	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, *J* = 12.8 Hz, 2H), 8.17 (s, 1H), 7.82 (d, *J* = 16.1 Hz, 1H), 7.50 (s, 1H), 7.38 – 7.23 (m, 5H), 6.72 (s, 1H), 5.35 (s, 2H), 4.91 (s, 1H), 4.20 – 3.49 (m, 13H), 4.05 (m, 1H),3.15 (d, *J* = 8.8 Hz, 2H), 2.74 (s, 1H), 1.93 (s, 2H), 1.78 (s, 2H), 1.63 (s, 6H), 1.52 (d, *J* = 12.2 Hz, 2H), 1.35 (s, 3H), 1.24 – 1.02 (m, 12H), 0.86 (s, 3H), 0.71 – 0.63 (m, 1H).	807.7
I-445	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, *J* = 18.5 Hz, 2H), 7.87 – 7.54 (m, 3H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 4.93 (s, 1H), 4.43 (s, 1H), 4.26 – 3.38 (m, 12H), 3.30 – 3.12 (m, 3H), 2.87 – 2.72 (m, 1H), 2.14 – 1.99 (m, 2H), 1.71 – 1.54 (m, 6H), 1.51 – 1.24 (m, 3H), 1.18 – 1.02 (m, 12H), 0.85 (s, 3H), 0.70 – 0.64 (m, 1H).	784.5
I-446	2A	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, *J*	767.6

[1125]

化合物编号	方法	^{1}HNMR	LCMS
		= 13.7 Hz, 2H), 8.15 (s, 1H), 7.82 (d, *J* = 13.9 Hz, 1H), 7.37 – 7.22 (m, 5H), 6.87 (s, 2H), 5.35 (s, 2H), 4.91 (s, 1H), 4.37 – 3.57 (m, 12H), 3.17 (s, 2H), 2.97 – 2.77 (m, 2H), 1.92 (s, 2H), 1.73 – 1.20 (m, 10H), 1.19 – 1.02 (m, 12H), 0.86 (s, 3H), 0.70 – 0.64 (m, 1H).	
I-447	34	^{1}H NMR (400 MHz, DMSO-d6) δ 9.29 – 9.23 (m, 1H), 8.57 – 8.47 (m, 1H), 8.44 – 8.30 (m, 1H), 4.86 (s, 1H), 4.35 – 4.22 (m, 1H), 4.17 – 3.36 (m, 12H), 3.28 – 3.08 (m, 7H), 3.06 – 2.74 (m, 1H), 1.75 – 1.53 (m, 8H), 1.52 – 1.32 (m, 2H), 1.30 – 1.00 (m, 16H), 0.92 – 0.79 (m, 2H).	696.5
I-448	32	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.38 (d, *J* = 3.4 Hz, 1H), 7.79 (d, *J* = 13.6 Hz, 1H), 5.73 – 5.55 (m, 2H), 4.54 (d, *J* = 22.0 Hz, 1H), 4.39 – 3.98 (m, 5H), 3.85 (d, *J* = 32.2 Hz, 3H), 3.53 – 3.40 (m, 4H), 3.28 – 3.16 (m, 1H), 2.05 (d, *J* = 9.6 Hz, 2H), 1.86 (s, 2H), 1.65 – 1.50 (m, 2H), 1.34 – 0.91 (m, 18H), 0.41 (dd, *J* = 38.4, 6.8 Hz, 4H).	601.4
I-449	2A	^{1}H NMR (400 MHz, 甲醇-d4) δ 8.87 (m, 1H), 8.21 (d, J = 15.2 Hz, 1H), 7.96 – 7.88 (m, 1H), 7.39 – 7.25 (m, 5H), 5.38 (d, J = 2.6 Hz, 2H), 4.99 (s, 1H), 4.60 (s, 1H), 4.47 – 3.71 (m, 11H), 3.35 (s, 3H), 3.21 (q, J = 5.4, 5.0 Hz, 1H), 3.00 (s, 1H), 2.16 (m, 2H), 1.88 (d, J = 6.6 Hz, 1H), 1.74 (m, 6H), 1.51 (dt, J = 8.0, 3.6 Hz, 1H), 1.39 – 1.12 (m, 13H), 1.04 (t, J = 4.6 Hz, 1H), 0.92 (m, 2H), 0.81 – 0.76 (m, 1H).	769.5
I-450	32	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.38 (d, *J* = 2.6 Hz, 1H), 7.81 – 7.62 (m, 2H), 4.42 – 4.25 (m, 3H), 4.23 – 4.04 (m, 3H), 4.04 – 3.82 (m, 5H), 3.75 (s, 2H), 3.67 – 3.42 (m, 2H), 3.28 – 3.22 (m, 1H), 3.04 (d, *J* = 8.6 Hz, 1H), 1.99 (d, *J* = 13.6 Hz, 1H), 1.90 – 1.62 (m, 5H), 1.56 (d, *J* = 7.8 Hz, 2H), 1.44 (t, *J* = 6.8 Hz, 1H), 1.38 (d, *J* = 7.4 Hz, 1H), 1.24 (d, *J* = 4.6 Hz, 3H), 1.21 – 1.14 (m, 7H), 1.13 (d, *J* = 6.0	587.45

[1126]

化合物编号	方法	^{1}HNMR	LCMS
		Hz, 2H), 1.06 (dt, J = 12.0, 5.6 Hz, 3H), 0.83 – 0.77 (m, 1H).	
I-451	33	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 4.85 (s, 1H), 4.70 – 4.32 (m, 4H), 4.26 – 3.99 (m, 3H), 3.88 – 3.65 (m, 6H), 3.46 – 3.38 (m, 2H), 3.25 (s, 5H), 3.18 – 3.06 (m, 2H), 3.01 – 2.93 (m, 1H), 2.62 (s, 3H), 2.36 – 2.32 (m, 3H), 1.86 – 1.63 (m, 4H), 1.57 – 1.27 (m, 9H), 1.11 – 0.98 (m, 9H), 0.88 – 0.82 (m, 1H), 0.71 – 0.63 (m, 1H).	714.5
I-452	33	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 12.3 Hz, 1H), 4.97 – 4.91 (m, 1H), 4.45 – 4.21 (m, 3H), 4.19 – 4.03 (m, 3H), 4.00 – 3.82 (m, 3H), 3.71 (d, 4H), 3.63 – 3.53 (m, 4H), 3.23 – 3.01 (m, 1H), 2.02 – 1.93 (m, 2H), 1.67 (t, J = 12.3 Hz, 4H), 1.49 (d, 2H), 1.45 – 1.41 (m, 2H), 1.32 (d, J = 19.2 Hz, 3H), 1.16 (dd, J = 18.1, 9.1 Hz, 10H), 1.02 (d, 4H), 0.98 (s, 2H), 0.82 – 0.75 (m, 1H).	684.4
I-453	33	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.39 (m, 2H), 5.65 – 5.48 (m, 1H), 4.83 (m, 1H), 4.16 (m, 10H), 3.79 (m, 3H), 3.65 (m, 3H), 3.55 (m, 2H), 3.40 (m, 2H), 2.98 (s, 1H), 1.79 (d, J = 27.6 Hz, 6H), 1.52 (d, J = 11.4 Hz, 4H), 1.39 (m, 5H), 1.10 – 1.08 (m, 3H), 1.06 (d, J = 9.6 Hz, 4H), 0.86 (m, 1H), 0.68 (m, 1H).	698.4
I-454	33	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.37 (m, 1H), 4.95 (s, 1H), 4.58 (m, 1H), 4.43 – 3.82 (m, 10H), 3.72 (m, 3H), 3.45 (m, 1H), 3.27 – 3.13 (m, 2H), 3.02 (s, 1H), 2.69 (s, 1H), 2.51 (s, 1H), 1.96 (m, 4H), 1.65 (m, 4H), 1.57 – 1.36 (m, 5H), 1.21 – 1.10 (m, 9H), 1.05 (s, 1H), 0.79(m, 1H).	724.4
I-455	33	H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.24 (m, 1H), 4.90 – 4.82 (m, 1H), 4.70 (s, 1H), 4.24 – 3.99 (m, 3H), 3.95 – 3.71 (m, 6H), 3.65 – 3.58 (m, 3H), 3.57 – 3.50 (m, 3H), 3.48 – 3.40 (m, 2H), 3.14 – 3.06 (m, 1H), 3.03 – 2.95 (m, 1H), 2.63 – 2.60 (m, 3H), 2.36 – 2.32 (m, 3H), 2.02 – 1.76 (m, 5H),	768.3

