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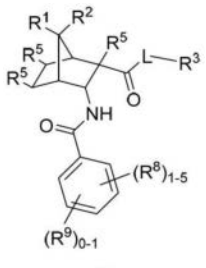
(54)发明名称

RXFP1激动剂

(57)摘要

本发明涉及RXFP1受体激动剂的式(I)化合物;含有所述化合物的组合物;及使用所述化合物的方法,例如用于治疗心脏衰竭、纤维变性疾病及相关疾病,诸如肺病(例如特发性肺纤维化)、肾病(例如慢性肾病)或肝病(例如非酒精性脂肪变性肝炎及门静脉高血压)的方法。



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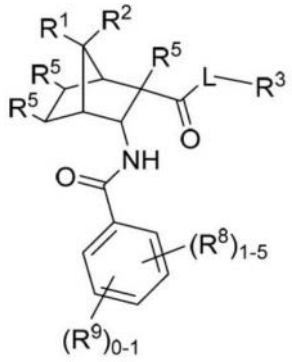
1.一种式(I)化合物：



(I)

或其药学上可接受的盐,其中：

L为-O-或-NH-；

R^1为经0至1个芳基或C_{3-6}环烷基取代基取代的C_{1-3}烷基；

R^2为H;其限制条件为,当R^1为经0个芳基或C_{3-6}环烷基取代的C_{1-3}烷基时,R^9不存在；

或R^1及R^2组合为=CR^6R^7或=NOC_{1-4}烷基,其中“=”为双键；

或R^1及R^2与该两者所连接的碳原子一起形成经0至1芳基取代基取代的二氧戊环基；

R^3为经0至5个卤基、CN、-OH或-OC_{1-3}烷基取代基取代的C_{1-8}烷基、经0至5个R^4取代的-$(CR^dR^d)_n$-C_{3-10}碳环基或包含1至4个选自O、S(=O)$_p$、N及NR^{4c}的杂原子且经0至5个R^4取代的-$(CR^dR^d)_n$-3元至12元杂环基；

R^4为卤基、CN、-OH、SF_5、-S(=O)$_p$$R^c$、经0至5个卤基、-OH或-$OC_{1-4}$烷基取代基取代的$C_{1-4}$烷基、经0至5个卤基取代基取代的-$OC_{1-4}$烷基、经0至5个$R^e$取代的-$(CR^dR^d)_n$-$C_{3-10}$碳环基或包含1至4个选自O、S(=O)$_p$、N及$NR^{4c}$的杂原子且经0至5个$R^e$取代的-$(CR^dR^d)_n$-4元至6元杂环基；

R^{4c}为H、C_{1-4}烷基或-S(=O)$_2$$CF_3$；

各R^5为H、卤基、-OH、经0至5个卤基取代基取代的C_{1-4}烷基、或经0至5个卤基取代基取代的-OC_{1-4}烷基；

R^6为H、卤基、CN、经0至3个R^{6a}取代的C_{1-7}烷基、经0至3个R^{6a}取代的C_{2-7}烯基、经0至3个R^{6a}取代的C_{2-7}炔基、-C(=O)OR^{6b}、-C(=O)N$R^{6b}R^{6b}$、经0至5个R^{14}取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$、N或NR^{14a}的杂原子且经0至5个R^{14}取代的3元至12元杂环基；

R^{6a}为卤基、-OH、-OC_{1-4}烷基、C_{1-4}烷基、芳基、或经0至4个卤基取代基取代的C_{3-6}环烷基；

R^{6b}为H、经0至1个芳基取代基取代的C_{1-4}烷基、或经0至4个卤基取代基取代的C_{3-6}环烷基；

R^7为H或C_{1-4}烷基；

或R^6及R^7与该两者所连接的碳原子一起形成环戊二烯基、二氢茚基或茚基；

R^8为H、卤基、CN、-NR^7R^7、经0至5个卤基或-OH取代基取代的C_{1-4}烷基、或经0至5个卤基取代的-OC_{1-4}烷基、-OH、C_{3-6}环烷基、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至9元杂环基、或经0至1个-OC_{1-3}烷基取代基取代的-OC_{1-4}烷基；

R^9为经0至3个R^{10}及0至2个R^{11}取代的芳基、或包含1至5个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至2个R^{11}取代的3元至12元杂环基；

R^{10}为卤基、CN、C_{1-4}烷基、=O、-OH或-OC_{1-4}烷基；

R^{11}为经0至4个R^{12}及0至2个R^{13}取代的C_{1-4}烷基、-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aC(=O)NR^aR^a$、-$NR^aS(=O)_pR^c$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aS(=O)_pR^c$、-$OC(=O)R^b$、-$S(=O)_pR^c$、-$S(=O)_pNR^aR^a$、经0至5个R^e取代的C_{3-6}碳环基、或包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^{11a}为H、经0至4个R^{11b}取代的C_{1-5}烷基、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、经0至5个R^e取代的C_{3-6}环烷基、经0至5个R^e取代的芳基、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至6元杂环基;

R^{11b}为卤基、-OH、-$C(=O)OH$、-$C(=O)OC_{1-4}$烷基或芳基;

R^{12}为卤基、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基、或C_{3-6}环烷基;

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aC(=O)NR^aR^a$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-$OC(=O)NR^aR^a$、-$OC(=O)NR^aOR^b$、-$S(=O)_pNR^aR^a$、-$S(=O)_pR^c$、经0至3个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_n$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_n$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^{14a}为H、$C(=O)C_{1-4}$烷基或经以下取代的C_{1-3}烷基:0至3个$Si(C_{1-3}$烷基$)_3$或经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-4}烷基或芳基;

R^a为H、-OC_{1-6}烷基、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^c为经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的C_{3-6}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^d为H、C_{1-4}烷基或C_{3-6}环烷基;

R^e为卤基、CN、NO_2、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、经0至5个R^g取代的-$(CH_2)_n$-C_{3-10}碳环基、包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^g取代的-$(CH_2)_n$-3元至12元杂环基、-$(CH_2)_nOR^f$、-$C(=O)OR^f$、-$C(=O)NR^fR^f$、-$NR^fC(=O)R^f$、-$S(=O)_pR^f$、-$S(=O)_pNR^fR^f$、-$NR^fS(=O)_pR^f$、-$NR^fC(=O)OR^f$、-$OC(=O)NR^fR^f$或-$(CH_2)_nNR^fR^f$;

R^f为H、经0至2个-OH或-OC_{1-4}烷基取代基取代的C_{1-6}烷基、C_{3-6}环烷基、芳基、或包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至12元杂环基;或R^f及R^f与该两者所连接的氮原子一起形成包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至12元杂环基;

R^g为卤基、CN、-OH、C_{1-6}烷基、C_{3-6}环烷基或芳基；

n为0、1、2或3；及

p为0、1或2。

2.根据权利要求1的化合物或其药学上可接受的盐，其中：

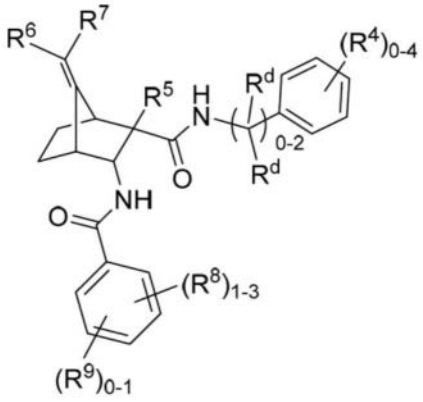
R^3为经0至4个卤基或-OH取代基取代的C_{1-6}烷基、经0至4个R^4取代的-$(CHR^d)_{0-1}$-C_{3-6}环烷基、经0至4个R^4取代的C_{6-9}螺环烷基、经0至4个R^4取代的C_{6-10}双环碳环基、或包含1至2个选自O、S(=O)$_p$、N及NR^{4c}的杂原子且经0至4个R^4取代的3元至6元杂环基；及

R^4为卤基或经0至4个卤基取代基取代的C_{1-3}烷基；

R^{4c}为H或C_{1-4}烷基；及

R^d为C_{1-3}烷基。

3.根据权利要求1的化合物，其具有式(II)：



(II)

或其药学上可接受的盐，其中：

R^4为卤基、经0至4个卤基取代基取代的-S(=O)$_p$$C_{1-4}$烷基、经0至4个卤基取代基取代的$C_{1-4}$烷基、或经0至4个卤基取代基取代的-O$C_{1-4}$烷基；

R^5为H或卤基；

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-7}烷基、经0至3个R^{6a}取代的C_{2-7}烯基、经0至3个R^{6a}取代的C_{2-7}炔基、C(=O)OR^{6b}、-C(=O)N$R^{6b}R^{6b}$、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的芳基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的4元至6元杂环基；

R^{6a}为卤基、-OH、C_{3-6}环烷基或芳基；

R^{6b}为H、经0至1个芳基取代基取代的C_{1-4}烷基、或经0至4个卤基取代基取代的C_{3-6}环烷基；

R^7为H或C_{1-3}烷基；

R^8为卤基、CN、-N(C_{1-2}烷基)$_2$、经0至5个卤基或-OH取代基取代的C_{1-4}烷基、或经0至4个卤基、-OH、芳基或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基；

R^9为经0至3个R^{10}及0至2个R^{11}取代的芳基、或包含1至4个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至1个R^{11}取代的3元至12元杂环基；

R^{10}为卤基、CN、C_{1-4}烷基、=O、-OH或-OC_{1-4}烷基；

R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-4}烷基、-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)

OR^b、$-NR^aC(=O)NR^aR^a$、$-NR^aS(=O)_pR^c$、$-C(=O)R^b$、$-C(=O)OR^b$、$-C(=O)NR^aR^a$、$-C(=O)NR^aS(=O)_pR^c$、$-OC(=O)R^b$、$-S(=O)_pR^c$、$-S(=O)_pNR^aR^a$、经0至5个R^e取代的C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至12元杂环基;

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基、$-C(=O)R^b$、$-C(=O)OR^b$、$-C(=O)NR^aR^a$、经0至5个R^e取代的C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至6元杂环基;

R^{11b}为-OH、-C(=O)OH或芳基;

R^{12}为卤基、$-C(=O)OR^b$、$-C(=O)NHR^a$、$-C(=O)NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为$-OR^b$、$-NR^aR^a$、$-NR^aC(=O)R^b$、$-NR^aC(=O)OR^b$、$-NR^aS(=O)_pR^c$、$-NR^aS(=O)_pNR^aR^a$、$-OC(=O)NR^aR^a$、$-OC(=O)NR^aOR^b$、$-S(=O)_pNR^aR^a$或$-S(=O)_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的$-OC_{1-4}$烷基、$-(CH_2)_{0-3}-NR^aR^a$、经0至3个R^e取代的$-(CH_2)_{0-3}-$芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的$-(CH_2)_{0-2}-$3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-4}烷基或经以下取代的C_{1-3}烷基:0至3个经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-3}烷基或芳基;

R^a为H、经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的$-(CH_2)_n-C_{3-10}$碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的$-(CH_2)_n-$3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的$-(CH_2)_n-C_{3-10}$碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的$-(CH_2)_n-$3元至12元杂环基;

R^c为经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^d为H或C_{1-4}烷基;

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、经0至4个R^g取代的$-(CH_2)_n-C_{3-6}$环烷基、经0至4个R^g取代的$-(CH_2)_n-$芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^g取代的$-(CH_2)_n-$4元至6元杂环基、$-(CH_2)_nOR^f$、$-C(=O)OR^f$、$-C(=O)NR^fR^f$、$-NR^fC(=O)R^f$、$-S(=O)_pR^f$、$-NR^fC(=O)OR^f$、$-OC(=O)NR^fR^f$或$-(CH_2)_nNR^fR^f$;

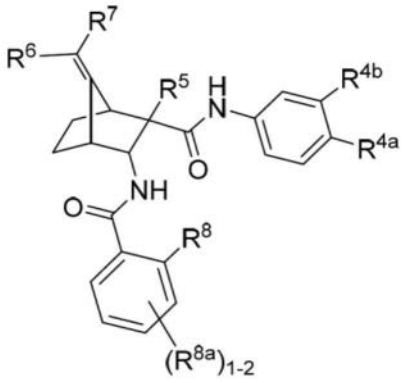
R^f为H、C_{1-5}烷基、C_{3-6}环烷基或芳基;或R^f及R^f与该两者所连接的氮原子一起形成杂环基;

R^g为卤基、CN、-OH、C_{1-5}烷基、C_{3-6}环烷基或芳基;

n为0、1、2或3;及

p为0、1或2。

4.根据权利要求1的化合物,其具有式(III):



(III)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基;

R^5为H或F;

R^6为卤基、经0至3个R^{6a}取代的C_{1-4}烷基、经0至1个苯基或-OH取代基取代的C_{2-4}烯基、-C(=O)OR^{6b}、C(=O)NHR^{6b}、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、萘基、或包含1至3个选自O、S、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂环基;

R^{6a}为卤基、-OH、C_{3-6}环烷基或苯基;

R^{6b}为H或C_{1-4}烷基;

R^7为H或C_{1-3}烷基;

或R^6及R^7与该两者所连接的碳原子一起形成环戊二烯基、二氢茚基或茚基;

R^8为-N(C_{1-4}烷基)$_2$或经0至1个-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基;

R^{8a}为卤基;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-3}烷基或经以下取代的C_{1-3}烷基:0至3个经0至2个卤基取代基取代的芳基;

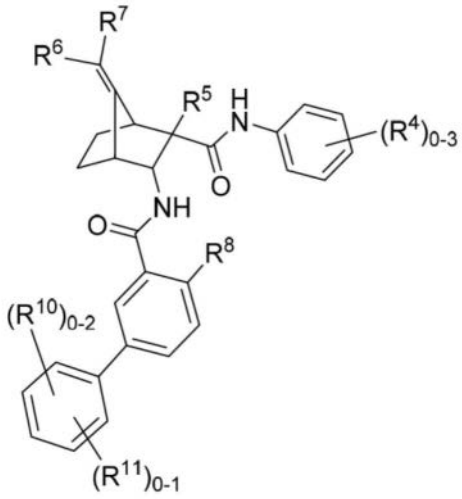
R^a为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的-$(CH_2)_n$-苯基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的-$(CH_2)_{0-1}$-苯基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^e为卤基、CN、NO_2、=O、C_{1-6}烷基或C(=O)OH;及

n为0、1、2或3。

5.根据权利要求3的化合物,其具有式(IV):



(IV)

或其药学上可接受的盐,其中:

R^4为卤基、经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的-OC_{1-4}烷基;

R^5为H或F;

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-6}烷基、经0至3个R^{6a}取代的C_{2-6}烯基、经0至3个R^{6a}取代的C_{2-6}炔基、-C(=O)OR^{6b}、C(=O)$NR^{6b}R^{6b}$、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基;

R^{6a}为卤基、C_{3-6}环烷基或苯基;

R^{6b}为H、经0至1个芳基取代基取代的C_{1-3}烷基、或经0至4个卤基取代基取代的C_{3-6}环烷基;

R^7为H或C_{1-2}烷基;

R^8为经0至4个卤基、-OH、芳基或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基;

R^{10}为卤基、CN、C_{1-3}烷基、-OH或-OC_{1-4}烷基;

R^{11}为经0至2个R^{12}及0至1个R^{13}取代的C_{1-4}烷基、-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)NR^aR^a、-NR^aS(=O)$_pR^c$、-C(=O)R^b、-C(=O)OR^b、-C(=O)NR^aR^a、-C(=O)NR^aS(=O)$_pR^c$、-OC(=O)R^b、-S(=O)$_pR^c$、-S(=O)$_pNR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至9元杂环基;

R^{12}为卤基、-C(=O)OR^b、-C(=O)NHR^a、-C(=O)$NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aS(=O)$_pR^c$、-NR^aS(=O)$_pNR^aR^a$、-OC(=O)NR^aR^a、-OC(=O)NR^aOR^b、-S(=O)$_pNR^aR^a$或-S(=O)$_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-3}烷基、经以下取代的C_{1-3}烷基:0至2个经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-2}烷基或苯基；

R^a为H、经0至4取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基；或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基；

R^b为H、经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基；

R^c为经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至12元杂环基；

R^e为卤基、CN、NO_2、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、-$(CH_2)_n$-C_{3-6}环烷基、-$(CH_2)_n$-芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的-$(CH_2)_n$-4元至6元杂环基、-$(CH_2)_n$$OR^f$、S(=O)$_p$$R^f$、C(=O)$NR^fR^f$、C(=O)$OR^f$、$NR^fC$(=O)$R^f$、S(=O)$_p$$NR^fR^f$、$NR^fS$(=O)$_p$$R^f$、$NR^fC$(=O)$OR^f$、OC(=O)$NR^fR^f$或-$(CH_2)_n$$NR^fR^f$；

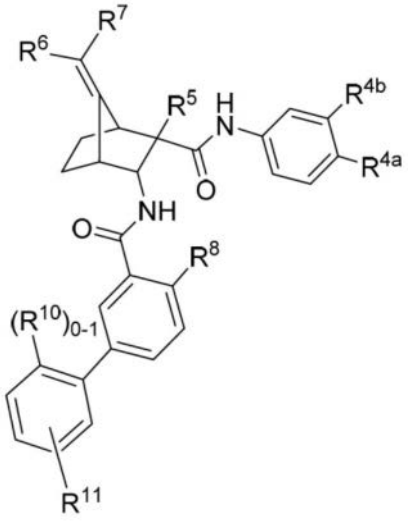
R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基；或R^f及R^f与该两者所连接的氮原子一起形成杂环基；

R^g为卤基、CN、-OH、C_{1-5}烷基、C_{3-6}环烷基或芳基；

n为0、1、2或3；及

p为0、1或2。

6.根据权利要求5的化合物，其具有式(V)：



(V)

或其药学上可接受的盐，其中：

R^{4a}为卤基或C_{1-2}烷基；

R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基；

R^5为H或F；

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-4}烷基、经0至3个R^{6a}取代的C_{2-4}烯基、-C(=O)OR^{6b}、C(=O)$NR^{6b}R^{6b}$、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、

$S(=O)_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基；

R^{6a}为卤基、-OH、C_{3-6}环烷基或苯基；

R^{6b}为H、经0至1个芳基取代基取代的C_{1-3}烷基或C_{3-6}环烷基；

R^7为H或C_{1-2}烷基；

R^8为经0至4个卤基、-OH、$-OC_{1-4}$烷基或芳基取代基取代的$-OC_{1-4}$烷基；

R^{10}为卤基或C_{1-3}烷基；

R^{11}为经0至2个R^{12}及0至1个R^{13}取代的C_{1-4}烷基、-OH、$-OC_{1-4}$烷基、$-NR^aC(=O)R^b$、$-NR^aC(=O)NR^aR^a$、$-NR^aS(=O)_pR^c$、$-C(=O)R^b$、$-C(=O)OR^b$、$-C(=O)NR^aR^a$、$-C(=O)NR^aS(=O)_pR^c$、$-OC(=O)R^b$、$-S(=O)_pR^c$、$-S(=O)_pNR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至3个R^e取代的4元至9元杂环基；

R^{12}为卤基、$-C(=O)OR^b$、$-C(=O)NHR^a$、$-C(=O)NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基；

R^{13}为$-OR^b$、$-NR^aR^a$、$-NR^aC(=O)R^b$、$-NR^aC(=O)OR^b$、$-NR^aS(=O)_pR^c$、$-NR^aS(=O)_pNR^aR^a$、$-OC(=O)NR^aR^a$或$-OC(=O)NR^aOR^b$；

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的$-OC_{1-4}$烷基、$-(CH_2)_{0-2}-NR^aR^a$、经0至3个R^e取代的$-(CH_2)_{0-1}-$芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至3个R^e取代的$-(CH_2)_{0-1}-$3元至9元杂环基；

R^{14a}为H、$C(=O)C_{1-3}$烷基、经以下取代的C_{1-3}烷基：0至1个经0至2个卤基取代基取代的芳基；

R^{15}为H、C_{1-2}烷基或苯基；

R^a为H、经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、经0至5个R^e取代的$-(CH_2)_n-C_{3-10}$碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的$-(CH_2)_n-$3元至12元杂环基；或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的3元至9元杂环基；

R^b为H、经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、经0至5个R^e取代的$-(CH_2)_n-C_{3-10}$碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的$-(CH_2)_n-$3元至12元杂环基；

R^c为经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、C_{3-6}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至9元杂环基；

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、$-(CH_2)_n-C_{3-6}$环烷基、$-(CH_2)_n-$芳基、包含1至4个选自O、$S(=O)_p$及N的杂原子的$-(CH_2)_n-$4元至6元杂环基、$-(CH_2)_nOR^f$、$S(=O)_pR^f$、$C(=O)NR^fR^f$、$C(=O)OR^f$、$NR^fC(=O)R^f$、$S(=O)_pNR^fR^f$、$NR^fS(=O)_pR^f$、$NR^fC(=O)OR^f$、$OC(=O)NR^fR^f$或$-(CH_2)_nNR^fR^f$；

R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基；或R^f及R^f与该两者所连接的氮原子一起形成杂环基；

R^g为卤基、CN、-OH、C_{1-6}烷基、C_{3-6}环烷基或芳基；

n为0、1、2或3；及

p为0、1或2。

7.根据权利要求6的化合物或其药学上可接受的盐，其中：

R^{4a}为卤基;

R^{4b}为CF_3;

R^6为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的C_{3-6}环烷基;

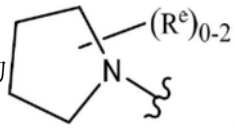
R^8为-OC_{1-4}烷基;

R^{10}为F;

R^{11}为-OH、-OC_{1-4}烷基、-$NR^aC(=O)R^b$、-$NR^aS(=O)_pR^c$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aS(=O)_pR^c$、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至9元杂环基;

R^{15}为H或C_{1-2}烷基;

R^a为H或经0至5个R^e取代的C_{1-4}烷基,

或R^a及R^a一起为  ;

R^b为H或经0至5个R^e取代的C_{1-4}烷基;

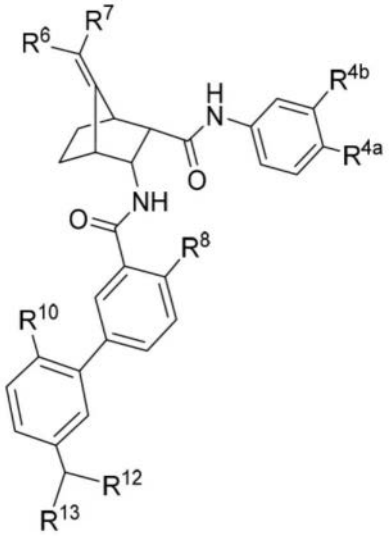
R^c为经0至5个R^e取代的C_{1-3}烷基或C_{3-6}碳环基;

R^e为卤基、=O、经0至5个R^g取代的C_{1-4}烷基、C(=O)OH、-OR^f或-NR^fR^f;及

R^f为H及C_{1-6}烷基;或R^f及R^f与该两者所连接的氮原子一起形成杂环基;及

R^g为卤基。

8.根据权利要求6的化合物,其具有式(VI):



(VI)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为CF_3;

R^6为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的C_{3-6}环烷基;

R^7为H;

R^8为经0至1个芳基取代基取代的-OC_{1-4}烷基;

R^{10}为卤基;

R^{12}为-C(=O)OH、-C(=O)OC_{1-4}烷基、-C(=O)NHC_{1-4}烷基、-C(=O)$NHOC_{1-3}$烷基、或经0至3个卤基取代基取代的C_{1-3}烷基;

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-OC(=O)NR^aR^a或-OC(=O)NR^aOR^b;

R^a为H、经0至5个卤基取代基取代的C_{1-4}烷基、经0至4个R^e取代的苯基、经0至4个R^e取代的C_{3-10}环烷基、经0至4个R^e取代的螺环烷基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至9元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-4}烷基、经0至4个卤基取代基取代的-$(CH_2)_n$-苯基、经0至4个卤基取代基取代的C_{3-6}环烷基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^c为经0至4个R^e取代的C_{1-4}烷基,

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-5}烷基、C_{3-6}环烷基、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至6元杂环基、或-OR^f;

R^f为H、C_{1-4}烷基、C_{3-6}环烷基或芳基;

R^g为卤基;

n为0或1;及

p为0、1或2。

9.根据权利要求8的化合物或其药学上可接受的盐,其中:

R^{4a}为F

R^{4b}为CF_3;

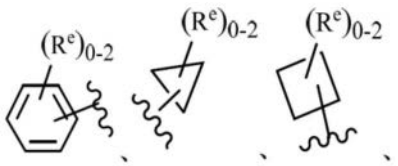
R^6为CF_3或C_{3-6}环烷基;

R^8为-OCH_3或-OCH_2-苯基;

R^{10}为F;

R^{12}为-C(=O)OH、-C(=O)OC_{1-4}烷基、-C(=O)NHC_{1-4}烷基、-C(=O)$NHOC_{1-3}$烷基、CH_3、CHF_2或CF_3;

R^{13}为-OH、-NR^aR^a、-NHC(=O)R^b、-NHS(=O)$_pC_{1-4}$烷基、-OC(=O)NR^aR^a或-OC(=O)$NHOC_{1-4}$烷基;

R^a为H、经0至4个F取代基取代的C_{1-4}烷基、 

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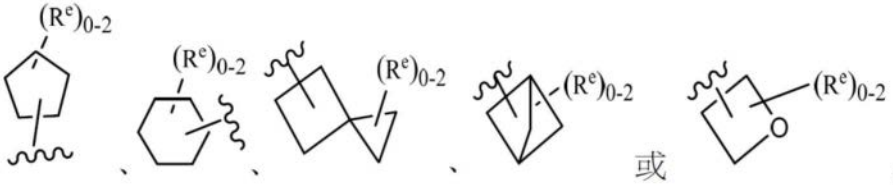
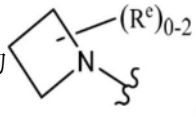
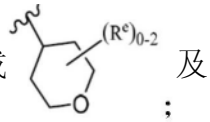


、、、或;

或R^a及R^a一起为 

,

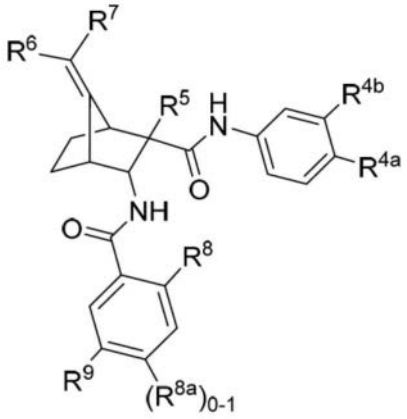
R^b为H、经0至5个R^e取代的C_{1-4}烷基、苯基，或  及

；

R^e为卤基、=O、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至6元杂环基或-OR^f；及

R^f为H、C_{1-3}烷基、C_{3-6}环烷基或苯基。

10.根据权利要求3的化合物，其具有式(VII)：



(VII)

或其药学上可接受的盐，其中：

R^{4a}为卤基；

R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的-OC_{1-4}烷基；

R^5为H或F；

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-6}烷基、经0至3个R^{6a}取代的C_{2-6}烯基、经0至3个R^{6a}取代的C_{2-6}炔基、经0至3个R^{14}取代的C_{3-6}环烷基、0至3个R^{14}经取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基；

R^{6a}为卤基、C_{3-6}环烷基或苯基；

R^7为H或C_{1-2}烷基；

R^8为卤基、CN或经0至4个卤基、-OH或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基；

R^{8a}为卤基或CN；

R^9为包含1至4个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至1个R^{11}取代的3元至12元杂环基；

R^{10}为卤基、CN、C_{1-3}烷基、=O、-OH或-OC_{1-3}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aC(=O)NR^aR^a$、-$NR^aS(=O)_pR^c$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aS(=O)_pR^c$、-$OC(=O)R^b$、-$S(=O)_pR^c$、-$S(=O)_pNR^aR^a$、经0至5个R^e取代的C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至6元杂环基；

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至6元杂环基；

R^{11b}为-OH、-C(=O)OH或芳基；

R^{12}为-C(=O)OR^b、-C(=O)NHR^a、-C(=O)$NHOR^b$或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aS(=O)$_pR^c$、-NR^aS(=O)$_pNR^aR^a$、-OC(=O)NR^aR^a、-S(=O)$_pNR^aR^a$或-S(=O)$_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-3}烷基或经以下取代的C_{1-3}烷基:0至2个经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-2}烷基或苯基;

R^a为H、经0至4取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^b为H、经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^c为经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至12元杂环基;

R^e为卤基、CN、=O、经0至4个R^g取代的C_{1-6}烷基、经0至4个R^g取代的C_{2-6}烯基、经0至4个R^g取代的C_{2-6}炔基、经0至4个R^g取代的-$(CH_2)_n$-C_{3-6}环烷基、经0至4个R^g取代的-$(CH_2)_n$-芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^g取代的-$(CH_2)_n$-4元至6元杂环基、-$(CH_2)_n$$OR^f$、C(=O)$OR^f$、C(=O)$NR^fR^f$、$NR^fC$(=O)$R^f$、S(=O)$_pR^f$、$NR^fS$(=O)$_pR^f$、$NR^fC$(=O)$OR^f$、OC(=O)$NR^fR^f$或-$(CH_2)_n$$NR^fR^f$;

R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基;

R^g为卤基、CN、-OH、C_{1-4}烷基、C_{3-6}环烷基或苯基;

n为0、1、2或3;及

p为0、1或2。

11.根据权利要求10的化合物或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基;

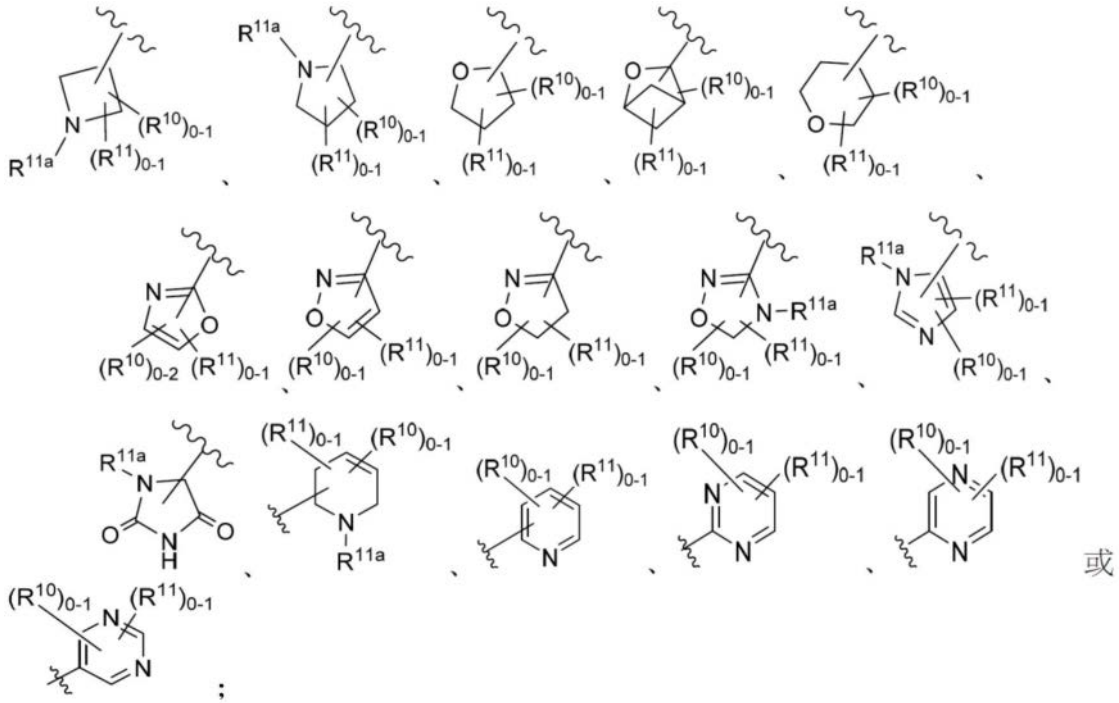
R^5为H;

R^6为经0至2个F取代基取代的C_{1-2}烷基或C_{3-6}环烷基;

R^8为-OC_{1-3}烷基;

R^{8a}为F或CN;

R^9为


或

；

R^{10}为卤基、CN、C_{1-2}烷基、=O、-OH或-OC_{1-2}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$或经0至5个R^e取代的C_{3-6}环烷基；

R^{11a}为H、-$C(=O)R^b$、-$C(=O)NR^aR^a$或经0至1个R^{11b}取代的C_{1-4}烷基；

R^{11b}为-OH或芳基；

R^{12}为-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$或经0至2个卤基或-OH取代基取代的C_{1-4}烷基；

R^{13}为-OH、经0至2个-OH取代基取代的-OC_{1-4}烷基、或-$S(=O)_2C_{1-4}$烷基；

R^a为H或C_{1-4}烷基，或R^a及R^a与该两者所连接的氮原子一起形成经0至4个R^e取代的3元至9元杂环基；

R^b为H、经0至1个R^e取代的C_{1-4}烷基或经0至1个R^e取代的C_{3-6}环烷基；

R^e为-OR^f；及

R^f为H或C_{1-4}烷基。

12.根据权利要求11的化合物或其药学上可接受的盐，其中：

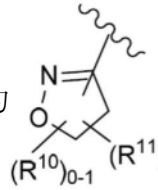
R^{4a}为卤基；

R^{4b}为CF_3；

R^5为H；

R^6为CF_3或C_{3-6}环丙基；

R^8为-OC_{1-3}烷基；

R^9为 
；

R^{10}为C_{1-2}烷基、-OH或-OC_{1-2}烷基;

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-C(=O)OR^b或-C(=O)NR^aR^a;

R^{12}为-C(=O)OR^b;

R^{13}为-OH;

R^a为H或C_{1-4}烷基;及

R^b为H或C_{1-4}烷基。

13.根据权利要求10的化合物或其药学上可接受的盐,其中:

R^{4a}为卤基;

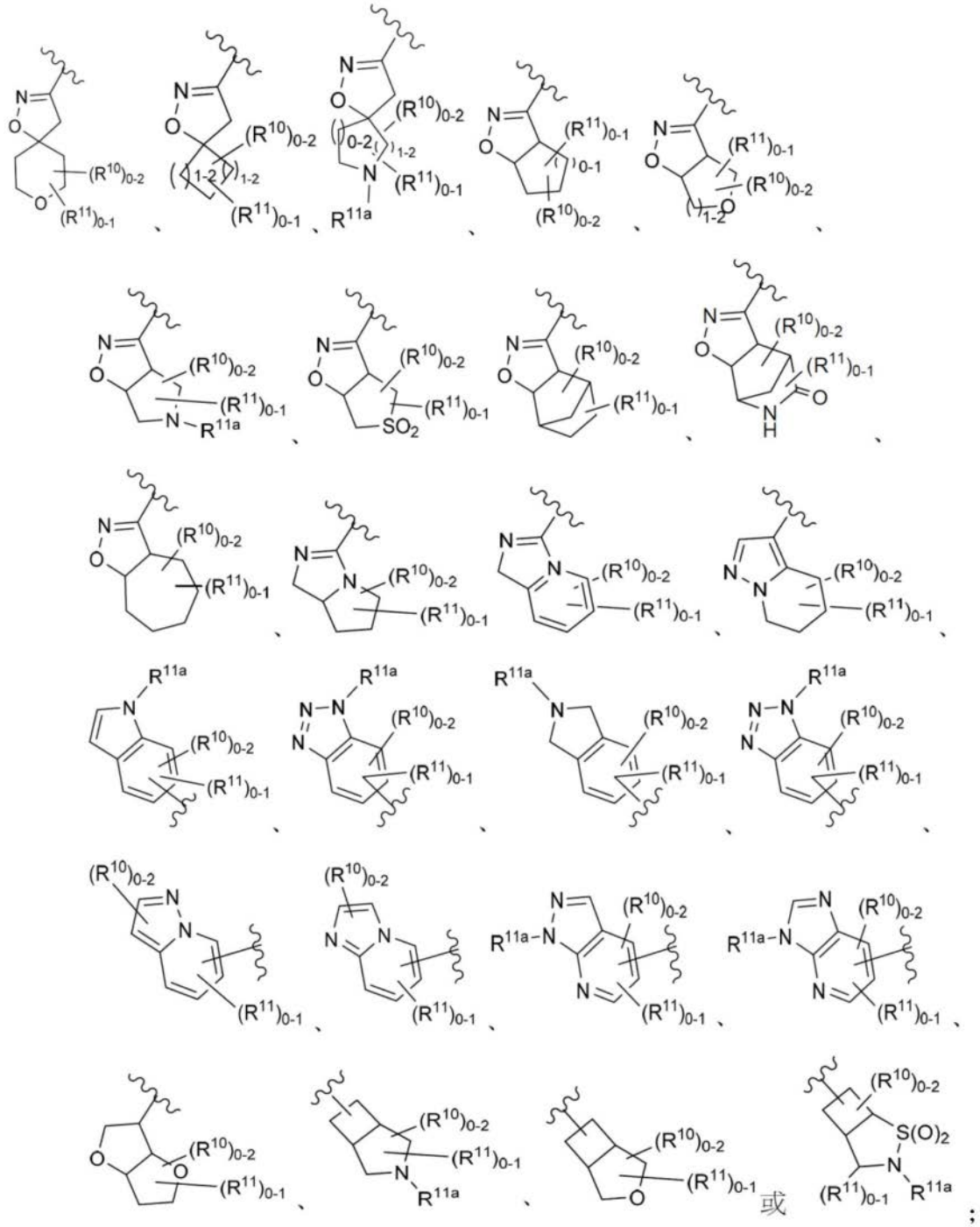
R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基;

R^5为H;

R^6为经0至3个F取代基取代的C_{1-3}烷基或C_{3-6}环烷基;

R^8为-OC_{1-3}烷基;

R^9为



R^{10}为卤基、C_{1-3}烷基、-OH或-OC_{1-3}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基；

