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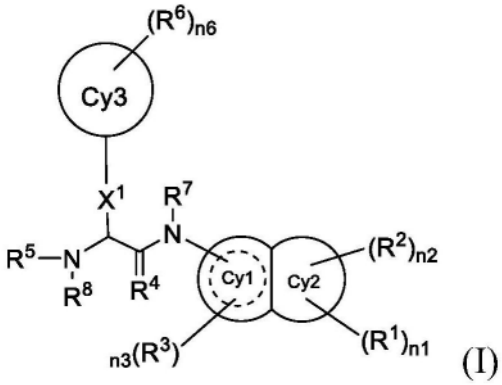
小分子IL-17A调节剂

(57)摘要

本文公开了用作小分子IL-17A调节剂的稠合双环化合物。本文公开了这些小分子IL-17A调节剂用于通过抑制来降低IL-17活性的用途,以及此类化合物用于治疗自身免疫性疾病或炎性疾病的用途。

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1.一种式(I)的化合物：



(I)

或其N-氧化物、或其药学上可接受的盐、或其立体异构体、或其氘代类似物,其中：

Cy1是5-6元芳族环,所述环包含0-3个独立地选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^3取代;

n3独立地是0、1、2或3;

Cy2是4-8元饱和或者部分或完全不饱和的环,所述环包含0-3个独立地选自氮、氧或任选氧化的硫的杂原子;所述环被至少一个取代基R^1和/或R^2取代;

n1是0或1;

n2是0、1或2;

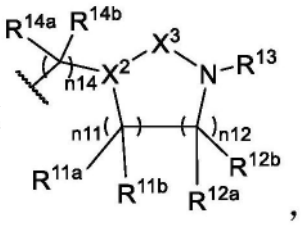
n1和n2不同时是0;

Cy1和Cy2彼此稠合;

Cy3是3-12元饱和或者部分或完全不饱和的环,所述环包含0-3个独立地选自氮、氧或任选氧化的硫的杂原子;所述环任选地被至少一个取代基R^6取代;

n6独立地是0、1、2、3、4或5,条件是满足化合价理论;

X^1是单键或$-CR^9R^{10}-$;

R^1独立地选自H或  ,

其中X^2是N或$C(R^{15})$;

X^3是-C(O)-、-S(O)-或$-S(O)_2-$;

n11和n12各自独立地是1、2或3;

n14是0或1;

R^{15}选自氢、卤素、$-C_{1-8}$烷基、$-C_3-C_8$环烷基、3元至8元杂环基、-CN、$-OR^{15a}$、$-NR^{15a}R^{15b}$或$-NR^{15a}COR^{15b}$;$-C_{1-8}$烷基、C_3-C_8环烷基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{15c}取代;

R^{15a}和R^{15b}各自独立地选自氢、$-C_{1-8}$烷基、$-C_{1-8}$卤代烷基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、C_{1-8}烷氧基$-C_{1-8}$烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基,$-C_{1-8}$烷基、$-C_{1-8}$卤代烷基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、C_{1-8}烷氧基$-C_{1-8}$烷基-、C_3-C_8环烷基、3元至8元杂环基、

C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{15d}取代;

R^{15c}和R^{15d}在每次出现时各自独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-OR^{11c}、-COR^{11c}、-CO_2R^{11c}、-$CONR^{11c}R^{11d}$、-$NR^{11c}R^{11d}$或-$NR^{11c}COR^{11d}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11e}取代,或

(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立地选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{11f}取代;

R^{11e}和R^{11f}在每次出现时各自独立地是氢、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{11g}、硫代基(=S)、-SR^{11g}、-CN、-SO_2R^{11g}、-$SO_2NR^{11g}R^{11h}$、-COR^{11g}、-CO_2R^{11h}、-$CONR^{11g}R^{11h}$、-$NR^{11g}R^{11h}$、-$NR^{11g}COR^{11h}$、-$NR^{11g}CO_2R^{11h}$或-$NR^{11g}SO_2R^{11h}$;-C_{1-8}烷基、-C_{1-8}烷氧基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11i}取代;

R^{11c}、R^{11d}、R^{11g}和R^{11h}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11j}取代;

R^{11i}和R^{11j}在每次出现时各自独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基取代;

R^{13}、R^{14a}和R^{14b}各自独立地选自氢、-C_{1-8}烷基、-C_3-C_8环烷基或3元至8元杂环基;-C_{1-8}烷基、-C_3-C_8环烷基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{13a}取代;

R^{13a}在每次出现时独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

R^2独立地选自H、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-COR^{2a}、-CO_2R^{2a}、-$CONR^{2a}R^{2b}$、-$NR^{2a}R^{2b}$或-$NR^{2a}COR^{2b}$,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2c}取代;或

当两个偕的或相邻的R^2与它们所连接的碳原子一起形成3元至8元不饱和或饱和的环时,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2c}取代;

R^{2a}和R^{2b}各自独立地选自氢、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂

环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2d}取代;或

R^{2a}和R^{2b}与它们所连接的氮原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

R^{2c}和R^{2d}在每次出现时各自独立地是氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{2e}、-SR^{2e}、-CN、-COR^{2e}、-CO_2R^{2e}、-$CONR^{2e}R^{2f}$、-$NR^{2e}R^{2f}$、-$NR^{2e}COR^{2f}$或-$NR^{2e}CO_2R^{2f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2g}取代;

R^{2e}和R^{2f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2h}取代;

R^{2g}和R^{2h}在每次出现时各自独立地是卤素、-OH、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

当n1和n2都是1时,R^1和R^2是偕的或相邻的;

R^3独立地选自氢、卤素、-C_{1-8}烷基、-C_{1-8}烷氧基、-C_3-C_8环烷基或-CN,其中-C_{1-8}烷基、-C_{1-8}烷氧基和-C_3-C_8环烷基中的每一者任选地被至少一个选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代;

R^4是氧代基(=O)或硫代基(=S);或

R^3和R^4与它们所连接的原子一起形成5元至6元芳族环,所述环包含1-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{3a}取代;

R^{3a}独立地选自氢、卤素、-C_{1-8}烷基、-C_{1-8}烷氧基、-C_3-C_8环烷基或-CN,其中-C_{1-8}烷基、-C_{1-8}烷氧基和-C_3-C_8环烷基中的每一者任选地被至少一个选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代;

R^5是C_6-C_{12}芳基、5元至12元杂芳基、-COR^{5a}、-CO_2R^{5a}、-$CONR^{5a}R^{5b}$,其中C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5c}取代;

R^{5a}和R^{5b}各自独立地选自-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5d}取代;或

R^{5a}和R^{5b}与它们所连接的原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{5d}取代;

R^{5c}和R^{5d}在每次出现时各自独立地选自氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{5e}、-SR^{5e}、-CN、-COR^{5e}、-CO_2R^{5e}、-$CONR^{5e}R^{5f}$、-$NR^{5e}R^{5f}$、-$NR^{5e}COR^{5f}$或-$NR^{5e}CO_2R^{5f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5g}取代;

R^{5e}和R^{5f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-

C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5h}取代;

R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

R^6是H、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-OR^{6a}、-$NR^{6a}R^{6b}$、-COR^{6a}、-CO_2R^{6a}、-$CONR^{6a}R^{6b}$、-COR^{6a}或-$NR^{6a}COR^{6b}$,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6c}取代;

R^{6a}和R^{6b}各自独立地选自氢、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6d}取代;

R^{6c}在每次出现时独立地是氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基5元至12元杂芳基、氧代基(=O)、-OR^{6e}、-SR^{6e}、-CN、-COR^{6e}、-CO_2R^{6e}、-$CONR^{6e}R^{6f}$、-$NR^{6e}R^{6f}$、-$NR^{6e}COR^{6f}$或-$NR^{6e}CO_2R^{6f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6g}取代;

R^{6e}和R^{6f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;

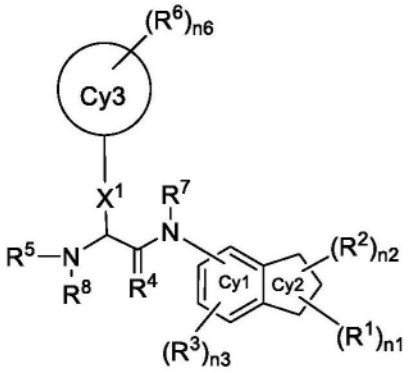
R^{6d}和R^{6g}各自独立地选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

R^7和R^8各自独立地是氢;

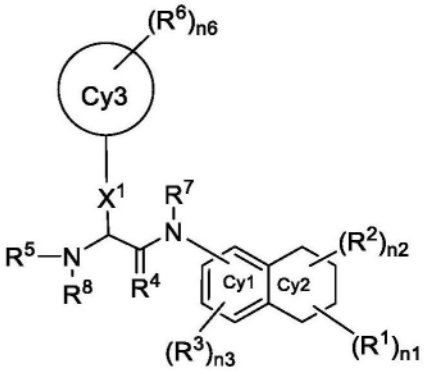
R^9和R^{10}各自独立地选自H、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基或5元至12元杂芳基,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{9a}取代;并且

R^{9a}在每次出现时独立地是卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基。

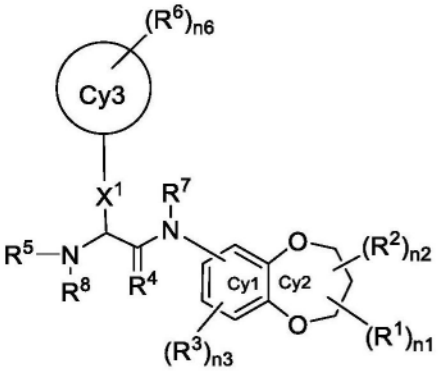
2.如权利要求1所述的化合物,其中所述化合物选自式(IIa)-(IIp):



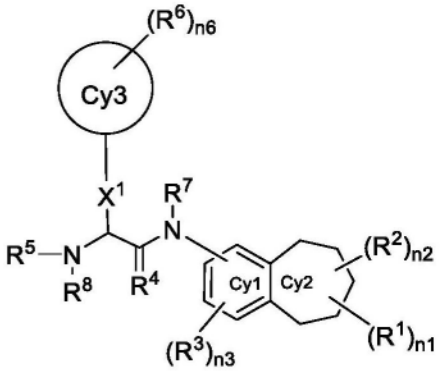
IIa



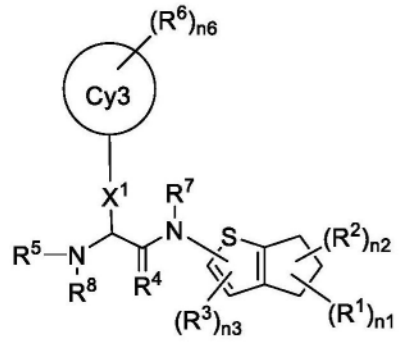
IIb



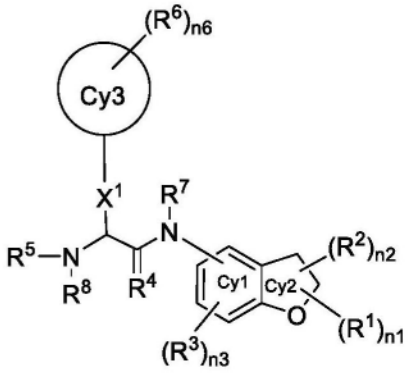
IIc



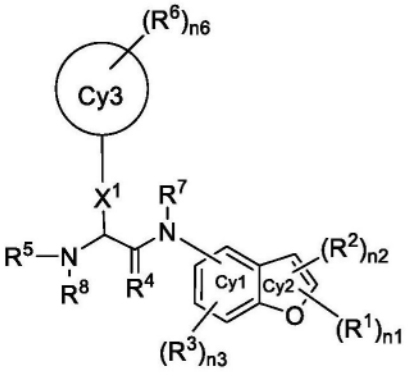
IId



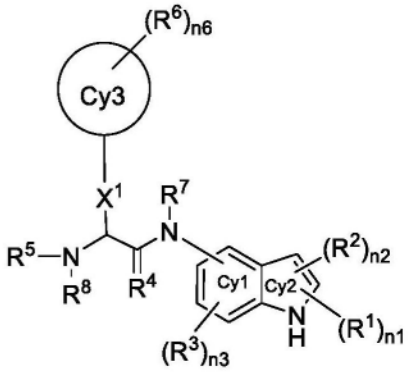
IIe



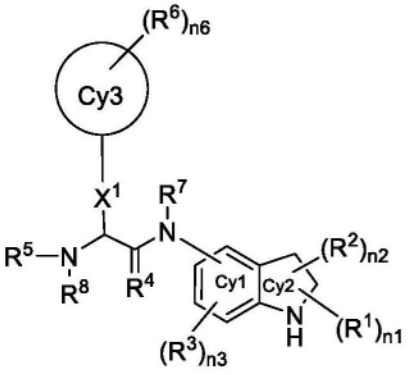
IIf



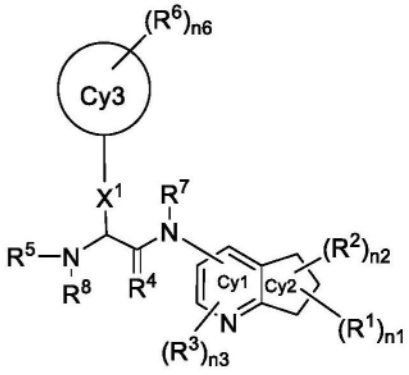
IIg



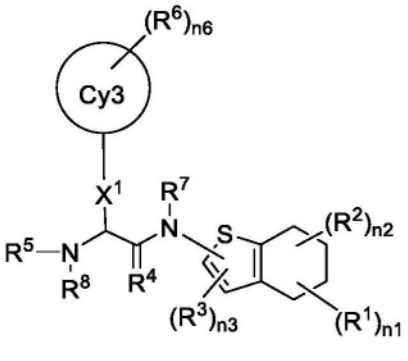
IIh



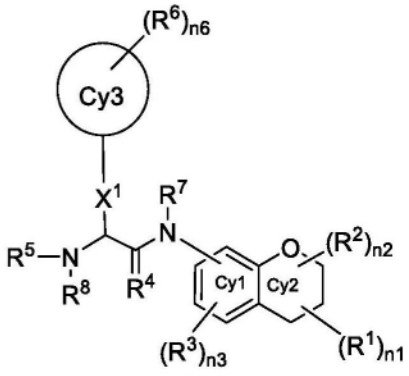
IIi



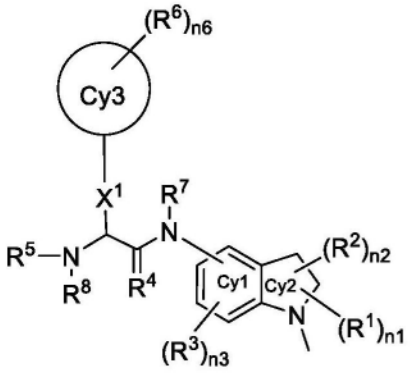
IIj



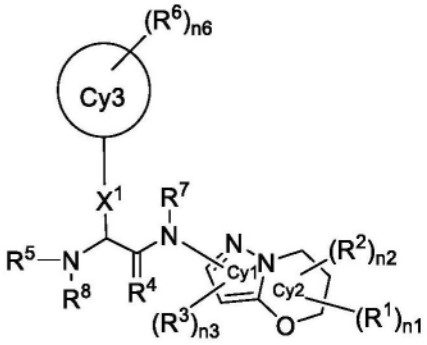
IIk



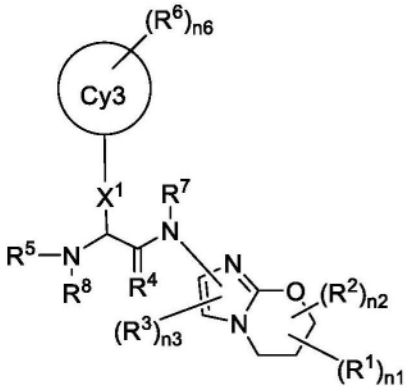
III



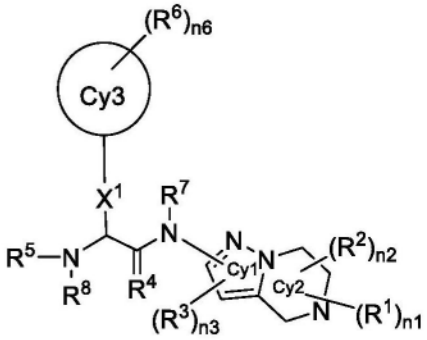
IIm



IIn



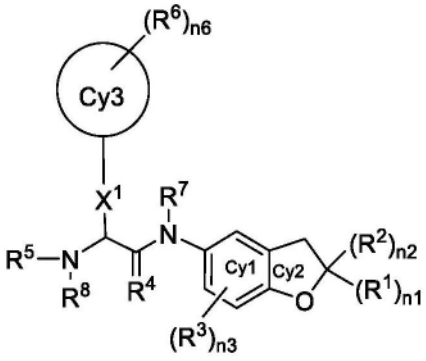
IIo



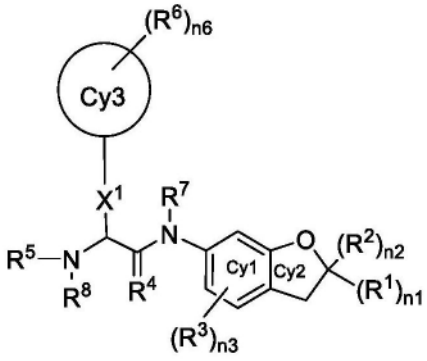
IIp

其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy3、n1、n2、n3、n6和X^1如权利要求1中所定义。

3.如权利要求1所述的化合物,其中所述化合物选自式(IIf1)-(IIf2):



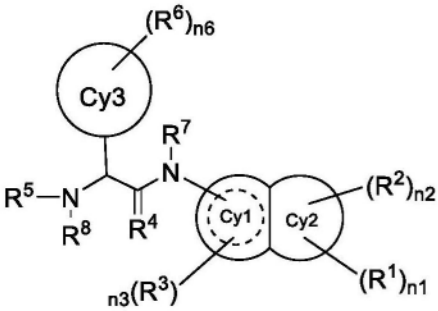
IIf1



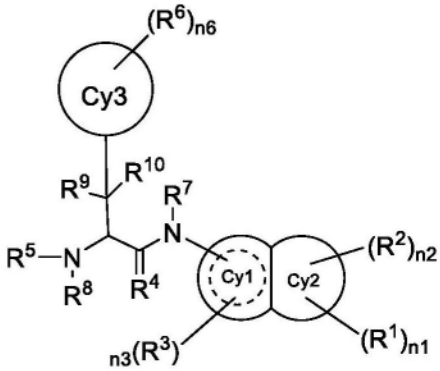
IIf2

其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy3、n1、n2、n3、n6和X^1如权利要求1中所定义。

4.如权利要求1所述的化合物,其中所述化合物选自式(IIIa)-(IIIb):



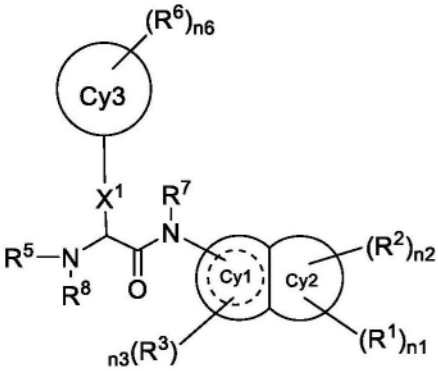
IIIa



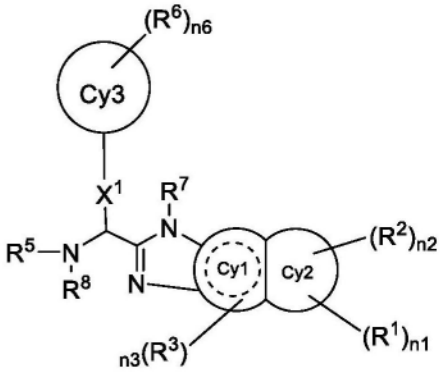
IIIb

其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n1、n2、n3、n6、R^9和R^{10}如权利要求1中所定义。

5.如权利要求1所述的化合物,其中所述化合物选自式(IVa)-(IVb):



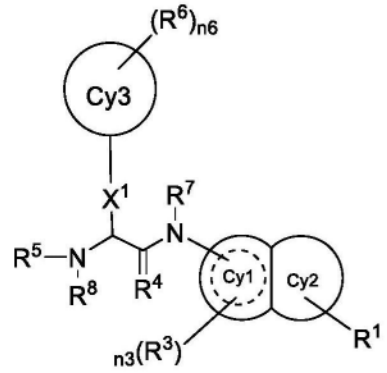
IVa



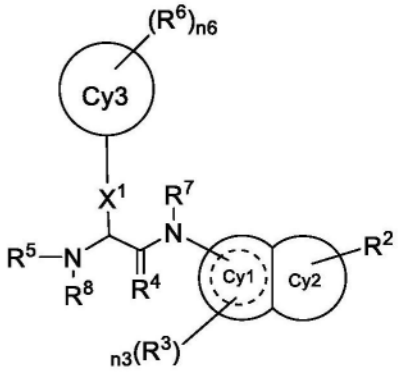
IVb

其中,X^1、R^1、R^2、R^3、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n1、n2、n3、n6、R^9和R^{10}如权利要求1中所定义。

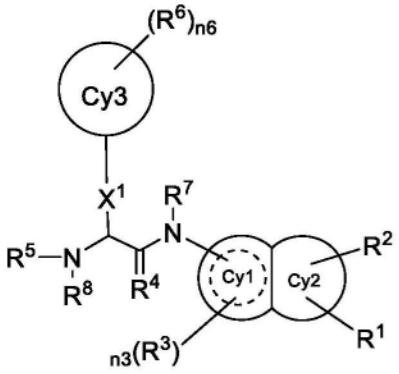
6.如权利要求1所述的化合物,其中所述化合物选自式(Va)-(Vc):



Va



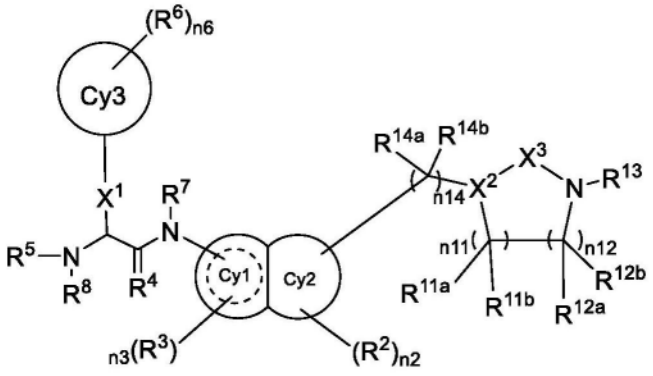
Vb



Vc

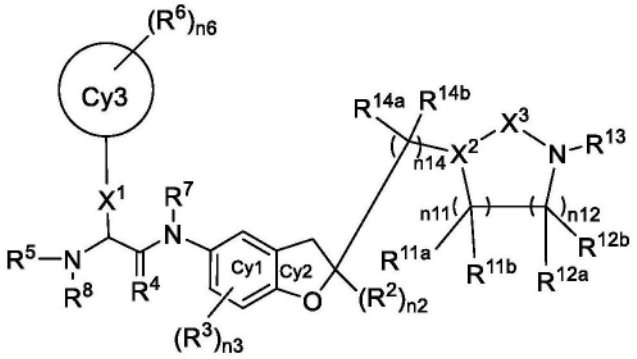
其中,X^1、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n3、n6、R^9和R^{10}如权利要求1中所定义。

7.如权利要求1所述的化合物,其中所述化合物是VIa,

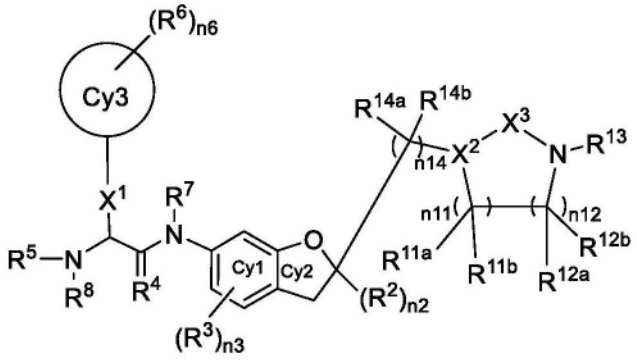


(VIa)

优选地,所述化合物选自VIb和Vic



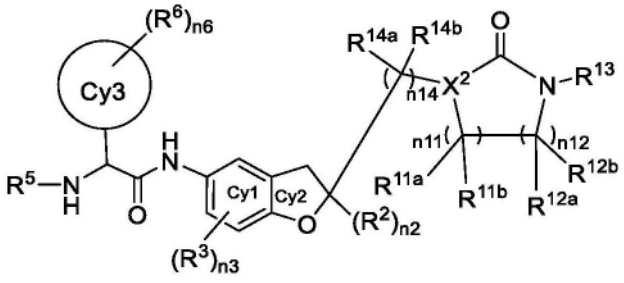
(VIb)



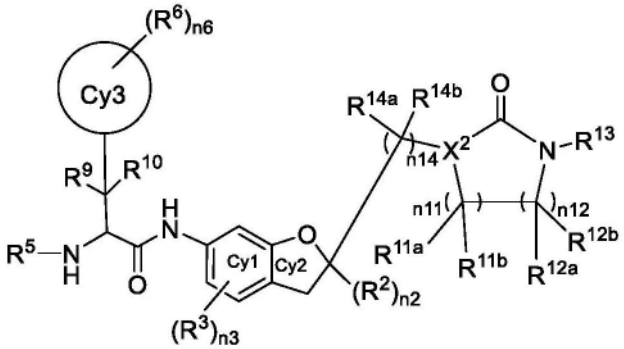
(VIc)

其中,X^1、X^2、X^3、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n2、n3、n6、R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、R^{14a}、R^{14b}、n11、n12和n14如权利要求1中所定义。

8.如权利要求1所述的化合物,其中所述化合物是VIIa或VIIb,

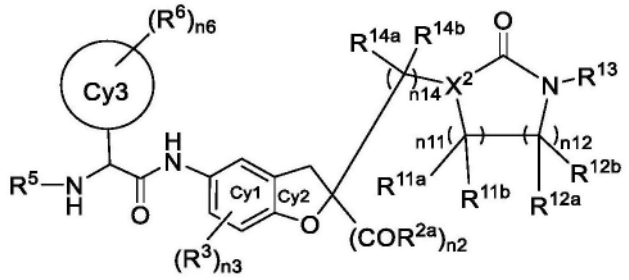


(VIIa)

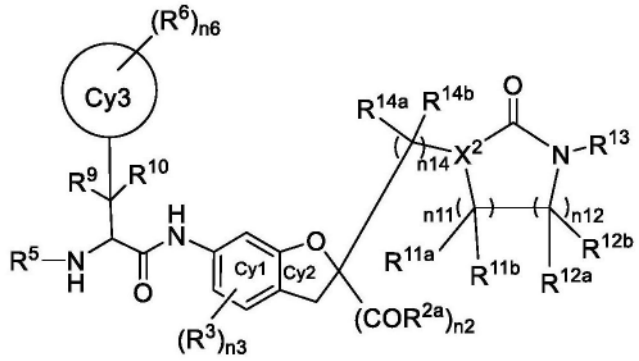


(VIIb);

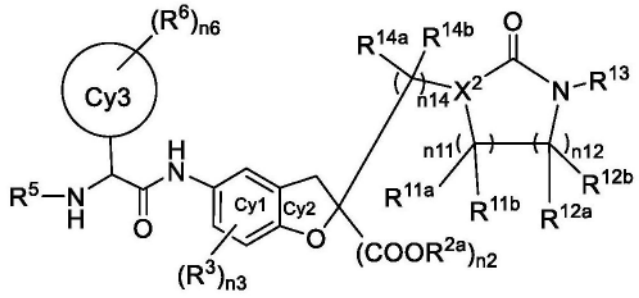
优选地,所述化合物选自VIIc、VIId、VIIe、VIIf、VIIg或VIIh,



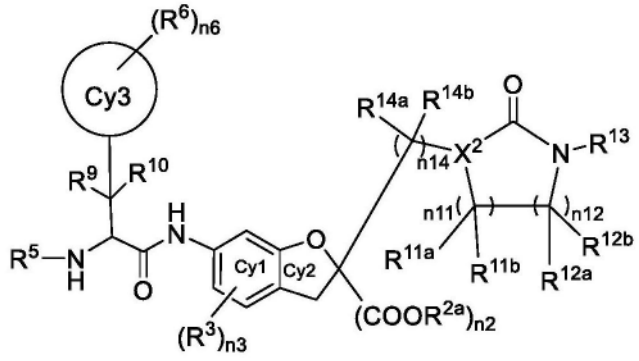
VIIc



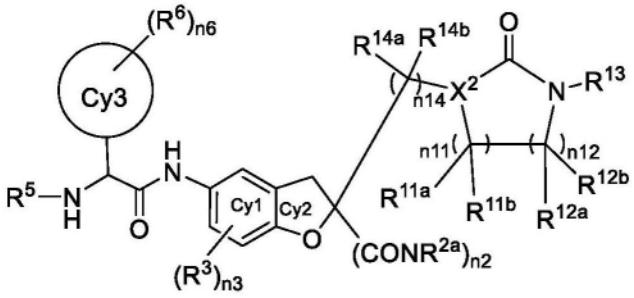
VIId



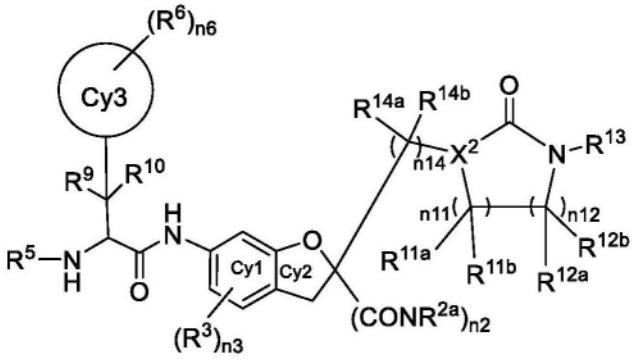
VIIe



VIIf



VIIg



VIIh;

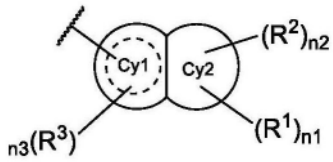
其中,X^2、R^{2a}、R^3、R^5、R^6、R^9、R^{10}、Cy1、Cy2、Cy3、n2、n3、n6、R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、R^{14a}、R^{14b}、n11、n12和n14如权利要求1中所定义。

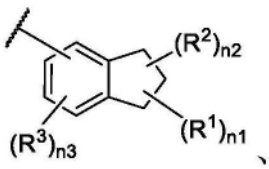
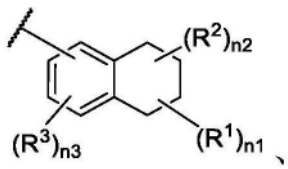
9.如前述权利要求中任一项所述的化合物,其中Cy1是5元或6元芳族环,所述环包含0、1或2个独立地选自氮、氧或硫的杂原子;所述环任选地被0、1、2或3个取代基R^3取代;

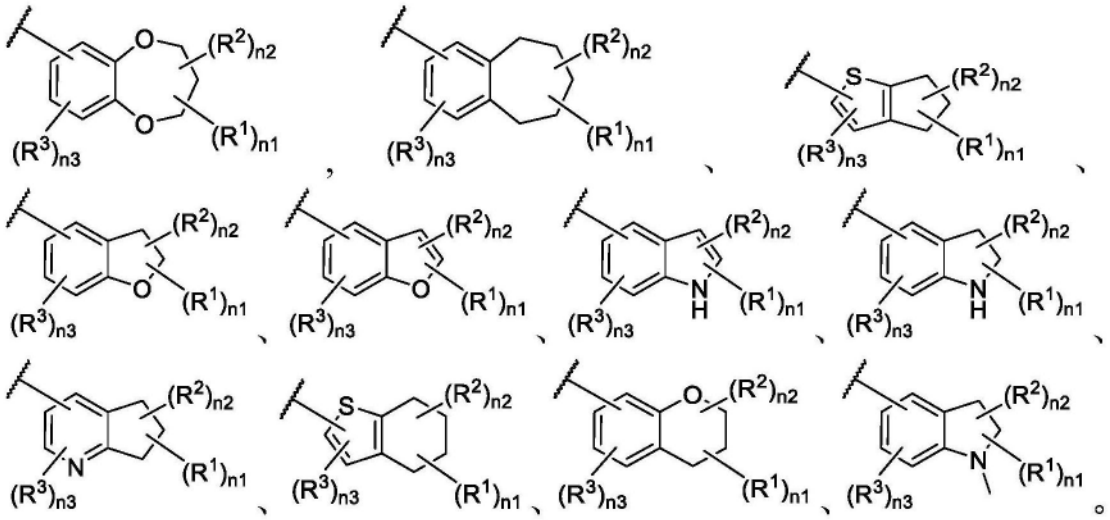
优选地,Cy1是苯基、吡啶基、噻吩基、咪唑基、呋喃基或吡唑基;苯基、吡啶基、噻吩基、咪唑基、呋喃基或吡唑基中的每一者任选地被0、1或2个取代基R^3取代。

10.如前述权利要求中任一项所述的化合物,其中Cy2是4元、5元、6元、7元或8元饱和或者部分或完全不饱和的环,所述环包含0、1、2或3个独立地选自氮或氧的杂原子;所述环被至少一个取代基R^1和/或R^2取代;

优选地,Cy2是5元、6元或7元饱和或者部分或完全不饱和的环,所述环包含0、1或2个独立选自氮或氧的杂原子;所述环被至少一个取代基R^1和/或R^2取代。

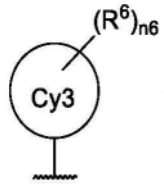
11.如前述权利要求中任一项所述的化合物,其中  部分选自:

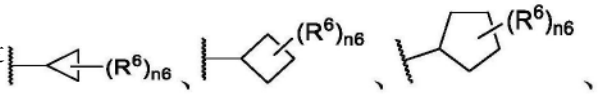
 、  、

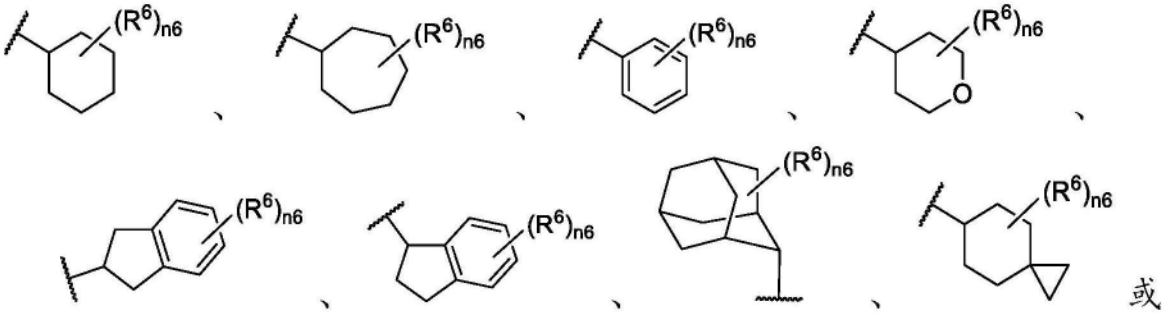


12.如前述权利要求中任一项所述的化合物,其中Cy3是3元、4元、5元、6元、7元、8元、9元、10元、11元或12元饱和或者部分或完全不饱和的环,所述环包含0、1、2或3个独立选自氮、氧或任选氧化的硫的杂原子;所述环任选地被0、1、2、3、4或5个取代基R^6取代;

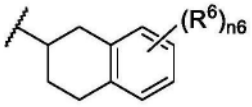
优选地,Cy3是3元、4元、5元、6元、7元、8元、9元、10元、11元或12元饱和或者部分或完全不饱和的环,所述环是包含0、1、2或3个独立选自氮、氧或任选氧化的硫的杂原子的单环、双环或三环;所述环任选地被0、1、2、3、4或5个取代基R^6取代;

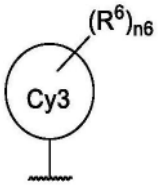
更优选地, 

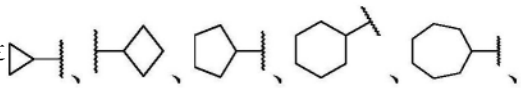
部分是 

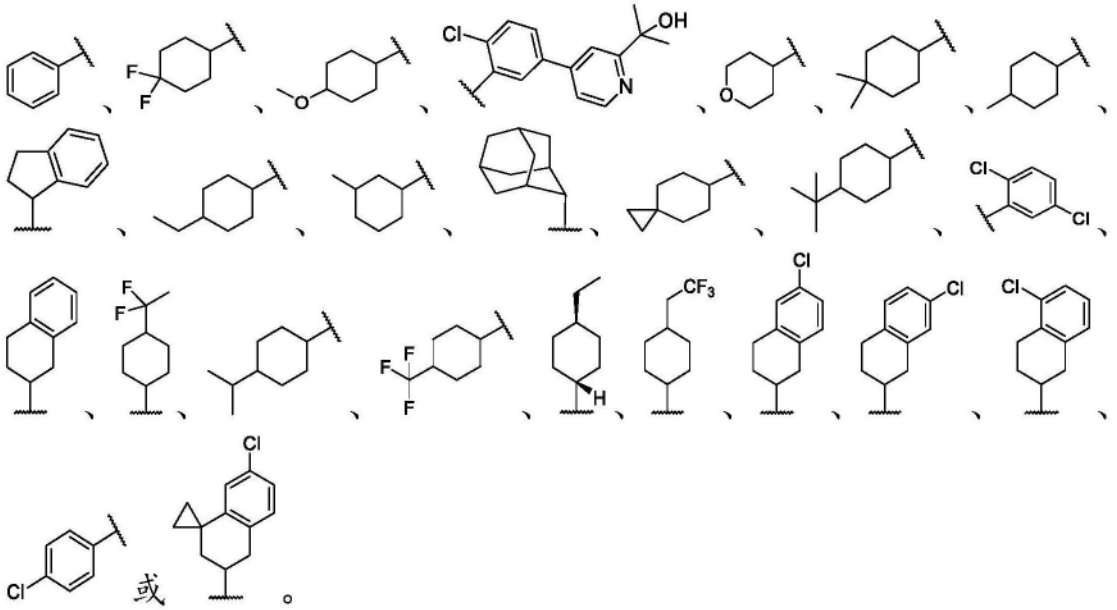


或

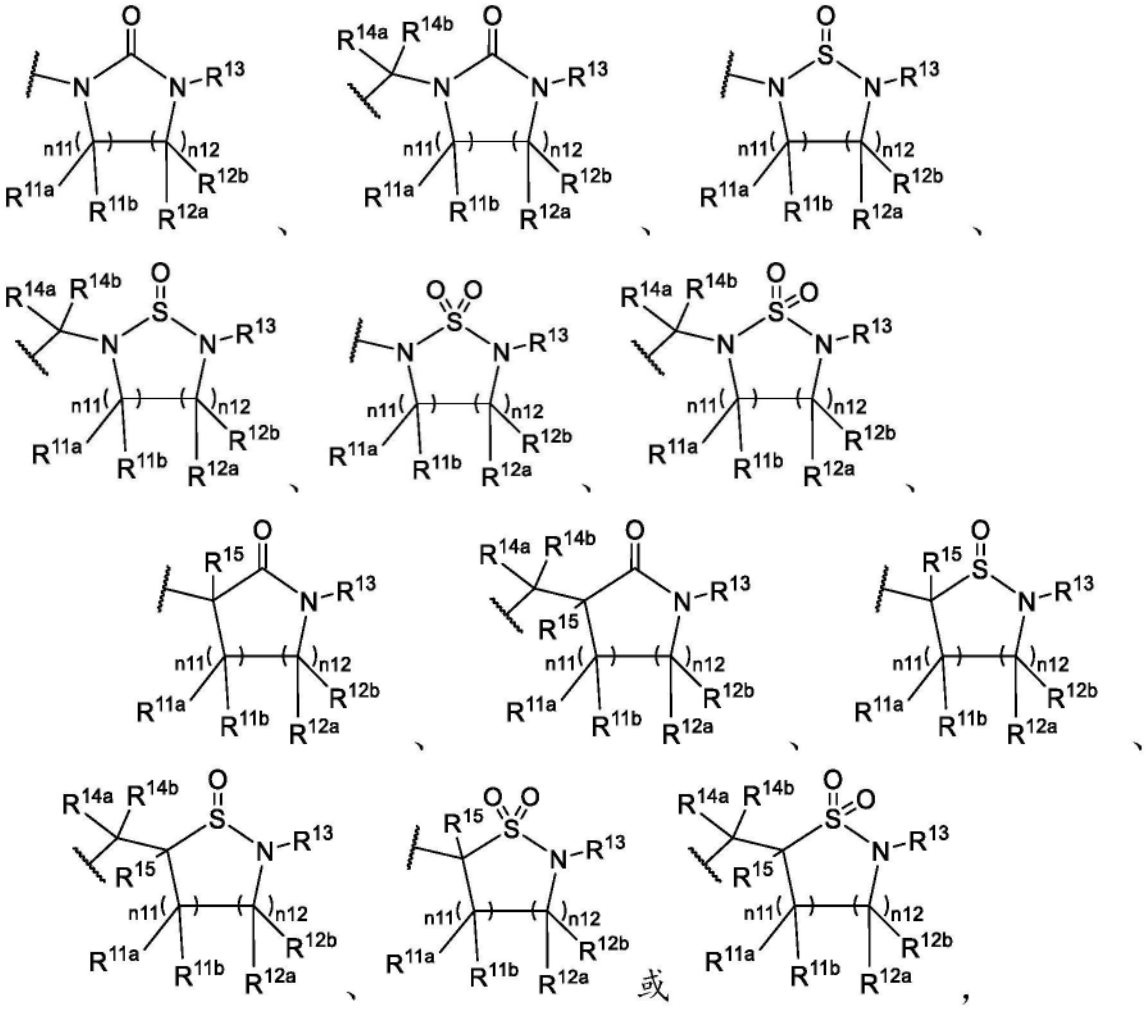

;

甚至更优选地, 

部分是 



13.如前述权利要求中任一项所述的化合物，其中R^1独立地选自H、



其中R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、n11和n12如权利要求1中所定义。

14.如前述权利要求中任一项所述的化合物，其中R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3

元至8元杂环基、-CN、-OR^{15a}、-$NR^{15a}R^{15b}$或-$NR^{15a}COR^{15b}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{15c}取代;

R^{15a}和R^{15b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{15d}取代;

R^{15c}和R^{15d}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基。

15.如前述权利要求中任一项所述的化合物,其中R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-CN、-OH、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基;

优选地,R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基;

更优选地,R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基;

甚至更优选地,R^{15}选自氢。

16.如前述权利要求中任一项所述的化合物,其中R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-

1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基和吡嗪基中的每一者任选地被至少一个取代基R^{11e}取代；

R^{11e}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基和吡嗪基中的每一者任选地被至少一个取代基R^{11i}取代；

R^{11c}、R^{11d}、R^{11g}和R^{11h}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环

己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11j}取代;

R^{11i}和R^{11j}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基中的每一者任选地被至少一个取代基-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基取代。

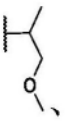
17.如前述权利要求中任一项所述的化合物,其中R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-

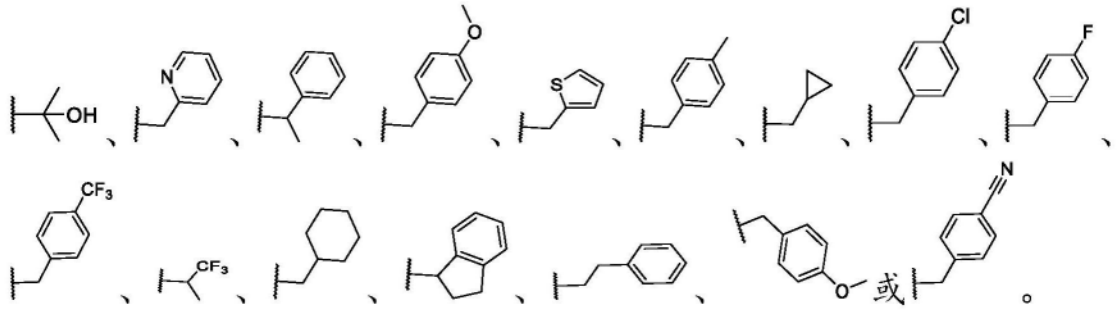
1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基和吡嗪基中的每一者任选地被至少一个取代基R^{11e}取代;

R^{11e}在每次出现时独立地是-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-OR^{11g}或-CN;

R^{11g}独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基;

优选地,R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自H、-CH_3、-CF_3、-CH_2CH_3、-CH_2CF_3、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、环丙基、环丁基、环戊基、环己基、环庚基、吡咯

烷基、四氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、苄基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、 



18.如前述权利要求中任一项所述的化合物,其中(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元不饱和或饱和的环,所述环包含0、1、2或3个独立地选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{11f}取代;

R^{11f}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{11g}、硫代基(=S)、-SR^{11g}、-CN、-SO_2R^{11g}、-$SO_2NR^{11g}R^{11h}$、-COR^{11g}、-CO_2R^{11h}、-$CONR^{11g}R^{11h}$、-$NR^{11g}R^{11h}$、-$NR^{11g}COR^{11h}$、-$NR^{11g}CO_2R^{11h}$或-$NR^{11g}SO_2R^{11h}$;

R^{11g}和R^{11h}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;

R^{11i}在每次出现时独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

优选地,(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元不饱和或饱和的环;

更优选地,(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元饱和的环。

19.如前述权利要求中任一项所述的化合物,其中R^{13}、R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基中的每一者任选地被至少一个取代基R^{13a}取代;

R^{13a}在每次出现时独立地是卤素、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-

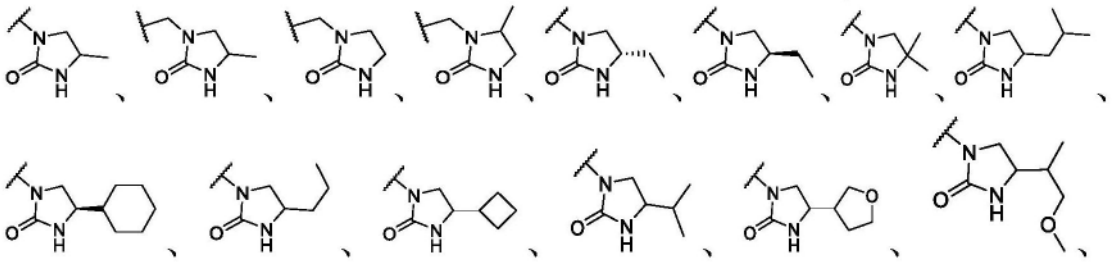
C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基;

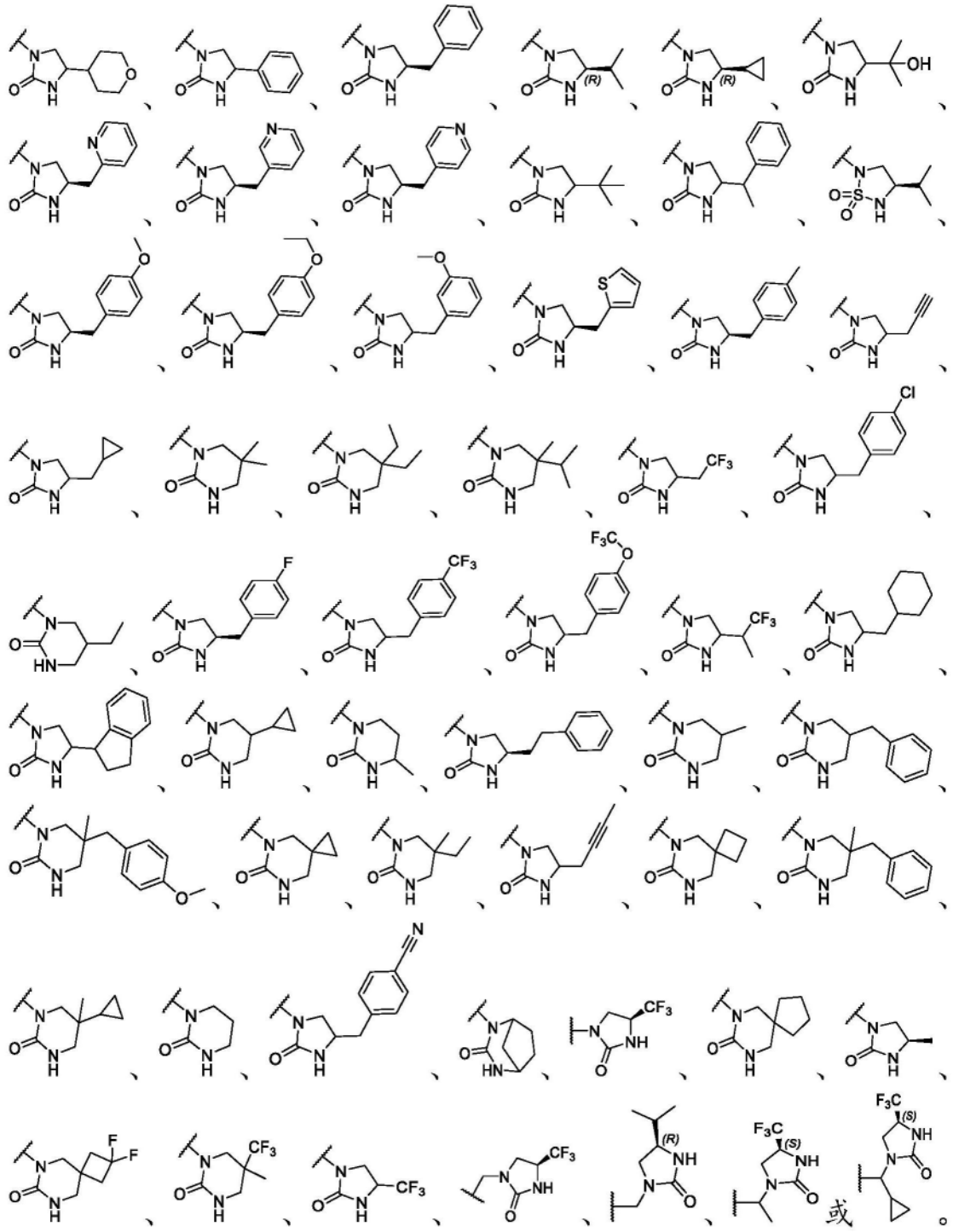
优选地,R^{13}、R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;

更优选地,R^{13}是氢、甲基、乙基、丙基或丁基;R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;

甚至更优选地,R^{13}是氢;R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、环丙基、环丁基、环戊基。

20.如前述权利要求中任一项所述的化合物,其中R^1选自





21.如前述权利要求中任一项所述的化合物,其中R^2独立地选自H、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-CN、-COR^{2a}、-CO_2R^{2a}、-$CONR^{2a}R^{2b}$、-$NR^{2a}R^{2b}$、-$NR^{2a}COR^{2b}$,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基和咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2c}取代;

R^{2a}和R^{2b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2d}取代;或

R^{2a}和R^{2b}与它们所连接的碳原子一起形成3元、4元、5元、6元、7元或8元不饱和或饱和的环,所述环包含0、1、2、3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

R^{2c}和R^{2d}在每次出现时各自独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、氧代基(=O)、-OR^{2e}、-SR^{2e}、-CN、-COR^{2e}、-CO_2R^{2e}、-$CONR^{2e}R^{2f}$、-$NR^{2e}R^{2f}$、-$NR^{2e}COR^{2f}$或-$NR^{2e}CO_2R^{2f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2g}取代;

R^{2e}和R^{2f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2h}取代;

R^{2g}和R^{2h}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基。

22.如前述权利要求中任一项所述的化合物,其中R^2独立地选自H、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-CN、-COR^{2a}、-CO_2R^{2a}或-$CONR^{2a}R^{2b}$,甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2c}取代;

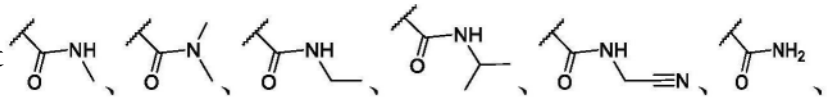
R^{2a}和R^{2b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2d}取代;或

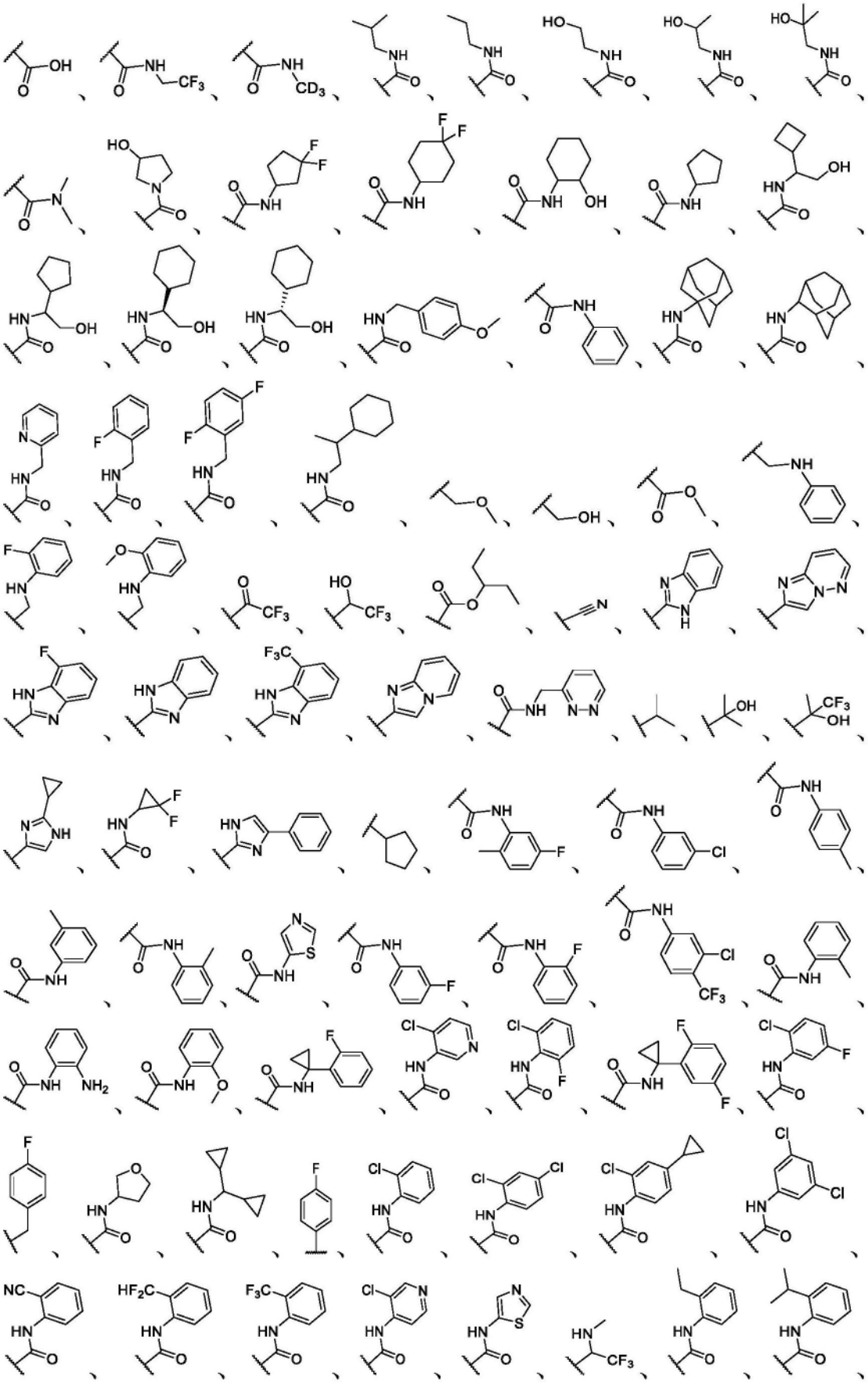
R^{2a}和R^{2b}与它们所连接的碳原子一起形成3元、4元、5元或6元不饱和或饱和的环,所述环包含0或1个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

R^{2c}和R^{2d}在每次出现时各自独立地是氢(H或D)、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-OR^{2e}、-CN或-$NR^{2e}R^{2f}$;甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2g}取代;

R^{2e}和R^{2f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基、环己基或苯基;甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基、环己基或苯基中的每一者任选地被至少一个取代基R^{2h}取代;

R^{2g}和R^{2h}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基或环己基;

优选地,R^2是 



-CH_3、  。

23.如前述权利要求中任一项所述的化合物,其中R^3独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或-CN,其中甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基中的每一者任选地被至少一个选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代;

优选地,R^3独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或-CN;

更优选地,R^3独立地选自氢、-F、-Cl、-Br、-I。

24.如前述权利要求中任一项所述的化合物,其中R^4是氧代基(=O)。

25.如前述权利要求中任一项所述的化合物,其中R^3和R^4与它们所连接的碳原子一起形成5元至6元芳族环,所述环包含1、2或3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{3a}取代;

R^{3a}独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-CN,其中甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基中的每一者任选地被至少一个选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代。

26.如前述权利要求中任一项所述的化合物,其中R^5是苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-COR^{5a}、-CO_2R^{5a}或-$CONR^{5a}R^{5b}$,其中苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5c}取代;

R^{5a}和R^{5b}各自独立地选自甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5d}取代;或

R^{5a}和R^{5b}与它们所连接的氮原子一起形成3元、4元、5元、6元、7元或8元不饱和或饱和的

环,所述环包含0、1、2或3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{5d}取代;

R^{5c}和R^{5d}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、氧代基(=O)、-OR^{5e}、-SR^{5e}、-CN、-COR^{5e}、-CO_2R^{5e}、-$CONR^{5e}R^{5f}$、-$NR^{5e}R^{5f}$、-$NR^{5e}COR^{5f}$或-$NR^{5e}CO_2R^{5f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5g}取代;

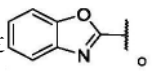
R^{5e}和R^{5f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5h}取代;

R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基。

27.如前述权利要求中任一项所述的化合物,其中R^5是吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基,其中吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5c}取代;

R^{5c}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;

优选地,R^5是苯并噁唑基;

更优选地,R^5是  。

28.如前述权利要求中任一项所述的化合物,其中R^5是-COR^{5a}、-CO_2R^{5a}或-$CONR^{5a}R^{5b}$;

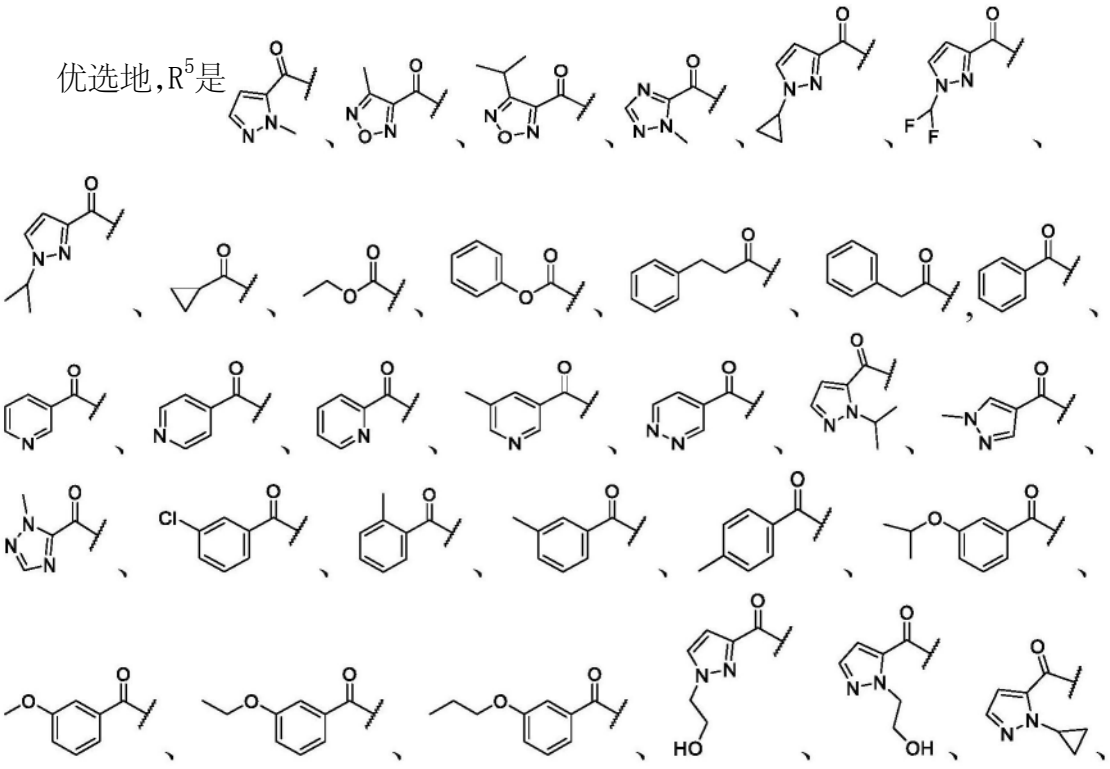
其中R^{5a}和R^{5b}各自独立地选自甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、

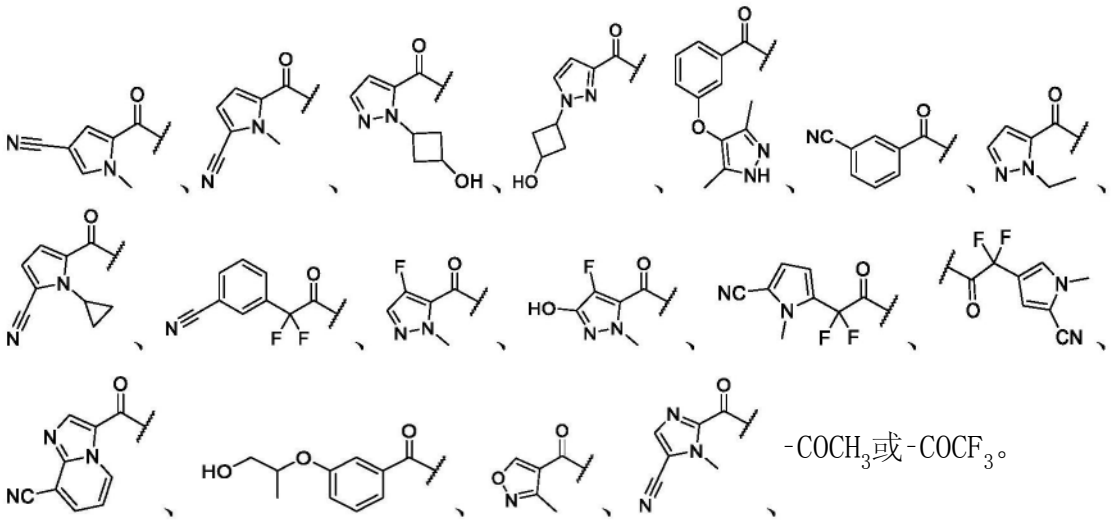
咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5d}取代;

R^{5d}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-OR^{5e}或-CN;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5g}取代;

R^{5e}选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5h}取代;

R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基;

优选地,R^5是 



-$COCH_3$或-$COCF_3$。

29.如前述权利要求中任一项所述的化合物,其中R^6是H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN、-OR^{6a}、-$NR^{6a}R^{6b}$、-COR^{6a}、-CO_2R^{6a}、-$CONR^{6a}R^{6b}$、-COR^{6a}或-$NR^{6a}COR^{6b}$,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基中的每一者任选地被至少一个取代基R^{6c}取代;

R^{6a}和R^{6b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6d}取代;

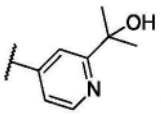
R^{6c}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基3元至8元杂环基、苯基、5元至12元杂芳基、氧代基(=O)、-OR^{6e}、-SR^{6e}、-CN、-COR^{6e}、-CO_2R^{6e}、-$CONR^{6e}R^{6f}$、-$NR^{6e}R^{6f}$、-$NR^{6e}COR^{6f}$或-$NR^{6e}CO_2R^{6f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6g}取代;

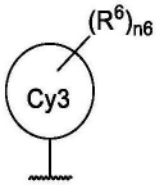
R^{6e}和R^{6f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;

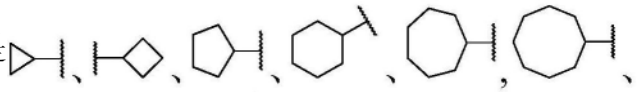
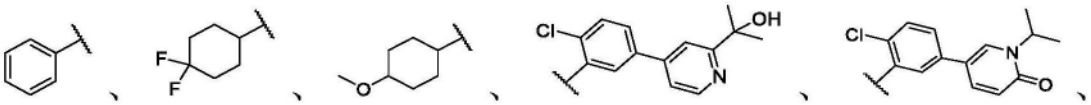
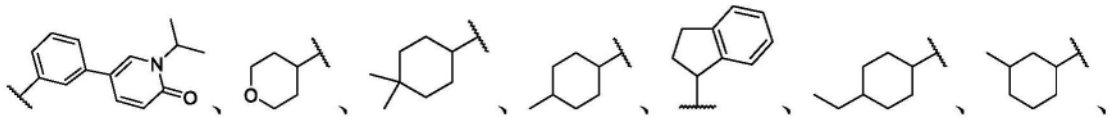
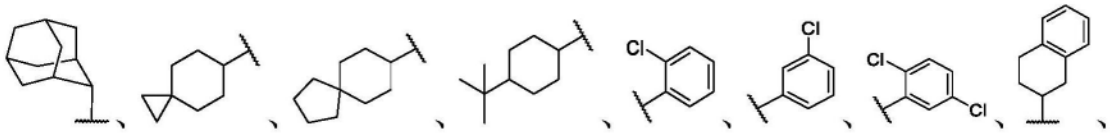
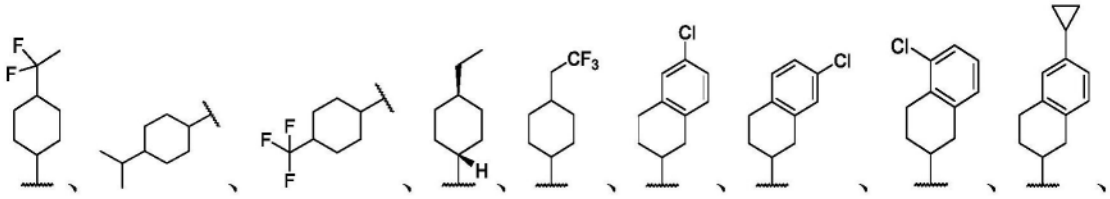
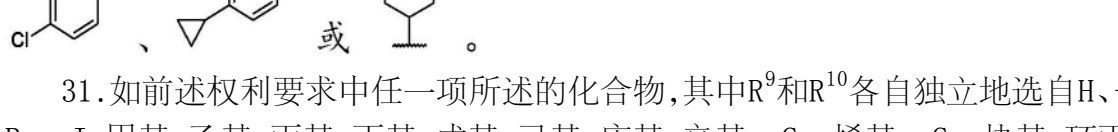
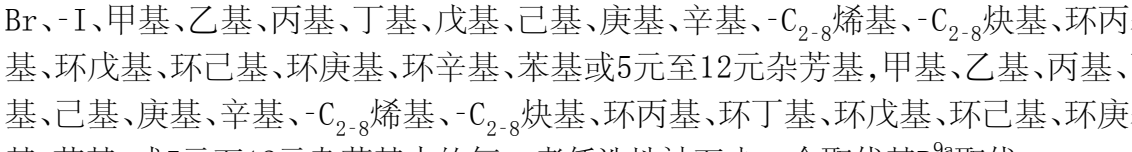
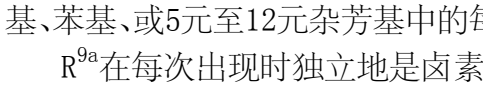
R^{6d}和R^{6g}各自独立地选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基。

30.如前述权利要求中任一项所述的化合物,其中R^6是H、-F、-Cl、-Br、-I、甲基、-CF_3、乙基、-CH_2CF_3、-CF_2CH_3、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、

环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧

基、 

；优选地， 

部分是  、  、  、  、  、  、  、  或  。

31.如前述权利要求中任一项所述的化合物，其中R^9和R^{10}各自独立地选自H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基，甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{9a}取代；

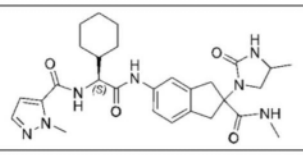
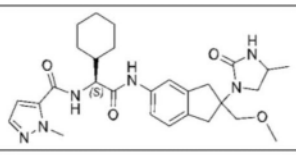
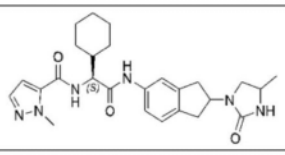
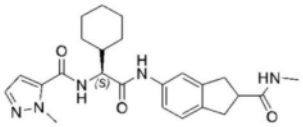
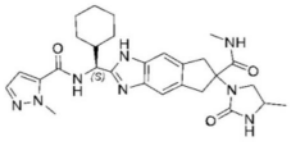
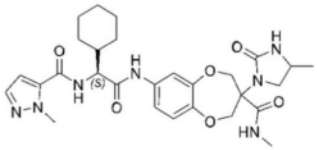
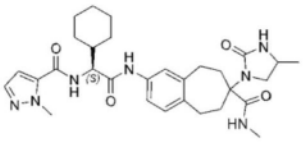
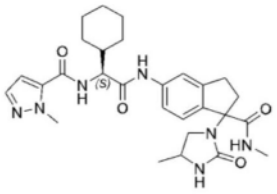
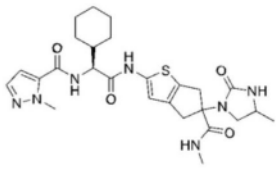
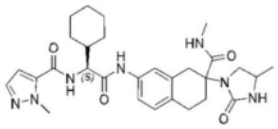
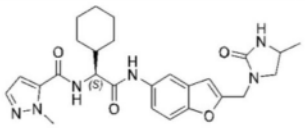
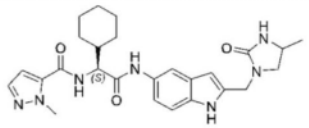
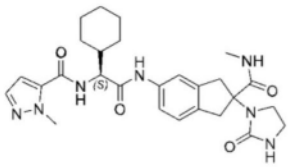
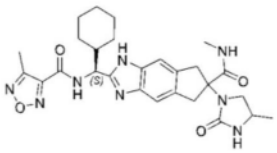
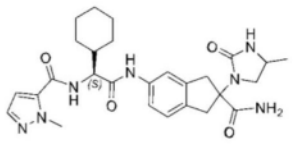
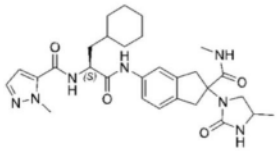
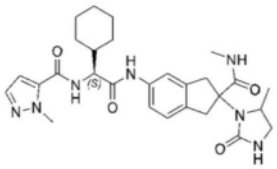
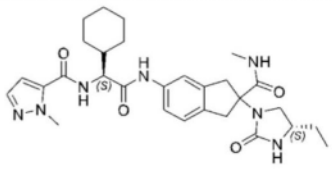
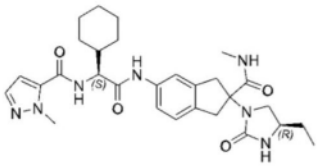
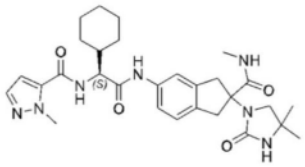
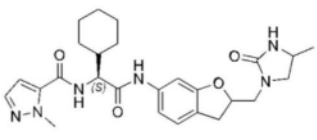
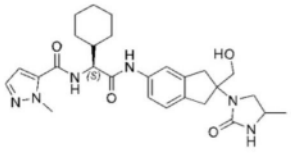
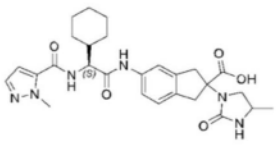
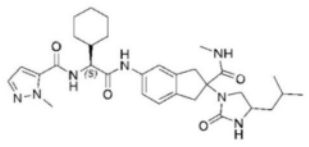
R^{9a}在每次出现时独立地是卤素、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基；

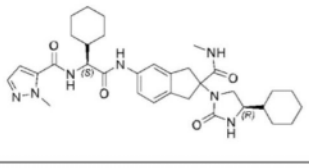
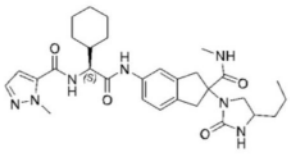
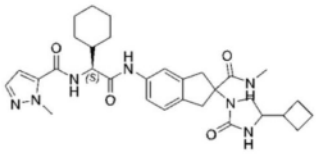
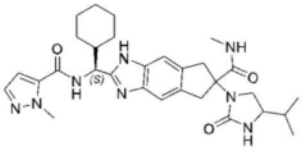
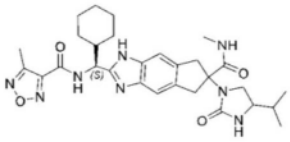
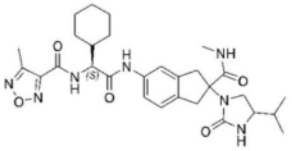
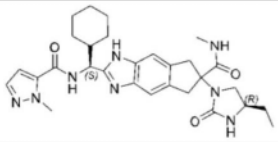
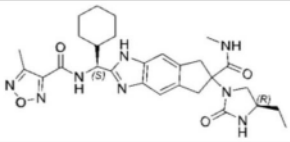
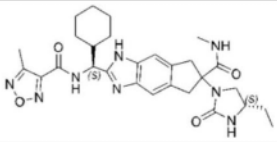
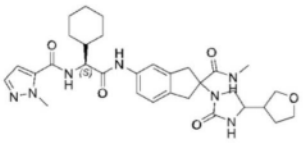
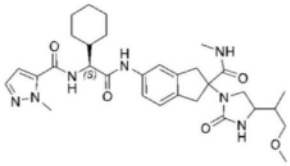
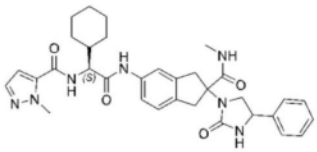
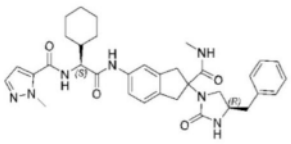
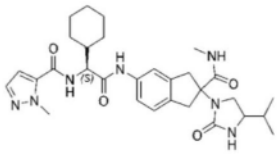
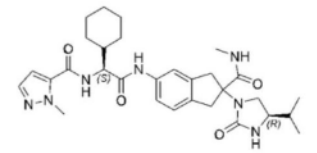
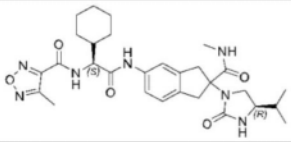
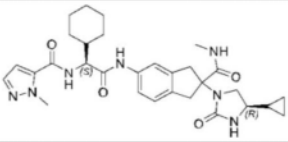
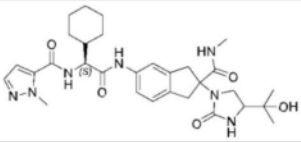
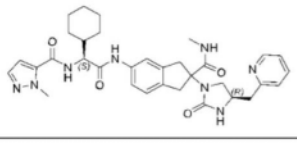
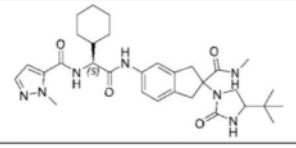
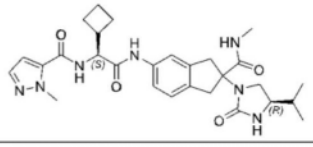
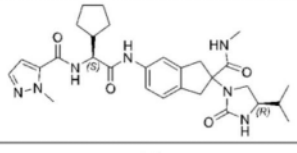
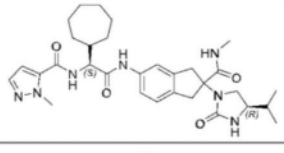
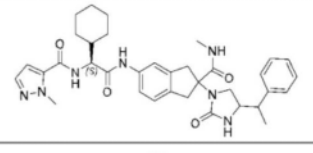
优选地，R^9和R^{10}各自独立地选自H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基；

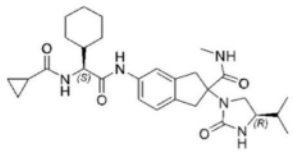
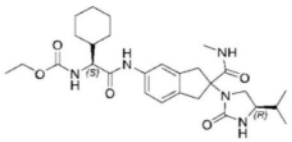
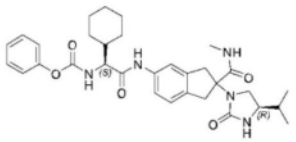
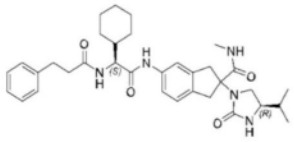
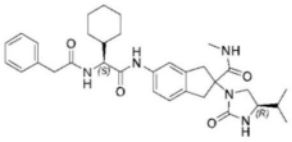
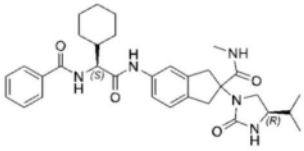
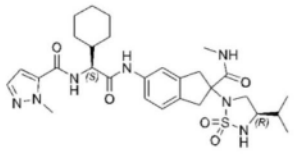
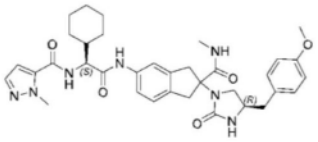
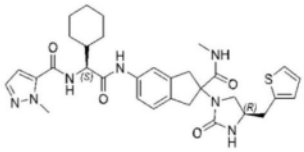
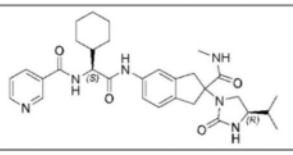
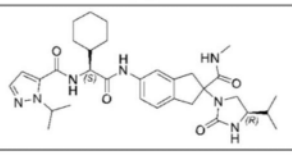
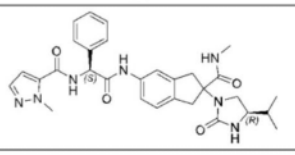
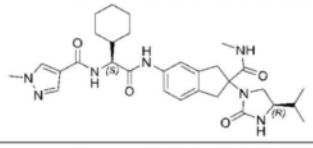
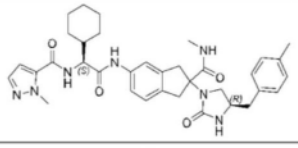
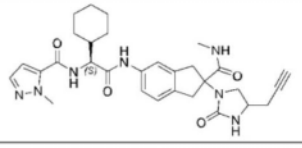
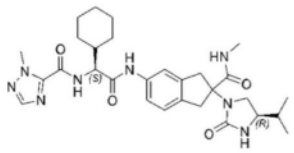
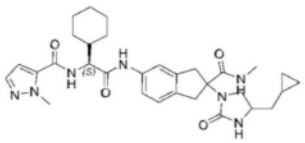
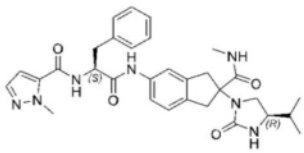
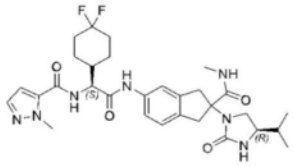
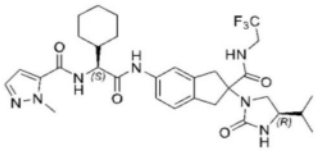
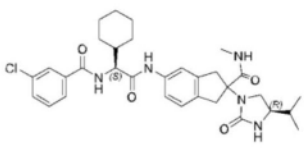
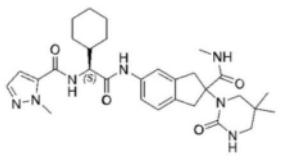
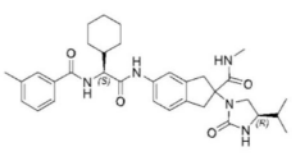
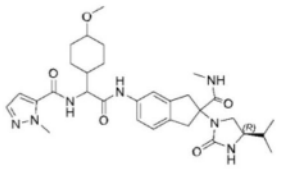
更优选地，R^9和R^{10}各自独立地选自H、甲基、乙基、丙基、丁基、戊基、环丙基、环丁基、环戊基；

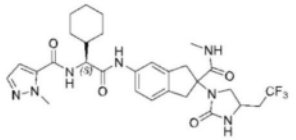
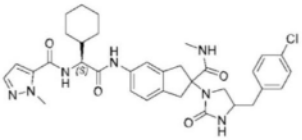
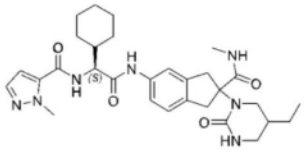
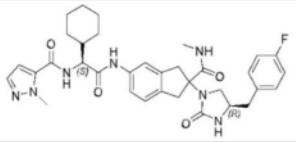
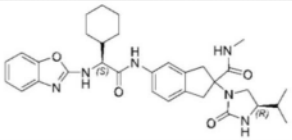
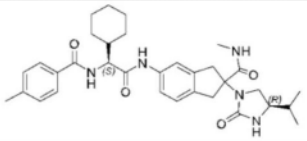
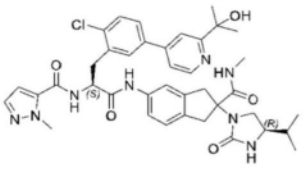
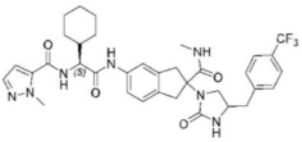
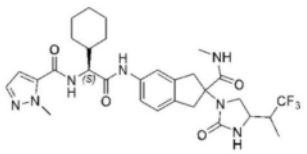
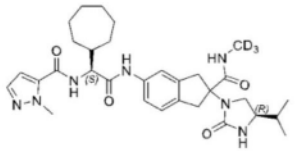
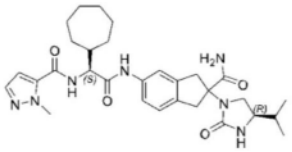
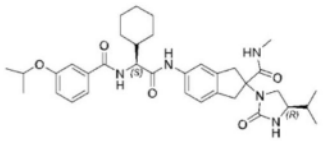
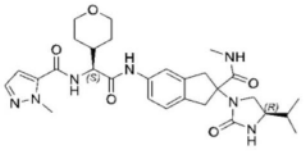
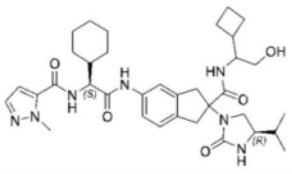
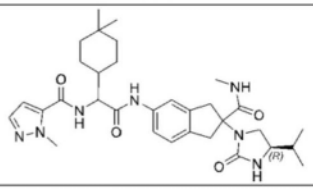
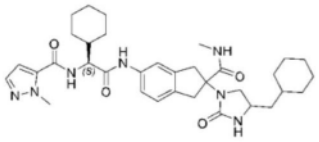
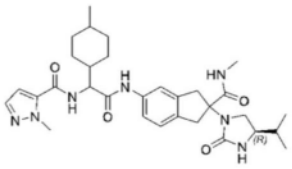
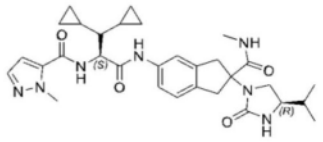
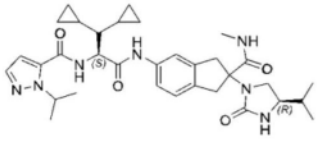
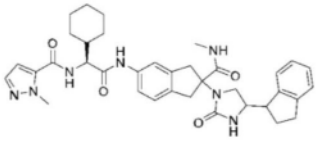
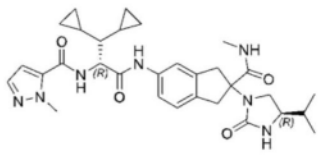
更优选地，R^9和R^{10}各自独立地选自H、环丙基。