[1127]

化合物编号	方法	^{1}HNMR	LCMS
		1.69 – 1.61 (m, 1H), 1.60 – 1.45 (m, 6H), 1.44 – 1.25 (m, 4H), 1.05 – 0.99 (m, 6H), 0.88 – 0.81 (m, 1H), 0.70 – 0.63 (m, 1H).	
I-456	33	^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 – 8.22 (m, 1H), 5.65 – 5.48 (m, 2H), 4.95 – 4.80 (m, 1H), 4.55 – 4.42 (m, 1H), 4.31 – 3.96 (m, 4H), 3.89 – 3.38 (m, 8H), 3.24 – 3.09 (m, 3H), 2.70 – 2.57 (m, 5H), 2.34 (s, 3H), 1.97 – 1.70 (m, 6H), 1.66 – 1.14 (m, 6H), 1.14 – 0.91 (m, 10H), 0.89 – 0.81 (m, 1H), 0.72 – 0.62 (m, 1H).	752.4
I-457	33	1H NMR (400 MHz, CD3OD) δ 9.16 (s, 1H), 8.39 – 8.36 (m, 2H), 4.96 – 4.92 (m, 1H), 4.64 – 4.56 (m, 2H), 4.40 – 3.89 (m, 9H), 3.73 – 3.35 (m, 7H), 3.24 – 3.23 (m, 1H), 3.04 – 3.02 (m, 1H), 1.98 – 1.97 (m, 4H), 1.81 – 1.63 (m, 5H), 1.50 – 1.29 (m, 4H), 1.20 – 1.11 (m, 9H), 1.09 – 1.05 (m, 1H), 0.80 – 0.79 (m, 1H) .	740.5
I-458	33	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.41 – 8.32 (m, 2H), 4.87 (s, 1H), 4.19 – 3.47 (m, 17H), 3.13 (d, J = 9.2 Hz, 1H), 2.99 (t, J = 8.6 Hz, 1H), 1.82 (s, 2H), 1.59 – 1.48 (m, 4H), 1.38 – 1.20 (m, 6H), 1.16 – 0.99 (m, 10H), 0.86 (s, 1H), 0.67 (t, J = 7.8, 4.0 Hz, 1H), 0.32 (s, 4H).	682.3
I-459	32	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 15.0 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.63 – 4.49 (m, 4H), 4.16 – 3.99 (m, 4H), 3.92 – 3.82 (m, 2H), 3.75 – 3.64 (m, 5H), 3.50 – 3.47 (m, 1H), 3.26 – 3.19 (m, 2H), 3.17 – 2.86 (m, 2H), 2.75 – 2.60 (m, 1H), 2.01 – 1.93 (m, 2H), 1.87 – 1.78 (m, 2H), 1.70 – 1.61 (m, 5H), 1.55 – 1.45 (m, 3H), 1.37 – 1.33 (m, 1H), 1.31 – 1.29 (m, 1H), 1.18 – 1.10 (m, 4H), 1.06 – 1.03 (m, 3H), 1.02 – 1.01 (m, 2H), 0.53 – 0.42 (m, 2H), 0.41 – 0.33 (m, 2H).	717.4
I-460	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.43 – 8.26 (m, 2H), 5.57 (q, J = 11.0 Hz, 1H), 4.88 (d, J = 29.0 Hz, 1H), 4.35 – 4.02 (m, 5H), 3.96 (m, 3H), 3.80 (d, J = 10.0	754.3

[1128]

化合物编号	方法	^{1}HNMR	LCMS
		Hz, 3H), 3.65 (m, 2H), 3.50 (d, *J* = 33.0 Hz, 3H), 3.27 – 2.63 (m, 5H), 1.91 (m, 1H), 1.75 (m, 5H), 1.59 – 1.47 (m, 2H), 1.43 – 1.23 (m, 5H), 1.13 – 0.97 (m, 9H), 0.86 (m, 1H), 0.72 – 0.64 (m, 1H).	
I-461	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.51 – 8.27 (m, 2H), 5.57 (q, *J* = 11.2 Hz, 1H), 4.96 – 4.78 (m, 1H), 4.30 – 3.52 (m, 16H), 3.25 – 2.80 (m, 4H), 1.96 – 1.61 (m, 7H), 1.57 – 1.51 (m, 1H), 1.42 – 1.24 (m, 5H), 1.12 – 1.00 (m, 10H), 0.86 (s, 1H), 0.71 – 0.64 (m, 1H).	736.4
I-462	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.46 – 8.27 (m, 2H), 7.88 – 7.71 (m, 1H), 4.45 (s, 1H), 4.33 – 4.21 (m, 3H), 4.20 – 4.02 (m, 3H), 3.99 – 3.72 (m, 5H), 3.69 – 3.48 (m, 1H), 3.23 – 3.12 (m, 1H), 3.08 – 2.99 (m, 1H), 2.62 (dd, J = 12.6, 4.4 Hz, 3H), 1.98 – 1.86 (m, 1H), 1.62 – 1.49 (m, 3H), 1.45 – 1.35 (m, 3H), 1.26 (d, J = 4.2 Hz, 1H), 1.17 – 1.10 (m, 3H), 1.07 (d, J = 3.3 Hz, 5H), 1.04 – 0.96 (m, 1H), 0.91 – 0.86 (m, 1H), 0.75 – 0.66 (m, 1H).	588.4
I-463	18	^{1}H NMR (DMSO, 400 MHz) δ 9.26 (1H, s)， 8.33 – 8.42 (1H, m), 8.01 – 8.12 (1H, m), 7.69 – 7.82 (1H, m), 3.67 – 4.27 (10H, m), 3.50 – 3.62 (1H, m), 3.43 (1H, t, *J*=3.2 Hz), 2.54 – 2.61 (3H, m), 2.03 (1H, d, *J*=12.4 Hz), 1.93 (1H, d, *J*=11.8 Hz), 1.85 (2H, d, *J*=7.2 Hz), 1.75 (3H, d, *J*=10.0 Hz), 1.62 (5H, m), 1.27 – 1.40 (3H, m), 1.02 – 1.12 (9H, m), 0.85 (1H, t, *J*=5.0 Hz), 0.63 – 0.70 (1H, m)	612.4
I-464	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.40-8.35 (m, 1H), 8.13-8.07 (m, 1H), 7.76-7.67 (m, 1H), 4.22-4.10 (m, 4H), 3.94-3.69 (m, 6H), 3.56-3.49 (m, 2H), 2.62-2.54 (m, 3H), 1.84-1.69 (m, 2H), 1.59-1.29 (m, 11H), 1.12-1.03 (m, 9H), 0.87-0.86 (m, 1H), 0.68-0.66 (m, 1H).	586.4
I-465	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 – 9.23 (m, 1H), 8.42 – 8.33 (m, 1H), 8.31 – 8.18 (m, 1H), 7.83 – 7.67 (m, 1H), 4.29 – 3.66 (m,	586.4

[1129]