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基或-C(=O)OC_{1-4}烷基；

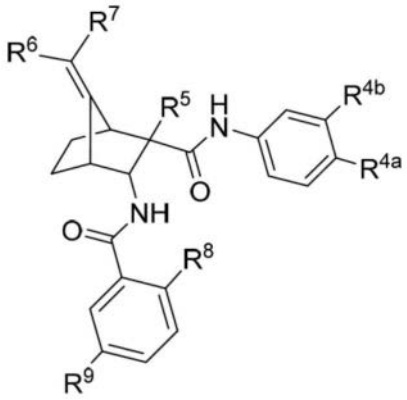
R^{11b}为-OH、-C(=O)OH或芳基；

R^{12}为-C(=O)OR^b或经0至3个卤基取代基取代的C_{1-3}烷基；

R^{13}为-OH；及

R^b为H或C_{1-4}烷基。

14.根据权利要求3的化合物，其具有式(VIII)：



(VIII)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

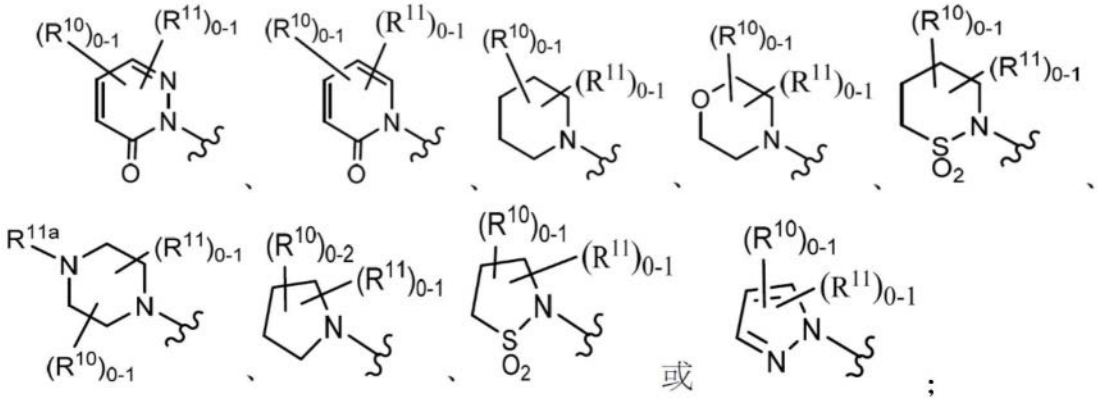
R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基;

R^{6}为经0至2个F取代基取代的C_{1-2}烷基、C_{3-6}环烷基或芳基;

R^{7}为H;

R^{8}为-OC_{1-3}烷基;

R^{9}为



或

;

R^{10}为卤基、CN、C_{1-4}烷基、=O、-OH或-OC_{1-4}烷基;

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-2}烷基、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$或-$C(=O)OR^b$;

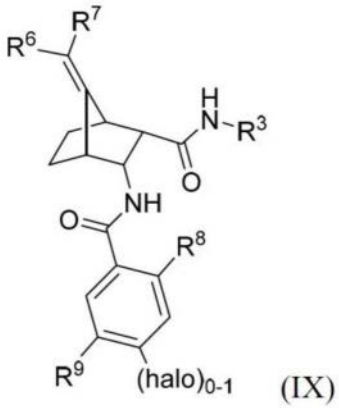
R^{12}为-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OH或-$NR^aC(=O)R^b$;

R^a为H或C_{1-4}烷基;及

R^b为H、C_{1-4}烷基、或包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至9元杂环基。

15.根据权利要求1的化合物,其具有式(IX):



(IX)

或其药学上可接受的盐,其中:

R^3为C_{1-5}烷基、CF_3、经0至4个R^4取代的-$(CR^dR^d)_{0-1}$-C_{3-6}环烷基或经0至4个R^4取代的苯基;

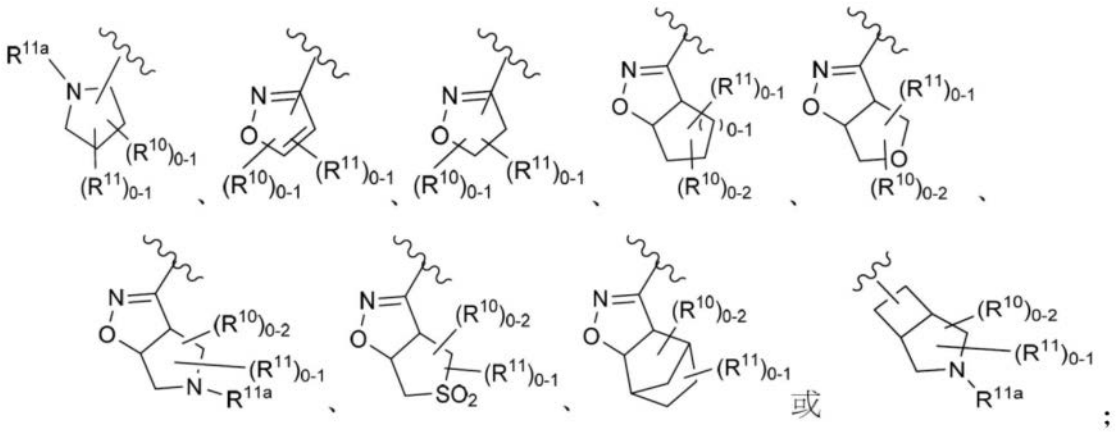
R^4为卤基、CN、CH_3或CF_3;

R^6为C_{1-6}烷基、CF_3或经0至2个F取代基取代的C_{3-6}环烷基;

R^7为H;

R^8为卤基、-N(C_{1-3}烷基)$_2$、经0至1个-OC_{1-4}烷基取代基取代的-OC_{1-3}烷基;

R^9为



或

;

R^{10}为卤基、C_{1-4}烷基、-OH或-OC_{1-4}烷基;

R^{11}为经0至2个R^{12}及0至2个R^{13}取代的C_{1-4}烷基、-C(=O)OR^b、-C(=O)NR^aR^a或经0至2个R^e取代的C_{3-6}环烷基;

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基、-C(=O)R^b或-C(=O)OC_{1-4}烷基;

R^{11b}为-OH;

R^{12}为经0至3个卤基取代基取代的C_{1-3}烷基或-C(=O)OR^b;

R^{13}为-OH;

R^a为H或C_{1-3}烷基;

R^b为H或经0至1个R^e取代的C_{1-4}烷基;

R^e为-OR^f;及

R^f为H或C_{1-6}烷基。

16.根据权利要求1的化合物,其具有式(X):

(X)

或其药学上可接受的盐,其中:

R^1为经C_{3-6}环烷基取代基取代的C_{1-2}烷基;

R^2为H;

或R^1及R^2经组合为=CR^6R^7;

R^3为经0至5个卤基、CN或-OC_{1-3}烷基取代基取代的C_{1-6}烷基、经0至5个R^4取代的-$(CHR^d)_n$-C_{3-10}碳环基、或包含1至3个选自O、S、N的杂原子且经0至3个R^4取代的5元至6元杂芳基;

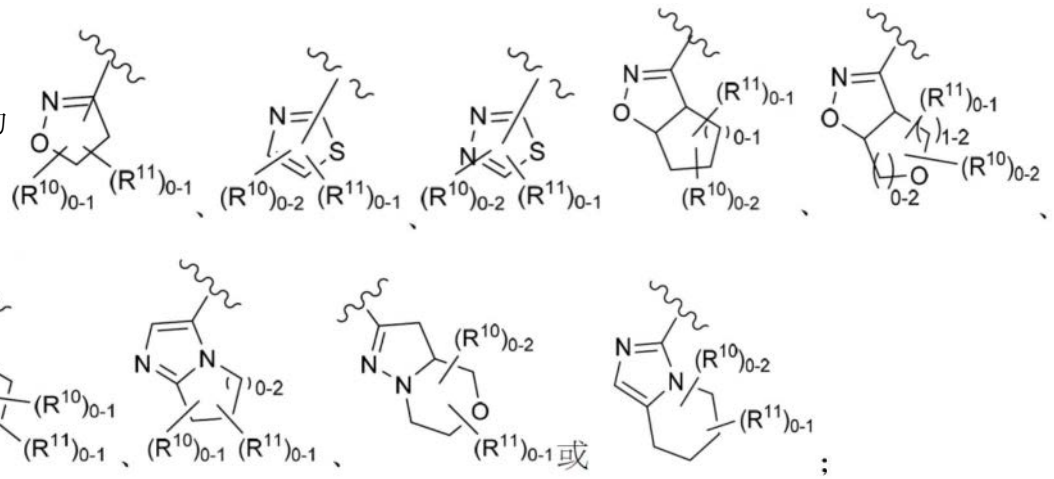
R^4为卤基、S(=O)$_2CF_3$、CN或经0至5个卤基取代基取代的C_{1-4}烷基;

R^6为卤基、经0至3个R^{6a}取代的C_{1-5}烷基、经0至3个R^{14}取代的C_{3-6}环烷基或包含1至3个选自O、S及N的杂原子且经0至3个R^{14}取代的5元至6元杂环基;

R^{6a}为卤基、-OH或C_{3-6}环烷基;

R^7为H;

R^8为H、卤基、CN、C_{1-4}烷基或经0至5个卤基、-OH、C_{3-6}环烷基或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基;

R^9为  ;

R^{10}为卤基、CN、C_{1-4}烷基或-OH;

R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NHC(=O)R^b或-C(=O)OR^b;

R^{12}为卤基;

R^{13}为-OR^b或C_{3-6}碳环基;

R^{14}为卤基、CN或经0至3个卤基取代基取代的C_{1-4}烷基;

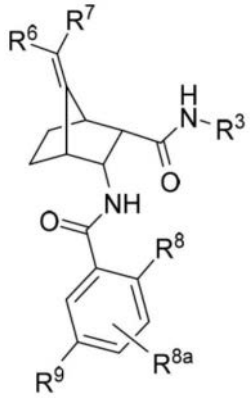
R^b为H或经0至5个R^e取代的C_{1-3}烷基;

R^d为H或C_{1-4}烷基;

R^e为-OH;及

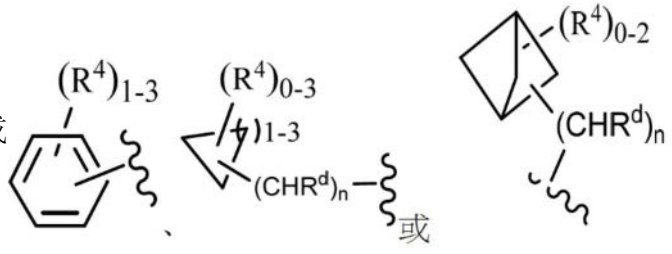
n为0或1。

17.根据权利要求16的化合物,其具有式(XI):



(XI)

或其药学上可接受的盐,其中:

R^3为C_{1-5}烷基或  ;

R^4为卤基、CN、-S(=O)$_2$$CF_3$、经0至5个卤基取代基取代的$C_{1-4}$烷基;

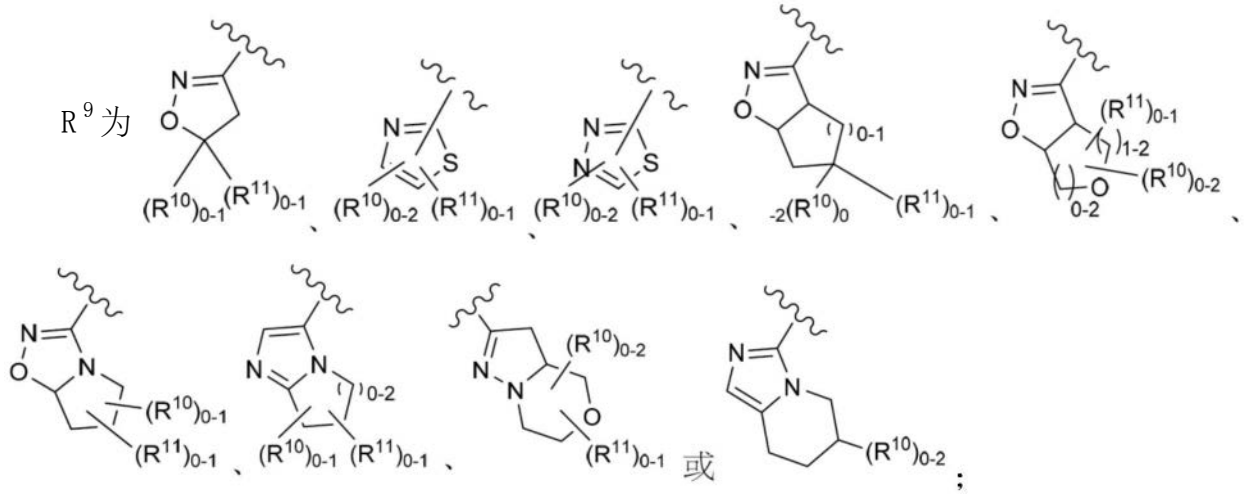
R^6为经0至2个R^{6a}取代的C_{1-5}烷基、经0至2个R^{14}取代的C_{3-6}环烷基、或包含1至3个选自O、S及N的杂原子且经0至2个R^{14}取代的5元至6元杂环基;

R^{6a}为卤基、-OH或C_{3-6}环烷基;

R^7为H;

R^8为经0至5个卤基、-OH、C_{3-6}环烷基或-OC_{1-3}烷基取代基取代的-OC_{1-3}烷基;

R^{8a}为H、卤基、CN或C_{1-3}烷基;

R^9为  ;

R^{10}为卤基、CN、C_{1-4}烷基或-OH;

R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NHC(=O)R^b或-C(=O)OR^b;

R^{12}为卤基;

R^{13}为-OR^b或C_{3-6}碳环基;

R^{14}为卤基或经0至3个卤基取代基取代的C_{1-4}烷基;

R^b为H或经0至5个R^e取代的C_{1-3}烷基;

R^d为H或C_{1-2}烷基;及

n为0或1。

18.一种药物组合物,其包含根据权利要求1的化合物或其药学上可接受的盐及药学上可接受的载剂。

19.一种用于治疗松弛素相关疾病的方法,该方法包括向有需要的患者施用治疗有效量的根据权利要求18的药物组合物。

20.根据权利要求19的方法,其中该疾病选自由以下组成的组:心绞痛、不稳定型心绞痛、心肌梗塞、心脏衰竭、急性冠状动脉疾病、急性心脏衰竭、慢性心脏衰竭及心脏医源性损伤。

21.根据权利要求20的方法,其中该疾病为心脏衰竭。

22.根据权利要求19的方法,其中该疾病为纤维化。

RXFP1激动剂

发明背景

[0001] 本发明涉及作为松弛素家族肽受体1(RXFP1)激动剂的新颖化合物、含有其的组合物,及其使用方法,例如用于治疗心脏衰竭、纤维变性疾病及相关疾病,诸如肺病(例如特发性肺纤维化)、肾病(例如慢性肾病)或肝病(例如非酒精性脂肪变性肝炎及门静脉高血压)的方法。

[0002] 人类松弛素激素(也称为松弛素或H2松弛素)为由53个氨基酸构成的6-kDa肽,其活性最初为在当Frederick Hisaw在1926年将来自猪黄体的粗提取物注射至原生天竺鼠中且观测到纤维软骨耻骨联合关节松弛时发现(Hisaw FL.,Proc.Soc.Exp.Biol.Med.,1926,23,661-663)。松弛素受体先前称为Lgr7,但现时常称为松弛素家族肽受体1(RXFP1),且在2002年使其脱孤成为松弛素受体(Hsu SY.,等人,Science,2002,295,671-674)。RXFP1在具有85%氨基酸一致性的小鼠与人类之间具有相当良好的保守性且基本上广泛地表达于人类及其他物种中(Halls ML.等人,Br.J.Pharmacol.,2007,150,677-691)。松弛素及RXFP1的细胞信号传导路径具有细胞类型依赖性且相当复杂(Halls ML.等人,Br.J.Pharmacol.,2007,150,677-691;Halls ML.等人,Ann.N Y Acad.Sci.,2009,1160,108-111;Halls ML.,Ann N Y Acad.Sci.,2007,1160,117-120)。最佳研究的路径为cAMP的细胞水平的松弛素依赖性增加,其中松弛素充当RXFP1激动剂以促进腺苷酸环化酶的GαS偶合及活化(Halls ML等人,Mol.Pharmacol.,2006,70,214-226)。

[0003] 自松弛素的初始发现以来,许多实验工作着重于描绘松弛素已在女性生殖生物学中发挥的作用及在哺乳动物妊娠期间出现的生理变化(Sherwood OD.,Endocr.Rev.,2004,25,205-234)。在人妊娠期间,为了满足胎儿强制性营养需求,女性身体会经历全身血管阻力(SVR)显著降低约30%且伴随心输出量增加约50%(Jeyabalan AC.,K.P.,Renal and Electolyte Disorders.2010,462-518)、(Clapp JF.&Capeless E.,Am.J.Cardio.,1997,80,1469-1473)。其他血管适应性包括:全局动脉顺应性的约30%增加,其对于维持高效心室-动脉耦合很重要,以及肾血流量(RBF)及肾小球过滤率(GFR)两者的约50%增加,其对于代谢废料消除很重要(Jeyabalan AC.,K.P.,Renal and Electolyte Disorders.2010,462-518),(Poppas A.等人,Circ.,1997,95,2407-2415)。在啮齿动物的临床前研究以及在多种患者环境中进行的临床研究提供证据表明,至少在某种程度上涉及松弛素会介导这些适应性生理变化(Conrad KP.,Regul.Integr.Comp.Physiol.,2011,301,R267-275),(Teichman SL.等人,Heart Fail.Rev.,2009,14,321-329)。重要的是,许多这些适应性反应可能有益于HF患者,为因为过度纤维化、不良动脉顺应性及不良肾功能为心脏衰竭患者共有的全部特征(Mohammed SF.等人,Circ.,2015,131,550-559)、(Wohlfahrt P.等人,Eur.J.Heart Fail.,2015,17,27-34)、(Damman K.等人,Prog.Cardiovasc.Dis.,2011,54,144-153)。

[0004] 心脏衰竭(HF),在血液动力学上定义为“全身灌流由于心泵功能减弱而不足以满足身体代谢需求”,表示对当今保健系统造成巨大负担,其中估计在美国的流行率为580万且在全球超过2300万(Roger VL.等人,Circ.Res.,2013,113,646-659)。据估计,到2030年,

美国将再有300万人患有HF,自2010以来增加25％。2010年与HF相关的估计直接成本(2008年,以美元为单位)为250亿美元,预计到2030年会增长至780亿美元(Heidenreich PA.等人,Circ.,2011,123,933-944)。令人惊奇的是,在美国,9例死亡中有1例的死亡证明上提及了HF(Roger VL.等人,Circ.,2012,125,e2-220),且在HF诊断之后的存活期随时间推移而提高(Matsushita K.等人,Diabetes,2010,59,2020-2026)、(Roger VL.等人,JAMA,2004,292,344-350),约50％具有HF的人的死亡率仍然较高,会在确诊后5年内死亡(Roger VL.等人,Circ.,2012,125,e2-220)、(Roger VL.等人,JAMA,2004,292,344-350)。

[0005] HF的症状由心输出量不足引起,且所述症状视晚期疾病而定可使人相当衰弱。HF的主要症状及病征包括:1)由肺水肿引起的呼吸困难(dyspnea)(难以呼吸),肺水肿由自左心室的低效正向流动及肺毛细管床中的压力增加引起;2)当右心室不能适应全身性静脉回流时,出现下肢水肿;及3)由于心脏衰竭而无法承受足够的心输出量(CO)以满足身体代谢需求造成的疲劳(Kemp CD.,&Conte JV.,Cardiovasc.Patool.,2011,21,365-371)。此外,与症状严重程度相关,HF患者通常被描述为“代偿”或“代偿不全”在代偿心脏衰竭中,症状为稳定的,且不存在水肿(fluid retention)及肺水肿的许多明显特征。代偿不全的心脏衰竭是指恶化(其可以肺水肿急性发作形式存在)、运动耐量降低且在运动时呼吸急促增加(Millane T.等人,BMJ,2000,320,559-562)。

[0006] 相比于不能满足代谢需求的不良心脏功效的简单定义,大量连带性疾病、多种风险因素及最终导致心脏衰竭的许多病理变化使得此疾病极其复杂(Jessup M.&Brozena S.,N.Engl.J.Med.,2003,348,3007-2018)。认为与HF的病理生理学有关的严重事件的范围为非常急性(诸如心肌梗塞)至更慢性损害(诸如终生高血压)。历史上,HF主要描述为“收缩性HF”,其中左心室(LV)收缩功能减少限制血液排出且因此导致射出分率降低(EF为心搏出量/舒张末期容积),或描述为“舒张性HF”,其中主动松弛降低且被动变刚度增加,从而在心脏舒张期间限制LV填充,但会维持总体EF(Borlaug BA.&Paulus WJ.,Eur HeartJ.,2011,32,670-679)。近年来,应理解,由于舒张及收缩LV功能不全并非这些两个群组所特有的,所以采用以下新术语:“射出分率降低型心脏衰竭”(HFrEF)及“射出分率正常型心脏衰竭”(HFpEF)(Borlaug BA.&Paulus WJ.,Eur Heart J.,2011,32,670-679)。尽管此两个患者群体具有极类似的病征及症状,但HFrEF及HFpEF是否表示两种不同形式的HF或共享常见发病机制的单一光谱的两个极值目前仍处于心血管界争论的中(Borlaug BA.&Redfield MM.,Circ.,2011,123,2006-2013)、(De Keulenaer GW.,&Brutsaert DL.,Circ.,2011,123,1996-2004)。

[0007] 目前正在研发具有0.09小时的相对短的第一阶段药物动力学半衰期的重组人类松弛素肽的静脉内(IV)调配物用于治疗HF(Novartis,2014)。塞雷拉辛(serelaxin)已给予正常健康志愿者(NHV)且证实会增加RBF(Smith MC.等人,J.Am.Soc.Nephrol.2006,17,3192-3197)及经估计GFR(Dahlke M.等人,J.Clin.Pharmacol.,2015,55,415-422)。亦在代偿稳定的HF患者中观测到RBF增加(Voors AA.等人,Cir.Heart Fail.,2014,7,994-1002)。在大型临床研究中,在急性代偿不全的HF(ADHF)患者中回应于住院48小时IV输注塞雷拉辛观测到肾功能恶化、HF恶化以及死亡较少的有利变化(Teerlink JR.等人,Lancet,2013,381,29-39),(Ponikowski P.等人,Eur.Heart,2014,35,431-441)。表明了长期给药塞雷拉辛可向HF患者提供持续益处,即在使用皮下泵向持续给予塞雷拉辛6个月的硬皮病患者中

观测到基于血清肌酐含量的肾功能改善(Teichman SL.等人,Heart Fail.Rev.,2009,14,321-329)。除了有可能作为治疗剂来治疗HF以外,亦已证明连续皮下施用释放素对肺(Unemori EN.等人,J.Clin.Invet.,1996,98,2739-2745)、肾(Garber SL.等人,Kidney Int.,2001,59,876-882)及肝损伤(Bennett RG.,Liver Int.,2014,34,416-426)的各种动物模型有效。

[0008] 概言之,有大量证据支持RXFP1介导在哺乳动物妊娠期间出现的适应性变化的松弛素依赖性促效作用,且这些变化在向HF患者给予松弛素时转变成有利的生理作用及结果。在肺、肾脏及肝脏损伤的各种疾病模型中的其他临床前动物研究提供证据表明,当长期施用时,松弛素可能对除HF以外的多种适应症提供治疗益处。更特别是,长期施用松弛素可有益于罹患肺病(例如特发性肺纤维化)、肾病(例如慢性肾病)或肝病(例如非酒精性脂肪变性肝炎及门静脉高血压)的患者。

发明内容

[0009] 本发明提供新颖的经取代的降冰片烷基化合物、其类似物,包括其立体异构体、互变异构体、药学上可接受的盐或溶剂合物,其适用作RXFP1受体激动剂。

[0010] 本发明亦提供制造本发明化合物的方法及中间体。

[0011] 本发明亦提供药物组合物,其包含药学上可接受的载剂及本发明化合物或其立体异构体、互变异构体、药学上可接受的盐或溶剂合物中的至少一者。

[0012] 本发明化合物可用于例如治疗和/或预防心脏衰竭、纤维变性疾病及相关疾病,诸如肺病(例如特发性肺纤维化)、肾病(例如慢性肾病)或肝病(例如非酒精性脂肪变性肝炎及门静脉高血压)。

[0013] 本发明化合物可以用于疗法中。

[0014] 本发明化合物可用于制造用于治疗和/或预防心脏衰竭的药剂。

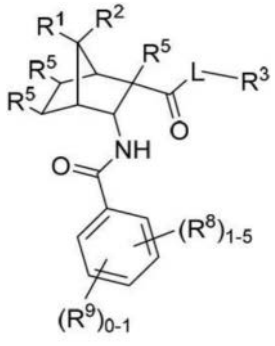
[0015] 本发明化合物可单独使用、与其他本发明化合物组合或与一种或多种、优选一至两种其他药剂组合使用。

[0016] 本发明的这些及其他特征将随继续公开而以扩展形式阐述。

具体实施方式

[0017] 本发明涵盖式(I)化合物,其为RXFP1受体激动剂;含有其的组合物;及其使用方法。

[0018] 在第一方面中,本发明尤其提供式(I)化合物:



(I)

或其药学上可接受的盐,其中:

L为-O-或-NH-;

R^1为经0至1个芳基或C_{3-6}环烷基取代基取代的C_{1-3}烷基;

R^2为H;其限制条件为,当R^1为经0个芳基或C_{3-6}环烷基取代基取代的C_{1-3}烷基时,R^9不存在;

或R^1及R^2组合为=CR^6R^7或=NOC_{1-4}烷基,其中"="为双键;或R^1及R^2与该两者所连接的碳原子一起形成经0至1个芳基取代基取代的二氧戊环基;

R^3为经0至5个卤基、CN、-OH或-OC_{1-3}烷基取代基取代的C_{1-8}烷基、经0至5个R^4取代的-$(CR^dR^d)_n$-C_{3-10}碳环基或包含1至4个选自O、S(=O)$_p$、N及NR^{4c}的杂原子且经0至5个R^4取代的-$(CR^dR^d)_n$-3元至12元杂环基;

R^4为卤基、CN、-OH、-SF_5、-S(=O)$_p$$R^c$、经0至5个卤基、-OH或-$OC_{1-4}$烷基取代基取代的$C_{1-4}$烷基、经0至5个卤基取代基取代的-$OC_{1-4}$烷基、经0至5个$R^e$取代的-$(CR^dR^d)_n$-$C_{3-10}$碳环基、或包含1至4个选自O、S(=O)$_p$、N及$NR^{4c}$的杂原子且经0至5个$R^e$取代的-$(CR^dR^d)_n$-4元至6元杂环基;

R^{4c}为H、C_{1-4}烷基或-S(=O)$_2$$CF_3$;

各R^5为H、卤基、-OH、经0至5个卤基取代基取代的C_{1-4}烷基、或经0至5个卤基取代基取代的-OC_{1-4}烷基;

R^6为H、卤基、CN、经0至3个R^{6a}取代的C_{1-7}烷基、经0至3个R^{6a}取代的C_{2-7}烯基、经0至3个R^{6a}取代的C_{2-7}炔基、-C(=O)OR^{6b}、-$CONR^{6b}R^{6b}$、经0至5个R^{14}取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$、N或NR^{14a}的杂原子且经0至5个R^{14}取代的3元至12元杂环基;

R^{6a}为卤基、-OH、-OC_{1-4}烷基、C_{1-4}烷基、芳基、或经0至4个卤基取代基取代的C_{3-6}环烷基;

R^{6b}为H、经0至1个芳基取代基取代的C_{1-4}烷基、或经0至4个卤基取代基取代的C_{3-6}环烷基;

R^7为H或C_{1-4}烷基;

或R^6及R^7与该两者所连接的碳原子一起形成环戊二烯基、二氢茚基或茚基;

R^8为H、卤基、CN、-NR^7R^7、经0至5个卤基或-OH取代基取代的C_{1-4}烷基、或经0至5个卤基取代的-OC_{1-4}烷基、-OH、C_{3-6}环烷基、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至9元杂环基或经0至1个-OC_{1-3}烷基取代基取代的-OC_{1}-$_3$烷基;

R^9为经0至3个R^{10}及0至2个R^{11}取代的芳基、或包含1至5个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至2个R^{11}取代的3元至12元杂环基;

R^{10}为卤基、CN、C_{1-4}烷基、=O、-OH或-OC_{1-4}烷基;

R^{11}为经0至4个R^{12}及0至2个R^{13}取代的C_{1-5}烷基、-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aC(=O)NR^aR^a、-NR^aS(=O)$_p$$R^c$、-C(=O)$R^b$、-C(=O)$OR^b$、-C(=O)$NR^aR^a$、-C(=O)$NR^aS$(=O)$_p$$R^c$、-OC(=O)$R^b$、-S(=O)$_p$$R^c$、-S(=O)$_p$$NR^aR^a$、经0至5个$R^e$取代的$C_{3-9}$碳环基、或包含1至4个选自O、S(=O)$_p$、N及$NR^{15}$的杂原子且经0至5个$R^e$取代的3元至12元杂环基;

R^{11a}为H、经0至4个R^{11b}取代的C_{1-5}烷基、-C(=O)R^b、-C(=O)OR^b、-C(=O)NR^aR^a、经0至5个R^e取代的C_{3-6}环烷基、经0至5个R^e取代的芳基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至6元杂环基;

R^{11b}为卤基、-OH、-C(=O)OH、-C(=O)OC_{1-4}烷基或芳基;

R^{12}为卤基、-C(=O)OR^b、-C(=O)NR^aR^a、-C(=O)NR^aOR^b、经0至3个卤基或-OH取代基取代的C_{1-4}烷基、或C_{3-6}环烷基;

R^{13}为-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aC(=O)NR^aR^a、-NR^aS(=O)$_pR^c$、-NR^aS(=O)$_pNR^aR^a$、-OC(=O)NR^aR^a、-OC(=O)NR^aOR^b、-S(=O)$_pNR^aR^a$、-S(=O)$_pR^c$、经0至3个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的$(CH_2)_n$-3元至12元杂环基;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_n$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_n$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-4}烷基或经以下取代的C_{1-3}烷基:0至3个Si(C_{1-3}烷基)$_3$或经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-4}烷基或芳基;

R^a为H、-OC_{1-6}烷基、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的$(CH_2)_nC_{3-10}$碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的$(CH_2)_n$-3元至12元杂环基;

R^c为经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的C_{2-6}烯基、经0至5个R^e取代的C_{2-6}炔基、经0至5个R^e取代的C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^d为H、C_{1-4}烷基或C_{3-6}环烷基;

R^e为卤基、CN、NO_2、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个-R^g取代的C_{2-6}烯基、经0至5个-R^g取代的C_{2-6}炔基、经0至5个R^g取代的-$(CH_2)_n$-C_{3-10}碳环基、包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^g取代的-$(CH_2)_n$-3元至12元杂环基、-$(CH_2)_nOR^f$、-C(=O)OR^f、-C(=O)NR^fR^f、-NR^fC(=O)R^f、-S(=O)$_pR^f$、-S(=O)$_pNR^fR^f$、-NR^fS(=O)$_pR^f$、-NR^fC(=O)OR^f、-OC(=O)NR^fR^f或-$(CH_2)_nNR^fR^f$;

R^f为H、经0至2个-OH或-OC_{1-4}烷基取代基取代的C_{1-6}烷基、C_{3-6}环烷基、芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至12元杂环基,及;或R^f及R^f与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至12元杂环基;

R^g为卤基、CN、-OH、C_{1-6}烷基、C_{3-6}环烷基或芳基;

n为0、1、2或3;及

p为0、1或2。

[0019] 在第一方面的范畴内的第二方面中,本发明提供式(I)化合物或其药学上可接受的盐,其中:

R^3为经0至4个卤基或-OH取代基取代的C_{1-6}烷基、经0至4个R^4取代的-$(CHR^d)_{0-1}$-C_{3-6}环烷基、经0至4个R^4取代的C_{6-9}螺环烷基、经0至4个R^4取代的C_{6-10}双环碳环基、或包含1至2个

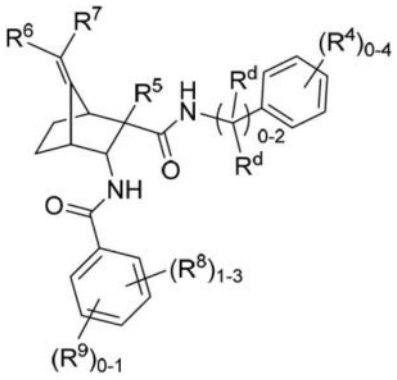
选自O、S(=O)$_p$、N及NR^{4c}的杂原子且经0至4个R^{4}取代的3元至6元杂环基;

R^{4}为卤基或经0至4个卤基取代基取代的C$_{1-3}$烷基;

R^{4c}为H或C$_{1-4}$烷基;

R^{d}为C$_{1-3}$烷基。

[0020] 在第一方面的范畴内的第三方面中,本发明提供式(II)化合物



(II)

或其药学上可接受的盐,其中:

R^{4}为卤基、经0至4个卤基取代基取代的-S(=O)$_p$C$_{1-4}$烷基、经0至4个卤基取代基取代的C$_{1-4}$烷基、经0至4个卤基取代基取代的-OC$_{1-4}$烷基;

R^{5}为H或卤基;

R^{6}为卤基、CN、经0至3个R^{6a}取代的C$_{1-7}$烷基、经0至3个R^{6a}取代的C$_{2-7}$烯基、经0至3个R^{6a}取代的C$_{2-7}$炔基、-C(=O)OR^{6b}、CONR^{6b}R^{6b}、经0至3个R^{14}取代的C$_{3-6}$环烷基、经0至3个R^{14}取代的C$_{3-6}$环烯基、经0至3个R^{14}取代的芳基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的4元至6元杂环基;

R^{6a}为卤基、-OH、C$_{3-6}$环烷基或芳基;

R^{6b}为H、经0至1个芳基取代基取代的C$_{1-4}$烷基、或经0至4个卤基取代基取代的C$_{3-6}$环烷基;

R^{7}为H或C$_{1-3}$烷基;

R^{8}为卤基、CN、-N(C$_{1-2}$烷基)$_2$、经0至5个卤基或-OH取代基取代的C$_{1-4}$烷基、或经0至4个卤基、-OH、芳基或-OC$_{1-4}$烷基取代基取代的-OC$_{1-4}$烷基;

R^{9}为经0至3个R^{10}及0至2个R^{11}取代的C$_6$芳基、或包含1至4个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至1个R^{11}取代的3元至12元杂环基;

R^{10}为卤基、CN、C$_{1-4}$烷基、=O、-OH或-OC$_{1-4}$烷基;

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C$_{1-4}$烷基、-OR^b、-NR^{a}R^a、-NR^{a}C(=O)R^b、-NR^{a}C(=O)OR^b、-NR^{a}C(=O)NR^{a}R^a、-NR^{a}S(=O)$_p$R^c、-C(=O)R^b、-C(=O)OR^b、-C(=O)NR^{a}R^a、-C(=O)NR^{a}S(=O)$_p$R^c、-OC(=O)R^b、-S(=O)$_p$R^c、-S(=O)$_p$NR^{a}R^a、经0至5个R^{e}取代的C$_{3-6}$环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^{e}取代的4元至12元杂环基;

R^{11a}为H、经0至2个R^{11b}取代的C$_{1-4}$烷基、-C(=O)R^b、-C(=O)OR^b、-C(=O)NR^{a}R^a、经0至5个R^{e}取代的C$_{3-6}$环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^{e}取代的4元至6元杂环基;

R^{11b}为-OH、-C(=O)OH或芳基;

R^{12}为卤基、-C(=O)OR^b、-C(=O)NHR^a、-C(=O)$NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aS(=O)$_pR^c$、-NR^aS(=O)$_pNR^aR^a$、-OC(=O)NR^aR^a、-OC(=O)NR^aOR^b、-S(=O)$_pNR^aR^a$或-S(=O)$_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-3}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-3}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-4}烷基或经以下取代的C_{1-3}烷基:0至3个经0至2个卤基取代基取代的芳基、;

R^{15}为H、C_{1-3}烷基或芳基;

R^a为H、经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^c为经0至5个R^e取代的C_{1-5}烷基、经0至5个R^e取代的C_{2-5}烯基、经0至5个R^e取代的C_{2-5}炔基、经0至5个R^e取代的C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^d为H或C_{1-4}烷基;

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、经0至5个R^g取代的-$(CH_2)_n$-C_{3-6}环烷基、经0至5个R^g取代的-$(CH_2)_n$-芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^g取代的-$(CH_2)_n$-3元至12元杂环基、-$(CH_2)_n$$OR^f$、-C(=O)$OR^f$、-C(=O)$NR^fR^f$、-$NR^fC$(=O)$R^f$、-S(=O)$_pR^f$、-$NR^fC$(=O)$OR^f$、-OC(=O)$NR^fR^f$或-$(CH_2)_n$$NR^fR^f$;

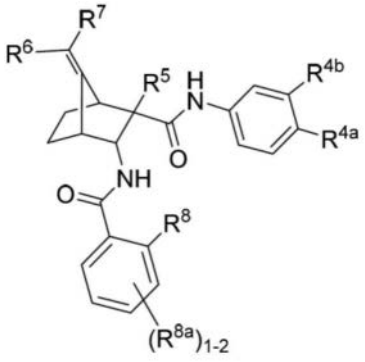
R^f为H、C_{1-5}烷基、C_{3-6}环烷基或芳基;或R^f及R^f与该两者所连接的氮原子一起形成杂环基;

R^g为卤基、CN、-OH、C_{1-5}烷基、C_{3-6}环烷基或芳基;

n为0、1、2或3;及

p为0、1或2。

[0021] 在第一方面的范畴内的第四方面中,本发明提供式(III)化合物:



(III)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基;

R^5为H或F;

R^6为卤基、经0至3个R^{6a}取代的C_{1-4}烷基、经0至1个苯基或-OH取代基取代的C_{2-4}烯基、-C(=O)OR^{6b}、C(=O)NHR^{6b}、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、经0至3个R^{14}取代的萘基、或包含1至3个选自O、S、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂环基;

R^{6a}为卤基、-OH、C_{3-6}环烷基或苯基;

R^{6b}为H或C_{1-4}烷基;

R^7为H或C_{1-3}烷基;

或R^6及R^7与该两者所连接的碳原子一起形成环戊二烯基、二氢茚基或茚基;

R^8为-N(C_{1-4}烷基)$_2$或经0至1个-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基;

R^{8a}为卤基;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-3}烷基或经以下取代的C_{1-3}烷基:0至3个经0至2个卤基取代基取代的芳基;