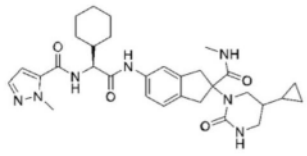
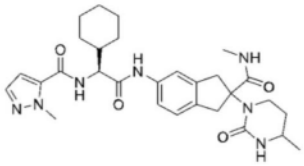
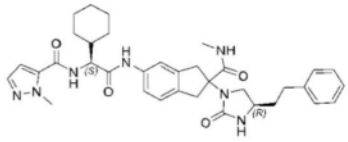
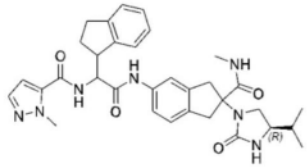
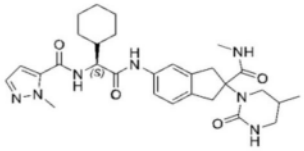
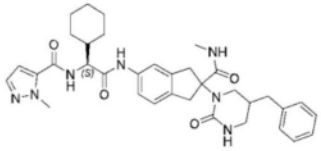
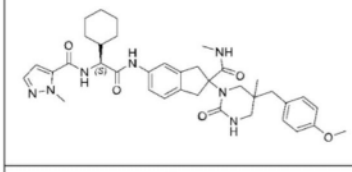
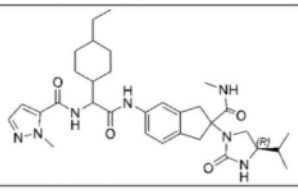
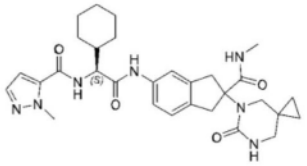
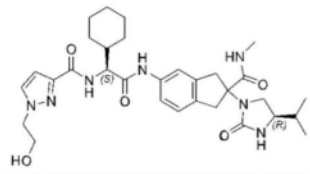
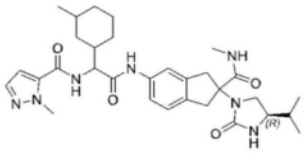
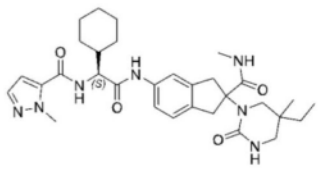
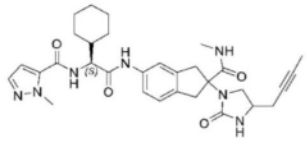
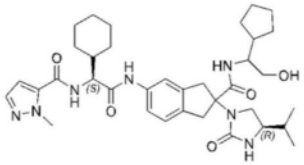
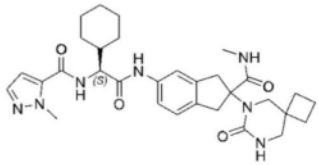
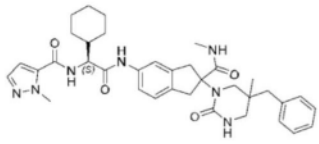
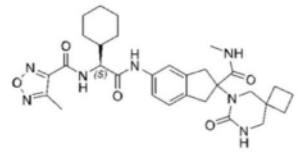
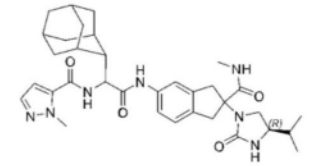
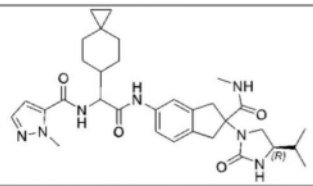
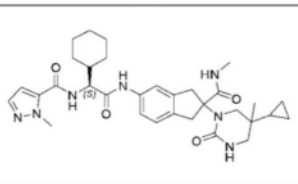
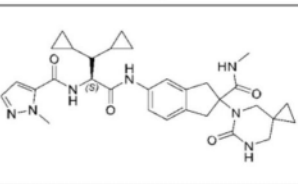
32.如前述权利要求中任一项所述的化合物，其中所述化合物选自

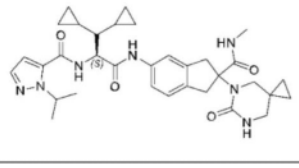
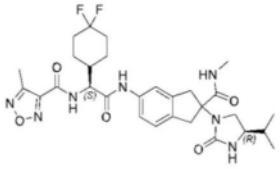
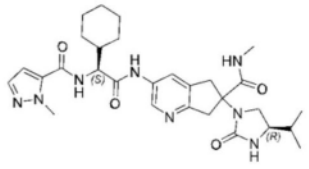
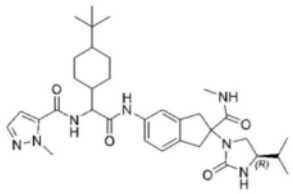
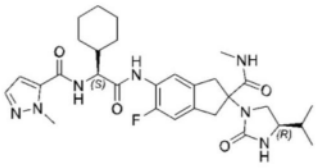
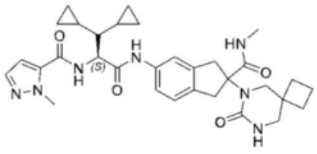
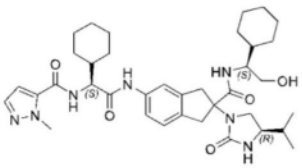
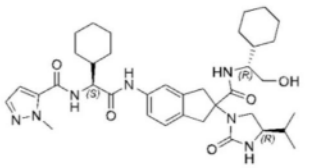
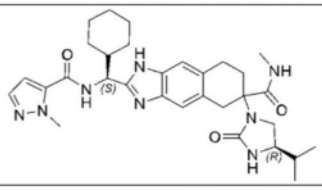
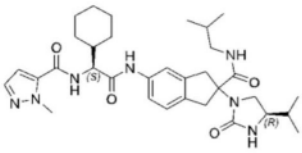
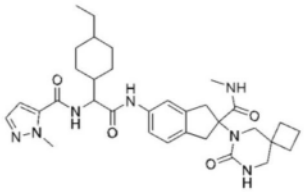
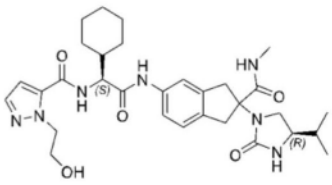
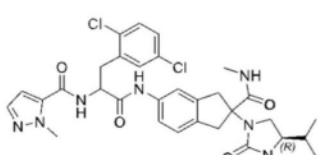
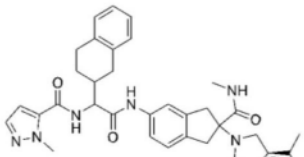
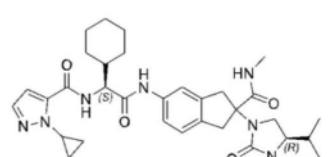
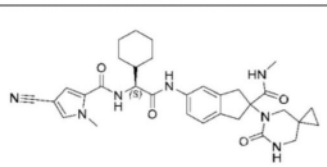
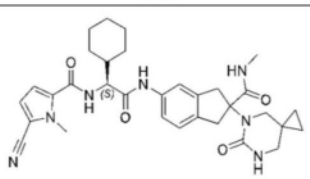
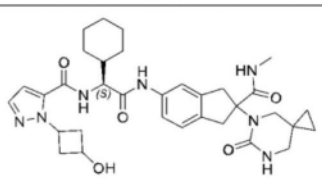
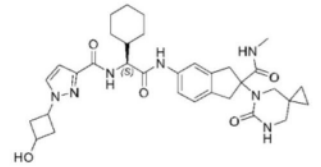
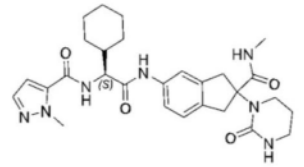
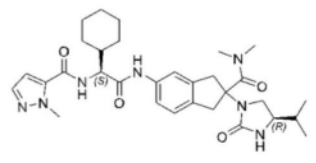
		
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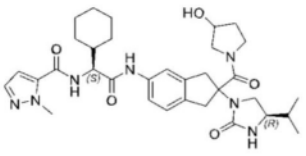
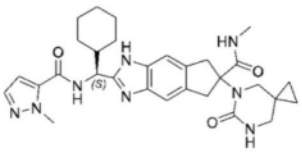
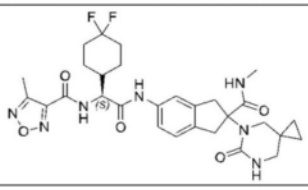
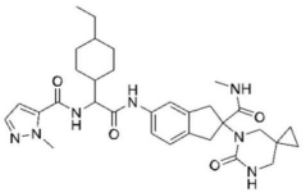
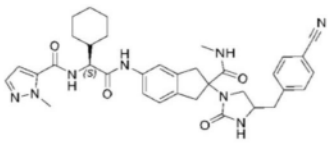
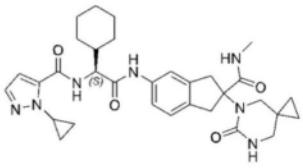
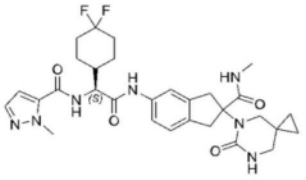
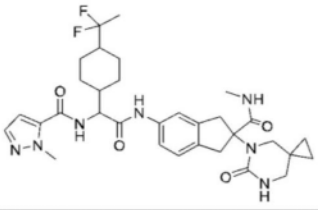
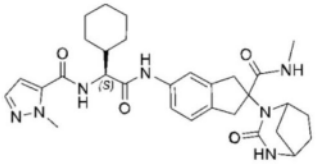
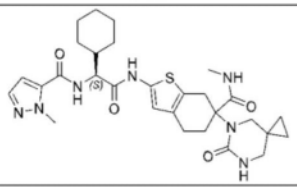
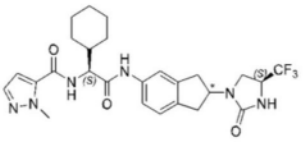
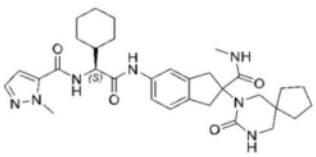
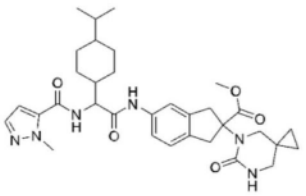
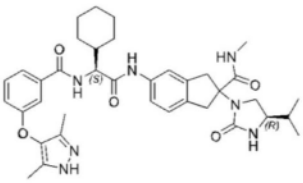
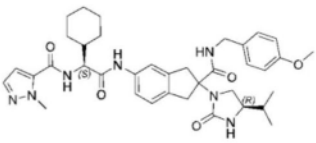
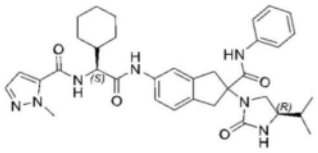
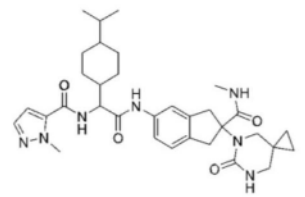
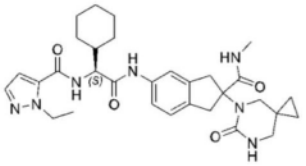
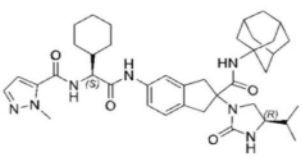
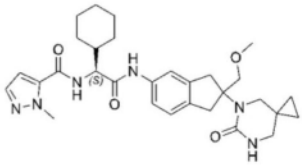
		
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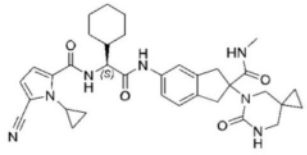
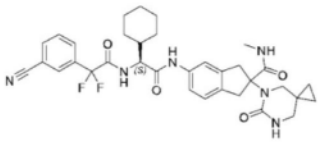
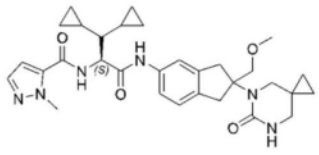
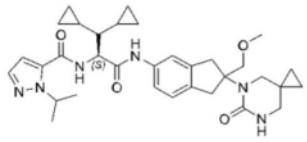
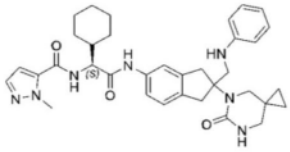
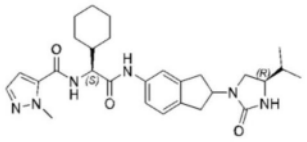
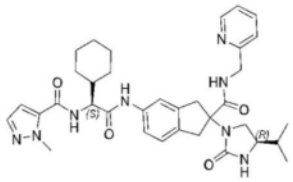
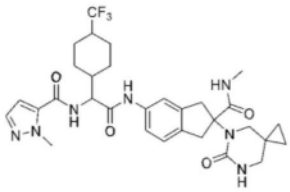
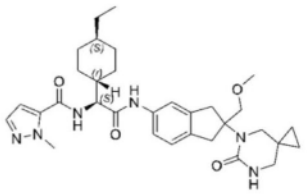
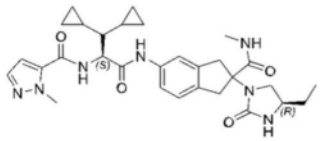
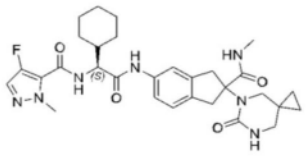
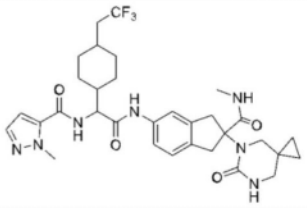
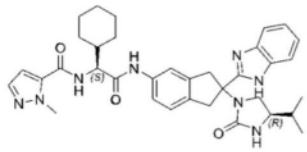
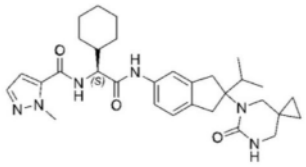
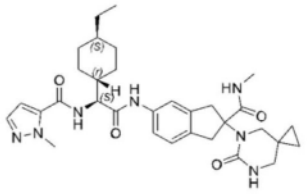
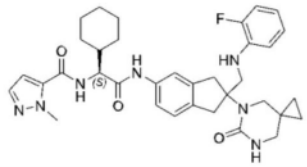
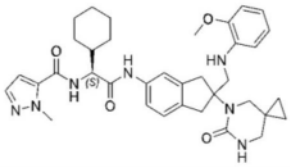
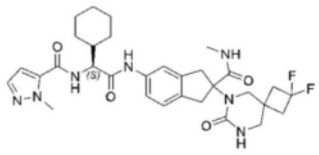
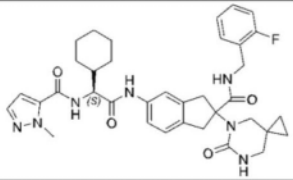
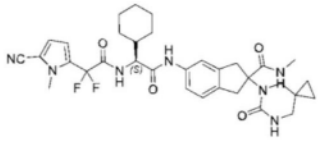
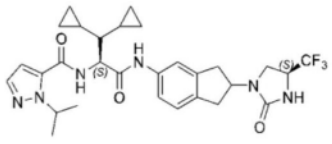
		
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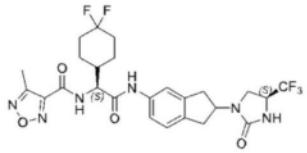
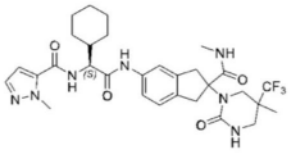
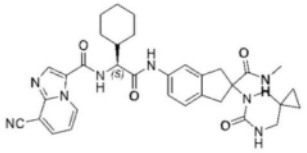
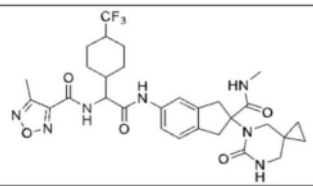
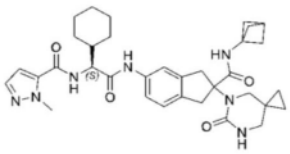
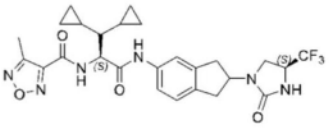
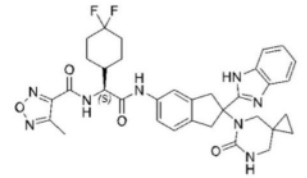
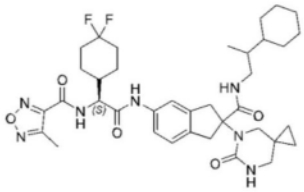
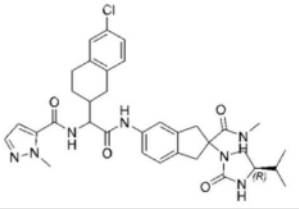
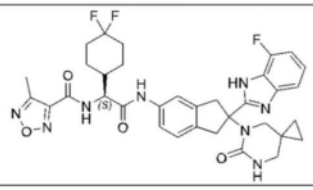
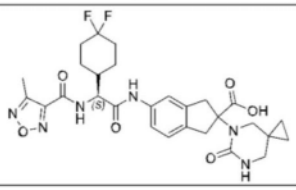
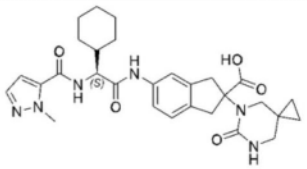
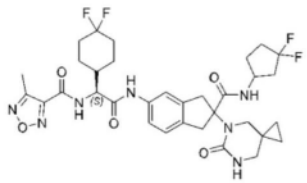
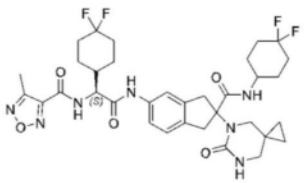
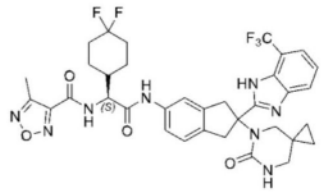
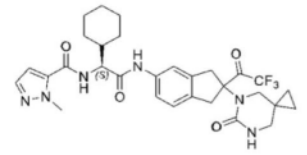
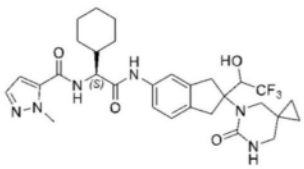
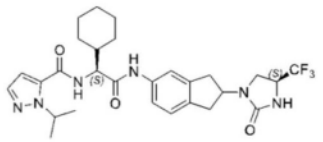
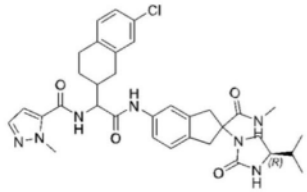
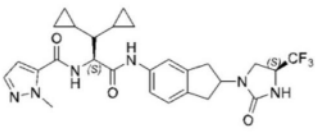
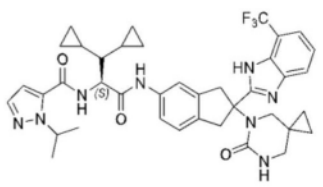
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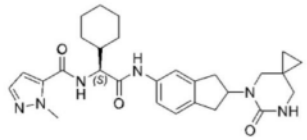
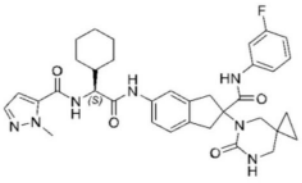
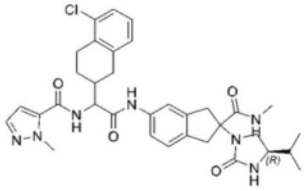
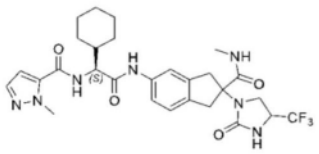
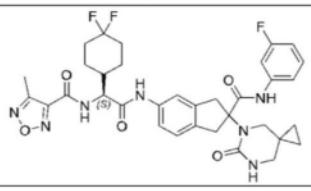
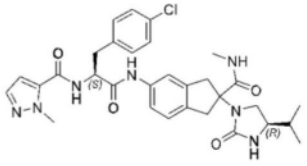
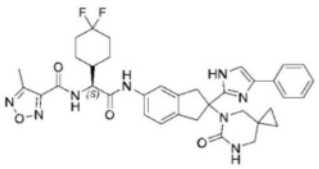
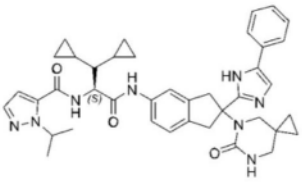
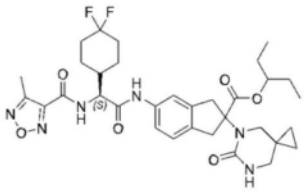
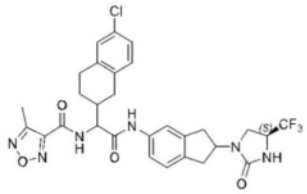
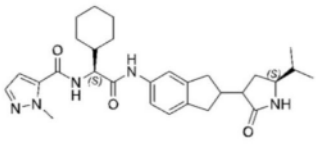
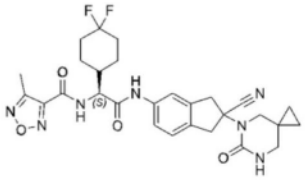
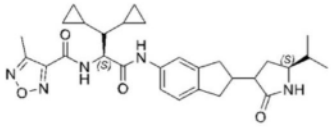
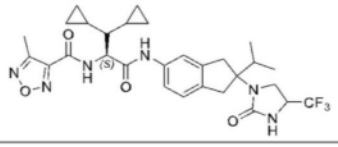
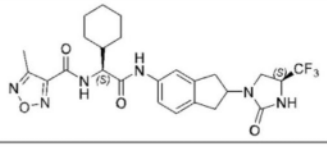
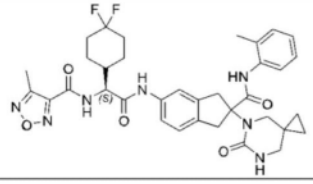
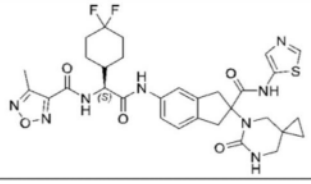
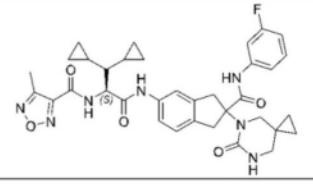
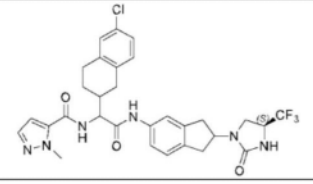
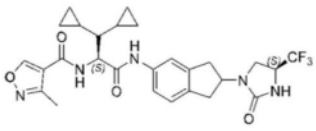
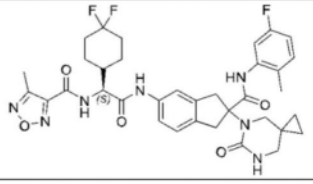
		
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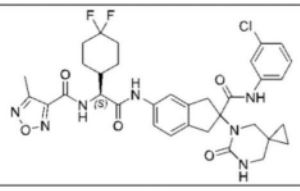
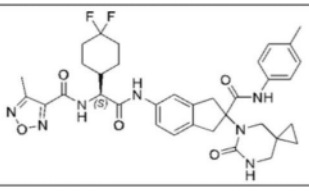
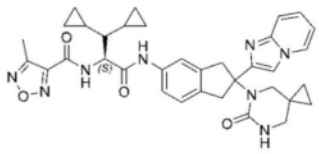
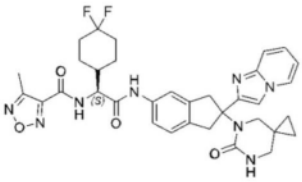
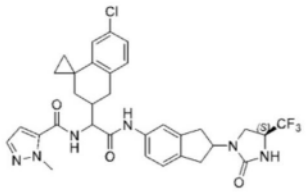
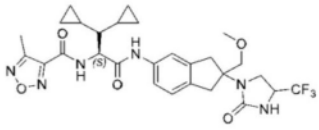
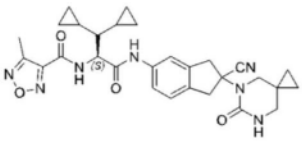
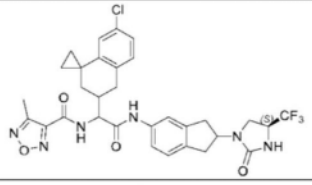
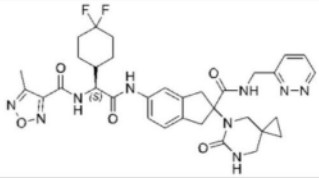
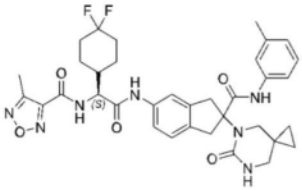
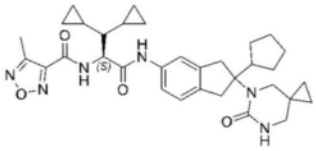
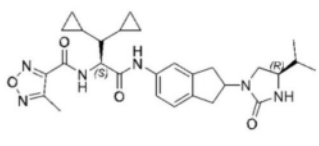
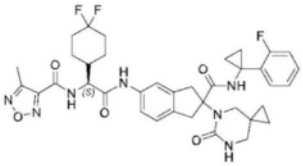
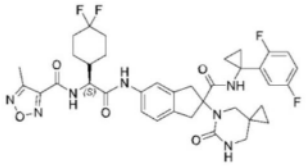
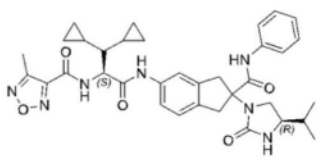
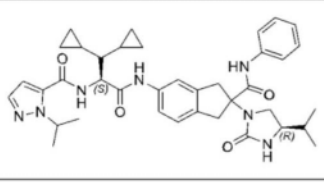
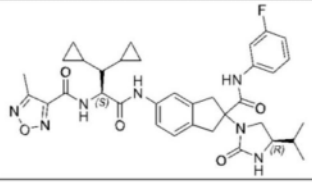
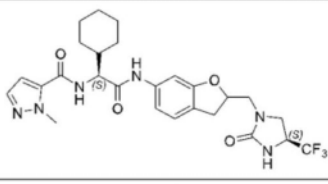
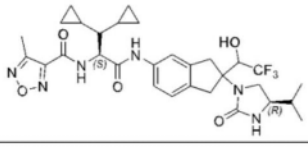
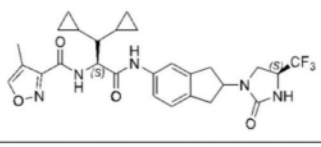
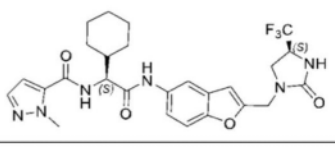
		
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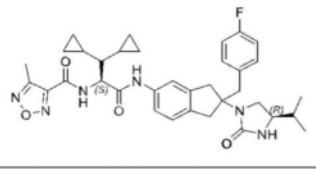
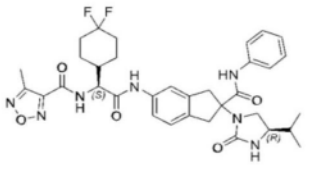
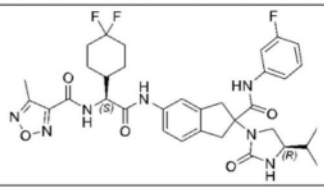
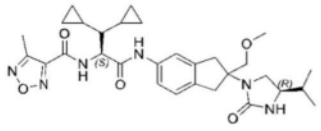
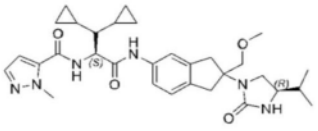
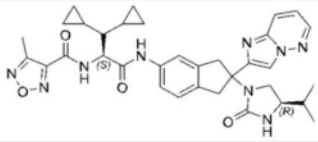
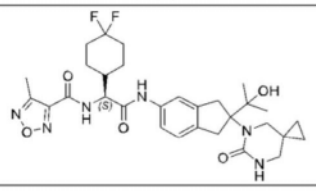
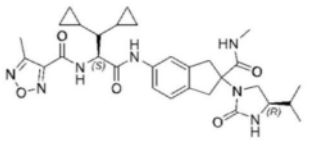
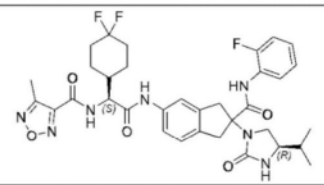
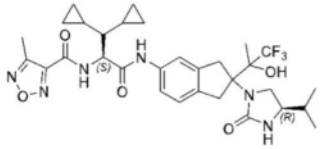
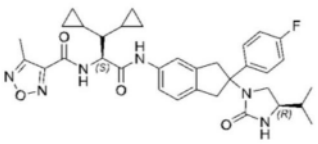
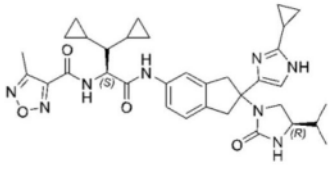
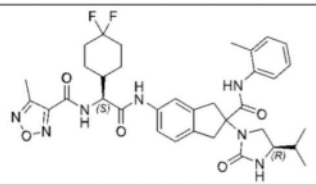
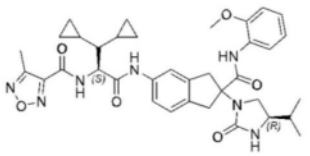
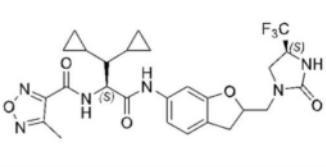
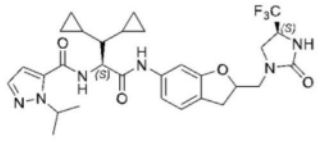
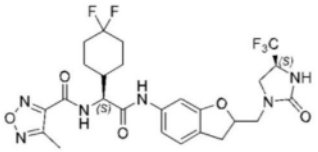
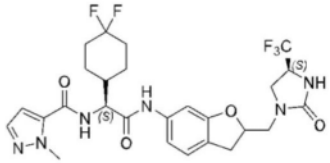
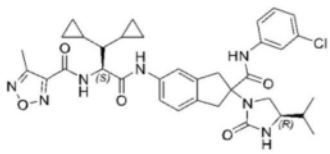
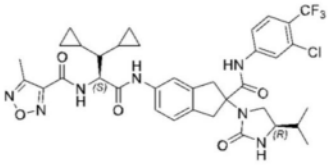
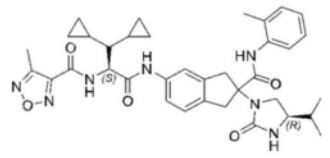
		
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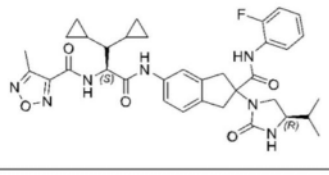
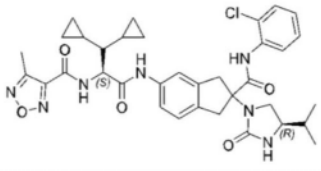
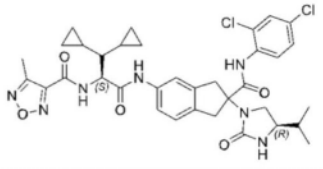
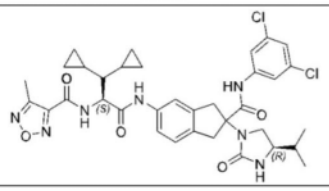
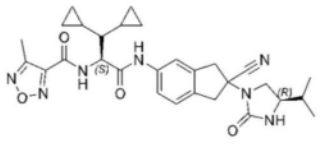
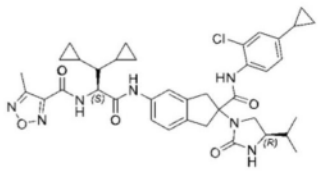
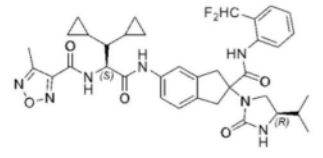
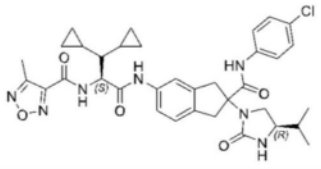
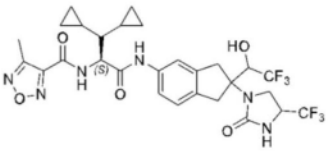
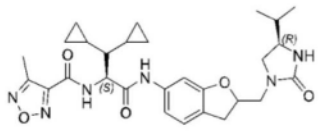
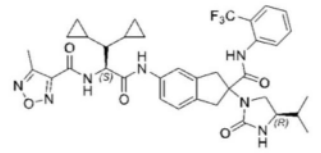
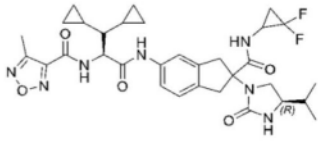
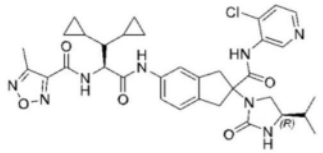
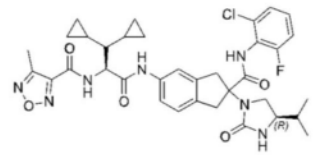
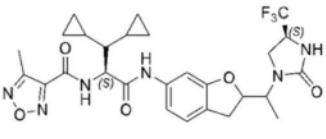
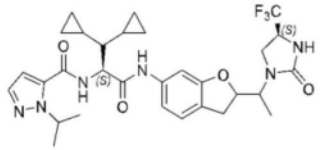
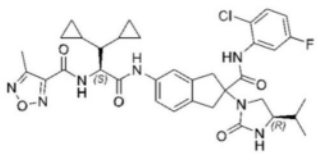
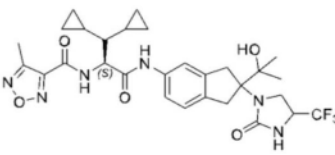
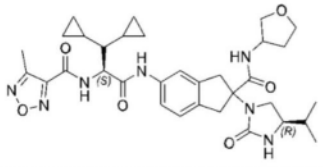
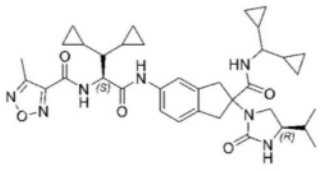
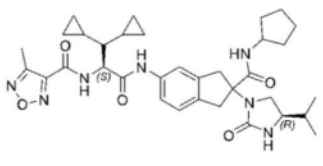
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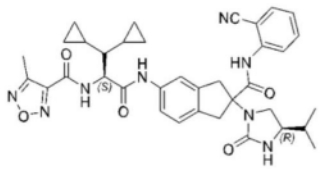
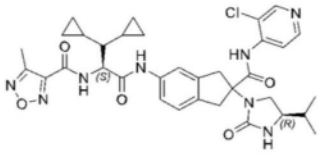
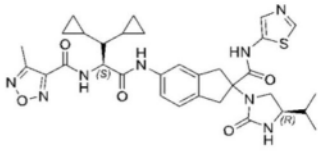
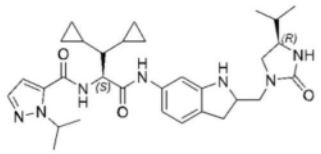
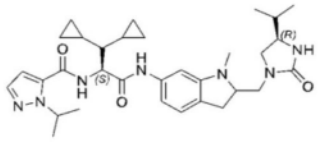
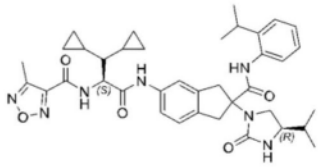
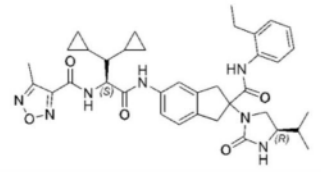
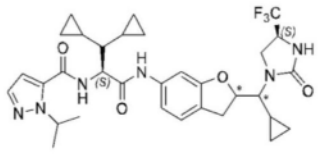
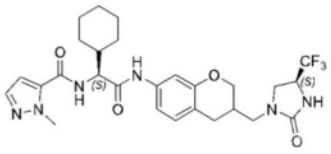
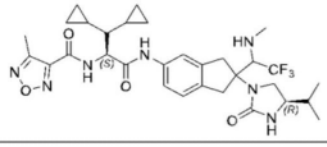
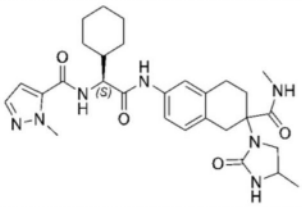
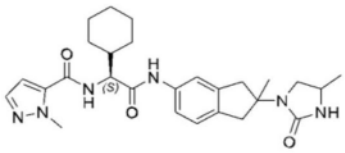
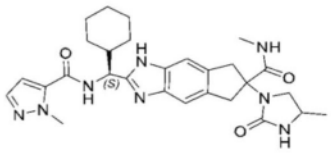
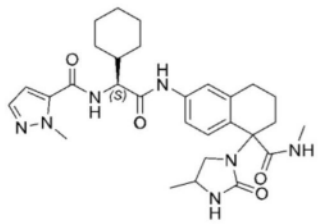
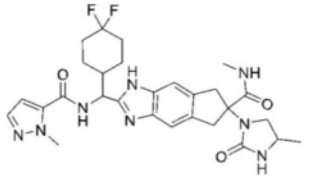
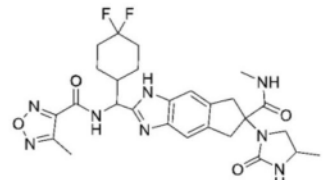
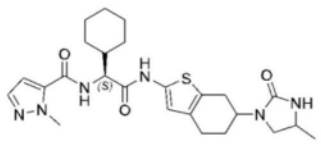
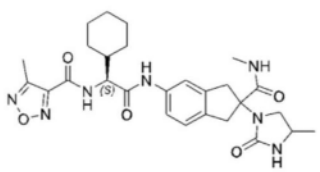
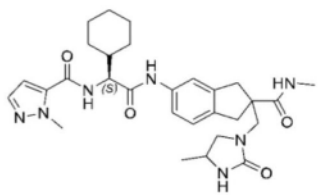
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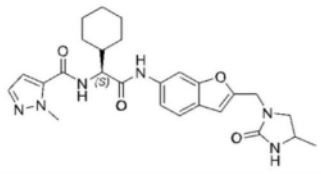
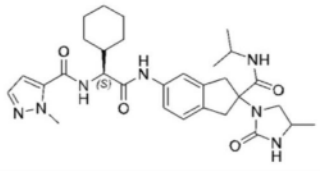
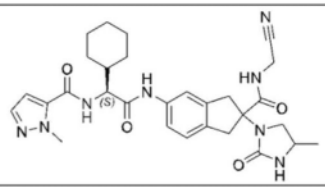
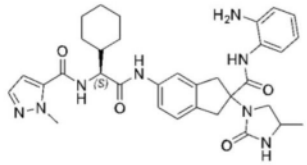
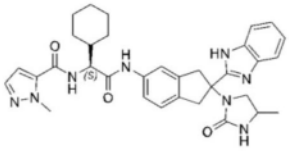
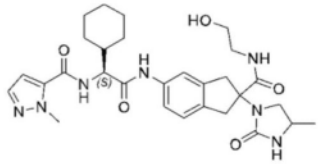
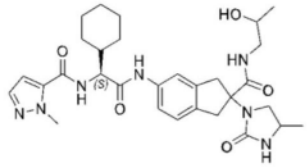
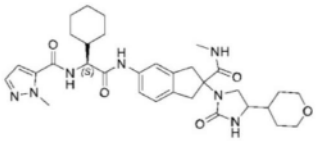
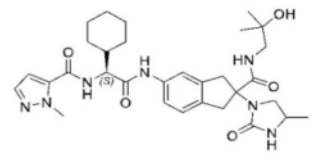
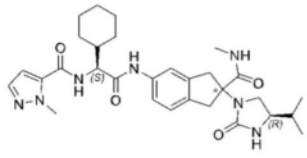
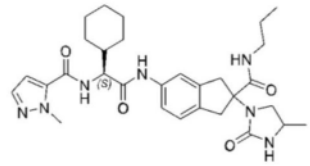
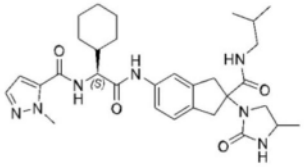
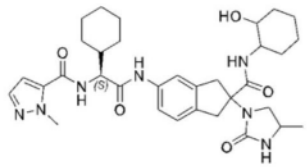
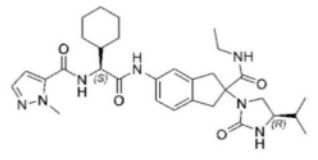
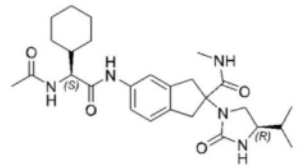
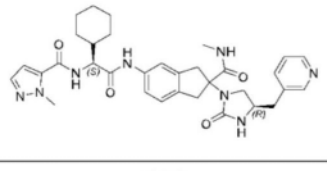
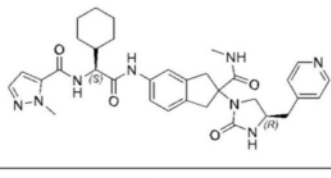
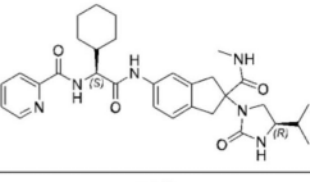
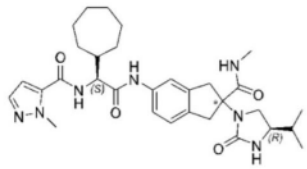
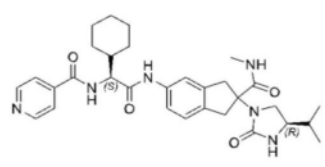
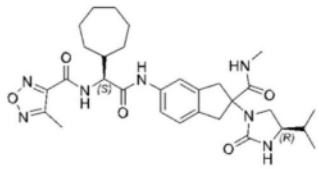
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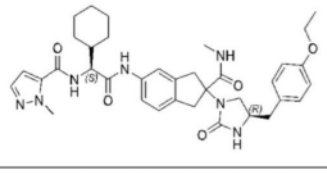
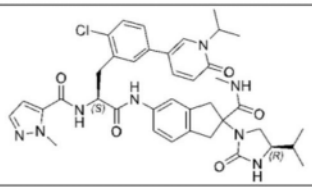
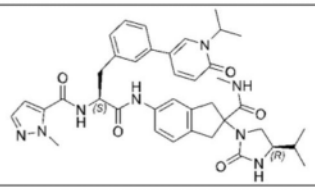
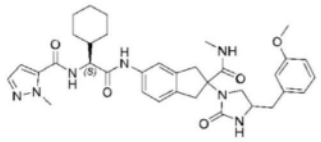
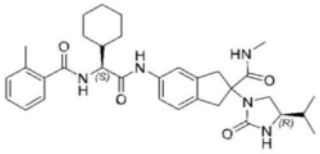
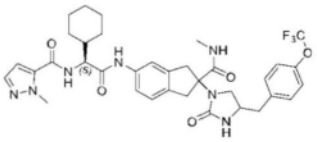
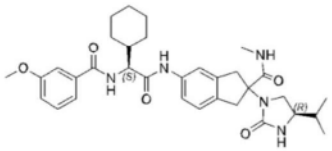
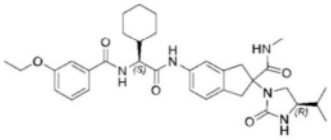
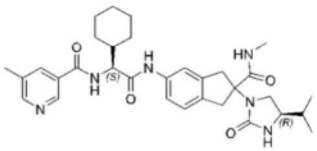
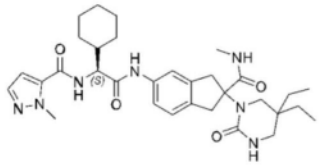
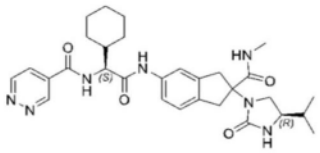
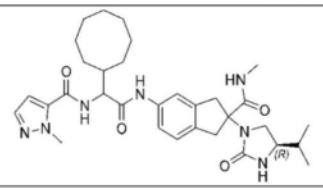
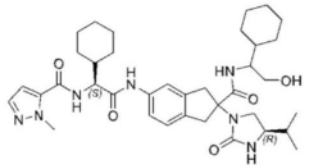
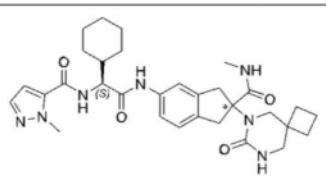
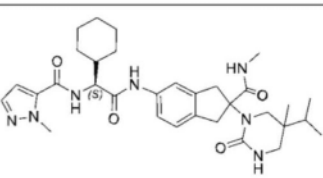
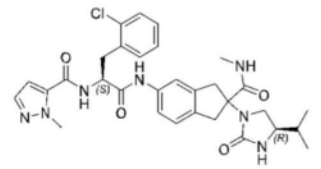
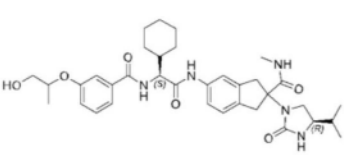
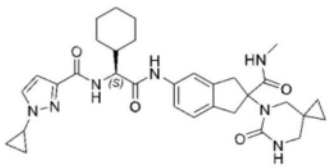
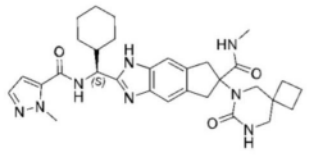
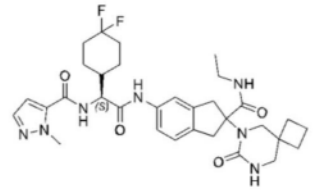
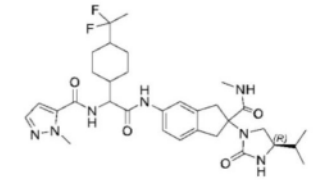
		
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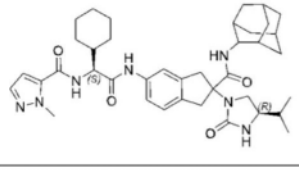
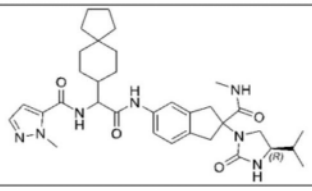
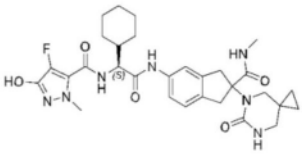
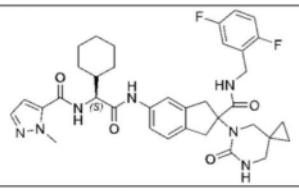
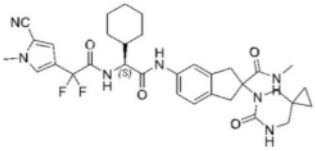
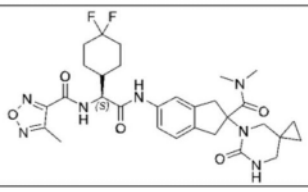
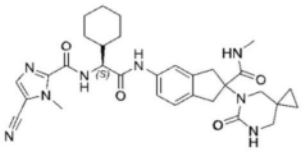
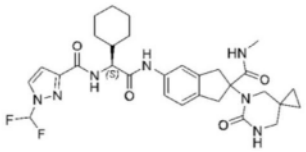
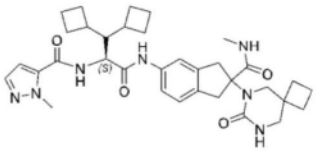
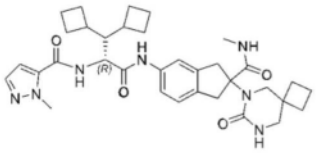
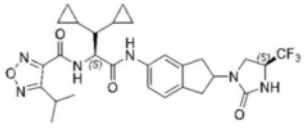
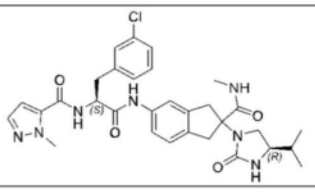
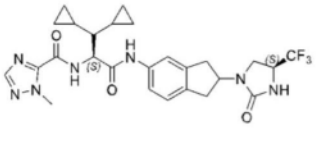
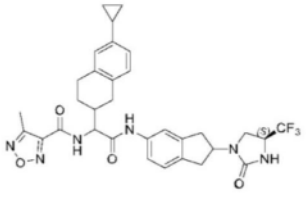
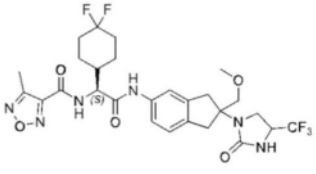
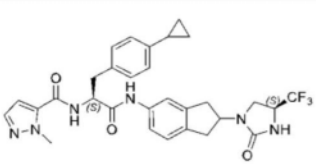
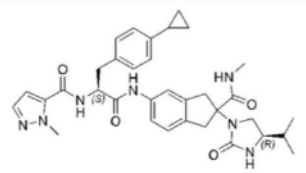
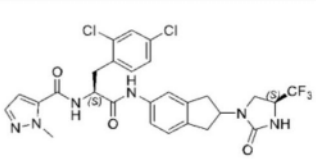
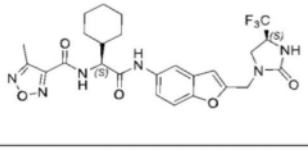
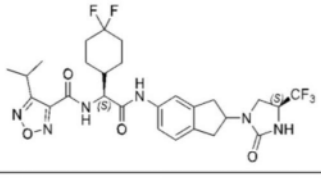
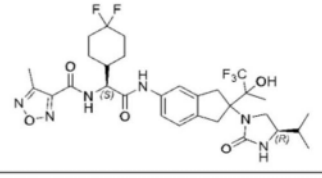
		
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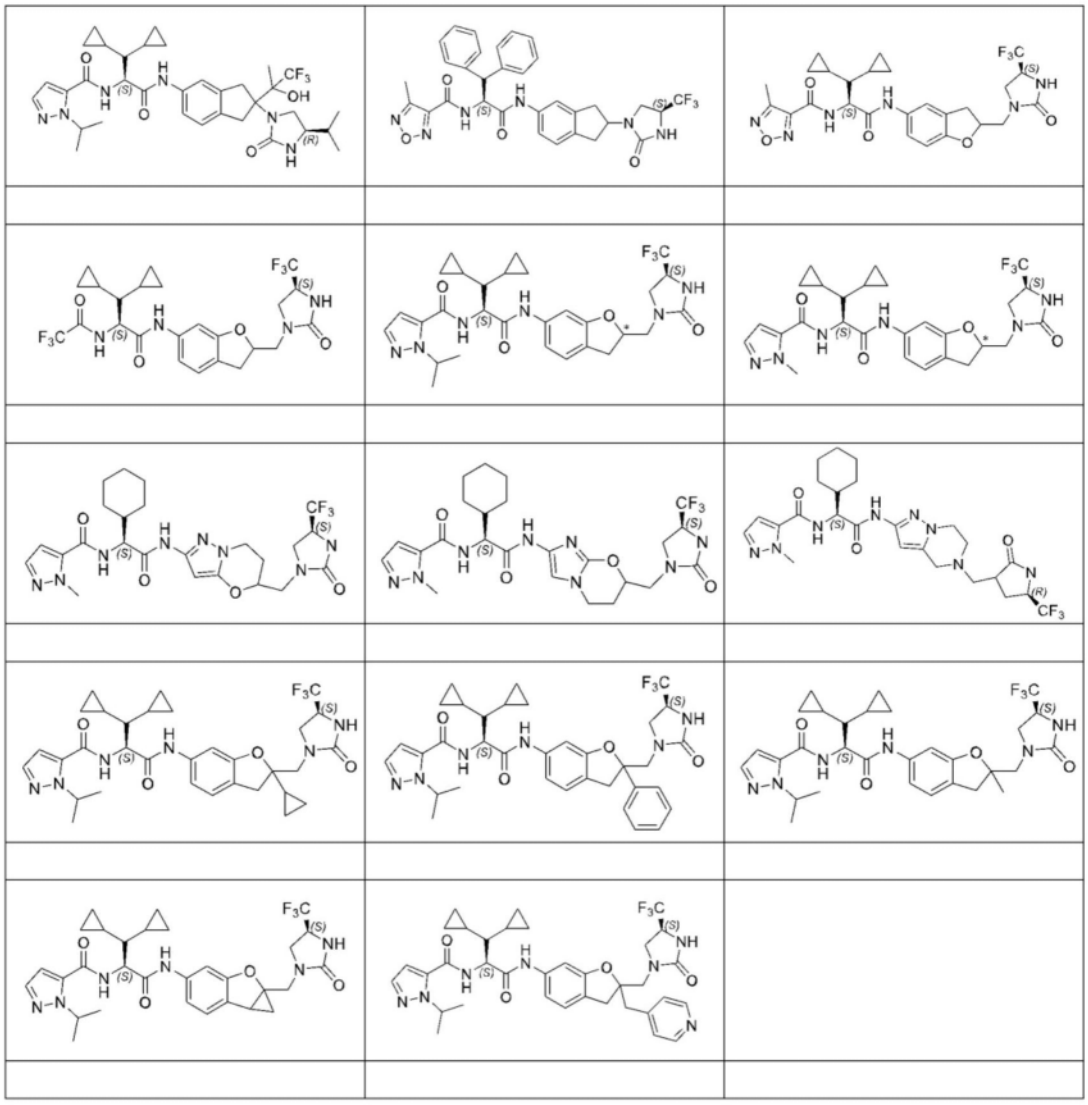
		
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33.一种药物组合物,其包含如权利要求1至32中任一项所述的化合物或其药学上可接受的盐、立体异构体、互变异构体或前药,以及药学上可接受的赋形剂。

34.一种通过抑制来降低IL-17活性的方法,其包括向个体施用如权利要求1至32中任一项所述的化合物或其药学上可接受的盐,包括式(I)的化合物或本文所例示的特定化合物。

35.如权利要求34所述的方法,其中所述疾病选自癌症。

36.如权利要求1至32中任一项所述的化合物或其药学上可接受的盐、立体异构体、互变异构体或前药在制备用于治疗能够受IL-17影响的疾病的药物中的用途。

37.如权利要求36所述的用途,其中所述疾病是自身免疫性疾病或炎性疾病。

38.如权利要求37所述的用途,其中所述疾病是慢性炎症、牛皮癣、脊椎关节炎、类风湿性关节炎或多发性硬化症。

小分子IL-17A调节剂

技术领域

[0001] 本文公开了用作小分子IL-17A调节剂的稠合双环化合物。本文公开了这些小分子IL-17A调节剂用于通过抑制来降低IL-17活性的用途,以及此类化合物用于治疗自身免疫性疾病或炎性疾病的用途。

背景技术

[0002] 白细胞介素-17(IL-17)家族是一组促炎细胞因子,其参与组织的免疫应答并在慢性炎症中起关键作用。IL-17的分泌可刺激其他促炎细胞因子(IL-1、IL-6、G-CSF、GM-CSF和TNF)和趋化因子(CXCL1、CXCL2、CXCL5、CCL2、CCL7、CCL20和IL-8)、基质金属蛋白酶(MMP1、MMP3、MMP9和MMP13)和抗微生物肽(β-防御素、S-100蛋白)的产生(Frontiers in Immunology(2020)11:947)。IL-17家族由7个成员组成,包括IL17A至IL17F和vIL-17A。IL-17A作为最广泛研究的建立者成员,与对抗各种微生物病原体和组织炎症的宿主防御相关(Gene(2017)614:8-14)。IL-17A由155个氨基酸组成,并且同源二聚体的分子量为30-35kDa(European Respiratory Journal(2005):159-172)。IL-17F(IL-17A的近亲)在其163个氨基酸上与IL-17A共享约50％的氨基酸序列同源性,并且经常与IL-17A共表达(Immunity(2004):467-476)。IL-17A和IL-17F均从T辅助细胞(Th17)分泌,并且以同源二聚体或IL-17A/F异源二聚体表达(European Respiratory Journal(2005):159-172)。IL-17受体家族由五个成员组成:IL-17RA、IL-17RB、IL-17RC、IL-17RD和IL-17RE。所有这五种受体共享命名为SEFIR结构域的共同细胞质基序(Frontiers in Immunology11(2020):947)。IL-17A和IL-17F通过相同受体复合物IL-17R的信号途径由两个亚基组成:IL-17RA和IL-17RG(Gene(2017)614:8-14)。相应的受体活化这些信号传导的下游途径,包括NFκB、MAPK和C/EBP,以诱导抗微生物肽、细胞因子和趋化因子的表达(Frontiers in Immunology(2020):947)。IL-17A促进组织炎症和骨重塑。其可作用于各种细胞类型:角质形成细胞、内皮细胞、成纤维细胞、破骨细胞、软骨细胞和成骨细胞(Archives of oral biology(2014):897-905)。

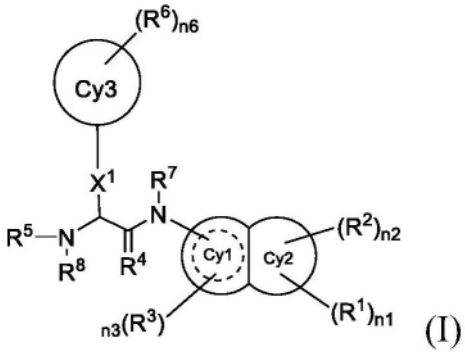
[0003] 在包括牛皮癣、脊椎关节炎、类风湿性关节炎和多发性硬化症的许多自身免疫性疾病中观察到增加分泌的IL-17A的异常自身免疫应答(Gene(2017)614:8-14)。这些疾病的一种潜在治疗是开发IL-17A抑制剂。目前,FDA批准几种靶向IL-17A的单克隆抗体用于治疗中度至重度斑块状牛皮癣(Expert Opin.Biol.Ther.(2019),19,45-54):司库奇尤单抗(secukinumab)(Cosentyx,Novartis)、依奇珠单抗(ixekizumab)(Taltz,Eli Lilly)和博达路单抗(brodalumab)(Kyntheum,LEO Pharma/AstraZeneca)。比美吉珠单抗(Bimekizumab)(UCB)是2021年由EC批准的双特异性抗IL-17A/IL-17F人源化单克隆抗体。然而,由于单克隆抗体具有许多缺点,诸如高的产品成本、非口服应用、差的组织穿透性和通常长的半衰期(Chem.Biol.(2014)21,1102-1114),仍在寻找将表现出相同生物学结果的小分子。已知一些公开内容描述了具有IL-17A抑制活性的小分子(WO2014066726、WO2018229079、WO2019138017、WO2019223718、WO2020182666、WO2020011731、WO2020127685、WO2020163554、WO2021055376、WO2021098844、2020163554WO2020146194、

WO2021204801、WO2021170627、WO2021098844、WO2021222404、WO2021220183)。靶向IL-17A和IL-17RA的蛋白质/蛋白质相互作用的几种小分子抑制剂现在已经推进到临床试验中。口服施用和灵活的治疗方案应该是有利于患者方便的主要方面。当发生与靶标相关的不良事件时,快速撤出小分子药物的可能性可能呈现批准的安全性。因此,一直需要开发具有不同结构、特别是可口服施用的小分子IL-17A调节剂。

发明内容

[0004] 在一个实施方案中,本文公开了式(I)的稠合双环化合物。该实施方案包括以下方面:

[0005] 方面1.一种式(I)的化合物:

[0006] 

(I)

[0007] 或其N-氧化物、或其药学上可接受的盐、或其立体异构体、或其氘代类似物,其中:

[0008] Cy1是5-6元芳族环,所述环包含0-3个独立地选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^3取代;

[0009] n3独立地是0、1、2或3;

[0010] Cy2是4-8元饱和或者部分或完全不饱和的环,所述环包含0-3个独立地选自氮、氧或任选氧化的硫的杂原子;所述环被至少一个取代基R^1和/或R^2取代;

[0011] n1是0或1;

[0012] n2是0、1或2;

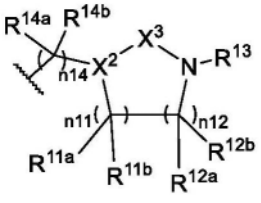
[0013] n1和n2不同时是0;

[0014] Cy1和Cy2彼此稠合;

[0015] Cy3是3-12元饱和或者部分或完全不饱和的环,所述环包含0-3个独立地选自氮、氧或任选氧化的硫的杂原子;所述环任选地被至少一个取代基R^6取代;

[0016] n6独立地是0、1、2、3、4或5,条件是满足化合价理论;

[0017] X^1是单键或-CR^9R^{10}-;

[0018] R^1独立地选自H或 

,

[0019] 其中X^2是N或C(R^{15});

[0020] X^3是-C(O)-、-S(O)-或-$S(O)_2$-;

[0021] n11和n12各自独立地是1、2或3;

[0022] n14是0或1;

[0023] R^{15}选自氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、-CN、-OR^{15a}、-$NR^{15a}R^{15b}$或-$NR^{15a}COR^{15b}$;-C_{1-8}烷基、C_3-C_8环烷基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{15c}取代;

[0024] R^{15a}和R^{15b}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基,-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{15d}取代;

[0025] R^{15c}和R^{15d}在每次出现时各自独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

[0026] R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-OR^{11c}、-COR^{11c}、-CO_2R^{11c}、-$CONR^{11c}R^{11d}$、-$NR^{11c}R^{11d}$或-$NR^{11c}COR^{11d}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11e}取代,或

[0027] (R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立地选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{11f}取代;

[0028] R^{11e}和R^{11f}在每次出现时各自独立地是氢、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{11g}、硫代基(=S)、-SR^{11g}、-CN、-SO_2R^{11g}、-$SO_2NR^{11g}R^{11h}$、-COR^{11g}、-CO_2R^{11h}、-$CONR^{11g}R^{11h}$、-$NR^{11g}R^{11h}$、-$NR^{11g}COR^{11h}$、-$NR^{11g}CO_2R^{11h}$或-$NR^{11g}SO_2R^{11h}$;-C_{1-8}烷基、-C_{1-8}烷氧基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11i}取代;

[0029] R^{11c}、R^{11d}、R^{11g}和R^{11h}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11j}取代;

[0030] R^{11i}和R^{11j}在每次出现时各自独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基取代;

[0031] R^{13}、R^{14a}和R^{14b}各自独立地选自氢、-C_{1-8}烷基、-C_3-C_8环烷基或3元至8元杂环基;-C_{1-8}烷基、-C_3-C_8环烷基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{13a}取代;

[0032] R^{13a}在每次出现时独立地是卤素、-OH、-CN、氧代基、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳

基或5元至12元杂芳基;

[0033] R^2独立地选自H、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-COR^{2a}、-CO_2R^{2a}、-$CONR^{2a}R^{2b}$、-$NR^{2a}R^{2b}$或-$NR^{2a}COR^{2b}$,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2c}取代;或

[0034] 当两个偕的或相邻的R^2与它们所连接的碳原子一起形成3元至8元不饱和或饱和的环时,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2c}取代;

[0035] R^{2a}和R^{2b}各自独立地选自氢、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2d}取代;或

[0036] R^{2a}和R^{2b}与它们所连接的氮原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

[0037] R^{2c}和R^{2d}在每次出现时各自独立地是氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{2e}、-SR^{2e}、-CN、-COR^{2e}、-CO_2R^{2e}、-$CONR^{2e}R^{2f}$、-$NR^{2e}R^{2f}$、-$NR^{2e}COR^{2f}$或-$NR^{2e}CO_2R^{2f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2g}取代;

[0038] R^{2e}和R^{2f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2h}取代;

[0039] R^{2g}和R^{2h}在每次出现时各自独立地是卤素、-OH、-C_{1-8}烷基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

[0040] 当n1和n2都是1时,R^1和R^2是偕的或相邻的;

[0041] R^3独立地选自氢、卤素、-C_{1-8}烷基、-C_{1-8}烷氧基、-C_3-C_8环烷基或-CN,其中-C_{1-8}烷基、-C_{1-8}烷氧基和-C_3-C_8环烷基中的每一者任选地被至少一个选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代;

[0042] R^4是氧代基(=O)或硫代基(=S);或

[0043] R^3和R^4与它们所连接的原子一起形成5元至6元芳族环,所述环包含1-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{3a}取代;

[0044] R^{3a}独立地选自氢、卤素、-C_{1-8}烷基、-C_{1-8}烷氧基、-C_3-C_8环烷基或-CN,其中-C_{1-8}烷基、-C_{1-8}烷氧基和-C_3-C_8环烷基中的每一者任选地被至少一个选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代;

[0045] R^5是C_6-C_{12}芳基、5元至12元杂芳基、-COR^{5a}、-CO_2R^{5a}、-$CONR^{5a}R^{5b}$,其中C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5c}取代;

[0046] R^{5a}和R^{5b}各自独立地选自-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5d}取代;或

[0047] R^{5a}和R^{5b}与它们所连接的原子一起形成3元至8元不饱和或饱和的环,所述环包含0-3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{5d}取代;

[0048] R^{5c}和R^{5d}在每次出现时各自独立地选自氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、-OR^{5e}、-SR^{5e}、-CN、-COR^{5e}、-CO_2R^{5e}、-$CONR^{5e}R^{5f}$、-$NR^{5e}R^{5f}$、-$NR^{5e}COR^{5f}$或-$NR^{5e}CO_2R^{5f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5g}取代;

[0049] R^{5e}和R^{5f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{5h}取代;

[0050] R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

[0051] R^6是H、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基、5元至12元杂芳基、-CN、-OR^{6a}、-$NR^{6a}R^{6b}$、-COR^{6a}、-CO_2R^{6a}、-$CONR^{6a}R^{6b}$、-COR^{6a}或-$NR^{6a}COR^{6b}$,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6c}取代;

[0052] R^{6a}和R^{6b}各自独立地选自氢、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6d}取代;

[0053] R^{6c}在每次出现时独立地是氢、卤素、-C_{1-8}烷基、-C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基5元至12元杂芳基、氧代基(=O)、-OR^{6e}、-SR^{6e}、-CN、-COR^{6e}、-CO_2R^{6e}、-$CONR^{6e}R^{6f}$、-$NR^{6e}R^{6f}$、-$NR^{6e}COR^{6f}$或-$NR^{6e}CO_2R^{6f}$;-C_{1-8}烷基、C_3-C_8环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6g}取代;

[0054] R^{6e}和R^{6f}各自独立地选自氢、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、C_3-C_{12}环烷基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;

[0055] R^{6d}和R^{6g}各自独立地选自卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

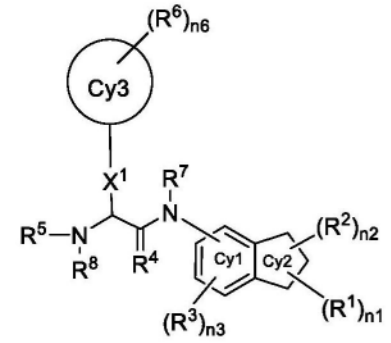
[0056] R^7和R^8各自独立地是氢;

[0057] R^9和R^{10}各自独立地选自H、卤素、-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基或5元至12元杂芳基,-C_{1-8}烷基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{9a}取代;并且

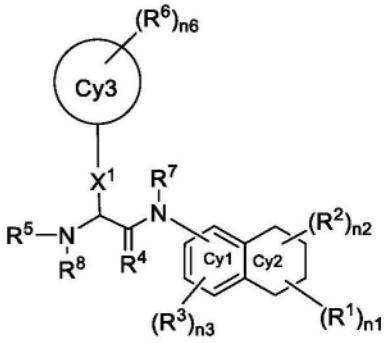
[0058] R^{9a}在每次出现时独立地是卤素、-OH、-C_{1-8}烷基、-C_{1-8}烷氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基。

[0059] 方面2.如方面1所述的化合物,其中所述化合物选自式(IIa)-(IIp):

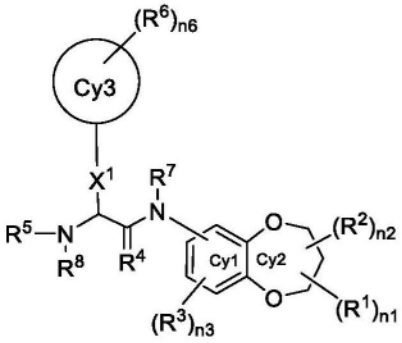
[0060]



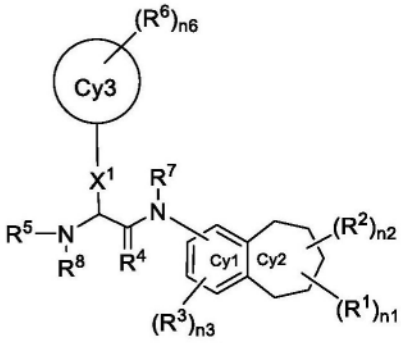
IIa



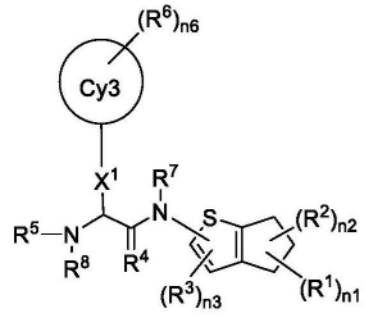
IIb



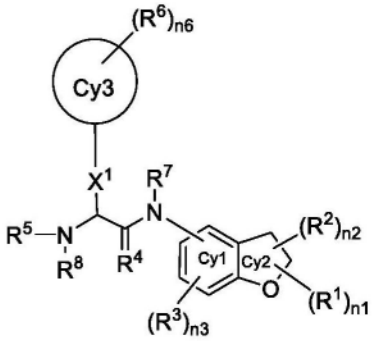
IIc



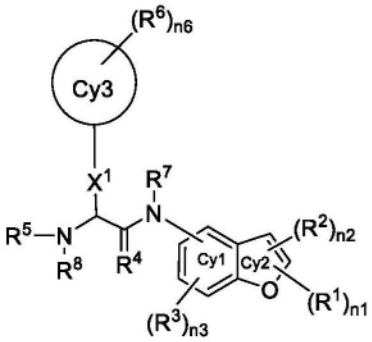
IId



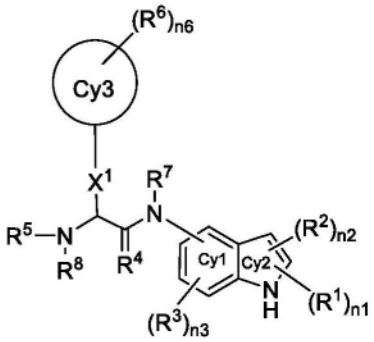
IIe



IIf

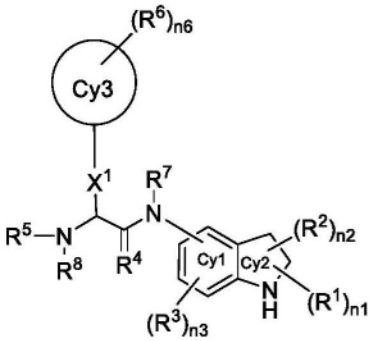


IIg

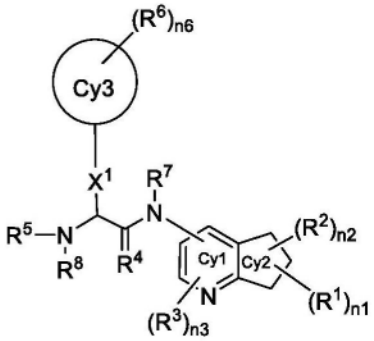


IIh

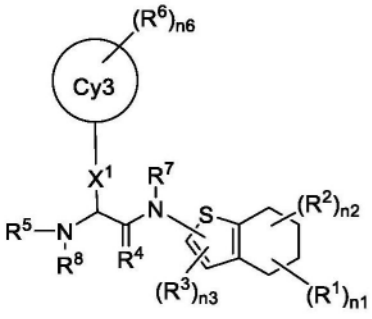
[0061]



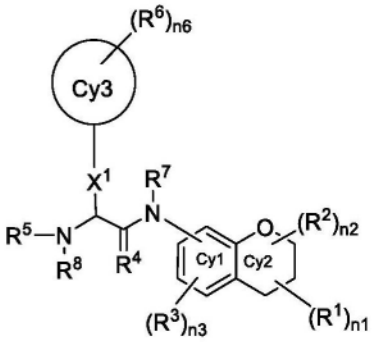
IIi



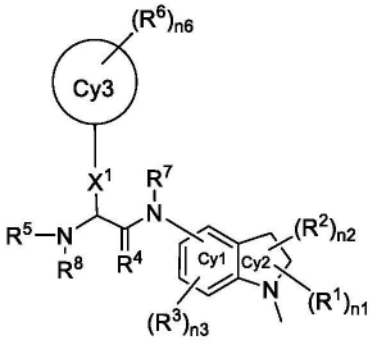
IIj



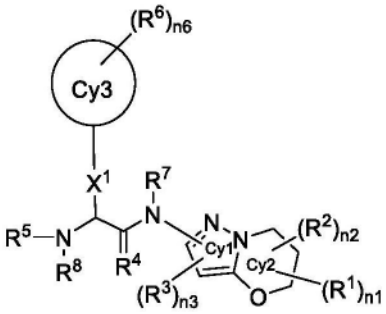
IIk



III

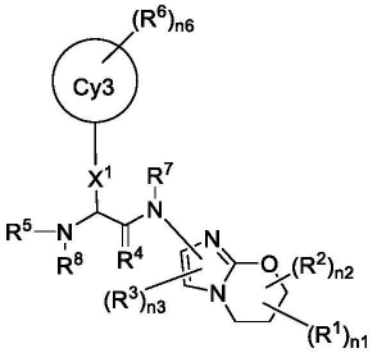


IIm

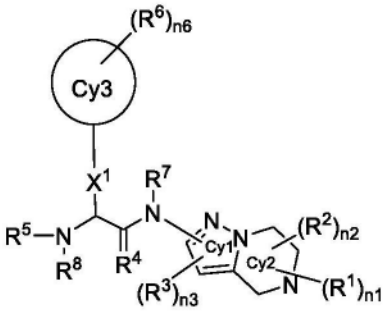


IIn

[0062]



IIo

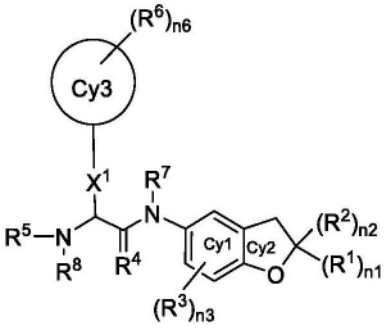


IIp

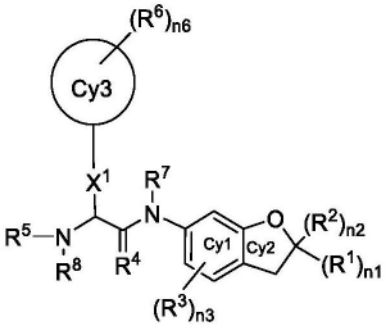
[0063] 其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy3、n1、n2、n3、n6和X^1如方面1中所定义。

[0064] 方面3.如方面1所述的化合物,其中所述化合物选自式(IIf1)-(IIf2):

[0065]



IIf1

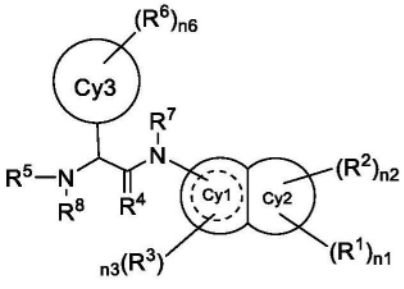


IIf2

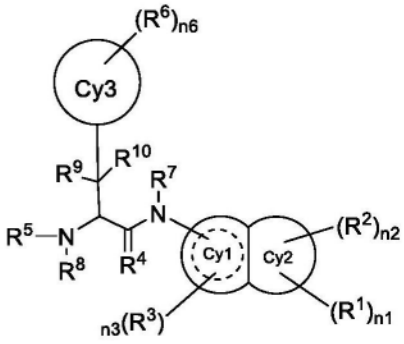
[0066] 其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy3、n1、n2、n3、n6和X^1如方面1中所定义。

[0067] 方面4.如方面1所述的化合物,其中所述化合物选自式(IIIa)-(IIIb):

[0068]



IIIa

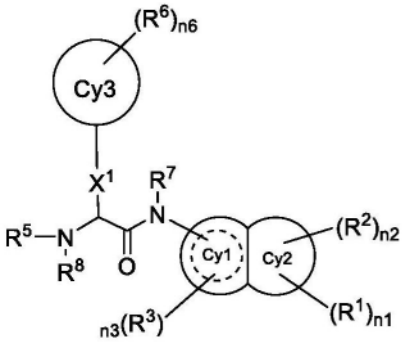


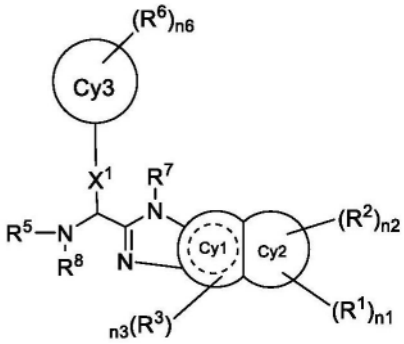
IIIb

[0069] 其中,R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n1、n2、n3、n6、R^9和R^{10}如方面1中所定

义。

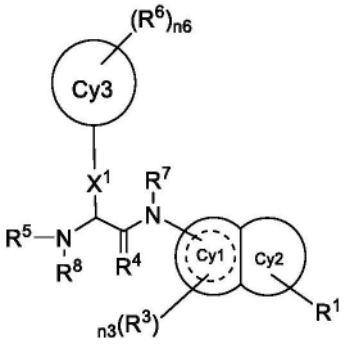
[0070] 方面5.如方面1所述的化合物,其中所述化合物选自式(IVa)-(IVb):

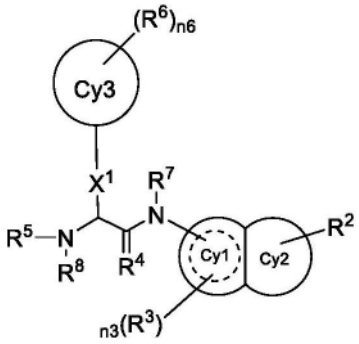
[0071] 
IVa


IVb

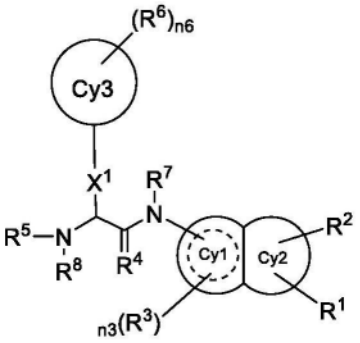
[0072] 其中,X^1、R^1、R^2、R^3、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n1、n2、n3、n6、R^9和R^{10}如方面1中所定义。

[0073] 方面6.如方面1所述的化合物,其中所述化合物选自式(Va)-(Vc):

[0074] 
Va

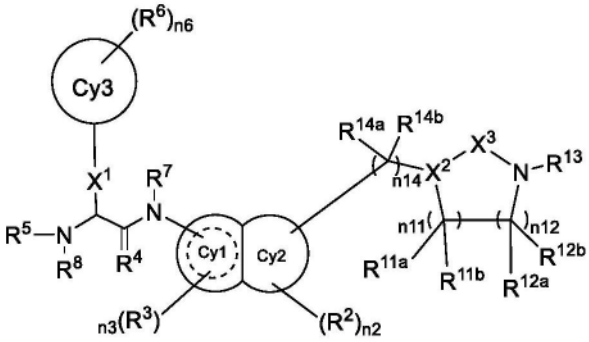

Vb

[0075]

[0076] 
Vc

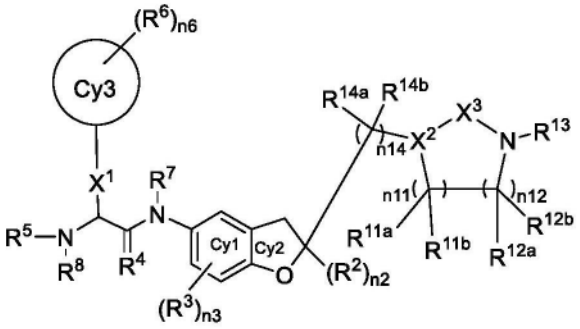
[0077] 其中,X^1、R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n3、n6、R^9和R^{10}如方面1中所定义。

[0078] 方面7.如方面1所述的化合物,其中所述化合物是VIa,

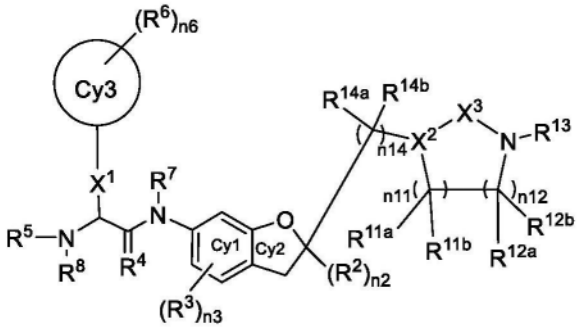
[0079] 

(VIa)

[0080] 优选地,所述化合物选自VIb和Vic

[0081] 

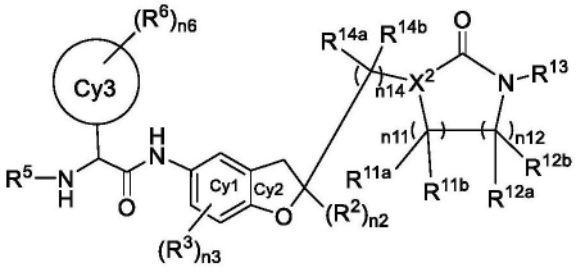
(VIb)

[0082] 

(VIc)

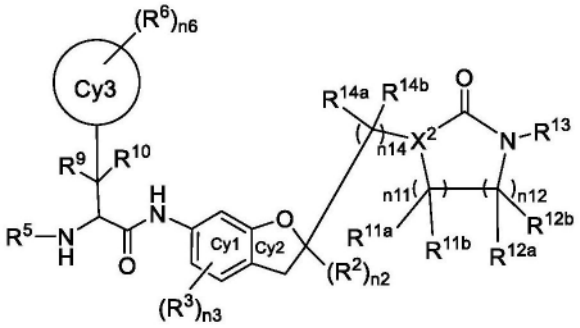
[0083] 其中,X^1、X^2、X^3、R^2、R^3、R^4、R^5、R^6、R^7、R^8、Cy1、Cy2、Cy3、n2、n3、n6、R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、R^{14a}、R^{14b}、n11、n12和n14如方面1中所定义。

[0084] 方面8.如方面1所述的化合物,其中所述化合物是VIIa或VIIb,



(VIIa)

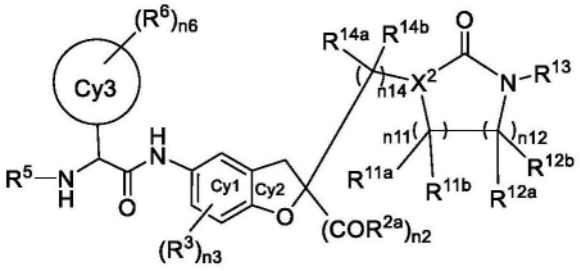
[0085]



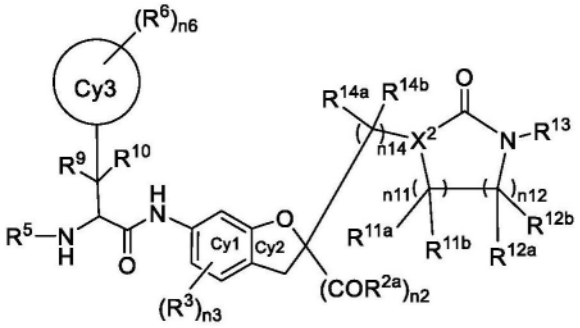
(VIIb);

[0086] 优选地,所述化合物选自VIIc、VIId、VIIe、VIIf、VIIg或VIIh,

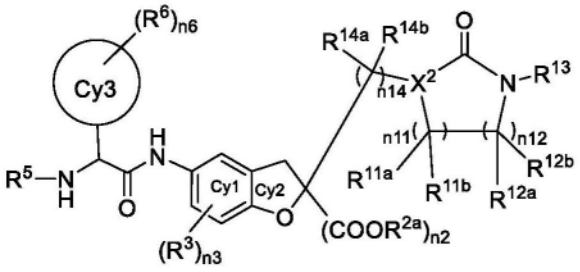
[0087]



VIIc

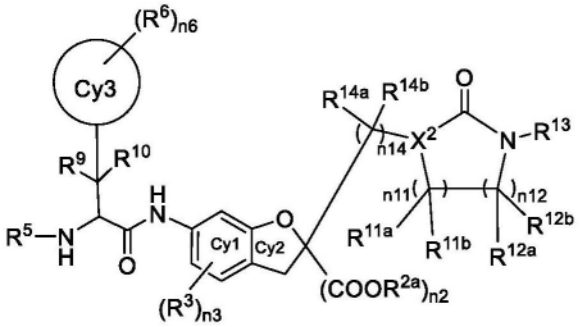


VIId

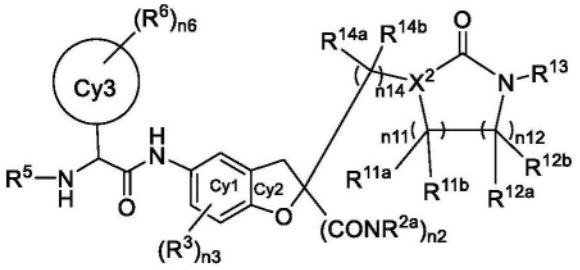


VIIe

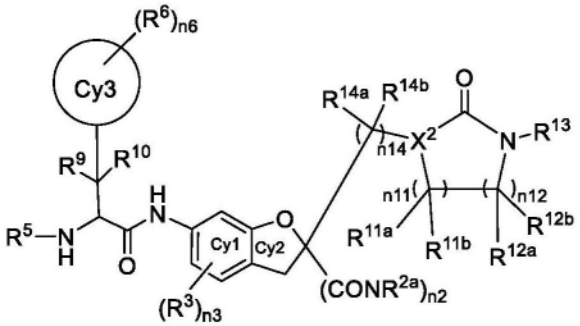
[0088]



VIIf



VIIg



VIIh;

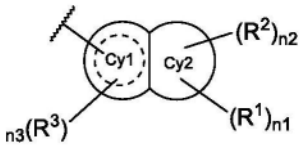
[0089] 其中,X^2、R^{2a}、R^3、R^5、R^6、R^9、R^{10}、Cy1、Cy2、Cy3、n2、n3、n6、R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、R^{14a}、R^{14b}、n11、n12和n14如方面1中所定义。

[0090] 方面9.如前述方面中任一项所述的化合物,其中Cy1是5元或6元芳族环,所述环包含0、1或2个独立地选自氮、氧或硫的杂原子;所述环任选地被0、1、2或3个取代基R^3取代;