化合物编号	方法	^{1}HNMR	LCMS
		11H), 3.36 – 3.28 (m, 1H), 3.19 – 2.98 (m, 1H), 2.62 – 2.55 (m, 3H), 2.19 – 2.09 (m, 2H), 2.04 – 1.94 (m, 1H), 1.64 – 1.54 (m, 1H), 1.49 – 1.37 (m, 2H), 1.33 – 1.18 (m, 4H), 1.12 – 1.01 (m, 10H), 0.89 – 0.83 (m, 1H), 0.71 – 0.62 (m, 1H), 0.60 – 0.51 (m, 1H).	
I-466	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.41 – 8.31 (m, 2H), 4.86 (s, 1H), 4.22 – 3.71 (m, 10H), 3.70 – 3.60 (m, 3H), 3.23 – 3.11 (m, 7H), 1.83 – 1.53 (m, 11H), 1.14 – 0.95 (m, 17H), 0.87 (s, 2H), 0.67 (s, 1H).	686.4
I-467	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.15 (s, 1H), 8.37 (d, J = 13.8Hz, 1H), 4.92 (s, 2H), 4.46 – 3.79 (m, 12H), 3.48 (s, 1H), 3.27 – 2.58 (m, 6H), 1.71 (m, 8H), 1.39 (s, 3H), 1.20 – 0.95 (m, 19H), 0.78 (s, 1H).	686.4
I-468	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.53 (s, 1H), 8.41 – 8.32 (m, 1H), 4.74 – 3.36 (m, 18H), 3.28 – 3.17 (m, 1H), 2.02 – 1.57 (m, 11H), 1.39 – 1.26 (m, 1H), 1.19 – 1.01 (m, 11H), 0.89 – 0.82 (m, 1H), 0.71 – 0.64 (m, 1H).	692.3
I-469	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.63 – 8.43 (m, 1H), 8.41 – 8.33 (m, 1H), 4.77 (s, 1H), 4.37 – 3.93 (m, 7H), 3.90 – 3.56 (m, 7H), 3.49 (m, 1H), 3.30 – 3.18 (m, 2H), 2.85 – 2.67 (m, 1H), 1.97 (s, 2H), 1.72 (t, J = 36.8 Hz, 9H), 1.40 (m, 2H), 1.07 (m, 10H), 0.86 (s, 1H), 0.68 (s, 1H).	692.3
I-470	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.70 – 8.56 (m, 1H), 8.47 -8.35 (m, 1H), 7.71 – 7.68 (m, 2H), 7.62 – 7.48 (m, 2H), 4.83 – 4.55 (m, 3H), 4.48 – 4.27 (m, 2H), 4.24 – 3.96 (m, 4H), 3.92 – 3.65 (m, 5H), 3.58 – 3.40 (m, 5H), 1.88 – 1.61 (m, 4H), 1.28 – 1.12 (m, 4H), 1.08 – 0.96 (m, 6H), 0.88 – 0.82 (m, 1H), 0.68 – 0.57 (m, 1H).	718.4
I-471	32	^{1}H NMR (400 MHz, 甲醇-d_4) δ 5.70 – 5.56 (m, 1H), 4.76 – 4.35 (m, 2H), 4.24 – 3.69 (m, 9H), 3.54 – 3.38 (m, 3H), 3.28 – 3.17 (m, 1H), 2.11 – 1.94 (m, 2H), 1.90 – 1.48 (m,	685.3

[1130]

化合物编号	方法	^{1}HNMR	LCMS
		5H), 1.34 – 0.85 (m, 17H), 0.50 – 0.31 (m, 4H).	
I-472	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 – 8.20 (m, 2H), 7.82 (d, *J* = 17.8 Hz, 1H), 7.57 (d, *J* = 22.6 Hz, 1H), 7.37 – 7.23 (m, 5H), 5.35 (s, 2H), 4.42 (dd, *J* = 8.8, 3.4 Hz, 1H), 4.25 – 4.10 (m, 1H), 4.07 – 3.85 (m, 3H), 3.78 – 3.59 (m, 4H), 3.56 – 3.40 (m, 2H), 3.17 (m, 4H), 1.67 (dd, *J* = 25.2, 13.2 Hz, 5H), 1.49 – 1.25 (m, 2H), 1.21 (d, *J* = 18.6 Hz, 4H), 1.09 – 1.01 (m, 14H), 0.84 (d, *J* = 12.4 Hz, 3H), 0.69 – 0.64 (m, 1H).	733.3
I-473	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.30 (dd, *J* = 40.8, 17.2 Hz, 2H), 7.82 (d, *J* = 18.2 Hz, 1H), 7.61 (d, *J* = 23.6 Hz, 1H), 7.37 – 7.23 (m, 5H), 5.35 (s, 2H), 4.42 (s, 1H), 4.26 – 3.80 (m, 8H), 3.78 – 3.57 (m, 5H), 3.24 – 3.08 (m, 3H), 1.68 (m,5H), 1.35 (m, 1H), 1.17 (d, *J* = 13.6 Hz, 7H), 1.09 – 1.01 (m, 15H), 0.85 (s, 3H), 0.67 (m, 1H).	761.5
I-474	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.36 (d, *J* = 14.8 Hz, 1H), 8.30 – 8.18 (m, 1H), 7.86 – 7.79 (m, 1H), 7.74 (d, *J* = 22.6 Hz, 1H), 7.38 – 7.23 (m, 5H), 5.35 (s, 2H), 4.43 – 4.35 (m, 1H), 4.24 – 4.04 (m, 2H), 3.98 – 3.85 (m, 2H), 3.83 – 3.59 (m, 5H), 3.58 – 3.37 (m, 2H), 3.23 – 3.12 (m, 2H), 1.73 – 1.59 (m, 5H), 1.50 – 1.41 (m, 1H), 1.38 – 1.34 (m, 1H), 1.30 – 1.11 (m, 6H), 1.08 – 0.99 (m, 8H), 0.89 – 0.79 (m, 6H), 0.66 (d, *J* = 7.2 Hz, 1H).	731.4
I-475	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 – 8.33 (m, 1H), 8.17 (s, 1H), 7.83 (d, *J* = 13.0 Hz, 1H), 7.37 – 7.22 (m, 5H), 5.35 (s, 2H), 4.52 (d, *J* = 8.6 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.99 – 3.87 (m, 3H), 3.74 (dd, *J* = 20.8, 13.2 Hz, 2H), 3.66 – 3.59 (m, 5H), 3.28 (d, *J* = 9.0 Hz, 1H), 3.13 (m, 2H), 3.07 – 3.01 (m, 1H), 1.65 (d, *J* = 12.4 Hz, 5H), 1.39 (d, *J* = 29.8 Hz, 2H), 1.20 – 1.10 (m, 4H), 1.06 (m, 8H), 0.85 (m, 3H), 0.67 (m, 1H).	648.3
I-476	16A	^{1}H NMR (400 MHz, 氯仿-d) δ 7.96 (t, *J* =	685.3

[1131]

化合物编号	方法	^{1}HNMR	LCMS
		7.6 Hz, 4H), 7.84 (s, 1H), 7.34 (q, *J* = 7.0 Hz, 7H), 6.56 (d, *J* = 26.2 Hz, 1H), 5.36 (s, 2H), 4.64 (d, *J* = 9.2 Hz, 3H), 4.19 – 3.89 (m, 9H), 3.16 (m, 1H), 2.82 (d, *J* = 4.6 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 1H), 1.12 (dd, *J* = 6.6, 3.0 Hz, 10H), 0.75 (d, *J* = 7.0 Hz, 1H).	
I-477	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.39 – 8.34 (m, 1H), 7.82 (d, *J* = 13.2 Hz, 1H), 7.37 – 7.23 (m, 5H), 5.35 (s, 2H), 4.40 (s, 1H), 4.14 (m, 2H), 3.99 – 3.83 (m, 3H), 3.72 (m, 2H), 3.60 (d, *J* = 9.2 Hz, 1H), 3.51 – 3.43 (m, 1H), 3.32 (s, 3H), 3.08 (t, *J* = 7.8 Hz, 1H), 1.73 – 1.58 (m, 5H), 1.45 (m, 1H), 1.32 (d, *J* = 23.6 Hz, 1H), 1.19 – 1.10 (m, 4H), 1.09 – 1.02 (m, 8H), 0.84 (d, *J* = 10.2 Hz, 3H), 0.69 – 0.63 (m, 1H).	634.3
I-478	16A	^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, *J* = 8.16 Hz, 1H), 8.21 (d, *J* = 11.6 Hz, 1H), 7.43-7.20 (m, 5H), 5.38 (s, 2H), 4.43-3.81 (m, 10H), 3.50-3.32 (m, 5H), 3.19 (d, *J* = 2.0 Hz, 1H), 2.47-2.44 (m, 2H), 1.74 (t, *J* = 13.2 Hz, 5H), 1.43 (d, *J* = 9.6 Hz, 9H), 1.30-1.22 (m, *J* = 24.0, 6.8 Hz, 5H), 1.15 (d, *J* = 8.0 Hz, 6H), 1.11 (s, 2H), 1.06-1.01 (m, 1H), 0.97-0.89 (m, 2H), 0.81-0.74 (m, 1H)	761.5
I-479			
I-480			
I-481			
I-482	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.46 – 8.30 (m, 2H), 7.82 (d, *J* = 16.2 Hz, 1H), 7.40 – 7.21 (m, 5H), 5.35 (s, 2H), 4.97 – 4.82 (m, 1H), 4.44 – 3.53 (m, 14H), 3.33 – 2.69 (m, 5H), 2.01 – 1.82 (m, 1H), 1.72 – 1.53 (m, 7H), 1.48 – 1.32 (m, 2H), 1.23 – 0.97 (m, 16H), 0.92 – 0.77 (m, 3H), 0.70 – 0.63 (m, 1H).	773.4
I-483	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 12.30 (s, 1H), 8.45 – 8.31 (m, 2H), 7.82 (d, *J* = 14.8 Hz, 1H), 7.39 – 7.22 (m, 5H), 5.35 (s, 2H), 4.96 – 4.85 (m, 1H), 4.56 – 3.36 (m, 12H), 3.27 – 3.08 (m, 2H), 3.05 – 2.59 (m, 2H), 2.41 – 2.14 (m, 1H), 2.05 – 1.87 (m, 1H),	745.3