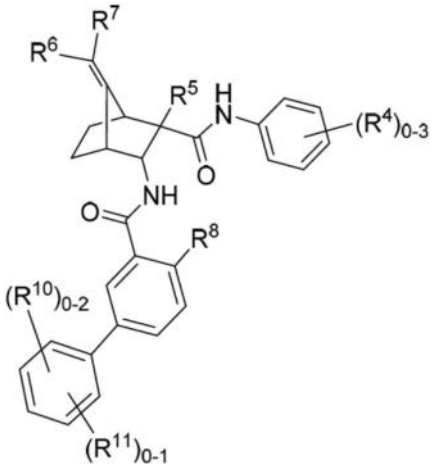
R^a为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的-$(CH_2)_n$-苯基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-6}烷基、经0至5个R^e取代的-$(CH_2)_{0-1}$-苯基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^e为卤基、CN、=O、C_{1-6}烷基或C(=O)OH;及

n为0、1、2或3。

[0022] 在第一至第三方面的范畴内的第五方面中,本发明提供式(IV)化合物:



(IV)

或其药学上可接受的盐,其中:

R^4为卤基、经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的-OC_{1-4}烷基;

R^5为H或F;

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-6}烷基、经0至3个R^{6a}取代的C_{2-6}烯基、经0至3个R^{6a}取代的C_{2-6}炔基、-C(=O)OR^{6b}、C(=O)$NR^{6b}R^{6b}$、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基;

R^{6a}为卤基、C_{3-6}环烷基或苯基;

R^{6b}为H、经0至1个芳基取代基取代的C_{1-3}烷基、或经0至4个卤基取代基取代的C_{3-6}环烷基;

R^7为H或C_{1-2}烷基;

R^8为经0至4个卤基、-OH、芳基或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基;

R^{10}为卤基、CN、C_{1-3}烷基、-OH或-OC_{1-4}烷基;

R^{11}为经0至2个R^{12}及0至1个R^{13}取代的C_{1-4}烷基、-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)NR^aR^a、-NR^aS(=O)$_pR^c$、-C(=O)R^b、-C(=O)OR^b、-C(=O)NR^aR^a、-C(=O)NR^aS(=O)$_pR^c$、-OC(=O)R^b、-S(=O)$_pR^c$、-S(=O)$_pNR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至9元杂环基;

R^{12}为卤基、-C(=O)OR^b、-C(=O)NHR^a、-C(=O)$NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OR^b、-NR^aR^a、-NR^aC(=O)R^b、-NR^aC(=O)OR^b、-NR^aS(=O)$_pR^c$、-NR^aS(=O)$_pNR^aR^a$、-OC(=O)NR^aR^a、-OC(=O)NR^aOR^b、-S(=O)$_pNR^aR^a$或-S(=O)$_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、C(=O)C_{1-3}烷基、经以下取代的C_{1-3}烷基:0至2个经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-2}烷基或苯基；

R^a为H、经0至4取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基；或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基；

R^b为H、经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基；

R^c为经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、C_{3-6}碳环基、或包含1至4个选自O、S(=O)$_p$及N的杂原子的3元至12元杂环基；

R^e为卤基、CN、NO_2、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、-$(CH_2)_n$-C_{3-6}环烷基、-$(CH_2)_n$-芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的-$(CH_2)_n$-3元至12元杂环基、-$(CH_2)_n$$OR^f$、S(=O)$_p$$R^f$、C(=O)$NR^fR^f$、C(=O)$OR^f$、$NR^f$C(=O)$R^f$、S(=O)$_p$$NR^fR^f$、$NR^f$S(=O)$_p$$R^f$、$NR^f$C(=O)$OR^f$、OC(=O)$NR^fR^f$或-$(CH_2)_n$$NR^fR^f$；

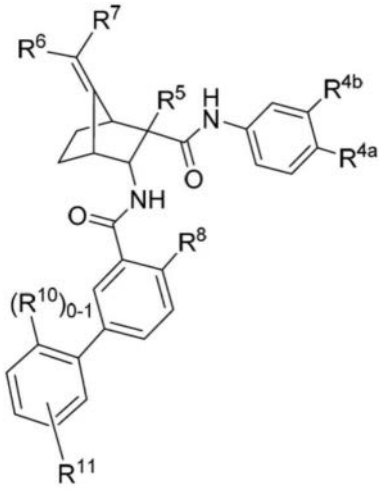
R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基；或R^f及R^f与该两者所连接的氮原子一起形成杂环基；

R^g为卤基、CN、-OH、C_{1-5}烷基、C_{3-6}环烷基或芳基；

n为0、1、2或3；及

p为0、1或2。

[0023] 在第五方面的范畴内的第六方面中，本发明提供式(V)化合物：



(V)

或其药学上可接受的盐，其中：

R^{4a}为卤基或C_{1-2}烷基；

R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基；

R^5为H或F；

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-4}烷基、经0至3个R^{6a}取代的C_{2-4}烯基、-C(=O)OR^{6b}、C(=O)O$NR^{6b}R^{6b}$、经0至3个R^{14}取代的C_{3-6}环烷基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基；

R^{6a}为卤基、-OH、C_{3-6}环烷基或苯基；

R^{6b}为H、经0至1个芳基取代基取代的C_{1-3}烷基或C_{3-6}环烷基；

R^{7}为H或C_{1-2}烷基；

R^{8}为经0至4个卤基、-OH、-OC_{1-4}烷基或芳基取代基取代的-OC_{1-4}烷基；

R^{10}为卤基或C_{1-3}烷基；

R^{11}为经0至2个R^{12}及0至1个R^{13}取代的C_{1-4}烷基、-OH、-OC_{1-4}烷基、-$NR^aC(=O)R^b$、-$NR^aC(=O)NR^aR^a$、-$NR^aS(=O)_pR^c$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aS(=O)_pR^c$、-$OC(=O)R^b$、-$S(=O)_pR^c$、-$S(=O)_pNR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至3个R^e取代的4元至9元杂环基；

R^{12}为卤基、-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$、或经0至3个卤基或-OH取代基取代的C_{1-4}烷基；

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-$OC(=O)NR^aR^a$或-$OC(=O)NR^aOR^b$；

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-1}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-1}$-3元至9元杂环基；

R^{14a}为H、$C(=O)C_{1-3}$烷基、经以下取代的C_{1-3}烷基：0至1个经0至2个卤基取代基取代的芳基；

R^{15}为H、C_{1-2}烷基或苯基；

R^a为H、经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至12元杂环基；或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的3元至9元杂环基；

R^b为H、经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、经0至5个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至5个R^e取代的-$(CH_2)_n$-3元至9元杂环基；

R^c为经0至5个R^e取代的C_{1-4}烷基、经0至5个R^e取代的C_{2-4}烯基、经0至5个R^e取代的C_{2-4}炔基、C_{3-6}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至9元杂环基；

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、-$(CH_2)_n$-C_{3-6}环烷基、-$(CH_2)_n$-芳基、包含1至4个选自O、$S(=O)_p$及N的杂原子的-$(CH_2)_n$-4元至6元杂环基、-$(CH_2)_nOR^f$、$S(=O)_pR^f$、$C(=O)NR^fR^f$、$C(=O)OR^f$、$NR^fC(=O)R^f$、$S(=O)_pNR^fR^f$、$NR^fS(=O)_pR^f$、$NR^fC(=O)OR^f$、$OC(=O)NR^fR^f$或-$(CH_2)_nNR^fR^f$；

R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基；或R^f及R^f与该两者所连接的氮原子一起形成杂环基；

R^g为卤基、CN、-OH、C_{1-6}烷基、C_{3-6}环烷基或芳基；

n为0、1、2或3；及

p为0、1或2。

[0024] 在式(V)的一个实施方案中，R^{4a}为F或CH_3；R^{4b}为CF_3；R^6为苯基或包含1至2个选自O及N的杂原子的5元杂芳基；R^7为H；R^8为-OC_{1-2}烷基；R^{10}为卤基；R^{11}为-CH_3、-CH_2CH_3、-CF_3-

OCF_3、-NHS(=O)$_2C_{1-2}$烷基、-C(=O)OH、-C(=O)OC_{1-4}烷基、经0至1个R^e取代的-C(=O)NHC_{1-4}烷基、或包含1至4个选自O、N及NR^{15}的杂原子且经0至3个R^e取代的5元杂环基;R^{15}为H、C_{1-2}烷基或苯基;且R^e为=O或C(=O)OH。

[0025] 在第六方面的范畴内的第七方面中,本发明提供式(V)化合物或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为CF_3;

R^6为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的C_{3-6}环烷基;

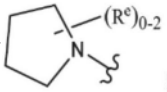
R^8为-OC_{1-4}烷基;

R^{10}为F;

R^{11}为-OH、-OC_{1-4}烷基、-NR^aC(=O)R^b、-NR^aS(=O)$_pR^c$、-C(=O)OR^b、-C(=O)NR^aR^a、-C(=O)NR^aS(=O)$_pR^c$、包含1至4个选自O、S(=O)$_p$、N及NR^{15}的杂原子且经0至5个R^e取代的4元至9元杂环基;

R^{15}为H或C_{1-2}烷基;

R^a为H或经0至5个R^e取代的C_{1-4}烷基;

或R^a及R^a一起为  ;

R^b为H或经0至5个R^e取代的C_{1-4}烷基;

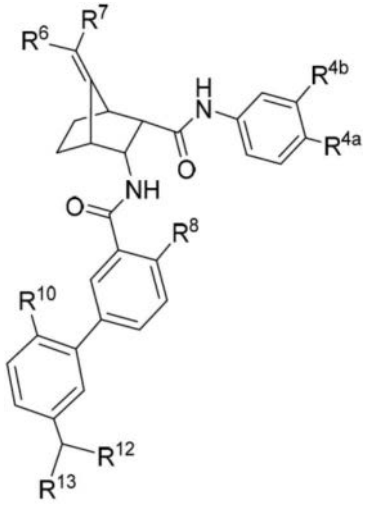
R^c为经0至5个R^e取代的C_{1-3}烷基或C_{3-6}碳环基;

R^e为卤基、=O、经0至5个R^g取代的C_{1-4}烷基、C(=O)OH、-OR^f或-NR^fR^f;及

R^f为H及C_{1-6}烷基;或R^f及R^f与该两者所连接的氮原子一起形成杂环基;及

R^g为卤基。

[0026] 在第六方面的范畴内的第八方面中,本发明提供式(VI)化合物:



(VI)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为CF_3;

R^6为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的C_{3-6}环烷基;

R^7为H;

R^8为经0至1个芳基取代基取代的-OC_{1-4}烷基;

R^{10}为卤基;

R^{12}为-C(=O)OH、-C(=O)OC_{1-4}烷基、-C(=O)NHC_{1-4}烷基、-C(=O)$NHOC_{1-3}$烷基、或经0至3个卤基取代基取代的C_{1-3}烷基;

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-OC(=O)NR^aR^a或-OC(=O)NR^aOR^b;

R^a为H、经0至5个卤基取代基取代的C_{1-4}烷基、经0至4个R^e取代的苯基、经0至4个R^e取代的C_{3-10}环烷基、经0至4个R^e取代的螺环烷基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至9元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^b为H、经0至5个R^e取代的C_{1-4}烷基、经0至4个R^e取代的-$(CH_2)_n$-苯基、经0至4个卤基取代基取代的C_{3-6}环烷基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^c为经0至4个R^e取代的C_{1-4}烷基,

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-5}烷基、C_{3-6}环烷基、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至6元杂环基、或-OR^f;

R^f为H、C_{1-4}烷基、C_{3-6}环烷基或芳基;

R^g为卤基;

n为0或1;及

p为0、1或2。

[0027] 在第八方面的范畴内的第九方面中,本发明提供式(VI)化合物或其药学上可接受的盐,其中:

R^{4a}为F

R^{4b}为CF_3;

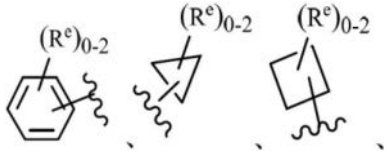
R^6为CF_3或C_{3-6}环烷基;

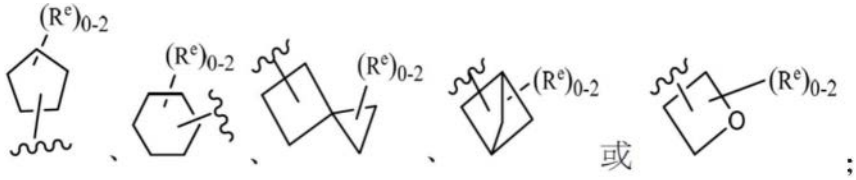
R^8为-OCH_3或-OCH_2-苯基;

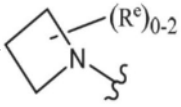
R^{10}为F;

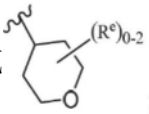
R^{12}为-C(=O)OH、-C(=O)OC_{1-4}烷基、-C(=O)NHC_{1-4}烷基、-C(=O)$NHOC_{1-4}$烷基、CH_3、CHF_2或CF_3;

R^{13}为-OH、-NR^aR^a、-NHC(=O)R^b、-NHS(=O)$_pC_{1-4}$烷基、-OC(=O)NR^aR^a或-OC(=O)$NHOC_{1-4}$烷基;

R^a为H、经0至4个F取代基取代的C_{1-4}烷基、 



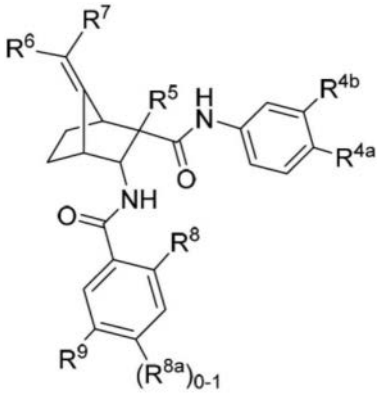
或R^a及R^a一起为  ，

R^b为H、经0至5个R^e取代的C_{1-4}烷基、苯基，或  及；

R^e为卤基、=O、芳基、包含1至4个选自O、S(=O)$_p$及N的杂原子的4元至6元杂环基或-OR^f；及

R^f为H、C_{1-3}烷基、C_{3-6}环烷基或苯基。

[0028] 在第三方面的范畴内的第十方面中，本发明提供式(VII)化合物：



(VII)

或其药学上可接受的盐，其中：

R^{4a}为卤基；

R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基或经0至3个卤基取代基取代的-OC_{1-4}烷基；

R^5为H或F；

R^6为卤基、CN、经0至3个R^{6a}取代的C_{1-6}烷基、经0至3个R^{6a}取代的C_{2-6}烯基、经0至3个R^{6a}取代的C_{2-6}炔基、经0至3个R^{14}取代的C_{3-6}环烷基、0至3个R^{14}经取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、或包含1至3个选自O、S(=O)$_p$、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂芳基；

R^{6a}为卤基、C_{3-6}环烷基或苯基；

R^7为H或C_{1-2}烷基；

R^8为卤基、CN或经0至4个卤基、-OH或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基；

R^{8a}为卤基或CN；

R^9为包含1至4个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至1个R^{11}取代的3元至12元杂环基；

R^{10}为卤基、CN、C_{1-3}烷基、=O、-OH或-OC_{1-3}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aC(=O)NR^aR^a$、-$NR^aS(=O)_pR^c$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、-$C(=O)NR^aS(=O)_pR^c$、-$OC(=O)R^b$、-$S(=O)_pR^c$、-$S(=O)_pNR^aR^a$、经0至5个R^e取代的C_{3-6}环烷基、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至6元杂环基;

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$、C_{3-6}环烷基、包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至4个R^e取代的4元至6元杂环基;

R^{11b}为-OH、-$C(=O)OH$或芳基;

R^{12}为-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-$OC(=O)NR^aR^a$、-$S(=O)_pNR^aR^a$或-$S(=O)_pR^c$;

R^{14}为卤基、CN、经0至3个卤基取代的C_{1-4}烷基、经0至3个卤基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H、$C(=O)C_{1-3}$烷基或经以下取代的C_{1-3}烷基:0至2个经0至2个卤基取代基取代的芳基;

R^{15}为H、C_{1-2}烷基或苯基;

R^a为H、经0至4取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基;或R^a及R^a与该两者所连接的氮原子一起形成包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至4个R^e取代的3元至12元杂环基;

R^b为H、经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、经0至4个R^e取代的-$(CH_2)_n$-C_{3-10}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至4个R^e取代的-$(CH_2)_n$-3元至12元杂环基;

R^c为经0至4个R^e取代的C_{1-5}烷基、经0至4个R^e取代的C_{2-5}烯基、经0至4个R^e取代的C_{2-5}炔基、C_{3-6}碳环基、或包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至12元杂环基;

R^e为卤基、CN、=O、经0至4个R^g取代的C_{1-6}烷基、经0至5个R^g取代的C_{2-6}烯基、经0至5个R^g取代的C_{2-6}炔基、经0至4个R^g取代的-$(CH_2)_n$-C_{3-6}环烷基、经0至4个R^g取代的-$(CH_2)_n$-芳基、包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至4个R^g取代的-$(CH_2)_n$-4元至6元杂环基、-$(CH_2)_nOR^f$、$C(=O)OR^f$、$C(=O)NR^fR^f$、$NR^fC(=O)R^f$、$S(=O)_pR^f$、$NR^fS(=O)_pR^f$、$NR^fC(=O)OR^f$、$OC(=O)NR^fR^f$或-$(CH_2)_nNR^fR^f$;

R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基;

R^g为卤基、CN、-OH、C_{1-4}烷基、C_{3-6}环烷基或芳基;

n为0、1、2或3;及

p为0、1或2。

[0029] 在第十方面的范畴内的第十一方面中,本发明提供式(VII)化合物或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基；

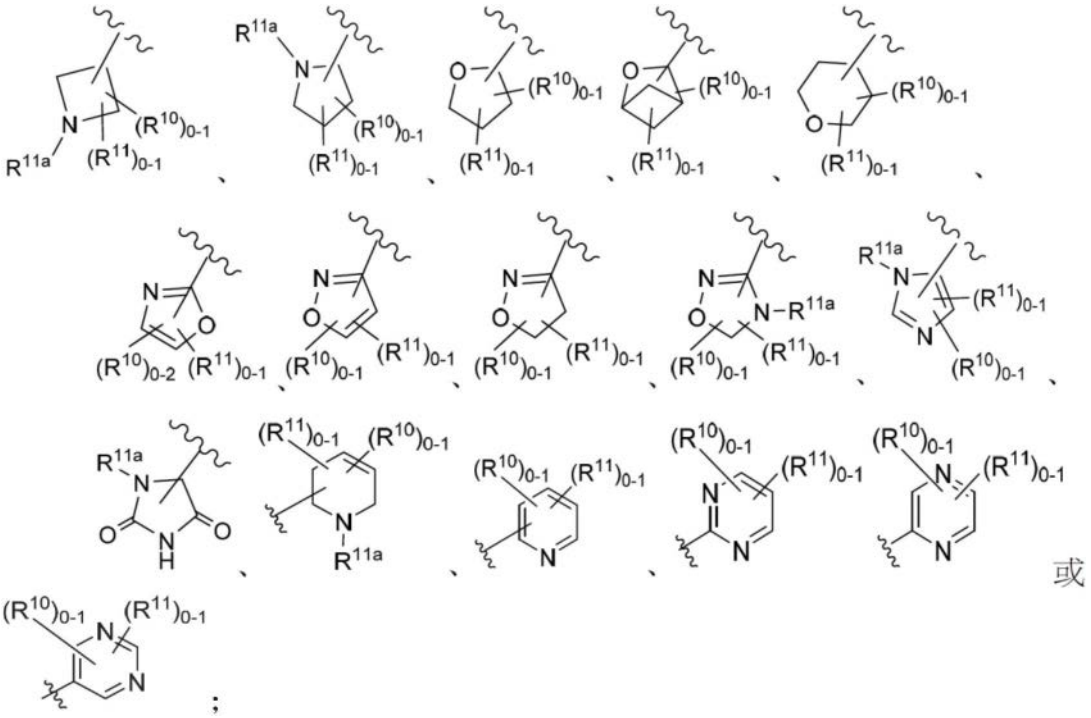
R^5为H；

R^6为经0至2个F取代基取代的C_{1-2}烷基或C_{3-6}环烷基；

R^8为-OC_{1-3}烷基；

R^{8a}为F或CN；

R^9为



或

；

R^{10}为卤基、CN、C_{1-2}烷基、=O、-OH或-OC_{1-2}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$C(=O)R^b$、-$C(=O)OR^b$、-$C(=O)NR^aR^a$或经0至5个R^e取代的C_{3-6}环烷基；

R^{11a}为H、-$C(=O)R^b$、-$C(=O)NR^aR^a$或经0至1个R^{11b}取代的C_{1-4}烷基；

R^{11b}为-OH或芳基；

R^{12}为-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$或经0至2个卤基或-OH取代基取代的C_{1-4}烷基；

R^{13}为-OH、经0至2个-OH取代基取代的-OC_{1-4}烷基、或-$S(=O)_2C_{1-4}$烷基；

R^a为H或C_{1-6}烷基，或R^a及R^a与该两者所连接的氮原子一起形成经0至4个R^e取代的3元至9元杂环基；

R^b为H、经0至1个R^e取代的C_{1-4}烷基或经0至1个R^e取代的C_{3-6}环烷基；

R^e为-OR^f；及

R^f为H或C_{1-4}烷基。

[0030] 在第十一方面的范畴内的第十二方面中，本发明提供式(VII)化合物或其药学上可接受的盐，其中：

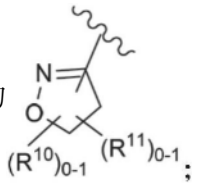
R^{4a}为卤基；

R^{4b}为CF_3；

R^5为H；

R^6为CF_3或C_{3-6}环丙基;

R^8为-OC_{1-3}烷基;

R^9为  ;

R^{10}为C_{1-2}烷基、-OH或-OC_{1-4}烷基;

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-2}烷基、-C(=O)OR^b或-C(=O)NR^aR^a;

R^{12}为-C(=O)OR^b;

R^{13}为-OH;

R^a为H或C_{1-4}烷基;及

R^b为H或C_{1-4}烷基。

[0031] 在第十方面的范畴内的第十三方面中,本发明提供式(VI)化合物或其药学上可接受的盐,其中:

R^{4a}为卤基;

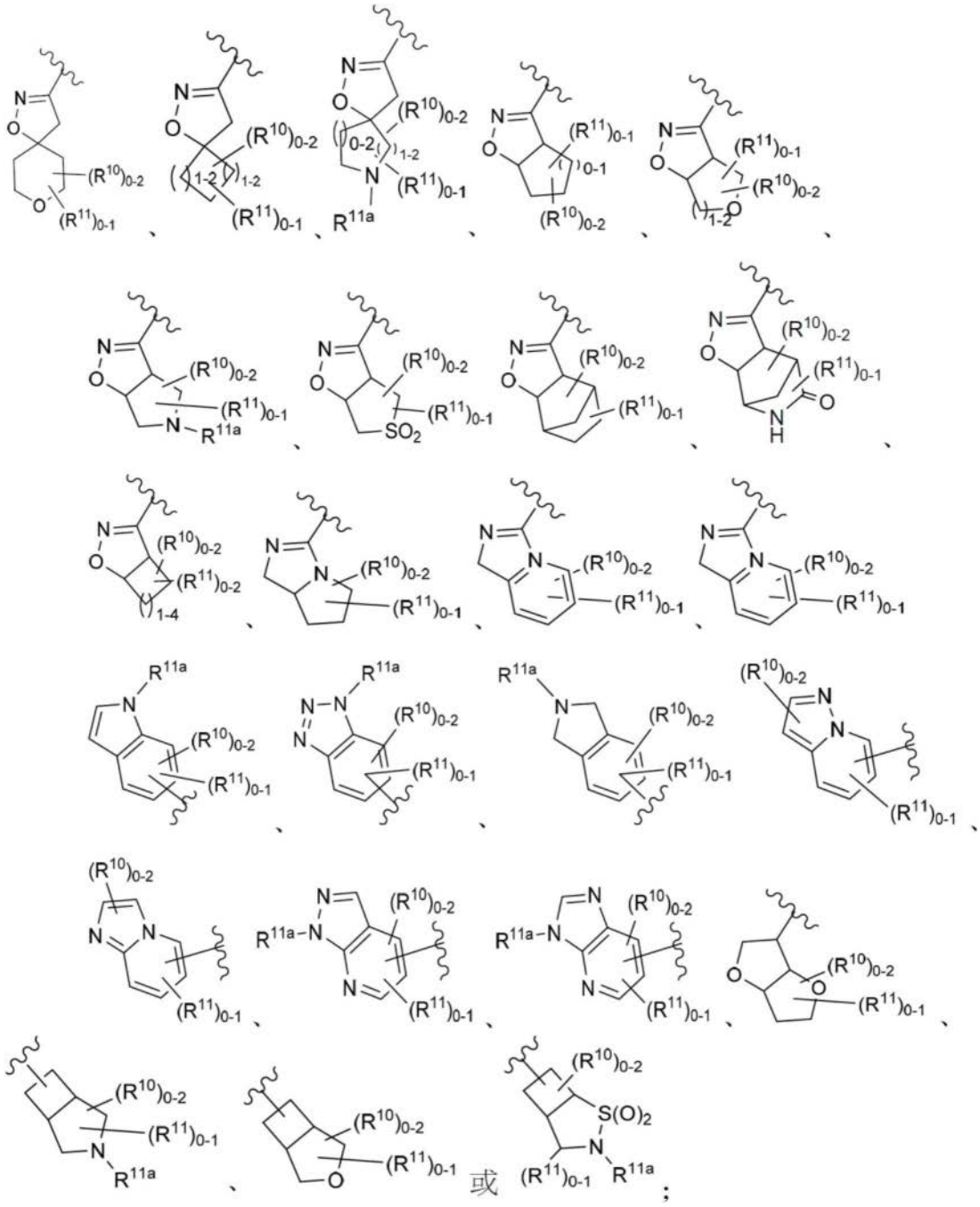
R^{4b}为经0至3个卤基取代基取代的C_{1-4}烷基;

R^5为H;

R^6为经0至3个F取代基取代的C_{1-3}烷基或C_{3-6}环烷基;

R^8为-OC_{1-3}烷基;

R^9为



R^{10}为卤基、C_{1-3}烷基、-OH或-OC_{1-3}烷基；

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-3}烷基或-C(=O)NH_2；

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基或-C(=O)OC_{1-4}烷基；

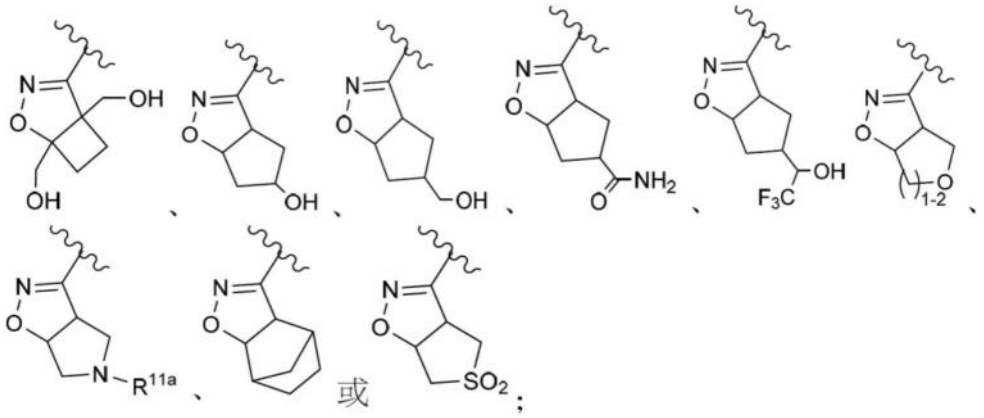
R^{11b}为-OH、-C(=O)OH或芳基；

R^{12}为C(=O)OR^b或经0至3个卤基取代基取代的C_{1-3}烷基；

R^{13}为-OH；及

R^b为H或C_{1-4}烷基。

[0032] 在式(VII)的一个实施方案中，R^{4a}为F；R^{4b}为CF_3；R^5为H；R^6为经0至3个F取代基取代的C_{1-4}烷基或C_{3-6}环烷基；R^8为-OCH_3或-$OCH_3(CH_2)_2OCH_3$；R^9为

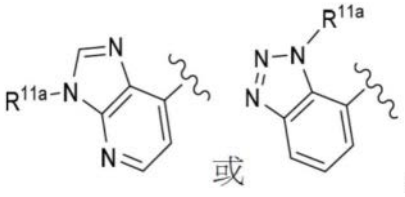


R^{11}为经0至1个R^{13}取代的C_{1-2}烷基;

R^{11a}为H、经0至2个R^{11b}取代的C_{1-3}烷基、经0至1个R^{11b}取代的-C(=O)C_{1-4}烷基、或-C(=O)OC_{1-4}烷基;且R^{11b}为-OH、-C(=O)OH或芳基;及

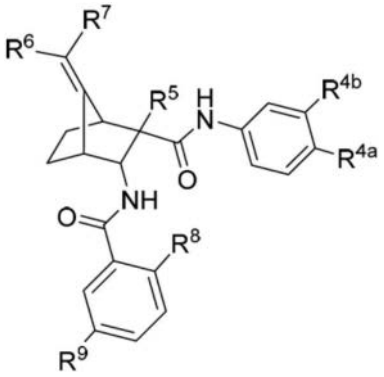
R^{13}为-OH。

[0033] 在式(VII)的一个实施方案中,R^{4a}为F;R^{4b}为CF_3;R^5为H;R^6为经0至3个F取代基取代的C_{1-3}烷基或C_{3-6}环烷基;R^8为-OCH_3;R^9为



R^{11a}为H或经0至1个R^{11b}取代的C_{1-2}烷基;且R^{11b}为-C(=O)OH。

[0034] 在第三方面的范畴内的第十四方面中,本发明提供式(VIII)化合物:



(VIII)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

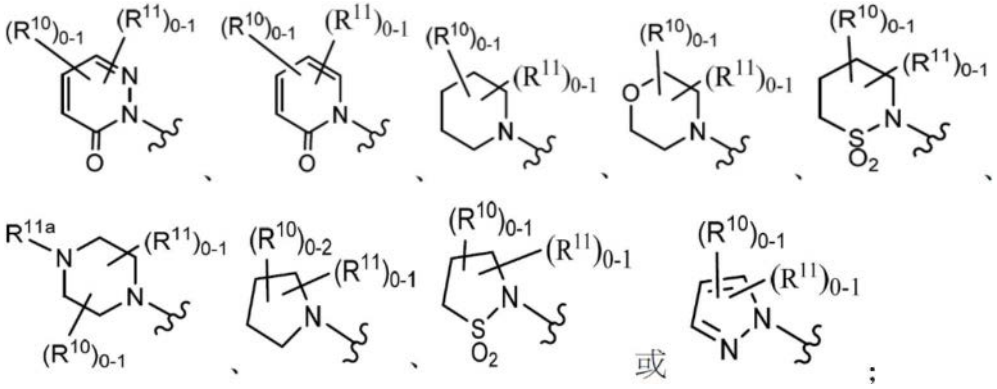
R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基;

R^6为经0至2个F取代基取代的C_{1-2}烷基、C_{3-6}环烷基或芳基;

R^7为H;

R^8为-OC_{1-3}烷基;

R^9为



R^{10}为卤基、CN、C_{1-4}烷基、=O、-OH或-OC_{1-4}烷基;

R^{11}为经0至1个R^{12}及0至1个R^{13}取代的C_{1-2}烷基、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$或-$C(=O)OR^b$;

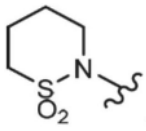
R^{12}为-$C(=O)OR^b$、-$C(=O)NHR^a$、-$C(=O)NHOR^b$或经0至3个卤基或-OH取代基取代的C_{1-4}烷基;

R^{13}为-OH或-$NR^aC(=O)R^b$;

R^a为H或C_{1-4}烷基;及

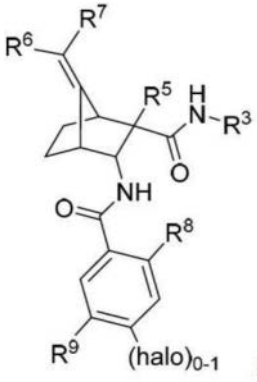
R^b为H、C_{1-4}烷基、或包含1至4个选自O、$S(=O)_p$及N的杂原子的3元至9元杂环基。

[0035] 在式(VIII)的一个实施方案中,R^{4a}为F;R^{4b}为CF_3;R^5为H;R^6为CF_3或环丙基;R^8为-OCH_3;R^9为



。

[0036] 在第一方面的范畴内的第十五方面中,本发明提供式(IX)化合物:



(IX)

或其药学上可接受的盐,其中:

R^3为C_{1-6}烷基、CF_3、经0至4个R^4取代的-$(CR_dR_d)_{0-1}$-C_{3-6}环烷基或经0至4个R^4取代的苯基;

R^4为卤基、CN、CH_3或CF_3;

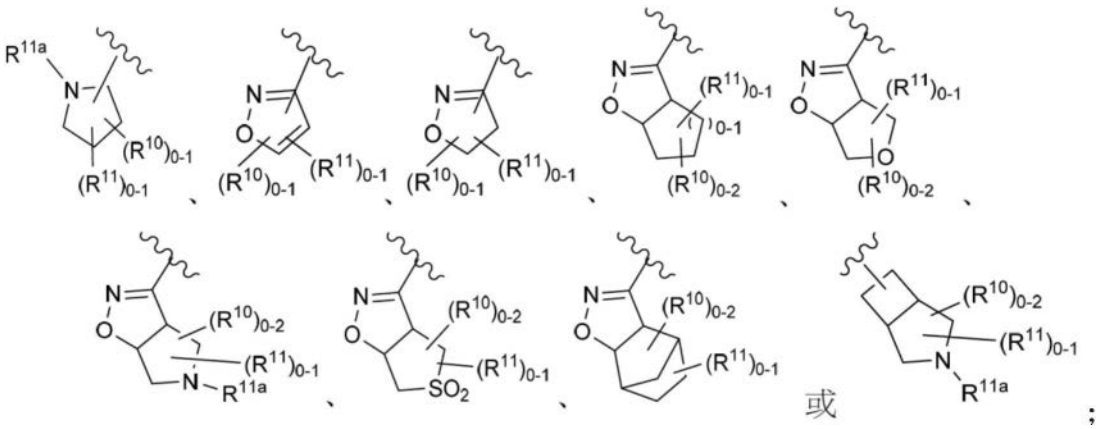
R^5为H;

R^6为C_{1-5}烷基、CF_3或经0至2个F取代基取代的C_{3-6}环烷基;

R^7为H;

R^8为卤基、-$N(C_{1-3}烷基)_2$、经0至1个-OC_{1-4}烷基取代基取代的-OC_{1-3}烷基;

R^9为



R^{10}为卤基、C_{1-4}烷基、-OH或-OC_{1-4}烷基；

R^{11}为经0至2个R^{12}及0至2个R^{13}取代的C_{1-4}烷基、-C(=O)OR^b、-C(=O)NR^aR^a或经0至2个R^e取代的C_{3-6}环烷基；

R^{11a}为H、经0至2个R^{11b}取代的C_{1-4}烷基、-C(=O)R^b或-C(=O)OC_{1-4}烷基；

R^{11b}为-OH；

R^{12}为经0至3个卤基取代基取代的C_{1-3}烷基或-C(=O)OR^b；

R^{13}为-OH；

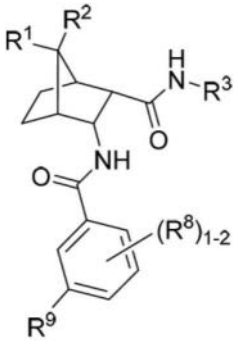
R^a为H或C_{1-3}烷基；

R^b为H或经0至1个R^e取代的C_{1-4}烷基；

R^e为-OR^f；及

R^f为H或C_{1-6}烷基。

[0037] 在第一方面的范畴内的第十六方面中，本发明提供式(X)化合物：



(X)

或其药学上可接受的盐，其中：

R^1为经C_{3-6}环烷基取代的C_{1-2}烷基；

R^2为H；

或R^1及R^2组合为=CR^6R^7；

R^3为经0至5个卤基、CN或-OC_{1-3}烷基取代基取代的C_{1-6}烷基、经0至5个R^4取代的-$(CHR^d)_n$-C_{3-10}碳环基、或包含1至3个选自O、S(=O)$_p$、N的杂原子且经0至3个R^4取代的5元至6元杂芳基；

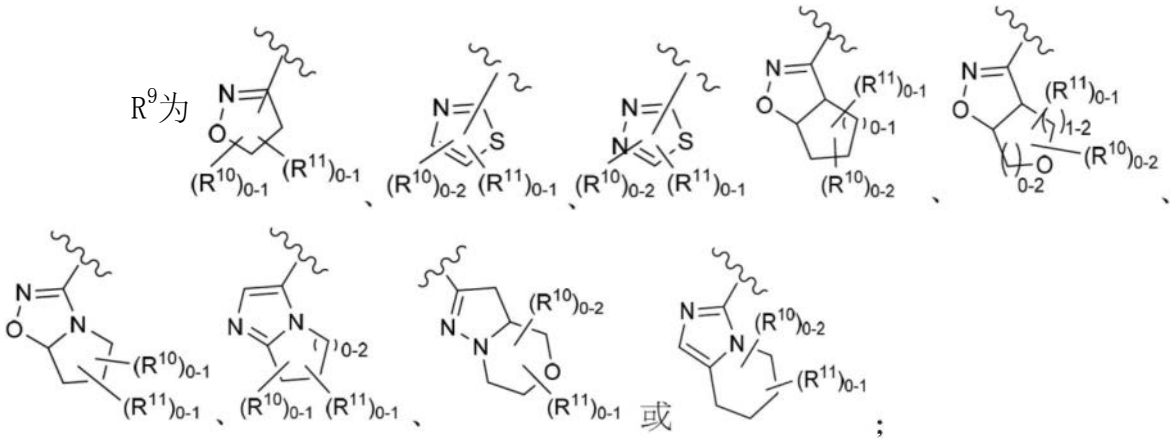
R^4为卤基、CN、S(=O)$_2CF_3$或经0至5个卤基取代基取代的C_{1-4}烷基；

R^6为卤基、经0至3个R^{6a}取代的C_{1-5}烷基、经0至3个R^{14}取代的C_{3-6}环烷基、或包含1至3个选自O、S及N的杂原子且经0至3个R^{14}取代的5元至6元杂环基；