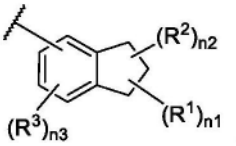
[0091] 优选地,Cy1是苯基、吡啶基、噻吩基、咪唑基、呋喃基或吡唑基;苯基、吡啶基、噻吩基、咪唑基、呋喃基或吡唑基中的每一者任选地被0、1或2个取代基R^3取代。

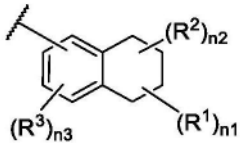
[0092] 方面10.如前述方面中任一项所述的化合物,其中Cy2是4元、5元、6元、7元或8元饱和或者部分或完全不饱和的环,所述环包含0、1、2或3个独立选自氮或氧的杂原子;所述环被至少一个取代基R^1和/或R^2取代;

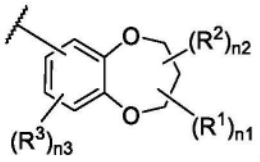
[0093] 优选地,Cy2是5元、6元或7元饱和或者部分或完全不饱和的环,所述环包含0、1或2个独立选自氮或氧的杂原子;所述环被至少一个取代基R^1和/或R^2取代。

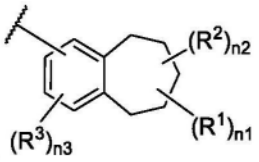
[0094] 方面11.如前述方面中任一项所述的化合物,其中 

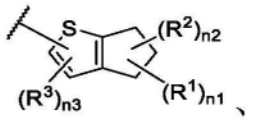
部分选自:

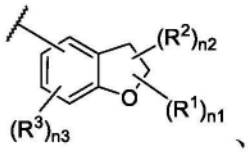


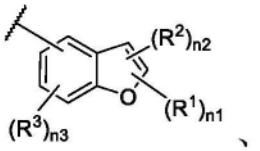
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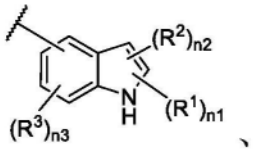
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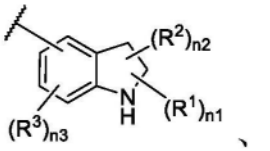
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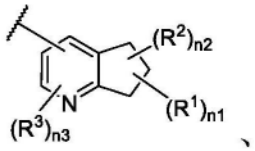
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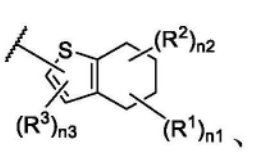
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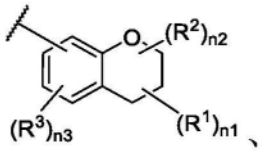
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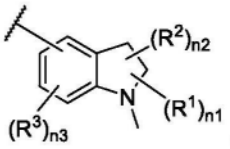
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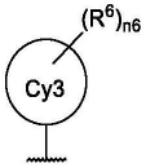
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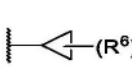
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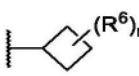
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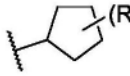
[0095] 方面12.如前述方面中任一项所述的化合物,其中Cy3是3元、4元、5元、6元、7元、8元、9元、10元、11元或12元饱和或者部分或完全不饱和的环,所述环包含0、1、2或3个独立选自氮、氧或任选氧化的硫的杂原子;所述环任选地被0、1、2、3、4或5个取代基R^6取代;

[0096] 优选地,Cy3是3元、4元、5元、6元、7元、8元、9元、10元、11元或12元饱和或者部分或完全不饱和的环,所述环是包含0、1、2或3个独立选自氮、氧或任选氧化的硫的杂原子的单环、双环或三环;所述环任选地被0、1、2、3、4或5个取代基R^6取代;

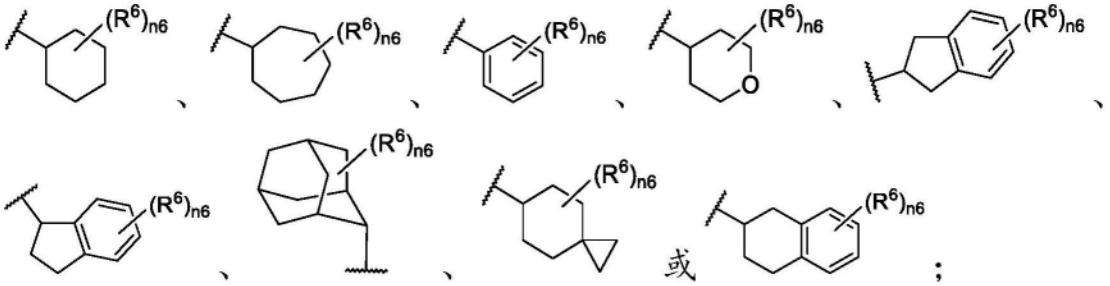
[0097] 更优选地, 

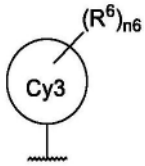
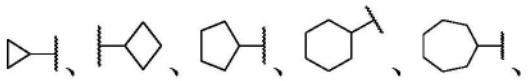
部分是 

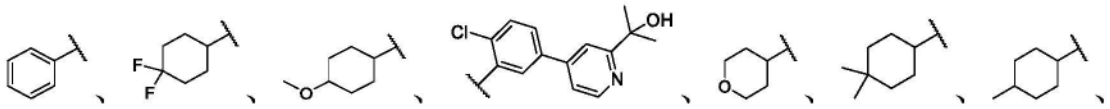
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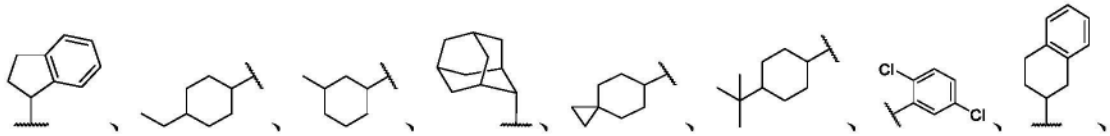
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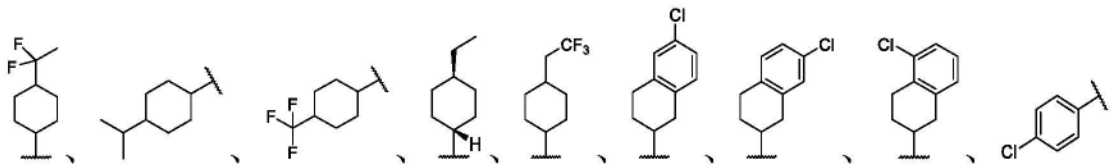
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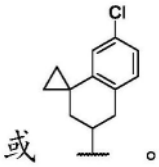


[0098] 甚至更优选地，  部分是 

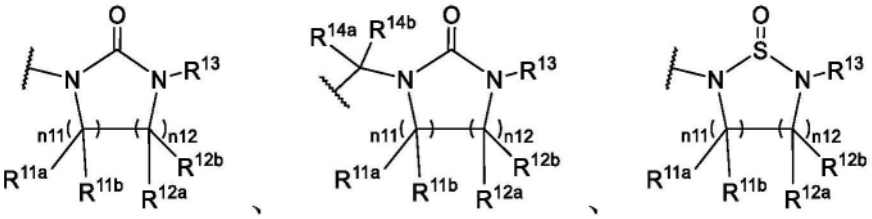


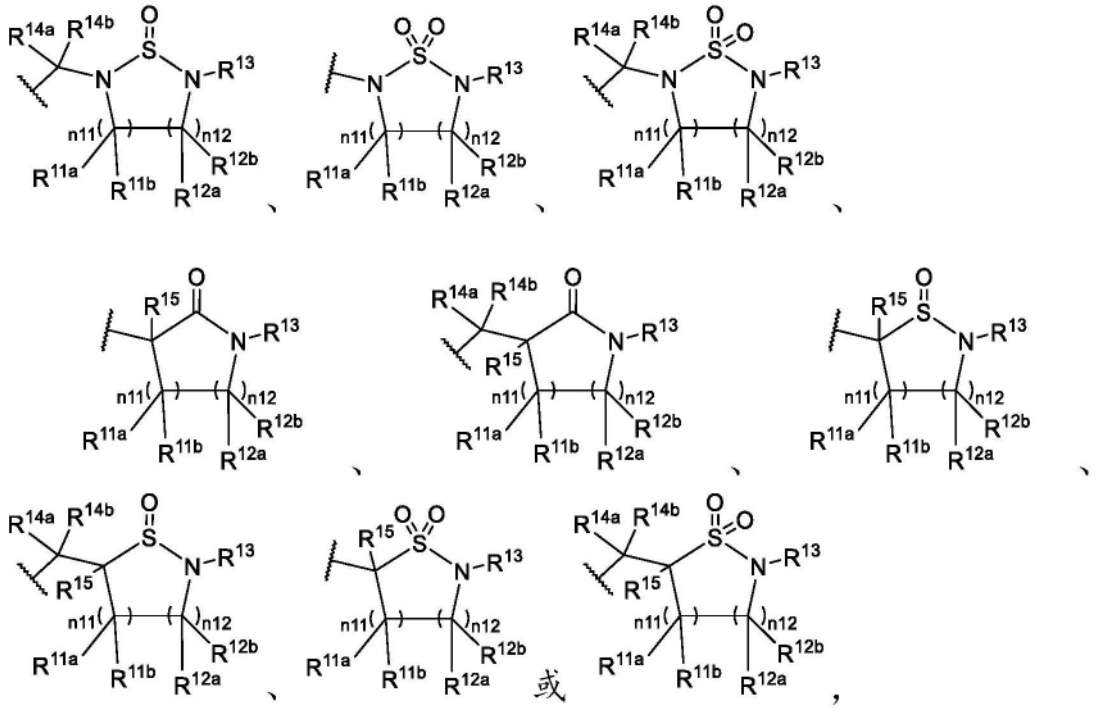






[0100] 方面13.如前述方面中任一项所述的化合物，其中R^1独立地选自H、





[0101] 其中R^{11a}、R^{11b}、R^{12a}、R^{12b}、R^{13}、n11和n12如方面1中所定义。

[0102] 方面14.如前述方面中任一项所述的化合物,其中R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-CN、$-OR^{15a}$、$-NR^{15a}R^{15b}$或$-NR^{15a}COR^{15b}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基和3元至8元杂环基中的每一者任选地被至少一个取代基R^{15c}取代;

[0103] R^{15a}和R^{15b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、$-C_{1-8}$卤代烷基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{15d}取代;

[0104] R^{15c}和R^{15d}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、$-C_{1-8}$卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、$-C_3$-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基。

[0105] 方面15.如前述方面中任一项所述的化合物,其中R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-CN、-OH、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基;

[0106] 优选地,R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基;

[0107] 更优选地,R^{15}选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛

基;

[0108] 甚至更优选地,R^{15}选自氢。

[0109] 方面16.如前述方面中任一项所述的化合物,其中R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基和吡嗪基中的每一者任选地被至少一个取代基R^{11e}取代;

[0110] R^{11e}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、

二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、氧代基(=O)、-OR^{11g}、硫代基(=S)、-SR^{11g}、-CN、-SO_2R^{11g}、-$SO_2NR^{11g}R^{11h}$、-COR^{11g}、-CO_2R^{11h}、-$CONR^{11g}R^{11h}$、-$NR^{11g}R^{11h}$、-$NR^{11g}COR^{11h}$、-$NR^{11g}CO_2R^{11h}$或-$NR^{11g}SO_2R^{11h}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、叶丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基和吡嗪基中的每一者任选地被至少一个取代基R^{11i}取代;

[0111] R^{11c}、R^{11d}、R^{11g}和R^{11h}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基和5元至12元杂芳基中的每一者任选地被至少一个取代基R^{11j}取代;

[0112] R^{11i}和R^{11j}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、叶丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、

丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基中的每一者任选地被至少一个取代基-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基取代。

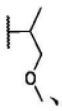
[0113] 方面17.如前述方面中任一项所述的化合物,其中R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、吖

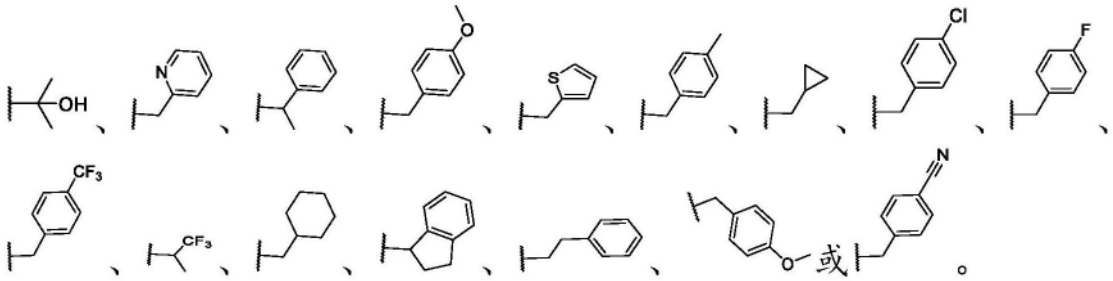
丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基和吡嗪基中的每一者任选地被至少一个取代基R^{11e}取代；

[0114] R^{11e}在每次出现时独立地是-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、丁-2-烯-1-基、丁-1-烯-1-基、戊-4-烯-1-基、戊-3-烯-1-基、戊-2-烯-1-基、戊-1-烯-1-基、己-5-烯-1-基、己-4-烯-1-基、己-3-烯-1-基、己-2-烯-1-基、己-1-烯-1-基、庚-6-烯-基、庚-5-烯-基、庚-4-烯-基、庚-3-烯-基、庚-2-烯-基、庚-1-烯-基、辛-7-烯-基、辛-6-烯-基、辛-5-烯-基、辛-4-烯-基、辛-3-烯-基、辛-2-烯-基、辛-1-烯-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、戊-4-炔-1-基、戊-3-炔-1-基、戊-2-炔-1-基、戊-1-炔-1-基、己-5-炔-1-基、己-4-炔-1-基、己-3-炔-1-基、己-2-炔-1-基、己-1-炔-1-基、庚-6-炔-基、庚-5-炔-基、庚-4-炔-基、庚-3-炔-基、庚-2-炔-基、庚-1-炔-基、辛-7-炔-基、辛-6-炔-基、辛-5-炔-基、辛-4-炔-基、辛-3-炔-基、辛-2-炔-基、辛-1-炔-基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、叶丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、$-OR^{11g}$或-CN；

[0115] R^{11g}独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基；

[0116] 优选地，R^{11a}、R^{11b}、R^{12a}和R^{12b}各自独立地选自H、$-CH_3$、$-CF_3$、$-CH_2CH_3$、$-CH_2CF_3$、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、环丙基、环丁基、环戊基、环己基、环庚基、吡咯烷基、四氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、苄基、乙烯基、丙烯基、烯丙基、丁-3-烯-1-基、乙炔基、丙-2-炔-1-基、丙-1-炔-1-基、丁-3-炔-1-基、丁-2-炔-1-基、丁-1-炔-1-基、





[0117] 方面18.如前述方面中任一项所述的化合物，其中(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元不饱和或饱和的环，所述环包含0、1、2或3个独立地选自氮、氧或硫的杂原子；所述环任选地被至少一个取代基R^{11f}取代；

[0118] R^{11f}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、$-C_{2-8}$烯基、$-C_{2-8}$炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基、5元至12元杂芳基、氧代基(=O)、$-OR^{11g}$、硫代基(=S)、$-SR^{11g}$、-CN、$-SO_2R^{11g}$、$-SO_2NR^{11g}R^{11h}$、$-COR^{11g}$、$-CO_2R^{11h}$、$-CONR^{11g}R^{11h}$、$-NR^{11g}R^{11h}$、$-NR^{11g}COR^{11h}$、$-NR^{11g}CO_2R^{11h}$或$-NR^{11g}SO_2R^{11h}$；

[0119] R^{11g}和R^{11h}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、C_{1-8}烷氧基-C_{1-8}烷基-、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、C_6-C_{12}芳基或5元至12元杂芳基;

[0120] R^{11i}在每次出现时独立地是-F、-Cl、-Br、-I、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基;

[0121] 优选地,(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元不饱和或饱和的环;

[0122] 更优选地,(R^{11a}和R^{11b})、(R^{12a}和R^{12b})、(R^{11a}和R^{12a})、(R^{11a}和R^{12b})、(R^{11b}和R^{12a})或(R^{11b}和R^{12b})与它们所连接的碳原子一起形成3元、4元、5元、6元或8元饱和的环。

[0123] 方面19.如前述方面中任一项所述的化合物,其中R^{13}、R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基中的每一者任选地被至少一个取代基R^{13a}取代;

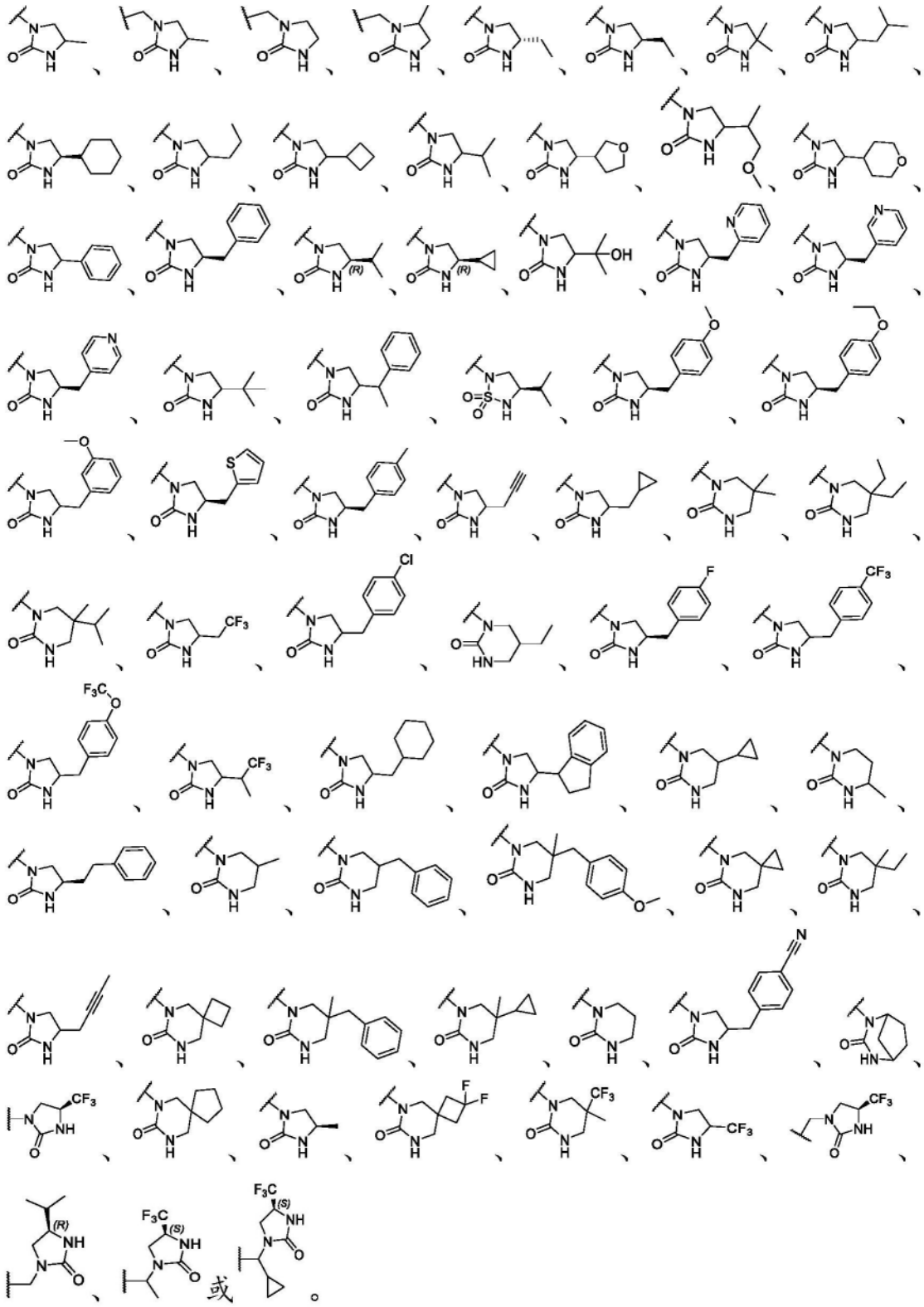
[0124] R^{13a}在每次出现时独立地是卤素、-OH、-CN、氧代基、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_{1-8}卤代烷基、-C_{1-8}烷氧基、-C_{2-8}烯基、-C_{2-8}炔基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基;

[0125] 优选地,R^{13}、R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;

[0126] 更优选地,R^{13}是氢、甲基、乙基、丙基或丁基;R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或3元至8元杂环基;

[0127] 甚至更优选地,R^{13}是氢;R^{14a}和R^{14b}各自独立地选自氢、甲基、乙基、丙基、丁基、环丙基、环丁基、环戊基。

[0128] 方面20.如前述方面中任一项所述的化合物,其中R^1选自



[0130] 方面21.如前述方面中任一项所述的化合物,其中R^2独立地选自H、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-CN、-COR^{2a}、-CO_2R^{2a}、-$CONR^{2a}R^{2b}$、-$NR^{2a}R^{2b}$、-$NR^{2a}COR^{2b}$,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-

C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基和咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2c}取代;

[0131] R^{2a}和R^{2b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2d}取代;或

[0132] R^{2a}和R^{2b}与它们所连接的碳原子一起形成3元、4元、5元、6元、7元或8元不饱和或饱和的环,所述环包含0、1、2、3个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

[0133] R^{2c}和R^{2d}在每次出现时各自独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、氧代基(=O)、-OR^{2e}、-SR^{2e}、-CN、-COR^{2e}、-CO_2R^{2e}、-$CONR^{2e}R^{2f}$、-$NR^{2e}R^{2f}$、-$NR^{2e}COR^{2f}$或-$NR^{2e}CO_2R^{2f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2g}取代;

[0134] R^{2e}和R^{2f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{2h}取代;

[0135] R^{2g}和R^{2h}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{1-8}卤代烷基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-C_3-C_8卤代环烷基、3元至8元杂环基、苯基或5元至12元杂芳基。

[0136] 方面22.如前述方面中任一项所述的化合物,其中R^2独立地选自H、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-CN、-COR^{2a}、-CO_2R^{2a}或-$CONR^{2a}R^{2b}$,甲基、乙基、丙基、丁基、戊基、己基、环丙

基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2c}取代;

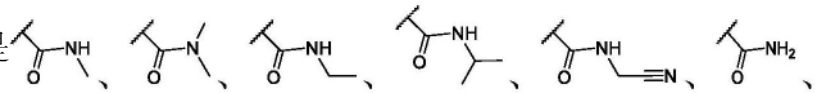
[0137] R^{2a}和R^{2b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、吖丙啶基、氮杂环丁烷基、吡咯烷基、二氢吡咯烷基、四氢呋喃基、二氢呋喃基、噁唑烷基、哌啶基、哌嗪基、吗啉基、四氢吡喃基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2d}取代;或

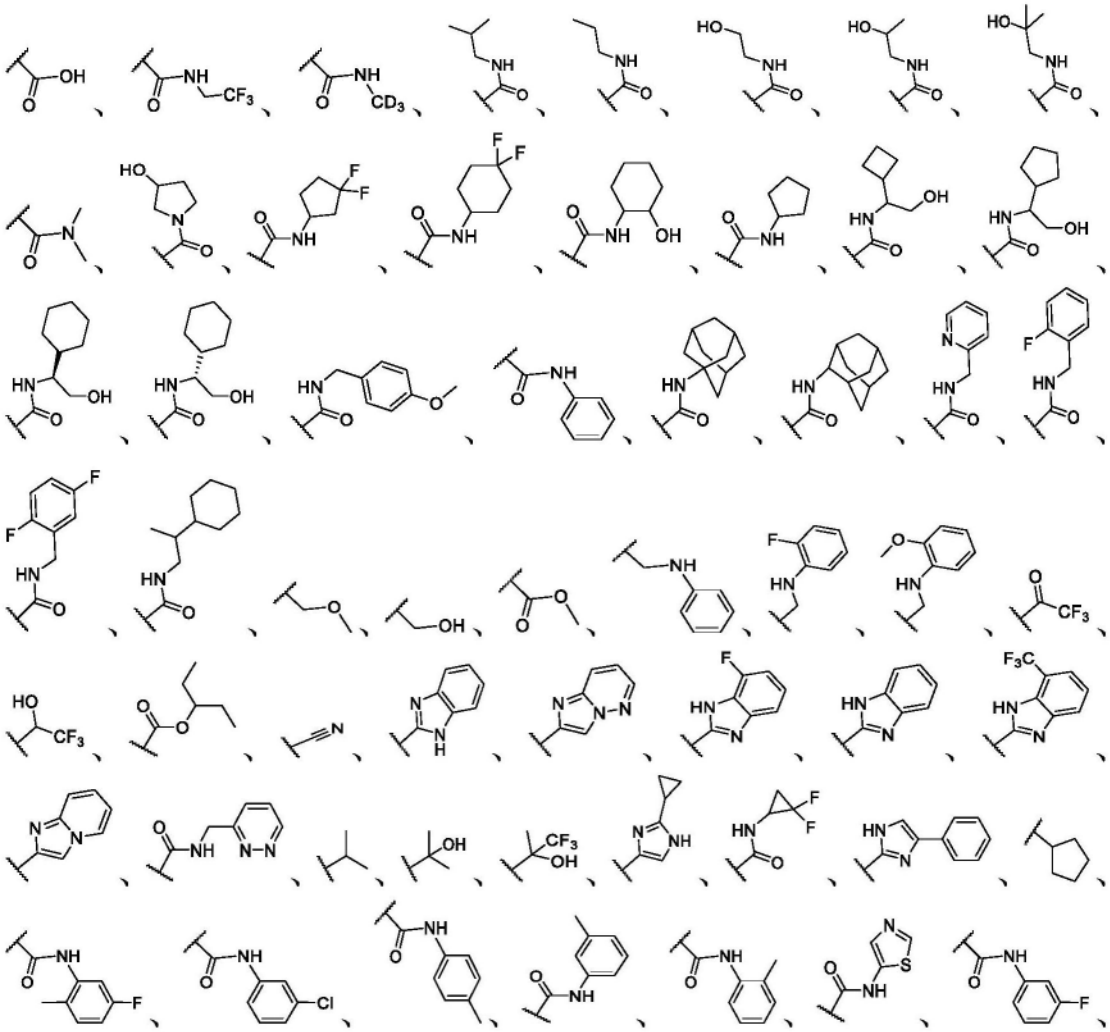
[0138] R^{2a}和R^{2b}与它们所连接的碳原子一起形成3元、4元、5元或6元不饱和或饱和的环,所述环包含0或1个独立选自氮、氧或硫的杂原子;所述环任选地被至少一个取代基R^{2d}取代;

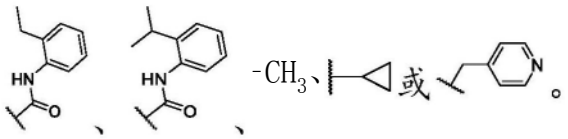
[0139] R^{2c}和R^{2d}在每次出现时各自独立地是氢(H或D)、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、$-OR^{2e}$、-CN或$-NR^{2e}R^{2f}$;甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{2g}取代;

[0140] R^{2e}和R^{2f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基、环己基或苯基;甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基、环己基或苯基中的每一者任选地被至少一个取代基R^{2h}取代;

[0141] R^{2g}和R^{2h}在每次出现时各自独立地是-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、环丙基、环丁基、环戊基或环己基;

[0142] 优选地,R^{2}是 

[0143] 

[0144] 

[0145] 方面23.如前述方面中任一项所述的化合物,其中R^3独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或-CN,其中甲基、

乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基中的每一者任选地被至少一个选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代；

[0146] 优选地，R^3独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基或-CN；

[0147] 更优选地，R^3独立地选自氢、-F、-Cl、-Br、-I。

[0148] 方面24.如前述方面中任一项所述的化合物，其中R^4是氧代基(=O)。

[0149] 方面25.如前述方面中任一项所述的化合物，其中R^3和R^4与它们所连接的碳原子一起形成5元至6元芳族环，所述环包含1、2或3个独立选自氮、氧或硫的杂原子；所述环任选地被至少一个取代基R^{3a}取代；

[0150] R^{3a}独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、-CN，其中甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基中的每一者任选地被至少一个选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、-C_6-C_{12}芳基或5元至12元杂芳基的取代基取代。

[0151] 方面26.如前述方面中任一项所述的化合物，其中R^5是苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、-COR^{5a}、-CO_2R^{5a}或-CONR^{5a}R^{5b}，其中苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5c}取代；

[0152] R^{5a}和R^{5b}各自独立地选自甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基；甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5d}取代；或

[0153] R^{5a}和R^{5b}与它们所连接的氮原子一起形成3元、4元、5元、6元、7元或8元不饱和或饱和的环，所述环包含0、1、2或3个独立选自氮、氧或硫的杂原子；所述环任选地被至少一个取代基R^{5d}取代；

[0154] R^{5c}和R^{5d}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊

基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、氧代基(=O)、-OR^{5e}、-SR^{5e}、-CN、-COR^{5e}、-CO_2R^{5e}、-$CONR^{5e}R^{5f}$、-$NR^{5e}R^{5f}$、-$NR^{5e}COR^{5f}$或-$NR^{5e}CO_2R^{5f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5g}取代;

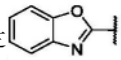
[0155] R^{5e}和R^{5f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5h}取代;

[0156] R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基。

[0157] 方面27.如前述方面中任一项所述的化合物,其中R^5是吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基,其中吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5c}取代;

[0158] R^{5c}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、环丙基、环丁基、环戊基、环己基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基;

[0159] 优选地,R^5是苯并噁唑基;

[0160] 更优选地,R^5是  。

[0161] 方面28.如前述方面中任一项所述的化合物,其中R^5是-COR^{5a}、-CO_2R^{5a}或-$CONR^{5a}R^{5b}$;

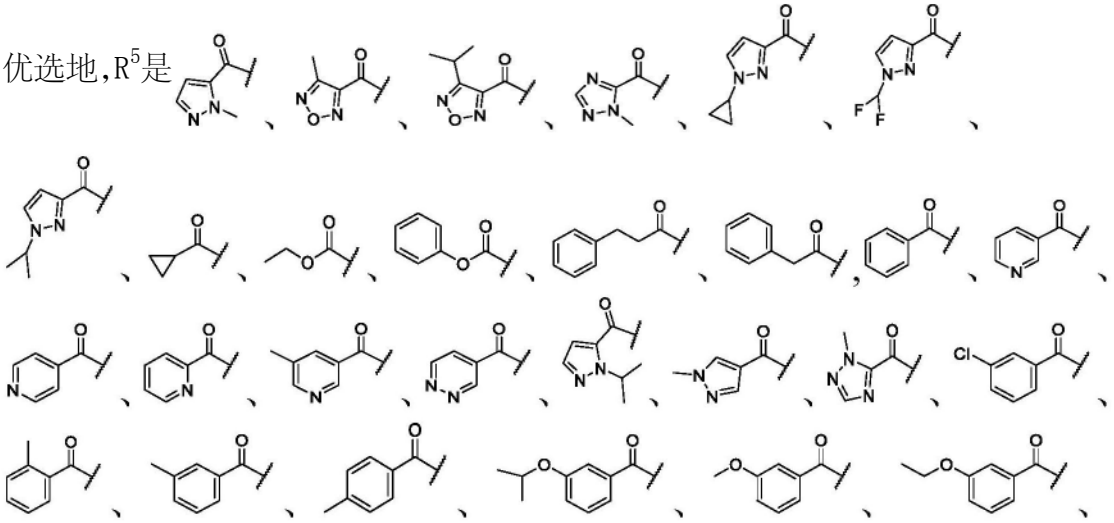
[0162] 其中R^{5a}和R^{5b}各自独立地选自甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、噁二唑基、三唑基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃

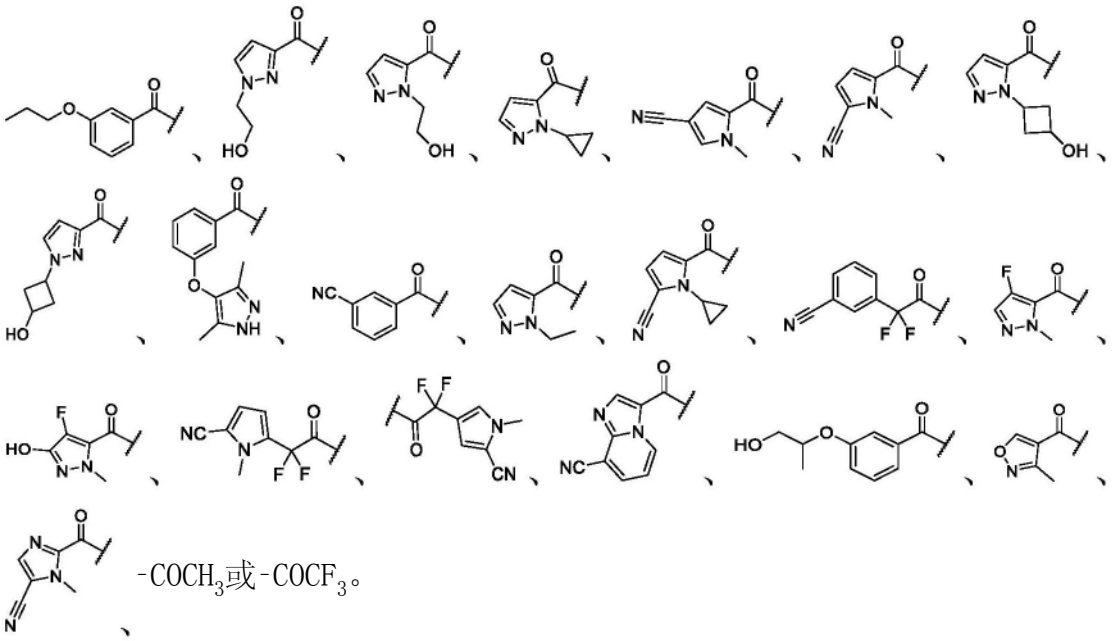
基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5d}取代；

[0163] R^{5d}在每次出现时独立地选自氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基、咪唑并吡啶基、$-OR^{5e}$或-CN；甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5g}取代；

[0164] R^{5e}选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基；甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并噁唑基、苯并咪唑基、咪唑并哒嗪基或咪唑并吡啶基中的每一者任选地被至少一个取代基R^{5h}取代；

[0165] R^{5g}和R^{5h}各自独立地选自卤素、-OH、-CN、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基；

[0166] 优选地，R^5是 

[0167] 

[0168] 方面29.如前述方面中任一项所述的化合物,其中R^6是H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN、-OR^{6a}、-$NR^{6a}R^{6b}$、-COR^{6a}、-CO_2R^{6a}、-$CONR^{6a}R^{6b}$、-COR^{6a}或-$NR^{6a}COR^{6b}$,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基中的每一者任选地被至少一个取代基R^{6c}取代;

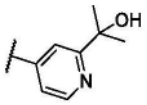
[0169] R^{6a}和R^{6b}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6d}取代;

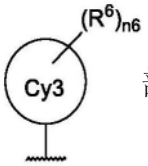
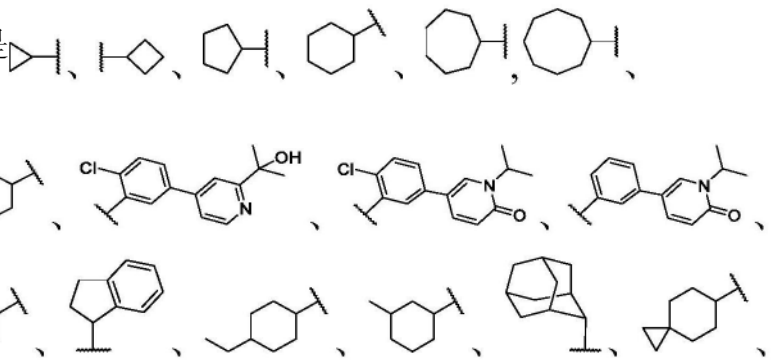
[0170] R^{6c}在每次出现时独立地是氢、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基3元至8元杂环基、苯基、5元至12元杂芳基、氧代基(=O)、-OR^{6e}、-SR^{6e}、-CN、-COR^{6e}、-CO_2R^{6e}、-$CONR^{6e}R^{6f}$、-$NR^{6e}R^{6f}$、-$NR^{6e}COR^{6f}$或-$NR^{6e}CO_2R^{6f}$;甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基、5元至12元杂芳基中的每一者任选地被至少一个取代基R^{6g}取代;

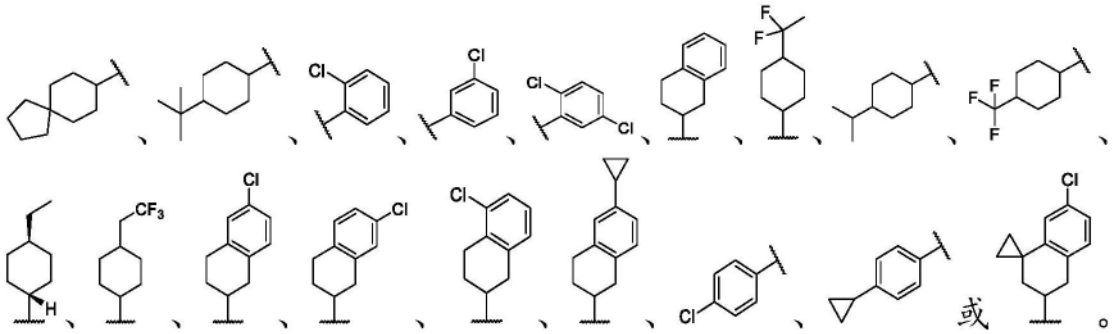
[0171] R^{6e}和R^{6f}各自独立地选自氢、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;

[0172] R^{6d}和R^{6g}各自独立地选自-F、-Cl、-Br、-I、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元

杂环基、苯基或5元至12元杂芳基。

[0173] 方面30.如前述方面中任一项所述的化合物,其中R^6是H、-F、-Cl、-Br、-I、甲基、-CF_3、乙基、-CH_2CF_3、-CF_2CH_3、丙基、丁基、戊基、己基、庚基、辛基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、吡咯基、吡唑基、咪唑基、噁唑基、呋喃基、噻吩基、噻唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、-CN、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、  ;

[0174] 优选地,  部分是 

[0175] 

[0176] 方面31.如前述方面中任一项所述的化合物,其中R^9和R^{10}各自独立地选自H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基,甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基、或5元至12元杂芳基中的每一者任选地被至少一个取代基R^{9a}取代;

[0177] R^{9a}在每次出现时独立地是卤素、-OH、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、甲氧基、乙氧基、丙氧基、丁氧基、戊氧基、己氧基、庚氧基、辛氧基、C_{1-8}烷氧基-C_{1-8}烷基-、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、3元至8元杂环基、苯基或5元至12元杂芳基;

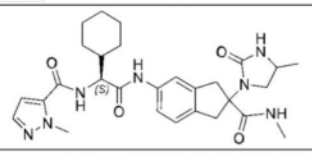
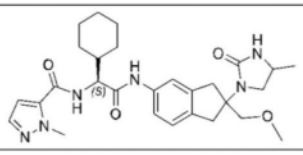
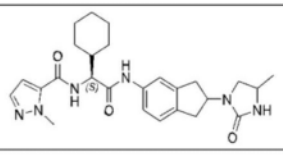
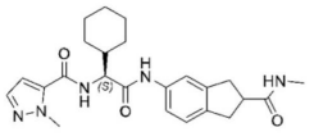
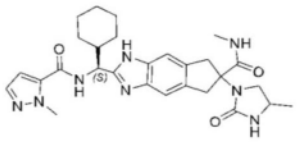
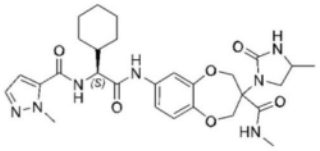
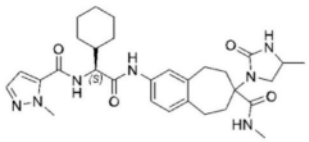
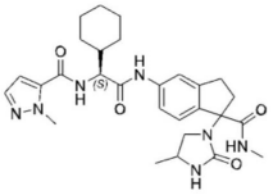
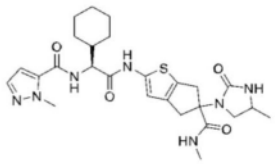
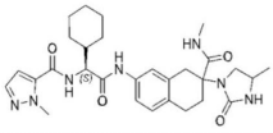
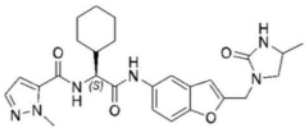
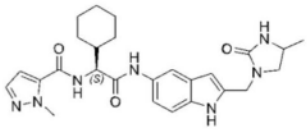
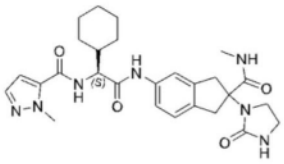
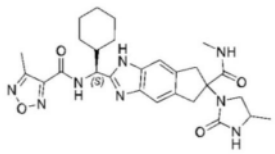
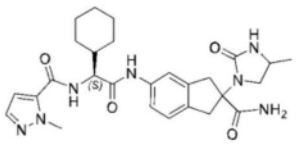
[0178] 优选地,R^9和R^{10}各自独立地选自H、-F、-Cl、-Br、-I、甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、-C_{2-8}烯基、-C_{2-8}炔基、环丙基、环丁基、环戊基、环己基、环庚基、环辛基、苯基或5元至12元杂芳基;

[0179] 更优选地,R^9和R^{10}各自独立地选自H、甲基、乙基、丙基、丁基、戊基、环丙基、环丁基、环戊基;

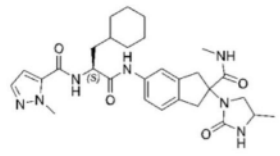
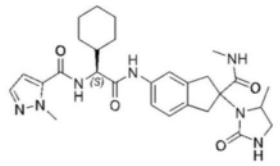
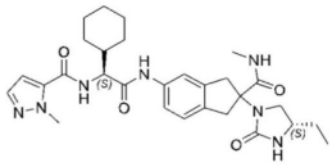
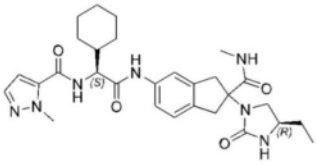
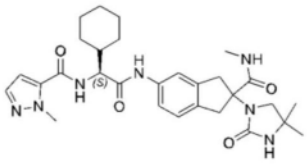
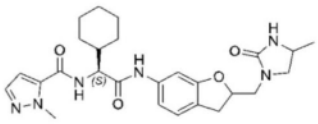
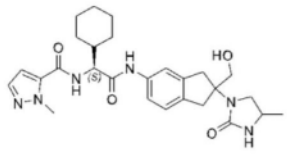
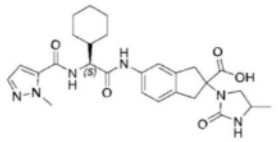
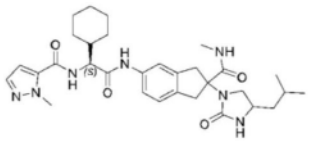
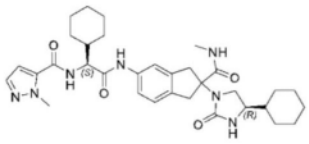
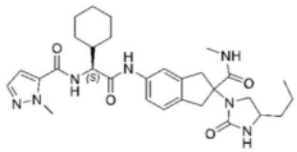
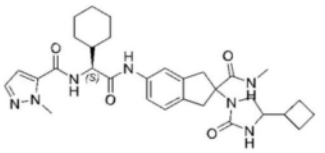
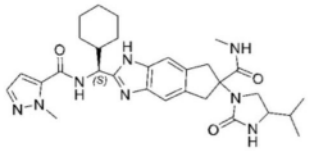
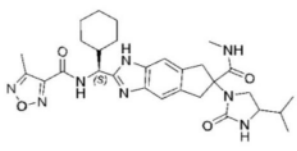
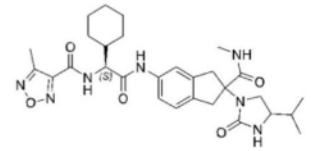
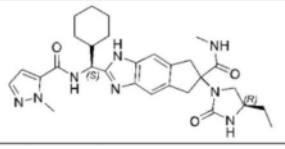
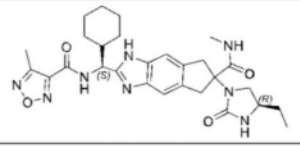
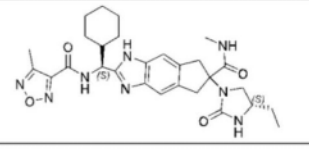
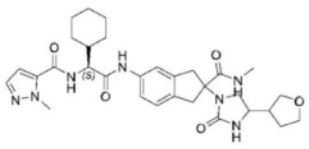
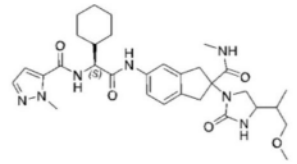
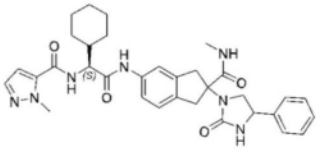
[0180] 更优选地,R^9和R^{10}各自独立地选自H、环丙基。

[0181] 方面32.如前述方面中任一项所述的化合物,其中所述化合物选自

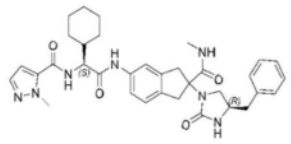
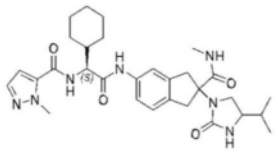
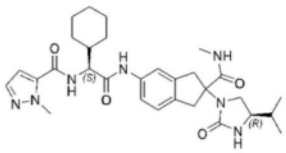
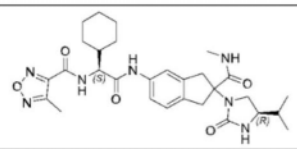
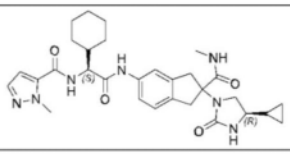
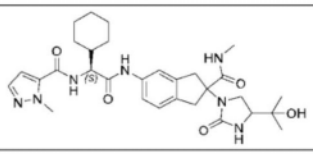
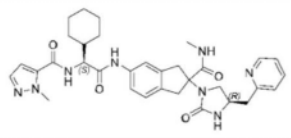
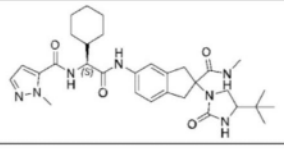
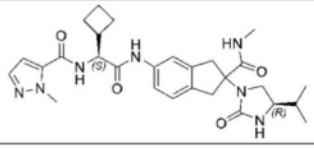
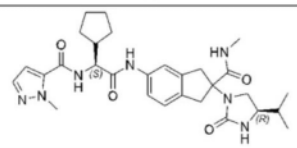
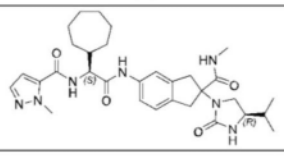
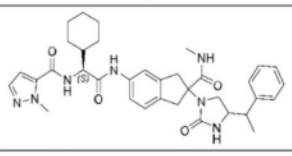
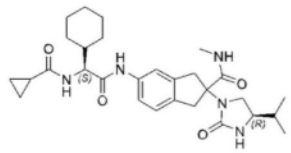
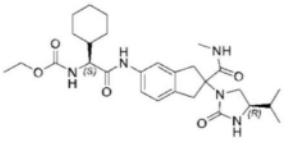
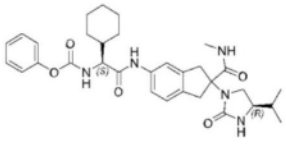
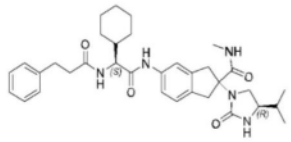
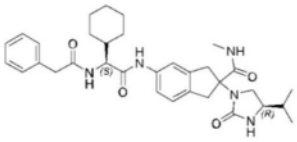
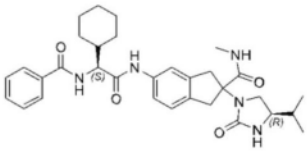
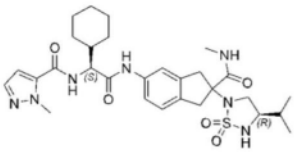
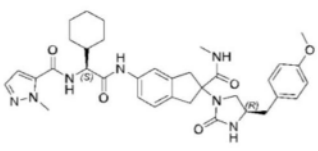
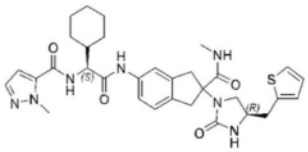
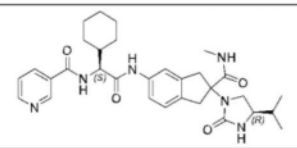
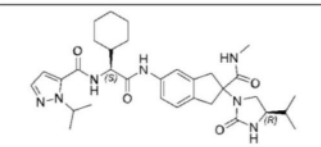
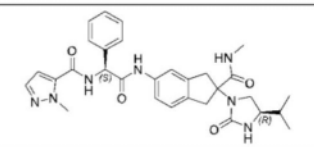
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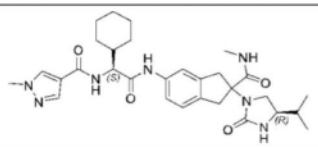
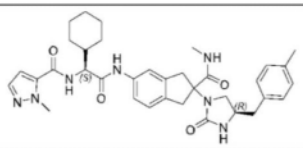
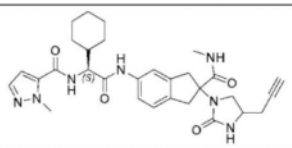
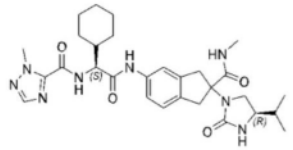
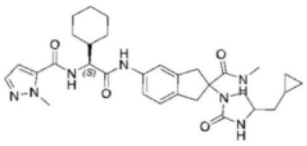
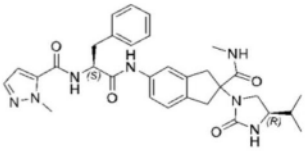
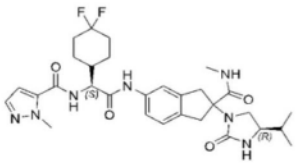
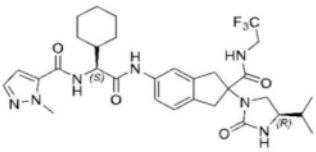
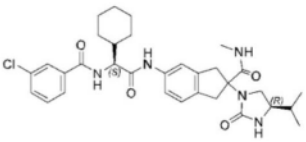
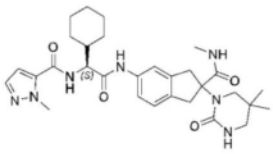
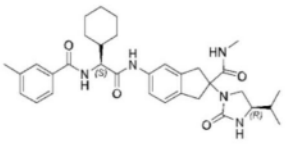
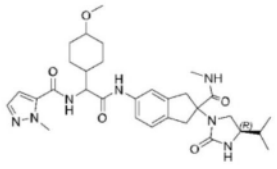
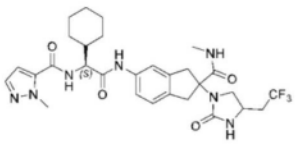
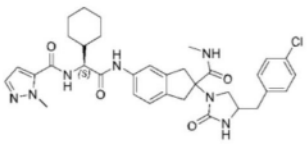
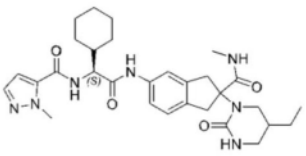
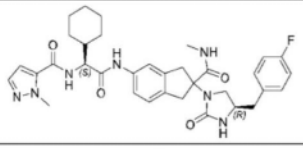
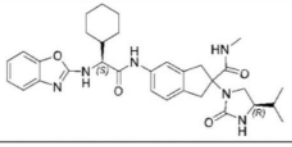
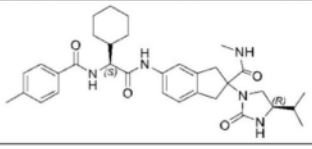
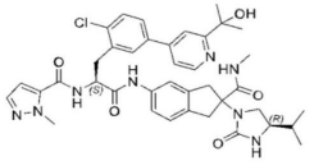
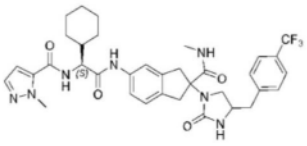
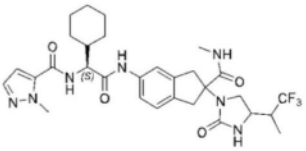
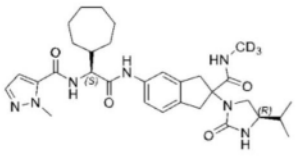
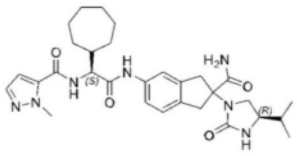
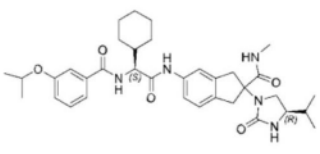
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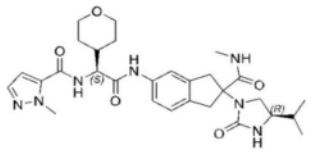
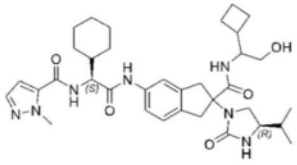
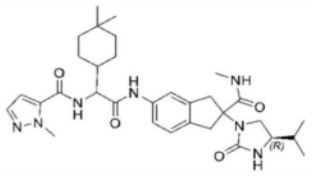
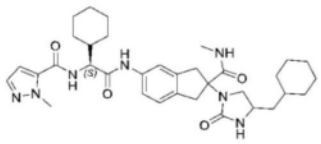
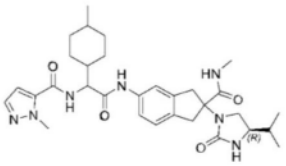
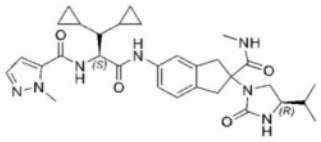
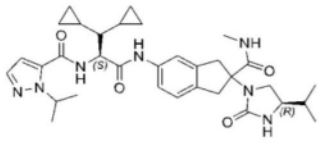
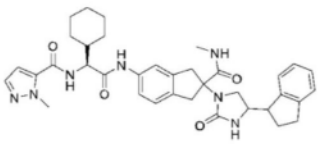
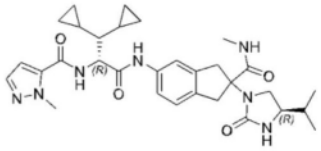
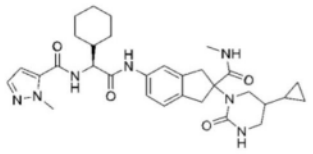
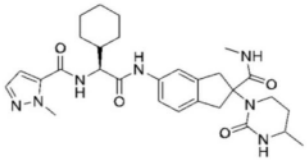
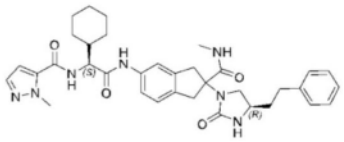
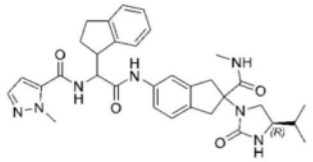
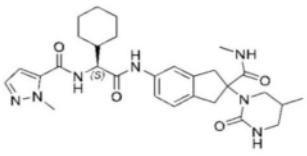
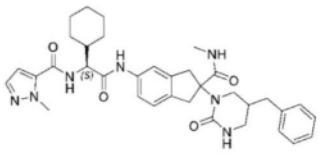
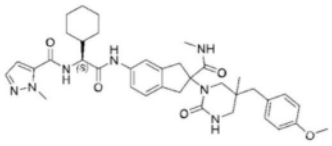
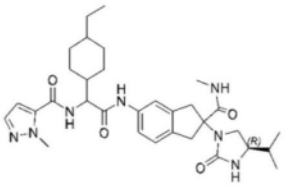
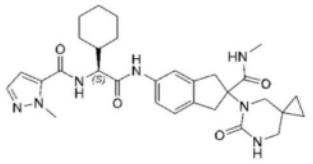
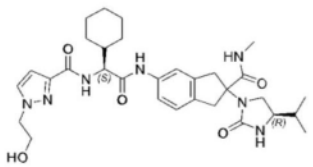
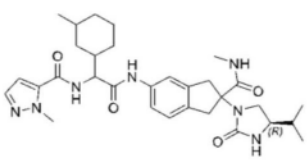
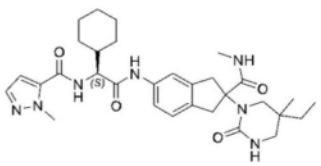
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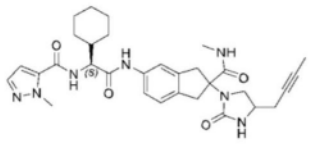
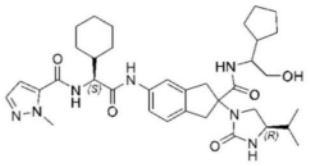
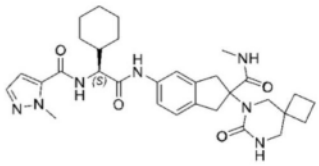
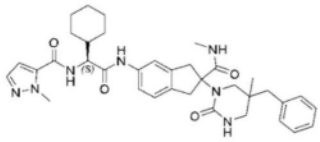
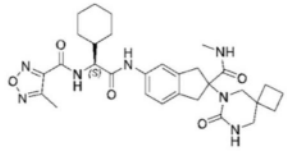
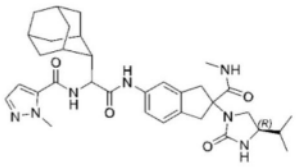
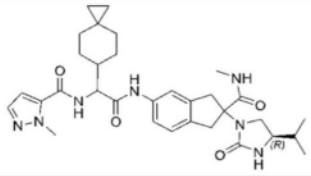
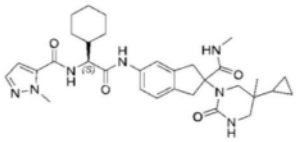
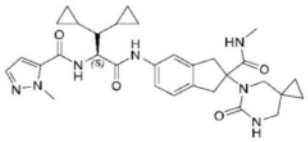
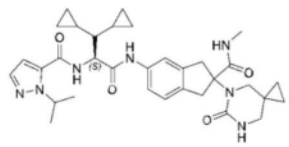
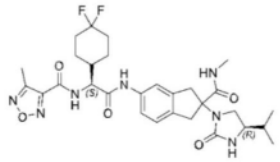
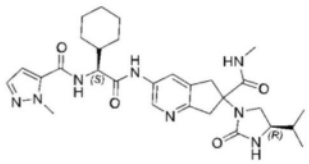
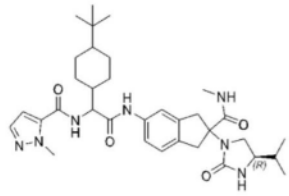
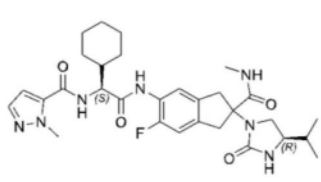
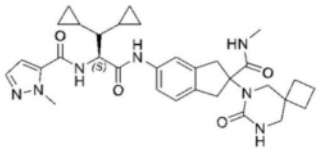
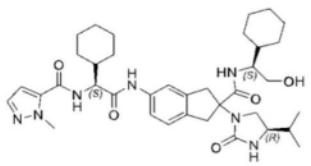
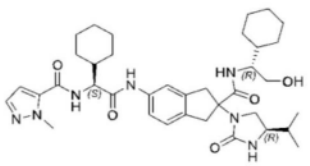
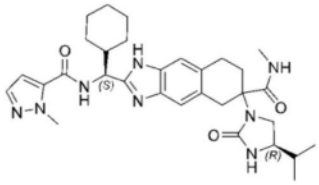
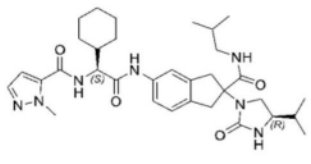
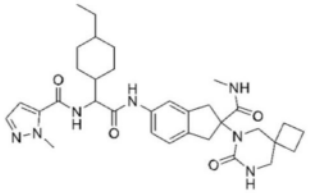
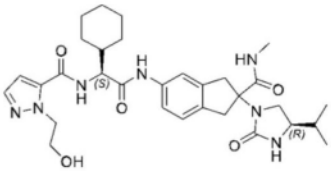
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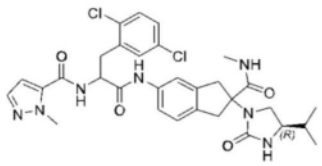
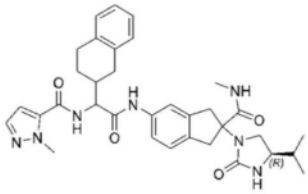
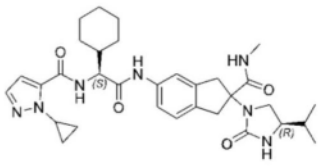
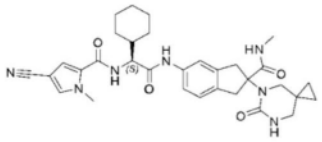
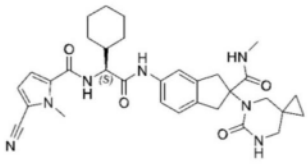
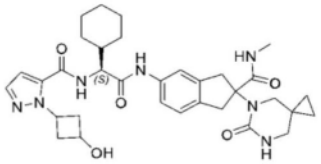
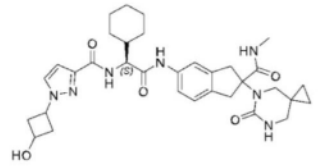
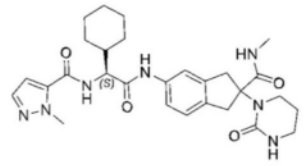
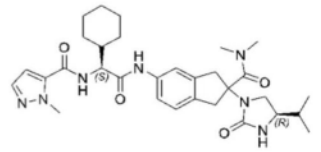
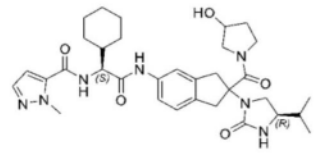
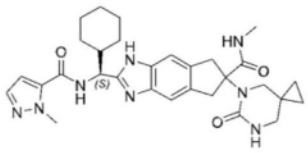
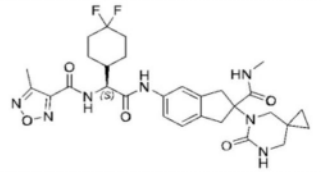
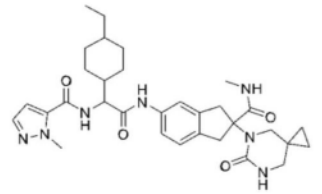
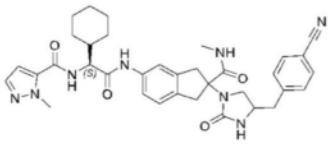
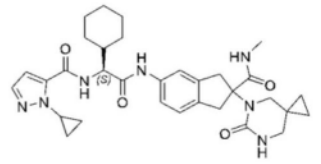
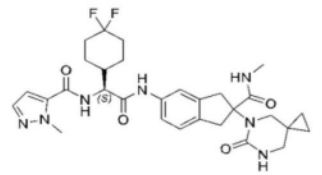
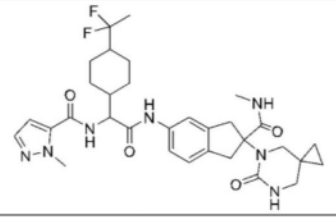
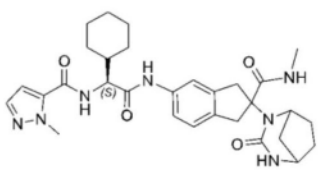
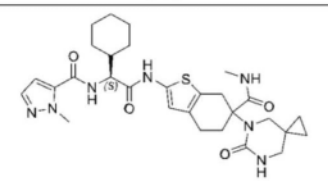
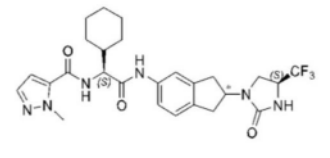
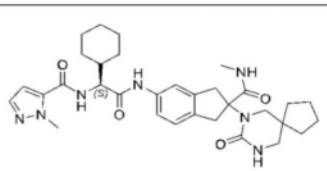
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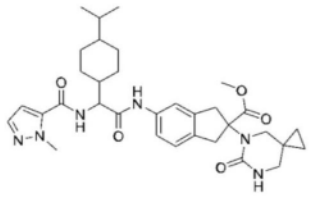
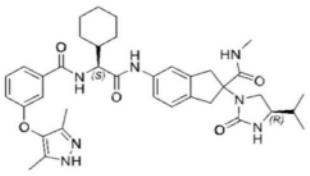
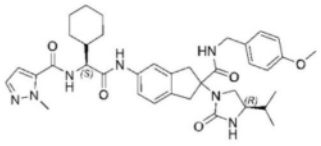
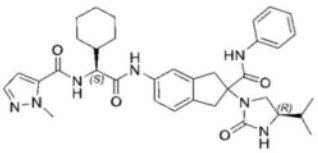
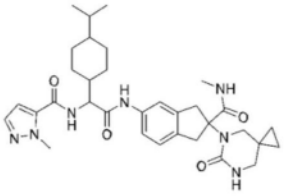
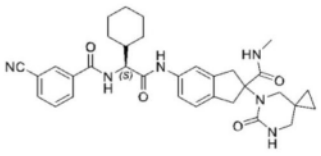
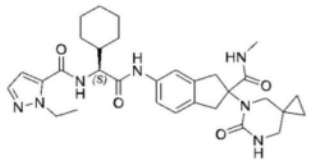
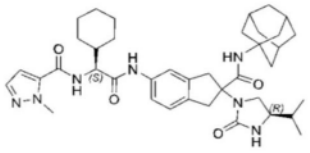
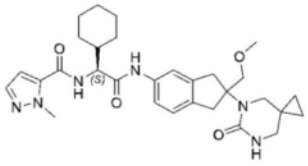
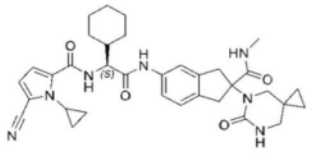
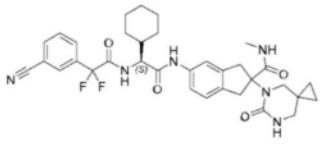
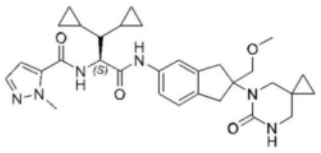
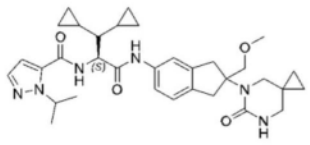
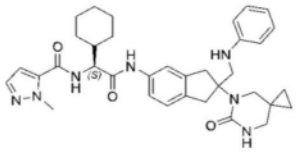
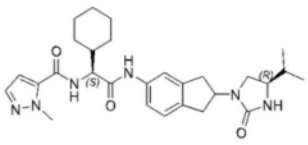
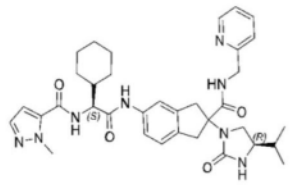
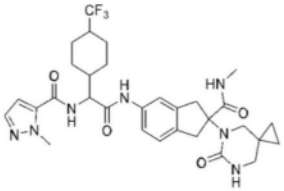
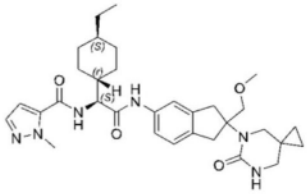
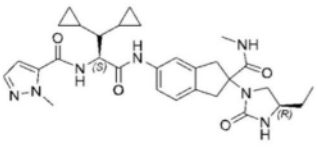
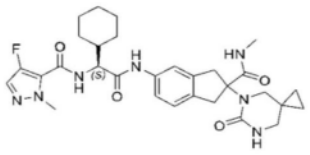
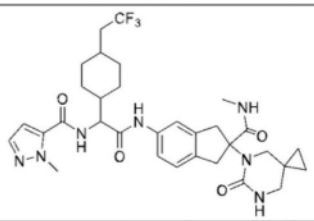
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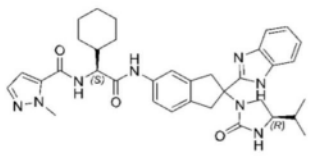
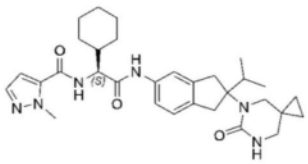
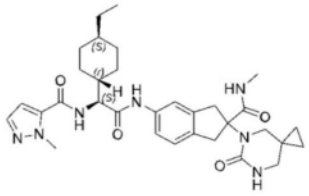
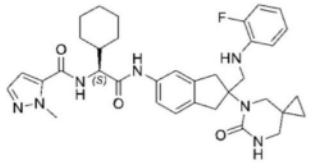
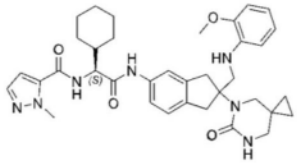
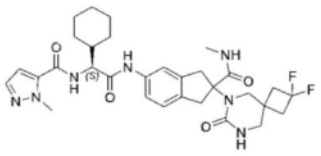
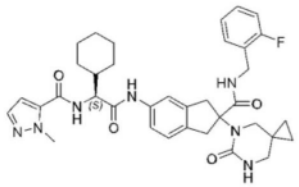
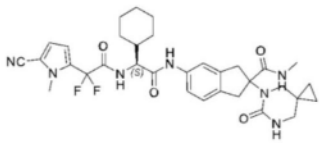
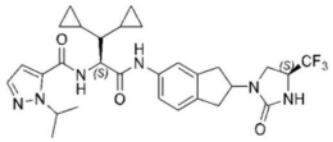
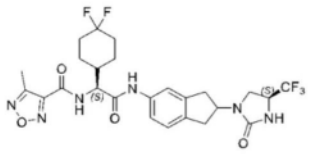
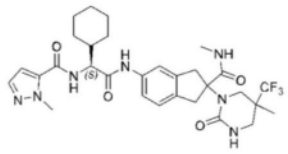
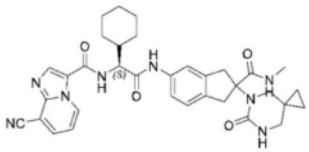
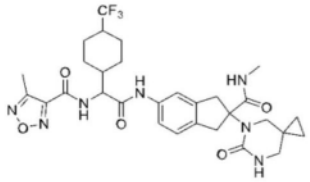
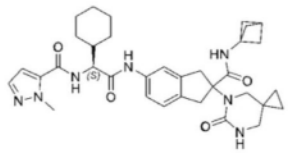
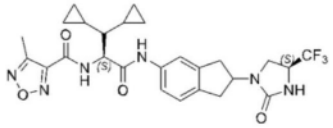
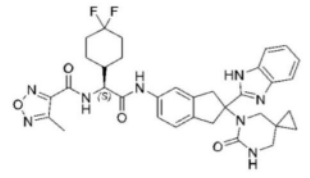
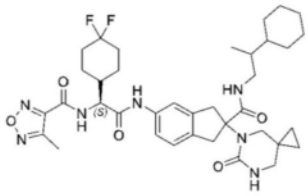
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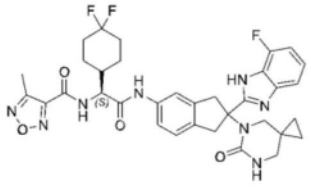
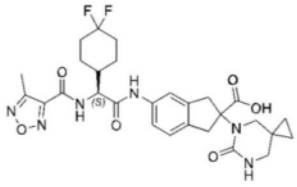
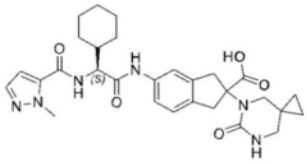
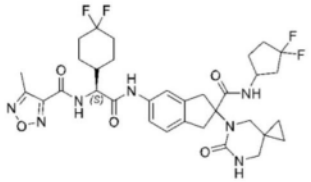
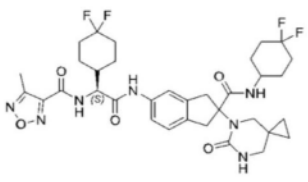
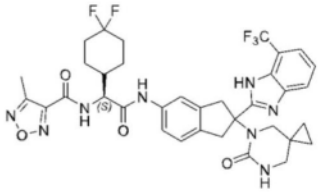
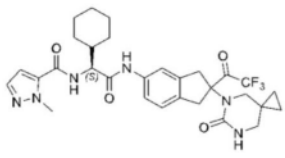
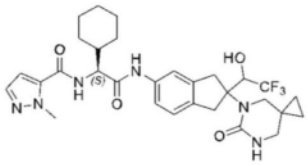
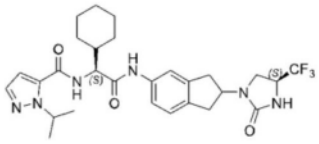
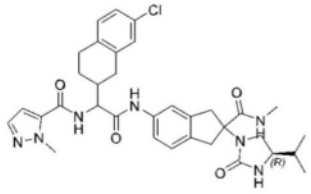
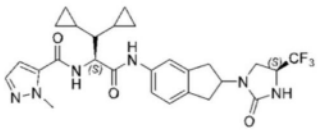
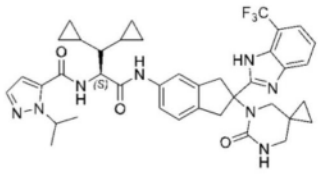
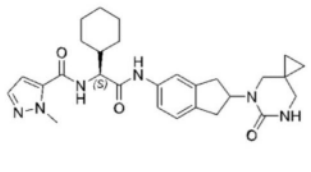
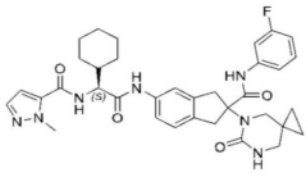
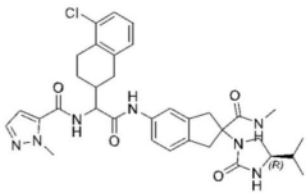
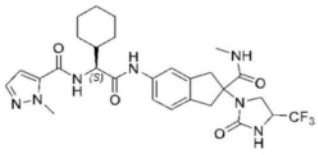
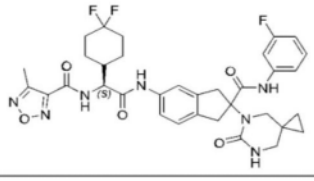
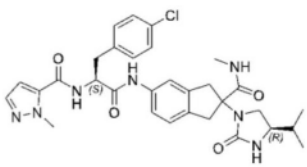
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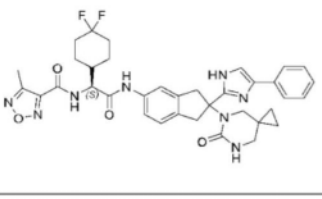
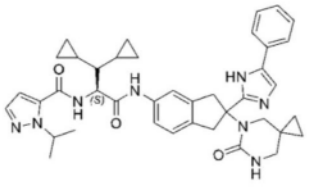
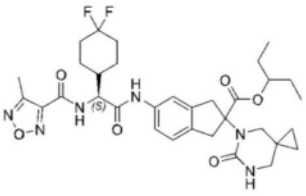
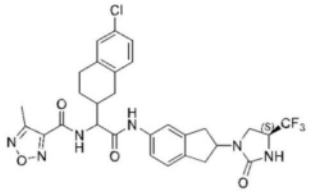
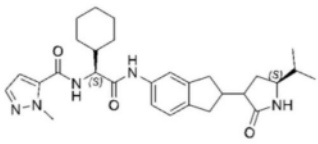
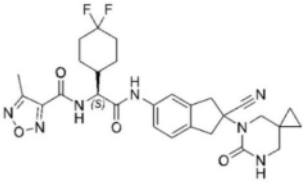
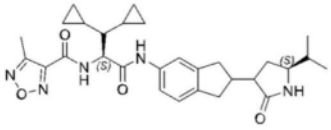
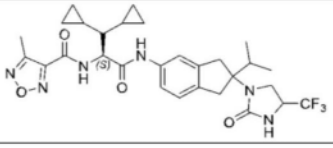
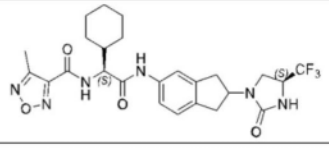
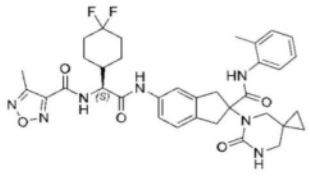
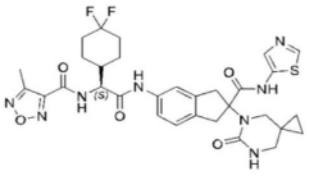
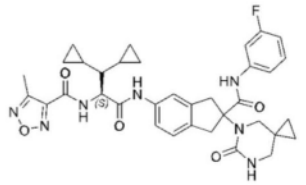
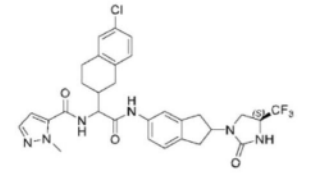
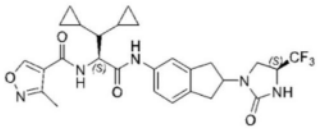
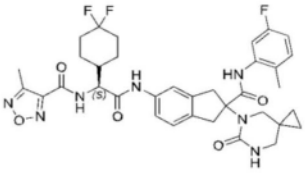
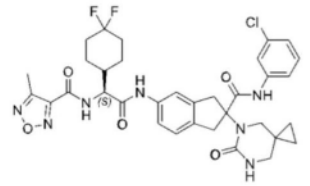
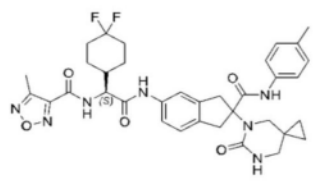
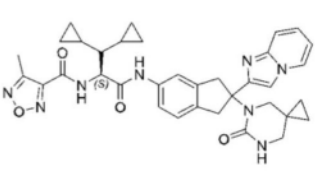
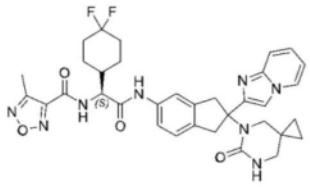
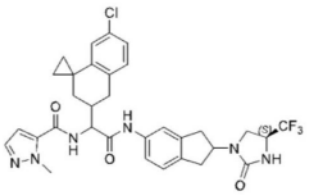
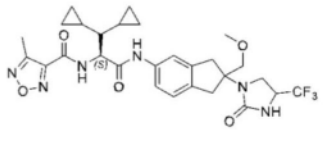
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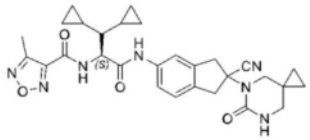
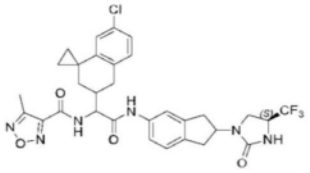
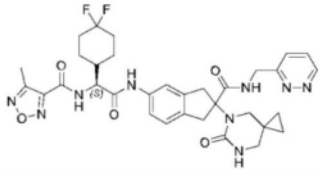
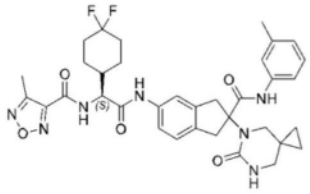
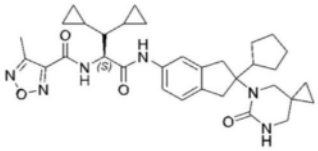
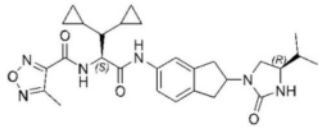
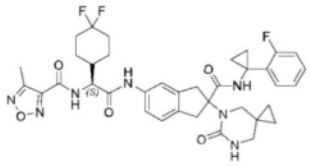
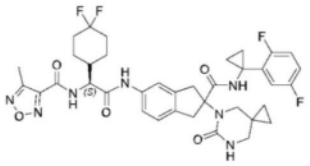
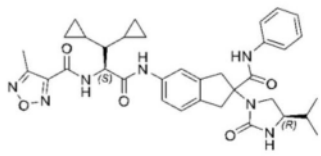
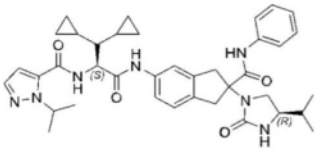
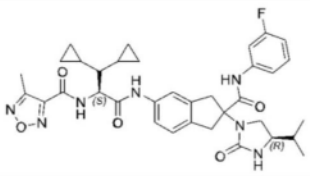
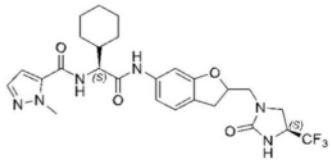
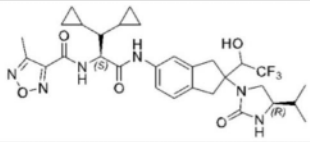
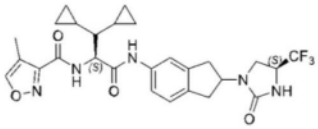
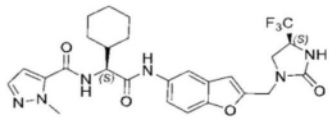
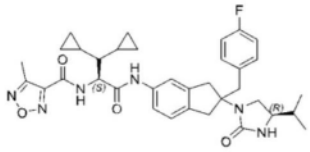
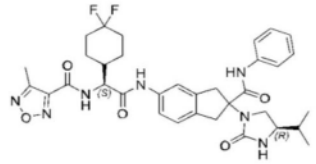
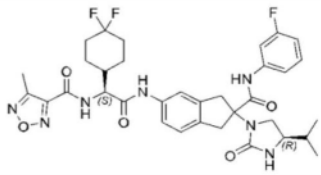
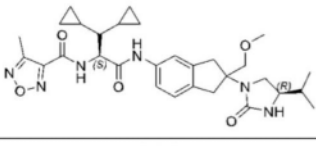
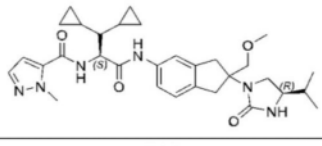
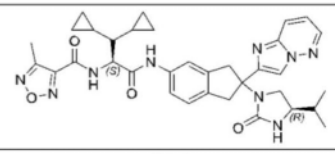
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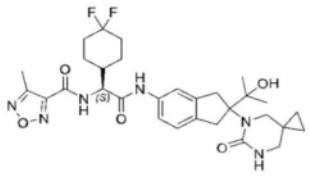
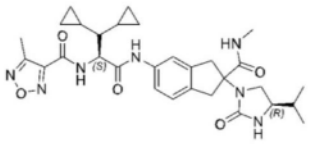
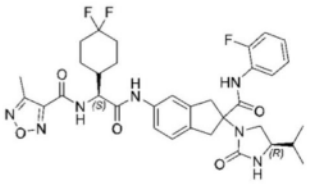
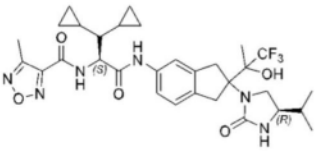
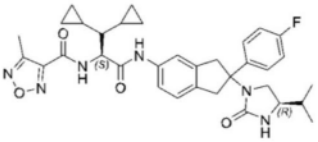
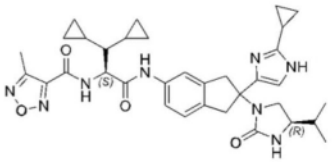
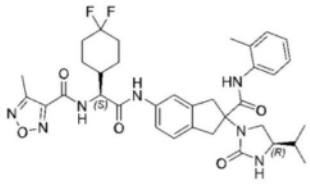
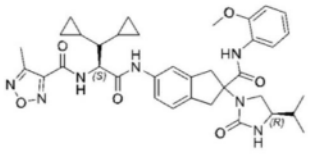
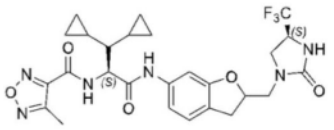
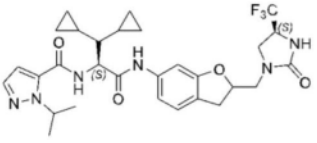
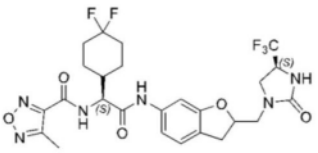
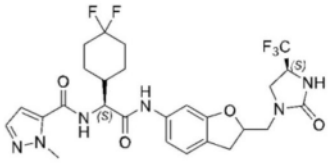
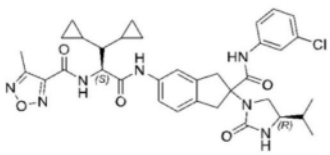
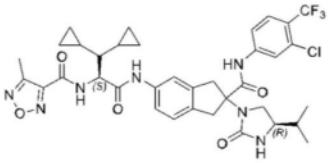
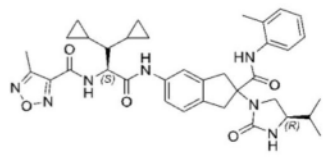
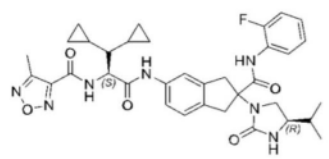
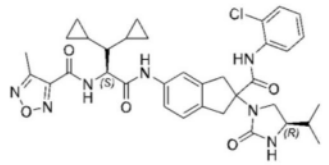
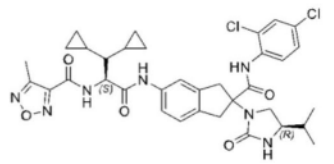
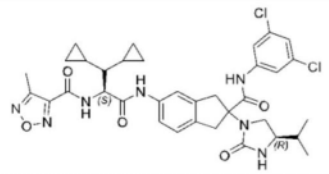
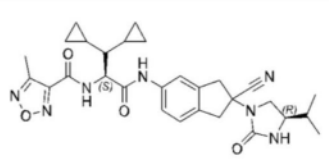
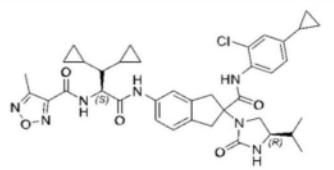
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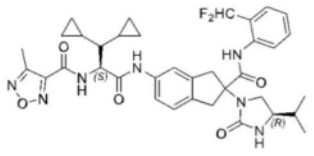
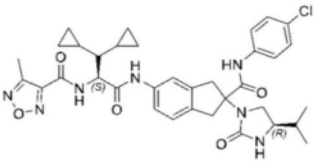
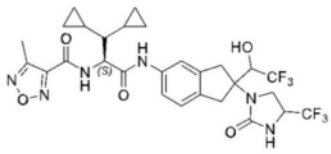
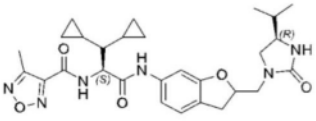
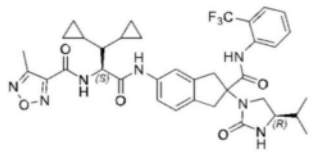
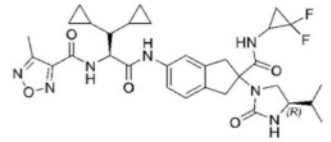
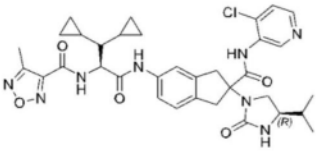
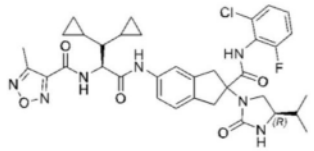
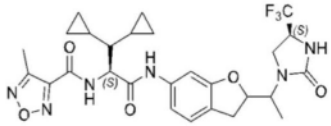
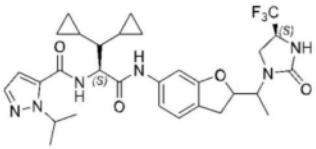
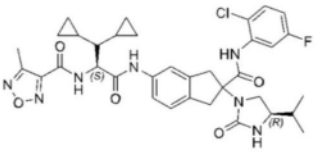
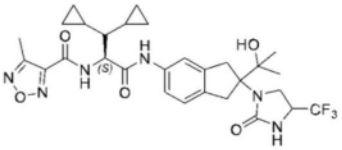
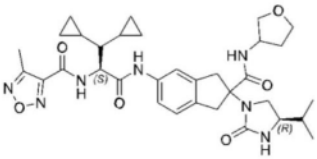
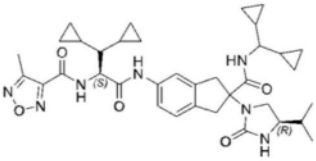
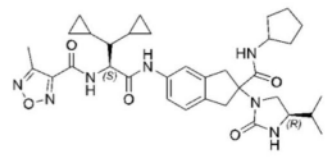
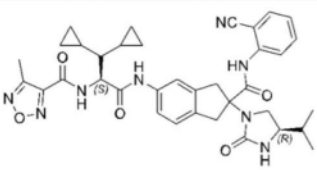
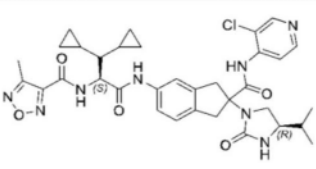
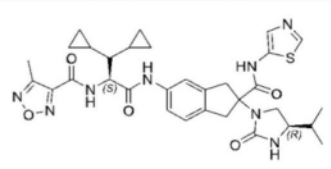
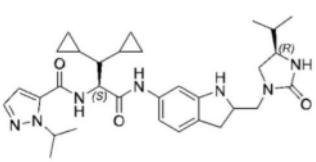
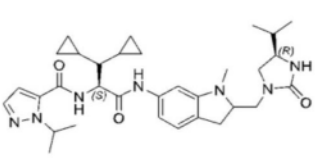
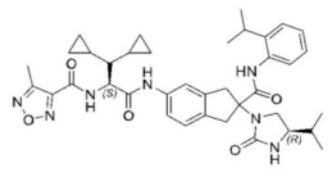
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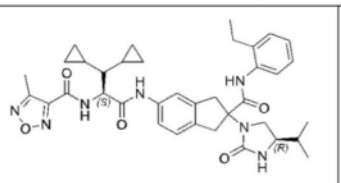
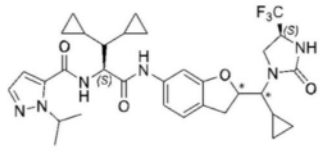
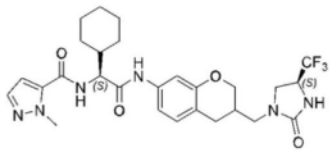
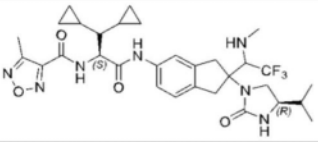
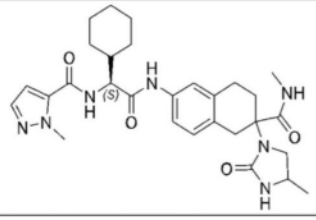
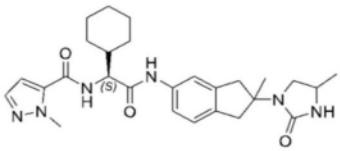
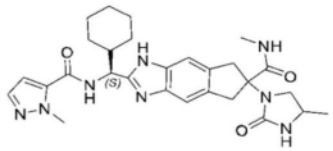
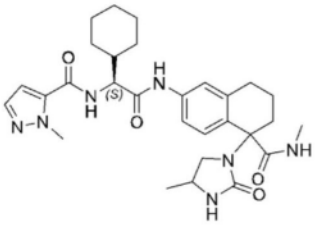
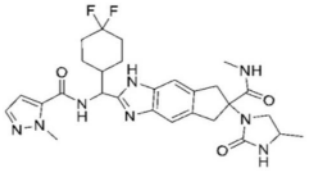
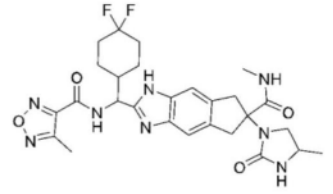
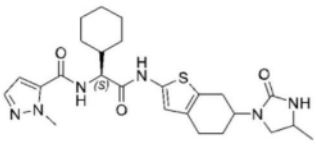
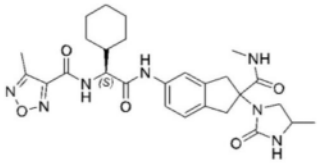
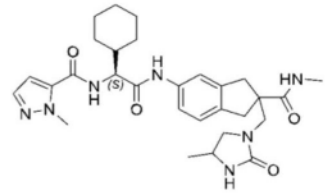
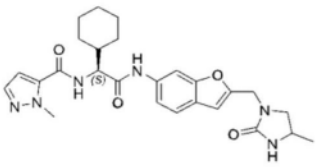
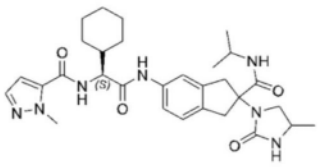
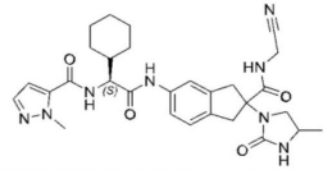
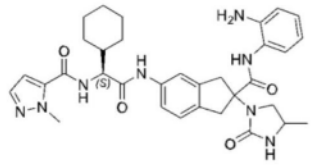
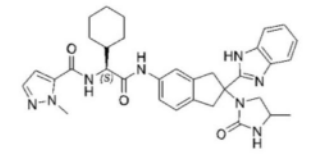
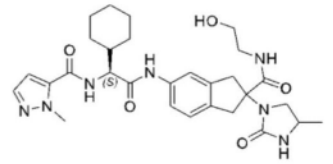
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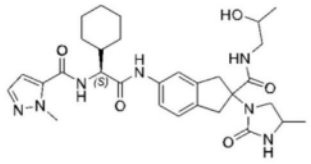
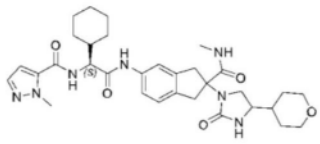
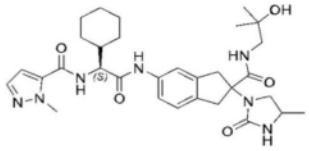
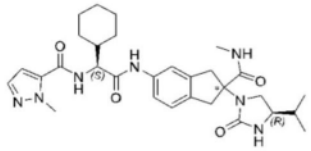
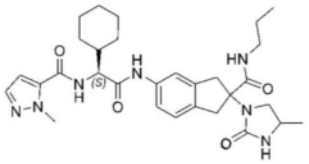
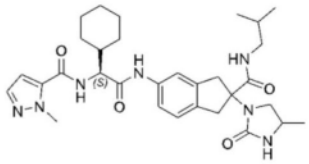
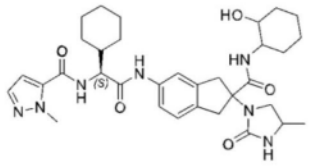
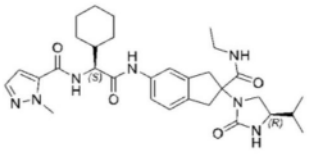
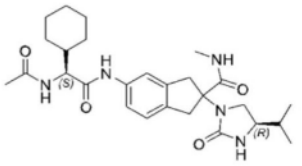
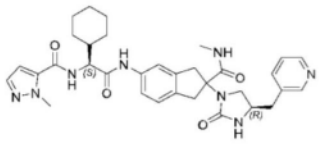
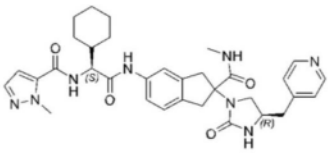
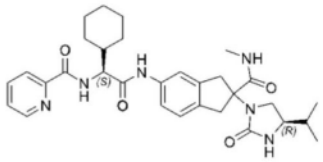
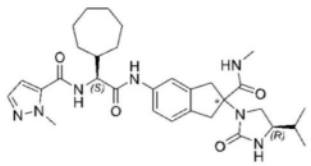
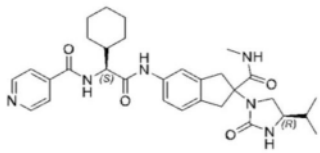
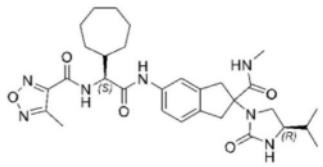
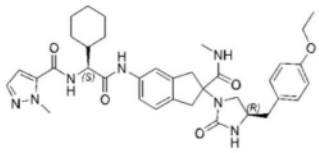
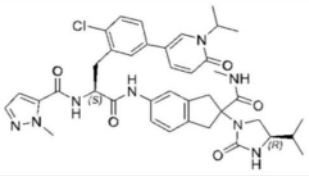
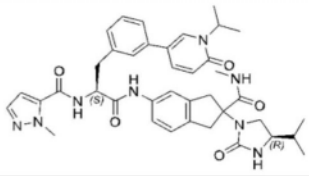
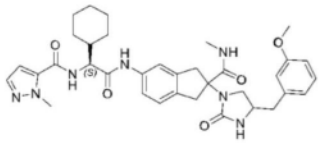
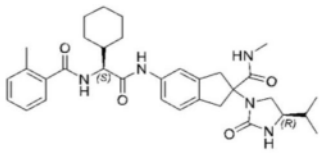
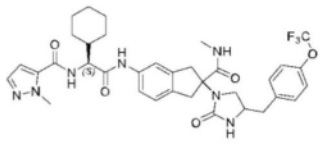
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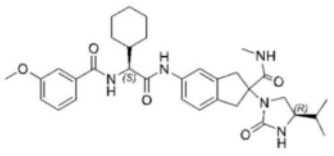
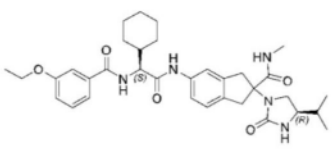
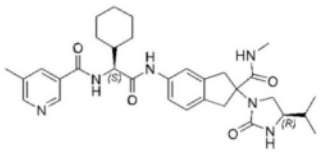
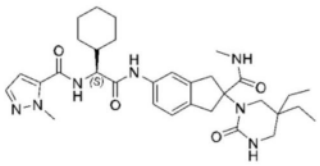
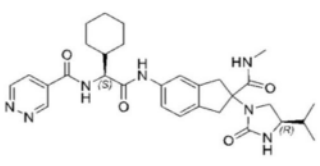
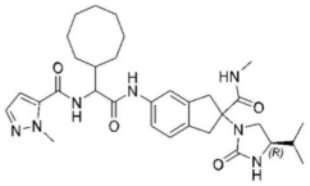
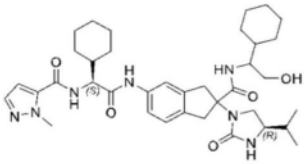
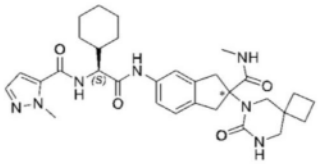
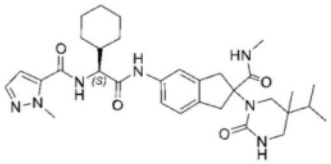
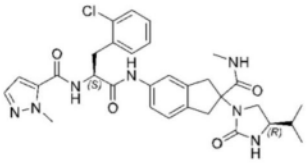
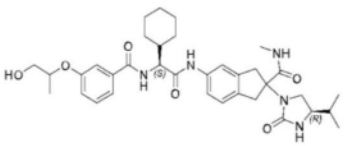
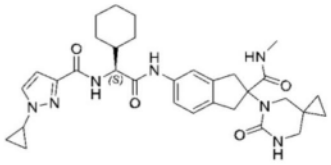
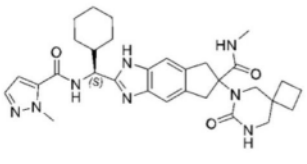
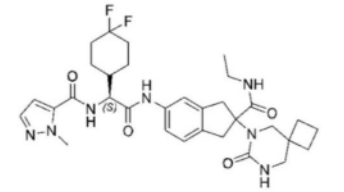
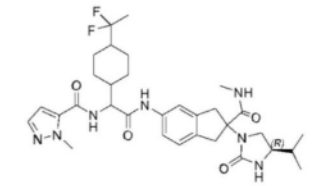
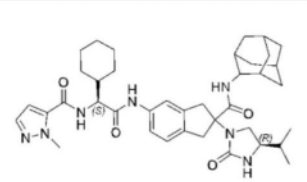
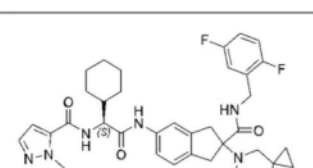
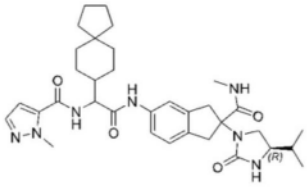
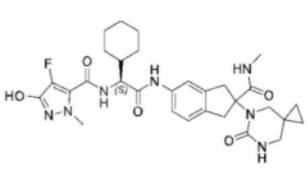
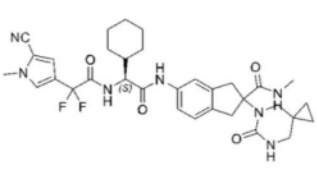
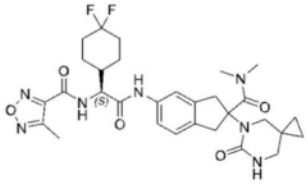
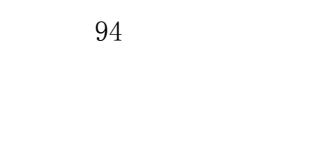
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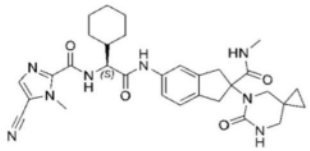
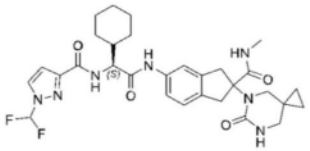
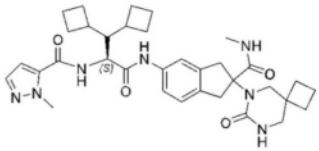
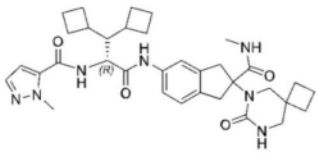
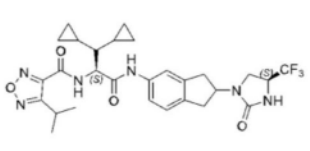
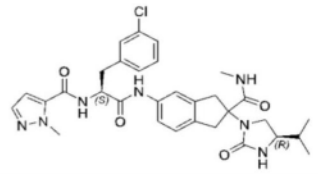
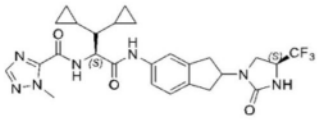
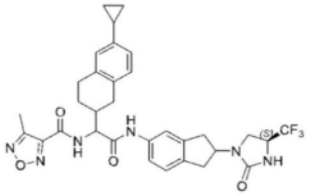
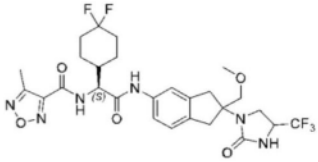
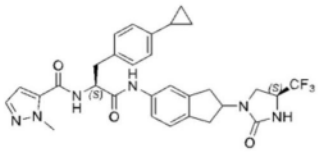
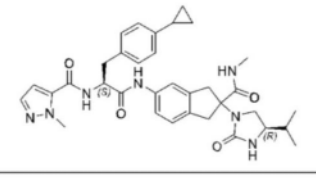
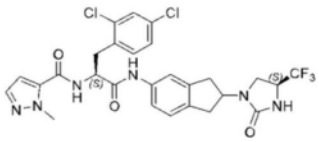
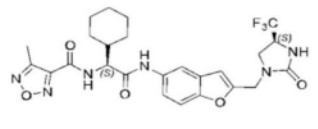
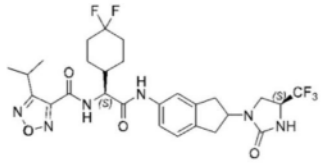
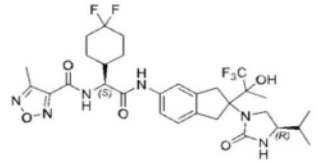
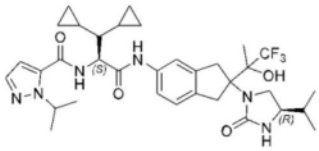
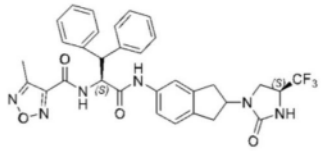
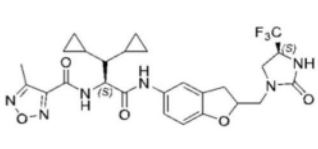
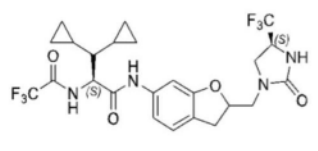
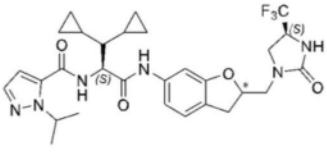
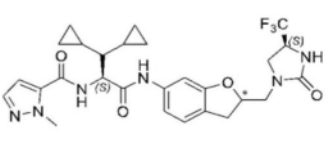
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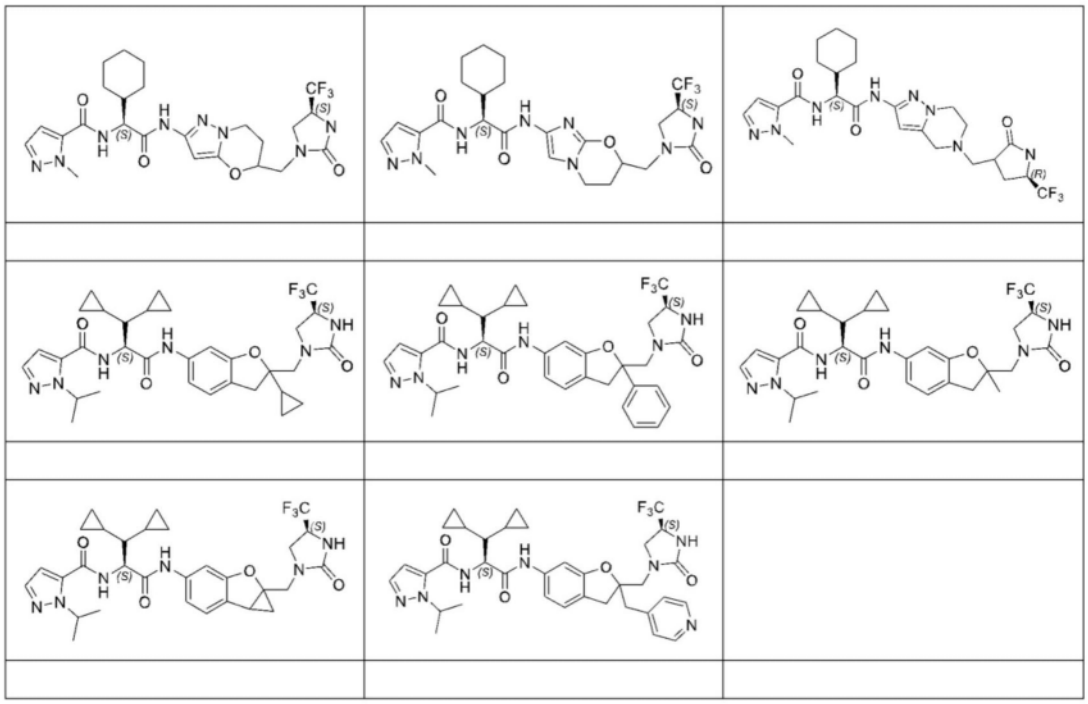
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[0201] 方面33.一种药物组合物,其包含如方面1至32中任一项所述的化合物或其药学上可接受的盐、立体异构体、互变异构体或前药,以及药学上可接受的赋形剂。