[1132]

化合物编号	方法	^{1}HNMR	LCMS
		1.78 – 1.53 (m, 7H), 1.49 – 1.27 (m, 3H), 1.24 – 0.99 (m, 12H), 0.91 – 0.79 (m, 3H), 0.70 – 0.64 (m, 1H).	
I-484	16A	^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 – 8.25 (m, 2H), 7.82 (d, *J* = 16.4 Hz, 1H), 7.39 – 7.21 (m, 5H), 5.35 (d, *J* = 3.4 Hz, 2H), 5.07 – 4.78 (m, 1H), 4.27 – 3.81 (m, 9H), 3.79 – 3.44 (m, 6H), 3.25 – 3.14 (m, 3H), 3.06 – 2.83 (m, 2H), 2.00 – 1.80 (m, 1H), 1.72 – 1.57 (m, 7H), 1.47 – 1.28 (m, 3H), 1.19 – 0.98 (m, 15H), 0.92 – 0.76 (m, 3H), 0.70 – 0.62 (m, 1H).	773.4
I-485			
I-486			
I-487			
I-488			
I-489			
I-490			
I-491			
I-492			
I-493	18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, *J* = 4.6 Hz, 1H), 8.84 – 8.67 (m, 1H), 8.38 (d, *J* = 3.2 Hz, 1H), 7.64 (m, 1H), 7.14 (m, 2H), 4.87 (m, 1H), 4.18 – 3.96 (m, 4H), 3.81 – 3.52 (m, 8H), 2.76 (d, *J* = 8.0 Hz, 1H), 2.64 (s, 1H), 1.89 – 1.78 (m, 4H), 1.70 (d, *J* = 12.4 Hz, 2H), 1.49 (s, 2H), 1.39 – 1.33 (m, 3H), 1.23 (d, *J* = 4.2 Hz, 3H), 1.11 – 0.98 (m, 5H), 0.86 (d, *J* = 7.3 Hz, 1H), 0.80 (m, 1H), 0.70 – 0.60 (m, 1H).	606.5
I-494	18	^{1}H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.38 (d, *J* = 28.1 Hz, 4H), 4.90 (s, 1H), 4.28 (s, 3H), 4.07 (s, 5H), 3.80 (s, 4H), 3.65 (s, 2H), 3.59 (s, 3H), 3.46 (s, 2H), 3.05 (s, 1H), 2.78 (s, 2H), 1.88 (s, 2H), 1.72 (s, 4H), 1.37 (d, *J* = 25.1 Hz, 3H), 1.20 (s, 4H), 1.12 (s, 1H), 1.09 (s, 2H), 1.05 (s, 4H), 0.93 (s, 1H), 0.89 (s, 1H), 0.86 (s, 1H), 0.68 (s, 1H).	612.3
I-495	18	^{1}H NMR (400 MHz, 甲醇-d_4) δ 9.19 – 9.09 (m, 1H), 8.40 – 8.26 (m, 1H), 7.70 – 7.56 (m, 1H), 7.24 – 7.05 (m, 2H), 5.17– 4.98 (m,	606.4

[1133]

化合物编号	方法	^{1}HNMR	LCMS
		1H), 4.59 – 3.64 (m, 10H), 3.52 – 3.35 (m, 1H), 2.70 – 2.64 (m, 1H), 2.04 – 1.69 (m, 9H), 1.66 – 1.21 (m, 7H), 1.21 – 0.91 (m, 6H), 0.90 – 0.64 (m, 2H).	
I-496	18	^{1}H NMR (400 MHz, CD_3OD) δ 9.19 – 9.09 (m, 1H), 8.40 – 8.28 (m, 1H), 7.70 – 7.58 (m, 1H), 7.22 – 7.05 (m, 2H), 5.18 – 4.97 (m, 1H), 4.63 – 3.73 (m, 10H), 3.72 – 3.32 (m, 6H), 2.76 – 2.64 (m, 1H), 1.99 – 1.81 (m, 4H), 1.81 – 1.72 (m, 1H), 1.64 – 1.24 (m, 6H), 1.23 – 0.64 (m, 8H).	622.4
I-497	18	^{1}H NMR (400 MHz, CD_3OD) δ 9.29 – 9.10 (m, 1H), 8.41 – 8.26 (m, 1H), 7.79 – 7.60 (m, 1H), 7.34 – 7.12 (m, 2H), 5.19 – 4.96 (m, 1H), 4.56 – 4.09 (m, 5H), 4.09 – 3.91 (m, 5H), 3.90 – 3.50 (m, 5H), 3.49 – 3.33 (m, 1H), 3.16– 2.68 (m, 1H), 2.03 – 1.42 (m, 9H), 1.22 – 0.96 (m, 6H), 0.93 – 0.67 (m, 2H).	608.4
I-498	35	^{1}HNMR (400 MHz, CD_3OD) δ 8.27 – 8.17 (m, 1H), 7.96 – 7.93 (m, 1H), 7.41 – 7.19 (m, 10H), 5.35 (d, J = 11.3 Hz, 2H), 4.70 – 3.58 (m, 13H), 2.72 (t, J = 2.8 Hz, 3H), 1.49 – 1.25 (m, 6H), 1.22 – 1.15 (m, 4H), 1.10 – 1.02 (m, 3H), 0.78 – 0.73 (m, 1H).	655.5
I-499A	35	^{1}HNMR (400 MHz, CD_3OD) δ 8.25 – 8.18 (m, 1H), 7.95 – 7.90 (m, 1H), 7.38 – 7.27 (m, 5H), 5.38 (s, 2H), 4.62 – 3.59 (m, 10H), 2.75 – 2.74 (m, 3H), 1.69 – 1.66 (m, 5H), 1.50 – 1.39 (m, 5H), 1.24 – 1.00 (m, 14H), 0.94 – 0.70 (m, 4H).	661.5
I-499B	35	^{1}H NMR (400 MHz, CD_3OD) δ 8.30 – 8.22 (m, 1H), 7.98 – 7.95 (m, 1H), 7.37 – 7.23 (m, 5H), 5.39 (s, 2H), 4.70 – 3.61 (m, 10H), 3.37 – 3.33 (m, 1H), 3.22 – 3.10 (m, 1H), 1.72 – 1.64 (m, 5H), 1.51 – 1.33 (m, 6H), 1.24 – 1.07 (m, 12H), 1.04 – 1.00 (m, 1H), 0.97 – 0.84 (m, 3H), 0.79 – 0.72 (m, 1H).	661.5
I-500	35	^{1}HNMR (400 MHz, CD_3OD) δ 8.29 – 8.17 (m, 1H), 8.01 – 7.84 (m, 1H), 7.38 – 7.19 (m, 10H), 5.38 (s, 2H), 4.65 – 3.78 (m, 13H), 2.77 – 2.70 (m, 3H), 1.46 – 1.31 (m, 1H),	659.4

[1134]

化合物编号	方法	^{1}HNMR	LCMS
		1.22 – 0.99 (m, 10H), 0.79 – 0.67 (m, 1H).	
I-501	35	^{1}HNMR (400 MHz, CD_3OD) δ 8.34 – 8.15 (m, 1H), 8.01 – 7.85 (m, 1H), 7.40 – 7.22 (m, 5H), 5.38 – 3.78 (m, 13H), 3.36 – 3.18 (m, 2H), 2.80 – 2.73 (m, 3H), 1.70 – 1.46 (m, 7H), 1.23 – 1.04 (m, 12H), 0.94 – 0.77 (m, 4H)	665.5