R^{6a}为卤基、-OH或C_{3-6}环烷基；

R^7为H；

R^8为H、卤基、CN、C_{1-4}烷基或经0至5个卤基、-OH、C_{3-6}环烷基或-OC_{1-4}烷基取代基取代的-OC_{1-4}烷基；

R^9为  ；

R^{10}为卤基、CN、C_{1-4}烷基或-OH；

R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NHC(=O)R^b或C(=O)OR^b；

R^{12}为卤基；

R^{13}为-OR^b或C_{3-6}碳环基；

R^{14}为卤基、CN或经0至3个卤基取代基取代的C_{1-4}烷基；

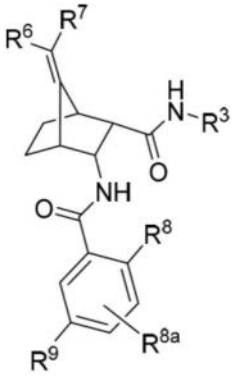
R^b为H或经0至5个R^e取代的C_{1-3}烷基；

R^d为H或C_{1-4}烷基；

R^e为-OH；及

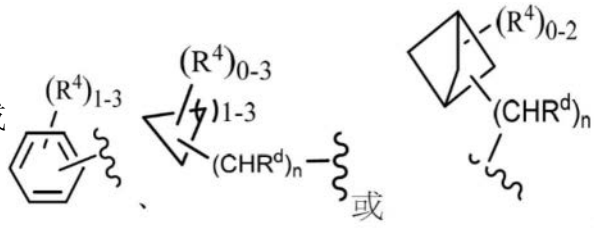
n为0或1。

[0038] 在第一方面的范畴内的第十七方面中，本发明提供式(XI)化合物：



(XI)

或其药学上可接受的盐，其中：

R^3为C_{1-5}烷基或  ；

R^4为卤基、CN、-S(=O)$_2CF_3$或经0至5个卤基取代基取代的C_{1-4}烷基；

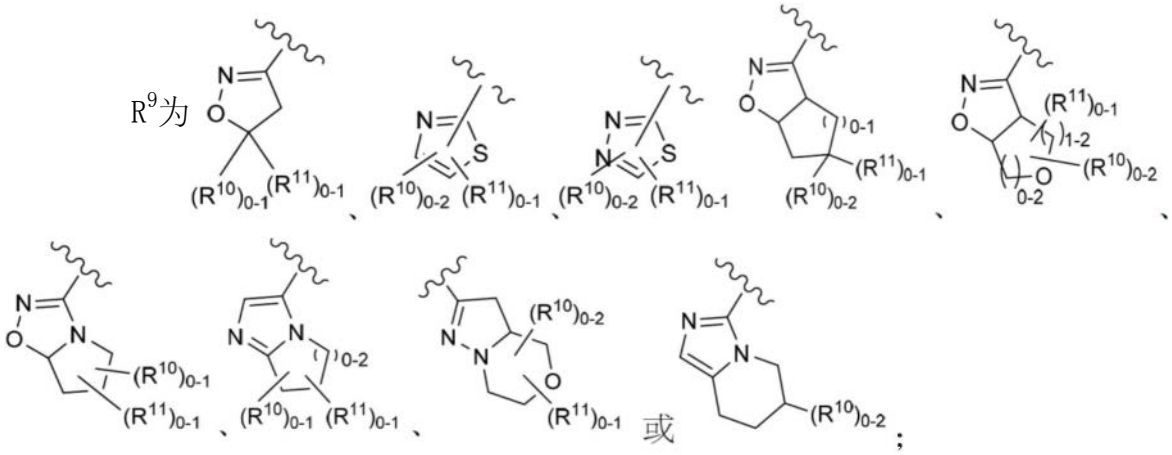
R^6为经0至4个R^{6a}取代的C_{1-5}烷基、经0至2个R^{14}取代的C_{3-6}环烷基、或包含1至3个选自O、S及N的杂原子且经0至2个R^{14}取代的5元至6元杂环基；

R^{6a}为卤基、-OH或C_{3-6}环烷基；

R^7为H；

R^8为经0至5个卤基、-OH、C_{3-6}环烷基或-OC_{1-3}烷基取代基取代的-OC_{1-3}烷基；

R^{8a}为H、卤基、CN或C_{1-3}烷基；

R^9为  ；

R^{10}为卤基、CN、C_{1-4}烷基或-OH；

R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基、-OR^b、-NHC(=O)R^b或-C(=O)OR^b；

R^{12}为卤基；

R^{13}为-OR^b或C_{3-6}碳环基；

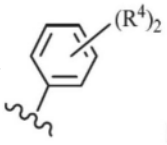
R^{14}为卤基或经0至3个卤基取代基取代的C_{1-4}烷基；

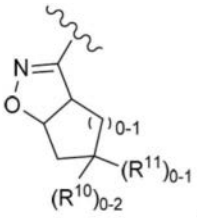
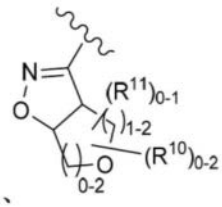
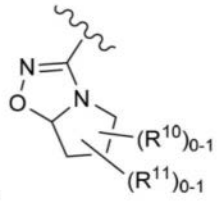
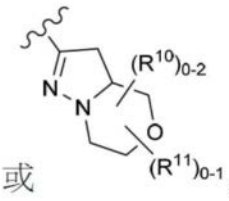
R^b为H或经0至5个R^e取代的C_{1-3}烷基；

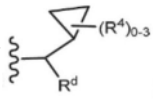
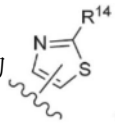
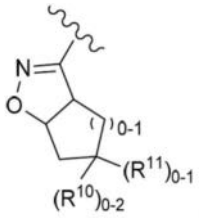
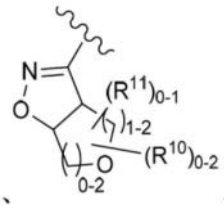
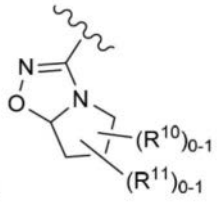
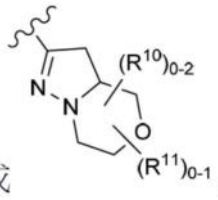
R^d为H或C_{1-2}烷基；及

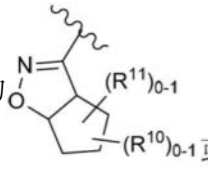
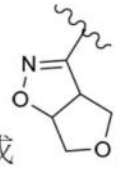
n为0或1。

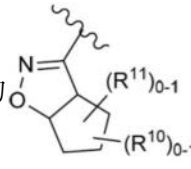
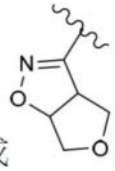
[0039] 对于式(I)化合物，可变取代基(包括R^1、R^2、R^3、R^4(R^{4a}、R^{4b}、R^{4c})、R^5、R^6、R^7、R^8(R^{8a})、R^9、R^{10}、R^{11}、R^{12}、R^{13}、R^{14}及R^{15})的任何例项的范畴可与可变取代基的任何其他例项的范畴独立地使用。因而，本发明包括不同方面的组合。

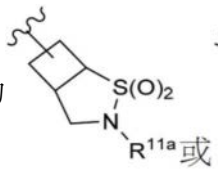
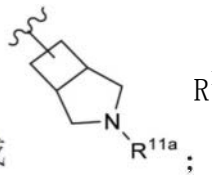
[0040] 在式(XI)的一个实施方案中，R^3为  R^4为卤基、CF_3或-OCF_3；R^6为C_{3-6}环烷基或经0至3个R^{6a}取代的C_{1-3}烷基；R^{6a}为卤基；R^7为H；R^8为经0至1个CF_3或-OCH_3取代基取代的-

OC_{1-3}烷基;R^9为  、  、  或  ;R^{10}为C_{1-4}烷基或-OH;R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基;R^{12}为卤基;且R^{13}为-OH。

[0041] 在式(XI)的另一个实施方案中,R^3为  ;R^4为卤基或经0至3个卤基取代基取代的C_{1-2}烷基;R^d为C_{1-2}烷基;R^6为  、经0至3个R^{6a}取代的C_{3-6}环烷基或经0至3个R^{6a}取代的C_{1-3}烷基;R^{6a}为卤基或-OH;R^{14}为经0至3个卤基取代基取代的C_{1-2}烷基;R^7为H;R^8为经0至1个C_{3-6}环烷基取代基取代的$-OC_{1-2}$烷基;R^{8a}为H或卤基;R^9为  、  、  或  ;R^{10}为C_{1-4}烷基或-OH;R^{11}为经0至3个R^{12}及0至1个R^{13}取代的C_{1-3}烷基;R^{12}为卤基;且R^{13}为-OH。

[0042] 在式(IX)的一个实施方案中,R^3为C_{1-4}烷基;R^6为CF_3或环丙基;R^7为H;R^8为$-OC_{1-2}$烷基;R^9为  或  ;R^{10}为-OH或$-OC_{1-4}$烷基;R^{11}为经0至2个R^{12}及0至2个R^{13}取代的C_{1-2}烷基;R^{12}为经0至3个卤基取代的C_{1-3}烷基或$-C(=O)OR^b$;且R^{13}为-OH。

[0043] 在式(IX)的另一个实施方案中,R^3为经0至1个R^4取代的环戊基、R^4为CN或C_{1-2}烷基;R^6为CF_3或环丙基;R^7为H;R^8为$-OC_{1-2}$烷基;R^9为  或  ;R^{10}为-OH或$-OC_{1-4}$烷基;R^{11}为经0至2个R^{12}及0至2个R^{13}取代的C_{1-2}烷基;R^{12}为经0至3个卤基取代基取代的C_{1-3}烷基或$-C(=O)OR^b$;且R^{13}为-OH。

[0044] 在式(IX)的另一个实施方案中,R^3为经0至2个R^4取代的苯基、R^4为卤基或CF_3;R^6为CF_3或环丙基;R^7为H;R^8为$-OC_{1-2}$烷基;R^9为  或  ;R^{11a}为H、经0至2个R^{11b}取代的C_{1-2}烷基;R^{11b}为-OH。

[0045] 在式(I)的另一个实施方案中,R^1及R^2与该两者所连接的碳原子形成二氧戊环基。

[0046] 在式(I)的另一个实施方案中,R^1及R^2组合为=NOC_{1-4}烷基,其中"="为双键。

[0047] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7,其中"="为双键。

[0048] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6及R^7皆为甲基。

[0049] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为甲基、乙基、丙基或丁基,其各自任选经-OH或卤基取代;R^7为H。

[0050] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为CF_3;R^7为H。

[0051] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为卤基;R^7为H。

[0052] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为经0至1个R^{14}取代的苯基;R^7为H;R^{14}为卤基、-OC_{1-4}烷基或苯基。

[0053] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为包含1至3个选自O及N的杂原子的5元杂环基;R^7为H。

[0054] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为C(=O)NH-苯基;R^7为H。

[0055] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为$C(=O)OC_{1-4}$烷基;R^7为H。

[0056] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为$C(=O)N(Me)_2$;R^7为H。

[0057] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为C_{3-6}环烷基;R^7为H。

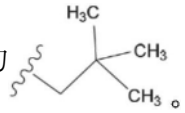
[0058] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为经卤基取代的-CH_2-C_{3-6}环烷基;R^7为H。

[0059] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6为环丙基;R^7为H。

[0060] 在式(I)的另一个实施方案中,R^1及R^2组合为=CR^6R^7;R^6及R^7与该两者所连接的碳原子形成环戊二烯基、二氢茚基或茚基。

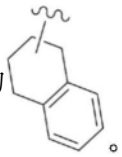
[0061] 在式(I)的一个实施方案中,R^3为经0至2个R^4取代的C_{1-6}烷基。

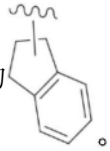
[0062] 在式(I)的另一个实施方案中,R^3为甲基、乙基、丙基或丁基或戊基。

[0063] 在式(I)的另一个实施方案中,R^3为 

。

[0064] 在式(I)的另一个实施方案中,R^3为经0至2个R^4取代的C_{3-6}环烷基。

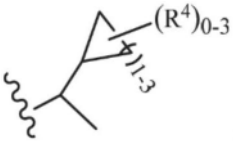
[0065] 在式(I)的另一个实施方案中,R^3为经0至2个R^4取代的C_{3-6}环烯基。在式(I)的另一个实施方案中,R^3为 
。

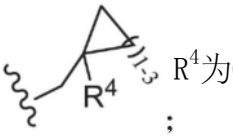
[0066] 在式(I)的另一个实施方案中,R^3为 
。

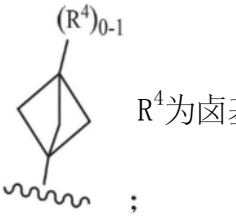
[0067] 在式(I)的另一个实施方案中,R^3为
。

[0068] 在式(I)的另一个实施方案中,R^3为经0至2个R^4取代的-$(CR^dR^d)_{1-2}$-苯基;R^4为卤基、CF_3或OCF_3;R^d为H或甲基。

[0069] 在式(I)的另一个实施方案中,R^3为经0至2个R^4取代的-(CHR^d)-C_{3-6}环烷基;R^4为卤基或C_{1-2}烷基;R_d为H或C_{1-2}烷基。

[0070] 在式(I)的另一个实施方案中,R^3为  ;R^4为卤基或C_{1-3}烷基。

[0071] 在式(I)的另一个实施方案中,R^3为  ;R^4为C_{1-2}烷基。

[0072] 在式(I)的另一个实施方案中,R^3为  ;R^4为卤基或CN。

[0073] 在式(I)的另一个实施方案中,R^3为包含1至2个选自O及N的杂原子的-$(CR^dR^d)_{1-2}$-5元杂环基;R^d为H或甲基。

[0074] 在式(I)的另一个实施方案中,R^4为卤基、CN、经0至3卤基取代的C_{1-2}烷基。

[0075] 在式(I)的另一实施方案中,R^3为环丙基、环丁基、经0至1个R^4取代的环戊基、或环己基;R^4为CN或C_{1-2}烷基。

[0076] 在式(I)的一个实施方案中,R^5为H、卤基或-OH。

[0077] 在式(I)的另一个实施方案中,R^5为H或-OH。

[0078] 在式(I)的一个实施方案中,R^6为经0至3个R^{6a}取代的C_{1-4}烷基或经0至3个R^{14}取代的C_{3-6}环烷基、或包含1至3个选自O、S、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂环基;R^{6a}为卤基、-OH或经0至3个卤基取代基取代的C_3-$_6$环烷基;R^{14}为卤基或经0至3个卤基取代基取代的C_{1-3}烷基。

[0079] 在式(I)的另一个实施方案中,R^6为经0至3个R^{14}取代的C_{3-6}环烷基;R^{14}为卤基取代基。

[0080] 在式(I)的另一个实施方案中,R^6为异丙基。

[0081] 在式(I)的一个实施方案中,R^7为H或C_{1-2}烷基。

[0082] 在式(I)的一个实施方案中,存在两个R^8变量。一个R^8为-OC_{1-3}烷基。有时称为R^{8a}的另一R^8为卤基或CN。

[0083] 在式(I)的一个实施方案中,R^9为经0至3个R^{10}及0至2个R^{11}取代的苯基。

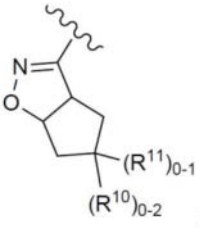
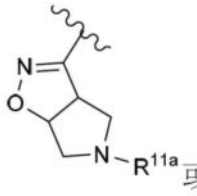
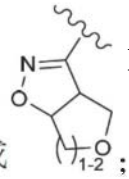
[0084] 在式(I)的另一实施方案中,R^9为经0至3个R^{10}及0至2个R^{11}取代的苯基;R^{10}为卤基;R^{11}为经0至4个R^{12}及0至2个R^{13}取代的C_{1-5}烷基;R^{12}为卤基或C(=O)OH;R^{13}为-OC(=O)NHR^a;R^a为C_{1-4}烷基、C_{3-6}烷基或苯基。

[0085] 在式(I)的另一实施方案中,R^9为经0至3个R^{10}及0至2个R^{11}取代的苯基;R^{10}为卤基;R^{11}为经0至4个R^{12}及0至2个R^{13}取代的C_{1-5}烷基;R^{12}为卤基或C(=O)OH;R^{13}为-NHC(=O)R^b;R^b为包含1至3个选自O、S及N的杂原子的3元至6元杂环基。

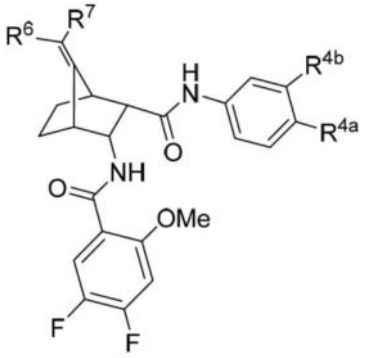
[0086] 在式(I)的另一个实施方案中,R^9为经0至1个R^{10}及0至1个R^{11}取代的苯基;R^{10}为卤基;R^{11}为包含1至4个选自O、$S(=O)_p$、N及NR^{15}的杂原子且经0至3个R^e取代的4元至9元杂环

基;R^e为-COOH或经0至5个R^g取代的C_{1-3}烷基;R^g为-OH。

[0087] 在式(I)的一个实施方案中,R^9为包含1至5个选自O、S(=O)$_p$、N及NR^{11a}的杂原子且经0至3个R^{10}及0至2个R^{11}取代的3元至12元杂环基。

[0088] 在式(I)的另一个实施方案中,R^9为  、  或  ;R^{10}为C_{1-2}烷基;R^{11}为经-OH取代基取代的C_{1-3}烷基,R^{11a}为经0至1个R^{11b}取代的-C(=O)C_{1-4}烷基;R^{11b}为-OH。

[0089] 在另一方面中,本发明提供式(IIIa)化合物:



(IIIa)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为经0至4个卤基取代基取代的C_{1-4}烷基;

R^6为卤基、经0至3个R^{6a}取代的C_{1-4}烷基、经0至1个苯基或-OH取代的C_{2-4}烯基、-C(=O)OR^b、C(=O)NHR^a、C_{3-6}环烷基、经0至3个R^{14}取代的C_{3-6}环烯基、经0至3个R^{14}取代的苯基、萘基、或包含1至3个选自O、S、N及NR^{14a}的杂原子且经0至3个R^{14}取代的5元至6元杂环基;

R^{6a}为卤基、-OH、C_{3-6}环烷基或苯基;

R^7为H;

或R^6及R^7与该两者所连接的碳原子一起形成环戊二烯基、二氢茚基或茚基;

R^{14}为卤基、CN、经0至3个卤基取代基取代的C_{1-4}烷基、经0至3个卤基取代基取代的-OC_{1-4}烷基、-$(CH_2)_{0-2}$-NR^aR^a、经0至3个R^e取代的-$(CH_2)_{0-2}$-芳基、经0至3个R^e取代的-O-芳基、或包含1至4个选自O、S(=O)$_p$及N的杂原子且经0至3个R^e取代的-$(CH_2)_{0-2}$-3元至12元杂环基;

R^{14a}为H或C_{1-3}烷基;

R^a为H或C_{1-3}烷基;

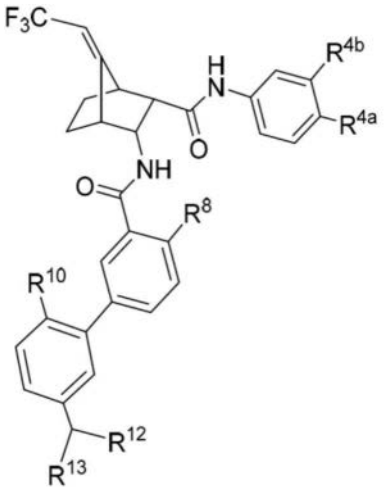
R^b为H或C_{1-3}烷基;及

p为0或2。

[0090] 在式(V)的一个实施方案中,R^{4a}为F或CH_3;R^{4b}为CF_3;R^6为苯基或包含1至2个选自O及N的杂原子的5元杂芳基;R^7为H;R^8为-OC_{1-2}烷基;R^{10}为卤基;R^{11}为-NHS(=O)$_2C_{1-2}$烷基、-C

(=O)OH、-C(=O)OC_{1-4}烷基、经0至1个R^e取代的-C(=O)NHC_{1-4}烷基、或包含1至4个选自O、N及NR^{15}的杂原子且经0至3个R^e取代的5元杂环基;R^{15}为H、C_{1-2}烷基或苯基;且R^e为=O或C(=O)OH。

[0091] 在另一方面中,本发明提供式(VIb)化合物:



(VIb)

或其药学上可接受的盐,其中:

R^{4a}为卤基;

R^{4b}为CF_3;

R^8为-OC_{1-4}烷基;

R^{10}为卤基;

R^{12}为-C(=O)OH、-C(=O)OC_{1-4}烷基、-C(=O)NHC_{1-4}烷基、-C(=O)$NHOC_{1-3}$烷基、或经0至3个卤基取代的C_{1-3}烷基;

R^{13}为-OR^b、-NR^aR^a、-$NR^aC(=O)R^b$、-$NR^aC(=O)OR^b$、-$NR^aS(=O)_pR^c$、-$NR^aS(=O)_pNR^aR^a$、-OC(=O)NR^aR^a、-OC(=O)NR^aOR^b、-$S(=O)_pNR^aR^a$或-$S(=O)_pR^c$;

R^a为H、经0至5个卤基取代基取代的C_{1-6}烷基、苯基、经0至4个R^e取代的C_{3-6}环烷基、螺环烷基、或经0至4个R^e取代的杂环基;或R^a及R^a与该两者所连接的氮原子一起形成经0至4个R^e取代的杂环基;

R^b为H、经0至5个R^e取代的C_{1-6}烷基、-$(CH_2)_n$-苯基、经0至4个卤基取代基取代的C_{3-6}环烷基、或包含1至4个选自O、$S(=O)_p$及N的杂原子且经0至4个R^e取代的3元至9元杂环基;

R^c为经0至4个R^e取代的C_{1-6}烷基,

R^e为卤基、CN、=O、经0至5个R^g取代的C_{1-5}烷基、C_{3-6}环烷基、芳基、4元至6元杂环基或-OR^f;

R^f为H、C_{1-6}烷基、C_{3-6}环烷基或芳基;

R^g为卤基;

n为0或1;及

p为0、1或2。

[0092] 在另一方面中,本发明提供式(VII)化合物或其药学上可接受的盐,其中:

R^{4a}为F;

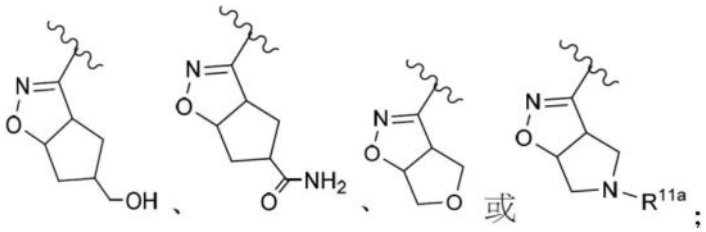
R^{4b}为CF_3；

R^5为H；

R^6为经0至3个F取代基取代的C_{1-3}烷基或C_{3-6}环烷基；

R^8为-OCH_3；

R^9为



；

R^{11a}为H、经0至2个R^{11b}取代的C_{1-3}烷基、经0至1个R^{11b}取代的-C(=O)C_{1-4}烷基、或-C(=O)OC_{1-4}烷基；及

R^{11b}为-OH、-C(=O)OH或芳基。

[0093] 除非另有指定，否则这些术语具有以下含义。

[0094] “卤基”包括氟、氯、溴及碘。

[0095] “烷基”或“亚烷基”意欲包括具有指定数目个碳原子的分支链与直链饱和脂族烃基。举例而言，“C_1至C_{10}烷基”或“C_{1-10}烷基”(或亚烷基)意欲包括C_1、C_2、C_3、C_4、C_5、C_6、C_7、C_8、C_9及C_{10}烷基。此外，例如“C_1至C_6烷基”或“C_1-C_6烷基”表示具有1至6个碳原子的烷基。烷基可未经取代或经取代，其中至少一个氢经另一化学基团置换。实施例甲基包括(但不限于)甲基(Me)、乙基(Et)、丙基(例如正丙基及异丙基)、丁基(例如正丁基、异丁基、叔丁基)及戊基(例如正戊基、异戊基、新戊基)。当使用“C_0烷基”或“C_0亚烷基”时，其意欲表示直接键。“烷基”亦包括氘代烷基，诸如CD_3。

[0096] “烯基”或“亚烯基”意欲包括具有一个或多个、优选一个至三个碳-碳双键的直链或分支链构型的烃链，碳-碳双键可存在于沿该链的任何稳定点处。举例而言，“C_2至C_6烯基”或“C_{2-6}烯基”(或亚烯基)意欲包括C_2、C_3、C_4、C_5及C_6烯基；诸如乙烯基、丙烯基、丁烯基、戊烯基及己烯基。

[0097] “炔基”或“亚炔基”意欲包括具有一个或多个、优选一至三个碳-碳三键的直链或分支链构型的烃链，碳-碳三键可存在于沿该链的任何稳定点处。举例而言，“C_2至C_6炔基”或“C_{2-6}炔基”(或亚炔基)意欲包括C_2、C_3、C_4、C_5及C_6炔基；诸如乙炔基、丙炔基、丁炔基、戊炔基及己炔基。

[0098] “碳环”、“碳环基”或“碳环残基”意指任何稳定3元、4元、5元、6元、7元或8元单环或双环，或7元、8元、9元、10元、11元、12元或13元双环或三环烃环，其中任一者可为饱和、部分不饱和、不饱和或芳族的。此类碳环基的例子包括(但不限于)环丙基、环丁基、环丁烯基、环戊基、环戊烯基、环己基、环庚烯基、环庚基、金刚烷基、环辛基、环辛烯基、环辛二烯基、[3.3.0]二环辛烷、[4.3.0]二环壬烷、[4.4.0]二环癸烷(十氢萘)、[2.2.2]二环辛烷、劳基、苯基、萘基、二氢茚基、金刚烷基、蒽基及四氢萘基(四氢萘)。如上文所示，碳环基定义亦包括桥接环(例如[2.2.2]二环辛烷)。当一个或多个碳原子连接两个非相邻碳原子时，产生桥接环。优选桥为一或两个碳原子。应注意，桥键始终将单环转化成三环。当环桥接时，关于环叙述的取代基亦可存在于桥上。当使用术语“碳环基”时，其意欲包括“芳基”、“环烷基”、“螺

环烷基”、“环烯基”。除非另外指定,否则优选碳环基为环丙基、环丁基、环戊基、环己基、苯基及二氢茚基。

[0099] “环烷基”意欲指环化烷基,包括单环、双环或多环环系统。“C_3至C_7环烷基”或“C_{3-7}环烷基”意欲包括C_3、C_4、C_5、C_6及C_7环烷基。单环环烷基的非限制性实施例包括环丙基、环丁基、环戊基、环己基、环庚基及环辛基。多环环烷基的非限制性实施例包括1-十氢萘基、降冰片烷基及金刚烷基。

[0100] “环烯基”意指环化烯基,包括在至少一个环中含有一个或多个双键的单环或多环环系统;但是若存在一个以上双键,则双键不能在所有环中形成完全非定域π电子系统(否则该基团将为如本文所定义的“芳基”)。“C_3至C_7环烯基”或“C_{3-7}环烯基”意欲包括C_3、C_4、C_5、C_6及C_7环烯基。

[0101] “螺环烷基”意指两个环经由单一原子连接的烃双环系统。环在大小及性质方面可不同,或在大小及性质方面相同。实施例包括螺戊烷、螺己烷、螺庚烷、螺辛烷、螺壬烷或螺癸烷。

[0102] “双环碳环基(bicyclic carbocyclyl)”或“双环碳环基(bicyclic carbocyclic group)”意指含有两个稠合环且由碳原子组成的稳定9元或10元碳环环系统。在两个稠合环中,一个环为与第二环稠合的苯并环;且第二个环为5元或6元饱和、部分不饱和或不饱和碳环。双环碳环基可在任何可产生稳定结构的碳原子处连接至其侧基。若所得化合物稳定,则本文中所描述的双环碳环基可在任何碳上经取代。双环碳环基的例子为(但不限于)萘基、1,2-二氢萘基、1,2,3,4-四氢萘基及二氢茚基。

[0103] “芳基”是指单环或多环芳族烃,其包括例如苯基、萘基及菲基。芳基部分是公知的且描述于例如Lewis,R.J.编,Hawley′s Condensed Chemical Dictionary,第13版,John Wiley&Sons,Inc.,New York(1997)中。

[0104] “苯甲基”意指其中一个氢原子经苯基置换的甲基,其中该苯基可任选经1至5个基团,优选1至3个基团取代。

[0105] “杂环(heterocycle)”、“杂环基(heterocyclyl)”或“杂环(heterocyclic ring)”意指稳定3元、4元、5元、6元或7元单环或双环、或7元、8元、9元、10元、11元、12元、13元或14元多环杂环,其为饱和、部分不饱和或完全不饱和的且含有碳原子及1个、2个、3个或4个独立地选自由N、O及S组成的组的杂原子;且包括其中任一上文所定义的杂环与苯环稠合的任何多环基团。氮及硫杂原子可任选经氧化(亦即,N→O及$S(O)_p$,其中p为0、1或2)。氮原子可经取代或未经取代(亦即N或NR,其中R为H或另一取代基(若定义))。杂环可在产生稳定结构的任何杂原子或碳原子处连接至其侧基。若所得化合物稳定,则本文所描述的杂环可在碳原子或氮原子上经取代。杂环基中的氮可任选经季铵化。优选的为,当杂环基中的S及O原子的总数超过1时,这些杂原子则彼此不相邻。优选的为,杂环基中的S及O原子的总数不超过1。杂环基的定义亦包括桥接环。当使用术语“杂环基”时,意欲包括“杂芳基”。

[0106] 杂环基的例子包括(但不限于)吖啶基、氮杂环丁基、吖辛基、苯并咪唑基、苯并呋喃基、苯并硫代呋喃基、苯并噻吩基、苯并噁唑基、苯并噁唑啉基、苯并噻唑基、苯并三唑基、苯并四唑基、苯并异噁唑基、苯并异噻唑基、苯并咪唑啉基、咔唑基、4aH-咔唑基、咔啉基、色满基、色烯基、噌啉基、十氢喹啉基、2H,6H-1,5,2-二噻嗪基、二氢呋喃并[2,3-b]四氢呋喃、呋喃基、呋咱基、咪唑烷基、咪唑啉基、咪唑基、1H-吲唑基、咪唑并吡啶基、假吲哚基

(indolenyl)、二氢吲哚基、吲嗪基、吲哚基、3H-吲哚基、靛红基(isatinoyl)、异苯并呋喃基、异色满基、异吲唑基、异二氢吲哚基、异吲哚基、异喹啉基、异噻唑基、异噻唑并吡啶基、异噁唑基、异噁唑并吡啶基、亚甲基二氧基苯基、吗啉基、萘啶基、八氢异喹啉基、噁二唑基、1,2,3-噁二唑基、1,2,4-噁二唑基、1,2,5-噁二唑基、1,3,4-噁二唑基、噁唑烷基、噁唑基、噁唑并吡啶基、噁唑烷基萘嵌间二氮杂苯基、羟吲哚基、嘧啶基、啡啶基、啡啉基、啡嗪基、啡噻嗪基、啡噁噻基、啡噁嗪基、呔嗪基、哌嗪基、哌啶基、哌啶酮基、4-哌啶酮基、胡椒基、喋啶基、嘌呤基、吡喃基、吡嗪基、吡唑烷基、吡唑啉基、吡唑并吡啶基、吡唑基、哒嗪基、吡啶并噁唑基、吡啶并咪唑基、吡啶并噻唑基、吡啶基、嘧啶基、吡咯烷基、吡咯啉基、2-吡咯烷酮基、2H-吡咯基、吡咯基、喹唑啉基、喹啉基、4H-喹嗪基、喹喔啉基、奎宁环基、四唑基、四氢呋喃基、四氢异喹啉基、四氢喹啉基、6H-1,2,5-噻二嗪基、1,2,3-噻二唑基、1,2,4-噻二唑基、1,2,5-噻二唑基、1,3,4-噻二唑基、噻蒽基、噻唑基、噻吩基、噻唑并吡啶基、噻吩并噻唑基、噻吩并噁唑基、噻吩并咪唑基、噻吩基(thiophenyl)、三嗪基、1,2,3-三唑基、1,2,4-三唑基、1,2,5-三唑基、1,3,4-三唑基及呫吨基。亦包含含有(例如)上述杂环基的稠合环及螺环化合物。

[0107] “双环杂环基(Bicyclic heterocyclyl)”、“双环杂环基(bicyclic heterocyclyl)”或“双环杂环基(bicyclic heterocyclic group)”意指稳定的9元或10元杂环系统,其含有两个稠环且由碳原子及1、2、3或4个独立地选自由N、O及S组成的组的杂原子组成。在两个稠合环中,一个环为5元或6元单环芳环,其包含5元杂芳基环、6元杂芳基环或苯并环,各稠合至第二环。第二环为5元或6元单环,其为饱和、部分不饱和或不饱和的且包含5元杂环基、6元杂环基或碳环基(限制条件为若第二环为碳环基,则第一环不为苯并环)。

[0108] 双环杂环基可在产生稳定结构的任何杂原子或碳原子处连接至其侧基。若所得化合物稳定,则本文中所描述的双环杂环基可在碳原子或氮原子上经取代。优选的为,当杂环基中的S及O原子的总数超过1时,这些杂原子则彼此不相邻。优选的为,杂环基中的S及O原子的总数不超过1。

[0109] 双环杂环基的例子为(但不限于)喹啉基、异喹啉基、呔嗪基、喹唑啉基、吲哚基、异吲哚基、吲哚啉基、1H-吲唑基、苯并咪唑基、1,2,3,4-四氢喹啉基、1,2,3,4-四氢异喹啉基、5,6,7,8-四氢喹啉基、2,3-二氢苯并呋喃基、色满基、1,2,3,4-四氢喹喔啉基及1,2,3,4-四氢喹唑啉基。

[0110] “杂芳基”意指稳定的单环及多环芳族烃,其包括至少一个杂原子环成员,诸如硫、氧或氮。杂芳基包括(但不限于)吡啶基、嘧啶基、吡嗪基、哒嗪基、三嗪基、呋喃基、喹啉基、异喹啉基、噻吩基、咪唑基、噻唑基、吲哚基、吡咯基、噁唑基、苯并呋喃基、苯并噻吩基、苯并噻唑基、异噁唑基、吡唑基、三唑基、四唑基、吲唑基、1,2,4-噻二唑基、异噻唑基、嘌呤基、咔唑基、苯并咪唑基、吲哚啉基、苯并二氧戊环基及苯并二噁烷。杂芳基经取代或未经取代。氮原子经取代或未经取代(亦即N或NR,其中R为H或另一取代基(若定义))。氮及硫杂原子可任选经氧化(亦即,N→O及$S(O)_p$,其中p为0、1或2)。

[0111] 如本文中所提及,术语“经取代”意谓至少一个氢原子置换为非氢基团,其限制条件为维持正常价数且取代产生稳定化合物。当取代基为酮基(亦即=O)时,则原子上的2个氢经置换。酮基取代基不存在于芳族部分上。当环系统(例如碳环或杂环)据称经羰基或双

键取代时,该羰基或双键意欲为该环的一部分(亦即在该环内)。如本文所用的环双键为在两个相邻环原子之间所形成的双键(例如,C=C、C=N或N=N)。

[0112] 在本发明化合物上存在氮原子(例如胺)的情况下,这些氮原子可通过用氧化剂(例如mCPBA和/或过氧化氢)处理而转化成N-氧化物,得到其他本发明化合物。因此,所展示及所主张的氮原子视为涵盖所展示的氮及其N-氧化物(N→O)衍生物。

[0113] 当任何变量在化合物的任何组分或式中出现一次以上时,其在每次出现时的定义独立于其在其他每次出现时的定义。因此,例如,若基团经展示经0至3个R基团取代,则该基团可任选经至多3个R基团取代,且R在每次出现时独立地选自R的定义。此外,取代基和/或变量的组合仅当这些组合产生稳定化合物时为容许的。

[0114] 若连至取代基之一键显示与连接环中的两个原子之一键交叉,则此类取代基可键合至该环上的任何原子。若所列取代基未指示此取代基键合至指定式的化合物的其余部分的原子,则此取代基可经此取代基中的任何原子键合。取代基和/或变量的组合仅在此类组合产生稳定化合物时为容许的。

[0115] 本发明包括化合物的所有药学上可接受的盐形式。药学上可接受的盐为相对离子不显著促成化合物的生理学活性或毒性且本身用作药理学等效物的盐。这些盐可根据常见有机技术、采用市售试剂制得。一些阴离子盐形式包括乙酸盐、醋硬脂酸盐、苯磺酸盐、溴化物、氯化物、柠檬酸盐、反丁烯二酸盐、葡萄糖醛酸盐、氢溴酸盐、盐酸盐、氢碘酸盐、碘化物、乳酸盐、顺丁烯二酸盐、甲磺酸盐、硝酸盐、双羟萘酸盐、磷酸盐、丁二酸盐、硫酸盐、酒石酸盐、甲苯磺酸盐及羟萘甲酸盐。一些阳离子盐形式包括铵、铝、苄星青霉素(benzathine)、铋、钙、胆碱、二乙胺、二乙醇胺、锂、镁、葡甲胺、4-苯基环已胺、哌嗪、钾、钠、缓血酸胺及锌。

[0116] 在整个说明书及随附权利要求书中,既定化学式或名称应涵盖其所有立体异构体及光学异构体及外消旋体(若这些异构体存在)。除非另外指明,否则所有手性(镜像异构体及非镜像异构体)及外消旋形式属于本发明的范畴内。镜像异构体及非镜像异构体为立体异构体的例子。术语“镜像异构体”是指彼此互为镜像且不可重叠的分子物种对之一。术语“非镜像异构体”是指不为镜像的立体异构体。术语“外消旋体”或“外消旋混合物”是指由等摩尔量的两种镜像异构体物质构成的组合物,其中该组合物缺乏光学活性。