[0202] 方面34.一种通过抑制来降低IL-17活性的方法,其包括向个体施用如方面1至32中任一项所述的化合物或其药学上可接受的盐,包括式(I)的化合物或本文所例示的特定化合物。

[0203] 方面35.如方面34所述的方法,其中所述疾病选自癌症。

[0204] 方面36.方面1至32中任一项所述的化合物或其药学上可接受的盐、立体异构体、互变异构体或前药在制备用于治疗能够受IL-17影响的疾病的药物中的用途。

[0205] 方面37.如方面36所述的用途,其中所述疾病是自身免疫性疾病或炎性疾病。

[0206] 方面38.如方面37所述的用途,其中所述疾病是慢性炎症、牛皮癣、脊椎关节炎、类风湿性关节炎或多发性硬化症。

具体实施方式

[0207] 以下术语在整个说明书中具有所指示的含义:

[0208] 如本文所用,包括所附方面,除非上下文另有明确规定,否则诸如“一个/种(a/an)”和“所述”的词语的单数形式包括其相应的复数引用。

[0209] 除非上下文另有明确规定,否则术语“或”用于意指术语“和/或”,并且可与术语“和/或”互换使用。

[0210] 术语“烷基”是指选自包含1个至18个,诸如1个至12个,进一步诸如1个至10个,再进一步诸如1个至8个、或1个至6个或1个至4个碳原子的直链和支链饱和烃基的烃基。包含1个至6个碳原子的烷基(即,C_{1-6}烷基)的实例包括但不限于甲基、乙基、1-丙基或正丙基(“n-Pr”)、2-丙基或异丙基(“i-Pr”)、1-丁基或正丁基(“n-Bu”)、2-甲基-1-丙基或异丁基(“i-Bu”)、1-甲基丙基或仲丁基(“s-Bu”)、1,1-二甲基乙基或叔丁基(“t-Bu”)、1-戊基,2-戊基,3-戊基,2-甲基-2-丁基,3-甲基-2-丁基、3-甲基-1-丁基、2-甲基-1-丁基、1-己基、2-己基、

3-己基、2-甲基-2-戊基、3-甲基-2-戊基、4-甲基-2-戊基、3-甲基-3-戊基、2-甲基-3-戊基、2,3-二甲基-2-丁基和3,3-二甲基-2-丁基。

[0211] 术语“环烷基”是指选自饱和环状烃基的烃基,其包括单环和多环(例如,二环和三环)基团,包括稠合、桥接或螺接的环烷基。

[0212] 单独或与其他术语组合使用的术语“芳基”是指选自以下的基团:

[0213] 5和6元碳环芳族环,例如,苯基;

[0214] 双环环系,诸如7元至12元双环环系,其中至少一个环为碳环和芳族,例如,萘基和茚满基;以及

[0215] 三环环系,诸如10元至15元三环环系,其中至少一个环为碳环和芳族,例如,芴基。

[0216] 术语“芳族烃环”和“芳基”在本文的整个公开内容中可互换使用。在一些实施方案中,单环或二环芳族烃环具有5至10个成环碳原子(即,C_{5-10}芳基)。单环或二环芳族烃环的实例包括但不限于苯基、萘-1-基、萘-2-基、薁基、菲基等。在一些实施方案中,芳族烃环为萘环(萘-1-基或萘-2-基)或苯基环。在一些实施方案中,芳族烃环为苯基环。

[0217] 术语“芳基-烷基-”是指进一步被芳基基团取代的如上定义的烷基基团。芳基-烷基基团的示例包括芳基-C_{1-8}烷基,诸如苯基乙基或苯基甲基(苄基)。

[0218] 术语“杂芳基”是指选自以下的基团:

[0219] 5、6或7元芳族单环,其包含至少一个选自氮(N)、硫(S)和氧(O)的杂原子,例如,1至4个(或在一些实施方案中,1至3个,在一些实施方案中,1至2个)杂原子,其余环原子为碳;

[0220] 7至12元二环,其包含至少一个选自N、O和S的杂原子,例如1至4个(或在一些实施方案中,1至3个,或在其他实施方案中,1或2个)杂原子,其余环原子为碳,并且其中至少一个环为芳族并且至少一个杂原子存在于芳族环中;以及

[0221] 11至14元三环,其包含至少一个选自N、O和S的杂原子,例如1至4个(或在一些实施方案中,1至3个,或在其他实施方案中,1或2个)杂原子,其余环原子为碳,并且其中至少一个环为芳族并且至少一个杂原子存在于芳族环中。

[0222] 当杂芳基中S和O原子的总数超过1时,那些杂原子彼此不相邻。在一些实施方案中,杂芳基中S和O原子的总数不超过2。在一些实施方案中,芳族杂环中S和O原子的总数不超过1。当杂芳基含有超过一个杂原子环成员时,杂原子可以是相同或不同的。杂芳基的一个或多个环中的氮原子可经氧化以形成N-氧化物。如本文所用的术语“C-连接的杂芳基”意指杂芳基通过来自杂芳基环的C-原子的键连接至核心分子

[0223] 术语“芳族杂环”和“杂芳基”在本文的整个公开内容中可互换使用。在一些实施方案中,单环或双环芳族杂环具有5元、6元、7元、8元、9元或10元成环成员,其中1个、2个、3个或4个杂原子环成员独立地选自氮(N)、硫(S)和氧(O)且其余环成员为碳。在一些实施方案中,单环或二环芳族杂环为包含1或2个独立地选自氮(N)、硫(S)和氧(O)的杂原子环成员的单环或二环。在一些实施方案中,单环或二环芳族杂环为5至6元杂芳基环,其为单环的并且具有1或2个独立地选自氮(N)、硫(S)和氧(O)的杂原子环成员。在一些实施方案中,单环或二环芳族杂环为8至10元杂芳基环,其为二环的并且具有1或2个独立地选自氮、硫和氧的杂原子环成员。

[0224] “杂环基”、“杂环”或“杂环状”是可互换的,并且包括非芳族杂环基,其包含一个或

多个选自氮、氧或任选地氧化的硫的杂原子作为环成员,其余环成员为碳,包括单环、稠合环、桥接环和螺环,即含有单环杂环基、桥接杂环基、螺杂环基和稠合杂环基。本文所用的术语“任选地氧化的硫”是指S、SO或SO_2。

[0225] 本文所公开的化合物可含有不对称中心,因此可作为对映异构体存在。“对映异构体”是指化合物的两种立体异构体,它们是彼此不可叠加的镜像。在本文所公开的化合物具有两个或更多个不对称中心的情况下,它们可另外作为非对映异构体存在。对映异构体和非对映异构体属于更广泛的立体异构体类别。旨在包括呈基本上纯的拆分的对映异构体、其外消旋混合物以及非对映异构体的混合物形式的所有此类可能的立体异构体。本文公开的化合物和/或其药学上可接受的盐的所有立体异构体意欲包括在内。除非另外特别指出,否则提及一种异构体适用于任何可能的异构体。只要未指定异构体组成,则包括所有可能的异构体。

[0226] 本文所用的术语“基本上纯的”是指目标立体异构体含有按重量计不超过35%、例如不超过30%、进一步例如不超过25%、甚至进一步例如不超过20%的任何其他立体异构体。在一些实施方案中,术语“基本上纯的”是指目标立体异构体含有按重量计不超过10%、例如不超过5%、例如不超过1%的任何其他立体异构体。

[0227] 除非另有说明,否则当本文所公开的化合物含有烯属双键时,此类双键意在包括E和Z几何异构体两者。

[0228] 当本文所公开的化合物含有二取代的环已基或环丁基时,在环已基或环丁基环上发现的取代基可以采取顺式和反式形式。顺式形式意指两个取代基都位于碳上2个取代基位置的上侧,而反式意指它们位于相对侧。

[0229] 将反应产物彼此分离和/或与起始材料分离可能是有利的。通过本领域中常用的技术将每个步骤或一系列步骤的所需产物分离和/或纯化(下文中分离)至所需的均一性程度。通常,这种分离包括多相萃取、从溶剂或溶剂混合物中结晶、蒸馏、升华或色谱。色谱可涉及任何数目的方法,包括例如:反相和正相色谱;尺寸排阻色谱;离子交换色谱;高压、中压和低压液相色谱方法和装置;小规模分析型色谱;模拟移动床(“SMB”)色谱和制备型薄层或厚层色谱,以及小规模薄层和快速色谱技术。本领域技术人员将应用最有可能实现所需分离的技术。“非对映异构体”是指具有两个或更多个手性中心但彼此不是镜像的化合物的立体异构体。基于它们的物理化学差异,通过本领域技术人员熟知的方法,例如通过色谱和/或分级结晶,可以将非对映异构体混合物分离成其单独的非对映异构体。可通过与适当的旋光活性化合物(例如,手性助剂,诸如手性醇或莫舍氏酰氯(Mosher’s acid chloride))反应将对映异构体混合物转化成非对映异构体混合物,分离非对映异构体并将单个非对映异构体转化(例如,水解)成相应的纯对映异构体,而分离对映异构体。还可通过使用手性HPLC柱分离对映异构体。

[0230] “药学上可接受的盐”是指在合理的医学判断范围内适用于与人和低等动物的组织接触而没有不适当的毒性、刺激、过敏反应等并且与合理的益处/风险比相称的那些盐。药学上可接受的盐可在本文所公开的化合物的最终分离和纯化期间原位制备,或者通过使游离碱官能团与适合的有机酸反应或通过使酸性基团与适合的碱反应来单独制备。

[0231] 另外,如果本文所公开的化合物是作为酸加成盐获得,则可通过使酸式盐的溶液碱化来获得游离碱。相反地,如果产物是游离碱,则加成盐(诸如药学上可接受的加成盐)可

以按照从碱化合物制备酸加成盐的常规方法,通过将游离碱溶解在合适的有机溶剂和/或水中并用酸处理溶液来制备。本领域技术人员将认识到可在没有过度实验的情况下用于制备无毒的药学上可接受的加成盐的各种合成方法。

[0232] 如本文所定义,“其药学上可接受的盐”包括至少一种式(I)的化合物的盐和式(I)的化合物的立体异构体的盐,诸如对映异构体的盐和/或非对映异构体的盐。

[0233] 当应用于动物、人、实验受试者、细胞、组织、器官或生物流体时,本文的术语“施用(administration)”、“施用(administering)”、“治疗(treating)”和“治疗(treatment)”意指外源性药物、治疗剂、诊断剂或组合物与动物、人、受试者、细胞、组织、器官或生物流体的接触。细胞的处理涵盖试剂与细胞的接触,以及试剂与流体的接触,其中所述流体与所述细胞接触。术语“施用”和“治疗”还意指例如通过试剂、诊断剂、结合化合物或通过另一细胞对细胞的体外和离体处理。本文中的术语“受试者”包括任何生物体,优选动物,更优选哺乳动物(例如,大鼠、小鼠、狗、猫和兔),且最优选人。

[0234] 术语“有效量”或“治疗有效量”是指活性成分(诸如化合物)当施用于受试者以治疗疾病、或疾病或病症的至少一种临床症状时,足以影响针对所述疾病、病症或症状的治疗的量。术语“治疗有效量”可随化合物,疾病,病症,和/或疾病或病症的症状,疾病、病症和/或疾病或病症的症状的严重性,待治疗受试者的年龄和/或待治疗受试者的体重而变化。在任何给定情况下,适当量对于本领域技术人员来说可以是显而易见的,或者可通过常规实验来确定。在一些实施方案中,“治疗有效量”是本文公开的至少一种化合物和/或其至少一种立体异构体和/或其至少一种药学上可接受的盐在受试者中有效“治疗”如上所定义的疾病或病症的量。在组合疗法的情况下,“治疗有效量”是指用于有效治疗疾病、病症或疾患的组合对象的总量。

[0235] 包含本文公开的化合物的药物组合物可以经由口服、吸入、直肠、肠胃外或局部施用而施用于有需要的受试者。对于口服施用,药物组合物可以是常规固体制剂,诸如片剂、粉末、颗粒、胶囊等;液体制剂,诸如水或油悬浮液;或其他液体制剂,诸如糖浆、溶液、悬浮液等;对于肠胃外施用,药物组合物可以是溶液、水溶液、油悬浮浓缩物、冻干粉等。优选地,药物组合物的剂型选自片剂、包衣片剂、胶囊、栓剂、鼻喷雾剂或注射剂,更优选片剂或胶囊。该药物组合物可以是使用准确剂量的单一单位施用。此外,该药物组合物还可以包含额外的活性成分。

[0236] 本文公开的药物组合物的所有制剂均可通过制药领域常规的方法制备。例如,可以将活性成分与一种或多种赋形剂混合,然后制备所需的制剂。“药学上可接受的赋形剂”是指适用于所需药物制剂的常规药物载体,例如:稀释剂;媒介物,诸如水、各种有机溶剂等;填充剂,诸如淀粉、蔗糖等;粘合剂,诸如纤维素衍生物、藻酸盐、明胶和聚乙烯吡咯烷酮(PVP);润湿剂,诸如甘油;崩解剂,诸如琼脂、碳酸钙和碳酸氢钠;吸收增强剂,诸如季铵化合物;表面活性剂,诸如十六醇;吸收载体,诸如高岭土和皂粘土;润滑剂,诸如滑石、硬脂酸钙、硬脂酸镁、聚乙二醇等。此外,药物组合物还包含其他药学上可接受的赋形剂,诸如分散剂、稳定剂、增稠剂、络合剂、缓冲剂、渗透增强剂、聚合物、芳香剂、甜味剂和染料。

[0237] 术语“疾病”是指任何疾病、不适、病痛、症状或适应症,并且可与术语“病症”或“疾患”互换。

[0238] 在本说明书和随后的各方面中,除非上下文另有要求,否则术语“包含

(comprise)”和诸如“包含(comprises)”和“包含(comprising)”的变型旨在指定其后特征的存在,但不排除一个或多个其他特征的存在或添加。当在本文中使用时,术语“包含”可用术语“含有”、“包括”或有时“具有”替代。

[0239] 贯穿本说明书和随后的方面,术语“C_{n-m}”表示包括端点的范围,其中n和m是整数并且表示碳的数目。实例包括C_{1-8}、C_{1-6}等。

[0240] 除非本文件中其他地方有明确定义,否则本文所用的所有其他技术和科学术语都具有本发明所属领域的普通技术人员通常所理解的含义。

[0241] 实施例

[0242] 本发明通过以下说明本发明的实施例进一步举例说明,但不限于此。

[0243] 在以下实施例中,使用以下缩写:

[0244]	AcOH或HOAc	乙酸
[0245]	aq.	水溶液
[0246]	BINAP	(2,2’-双(二苯基膦基)-1,1’-联萘基)
[0247]	BH_3	硼烷
[0248]	盐水	饱和氯化钠水溶液
[0249]	Boc_2O	碳酸二叔丁酯
[0250]	BSA	牛血清白蛋白
[0251]	CDI	1,1’-羰基二咪唑
[0252]	DAST	二乙氨基三氟化硫
[0253]	DBN	1,5-二氮杂双环[4.3.0]壬-5-烯
[0254]	DBU	1,8-二氮杂双环[5.4.0]十一碳-7-烯
[0255]	DCE	1,2-二氯乙烷
[0256]	DCM	二氯甲烷
[0257]	DMAP	4-二甲基氨基吡啶
[0258]	CH_3MgBr	甲基溴化镁
[0259]	DIPEA	N,N-二异丙基乙胺
[0260]	DMF	N,N-二甲基甲酰胺
[0261]	DMAC	二甲基乙酰胺
[0262]	DMSO	二甲亚砜
[0263]	DPPA	二苯基磷酰叠氮化物
[0264]	EA	乙酸乙酯
[0265]	EDCI	1-乙基-3-(3-二甲基氨基丙基)碳二亚胺盐酸盐
[0266]	EDTA	乙二胺四乙酸
[0267]	EtOH	乙醇
[0268]	h或hr	小时
[0269]	HATU	1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐
	Hex	己烷
[0270]	^1H NMR	质子核磁共振

[0271]	H_2O_2	过氧化氢
[0272]	HOBt	羟基苯并三唑
[0273]	IPA(i-PrOH)	异丙醇
[0274]	KOAc	乙酸钾
[0275]	LAH	氢化铝锂
[0276]	LC-MS	液相色谱-质谱
[0277]	LDA	二异丙基氨基锂
[0278]	MeOH	甲醇
[0279]	MsOH	甲磺酸
[0280]	Min	分钟
[0281]	n-BuLi	正丁基锂
[0282]	NaH	氢化钠
[0283]	$NaBH(OAc)_3$	三乙酰氧基硼氢化钠
[0284]	(STAB)	
[0285]	$NaBH_3CN$	氰基硼氢化钠
[0286]	NH_4Cl	氯化铵
[0287]	Pd/C	钯/碳粉末
[0288]	$Pd(dppf)Cl_2$	[1,1'-双(二苯基膦基)二茂铁]二氯钯(II)
[0289]	$Pd(PPh_3)_4$	四(三苯基膦)钯(0)
[0290]	$Pd(OAc)_2$	乙酸钯
[0291]	$Pd(OH)_2/C$	氢氧化钯/碳粉末
[0292]	PE	石油醚
[0293]	pH	-lg(氢离子浓度)
[0294]	制备型HPLC	制备型高压液相色谱
[0295]	制备型MPLC	制备型中压液相色谱
[0296]	制备型SFC	制备型超临界流体色谱
[0297]	制备型TLC	制备型薄层色谱
[0298]	p-TsOH	对甲苯磺酸
[0299]	r.t.或RT	室温
[0300]	sat.	饱和的
[0301]	t-BuOK	叔丁醇钾
[0302]	TBS	叔丁基二甲基甲硅烷基
[0303]	THF	四氢呋喃
[0304]	TEA	三乙胺
[0305]	TFA	三氟乙酸
[0306]	TsCl	4-甲苯磺酰氯
[0307]	TMSCN	三甲基甲硅烷基氰化物
[0308]	$TMSCF_3$	(三氟甲基)三甲基硅烷
[0309]	TBAF	四丁基氟化铵

[0310] TBSOTf 三氟甲磺酸叔丁基二甲基甲硅烷基酯

[0311] $TiCl_4$ 四氯化钛

[0312] TIPT 丙基膦酸酐溶液

[0313] TMSI 三甲基碘硅烷

[0314] 以下实施例仅仅意图是示例性的,并且不应视为以任何方式进行限制。已经努力确保关于所用数字(例如量、温度等)的准确性,但应考虑一些实验误差和偏差。除非另外指示,否则温度以摄氏度为单位。试剂从例如Sigma-Aldrich、Alfa Aesar或TCI的商业供应商购买,并且除非另外指示,否则未经进一步纯化即使用。

[0315] 除非另外指示,否则以下阐述的反应是在正压氮气或氩气下或用干燥管在无水溶剂中进行;反应烧瓶装有橡胶隔片,用于经由注射器引入底物和试剂;并且玻璃器皿烘干和/或加热干燥。

[0316] 在以400MHz操作的Agilent仪器上记录^{1}H NMR谱。使用$CDCl_3$、CD_2Cl_2、CD_3OD,D_2O、d_6-DMSO、d_6-丙酮或$(CD_3)_2CO$作为溶剂,并且四甲基硅烷(0.00ppm)或残余溶剂($CDCl_3$:7.25ppm;CD_3OD:3.31ppm;D_2O:4.79ppm;d_6-DMSO:2.50ppm;d6-丙酮:2.05;$(CD_3)_2CO$:2.05)作为参考标准,获得^{1}HNMR谱。当报告峰多重性时,使用以下缩写:s(单峰)、d(双峰)、t(三重峰)、q(四重峰)、qn(五重峰)、sx(六重峰)、m(多重峰)、br(宽峰)、dd(双二重峰)、dt(双三重峰)。耦合常数在给出时是以赫兹(Hz)报告。

[0317] LC-MS光谱仪(Agilent 1260)检测器:MWD(190-400nm),质量检测器:6120SQ

[0318] 流动相:A:含0.1%甲酸的乙腈,B:含0.1%甲酸的水

[0319] 柱:Poroshell 120EC-C18,4.6×50mm,2.7μm

[0320] 梯度法:流速:1.8mL/min

[0321]

时间(min)	A (%)	B (%)
0.00	5	95
1.5	95	5

[0322]

2.0	95	5
2.1	5	95
3.0	5	95

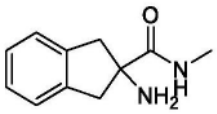
[0323] 在室温和214nm和254nm的UV检测下,在柱(150×21.2mm ID,5μm,Gemini NX-C18)和(150×19mm,5μm,SunFire Prep C18OBD™)上以不同的流速和注射体积进行制备型HPLC。

[0324] 在室温和214nm和254nm的UV检测下,在柱(C18 spherical20-35μm)上以不同的流速和注射体积进行组合闪式色谱(Combi Flash)。

[0325] 中间体(Int)的制备:

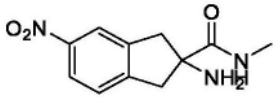
[0326] Int A1:5-((S)-2-氨基-2-环已基乙酰氨基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺

[0327] 步骤1:2-氨基-N-甲基-2,3-二氢-1H-茚-2-甲酰胺

[0328] 

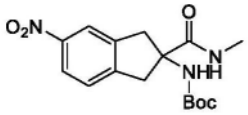
[0329] 将2-氨基-2,3-二氢-1H-茚-2-甲酸甲酯(3.8g,20mmol)在$MeNH_2$溶液(在EtOH中,33%,wt,20mL)中的混合物在密封管中加热至80℃持续4小时。将反应物冷却至环境温度并真空浓缩,得到标题化合物(3.7g,产率:97.32%)。

[0330] 步骤2:2-氨基-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺

[0331] 

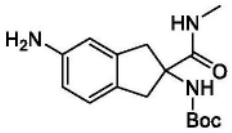
[0332] 在0℃下,向H_2SO_4(3mL)和HNO_3(3mL)的混合物中缓慢分批添加2-氨基-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(3.7g,19.46mmol,在6mL HOAc中的溶液)并搅拌15分钟。在0℃下将反应混合物倒入$NaHCO_3$溶液(水溶液,200mL)中,然后用DCM(200mL)稀释。将有机层分离,干燥,真空浓缩。将残余物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=20/0至20/1)纯化,得到标题化合物(3.28g,产率:71.56%)。

[0333] 步骤3:(2-(甲基氨基甲酰基)-5-硝基-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯

[0334] 

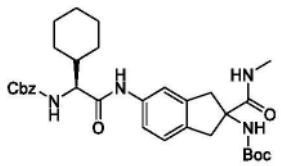
[0335] 将2-氨基-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺(1.18g,5mmol)和Boc_2O(1.15g,5.25mmol)在DCM(50mL)中的混合物搅拌过夜。将混合物用盐水(50mL)淬灭,分离并将有机相经Na_2SO_4干燥,真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题产物(1.31g,产率:77.52%)。MS(ESI,m/e)$[M+1]^+$336.3。

[0336] 步骤4:(5-氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯

[0337] 

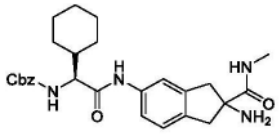
[0338] 向(2-(甲基氨基甲酰基)-5-硝基-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(1.31g,3.90mmol)和Pd/C(150mg)在MeOH(50mL)中的混合物用H_2气球鼓泡并搅拌过夜。将混合物过滤,真空浓缩,通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题产物(1.06g,产率:88.99%)。MS(ESI,m/e)$[M+1]^+$306.0。

[0339] 步骤5:(5-((S)-2-(((苄氧基)羰基)氨基)-2-环己基乙酰氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0340] 

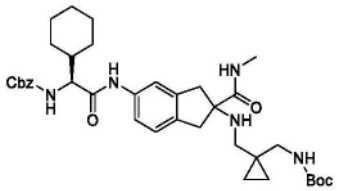
[0341] 将(S)-2-(((苄氧基)羰基)氨基)-2-环己基乙酸(909mg,3.0mmol)、(5-氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(915mg,3.0mmol)、HATU(1.14g,3.0mmol)和TEA (606mg,6.0mmol)在DCM(100mL)中的混合物在室温下搅拌4小时。将混合物用$NaHCO_3$水溶液(150mL)淬灭,分离并将有机相经Na_2SO_4干燥,真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题产物(1.41g,产率:80.67%)。MS(ESI,m/e)$[M+1]^+$579.3。

[0342] 步骤6:((1S)-2-((2-氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯

[0343] 

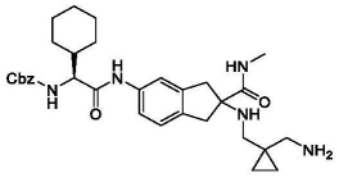
[0344] 将(5-((S)-2-(((苄氧基)羰基)氨基)-2-环己基乙酰氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(5g,8.6mmol)在DCM(50mL)和TFA(20mL)中的混合物在20℃下搅拌2小时。然后减压浓缩反应混合物。将残余物用H_2O(50mL)稀释并将水相用Na_2CO_3碱化至pH约8-9。用EtOAc(50mL×3)萃取混合物。将合并的有机层经Na_2SO_4干燥,过滤并真空浓缩,得到((1S)-2-((2-氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯(4g,粗物质)。MS(ESI,m/e)$[M+H]^+$479.3。

[0345] 步骤7:((1S)-2-((2-(((1-(((叔丁氧基羰基)氨基)甲基)环丙基)甲基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯

[0346] 

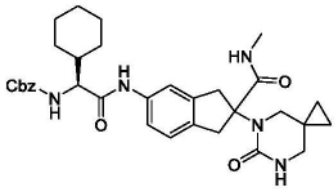
[0347] 在0℃下,向((1S)-2-((2-氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯(0.8g,1.7mmol)和((1-甲酰基环丙基)甲基)氨基甲酸叔丁酯(0.5g,2.5mmol)在DCM(15mL)中的溶液中添加AcOH(0.2g,3.4mmol)和NaBH(OAc)3(0.931g,4.2mmol)。将混合物在25℃下搅拌3小时。然后将反应混合物用$NaHCO_3$水溶液(20mL)稀释并用DCM(10mL×3)萃取,用盐水洗涤,经Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化。得到标题化合物(0.65g,产率:59%)。

[0348] 步骤8:((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯

[0349] 

[0350] 将((1S)-2-((2-(((1-(((叔丁氧基羰基)氨基)甲基)环丙基)甲基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯(0.65g,0.982mmol)在HCl/EtOAc(10mL)中的混合物在25℃下搅拌2小时。将反应混合物减压浓缩,得到((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯(0.55g,HCl盐)。MS(ESI,m/e)$[M+H]^+$562.3。

[0351] 步骤9:((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸苄酯

[0352] 

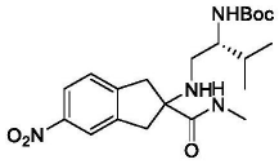
[0353] 向((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)氨基甲酸苄酯(0.55g,0.98mmol)在THF(10mL)中的溶液中添加TEA (0.198g,1.9mmol)和CDI(0.317g,1.9mmol)。将混合物在60℃下搅拌8小时。将反应混合物倒入冰/水(10mL)中,用EtOAc(10mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na2SO4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸苄酯(0.46g,产率:80%)。

[0354] 步骤10:5-((S)-2-氨基-2-环己基乙酰氨基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺(IntA1)。

[0355] 向((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸苄酯(0.41g,0.698mmol)在MeOH(10mL)和MeNH2.H2O(1mL)中的溶液中添加Pd(OH)2(0.1g,0.698mmol)。将混合物在50℃下在H_2(15Psi)下搅拌1小时。将反应混合物用水(5mL)稀释并用EtOAc(5mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na2SO4干燥,过滤并减压浓缩,得到5-((S)-2-氨基-2-环己基乙酰氨基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺(280mg,产率:87%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.08-9.41(m,1H),7.50(s,1H),7.40-7.22(m,2H),7.06(d,J=8.4Hz,1H),6.42(s,1H),3.55-3.39(m,3H),3.12-2.93(m,5H),2.91-2.81(m,2H),2.56(d,J=4.8Hz,3H),2.00-1.81(m,1H),1.69(d,J=10.0Hz,3H),1.62-1.45(m,3H),1.23-0.97(m,5H),0.45-0.32(m,2H),0.19-0.44(m,2H)。MS(ESI,m/e)[M+H]$^+$454.3。

[0356] Int A2:5-((S)-2-氨基-2-环己基乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺

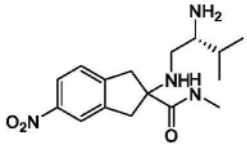
[0357] 步骤1:((2R)-3-甲基-1-((2-(甲基氨基甲酰基)-5-硝基-2,3-二氢-1H-茚-2-基)氨基)丁-2-基)氨基甲酸叔丁酯

[0358] 

[0359] 向2-氨基-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺(10g,42.51mmol)和(R)-(3-甲基-1-氧代丁-2-基)氨基甲酸叔丁酯(15.4g,78.52mmol)在MeOH(100mL)中的溶液中添加$NaBH_3CN$(5.17g,858.02mmol)。将混合物在25℃下搅拌12小时。然后减压浓缩反应混合物。将残余物在水(50mL)中稀释并用DCM(50mL×3)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=10/1至0/1)纯化,得到((2R)-3-甲基-1-((2-(甲基氨基甲酰基)-5-硝基-2,3-二氢-1H-茚-

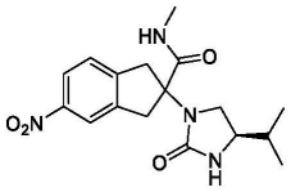
2-基)氨基)丁-2-基)氨基甲酸叔丁酯(13g,产率:73%)。^{1}H NMR(400MHz,DMSO-d_6)δppm 8.08(d,J=10.0Hz,2H),7.63-7.61(m,1H),7.34(d,J=8.0Hz,1H),7.19(d,J=3.2Hz,1H),4.31(s,1H),3.70-3.59(m,3H),3.44(s,1H),3.02-2.99(m,2H),2.88(d,J=4.8Hz,1H),2.58-2.55(m,1H),2.35-2.33(m,1H),1.68-1.66(m,2H),1.45(s,9H),0.89-0.85(m,6H)。

[0360] 步骤2:2-(((R)-2-氨基-3-甲基丁基)氨基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺

[0361] 

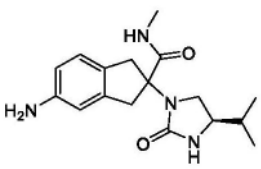
[0362] 向((2R)-3-甲基-1-((2-(甲基氨基甲酰基)-5-硝基-2,3-二氢-1H-茚-2-基)氨基)丁-2-基)氨基甲酸叔丁酯(7.8g,18.55mmol)在DCM(80mL)中的溶液中添加TFA (10mL)。将混合物在20℃下搅拌13小时。在浓缩去除TFA后,将反应混合物通过饱和$NaHCO_3$(50mL)淬灭,然后用DCM(100mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到2-(((R)-2-氨基-3-甲基丁基)氨基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺(4.5g,产率:76%)。MS(ESI,m/e)$[M+H]^+$321.2。

[0363] 步骤3:2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺

[0364] 

[0365] 将2-(((R)-2-氨基-3-甲基丁基)氨基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺(4g,12.48mmol)、TEA(0.5mL)和CDI(3.04g,18.73mmol)在THF(40mL)中的混合物在回流下搅拌1小时。将反应混合物减压浓缩,然后用水(50mL)稀释并用DCM(50mL×3)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺(3.5g,产率:80%)。^{1}H NMR(400MHz,DMSO-d_6)δppm 8.08(d,J=7.2Hz,2H),7.69(s,1H),7.37-7.33(m,1H),7.12(s,1H),7.05(s,1H),4.75(s,1H),3.87-3.83(m,2H),3.63-3.55(m,2H),3.44-3.39(m,2H),3.14-3.12(m,1H),2.77(d,J=7.6Hz,3H),1.63-1.62(m,1H),0.89-0.83(m,6H)。

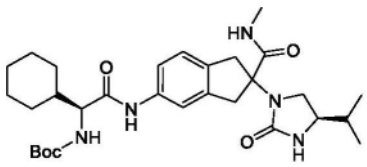
[0366] 步骤4:5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺

[0367] 

[0368] 向2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-

甲酰胺(8.1g,25.58mmol)在CH_3OH(80mL)中的溶液中添加Pd/C(1g)。将反应混合物用H_2吹扫3次并在H_2气氛(50psi)下在50℃下氢化12小时。将反应混合物过滤并将滤液真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(6.1g,产率:70%)。MS(ESI,m/e)$[M+H]^+$317.3。

[0369] 步骤5:((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸叔丁酯

[0370] 

[0371] 在0℃下,向5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(1.5g,4.74mmol)、TEA (719.59mg,7.11mmol)和(S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酸(1.45g,5.69mmol)在DCM(20mL)中的溶液中添加HATU(2.16g,5.69mmol)。将混合物在20℃下搅拌3小时。然后将反应混合物通过H_2O(50mL)淬灭并用DCM(50mL×3)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=100/1至1/1)纯化,得到((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸叔丁酯(2.5g,产率:95%)。^1H NMR(400MHz,DMSO-d_6)δppm 9.75(s,1H),7.52-7.45(m,2H),7.34-7.26(m,1H),7.16-7.08(m,1H),6.82-6.75(m,2H),3.92-3.90(m,1H),3.56-3.48(m,2H),3.21-3.18(m,2H),3.11-3.08(m,2H),2.90-2.88(m,1H),2.56(d,J=4.4Hz,3H),1.75-1.50(m,6H),1.42(s,9H),1.15-1.02(m,4H),0.74-0.65(m,6H)。

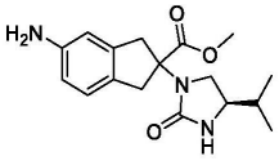
[0372] 步骤6:5-((S)-2-氨基-2-环己基乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(IntA2)

[0373] 将((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸叔丁酯(2.5g,4.5mmol)在DCM(20mL)和TFA(5m)中的溶液在20℃下搅拌3小时。在真空浓缩以去除TFA后,将反应混合物通过饱和$NaHCO_3$(50mL)淬灭并用DCM(100mL×3)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型MPLC(SiO_2柱,洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到5-((S)-2-氨基-2-环己基乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(1270mg,产率:62%)。^1H NMR(400MHz,DMSO-d_6)δppm 10.25(s,1H),7.55-7.44(m,4H),7.37-7.31(m,1H),7.15(d,J=8.0Hz,1H),6.77(d,J=11.2Hz,1H),3.60-3.48(m,3H),3.36-3.34(m,3H),3.22-3.16(m,2H),2.84-2.82(m,1H),2.56(d,J=4.4Hz,3H),1.75-1.50(m,6H),1.45(s,1H),1.15-1.02(m,5H),0.74-0.67(m,6H).MS(ESI,m/e)$[M+H]^+$456.3。

[0374] Int A3:5-((S)-2-氨基-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-(邻甲苯基)-2,3-二氢-1H-茚-2-甲酰胺

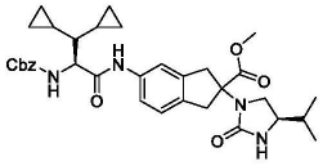
[0375] 步骤1:5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸

甲酯

[0376] 

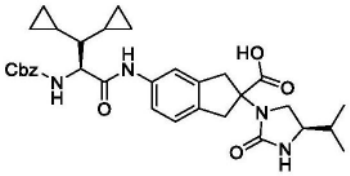
[0377] 在室温下,在N_2下,向2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-5-硝基-2,3-二氢-1H-茚-2-甲酸甲酯(5.9g,16.9mmol,通过与Int A2中所述的2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺类似的程序制备)在MeOH(60mL)中的溶液中添加雷尼镍(0.6g,1.69mmol)。将混合物在H_2气氛(15psi)下在60℃下氢化1小时。将反应混合物通过硅藻土垫过滤并用MeOH(50mL)洗涤。将滤液真空浓缩,得到5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯(2.5g,粗物品),将其直接用于下一步骤。MS(ESI,m/e)$[M+H]^+$318.1。

[0378] 步骤2:5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯

[0379] 

[0380] 在0℃下,向5-氨基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯(2.5g)、DIEA(3.05g,23.6mmol)和(S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酸(2.39g,7.88mmol)在DCM(25mL)中的溶液中添加HATU(3.0g,7.88mmol)。将混合物在室温下搅拌持续12小时。将反应混合物用水(30mL)稀释,然后用DCM(30mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化,得到5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯(2.5g,产率:53%)。MS(ESI,m/e)$[M+H]^+$603.3。

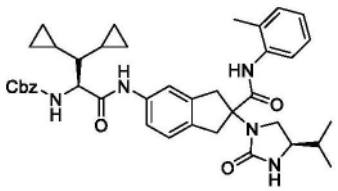
[0381] 步骤3:5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸

[0382] 

[0383] 在N_2下,向5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯(2.5g,4.13mmol)在THF(47mL)中的溶液中添加H_2O(10mL)、$LiOH.H_2O$(654mg,8.26mmol)。将混合物在室温下搅拌2小时。将反应混合物在搅拌下用HCl酸(30mL,0.5M)稀释,然后用EtOAc(35mL×3)萃取。将合并的有机相用盐水(40mL)洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩,得到5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸(1.0g,产率:50%)。^{1}H NMR(400MHz,DMSO-d_6)δppm 12.5(s,1H),9.84(s,

1H),7.23-7.53(m,8H),7.13-7.11(m,1H),6.75(d,J=2.4Hz,1H),5.06(s,2H),4.29-4.44(m,1H),3.42-3.52(m,2H),3.36(s,2H),3.16-3.24(m,1H),3.04-3.13(m,1H),1.50-1.47(m,1H),0.70-0.92(m,9H),0.08-0.61(m,10H)。MS实验值:$[M+H]^+$589.4。

[0384] 步骤4:((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)氨基甲酸苄酯

[0385] 

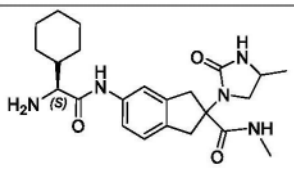
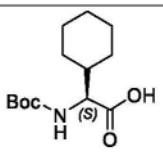
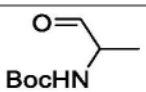
[0386] 在0℃下,向5-((S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸(0.15g,254.80umol)在DCM(5mL)中的溶液中添加邻甲苯胺(0.027g,0.255mmol)、DIEA(65.86mg,509.60umol)和HATU(116.24mg,305.76umol)。将混合物在室温下搅拌12小时。将反应混合物用H_2O(5mL)稀释,然后用DCM(5mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型TLC(硅胶,洗脱液:石油醚/乙酸乙酯(v/v)=5:1,R_f=0.1)纯化,得到((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(0.105g,产率:61%)。

[0387] 步骤5:5-((S)-2-氨基-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-(邻甲苯基)-2,3-二氢-1H-茚-2-甲酰胺(IntA3)

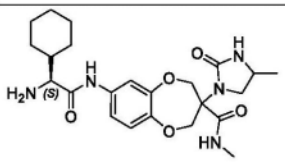
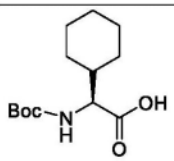
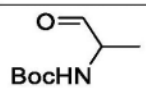
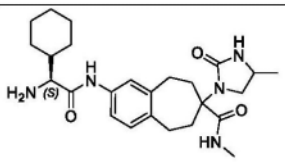
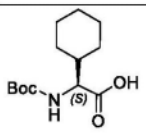
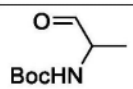
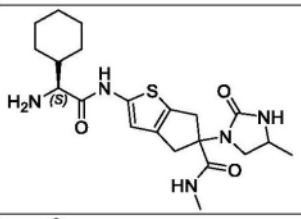
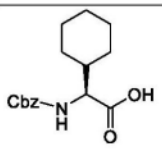
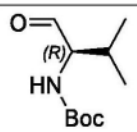
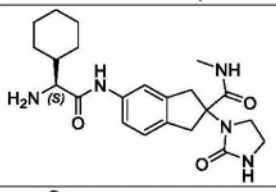
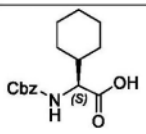
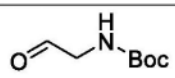
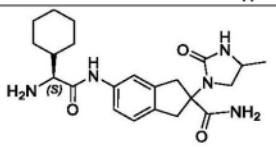
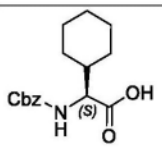
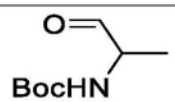
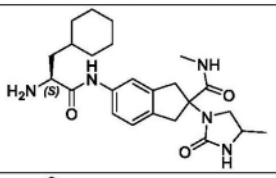
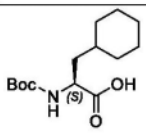
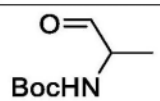
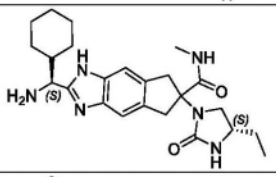
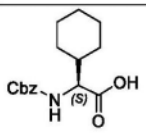
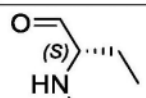
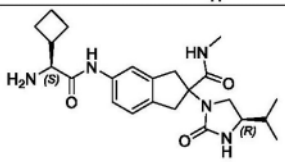
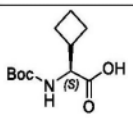
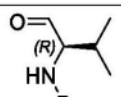
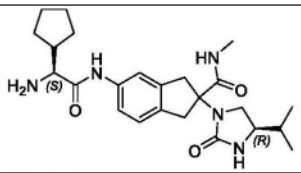
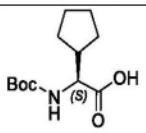
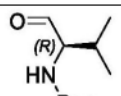
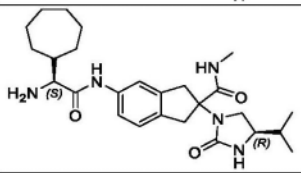
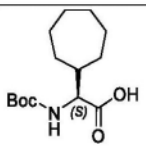
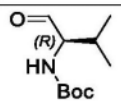
[0388] 在20℃下,在H_2下,向((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(0.105g,0.155mmol)在MeOH(1mL)和MeNH2.H2O(0.1mL)中的溶液中添加Pd(OH)2/C(0.1g,0.155mmol)。将混合物在50℃下在H_2(20Psi)气氛下搅拌1小时。将反应混合物过滤,并且将滤液真空浓缩。将粗产物通过制备型TLC(硅胶,洗脱液:乙酸乙酯/MeOH(v/v)=10/1,R_f=0.2)纯化,得到标题化合物Int A3(65mg,产率:77%)。MS实验值:$[M+H]^+$544.5。

[0389] 根据本领域技术人员已知的与中间体Int A1或Int A2或Int A3类似的方法/程序合成在2,3-二氢-1H-茚核心片段的2位处具有甲酰胺基团的另一关键中间体;醛和氨基酸的不同材料也列于表中。

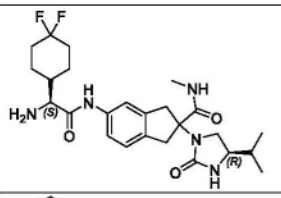
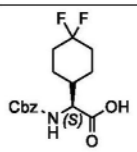
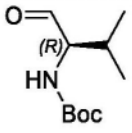
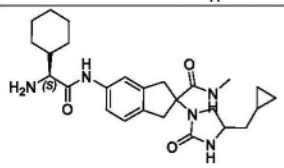
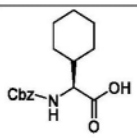
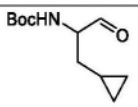
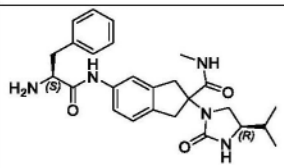
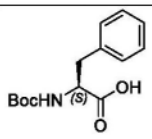
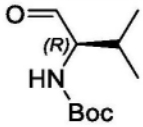
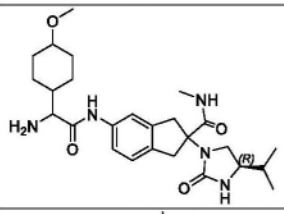
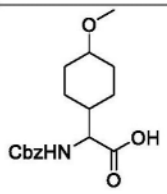
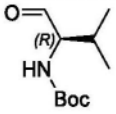
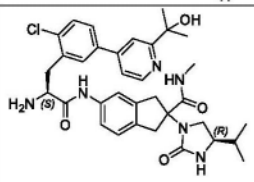
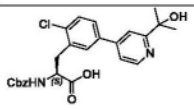
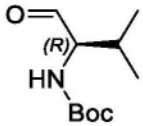
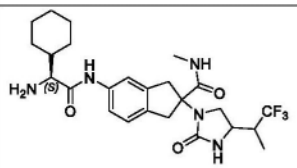
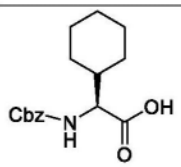
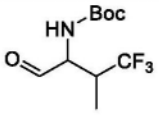
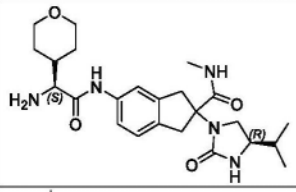
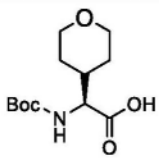
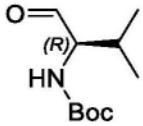
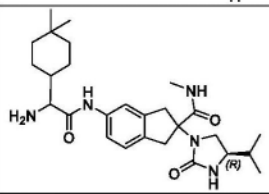
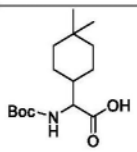
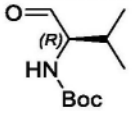
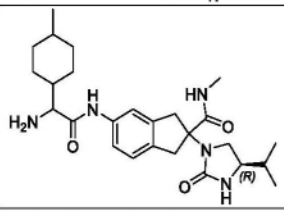
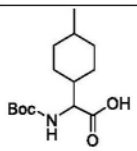
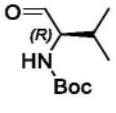
[0390]

Int	结构	被保护的氨基酸	醛	数据
A4				MS (ESI, m/e) $[M+1]^+$ 428.2

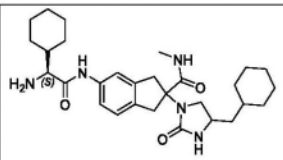
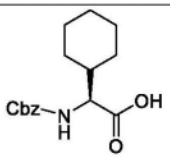
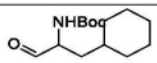
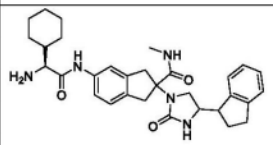
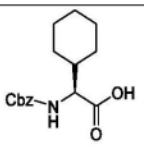
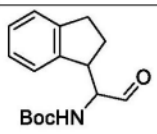
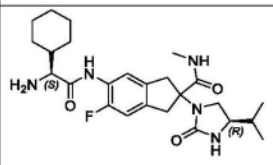
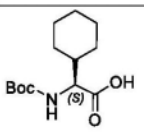
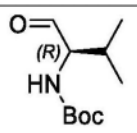
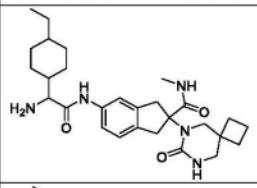
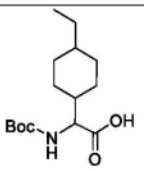
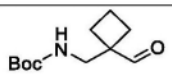
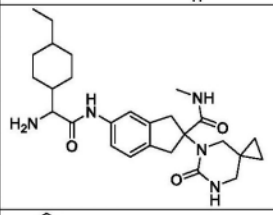
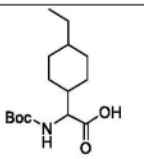
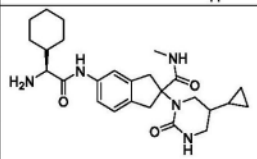
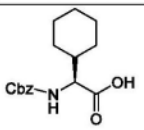
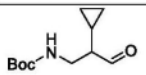
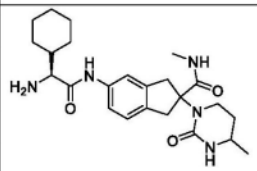
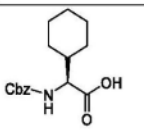
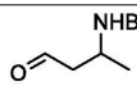
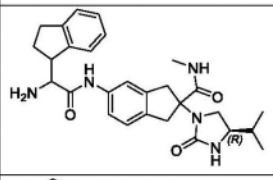
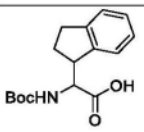
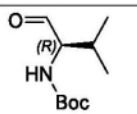
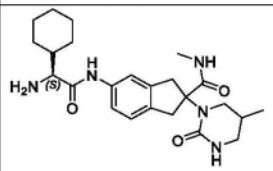
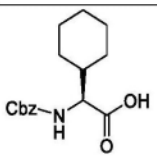
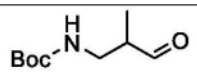
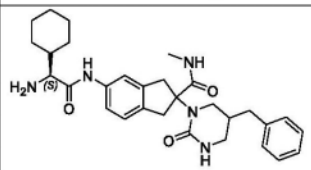
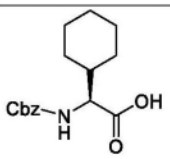
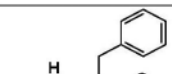
[0391]

A5				MS (ESI, m/e) $[M+1]^+$ 460.3
A6				MS (ESI, m/e) $[M+1]^+$ 456.3
A7				MS (ESI, m/e) $[M+1]^+$ 434.4。
A8				MS (ESI, m/e) $[M+1]^+$ 414.3
A9				MS (ESI, m/e) $[M+1]^+$ 414.2
A10				MS (ESI, m/e) $[M+1]^+$ 442.3
A11				MS (ESI, m/e) $[M+1]^+$ 439.2
A12				MS (ESI, m/e) $[M+1]^+$ 428.2
A13				MS (ESI, m/e) $[M+1]^+$ 442.3
A14				MS (ESI, m/e) $[M+1]^+$ 470.3

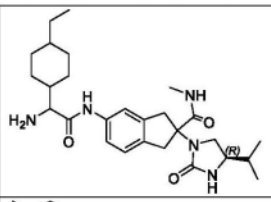
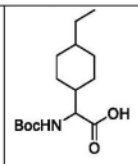
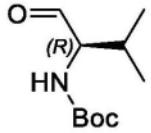
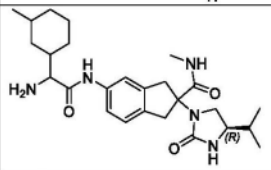
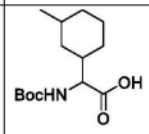
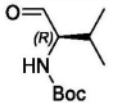
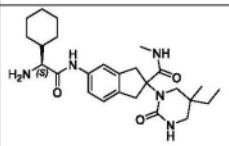
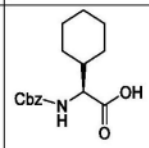
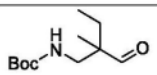
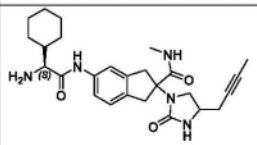
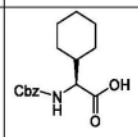
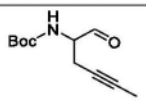
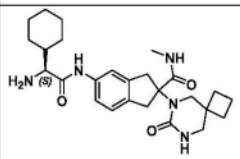
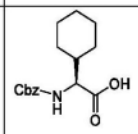
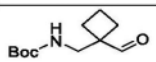
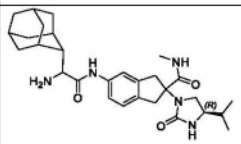
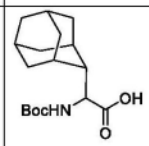
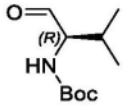
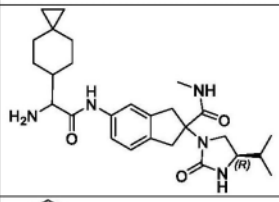
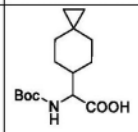
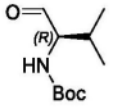
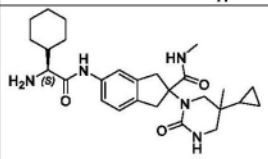
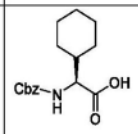
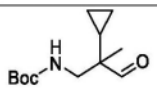
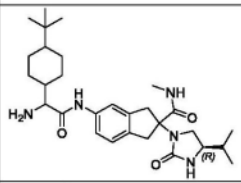
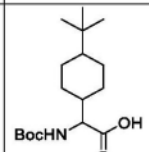
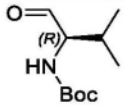
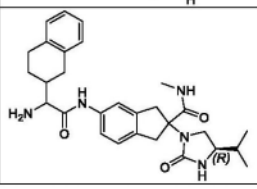
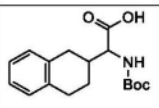
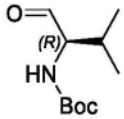
[0392]

A15				MS (ESI, m/e) $[M+1]^+$ 492.2。
A16				MS (ESI, m/e) $[M+1]^+$ 468.2。
A17				MS (ESI, m/e) $[M+1]^+$ 464.3。
A18				MS (ESI, m/e) $[M+1]^+$ 486.3。
A19				MS (ESI, m/e) $[M+1]^+$ 633.4。
A20				MS (ESI, m/e) $[M+1]^+$ 510.2。
A21				MS (ESI, m/e) $[M+1]^+$ 458.3。
A22				MS (ESI, m/e) $[M+1]^+$ 484.3
A23				MS (ESI, m/e) $[M+1]^+$ 470.3

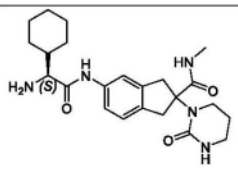
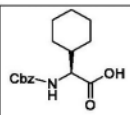
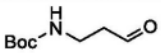
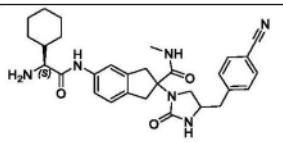
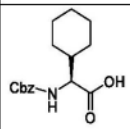
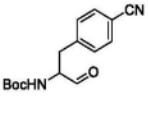
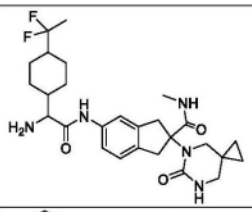
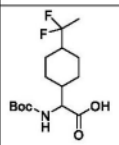
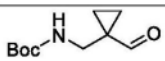
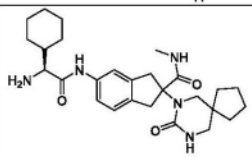
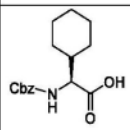
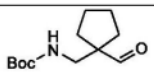
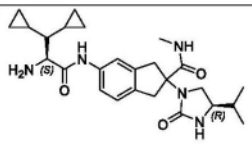
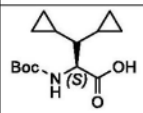
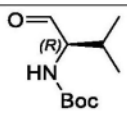
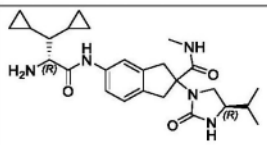
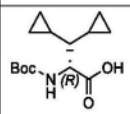
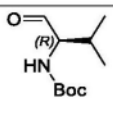
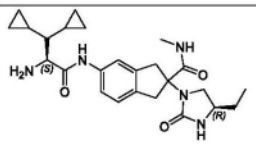
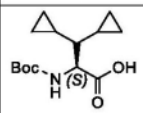
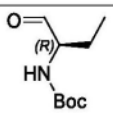
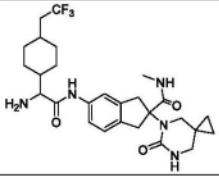
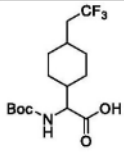
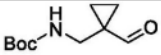
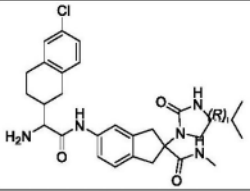
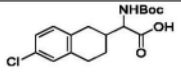
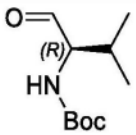
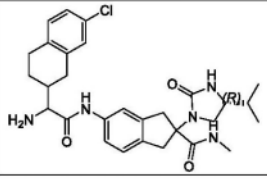
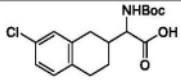
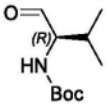
[0393]

A24				MS (ESI, m/e) $[M+1]^+$ 510.4。
A25				MS (ESI, m/e) $[M+1]^+$ 530.3。
A26				MS (ESI, m/e) $[M+1]^+$ 474.3
A27				MS (ESI, m/e) $[M+1]^+$ 496.3
A28				MS (ESI, m/e) $[M+1]^+$ 482.3
A29				MS (ESI, m/e) $[M+1]^+$ 468.4。
A30				MS (ESI, m/e) $[M+1]^+$ 442.2。
A31				MS (ESI, m/e) $[M+1]^+$ 490.3。
A32				MS (ESI, m/e) $[M+1]^+$ 442.2。
A33				MS (ESI, m/e) $[M+1]^+$ 518.4。

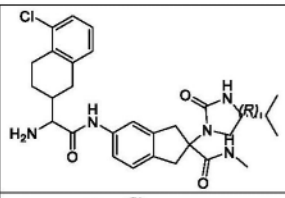
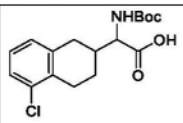
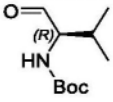
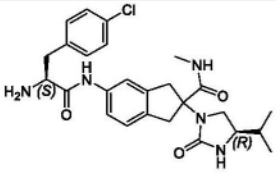
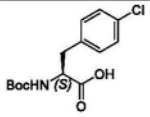
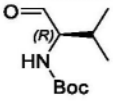
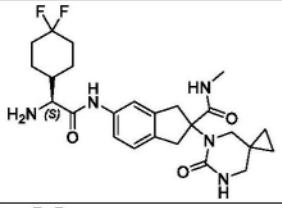
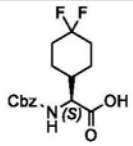
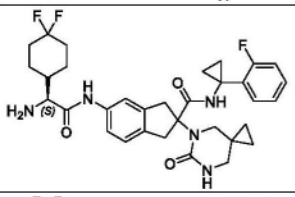
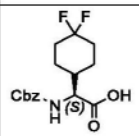
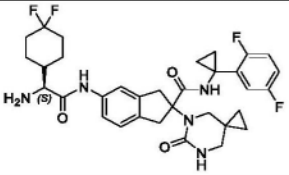
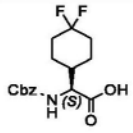
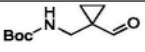
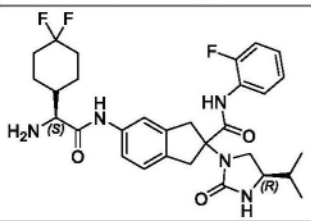
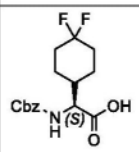
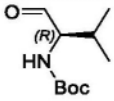
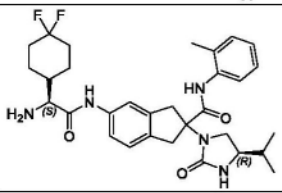
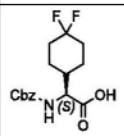
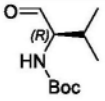
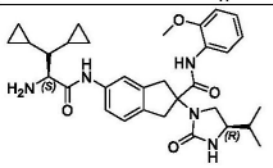
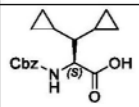
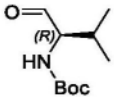
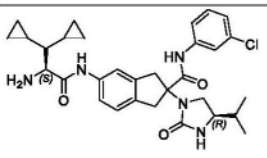
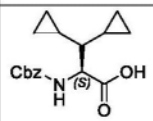
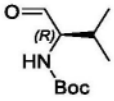
[0394]

A34				MS (ESI, m/e) $[M+1]^+$ 484.3。
A35				MS (ESI, m/e) $[M+1]^+$ 470.3。
A36				MS (ESI, m/e) $[M+1]^+$ 470.3。
A37				MS (ESI, m/e) $[M+1]^+$ 466.3。
A38				MS (ESI, m/e) $[M+1]^+$ 468.3。
A39				MS (ESI, m/e) $[M+1]^+$ 508.3
A40				MS (ESI, m/e) $[M+1]^+$ 482.4。
A41				MS (ESI, m/e) $[M+1]^+$ 482.3
A42				MS (ESI, m/e) $[M+1]^+$ 512.5。
A43				MS (ESI, m/e) $[M+1]^+$ 504.3。

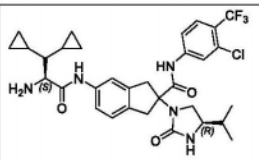
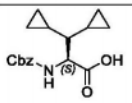
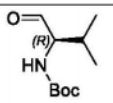
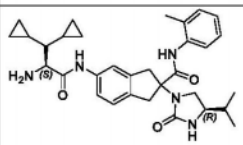
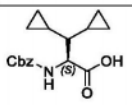
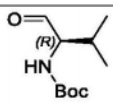
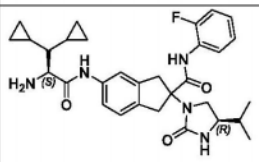
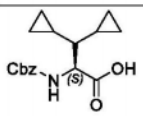
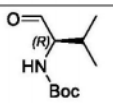
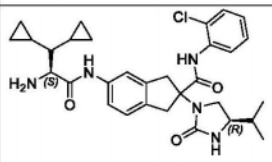
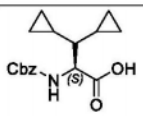
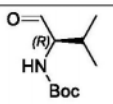
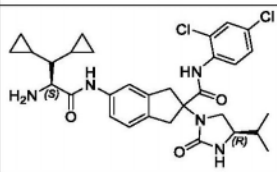
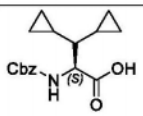
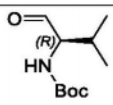
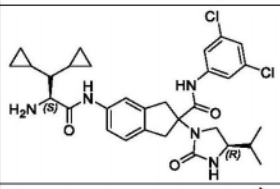
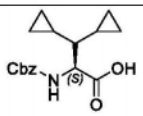
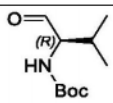
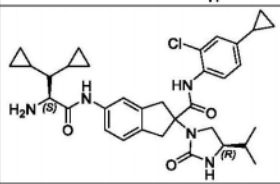
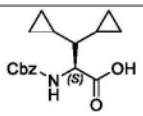
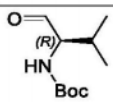
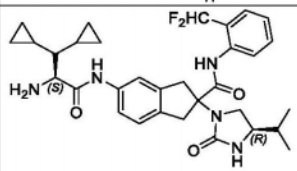
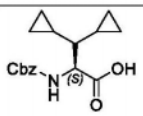
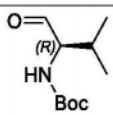
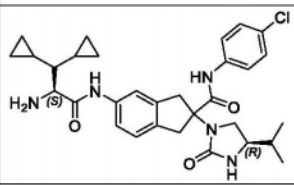
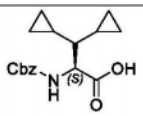
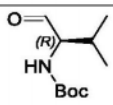
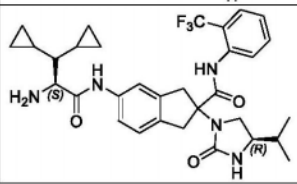
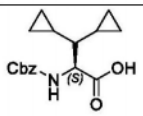
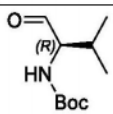
[0395]