[1135] 实施例A1:CDK2/细胞周期蛋白E1 Caliper测定

[1136] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开化合物存在下对CDK2/细胞周期蛋白E1活性的抑制。在测定中,CDK2/细胞周期蛋白E1(Eurofins,14-475)催化荧光标记肽5-FAM-QSPKKG-CONH2(PerkinElmer,FL Peptide 18)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK2/细胞周期蛋白E1的抑制作用(以%活性和IC50值表示)。反应含有50mM HEPES pH 7.5、10mM MgCl2、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、2.5nM CDK2/细胞周期蛋白E1、100μM ATP和1.5μM荧光肽底物。

[1137] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的3.25nM CDK2/细胞周期蛋白E1和130μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为2.5nM CDK2/细胞周期蛋白E1、100μM ATP和1.5μM荧光肽。100分钟后添加EDTA(400mM最终EDTA浓度)停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合到四参数方程以确定每种化合物的IC50。

[1138] Caliper测定的结果报告在下表3中。IC_{50}小于或等于0.01μM的化合物指定为"A"。IC_{50}大于0.01μM且小于或等于0.1μM的化合物指定为"B"。IC_{50}大于0.1μM且小于或等于1.0μM的化合物指定为"C"。IC_{50}大于1.0μM且小于或等于10.0μM的化合物指定为"D"。IC_{50}大于10.0μM的化合物指定为"E"。

[1139] 实施例A2:BrdU细胞增殖测定

[1140] 使用BrdU测定作为基于增殖细胞的DNA复制过程的增殖测量。BrdU(嘧啶类似物)被添加到细胞培养物中并掺入增殖细胞的DNA中。然后通过比色ELISA测量BrdU类似物的存在。细胞固定和透化后,添加识别BrdU的过氧化物酶缀合的抗体并孵育,然后彻底清洗以除去未结合的抗体。为了确定结合的抗体量的数量,添加过氧化物酶底物并产生可在450nm测量的颜色。

[1141] 在第-1天,将Kuramochi细胞(Sekisui XenoTech JCRB0098)以2,000个细胞/孔接种在150μL培养基的96孔板(Corning,CLS3596)的第2-12列中,并使其在37度及5%CO_2粘附过夜。

[1142] 在第0天,通过添加10mM化合物并为了每种化合物的10点剂量反应进行3倍连续的稀释来制备源板。使用多通道移液器,在Nunc 96DeepWell™板(未处理的96DeepWell板,2mL/孔,无菌,天然,60/cs)(Sigma Z717274)的每个孔中将2μL源板内容物冲压到具有500μL RPMI 1640培养基、GlutaMAX补充剂(Life Technologies,61870127)的中间板中并充分

混合。将该中间板的每个孔中的50μL添加到先前接种的Kuramochi细胞的96孔板的4个孔中。

[1143] 在第4天,根据制造商的说明(Roche,11647229001)使用BrdU ELISA细胞增殖测定对板进行显影。简而言之,将BrdU在Gibco®、Opti-MEM®中稀释至1:100,并添加20μL/孔,在350rpm振荡10分钟,然后返回培养箱孵育1小时。孵育后,弃去培养基,并将细胞通过添加200μL固定/变性溶液固定。将抗BrdU过氧化物酶抗体在OptiMEM中稀释至1:1000,以100μL/孔添加,并振荡(350rpm)孵育1小时。用PBS洗涤3次以去除任何未结合的抗体,然后向每个孔中添加100μL底物溶液。然后添加25μL/孔的1M硫酸溶液以终止反应,并使用设置为读取450nm吸光度的Envision分光光度计(Perkin Elmer)读取板。从所有样品中减去空孔的背景吸光度值,然后标准化为DMSO处理的孔。

[1144] BrdU细胞增殖测定的结果报告在下表3中。IC_{50}小于或等于0.5μM的化合物指定为"A"。IC_{50}大于0.5μM且小于或等于5.0μM的化合物指定为"B"。IC_{50}大于5.0μM且小于或等于10.0μM的化合物指定为"C"。IC_{50}大于10.0μM的化合物指定为"D"。

[1145] 实施例A3:HotSpot™激酶抑制测定

[1146] 使用HotSpot™测定(Reaction Biology Corporation专有)评估在本公开化合物存在下对CDK2/CCNE1活性的抑制。在该测定中,CDK2/细胞周期蛋白E1(Signalchem C29-18G)催化放射性磷酸盐转移至组蛋白H1(Sigma,H5505)的氨基酸残基,其通过辐射进行检测。减去源自含有无活性酶的对照反应的背景后,激酶活性数据表示为与不存在抑制剂的反应相比在测试样品中剩余激酶活性的百分比。反应含有20mM HEPES pH 7.5、10mM $MgCl_2$、1mM EGTA、2mM DTT、0.02%Brij35、0.02mg/mL BSA、0.1mM Na_3VO_4、1%DMSO、1.5nM CDK2/细胞周期蛋白E1、10μM ATP和20μM组蛋白H1。

[1147] 将CDK2/细胞周期蛋白E1和组蛋白H1在反应缓冲液中混合。通过声学传递向该混合物中加入在100%DMSO中的抑制剂的剂量滴定。将化合物混合物孵育20分钟,然后通过添加ATP和^{33}P ATP的混合物(最终浓度为10μM总ATP、20μM组蛋白H1和1.5nM CDK2/细胞周期蛋白E1)来引发激酶反应。反应进行120分钟,然后点样在P81离子交换滤纸上,并用0.75%磷酸充分洗涤。将所得放射性计数标准化为收率%活性,绘制化合物浓度图,并拟合到四参数方程以确定每种化合物的IC_{50}。

[1148] HotSpot™测定的结果报告在下表3中。IC_{50}小于或等于1.0μM的化合物指定为"A"。IC_{50}大于1.0μM且小于或等于10μM的化合物指定为"B"。IC_{50}大于10μM且小于或等于100μM的化合物指定为"C"。IC_{50}大于100μM的化合物指定为"D"。

[1149] 实施例A4:IncuCyte®细胞增殖测定

[1150] IncuCyte®测定用于测量公开的化合物对细胞增殖的影响。在化合物处理后立即和72小时后拍摄细胞的荧光显微镜图像。使用图像分析软件来获得作为化合物浓度的函数的细胞计数。将用mApple-H2B标记的Kuramochi细胞接种到384孔分析准备板上。将板置于IncuCyte®(Sartorius)中并在0小时和72小时进行扫描。IncuCyte®软件用于计算在每个孔中荧光核的数量。将用增加的化合物浓度(10pts、1/2log稀释、20μM最高浓度)处理的孔中从0小时到72小时的细胞计数中的倍数变化标准化为DMSO对照孔。将标准化的细胞计数与剂量反应曲线拟合并计算GI_{50}。

[1151] IncuCyte®细胞增殖测定的结果报告在下表3中。IC_{50}小于或等于0.5μM的化合物

指定为“A”。IC_{50}大于0.5μM且小于或等于5.0μM的化合物指定为“B”。IC_{50}大于5.0μM且小于或等于20.0μM的化合物指定为“C”。IC_{50}大于20.0μM的化合物指定为“D”。

[1152] 表3.测定结果

[1153]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-1			B	
I-2			C	
I-3A	C		A	
I-3B	E		B	D
I-4A			C	
I-4B			D	
I-5A			A	
I-5B			B	
I-6			D	
I-7		D	A	
I-8A	D		B	
I-8B	D		C	
I-9	C	D		
I-10	C		A	
I-11	C		A	
I-12		B	A	
I-13	C		A	
I-14	D		B	
I-15	C	D		
I-16A	E	D		
I-16B	E	D		
I-17A		D		
I-17B	E	D		
I-18	D			D
I-19A	C	D		
I-19B	E	D		
I-20	B	D		
I-21	B	D		