[0117] 本发明包括化合物、滞转异构体及旋转异构体的所有互变异构象式。

[0118] 术语“相对离子”用于表示带负电的物质,诸如氯离子、溴离子、氢氧根、乙酸根及硫酸根。

[0119] 用于制备本发明化合物的所有方法及其中制备的中间体视为本发明的一部分。

[0120] 符号“R”及“S”代表手性碳原子周围的取代基的构型。异构体描述词“R”及“S”如本文所述用于表明相对于核心分子的原子构型且意欲如文献(IUPAC Recommendations 1996,Pure and Applied Chemistry,68:2193-2222(1996))中所定义般使用。

[0121] 术语“手性”是指分子的使其不可能叠印于其镜像上的结构特征。术语“同手性”是指镜像异构纯度的状态。术语“光学活性”是指同手性分子或手性分子的非外消旋混合物使偏振光平面旋转的程度。

[0122] 本发明意欲包括存在于化合物中的原子的所有同位素。同位素包括具有相同原子数但质量数不同的那些原子。作为一般实施例且非限制性地,氢的同位素包括氘及氚。碳的同位素包括^{13}C及^{14}C。本发明的同位素标记化合物一般可通过本领域技术人员已知的常规

技术或通过类似于本文所述的方法,使用经适当同位素标记的试剂代替原来使用的未经标记的试剂来制备。此类化合物可具有多种潜在用途,例如在测定生物活性时用作标准物及试剂。在稳定同位素的情况下,此类化合物可具有有利地调节生物学、药理学或药物动力学特性的潜能。

生物方法

[0123] RXFP1环单磷酸腺苷(cAMP)分析。将人类胚胎肾细胞293(HEK293)细胞及稳定表达人类RXFP1的HEK293细胞在补充有10%合格FBS及300μg/ml潮霉素(Life Technologies)的MEM培养基中培养。将细胞解离且悬浮于分析缓冲液中。分析缓冲液为含有20mMHEPES、0.05%BSA及0.5mM IBMX的HBSS缓冲液(具有钙及镁)。将细胞(每孔3000个细胞,除稳定表达人类RXFP1的HEK293细胞的每孔1500个细胞外)添加至384孔Proxiplates(Perkin-Elmer)中。将细胞立即用DMSO(最终2%)中的测试化合物以0.010nM至50μM范围内的最终浓度处理。将细胞在室温下培育30min。根据制造商说明书使用HTRF HiRange cAMP分析试剂试剂盒(Cisbio)测定细胞内cAMP的含量。分别在所供应裂解缓冲液中制备穴状化合物结合的抗cAMP及d2荧光团标记的cAMP的溶液。反应完成后,用等体积的d2-cAMP溶液及抗cAMP溶液裂解细胞。在1h室温培育后,使用Envision(Perkin-Elmer)在400nm激发及590nm及665nm的双重发射下来量测时差式荧光强度。通过绘制665nm发射的荧光强度与590nm发射的强度对照cAMP浓度的比率,以2.7μM至0.1pM的浓度范围下之外部cAMP标准建构校准曲线。随后通过根据cAMP含量对化合物浓度的绘图拟合4参数逻辑方程式来测定化合物抑制cAMP产生的效力及活性。

[0124] 在上文所描述的人类RXFP1(hRXFP1)HEK293 cAMP分析中测试下文所公开的例子,且发现其具有促效活性。表1列出针对实施例量测的hRXFP1 HEK293 cAMP分析中的EC_{50}值。

表1

实施例	EC_{50}	实施例	EC_{50}	实施例	EC_{50}
5	2,200	319	13	653	285.3
6	140	320	1,949	654	299.5
7	270	321	91	655	303.2
8	110	322	1,088	656	311.4
9	310	323	854	657	312
10	1,100	324	2,244	658	314.1
11	230	325	4,835	659	347.3
12	410	326	2,270	660	349.9
13	1,100	327	2,039	661	359.1
14	220	328	673	662	359.9
15	110	329	4,810	664	367.2
16	770	330	369	665	372.6
17	120	331	601	666	373.2
18	630	331	534	667	384.1
19	720	333	1,362	669	416.4
20	940	334	1,371	670	447.6
21	55	335	3,561	671	450.8
22	700	336	1,933	672	454.9
23	1,400	337	2,075	673	476.6
24	94	338	750	674	481
25	200	339	67	675	485.2
26	77	340	62	676	485.8

27	380	341	1,175	677	500.5
28	400	342	390	678	507.4
29	110	343	707	679	562.7
30	55	344	757	680	581.6
33	310	345	1,405	681	605.7
34	4,600	346	169	682	612.2
35	30	347	62	683	626.1
36	19	348	1,307	684	642.1
37	15	349	2,792	685	644.8
38	360	350	2,521	686	653.2
39	88	351	2,871	687	658
40	20	352	64	688	675
41	27	353	11	689	683.6
42	130	354	11	690	711.6
43	70	355	3	691	734.7
44	26	356	5	692	789
45	59	357	211	693	791.4
46	120	358	18	694	796.3
47	47	359	2	695	836.1
48	220	360	1,944	696	965.8
49	200	361	747	697	972
50	150	362	807	698	1,007
51	790	363	254	699	1,026
52	3,000	364	2,231	700	1,046
53	240	365	234	701	1,086
54	160	366	1,663	702	1,150
55	230	367	267	703	1,194
56	270	368	639	704	1,298

57	550	369	65	705	1,302
58	1,100	370	788	706	1,305
59	890	371	338	707	1,333
60	920	372	12	708	1,357
61	570	373	9	710	1,470
62	710	374	59	711	1,561
63	510	375	213	712	1,599
64	520	376	662	713	1,673
65	2,000	377	1,042	714	1,745
66	1,700	378	16	715	1,960
67	1,700	379	26	716	1,982
68	3,200	380	23	717	2,319
69	3,700	381	20	718	2,347
70	2,900	382	118	719	2,491
71	350	383	127	720	3,139
72	250	384	123	721	3,907
73	2,400	385	8	722	4,181
74	3,800	386	71	723	4,984
75	2,600	387	11	724	4,995
76	400	388	152	725	360
77	330	389	54	726	417
78	1,900	390	37	727	381
79	11	391	49	728	41
80	11	392	50	729	82
81	39	393	73	730	263
82	41	394	49	731	10
83	66	395	104	732	99
84	110	396	320	733	6.3

85	130	397	912	734	23
86	150	398	37	735	1.3
87	160	399	42	736	2.4
88	190	400	31	737	3.2
89	330	401	786	738	3.3
90	330	402	70	739	3.4
91	360	403	1,394	740	3.4
92	380	404	45	741	1.7
93	390	406	48	742	4.7
94	400	407	21	743	5
95	420	408	3	744	2.5
96	460	409	9	745	1.2
97	490	410	168	748	3.3
98	510	411	435	749	3.3
99	540	412	85	750	3.5
100	560	413	39	751	2.2
101	580	414	364	752	2.5
102	590	415	1,200	753	3.3
103	910	416	1	754	3.6
104	1,600	417	172	755	5
105	1,200	418	170	756	0.4
106	2,700	419	17	757	0.9
107	180	420	1	758	0.9
108	330	421	831	759	1
109	390	422	55	760	1.2
110	800	423	28	761	1.9
111	860	424	11	762	2
113	1,800	425	19	763	2.1

114	1,100	426	45	764	2.3
115	1,100	427	54	765	2.5
119	3,900	428	6	766	2.7
120	7	429	2	767	3
121	16	430	194	768	3
122	13	431	250	769	3.3
123	210	432	2	770	3.6
124	210	433	2	771	3.8
125	240	434	24	772	3.8
126	23	435	49	773	3.9
127	49	436	4	774	4.1
128	55	437	31	775	4.4
129	60	438	24	776	5
130	440	439	30	777	13.9
131	130	440	25	778	1.1
132	220	441	360	779	1.6
133	1,700	442	25	780	1.8
134	1,400	443	5	781	2.7
135	370	444	410	782	3.2
136	270	445	0.5	783	3.4
137	480	446	0.6	784	3.4
138	370	447	0.8	785	4
139	550	448	1.2	786	4
140	700	449	1.6	787	4.2
141	720	450	1.6	788	4.3
142	2,900	452	1.8	789	4.4
143	2,800	453	1.9	790	4.9
144	2,100	454	1.9	791	0.8

145	1,300	455	2	792	1.4
146	2,200	457	2.1	793	2.2
147	1,800	458	2.2	794	3.2
148	910	459	2.5	795	3.5
149	4,500	460	2.5	796	3.7
150	190	461	2.6	797	4.1
151	240	462	3	798	4.7
152	8	463	3.1	799	4.7
153	140	464	3.2	800	1
154	33	465	3.5	801	2
155	87	466	3.9	802	3
156	11	467	4	803	3.5
157	610	469	4.3	804	4
158	100	471	4.5	805	4.1
159	21	472	4.7	806	4.9
160	26	473	4.9	807	2.1
161	110	474	5	808	4.2
162	40	475	5.6	809	4.6
163	13	476	6.1	810	4.7
164	14	477	6.4	811	0.6
165	40	478	6.5	812	0.8
166	11	480	6.7	813	1
167	16	481	6.7	814	1.2
168	11	482	6.8	815	1.5
169	44	483	7.3	816	1.6
170	59	484	7.4	817	1.9
171	5	485	7.8	818	2.2
172	5	486	7.8	819	2.3

173	7	488	8.2	820	2.4
174	8	489	8.5	821	2.5
175	17	491	8.7	822	2.5
176	57	493	9.5	823	2.6
177	5	494	10.4	824	2.9
178	11	495	10.5	825	2.9
179	5	496	10.5	826	3
180	5	497	10.6	827	3.1
181	6	499	11	828	3.3
182	5	500	11	829	3.4
183	5	501	11.6	830	3.4
184	11	502	11.9	831	3.5
185	15	504	12.1	832	3.6
186	25	505	12.1	833	3.7
187	19	506	12.7	834	3.8
188	20	507	12.9	835	3.9
189	10	508	13	836	4.1
190	74	509	15.2	837	4.3
191	42	510	15.2	838	4.4
192	135	511	15.3	839	4.4
193	300	512	15.7	840	4.5
194	5	513	16.5	841	4.7
195	29	514	17.2	842	4.9
196	45	515	17.2	843	0.9
197	51	516	17.6	844	1.2
198	76	517	18	845	1.3
199	128	518	18.4	846	1.8
200	37	520	19.3	847	2.5

201	76	521	19.5	848	2.5
202	180	522	21.1	849	2.7
203	322	523	21.3	850	2.7
204	3,200	524	21.9	851	2.8
205	1	526	22.4	852	3.1
206	1	527	22.4	853	3.6
207	1	528	22.4	854	3.9
208	1	530	22.7	855	4.5
209	1	531	22.7	856	4.7
210	1	532	22.9	857	5
211	1	533	23.4	858	1.3
212	1	534	23.9	859	1.8
213	2	535	24	862	3.4
214	2	536	24.7	864	3.8
215	2	537	26	866	4.8
216	2	538	26.3	867	3.7
217	2	539	29.3	868	3.8
218	2	540	29.4	869	1.4
219	3	541	30	870	2.2
220	8	543	30.5	871	4.8
221	26	545	31.5	872	8
222	1	546	32.1	873	3.3
223	2	548	32.6	875	1.8
224	2	549	33	876	0.9
225	3	550	34.9	878	5.1
226	3	551	36.6	879	0.9
227	3	552	36.7	880	1.6
228	3	553	37.4	881	3.1

229	7	554	37.6	883	2.5
230	1	555	41.4	884	1
231	1	556	41.7	886	2.7
232	1	558	44.3	887	5.5
233	2	559	44.9	888	2.7
234	1	560	45.3	889	8.5
235	1	564	47.3	890	2.4
236	3	565	50.7	891	3.7
237	2	566	56.3	892	9.9
238	1	567	58.1	893	2.2
239	1	568	59.4	894	1.3
240	1	570	62.7	895	0.2
241	3	571	65.3	896	8.2
242	3	572	66.4	897	1
243	4	573	67.4	898	3.9
244	7	574	67.8	899	3
245	3	575	68.8	901	4.5
246	9	576	69.2	902	8.7
247	73	577	70.7	905	7
248	4	578	70.8	906	6.8
249	5	579	71.6	907	0.1
250	12	580	72.8	908	3.5
251	36	582	74.9	909	4
252	11	583	74.9	910	3.4
253	17	584	77.3	911	7.6
254	71	585	78.3	913	9
255	3	586	79.1	914	7.8
256	14	587	80.8	915	4

257	16	588	82	916	3.6
258	283	589	83.5	917	1.3
259	815	590	86.1	918	5.5
260	2,972	591	86.6	919	3.6
261	1,883	592	87.1	920	2.4
262	139	593	89.8	921	8.2
263	294	594	91.4	922	2.2
264	3,183	595	92.7	923	4.7
265	5	596	101.9	924	5.7
266	3,947	597	101.9	925	5.2
267	505	598	102	926	2.8
268	15	599	104.2	927	0.4
269	370	600	106.3	928	1.4
270	25	601	108	929	1.6
271	664	602	110	930	1.1
272	3,826	603	111.7	931	2.5
274	16	605	118.3	932	3.9
275	25	606	120.7	933	0.9
276	72	607	128.4	934	1.4
277	12	609	130.4	935	2.5
278	32	610	132.2	936	1.4
279	15	611	132.7	937	5.8
280	12	612	133.7	938	1.7
281	15	613	137.1	939	0.6
282	25	614	138.3	940	4.1
283	69	615	139.2	941	1.2
284	109	616	141.4	942	1.3
285	7	617	153	943	1.7

286	5	618	154.7	944	1.9
287	7	619	156.4	945	5.4
288	127	620	163	946	0.9
289	548	621	163.9	947	8.6
290	20	622	167.7	948	8.6
291	506	623	168.7	949	3.6
292	1,858	624	168.7	950	4.9
293	32	626	171.3	951	1
294	47	627	175.6	952	1.5
295	53	628	177	953	7
296	205	629	179.5	954	5.3
297	73	630	185.1	955	0.1
298	70	631	185.3	956	6.1
299	227	632	190.1	957	5.3
300	575	633	190.4	958	0.9
301	850	634	190.7	959	6.1
302	889	635	191	960	0.4
303	1,697	636	195.8	961	1
304	1,713	637	206.1	962	3.1
305	1,384	638	207.2	963	2.9
306	540	639	212.2	964	6.2
307	958	640	213.7	965	4.8
308	2,391	641	216.6	966	6.9
309	4,380	642	219	967	2.1
310	162	644	238.4	969	3.6
311	38	645	239.1	970	2
312	9	646	240.4	971	2.8
313	90	647	241.4	972	1.9

314	5	648	241.9	973	5.8
315	60	649	250.4	974	4.5
316	81	650	261.6	975	1,000
317	31	651	269.4	976	710
318	11	652	277.9		

药物组合物及使用方法

[0125] 式(I)化合物为RXFP1受体激动剂,且可用于治疗医学适应症,诸如心脏衰竭、纤维变性疾病及相关疾病,诸如肺病(例如特发性肺纤维化)、肾病(例如慢性肾病)或肝病(例如非酒精性脂肪变性肝炎及门静脉高血压)。式(I)化合物还可用于治疗动脉僵化、动脉弹性降低、动脉顺应性和扩张性降低所导致或引起的疾病,包括高血压、肾病、外周动脉疾病、颈动脉和脑血管疾病(即中风和痴呆)、糖尿病、导致终末器官损伤的微血管疾病、冠状动脉疾病和心力衰竭。本文所述化合物还可用于治疗先兆子痫。

[0126] 本发明的另一方面为一种药物组合物,其包含式(I)化合物及药学上可接受的载剂。

[0127] 本发明的另一方面为一种药物组合物,其包含用于治疗松弛素相关病症的式(I)化合物及药学上可接受的载剂。

[0128] 本发明的另一方面为一种治疗与松弛素相关的疾病的方法,其包含施用有效量的式(I)化合物。

[0129] 本发明的另一方面为一种治疗心血管疾病的方法,其包含向有需要的患者施用有效量的式(I)化合物。

[0130] 本发明的另一方面为一种治疗心脏衰竭的方法,其包含向有需要的患者施用有效量的式(I)化合物。

[0131] 本发明的另一方面为一种治疗纤维化的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0132] 本发明的另一方面为一种治疗与纤维化相关的疾病的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0133] 本发明的另一方面为一种治疗特发性肺纤维化的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0134] 本发明的另一方面为一种治疗肾病(例如慢性肾病)的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0135] 本发明的另一方面为一种治疗或预防肾衰竭的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0136] 本发明的另一方面为一种改善、稳定或恢复有需要的患者的肾功能的方法,其包含向该患者施用治疗有效量的式(I)化合物。

[0137] 本发明的另一方面为一种治疗特发性肺纤维化的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0138] 本发明的另一方面为一种治疗肾病(例如慢性肾病)的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0139] 本发明的另一方面为一种治疗非酒精性脂肪变性肝炎及门静脉高血压的方法,其包含向有需要的患者施用治疗有效量的式(I)化合物。

[0140] 本发明的另一方面为式(I)化合物用于预防和/或治疗松弛素相关病症的用途。

[0141] 本发明的另一方面为式(I)化合物用于预防和/或治疗松弛素相关病症。

[0142] 除非另有指定,否则以下术语具有所陈述的含义。

[0143] 如本领域技术人员所理解,术语“患者”或“个体”是指可能受益于使用RXFP1激动剂的治疗的任何人类或非人类有机体。例示性个体包括任何年龄的具有心血管疾病风险因素的人类。常见风险因素包括(但不限于)年龄、性别、体重、家族病史、睡眠呼吸暂停、酒精或烟草使用、缺乏运动性心律不整或胰岛素抗性的征象,诸如黑棘皮病(acanthosis nigricans)、高血压、血脂异常或多囊性卵巢综合征(PCOS)。

[0144] “治疗(treating)”或“治疗(treatment)”涵盖治疗如此领域的从业者所了解的疾病病况,且包括以下:(a)抑制疾病病况,亦即遏制其发展;(b)缓解疾病病况,亦即使得疾病病况消退;和/或(c)预防在哺乳动物中出现疾病病况,尤其在此类哺乳动物易感染疾病病况但尚未诊断为患有该疾病病况时如此。

[0145] 如本领域技术人员所了解,“预防(preventing/prevention)”涵盖预防性治疗(亦即防治和/或风险降低)亚临床疾病病况,旨在降低出现临床疾病病况的机率。基于已知相较于一般群体增加罹患临床疾病病况的风险的因素而选择用于预防性疗法的患者。“防治”疗法可分成(a)初级预防及(b)次级预防。初级预防定义为在尚未呈现临床疾病病况的个体中治疗,而次级预防定义为预防第二次出现相同或类似临床疾病病况。“风险降低(risk reduction)”或“降低风险(reducing risk)”涵盖降低临床疾病病况发展的发生率的疗法。因而,初级及次级预防疗法为风险降低的例子。

[0146] 如本领域技术人员所了解,“治疗有效量”意欲包括当单独或与其他药剂组合施用时有效治疗病症的本发明化合物的量。在应用于组合时,该术语是指无论组合、依序或是同时施用,均产生预防或治疗效果的活性成分的组合量。

[0147] “心血管系统病症”或“心血管病症”包括例如以下病症:高血压(hypertension)(高血压(high blood pressure))、周边及心血管病症、冠心病、稳定型及不稳定型心绞痛、心脏病发作、心肌功能不全、异常心律(或心律不整)、持续缺血性功能障碍(“冬眠心肌(hibernating myocardium)”)、暂时缺血后功能障碍(“顿抑心肌(stunned myocardium)”)、心脏衰竭、末梢血流紊乱、急性冠状动脉综合征、心脏衰竭、心肌疾病(心肌病(cardiomyopathy))、心肌梗塞及血管疾病(vascular disease)(血管疾病(blood vessel disease))。

[0148] “心脏衰竭”包括心脏衰竭的急性及慢性表达,以及更具体或相关类型的疾病,诸如晚期心脏衰竭、急性期后心脏衰竭、心肾综合征、心脏衰竭伴肾功能受损、慢性心脏衰竭、射出分率中程型慢性心脏衰竭(HFmEF)、代偿型心脏衰竭、代偿不全型心脏衰竭、右心衰竭、左心衰竭、全身衰竭、缺血性心肌症、扩张型心肌症、与先天性心脏缺损相关的心脏衰竭、心脏瓣膜缺损、与心脏瓣膜缺损相关的心脏衰竭、二尖瓣狭窄、二尖瓣闭锁不全、主动脉瓣狭窄、主动脉瓣闭锁不全、三尖瓣狭窄、三尖瓣闭锁不全、肺狭窄、肺瓣膜闭锁不全、与合并心

脏瓣膜缺损相关的心脏衰竭、心肌发炎(心肌炎)、慢性心肌炎、急性心肌炎、病毒性心肌炎、糖尿病性心脏衰竭、酒精性心肌病、与心脏储积病症相关的心脏衰竭、舒张性心脏衰竭、收缩性心脏衰竭、急性心脏衰竭恶化期、射出分率正常型心脏衰竭(HFpEF)、射出分率降低型心脏衰竭(HFrEF)、慢性射出分率降低型心脏衰竭(HFrEF)、长期射出分率正常型心脏衰竭(HFpEF)、心肌梗死后重塑(postmyocardial remodeling)、心绞痛、高血压、肺高血压及肺动脉高血压。

[0149] “纤维变性病症”涵盖特征为纤维化的疾病及病症,尤其包括以下疾病及病症:肝纤维化、肝硬化、NASH、肺纤维化(pulmonary fibrosis)或肺部纤维化(lung fibrosis)、心脏纤维化、心内膜心肌纤维化、肾病、小球体肾炎、间质性肾纤维化、由糖尿病引起的纤维变性损伤、骨髓纤维化及类似纤维变性病症、硬皮病、硬斑病、瘢痕瘤、肥大性瘢痕形成(亦在手术操作后)、痣、糖尿病性视网膜病变、增生性玻璃体视网膜病变及结缔组织病症(例如类肉瘤病)。

[0150] 松弛素相关病症包括(但不限于)心血管系统病症及纤维变性病症。

[0151] 本发明化合物可通过任何适合的手段施用,例如经口,诸如片剂、胶囊(其各自包括持续释放或定时释放调配物)、丸剂、散剂、颗粒剂、酏剂、酊剂、悬浮液(包括纳米悬浮液、微悬浮液、喷雾干燥分散液)、糖浆及乳液;舌下;经颊;非经肠,诸如通过皮下、静脉内、肌肉内或胸骨内注射,或输注技术(例如作为无菌可注射水溶液或非水溶液或悬浮液);经鼻,包括向鼻膜施用,诸如通过吸入喷雾施用;表面,诸如以乳霜或软膏形式;或经直肠,诸如以栓剂形式施用。其可单独施用,但一般将与基于所选施用途径及标准药物实践而选择的药物载剂一起施用。

[0152] “药物组合物”意谓包含本发明化合物与至少一种其他药学上可接受的载剂的组合的组合物。“药学上可接受的载剂”是指本领域一般接受用于向动物(尤其哺乳动物)递送生物活性剂的介质,视施用模式的性质及剂型而定,包括(亦即)佐剂、赋形剂或媒剂,诸如稀释剂、防腐剂、填充剂、流动调节剂、崩解剂、湿润剂、乳化剂、悬浮剂、甜味剂、调味剂、芳香剂、抗细菌剂、抗真菌剂、润滑剂及分散剂。

[0153] 药学上可接受的载剂根据一般本领域技术人员见识内的许多因素来调配。这些因素包括但不限于:所调配的活性剂的类型及性质;要施用含该药剂的组合物的个体;组合物的预期施用途径;以及所靶向的治疗适应症。药学上可接受的载剂包括水性及非水性液体介质,以及各种固体及半固体剂型。此类载剂可包括除活性剂之外的许多不同成分及添加剂,此类其他成分出于一般本领域技术人员熟知的多种原因包括于调配物中,例如稳定活性剂、黏合剂等。对于适合的药学上可接受的载剂及其选择所设计的因素的描述见于多种容易获得的来源,诸如Allen,L.V.,Jr.等人,Remington:The Science and Practice of Pharmacy(2卷),第22版,Pharmaceutical Press(2012)。

[0154] 本发明化合物的给药方案当然将视已知因素而变化,诸如特定药剂的药效学特征及其施用模式及途径;接受者的物种、年龄、性别、健康状况、医学条件及体重;症状的性质及程度;同时发生的治疗的种类;治疗频率;施用途径;患者的肾功能及肝功能;以及所需作用。

[0155] 借助于一般导引,各活性成分在用于指定作用时的每日口服剂量将在每天约0.01至约5000mg之间,优选每天约0.1至约1000mg之间,且最佳每天约0.1至约250mg之间的范围

内。静脉内施用时,在恒定速率输注期间最佳剂量将在每分钟约0.01至约10mg/kg的范围内。本发明化合物可以单次日剂量形式施用,或每日总剂量可分成每日两次、三次或四次分次剂量施用。

[0156] 化合物通常以与针对预期施用形式(例如口服片剂、胶囊、酏剂及糖浆)适当选择且与常规药物实践相符的适合药物稀释剂、赋形剂或载剂(在本文中统称为药物载剂)的混杂物形式施用。

[0157] 适合于施用的剂型(药物组合物)可含有每剂量单位约1毫克至约2000毫克的活性成分。在这些药物组合物中,活性成分通常将以按该组合物的总重量计约0.1-95重量%的量存在。用于经口施用的典型胶囊含有本发明化合物中的至少一者(250mg)、乳糖(75mg)及硬脂酸镁(15mg)。混合物通过60目筛且装入1号明胶胶囊中。通过将本发明化合物中的至少一者(250mg)以无菌方式放入小瓶中、以无菌方式冷冻干燥及密封来制造典型可注射制剂。对于使用,将小瓶的内含物与2mL生理食盐水混合产生可注射制剂。

[0158] 化合物可与适用于治疗疾病或病症的其他适合治疗剂组合使用,所述治疗剂包括:抗动脉粥样硬化剂、抗脂质异常剂、抗糖尿病剂、抗高血糖剂、抗高胰岛素剂、抗血栓剂、抗视网膜病变剂、抗神经病剂、抗肾病剂、抗缺血剂、抗高血压剂、抗肥胖剂、抗高血脂剂、抗高三酸甘油酯剂、抗高胆固醇剂、抗再狭窄药剂、抗胰脏病剂、降脂剂、厌食剂、记忆增强剂、抗痴呆剂、认知促进剂、食欲抑制剂、治疗心脏衰竭的药剂、治疗周边动脉疾病的药剂、治疗恶性肿瘤的药剂及消炎剂。

[0159] 其他治疗剂可包括ACE抑制剂、β-阻断剂、利尿剂、盐皮质激素受体拮抗剂、利阿诺定(ryanodine)受体调节剂、SERCA2a活化剂、肾素抑制剂、钙离子通道阻断剂、腺苷A1受体激动剂、部分腺苷A1受体、多巴胺β-羟化酶抑制剂、血管收缩素II受体拮抗剂、具有用于选择细胞信号传导路径的偏压促效作用的血管收缩素II受体拮抗剂、血管收缩素II受体拮抗剂与脑啡肽酶酶抑制剂的组合、脑啡肽酶酶抑制剂、可溶性鸟苷酸环化酶活化剂、肌凝蛋白ATP酶活化剂、rho-激酶1抑制剂、rho-激酶2抑制剂、爱帕琳肽(apelin)受体激动剂、硝酰基供体化合物、钙依赖性激酶II抑制剂、抗纤维化剂、半乳糖凝集素-3抑制剂、血管加压素受体拮抗剂、RXFP1受体调节剂、利尿钠肽受体激动剂、瞬时受体电位辣椒素-4通道阻断剂、抗心律不整剂、I_f“起搏电流”通道阻断剂、硝酸盐、毛地黄(digitalis)化合物、强心剂(inotropic agent)及β-受体激动剂、细胞膜再密封剂(例如泊洛沙姆(Poloxamer)188)抗高血脂剂、血浆HDL增强剂、抗高胆固醇血症剂、胆固醇生物合成抑制剂(诸如HMG CoA还原酶抑制剂)、LXR激动剂、FXR激动剂、普罗布考(probucol)、雷诺昔芬(raloxifene)、烟碱酸、烟碱酰胺、胆固醇吸收抑制剂、胆酸螯合剂、阴离子交换树脂、四级胺、消胆胺(cholestyramine)、考来替泊(colestipol)、低密度脂蛋白受体诱导剂、氯贝特(clofibrate)、非诺贝特(fenofibrate)、苯扎贝特(bezafibrate)、环丙贝特(ciprofibrate)、吉非贝齐(gemfibrizol)、维生素B6、维生素B12、抗氧化剂维生素、抗糖尿病剂、血小板凝集抑制剂、血纤维蛋白原受体拮抗剂、阿司匹林(aspirin)及纤维酸衍生物、PCSK9抑制剂、阿司匹林及P2Y12抑制剂,诸如氯吡格雷(Clopidogrel)。

[0160] 其他治疗剂亦可包括尼达尼布(nintedanib)、吡非尼酮(Pirfenidone)、LPA1拮抗剂、LPA1受体拮抗剂、GLP1类似物、曲罗芦单抗(tralokinumab)(IL-13,AstraZeneca)、维莫德吉(vismodegib)(刺猬拮抗剂,Roche)、PRM-151(正五聚素蛋白-2,TGFβ-1,Promedior)、

SAR-156597(双特异性Mab IL-4&IL-13,Sanofi)、辛妥珠单抗(simtuzumab)((抗赖氨酰氧化酶样2(抗LOXL2)抗体,Gilead)、CKD-942、PTL-202(PDE抑制剂/己酮可可碱(pentoxifylline)/NAC经口控制释放,Pacific Ther.)、奥米昔布(omipalisib)(经口PI3K/mTOR抑制剂,GSK)、IW-001(适度经口V型牛胶原蛋白溶液,ImmuneWorks)、STX-100(整合素αV/β-6 ant,Stromedix/Biogen)、阿克姆(Actimmune)(IFNγ)、PC-SOD(中度歧化酶(midismase);吸入型,LTT Bio-Pharma/CKD Pharm)、来瑞组单抗(lebrikizumab)(抗IL-13SC人源化mAb,Roche)、AQX-1125(SHIP1活化剂,Aquinox)、CC-539(JNK抑制剂,Celgene)、FG-3019(FibroGen)、SAR-100842(Sanofi)及奥贝胆酸(OCA或INT-747,Intercept)。

[0161] 以上其他治疗剂与本发明化合物组合使用时可以例如Physicians′Desk Reference(如以上所陈述的专利中)中所指示的量或另外由本领域的从业者确定的量使用。

[0162] 尤其当以单个剂量单元形式提供时,组合的活性成分之间可能存在化学相互作用。因此,当本发明化合物及第二治疗剂在单个剂量单元中组合时,其经调配使得尽管活性成分在单个剂量单元中组合,但活性成分之间的物理接触降至最低(亦即降低)。举例而言,一种活性成分可包覆肠溶包衣。通过对活性成分中之一种包覆肠溶包衣,不仅可使组合的活性成分之间的接触降至最低,而且可控制这些组分中之一者在胃肠道中的释放,使得这些组分中之一者不在胃中释放,而是在肠中释放。活性成分中之一者亦可包覆有影响在整个胃肠道中持续释放的物质,且亦用以使组合的活性成分之间的物理接触降至最低。此外,持久释放的组分可另外包覆肠溶包衣,使得此组分的释放仅在肠道中发生。另一方法将涉及组合产物的调配,其中一种组分包覆有持续和/或肠释放聚合物,且另一组分亦包覆有诸如低黏度级别的羟丙基甲基纤维素(HPMC)的聚合物或本领域已知的其他适当物质,以进一步分离活性组分。聚合物包衣用以形成与另一组分的相互作用的其他障壁。

[0163] 本发明化合物亦适用作涉及RXFP1的测试或分析中的标准或参考化合物,例如作为质量标准或对照。此类化合物可提供于例如用于涉及RXFP1活性的药物研究的市售试剂盒中。举例而言,本发明化合物可在分析中用作参考物以使其已知活性与具有未知活性的化合物相比较。此将确保实验者正确进行分析法且提供比较基础,尤其当测试化合物为参考化合物的衍生物时。当研发新的分析或方案时,根据本发明的化合物可用以测试其有效性。本发明化合物亦可用于涉及RXFP1的诊断分析中。

[0164] 本发明亦涵盖一种制品。如本文中所使用,制品意欲包括但不限于试剂盒及套装。本发明制品包含:(a)第一容器;(b)位于该第一容器内的药物组合物,其中该组合物包含第一治疗剂,该第一治疗剂包含本发明化合物或其药学上可接受的盐形式;以及(c)药品说明书,其陈述该药物组合物可用于治疗血脂异常及其后遗症。在另一实施方案中,药品说明书陈述该药物组合物可与第二治疗剂组合(如上文所定义)用于治疗血脂异常及其后遗症。制品可进一步包含:(d)第二容器,其中组分(a)及(b)位于第二容器中,且组分(c)位于第二容器内或外。位于第一及第二容器内意谓各别容器将物品固持于其边界内。

[0165] 第一容器为用以容纳药物组合物的盛器。此容器可用于制造、储存、运送和/或个别/整体出售。第一容器意欲涵盖瓶、罐、小瓶、烧瓶、注射器、管(例如用于乳膏制剂)或任何其他用于制造、容纳、储存或分配药物产品的容器。

[0166] 第二容器为用以容纳第一容器及任选选用的药品说明书的容器。第二容器的例子

包括(但不限于)盒(例如卡纸板或塑料)、板条箱、纸盒、袋(例如纸或塑料袋)、小袋及大袋。药品说明书可经由胶带、胶、卡钉(staple)或另一附着方法物理附着于第一容器之外部,或其可留在第二容器内部而不借助于任何物理方式附着于第一容器。或者,药品说明书位于第二容器之外部。当位于第二容器之外部时,药品说明书优选经胶带、胶、卡钉或另一附着方法物理附着。或者,其可与第二容器外部相邻或接触但不以物理方式附着。

[0167] 药品说明书为叙述与位于第一容器内的药物组合物有关的信息的标记、卷标、标记物等。所叙述信息通常将由控管出售制品的地区的监管机构(例如美国食品与药物管理局(United States Food and Drug Administration))决定。优选地,药品说明书具体叙述药物组合物已审批通过的适应症。药品说明书可由个人可读取其中或其上所含的信息的任何材料制成。优选地,药品说明书为上面已形成所需信息(例如印刷或涂覆)的可印刷材料(例如纸、塑料、卡纸板、箔、胶黏纸或塑料等)。

化学方法

[0168] 本发明化合物可通过本领域已知的多种方法制备,包括以下流程及特定实施方案部分中的方法。合成流程中所示的结构编号及变量编号与权利要求书或说明书其余部分的结构或变量编号不同,且不应混淆。流程中的变量仅欲说明如何制备一些本发明化合物。

[0169] 本发明不限于前述说明性实施例,且所述实施例应在所有方面被视为说明性的而非限定性的,且因此意欲涵盖权利要求书的等效意义及范围内出现的所有变化。

[0170] 亦将认识到,在本领域中,任何合成途径的规划中的另一主要考虑因素为审慎选择用于保护本发明中所描述的化合物中存在的反应性官能基的保护基。向经培训的从业者描述多种替代方式的权威性说明为Greene,T.W.等人,Protecting Groups in Organic Synthesis,第4版,Wiley(2007))。

[0171] 缩写定义如下:“1×”:一次;“2×”:两次;“3×”:三次;“℃”:摄氏度;“aq”:水溶液;“eq”或“equiv.”:当量;“g”:公克;“mg”:毫克;“L”:公升;“mL”:毫升;“μL”:微升;“N”:正常;“M”:摩尔;“nM”:纳摩尔;“pM”:皮摩尔;“mol”:摩尔;“mmol”:毫摩尔;“min”:分钟;“h”:小时;“rt”:室温;“RT”:保留时间;“atm”:大气压;“psi”:磅/平方时;“conc.”:浓缩物;“aq”:“水溶液”;“sat.”:饱和;“MW”:分子量;“MS”或“Mass Spec”:质谱;“ESI”:电喷雾电离质谱;“LC-MS”:液相色谱质谱;“HPLC”:高压液相色谱;“RPHPLC”:反相HPLC;“NMR”:核磁共振光谱;“SFC”:超临界流体色谱;“^{1}H”:质子;“δ”:德耳塔(δ);“s”:单重峰;“d”:双重峰;“t”:三重峰;“q”:四重峰;“m”:多重峰;“br”:宽峰;“Hz”:赫兹;“MHz”:百万赫;且“α”、“β”、“R”、“S”、“E”及“Z”为本领域技术人员熟悉的立体化学标示。

AcCl 乙酰氯

AcOH 乙酸

AIBN 偶氮二异丁腈

BHFFT 双(四亚甲基)氟甲脒鎓六氟磷酸盐

Boc 叔丁氧羰基

BuLi 丁基锂

DAST 二乙基氨基硫三氟化物

DCE 二氯乙烷

DCM 二氯甲烷

DIEA 二乙丙基乙胺

DMAP 4-二甲氨基吡啶

DMF 二甲基甲酰胺

DPPA 二苯基磷酰基叠氮化物

Et_2O 二乙醚

EtOAc 乙酸乙酯

EtOH 乙醇

HATU (1-[双(二甲氨基)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)

HMPA 六甲基磷酰胺

IPA 异丙醇

i-Pr 异丙基

KHMDS 双(三甲基硅基)氨基钾\

LDA 二异丙氨基锂

MeCN 乙腈

MeOH 甲醇

Me 甲基

NBS N-溴代丁二酰亚胺

Pd/C 钯/碳

pTsOH 对甲苯磺酸

PyBroP 溴三吡咯烷鏻六氟磷酸盐

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

TBAF 四正丁基氟化铵

t-Bu 叔丁基

Teoc 甲酸2-(三甲基硅基)乙酯

TFA 三氟乙酸

TFAA 三氟乙酸酐

THF 四氢呋喃

TsOH 甲苯磺酸

XPhos-Pd-G2 第2代XPhos预催化剂CAS编号1310584-14-5

[0172] 除了另外标记处以外,在例示性实施例中使用以下方法。经由正相或反相色谱进行中间体及最终产物的纯化。除非另有指示,否则使用预填充的SiO_2滤筒,用已烷及乙酸乙酯或DCM及MeOH的梯度洗脱来进行正相色谱。使用C18柱,通过UV220nm或制备型LCMS检测,用以下梯度洗脱来进行反相制备型HPLC:溶剂A(90%水、10%甲醇、0.1%TFA)及溶剂B(10%水、90%甲醇、0.1%TFA)的梯度;或溶剂A(95%水、5%ACN、0.1%TFA)及溶剂B(5%水、95%ACN、0.1%TFA)的梯度;或溶剂A(95%水、2%ACN、0.1%HCOOH)及溶剂B(98%ACN、2%水、0.1%HCOOH)的梯度;或溶剂A(95%水、5%ACN、10mM NH_4OAc)及溶剂B(98%ACN、2%水、10mM NH_4OAc)的梯度;或溶剂A(98%水、2%ACN、0.1%NH_4OH)及溶剂B(98%ACN、2%水、0.1%NH_4OH)的梯度。