A44				MS (ESI, m/e) $[M+1]^+$ 428.3。
A45				MS (ESI, m/e) $[M+1]^+$ 529.3。
A46				MS (ESI, m/e) $[M+1]^+$ 519.4
A47				MS (ESI, m/e) $[M+1]^+$ 482.1。
A48				MS (ESI, m/e) $[M+1]^+$ 468.3
A49				MS (ESI, m/e) $[M+1]^+$ 468.3
A50				MS (ESI, m/e) $[M+1]^+$ 454.3。
A51				MS (ESI, m/e) $[M+1]^+$ 536.5。
A52				MS (ESI, m/e) $[M+1]^+$ 538.3。
A53				MS (ESI, m/e) $[M+1]^+$ 538.1。

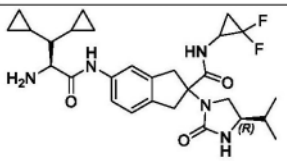
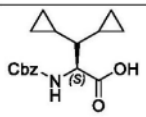
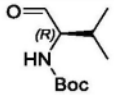
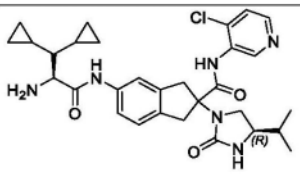
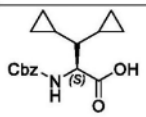
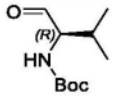
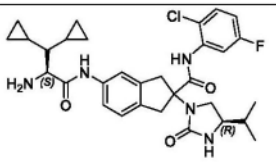
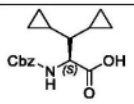
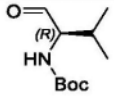
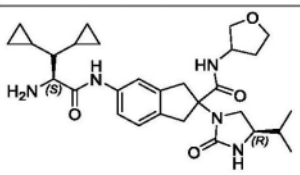
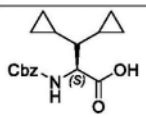
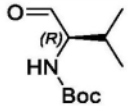
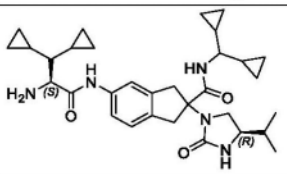
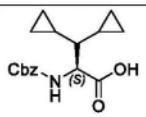
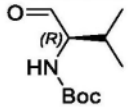
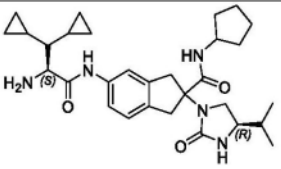
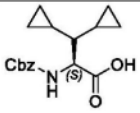
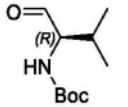
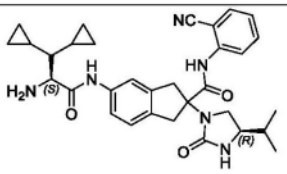
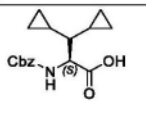
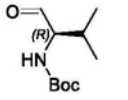
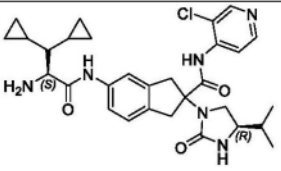
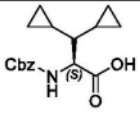
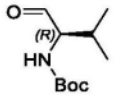
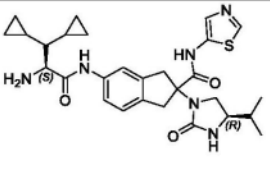
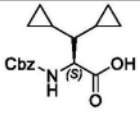
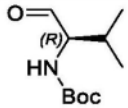
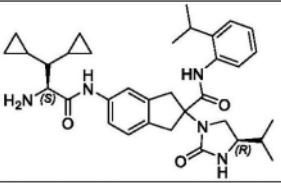
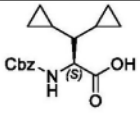
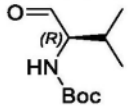
[0396]

A54				MS (ESI, m/e) $[M+1]^+$ 538.3。
A55				MS (ESI, m/e) $[M+1]^+$ 498.0。
A56				MS (ESI, m/e) $[M+1]^+$ 490.3
A57				MS (ESI, m/e) $[M+1]^+$ 610.4。
A58				MS (ESI, m/e) $[M+1]^+$ 628.4。
A59				MS (ESI, m/e) $[M+1]^+$ 572.3。
A60				MS (ESI, m/e) $[M+1]^+$ 568.3。
A61				MS (ESI, m/e) $[M+1]^+$ 560.5。
A62				MS (ESI, m/e) $[M+1]^+$ 564.4。

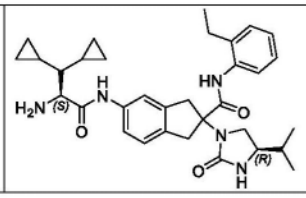
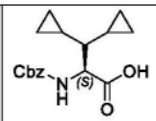
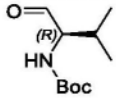
[0397]

A63				MS (ESI, m/e) $[M+1]^+$ 632.3。
A64				MS (ESI, m/e) $[M+1]^+$ 544.4。
A65				MS (ESI, m/e) $[M+1]^+$ 548.4。
A66				MS (ESI, m/e) $[M+1]^+$ 564.3。
A67				MS (ESI, m/e) $[M+1]^+$ 598.2。
A68				MS (ESI, m/e) $[M+1]^+$ 598.3。
A69				MS (ESI, m/e) $[M+1]^+$ 604.2。
A70				MS (ESI, m/e) $[M+1]^+$ 580.3。
A71				MS (ESI, m/e) $[M+1]^+$ 564.3。
A72				MS (ESI, m/e) $[M+1]^+$ 598.4。

[0398]

A73				MS (ESI, m/e) $[M+1]^+$ 530.3。
A74				MS (ESI, m/e) $[M+1]^+$ 565.3。
A75				MS (ESI, m/e) $[M+1]^+$ 582.3。
A76				MS (ESI, m/e) $[M+1]^+$ 524.4。
A77				MS (ESI, m/e) $[M+1]^+$ 548.4。
A78				MS (ESI, m/e) $[M+1]^+$ 522.3。
A79				MS (ESI, m/e) $[M+1]^+$ 555.3。
A80				MS (ESI, m/e) $[M+1]^+$ 565.4。
A81				MS (ESI, m/e) $[M+1]^+$ 537.3。
A82				MS (ESI, m/e) $[M+1]^+$ 572.4。

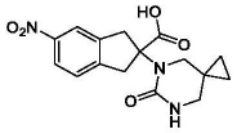
[0399]

A83				MS (ESI, m/e) $[M+1]^+$ 558.4。

[0400] 受保护的氨基酸或醛是可商购的,文献中已知的或可以如所示制备中概述的合成。

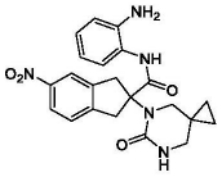
[0401] Int B1:5-(5-氨基-2-(1H-苯并[d]咪唑-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮

[0402] 步骤1:5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2,3-二氢-1H-茚-2-甲酸

[0403] 

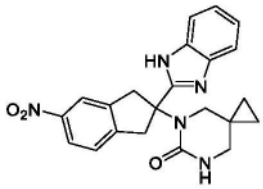
[0404] 向N-甲基-5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺(2.1g,6.1mol,通过与如Int A2中所述的2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺类似的程序制备)在DCM(15mL)中的溶液中添加TFA(5mL)并在室温下搅拌4小时。将反应混合物冷却至室温并在真空中浓缩以去除TFA和溶剂。将残余物用DCM(50mL)稀释,用饱和$NaHCO_3$(20mL)洗涤,然后用饱和NH4Cl(20mL)洗涤。将有机溶液经无水Na_2SO_4干燥,过滤并真空浓缩,得到5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸(2g,产率:98%)。MS实验值:$[M+H]^+$332.4。

[0405] 步骤2:N-(2-氨基苯基)-5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2,3-二氢-1H-茚-2-甲酰胺

[0406] 

[0407] 在0℃下,向5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸(0.5g,1.51mmol)、苯-1,2-二胺(0.26g,1.51mmol)和TEA(0.3g,3mmol)在DCM(10mL)中的溶液中添加HATU(0.0.65g,1.7mmol)。将混合物在室温下搅拌4小时。将反应混合物用水(15mL)稀释,用EtOAc(20mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1至1/1)纯化,得到N-(2-氨基苯基)-5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺(0.18g,产率:28%)。MS实验值:$[M+H]^+$422.4。

[0408] 步骤3:5-(2-(1H-苯并[d]咪唑-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮

[0409] 

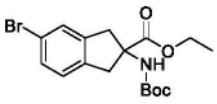
[0410] 将N-(2-氨基苯基)-5-硝基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺(0.18g,0.45mmol)在AcOH(8mL)中的溶液加热至50℃并搅拌4小时。将反应混合物用水(15mL)稀释,用EtOAc(20mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=50/1至5/1)纯化,得到5-(2-(1H-苯并[d]咪唑-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(80mg,产率:44%)。MS实验值:$[M+H]^+$404.2。

[0411] 步骤4:5-(5-氨基-2-(1H-苯并[d]咪唑-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(IntB1)

[0412] 在N_2下,向5-(2-(1H-苯并[d]咪唑-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(80mg,0.09mmol)在MeOH(10mL)中的溶液中添加雷尼镍(11mg)和NH3·H_2O(1mL)。将悬浮液在真空下脱气并用H_2吹扫三次。将混合物在50℃在H_2气氛下搅拌1小时。将反应混合物过滤并真空浓缩,得到5-(5-氨基-2-(1H-苯并[d]咪唑-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(70mg,产率:54%)。^{1}H NMR(400MHz,DMSO-d6)δppm 11.89(s,1H),7.55-7.38(m,2H),7.07(s,2H),6.79(d,J=6.8Hz,1H),6.47-6.11(m,3H),4.79(s,2H),4.06-3.82(m,2H),3.27-3.09(m,4H),2.86(d,J=7.2Hz,2H),0.49-0.27,4H)。$[M+H]^+$374.2。

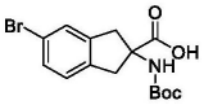
[0413] Int B2:5-(5-氨基-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮

[0414] 步骤1:5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸乙酯。

[0415] 

[0416] 向2-氨基-5-溴-2,3-二氢-1H-茚-2-甲酸乙酯(4g,14.1mmol)在DCM(60mL)中的溶液中添加Boc_2O(7.7g,35.3mmol)。将混合物加热至回流搅拌15小时。将反应混合物冷却至室温并浓缩。将残余物通过硅胶柱色谱(洗脱液:EtOAc/PE(v/v)=1/5)纯化,得到5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸乙酯(4.8g,产率:91%)。MS(ESI)m/e[M-56+1]$^+$328.1。

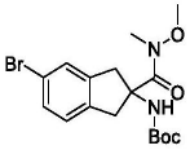
[0417] 步骤2:5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸。

[0418] 

[0419] 在室温下,在搅拌下,向5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸乙酯(3.45g,9.0mmol)在THF(45mL)中的溶液中逐滴添加NaOH溶液(1.44g于15mL H_2O)。将所得混合物加热至55℃并搅拌16小时。将反应混合物冷却至室温并真空浓缩。将残余物用水稀释并将混合物用HCl酸(1N)调节至pH约5,然后用EtOAc(50×3mL)萃取。将有机层用盐水洗涤,干燥并真空浓缩。将粗产物在EtOAc/PE(1:1)中在室温下搅拌10分钟。通过过滤收

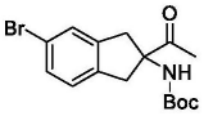
集固体并真空干燥,得到5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸(3g,产率:93%)。MS(ESI)m/e[M+23]$^+$378.1。

[0420] 步骤3:(5-溴-2-(甲氧基(甲基)氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0421] 

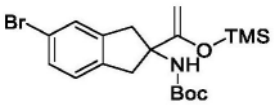
[0422] 在室温下,向5-溴-2-((叔丁氧基羰基)氨基)-2,3-二氢-1H-茚-2-甲酸(2.3g,6.5mmol)在DCM(50mL)中的溶液中逐滴添加N,O-二甲基羟胺盐酸盐(698mg,7.1mmol)和HATU(2.7g,7.1mmol)、DIPEA(3.3g,25.9mmol)。将所得混合物在室温下搅拌2小时。用EtOAc稀释反应混合物。将有机层用饱和$NaHCO_3$溶液(水溶液)和盐水洗涤,干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:EtOAc/PE(v/v)=1/2)纯化,得到(5-溴-2-(甲氧基(甲基)氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(2.3g,产率:88%)。MS(ESI)m/e[M-56+1]$^+$343.2。

[0423] 步骤4:(2-乙酰基-5-溴-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0424] 

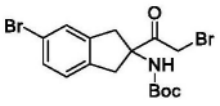
[0425] 在低于-10℃下,在N_2气氛下,向(5-溴-2-(甲氧基(甲基)氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(1.55g,3.9mmol)在THF(25mL)中的溶液中添加CH_3MgCl(4mL,11.7mmol)。将所得混合物在0℃下搅拌1小时。将反应混合物在0℃下倒入饱和NH_4Cl水溶液(30mL)中并用EtOAc(30mL×3)萃取。将合并的有机层用盐水洗涤,干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:EtOAc/PE(v/v)=1/6)纯化,得到(2-乙酰基-5-溴-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(1.3g,产率:94%)。MS(ESI)m/e[M+23]$^+$376.1。

[0426] 步骤5:(5-溴-2-(1-((三甲基甲硅烷基)氧基)乙烯基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0427] 

[0428] 将(2-乙酰基-5-溴-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(1.1g,3.1mmol)溶解于THF(15mL)中并在N_2气氛下冷却至-70℃。在-70℃下,在N_2气氛下,在搅拌下,向这种溶液中逐滴添加LDA(3.1mL,6.2mmol)。在所得混合物搅拌30分钟后,在-70℃添加TMSCl(680mg,6.2mmol)。在-60℃下进一步搅拌1小时后,将反应混合物在低于-20℃下通过NH_4Cl(水溶液)淬灭,然后用EtOAc稀释。将有机层分离,用水和盐水洗涤,干燥并真空浓缩,得到粗产物(1.5g),将其直接用于下一步骤中。

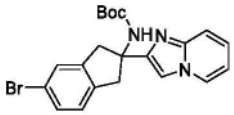
[0429] 步骤6:(5-溴-2-(2-溴乙酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0430] 

[0431] 在0℃下,向(5-溴-2-(1-((三甲基甲硅烷基)氧基)乙烯基)-2,3-二氢-1H-茚-2-

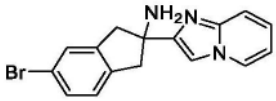
基)氨基甲酸叔丁酯(1.5g,粗物质)在THF(20mL)中的溶液中分几份添加NBS(625mg,3.5mmol)。将混合物在0℃下搅拌1小时。将反应混合物通过$NaHCO_3$(水溶液)淬灭并用EtOAc(30mL)稀释。将有机层分离,用水和盐水洗涤,干燥并浓缩。将残余物通过硅胶柱色谱(洗脱液:EtOAc/PE(v/v)=1/7)纯化,得到(5-溴-2-(2-溴乙酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(740mg,两步的产率:55%)。MS(ESI)m/e[M+23]$^+$456.1。

[0432] 步骤7:(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯。

[0433] 

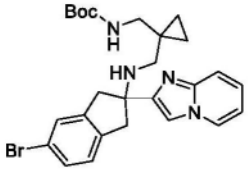
[0434] 将(5-溴-2-(2-溴乙酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(740mg,1.72mmol)和吡啶-2-胺(162mg,1.72mmol)在MeOH(10mL)中的溶液加热至80℃并在N_2气氛下搅拌24小时。将反应混合物冷却至室温并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:EtOAc/PE(v/v)=1/2)纯化,得到(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(250mg,产率:34%)。MS(ESI)m/e[M+1]$^+$428.2。

[0435] 步骤8:5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺。

[0436] 

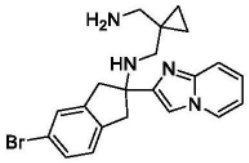
[0437] 在室温下,向(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(250mg,0.59mmol)在DCM(16mL)中的溶液中逐滴添加HCl(4N于二噁烷中,4mL)。将所得混合物在室温下搅拌2小时。然后将反应混合物真空浓缩,得到5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺(180mg,粗物质),为HCl盐。MS(ESI)m/e[M+1]$^+$328.1。

[0438] 步骤9:((1-(((5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)-甲基)氨基甲酸叔丁酯。

[0439] 

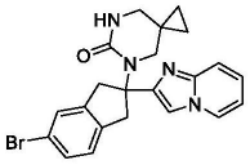
[0440] 将5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺(180mg,0.55mmol)和((1-甲酰基环丙基)甲基)氨基甲酸叔丁酯(154mg,0.77mmol)在DCM(10mL)中的混合物在室温下搅拌1小时。然后在0℃下向这种混合物中分批添加$NaBH_3CN$(351mg,1.66mmol)。将所得混合物在室温下搅拌过夜。将反应混合物通过$NaHCO_3$(水溶液)淬灭并用EtOAc(30mL)萃取。将有机层用盐水洗涤,干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/EtOAc(v/v)=1/1)纯化,得到((1-(((5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)-甲基)氨基甲酸叔丁酯(200mg,两步的产率:67%)。MS(ESI)m/e[M+1]$^+$511.3。

[0441] 步骤10:N-((1-(氨基甲基)环丙基)甲基)-5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺。

[0442] 

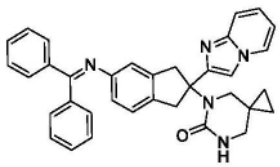
[0443] 在0℃下,向((1-(((5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)-甲基)氨基甲酸叔丁酯(200mg,0.39mmol)在DCM(9mL)中的溶液中逐滴添加HCl(4N于二噁烷中,3mL)。所得混合物在室温下搅拌2h。然后浓缩反应混合物,并且得到N-((1-(氨基甲基)环丙基)甲基)-5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺HCl盐(200mg,粗物质),将其直接用于下一步骤中。MS(ESI)m/e[M+1]$^+$411.2。

[0444] 步骤11:5-(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮。

[0445] 

[0446] 向N-((1-(氨基甲基)环丙基)甲基)-5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-胺(200mg)和TEA(1mL)在THF(10mL)中的溶液中添加CDI(198mg,1.22mmol)。将混合物加热至60℃并搅拌1小时。将反应混合物冷却至室温,用EtOAc稀释,用水和盐水洗涤,干燥并真空浓缩。将粗产物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=15/1)纯化,得到5-(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(100mg,两步的产率:58%)。MS(ESI)m/e[M+1]$^+$437.2。

[0447] 步骤12:5-(5-((二苯基亚甲基)氨基)-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮。

[0448] 

[0449] 向5-(5-溴-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(100mg,0.23mmol)在二噁烷(15mL)中的溶液中添加二苯基甲亚胺(62.3mg,0.34mmol)、Pd_2dba_3(21mg,0.02mmol)、Xantphos(27mg,0.04mmol)和Cs_2CO_3(150mg,0.46mmol)。将混合物用N_2脱气,加热至100℃,然后在N_2气氛下搅拌6小时。将反应混合物冷却至室温并用DCM/MeOH(v/v=15/1)稀释。在滤出固体后,将滤液浓缩并通过制备型TLC(洗脱液:DCM/MeOH(v/v)=20/1)纯化,得到5-(5-((二苯基亚甲基)氨基)-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(58mg,产率:47%)。MS(ESI)m/e[M+1]$^+$538.4。

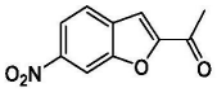
[0450] 步骤13:5-(5-氨基-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(IntB2)

[0451] 在室温下,向5-(5-((二苯基亚甲基)氨基)-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(58mg,0.11mmol)在THF(5mL)中的溶液中添加HCl(3N,1mL)并搅拌30分钟。将所得反应混合物倒入饱和$NaHCO_3$水溶液中,然后用EA

(30×3mL)萃取。将合并的有机层用盐水洗涤,干燥,过滤并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=10/1)纯化,得到5-(5-氨基-2-(咪唑并[1,2-a]吡啶-2-基)-2,3-二氢-1H-茚-2-基)-5,7-二氮杂螺[2.5]辛-6-酮(22mg,产率:55%)。MS(ESI)m/e[M+1]$^+$374.3。

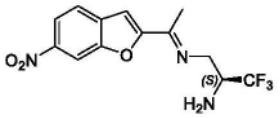
[0452] Int C1:(4S)-1-(1-(6-氨基-2,3-二氢苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮

[0453] 步骤1:1-(6-硝基苯并呋喃-2-基)乙-1-酮

[0454] 

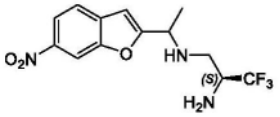
[0455] 向2-羟基-4-硝基苯甲醛(2g,12mmol)和1-氯丙-2-酮(1.1g,12mmol)在CH_3CN(20mL)中的溶液中添加K_2CO_3(3.3g,24mmol)。将混合物在室温下搅拌4小时。将反应混合物倒入水(40mL)中,然后用EtOAc(20mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=100/1至10/1)纯化,得到1-(6-硝基苯并呋喃-2-基)乙酮(0.61g,产率:25%)。MS(ESI)m/e[M+1]$^+$206.2。

[0456] 步骤2:(S)-1,1,1-三氟-3-((1-(6-硝基苯并呋喃-2-基)亚乙基)氨基)丙-2-胺

[0457] 

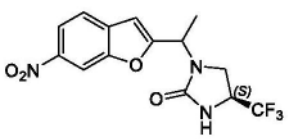
[0458] 向1-(6-硝基苯并呋喃-2-基)乙酮(0.4g,1.9mmol)和(S)-3,3,3-三氟丙烷-1,2-二胺盐酸盐(0.164g,2.9mmol)在DCM(10mL)中的溶液中添加TEA(0.101g,19.5mmol)和4A MS(1g)。将混合物在45℃下搅拌3小时。在过滤反应混合物后,减压浓缩滤液。将粗产物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=100/1至0/1)纯化,得到(S)-3,3,3-三氟-N1-(1-(6-硝基苯并呋喃-2-基)亚乙基)丙烷-1,2-二胺(0.5g,产率:81%)。MS(ESI)m/e[M+1]$^+$316.1。

[0459] 步骤3:(2S)-3,3,3-三氟-N1-(1-(6-硝基苯并呋喃-2-基)乙基)丙烷-1,2-二胺

[0460] 

[0461] 向(S)-3,3,3-三氟-N1-(1-(6-硝基苯并呋喃-2-基)亚乙基)丙烷-1,2-二胺(0.5g,1.6mmol)在MeOH(10mL)中的溶液中添加$NaBH_3CN$(1g,16mmol)。将混合物在70℃下搅拌12小时。将混合物倒入水(20mL)中,然后用EtOAc(10mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物纯化。将粗产物通过硅胶柱色谱(洗脱液:DCM/CH_3OH(v/v)=100/1至10/1)纯化,得到(2S)-3,3,3-三氟-N1-(1-(6-硝基苯并呋喃-2-基)乙基)丙烷-1,2-二胺(0.32g,产率:64%)。MS(ESI)m/e[M+1]$^+$318.2。

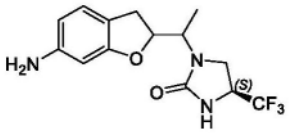
[0462] 步骤4:(4S)-1-(1-(6-硝基苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮

[0463] 

[0464] 在20℃下,向(2S)-3,3,3-三氟-N1-(1-(6-硝基苯并呋喃-2-基)乙基)丙烷-1,2-二胺(1.2g,3.8mmol)在THF(15mL)中的溶液中添加CDI(0.92g,5.7mmol)和TEA(0.5mL)。将

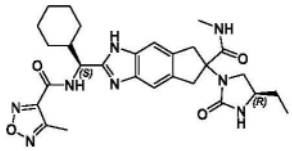
混合物在60℃下搅拌6小时。将反应混合物用EtOAc(30mL)稀释,然后用盐水洗涤。将有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:PE/EAE(v/v)=100/1至10/1)纯化,得到(4S)-1-(1-(6-硝基苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮(0.34g,产率:26%)。MS(ESI)m/e[M+1]$^+$344.3。

[0465] 步骤5:(4S)-1-(1-(6-氨基-2,3-二氢苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮(Int C1)

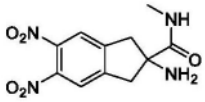
[0466] 

[0467] 在室温下,向(4S)-1-(1-(6-硝基苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮(0.32g,0.932mmol)在i-PrOH(5mL)中的溶液中添加Pd/C(0.1g,0.932mmol)。将混合物加热至50℃并搅拌并在H_2(15Psi)气氛下氢化2小时。过滤反应混合物并真空浓缩滤液。获得(4S)-1-(1-(6-氨基-2,3-二氢苯并呋喃-2-基)乙基)-4-(三氟甲基)咪唑烷-2-酮(282mg)。^{1}H NMR(400MHz,$CDCl_3$)δppm 7.02-6.84(m,1H),6.79-6.12(m,2H),5.10-4.92(m,1H),4.91-4.72(m,1H),4.20-4.09(m,1H),4.06-3.90(m,1H),3.83-3.66(m,1H),3.65-3.49(m,2H),3.48-2.80(m,1H),1.58-1.12(m,3H)。MS(ESI,m/e)[M+H]$^+$316.1。

[0468] 实施例32:N-((1S)-环己基(6-((R)-4-乙基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)-4-甲基-1,2,5-噁二唑-3-甲酰胺

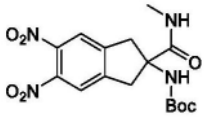
[0469] 

[0470] 步骤1:2-氨基-N-甲基-5,6-二硝基-2,3-二氢-1H-茚-2-甲酰胺

[0471] 

[0472] 在0℃下,向H_2SO_4(100mL)和HNO_3(25mL)的混合物中分批缓慢添加2-氨基-N-甲基-2,3-二氢-1H-茚-2-甲酰胺(19g,100mmol,溶解于10mL HOAc中)。在添加后,将混合物在室温下搅拌4小时。将反应混合物在0-10℃下小心地倒入饱和$NaHCO_3$(水溶液,500mL)中,然后用DCM(500mL)萃取。分离有机层并通过硅胶柱色谱(洗脱液:DCM至DCM/MeOH(v/v)=20/1)纯化,得到标题化合物(16.81g,产率:60.0%)。

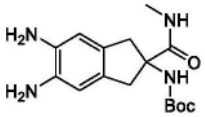
[0473] 步骤2:(2-(甲基氨基甲酰基)-5,6-二硝基-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯

[0474] 

[0475] 将2-氨基-N-甲基-5,6-二硝基-2,3-二氢-1H-茚-2-甲酰胺(16.81g,60mmol)和Boc_2O(26.16g)在DCM(200mL)中的混合物在室温下搅拌过夜。将反应混合物用PE(200mL)稀释,用盐水(500mL)洗涤,经Na_2SO_4干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题产物(19.76g,产率:86.7%)。MS(ESI,m/e)[M+1]$^+$

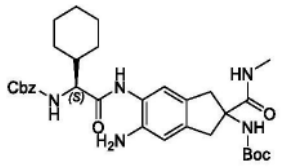
381.3。

[0476] 步骤3:(5,6-二氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯

[0477] 

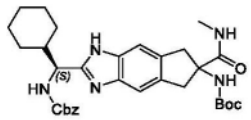
[0478] 向(2-(甲基氨基甲酰基)-5,6-二硝基-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(19.76g,52mmol)和Pd/C(1.5g)在MeOH(500mL)中的混合物用H_2气球鼓泡并在H_2气氛下搅拌过夜。将反应混合物过滤并真空浓缩滤液,然后通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题化合物(14.7g,产率:88.46%)。MS(ESI,m/e)[M+1]$^+$321.3。

[0479] 步骤4:((1S)-2-((6-氨基-2-((叔丁氧基羰基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环已基-2-氧代乙基)氨基甲酸苄酯

[0480] 

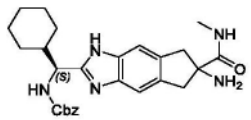
[0481] 将(S)-2-(((苄氧基)羰基)氨基)-2-环已基乙酸(13.4g,46mmol)、(5,6-二氨基-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-2-基)氨基甲酸叔丁酯(14.70g,46mmol)、HATU(19g,50mmol)和TEA (10g,100mmol)在DCM(500mL)中的混合物在室温下搅拌过夜。将反应混合物用$NaHCO_3$(水溶液,500mL)淬灭。将有机层分离,用盐水(500mL)洗涤,经Na_2SO_4干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题化合物(9.0g,产率:32.95%)。MS(ESI,m/e)[M+1]$^+$594.3。

[0482] 步骤5:((1S)-(6-((叔丁氧基羰基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环已基)甲基)氨基甲酸苄酯

[0483] 

[0484] 将((1S)-2-((6-氨基-2-((叔丁氧基羰基)氨基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环已基-2-氧代乙基)氨基甲酸苄酯(9.0g)和AcOH(50mL)的混合物加热至100℃并搅拌过夜。将反应混合物真空浓缩,将残余物用$NaHCO_3$(水溶液,250mL)稀释并用DCM(250mL)萃取,用盐水(500mL)洗涤,经Na_2SO_4干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题化合物(1.63g,产率:39.36%)。MS(ESI,m/e)[M+1]$^+$576.3。

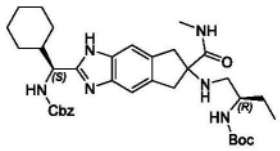
[0485] 步骤6:((1S)-(6-氨基-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环已基)甲基)氨基甲酸苄酯

[0486] 

[0487] 向((1S)-(6-((叔丁氧基羰基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环已基)甲基)氨基甲酸苄酯(5.0g,8.69mmol)在DCM(100mL)中的溶液

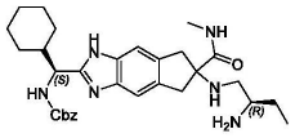
中添加HCl酸(4M,在二噁烷中,100mL)。将混合物在室温下搅拌过夜。将反应混合物减压浓缩以去除溶剂。将残余物用$NaHCO_3$(水溶液,250mL)稀释并用DCM(250mL)萃取。将有机层用盐水(200mL)洗涤,经Na_2SO_4干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题化合物(1.63g,产率:39.36%)。MS(ESI,m/e)$[M+1]^+$476.2。

[0488] 步骤7:((1S)-(6-(((R)-2-((叔丁氧基羰基)氨基)丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯

[0489] 

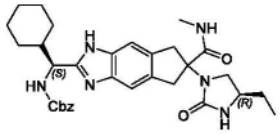
[0490] 将((1S)-(6-氨基-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯(300mg,0.63mmol)、(R)-(3-甲基-1-氧代丁-2-基)氨基甲酸叔丁酯(252mg,1.26mmol)和$NaBH(OAc)_3$(267mg,1.26mmol)在DCM(50mL)中的混合物在室温下搅拌2小时。将反应混合物用$NaHCO_3$(水溶液,100mL)淬灭并用DCM(50mL)萃取。将有机层经Na_2SO_4干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1)纯化。得到((1S)-(6-(((R)-2-((叔丁氧基羰基)氨基)丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯(310mg,产率:71.4%)。MS(ESI,m/e)$[M+1]^+$647.4。

[0491] 步骤8:((1S)-(6-(((R)-2-氨基丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯

[0492] 

[0493] 将((1S)-(6-(((R)-2-((叔丁氧基羰基)氨基)丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯(310mg,0.45mmol)和TFA(2mL)在DCM(5mL)中的混合物搅拌2小时。将混合物真空浓缩,得到((1S)-(6-(((R)-2-氨基丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯(236mg,粗物质),将其直接用于下一步骤中。MS(ESI,m/e)$[M+1]^+$547.3。

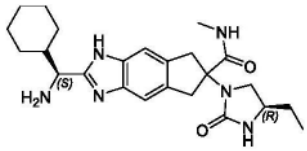
[0494] 步骤9:((1S)-环己基(6-((R)-4-乙基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)氨基甲酸苄酯

[0495] 

[0496] 将((1S)-(6-(((R)-2-氨基丁基)氨基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)(环己基)甲基)氨基甲酸苄酯(236mg,0.44mmol)、TEA (0.5mL)和CDI(142mg,0.88mmol)在THF(20mL)中的混合物加热至60℃并搅拌2小时。将反应混合物用盐水(50mL)淬灭,用EA (50×2mL)萃取。将合并的层经Na_2SO_4干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化。得到((1S)-环己基(6-((R)-4-乙

基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)氨基甲酸苄酯(236mg,产率:93.18%)。MS(ESI,m/e)[M+1]$^+$573.3。

[0497] 步骤10:2-((S)-氨基(环己基)甲基)-6-((R)-4-乙基-2-氧代咪唑烷-1-基)-N-甲基-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺

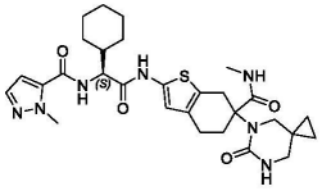
[0498] 

[0499] 向((1S)-环己基(6-((R)-4-乙基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)氨基甲酸苄酯(236mg,0.41mmol)和Pd/C(20mg)在MeOH(50mL)中的混合物用H_2气球鼓泡并在H_2气氛下搅拌过夜以用于脱保护。然后将反应混合物过滤并真空浓缩滤液。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化,得到标题胺化合物(142mg,产率:55.66%)。MS(ESI,m/e)[M+1]$^+$439.3。

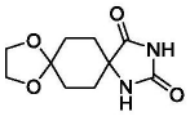
[0500] 步骤11:N-((1S)-环己基(6-((R)-4-乙基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)-4-甲基-1,2,5-噁二唑-3-甲酰胺(实施例32)

[0501] 向2-((S)-氨基(环己基)甲基)-6-((R)-4-乙基-2-氧代咪唑烷-1-基)-N-甲基-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺(22mg,0.05mmol)在DCM(10mL)中的溶液中添加4-甲基-1,2,5-噁二唑-3-甲酸(7mg,0.05mmol)、HATU(19mg,0.05mmol)和TEA(10mg,0.1mmol)。将混合物在室温下搅拌1小时。将反应混合物用$NaHCO_3$水溶液(50mL)淬灭并用DCM(20mL)稀释。将有机层经Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1至20/1)纯化。得到标题化合物(13mg,产率:47.4%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:12.20(br,1H),9.42(d,J=8.8Hz,1H),7.55-7.25(m,3H),6.69(s,1H),5.05(t,J=8.4Hz,1H),3.65-3.40(m,4H),3.32-3.23(m,2H),2.93-2.87(m,1H),2.58(d,J=4.4Hz,3H),2.10-1.55(m,5H),1.42-1.27(m,3H),1.21-0.95(m,5H),0.71(t,J=7.2Hz,3H)。MS(ESI,m/e)[M+1]$^+$549.4。

[0502] 实施例145:N-((1S)-1-环己基-2-((6-(甲基氨基甲酰基)-6-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

[0503] 

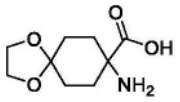
[0504] 步骤1:9,12-二氧杂-1,3-二氮杂二螺[4.2.4^8.2^5]十四烷-2,4-二酮

[0505] 

[0506] 将1,4-二氧杂螺[4.5]癸-8-酮(9.55g,61.2mmol)、NaCN(3g,61.2mmol)和$(NH_4)_2CO_3$(23.5g,244.8mmol)在H_2O(100mL)和EtOH(5mL)中的混合物在60℃下搅拌过夜。将反应

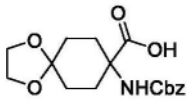
混合物冷却至室温并静置1天。过滤沉淀,然后在空气中干燥滤饼,得到9,12-二氧杂-1,3-二氮杂二螺[4.2.4^8.2^5]十四烷-2,4-二酮(7.38g,粗物质)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.59(s,1H),8.44(s,1H),3.87(s,4H),1.95-1.78(m,2H),1.73-1.69(m,4H),1.59-1.56(m,2H)。

[0507] 步骤2:8-氨基-1,4-二氧杂螺[4.5]癸烷-8-甲酸

[0508] 

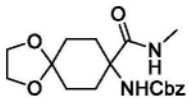
[0509] 将9,12-二氧杂-1,3-二氮杂二螺[4.2.4^8.2^5]十四烷-2,4-二酮(2g)在NaOH溶液(6N,15mL)中的溶液在140℃下在密封管中搅拌3小时。将反应混合物冷却至室温并用6N HCl酸酸化至pH=4。在将混合物真空浓缩以去除溶剂后,将残余物用DCM/MeOH=10/1(80mL)溶解并搅拌10分钟。将混合物过滤并浓缩滤液,得到8-氨基-1,4-二氧杂螺[4.5]癸烷-8-甲酸(1.13g,粗物质)。MS(ESI)m/e[M+1]$^+$202.1

[0510] 步骤3:8-(((苄氧基)羰基)氨基)-1,4-二氧杂螺[4.5]癸烷-8-甲酸

[0511] 

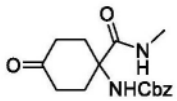
[0512] 将8-氨基-1,4-二氧杂螺[4.5]癸烷-8-甲酸(1.13g)、CbzCl(966mg)和Et_3N(1.15g,3.06mmol)在THF(30mL)和H_2O(30mL)中的混合物在室温下搅拌3小时。将反应混合物用MTBE(30mL)稀释并搅拌10分钟。收集水相并真空浓缩。将得到的固体在空气中干燥,得到8-(((苄氧基)羰基)氨基)-1,4-二氧杂螺[4.5]癸烷-8-甲酸(1.86g,粗物质)。MS(ESI)m/e[M+1]$^+$337.1。

[0513] 步骤4:(8-(甲基氨基甲酰基)-1,4-二氧杂螺[4.5]癸烷-8-基)氨基甲酸苄酯

[0514] 

[0515] 将8-(((苄氧基)羰基)氨基)-1,4-二氧杂螺[4.5]癸烷-8-甲酸(1.86g)、甲胺盐酸盐(385mg,5.7mmol)、HATU(2.17g,5.7mmol)和Et_3N(1.15g,11.4mmol)在DCM(60mL)中的混合物在室温下搅拌过夜。将反应混合物浓缩,然后将残余物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=50/1)纯化。得到(8-(甲基氨基甲酰基)-1,4-二氧杂螺[4.5]癸-8-基)氨基甲酸苄酯(1.77g)。MS(ESI)m/e[M+1]$^+$349.2。

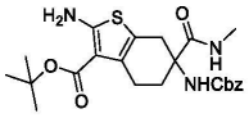
[0516] 步骤5:(1-(甲基氨基甲酰基)-4-氧代环己基)氨基甲酸苄酯

[0517] 

[0518] 将(8-(甲基氨基甲酰基)-1,4-二氧杂螺[4.5]癸烷-8-基)氨基甲酸苄酯(1.77g,5.7mmol)在TFA(10mL)中的溶液在室温下搅拌3小时。将反应混合物浓缩以去除TFA。将残余物用$NaHCO_3$水溶液中和,然后用DCM(50mL×3)萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。得到(1-(甲基氨基甲酰基)-4-氧代环己基)氨基甲酸苄酯(615mg,粗物质)。MS(ESI)m/e[M+1]$^+$305.1

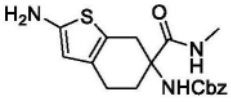
[0519] 步骤6:2-氨基-6-(((苄氧基)羰基)氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯

并[b]噻吩-3-甲酸叔丁酯

[0520] 

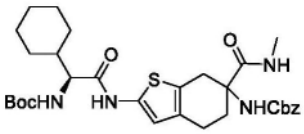
[0521] 将(1-(甲基氨基甲酰基)-4-氧代环己基)氨基甲酸苄酯(615mg,2.02mmol)、2-氰基乙酸叔丁酯(500mg,2.02mmol)、硫(65mg,2.02mmol)和吗啉(176mg,2.02mmol)在EtOH(25mL)中的混合物在80℃下搅拌过夜。将混合物冷却至室温并真空浓缩。将残余物通过制备型TLC(洗脱液:EA/PE(v/v)=1/1)纯化。得到2-氨基-6-(((苄氧基)羰基)氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-3-甲酸叔丁酯(287mg)。MS(ESI)m/e[M+1]$^+$ 460.3。

[0522] 步骤7:(2-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯

[0523] 

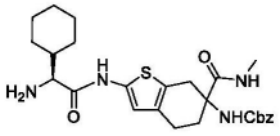
[0524] 向2-氨基-6-(((苄氧基)羰基)氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-3-甲酸叔丁酯(287mg,0.625mmol)在THF(30mL)中的溶液中添加HCl酸(6N,10mL)。将混合物在60℃下搅拌4小时。在冷却至室温后,将反应混合物用$NaHCO_3$水溶液中和,然后用DCM(50mL×3)萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过制备型TLC(洗脱液:MeOH/DCM(v/v)=1/10)纯化,得到(2-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(237mg)。MS(ESI)m/e[M+1]$^+$360.2。

[0525] 步骤8:(2-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯

[0526] 

[0527] 向(2-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(237mg,0.625mmol)在DCM(15mL)中的溶液中添加(S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酸(161mg,0.625mmol)、HATU(238mg,0.625mmol)和Et_3N(189mg,1.875mmol)。将混合物在室温下搅拌过夜。将反应混合物浓缩,并且将残余物通过制备型TLC(MeOH/DCM=1/10)纯化。得到(2-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(223mg)。MS(ESI)m/e[M+1]$^+$599.3。

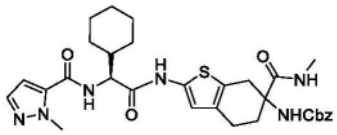
[0528] 步骤9:(2-((S)-2-氨基-2-环己基乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯

[0529] 

[0530] 将(2-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(223mg,0.372mmol)在TFA(5mL)中的

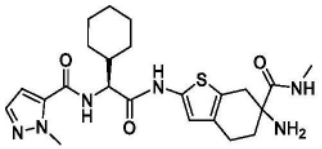
溶液在室温下搅拌1小时。真空浓缩反应物,得到粗标题化合物(300mg)。MS(ESI)m/e[M+1]$^+$ 499.4。

[0531] 步骤10:(2-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-6-(甲基氨甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯

[0532] 

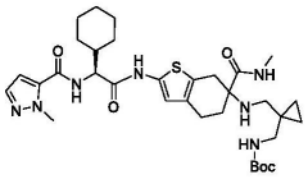
[0533] 向(2-((S)-2-氨基-2-环己基乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(300mg)在DCM(15mL)中的溶液中添加1-甲基-1H-吡唑-5-甲酸(47mg,0.372mmol)、HATU(141mg,0.372mmol)和Et_3N(190mg,1.86mmol)。将混合物在室温下搅拌48小时。真空浓缩反应混合物。将残余物通过制备型TLC(洗脱液:MeOH/DCM(v/v)=1/10)纯化,得到(2-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-6-(甲基氨甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(90mg)。MS(ESI)m/e[M+1]$^+$ 607.4。

[0534] 步骤11:N-((1S)-2-((6-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

[0535] 

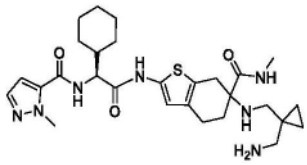
[0536] 向(2-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰氨基)乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基甲酸苄酯(80mg,0.13mmol)在DCM(10mL)中的溶液中添加TMSI(1mL,1mol/L)。将混合物在室温下搅拌30分钟。将反应混合物用$NaHCO_3$水溶液中和并用DCM(50mL×3)萃取。将有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。得到N-((1S)-2-((6-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(63mg,粗物质)。MS(ESI)m/e[M+1]$^+$473.2。

[0537] 步骤12:((1-(((2-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰氨基)乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基)甲基)环丙基)甲基)氨基甲酸叔丁酯

[0538] 

[0539] 将N-((1S)-2-((6-氨基-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(30mg,0.063mmol)、((1-甲酰基环丙基)甲基)氨基甲酸叔丁酯(13mg,0.063mmol)和$NaBH(OAc)_3$(14mg,0.063mmol)在DCM(10mL)中的混合物在室温下搅拌过夜。真空浓缩反应混合物。将残余物通过制备型TLC(洗脱液:MeOH/DCM(v/v)=1/15)纯化,得到所需产物(10mg)。MS(ESI)m/e[M+1]$^+$656.5。

[0540] 步骤13:N-((1S)-2-((6-(((1-(氨基甲基)环丙基)甲基)氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

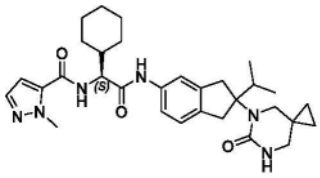
[0541] 

[0542] 将((1-(((2-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰氨基)乙酰氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-6-基)氨基)甲基)环丙基)甲基)氨基甲酸叔丁酯(10mg)在TFA(2mL)中的混合物在室温下搅拌30分钟。将反应物浓缩,得到呈白色固体状的所需产物(10mg)。MS(ESI)m/e[M+1]$^+$556.4。

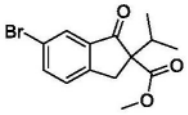
[0543] 步骤14:N-((1S)-1-环己基-2-((6-(甲基氨基甲酰基)-6-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(实施例145)

[0544] 向N-((1S)-2-((6-(((1-(氨基甲基)环丙基)甲基)氨基)-6-(甲基氨基甲酰基)-4,5,6,7-四氢苯并[b]噻吩-2-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(10mg)和Et_3N(30mg)在DMF(2mL)中的溶液中添加CDI(3mg)。将混合物在60℃下搅拌2小时。真空浓缩反应混合物并将残余物通过制备型TLC(洗脱液:MeOH/DCM(v/v)=1/15)纯化。得到标题化合物实施例145(2mg)。MS(ESI)m/e[M+1]$^+$582.2。

[0545] 实施例170:N-((1S)-1-环己基-2-((2-异丙基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

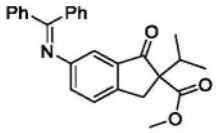
[0546] 

[0547] 步骤1:6-溴-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯

[0548] 

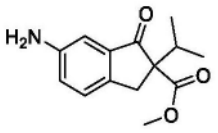
[0549] 在N_2保护下,在20分钟内,向6-溴-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(27g)在无水DMF(250ml)中的溶液中分批添加氢化钠(8g含60%悬浮液的油,200mmol)。将混合物搅拌45分钟。在15分钟内逐滴添加2-碘丙烷(34g,200mmol),然后将混合物在室温下搅拌18小时。将反应混合物减压浓缩并将残余物分配在EA (150mL)与HCl酸(2N,50mL)之间。将有机层分离,干燥并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=10/1)纯化。得到6-溴-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(10g,产率:33%)。MS(ESI,m/e)[M+1]$^+$311.0/313.0。

[0550] 步骤2:6-((二苯基亚甲基)氨基)-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯

[0551] 

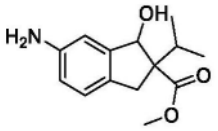
[0552] 将6-溴-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(3.11g,10mmol)、二苯基甲亚胺(2.7g,15mmol)、BINAP(1.87g,0.3mmol)、$Pd_2(dba)_3$(1.4g,0.15mmol)和Cs_2CO_3(10g,30mmol)在甲苯(50ml)中的混合物用N_2脱气。将混合物加热至100℃并在N_2气氛下搅拌12小时。将反应混合物冷却至室温并用H_2O、盐水洗涤。将有机层经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:己烷/EtOAc(v/v)=10/1)纯化。得到6-((二苯基亚甲基)氨基)-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(2.2g,产率:53.5%)。MS(ESI,m/e)$[M+1]^+$412.1

[0553] 步骤3:6-氨基-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯

[0554] 

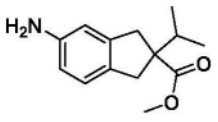
[0555] 将6-((二苯基亚甲基)氨基)-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(2.2g)溶解于HCl酸(1N,15mL)中并搅拌1小时。将反应混合物用$NaHCO_3$碱化至pH=8-9并用EtOAc(30mL×3)萃取。将合并的有机层用H_2O、盐水洗涤,经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:己烷/EtOAc(v/v)=1/1)纯化。得到6-氨基-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(1g,产率:76.9%)。MS(ESI,m/e)$[M+1]^+$248.1。

[0556] 步骤4:6-氨基-1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0557] 

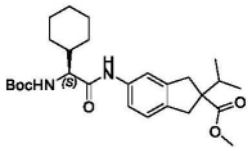
[0558] 在0℃下,向6-氨基-2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(1g,4mmol)在MeOH(50mL)中的溶液中分批添加$NaBH_4$(154mg,12mmol)。将反应混合物搅拌1小时,然后减压浓缩。将残余物分配在乙酸乙酯与水之间。将有机层经$MgSO_4$干燥并真空浓缩。得到6-氨基-1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(1g,粗物质)。MS(ESI,m/e)$[M+1]^+$250.1。

[0559] 步骤5:5-氨基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0560] 

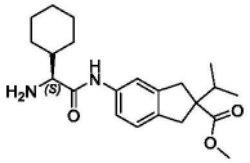
[0561] 向6-氨基-1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(249mg,1mmol)在TFA(10mL)中的溶液中添加三乙基硅烷(2mL)。将混合物在室温下搅拌1小时。在将反应混合物浓缩以去除TFA后,将残余物溶解于DCM(25mL)中并用饱和$NaHCO_3$水溶液洗涤。将有机层经$MgSO_4$干燥并真空浓缩。得到5-氨基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(240mg,粗物质)。MS(ESI,m/e)$[M+1]^+$234.1。

[0562] 步骤6:5-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0563] 

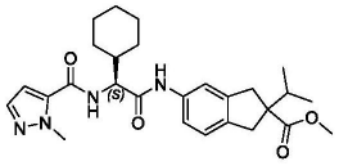
[0564] 向5-氨基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(466mg,2mmol)在DCM(25mL)中的溶液中添加(S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酸(819mg,3mmol)、HATU(1.35g,3.6mmol)和TEA(1mL)。将混合物在室温下搅拌1小时。将反应混合物浓缩以去除溶剂并将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=15:1)纯化。得到5-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(623mg,产率:56%)。MS(ESI,m/e)[M+1]$^+$473.3。

[0565] 步骤7:5-((S)-2-氨基-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0566] 

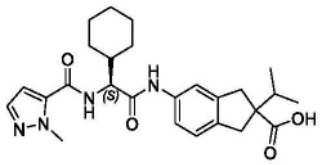
[0567] 将5-((S)-2-((叔丁氧基羰基)氨基)-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(623mg,1.32mmol)溶解于HCl溶液(10mL,2M于二噁烷中)中并在室温下搅拌1小时。在真空中浓缩反应混合物以去除溶剂后,得到HCl的5-((S)-2-氨基-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯盐(491mg,粗物质)。MS(ESI,m/e)[M+1]$^+$373.1。

[0568] 步骤8:5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0569] 

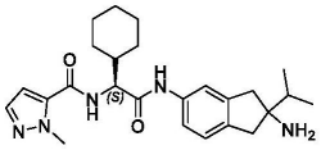
[0570] 向5-((S)-2-氨基-2-环己基乙酰氨基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(491mg,粗物质)和TEA (1.0mL)在DCM(25mL)中的溶液中添加1-甲基-1H-吡唑-5-甲酸(200mg,1.58mmol)和HATU(752mg,1.98mmol)。将混合物在室温下搅拌2小时。将反应混合物用$NaHCO_3$水溶液(50mL)淬灭并用DCM(20mL)稀释。有机层经Na_2SO_4干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=15:1)纯化。得到5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(200mg,产率:32%)。MS(ESI,m/e)[M+1]$^+$481.1。

[0571] 步骤9:5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸

[0572] 

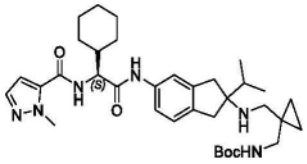
[0573] 向5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(200mg,0.42mmol)在甲醇(5mL)中的溶液中添加NaOH水溶液(2mL,1.0N)。将混合物在室温下搅拌过夜。将反应混合物用稀HCl酸酸化至pH=5-6并用EtOAc(15mL×3)萃取。将有机层用H_2O、盐水洗涤,经$MgSO_4$干燥,过滤并真空浓缩。得到5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸(100mg,粗物质)。MS(ESI,m/e)$[M+1]^+$467.0。

[0574] 步骤10:N-((1S)-2-((2-氨基-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

[0575] 

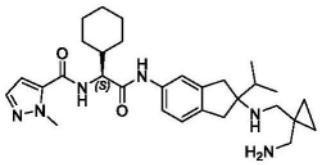
[0576] 向5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-甲酸(60mg,0.13mmol)在甲苯(5mL)中的溶液中添加DPPA(53mg)和TEA(0.1mL)。将混合物加热至90℃并搅拌1小时。将反应混合物冷却并浓缩以去除溶剂。将残余物溶于HCl酸(5mL,1N)中,然后搅拌1小时。将混合物用$NaHCO_3$水溶液碱化至pH约9并用EtOAc(10mL×3)萃取。将有机层用H_2O、盐水洗涤,经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:已烷/EtOAc(v/v)=1/1)纯化。得到N-((1S)-2-((2-氨基-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(30mg,产率:54%)。MS(ESI,m/e)$[M+1]^+$438.1。

[0577] 步骤11:((1-(((5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)甲基)氨基甲酸叔丁酯

[0578] 

[0579] 将N-((1S)-2-((2-氨基-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(30mg,0.069mmol)、((1-甲酰基环丙基)甲基)氨基甲酸叔丁酯(14mg,0.069mmol)和$NaBH(OAc)_3$(50mg)在DCM(5mL)中的混合物在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释,然后用H_2O、盐水洗涤。将有机层分离并经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=15:1)纯化。得到((1-(((5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)甲基)氨基甲酸叔丁酯(20mg,产率:47%)。MS(ESI,m/e)$[M+1]^+$621.1。

[0580] 步骤12:N-((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺

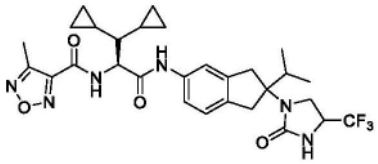
[0581] 

[0582] 将((1-(((5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-异丙基-2,3-二氢-1H-茚-2-基)氨基)甲基)环丙基)甲基)氨基甲酸叔丁酯(20mg)溶解于HCl溶液(10mL,2M于二噁烷中)中并在室温下搅拌1小时。真空浓缩反应混合物,得到HCl的N-((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺盐(20mg粗物质)。MS(ESI,m/e)[M+1]$^+$521.3。

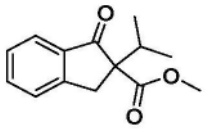
[0583] 步骤13:N-((1S)-1-环己基-2-((2-异丙基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(实施例170)

[0584] 向N-((1S)-2-((2-(((1-(氨基甲基)环丙基)甲基)氨基)-2-异丙基-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺(20mg)和TEA(0.5mL)在THF(5mL)中的溶液中添加CDI(20mg)。将混合物加热至回流搅拌3小时。将反应混合物冷却至室温并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=15:1)纯化。得到标题化合物(10mg,2步的产率:28.6%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.05(s,1H),8.45(d,J=8.0Hz,1H),7.45(t,J=8.6Hz,2H),7.29(s,1H),7.04(d,J=10.4Hz,2H),6.05(s,1H),4.44-4.31(m,1H),4.03(s,3H),3.21-2.92(m,4H),2.86(s,2H),2.67(s,2H),1.94-1.49(m,8H),128-1.15(m,4H),0.70(d,J=6.6Hz,6H),0.52-0.38(m,4H)。MS(ESI,m/e)[M+1]$^+$547.7。

[0585] 实施例212:N-((2S)-1,1-二环丙基-3-((2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺

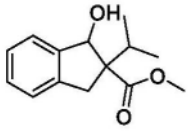
[0586] 

[0587] 步骤1:2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯

[0588] 

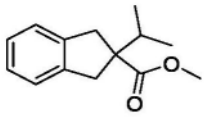
[0589] 在0℃下,在20分钟内,向1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(14g,73.6mmol)在无水DMF(250ml)中的溶液中逐份添加氢化钠(8.8g含60%悬浮液的油,222mmol)。在将混合物进一步搅拌45分钟后,在15分钟内逐滴添加2-碘丙烷(25g,148mmol)。然后将混合物加热至90℃并搅拌18小时。将反应混合物冷却至室温,然后倒入冰/水(100mL)中,用EA (100mL×3)萃取。将合并的有机层经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=10/1)纯化。得到2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(8g,50%)。MS(ESI,m/e)[M+1]$^+$233.1。

[0590] 步骤2:1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0591] 

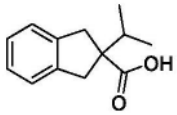
[0592] 在0℃下,向2-异丙基-1-氧代-2,3-二氢-1H-茚-2-甲酸甲酯(1.8g,7.8mmol)在MeOH(50mL)中的溶液中分批添加$NaBH_4$(1.2g,32mmol)。将混合物搅拌1小时,然后减压浓缩。将残余物分配在乙酸乙酯与水之间。将有机层经$MgSO_4$干燥,过滤并真空浓缩。得到1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(1.8g,粗物质),将其直接用于下一步骤中。MS(ESI,m/e)$[M-17]^+$217.1。

[0593] 步骤3:2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯

[0594] 

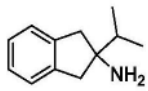
[0595] 向1-羟基-2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(1.7g,7.2mmol)在TFA(25mL)中的溶液中添加三乙基硅烷(5mL)。将混合物在室温下搅拌1小时。然后将反应混合物减压浓缩以去除溶剂。将残余物溶解于DCM(25mL)中并用饱和$NaHCO_3$水溶液(10mL)洗涤。将有机层用盐水洗涤,经$MgSO_4$干燥并真空浓缩。得到2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(1.5g,粗物质),将其直接用于下一步骤中。MS(ESI,m/e)$[M+1]^+$219.1。

[0596] 步骤4:2-异丙基-2,3-二氢-1H-茚-2-甲酸

[0597] 

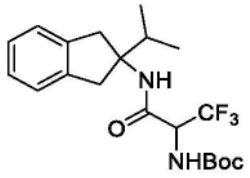
[0598] 向2-异丙基-2,3-二氢-1H-茚-2-甲酸甲酯(218mg,1mmol)在甲醇(3mL)中的溶液中添加NaOH水溶液(1.0N,2mL,2mmol)。将混合物在室温下搅拌过夜。然后将反应混合物用HCl酸(2.0N)酸化并用EtOAc(10mL×3)萃取。将合并的有机层用盐水、H_2O洗涤,经$MgSO_4$干燥,过滤并真空浓缩。得到2-异丙基-2,3-二氢-1H-茚-2-甲酸(200mg,粗物质)。MS(ESI,m/e)$[M+1]^+$205.1。

[0599] 步骤5:2-异丙基-2,3-二氢-1H-茚-2-胺

[0600] 

[0601] 向2-异丙基-2,3-二氢-1H-茚-2-甲酸(1.2g,6.8mmol)在甲苯(25mL)中的溶液中添加DPPA(2.75g)和TEA (3mL)。将混合物加热至90℃并搅拌1小时。减压浓缩反应混合物。将残余物稀释到HCl酸(1N,15mL)中,然后搅拌1小时。将混合物用$NaHCO_3$碱化至pH约8-9并用EtOAc(10mL×3)萃取。将合并的有机层用H_2O、盐水洗涤,经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:己烷/EtOAc(v/v)=4/1)纯化。得到2-异丙基-2,3-二氢-1H-茚-2-胺(700mg,产率:69%)。MS(ESI,m/e)$[M+1]^+$176.1

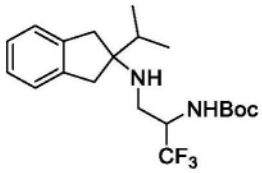
[0602] 步骤6:(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙烷-2-基)氨基甲酸叔丁酯

[0603] 

[0604] 在0℃下,向2-(((苄氧基)羰基)氨基)-3,3,3-三氟丙酸(1.17g,4.8mmol)、HATU

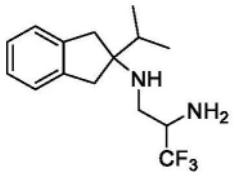
(1.98g,5.2mmol)在DCM(30mL)中的混合物中添加2-异丙基-2,3-二氢-1H-茚-2-胺(700mg,4mmol)和TEA (1.6g,15.4mmol)。将混合物在室温下搅拌1.5小时。将反应混合物用DCM稀释并用$NaHCO_3$水溶液淬灭。将有机层用盐水洗涤,干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:已烷/EtOAc(v/v)=5/1)纯化。得到(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙-2-基)氨基甲酸叔丁酯(750mg,产率:46%)。MS(ESI,m/e)$[M+1]^+$ 401.1。

[0605] 步骤7:(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸叔丁酯

[0606] 

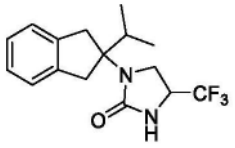
[0607] 向(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙-2-基)氨基甲酸叔丁酯(750mg,1.8mmol)在THF(10mL)中的溶液中逐滴添加BH_3-Me_2S(10mL)。将混合物加热至70℃并搅拌4小时。将反应混合物用MeOH(10mL)淬灭。在去除溶剂后,将残余物通过硅胶柱色谱(洗脱液:已烷/EtOAc(v/v)=4/1)纯化。得到(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸叔丁酯(500mg,72%)。MS(ESI,m/e)$[M+1]^+$ 387.2

[0608] 步骤8:3,3,3-三氟-N^1-(2-异丙基-2,3-二氢-1H-茚-2-基)丙烷-1,2-二胺

[0609] 

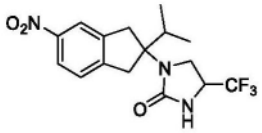
[0610] 向(1,1,1-三氟-3-((2-异丙基-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸叔丁酯(500mg)在THF中的溶液中添加含HCl的二噁烷(2M,10mL)。将混合物在室温下搅拌1小时。在真空去除溶剂后,得到3,3,3-三氟-N^1-(2-异丙基-2,3-二氢-1H-茚-2-基)丙烷-1,2-二胺盐(450mg,粗物质),将其直接用于下一步骤中。

[0611] 步骤9:1-(2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮

[0612] 

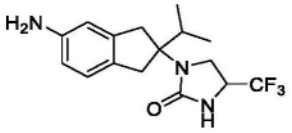
[0613] 向3,3,3-三氟-N1-(2-异丙基-2,3-二氢-1H-茚-2-基)丙烷-1,2-二胺(400mg,1.4mmol)和TEA (1.5mL)在THF(15mL)中的溶液中添加CDI(324mg,2mmol)。将混合物加热至回流搅拌3小时。在冷却至室温后,将反应混合物减压浓缩。将残余物通过硅胶柱色谱(洗脱液:已烷/EtOAc(v/v)=5/1)纯化。得到1-(2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(150mg,2步的产率:34%)。MS(ESI,m/e)$[M+1]^+$313.0。

[0614] 步骤10:1-(2-异丙基-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮

[0615] 

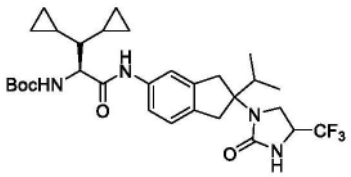
[0616] 在0℃下,向H_2SO_4(2mL)和HNO_3(3mL)的混合物中分批添加1-(2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(80mg,0.25mmol)在HOAc(2mL)中的溶液。将混合物在0℃下搅拌5分钟,然后用饱和$NaHCO_3$水溶液(10mL)淬灭并用DCM(10mL×3)萃取。将有机层用H_2O、盐水洗涤,经$MgSO_4$干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:己烷/EtOAc(v/v)=4/1)纯化。得到1-(2-异丙基-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,产率:44%)。MS(ESI,m/e)$[M+1]^+$358.0。

[0617] 步骤11:1-(5-氨基-2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮

[0618] 

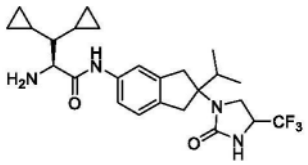
[0619] 向1-(2-异丙基-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,0.11mmol)在MeOH(10mL)中的溶液中添加Pd/C(10mg)。将混合物在H_2气氛下搅拌1小时。将反应混合物过滤并真空浓缩滤液。得到1-(5-氨基-2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,粗物质)。MS(ESI,m/e)$[M+1]^+$328.0。

[0620] 步骤12:((2S)-1,1-二环丙基-3-((2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)氨基甲酸叔丁酯

[0621] 

[0622] 向1-(5-氨基-2-异丙基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,0.11mmol)在DCM中的溶液中添加(S)-2-((叔丁氧基羰基)氨基)-3,3-二环丙基丙酸(30mg,0.11mmol)、HATU(63mg,0.17mmol)和TEA(0.1mL)。将混合物在室温下搅拌1小时。将反应混合物浓缩并通过制备型TLC纯化,得到((2S)-1,1-二环丙基-3-((2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸叔丁酯(30mg,产率:47%)。MS(ESI,m/e)$[M+1]^+$579.1。

[0623] 步骤13:(2S)-2-氨基-3,3-二环丙基-N-(2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺

[0624] 

[0625] 向((2S)-1,1-二环丙基-3-((2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸叔丁酯(30mg)在THF中的溶液中添加含HCl的二噁烷(2M,10mL)。将混合物在室温下搅拌1小时。在真空去除溶剂后,得到(2S)-

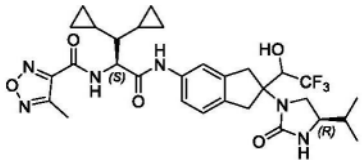
2-氨基-3,3-二环丙基-N-(2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺(20mg,粗物质)。MS(ESI,m/e)[M+1]$^+$479.1。

[0626] 步骤14:N-((2S)-1,1-二环丙基-3-((2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺(实施例212)

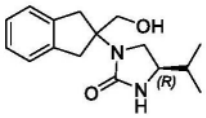
[0627] 向(2S)-2-氨基-3,3-二环丙基-N-(2-异丙基-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺(20mg,0.042mmol)在DCM(10mL)中的溶液中添加4-甲基-1,2,5-噁二唑-3-甲酸(5mg,0.042mmol)、HATU(24mg,0.063mmol)和TEA (0.1mL)。将混合物在室温下搅拌1小时。将反应混合物浓缩以去除溶剂。将残余物通过制备型TLC(洗脱液:DCM/CH3OH(v/v)=20/1)纯化。得到标题化合物实施例212(8mg,产率:32%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.06(s,1H),9.02(d,J=8.8Hz,1H),7.46(d,J=7.8Hz,1H),7.33(d,J=8.2Hz,1H),7.22(s,1H),7.12(d,J=8.0Hz,1H),4.89-4.80(m,1H),4.24(s,1H),3.65(d,J=10.6Hz,1H),3.49-3.41(m,2H),3.09-3.01(m,3H),2.59-2.53(m,1H),2.48(s,3H),0.94-0.76(m,9H),0.50-0.11(m,8H)。MS(ESI,m/e)[M+1]$^+$589.5。

[0628] 实施例238

[0629] N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺

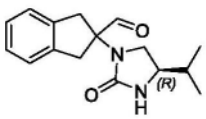
[0630] 

[0631] 步骤1:(R)-1-(2-(羟基甲基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮。

[0632] 

[0633] 在0℃下,在N_2气氛下,在搅拌下,向(R)-2-(4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸甲酯(430mg,1.4mmol,通过与中间体A2中所述的2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5-硝基-2,3-二氢-1H-茚-2-甲酰胺类似的程序制备)在THF(8mL)中的溶液中逐滴添加LAH(2.5M,1.5mL,3.7mmol)的溶液。在添加后,将混合物在0℃下搅拌1小时。将反应混合物通过Na_2SO_4水溶液淬灭并用EA(15mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=20/1)纯化,得到(R)-1-(2-(羟基甲基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮(270mg,产率:69%)。MS(ESI)m/e[M+1]$^+$275.1。

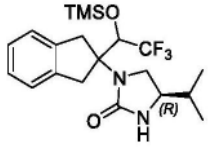
[0634] 步骤2:(R)-2-(4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲醛。

[0635] 

[0636] 向(R)-1-(2-(羟基甲基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮(270mg,1.0mmol)在DCM(20mL)中的溶液中。将所得溶液在氮气气氛下冷却至0℃,在0℃下在氮气气

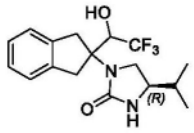
氛下分批添加戴斯马丁试剂(Dess-Martin reagent)(636mg,1.5mmol)。将混合物在室温下搅拌2小时。将反应混合物通过$Na_2S_2O_3$水溶液(5mL)在0℃下淬灭,然后用$NaHCO_3$水溶液(10mL)稀释并用EA(15mL×3)萃取。将合并的有机层用盐水洗涤,干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=30/1)纯化,得到(R)-2-(4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲醛(240mg,产率:88%)。MS(ESI)m/e[M+1]$^+$273.1。

[0637] 步骤3:(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-((三甲基甲硅烷基)氧基)乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮。

[0638] 

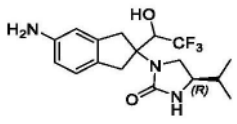
[0639] 在氮气气氛下,向(R)-2-(4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲醛(240mg,0.88mmol)在THF(10mL)中的溶液中添加CsF(174mg,1.15mmol)。将所得混合物冷却至0℃。向这种混合物中添加TMS-CF_3(163mg,1.15mmol)。将混合物在室温下搅拌30分钟。将反应混合物用EtOAc(50mL)稀释,然后用盐水洗涤。将有机层分离,经Na_2SO_4干燥并真空浓缩。得到(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-((三甲基甲硅烷基)氧基)乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮(300mg,粗物质),将其直接用于下一步骤中。

[0640] 步骤4:(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮。

[0641] 

[0642] 将(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-((三甲基甲硅烷基)氧基)乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮(300mg,粗物质)溶解于THF(10mL)中并冷却至0℃。向这种溶液中添加TBAF(0.1mL,1M)。将混合物在0℃下搅拌1小时。将反应混合物用EtOAc(50mL)稀释,然后用盐水洗涤。将有机层分离,经Na_2SO_4干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:DCM/MeOH(v/v)=25/1)纯化,得到(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮(60mg,两步的产率:20%)。MS(ESI)m/e[M+1]$^+$343.2。

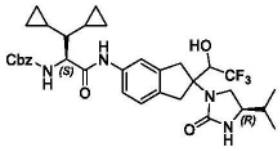
[0643] 步骤5:(4R)-1-(5-氨基-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮。

[0644] 

[0645] 在-5℃下,向H_2SO_4(1mL)和HNO_3(1.5mL)的混合物中分批添加(4R)-4-异丙基-1-(2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)咪唑烷-2-酮(60mg)在AcOH(2mL)中的溶液。将混合物在-5℃下进一步搅拌5分钟。将反应混合物倒入水/冰中,然后用EtOAc(15mL×3)萃取。将合并的有机层用水、$NaHCO_3$水溶液和盐水洗涤,干燥并真空浓缩。得到(4R)-1-(5-氨基-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮(70mg,粗物质)。将粗硝基产物溶解在MeOH(10mL)中,在室温下在Pd/C(35mg)存在下用H_2搅拌并氢化1小时。得到(4R)-1-(5-氨基-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-

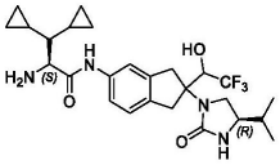
茚-2-基)-4-异丙基咪唑烷-2-酮(40mg,粗物质)。MS(ESI)m/e[M+1]$^+$358.3。

[0646] 步骤6:((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯。

[0647] 

[0648] 向(4R)-1-(5-氨基-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-2-基)-4-异丙基咪唑烷-2-酮(40mg,粗物质)在DCM(5mL)中的溶液中添加(S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酸(34mg,0.11mmol)、DIPEA(43.4mg,0.34mmol)和HATU(55.4mg,0.15mmol)。将混合物在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释,然后用$NaHCO_3$水溶液洗涤。将有机层用盐水洗涤,干燥并真空浓缩。将粗产物通过制备型TLC(洗脱液:EA/PE(v/v)=1/1)纯化。得到((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(30mg,产率:42%)。MS(ESI)m/e[M+1]$^+$643.5。

[0649] 步骤7:(2S)-2-氨基-3,3-二环丙基-N-(2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)丙酰胺

[0650] 

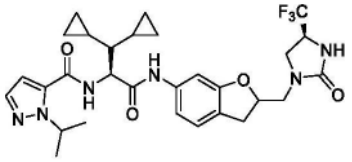
[0651] 向((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(30mg,0.05mmol)在MeOH中的溶液中添加Pd/C(30mg)。然后将这种混合物用H_2脱气并在H_2气氛下在室温下搅拌1小时。将反应混合物用DCM稀释并过滤。浓缩滤液,得到(2S)-2-氨基-3,3-二环丙基-N-(2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)丙酰胺(29mg,粗物质)。MS(ESI)m/e[M+1]$^+$509.4。

[0652] 步骤8:N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺(实施例238)。

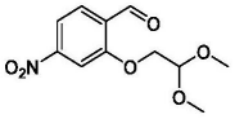
[0653] 向(2S)-2-氨基-3,3-二环丙基-N-(2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1H-茚-5-基)丙酰胺(29mg,粗物质)在DCM(5mL)中的溶液中添加4-甲基-1,2,5-噁二唑-3-甲酸(7.3mg,0.06mmol)、DIPEA(22mg,0.17mmol)和HATU(33mg,0.09mmol)。将混合物在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释,然后用$NaHCO_3$水溶液洗涤。将有机层用盐水洗涤,干燥并真空浓缩。将残余物首先通过制备型TLC纯化。然后将粗产物通过制备型HPLC(流动相:MeCN/水(0.1% FA);柱:SunFire;洗脱液:60%-80% MeCN)纯化。得到标题化合物实施例238(8.16mg,两步28%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.12(s,1H),9.05(d,J=8.8Hz,1H),7.54-7.50(m,1H),7.43-7.32(m,1H),7.24-7.11(m,1H),6.90-6.76(m,1H),4.87-4.75(m,2H),3.53-3.38(m,3H),3.31-3.14(m,4H),2.97-2.89(m,1H),2.49(s,3H),1.37-1.24(m,1H),0.93-0.67(m,3H),

0.63-0.50(m,6H),0.49-0.35(m,2H),0.33-0.08(m,6H)。MS(ESI)m/e[M+1]$^+$619.5。

[0654] 实施例256:N-((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺

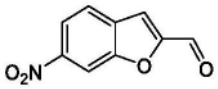
[0655] 

[0656] 步骤1:2-(2,2-二甲氧基乙氧基)-4-硝基苯甲醛

[0657] 

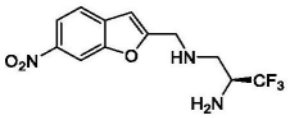
[0658] 在室温下,向2-羟基-4-硝基苯甲醛(10g,29.92mmol)在DMA(100mL)中的溶液中缓慢添加2-溴-1,1-二甲氧基乙烷(40g,239.35mmol)、K_2CO_3(33g,239.35mmol)。将混合物在140℃下搅拌12小时。将反应混合物倒入冰水(500mL)中。通过过滤收集沉淀并用水(500mL)洗涤。在真空干燥滤饼后,得到2-(2,2-二甲氧基乙氧基)-4-硝基苯甲醛(10g,产率:66%)。^{1}H NMR(400MHz,$CDCl_3$)δppm 10.55(s,1H),8.04-7.96(m,1H),7.94-7.86(m,2H),4.81(t,J=5.2Hz,1H),4.23(d,J=5.2Hz,2H),3.52-3.44(m,6H)。

[0659] 步骤2:6-硝基苯并呋喃-2-甲醛

[0660] 

[0661] 将2-(2,2-二甲氧基乙氧基)-4-硝基苯甲醛(10g,39.18mmol)在AcOH(100mL)中的溶液加热至60℃并搅拌12小时。减压浓缩反应混合物。将残余物倒入饱和Na_2CO_3水溶液(100mL)中,然后用DCM(100mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。得到6-硝基苯并呋喃-2-甲醛(6g,产率:80%)。^{1}H NMR(400MHz,$CDCl_3$)δppm 9.99(s,1H),8.52(s,1H),8.28(dd,J=2.0,8.8Hz,1H),7.92(d,J=8.8Hz,1H),7.65(d,J=0.4Hz,1H)。

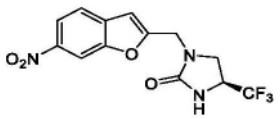
[0662] 步骤3:(S)-3,3,3-三氟-N^1-((6-硝基苯并呋喃-2-基)甲基)丙烷-1,2-二胺

[0663] 

[0664] 在20℃下,向6-硝基苯并呋喃-2-甲醛(2g,10.46mmol)在i-PrOH(40mL)中的溶液中添加(S)-3,3,3-三氟丙烷-1,2-二胺盐酸盐(2.58g,15.70mmol)和TEA(4.24g,41.85mmol)。将混合物在60℃下搅拌2小时。在TLC指示醛反应物完全消耗后,在0℃下将AcOH(3.14g,52.30mmol)和$NaBH_3CN$(1.64g,26.16mmol)添加到反应混合物(主要含有(S)-1,1,1-三氟-3-(((6-硝基苯并呋喃-2-基)亚甲基)氨基)丙-2-胺在i-PrOH中的亚胺中间体)中。在添加后,将反应混合物在80℃下进一步搅拌12小时。将反应混合物冷却,然后倒入饱和$NaHCO_3$水溶液(20mL)中并用DCM(50mL×3)萃取。将合并的层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1

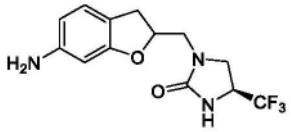
至0/1)纯化。得到(S)-3,3,3-三氟-N^1-((6-硝基苯并呋喃-2-基)甲基)丙烷-1,2-二胺(2.3g,70%产率)。^{1}H NMR(400MHz,$CDCl_3$)δppm 8.37(d,J=1.2Hz,1H),8.18(dd,J=2.0,8.4Hz,1H),7.63(d,J=8.4Hz,1H),6.74(s,1H),4.05(s,2H),3.36(s,1H),3.37(s,1H),3.00(dd,J=3.6,12.4Hz,1H),2.75(dd,J=8.8,12.0Hz,1H)。MS(ESI,m/e)$[M+1]^+$303.2。

[0665] 步骤4:(S)-1-((6-硝基苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮

[0666] 

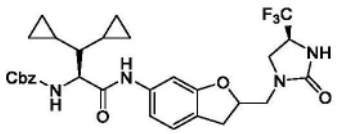
[0667] 在室温下,向(S)-3,3,3-三氟-N^1-((6-硝基苯并呋喃-2-基)甲基)丙烷-1,2-二胺(2.3g,7.58mmol)在THF(20mL)中的溶液中添加CDI(1.84g,11.38mmol)。将混合物在80℃下搅拌2小时。将反应混合物冷却并倒入水(20mL)中,用DCM(20mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=50/1至1/1)纯化。得到(S)-1-((6-硝基苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮(1.5g,产率:60%)。^{1}H NMR(400MHz,$CDCl_3$)δppm 8.42-8.35(m,1H),8.23-8.15(m,1H),7.67-7.62(m,1H),6.81-6.75(m,1H),5.01-4.94(m,1H),4.68-4.54(m,1H),4.24-4.17(m,1H),3.84-3.62(m,2H)。

[0668] 步骤5:(4S)-1-((6-氨基-2,3-二氢苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮

[0669] 

[0670] 在室温下,向(S)-1-((6-硝基苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮(1.5g,4.56mmol)在i-PrOH(10mL)中的溶液中添加Pd/C(180mg)。将混合物搅拌并在H_2气氛(50psi)下在50℃下氢化12小时。将反应混合物过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:石油醚/乙酸乙酯(v/v)=100/1至0/1)纯化。得到(4S)-1-((6-氨基-2,3-二氢苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮(810mg,产率:59%)。^{1}H NMR(400MHz,$CDCl_3$)δppm 6.92(d,J=7.6Hz,1H),6.30-6.11(m,2H),5.16-4.88(m,2H),4.18-4.07(m,1H),3.84-3.71(m,1H),3.67-3.54(m,3H),3.47-3.29(m,1H),3.18(ddd,J=3.2,9.6,15.2Hz,1H),2.86(dt,J=7.2,16.4Hz,1H)。MS(ESI,m/e)$[M+1]^+$302.1。

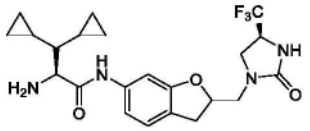
[0671] 步骤6:((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙-2-基)氨基甲酸苄酯

[0672] 

[0673] 向(4S)-1-((6-氨基-2,3-二氢苯并呋喃-2-基)甲基)-4-(三氟甲基)咪唑烷-2-酮(301mg,1.0mmol)在DCM(100mL)中的溶液中添加(S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酸(303mg,1.0mmol)、HATU(380mg,1.0mmol)和TEA(202mg,2.0mmol)。将混合物在室温下搅拌4小时。然后将反应混合物用$NaHCO_3$(水溶液,150mL)淬灭。将有机层分离,用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/

v)＝50/1)纯化。得到((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙烷-2-基)氨基甲酸苄酯(469mg,80%)。MS(ESI,m/e)[M+1]$^+$587.2。

[0674] 步骤7:(2S)-2-氨基-3,3-二环丙基-N-(2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)丙酰胺

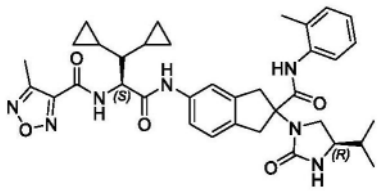
[0675] 

[0676] 向((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙烷-2-基)氨基甲酸苄酯(469mg,0.8mmol)和Pd/C(50mg)在MeOH(50mL)中的混合物用H_2气球鼓泡并搅拌2小时。将混合物过滤并真空浓缩。得到粗产物(2S)-2-氨基-3,3-二环丙基-N-(2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)丙酰胺(226mg,粗产物),将其直接用于下一步骤中。MS(ESI,m/e)[M+1]$^+$453.2。

[0677] 步骤8:N-((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺(实施例256)

[0678] 向(2S)-2-氨基-3,3-二环丙基-N-(2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)丙酰胺(226mg,0.5mmol)在DCM(50mL)中的溶液中添加1-异丙基-1H-吡唑-5-甲酸(14mg,0.09mmol)、HATU(40mg,0.09mmol)和DIEA(23mg,0.18mmol)。将混合物在室温下搅拌4小时。将反应混合物用饱和$NaHCO_3$水溶液(50mL)淬灭。将有机层分离,用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将残余物通过制备型TLC(洗脱液:MeOH/DCM(v/v)＝1/20)纯化,得到粗产物。将粗产物通过制备型HPLC纯化。得到N-((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺(16.85mg,32.3%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.09(d,J＝5.0Hz,1H),8.42(d,J＝8.7Hz,1H),7.52-7.50(m,2H),7.18(d,J＝4.4Hz,1H),7.10(t,J＝8.4Hz,1H),7.00(d,J＝7.8Hz,1H),6.92(s,1H),5.44-5.37(m,1H),4.95-4.93(m,1H),4.76(t,J＝8.2Hz,1H),4.35(s,1H),3.79-3.66(m,1H),3.58-3.37(m,2H),3.30-3.14(m,2H),2.87-2.82(m,1H),1.38-1.33(m,6H),0.89-0.67(m,3H),0.45-0.06(m,8H)。MS(ESI,m/e)[M+1]$^+$589.5。

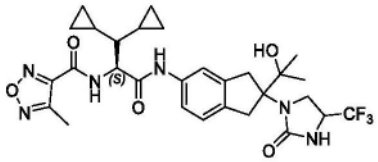
[0679] 实施例261:N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺

[0680] 

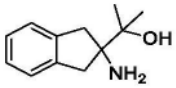
[0681] 在0℃下,向5-((S)-2-氨基-3,3-二环丙基丙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-(邻甲苯基)-2,3-二氢-1H-茚-2-甲酰胺(65mg,0.12mmol)在DCM(5mL)中

的溶液中添加4-甲基-1,2,5-噁二唑-3-甲酸(23mg,0.18mmol)、HATU(68mg,0.18mmol)和DIEA(31mg,0.24mmol)。将混合物在室温下搅拌12小时。将反应混合物用水(3mL)稀释,用DCM(5mL×3)萃取。将合并的有机层用盐水洗涤,经无水Na_2SO_4干燥,过滤并真空浓缩。将粗产物通过制备型HPLC(柱:Phenomenex Luna C18 75*30mm*3um;流动相:[水(NH4HCO3)-ACN];B%:40%-70%,8min)纯化。得到N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺(15.5mg,产率:19.8%)。^{1}H NMR(400MHz,DMSO-d_6)δ ppm 10.10(s,1H),9.07-8.96(m,2H),7.56-7.47(m,1H),7.46-7.32(m,2H),7.19(d,J=7.6Hz,2H),7.16-7.10(m,1H),7.08-7.03(m,1H),7.02(s,1H),4.86(t,J=8.0Hz,1H),3.70(t,J=17.6Hz,1H),3.62-3.49(m,2H),3.48-3.38(m,1H),3.30-3.25(m,1H),3.22(d,J=16.4Hz,1H),2.94(td,J=7.6,12.4Hz,1H),2.49(s,3H),2.17(s,3H),1.55-1.42(m,1H),0.93-0.84(m,1H),0.82-0.68(m,8H),0.52-0.36(m,2H),0.34-0.11(m,6H)。MS(ESI,m/e)[M+1]$^+$654.2。

[0682] 实施例279:N-((2S)-1,1-二环丙基-3-((2-(2-羟基丙烷-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺

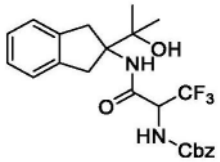
[0683] 

[0684] 步骤1:2-(2-氨基-2,3-二氢-1H-茚-2-基)丙-2-醇。

[0685] 

[0686] 将2-氨基-2,3-二氢-1H-茚-2-甲酸甲酯(1g,5.2mmol)溶解于THF(20mL)中并在N_2气氛下冷却至0℃。在低于10℃下,在搅拌下,向这种溶液中逐滴添加CH_3MgBr(26.2mL,26.2mmol)。将混合物温热至室温并搅拌30分钟。将反应混合物用NH_4Cl水溶液在0℃下淬灭并用DCM(30mL×3)萃取。将合并的有机层用盐水洗涤,干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=10/1)纯化。得到2-(2-氨基-2,3-二氢-1H-茚-2-基)丙-2-醇(980mg,产率:98%)。MS(ESI)m/e[M+1]$^+$192.2。

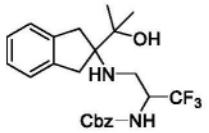
[0687] 步骤2:(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯。

[0688] 

[0689] 在0℃下,向2-(((苄氧基)羰基)氨基)-3,3,3-三氟丙酸(1.4g,5.1mmol)、EDCI(2.5g,12.8mmol)和HOBt(727mg,5.4mmol)在DCM(30mL)中的混合物中添加2-(2-氨基-2,3-二氢-1H-茚-2-基)丙-2-醇(980mg,5.1mmol)和TEA(1.6g,15.4mmol)。将混合物温热至室温并搅拌1.5小时。将反应混合物用DCM稀释并用$NaHCO_3$(水溶液)淬灭。将有机层用盐水洗涤,

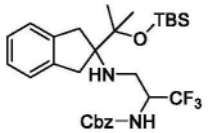
干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=1/1)纯化。得到(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(400mg,产率:17%)。MS(ESI)m/e[M+1]$^+$451.3。

[0690] 步骤3:(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸苄酯。

[0691] 

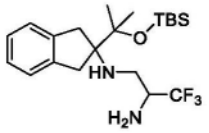
[0692] 在搅拌下,将(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(400mg,0.89mmol)添加BH_3-THF(1M,10mL)中。将混合物加热至60℃并搅拌6小时。将反应混合物冷却至室温并在0℃下通过MeOH(5mL)淬灭。将混合物真空浓缩。将残余物通过硅胶柱色谱(洗脱液:DCM/MeOH(v/v)=25/1)纯化。得到(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸苄酯(110mg,产率:28%)。MS(ESI)m/e[M+1]$^+$437.3。

[0693] 步骤4:(3-((2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-1,1,1-三氟丙-2-基)氨基甲酸苄酯。

[0694] 

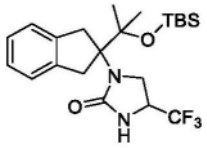
[0695] 在0℃下,在N_2气氛下,向(1,1,1-三氟-3-((2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)丙-2-基)氨基甲酸苄酯(110mg,0.25mmol)在DCM(5mL)中的溶液中逐滴添加2,6-二甲基吡啶(40.5mg,0.38mmol)和TBS-OTf(86.6mg,0.33mmol)。将混合物在0℃下搅拌1小时。将反应混合物通过$NaHCO_3$水溶液(10mL)在0℃下淬灭并用EtOAc(10mL×3)萃取。将合并的有机层用盐水洗涤,干燥并真空浓缩。将残余物通过硅胶柱色谱(洗脱液:PE/EA(v/v)=3/1)纯化。得到(3-((2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-1,1,1-三氟丙-2-基)氨基甲酸苄酯(110mg,产率:79%)。MS(ESI)m/e[M+1]$^+$551.4。

[0696] 步骤5:N^1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)-3,3,3-三氟丙烷-1,2-二胺。

[0697] 

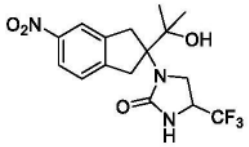
[0698] 向(3-((2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)氨基)-1,1,1-三氟丙-2-基)氨基甲酸苄酯(110mg,0.2mmol)在MeOH(5mL)中的溶液中添加Pd/C(55mg)。然后将这种混合物用H_2脱气并在H_2气氛下在室温下搅拌1小时。将反应混合物用DCM(5mL)稀释,然后过滤。将滤液真空浓缩。得到N^1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)-3,3,3-三氟丙烷-1,2-二胺(84mg,粗物质),将其直接用于下一步骤中。MS(ESI)m/e[M+1]$^+$417.4。

[0699] 步骤6:1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙烷-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮。

[0700] 

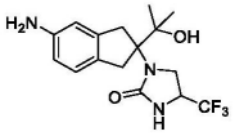
[0701] 在室温下,向N^1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙-2-基)-2,3-二氢-1H-茚-2-基)-3,3,3-三氟丙烷-1,2-二胺(84mg,0.2mmol)在THF(6mL)中的溶液中添加CDI(82mg,0.5mmol)和TEA(102mg,1.0mmol)。将混合物加热至60℃并搅拌2小时。然后将反应混合物冷却至室温,用EtOAc(20mL)稀释并用盐水洗涤。将有机层干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:EtOAc/DCM(v/v)=2/1)纯化。得到1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙烷-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(80mg,粗物质)。MS(ESI)m/e[M+1]$^+$443.3。

[0702] 步骤7:1-(2-(2-羟基丙-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮。

[0703] 

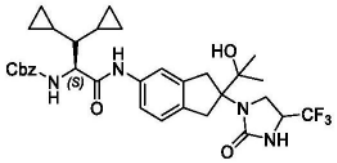
[0704] 在-5℃下,向H_2SO_4(2mL)和HNO_3(3mL)的混合物中分批添加(1-(2-(2-((叔丁基二甲基甲硅烷基)氧基)丙烷-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(80mg)在AcOH(2mL)中的溶液。将混合物在-5℃下进一步搅拌5分钟。将反应混合物倒入水/冰中,然后用EtOAc(15mL×3)萃取。将合并的有机层用水、$NaHCO_3$水溶液和盐水洗涤,干燥并真空浓缩。得到1-(2-(2-羟基丙-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(50mg,粗物质)。MS(ESI)m/e[M+23]$^+$374.2。

[0705] 步骤8:1-(5-氨基-2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮。

[0706] 

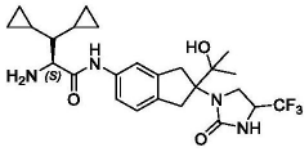
[0707] 向1-(2-(2-羟基丙-2-基)-5-硝基-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(50mg,粗物质)在MeOH(6mL)中的溶液中添加Pd/C(30mg)。然后将混合物用H_2脱气并在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释并过滤。真空浓缩滤液。得到1-(5-氨基-2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,粗物质)。MS(ESI)m/e[M+1]$^+$344.2。

[0708] 步骤9:((2S)-1,1-二环丙基-3-((2-(2-羟基丙烷-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)氨基甲酸苄酯。

[0709] 

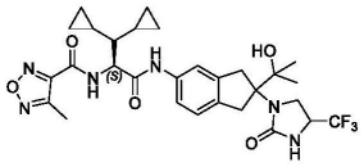
[0710] 向1-(5-氨基-2-(2-羟基丙-2-基)-2,3-二氢-1H-茚-2-基)-4-(三氟甲基)咪唑烷-2-酮(40mg,0.11mmol)在DCM(5mL)中的溶液中添加(S)-2-(((苄氧基)羰基)氨基)-3,3-二环丙基丙酸(35mg,0.11mmol)、DIPEA(45mg,0.35mmol)和HATU(66mg,0.17mmol)。将混合物在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释并用$NaHCO_3$水溶液洗涤。将有机层用盐水洗涤,干燥并真空浓缩。将残余物通过制备型TLC(洗脱液:EtOAc/DCM(v/v)=1/1)纯化。得到((2S)-1,1-二环丙基-3-((2-(2-羟基丙烷-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)氨基甲酸苄酯(30mg,3步产率:41%)。MS(ESI)m/e[M+1]$^+$629.1。

[0711] 步骤10:(2S)-2-氨基-3,3-二环丙基-N-(2-(2-羟基丙-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺。

[0712] 

[0713] 向((2S)-1,1-二环丙基-3-((2-(2-羟基丙-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)氨基甲酸苄酯(30mg,0.05mmol)在MeOH(6mL)中的溶液中添加Pd/C(30mg)。然后将混合物用H_2脱气并在H_2气氛下搅拌1小时。将反应混合物用DCM(10mL)稀释并过滤。真空浓缩滤液。得到(2S)-2-氨基-3,3-二环丙基-N-(2-(2-羟基丙-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺(28mg,粗物质)。MS(ESI)m/e[M+1]$^+$495.2。

[0714] 步骤11:N-((2S)-1,1-二环丙基-3-((2-(2-羟基丙-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺(实施例279)。

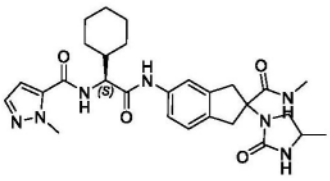
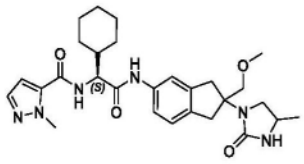
[0715] 

[0716] 向(2S)-2-氨基-3,3-二环丙基-N-(2-(2-羟基丙-2-基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)丙酰胺(28mg,粗物质)在DCM(5mL)中的溶液中添加4-甲基-1,2,5-噁二唑-3-甲酸(7.3mg,0.06mmol)、DIPEA(22mg,0.17mmol)和HATU(33mg,0.09mmol)。将混合物在室温下搅拌1小时。将反应混合物用DCM(15mL)稀释,然后用$NaHCO_3$水溶液洗涤。将有机层用盐水洗涤,干燥并真空浓缩。将残余物首先通过制备型TLC纯化。将粗产物通过制备型HPLC(流动相:MeCN/水(0.1% FA);柱:SunFire;洗脱液:50%-68% MeCN)纯化。得到标题化合物实施例279(10mg,两步的产率:29%)。^{1}H NMR(400MHz,DMSO-d_6)δppm:10.06(s,1H),9.01(d,J=8.8Hz,1H),7.46(t,J=9.4Hz,1H),7.34-7.30(m,2H),7.12(d,J=7.8Hz,1H),5.21(s,1H),4.85(t,J=7.8Hz,1H),4.23(s,1H),3.83-3.57(m,3H),

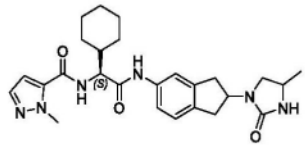
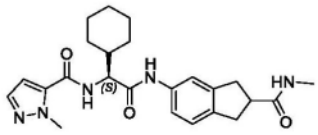
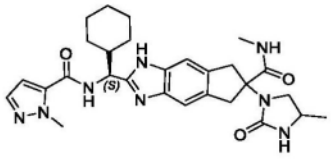
3.43-3.18(m,3H),2.48(s,3H),1.10(s,6H),0.93-0.62(m,3H),0.52-0.11(m,8H)。MS(ESI)m/e[M+1]$^+$605.2。

[0717] 根据与本领域技术人员已知的实施例32或实施例170、实施例212、实施例238、实施例256、实施例261、实施例279类似的方法合成其他实施例。相应的化合物名称、结构和光谱数据列于表中。

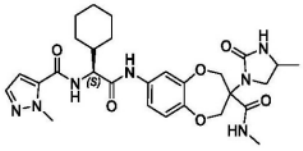
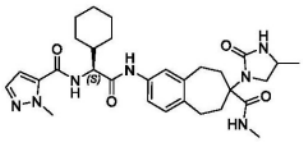
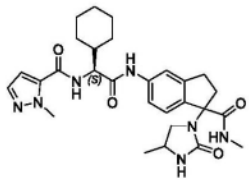
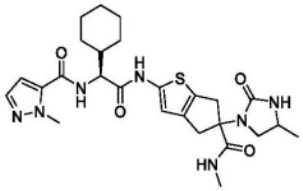
[0718]

Ex.	结构	化合物名称	数据
1		N-((1S)-1-环己基-2-((2-(4-甲基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.54-7.25 (m, 4H), 7.10-7.05 (m, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.57 (s, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.55-3.36 (m, 4H), 3.33-3.05 (m, 2H), 2.76-2.69 (m, 1H), 2.54 (d, J = 4.0 Hz, 3H), 1.85-1.50 (m, 6H), 1.21-1.10 (m, 5H), 1.03-0.95 (m, 3H)。MS (ESI, m/e) [M+1]$^+$ 536.5。
2		N-((1S)-1-环己基-2-((2-(甲氧基甲基)-2-(4-甲基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.49-7.28 (m, 3H), 7.09-7.04 (m, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.35 (s, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.59-3.44 (m, 4H), 3.33-3.15 (m, 5H), 3.06-2.95 (m, 3H), 1.85-1.50 (m, 6H), 1.21-1.10 (m, 5H), 1.01 (d, J =

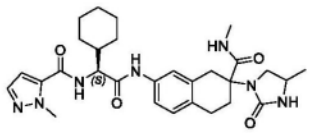
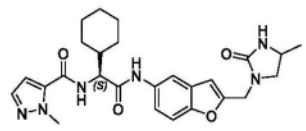
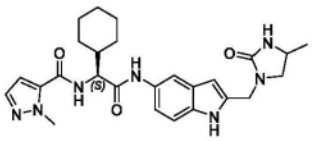
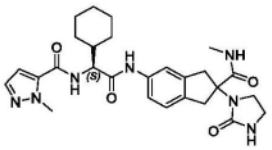
[0719]

		酰胺	6.0 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 523.3。
3		N-((1S)-1-环己基-2-((2-(4-甲基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.59-7.28 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.43 (s, 1H), 4.59-4.50 (m, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.57-3.47 (m, 1H), 3.33-3.15 (m, 2H), 3.06-2.85 (m, 2H), 2.84-2.70 (m, 2H), 2.64-2.55 (m, 1H), 1.85-1.50 (m, 6H), 1.21-1.10 (m, 4H), 1.03-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 479.2。
4		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.04 (s, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.85-7.82 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 4.0 Hz, 1H), 7.30-7.26 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 4.35-4.31 (m, 1H), 3.98 (s, 3H), 3.27 (s, 1H), 3.13-3.05 (m, 1H), 2.97-2.91 (m, 4H), 2.56 (d, J = 8.0 Hz, 1H), 1.79-1.77 (m, 2H), 1.68-1.65 (m, 2H), 1.58-1.51 (m, 2H), 1.19-1.11 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 438.1。
5		2-((S)-环己基(1-甲基-1H-吡唑-5-甲酰胺基)甲基)-N-甲基-6-(4-甲基-2-氧代咪唑烷-1-基)-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.23 (br, 1H), 8.74 (d, J = 8.8 Hz, 1H), 7.50-7.45 (m, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.02 (d, J = 1.6 Hz, 1H), 6.52 (s, 1H), 4.97 (t, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.59-3.40 (m, 4H), 3.32-3.15 (m, 2H), 2.73 (t, J = 7.6 Hz, 1H), 2.54 (d, J = 4.4 Hz, 3H), 2.11-2.00 (m, 1H), 1.85-1.78 (m, 1H), 1.72-1.52 (m, 3H), 1.38-1.30 (m, 1H), 1.21-0.95 (m, 9H)。MS (ESI, m/e) $[M+1]^+$ 533.5。

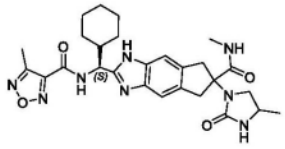
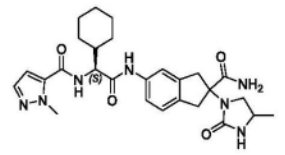
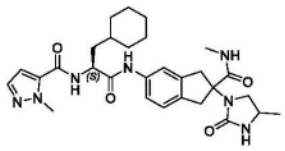
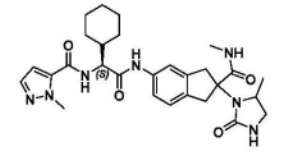
[0720]

6		N-((1S)-1-环己基-2-((3-(4-甲基-2-氧代咪唑烷-1-基)-3-(甲基氨基甲酰基)-3,4-二氢-2H-苯并[b][1,4]二氧庚环-7-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 4.4 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.31 (s, 1H), 7.11-7.00 (m, 2H), 6.84 (d, J = 8.8 Hz, 1H), 6.60 (s, 1H), 4.50-4.25 (m, 5H), 3.98 (s, 3H), 3.74-3.63 (m, 2H), 3.27 (s, 3H), 3.18-3.12 (m, 1H), 2.55-2.53 (m, 3H), 1.78-1.75 (m, 2H), 1.65-1.54 (m, 4H), 1.20-1.05 (m, 6H). MS (ESI, m/e) $[M+1]^+$ 568.3。
7		N-((1S)-1-环己基-2-((7-(4-甲基-2-氧代咪唑烷-1-基)-7-(甲基氨基甲酰基)-6,7,8,9-四氢-5H-苯并[7]轮烯-2-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.01 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.39-7.27 (m, 3H), 7.04-6.97 (m, 2H), 6.40 (s, 1H), 4.32 (t, J = 8.8 Hz, 1H), 4.03 (s, 3H), 3.60-3.40 (m, 2H), 2.95-2.50 (m, 8H), 2.38-2.20 (m, 1H), 1.90-1.50 (m, 8H), 1.21-1.10 (m, 6H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 564.3。
8		N-((1S)-1-环己基-2-((1-(4-甲基-2-氧代咪唑烷-1-基)-1-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.80-7.76 (m, 1H), 7.57-7.28 (m, 4H), 7.06 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 27.6 Hz, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.69-3.45 (m, 1H), 3.30-2.72 (m, 5H), 2.55 (t, J = 4.8 Hz, 3H), 2.30-1.91 (m, 2H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 536.3。
9		N-((1S)-1-环己基-2-((5-(4-甲基-2-氧代咪唑烷-1-基)-5-(甲基氨基甲酰基)-5,6-二氢-4H-环戊二烯并[b]噻吩-2-基)氨基)-2-氧	MS (ESI) m/e $[M+1]^+$ 542.2

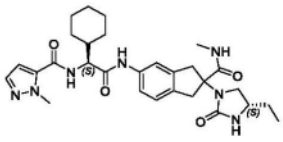
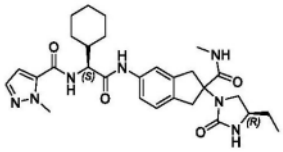
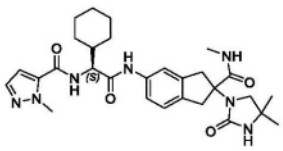
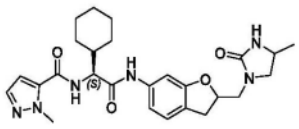
[0721]

		代乙基)-1-甲基-1H-吡唑-5-甲酰胺	
10		N-((1S)-1-环己基-2-((7-(4-甲基-2-氧代咪唑烷-1-基)-7-(甲基氨基甲酰基)-5,6,7,8-四氢萘-2-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.45-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.28-7.25 (m, 1H), 7.02-7.01 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.38 (s, 1H), 4.36-4.31 (m, 1H), 3.46-3.41 (m, 1H), 3.24-3.18 (m, 2H), 3.08-2.83 (m, 5H), 2.56-2.53 (m, 5H), 1.98-1.92 (m, 1H), 1.79-1.77 (m, 2H), 1.68-1.66 (m, 2H), 1.58-1.52 (m, 2H), 1.19-1.11 (m, 4H), 1.01-0.99 (m, 4H). MS (ESI, m/e) $[M+1]^+$ 550.3。
11		N-((1S)-1-环己基-2-((2-((4-甲基-2-氧代咪唑烷-1-基)甲基)苯并呋喃-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23 (s, 1H), 8.51 (d, J = 8.2 Hz, 1H), 7.99-7.94 (m, 1H), 7.52-7.36 (m, 3H), 7.10-7.03 (m, 1H), 6.75 (s, 1H), 6.69 (s, 1H), 4.47-4.29 (m, 3H), 4.03 (s, 3H), 3.70-3.59 (m, 1H), 3.48-3.40 (m, 1H), 2.89-2.78 (m, 1H), 1.95-1.77 (m, 2H), 1.77-1.55 (m, 4H), 1.30-1.22 (m, 5H), 1.12-1.05 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 493.3
12		N-((1S)-1-环己基-2-((2-((4-甲基-2-氧代咪唑烷-1-基)甲基)-1H-吲哚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.71 (s, 1H), 7.47 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.31 (s, 1H), 4.48-4.41 (m, 2H), 4.09 (s, 3H), 3.79-3.75 (m, 1H), 3.52-3.47 (m, 1H), 3.00-2.88 (m, 1H), 1.94-1.72 (m, 5H), 1.41-1.32 (m, 6H), 1.18 (d, J = 6.2 Hz, 4H)。MS (ESI, m/e) $[M+1]^+$ 492.2。
13		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代咪唑烷-1-基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.64-7.30 (m, 4H), 7.14-6.95 (m, 2H), 6.46 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.50-3.40 (m, 2H), 3.33-3.09 (m, 6H), 2.58 (d, J =

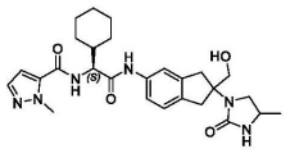
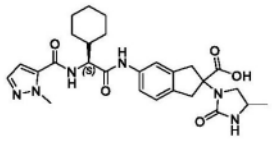
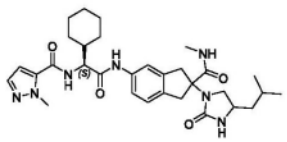
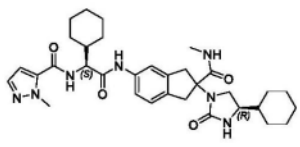
[0722]

		-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	4.4 Hz, 3H), 1.90-1.55 (m, 6H), 1.21-0.95 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 522.4。
14		N-((1S)-环己基(6-(4-甲基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.20 (d, J = 18.0 Hz, 1H), 9.40 (t, J = 6.4 Hz, 1H), 7.55-7.48 (m, 1H), 7.35 (d, J = 3.2 Hz, 1H), 7.27 (d, J = 4.0 Hz, 1H), 6.57 (s, 1H), 5.05 (t, J = 8.0 Hz, 1H), 3.65-3.40 (m, 4H), 3.32-3.20 (m, 2H), 2.83-2.69 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.11-1.96 (m, 2H), 1.90-1.55 (m, 4H), 1.21-0.95 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 535.4。
15		N-((1S)-2-((2-氨基甲酰基-2-(4-甲基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.57-7.30 (m, 3H), 7.14-6.95 (m, 4H), 6.63 (s, 1H), 4.38 (t, J = 8.8 Hz, 1H), 4.03 (s, 3H), 3.60-3.40 (m, 4H), 3.33-3.09 (m, 2H), 2.83-2.75 (m, 1H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 522.2。
16		N-((2S)-3-环己基-1-((2-(4-甲基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.58 (d, J = 8.0 Hz, 1H), 7.59-7.22 (m, 3H), 7.14-7.05 (m, 2H), 6.61 (s, 1H), 4.63-4.40 (m, 1H), 4.03 (s, 3H), 3.63-3.40 (m, 4H), 3.33-3.05 (m, 2H), 2.87-2.69 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.05-2.00 (m, 2H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H), 0.93-0.85 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 550.2。
17		N-((1S)-1-环己基-2-((2-(5-甲基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.77-7.30 (m, 4H), 7.14-7.05 (m, 2H), 6.48 (s, 1H), 4.38 (t, J = 8.0 Hz, 1H), 4.02 (s, 3H), 3.93-3.78 (m, 1H), 3.76-3.68 (m, 1H), 3.63-3.40 (m, 3H), 3.33-3.05 (m, 1H),

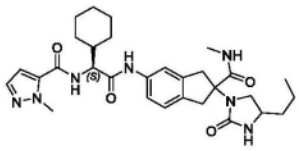
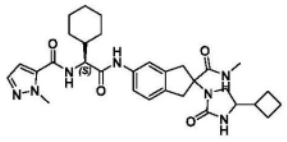
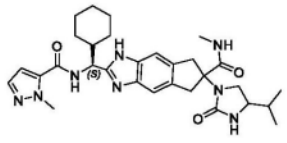
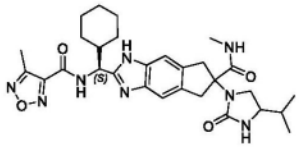
[0723]

		基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	2.88-2.76 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 536.3。
18		N-((1S)-1-环己基-2-((2-((S)-4-乙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.58-7.29 (m, 4H), 7.12 (d, J = 7.6 Hz, 1H), 7.10 (s, 1H), 6.74 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.55-3.35 (m, 4H), 3.33-3.11 (m, 2H), 2.90-2.83 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.54 (m, 6H), 1.38-1.30 (m, 2H), 1.20-0.95 (m, 5H), 0.74 (t, J = 7.2 Hz, 1H)。MS (ESI, m/e) $[M+1]^+$ 550.4。
19		N-((1S)-1-环己基-2-((2-((R)-4-乙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.58-7.29 (m, 4H), 7.13-7.05 (m, 2H), 6.73 (s, 1H), 4.37 (t, J = 8.8 Hz, 1H), 4.02 (s, 3H), 3.55-3.35 (m, 4H), 3.33-3.11 (m, 2H), 2.85 (t, J = 7.2 Hz, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.54 (m, 6H), 1.38-1.30 (m, 2H), 1.20-0.95 (m, 5H), 0.74 (t, J = 7.2 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 550.4。
20		N-((1S)-1-环己基-2-((2-(4,4-二甲基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.60-7.28 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.62 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.49-3.42 (m, 2H), 3.24-3.00 (m, 4H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.57 (m, 6H), 1.20-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 550.4。
21		N-((1S)-1-环己基-2-((2-((4-甲基-2-氧代咪唑烷-1-基)甲基)-2,3-二氢苯	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (d, J = 3.2 Hz, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.27-7.16 (m, 1H), 7.14-7.05 (m, 2H), 7.05-6.91 (m, 1H),

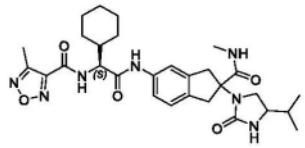
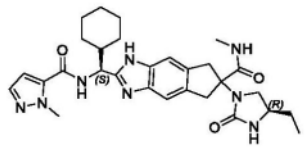
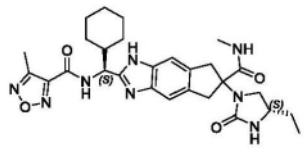
[0724]

		并呋喃-6-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	6.50 (d, J = 18.4 Hz, 1H), 4.96-4.83 (m, 1H), 4.42-4.32 (m, 1H), 4.03 (s, 3H), 3.64-3.45 (m, 2H), 3.30-3.11 (m, 3H), 3.03-2.80 (m, 2H), 1.91-1.47 (m, 6H), 1.21-1.05 (m, 5H), 1.05-0.95 (m, 1H), 0.93-0.85 (m, 2H)。MS (ESI, m/e) $[M+1]^{+\cdot}$ 495.3。
22		N-((1S)-1-环己基-2-((2-(羟基甲基)-2-(4-甲基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.57-7.30 (m, 3H), 7.14-7.05 (m, 2H), 6.37 (s, 1H), 4.99 (t, J = 5.2 Hz, 1H), 4.38 (t, J = 8.0 Hz, 1H), 4.02 (s, 3H), 3.63-3.40 (m, 3H), 3.33-3.05 (m, 6H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 509.3。
23		5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-(4-甲基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-2-甲酸	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.46 (br, 1H), 10.12 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.57-7.30 (m, 3H), 7.14-7.05 (m, 2H), 6.61 (s, 1H), 4.38 (t, J = 8.0 Hz, 1H), 3.92 (s, 3H), 3.63-3.40 (m, 4H), 3.33-3.05 (m, 2H), 3.00-2.88 (m, 1H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 523.3。
24		N-((1S)-1-环己基-2-((2-(4-异丁基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.57-7.25 (m, 4H), 7.14-7.05 (m, 2H), 6.70 (s, 1H), 4.35 (t, J = 7.6 Hz, 1H), 4.02 (s, 3H), 3.63-3.40 (m, 3H), 3.33-3.05 (m, 3H), 2.75-2.68 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.55 (m, 6H), 1.21-1.10 (m, 5H), 1.07-0.95 (m, 9H)。MS (ESI, m/e) $[M+1]^+$ 578.4。
25		N-((1S)-1-环己基-2-((2-((R)-4-环己基-2-氧代咪唑烷-1-基)-2-(甲基氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.10 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.53 (s, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.39-7.31 (m, 1H), 7.14-7.09 (m, 1H), 7.06 (s, 1H), 6.76-6.70 (m, 1H),

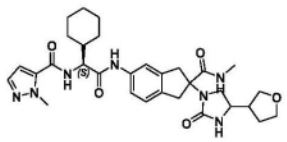
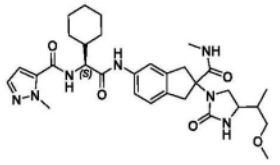
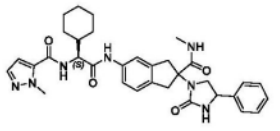
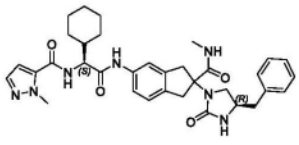
[0725]

		基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	4.41-4.33 (m, 1H), 4.02 (s, 3H), 3.58-3.35 (s, 2H), 3.22-3.16 (m, 1H), 3.05-2.94 (m, 4H), 2.57 (d, J = 4.4 Hz, 3H), 1.86-1.77 (m, 2H), 1.31-0.93 (m, 20H)。MS (ESI, m/e) [M+1]+ 604.4。
26		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-丙基咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.11 (s, 1H), 8.47 (d, J = 8.2 Hz, 1H), 7.57-7.48 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.42-7.30 (m, 1H), 7.15-7.08 (m, 1H), 7.08-7.04 (m, 1H), 6.71 (s, 1H), 4.42-4.30 (m, 1H), 4.02 (s, 3H), 3.54-3.35 (m, 5H), 3.29-3.09 (m, 2H), 2.90-2.76 (m, 1H), 2.57 (d, J = 4.4 Hz, 3H), 2.03 -1.52 (m, 7H), 1.35-1.27 (m, 2H), 1.20-1.07 (s, 5H), 0.84-0.77 (m, 3H)。MS (ESI, m/e) $[M+1]^{+\cdot}$ 564.4.
27		N-((1S)-2-((2-(4-环丁基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.48 (d, J = 8.4 Hz. 1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.76 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 3H), 3.21-3.01 (m, 2H), 2.54-2.51 (m, 3H), 2.24-2.21 (m, 1H),1.81-1.57 (m, 13H), 1.05-1.02 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 576.4。
28		2-((S)-环己基(1-甲基-1H-吡唑-5-甲酰胺基)甲基)-6-(4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.18 (br, 1H), 8.79 (s, 1H), 7.55-7.20 (m, 4H), 7.07 (s, 1H), 6.73 (s, 1H), 5.02 (t, J = 5.6 Hz, 1H), 4.02 (s, 3H), 3.64-3.40 (m, 4H), 3.32-3.14 (m, 2H), 2.97-2.89 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.15-1.95 (m, 2H), 1.90-1.35 (m, 6H), 1.21-0.95 (m, 5H), 0.71 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 561.3。
29		N-((1S)-环己基(6-(4-异丙基-2-氧代咪唑烷-1-基)-6-(甲基氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.18 (br, 1H), 9.41 (d, J = 9.2 Hz, 1H), 7.59-7.20 (m, 3H), 6.73 (s, 1H), 5.06 (t, J =

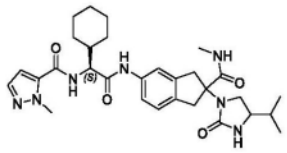
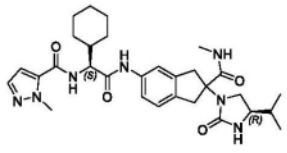
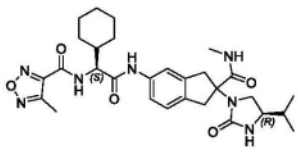
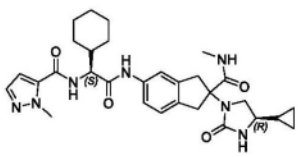
[0726]

		基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	8.0 Hz, 1H), 3.67-3.40 (m, 4H), 3.32-3.14 (m, 2H), 2.97-2.89 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.11-1.95 (m, 2H), 1.90-1.39 (m, 6H), 1.21-0.95 (m, 4H), 0.71 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 563.3。
30		N-((1S)-1-环己基-2-((2-(4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.14 (s, 1H), 9.09 (d, J = 8.0 Hz, 1H), 7.59-7.29 (m, 3H), 7.13 (d, J = 8.4 Hz, 1H), 6.78 (s, 1H), 4.45 (t, J = 8.0 Hz, 1H), 3.59-3.46 (m, 2H), 3.32-3.10 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.39 (m, 7H), 1.21-0.95 (m, 5H), 0.75 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 566.3。
31		2-((S)-环己基(1-甲基-1H-吡唑-5-甲酰胺基)甲基)-6-((R)-4-乙基-2-氧代咪唑烷-1-基)-N-甲基-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.20 (br, 1H), 8.78 (d, J = 8.0 Hz, 1H), 7.55-7.20 (m, 4H), 7.07 (s, 1H), 6.69 (s, 1H), 5.01 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.65-3.40 (m, 4H), 3.32-3.23 (m, 2H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.10-1.55 (m, 5H), 1.42-1.27 (m, 3H), 1.21-0.95 (m, 5H), 0.70 (t, J = 7.2 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 547.3。
33		N-((1S)-环己基(6-((S)-4-乙基-2-氧代咪唑烷-1-基)-6-(甲基氨基甲酰基)-1,5,6,7-四氢茚并[5,6-d]咪唑-2-基)甲基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.28 (br, 1H), 9.42 (d, J = 8.8 Hz, 1H), 7.55-7.50 (m, 1H), 7.32 (s, 2H), 6.69 (s, 1H), 5.06 (t, J = 8.8 Hz, 1H), 3.62-3.40 (m, 4H), 3.32-3.23 (m, 2H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.14-1.55 (m, 5H), 1.42-1.27 (m, 3H), 1.21-0.95 (m, 5H), 0.71 (t, J = 7.2 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 549.4。

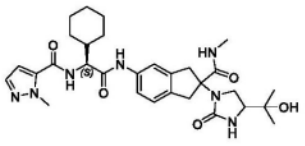
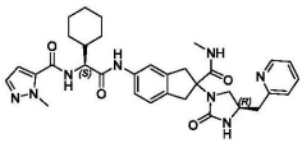
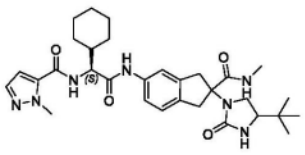
[0727]

34		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(四氢呋喃-3-基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.53 (d, J = 8.4 Hz. 1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.76 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 6H), 3.21-3.01 (m, 4H), 2.54-2.51 (m, 3H),1.81-1.57 (m, 7H), 1.31-1.17 (m, 5H), 1.05-1.02 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 592.3。
35		N-((1S)-1-环己基-2-((2-(4-(1-甲氧基丙烷-2-基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.53 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.76 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 3H), 3.21-3.01 (m, 10H), 2.54-2.51 (m, 3H),1.81-1.57 (m, 7H), 1.31-1.17 (m, 6H), 1.05-1.02 (m, 2H), 0.63-0.55 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 594.3。
36		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-苯基咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	MS (ESI, m/e) $[M+1]^+$ 598.3。
37		N-((1S)-2-((2-((R)-4-苄基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (d, J = 20.0 Hz, 1H), 8.52-8.47 (m, 1H), 7.59-7.45 (m, 2H), 7.41-7.34 (m, 1H), 7.25-7.12 (m, 4H), 7.09-7.02 (m, 3H), 6.93 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 4.0 Hz, 1H), 4.42-4.36 (m, 1H), 4.02 (d, J = 8.0 Hz, 1H), 3.69-3.63 (m, 1H), 3.50-3.41 (m, 2H), 3.31-3.27 (m, 2H), 3.12-3.05 (m, 2H), 2.98-2.95 (m, 1H), 2.72-2.65 (m, 1H), 2.55-2.53 (m, 3H), 1.90-1.79 (m, 2H),

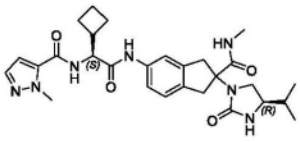
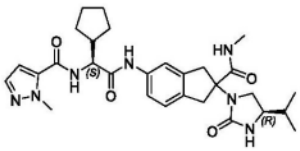
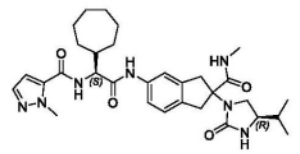
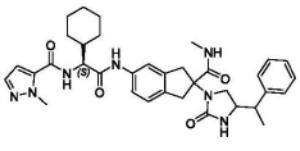
[0728]

			1.75-1.54 (m, 4H), 1.35-1.10 (m, 8H), 1.02-0.78 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 612.3。
38		N-((1S)-1-环己基-2-((2-(4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.57-7.29 (m, 4H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 4.37 (t, J = 8.8 Hz, 1H), 4.02 (s, 3H), 3.58-3.45 (m, 2H), 3.33-3.11 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.54 (m, 6H), 1.48-1.40 (m, 2H), 1.20-0.95 (m, 5H),), 0.75 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 564.3。
39		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.59-7.29 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.77 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.57-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.39 (m, 7H), 1.21-0.95 (m, 5H), 0.74 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 564.3。
40		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 9.09 (d, J = 8.0 Hz, 1H), 7.55-7.27 (m, 3H), 7.13 (d, J = 8.4 Hz, 1H), 6.78 (s, 1H), 4.46 (t, J = 8.0 Hz, 1H), 3.57-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.39 (m, 7H), 1.21-1.00 (m, 5H), 0.77-0.50 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 566.5。
41		N-((1S)-1-环己基-2-((2-((R)-4-环丙基-2-氧代咪唑烷-1-基)-2-(甲基氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.58-7.27 (m, 4H), 7.15-7.10 (m, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.73 (s, 1H), 4.37 (t, J = 8.0 Hz, 1H), 4.02 (s,

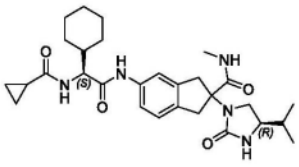
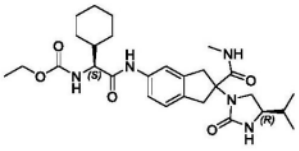
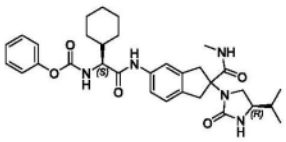
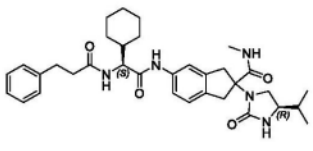
[0729]

		基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	3H), 3.56-3.35 (m, 3H), 3.30-3.10 (m, 2H), 3.04-2.89 (m, 2H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.55 (m, 6H), 1.20-0.78 (m, 5H), 0.38-0.28 (m, 2H), 0.15-0.09 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 562.3。
42		N-((1S)-1-环己基-2-((2-(4-(2-羟基丙-2-基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.53 (d, J = 8.4 Hz.1H), 7.49-7.22 (m, 4H), 7.08-7.02 (m, 2H), 6.76 (s, 1H), 4.59-4.56 (m, 1H), 4.39-4.35 (m, 1H), 4.03 (s, 3H), 3.46-3.41 (m, 3H), 3.21-3.01 (m, 2H), 2.54-2.51 (m, 3H), 1.91-1.57 (m, 7H), 1.31-1.17 (m, 2H), 1.05-1.02 (m, 2H), 0.87-0.81 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 580.3。
43		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-((R)-2-氧代-4-(吡啶-2-基甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	MS (ESI, m/e) $[M+1]^+$ 613.4。
44		N-((1S)-2-((2-(4-(叔丁基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (d, J = 4.0 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.56-7.47 (m, 2H), 7.46 (d, J = 4.0 Hz, 1H), 7.42-7.30 (m, 1H), 7.12-7.10 (m, 1H), 7.06 (d, J = 4.0 Hz, 1H), 6.79 (s, 1H), 4.40-4.35 (m, 1H), 4.02 (s, 3H), 3.60-3.50 (m, 1H), 3.45-3.41 (m, 1H), 3.30-3.28 (m, 1H), 3.24-3.10 (m, 2H), 2.99-2.94 (m, 1H), 2.57 (d, J = 4.0 Hz, 3H), 1.83-1.81 (m, 2H), 1.73-1.68 (m, 2H), 1.62-1.53 (m, 2H), 1.23-0.79 (m, 6H), 0.66 (s, 9H)。MS (ESI, m/e) $[M+1]^+$ 578.4。

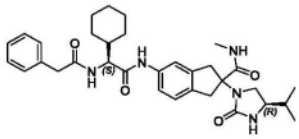
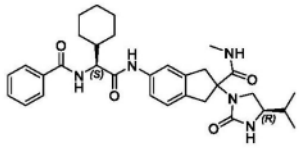
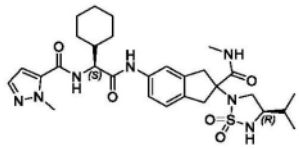
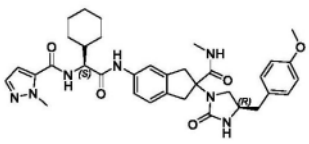
[0730]

45		N-((1S)-1-环丁基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.50 (d, J = 7.6 Hz, 1H), 7.58-7.27 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 1.6 Hz, 1H), 6.77 (s, 1H), 4.54 (t, J = 9.6 Hz, 1H), 4.03 (s, 3H), 3.57-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.93-2.87 (m, 1H), 2.80-2.67 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.10-1.75 (m, 1H), 1.50-1.40 (m, 1H), 0.72-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 536.5。
46		N-((1S)-1-环戊基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.61 (d, J = 8.0 Hz, 1H), 7.58-7.30 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 6.77 (s, 1H), 4.37 (t, J = 9.2 Hz, 1H), 4.03 (s, 3H), 3.57-3.45 (m, 2H), 3.32-3.12 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.40-2.30 (m, 1H), 1.89-1.80 (m, 1H), 1.70-1.28 (m, 9H), 0.75 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 550.5。
47		N-((1S)-1-环庚基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.57-7.30 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.77 (s, 1H), 4.45 (t, J = 8.0 Hz, 1H), 4.03 (s, 3H), 3.57-3.45 (m, 2H), 3.32-3.12 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.13-2.04 (m, 1H), 1.78-1.28 (m, 14H), 0.74 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 578.4。
48		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(1-苯基乙基)咪唑烷-1-基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.22-10.19 (m, 1H), 8.58-8.54 (m, 1H), 7.73-7.56 (m, 1H), 7.54-7.50 (m, 1H), 7.47-7.40 (m, 1H), 7.32-7.24 (m, 3H), 7.22-7.10 (m, 4H), 7.08-7.02 (m, 1H), 6.86-6.72 (m, 1H), 4.47-4.43 (m, 1H),

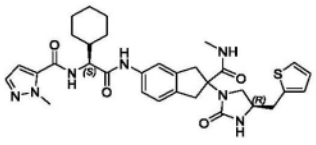
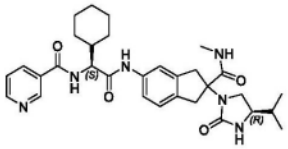
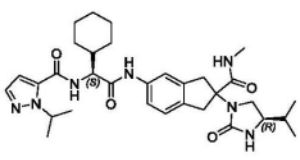
[0731]

		-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	4.10-4.07 (m, 3H), 3.17-3.02 (m, 3H), 2.89-2.76 (m, 1H), 2.61-2.59 (m, 2H), 2.09-2.02 (m, 1H), 1.95-1.86 (m, 2H), 1.80-1.73 (m, 2H), 1.71-1.62 (m, 2H), 1.42 (s, 1H), 1.30-1.20 (m, 9H), 1.14-1.05 (m, 2H). MS (ESI, m/e) $[M+1]^+$ 626.4。
49		5-((S)-2-环己基-2-(环丙烷甲酰胺基)乙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.00 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H),7.55-7.25 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.29 (t, J = 8.0 Hz, 1H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.81-1.40 (m, 7H), 1.21-0.80 (m, 7H), 0.74 (d, J = 6.8 Hz, 3H), 0.72-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 524.4。
50		((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸乙酯	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.94 (s, 1H), 7.55-7.20 (m, 4H), 7.11 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 4.02-3.93 (m, 3H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.8 Hz, 3H), 1.78-1.40 (m, 7H), 1.21-0.93 (m, 8H), 0.74 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 528.3。
51		((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)氨基甲酸苯酯	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.58-7.08 (m, 9H), 6.77 (s, 1H), 4.03 (t, J = 8.4 Hz, 1H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.8 Hz, 3H), 1.85-1.40 (m, 7H), 1.21-1.03 (m, 5H), 0.77-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 576.4。
52		5-((S)-2-环己基-2-(3-苯基丙酰胺基)乙酰胺基)-2-((R)-4-异丙基-2-氧代咪	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.98 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.55-7.08 (m, 9H), 6.76 (s, 1H), 4.27 (t, J = 8.0 Hz, 1H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87

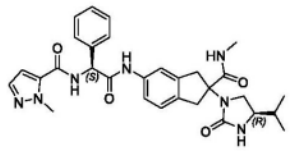
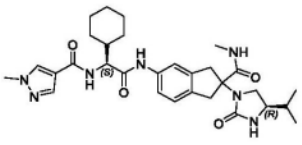
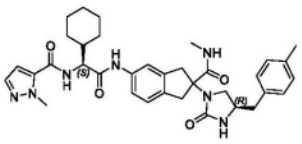
[0732]

		唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	(m, 1H), 2.84-2.78 (m, 2H), 2.58 (d, J = 4.8 Hz, 3H), 2.48-2.38 (m, 2H), 1.70-1.40 (m, 7H), 1.21-0.83 (m, 5H), 0.74 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 588.4。
53		5-((S)-2-环己基-2-(2-苯基乙酰氨基)乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.99 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.55-7.17 (m, 8H), 7.11 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.28 (t, J = 8.0 Hz, 1H), 3.59-3.45 (m, 4H), 3.32-3.10 (m, 4H), 2.94-2.86 (m, 1H), 2.58 (d, J = 4.8 Hz, 3H), 1.75-1.40 (m, 7H), 1.21-0.95 (m, 5H), 0.77-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 574.4。
54		5-((S)-2-苯甲酰氨基-2-环己基乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.58-7.29 (m, 6H), 7.12 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.41 (t, J = 8.4 Hz, 1H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.90 (t, J = 8.0 Hz, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.93-1.55 (m, 6H), 1.48-1.38 (m, 1H), 1.21-0.95 (m, 5H), 0.76-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 560.3。
55		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-1,1-二氧化-1,2,5-噻二唑烷-2-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.77-7.72 (m, 1H), 7.54-7.33 (m, 4H), 7.11 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 4.37 (t, J = 8.8 Hz, 1H), 4.02 (s, 3H), 3.55-3.40 (m, 5H), 3.26-3.10 (m, 2H), 2.60 (d, J = 4.4 Hz, 3H), 2.04-1.56 (m, 7H), 1.20-0.95 (m, 5H), 0.91 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 600.3。
56		N-((1S)-1-环己基-2-((2-((R)-4-(4-甲氧基苄	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.16-10.12 (m, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.57-7.51 (m, 1H), 7.47-7.45 (m, 1H), 7.41-7.33 (m, 1H),

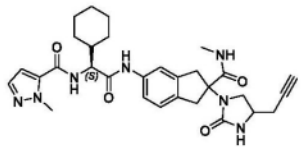
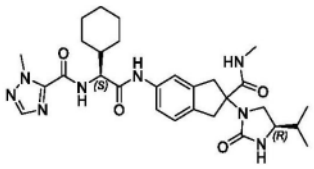
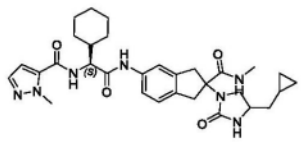
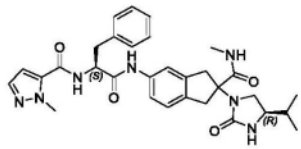
[0733]

		基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	7.16-7.09 (m, 2H), 7.07-7.05 (m, 1H), 6.95-6.88 (m, 2H), 6.81-6.76 (m, 2H), 6.70 (s, 1H), 4.42-4.36 (m, 1H), 4.02 (d, J = 4.0 Hz, 3H), 3.70-3.68 (m, 2H), 3.64 (s, 1H), 3.47-3.38 (m, 2H), 3.29-3.25 (m, 1H), 3.12-3.06 (m, 2H), 2.99-2.95 (m, 1H), 2.66-2.59 (m, 2H), 2.54-2.52 (m, 3H), 2.45-2.34 (m, 1H), 1.89-1.81 (m, 2H), 1.73-1.56 (m, 4H), 1.23-1.15 (m, 6H), 1.04-0.99 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 642.5。
57		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-((R)-2-氧代-4-(噻吩-2-基甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15-10.12 (m, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.55-7.45 (m, 2H), 7.39-7.24 (m, 3H), 7.11-7.07 (m, 2H), 6.93-6.90 (m, 1H), 6.78-6.69 (m, 2H), 4.40-4.35 (m, 1H), 4.02 (d, J = 4.0 Hz, 3H), 3.74-3.64 (m, 1H), 3.45-3.41 (m, 1H), 3.13-3.00 (m, 3H), 2.89-2.79 (m, 2H), 2.56-2.54 (m, 3H), 2.03-1.95 (m, 1H), 1.87-1.82 (m, 1H), 1.73-1.57 (m, 4H), 1.23-1.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 618.4。
58		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)烟酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.04 (s, 1H), 8.88-8.73 (m, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.57-7.29 (m, 4H), 7.12 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.47-4.40 (m, 1H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.94-1.40 (m, 7H), 1.21-0.95 (m, 5H), 0.74 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 561.4。
59		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.57-7.30 (m, 4H), 7.12 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 1.0 Hz, 1H), 6.77 (s, 1H), 5.45-5.35 (m, 1H),

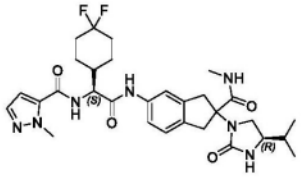
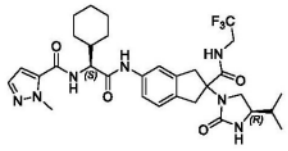
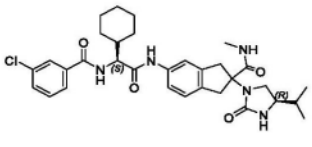
[0734]

		基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-异丙基-1H-吡唑-5-甲酰胺	4.38-4.32 (m, 1H), 3.59-3.45 (m, 2H), 3.30-3.12 (m, 4H), 2.93-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.40 (m, 7H), 1.35 (t, J = 7.2 Hz, 6H), 1.20-0.95 (m, 5H), 0.75 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 592.5。
60		N-((1S)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代-1-苯基乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.32 (s, 1H), 9.01 (d, J = 7.6 Hz, 1H), 7.57-7.30 (m, 9H), 7.13 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 5.80 (d, J = 7.6 Hz, 1H), 4.04 (s, 3H), 3.59-3.44 (m, 2H), 3.30-3.12 (m, 4H), 2.93-2.87 (m, 1H), 2.57 (d, J = 4.4 Hz, 3H), 1.48-1.38 (m, 1H), 0.76-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 558.3。
61		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-4-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.24 (s, 1H), 8.10-8.05 (m, 3H), 7.93 (s, 1H), 7.57-7.30 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 4.43-4.35 (m, 1H), 3.85 (s, 3H), 3.59-3.45 (m, 2H), 3.32-3.10 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.85-1.40 (m, 7H), 1.21-0.95 (m, 5H), 0.74 (d, J = 6.4 Hz, 3H), 0.69 (d, J = 6.4 Hz, 3H). MS (ESI, m/e) $[M+1]^+$ 564.4。
62		N-((1S)-1-环己基-2-((2-((R)-4-(4-甲基苄基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.17-10.12 (m, 1H), 8.51-8.47 (m, 1H), 7.58-7.46 (m, 2H), 7.41-7.34 (m, 1H), 7.20-6.99 (m, 5H), 6.91-6.89 (m, 1H), 6.85-6.81 (m, 1H), 6.70 (s, 1H), 4.43-4.36 (m, 1H), 4.02-4.01 (m, 3H), 3.65-3.59 (m, 1H), 3.46-3.40 (m, 2H), 3.31-3.26 (m, 2H), 3.13-3.04 (m, 2H), 2.98-2.92 (m, 1H), 2.68-2.60 (m, 1H), 2.55-2.53 (m, 3H), 2.47-2.31 (m, 1H), 2.23-2.15 (m, 3H), 1.89-1.82 (m, 1H), 1.75-1.54 (m, 3H),

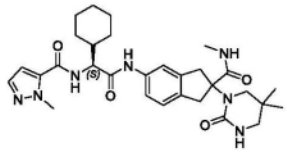
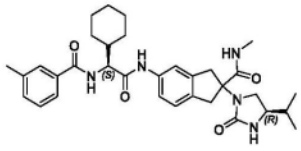
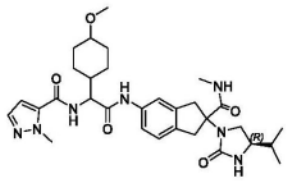
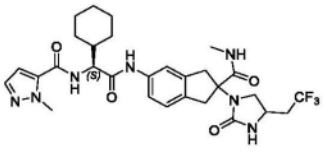
[0735]

			1.23-1.14 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 626.4。
63		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(丙-2-炔-1-基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO- d_6) δ ppm: 10.10 (s, 1H), 8.46 (d, J = 8.6 Hz, 1H), 7.58-7.47 (m, 2H), 7.46 (d, J = 1.8 Hz, 1H) 7.41-7.28 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.07-7.03 (m, 1H), 6.74 (s, 1H), 4.42-4.31 (m, 1H), 4.02 (s, 3H), 3.65-3.54 (m, 1H), 3.52-3.37 (m, 3H), 3.23-3.05 (m, 3H), 2.84-2.78 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 2.39-2.22 (m, 2H), 2.03-1.50 (m, 7H), 1.21-1.08 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 560.4。
64		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-1,2,4-三唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.38 (d, J = 7.2 Hz, 1H), 8.24 (s, 1H), 7.55-7.27 (m, 3H), 7.13 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.52-4.45 (m, 1H), 4.13 (s, 3H), 3.58-3.45 (m, 2H), 3.32-3.12 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.40 (m, 7H), 1.21-0.95 (m, 5H), 0.76 (d, J = 6.4 Hz, 3H), 0.71 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 565.5。
65		N-((1S)-1-环己基-2-((2-(4-(环丙基甲基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.47-8.44 (m, 1H), 7.53-7.46 (m, 3H), 7.21-7.06 (m, 3H), 6.68-6.65 (m, 2H), 4.40-4.35 (m, 1H), 4.02 (s, 3H), 3.54-3.38 (m, 3H), 3.31-3.29 (m, 2H), 2.98-2.91 (m, 2H), 2.68-2.65 (m, 1H), 2.59-2.56 (m, 3H), 2.34-2.31 (m, 1H), 2.02-1.95 (m, 6H), 1.85-1.81 (m, 1H), 1.75-1.67 (m, 2H), 1.48-1.44 (m, 2H), 1.23-1.14 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 576.5。
66		N-((2S)-1-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.74 (d, J = 8.0 Hz, 1H), 7.54-7.25 (m, 8H), 7.20-7.12 (m, 2H), 6.95 (s, 1H), 6.77 (s, 1H), 4.83-4.77 (m, 1H), 3.94 (s, 3H), 3.59-3.34 (m,

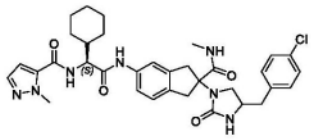
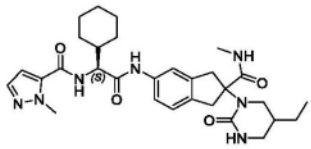
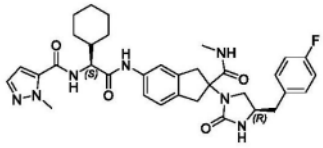
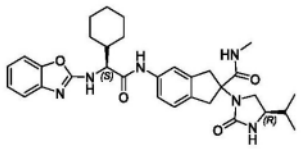
[0736]

		二氢-1H-茚-5-基)氨基)-1-氧代-3-苯基丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	2H), 3.31 (s, 1H), 3.24-3.12 (m, 3H), 3.07-3.01 (m, 1H), 2.92-2.88 (m, 1H), 2.57 (d, *J* = 4.0 Hz, 1H), 1.48-1.40 (m, 1H), 1.23-1.16 (m, 1H), 0.76-0.69 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 572.3。
67		N-((1S)-1-(4,4-二氟环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 8.62 (d, *J* = 12.0 Hz, 1H), 7.56-7.46 (m, 3H), 7.41-7.30 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.76 (s, 1H), 4.49-4.45 (m, 1H), 4.03 (s, 3H), 3.57-3.45 (m, 2H), 3.30 (s, 1H), 3.23-3.15 (m, 2H), 3.12-3.05 (m, 2H), 2.93-2.88 (m, 1H), 2.57 (d, *J* = 8.0 Hz, 1H), 2.07-1.99 (m, 3H), 1.92-1.65 (m, 4H), 1.46-1.42 (m, 2H), 1.35-1.23 (m, 1H), 0.75-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 600.4。
68		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((2,2,2-三氟乙基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.23-8.17 (m, 1H), 7.57-7.32 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 6.90 (s, 1H), 4.42-4.35 (m, 1H), 4.02 (s, 3H), 3.95-3.74 (m, 2H), 3.64-3.38 (m, 3H), 3.32-3.07 (m, 3H), 2.87-2.80 (m, 1H), 1.90-1.40 (m, 7H), 1.21-0.95 (m, 5H), 0.76 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 632.5。
69		5-((S)-2-(3-氯苯甲酰氨基)-2-环己基乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.63 (d, *J* = 8.2 Hz, 1H), 8.00-7.94 (m, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.64-7.46 (m, 4H), 7.42-7.28 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.74 (s, 1H), 4.47-4.35 (m, 1H), 3.60-3.43 (m, 2H), 3.31-3.05 (m, 4H), 2.95-2.85 (m, 1H), 2.57 (d, *J* = 4.4 Hz, 3H), 1.94-1.53 (m, 6H), 1.50-1.38 (m, 1H), 1.20-1.01 (m, 5H), 0.78-0.62 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 594.4。

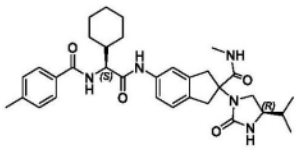
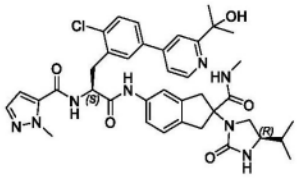
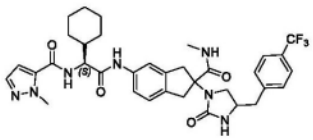
[0737]

70		N-((1S)-1-环己基-2-((2-(5,5-二甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.43 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.07-3.01 (m, 4H), 2.98-2.96 (m, 2H), 2.54-2.51 (m, 3H).1.81-1.67 (m, 7H), 1.05-1.02 (m, 6H), 0.79-0.72 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 564.5。
71		5-((S)-2-环己基-2-(3-甲基苯甲酰氨基)乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.73-7.62 (m, 2H), 7.53-7.32 (m, 5H), 7.10-7.05 (m, 1H), 6.75 (s, 1H), 4.45-4.41 (m, 1H), 3.46-3.41 (m, 2H), 3.22-3.16 (m, 2H), 2.98-2.96 (m, 1H), 2.64-2.60 (m, 3H), 2.31 (s, 3H), 1.81-1.67 (m, 7H), 1.21-1.02 (m, 5H), 0.65-0.55 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 574.5。
72		N-(2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4-甲氧基环己基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.60-7.44 (m, 3H), 7.44-7.26 (m, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.07-7.03 (m, 1H), 6.76 (s, 1H), 4.43-4.31 (m, 1H), 4.02 (s, 3H), 3.53-3.44 (m, 2H), 3.23-3.15 (m, 5H), 3.12-3.04 (m, 2H), 2.94-2.88 (m, 1H), 2.57 (d, J = 4.6 Hz, 3H), 2.08-1.75 (m, 4H), 1.65-1.52 (m, 1H), 1.50-1.28 (m, 4H), 1.20-1.14 (m, 2H), 0.78-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 594.5。
73		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(2,2,2-三氟乙基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.64-7.30 (m, 4H), 7.12 (d, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.78 (s, 1H), 4.42-4.35 (m, 1H), 4.02 (s, 3H), 3.83-3.74 (m, 1H), 3.53-3.38 (m, 3H), 3.22-3.12 (m, 2H), 3.09-2.99 (m, 1H), 2.59 (d, J =

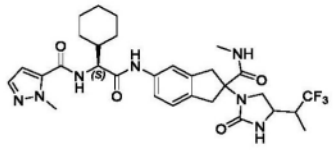
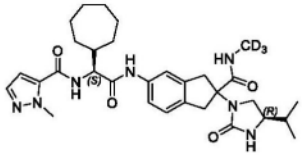
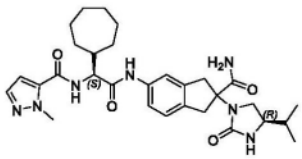
[0738]

		基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	4.4 Hz, 3H), 2.56-2.40 (m, 2H), 1.90-1.54 (m, 6H), 1.21-0.95 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 604.4。
74		N-((1S)-2-((2-(4-(4-氯苄基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18-10.08 (m, 1H), 8.55-8.40 (m, 1H), 7.57-7.48 (m, 1H), 7.47-7.43 (m, 1H), 7.43-7.32 (m, 1H), 7.32-7.15 (m, 3H), 7.15-6.95 (m, 4H), 6.72 (s, 1H), 4.48-4.30 (m, 1H), 4.06-3.90 (m, 3H), 3.72-3.58 (s, 1H), 3.50-3.38 (m, 1H), 3.16-2.82 (m, 4H), 2.70-2.60 (m, 1H), 2.59-2.52 (m, 3H), 2.48-2.38 (m, 1H), 1.95-1.44 (m, 7H), 1.20-0.98 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 646.5。
75		N-((1S)-1-环己基-2-((2-(5-乙基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.62-7.25 (m, 4H), 7.20-6.94 (m, 2H), 6.34 (s, 1H), 4.38 (t, J = 8.2 Hz, 1H), 4.02 (s, 3H), 3.60-3.32 (m, 3H), 3.21-3.02 (m, 3H), 2.84-2.68 (m, 2H), 2.54 (d, J = 3.6 Hz, 3H), 1.83-1.59 (m, 7H), 1.15-0.99 (m, 7H), 0.71 (d, J = 6.2 Hz, 3H)。MS (ESI) m/e $[M+1]^+$ 564.4。
76		N-((1S)-1-环己基-2-((2-((R)-4-(4-氟苄基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, 甲醇-d_4) δ ppm: 7.48-7.29 (m, 3H), 7.18-7.11 (m, 1H), 7.02-6.84 (m, 5H), 4.44 (d, J = 8.8 Hz, 1H), 4.11-4.05 (m, 3H), 3.85-3.75 (m, 1H), 3.67-3.37 (m, 4H), 3.20-3.07 (m, 3H), 2.85-2.71 (m,3H), 1.98-1.65 (m, 6H), 1.36-1.07 (m, 6H)。MS (ESI, m/e) [M+1]+ 630.5。
77		5-((S)-2-(苯并[d]噁唑-2-基氨基)-2-环己基乙酰氨基)-2-((R)-4-异	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.53-7.32 (m, 4H), 7.15-7.05 (m, 3H), 6.75 (s, 1H), 4.30-4.25 (m, 1H), 3.46-3.41 (m, 2H), 3.22-3.16

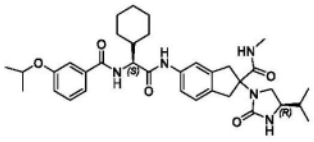
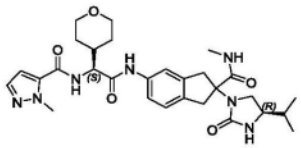
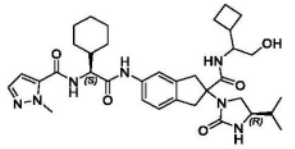
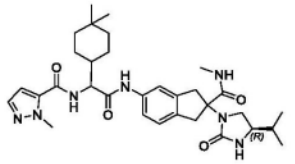
[0739]

		丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	(m, 2H), 2.98-2.96 (m, 1H), 2.64-2.60 (m, 3H), 1.99-1.97 (m, 1H), 1.81-1.67 (m, 7H), 1.53-1.47 (m, 2H), 1.21-1.02 (m, 5H), 0.65-0.55 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 573.5。
78		5-((S)-2-环己基-2-(4-甲基苯甲酰氨基)乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.58-7.46 (m, 2H), 7.42-7.29 (m, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 1H), 6.75 (s, 1H), 4.44-4.34 (m, 1H), 3.53-3.44 (m, 2H), 3.30-3.25 (m 1H), 3.23-3.12 (m, 2H), 2.95-2.87 (m, 1H), 2.57 (d, J = 4.4 Hz, 3H), 2.36 (s, 3H), 1.94-1.51 (m, 7H), 1.48-1.41 (m, 1H), 1.19-1.01 (m, 5H), 0.75-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 574.5。
79		N-((2S)-3-(2-氯-5-(2-(2-羟基丙烷-2-基)吡啶-4-基)苯基)-1-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 10.04 (s, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.51 (s, 1H), 7.92 (s, 2H), 7.67-7.31 (m, 7H), 7.11 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 4.98 (s, 1H), 3.91 (s, 3H), 3.57-3.16 (m, 6H), 3.11-3.06 (m, 2H), 2.88 (s, 1H), 2.57 (d, J = 2.8 Hz, 3H), 1.48 (s, 6H), 1.46-1.39 (m, 1H), 0.77-0.64 (m, 6H)。MS (ESI) m/e $[M+1]^+$ 742.4。
80		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(4-(三氟甲基)苄基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 8.46 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.38-7.31 (m, 2H), 7.25 (d, J = 7.4 Hz, 2H), 7.14-7.02 (m, 2H), 6.75 (d, J = 5.2 Hz, 1H), 4.39 (d, J = 7.6 Hz, 1H), 4.02 (d, J = 3.2 Hz, 3H), 3.73 (s, 1H), 3.46-3.32 (m, 3H), 3.12-3.06 (m, 2H), 2.97 (s, 1H), 2.78 (s, 1H), 2.62 (s, 1H), 2.55 (d, J = 3.2 Hz, 3H), 1.84 (s, 2H),

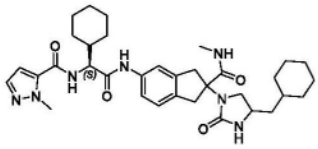
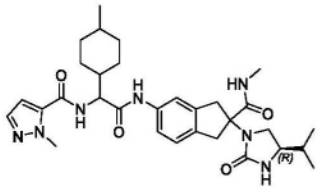
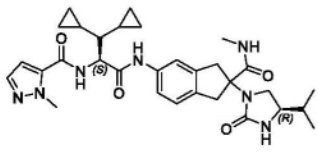
[0740]

			1.69 (s, 2H), 1.60 (s, 2H), 1.15 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 11.2 Hz, 1H)。MS (ESI) m/e $[M+1]^+$ 680.4
81		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(1,1,1-三氟丙-2-基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.61-7.50 (m, 2H), 7.46 (d, J = 4.0 Hz, 1H), 7.41-7.31 (m, 1H), 7.13-7.11 (m, 1H), 7.06 (d, J = 4.0 Hz, 1H), 6.79 (s, 1H), 4.40-4.35 (m, 1H), 4.02 (s, 3H), 3.77-3.72 (m, 1H), 3.77-3.72 (m, 1H), 3.64-3.50 (m, 2H), 3.30-3.24 (m, 2H), 3.19-3.12 (m, 1H), 3.05-3.01 (m, 1H), 2.57 (d, J = 4.0 Hz, 3H), 1.87-1.81 (m, 2H), 1.74-1.70 (m, 2H), 1.62-1.55 (m, 2H), 1.23-1.15 (m, 6H), 0.96-0.92 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 618.5。
82		N-((1S)-1-环庚基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((甲基-d_3)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.58-7.30 (m, 4H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.75 (s, 1H), 4.48-4.43 (m, 1H), 4.01 (s, 3H), 3.57-3.45 (m, 2H), 3.25-3.12 (m, 4H), 2.95-2.89 (m, 1H), 2.13-2.06 (m, 1H), 1.77-1.28 (m, 14H), 0.75 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 581.5。
83		N-((1S)-2-((2-氨基甲酰基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环庚基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.57-7.31 (m, 3H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 7.05-6.93 (m, 2H), 6.77 (s, 1H), 4.48-4.43 (m, 1H), 4.01 (s, 3H), 3.57-3.35 (m, 4H), 3.25-3.12 (m, 2H), 2.98-2.89 (m, 1H), 2.13-2.06 (m, 1H), 1.77-1.28 (m, 14H), 0.76 (d, J = 6.4 Hz, 3H) , 0.71 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 564.5。

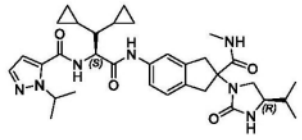
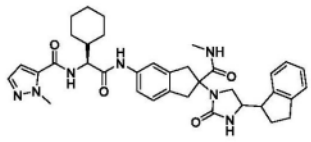
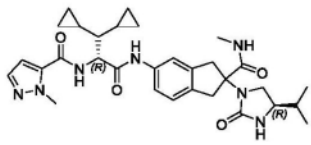
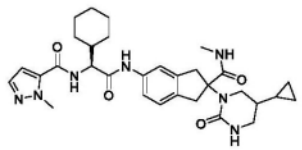
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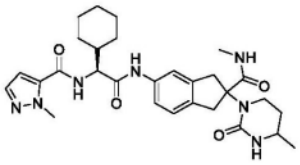
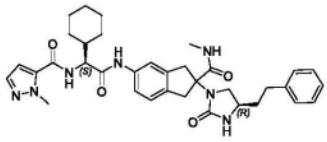
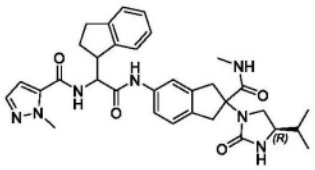
84		5-((S)-2-环己基-2-(3-异丙氧基苯甲酰氨基)乙酰氨基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.45 (d, J = 7.2 Hz, 1H), 7.57-7.28 (m, 3H), 7.12 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 6.75 (s, 1H), 4.73-4.65 (m, 1H), 4.43-4.38 (m, 1H), 3.58-3.44 (m, 2H), 3.32-3.07 (m, 4H), 2.94-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.95-1.40 (m, 7H), 1.30-1.26 (m, 6H), 1.20-1.11 (m, 4H), 1.08-0.95 (m, 1H), 0.74 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 618.5。
85		N-((1S)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代-1-(四氢-2H-吡喃-4-基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.58-7.43 (m, 3H), 7.43-7.29 (m, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.75 (s, 1H), 4.47-4.35 (m, 1H), 4.03 (s, 3H), 3.93-3.82 (m, 2H), 3.60-3.42 (m, 2H), 3.26-3.04 (m, 7H), 2.95-2.85 (m, 1H), 2.57 (d, J = 4.6 Hz, 3H), 2.15-2.00 (m, 1H), 1.75-1.65 (m, 1H), 1.52-1.40 (m, 3H), 0.76-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 566.5。
86		N-((1S)-2-((2-((1-环丁基-2-羟基乙基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.45-7.42 (m, 3H), 7.13-7.10 (m, 4H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.56-3.51 (s, 4H), 3.26-3.21 (m, 4H), 2.89-2.85 (m, 1H),1.91-1.67 (m, 14H), 1.20-1.04 (m, 4H), 0.84-0.75 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 648.5。
87		N-(1-(4,4-二甲基环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.53 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.76 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.07-3.01 (m, 3H), 2.54-2.51

[0742]

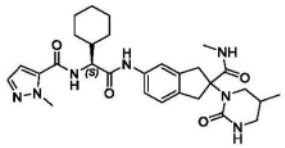
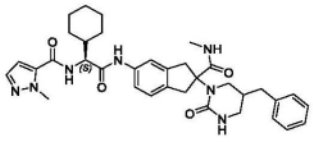
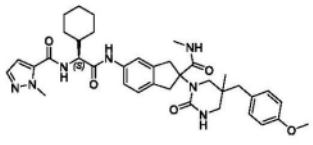
		基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	(m, 3H),1.81-1.67 (m, 2H), 1.51-1.17 (m, 7H), 1.05-1.02 (m, 2H), 0.79-0.72 (m, 6H), 0.63-0.55 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 592.5。
88		N-((1S)-1-环己基-2-((2-(4-(环己基甲基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.43 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.65 (s, 1H), 4.40-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 4H), 3.07-3.01 (m, 2H), 2.78-2.76 (m, 1H), 2.54-2.51 (m, 3H).1.81-1.67 (m, 11H), 1.05-1.02 (m, 8H), 0.79-0.72 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 618.6。
89		N-(2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4-甲基环己基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.58-7.30 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.75 (s, 1H), 4.40-4.34 (m, 1H), 4.02 (s, 3H), 3.59-3.46 (m, 2H), 3.27-3.12 (m, 4H), 2.95-2.87 (m, 1H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.54 (m, 5H), 1.50-1.25 (m, 3H), 1.21-0.85 (m, 6H), 0.75 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 578.5。
90		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.42 (d, J = 8.8 Hz, 1H), 7.52-7.46 (m, 4H), 7.17 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 6.74 (s, 1H), 4.82-4.78 (m, 1H), 4.05 (s, 3H), 3.50-3.47 (m, 2H), 3.28-3.21 (m, 3H), 3.03-2.98 (m, 1H), 2.58-2.52 (m, 3H), 1.49-1.34 (m, 1H), 0.93-0.68 (m, 9H), 0.45-0.07 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 576.5。

[0743]

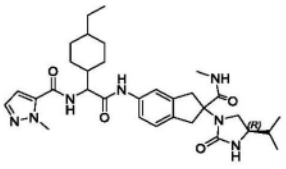
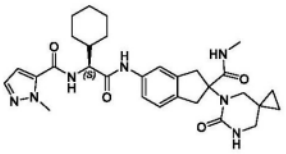
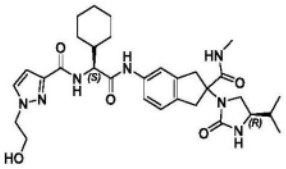
91		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H), 8.42 (d, J = 8.8 Hz, 1H), 7.52-7.46 (m, 4H), 7.17 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.74 (s, 1H), 5.48-5.34 (m, 1H), 4.82-4.78 (m, 1H), 3.50-3.47 (m, 2H), 3.28-3.21 (m, 3H), 3.17-3.15 (m, 1H), 3.03-2.98 (m, 1H), 2.58-2.52 (m, 3H), 1.49-1.34 (m, 7H), 0.93-0.68 (m, 10H), 0.45-0.07 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 604.5。
92		N-((1S)-1-环己基-2-((2-(4-(2,3-二氢-1H-茚-1-基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (d, J = 8.8 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.59-7.30 (m, 4H), 7.18-7.00 (m, 6H), 6.82 (d, J = 4.4 Hz, 1H), 4.44-4.37 (m, 1H), 4.02 (s, 3H), 3.74-3.46 (m, 3H), 3.27-3.00 (m, 5H), 2.86-2.65 (m, 2H), 2.58-2.54 (m, 3H), 2.04-1.54 (m, 6H), 1.20-0.95 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 638.5。
93		N-((2R)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 7.57-7.50 (m, 1H), 7.50-7.43 (m, 2H), 7.40-7.32 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.08-7.02 (m, 1H), 6.74 (s, 1H), 4.85-4.74 (m, 1H), 4.04 (s, 3H), 3.61-3.45 (m, 2H), 3.29-3.27 (m, 1H), 3.25-3.12 (m, 2H), 2.92-2.82 (m, 1H), 2.60-2.55 (m, 3H), 2.04-1.91 (m, 1H), 1.53-1.35 (m, 1H), 0.85-0.65 (m, 9H), 0.48-0.05 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 576.5。
94		N-((1S)-1-环己基-2-((2-(5-环丙基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 19.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.39-7.28 (m, 2H), 7.10 (d, J = 8.2 Hz, 1H), 7.08-7.03 (m, 1H), 6.34 (s, 1H), 4.44-4.30 (m,

		二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	1H), 4.02 (s, 3H), 3.66-3.52 (m, 1H), 3.47-3.38 (m, 1H), 3.21-2.81 (m, 6H), 2.54 (d, *J* = 4.6 Hz, 3H), 1.93-1.52 (m, 6H), 1.21-0.94 (m, 6H), 0.54-0.41 (m, 1H), 0.39-0.29 (m, 1H), 0.29-0.18 (m, 1H), 0.11-0.04 (m, 1H), 0.00--0.1 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 576.5。
95		N-((1S)-1-环己基-2-((2-(4-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.40-7.34 (m, 1H), 7.34-7.28 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.32 (s, 1H), 4.42-4.34 (m, 1H), 4.02 (s, 3H), 3.58-3.40 (m, 2H), 3.22-3.02 (m, 4H), 2.54 (d, *J* = 4.6 Hz, 3H), 2.02-1.50 (m, 8H), 1.43-1.32 (m, 1H), 1.23-1.07 (m, 4H), 1.07-0.95 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 550.5。
[0744] **96**		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-((R)-2-氧代-4-苯乙基咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13-10.10 (m, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.46-7.45 (m, 1H), 7.43-7.33 (m, 1H), 7.26-7.21 (m, 1H), 7.16-7.10 (m, 4H), 7.07-7.06 (m, 1H), 6.79 (s, 1H), 4.41-4.36 (m, 1H), 4.02 (d, *J* = 4.0 Hz, 3H), 3.54-3.40 (m, 4H), 3.26-3.13 (m, 2H), 2.93-2.88 (m, 1H), 2.58 (d, *J* = 4.0 Hz, 3H), 2.47-2.45 (m, 1H), 1.87-1.81 (m, 2H), 1.73-1.69 (m, 2H), 1.63-1.56 (m, 2H), 1.23-1.15 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 626.5。
97		N-(1-(2,3-二氢-1H-茚-1-基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.28 (s, 0.19H), 10.02 (s, 0.78H), 9.03 (d, *J* = 8.0 Hz, 0.2H), 8.65 (d, *J* = 8.0 Hz, 0.8H), 7.63-7.28 (m, 5H), 7.22-7.05 (m, 4H), 7.01-6.99 (m, 0.8H), 6.81 (s, 1H), 4.96-4.92 (m, 0.8H), 4.66-4.61 (m, 0.2H), 4.05-4.02 (m, 3H),

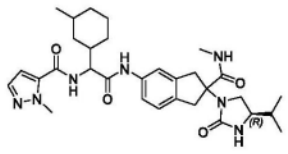
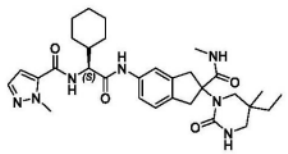
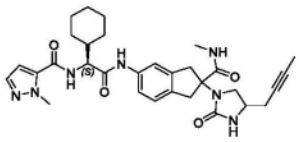
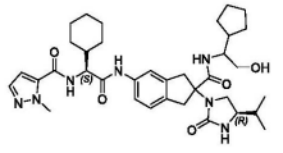
[0745]

		基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	3.85-3.80 (m, 1H), 3.65-3.52 (m, 2H), 3.31-3.19 (m, 2H), 3.08-2.82 (m, 3H), 2.66-2.62 (m, 3H), 2.20-2.03 (m, 2H), 1.53-1.48 (m, 2H), 0.81-0.75 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 598.5。
98		N-((1S)-1-环己基-2-((2-(5-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.43 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.07-3.01 (m, 4H), 2.98-2.96 (m, 2H), 2.54-2.51 (m, 3H).1.81-1.67 (m, 7H), 1.05-1.02 (m, 6H), 0.79-0.72 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 550.5。
99		N-((1S)-2-((2-(5-苄基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (d, J = 4.0 Hz, 1H), 8.47 (d, J = 7.4 Hz, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 7.38-7.33 (m, 2H), 7.22-7.18 (m, 2H), 7.15-7.03 (m, 3H), 7.00-6.95 (m, 2H), 6.35 (s, 1H), 4.40 (t, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.62 (t, J = 15.6 Hz, 1H), 3.37-3.32 (m, 1H), 3.17-3.01 (m, 5H), 2.97 (s, 1H), 2.83-2.75 (m, 2H), 2.54 (d, J = 4.0 Hz, 3H), 2.43-2.41 (m, 2H), 2.05 (s, 1H), 1.85 (s, 2H), 1.70 (s, 2H), 1.61 (s, 2H), 1.23-1.16 (m, 3H), 1.05-0.99 (m, 1H)。MS (ESI) m/e $[M+1]^+$ 626.4
100		N-((1S)-1-环己基-2-((2-(5-(4-甲氧基苄基)-5-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.45-8.43(m, 1H), 7.56-7.27 (m, 4H), 7.11-7.06 (m, 2H), 6.89-6.66 (m, 4H), 6.41 (d, J = 7.4 Hz, 1H), 4.39 (t, J = 74 Hz, 1H), 4.02 (d, J = 5.8 Hz, 3H), 3.75-3.62 (m, 4H), 3.50-3.38 (m, 2H), 3.20-2.91 (m, 5H), 2.80 (d, J = 11.2 Hz, 1H), 2.68 (d, J = 9.8 Hz, 1H), 2.55 (d, J = 4.4 Hz, 3H), 2.40 (d, J = 13.4 Hz, 1H), 2.24 (d, J = 13.4 Hz,

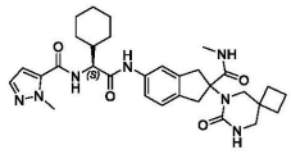
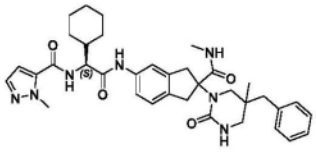
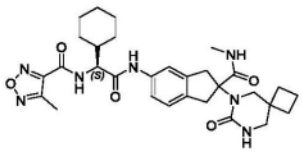
[0746]

			1H), 1.84 (s, 2H), 1.70 (s, 2H), 1.59 (s, 2H), 1.16 (s, 2H), 1.02 (s, 1H), 0.64-0.55 (m, 3H)。MS (ESI) m/e $[M+1]^+$ 670.4。
101		N-(1-(4-乙基环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.55-7.47 (m, 2H), 7.45 (d, J = 4.0 Hz, 1H), 7.40-7.29 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 4.0 Hz, 1H), 6.74 (s, 1H), 4.38-4.34 (m, 1H), 4.03-4.02 (m, 3H), 3.57-3.45 (m, 2H), 3.23-3.12 (m, 3H), 2.92-2.89 (m, 1H), 2.58 (d, J = 4.0 Hz, 3H), 1.88-1.75 (m, 4H), 1.61-1.58 (m, 1H), 1.47-1.42 (m, 2H), 1.24-1.15 (m, 5H), 1.07-1.00 (m, 2H), 0.85-0.82 (m, 3H), 0.85-0.82 (m, 3H), 0.75-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 592.6。
102		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.06 (s, 1H), 8.44 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.33-7.29 (m, 2H), 7.11-7.02 (m, 2H), 6.42 (s, 1H), 4.38 (t, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.55-3.45 (m, 2H), 3.21-2.98 (m, 5H), 2.85 (s, 2H), 2.56 (d, J = 4.4 Hz, 3H), 1.88-1.52 (m, 6H), 1.35-1.01 (m, 5H), 0.39 (s, 2H), 0.24-0.11 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 562.5
103		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-(2-羟乙基)-1H-吡唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.14 (s, 1H), 8.39-8.31 (m, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.58-7.51 (m, 1H), 7.39-7.31 (m, 1H), 7.11 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 6.65 (d, J = 2.2 Hz, 1H), 4.7-4.92(m, 1H), 4.56-4.52 (m, 1H), 4.25-4.21 (m, 2H), 3.85-3.75 (m, 2H), 3.71-3.51 (m, 4H), 3.9-3.05 (m, 4H), 2.65-2.55 (m, 3H), 1.81-1.61 (m, 6H), 1.35-1.1 (s, 5H), 0.85-0.69 (m, 6H)。MS

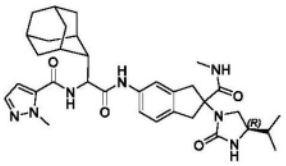
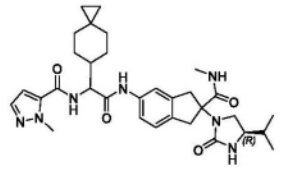
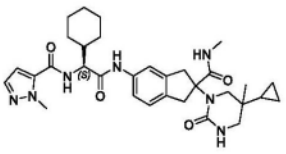
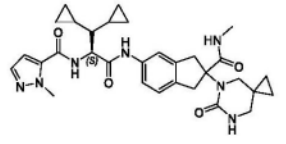
[0747]