[1154]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-22	B	B		
I-23A	D	D		
I-23B	E	D		
I-24A	C	D		
I-24B	E	D		
I-25A	E	D		
I-25B	E	D		
I-26A	D	D		
I-26B	E	D		
I-27A	D	D		
I-27B	E	D		
I-28	C	D		
I-29	C	D		
I-30	B	D		
I-31	C	D		
I-32	B	D		
I-33A	C	D		
I-33B	E	D		
I-34A	E	D		
I-34B	E	D		
I-35	E			D
I-36A	E	D		
I-36B	E	D		
I-37A	E	D		
I-37B	E	D		
I-38A	E	D		
I-38B	E	D		
I-39A	C	D		
I-39B	E	D		
I-40A	E	D		
I-40B	E	D		

[1155]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-41A	E	D		
I-41B	E	D		
I-42A	D	D		
I-42B	E	D		
I-43A	E	D		
I-43B	E	D		
I-44A	E	D		
I-44B	E	D		
I-45A	E	D		
I-45B	E	D		
I-46A	E	D		
I-46B	E	D		
I-47A	E	D		
I-47B	E	D		
I-48A	E	D		
I-48B	E	D		
I-49A	E	D		
I-49B	E	D		
I-50A	E	D		
I-50B	E	D		
I-51A	E	C		C
I-51B	E	D		
I-52	B	B		B
I-53A	E	D		
I-53B	E	D		
I-54A	C	D		
I-54B	E	D		
I-55A	E	D		
I-55B	E	D		
I-56A	C	D		
I-56B	D	D		

[1156]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-57	B	D		
I-58A	C	D		
I-58B	D	D		
I-59A	E	D		
I-59B	E	D		
I-60A	D	D		
I-60B	E	D		
I-61A	D	D		
I-61B	E	D		
I-62A	C	D		
I-62B	E	D		
I-63A	D	C		
I-63B	D	D		
I-64	B	B		
I-65A	B	D		
I-65B	E	D		
I-66A	B	D		
I-66B	D	D		
I-67A	C	D		
I-67B	E	D		
I-68A	E	D		
I-68B	E	D		
I-69A	C	D		
I-69B	E	D		
I-70A	E	D		
I-70B	E	D		
I-71A	C	D		
I-71B	E	D		
I-72A	E	D		
I-72B	E	D		
I-73A	D	D		

[1157]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-73B	E	D		
I-74A	D	D		
I-74B	E	D		
I-75A	D	B		
I-75B	D	D		
I-76A	D	D		
I-76B	E	D		
I-77A	E	D		
I-77B	E	D		
I-78A	E	D		
I-78B	E	D		
I-79A	E	D		
I-79B	E	D		
I-80A	E	D		
I-80B	E	D		
I-81A	C			
I-81B	D	C		
I-82A	E	D		
I-82B	E	D		
I-83A	D	D		
I-83B	E	D		
I-84A	D			
I-84B	D	C		
I-85	B	B		
I-86	B	D		
I-87A	C	D		
I-87B	E	D		
I-88 混合物			C	
I-88A	E	D		
I-88B	E	D		
I-89A	D	D		

[1158]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-89B	E	D		
I-90A	C	D		
I-90B	E	D		
I-91A	E	D		
I-91B	E	D		
I-92A	E	D		
I-92B	E	D		
I-93	D	D		
I-94A	E	D		
I-94B	E	D		
I-95A	C	D		
I-95B	E	D		
I-96A	C	D		
I-96B	E	D		
I-97	B	B		B
I-98	B	D		
I-99	B	B		C
I-100A	D	D		
I-100B	E	D		
I-101A	C	D		
I-101B	E	D		
I-102A	E	D		
I-102B	E	D		
I-103A	C	D		
I-103B	E	D		
I-104	B	A		B
I-105	A	A		A
I-106	B	B		
I-107	A	A		A
I-108A	C	D		
I-108B	E	D		

[1159]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-109A	E	D		
I-109B	E	D		
I-110A	B	B		
I-110B	C	C		C
I-111	B	A		B
I-112A	D	D		
I-112B	E	D		
I-113A	D	D		
I-113B	E	D		
I-114A	C	D		
I-114B	E	D		
I-115	C	D		C
I-116A	E	D		
I-116B	E	D		
I-117A	D	D		
I-117B	E	D		
I-118	E	D		D
I-119A	C	D		
I-119B	D	D		
I-120A	C	D		
I-120B	D	D		
I-121A	B	C		
I-121B	D	D		
I-122A	E	D		
I-122B	E	D		
I-123A	A	A		B
I-123B	C	D		
I-124	C	D		
I-125A	A	A		A
I-125B	B	B		B
I-126A	E	D		

[1160]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-126B	E	D		
I-127A	D	D		
I-127B	E	D		
I-128A	E	D		
I-128B	E	D		
I-129A	B	B		B
I-129B	D	D		
I-130A	B	C		C
I-130B	C	D		
I-131A	E	D		D
I-131B	E	D		
I-132	B	B		B
I-133A	D	D		
I-133B	D	D		D
I-134A	E	D		D
I-134B	E	D		D
I-135A	B	B		B
I-135B	C	D		C
I-136A	B	B		C
I-136B	C	D		
I-137A	C	D		D
I-137B	D	D		D
I-138	A	A		A
I-139	C	D		
I-140A	C	D		C
I-140B	E	D		
I-141A	B	B		
I-141B	C	B		C
I-142A	E	D		
I-142B	E	D		
I-143	E	D		

[1161]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-144A	B	D		
I-144B	D	D		
I-145A	B	B		
I-145B	D	D		
I-146	E	D		
I-147	A			
I-148A	E	D		
I-148B	E	D		
I-149 混合物	A	A		A
I-149A	A	A		A
I-149B	C	D		
I-150A	A	B		
I-150B	D	D		
I-151A		B		B
I-151B	D	D		
I-152 混合物	A	A		A
I-152A	A	A		A
I-152B	D	D		C
I-153 混合物	A	A		A
I-153A		A		A
I-153B	D	D		
I-154A		B		B
I-154B	D	D		
I-155A	C	D		
I-155B	D	D		
I-156A	B	C		
I-156B	E	D		D
I-157A	B	B		B
I-157B	C	D		
I-158A	E	D		

[1162]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-158B	E	D		
I-159	E	D		
I-160A	B	B		
I-160B	E	D		
I-161A	E	D		
I-161B	E	D		
I-162A	B	B		C
I-162B	E	D		
I-163A	E	D		D
I-163B	E	D		
I-164A	A	A		A
I-164B	B	B		B
I-165	E	D		
I-166A	A	A		A
I-166B	C	B		
I-167	C	D		
I-168	D	D		
I-169	E	D		
I-170	A	B		
I-171A	C	D		
I-171B	E	D		
I-172	A	A		
I-173A	A	A		B
I-173B	D	D		
I-174A	B	B		B
I-174B	C	D		
I-175A	A	A		A
I-175B	C	D		C
I-176A	B	D		D
I-176B	D	D		
I-177A	C	B		C

[1163]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-177B	D	D		
I-178A	C	D		C
I-178B	E	D		
I-179	D	D		
I-180	C	D		
I-181	D	D		
I-182	D	C		
I-183	E	D		
I-184	C			
I-185A	E	D		
I-185B	E	D		
I-186A	B	B		
I-186B	E	D		
I-187A	E	D		
I-187B	E	D		
I-188A	B	D		
I-188B	D	D		
I-189A	C	D		C
I-189B	E	D		D
I-190A	B	A		A
I-190B	C	B		C
I-191A	E	D		D
I-191B	E	D		D
I-192A	A	A		A
I-192B	D	D		
I-193		A		A
I-194 混合物	A	A		A
I-194A		A		A
I-194B		B		C
I-195	A	A		A

[1164]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-196 混合物	A	A		B
I-196A	A	A	A	A
I-196B	A	A		B
I-197	A	B		A
I-198	A	A		A
I-199	C	D		
I-200	A	B		
I-201A	E	D		
I-201B	E	D		
I-202	A	B		
I-203	A	B		B
I-204	D	D		
I-205A	C	D		
I-205B	D	D		
I-206	C	D		
I-207	D	A		C
I-208A	B	A		A
I-208B	C	D		
I-209A	D	D		
I-209B	E	D		
I-210	E	D		
I-211	D	D		
I-212	D	D		
I-213A	B	B		B
I-213B	E	D		D
I-214	D	D		
I-215	D	D		
I-216	C	D		
I-217	A	A		
I-218	A	C		
I-219	A	B		