[0173] 用于实施例的表征中的LC/MS方法列于下文。

[0174] 方法A:

仪器:Waters Acquity联合WatersMICROMASS®ZQ质谱仪

线性梯度:2至98%B,经1min,其中在98%B下的保持时间为0.5min

UV观测:220nm

柱:Waters BEH C18,2.1×50mm

流动速率:0.8mL/min(方法A)

移动相A:0.05%TFA,100%水

移动相B:0.05%TFA,100%乙腈

[0175] 方法B:

仪器:Shimadzu Prominence HPLC联合Shimadzu LCMS-2020质谱仪

线性梯度:0至100%B,经3min,其中在100%B下的保持时间为0.75min

UV观测:220nm

柱:Waters Xbridge C18,2.1×50mm,1.7μm粒子

流动速率:1mL/min

移动相A:10mM乙酸铵,95:5水:乙腈

移动相B:10mM乙酸铵,5:95水:乙腈

[0176] 方法C:

仪器:Shimadzu Prominence HPLC联合Shimadzu LCMS-2020质谱仪

线性梯度:0至100%B,经3min,其中在100%B下的保持时间为0.75min

UV观测:220nm

柱:Waters Xbridge C18,2.1×50mm,1.7μm粒子

流动速率:1mL/min

移动相A:0.1%TFA,95:5水:乙腈

移动相B:0.1%TFA,5:95水:乙腈

[0177] 方法D:

仪器:Waters Acquity联合WatersMICROMASS®ZQ质谱仪

线性梯度:10%B至98%B,经1min,其中在98%B下的保持时间为0.5min

UV观测:220nm

柱:Waters Acquity GEN C18,2.1×50mm,1.7μm粒子

流动速率:1mL/min

移动相A:0.05%TFA,100%水

移动相B:0.05%TFA,100%乙腈

[0178] 方法E:

仪器:Shimadzu Prominence HPLC联合Shimadzu LCMS-2020质谱仪

线性梯度:0至100%B,经1min,其中在100%B下的保持时间为0.5min

UV观测:220nm

柱:Waters Acquity BEH C18,2.1×50mm,1.7μm粒子

流动速率:1mL/min

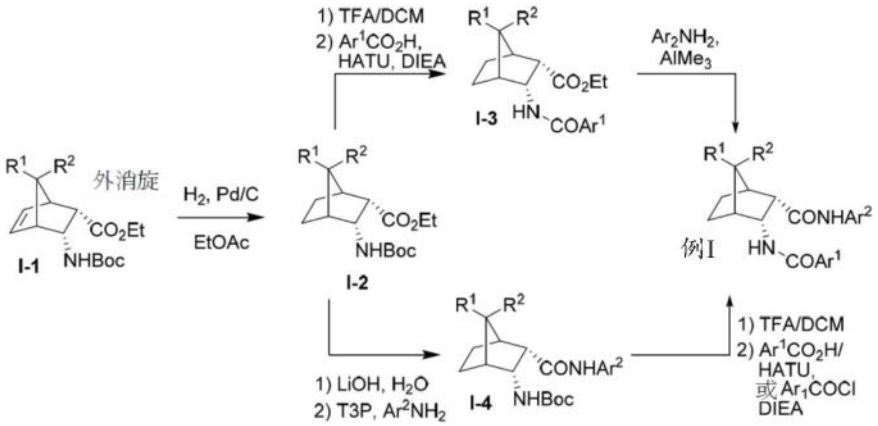
移动相A:10mM乙酸铵,95:5水:乙腈

移动相B:10mM乙酸铵,5:95水:乙腈

[0179] 实施例的表征中采用的NMR。使用在如下频率下操作的Bruker或JEOL®傅立叶变换光谱仪获得^{1}H NMR光谱:^{1}H NMR:400MHz(Bruker或JEOL®)或500MHz(Bruker或JEOL®)。光谱数据以如下格式报导:化学位移(多重性、偶合常数及氢的数目)。以四甲基硅烷内标(δ单元,四甲基硅烷=0ppm)的ppm下场和/或参考溶剂峰指定化学位移,其在^{1}H NMR光谱中呈现为2.51ppm(对于DMSO-d_6)、3.30ppm(对于CD3OD)、1.94ppm(对于CD3CN)及7.24ppm(对于$CDCl_3$)。

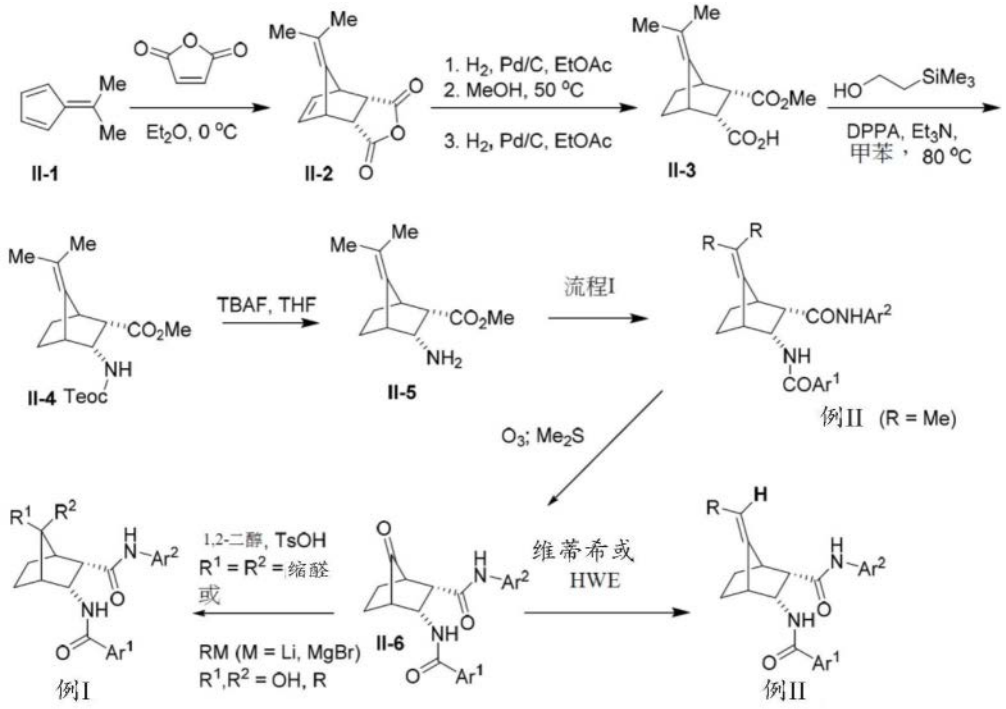
[0180] 流程I描述降冰片烷基实施例可如何以降冰片烷基中间体I-1为起始物质来制备或如何如后续流程中所描述来制备,所述降冰片烷基中间体为市售的(R^1=R^2=H)。以经保护的氨基酯(诸如I-1)为起始物质,可在氢化条件(例如Pd/C、H_2)下还原烯烃。所得受Boc保护的胺I-2接着可使用TFA脱除保护基,随后采用各种酰胺键形成条件(例如HATU或BOP-Cl,DIEA)用苯甲酸进行后续酰化,得到I-3。酯I-3可随后通过用适合的胺及$AlMe_3$处理而直接转化为通式结构I的例子。或者,酰胺键形成反应的顺序可颠倒,以I-2的皂化开始,随后用T3P®及适当胺处理,得到I-4。根据先前所描述的条件的脱除保护基及酰化接着亦得到通式结构I的例子。另外,初始氢化步骤可延迟至该顺序中的任何点,而不改变流程1中所描述的步骤的结果。

流程I



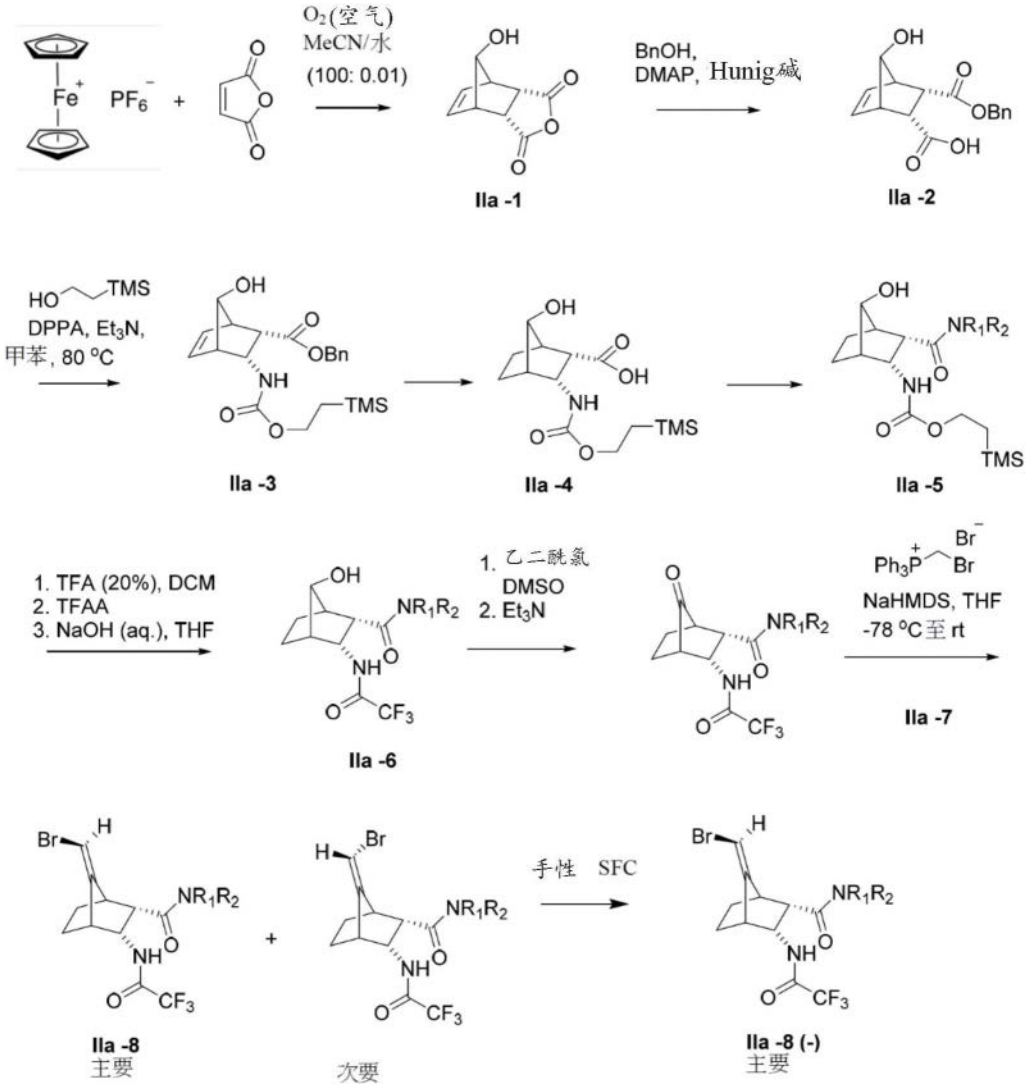
[0181] 流程II展示一种用于以II-1为起始物质产生在C7位置具有取代的降冰片烷基类似物的方法。用苹果酸酐处理II-1得到II-2,其选择性地经氢化且溶剂化以产生II-3。II-3与DPPA在三甲基硅烷醇存在下发生柯提斯反应(Curtius reaction),以便形成II-4。在标准条件下使Teoc基团脱除保护基使胺II-5形成,胺II-5可经直接加工为通式结构II的例子。或者,可用臭氧处理结构II,得到酮II-6,酮II-6又可经由多种标准变换而官能化,包括(但不限于)有机金属添加(例如,R-Li、R-MgBr)、维蒂希(Wittig)或霍纳-沃兹沃思-埃蒙斯(Horner-Wadsworth Emmons;HWE)烯化或缩醛形成。这些产物可充当通式结构I或II本身的例子,或可替代地可充当中间体以用于进一步加工。另外,臭氧化反应步骤可出于策略原因而在合成顺序中较早进行,而不改变流程II中概述的合成步骤的结果。

流程II



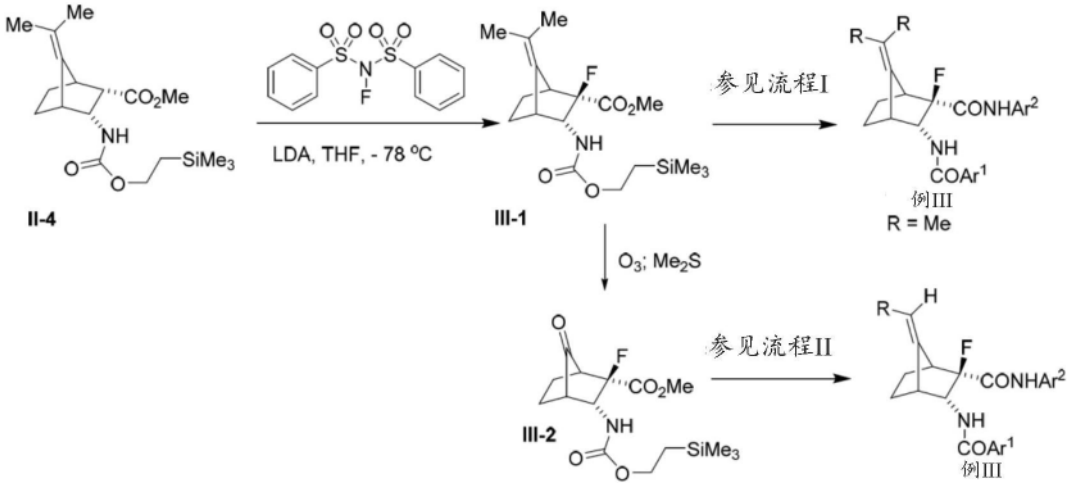
流程IIa

[0182] 降冰片烷基中间体IIa-8亦可通过流程IIa中所示的通用途径由呋喃-2,5-二酮及六氟磷酸二茂铁制备。进行狄耳士-阿尔德缩合(Diels Alder condensation),随后水解得到IIa-2,经柯提斯重排反应得到中间体胺,其在氢化条件还原且随后受保护,得到中间体IIa-3使苯甲基酯裂解且与NHR_1R_2发生交叉偶合,产生具有通式结构IIa-5的中间体。C7羟基转化成酮,随后进行维蒂希烯化,产生主要异构体中间体IIa-8。通过色谱将主要异构体与次要异构体分离且外消旋体经分离成镜像纯IIa-8(-)。



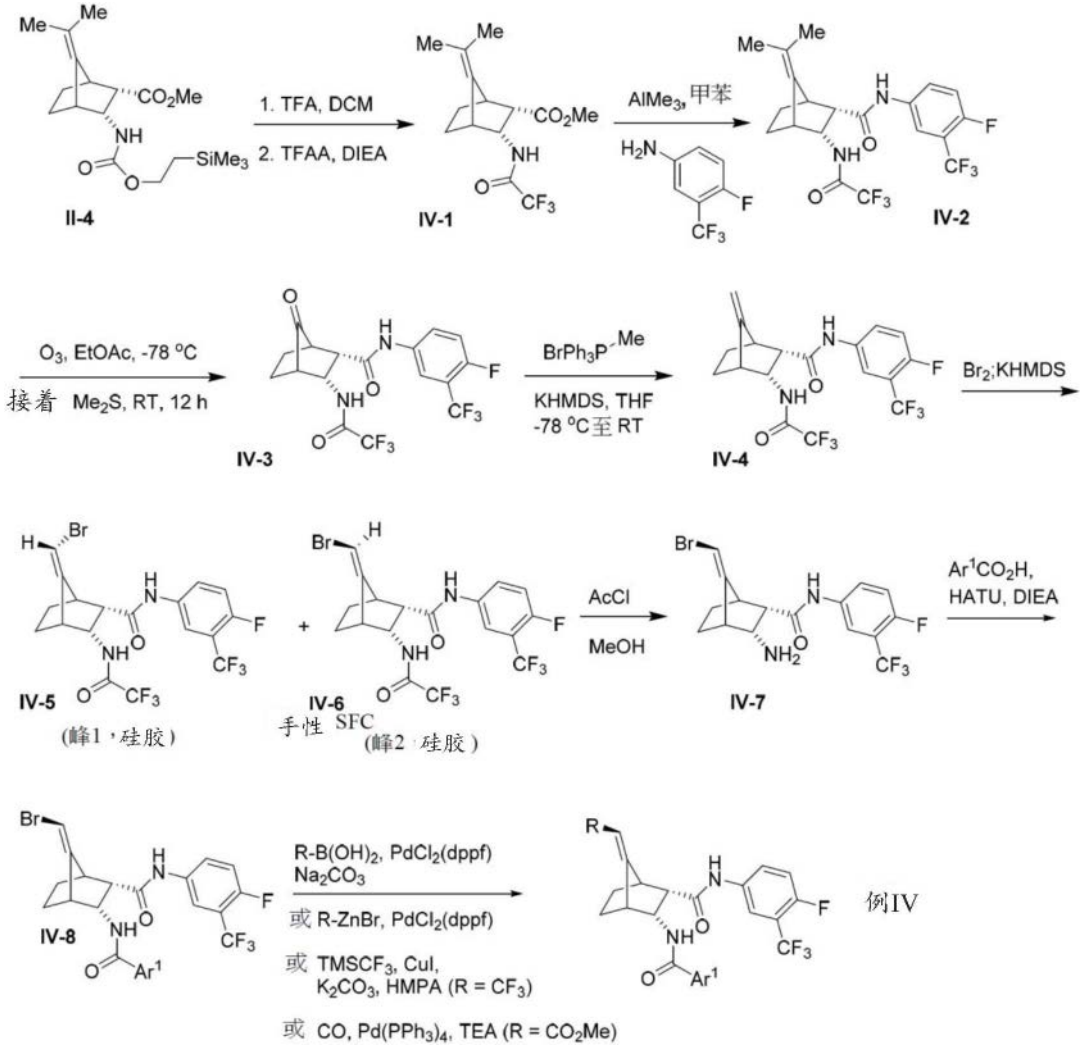
[0183] 流程III展示降冰片烷基核心可如何氟化。以II-4为起始物质,将该物质用LDA去质子化且用N-氟-二苯亚磺酰胺氟化,随后根据流程I中所概述的路径加工为通式结构III的例子。或者,III-1可与流程II中类似用臭氧处理,得到III-2。中间体III-2可随后用维蒂希或HWE条件处理且如流程II中加工,得到通式结构(III)的例子。

流程III



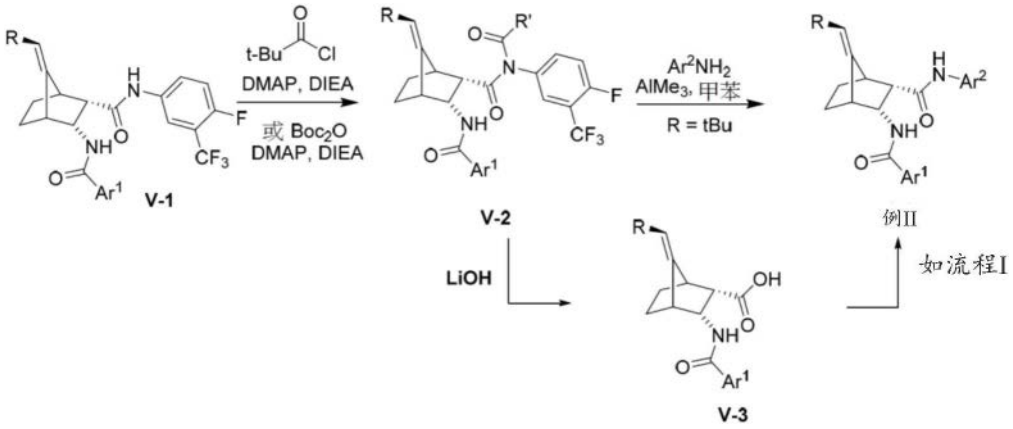
[0184] 流程IV展示由常见中间体溴化物制备多种不同的经C-7亚甲基取代的降冰片烷基核心。经由标准Teoc脱除保护基、TFA酰化程序将II-4转化成IV-1。根据流程I中所概述的AlMe3程序将酯IV-1转化成酰胺IV-2,且与流程II中一样使IV-2发生臭氧化反应,得到酮IV-3。维蒂希甲基化得到烯烃IV-4,其经溴及KHMDS处理,得到呈通过硅胶色谱分离的异构体混合物形式的IV-5及IV-6。随后对异构体IV-6进行手性SFC纯化,产生IV的单一镜像异构体,接着使其脱除保护基,得到IV-7。胺IV-7可随后根据流程1中所概述的方法酰化,得到IV-8。溴乙烯亦可进一步官能化(例如铃木、根岸及Semmelhack反应条件及其他),其产生通式结构IV的不同实施例或可随后进一步加工的对应中间体。或者,可对IV-6进行溴乙烯官能化步骤,且以通式结构IV的例子类似的方式处理所得物质。

流程IV



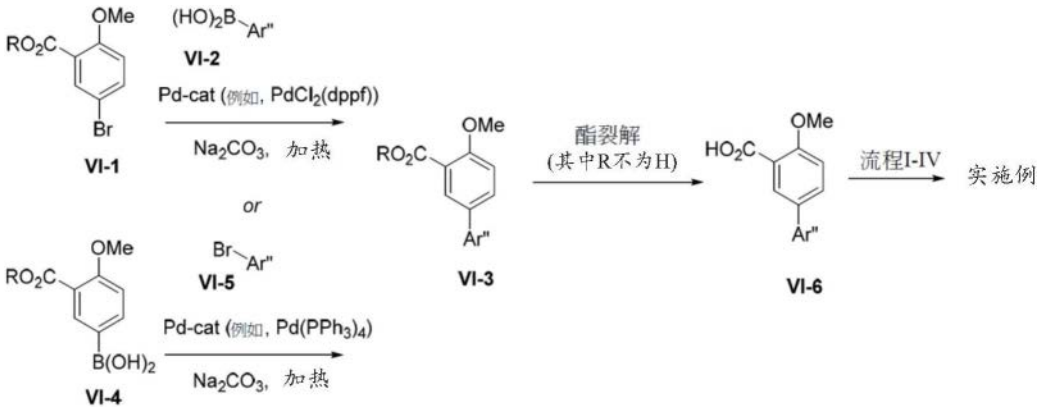
[0185] 流程V展现在高度加工的甲酸降冰片烷基酯上引入不同酰胺的方法。根据流程I-IV中所描述的方法制备的中间体V-1可用特戊酰氯、DMAP及DIEA处理,得到V-2。所得酰亚胺可在$AlMe_3$存在下用胺直接置换,得到通式结构II的例子。或者,可经由使用氢氧化物(例如LiOH、NaOH等)水解V-2,得到V-3,其可根据流程I中所概述的方法进一步官能化,得到通式结构II的例子。

流程V



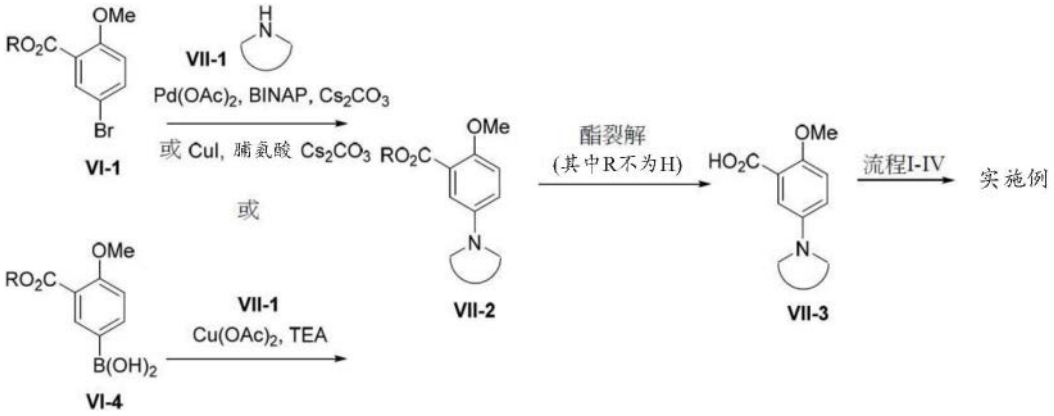
[0186] 流程VI描述用于流程I-IV中的双环苯甲酸酯(Ar1＝-Ar′-Ar″,其中Ar″＝经取代的苯基、杂芳基或杂环烯烃)的合成。在铃木反应条件下用芳基、杂芳基及杂环乙烯基硼酸(或酯)VI-2、钯催化剂(例如$Pd(PPh_3)_4$、$PdCl_2$(dppf)等)、适当的碱(例如,Na_2CO_3、K_3PO_4等)处理芳基溴化物VI-1(其中R可为H、Me、Bn、tBu及其他),得到双环VI-3。或者,可在类似条件下使用芳基硼酸VI-4及卤化物VI-5来颠倒偶合搭配物,以同样产生VI-3。在VI-3,R≠H的情况下,可采用皂化条件(例如LiOH,针对R＝Me的水)、酸性条件(例如,针对R＝tBu的TFA/DCM)或氢解条件(例如Pd/C,针对R＝Bn的H_2)裂解苯甲酸酯,得到VI-6。接着可如流程I-IV中所概述使苯甲酸VI-6与降冰片烷基核心偶合,得到通式结构I或II的例子或可进一步加工为实施例的中间体。

流程VI



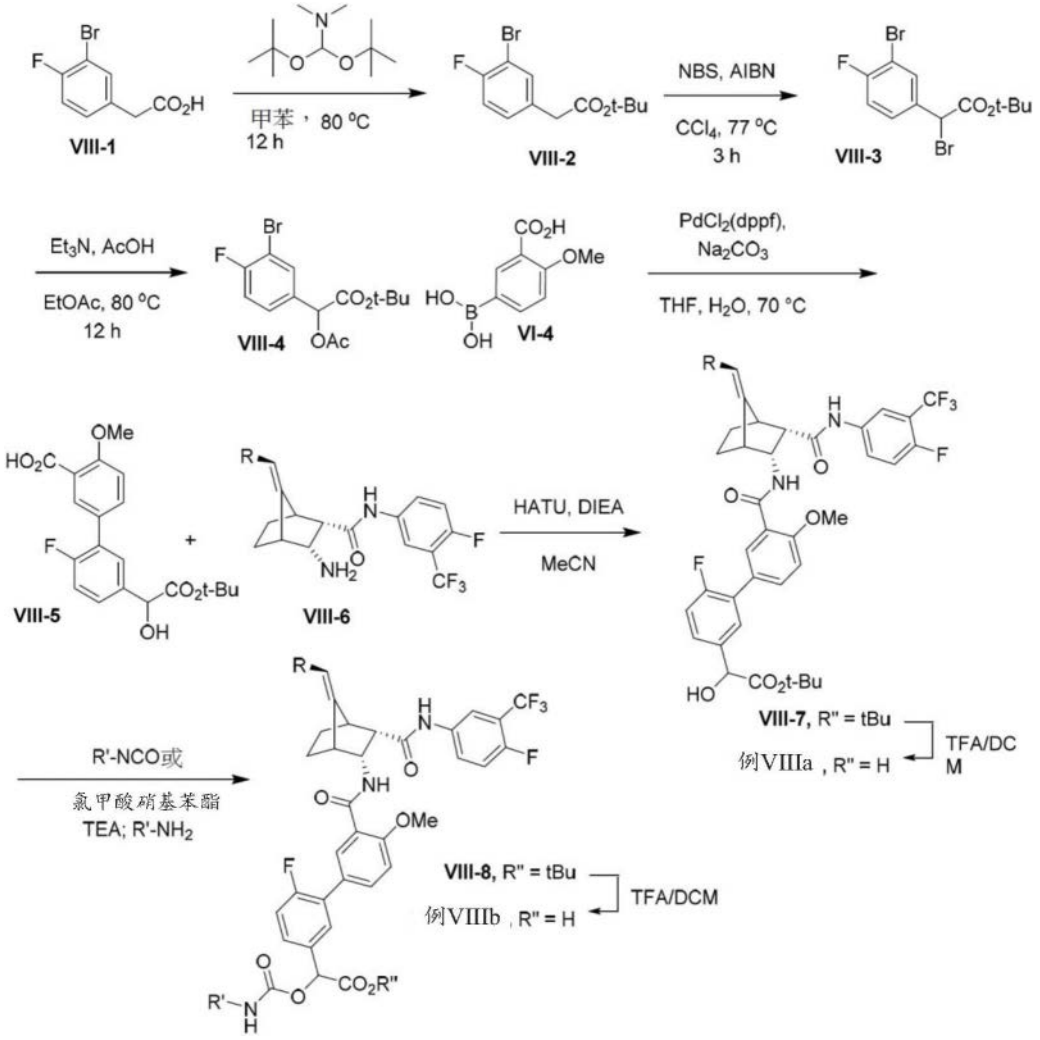
[0187] 流程VII概述由苯甲酸酯中间体VI-1或VI-4合成N-键联的氮杂环双环苯甲酸酯。在布赫瓦尔德-哈特维希(Hartwig-Buchwald)反应条件(例如$Pd(OAc)_2$、BINAP、Cs_2CO_3及其他)或乌耳曼Ullman)反应条件(例如CuI、脯氨酸、Cs_2CO_3及其他)下用胺VII-1处理VI-1,得到双环VII-2。或者,可根据Chan-Evans-Lam条件(例如$Cu(OAc)_2$、TEA、O_2及其他)由VI-4制备VII-2。中间体VII-2可随后在需要时经由酯裂解以与流程VI中的VI-3类似的方式进一步官能化,且根据流程I-IV进一步操作,直接得到通式结构I或II的例子或可进一步加工成实施例的中间体。

流程VII



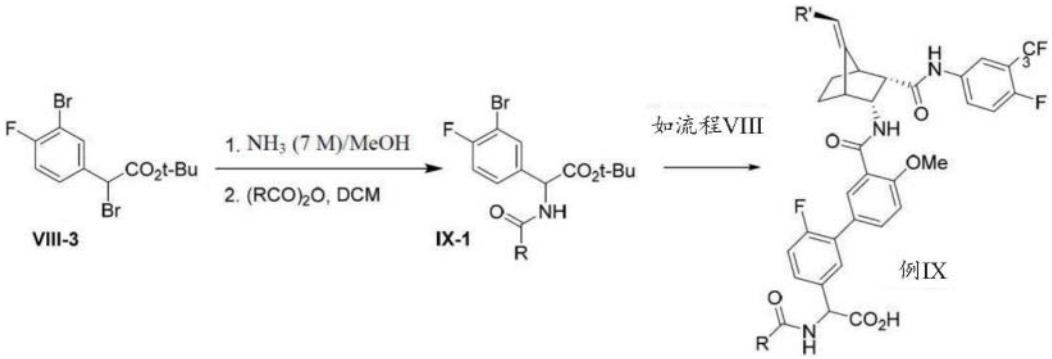
[0188] 流程VIII说明得到基于杏仁酸的联芳基类似物的通用途径。将市售VIII-1转化为叔丁酯VIII-2,接着溴化,得到VIII-3。溴化物经乙酸置换得到中间体VIII-4,接着如流程VI中所描述进行铃木反应,得到VIII-5(乙酸酯裂解伴随联芳基形成)。如流程I中所描述将所得酸直接与降冰片烷基中间体VIII-6偶合,得到VIII-7。接着可裂解(TFA/DCM)叔丁酯VIII-7,得到通式结构VIIIa的例子。或者,VIII-7中的羟基可用适当异氰酸根或两步氨基甲酸酯形成方案(例如氯甲酸硝苯酯、TEA,接着胺)加工,得到IVII-8,其接着可经裂解(TFA/DCM),得到通式结构VIIIb的例子。

流程VIII



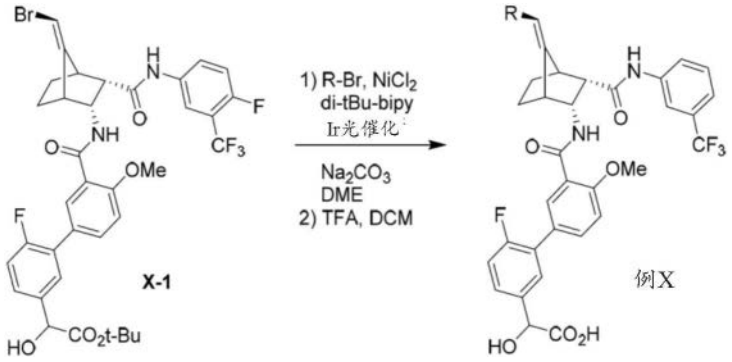
[0189] 流程IX展示对流程VIII中允许制备基于苯基甘氨酸的联芳基类似物的步骤的修改。用氨处理中间体VIII-3,接着进行酰化,得到中间体IX-1,其根据流程VIII中所概述的方法加工,得到通式结构IX的例子。

流程IX



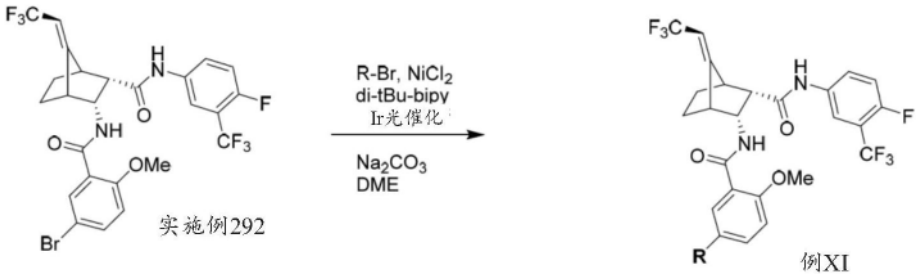
[0190] 流程X描述一种可由中间体X-1制备具有不同脂族C-7取代基的类似物的方法,该中间体X-1本身根据流程VIII中概述的途径制备。在MacMillan等人(J.Am.Chem.Soc.2016,138,8084-8087)中概述的条件下用烷基溴化物处理中间体X-1,随后对tBu酯进行后续脱除保护基,产生通式结构X的例子。

流程X



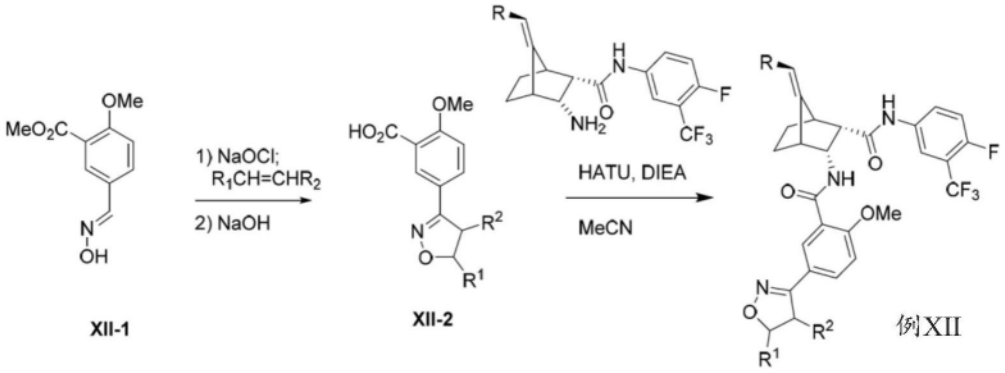
[0191] 流程XI表明制备可由实施例292制备的具有不同脂族芳基取代基(R)的类似物的途径。在MacMillan等人(J.Am.Chem.Soc.2016,138,8084-8087)中概述的条件下用烷基溴化物处理实施例292,得到通式结构XI的类似物。

流程XI



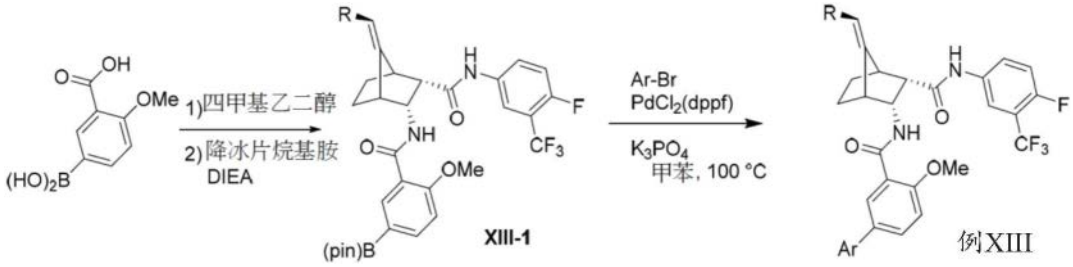
[0192] 流程XII描述一种产生经取代的异噁唑啉类似物的途径。用NaOCl处理XII-1,随后通过后续酯皂化用经取代的烯烃处理,得到中间体XII-2。这些中间体为根据流程1中所概述的方法与降冰片烷基胺偶合,得到通式结构XII的例子。

流程XII



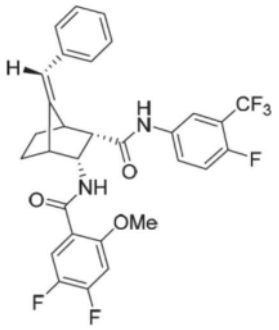
[0193] 流程XIII描述用于产生具有不同芳基取代基(Ar)的类似物的途径。用四甲基乙二醇处理硼酸VI-4,随后与降冰片烷基酰胺(根据以上流程制备)进行酰胺偶合,得到XIII-1。在标准无水铃木条件下用芳基卤化物处理XIII-1,以便形成类似物XIII。