			(ESI, m/e) [M+1]+ 594.8。
104		N-(2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-(3-甲基环己基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.46-7.44 (m, 1H), 7.40-7.30 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.07-7.05 (m, 1H), 6.75 (s, 1H), 4.39-4.34 (m, 1H), 4.04-4.01 (m, 3H), 3.57-3.45 (m, 2H), 3.23-3.12 (m, 2H), 2.94-2.88 (m, 1H), 2.58 (d, J = 4.0 Hz, 3H), 1.90-1.78 (m, 2H), 1.74-1.69 (m, 1H), 1.65-1.54 (m, 2H), 1.49-1.40 (m, 1H), 1.35-1.20 (m, 4H), 1.10-0.99 (m, 1H), 0.87-0.82 (m, 5H), 0.74-0.68 (m, 6H)。MS (ESI, m/e) [M+1]$^+$ 578.5。
105		N-((1S)-1-环己基-2-((2-(5-乙基-5-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.57-7.28 (m, 4H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.33 (s, 1H), 4.44-4.37 (m, 1H), 4.03 (s, 3H), 3.59-3.46 (m, 2H), 3.17-3.06 (m, 2H), 2.98-2.92 (m, 2H), 2.78-2.70 (m, 2H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.54 (m, 6H), 1.20-0.95 (m, 7H), 0.65-0.55 (m, 6H)。MS (ESI, m/e) [M+1]$^+$ 578.5。
106		N-((1S)-2-((2-(4-(丁-2-炔-1-基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.49-7.42 (m, 3H), 7.42-7.35 (m, 2H), 7.06 (s, 1H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 4H), 3.22-3.16 (m, 2H), 2.98-2.96 (m, 1H), 2.54-2.52(m, 3H), 2.24-2.22 (m, 2H), 1.81-1.67 (m, 2H), 1.21-1.02 (m, 5H), 1.16-1.14 (m, 5H)。MS (ESI, m/e) [M+1]$^+$ 574.5。
107		N-((1S)-1-环己基-2-((2-((1-环戊基-2-羟基乙基)氨基甲酰基)-2-((R)-4-异	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.45-7.42 (m, 3H), 7.13-7.10 (m, 4H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.56-3.51 (s, 3H), 3.46-3.41 (m,

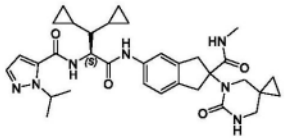
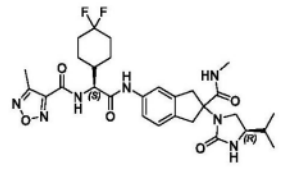
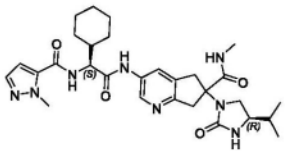
[0748]

		丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	3H), 1.91-1.67 (m, 17H), 1.20-1.04 (m, 6H), 0.84-0.75 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 662.6
108		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(7-氧代-6,8-二氮杂螺[3.5]壬-6-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 3.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.31 (s, 1H), 4.39 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.57-3.47 (m, 2H), 3.20-2.91 (m, 6H), 2.55 (d, J = 4.2 Hz, 3H), 1.82 (d, J = 10.8 Hz, 2H), 1.77-1.52 (m, 8H), 1.45-1.39 (m, 2H), 1.19-1.16 (m, 5H)。MS (ESI) m/e $[M+1]^+$ 576.4。
109		N-((1S)-2-((2-(5-苄基-5-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.17-10.02 (m, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.55-7.29 (m, 4H), 7.23-7.05 (m, 5H), 6.92 (t, J = 5.8 Hz, 2H), 6.42 (s, 1H), 4.40 (t, J = 7.6 Hz, 1H), 4.03 (d, J = 4.4 Hz, 3H), 3.62-3.56 (m, 2H), 3.17-2.99 (m, 4H), 2.82 (d, J = 10.0 Hz, 1H), 2.70 (d, J = 10.0 Hz, 1H), 2.56 (d, J = 4.2 Hz, 3H), 2.45 (d, J = 12.8 Hz, 1H), 2.29 (d, J = 12.8 Hz, 1H), 2.01-1.97 (m, 1H), 1.84 (s, 2H), 1.70 (s, 2H), 1.61 (s, 2H), 1.16 (s, 3H), 1.01 (d, J = 11.0 Hz, 1H), 0.59 (s, 3H)。MS (ESI) m/e $[M+1]^+$ 640.4。
110		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(7-氧代-6,8-二氮杂螺[3.5]壬-6-基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.03 (d, J = 8.2 Hz, 1H), 7.59-6.93 (m, 4H), 6.31 (s, 1H), 4.47 (t, J = 8.2 Hz, 1H), 3.56-3.49 (m, 2H), 3.19 (s, 2H), 3.15-3.09 m, 2H), 2.94 (s, 2H), 2.55 (d, J = 4.4 Hz, 3H), 2.47 (s, 3H), 1.86-1.50 (m, 10H), 1.43 (s, 2H), 1.21-1.12

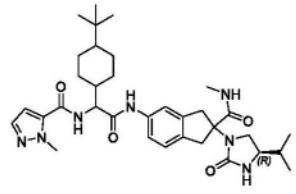
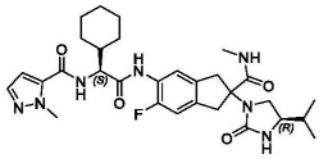
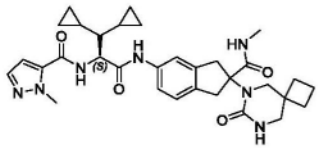
[0749]

		基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 3H), 1.03 (d, J = 10.4 Hz, 1H), 0.89-0.80 (m, 1H)。MS (ESI) m/e $[M+1]^+$ 578.4。
111		N-(1-((1R，3S，5R，7R)-金刚烷-2-基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.24 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.49-7.42 (m, 4H), 7.42-7.35 (m, 1H), 7.13-7.10 (m, 2H), 6.76 (m, 1H), 4.92-4.86 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.22-3.16 (m, 4H), 2.58-2.56 (m, 3H), 2.40-2.36 (m, 2H), 1.81-1.67 (m, 11H), 1.55-1.52 (m, 3H), 0.74-0.65 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 616.3。
112		N-(2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代-1-(螺[2.5]辛烷-6-基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.53 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.07-3.01 (m, 3H), 2.98-2.96 (m, 3H), 2.64-2.60(m, 3H).1.81-1.67 (m, 6H), 1.05-1.02 (m, 3H), 0.91-0.72 (m, 8H), 0.26-0.14 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 590.3。
113		N-((1S)-1-环己基-2-((2-(5-环丙基-5-甲基-2-氧代四氢嘧啶-1(2H)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (s, 1H), 8.43 (d, J = 8.4 Hz.1H), 7.49-7.42 (m, 4H), 7.08-7.02 (m, 2H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 2H), 3.07-3.01 (m, 3H), 2.98-2.96 (m, 3H), 2.64-2.60 (m, 3H).1.81-1.67 (m, 6H), 1.05-1.02 (m, 4H), 0.51-0.42 (m, 4H), 0.26-0.14 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 590.4。
114		N-((2S)-1,1-二环丙基-3-((2-(甲基氨基甲酰	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.16 (d, J = 4.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.44-7.38 (m, 2H), 7.16-7.12 (m, 2H),

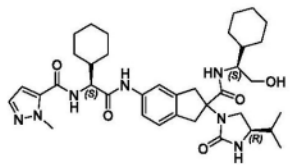
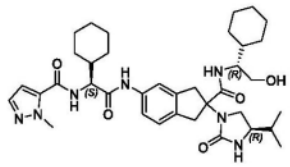
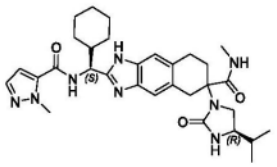
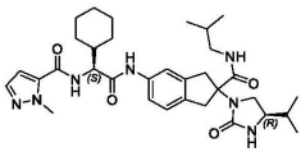
[0750]

		基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	6.48 (s, 1H), 4.88-4.83 (m, 1H), 4.11 (s, 3H), 3.57 (d, *J* = 16.0 Hz, 2H), 3.51-3.46 (m, 1H), 3.16-3.07 (m, 3H), 3.03-2.87 (m, 3H), 2.63 (d, *J* = 4.0 Hz, 3H), 0.91-0.77 (m, 3H), 0.51-0.31 (m, 6H), 0.25-0.06 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 574.5
115		N-((2S)-1,1-二环丙基-3-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (d, *J* = 8.0 Hz, 1H), 8.41-8.38 (m, 1H), 7.50 (d, *J* = 4.0 Hz, 1.5H), 7.43 (s, 0.5H), 7.38-7.31 (m, 2H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.93-6.91(m, 1H), 6.40 (d, *J* = 4.0 Hz, 1H), 5.43-5.39 (m, 1H), 4.80-4.75(m, 1H), 4.54-4.38 (m, 1H), 3.10-3.01 (m, 4H), 2.57 (d, *J* = 4.0 Hz, 3H), 2.54 (s, 3H), 2.03-1.96 (m, 2H), 1.38-1.34 (m, 6H), 0.87-0.84 (m, 3H), 0.45-0.08 (m, 10H)。MS (ESI, m/e) $[M+1]^+$ 602.4
116		N-((1S)-1-(4,4-二氟环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.78 (d, *J* = 8.0 Hz, 1H), 7.58-7.45 (m, 2H), 7.42-7.28 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 4.58-4.53 (m, 1H), 3.60-3.42 (m, 4H), 3.25-2.82 (m, 2H), 2.94-2.87 (m, 1H), 2.58 (d, *J* = 4.8 Hz, 3H), 2.12-1.65 (m, 7H), 1.52-1.30 (m, 3H), 0.78-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 602.4。
117		3-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-6-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-6,7-二氢-5H-环戊二烯并[b]吡啶-6-甲	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.33 (s, 1H), 8.53-8.3 (m, 2H), 7.49-7.42 (m, 1H), 7.42-7.35 (m, 1H), 7.06 (s, 1H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 4H), 3.22-3.16 (m, 2H), 2.98-2.96 (m, 1H), 2.64-2.60(m, 3H).1.81-1.67 (m, 8H), 1.21-1.02 (m, 5H), 1.16-1.14 (m, 6H)。MS (ESI, m/e) $[M+1]^+$

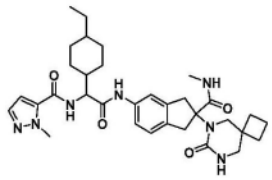
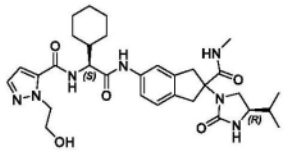
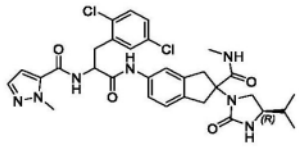
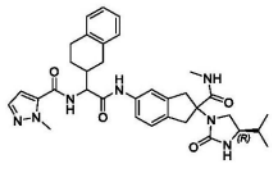
[0751]

		酰胺	565.5。
118		N-(1-(4-(叔丁基)环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.55-7.29 (m, 4H), 7.11 (d, J = 8.1 Hz, 1H), 7.05 (s, 1H), 6.74 (s, 1H), 4.35 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.59-3.43 (m, 2H), 3.22-3.12 (m, 3H), 2.94-2.88 (m, 2H), 2.57 (d, J = 4.2 Hz, 3H), 1.90 (s, 1H), 1.76 (s, 3H), 1.65 (d, J = 13.2 Hz, 1H), 1.46-1.42 (m, 1H), 1.20-1.10 (m, 2H), 0.94 (s, 3H), 0.82 (s, 9H), 0.74 (d, J = 6.4 Hz, 3H), 0.69 (d, J = 6.5 Hz, 3H)。MS (ESI) m/e [M+1]$^+$ 620.4。
119		N-((1S)-1-环己基-2-((6-氟-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.78 (d, J = 4.8 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.60-7.45 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.77 (s, 1H), 4.56-4.48 (m, 1H), 4.03 (s, 3H), 3.60-3.42 (m, 3H), 3.25-2.82 (m, 4H), 2.58 (d, J = 4.4 Hz, 3H), 1.90-1.42 (m, 9H), 1.20-1.02 (m, 3H), 0.80-0.68 (m, 6H)。MS (ESI, m/e) [M+1]$^+$ 582.5。
120		N-((2S)-1,1-二环丙基-3-((2-(甲基氨基甲酰基)-2-(7-氧代-6,8-二氮杂螺[3.5]壬-6-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.55-7.34 (m, 4H), 7.13 (d, J = 8.0 Hz, 1H), 7.07-7.06 (m, 1H), 6.29 (s, 1H), 4.82-4.78 (m, 1H), 4.04 (s, 3H), 3.56-3.45 (m, 2H), 3.19-3.04 (m, 5H), 2.93 (s, 2H), 2.55 (d, J = 4.0 Hz, 3H), 1.72-1.59 (m, 3H), 1.53-1.47 (m, 1H), 1.40-1.34 (m, 2H), 0.87-0.72 (m, 3H), 0.46-0.43 (m, 1H), 0.37-0.34 (m, 2H), 0.29-0.24 (m, 1H), 0.20-0.16 (m, 2H), 0.10-0.05 (m, 1H)。MS (ESI, m/e) [M+1]$^+$ 588.5。

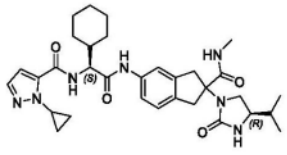
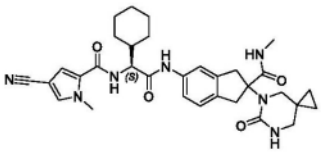
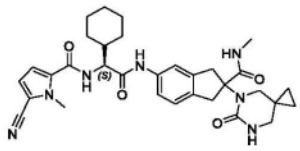
[0752]

121		N-((1S)-1-环己基-2-((2-(((S)-1-环己基-2-羟基乙基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.45-7.42 (m, 3H), 7.13-7.10 (m, 4H), 4.39-4.36 (m, 2H), 4.02 (s, 3H), 3.56-3.51 (s, 5H), 3.46-3.41 (m, 2H), 3.27-3.21 (m, 1H), 2.89-2.85 (m, 1H), 1.81-1.67 (m, 13H), 1.55-1.52 (m, 7H), 1.16-1.14 (m, 2H), 0.84-0.75 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 677.2。
122		N-((1S)-1-环己基-2-((2-(((R)-1-环己基-2-羟基乙基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.45-7.42 (m, 3H), 7.13-7.10 (m, 4H), 4.39-4.36 (m, 2H), 4.02 (s, 3H), 3.56-3.51 (s, 5H), 3.46-3.41 (m, 2H), 3.27-3.21 (m, 1H), 2.89-2.85 (m, 1H), 1.81-1.67 (m, 14H), 1.55-1.52 (m, 7H), 1.16-1.14 (m, 1H), 0.84-0.75 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 677.3。
123		2-((S)-环己基(1-甲基-1H-吡唑-5-甲酰胺基)甲基)-6-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-5,6,7,8-四氢-1H-萘并[2,3-d]咪唑-6-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.11 (br, 1H), 8.77 (d, J = 8.8 Hz, 1H), 7.60-7.10 (m, 4H), 7.08-7.05 (m, 1H), 6.52 (s, 1H), 5.06-4.98 (m, 1H), 4.02 (s, 3H), 3.65-3.56 (m, 1H), 3.25-3.10 (m, 3H), 2.85-2.60 (m, 6H), 2.15-2.03 (m, 2H), 1.90-1.42 (m, 6H), 1.20-0.92 (m, 5H), 0.84-0.45 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 575.7。
124		N-((1S)-1-环己基-2-((2-(异丁基氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 7.60-7.30 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.85 (s, 1H), 4.45-4.38 (m, 1H), 4.02 (s, 3H), 3.65-3.42 (m, 4H), 3.25-2.82 (m, 5H), 1.90-1.42 (m, 7H),

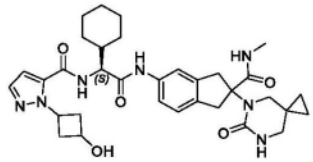
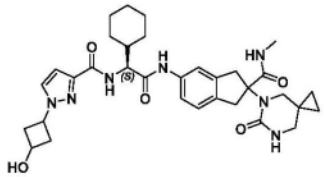
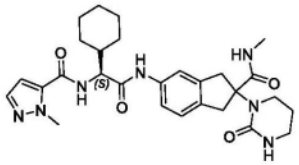
[0753]

		基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	1.20-0.92 (m, 5H), 0.84-0.70 (m, 12H)。MS (ESI, m/e) $[M+1]^+$ 606.5。
125		N-(1-(4-乙基环己基)-2-((2-(甲基氨基甲酰基)-2-(7-氧代-6,8-二氮杂螺[3.5]壬-6-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.58-7.30 (m, 4H), 7.11 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.31(s, 1H), 4.40-4.35 (m, 1H), 4.03 (s, 3H), 3.58-3.48 (m, 2H), 3.25-3.08 (m, 4H), 2.96-2.92 (m, 2H), 2.55 (d, J = 4.4 Hz, 3H), 2.10-1.56 (m, 11H), 1.50-1.38 (m, 3H), 1.22-0.95 (m, 5H), 0.90-0.78 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 604.4。
126		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-(2-羟乙基)-1H-吡唑-5-甲酰胺	MS (ESI, m/e) [M+1]+ 594.6。
127		N-(3-(2,5-二氯苯基)-1-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.78 (d, J = 8.2 Hz, 1H), 7.46-7.31 (m, 7H), 7.16-7.12 (m, 1H), 6.95 (s, 2H), 6.75 (s, 1H), 4.92-4.89 (m, 1H), 3.95 (s, 3H), 3.57-3.38 (m, 3H), 3.16-3.12 (m, 3H), 2.90-2.87 (m, 1H), 2.87-2.85 (m, 1H), 1.49-1.47 (m, 1H), 1.16-1.14 (m, 2H), 0.81-0.69 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 640.4。
128		N-(2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23 (s, 1H), 8.66 (d, J = 8.2 Hz, 1H), 7.51-7.47 (m, 4H), 7.07-7.00 (m, 6H), 6.76 (s, 1H), 4.52-4.46 (m, 1H), 4.03 (s, 3H), 3.57-3.38 (m, 2H),

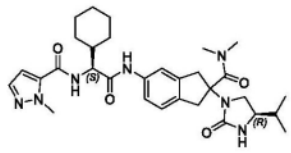
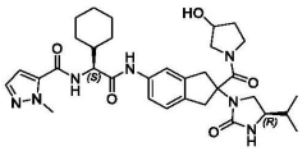
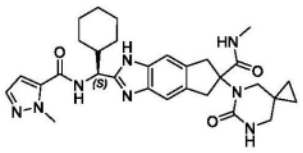
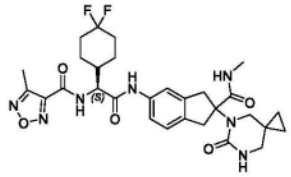
[0754]

		基)氨基)-2-氧代-1-(1,2,3,4-四氢萘-2-基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	3.16-3.12 (m, 3H), 2.90-2.87 (m, 4H), 2.60-2.52 (m, 4H), 1.84-1.82 (m, 1H), 1.70 (s, 2H), 1.71-1.68 (m, 1H), 1.49-1.47 (m, 2H), 0.81-0.69 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 612.8。
129		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-环丙基-1H-吡唑-5-甲酰胺 化学式：C32H43N7O4	1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.57-7.46 (m, 2H), 7.40 (s, 1H), 7.36-7.27 (m, 1H), 7.13-7.08 (m, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.75 (s, 1H), 4.45-4.39 (m, 2H), 3.54-3.44 (m, 2H), 3.22-3.11 (m, 3H), 2.95-2.85 (m, 2H), 2.57 (d, J = 4.4 Hz, 3H), 1.87-1.79 (m, 2H), 1.75-1.67 (m, 2H), 1.67-1.51 (m, 2H), 1.51-1.39 (m, 1H), 1.21-1.11 (m, 4H), 1.10-0.98 (m, 3H), 0.98-0.87 (m, 2H), 0.71 (dd, J = 19.4, 6.6 Hz, 6H)。MS (ESI, m/e) $[M+1]^+$ 590.5。
130		4-氰基-N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡咯-2-甲酰胺	1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.01 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.51 (s, 1H),7.44-7.38 (m, 1H), 7.38-7.28 (m, 2H), 7.07 (d, J = 8.2 Hz, 1H), 6.42 (s, 1H), 4.34 (t, J = 8.6 Hz, 1H), 3.85 (s, 3H), 3.57-3.45 (m, 2H), 3.12-2.94 (m, 4H), 2.87 (t, J = 7.8 Hz, 2H), 2.55 (t, J = 4.6 Hz, 3H), 1.87-1.52 (m, 6H), 1.24-0.92 (m, 5H), 0.39 (s, 2H), 0.19 (t, J = 9.4 Hz, 2H)。MS (ESI, m/e) $[M+1]^+$ 586.4
131		5-氰基-N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡咯-2-甲酰胺	1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 7.39-7.24 (m, 2H), 7.12-7.01 (m, 2H), 6.98 (d, J = 4.4 Hz, 1H), 6.42 (s, 1H), 4.37 (t, J = 8.6 Hz, 1H), 3.93 (s, 3H), 3.56-3.38 (m, 2H), 3.15-2.95 (m, 4H), 2.89-2.79 (m, 2H), 2.56 (d, J = 4.5 Hz, 3H), 1.91-1.50 (m, 6H), 1.26-0.91 (m, 5H), 0.39 (s, 2H), 0.18 (q, J = 9.4 Hz, 2H)。MS (ESI, m/e)

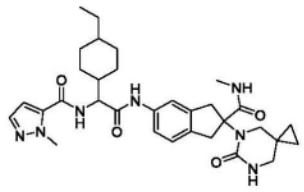
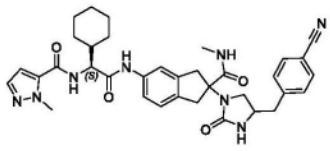
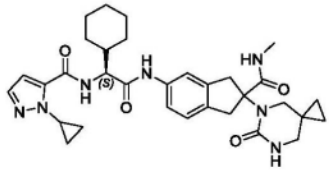
[0755]

			$[M+1]^+$ 586.5
132		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-(3-羟基环丁基)-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.54-7.52 (m, 2H), 7.37-7.29 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 4.0 Hz, 1H), 6.42 (s, 1H), 5.21 (d, J = 4.0 Hz, 1H), 5.15-5.06 (m, 1H), 4.37-4.33 (m, 1H), 3.95-3.86 (m, 1H), 3.54-3.43 (m, 2H), 3.11-2.95 (m, 4H), 2.88-2.84 (m, 2H), 2.66-2.60 (m, 2H), 2.56 (d, J = 8.0 Hz, 3H), 2.43-2.33 (m, 2H), 1.87-1.79 (m, 2H), 1.74-1.69 (m, 2H), 1.62-1.52 (m, 2H), 1.24-1.14 (m, 4H), 1.02-0.98 (m, 1H), 0.39 (s, 2H), 0.22-0.15 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 618.7
133		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-(3-羟基环丁基)-1H-吡唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.64 (d, J = 12.0 Hz, 1H), 7.52 (s, 1H), 7.35-7.32 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 12.0 Hz, 1H), 6.69 (d, J = 4.0 Hz, 1H), 6.41 (s, 1H), 5.35 (d, J = 4.0 Hz, 1H), 4.55-4.51 (m, 1H), 4.48-4.40 (m, 1H), 4.02-3.93 (m, 1H), 3.53-3.44 (m, 2H), 3.11-3.05 (m, 2H), 3.01-2.96 (m, 2H), 2.85 (s, 2H), 2.79-2.73 (m, 2H), 2.57 (d, J = 4.0 Hz, 3H), 2.38-2.30 (m, 2H), 1.77-1.61 (m, 6H), 1.24-1.08 (m, 4H), 1.00-0.97 (m, 1H), 0.39 (s, 2H), 0.20-0.17 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 618.6
134		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代四氢嘧啶-1(2H)-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.55-7.45 (m, 2H), 7.39-7.29 (m, 2H), 7.10-7.06 (m, 2H), 6.32 (s, 1H), 4.39-4.35 (m, 1H), 4.02 (s, 3H), 3.53-3.44 (m, 2H), 3.14-3.08 (m, 3H), 3.04-2.99 (m, 2H), 2.55 (d, J = 4.0 Hz, 3H), 2.03-1.97 (m, 1H), 1.87-1.81 (m, 2H), 1.75-1.67 (m, 4H),

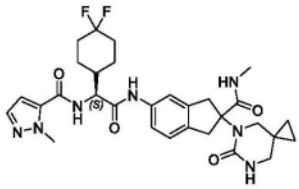
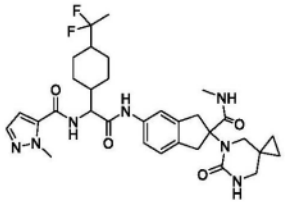
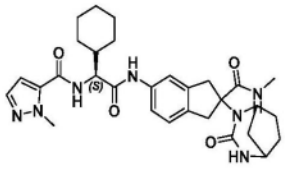
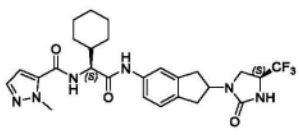
[0756]

		-1H-吡唑-5-甲酰胺	1.62-1.57 (m, 2H), 1.23-1.15 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 536.4。
135		N-((1S)-1-环己基-2-((2-(二甲基氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 7.56-7.30 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.76 (s, 1H), 4.45-4.38 (m, 1H), 4.02 (s, 3H), 3.68-3.42 (m, 3H), 3.25-2.82 (m, 9H), 1.90-1.42 (m, 7H), 1.20-0.97 (m, 5H), 0.82-0.74 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 578.6。
136		N-((1S)-1-环己基-2-((2-(3-羟基吡咯烷-1-羰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.56-7.28 (m, 3H), 7.16-7.08 (m, 2H), 6.77-6.72 (m, 2H), 5.00-4.79 (m, 1H), 4.42-4.19 (m, 2H), 4.02 (s, 3H), 3.78-3.42 (m, 5H), 3.25-2.86 (m, 4H), 1.95-1.55 (m, 9H), 1.50-1.36 (m, 1H), 1.20-0.86 (m, 5H), 0.82-0.70 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 620.9。
137		2-((S)-环己基(1-甲基-1H-吡唑-5-甲酰胺基)甲基)-N-甲基-6-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-1,5,6,7-四氢茚并[5,6-d]咪唑-6-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.78 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.35-7.25 (m, 3H), 7.08 (s, 1H), 6.40 (s, 1H), 5.09-5.02 (m, 1H), 4.05 (s, 3H), 3.68-3.55 (m, 2H), 3.25-2.82 (m, 6H), 2.56 (d, J = 4.8 Hz, 3H), 2.15-1.62 (m, 8H), 1.40-1.32 (m, 1H), 0.45-0.14 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 559.6。
138		N-((1S)-1-(4,4-二氟环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 9.32 (s, 1H), 7.52-7.25 (m, 3H), 7.12-7.06 (m, 1H), 6.65 (s, 1H), 4.57-4.53 (m, 2H), 3.65-3.30 (m, 4H), 3.28-3.10 (m, 7H), 2.49-2.45 (m, 3H), 2.01-1.63 (m, 9H), 1.55-1.43 (m, 2H), 0.78-0.70 (m, 2H), 0.58-0.41 (m, 2H)。MS (ESI, m/e) $[M+1]^+$

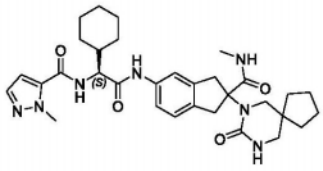
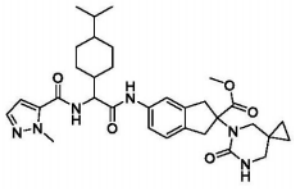
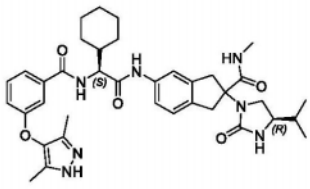
[0757]

		基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	600.4
139		N-(1-(4-乙基环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.75 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.40-7.30 (m, 3H), 7.07 (s, 1H), 6.29 (s, 1H), 5.07-5.02 (m, 1H), 4.01 (s, 3H), 3.68-3.58 (m, 2H), 3.25-3.06 (m, 6H), 2.95-2.92 (m, 2H), 2.55 (d, J = 4.8 Hz, 3H), 2.10-1.56 (m, 8H), 1.40-1.32 (m, 3H), 1.22-0.85 (m, 7H)。MS (ESI, m/e) [M+1]$^+$ 590.6。
140		N-((1S)-2-((2-(4-(4-氰基苄基)-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19-10.04 (m, 1H), 8.46 (t, J = 7.2 Hz, 1H), 7.71-7.67 (m, 2H), 7.55-7.34 (m, 3H), 7.32-7.18 (m, 3H), 7.12-7.01 (m, 2H), 6.74 (d, J = 3.0 Hz, 1H), 4.39 (d, J = 3.6 Hz, 1H), 4.07-4.02 (m, 3H), 3.73 (d, J = 5.2 Hz, 1H), 3.54-3.45 (m, 1H), 3.10-3.06 (m, 4H), 2.95 (s, 1H), 2.79-2.73 (m, 1H), 2.68-2.60 (m, 1H), 2.55 (d, J = 2.6 Hz, 3H), 1.84 (s, 2H), 1.70 (s, 2H), 1.60 (s, 2H), 1.19-1.16 (m, 4H), 1.06-0.99 (m, 1H)。MS (ESI) m/e [M+1]$^+$ 637.5。
141		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-环丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm: 10.07 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.31 (dd, J = 14.2, 6.6 Hz, 2H), 7.08 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.42 (s, 1H), 4.45-4.38 (m, 2H), 3.54-3.43 (m, 2H), 3.11-2.95 (m, 4H), 2.86 (s, 2H), 2.56 (d, J = 4.6 Hz, 3H), 1.85-1.59 (m, 6H),1.27-1.11 (m, 4H), 1.06-0.90 (m, 5H), 0.39 (s, 2H), 0.20-0.16 (m, 2H)。MS (ESI, m/e) [M+1]$^+$ 588.5

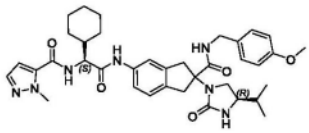
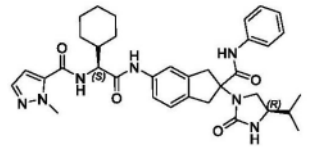
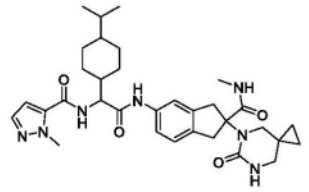
[0758]

142		N-((1S)-1-(4,4-二氟环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.61 (d, J = 8.8 Hz, 1H), 7.53-7.30 (m, 4H), 7.09 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 6.42 (s, 1H), 4.53-4.43 (m, 1H), 4.03 (s, 3H), 3.58-3.42 (m, 2H), 3.25-2.82 (m, 6H), 2.56 (d, J = 4.8 Hz, 3H), 2.10-1.62 (m, 8H), 1.50-1.32 (m, 2H), 0.45-0.14 (m, 4H)。MS (ESI, m/e) [M+1]$^+$ 598.5。
143		*N*-(1-(4-(1,1-二氟乙基)环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.93 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.38-7.29 (m, 2H), 7.26-7.10 (m, 2H), 6.93 (d, J = 8.2 Hz, 1H), 6.91-6.89 (m, 1H), 6.27 (s, 1H), 4.24 (t, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.39-3.28 (m, 2H), 2.98-2.78 (m, 4H), 2.75-2.67 (m, 2H), 2.41 (d, J = 4.6 Hz, 3H), 1.83-1.47 (m, 6H), 1.38 (t, J = 19.4 Hz, 3H), 1.05-0.83 (m, 4H), 0.28-0.21 (m, 2H), 0.08-0.01 (m, 2H)。MS (ESI, m/e) [M+1]$^+$ 626.4。
144		*N*-((1*S*)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(3-氧代-2,4-二氮杂双环[3.2.1]辛-2-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (d, J = 4.4 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.63-7.25 (m, 3H), 7.25-6.91 (m, 3H), 6.57 (s, 1H), 4.38 (t, J = 8.6 Hz, 1H), 4.03 (s, 3H), 3.82 (s, 1H), 3.70 (t, J = 14.8 Hz, 1H), 3.44 (s, 1H), 3.41-3.36 (m, 1H), 3.19-3.12(m, 1H), 3.06-2.95 (m, 1H), 2.56-2.53 (m, 3H), 1.84-1.70 (m, 6H), 1.64-1.44 (m, 6H), 1.21-1.10 (m, 4H), 1.05-0.96 (t, J = 11.8 Hz, 1H)。MS (ESI, m/e) [M+1]$^+$ 562.5。
146		N-((1S)-1-环己基-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.43 (s, 2H), 7.18-7.02 (m, 2H), 7.05 (s, 1H), 4.57 (s, 1H), 4.39-4.37 (m, 2H), 4.03 (s, 3H), 3.23 (s, 1H), 2.98-2.90 (m, 5H),

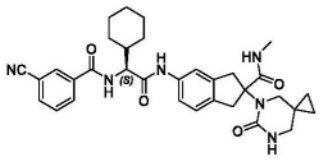
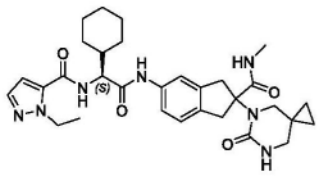
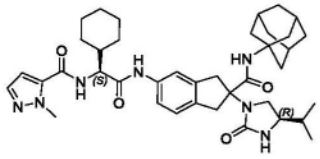
[0759]

		-1H-茚-5-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	1.84-1.82 (m, 2H), 1.70-1.59 (s, 4H), 1.14-1.02 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 533.4。
147		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(8-氧代-7,9-二氮杂螺[4.5]癸-7-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.49-7.42 (m, 4H), 7.42-7.35 (m, 2H), 6.36 (s, 1H), 4.39-4.36 (m, 1H), 4.02 (s, 3H), 3.46-3.41 (m, 3H), 3.22-3.16 (m, 3H), 2.98-2.96 (m, 3H), 2.64-2.60(m, 3H).1.81-1.67 (m, 8H), 1.55-1.52 (m, 3H), 1.16-1.14 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 590.5。
148		5-(2-(4-异丙基环己基)-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸甲酯	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.55-7.51 (m, 1H), 7.47-7.44 (m, 1H), 7.41-7.31 (m, 1H), 7.11-7.07 (m, 2H), 6.47 (s, 1H), 4.38-4.33 (m, 1H), 4.04-4.02 (m, 3H), 3.54 (s, 3H), 3.47-3.37 (m, 2H), 3.19-3.12 (m, 2H), 3.00-2.98 (m, 2H), 2.86 (s, 2H), 2.01-1.61 (m, 6H), 1.40-1.36 (m, 2H), 1.02-0.91 (m, 3H), 0.85-0.82 (m, 6H), 0.46-0.44 (m, 2H), 0.32-0.26 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 605.5。
149		5-((S)-2-环己基-2-(3-((3,5-二甲基-1H-吡唑-4-基)氧基)苯甲酰胺基)乙酰胺基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-N-甲基-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:12.23 (s, 1H), 10.03 (s, 1H), 8.44 (d, J = 8.2 Hz, 1H), 7.60-7.45 (m, 3H), 7.41-7.35 (m, 2H), 7.10 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 4.38 (t, J = 8.8 Hz, 1H), 3.59--3.49 (m, 2H), 3.24-3.16 (m, 2H), 2.90 (t, J = 7.8 Hz, 2H), 2.57 (d, J = 4.6 Hz, 3H), 2.12-1.82 (m, 9H),1.78-1.68(m,2H) 1.68-1.61 (m, 5H), 1.52-1.42 (m, 2H), 1.19-1.11 (m, 5H), 0.75-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 670.7

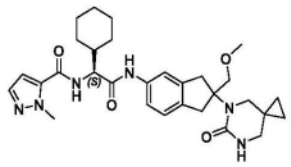
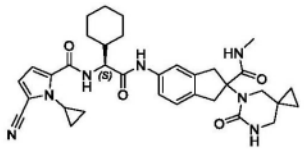
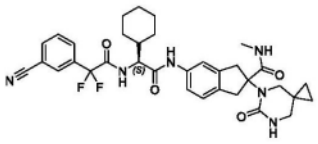
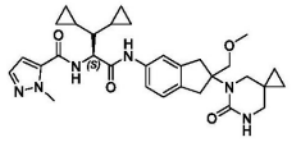
[0760]

150		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((4-甲氧基苄基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.04-8.02 (m, 1H), 7.57 (s, 0.5H), 7.48 (s, 0.5H), 7.45 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.2 Hz, 0.5H), 7.32 (d, J = 7.8 Hz, 0.5H), 7.15-7.12 (m, 3H), 7.06 (d, J = 2.0 Hz, 1H), 6.85-6.78 (m, 3H), 4.39-4.35 (m, 1H), 4.23-4.19 (m, 2H), 4.02 (s, 3H), 3.64-3.34 (m, 4H), 3.21-3.18 (m, 2H), 2.96-2.85 (m, 1H), 1.85-1.82 (m, 2H), 1.72-1.70 (m, 2H), 1.61-1.58 (m, 2H), 1.47-1.35 (m, 1H), 1.22-1.18 (m, 5H), 1.02-0.98 (m, 1H), 0.75-0.68 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 670.6。
151		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.45 (d, J = 3.4 Hz, 1H), 8.44 (d, J = 8.2 Hz, 1H), 7.62-7.55 (m, 3H), 7.51 (s, 0.5H), 7.45-7.42 (m, 1H), 7.35-7.24 (m, 3H), 7.16-7.12 (m, 1H), 7.07-7.00 (m, 2H), 6.92 (s, 1H), 4.42-4.36 (m, 1H), 4.03 (s, 3H), 3.77-3.64 (m, 1H), 3.57-3.38 (m, 3H), 3.16-3.12 (m, 1H), 2.90-2.87 (m, 1H), 1.84-1.82 (m, 2H), 1.70 (s, 2H), 1.61-1.58 (m, 2H), 1.49-1.47 (m, 1H), 1.16-1.14 (m, 4H), 1.02-1.0 (m, 1H), 0.81-0.69 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 626.5。
152		N-(1-(4-异丙基环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.52-7.45 (m, 2H), 7.39-7.28 (m, 2H), 7.09-7.06 (m, 2H), 6.41 (s, 1H), 4.38-4.33 (m, 1H), 4.04-4.02 (m, 3H), 3.54-3.43 (m, 2H), 3.11-3.05 (m, 2H), 3.00-2.95 (m, 2H), 2.90-2.82 (m, 2H), 2.56 (d, J = 8.0 Hz, 3H), 2.03-1.61 (m, 5H), 1.47-1.34 (m, 2H), 1.23-1.11 (m, 2H), 1.02-0.93 (m, 2H), 0.88-0.82

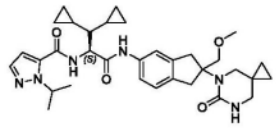
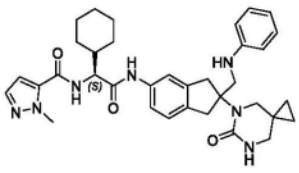
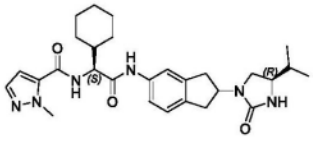
[0761]

			(m, 6H), 0.42-0.38 (m, 2H), 0.22-0.17 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 604.7。
153		5-((S)-2-(3-氰基苯甲酰胺基)-2-环己基乙酰胺基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.07 (s, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 33.8 Hz, 1H), 7.42-7.25 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.41 (s, 1H), 4.43 (s, 1H), 3.53-3.46 (m, 2H), 3.13-2.99 (m, 4H), 2.85 (s, 2H), 2.56 (d, J = 4.5 Hz, 3H), 1.95-1.54 (m, 6H), 1.28-1.11 (m, 5H), 0.39 (s, 2H). 0.20-0.16 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 583.5
154		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-乙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.05 (s, 1H), 8.43 (d, J = 8.2 Hz, 1H), 7.53-7.43 (m, 2H), 7.40-7.27 (m, 2H), 7.07 (d, J = 8.2 Hz, 1H), 7.01 (s, 1H), 6.41 (s, 1H), 4.52-4.47 (m, 2H), 4.38 (t, J = 8.6 Hz, 1H), 3.66-3.58 (m, 1H), 3.52-3.48 (m, 2H), 3.2-2.91 (m, 5H), 2.86 (q, J = 11.8 Hz, 2H), 2.56 (d, J = 4.6 Hz, 3H), 1.89-1.52 (m, 6H), 1.22-0.94 (m, 6H), 0.39 (s, 2H), 0.18 (q, J = 9.2 Hz, 2H)。MS (ESI, m/e) $[M+1]^+$ 576.5
155		N-((1S)-2-((2-(((3R，5R)-金刚烷-1-基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.46-7.41 (m, 3H), 7.11-7.06 (m, 2H), 6.97 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.39-4.35 (m, 1H), 4.02 (s, 3H), 3.52-3.43 (m, 2H), 3.39-3.36 (m, 1H), 3.16-3.09 (m, 1H), 2.94-2.91 (m, 1H), 1.99-1.96 (m, 5H), 1.88-1.86 (m, 9H), 1.70 (s, 2H), 1.61-1.56 (m, 9H), 1.15 (s, 3H), 0.85-0.76 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 684.9。

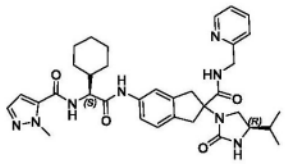
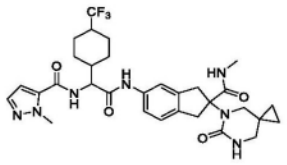
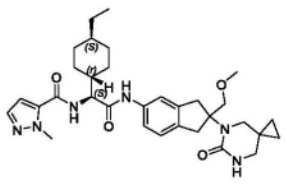
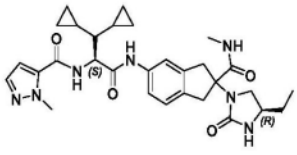
[0762]

156		N-((1S)-1-环己基-2-((2-(甲氧基甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.50-7.33 (m, 3H), 7.12-7.06 (m, 2H), 6.18 (s, 1H), 4.42-4.35 (m, 1H), 4.03 (s, 3H), 3.45-3.36 (m, 2H), 3.25-3.07 (m, 9H), 2.95-2.82 (m, 2H), 1.85-2.56 (m, 6H), 1.22-0.88 (m, 5H), 0.58-0.44 (m, 4H)。MS (ESI, m/e) [M+1]$^+$ 549.9。
157		5-氰基-N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-环丙基-1H-吡咯-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.05 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 33.0 Hz, 1H), 7.33 (dd, J = 18.6, 13.6 Hz, 2H), 7.08 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 4.2 Hz, 1H), 6.64 (d, J = 4.1 Hz, 1H), 6.43 (s, 1H), 4.38 (t, J = 8.4 Hz, 1H), 3.61-3.40 (m, 3H), 3.13-2.99 (m, 9H), 2.85 (d, J = 7.2 Hz, 2H), 2.56 (d, J = 4.4 Hz, 3H), 1.88-1.50 (m, 6H), 1.07-0.81 (m, 5H), 0.39 (s, 2H), 0.17 (d, J = 13.4 Hz, 2H)。MS (ESI, m/e) [M+1]$^+$ 612.5
158		5-((S)-2-(2-(3-氰基苯基)-2,2-二氟乙酰氨基)-2-环己基乙酰氨基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2,3-二氢-1H-茚-2-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.11 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.42 (s, 1H), 4.26-4.22 (m, 1H), 3.54-3.46 (m, 2H), 3.10-2.99 (m, 2H), 2.90-2.82 (m, 2H), 2.56 (d, J = 4.0 Hz, 3H), 1.68-1.58 (m, 4H), 1.52-1.43 (m, 4H), 0.40-0.38 (m, 2H), 0.20-0.15 (m, 2H)。MS (ESI, m/e) [M+1]$^+$ 633.7
159		N-((2S)-1,1-二环丙基-3-((2-(甲氧基甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.55-7.28 (m, 3H), 7.22-7.06 (m, 3H), 6.17 (s, 1H), 4.58-4.52 (m, 1H), 4.01 (s, 3H), 3.65-3.49 (m, 2H), 3.25-3.07 (m, 9H), 2.85-2.70

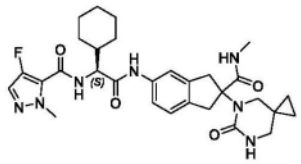
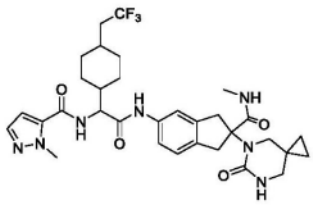
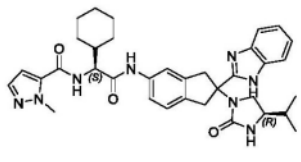
[0763]

		基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	(m, 2H), 0.92-0.78 (m, 2H), 0.58-0.14 (m, 12H)。MS (ESI, m/e) $[M+1]^+$ 561.8。
160		N-((2S)-1,1-二环丙基-3-((2-(甲氧基甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.04 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.55-7.28 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.18 (s, 1H), 5.55-5.42 (m, 1H), 4.88-4.72 (m, 1H), 3.65-3.49 (m, 2H), 3.25-3.07 (m, 9H), 2.85-2.70 (m, 2H), 1.48-1.30 (m, 6H), 0.92-0.78 (m, 2H), 0.58-0.14 (m, 12H)。MS (ESI, m/e) $[M+1]^+$ 589.7。
161		*N*-((1S)-1-环己基-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2-((苯基氨基)甲基)-2,3-二氢-1*H*-茚-5-基)氨基)乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.41-7.32 (m, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 6.99 (t, J = 7.8 Hz, 2H), 6.49-6.44 (m, 3H), 6.32 (s, 1H), 5.86 (t, J = 6.2 Hz, 1H), 4.39 (t, J = 8.6 Hz, 1H), 4.03 (s, 3H), 3.41-3.19 (m, 4H), 3.16-3.06 (m, 4H), 2.89-2.74 (m, 2H), 1.88-1.81 (m, 2H), 1.72-1.70 (m, 2H), 1.63-1.57 (m, 2H), 1.23-1.11 (m, 4H), 1.04-0.97 (m, 1H), 0.41-0.34 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 611.0。
162		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.58-7.54 (m, 1H), 7.43-7.41 (m, 2H), 7.18-7.02 (m, 2H), 6.64 (s, 1H), 4.57 (s, 1H), 4.39-4.37 (m, 1H), 4.03 (s, 3H), 3.23 (s, 2H), 2.98-2.90 (m, 5H), 1.84-1.82 (m, 2H), 1.70 (s, 2H), 1.58-1.53 (m, 3H), 1.15 (s, 3H), 0.88-0.70 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 507.5。

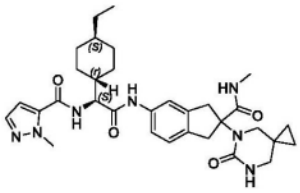
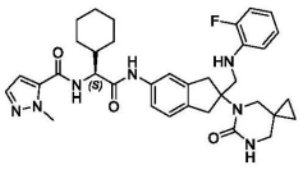
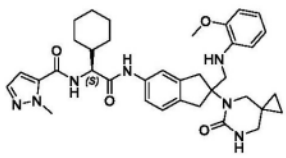
[0764]

163		N-((1S)-1-环己基-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((吡啶-2-基甲基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.51-8.42 (m, 2H), 8.27 (s, 1H), 7.66-7.64 (m, 2H), 7.46-7.43 (m, 2H), 7.36-7.34 (m, 2H), 7.24-7.18 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 4.44-4.27 (m, 3H), 4.01 (s, 3H), 3.66-3.48 (m, 2H), 3.22-3.18 (m, 2H), 2.96-2.93 (m, 1H), 1.83 (s, 2H), 1.68-1.63 (m, 5H), 1.47-1.43 (m, 1H), 1.15 (s, 4H), 1.00 (s, 1H), 0.78-0.70 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 642.2。
164		1-甲基-N-(2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代-1-(4-(三氟甲基)环己基)乙基)-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.96 (s, 1H), 8.34 (d, J = 4.0 Hz, 1H), 7.34-7.25 (m, 2H), 7.20-7.09 (m, 2H), 6.89-6.87 (m, 2H), 6.23 (s, 1H), 4.22-4.18 (m, 1H), 3.84-3.83 (m, 3H), 3.34-3.23 (m, 2H), 2.91-2.85 (m, 2H), 2.83-2.75 (m, 2H), 2.69-2.63 (m, 2H), 2.36-2.34 (m, 3H), 2.07-1.98 (m, 1H), 1.81-1.65 (m, 4H), 1.51-1.48 (m, 1H), 1.09-0.97 (m, 4H), 0.21-0.15 (m, 2H), 0.04-0.00 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 630.6。
165		N-((1S)-1-((1r,4S)-4-乙基环己基)-2-((2-(甲氧基甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.48-7.45 (m, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 4.0 Hz, 1H), 6.18 (s, 1H), 4.37-4.33 (m, 1H), 4.02 (s, 3H), 3.41 (s, 2H), 3.22-3.18 (m, 6H), 3.12-3.03 (m, 2H), 2.89-2.82 (m, 2H), 2.03-1.97 (m, 1H), 1.88-1.74 (m, 4H), 1.61-1.58 (m, 1H), 1.23-1.11 (m, 5H), 1.06-0.97 (m, 2H), 0.86-0.82 (m, 3H), 0.56-0.48 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 577.7
166		N-((2S)-1,1-二环丙基-3-((2-((R)-4-乙基-2-氧代咪唑烷-1-基)-2-(甲	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.07 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 7.55-7.45 (m, 3H), 7.41-7.30 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H),

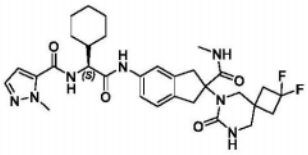
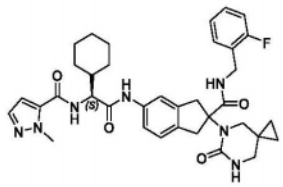
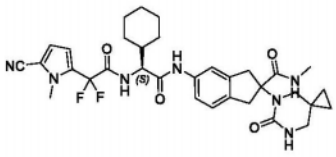
[0765]

		基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	6.71 (s, 1H), 4.79 (t, J = 9.0 Hz, 1H), 4.04 (s, 3H), 3.58-3.51 (m, 2H), 3.47-3.37 (m, 2H), 3.31-3.21 (m, 2H), 2.91-2.86 (m, 1H), 2.58 (d, J = 3.0 Hz, 3H), 2.06-1.92 (m, 1H), 1.41-1.31 (m, 3H), 0.87-0.76 (m, 5H), 0.42-0.19 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 562.5
167		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-氟-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.01, (s, 1H), 8.02 (s, 1H), 7.59 (d, J = 4.4 Hz, 1H), 7.47 (s, 1H), 7.38-7.25 (m, 2H), 7.09 (d, J = 8.2 Hz, 1H), 6.43 (s, 1H), 4.47 (s, 1H), 3.92 (s, 2H), 3.58-3.38 (m, 2H), 3..18-3.11 (m, 5H), 2.86 (s, 2H), 2.55 (d, J = 4.8 Hz, 3H), 1.81-1.52 (m, 6H), 1.28-1.12 m, 6H), 0.40 (s, 2H), 0.21-0.17 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 580.5
168		1-甲基-*N*-(2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代-1-(4-(2,2,2-三氟乙基)环己基)乙基)-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 16.4 Hz, 2H), 7.41-7.25 (m, 2H), 7.07 (d, J = 12.4 Hz, 2H), 6.43 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.56-3.40 (m, 3H), 3.11-2.95 (m, 4H), 2.91-2.80 (m, 2H), 2.56 (d, J = 4.4 Hz, 3H), 2.23-2.09 (m, 2H), 1.87-1.78 (m, 4H), 1.61-1.52 (m, 2H), 1.22-1.16 (m, 1H), 1.11-0.98 (m, 2H), 0.44-0.36 (m, 2H), 0.21-0.13 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 644.5。
169		N-((1S)-2-((2-(1H-苯并[d]咪唑-2-基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.20-11.97 (m, 1H), 10.07 (s, 1H), 8.42 (d, J = 8.2 Hz, 1H), 7.54-7.50 (m, 4H), 7.35-7.30 (m, 1H), 7.16-7.13 (m, 3H), 7.04 (s, 1H), 6.77 (s, 1H), 4.38-4.36 (m, 1H), 4.03-3.84 (m, 5H), 3.64-3.52 (m, 3H), 3.25-3.11 (m, 2H), 1.82 (s, 2H), 1.65-1.58 (m, 4H), 1.45-1.44 (m, 1H), 1.18-0.93 (m, 5H), 0.76-0.72 (m, 6H)。MS

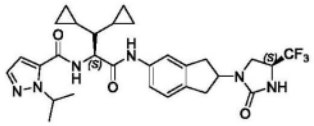
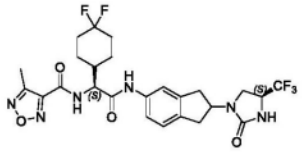
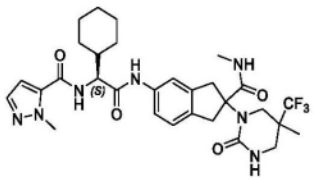
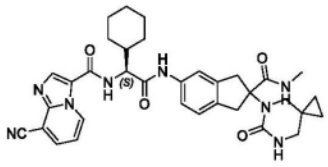
[0766]

			(ESI, m/e) $[M+1]^+$ 623.6。
171		N-((1S)-1-((1r,4S)-4-乙基环己基)-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.54-7.45 (m, 2H), 7.40-7.29 (m, 2H), 7.10-7.06 (m, 2H), 6.43 (s, 1H), 4.38-4.33 (m, 1H), 4.03 (s, 3H), 3.53-3.42 (m, 2H), 3.11-2.95 (m, 2H), 2.89-2.82 (m, 2H), 2.56 (d, J = 4.0 Hz, 3H), 1.88-1.75 (m, 4H), 1.61-1.57 (m, 1H), 1.23-1.11 (m, 5H), 1.06-0.97 (m, 2H), 0.90-0.77 (m, 3H), 0.43-0.36 (m, 2H), 0.21-0.15 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 590.5。
172		*N*-((1*S*)-1-环己基-2-((2-(((2-氟苯基)氨基)甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 10.2 Hz, 1H), 7.45 (d, J = 1.4 Hz, 1H), 7.37 (dd, J = 13.2, 8.4 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 6.95 (dd, J = 12.2, 7.8 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 6.58 (t, J = 8.6 Hz, 1H), 6.49-6.44 (m, 2H), 5.99 (s, 1H), 4.38 (t, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.44-3.40 (m, 2H), 3.26-3.07 (m, 6H), 2.90-2.78 (m, 2H), 1.88-1.80 (m, 2H), 1.72-1.69 (m, 2H), 1.62-1.55 (m, 2H), 1.20-1.12 (m, 4H), 1.05-0.92 (m, 1H), 0.44-0.38 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 628.5。
173		*N*-((1*S*)-1-环己基-2-((2-(((2-甲氧基苯基)氨基)甲基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 10.4 Hz, 1H), 7.46 (s, 1H), 7.41-7.33 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.66 (t, J = 7.4 Hz, 1H), 6.48 (t, J = 7.6 Hz, 1H), 6.41 (s, 1H), 6.35 (d, J = 7.8Hz, 1H), 5.33 (d, J = 4.6 Hz, 1H), 4.38 (t, J = 8.6 Hz, 1H), 4.02 (s, 3H), 3.73 (s, 3H), 3.20-3.12 (m, 6H), 2.87 (s, 2H), 2.04-1.94 (m, 2H), 1.86-1.80 (m, 2H),

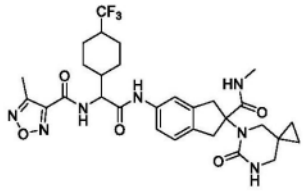
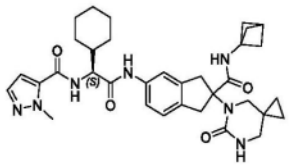
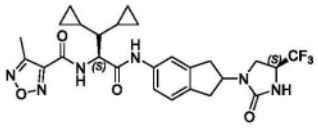
[0767]

			1.72-1.69 (m, 2H), 1.62-1.59 (m, 2H), 1.17-1.14 (s, 4H), 0.85 (t, J = 6.0 Hz, 1H), 0.49 (d, J = 9.2 Hz, 4H)。MS (ESI, m/e) $[M+1]^+$ 640.5。
174		N-((1S)-1-环己基-2-((2-(2,2-二氟-7-氧代-6,8-二氮杂螺[3.5]壬烷-6-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.10 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 8.23 (s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.46 (s, 1H), 7.37 (d, J = 4.6 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 6.48 (s, 1H), 4.38 (d, J = 4.2 Hz, 1H), 4.02 (s, 3H), 3.55-3.44 (m, 2H), 3.25 (s, 1H), 3.11-3.07 (m, 2H), 3.02 (s, 1H), 2.65 (d, J = 14.8 Hz, 2H), 2.55 (d, J = 4.4 Hz, 3H), 2.37-2.24 (m, 2H), 2.20-2.01 (m, 2H), 1.83 (s, 2H), 1.69 (s, 2H), 1.59 (d, J = 18.8 Hz, 2H), 1.15 (s, 4H), 1.05-0.98 (m, 1H)。MS (ESI) m/e $[M+1]^+$ 612.5。
175		N-((1S)-1-环己基-2-((2-((2-氟苄基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.47 (d, J = 8.2 Hz, 1H), 8.03 (s, 1H), 7.60-7.20 (m, 5H), 7.17-7.02 (m, 4H), 6.59 (s, 1H), 4.43-4.26 (m, 3H), 4.03 (s, 3H), 3.65-3.54 (m, 2H), 3.23-2.96 (m, 4H), 2.89-2.85 (m, 2H), 1.83-1.82 (m, 2H), 1.70 (s, 2H), 1.59-1.56 (m, 2H), 1.15 (s, 4H), 0.39 (s, 2H), 0.21-0.18 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 656.5。
176		5-((S)-2-(2-(5-氰基-1-甲基-1H-吡咯-2-基)-2,2-二氟乙酰氨基)-2-环己基乙酰氨基)-N-甲基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酰胺	MS (ESI, m/e) $[M+1]^+$ 636.7

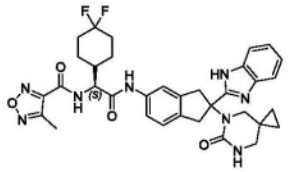
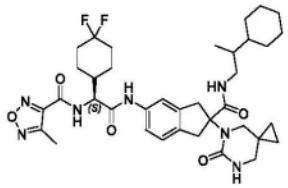
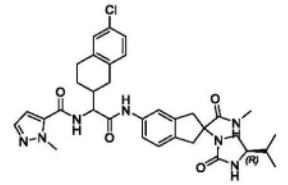
[0768]

177		N-((2S)-1,1-二环丙基-3-氧代-3-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 8.42 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.52-7.46 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 5.48-5.34 (m, 1H), 4.82-4.78 (m, 1H), 4.66-4.54 (m, 1H), 4.31 (s, 1H), 3.50-3.47 (m, 1H), 3.17-3.15 (m, 1H), 3.03-2.98 (m, 2H), 2.88-2.80 (m, 2H), 1.39-1.34 (m, 6H), 0.93-0.68 (m, 3H), 0.45-0.07 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 573.6。
178		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.22 (s, 1H), 9.23 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 4.59-4.56 (m, 2H), 4.32 (s, 1H), 3.50-3.46 (m, 1H), 3.16-3.12 (m, 1H), 3.04-3.0 (m, 2H), 2.95-2.86 (m, 3H), 2.47 (s, 3H), 2.04 (s, 3H), 1.93-1.64 (m, 4H), 1.52-1.27 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 571.5。
179		*N*-((1*S*)-1-环己基-2-((2-(5-甲基-2-氧代-5-(三氟甲基)四氢嘧啶-1(2*H*)-基)-2-(甲基氨基甲酰基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.60-7.23 (m, 4H), 7.11 (d, J = 8.2 Hz, 1H), 7.07 (s, 1H), 6.68 (s, 1H), 4.38 (t, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.69-3.46 (m, 3H), 3.27 (d, J = 12.2 Hz, 1H), 3.15-3.08 (m, 3H), 2.91 (d, J = 9.8 Hz, 1H), 2.55 (d, J = 4.4 Hz, 3H), 1.86-1.81 (m, 2H), 1.72-1.69 (m, 2H), 1.62-1.54 (m, 2H), 1.18-1.12 (m, 4H), 1.06-0.94 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 618.5。
180		8-氰基-N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.14 (s, 1H), 9.68 (d, J = 7.0 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 8.72 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.50 (s,1H), 7.34-7.24 (m, 3H), 7.08 (d, J = 8.0 Hz, 1H), 6.43 (s, 1H), 4.48

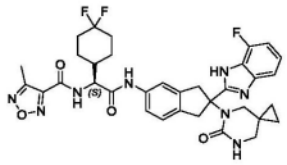
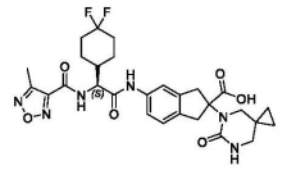
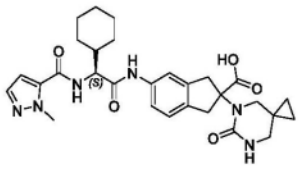
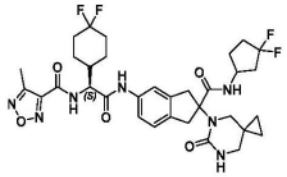
[0769]

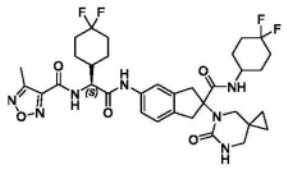
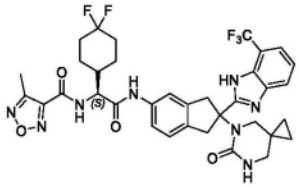
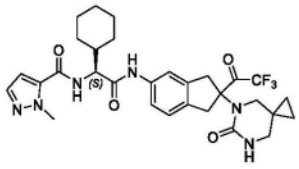
		[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)咪唑并[1,2-a]吡啶-3-甲酰胺	(t, J = 9.0 Hz,1H), 3.56-3.46 (m, 2H), 3.12-2.91 (m, 4H), 2.85 (s, 2H), 2.55 (d, J = 4.6 Hz, 3H), 1.95-1.55 (m, 6H), 1.29-0.93 (m, 5H), 0.39 (s, 2H), 0.24-0.07 (m, 2H)。(ESI, m/e) $[M+1]^+$ 623.6
181		4-甲基-N-(2-((2-(甲基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代-1-(4-(三氟甲基)环己基)乙基)-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.16 (s, 1H), 9.13-9.11 (m, 1H), 7.52-7.43 (m, 1H), 7.40-7.26 (m, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 4.49-4.45 (m, 1H), 3.54-3.43 (m, 2H), 3.11-3.05 (m, 2H), 3.01-2.98 (m, 2H), 2.89-2.84 (m, 2H), 2.56 (d, J = 4.0 Hz, 3H), 2.48 (s, 3H), 2.27-2.15 (m,1H), 2.01-1.84 (m, 4H), 1.74-1.68 (m, 1H), 1.23-1.16 (m, 4H), 0.43-0.36 (m, 2H), 0.21-0.15 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 632.6。
182		N-((1S)-2-((2-(二环[1.1.1]戊-1-基氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-1-环己基-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.47 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 7.53 (s, 1H), 7.46-7.43 (m, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.09-7.06 (m, 2H), 6.56 (s, 1H), 4.39-4.35 (m, 1H), 4.03 (s, 3H), 3.50-3.45 (m, 2H), 3.12-2.78 (m, 8H), 2.35 (s, 1H), 1.94 (s, 6H), 1.83 (s, 2H), 1.72-1.70 (m, 2H), 1.63-1.60 (m, 2H), 1.16-1.10 (s, 3H), 0.42 (s, 2H), 0.25-0.18 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 614.5。
183		N-((2S)-1,1-二环丙基-3-氧代-3-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.99 (s, 1H), 8.91 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.35 (s, 1H), 7.18 (d, J = 12.0 Hz, 1H), 7.05 (d, J = 12.0 Hz, 1H), 4.74-4.70 (m, 1H), 4.48-4.45 (m, 1H), 4.24-4.14 (m, 1H), 3.38-3.33 (m, 1H), 3.04-3.00 (m, 1H), 2.91-2.85 (m, 2H), 2.79-2.73 (m, 1H), 2.70-2.65 (m,1H), 2.35 (s, 3H), 0.74-0.58 (m, 3H), 0.35-0.30 (m, 1H),

[0770]

			0.27-0.23 (m, 1H), 0.21-0.01 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 547.4。
184		N-((1S)-2-((2-(1H-苯并[d]咪唑-2-基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4,4-二氟环己基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.94 (s, 1H), 10.17 (s, 1H), 9.22 (d, J = 8.0 Hz, 1H), 7.55-7.22 (m, 4H), 7.15 -7.04 (m, 3H), 6.41 (s, 1H), 4.56-4.48 (m, 1H), 4.19-4.07 (m, 2H), 3.49-3.36 (m, 2H), 3.30-3.22 (m, 2H), 2.96-2.87 (m, 2H), 2.48 (s, 3H), 2.10-1.60 (m, 7H), 1.50-1.30 (m, 2H), 0.48-0.34 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 659.5。
185		N-((1S)-2-((2-((2-环己基丙基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4,4-二氟环己基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.24 (d, J = 8.0 Hz, 1H), 7.55-7.26 (m, 3H), 7.11 (d, J = 8.0 Hz, 1H), 6.67 (s, 1H), 4.58-4.50 (m, 1H), 3.58 (t, J = 17.2 Hz, 2H), 3.18-2.97 (m, 5H), 2.93-2.83 (m, 3H), 2.48 (s, 3H), 2.10-1.65 (m, 8H), 1.59-1.30 (m, 7H), 1.19-0.95 (m, 6H), 0.50-0.28 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 710.6。
186		N-(1-(6-氯-1,2,3,4-四氢萘-2-基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.22 (d, J = 11.8 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 7.59-7.38 (m, 3H), 7.37 (d, J = 25.8 Hz, 1H), 7.20-7.04 (m, 5H), 6.78 (s, 1H), 4.55 (t, J = 8.8 Hz, 1H), 4.04 (s, 3H), 3.58-3.46 (m, 2H), 3.33-3.29 (m, 3H), 3.23-3.08 (m, 2H), 2.91-2.79 (m, 2H), 2.79-2.69 (m, 2H), 2.57 (d, J = 4.2 Hz, 3H), 2.38-2.28 (m, 1H), 1.99-1.88 (m , 1H), 1.48-1.38 (m, 2H), 0.72 (dd, J = 19.4, 6.2 Hz, 6H)。MS (ESI，m/e)[M ＋1]＋646.5

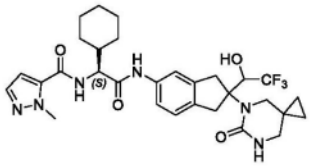
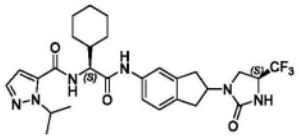
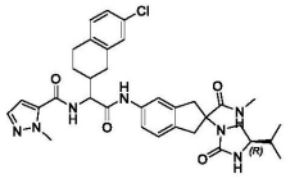
[0771]

187		N-((1S)-1-(4,4-二氟环己基)-2-((2-(7-氟-1H-苯并[d]咪唑-2-基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:12.32 (d, J = 12.6 Hz, 1H), 10.19 (s, 1H), 9.21 (d, J = 8.6 Hz, 1H), 7.59-7.49 (m, 1H), 7.42-7.22 (m, 2H), 7.15 (d, J = 8.6 Hz, 2H), 6.93 (s, 1H), 6.44 (s, 1H), 4.52 (t, J = 8.4 Hz, 1H), 4.14-4.00 (m, 2H), 3.56-3.49 (m, 2H) 3.27 (s, 2H), 2.87 (s, 2H), 2.46 (s, 3H), 2.05-2.01 (m, 3H), 1.85-1.61 (m, 4H), 1.43-1.28 (m, 2H), 0.44-0.39 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 678.1
188		5-((S)-2-(4,4-二氟环己基)-2-(4-甲基-1,2,5-噁二唑-3-甲酰胺基)乙酰胺基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.05 (s, 1H), 10.20 (s, 1H), 9.24 (d, J = 8.0 Hz, 1H), 7.55-7.26 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 6.45 (s, 1H), 4.58-4.50 (m, 1H), 3.49-3.36 (m, 2H), 3.20-3.12 (m, 2H), 3.06-2.97 (m, 2H), 2.86 (s, 2H), 2.48 (s, 3H), 2.10-1.65 (m, 7H), 1.50-1.30 (m, 2H), 0.50-0.24 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 587.6。
189		5-((S)-2-环己基-2-(1-甲基-1H-吡唑-5-甲酰胺基)乙酰胺基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.03 (s, 1H), 10.10 (s, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, J = 7.4 Hz, 0H), 7.30 (d, J = 8.0 Hz, 0.5H), 7.12-7.01 (m, 2H), 6.44 (s, 1H), 4.39-4.36 (m, 1H), 4.03 (s, 3H), 3.46-3.40 (m, 1H), 3.16-3.14 (m, 2H), 3.10-3.01 (m, 2H), 2.86-2.84 (m, 2H), 1.84-1.80 (m, 2H), 1.72-1.70 (m, 2H), 1.63-1.60 (m, 2H), 1.19-1.10 (m, 6H), 0.43 (s, 2H), 0.29-0.21 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 549.5。
190		N-((1S)-1-(4,4-二氟环己基)-2-((2-((3,3-二氟环戊基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.22 (d, J = 8.2 Hz, 1H), 7.52-7.43 (m, 2H), 7.38 (d, J = 8.6 Hz, 0.5H), 7.28 (d, J = 8.2 Hz, 0.5H), 7.11 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 4.56-4.51 (m, 1H), 4.19-4.06 (m, 1H), 3.57-3.43 (m, 2H),

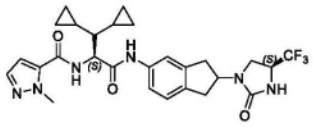
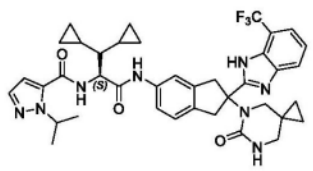
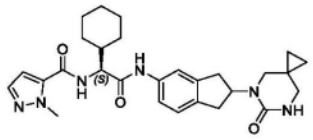
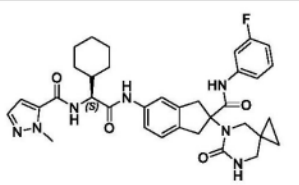
		[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	3.10-3.01 (m, 5H), 2.89-2.86 (m, 3H), 2.47 (s, 2H), 2.34-2.30 (m, 1H), 2.08-1.97 (m, 5H), 1.87 (s, 1H), 1.70-1.65 (m, 2H), 1.49-1.20 (m, 3H), 0.42 (s, 2H), 0.40 -0.20 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 690.6。
191		N-((1S)-1-(4,4-二氟环己基)-2-((2-((4,4-二氟环己基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.23 (d, J = 8.4 Hz, 1H), 7.55-7.32 (m, 3H), 7.10-7.05 (m, 1H), 6.62 (s, 1H), 4.56-4.51 (m, 1H), 3.56-3.51 (s, 3H), 3.27-2.95 (m, 4H), 2.89-2.85 (m, 1H), 2.47 (s, 1H), 1.95-1.67 (m, 14H), 1.55-1.42 (m, 4H), 0.45-0.43 (m, 2H), 0.34-0.25 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 704.6。
192		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(7-(三氟甲基)-1H-苯并[d]咪唑-2-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.49 (s, 1H), 10.19 (s, 1H), 9.21 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.57-7.50(m, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.39-7.23 (m, 2H), 7.15 (d, J = 8.2 Hz, 1H), 6.39 (s, 1H), 4.52 (t, J = 8.2 Hz, 1H), 4.14-4.02 (m, 2H), 3.45 (s, 2H), 2.86 (s, 2H), 2.69 (s, 2H), 2.46 (s, 3H), 2.00 (d, J = 7.6 Hz, 4H), 1.89-1.62 (m, 5H), 1.48-1.29 (m, 4H)。MS (ESI) m/e $[M+1]^+$ 727.7。
193		*N*-((1*S*)-1-环己基-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2-(2,2,2-三氟乙酰基)-2,3-二氢-1*H*-茚-5-基)氨基)乙基)-1-甲基-1*H*-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 7.63-7.44 (m, 2H), 7.43-7.33 (m, 1H), 7.25 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 4.36 (t, J = 8.6 Hz, 1H), 4.02 (s, 3H), 3.52-3.42 (m, 2H), 3.17-3.06 (m, 2H), 2.92-2.85 (m, 4H), 1.87-1.82 (m, 2H), 1.72-1.69 (m, 2H), 1.62-1.57 (m, 2H), 1.18-1.11 (m, 4H), 1.06-0.94 (m, 1H),

[0772]

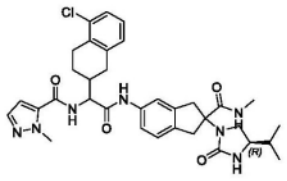
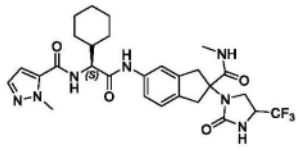
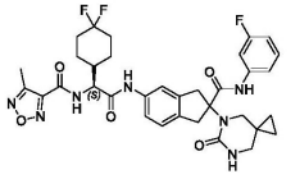
[0773]

		吡唑-5-甲酰胺	0.51 (d, J = 9.6 Hz, 4H)。MS (ESI, m/e) $[M+1]^+$ 601.4。
194		*N*-((1*S*)-1-环己基-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1*H*-茚-5-基)氨基)乙基)-1-甲基-1*H*-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.52 (d, J = 8.2 Hz, 1H), 7.61-7.45 (m, 2H), 7.38 (dt, J = 15.8, 8.2 Hz, 1H), 7.13 (dd, J = 7.8, 4.4 Hz, 1H), 7.07 (s, 1H), 6.72 (d, J = 15.6 Hz, 1H), 4.69 (s, 1H), 4.38 (t, J = 8.6 Hz, 1H), 4.03 (s, 3H), 3.53-3.35 (m, 3H), 3.26-3.03 (m, 3H), 2.95-2.72 (m, 2H), 2.70-2.57 (m, 1H), 1.86-1.81 (m, 2H), 1.72-1.69 (m, 2H), 1.62-1.54 (m, 2H), 1.18-1.12 (m, 4H), 1.04-0.96 (m, 1H), 0.38-0.32 (m, 2H), 0.21-0.07 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 603.4。
195		N-((1S)-1-环己基-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.46 (d, J = 4.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.49 (s, 2H), 7.38-7.33 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 5.42-5.36 (m, 1H), 4.61-4.58 (m, 1H), 4.38-4.28 (m, 2H), 3.50-3.45 (m, 1H), 3.16-3.11 (m, 1H), 3.04-2.98 (m, 2H), 2.91-2.85 (m, 1H), 2.82-2.77 (m,1H), 1.89-1.77 (m, 2H), 1.77-1.67 (m, 2H), 1.62-1.55 (m, 2H), 1.37-1.33 (m, 6H), 1.23-1.15 (m, 4H), 1.02-0.97 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 561.5
196		N-(1-(7-氯-1,2,3,4-四氢萘-2-基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.22 (d, J = 12.6 Hz, 1H), 8.66 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 8.8 Hz, 4H), 7.20-7.06 (m, 5H), 6.78 (s, 1H), 4.55 (s, 1H), 4.09-4.04 (m, 2H), 3.61-3.45 (m, 2H), 3.24-3.02 (m, 4H), 2.88-2.78 (m, 5H), 2.57 (s, 3H), 2.45-2.35 (m, 2H), 2.05-1.99 (m, 1H), 1.49-1.42 (m, 2H), 0.79-0.66 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 646.4

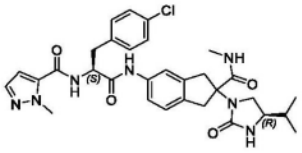
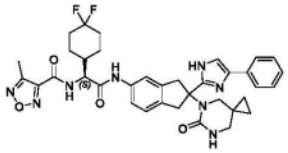
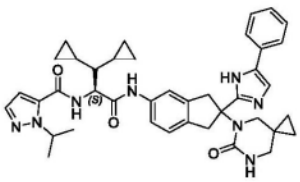
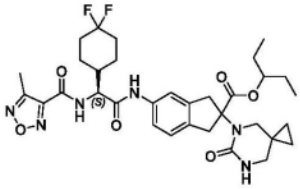
[0774]

197		N-((2S)-1,1-二环丙基-3-氧代-3-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.59-7.52 (m, 1H), 7.47 (s, 2H), 7.40-7.33 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 4.0 Hz, 1H), 4.82-4.78 (m, 1H), 4.61-4.58 (m, 1H), 4.38-4.28 (m, 1H), 4.01 (s, 3H), 3.51-3.46 (m, 1H), 3.16-2.98 (m, 3H), 2.94-2.78 (m, 2H), 0.87-0.73 (m, 3H), 0.46-0.43 (m, 1H), 0.39-0.34 (m, 2H), 0.30-0.26 (m, 1H), 0.22-0.18 (m, 3H), 0.11-0.07 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 545.6
198		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(7-(三氟甲基)-1H-苯并[d]咪唑-2-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.48 (s, 1H), 10.06 (d, J = 5.6 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.50-7.38 (m, 3H), 7.33-7.22 (m, 2H), 7.14 (d, J = 8.2 Hz, 1H), 6.91 (s, 1H), 6.38 (s, 1H), 5.41-5.36 (m, 1H), 4.76 (t, J = 8.2 Hz, 1H), 4.14-3.95 (m, 2H), 3.49-3.40 (m, 2H), 2.86 (s, 2H), 2.69 (s, 2H), 1.36 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.23 (s, 1H), 0.86-0.67 (m, 4H), 0.34 (s, 3H), 0.28 (d, J = 8.8 Hz, 1H), 0.18 (s, 3H), 0.07 (s, 1H)。MS (ESI) m/e $[M+1]^+$ 729.5。
199		N-((1S)-1-环己基-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.47-8.45(m, 1H), 7.57-7.54 (m, 2H), 7.34-7.29 (m, 1H), 7.09-7.05 (m, 2H), 6.34 (s, 1H), 4.35-4.30 (m, 1H), 4.03 (s, 1H), 2.89-2.85 (m, 6H), 2.05-2.01 (m, 2H), 1.91-1.63 (m, 4H), 1.49-1.20 (m, 3H), 0.45 (s, 4H)。MS (ESI, m/e) $[M+1]^+$ 505.6。
200		N-((1S)-1-环己基-2-((2-((3-氟苯基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 9.45 (s, 1H), 8.47-8.45(m, 1H), 7.57-7.54 (m, 2H), 7.48-7.39 (m, 2H), 7.35-7.30 (m, 3H),

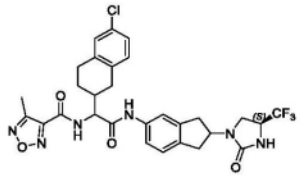
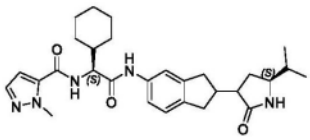
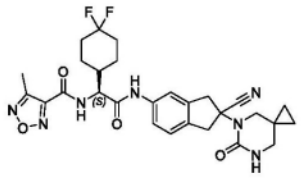
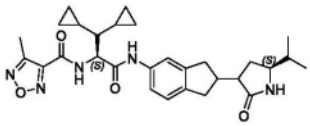
[0775]

		[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	6.86-6.84 (m, 3H), 6.64 (s, 1H), 4.35-4.30 (m, 1H), 4.03 (s, 1H),3.70-3.54 (m, 2H), 3.24-3.03 (m, 5H), 2.89-2.85 (m, 2H), 2.05-2.01 (m, 3H), 1.91-1.63 (m, 4H), 1.49-1.20 (m, 3H), 0.45 (s, 2H), 0.30-0.20 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 642.8。
201		N-(1-(5-氯-1,2,3,4-四氢萘-2-基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.26-10.21 (m, 1H), 8.68 (d, J = 8.6 Hz, 1H), 7.6-7.25 (m, 4H), 7.24 (d, J = 7.2 Hz, 1H), 7.18-6.97 (m, 4H), 6.78 (s, 1H), 4.55 (s, 1H), 4.05 (s, 3H), 3.60-3.45 (m, 2H), 3.24-3.12 (m, 3H), 2.90 (s, 3H), 2.70 (d, J = 26.4 Hz,2H), 2.57 (d, J = 4.2 Hz, 3H), 2.35-2.32 (m, 2H), 2.05-2.02 (m, 1H), 1.62-1.33 (m, 2H), 0.77-0.52 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 646.4
202		N-((1S)-1-环己基-2-((2-(甲基氨基甲酰基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	MS (ESI) m/e $[M+1]^+$ 590.4。
203		N-((1S)-1-(4,4-二氟环己基)-2-((2-((3-氟苯基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.22 (s, 1H), 9.47 (s, 1H), 9.24 (d, J = 8.0 Hz, 1H), 7.57 (s, 2H), 7.54 (s, 1H), 7.48-7.39 (m, 1H), 7.35-7.30 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 6.86-6.84 (m, 1H), 6.64 (s, 1H), 4.55-4.52 (m, 1H), 3.70-3.54 (m, 2H), 3.24-3.03 (m, 5H), 2.89-2.85 (m, 2H), 2.47 (s, 3H), 2.05-2.01 (m, 3H), 1.91-1.63 (m, 4H), 1.49-1.20 (m, 4H), 0.45 (s, 2H), 0.30-0.20 (m, 2H)。

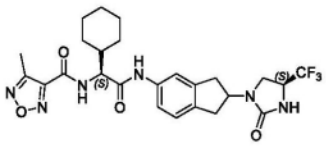
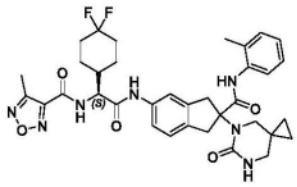
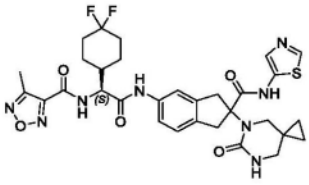
[0776]

		-3-甲酰胺	
204		N-((2S)-3-(4-氯苯基)-1-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-1-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.16 (s, 1H), 8.75 (d, J = 8.2 Hz, 1H), 7.54-7.52 (m, 1H), 7.45-7.35(m, 6H), 7.13 (d, J = 8.2 Hz, 1H), 6.95 (s, 1H), 6.77 (s, 1H), 4.78 (s, 1H), 3.94 (s, 3H), 3.58-3.44 (m, 2H), 3.22-3.10 (m, 3H), 3.04-2.80 (m, 2H), 2.59-2.54 (m, 3H), 1.47-1.40 (m, 1H), 1.29-1.26 (m, 5H), 0.77-0.67 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 606.5。
205		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(4-苯基-1H-咪唑-2-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.69 (s, 1H), 10.16 (s, 1H), 9.21 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.65-7.47 (m, 2H), 7.37-7.20 (m, 4H), 7.15-7.07 (m, 2H), 6.34 (s, 1H), 4.58-4.47 (m, 1H), 4.17-4.05 (m, 2H), 3.28-3.20 (m, 4H), 2.86 (s, 2H), 2.48 (s, 3H), 2.10-1.60 (m, 8H), 1.50-1.30 (m, 2H), 0.50-0.40 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 685.7。
206		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2-(5-苯基-1H-咪唑-2-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.68 (s, 1H), 10.02 (s, 1H), 8.40 (d, J = 8.6 Hz, 1H) 7.64-7.52 (m, 2H), 7.50-7.35 (m, 4H), 7.30-7.14 (m, 2H), 6.91 (s, 1H), 6.33 (s, 1H), 4.77-4.74 (m, 1H), 4.10-4.04 (m, 1H), 3.65-3.40 (m, 4H), 2.91-2.84 (m, 2H), 1.40-1.33 (m, 6H), 0.89-0.70 (m, 3H), 0.45-0.11 (m, 12H)。MS (ESI, m/e) $[M+1]^+$ 687.6
207		5-((S)-2-(4,4-二氟环己基)-2-(4-甲基-1,2,5-噁二唑-3-甲酰胺基)乙酰胺基)-2-(6-氧代-5,7-二氮	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 9.32 (s, 1H), 7.52-7.25 (m, 2H), 7.12-7.06 (m, 1H), 6.65 (s, 1H), 4.57-4.53 (m, 2H), 3.65-3.30 (m, 3H), 3.28-3.10 (m, 2H), 2.89-2.80 (m, 2H), 2.49-2.45 (m, 3H), 2.01-1.63 (m, 7H),

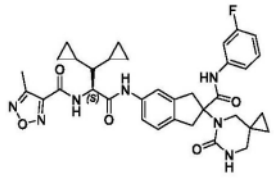
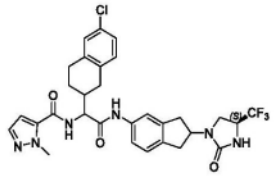
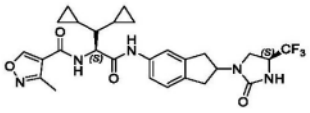
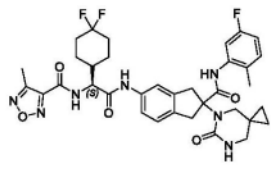
[0777]

		杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-2-甲酸戊-3-基酯	1.55-1.43 (m, 5H), 0.78-0.70 (m, 6H), 0.58-0.41 (m, 4H), MS (ESI, m/e) $[M+1]^+$ 657.7
208		N-(1-(6-氯-1,2,3,4-四氢萘-2-基)-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23-10.18 (m, 1H), 9.33-9.29 (m, 1H), 7.57-7.42 (m, 3H), 7.12-7.01 (s, 4H), 4.57-4.53 (m, 2H), 4.32-4.30 (m, 1H), 3.65-3.30 (m, 2H), 3.28-3.10 (m, 5H), 2.85-2.80 (m, 3H), 2.35-2.30 (m, 1H), 1.87-1.83 (m, 1H), 1.55-1.23 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 617.3
209		N-((1S)-1-环己基-2-((2-((5S)-5-异丙基-2-氧代吡咯烷-3-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.85-7.80 (m, 1H), 7.58-7.50 (m, 2H), 7.32-7.28 (s, 1H), 7.11-6.98 (m, 3H), 4.47-4.43 (m, 1H), 4.05 (s, 3H), 3.61-3.56 (m, 1H), 3.24-3.22 (m, 4H), 3.10-3.05 (m, 4H), 2.49-2.28 (m, 1H), 1.95-1.65 (m, 5H), 1.82-1.58 (m, 3H), 1.24-1.20 (m, 5H), 0.89-0.79 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 506.4。
210		N-((1S)-2-((2-氰基-2-(6-氧代-5,7-二氮杂螺[2.5]辛烷-5-基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4,4-二氟环己基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.30 (s, 1H), 9.27 (d, J = 8.0 Hz, 1H), 7.64-7.55 (m, 1H), 7.48-7.37 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 4.58-4.53 (m, 1H), 3.75-3.64 (m, 2H), 3.28-3.23 (m, 2H), 3.16 (s, 2H), 2.93 (s, 2H), 2.48 (s, 3H), 2.10-1.64 (m, 7H), 1.50-1.30 (m, 2H), 0.60-0.52 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 568.6。
211		N-((2S)-1,1-二环丙基-3-((2-((5S)-5-异丙基-2-氧代吡咯烷-3-基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H), 9.03 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.47-7.45 (m, 1H), 7.35-7.16 (m, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.85-4.82 (m, 1H), 3.23-2.55 (m, 7H), 2.48 (s, 3H),

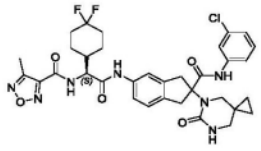
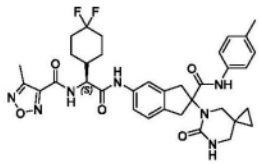
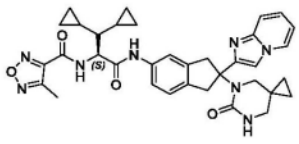
[0778]

		基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	2.47-2.38 (m, 1H), 1.89-1.82 (m, 1H), 1.59-1.42 (m, 1H), 0.90-0.69 (m, 7H), 0.51- 0.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 520.6。
213		N-((1S)-1-环己基-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 9.07 (d, J = 8.0 Hz, 1H), 7.60-7.57 (m, 1H), 7.47 (s, 1H), 7.36-7.32 (m, 1H), 7.19-7.16 (m, 1H), 4.63-4.56 (m, 1H), 4.48-4.44 (m, 1H), 4.35-4.28 (m, 1H), 3.50-3.45 (m, 1H), 3.15-3.12 (m, 1H), 3.04-2.98 (m, 2H), 2.91-2.86 (m, 1H), 2.83-2.77 (m, 1H), 2.47 (s, 3H), 1.87-1.79 (m, 2H), 1.74-1.68 (m, 2H), 1.65-1.55 (m, 2H), 1.23-1.05 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 535.3
214		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(邻甲苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 9.24 (d, J = 8.4 Hz, 1H), 9.06 (d, J = 4.4 Hz, 1H), 7.58-7.47 (m, 2H), 7.44-7.30 (m, 1H), 7.21-7.11 (m, 3H), 7.02 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 4.58-4.53 (m, 1H), 3.75-3.62 (m, 2H), 3.28-3.20 (m, 2H), 3.10-3.00 (m, 2H), 2.87 (s, 2H), 2.48 (s, 3H), 2.20 (s, 3H), 2.10-1.64 (m, 7H), 1.50-1.30 (m, 2H), 0.50-0.34 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 676.4。
215		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(噻唑-5-基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.68 (s, 1H), 10.22 (s, 1H), 9.32 (s, 1H), 8.52 (s, 1H), 7.58-7.25 (m, 3H), 7.12-7.06 (m, 1H), 6.65 (s, 1H), 4.57-4.53 (m, 1H), 3.65-3.30 (m, 3H), 3.28-3.10 (m, 3H), 2.89-2.80 (m, 2H), 2.49-2.45 (m, 3H), 2.01-1.63 (m, 9H), 1.55-1.23 (m, 3H), 0.48-0.30 (m, 2H), 0.28-0.21 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 669.4

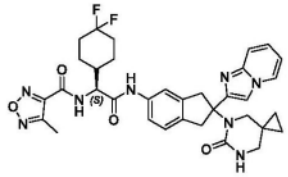
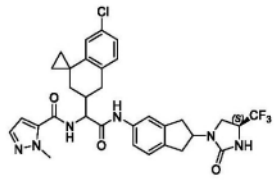
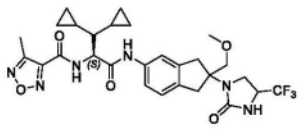
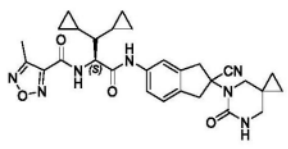
[0779]

216		N-((2S)-1,1-二环丙基-3-((2-((3-氟苯基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.44 (s, 1H), 9.02 (d, J = 8.6 Hz, 1H) 7.64-7.52 (m, 2H), 7.50-7.35 (m, 4H), 7.30-7.14 (m, 1H), 6.85 (s, 1H), 6.61 (s, 1H), 4.87-4.83 (m, 1H), 3.65-3.40 (m, 2H), 3.28-3.26 (m, 4H), 3.01-2.94 (m, 2H), 2.79-2.65 (m, 3H), 0.89-0.70 (m, 3H), 0.45-0.11 (m, 12H)。MS (ESI, m/e) $[M+1]^+$ 656.3
217		N-(1-(6-氯-1,2,3,4-四氢萘-2-基)-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23-10.18 (m, 1H), 8.70-8.63 (m, 1H), 7.57-7.42 (m, 4H), 7.12-7.01 (s, 5H), 4.57-4.53 (m, 3H), 4.03 (s, 3H), 3.65-3.30 (m, 1H), 3.28-3.10 (m, 4H), 2.85-2.80 (m, 6H), 2.35-2.30 (m, 1H), 1.87-1.83 (m, 1H),1.55-1.23 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 615.3
218		N-((2S)-1,1-二环丙基-3-氧代-3-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-3-甲基异噁唑-4-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 9.45 (s, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.36-7.32 (m, 1H), 7.19-7.15 (m, 1H), 4.82-4.78 (m, 1H), 4.63-4.56 (m, 1H), 4.37-4.28 (m, 1H), 3.51-3.46 (m, 1H), 3.16-3.13 (m, 1H), 3.04-2.96 (m, 3H), 2.91-2.86 (m, 1H), 2.83-2.78 (m, 1H), 2.38 (s, 3H), 0.91-0.76 (m, 2H), 0.67-0.63 (m, 1H), 0.47-0.42 (m, 1H), 0.39-0.33 (m, 1H), 0.31-0.26 (m, 2H), 0.22-0.17 (m, 2H), 0.12-0.07 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 546.3
219		N-((1S)-1-(4,4-二氟环己基)-2-((2-((5-氟-2-甲基苯基)氨基甲酰	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.22 (s, 1H), 9.22 (dd, J = 20.4 Hz, 5.2 Hz, 1H), 7.58-7.53 (m, 2H), 7.47-7.30 (m, 1H), 7.24-7.13 (m, 1H), 6.88-6.83 (m, 1H), 4.58-4.53

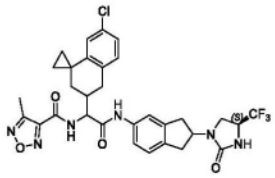
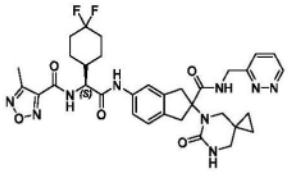
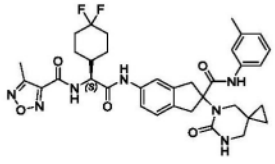
[0780]

		基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 1H), 3.75-3.62 (m, 2H), 3.28-3.20 (m, 2H), 3.10-3.00 (m, 2H), 2.90 (s, 2H), 2.69 (s, 1H), 2.48 (s, 3H), 2.19 (s, 3H), 2.13-1.64 (m, 7H), 1.52-1.30 (m, 2H), 0.53-0.37 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 694.4。
220		N-((1S)-2-((2-((3-氯苯基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-1-(4,4-二氟环己基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 9.32 (s, 1H), 9.22 (d, J = 8.6 Hz, 1H), 7.39-7.15 (m, 4H), 7.12-7.06 (m, 1H), 6.65 (s, 1H),4.57-4.53 (m, 1H), 3.65-3.30 (m, 2H), 3.28-3.10 (m, 4H),2.85-2.80 (m, 2H), 2.49-2.45 (m, 3H), 2.16 (s, 3H), 2.01-1.83 (m, 8H),1.55-1.23 (m, 2H), 0.48-0.30 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 696.4
221		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(对甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 9.32 (s, 1H), 9.22 (d, J = 8.6 Hz, 1H), 7.39-7.15 (m, 4H), 7.12 (s, 3H), 6.65 (s, 1H),4.57-4.53 (m, 1H), 3.65-3.30 (m, 2H), 3.28-3.10 (m, 4H),2.85-2.80 (m, 2H), 2.75 (s, 3H), 2.49-2.45 (m, 3H), 2.16 (s, 3H), 2.01-1.83 (m, 6H),1.55-1.23 (m, 2H), 0.48-0.30 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 676.4
222		*N*-((2*S*)-1,1-二环丙基-3-((2-(咪唑并[1,2-*a*]吡啶-2-基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.03 (d, J = 4.6 Hz, 1H), 9.01 (dd, J = 8.8, 5.4 Hz, 1H), 8.40 (d, J = 6.8 Hz, 1H), 7.70 (s, 1H), 7.49-7.36 (m, 2H), 7.33-7.21 (m, 1H), 7.13-7.08 (m, 2H), 6.77 (t, J = 6.6 Hz, 1H), 6.12 (s, 1H), 4.82 (t, J = 7.6 Hz, 1H), 3.92 (t, J = 14.8 Hz, 2H), 3.43-3.39 (m, 4H), 2.85 (s, 2H), 2.46 (s, 3H), 0.86-0.68 (m, 3H), 0.57-0.42 (m, 5H), 0.40-0.09 (m, 7H)。MS

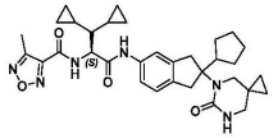
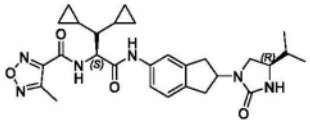
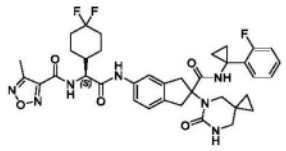
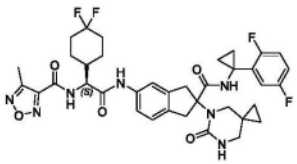
[0781]

		-1,2,5-噁二唑-3-甲酰胺	(ESI, m/e) $[M+1]^+$ 635.2。
223		*N*-((1*S*)-1-(4,4-二氟环己基)-2-((2-(咪唑并[1,2-*a*]吡啶-2-基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.19 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 6.8 Hz, 1H), 7.70 (s, 1H), 7.59-7.34 (m, 2H), 7.31-7.24 (m, 1H), 7.13-7.08 (m, 2H), 6.78 (t, *J* = 6.8 Hz, 1H), 6.12 (s, 1H), 4.51 (t, *J* = 8.4 Hz, 1H), 3.94 (dd, *J* = 15.6, 9.8 Hz, 2H), 3.45-3.35 (m, 4H), 2.86 (s, 2H), 2.45 (s, 3H), 2.02-1.98 (m, 2H), 1.91-1.59 (m, 5H), 1.47-1.28 (m, 2H), 0.55 (s, 2H), 0.46 (s, 2H)。MS (ESI, m/e) $[M+1]^+$ 659.5。
224		N-(1-(7'-氯-3',4'-二氢-2'H-螺[环丙烷-1,1'-萘]-3'-基)-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23-10.18 (m, 1H), 8.70-8.63 (m, 1H), 7.57-7.42 (m, 4H), 7.12-7.01 (s, 4H), 6.75 (s, 1H), 4.57-4.53 (m, 3H), 4.03 (s, 3H), 3.65-3.30 (m, 1H), 3.28-3.10 (m, 4H), 2.85-2.80 (m, 4H), 1.87-1.83 (m, 1H),1.55-1.23 (m, 1H), 0.89-0.70 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 641.3
225		N-((2S)-1,1-二环丙基-3-((2-(甲氧基甲基)-2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 9.01 (d, *J* = 8.0 Hz, 1H), 7.52-7.29 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 4.90-4.82 (m, 1H), 4.31 (s, 1H), 3.85 (s, 1H), 3.58 (s, 1H), 3.43-3.33 (m, 4H), 3.22 (s, 3H), 3.11-3.04 (m, 2H), 2.53 (s, 3H), 0.85 (s, 2H), 0.78-0.72 (m, 1H), 0.46 (s, 1H), 0.38 (s, 1H), 0.31 (s, 1H), 0.25 (s, 2H), 0.16 (s, 1H)。MS (ESI) m/e $[M+1]^+$ 591.4。
226		N-((2S)-1-((2-氰基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.07 (d, *J* = 9.2 Hz, 1H), 7.58-7.53 (m, 1H), 7.47-7.38 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 4.88-4.83 (m, 1H), 3.75-3.65

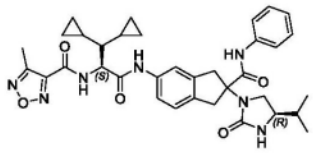
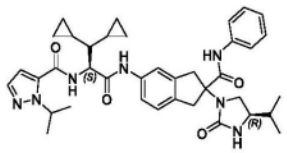
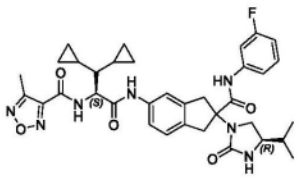
[0782]

		-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 2H), 3.38-3.25 (m, 2H), 3.15 (s, 2H), 2.93 (s, 2H), 2.48 (s, 3H), 2.03-1.94 (m, 1H), 0.90-0.69 (m, 4H), 0.51-0.11 (m, 10H)。MS (ESI, m/e) $[M+1]^+$ 544.6。
227		N-(1-(7'-氯-3',4'-二氢-2'H-螺[环丙烷-1,1'-萘]-3'-基)-2-氧代-2-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.24 (s, 1H), 9.38 -9.28 (m, 1H), 7.67-7.57 (m, 1H), 7.48 (s, 1H), 7.41-7.32 (m, 1H), 7.22-7.17 (m, 1H), 7.10 -7.03 (m, 1H), 6.73 (s, 1H), 4.72-4.56 (m, 2H), 4.38-4.28 (m, 1H), 3.55-3.45 (m, 1H), 3.20-3.13 (m, 2H), 3.08-2.70 (m, 7H), 2.48 (s, 3H), 2.05-1.80 (m, 2H), 1.48-1.24 (m, 2H), 0.99-0.65 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 643.3。
228		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-((哒嗪-3-基甲基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 9.24 (d, J = 8.6 Hz, 1H), 9.09 (d, J = 8.6 Hz, 1H), 8.24 (s, 1H), 7.57-7.42 (m, 4H), 7.12 (s, *2*H), 6.65 (s, 1H),4.57-4.53 (m, 3H), 3.65-3.30 (m, 2H), 3.28-3.10 (m, 5H),2.85-2.80 (m, 2H), 2.49-2.45 (m, 3H), 2.01-1.83 (m, 6H),1.55-1.23 (m, 2H), 0.48-0.30 (m, 2H), 0.17-0.12 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 678.7
229		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2-(间甲苯基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (s, 1H), 9.32 (s, 1H), 9.22 (d, J = 8.6 Hz, 1H), 7.57-7.42 (m, 4H), 7.12 (s, *2*H), 6.85 (s, 1H), 6.65 (s, 1H),4.57-4.53 (m, 1H), 3.65-3.30 (m, 2H), 3.28-3.10 (m, 4H),2.85-2.80 (m, 2H), 2.75 (s, 3H), 2.49-2.45 (m, 3H), 2.16 (s, 3H), 2.01-1.83 (m, 5H),1.55-1.23 (m, 2H), 0.48-0.30 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 676.3

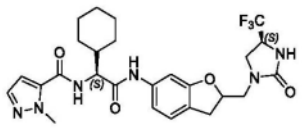
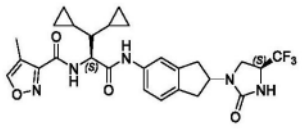
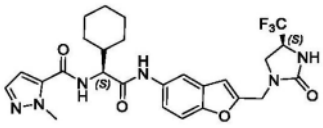
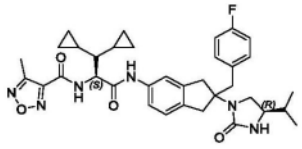
[0783]

230		N-((2S)-1-((2-环戊基-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	MS (ESI, m/e) $[M+1]^+$ 587.4
231		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 9.03 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 20.8 Hz, 1H), 7.34 (dd, J = 18.4, 8.8 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 6.65 (s, 1H), 4.85 (t, J = 8.0 Hz, 1H), 4.60-4.54 (m, 1H), 3.24-3.22 (m, 2H), 2.97-2.80 (m, 6H), 2.49-2.47 (m, 3H), 1.52-1.48 (m, 1H), 0.83-075 (m, 8H), 0.46-0.20 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 521.5。
232		N-((1S)-1-(4,4-二氟环己基)-2-((2-((1-(2-氟苯基)环丙基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 9.22 (d, J = 8.2 Hz, 1H), 8.21 (s, 1H), 7.49-7.20 (m, 4H), 7.10-7.01 (m, 3H), 6.64 (s, 1H), 4.53 (t, J = 8.0 Hz, 1H), 3.47-3.40 (m, 2H), 3.08-2.96 (m, 4H), 2.87 (d, J = 10.6 Hz, 2H), 2.82-2.78 (m, 1H), 2.47 (s, 3H), 2.08-1.98 (m, 2H), 1.90-1.64 (m, 4H), 1.46-1.29 (m, 2H), 1.18 (s, 2H), 1.03-0.99 (m, 2H), 0.39 (s, 2H), 0.17-0.13 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 720.6。
233		N-((1S)-1-(4,4-二氟环己基)-2-((2-((1-(2,5-二氟苯基)环丙基)氨基甲酰基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.18 (s, 1H), 9.22 (d, J = 8.4 Hz, 1H), 8.23 (s, 1H), 7.52-7.25 (m, 3H), 7.15-7.01 (m, 3H), 6.65 (s, 1H), 4.54 (t, J = 8.2 Hz, 1H), 3.51-3.47 (m, 2H), 3.08-2.95 (m, 4H), 2.89 (d, J = 13.4 Hz, 2H), 2.82 (d, J = 10.2 Hz, 1H), 2.47 (s, 3H), 2.05-2.02 (m, 2H), 1.76-1.65

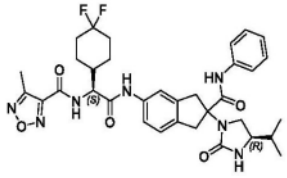
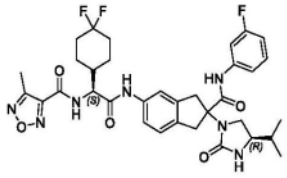
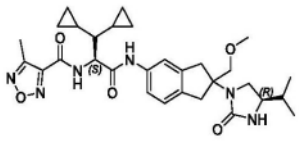
[0784]

		-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 4H), 1.43-1.35 (m, 2H), 1.29 (s, 2H), 1.04 (s, 2H), 0.39 (s, 2H), 0.15-0.12 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 738.6。
234		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.48 (s, 1H), 9.04 (d, J = 8.8 Hz, 1H), 7.62-7.46 (m, 3H), 7.44-7.26 (m, 3H), 7.20-7.15 (m, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.93 (s, 1H), 4.88-4.83 (m, 1H), 3.79-3.67 (m, 1H), 3.60-3.53 (m, 1H), 3.45-3.34 (m, 2H), 3.32-3.25 (m, 1H), 3.18-3.11 (m, 1H), 2.87-2.80 (m, 1H), 2.03-1.94 (m, 1H), 1.53-1.44 (m, 1H), 0.90-0.69 (m, 8H), 0.51-0.11 (m, 9H)。MS (ESI, m/e) $[M+1]^+$ 640.7。
235		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.48 (s, 1H), 8.43 (d, J = 8.8 Hz, 1H), 7.63-7.48 (m, 4H), 7.44-7.28 (m, 3H), 7.18-7.14 (m, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.93 (s, 1H), 5.44-5.38 (m, 1H), 4.88-4.83 (m, 1H), 3.79-3.67 (m, 1H), 3.60-3.53 (m, 1H), 3.48-3.38 (m, 2H), 3.32-3.25 (m, 2H), 3.15-3.07 (m, 1H), 2.87-2.83 (m, 1H), 1.53-1.34 (m, 7H), 0.93-0.69 (m, 9H), 0.50-0.05 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 666.8。
236		N-((2S)-1,1-二环丙基-3-((2-((3-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.68 (s, 1H), 9.04 (d, J = 8.8 Hz, 1H), 7.63-7.46 (m, 2H), 7.42-7.28 (m, 3H), 7.20-7.15 (m, 1H), 6.94 (s, 1H), 6.85 (t, J = 7.6 Hz, 1H), 4.88-4.83 (m, 1H), 3.79-3.67 (m, 1H), 3.60-3.53 (m, 1H), 3.45-3.34 (m, 2H), 3.32-3.25 (m, 2H), 3.15-3.07 (m, 1H), 2.87-2.80 (m, 1H), 2.48 (s, 3H), 1.53-1.44 (m, 1H), 0.90-0.69 (m, 9H), 0.51-0.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$

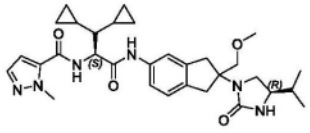
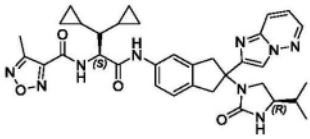
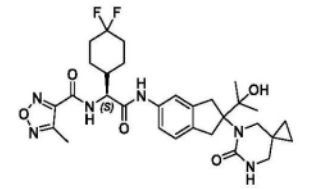
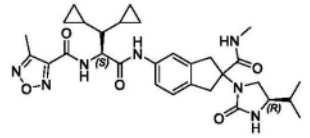
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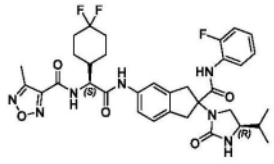
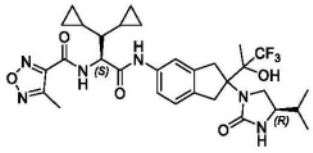
		-3-甲酰胺	658.6。
237		N-((1S)-1-环己基-2-氧代-2-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (d, J = 8.8 Hz, 1H), 8.48 (d, J = 7.4 Hz, 1H), 7.51-7.45 (m, 2H), 7.20 (d, J = 22.6 Hz, 1H), 7.12-6.98 (m, 3H), 4.94-4.92 (m, 1H), 4.36 (t, J = 8.2 Hz, 2H), 4.02 (s, 3H), 3.79-3.64 (m, 1H), 3.58-3.33 (m, 2H), 3.30-3.14 (m, 3H), 2.86-2.79 (m, 1H), 1.83-1.80 (m, 2H), 1.69-1.67 (m, 2H), 1.59-1.56 (m, 2H), 1.15-1.14 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 549.4。
239		N-((2S)-1,1-二环丙基-3-氧代-3-((2-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)丙-2-基)-4-甲基异噁唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 8.85 (s, 1H), 8.38 (d, J = 12.0 Hz, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.33-7.31 (m, 1H), 7.19-7.17 (m, 1H), 4.84-4.81 (m, 1H), 4.63-4.56 (m, 1H), 4.38-4.28 (m, 1H), 3.52-3.47 (m, 1H), 3.17-3.13 (m, 1H), 3.04-2.98 (m, 2H), 2.92-2.78 (m, 2H), 2.11 (s, 3H), 0.95-0.71 (m, 3H), 0.46-0.13 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 546.3
240		N-((S)-1-环己基-2-氧代-2-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)苯并呋喃-5-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.26 (s, 1H), 9.10 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.66 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 6.77 (s, 1H), 4.49 (t, J = 8.4 Hz, 1H), 3.65 (t, J = 9.8 Hz, 1H), 3.44-3.31 (m, 1H), 3.33 (s, 3H), 2.47 (s, 3H), 1.93-1.57 (m, 6H), 123-1.04 (m, 5H)。MS (ESI, m/e) [M+1]+547.5
241		N-((2S)-1,1-二环丙基-3-((2-(4-氟苄基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-	MS (ESI, m/e) [M+1]+629.6

[0786]

		基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	
242		N-((1S)-1-(4,4-二氟环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(苯基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23 (s, 1H), 9.47 (s, 1H), 9.24 (d, J = 5.2 Hz, 1H), 7.63 -7.47 (m, 3H), 7.38-7.27 (m, 3H), 7.20-7.15 (m, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.95 (s, 1H), 6.85 (t, J = 8.0 Hz, 1H), 4.58-4.53 (m, 1H), 3.72 (t, J = 15.6 Hz, 1H), 3.59-3.42 (m, 3H), 3.32-3.28 (m, 1H), 3.18-3.10 (m, 1H), 2.93-2.83 (m, 1H), 2.48 (s, 3H), 2.13-1.65 (m, 7H), 1.54-1.30 (m, 3H), 0.85-0.78 (m, 3H), 0.75 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 664.7。
243		N-((1S)-1-(4,4-二氟环己基)-2-((2-((3-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23 (s, 1H), 9.67 (s, 1H), 9.24 (d, J = 6.0 Hz, 1H), 7.63-7.47 (m, 2H), 7.45-7.27 (m, 3H), 7.17(t, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.85 (t, J = 8.0 Hz, 1H), 4.58-4.53 (m, 1H), 3.79-3.68 (m, 1H), 3.69-3.53 (m, 1H), 3.47-3.39 (m, 2H), 3.32-3.28 (m, 1H), 3.15-3.07 (m, 1H), 2.93-2.83 (m, 1H), 2.48 (s, 3H), 2.13-1.65 (m, 7H), 1.54-1.30 (m, 3H), 0.85-0.78 (m, 3H), 0.75 (d, J = 6.4 Hz, 3H)。MS (ESI, m/e) $[M+1]^+$ 682.6。
244		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲氧基甲基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 9.01 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 4.85 (t, J = 7.8 Hz, 1H), 3.53 (d, J = 10.6 Hz, 2H), 3.41 (d, J = 9.6 Hz, 1H), 3.27-3.16 (m, 6H), 3.04 (t, J = 14.8 Hz, 2H), 2.48 (s, 3H), 1.55-1.41 (m, 1H), 0.85 (s, 1H), 0.80-0.75 (m, 6H), 0.46 (s, 1H), 0.38 (s, 1H), 0.25-0.14 (m, 6H)。MS (ESI) m/e $[M+1]^+$ 565.7。

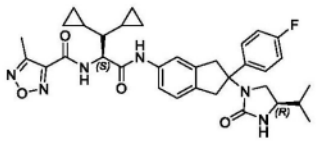
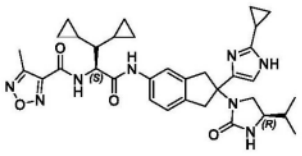
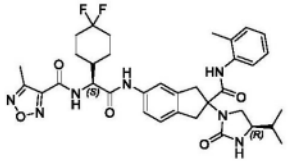
[0787]

245		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(甲氧基甲基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 7.52-7.29 (m, 3H), 7.11 (d, J = 7.8 Hz, 1H), 7.05 (s, 1H), 6.53 (s, 1H), 4.79 (t, J = 8.0 Hz, 1H), 4.04 (s, 3H), 3.59-3.49 (m, 2H), 3.45-3.36 (m, 2H), 3.27-3.17 (m, 6H), 3.07-3.01 (m, 2H), 1.48 (d, J = 6.0 Hz, 1H), 0.84 (s, 1H), 0.80-0.70 (m, 6H), 0.44 (s, 1H), 0.35 (d, J = 6.2 Hz, 2H), 0.31-0.25 (m, 1H), 0.21 (s, 3H), 0.10 (s, 1H)。MS (ESI) m/e [M+1]$^+$ 563.5。
246		N-((2S)-1,1-二环丙基-3-((2-(咪唑并[1,2-b]哒嗪-2-基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.04 (s, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.43 (s, 1H), 8.12-7.99 (m, 2H), 7.47 (d, J = 24.2 Hz, 1H), 7.32-7.27 (m, 1H), 7.15 (d, J = 5.8 Hz, 2H), 6.61 (s, 1H), 4.83 (s, 1H), 3.90-3.72 (m, 2H), 3.57-3.54 (m, 3H), 3.30-3.15 (m, 2H), 2.47 (s, 3H), 1.48-1.39 (m, 1H), 0.84 (d, J = 6.6 Hz, 1H), 0.76-0.72 (m, 6H), 0.44 (s, 1H), 0.37 (s, 1H), 0.31 (s, 1H), 0.23-0.18 (m, 5H)。MS (ESI) m/e [M+1]$^+$ 638.5。
247		*N*-((1*S*)-1-(4,4-二氟环己基)-2-((2-(2-羟基丙-2-基)-2-(6-氧代-5,7-二氮杂螺[2.5]辛-5-基)-2,3-二氢-1*H*-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.17 (s, 1H), 9.22 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 5.8 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.83 (s, 1H), 6.61 (s, 1H), 4.54 (t, J = 8.4 Hz, 1H), 3.31-3.22 (m, 4H), 2.88 (s, 2H), 2.52 (d, J = 15.8 Hz, 2H), 2.47 (s, 3H), 2.07-2.01 (m, 3H), 1.95-1.61 (m, 4H), 1.54-1.26 (m, 2H), 0.91 (s, 6H), 0.52 (s, 4H)。MS (ESI, m/e) [M+1]$^+$ 601.3。
248		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 9.01 (d, J = 8.8 Hz, 1H), 7.57-7.44 (m, 2H), 7.38-7.32 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H),

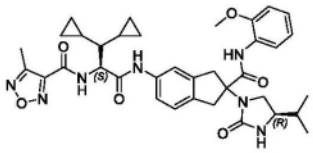
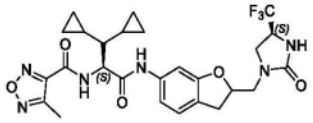
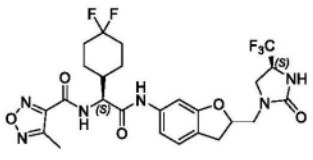
		唑烷-1-基)-2-(甲基氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	4.88-4.83 (m, 1H), 3.59-3.36 (m, 4H), 3.32-3.18 (m, 2H), 2.85-2.80 (m, 1H), 2.56-2.53 (m, 3H), 2.53 (s, 3H), 1.49-1.40 (m, 1H), 0.90-0.65 (m, 8H), 0.51-0.09 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 578.8。
249		N-((1S)-1-(4,4-二氟环己基)-2-((2-((2-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.22 (s, 1H), 9.33-9.18 (m, 2H), 7.85 (s, 1H), 7.61-7.31 (m, 2H), 7.28-7.06 (m, 5H), 4.55 (t, J = 8.4Hz, 1H), 3.70-3.36 (m, 3H), 3.31-3.19 (m, 1H), 3.04-2.94 (m, 1H), 2.69 (s, 1H), 2.47 (s, 3H), 2.10-1.96 (m, 3H), 1.88-1.70 (m, 2H), 1.55-1.42 (m, 3H), 1.36-1.16 (m, 2H), 0.82-0.73 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 682.8。
250		*N*-((2*S*)-1,1-二环丙基-3-((2-((*R*)-4-异丙基-2-氧代咪唑烷-1-基)-2-(1,1,1-三氟-2-羟基丙-2-基)-2,3-二氢-1*H*-茚-5-基)氨基)-3-氧代丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	异构体 A：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.05 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.14 (s, 1H), 4.87 (t, J = 8.2 Hz, 1H), 3.61-3.55 (m, 2H), 3.43-3.17 (m, 5H), 2.91 (s, 1H), 2.49 (s, 3H), 1.35 (s, 3H), 1.15-1.08 (m, 1H), 0.95-0.74 (m, 2H), 0.73-0.67 (m, 1H), 0.51-0.33 (m, 8H), 0.33-0.04 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 633.4。保留时间$_{(制备型\ HPLC)}$: 8.0 min。
			异构体 B：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.14 (d, J = 5.2 Hz, 1H), 9.06 (d, J = 8.8 Hz, 1H), 7.64-7.33 (m, 2H), 7.28-7.20 (m, 1H), 7.17-7.18 (m, 1H), 4.87 (s, 1H), 3.63-3.56 (m, 2H), 3.39-3.21 (m, 5H), 3.09-2.96 (m, 1H), 2.50 (s, 3H), 1.24-1.11 (m, 4H), 0.99-0.65 (m, 6H), 0.55-0.10 (m, 11H). MS (ESI, m/e) $[M+1]^+$ 633.3。保

[0788]

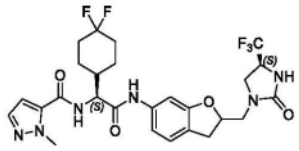
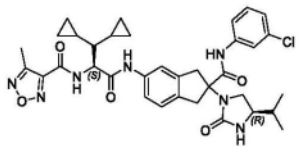
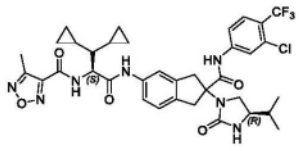
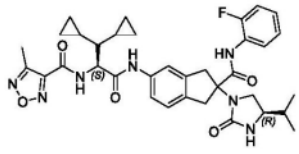
[0789]

			留时间(制备型HPLC): 8.8 min。 异构体C：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.04 (d, J = 8.8 Hz, 1H), 7.56 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.08 (s, 1H), 4.85 (t, J = 7.8 Hz, 1H), 3.59-3.52 (m, 1H), 3.41-3.36 (m, 2H), 3.23-3.00 (m, 5H), 2.49 (s, 3H), 1.41-1.36 (m, 4H), 0.97-0.66 (m, 8H), 0.51-0.12 (m, 9H). MS (ESI, m/e) $[M+1]^+$ 633.4。保留时间(制备型HPLC): 9.4 min。
251		N-((2S)-1,1-二环丙基-3-((2-(4-氟苯基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.03 (d, J = 8.0 Hz, 1H), 7.57-7.29 (m, 4H), 7.19-7.15 (m, 1H), 7.11-7.07 (m, 1H), 6.61 (s, 1H), 4.87-4.83 (m, 1H), 3.85-3.64 (m, 2H), 3.36-3.37 (m, 3H), 3.23-3.16 (m, 1H), 2.97-2.91 (m, 1H), 2.48 (s, 3H), 0.89-0.67 (m, 10H), 0.49-0.14 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 615.6
252		N-((2S)-1,1-二环丙基-3-((2-(2-环丙基-1H-咪唑-4-基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.05 (s, 1H), 9.08-9.00 (m, 1H), 7.78 (s, 1H), 7.57-7.48 (m, 2H), 7.43-7.30 (m, 2H), 7.23-6.93 (m, 1H), 4.88-4.83 (m, 1H), 3.79-3.36 (m, 6H), 3.32-3.18 (m, 1H), 2.48 (s, 3H), 2.05-1.88 (m, 2H), 1.52-1.45 (m, 2H), 0.96-0.70 (m, 10H), 0.51-0.06 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 627.8。
253		N-((1S)-1-(4,4-二氟环己基)-2-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(邻甲苯	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.23 (s, 1H), 9.25 (d, J = 8.6 Hz, 1H), 9.03 (d, J = 8.6 Hz, 1H), 7.54-7.42 (m, 3H), 7.20-7.01 (m, 5H), 4.57-4.53 (m, 4H), 3.65-3.30 (m, 1H), 3.28-3.26 (m, 1H), 2.75 (s, 3H),

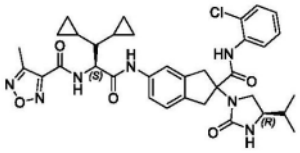
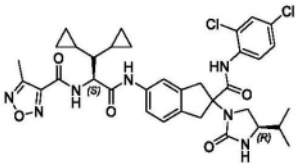
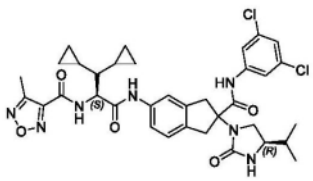
[0790]

		基氨甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-2-氧代乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	2.49-2.45 (m, 3H), 2.16 (s, 3H), 2.01-1.83 (m, 5H), 1.55-1.23 (m, 5H), 0.79-0.50 (m,6H)。MS (ESI, m/e) $[M+1]^+$ 678.5
254		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((2-甲氧基苯基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:10.13 (s, 1H), 9.04 (d, J = 8.8Hz, 1H), 8.88 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.56-7.33 (m, 2H), 7.24-7.12 (m, 2H), 7.02 (d, J = 4.0 Hz, 2H), 6.89 (s, 1H), 4.88-4.84 (m, 1H), 3.79(s, 3H), 3.72-3.47 (m, 2H), 3.42-3.36 (m, 2H), 3.38-3.15 (m, 2H), 3.15-3.10 (m, 1H), 2.48 (s, 3H), 1.60-1.51 (m, 1H), 0.91-0.70 (m, 7H), 0.52-0.11 (m, 10H)。MS (ESI, m/e) $[M+1]^+$ 670.8
255		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (d, J = 5.0 Hz, 1H), 9.05 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 5.8 Hz, 1H), 7.18-7.08 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 4.96-4.92 (m, 1H), 4.84 (t, J = 7.8 Hz, 1H), 4.36 (s, 1H), 3.79-3.66 (m, 1H), 3.59-3.38 (m, 2H), 3.30-3.14 (m, 2H), 2.87-2.82 (m, 1H), 2.48 (s, 3H), 0.90-0.66 (m, 3H), 0.47-0.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 563.5。
257		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)乙基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.21 (d, J = 7.8 Hz, 1H), 9.23 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 5.8 Hz, 1H), 7.22-7.08 (m, 2H), 7.01-6.96 (m, 1H), 4.95-4.94 (m, 1H), 4.52 (t, J = 8.2 Hz, 1H), 4.36 (s, 1H), 3.79-3.67 (m, 1H), 3.57-3.41 (m, 2H), 3.28-3.16 (m, 2H), 2.86-2.82 (m, 1H), 2.47 (s, 3H), 2.04-2.00 (m, 3H), 1.86-1.65 (m, 4H), 1.47-1.30 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 587.6。

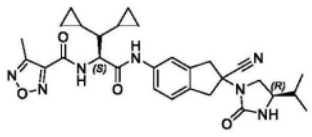
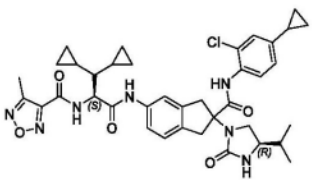
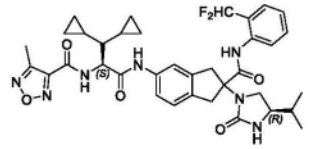
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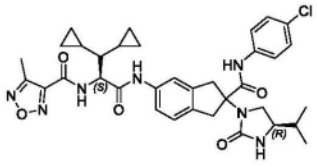
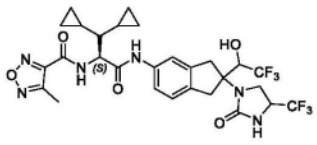
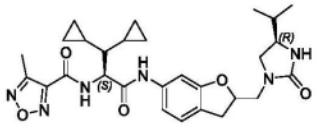
258		N-((1S)-1-(4,4-二氟环己基)-2-氧代-2-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.18 (d, J = 7.5 Hz, 1H), 8.62 (d, J = 7.5 Hz, 1H), 7.54-7.44 (m, 2H), 7.23-6.99 (m, 4H), 4.95-4.93 (m, 1H), 4.48-4.37 (m, 2H), 4.03 (s, 3H), 3.79-3.67 (m, 1H), 3.57-3.41 (m, 2H), 3.29-3.15 (m, 2H), 2.84 (d, J = 17.2 Hz, 1H), 2.05-2.01 (m, 3H), 1.88-1.63 (m, 4H), 1.43-1.29 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 585.6。
259		N-((2S)-1-((2-((3-氯苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.65 (s, 1H), 9.08-9.00 (m, 1H), 7.78 (s, 1H), 7.57-7.48 (m, 2H), 7.43-7.30 (m, 2H), 7.23-7.09 (m, 2H), 6.93 (s, 1H), 4.88-4.83 (m, 1H), 3.79-3.36 (m, 4H), 3.32-3.18 (m, 2H), 2.85-2.80 (m, 1H), 2.48 (s, 3H), 1.52-1.45 (m, 1H), 0.96-0.70 (m, 9H), 0.51-0.09 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 674.3。
260		N-((2S)-1-((2-((3-氯-4-(三氟甲基)苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 10.01 (s, 1H), 9.08-9.04 (m, 1H), 8.06 (s, 1H), 7.77-7.75 (m, 2H), 7.53-7.30 (m, 2H), 7.25-7.20 (m, 1H), 6.99 (s, 1H), 4.88-4.83 (m, 1H), 3.79-3.36 (m, 4H), 3.32-3.18 (m, 1H), 2.85-2.80 (m, 1H), 2.48 (s, 3H), 0.96-0.70 (m, 10H), 0.51-0.09 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 742.3。
262		N-((2S)-1,1-二环丙基-3-((2-((2-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.29 (d, J = 8.6 Hz, 1H),9.02 (d, J = 8.6 Hz, 1H) 7.84-7.80 (m, 1H), 7.50-7.35 (m, 4H), 7.30-7.14 (m, 3H), 4.87-4.83 (m, 1H), 3.65-3.30 (m, 4H), 3.28-3.26

[0792]

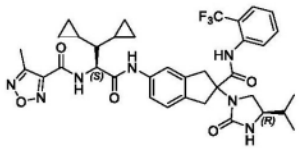
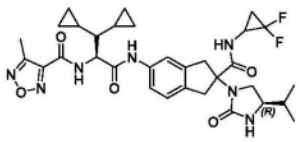
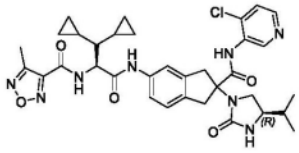
		二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 2H), 3.01-2.94 (m, 1H), 2.49-2.45 (m, 3H), 1.55-1.53 (m, 1H), 0.79-0.70 (m,9H), 0.45-0.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 658.3
263		N-((2S)-1-((2-((2-氯苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.13 (s, 1H), 9.17 (d, J = 8.6 Hz, 1H),9.06 (d, J = 8.6 Hz, 1H) 7.96-7.94 (m, 2H), 7.50-7.35 (m, 4H), 7.30-7.14 (m, 3H), 4.89-4.87 (m, 1H), 3.65-3.30 (m, 4H), 3.28-3.26 (m, 2H), 3.01-2.94 (m, 1H), 2.49-2.45 (m, 3H), 1.55-1.53 (m, 1H), 0.79-0.70 (m,9H), 0.29-0.11 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 674.3
264		N-((2S)-1,1-二环丙基-3-((2-((2,4-二氯苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 9.23 (d, J = 6.0 Hz, 1H), 9.03 (d, J = 8.8 Hz, 1H), 7.96-7.88 (dd, J = 5.2, 8.8 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.56-7.46 (m, 1H), 7.45-7.33 (m, 2H), 7.23-7.11 (m, 2H), 4.85 (t, J = 7.6 Hz, 1H), 3.71-3.61 (m, 1H), 3.59-3.48 (m, 2H), 3.44-3.33 (m, 2H), 3.27-3.20 (m, 1H), 3.01-2.93 (m, 1H), 2.48 (s, 3H), 1.56-1.47 (m, 1H), 0.91-0.84 (m, 1H), 0.81-0.72 (m, 8H), 0.49-0.35 (m, 2H), 0.33-0.13 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 708.6。
265		N-((2S)-1,1-二环丙基-3-((2-((3,5-二氯苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.80 (s, 1H), 9.02 (dd, J = 3.6, 8.4 Hz, 1H), 7.75 (s, 2H), 7.56-7.46 (m, 1H), 7.44-7.31 (m, 1H), 7.25 (s, 1H), 7.19-7.15 (m, 1H), 6.96 (s, 1H), 4.92-4.80 (m, 1H), 3.77-3.72 (m, 1H), 3.61-3.51 (m, 1H), 3.47-3.33 (m, 2H), 3.28 (s, 1H), 3.07-3.02 (m, 1H), 2.85-2.78 (m, 1H), 2.49 (s, 3H),

[0793]

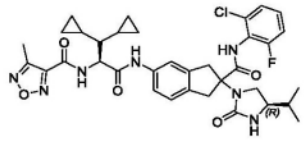
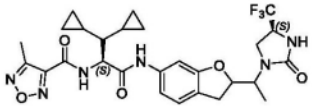
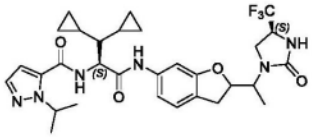
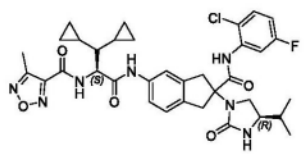
		-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	1.48-1.45 (m, 1H), 0.88-0.84 (m, 1H), 0.82-0.69 (m, 8H), 0.51-0.36 (m, 2H), 0.33-0.12 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 708.2。
266		N-((2S)-1-((2-氰基-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07-9.93 (m, 1H), 8.54-8.45 (m, 1H), 8.23-8.11 (m, 1H), 8.08-7.92 (m, 1H), 7.87-7.69 (m, 1H), 6.91-6.80 (m, 1H), 5.56-5.42 (m, 1H), 4.34-3.92 (m, 6H), 3.79-3.68 (m, 1H), 3.09-3.03 (m, 3H), 2.26-2.14 (m, 1H), 1.82-1.76 (m, 1H), 1.49-1.42 (m, 6H), 1.07-0.69 (m, 10H)。MS (ESI, m/e) $[M+1]^+$ 546.5。
267		N-((2S)-1-((2-((2-氯-4-环丙基苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.11-8.99 (m, 2H), 7.79-7.71 (m, 1H), 7.54-7.33 (m, 2H), 7.21-7.16 (m, 2H), 7.13-7.10 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.85 (t, J = 8.0 Hz,1H), 3.76-3.44 (m, 4H), 3.42-3.40 (m, 1H), 3.27-3.21 (m, 1H), 3.02-2.91 (m, 1H), 2.50-2.48 (m, 3H), 1.96-1.86 (m, 1H), 1.57-1.46 (m, 1H), 0.94-0.92 (m, 2H), 0.89-0.84 (m, 1H), 0.82-0.71 (m, 8H), 0.67-0.64 (m, 2H), 0.49-0.36 (m, 2H), 0.33-0.13 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 714.3。
268		N-((2S)-1,1-二环丙基-3-((2-((2-(二氟甲基)苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 9.58 (d, J = 8.4 Hz, 1H), 9.05 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.57-7.42 (m, 2H), 7.42-7.31 (m, 3H), 7.23-7.15 (m, 1H), 7.11-7.05 (m, 1H), 4.85 (t, J = 8.0 Hz, 1H), 3.62-3.52 (m, 1H), 3.79-3.51 (m, 1H), 3.44 (d, J = 6.0 Hz, 1H), 3.39 (s, 1H), 3.33-3.22 (m, 4H), 3.09 (d, J = 16.8 Hz, 1H), 2.89-2.80 (m, 1H), 2.48 (s, 3H), 1.51-1.42 (m, 1H), 0.91-0.79 (m, 1H), 0.78-0.67 (m, 8H),

		-3-甲酰胺	0.50-0.28 (m, 2H), 0.28-0.10 (m, 4H)。MS (ESI, m/e) $[M+1]^+$ 690.3。
269		N-((2S)-1-((2-((4-氯苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.62 (s, 1H), 9.08-8.99 (m, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.55-7.45 (m, 1H), 7.37-7.32 (m, 3H), 7.17 (dd, J = 4.8, 8.0 Hz, 1H), 6.93 (s, 1H), 4.89-4.81 (m, 1H), 3.79-3.67 (m, 1H), 3.60-3.51 (m, 1H), 3.43 (s, 1H), 3.39-3.37 (m, 1H), 3.31-3.27 (m, 1H), 3.10 (d, J = 16.8 Hz, 1H), 2.84 (q, J = 8.0 Hz, 1H), 2.48 (s, 3H), 2.07 (s, 1H), 1.51-1.41 (m, 1H), 0.91-0.82 (m, 1H), 0.78-0.75 (m, 4H), 0.72-0.69 (m, 4H), 0.50-0.42 (m, 1H), 0.41-0.35 (m, 1H), 0.34-0.17 (m, 6H), 0.17-0.11 (m, 1H)。MS (ESI, m/e) $[M+1]^+$ 674.3。
[0794] **270**		*N*-((2*S*)-1,1-二环丙基-3-氧代-3-((2-(2-氧代-4-(三氟甲基)咪唑烷-1-基)-2-(2,2,2-三氟-1-羟基乙基)-2,3-二氢-1*H*-茚-5-基)氨基)丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.02 (d, J = 8.8 Hz, 1H), 7.67-7.30 (m, 3H), 7.18 (dd, J = 18.6, 8.4 Hz, 1H), 7.09-6.92 (m, 1H), 4.93-4.84 (m, 2H), 4.27 (s, 1H), 3.71-3.63 (m, 1H), 3.52-3.40 (m, 2H), 3.33-3.05 (m, 3H), 2.49 (s, 3H), 0.96-0.66 (m, 3H), 0.47-0.13 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 645.4。
271		N-((2S)-1,1-二环丙基-3-((2-(((R)-4-异丙基-2-氧代咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-6-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.04 (d, J = 8.6 Hz, 1H), 7.19-7.04 (m, 2H), 6.99-6.9 (m, 1H), 6.68 (s, 1H), 4.89-4.87 (m, 2H), 3.50-3.02 (m, 8H), 2.89-2.80 (m, 1H), 2.49-2.45 (m, 2H), 1.55-1.33 (m, 1H), 0.79-0.70 (m,10H), 0.29-0.11 (m, 9H)。MS (ESI, m/e) $[M+1]^+$ 537.5

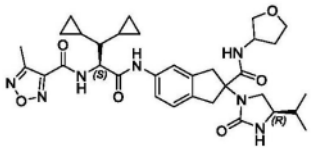
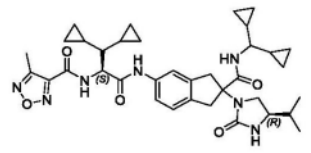
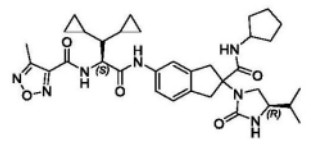
[0795]

272		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((2-(三氟甲基)苯基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.21-9.16 (m, 1H), 9.01 (d, J = 8.8 Hz, 1H), 7.80-7.73 (m, 1H), 7.73-7.64 (m, 2H), 7.56-7.47 (m, 1H), 7.42-7.33 (m, 2H), 7.20-7.11 (m, 2H), 4.89-4.83 (m, 1H), 3.72-3.61 (m, 1H), 3.57-3.48 (m, 2H), 3.46-3.39 (m, 1H), 3.35 (d, J = 6.8 Hz, 1H), 3.20 (dd, J = 2.8, 16.8 Hz, 1H), 2.97-2.88 (m, 1H), 2.48 (s, 3H), 1.54-1.47 (m, 1H), 0.91-0.84 (m, 1H), 0.83-0.69 (m, 8H), 0.50-0.13 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 708.3。
273		N-((2S)-1,1-二环丙基-3-((2-((2,2-二氟环丙基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 9.00 (d, J = 8.8 Hz, 1H), 8.02-7.91 (dd, J = 3.2, 29.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.41-7.31 (m, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 4.89-4.82 (dd, J = 2.0, 7.2 Hz, 1H), 3.65-3.36 (m, 3H), 3.27-3.17 (m, 3H), 2.94-2.74 (m, 1H), 2.48 (s, 3H), 1.91-1.79 (m, 1H), 1.57-1.38 (m, 2H), 0.87-0.66 (m, 10H), 0.49-0.36 (m, 2H), 0.31-0.12 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 640.3。
274		N-((2S)-1-((2-((4-氯吡啶-3-基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.09 (s, 1H), 9.46-9.36 (m, 1H), 9.01 (d, J = 8.8 Hz, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 7.60 (d, J = 5.2 Hz, 1H), 7.56-7.47 (m, 1H), 7.44-7.33 (m, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.11 (s, 1H), 4.86 (dd, J = 7.2, 8.8 Hz, 1H), 3.76-3.64 (m, 1H), 3.61-3.48 (m, 2H), 3.47-3.40 (m, 1H), 3.21 (dd, J = 3.6, 16.8 Hz, 2H), 2.99-2.91 (m, 1H), 2.48 (s, 3H), 1.55-1.46 (m, 1H), 0.92-0.84 (m, 1H), 0.81-0.72 (m, 8H), 0.50-0.43 (m, 1H), 0.41-0.38 (m, 1H), 0.34-0.30 (m, 1H), 0.29-0.12 (m, 5H)。MS

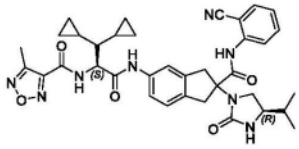
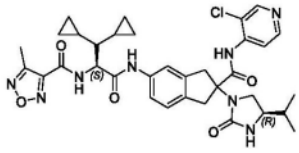
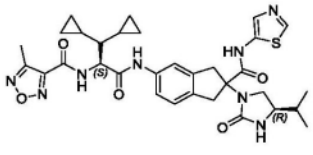
[0796]

			(ESI, m/e) $[M+1]^+$ 675.3。
275		N-((2S)-1-((2-((2-氯-6-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.40 (d, J = 8.4 Hz, 1H), 9.01 (d, J = 8.4 Hz, 1H), 7.55-7.46 (m, 1H), 7.40-7.31 (m, 2H), 7.32-7.31 (m, 1H), 7.28-7.22 (m, 1H), 7.20-7.15 (m, 1H), 6.97 (s, 1H), 4.86 (t, J = 7.6 Hz, 1H), 3.70-3.49 (m, 4H), 3.30-3.26 (m, 1H), 3.01-2.89 (m, 1H), 2.49-2.48 (m, 3H), 1.55-1.42 (m, 1H), 0.91-0.84 (m, 1H), 0.80-0.76 (m, 4H), 0.75-0.70 (m, 4H), 0.32 (br s, 3H), 0.30-0.13 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 692.2
276		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(1-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)乙基)-2,3-二氢苯并呋喃-6-基)氨基)丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12-10.10 (m, 1H), 9.05 (m, 1H), 7.49-7.45 (m, 1H), 7.22 (s, 1H), 7.16-7.04 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.95-4.84 (m, 2H), 4.42 (s, 1H), 3.99-3.67 (m, 2H), 3.52-3.41 (m, 1H), 3.25-3.09 (m, 1H), 2.94-2.80 (m, 1H), 2.48 (s, 2H), 1.26-1.09 (m, 4H), 0.79-0.70 (m, 3H), 0.43-0.11(m, 8H)。MS (ESI, m/e) $[M+1]^+$ 577.4。
277		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(1-((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)乙基)-2,3-二氢苯并呋喃-6-基)氨基)丙-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.12-10.10 (m, 1H), 8.43 (d, J = 8.8 Hz, 1H), 7.52-7.45 (m, 2H), 7.27-6.88 (m, 4H), 5.46-5.33 (m, 1H), 4.85-4.80 (m, 2H), 4.44-4.40 (m, 1H), 3.85-3.70 (m, 2H), 3.55-3.50 (m, 1H), 3.27-3.10 (m, 1H), 2.92-2.87 (m, 1H), 1.36 (dd, J = 13.8, 6.6 Hz, 6H), 1.25-1.19 (m, 1H), 1.15-1.09 (m, 2H), 0.88-0.68 (m, 3H), 0.49-0.03 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 603.4。
278		N-((2S)-1-((2-((2-氯-5-氟苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 9.22 (d, J = 6.4 Hz, 1H), 9.01 (d, J = 9.2 Hz, 1H), 7.95-7.86 (m, 1H), 7.58-7.47 (m, 2H), 7.44-7.34 (m, 1H), 7.22-7.16 (m, 2H),

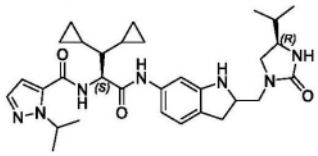
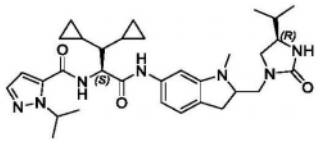
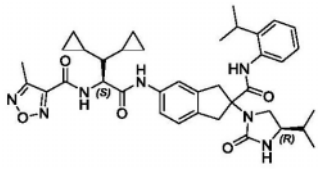
[0797]

		唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	7.05-6.98 (m, 1H), 4.85 (dd, *J* = 7.2, 8.4 Hz, 1H), 3.70-3.55 (m, 2H), 3.54-3.49 (m, 1H), 3.42-3.36 (m, 1H), 3.29-3.23 (m, 1H), 3.01-2.98 (m, 1H), 2.48 (s, 3H), 1.54-1.51 (m, 1H), 0.91-0.85 (m, 1H), 0.82-0.72 (m, 8H), 0.50-0.10 (m, 9H)。MS (ESI, m/e) $[M+1]^+$ 692.3。
280		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((四氢呋喃-3-基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 9.00 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 7.46 (d, *J* = 16.8 Hz, 1H), 7.35 (dd, *J* = 7.6, 18.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 4.93-4.78 (t, *J* = 7.6 Hz, 1H), 4.26-4.22 (m, 1H), 3.79-3.69 (m, 2H), 3.68-3.52 (m, 2H), 3.49-3.40 (m, 2H), 3.36 (s, 1H), 3.31-3.20 (m, 2H), 3.15-3.04 (m, 1H), 2.86-2.80 (m, 1H), 2.48 (s, 3H), 2.10-1.97 (m, 1H), 1.80-1.70 (m, 1H), 1.48-1.37 (m, 1H), 0.91-0.83 (m, 1H), 0.81-0.65 (m, 8H), 0.50-0.35 (m, 2H), 0.34-0.12 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 634.2。
281		N-((2S)-1,1-二环丙基-3-((2-((二环丙基甲基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.81 (s, 1H), 8.47 (s, 1H), 7.87-7.81 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.27-7.11 (m, 2H), 6.76-6.66 (m, 1H), 5.76-5.56 (m, 1H), 5.35-5.26 (m, 1H), 5.08-4.83 (m, 1H), 3.99-3.96 (m, 1H), 3.45-3.41 (m, 1H), 3.38-3.33 (m, 2H), 3.32-3.18 (m, 4H), 2.48 (s, 3H), 1.75-1.52 (m, 3H), 1.01-0.29 (m, 22H)。
282		N-((2S)-1-((2-(环戊基氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 9.01 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 14.8 Hz, 1H), 7.37-7.30 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 4.88-4.83 (m, 1H), 3.99-3.96 (m, 1H), 3.45-3.41 (m, 1H), 3.38-3.33 (m, 4H),

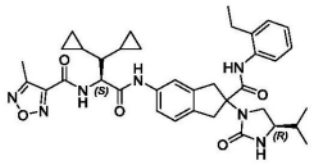
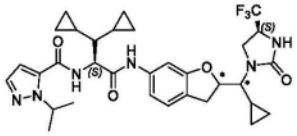
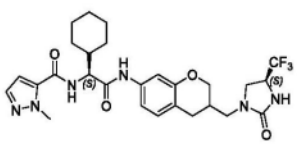
[0798]

		基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	3.32-3.18 (m, 3H), 2.96-2.93 (m, 1H), 2.48 (s, 3H), 1.81-1.70 (m, 2H), 1.69-1.65 (m, 2H), 1.55-1.35 (m, 5H), 0.95-0.70 (m, 7H), 0.51-0.19 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 632.6。
283		N-((2S)-1-((2-((2-氰基苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.14-10.09 (m, 1H), 9.70 (d, J = 3.6 Hz, 1H), 9.02 (d, J = 9.2 Hz, 1H), 7.83-7.79 (m, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.56-7.48 (m, 1H), 7.44-7.31 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 4.91-4.81 (m, 1H), 3.74 (t, J = 17.6 Hz, 1H), 3.61-3.54 (m, 1H), 3.53-3.39 (m, 2H), 3.31-3.27 (m, 1H), 3.16 (dd, J = 3.2, 16.8 Hz, 1H), 2.91-2.82 (m, 1H), 2.49 (br s, 3H), 1.55-1.46 (m, 1H), 0.92-0.85 (m, 1H), 0.81-0.70 (m, 8H), 0.51-0.44 (m, 1H), 0.42-0.36 (m, 1H), 0.35-0.30 (m, 1H), 0.29-0.13 (m, 5H)。MS (ESI, m/e) $[M+1]^+$ 665.3。
284		N-((2S)-1-((2-((3-氯吡啶-4-基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3,3-双环丙基-1-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.32-8.31 (m, 1H), 8.42-8.26 (m, 1H), 7.89-7.78 (m, 1H), 7.57-7.45 (m, 1H), 7.34 (s, 1H), 7.25-7.19 (m, 1H), 5.08-4.83 (m, 1H), 3.92-3.17 (m, 7H), 2.64-2.52 (m, 3H), 1.77-1.70 (m, 1H), 1.55-1.43 (m, 1H), 1.36-1.22 (m, 2H), 1.00-0.86 (m, 6H), 0.83-0.76 (m, 2H), 0.60-0.49 (m, 2H), 0.45-0.30 (m, 2H), 0.28-0.14 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 675.3。
285		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-(噻唑-5-基氨基甲酰基)-2,3-二氢	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.11-8.88 (m, 1H), 8.53 (s, 1H), 7.67 (s, 1H), 7.57-7.45 (m, 1H), 7.45-7.24 (m, 2H), 7.18-7.14 (m, 1H), 6.95-6.91 (m, 1H), 3.48-3.39 (m, 1H), 3.30-3.23 (m, 2H), 3.17-3.05 (m, 1H), 2.85-2.80 (m, 1H), 2.45-2.40

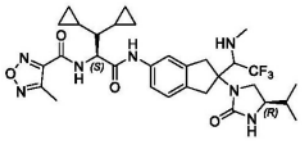
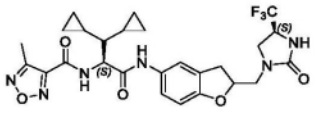
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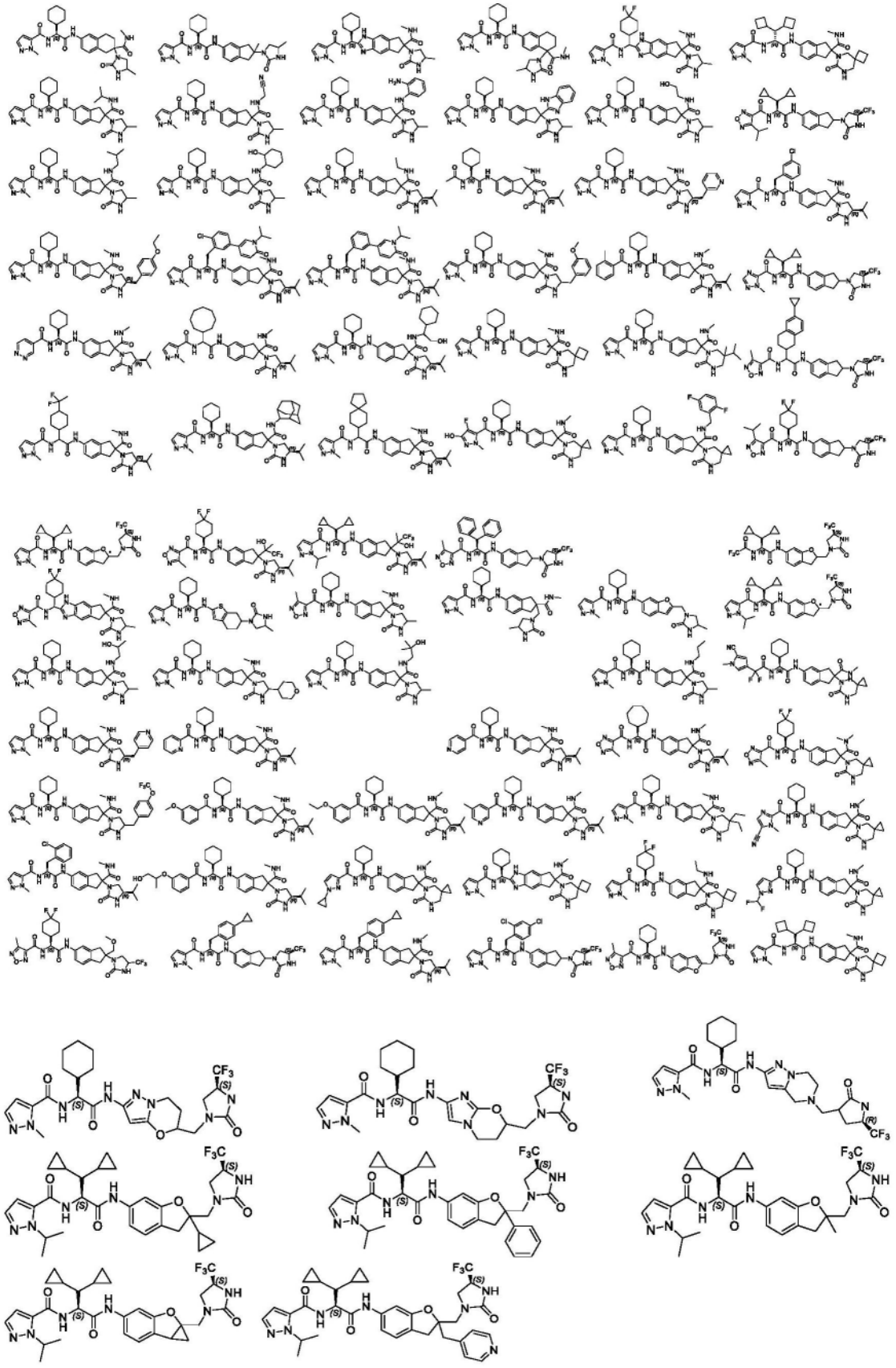
		-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	(m, 3H), 1.50-1.42 (m, 1H), 0.90-0.83 (m, 1H), 0.83-0.73 (m, 5H), 0.71-0.69 (m, 3H), 0.50-0.43 (m, 1H), 0.41-0.35 (m, 1H), 0.34-0.11 (m, 6H)。MS (ESI, m/e) $[M+1]^+$ 647.3。
286		N-((2S)-1,1-二环丙基-3-((2-(((R)-4-异丙基-2-氧代咪唑烷-1-基)甲基)二氢吲哚-6-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.83 (s, 1H), 8.37 (d, J = 9.2 Hz, 1H), 7.49 (s, 1H), 6.95-6.81 (m, 3H), 6.69 (d, J = 7.8 Hz, 1H), 6.62 (s, 1H), 5.73 (s, 1H), 5.40 (s, 1H), 4.76 (t, J = 9.4 Hz, 1H), 3.25-2.87 (m, 8H), 1.55-1.43 (m, 1H), 1.51-1.42 (m, 6H), 0.91-0.72 (m, 10H), 0.44-0.10 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 562.5。
287		N-((2S)-1,1-二环丙基-3-((2-(((R)-4-异丙基-2-氧代咪唑烷-1-基)甲基)-1-甲基吲哚啉-6-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.89 (d, J = 7.2 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1 H), 7.50 (s, 1 H), 6.95-6.74 (m, 4 H), 6.64 (d, J = 9.4 Hz, 1 H), 5.41 (s, 1 H), 4.77 (t, J = 8.4 Hz, 1 H), 3.55-3.37 (m, 3 H), 3.28-2.90 (m, 4 H), 2.69 (d, J = 4.4 Hz, 3 H),2.66-2.62 (m, 1 H), 1.36 (dd, J = 11.6, 6.6 Hz, 6H), 0.89-0.65 (m, 10 H), 0.35-0.11 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 576.5。
288		N-((2S)-1,1-二环丙基-3-((2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2-((2-异丙基苯基)氨基甲酰基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.70-8.57 (m, 1H), 8.41-8.28 (m, 1H), 7.81-7.75 (m, 1H), 7.72-7.68 (m, 1H), 7.52-7.45 (m, 1H), 7.39-7.27 (m, 1H), 7.23-7.18 (m, 2H), 7.04 (br s, 2H), 7.05-7.03 (m, 1H), 5.63-5.21 (m, 1H), 4.96-4.86 (m, 1H), 4.11-3.93 (m, 1H), 3.90-3.79 (m, 1H), 3.59-3.26 (m, 4H), 2.88-2.78 (m, 1H), 2.77-2.67 (m, 1H), 2.60-2.58 (m, 3H), 1.71-1.65 (m, 1H), 1.13-1.05 (m, 6H), 0.99-0.75 (m, 12H), 0.62-0.50 (m, 2H), 0.35-0.27 (m, 2H)。MS (ESI, m/e) $[M+1]^+$ 682.5。

[0800]

289		N-((2S)-1,1-二环丙基-3-((2-((2-乙基苯基)氨基甲酰基)-2-((R)-4-异丙基-2-氧代咪唑烷-1-基)-2,3-二氢-1H-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.08 (s, 1H), 9.05-8.99 (m, 2H), 7.57-7.47 (m, 1H), 7.46-7.34 (m, 2H), 7.23-7.17 (m, 2H), 7.16-7.08 (m, 2H), 7.06-7.02 (m, 1H), 4.86 (dd, J = 7.2, 8.4 Hz, 1H), 3.70-3.67 (m, 1H), 3.62-3.50 (m, 2H), 3.46-3.39 (m, 1H), 3.03-2.90 (m, 1H), 1.54-1.44 (m, 1H), 1.09 (t, J = 7.6 Hz, 3H), 0.92-0.83 (m, 1H), 0.79-0.72 (m, 8H), 0.51-0.12 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 668.7。
290		N-((S)-1,1-二环丙基-3-((2-(环丙基((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)-l3-甲基)-2,3-二氢-2l3-苯并呋喃-6-基)氨基)-3-氧代丙烷-2-基)-1-异丙基-1H-吡唑-5-甲酰胺	异构体 A：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.42 (d, J = 8.8 Hz, 1H), 7.53-7.50 (m, 2H), 7.22-6.89 (m, 4H), 5.43-5.40 (m, 1H), 4.99-4.97 (m, 1H), 4.77 (s, 1H), 4.39-4.37 (m, 1H), 3.87-3.85 (m, 1H), 3.08-3.04(m, 3H), 1.38-1.33 (m, 6H), 1.12-0.99 (m, 1H), 0.79-0.70 (m, 4H), 0.52-0.04 (m, 11H)。MS (ESI, m/e) $[M+1]^+$ 629.4。保留时间(制备型 HPLC): 7.4 min 异构体 B：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.11 (s, 1H), 8.44 (d, J = 8.8 Hz, 1H), 7.51-7.40 (m, 2H), 7.27 (s, 1H), 7.17-7.08 (m, 1H), 7.02-6.88 (m, 2H), 5.48-5.31 (m, 1H), 4.98-4.95 (m, 1H), 4.78-4.76 (m, 1H), 4.40-4.35 (m, 1H), 3.85 (s, 1H), 3.63-3.60 (m, 1H), 3.24-2.99 (m, 3H), 1.40-1.30 (m, 6H), 1.05 (s, 1H), 0.91-0.69 (m, 3H), 0.54-0.50 (m, 3H), 0.40-0.15 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 629.4。保留时间(制备型 HPLC): 8.2 min
291		N-((1S)-1-环己基-2-氧代-2-((3-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)色满	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.15 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.58-7.50 (m, 2H), 7.31-6.98 (m, 4H), 4.47-4.43 (m, 2H), 4.20-4.05 (m, 4H), 3.80-3.77 (m, 2H),

[0801]

		-7-基)氨基)乙基)-1-甲基-1H-吡唑-5-甲酰胺	3.53-3.50 (m, 1H), 3.24-3.22 (m, 1H), 3.09-3.08 (m, 1H), 2.76-2.73 (m, 1H), 2.49-2.28 (m, 2H), 1.95-1.65 (m, 6H), 1.82-1.58 (m, 4H), 1.24-1.20 (m, 3H)。MS (ESI, m/e) $[M+1]^+$ 563.4。
292		*N*-((2*S*)-1,1-二环丙基-3-((2-((*R*)-4-异丙基-2-氧代咪唑烷-1-基)-2-(2,2,2-三氟-1-(甲基氨基)乙基)-2,3-二氢-1*H*-茚-5-基)氨基)-3-氧代丙烷-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	异构体 A：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.03 (d, J = 8.6 Hz, 1H), 7.61-7.28 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 4.85 (t, J = 8.0 Hz, 1H), 4.01 (s, 1H), 3.51-3.36 (m, 2H), 3.27-3.11 (m, 3H), 3.07-3.00 (m, 2H), 2.81-2.77 (m, 1H), 2.48 (s, 3H), 1.35-1.23 (m, 3H), 0.93-0.58 (m, 10H), 0.48-0.14 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 632.4。保留时间(制备型 HPLC): 7.9 min。
			异构体 B：^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.10 (s, 1H), 9.04 (d, J = 8.8 Hz, 1H), 7.53 (t, J = 14.6 Hz, 1H), 7.43-7.27 (m, 1H), 7.20-7.12 (m, 1H), 6.55 (s, 1H), 4.85 (t, J = 7.8 Hz, 1H), 4.14-4.08 (m, 1H), 3.52-3.45 (m, 3H), 3.26-3.17 (m, 2H), 3.19-3.03 (m, 2H), 2.84-2.76 (m, 1H), 2.59 (s, 1H), 2.48 (s, 3H), 1.26-1.18 (m, 3H), 0.92-0.66 (m, 4H), 0.50-0.45 (m, 6H), 0.37-0.11 (m, 7H)。MS (ESI, m/e) $[M+1]^+$ 632.4。保留时间(制备型 HPLC): 9.4 min。
293		N-((2S)-1,1-二环丙基-3-氧代-3-((2-(((S)-2-氧代-4-(三氟甲基)咪唑烷-1-基)甲基)-2,3-二氢苯并呋喃-5-基)氨基)丙-2-基)-4-甲基-1,2,5-噁二唑-3-甲酰胺	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.00 (d, J = 8.8 Hz, 1H), 9.01-8.96 (m, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 7.24 (t, J = 8.4 Hz, 1H), 6.70 (t, J = 8.8 Hz, 1H), 4.98-4.80 (m, 2H), 4.42-4.30 (m, 1H), 3.79-3.65 (m, 1H), 3.59-3.37 (m, 2H), 3.32-3.15 (m, 2H), 2.95-2.85 (m, 1H), 2.42 (s, 3H), 0.90-0.68 (m, 3H), 0.49-0.12 (m, 8H)。MS (ESI, m/e) $[M+1]^+$ 563.4。

[0802] 

[0803] 生物测定：

[0804] 利用本文所述的测定来确定本公开的化合物的生物活性。值可以根据每日测定性能而波动，这种波动是本领域技术人员已知的。这些结果显示本公开的化合物能够抑制IL-

17A的生物作用。

[0805] 人IL-17A生物化学测定

[0806] 在基于均相时间分辨荧光的测定中,测试了本文公开的化合物用其受体人IL-17RA (Cat:CI53,新蛋白)阻断人IL-17A(Cat:C774,新蛋白)蛋白。在室温下,在含有20mM HEPES,pH 7.5、50mM NaCl、0.1% BSA、0.2mM DTT、0.005% Tween20的测定缓冲液中,将0.4nM重组人IL-17A蛋白与本文公开的化合物的系列稀释液(最大浓度为10uM,2.7倍系列稀释,10个点)一起预温育3小时。然后将0.3nM重组人IL-17RA添加到板中并在室温下进一步温育1小时。此后,将Mab抗-6His Tb穴状化合物Gold(Cat:61HI2TLB,Cisbio Bioassays)和MAb抗人IgG-XL665(Cat:61HFCXLB,Cisbio Bioassays)添加到板中并在室温下进一步温育1小时。在BMG PHERAstar FSX仪器上读取HTRF信号(ex337 nm,em620 nm/665nm)。基于620nm处的荧光与665nm处的荧光的比率计算在递增浓度的化合物存在下人IL-17A与其受体人IL-17RA的相互作用的抑制百分比。通过Dotmatics将数据拟合到四参数逻辑方程,得到每种化合物的IC50。

[0807] 人结肠直肠腺癌上皮细胞中的GROα释放测定

[0808] 该测定的目的是测试化合物中和IL17A蛋白的能力。IL17可刺激人上皮细胞分泌GROα。在这个测定中测试本发明的一种化合物中和IL-17诱导的人结肠直肠腺癌上皮细胞系HT-29的GROα分泌的能力。

[0809] 用最终浓度为10ng/mL的IL-17A (Novoprotein,#C774)刺激HT-29细胞(人结肠直肠腺癌上皮细胞,ATCC)。使用来自Invitrogen的ELISA试剂盒(#88-52122)测量所得GROα应答。HT-29细胞在完全培养基(McCoy's 5A培养基+10% FBS)中培养并使用标准技术维持在组织培养瓶中。在第1天,使用TrypLE(Gibco,#12605036)分离细胞并用完全培养基中和。将细胞以11,00rmp离心4分钟。将细胞沉淀重悬于完全培养基中并将50,000个HT-29细胞以每孔135μL完全培养基接种到96孔测定板(Corning,3599)中。将细胞在37℃/5%CO_2下温育过夜以粘附板。在第2天,制备测试化合物在DMSO中的4倍连续稀释液。化合物的最高浓度为10μM。将2μL系列稀释的化合物从系列稀释板转移到试剂板中,该试剂板含有198μL每孔具有100ng/mL IL-17A的完全培养基。将化合物与IL-17A一起温育15分钟。将来自试剂板的15μL混合物转移到细胞测定板中。将板在37℃/5% CO_2下温育48小时。在温育后,在第4天,用GROαELISA作为制造商的说明书测量GROα水平。从测定板到ELISA板收集50μL上清液。在酶标仪上在450nm下读取ELISA板并与标准校准曲线比较。

[0810] 使用GraphPad Prism处理数据。由标准曲线计算GROα浓度。使用方程对数浓度(抑制剂)对应答测定IC50并拟合至四个参数。

[0811]

EX	生物化学测定	细胞测定	EX	生物化学测定	细胞测定
	IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)		IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)
1	378.7	897.5	149	92	44.3
2	1,100	2,565	150	20	46.5
3	3,190	8,434	151	31	99.6
4	>10,000		152	10	31.0
5	410	352.7	153	95	258.2
6	17,000		154	28	71.4
7	51,000		155	129	210.9
8	>10,000		156	68.3	305.3
9	8,000	>10,000	157	37	398.3
10	19,000		158	123.1	48.5
11	1,700	6,522	159	53.2	186.7
12	13,000	>10,000	160	110.5	93.1
13	1,800	1,495	161	120.7	145.5

[0812]

EX	生物化学测定	细胞测定	EX	生物化学测定	细胞测定
	IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)		IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)
14	150	300.3	162	539.9	1,063
15	550	1,235	163	19.0	38.8
16	5,000		164	35.2	111.8
17	2,500	2,636	165	173.4	322.2
18	1,000	2,553	166	168.8	135
19	60	262.3	167	127	219.6
20	980	475.6	168	32.8	60.5
21	2,400		169	56.4	65.2
22	950	7,117	170	168.6	226.7
23	640	3,662	171	7.0	9.7
24	2,342		172	400.3	376.9
25	6,300		173		153.1
26	360	1,082	174	264	485.1
27	160	981.5	175	22.4	10.1
28	394	76.5	176	69.9	290.3
29	160	146.5	177	53.3	59.4
30	58	576.3	178	3,654	2,207
31	203	115.8	179	10.9	51.6
32	62	135.3	180	3,681	
33	2,036		181	192.6	153.9
34	8,400		182	26.9	52.9
35	293	2,023	183	767.7	370.4
36	2,429		184	150.9	57.3
37	112	1,483	185	118.8	275.2
38	46	155.6	186	6.3	15.1
39	22.6	56.4	187	248.6	245.7
40	25	143.2	188	44.9	450.1
41	100	494.8	189	15.3	124.5
42	3,171		190	87.1	139.3
43	1,464	2,382	191	76.9	168.4
44	47	231.3	192	1,665	1,242
45	5,126		193	50.7	140.2
46	260	532.6	194	33.8	21.0

[0813]

EX	生物化学测定	细胞测定	EX	生物化学测定	细胞测定
	IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)		IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)
47	11	11.6	195	128.4	383.4
48	161	1,270	196	19.8	58.5
49	1,806		197	80.6	397
50	1,583		198	1,127	316.5
51	686	2,050	199	570.4	2,772
52	1,307		200	31.2	107.1
53	223	734.8	201	6.5	39.5
54	24	136.7	202	346	518.9
55	1,052	1,824	203	63.9	135.2
56	20	23.7	204	405.8	2,240
57	334	2,148	205	246.4	193.1
58	595	1,441	206	269.7	32.5
59	93	34.5	207	347.2	860.8
60	2,012		208	717.9	2,170
61	857	4,962	209	1,065	2,179
62	24	211.6	210	91.6	294.5
63	85	325.7	211	465	3,685
64	1,816		212	686.6	1,032
65	713	2,028	213	1,762	4,518
66	2,124		214	37.3	101.8
67	70	365	215	33.6	133.8
68	30	37.0	216	23.3	58.9
69	120	432.3	217	62.5	394
70	26	70.6	218	141.1	385.4
71	21	217.4	219	106.8	297.1
72	3,627		220	169	80.6
73	391		221	47.8	111.4
74	32	341.8	222	34.3	66.6
75	33	186.3	223	118	606.5
76	90	736	224	47.8	85.1
77	490		225	1,272	2,320
78	532		226	50.4	225.3
79	79	1,301	227	112	167.7

[0814]

EX	生物化学测定	细胞测定	EX	生物化学测定	细胞测定
	IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)		IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)
80	157	971.1	228	15.9	49.1
81	75	701.6	229	28.6	85.1
82	32	156.2	230	4,458	9,470
83	22	189.5	231	1,078	1,970
84	37	94.4	232	117.1	158
85	10,076		233	77.8	90.1
86	22	23.5	234	339.9	207
87	36	352.5	235	229.3	214
88	2,059		236	244.8	537.3
89	18	29.7	237	27.1	53.3
90	37	48.6	238	221.9	137
91	71	43.0	239	977.4	3,213
92	3,038		240	200.4	263.9
93	830		241	2,917	5,799
94	40	118	242	250.3	651.6
95	4,232		243	290	316.6
96	2,315		244	2,126	1,574
97	535	1,859	245	52.4	92.5
98	628	3,279	246	257.2	1,222
99	278	2,477	247	20.9	40.8
100	886	2,563	248	126.5	427
101	7.5	45.2	249	226	695.1
102	9.5	17.3	250	75.9	190
103	2,698			>10,000	
104	12	23.6		139.9	271.2
105	15	55.5	251	1,514	1,510
106	48	202.4	252	828.9	1,165
107	25	34.5	253	355	330.6
108	5.8	42.3	254	178.1	318.4
109	3,453		255	165	665.8
110	15	76.5	256	50.2	82.0
111	55	111.5	257	938	2,503
112	41	180.7	258	107.9	208.6

[0815]

EX	生物化学测定	细胞测定	EX	生物化学测定	细胞测定
	IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)		IL-17A/IL-17RA IC50 (nM)	HT29 细胞 /CXCL1 IC50 (nM)
113	53	456.6	259	1,020	1,973
114	73.9	57.2	260	>10,000	
115	258	72.4	261	58	143.4
116	69.1	415.2	262	99.4	446.7
117	924.9	1,063	263	97.1	447.4
118	192	581.2	264	2,540	
119	73	143.6	265	8,070	
120	19	72.4	266	912	658.8
121	16	32.3	267	>10,000	
122	10	13.0	268	88.1	248.1
123	441	61.6	269	416	1,068
124	19	32.5	270	200	350.3
125	5.6	25.8	271	268	1,385
126	72	3,955	272	295	650.3
127	698		273	34.7	66.1
128	89.8	277	274	42.4	67.6
129	44	119.2	275	61.3	133.4
130	19	59.6	276	573	1,464
131	5.5	14.9	277	560	1,284
132	66	177.9	278	333	122.5
133	320		279	64.8	69.1
134	311		280	17.3	48.1
135	186	244.8	281	16.5	67.4
136	108	279.1	282	33.7	95.3
137	413	1,490	283	32.5	34.6
138	53.1	101	284	268.5	353.6
139	10.0	21.9	285	71.4	90.2
140	277		286	143.6	429.9
141	16	41.1	287	61.5	221.8
142	107	197.2	288	109.6	408.4
143	163	771.5	289	24.5	81.4
144	48.6	181.7	290 异构体 1	18.6	60.3
145	139	454.1	290 异构体 2	641.3	271.3
146	203.6	767.7	291	1,552	1,060
147	22.4	61.8	292 异构体 1	287.3	206
148	62	163.8	292 异构体 2	212.8	495.5
			293	> 10,000	

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