[1165]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-220	B	D		
I-221	E	D		
I-222	B	D		
I-223	E	D		
I-224A	D	D		D
I-224B	E	D		
I-225	C	D		
I-226	D	D		
I-227A	C	D		D
I-227B	E	D		
I-228A	A	D		D
I-228B	C	D		
I-229A	E	B		B
I-229B	E	D		
I-230	D	D		
I-231A	D	D		D
I-231B	E	D		
I-232A	B	B		B
I-232B	D	D		
I-233	E	D		
I-234	E	D		
I-235	C	D		
I-236	D	D		
I-237	C	D		
I-238	B	D		
I-239	A	D		
I-240	A	D		
I-241	D	D		
I-242	D	D		
I-243	E	D		
I-244	D	D		

[1166]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-245	D	D		
I-246	C	B		C
I-247	C	D		
I-248	E	D		
I-249	B	B		B
I-250	E	D		
I-251	C	D		
I-252	C	C	A	C
I-253	C	C	B	C
I-254	E	D		
I-255	E	D		
I-256	C	C	B	
I-257	D	D		D
I-258	E	D		D
I-259	E	D		D
I-260	E	D		D
I-261	E	D		D
I-262	C	D		D
I-263	A	B		B
I-264	D	D		D
I-265	D	D		D
I-266	D	D		D
I-267	D	D		D
I-268	E	D		D
I-269	C	D		C
I-270	B	D		C
I-271	A	A		A
I-272	B	B		B
I-273	E	D		D
I-274	C	C		C
I-275	C	D		D

[1167]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-276	D	D		D
I-277	D	D		D
I-278	D	D		D
I-279	B	B		B
I-280	A	B		B
I-281	A	B	A	A
I-282	A	A		A
I-283	D	D		D
I-284	B	B		B
I-285	C			D
I-286	B	B		B
I-287	C	D		C
I-288	B	D		C
I-289	A	A		A
I-290	C	D		C
I-291	C			D
I-292	B			D
I-293	D	D		D
I-294	E	D		D
I-295	C	C		C
I-296	B	B		B
I-297	B			D
I-298	E	D		D
I-299	B	D		D
I-300	A			A
I-301	A			D
I-302	B	D		D
I-303	E	D		
I-304	A	B		B
I-305	E	B		
I-306	D	D		D

[1168]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-307	B	B		B
I-308	A	A		B
I-309	B	B		B
I-310				C
I-311	A	A		A
I-312	B			B
I-313	A			B
I-314	A			A
I-315	A			B
I-316	C			D
I-317	A	B		B
I-318	A	B		B
I-319	A	A		B
I-320	A			B
I-321	B	B		B
I-322	A	B		B
I-323	D	D		D
I-324	D	D		D
I-325	D	D		D
I-326	A	A		A
I-327	B			C
I-328	A	B		B
I-329	A			B
I-330	A	C		B
I-331	A			A
I-332	A			C
I-333	B			C
I-334	C			D
I-335	A			B
I-336	A	D		C
I-337	A			B

[1169]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-338	E			D
I-339	D			D
I-340	D			D
I-341	C	D		D
I-342	B	B		B
I-343	A			D
I-344	E	D		D
I-345	E	D		D
I-346	E	D		D
I-347	E			D
I-348	D			D
I-349	E			D
I-350	E			D
I-351	E			D
I-352	E			D
I-353	A			C
I-354	A	B		A
I-355	A	B		A
I-356	E	D		D
I-357	B	C		C
I-358	E	D		D
I-359	E	D		D
I-360	A	B		B
I-361	A	B		B
I-362	B	B		C
I-363	D	C		C
I-364	E	D		C
I-365	D	D		D
I-366	D	B		B
I-367	A	B	A	B
I-368	C	D		C

[1170]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-369	A	B		B
I-370	A	A		A
I-371	E	D		D
I-372	A	A		A
I-373	E	D		D
I-374	A	B		B
I-375	C	D		D
I-376	D	D	B	D
I-377	C	D	A	D
I-378	E	D	C	D
I-379	E	D		D
I-380	A	A		A
I-381	E	D		D
I-382	D	D		D
I-383	A	C		B
I-384	E	D		D
I-385	A	A		A
I-386	A	A		A
I-387	E			D
I-388	E			B
I-389	A			B
I-390	A			A
I-391	A			B
I-392	D			D
I-393	B			C
I-394	A			A
I-395	B			B
I-396	A			B
I-397	A			B
I-398	A	A		A
I-399	A	B		B

[1171]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-400	E	D		D
I-401	B	B		B
I-402	B	B		B
I-403	B	D		D
I-404	B			D
I-405	E			D
I-406	A	B		B
I-407	E			D
I-408	B			B
I-409	A			B
I-410	B			B
I-411	B			D
I-412	B			D
I-413	C			D
I-414	B			B
I-415	B			B
I-416	B			C
I-417	E			D
I-418	E			D
I-419	C			D
I-420	E			D
I-421	D			D
I-422	D	D		D
I-423	D			D
I-424	B	D		D
I-425	C	D		D
I-426	C	D		D
I-427	D	D		D
I-428	C	D		D
I-429	D	D		D
I-430	C	D		D

[1172]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-431	C			D
I-432	C	D		D
I-433	D			D
I-434	C			D
I-435	A			B
I-436	E			D
I-437	E			D
I-438	A			B
I-439	A			A
I-440	B			D
I-441	C			D
I-442	A			C
I-443	A			A
I-444	A			A
I-445	A			A
I-446	A			B
I-447	C	D		
I-448	D			D
I-449	A			A
I-450	C			D
I-451	B			C
I-452	A			A
I-453	A			C
I-454	A			B
I-455	B			B
I-456	A			B
I-457	B			B
I-458	A			B
I-459	B			C
I-460	A			B
I-461	A			B

[1173]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-462	C	D		D
I-463	B	B		B
I-464	B	B		B
I-465	A	B		A
I-466	A	B	A	B
I-467	A	B		B
I-468	A	A		A
I-469	A	B		A
I-470	A			B
I-471	D			D
I-472	A			
I-473	A			
I-474	A			
I-475	A			
I-476	D			D
I-477	A			D
I-478	A			A
I-479				
I-480				
I-481				
I-482	A			
I-483	A			
I-484	A			
I-485				
I-486				
I-487				
I-488				
I-489				
I-490				
I-491				
I-492				

[1174]

化合物编号	Caliper 测定 (CDK2/CCNE1): IC50 (μM)	BrdU - KURAMOCHI.1: IC50 (μM)	Kinase 测定 (CDK2/CCNE): IC50 (μM)	IncuCyte®测定: IC50 (μM)
I-493	B			C
I-494	C	D		D
I-495	B			B
I-496	B	D		C
I-497	D			D
I-498	D			D
I-499A	D			D
I-499B	E			D
I-500	C			
I-501	B			B

[1175] 实施例A5:CDK1/细胞周期蛋白B1 Caliper测定

[1176] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开的化合物存在下CDK1/细胞周期蛋白B1活性的抑制作用。在测定中,CDK1/细胞周期蛋白B1(Carna Biosciences,04-102)催化荧光标记肽5-FAM-GGGPATPKKAKKL-CONH2(PerkinElmer,FL Peptide 29)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK1/细胞周期蛋白B1的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、1.25nM CDK1/细胞周期蛋白B1、10μM ATP和1.5μM荧光肽底物。

[1177] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的1.625nM CDK1/细胞周期蛋白B1和13μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为1.25nM CDK1/细胞周期蛋白B1、10μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)90分钟后停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1178] 在实施例A5的上述方法中测试本发明的某些化合物,并发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK1/细胞周期蛋白B1的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK1/细胞周期蛋白B1大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK1/细胞周期蛋白B1大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK1/细胞周期蛋白B1大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK1/细胞周期蛋白B1大于200倍以上。

[1179] 实施例A6:CDK2/细胞周期蛋白A2 Caliper测定

[1180] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开化合物存在下对CDK2/细胞周期蛋白A2活性的抑制作用。在测定中,CDK2/细胞周期蛋白A2(Carna

Biosciences,04-103)催化荧光标记肽5-FAM-QSPKKG-CONH2(PerkinElmer,FL Peptide 18)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK2/细胞周期蛋白A2的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、1.5nM CDK2/细胞周期蛋白A2、10μM ATP和1.5μM荧光肽底物。