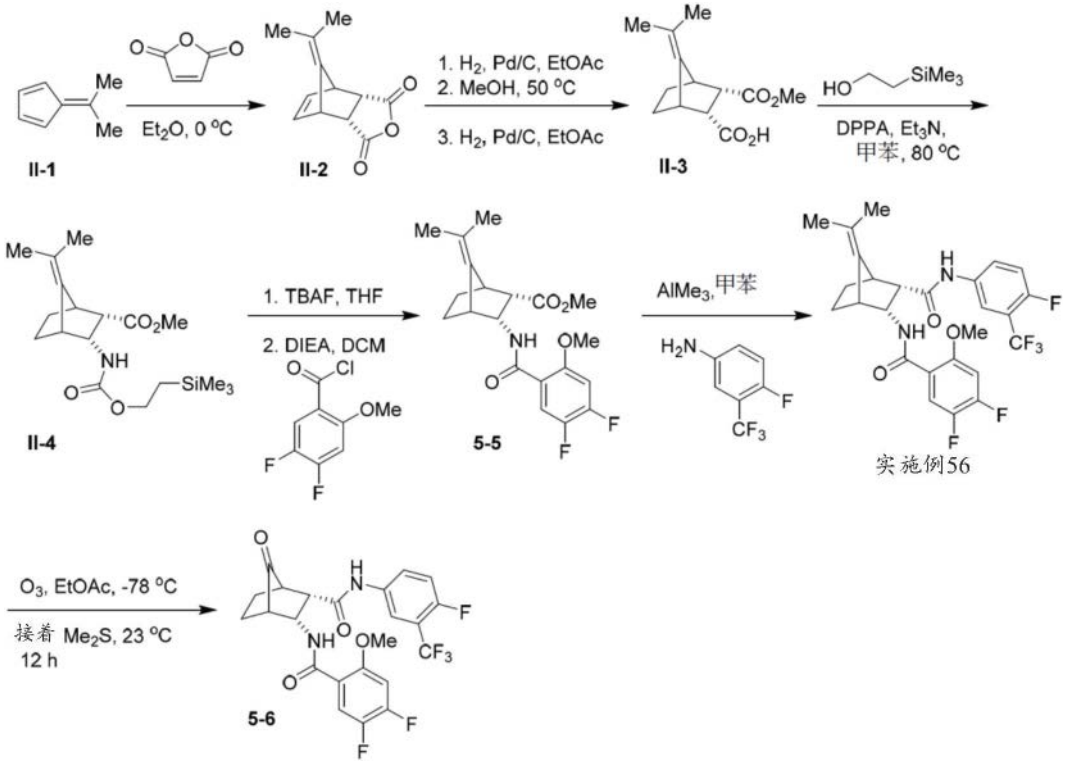
流程XIII



实施例

[0194] 实施例5





中间体II-2:在0℃向反应容器中添加Et_2O(100mL)、5-丙烷-2-亚基)环戊-1,3-二烯(II-1,10g,94mmol)及呋喃-2,5-二酮(10g,102mmol)。将反应混合物在0℃搅拌18h,在减压下浓缩且经由硅胶色谱纯化,得到II-2(3.74g,18.3mmol,19.0%产率)。中间体II-2为已知化合物;请参见:2011年12月29目的PCT国际申请案2011163502。

[0195] 中间体II-3:向反应容器中添加II-2(2.74g,13.4mmol)、EtOAc(100mL)、吡啶(0.540mL,6.71mmol)及Pd/C(70mg,0.070mmol)。将反应混合物在23℃在1atm H_2(H_2气球)下搅拌60min,经硅藻土过滤,且在减压下浓缩。将所得中间体溶解于甲醇(50mL)中且在50℃加热12h。在减压下浓缩反应混合物(与甲苯3×15mL共沸),产生II-3(3.21g,13.5mmol,100%产率),其不经进一步纯化即使用。

[0196] 中间体II-4:向反应容器中添加II-3(3.2g,13mmol)、Et_3N(3.38mL,24.3mmol)、甲苯(75mL)及二苯基磷酰基叠氮化物(4.35mL,20.2mmol)。在23℃搅拌反应混合物1h。随后在85℃加热反应混合物30min且添加2-(三甲基硅基)乙醇(4.83mL,33.7mmol)。在85℃搅拌66h之后,使反应混合物冷却至23℃且经由硅胶色谱纯化,得到外消旋II-4(3.71g,10.5mmol,78.0%产率)LC-MS RT=1.25min;(M+H)=354.1。方法A。使用手性SFC将外消旋II-4分离成个别镜像异构体。制备型色谱条件:仪器:Thar 350SFC;柱:Whelko-RR,5×50cm,10微米;移动相:13%IPA/87%CO_2;流动条件:300mL/min,100巴,35℃;检测器波长:220nm;注射详情:注射4次3.5mL 59g/490mL MeOH:DCM(4:1)120mg/mL于IPA中。分析型色谱条件:仪器:Thar分析型SFC;柱:Whelko-RR(0.46×25cm,5微米;移动相:5%IPA/95%CO_2;流动条件:3mL/min,140巴,40℃;检测器波长:200-400nm UV。峰1,RT=3.496min,>99%ee;峰2,RT=4.417min,>99%ee。收集中间体II-4产物峰#1且继续使用以产生手性5-5。

[0197] 中间体5-5:向反应容器中添加手性II-4(3.71g,10.5mmol)、THF(80mL)及TBAF(31.5mL,31.5mmol)。将反应混合物在23℃搅拌12h,用EtOAc(15mL)稀释,且用饱和$NaHCO_3$(15mL)洗涤有机部分。收集有机相,经Na_2SO_4干燥,在减压下浓缩且溶解于DCM(50mL)中。冷

却至0℃之后,添加DIEA(5.50mL,31.5mmol)及4,5-二氟-2-甲氧基苯甲酰氯(2.4g,12mmol)。将反应混合物在0℃搅拌1h,随后升温至23℃,在减压下浓缩,且经由硅胶色谱纯化残余物,得到5-5(2.9g,7.7mmol,产率74%)。LC-MS RT=1.13min;(M+H)=380.1。方法A。

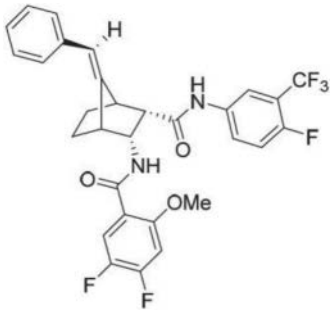
[0198] 实施例56:向反应容器中添加4-氟-3-(三氟甲基)苯胺(4.87g,27.2mmol)、甲苯(40mL)及三甲基铝(13.59mL,27.20mmol)。在23℃搅拌30min之后,添加含5-6(2.95g,7.76mmol)的甲苯(80mL)。在65℃搅拌反应混合物30min。在冷却至23℃之后,将反应混合物用EtOAc(50mL)稀释且用罗谢尔盐饱和水溶液洗涤。将有机层经Na_2SO_4干燥,过滤,在减压下浓缩且经由硅胶色谱纯化,得到实施例56(3.23g,6.14mmol,79.0%产率)。LCMS RT=1.23min;(M+H)=527.1;方法A。

[0199] 中间体5-6:向反应容器中添加实施例56(110mg,0.210mmol)及EtOAc(5mL)。使反应混合物冷却至-78℃,且使O_3鼓泡通过溶液10min(直至出现蓝色)。在使N_2鼓泡以移除过量O_3之后,随后添加二硫二甲烷(0.370mL,4.18mmol)且使反应混合物升温至23℃且搅拌12h。在减压下浓缩反应混合物,得到残余物5-6(100mg,0.20mmol,96%产率),其不经进一步纯化即使用。LC-MS RT=1.08min;(M+H)=501.1;方法A。

[0200] 针对实施例5的程序:向反应容器中添加苯甲基膦酸二乙酯(0.290mL,1.40mmol)、THF(10mL)。使混合物冷却至-78℃且添加KHMDS(1.4mL,1.4mmol)。在-78℃搅拌此混合物15min且在-78℃添加5-6。在-78℃搅拌10min之后,使混合物升温至23℃,在23℃搅拌1h,用饱和$NaHCO_3$淬灭且用EtOAc萃取。收集有机相,经Na_2SO_4干燥,过滤,浓缩,且经由硅胶色谱纯化,得到E-异构体实施例5(59mg,0.10mmol,51%产率)及Z-异构体实施例6(34mg,0.060mmol,29%产率)。1H NMR(400MHz,$CDCl_3$)δ9.53(d,J=7.7Hz,1H),8.03(dd,J=11.2,9.5Hz,1H),7.93(dd,J=6.1,2.5Hz,1H),7.83(s,1H),7.55-7.47(m,1H),7.37-7.21(m,5H),7.10(t,J=9.4Hz,1H),6.78(dd,J=11.6,6.1Hz,1H),6.31(s,1H),4.83-4.72(m,1H),4.00(s,3H),3.46-3.39(m,1H),3.12(dd,J=10.7,4.1Hz,1H),2.89(t,J=4.0Hz,1H),2.31-2.20(m,1H),1.94-1.84(m,1H),1.79-1.65(m,2H)。LC-MS RT:1.25min;MS(ESI)m/z=575.2(M+H)+;方法A。

[0201]

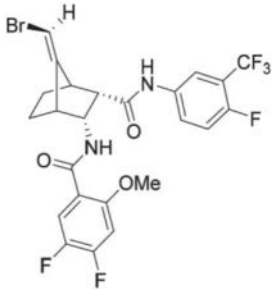
实施例6



针对实施例6的程序:实施例6经制备作为实施例5的副产物。1H NMR(400MHz,$CDCl_3$)δ9.51(d,J=7.7Hz,1H),8.03(dd,J=11.4,9.5Hz,1H),7.94(dd,J=6.2,2.6Hz,1H),7.72(s,1H),7.53(dt,J=8.5,3.7Hz,1H),7.37-7.30(m,4H),7.25-7.19(m,1H),7.12(t,J=9.4Hz,1H),6.78(dd,J=11.7,6.2Hz,1H),6.33(s,1H),4.83(ddd,J=10.9,7.6,3.9Hz,1H),3.99(s,3H),3.49(br.s.,1H),3.16(dd,J=10.8,3.7Hz,1H),2.87(br.s.,1H),

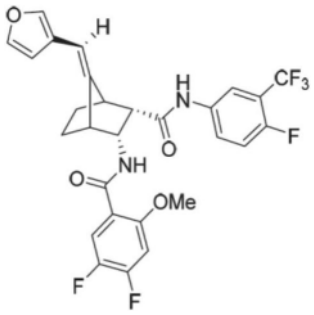
2.22(t,J＝8.8Hz,1H),1.91(t,J＝8.7Hz,1H),1.69(d,J＝6.4Hz,2H)。LC-MS RT:1.25min;MS(ESI)m/z＝575.2(M+H)+;方法A。

[0202] 实施例11



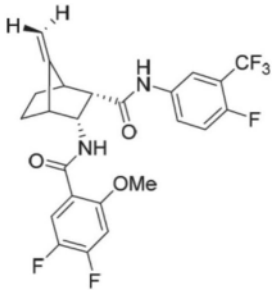
针对实施例11的程序:实施例11为根据针对实施例5所描述的方法,采用溴(溴甲基)三苯基磷烷,由5-6制备。1H NMR(500MHz,$CDCl_3$)δ9.31(d,J＝8.0Hz,1H),8.01(dd,J＝11.3,9.4Hz,1H),7.94-7.86(m,2H),7.51(dt,J＝8.7,3.6Hz,1H),7.10(t,J＝9.4Hz,1H),6.78(dd,J＝11.6,6.1Hz,1H),5.98(s,1H),4.87-4.76(m,1H),3.97(s,3H),3.28(t,J＝3.7Hz,1H),3.16-3.09(m,1H),2.93(t,J＝3.7Hz,1H),2.35-2.25(m,1H),1.91-1.82(m,1H),1.75-1.63(m,2H)。LC-MS RT:1.22min;MS(ESI)m/z＝578.9(M+H)+;方法A。

[0203] 实施例12



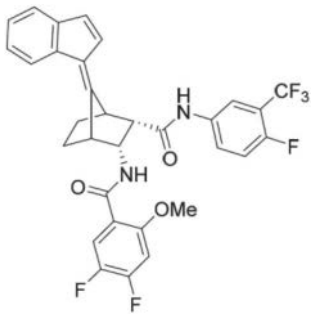
针对实施例12的程序:向反应容器添加实施例11(10mg,0.020mmol),随后添加呋喃-3-基硼酸(9.7mg,0.090mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(4.2mg,5.2μmol)、THF(2mL)及Na_2CO_3(0.5mL,1.00mmol)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在60℃搅拌2h。在使反应混合物冷却至23℃之后,浓缩反应混合物且经由制备型RP-HPLC纯化残余物,得到实施例12(7.7mg,0.010mmol,77%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.54(d,J＝7.4Hz,1H),8.03(dd,J＝11.3,9.4Hz,1H),7.94(dd,J＝6.3,2.8Hz,1H),7.69(s,1H),7.53(dt,J＝8.9,3.4Hz,1H),7.44(d,J＝0.8Hz,1H),7.39(t,J＝1.7Hz,1H),7.12(t,J＝9.4Hz,1H),6.79(dd,J＝11.6,6.3Hz,1H),6.54(d,J＝1.1Hz,1H),6.08(s,1H),4.82-4.73(m,1H),4.00(s,3H),3.37(t,J＝3.6Hz,1H),3.12(dd,J＝10.7,3.9Hz,1H),2.84(t,J＝3.3Hz,1H),2.20-2.14(m,1H),1.90(t,J＝8.5Hz,1H),1.69-1.65(m,2H)。LC-MS RT:1.22min;MS(ESI)m/z＝565.0(M+H)+;方法C。

[0204] 实施例13



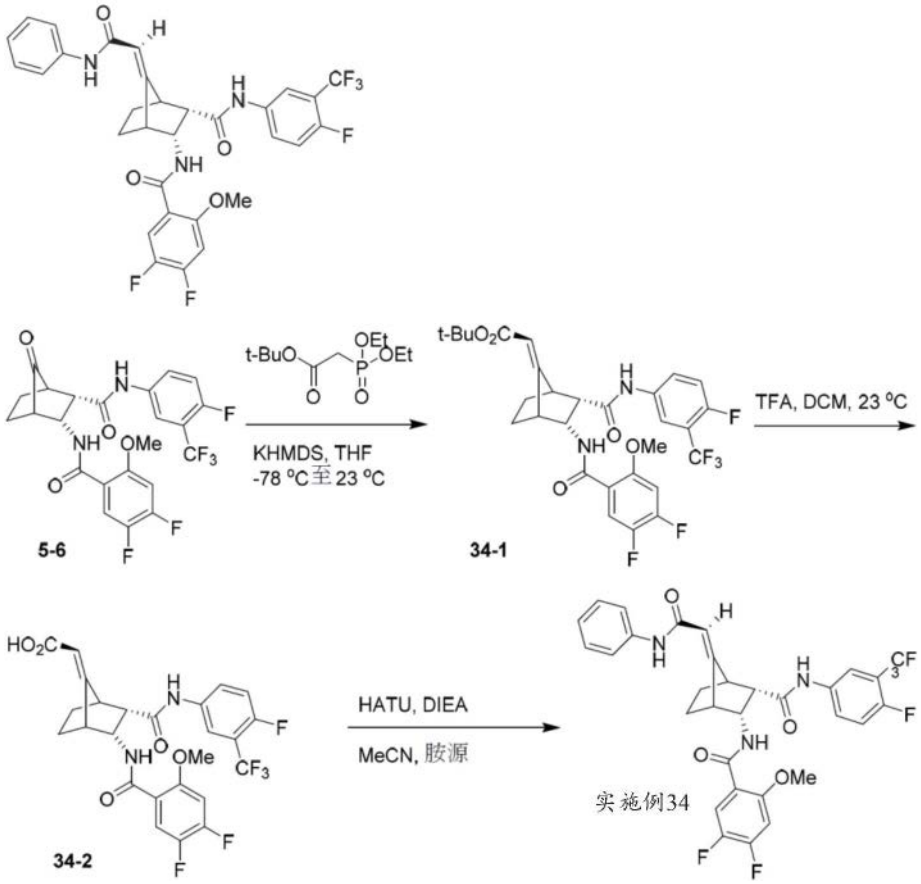
针对实施例13的程序:实施例13为根据针对实施例12所描述的方法,采用[1,1′-联苯]-4-基硼酸,由5-6(5.0mg,8.7μmol)制备。在形成实施例13的情况下,未获得交叉偶合产物,但观测到去卤化副产物且将其分离(2.3mg,4.6μmol,53%)。^{1}H NMR(500MHz,$CDCl_3$)δ 9.44(d,J=6.6Hz,1H),8.05(dd,J=11.3,9.5Hz,1H),7.99-7.93(m,1H),7.76(bs,1H),7.58-7.50(m,1H),7.13(t,J=9.3Hz,1H),6.80(dd,J=11.6,6.1Hz,1H),4.86(s,1H),4.85(s,1H),4.79-4.73(m,1H),3.11(dd,J=10.8,4.0Hz,1H),2.83(br.s.,1H),2.79(br.s.,1H),2.24-2.15(m,1H),1.88-1.80(m,1H),1.69-1.63(m,2H)。LC-MS RT:1.17min;MS(ESI)m/z=499.1(M+H)+;方法C。

[0205] 实施例33



针对实施例33的程序:向反应容器中添加1H-茚(34.8mg,0.300mmol)及THF(2mL)。使反应混合物冷却至-78℃且添加nBuLi(0.19mL,0.30mmol)。在-78℃搅拌10min且在23℃搅拌10min之后,将反应混合物再次冷却至-78℃且添加5-6(15mg,0.030mmol)。使反应混合物升温至23℃,搅拌15min,且通过添加饱和$NaHCO_3$淬灭且用EtOAc萃取。将有机相经Na_2SO_4干燥,过滤,浓缩且溶解于Et_2O(2mL)中。在添加柏杰士试剂(Burgess reagent)(14.3mg,0.0600mmol)(添加1equiv.且接着在3h之后再添加1equiv.)之后,在45℃搅拌反应混合物12h。浓缩所得溶液且经由硅胶色谱纯化,得到E-异构产物(3.4mg,5.6μmol,19%产率)及Z-异构体实施例33(4.6mg,7.5μmol,25%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.63(d,J=7.7Hz,1H),8.07(dd,J=11.3,9.4Hz,1H),8.00(dd,J=6.2,2.6Hz,1H),7.87(d,J=7.4Hz,1H),7.80(s,1H),7.57(dt,J=8.7,3.5Hz,1H),7.37(d,J=7.4Hz,1H),7.32-7.26(m,1H),7.25-7.21(m,1H),7.17(t,J=9.4Hz,1H),6.90(d,J=5.5Hz,1H),6.83(dd,J=11.6,6.1Hz,1H),6.67(d,J=5.5Hz,1H),4.94-4.86(m,1H),4.04(s,3H),3.98(t,J=4.0Hz,1H),3.43(t,J=3.9Hz,1H),3.19(dd,J=10.9,4.0Hz,1H),2.40-2.33(m,1H),2.14-2.07(m,1H),1.84-1.70(m,2H)。LC-MS RT:1.27min;MS(ESI)m/z=599.1(M+H)+;方法A。

[0206] 实施例34

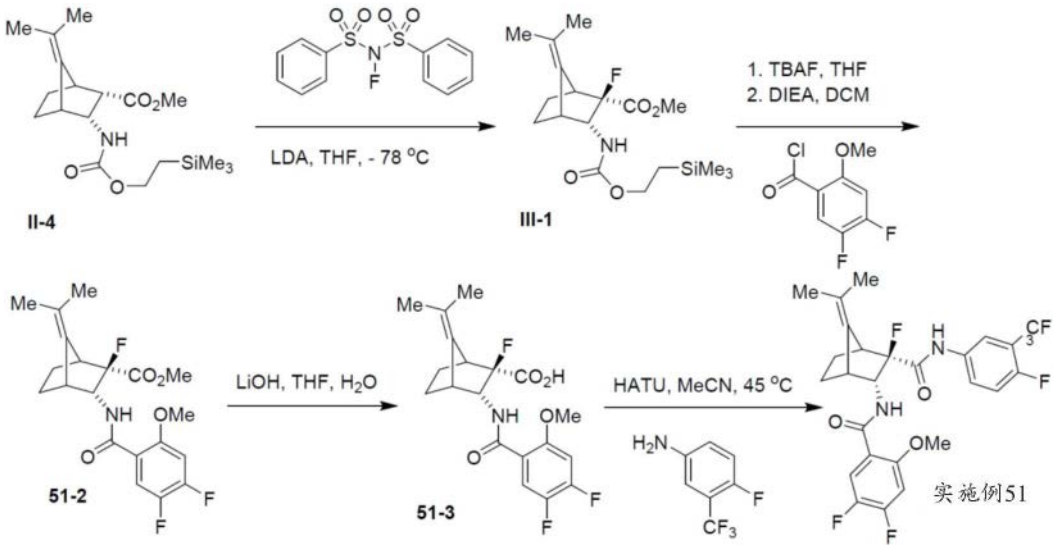


中间体34-1:中间体34-1为以与实施例5中的一般维蒂希反应相同的方式由5-6及2-(二乙氧基磷酰基)乙酸叔丁酯制备。LC-MS RT＝1.25min;(M+H)＝599.1;方法A。

[0207] 中间体34-2:向反应容器中添加34-1(50mg,0.080mmol)、DCM(2mL)及TFA(0.200mL,2.59mmol)。在23℃搅拌12h之后,在减压下浓缩反应内容物,得到34-2(46mg,0.080mmol,98％产率),其不经进一步纯化即使用。LC-MS RT＝1.08min,(M+H)＝543.1;方法A。

[0208] 针对实施例34的程序:向反应容器中添加34-2(5mg,9μmol)、MeCN(1mL)、DIEA(5μl、0.03mmol)及HATU(7mg,0.02mmol)。在23℃搅拌反应混合物3h,在减压下浓缩溶液,且经由制备型HPLC纯化残余物,得到实施例34(3.8mg,6.8mmol,74％产率)。LC-MS RT:1.18min;MS(ESI)m/z＝618.1(M+H)+;方法B。

[0209] 实施例51



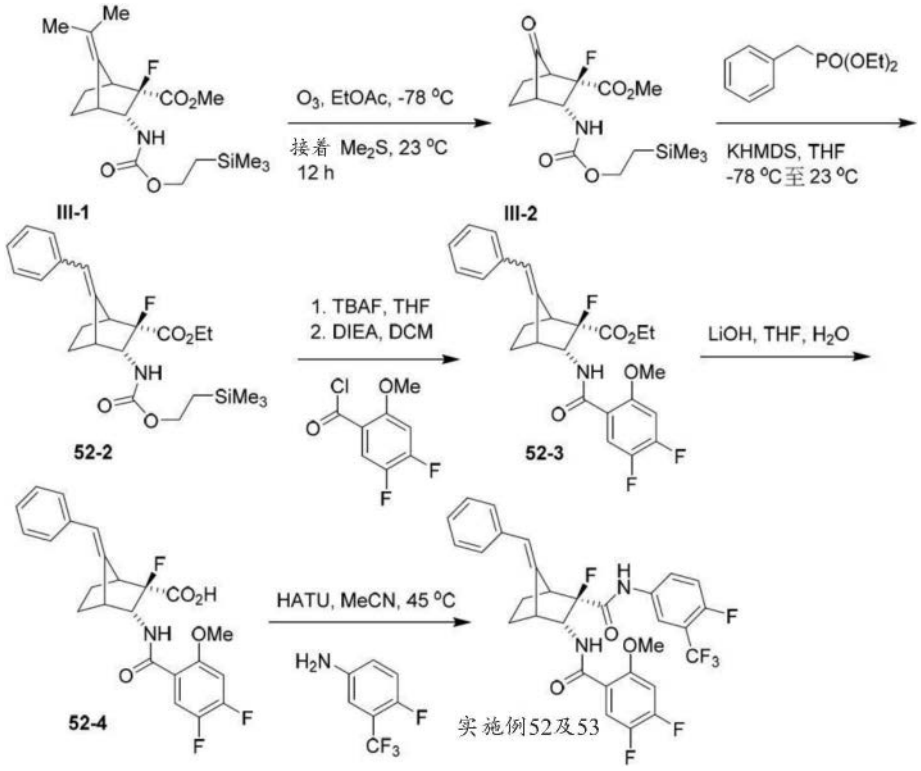
中间体III-1:向反应容器中添加II-4(100mg,0.28mmol)及THF(5mL)。在冷却至-78℃之后,添加LDA(在0℃由BuLi(0.53mL,0.85mmol)及二异丙胺(0.12mL,0.85mmol)制备)且在-78℃搅拌反应混合物15min。随后,在-78℃添加N-氟-N-(苯基磺酰基)苯磺酰胺(223mg,0.710mmol)。在-78℃搅拌1h之后,通过添加饱和$NaHCO_3$淬灭反应混合物且用EtOAc萃取水性部分。将合并的有机部分经Na_2SO_4干燥,在减压下浓缩,且经由硅胶色谱纯化,得到III-1(59.5mg,0.160mmol,57.0%产率)(第1峰)以及反式异构体(17.5mg,0.0500mmol,17.0%产率)(第2峰)。LC-MS RT=1.21min,(M+H)=372.1;方法A。

[0210] 中间体51-2:向反应容器中添加III-1(20mg,0.050mmol)、THF(1mL)及TBAF(0.270mL,0.270mmol)。将反应混合物在23℃搅拌3h,用EtOAc稀释,且用饱和$NaHCO_3$洗涤有机部分。收集有机相,经Na_2SO_4干燥,在减压下浓缩且再溶解于DCM(1mL)中。随后添加DIEA(0.02mL,0.11mmol)及4,5-二氟-2-甲氧苯甲酰氯(16.7mg,0.0800mmol)。在23℃搅拌1h之后,在减压下浓缩反应混合物且经由硅胶色谱纯化,得到51-2(7.2mg,0.020mmol,34%产率)。LC-MS RT=1.11min,(M+H)=398.1;方法A。

[0211] 中间体51-3:向反应容器中添加51-2(7.5mg,0.020mmol)、THF(1mL)、水(0.5mL)及单水合氢氧化锂(4.0mg,0.090mmol)。在23℃搅拌反应混合物1h,用EtOAc(10mL)稀释,且用10mL含有0.1mmol HCl的饱和NH_4Cl洗涤有机部分。将有机相经Na_2SO_4干燥,过滤且在减压下浓缩,得到51-3(7.5mg,0.020mmol,100%产率),其不经进一步纯化即使用。LC-MS RT=0.98min,(M+H)=384.1;方法A。

[0212] 针对实施例51的程序:向反应容器中添加51-3(7.0mg,0.020mmol)、4-氟-3-(三氟甲基)苯胺(6.5mg,0.040mmol)、MeCN(1mL)、DIEA(6μl,0.04mmol)及HATU(14mg,0.040mmol)。在50℃搅拌反应混合物1h,使其冷却至23℃,在减压下浓缩,且经由硅胶色谱纯化,得到实施例51(4.7mg,8.3mmol,45%产率)。1H NMR(500MHz,$CDCl_3$)δ9.21(d,J=8.3Hz,1H),8.33(d,J=8.8Hz,1H),8.09(dd,J=6.2,2.6Hz,1H),8.02(dd,J=11.3,9.4Hz,1H),7.54(dt,J=8.8,3.4Hz,1H),7.18(t,J=9.2Hz,1H),6.78(dd,J=11.7,6.2Hz,1H),4.70-4.54(m,1H),3.13(t,J=3.9Hz,1H),2.98(dd,J=9.4,3.9Hz,1H),2.07-2.00(m,1H),1.79(s,3H),1.74(s,3H),1.57-1.43(m,3H)。LC-MS RT:1.23min;MS(ESI)m/z=545.1(M+H)+;方法A。

[0213] 实施例52

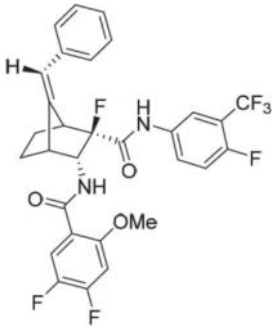


中间体III-2:向反应容器中添加III-1(50mg,0.14mmol)及EtOAc(3mL)。使反应混合物冷却至-78℃,且使O_3鼓泡通过溶液10min。随后添加二硫二甲烷(0.24mL,2.7mmol)且使反应混合物升温至23℃且搅拌12h。在减压下浓缩之后,将残余物溶解于EtOAc中且经由硅胶过滤。在减压下浓缩滤液,得到III-2(50.5mg,0.15mmol,100%产率),其不经进一步纯化即使用。LCMS RT=1.24min,(M+H)=346.0;方法A。

[0214] 中间体52-2:向反应容器中添加苯甲基膦酸二乙酯(0.14mL,0.65mmol)、THF(5mL)。使反应混合物冷却至-78℃且添加KHMDS(0.65mL,0.65mmol)。在-78℃搅拌此混合物20min且在-78℃添加III-2(45mg,0.13mmol)。在-78℃搅拌5min且在23℃搅拌1h之后,通过添加饱和$NaHCO_3$淬灭反应混合物且用EtOAc萃取水性部分。合并有机部分,经Na_2SO_4干燥,在减压下浓缩,且经由硅胶色谱纯化,得到52-2(17.4mg,0.0400mmol,31.0%产率,烯烃异构体的1.45:1混合物)。LC-MS RT=1.27min,(M+H-Et)=406.0;方法A。

[0215] 中间体52-3:中间体52-3为利用针对中间体51-2的合成所描述的程序来制备。

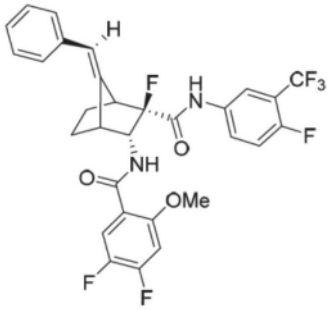
[0216] 中间体52-4:中间体52-4为利用针对中间体51-3的合成所描述的程序来制备。



[0217] 针对实施例52的程序:实施例52为根据实施例51所描述的方法由52-4制备。^1H

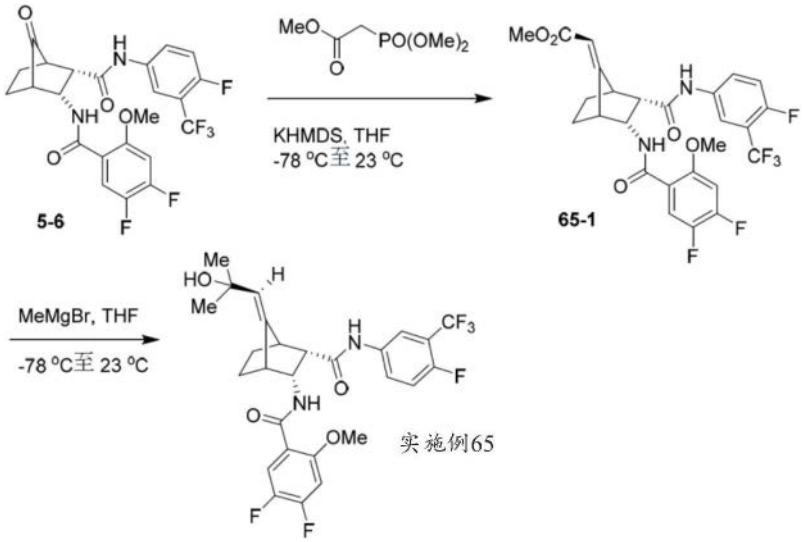
NMR(500MHz,$CDCl_3$)δ9.25(d,J=8.0Hz,1H),8.33(d,J=8.5Hz,1H),8.10(dd,J=6.2,2.6Hz,1H),8.04(dd,J=11.1,9.5Hz,1H),7.58-7.50(m,1H),7.39-7.31(m,4H),7.18(t,J=9.4Hz,1H),6.79(dd,J=11.6,6.1Hz,1H),6.56(s,1H),4.92-4.73(m,1H),4.00(s,3H),3.41(dd,J=8.7,3.4Hz,1H),3.06(t,J=3.9Hz,1H),2.24-2.13(m,1H),1.79-1.72(m,1H),1.71-1.57(m,3H)。LC-MS RT:1.27min;MS(ESI)m/z=593.0(M+H)+;方法A。

[0218] 实施例53



针对实施例53的程序:实施例53为根据实施例51所描述的方法由52-4制备。1H NMR(500MHz,$CDCl_3$)δ9.28(d,J=7.4Hz,1H),8.33(d,J=8.3Hz,1H),8.11(d,J=4.1Hz,1H),8.02(t,J=10.3Hz,1H),7.55(d,J=7.7Hz,1H),7.40-7.31(m,4H),7.19(t,J=9.2Hz,1H),6.79(dd,J=11.6,6.1Hz,1H),6.45(s,1H),4.89-4.72(m,1H),4.01(s,3H),3.61(br.s.,1H),2.85(d,J=6.1Hz,1H),2.25-2.13(m,1H),1.85-1.76(m,1H),1.75-1.58(m,3H)。LC-MS RT:1.27min;MS(ESI)m/z=593.0(M+H)+;方法A。

[0219] 实施例65

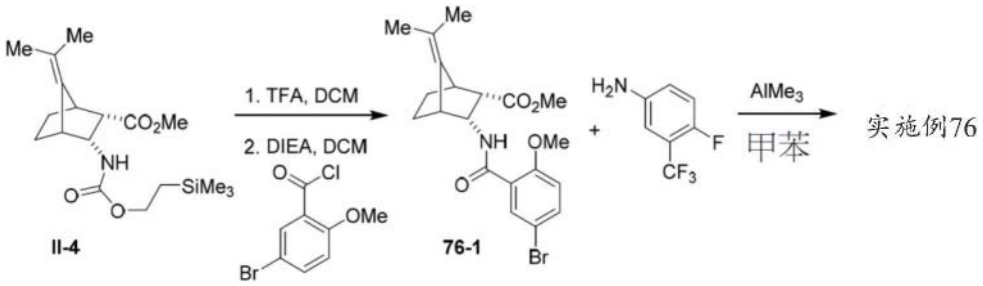


中间体65-1:中间体65-1为以与实施例5中所描述的维蒂希反应类似的方式由5-6及2-(二甲氧基磷酰基)乙酸甲酯制备。

[0220] 针对实施例65的程序:向反应容器中添加65-1(5.0mg,9.0mmol)及THF(1mL)。在冷却反应混合物至-78℃之后,添加氯化甲基镁(0.06mL,0.2mmol)。使反应混合物升温至23℃,在23℃搅拌2h。通过添加饱和$NaHCO_3$淬灭反应物且用EtOAc萃取溶液。将有机层经Na_2SO_4干燥,过滤,在减压下浓缩,且经由制备型RP-HPLC纯化来纯化,得到实施例65(3.2mg,5.3μmol,59%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.46(d,J=7.7Hz,1H),8.03-7.91(m,3H),7.53(dt,J=8.6,3.5Hz,1H),7.10(t,J=9.4Hz,1H),6.78(dd,J=11.6,6.3Hz,1H),5.49(s,

1H),4.77-4.67(m,1H),3.98(s,3H),3.49(t,J＝4.0Hz,1H),3.07(dd,J＝11.0,4.1Hz,1H),2.69(t,J＝3.9Hz,1H),2.17-2.09(m,1H),1.89-1.81(m,1H),1.68-1.55(m,2H),1.42(s,6H)。LC-MS RT:1.14min;MS(ESI)m/z＝557.0(M+H)+;方法C。

[0221] 实施例76

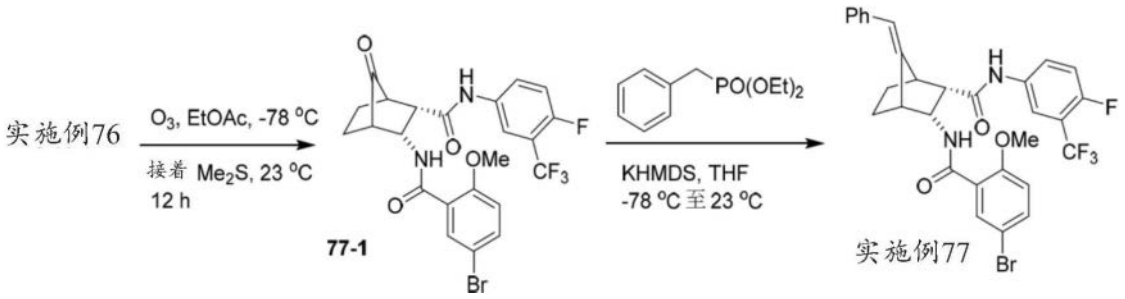


中间体76-1:向含有II-4(1.77g,5.00mmol)的20mL小瓶中添加DCM(20mL)。随后添加TFA(2.02mL,26.3mmol)且在23℃搅拌反应混合物48h。在减压下浓缩所得溶液且在高真空下干燥5小时。残余物不经进一步纯化即继续用于酰化步骤。以下列方式制备5-溴-2-甲氧苯甲酰氯:向装有5-溴-2-甲氧基苯甲酸(1.39g,6.00mmol)的100mL烧瓶中添加DCM(30mL),随后添加乙二酰氯(0.6mL,7mmol)及DMF(0.05mL,0.6mmol)。在23℃搅拌溶液18h且以与针对中间体5-5所描述相同的方式转化成酰胺,得到76-1(878mg,2.10mmol,56.0%产率)。^{1}H NMR(500MHz,DMSO-d_6)δ9.49(d,J＝7.0Hz,1H),8.04-7.87(m,1H),7.74-7.59(m,1H),7.17(d,J＝8.8Hz,1H),4.26(br.s.,1H),3.98(s,3H),3.63(s,1H),3.51(br.s.,1H),3.42(d,J＝18.1Hz,3H),3.13-3.01(m,1H),2.92(d,J＝13.5Hz,2H),1.67(s,5H),1.64-1.47(m,3H),1.36(br.s.,2H)。

[0222] 针对实施例76的程序:实施例76为根据针对实施例56所描述的方法,采用4-氟-3-(三氟甲基)苯胺,由76-1制备。^{1}H NMR(500MHz,DMSO-d6)δ10.52(s,1H),9.88(d,J＝7.0Hz,1H),8.19(d,J＝4.3Hz,1H),7.97(d,J＝2.7Hz,1H),7.78(d,J＝8.5Hz,1H),7.65(dd,J＝8.7,2.6Hz,1H),7.47(t,J＝9.8Hz,1H),7.16(d,J＝8.9Hz,1H),4.31(br.s.,1H),3.98(s,3H),3.55-3.40(m,3H),3.09(dd,J＝10.7,4.0Hz,1H),3.02(br.s.,1H),2.91(br.s.,1H),1.80(t,J＝8.9Hz,1H),1.75-1.62(m,7H),1.33(d,J＝6.1Hz,2H)。