[1181] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的2nM CDK2/细胞周期蛋白A2和13μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为1.5nM CDK2/细胞周期蛋白A2、10μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在CaliperLabChip®EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1182] 在实施例A6的上述方法中测试本发明的某些化合物,并发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK2/细胞周期蛋白A2的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白A2大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白A2大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白A2大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白A2大于200倍以上。

[1183] 实施例A7:CDK3/细胞周期蛋白E1 Caliper测定

[1184] 使用CaliperLabChip®EZ Reader迁移率变化测定评估在本公开的化合物存在下对CDK3/细胞周期蛋白E1活性的抑制作用。在测定中,CDK3/细胞周期蛋白E1(Carna BioscienceS,04-104)催化荧光标记肽5-FAM-GGGPATPKKAKKL-CONH2(PerkinElmer,FL peptide 29)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK3/细胞周期蛋白E1的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、0.31nM CDK3/细胞周期蛋白E1、1mM ATP和1.5μM荧光肽底物。

[1185] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的0.4nM CDK3/细胞周期蛋白E1和1.3mM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为0.31nM CDK3/细胞周期蛋白E1、1mM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在CaliperLabChip®EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1186] 在实施例A7的上述方法中测试本发明的某些化合物,并发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK3/细胞周期蛋白E1的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK3/细胞周期蛋白E1大于2倍以上。

[1187] 实施例A8:CDK4/细胞周期蛋白D3 Caliper测定

[1188] 使用CaliperLabChip®EZ Reader迁移率变化测定评估在本公开化合物存在下对

CDK4/细胞周期蛋白D3活性的抑制作用。在测定中,CDK4/细胞周期蛋白D3(Carna Biosciences,04-105)催化荧光标记肽5-FAM-RRRFRPASPLRGPPK-COOH(PerkinElmer,FL Peptide 34)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK4/细胞周期蛋白D3的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、5nM CDK4/细胞周期蛋白D3、100μM ATP和1.5μM荧光肽底物。

[1189] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的6.5nM CDK4/细胞周期蛋白D3和130μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为5nM CDK4/细胞周期蛋白D3、100μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1190] 在实施例A8的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK4/细胞周期蛋白D3的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK4/细胞周期蛋白D3大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK4/细胞周期蛋白D3大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK4/细胞周期蛋白D3大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK4/细胞周期蛋白D3大于200倍以上。

[1191] 实施例A9:CDK5/p35 Caliper测定

[1192] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开的化合物存在下对CDK5/p35活性的抑制作用。在测定中,CDK5/p35(Signalchem,C33-10BG)催化荧光标记的肽5-FAM-GGGPATPKKAKKL-CONH2(PerkinElmer,FL Peptide 29)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK5/p35的抑制作用(以%活性和IC50值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、60pM CDK5/p35、10μM ATP和1.5μM荧光肽底物。

[1193] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的78pM CDK5/p35和13μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为60pM CDK5/p35、10μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)60分钟后停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1194] 在实施例A9的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK5/p35的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK5/p35大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK5/p35大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK5/p35大于200倍以上。

[1195] 实施例A10:CDK6/细胞周期蛋白D3 Caliper测定

[1196] 使用CaliperLabChip®EZ Reader迁移率变化测定评估在本公开的化合物存在下对CDK6/细胞周期蛋白D3活性的抑制作用。在测定中,CDK6/细胞周期蛋白D3(Carna Biosciences,04-107)催化荧光标记肽5-FAM-RRRFRPASPLRGPPK-COOH(PerkinElmer,FL Peptide 34)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK6/细胞周期蛋白D3的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、5nM CDK6/细胞周期蛋白D3、100μM ATP和1.5μM荧光肽底物。

[1197] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的6.5nM CDK6/细胞周期蛋白D3和130μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为5nM CDK6/细胞周期蛋白D3、100μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在CaliperLabChip®EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1198] 在实施例A10的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK6/细胞周期蛋白D3的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK6/细胞周期蛋白D3大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK6/细胞周期蛋白D3大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK6/细胞周期蛋白D3大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK6/细胞周期蛋白D3大于200倍以上。

[1199] 实施例A11:CDK7/细胞周期蛋白H/MAT1 Caliper测定

[1200] 使用CaliperLabChip®EZ Reader迁移率变化测定评估在本公开的化合物存在下对CDK7/细胞周期蛋白H/MAT1活性的抑制作用。在测定中,CDK7/细胞周期蛋白H/MAT1(Carna Biosciences,04-108)催化荧光标记肽5-FAM-FLAKSFGSPNRAYKK-COOH(Pharmaron,CDK7tide)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK7/细胞周期蛋白H/MAT1的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、5nM CDK7/细胞周期蛋白H/MAT1、40μM ATP和1.5μM荧光肽底物。

[1201] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的6.5nM CDK7/细胞周期蛋白H/MAT1和52μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为5nM CDK7/细胞周期蛋白H/MAT1、40μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在CaliperLabChip®EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1202] 在实施例A11的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK7/细胞周期蛋白H/MAT1的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK7/细胞周期蛋白H/MAT1大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对

于CDK7/细胞周期蛋白H/MAT1大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK7/细胞周期蛋白H/MAT1大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK7/细胞周期蛋白H/MAT1大于200倍以上。

[1203] 实施例A12:CDK9/细胞周期蛋白T1 Caliper测定

[1204] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开化合物存在下对CDK9/细胞周期蛋白T1活性的抑制作用。在测定中,CDK9/细胞周期蛋白T1(Carna Biosciences,04-110)催化荧光标记肽5-FAM-RRRFRPASPLRGPPK-COOH(PerkinElmer,FL Peptide 34)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK9/细胞周期蛋白T1的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、2.5nM CDK9/细胞周期蛋白T1、10μM ATP和1.5μM荧光肽底物。

[1205] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的3.25nM CDK9/细胞周期蛋白T1和13μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为2.5nM CDK9/细胞周期蛋白T1、10μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)120分钟后停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的IC_{50}。

[1206] 在实施例A12的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK9/细胞周期蛋白T1的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK9/细胞周期蛋白T1大于5000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK9/细胞周期蛋白T1大于1000倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK9/细胞周期蛋白T1大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK9/细胞周期蛋白T1大于200倍以上。

[1207] 实施例A13:CDK2/细胞周期蛋白E2 Caliper测定

[1208] 使用Caliper LabChip® EZ Reader迁移率变化测定评估在本公开化合物存在下对CDK2/细胞周期蛋白E2活性的抑制作用。在测定中,CDK2/细胞周期蛋白E2(Biortus,BP469/4624/691)催化荧光标记肽5-FAM-QSPKKG-CONH2(PerkinElmer,FL Peptide 18)的磷酸化,其诱导了在毛细管电泳迁移率中的差异。测量肽底物和产物,并使用转化率来确定CDK2/细胞周期蛋白E2的抑制作用(以%活性和IC_{50}值表示)。反应包含50mM HEPES pH 7.5、10mM $MgCl_2$、1mM EDTA、2mM DTT、0.01%Brij35、0.5mg/mL BSA、0.1%DMSO、5nM CDK2/细胞周期蛋白E2、200μM ATP和1.5μM荧光肽底物。

[1209] 将在100%DMSO中的抑制剂的剂量滴定与在反应缓冲液中的6.5nM CDK2/细胞周期蛋白E2和260μM ATP结合。将混合物孵育30分钟,然后添加荧光肽底物以引发激酶反应。最终条件为5nM CDK2/细胞周期蛋白E2、200μM ATP和1.5μM荧光肽。在添加EDTA(400mM最终EDTA浓度)90分钟后停止反应。在Caliper LabChip® EZ Reader II上分析停止的反应。将转化率标准化为收率%活性,绘制化合物浓度图,并拟合四参数方程以确定每种化合物的

IC_{50}。

[1210] 在实施例A13的上述方法中测试本发明的某些化合物,发现其对CDK2/细胞周期蛋白E1的抑制相对于对CDK2/周期蛋白E2的抑制有选择性。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白E2大于1000倍。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白E2大于500倍以上。在一些实施方案中,发现测试的化合物对CDK2/细胞周期蛋白E1的选择性相对于CDK2/细胞周期蛋白E2大于200倍以上。