LC-MS RT:2.69min;MS(ESI)m/z＝569.1(M-H)+;方法B。

[0223] 实施例77

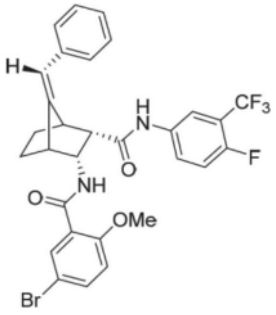


中间体77-1:中间体77-1为以与针对中间体5-6所描述的相同通用方式,由实施例76制备。LC-MS RT＝1.0min;(M+H)＝544.0;方法A。

[0224] 针对实施例77的程序:实施例77为根据针对实施例5所描述的通用方法,使用苯甲基膦酸二乙酯,由77-1制备。1H NMR(500MHz,DMSO-d6)δ10.66-10.50(m,1H),10.06-9.88

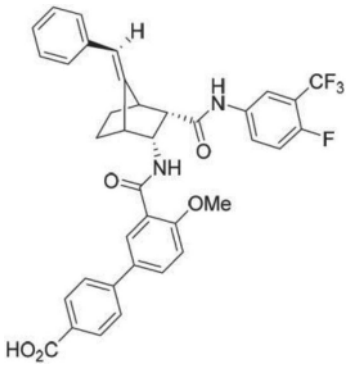
(m,1H),8.27-8.13(m,1H),8.06-7.94(m,1H),7.86-7.73(m,1H),7.71-7.59(m,1H),7.53-7.43(m,1H),7.43-7.31(m,4H),7.31-7.21(m,1H),7.21-7.09(m,1H),6.47-6.22(m,1H),4.55-4.37(m,1H),4.09-3.95(m,3H),3.33-3.19(m,1H),2.90-2.76(m,1H),2.02-1.88(m,1H),1.87-1.71(m,1H),1.64-1.42(m,2H),1.06-0.91(m,1H)。LC-MS RT:2.83min;MS(ESI)m/z=617.20(M-H)+;方法B。

[0225] 实施例78



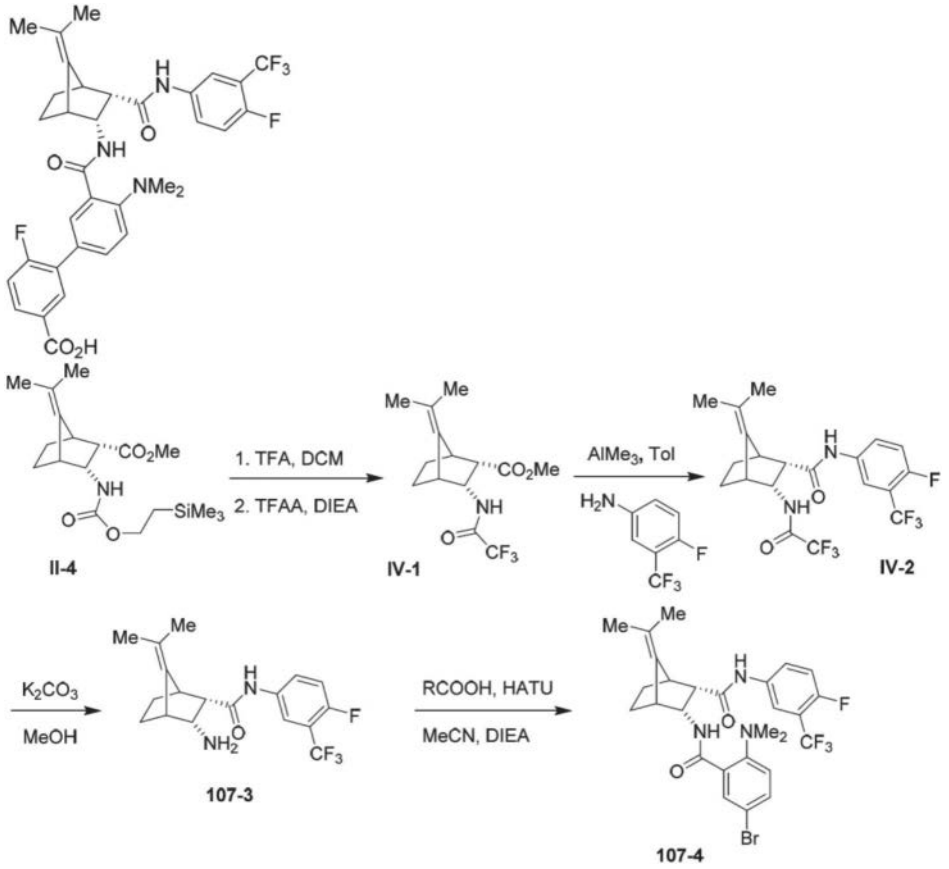
针对实施例78的程序:在实施例77的生产中制备呈副产物形式的例子78。^{1}H NMR(500MHz,DMSO-d6)δ10.66-10.50(m,1H),10.06-9.88(m,1H),8.27-8.13(m,1H),8.06-7.94(m,1H),7.86-7.73(m,1H),7.71-7.59(m,1H),7.53-7.43(m,1H),7.43-7.31(m,4H),7.31-7.21(m,1H),7.21-7.09(m,1H),6.47-6.22(m,1H),4.55-4.37(m,1H),4.09-3.95(m,3H),3.33-3.19(m,1H),2.90-2.76(m,1H),2.02-1.88(m,1H),1.87-1.71(m,1H),1.64-1.42(m,2H),1.06-0.91(m,1H)。LC-MS RT:2.82min;MS(ESI)m/z=617.35(M-H)+;方法B。

[0226] 实施例79



针对实施例79的程序:向装有实施例77(15mg,0.024mmol)的0.5至2.0mL微波反应小瓶中添加4-溴苯甲酸(6mg,0.04mmol),随后添加THF(490μl)及K_3PO_4(97μl,0.049mmol)于水中的溶液。最后,添加XPhos-Pd-G2(CAS 1310584-14-5)(2mg,0.002mmol,小刮勺尖端)。将小瓶加盖且在微波中加热至100℃持续30min。将反应物用DMF稀释至2mL总体积,过滤,且通过制备型RP-HPLC纯化,得到实施例79(5.2mg,0.01mmol,33%产率)。1H NMR(500MHz,DMSO-d6)δ9.95(d,J=7.0Hz,1H),8.26(d,J=4.3Hz,1H),7.94(d,J=6.7Hz,1H),7.81(br.s.,1H),7.50(t,J=8.2Hz,3H),7.44-7.32(m,6H),7.25(br.s.,2H),7.18(d,J=8.2Hz,1H),7.04(t,J=7.5Hz,1H),6.39(s,1H),4.52(br.s.,1H),3.28(br.s.,1H),2.93(br.s.,1H),2.02-1.79(m,3H),1.53(br.s.,3H)。LC-MS RT:2.2min;MS(ESI)m/z=659.4(M-H)+;方法B。

[0227] 实施例107



中间体IV-1:将II-4脱除保护基得到中间体IV-1为利用与76-1中所描述的相同条件。如下进行三氟乙酰基保护基的安装:将II-4脱除保护基得到对应的胺中间体且添加胺(1.7g,8.1mmol),添加DCM(41mL)且经由冰浴使烧瓶冷却至0℃。添加TFAA(1.26mL,8.90mmol)及DIEA(5.7mL,33mmol)。5min之后,自冰浴中移出反应烧瓶,且在23℃搅拌30min。将反应混合物用饱和$NaHCO_3$(50mL)淬灭且用EtOAc(3×50mL)萃取。将合并的有机部分经Na_2SO_4干燥,过滤且在减压下浓缩,得到IV-1(2.48g,8.12mmol,100%产率),其不经进一步纯化即使用。LC-MS RT=1.11min;MS(ESI)m/z=306.1$(M+H)^+$;方法A。

[0228] 中间体IV-2:中间体IV-2为以如针对5-6所描述的相同方式由IV-1制备。(2.5g,5.5mmol,63%产率);LC-MS RT=1.20min;MS(ESI)m/z=453.0$(M+H)^+$;方法A。

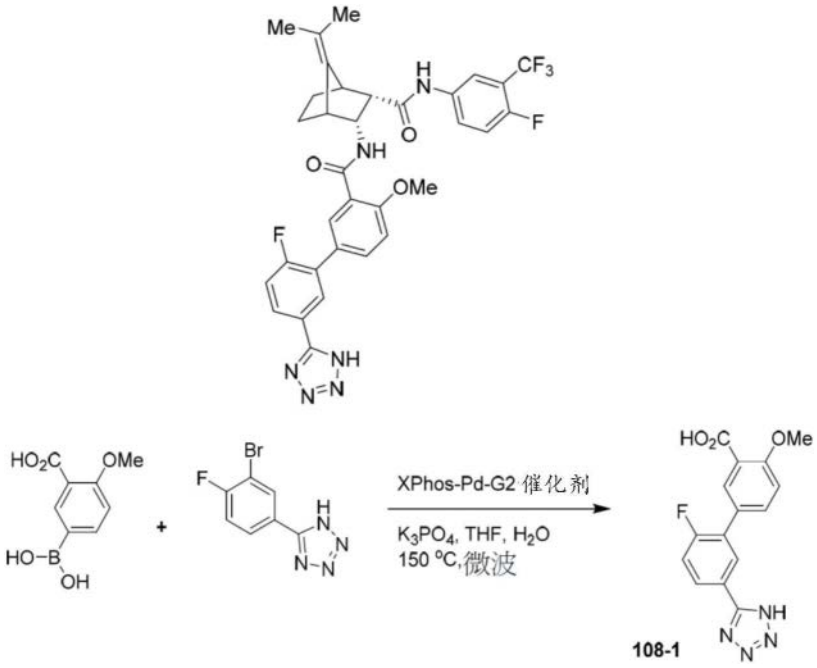
[0229] 中间体107-3:将中间体IV-2(133mg,0.290mmol)溶解于水(2.9mL)及MeOH(2.9mL)中。添加K_2CO_3(2.03g,1.47mmol)且在40℃搅拌反应混合物4h。使反应混合物冷却至室温,随后添加水(5mL)。用EtOAc(3×10mL)萃取所得混合物。将合并的有机萃取物经Na_2SO_4干燥,过滤且在减压下浓缩,得到107-3(105mg,0.290mmol,100%产率),其不经进一步纯化即使用。LC-MS RT=0.82min;MS(ESI)m/z=357.1$(M+H)^+$;方法A。

[0230] 中间体107-4为使用针对76-1使用的样本程序由107-3制备。

[0231] 针对实施例107的程序:实施例107为根据针对实施例79所描述的方法,采用3-溴-4-氟苯甲酸,由107-4制备。^1H NMR(500MHz,DMSO-d6)δ10.64(s,1H),10.34(br d,J=7.3Hz,1H),8.23(dd,J=6.1,1.8Hz,1H),7.99(br d,J=7.6Hz,1H),7.93(s,1H),7.91-7.86(m,1H),7.80(br d,J=8.2Hz,1H),7.61(br d,J=8.2Hz,1H),7.44(br t,J=9.8Hz,1H),7.33(d,J=8.5Hz,1H),7.24(br t,J=9.6Hz,1H),4.46-4.38(m,1H),3.13(br dd,J=10.4,4.0Hz,1H),3.03(br s,1H),2.93(br s,1H),2.71(s,6H),1.94-1.87(m,2H),1.84-

1.75(m,1H),1.71(s,6H),1.45-1.30(m,2H)。LC-MS RT:2.2min;MS(ESI)m/z＝642.2(M+H)+;方法B。

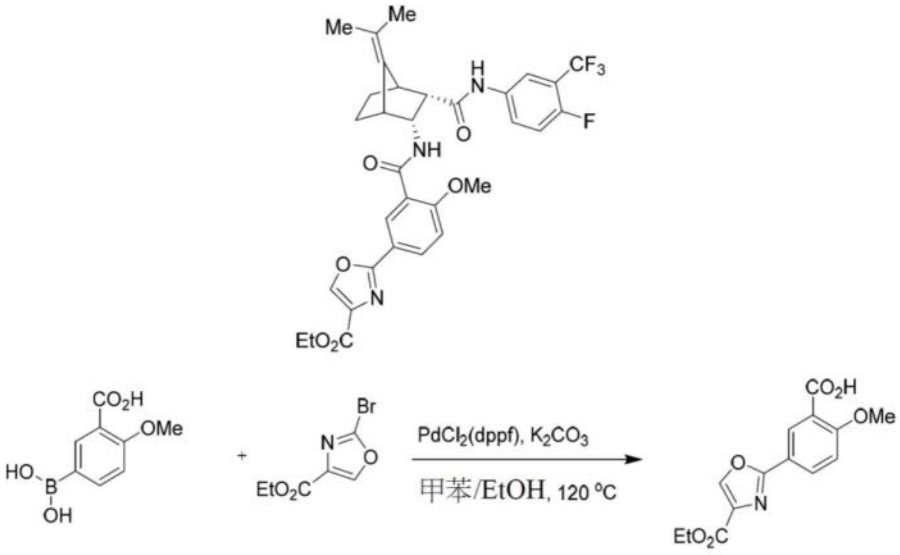
[0232] 实施例108



中间体108-1:向小瓶中添加5-(3-溴-4-氟苯基)-1H-四唑(50mg,0.21mmol)、5-溴-2-甲氧基苯甲酸(60.5mg,0.309mmol)、XPhos-Pd-G2催化剂(32mg,0.042mmol)及K_3PO_4(131mg,0.617mmol),随后添加THF(1.8mL)及水(257μl)。将反应混合物用氮气脱气2min,接着密封且在微波照射下在150℃加热2.5h。使反应混合物分配于1N HCl(5mL)之间且用EtOAc(3×5mL)萃取。将合并的有机部分经Na_2SO_4干燥,过滤且在减压下浓缩。通过制备型RP-HPLC纯化所得残余物,得到108-1(13mg,0.041mmol,20%产率)。LC-MS RT＝0.77min;MS(ESI)m/z＝315.1$(M+H)^+$;方法A。

[0233] 针对实施例108的程序:向反应容器中添加107-3(10mg,0.03mmol)、108-1(13.2mg,0.0400mmol)、MeCN(1mL)、DIEA(0.02mL,0.1mmol)及HATU(16mg,0.040mmol)。将反应混合物在23℃搅拌3h,在减压下浓缩,且进行制备型RP-HPLC纯化,得到实施例108(12.3mg,0.0200mmol,65.0%产率)。1H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.93(d,J＝7.0Hz,1H),8.26-8.19(m,2H),8.17(br d,J＝6.4Hz,1H),8.09-8.02(m,1H),7.83-7.75(m,2H),7.54(dd,J＝10.2,9.0Hz,1H),7.47(t,J＝9.8Hz,1H),7.34(d,J＝8.5Hz,1H),4.41-4.34(m,1H),4.05(s,3H),3.11(dd,J＝10.8,4.1Hz,1H),3.05-3.02(m,1H),2.99-2.92(m,1H),1.86-1.80(m,1H),1.77-1.69(m,7H),1.41-1.31(m,2H)。LC-MS RT:2.17min;MS(ESI)m/z＝653.6(M+H)+;方法B。

[0234] 实施例110

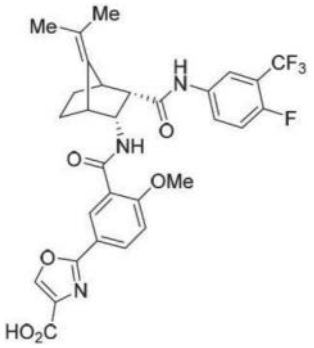


110-1

中间体110-1:向小瓶中添加5-溴-2-甲氧基苯甲酸(100mg,0.51mmol)、2-溴噁唑-4-甲酸乙酯(75mg,0.34mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(28mg,0.030mmol)、K_2CO_3(470mg,3.40mmol)、甲苯(1.7mL)及乙醇(1.7mL)。在120℃加热反应混合物3h,其后其变成凝胶。将反应混合物用DMF稀释,过滤且通过制备型RP-HPLC纯化,得到110-1(24mg,0.080mmol,24%产率)。RT=0.73min;MS(ESI)m/z=292.1$(M+H)^+$;方法A。

[0235] 针对实施例110的程序:实施例110为根据针对实施例108所描述的方法,采用110-1,由107-3制备。1H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.93(d,J=7.0Hz,1H),8.88(s,1H),8.58(d,J=2.4Hz,1H),8.20(dd,J=6.4,2.1Hz,1H),8.12(dd,J=8.7,2.3Hz,1H),7.81(br dd,J=8.4,4.1Hz,1H),7.48(t,J=9.8Hz,1H),7.37(d,J=8.9Hz,1H),4.41-4.35(m,1H),4.31(q,J=7.0Hz,2H),4.08(s,3H),3.12(br dd,J=10.7,4.0Hz,1H),3.07-3.02(m,1H),2.98-2.93(m,1H),1.86-1.79(m,1H),1.78-1.69(m,7H),1.38-1.33(m,2H),1.31(t,J=7.0Hz,3H)。LC-MS RT:2.61min;MS(ESI)m/z=630.5(M+H)+;方法B。

[0236] 实施例113

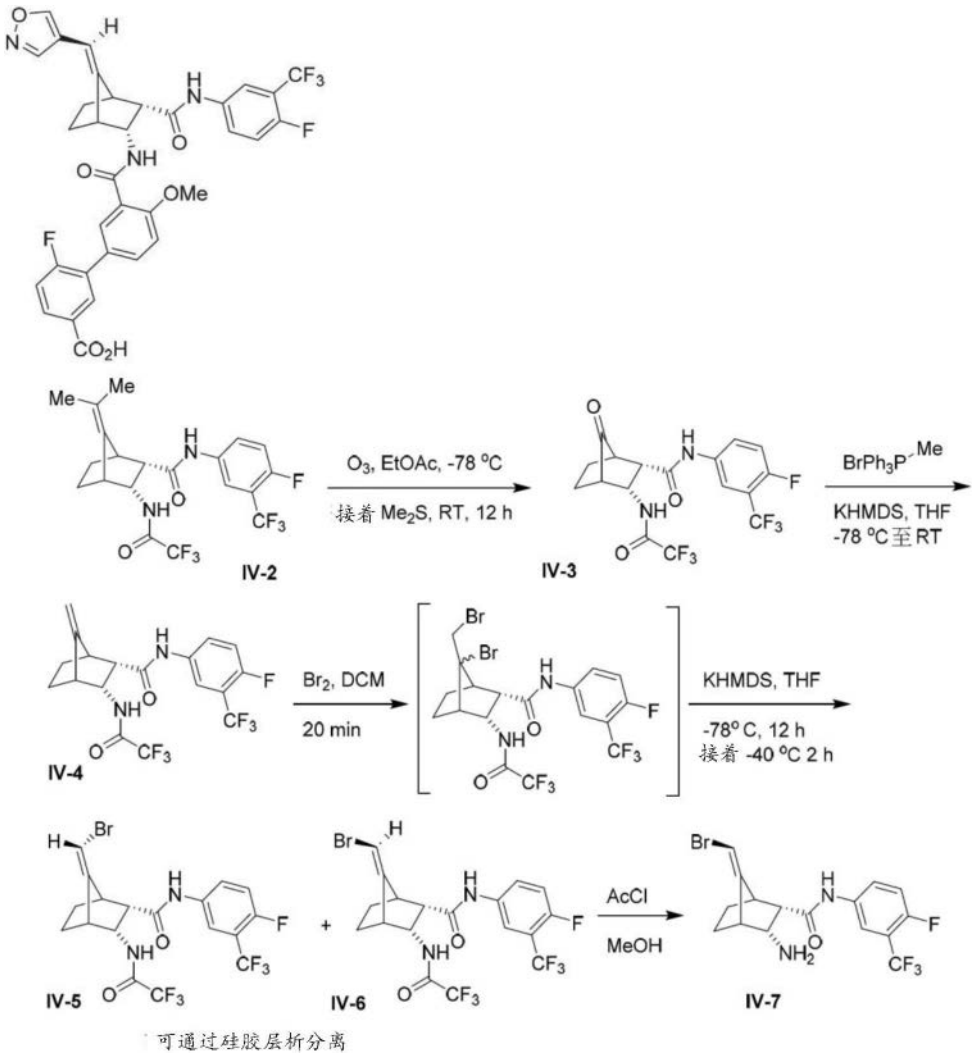


针对实施例113的程序:向含有实施例110(11.5mg,0.02mmol)于THF(180μl)/水(90μl)/MeOH(90μl)中的小瓶中添加1.5M氢氧化锂溶液(61μl,0.09mmol),且在23℃搅拌反应物5min。通过添加1N HCl(1mL)淬灭反应混合物且用EtOAc(3×5mL)萃取。将合并的有机物经Na_2SO_4干燥且在减压下浓缩。经由制备型RP-HPLC纯化所得粗产物,得到实施例113(6.3mg,0.01mmol,56%产率)。1H NMR(500MHz,DMSO-d6)δ10.57(s,1H),9.93(d,J=7.3Hz,1H),8.57(s,1H),8.54(d,J=2.1Hz,1H),8.18(dd,J=6.1,2.1Hz,1H),8.10(dd,J=8.7,

2.3Hz,1H),7.79(dd,J＝8.1,3.8Hz,1H),7.46(t,J＝9.8Hz,1H),7.35(d,J＝8.9Hz,1H),4.41-4.30(m,1H),4.06(s,3H),3.10(dd,J＝10.7,4.0Hz,1H),3.05-2.99(m,1H),2.98-2.91(m,1H),1.81(t,J＝8.7Hz,1H),1.76-1.65(m,7H),1.41-1.28(m,2H)。LC-MS RT:1.92min;MS(ESI)m/z＝601.9(M+H)+;方法B。

[0237] 针对实施例114的程序:实施例114为根据针对实施例108所描述的方法,采用5-氰基-2-氟苯甲酸,由14-3制备。1H NMR.LC-MS RT:2.53min;MS(ESI)m/z＝504.1(M+H)+;方法C。

[0238] 实施例120



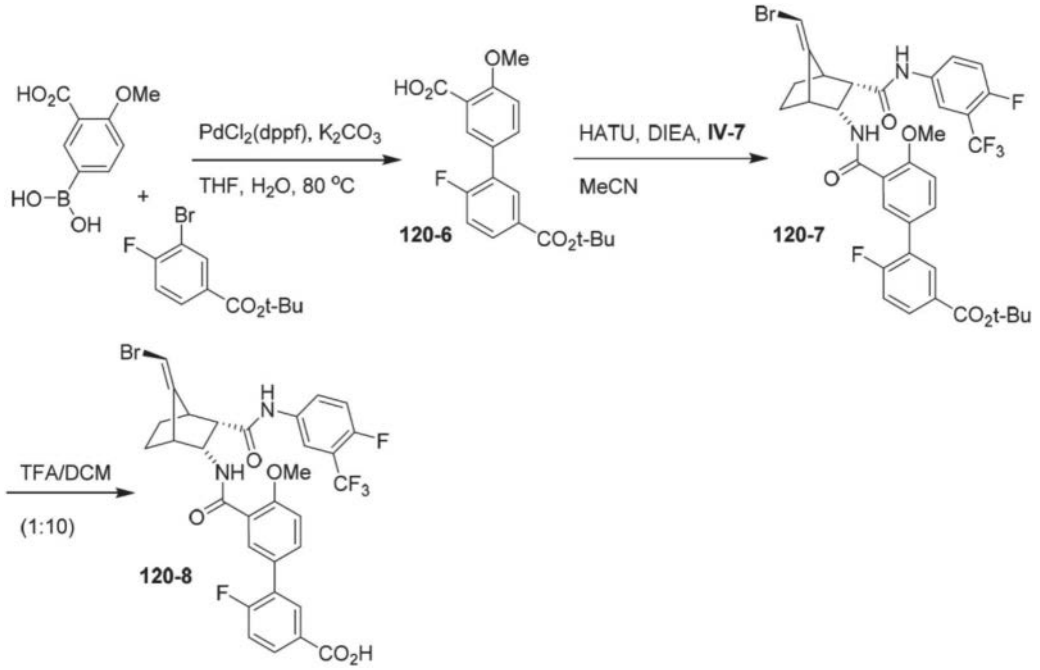
中间体IV-3:中间体IV-3为以如针对5-6所描述的相同方式由IV-2制备。(101g,0.240mmol,97.0%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.61(br d,J＝6.3Hz,1H),7.76(dd,J＝5.9,2.6Hz,1H),7.71(dt,J＝8.9,3.4Hz,1H),7.66(s,1H),7.23(t,J＝9.4Hz,1H),4.70(dt,J＝10.3,5.3Hz,1H),3.33(dd,J＝10.5,4.4Hz,1H),2.54(t,J＝4.3Hz,1H),2.42(t,J＝4.1Hz,1H),2.20-2.10(m,1H),2.06-1.99(m,1H),1.96-1.81(m,2H)。

[0239] 中间体IV-4:向反应容器中添加溴(甲基)三苯基磷烷(419mg,1.17mmol)(通过研磨市售材料的精细粉末)及THF(7mL)。使反应混合物冷却至-78℃且添加KHMDS(1.2mL,1.17mmol)。在-78℃剧烈搅拌此反应混合物30min且在-78℃添加IV-3(100mg,0.240mmol)。在-78℃再搅拌10min之后,使反应混合物升温至23℃且搅拌1.5h。使反应混合物冷却至-40

℃且通过添加饱和$NaHCO_3$淬灭。用EtOAc萃取溶液。将有机相经Na_2SO_4干燥,过滤,在减压下浓缩,且经由硅胶色谱纯化,得到IV-4(71mg,0.17mmol,71％产率)。LCMS RT＝1.16min;(M+H)＝425.0;方法A。

[0240] 中间体IV-5及IV-6:向反应容器中添加IV-4(71mg,0.17mmol)、DCM(3mL)及Br_2(0.03mL,0.6mmol)。在23℃搅拌反应混合物20min且在减压下用饱和$Na_2S_2O_3$捕获剂浓缩以淬灭过量Br_2。将所得二溴化物溶解于THF(3mL)中。在将烧瓶冷却至-78℃之后,添加KHMDS(1.0mL,1.0mmol)。使反应混合物在-78℃保持12h且在-40℃保持2h,随后通过在-40℃添加饱和$NaHCO_3$淬灭。用EtOAc萃取所得溶液。收集有机相,经Na_2SO_4干燥,过滤,在减压下浓缩,且经由硅胶色谱纯化,得到IV-6(27mg,0.050mmol,32％产率)(Z-异构体,峰2。LCMS RT＝1.19min;(M+H)＝504.9;方法A,及相对应的E-异构体IV-5(28mg,0.060mmol,33％产率)(峰1)。IV-6为如上文所概述以外消旋体形式产生且使用手性SFC分离成个别镜像异构体。制备型色谱条件:仪器:Thar 350SFC;柱:Chiralcel OD-H,5×50cm,5微米;移动相:20％MeOH/80％CO_2;流动条件:340mL/min,100巴,35℃;检测器波长:220nm;注射详情:3.75mL 30mg/mL于MeOH中。峰1,RT＝7.81min,＞99％ee;峰2,RT＝10.97min,＞99％ee。收集中间体IV-6产物峰#1(1.9公克)且继续使用以产生手性IV-7。

[0241] 中间体IV-7:向反应物中添加MeOH(3mL)及AcCl(0.3mL,4.2mmol)。在搅拌5min之后,添加手性IV-6(来自手性SFC的第1洗脱峰,75mg,0.15mmol)且在40℃搅拌反应混合物48h。在减压下浓缩所得溶液,得到IV-7(67mg,0.16mmol,100％),其不经进一步纯化即使用。LC-MS RT＝0.78min;(M+H)＝408.9;方法A。



[0242] 中间体120-6:向小瓶中添加5-溴-2-甲氧基苯甲酸(500mg,2.55mmol)、3-溴-4-氟苯甲酸叔丁酯(842mg,3.06mmol)、3-溴-4-氟苯甲酸叔丁酯(842mg,3.06mmol)、K_2CO_3(1.76g,12.8mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(313mg,0.380mmol)及THF(22.3mL)。将反应混合物用氮气脱气2min,接着在80℃加热18h。冷却至室温之后,用1NHCl(25mL)稀释反应混合物且用EtOAc(3×25mL)萃取溶液。将合并的有机部分经Na_2SO_4干燥,过滤,在减压下浓缩,且将所得残余物溶解于DMF中且通过制备型RP-HPLC纯化,得到120-6(586mg,1.69mmol,

66.0%产率)。LC-MS RT=1.02min;(M+H)=347.1;方法A。

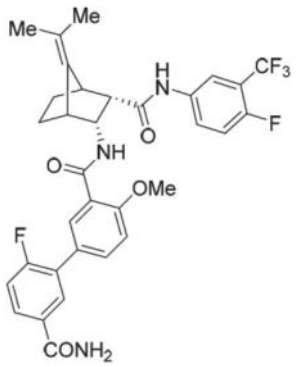
[0243] 可用替代性芳基卤化物进行铃木反应,且以与联芳基类似物产生类似的方式进行其余步骤。

[0244] 中间体120-7:在反应容器中添加IV-7(7mg,0.02mmol)及120-6(6.6mg,0.020mmol)、MeCN(1mL)、DIEA(9.64uL、0.0600mrnol)及HATU(12.0mg,0.0300mmol)。将反应混合物在23℃搅拌3h,在减压下浓缩且经由硅胶色谱纯化,得到120-7(10mg,0.014mmol,86%产率)。LC-MS RT=1.33min;(M+H)=735.2;方法A。

[0245] 中间体120-8:中间体120-8为以与中间体34-2相同的方式由120-7制备(5mg,0.07mmol,100%产率)。LC-MS RT=1.15min;(M+H)=679.08;方法A。

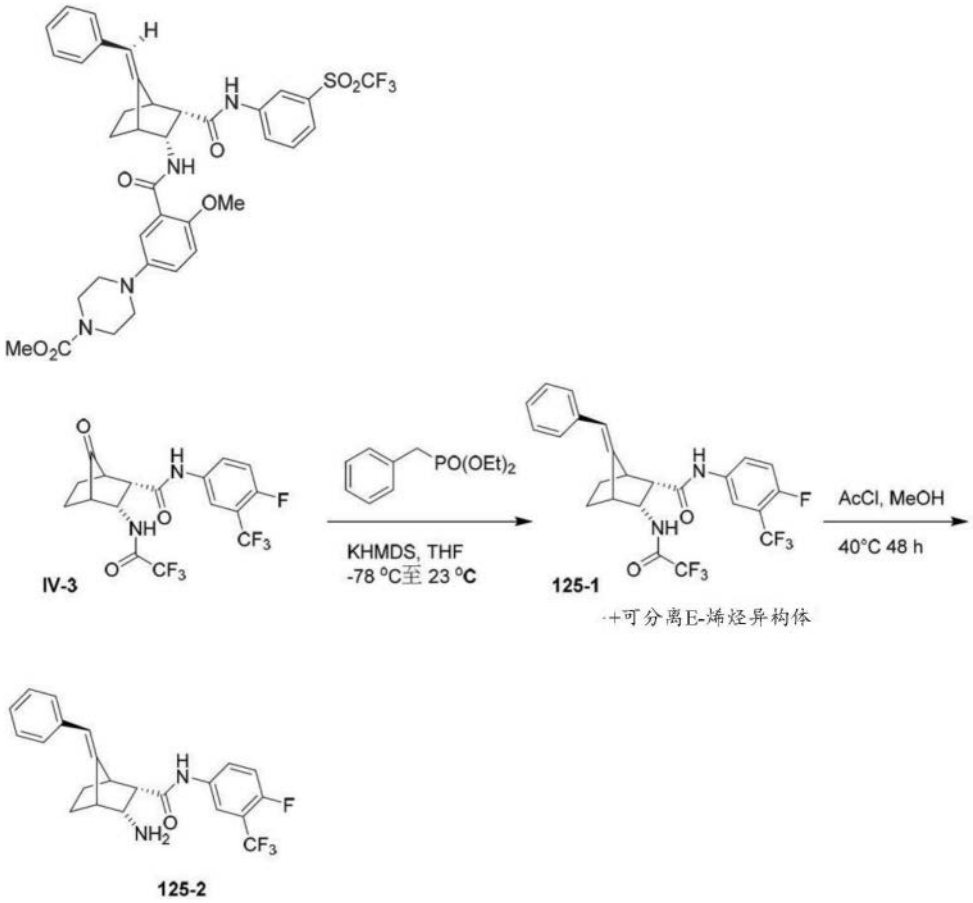
[0246] 针对实施例120的程序:向含有120-8(10mg,0.01mmol)的反应容器中添加4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)异噁唑(13.3mg,0.07mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(3mg,0.004mmol,小刮勺尖端)及Na_2CO_3(0.5mL,1.0mmol)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在60℃搅拌2h。在冷却至23℃之后,在减压下浓缩反应混合物且经由制备型RP-HPLC纯化,得到中间体叔丁酯。用10:1 DCM/TFA处理酯,随后通过反相HPLC纯化,得到实施例120(7.0mg,0.01mrnol,72%产率)。1H NMR(500MHz,$CDCl_3$)δ10.03(br d,J=6.3Hz,1H),8.50(br s,1H),8.43(br s,1H),8.31(br s,1H),8.21(br d,J=5.2Hz,1H),8.10-7.91(m,3H),7.73(br d,J=8.3Hz,1H),7.53(br d,J=3.9Hz,1H),7.27-7.19(m,1H),7.19-7.08(m,2H),6.06(s,1H),4.86(br s,1H),4.11(br s,3H),3.31(br s,1H),3.22(br d,J=7.2Hz,1H),2.93(br s,1H),2.37-2.25(m,1H),2.03(br d,J=11.8Hz,1H),1.75-1.65(m,2H)。LC-MS RT:1.14min;MS(ESI)m/z=668.3(M+H)+;方法A。

[0247] 实施例121



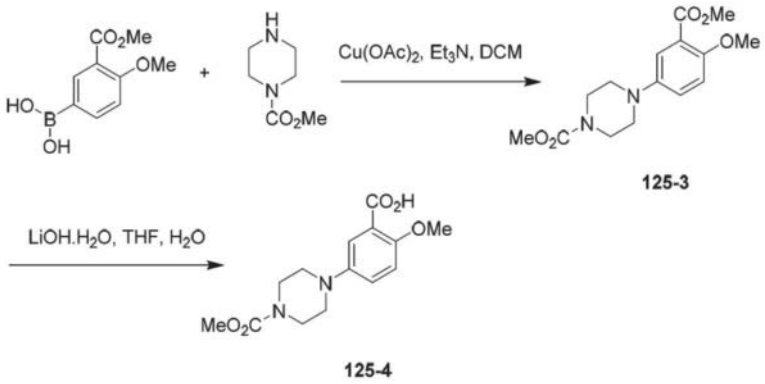
针对实施例121的程序:向反应容器中添加实施例87(3mg,4.77μmol)、乙磺酰胺(1.6mg,0.01mmol)、MeCN(1mL)、DIEA(3μl,0.017mmol)及BOP-Cl(4mg,0.01mmol)。将反应物在40℃搅拌12h,在减压下浓缩且经由制备型RP-HPLC纯化,以仅产生初级酰胺副产物121(3.0mg,0.0040mmol,93%产率)。1H NMR(500MHz,$CDCl_3$)δ9.65(br d,J=8.0Hz,1H),8.41(d,J=2.2Hz,1H),7.96(dd,J=7.2,2.2Hz,2H),7.90-7.83(m,2H),7.73(dt,J=8.5,2.2Hz,1H),7.56(dt,J=8.7,3.5Hz,1H),7.25(dd,J=9.9,8.8Hz,1H),7.16-7.06(m,2H),6.69-6.68(m,1H),4.72(br t,J=11.0Hz,1H),4.08(s,3H),3.06(br d,J=8.8Hz,3H),2.21-2.14(m,1H),1.84(br t,J=8.7Hz,1H),1.76(s,3H),1.75(s,3H),1.64-1.54(m,2H)。LC-MS RT:1.26min;MS(ESI)m/z=628.3(M+H)+;方法A。

[0248] 实施例125



中间体125-1:中间体125-1为以与实施例5相同的方式由IV-3制备且经由硅胶色谱纯化(49mg,0.10mmol,30%产率)。RT=1.23min;MS(ESI)m/z=501.1(M+H)$^+$;方法A。

[0249] 中间体125-2:中间体125-2为以与中间体IV-7相同的方式由125-1制备(73mg,0.18mmol,96%产率)。RT=0.87min;MS(ESI)m/z=405.1(M+H)$^+$;方法A。



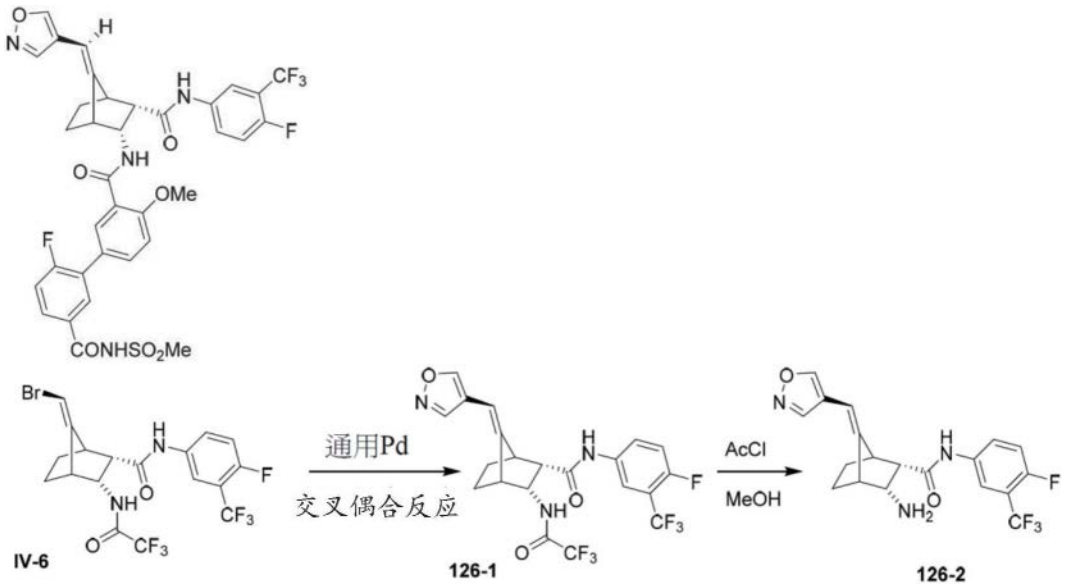
[0250] 中间体125-3:向反应容器中添加哌嗪-1-甲酸甲酯(103mg,0.710mmol)、DCE(1mL)、MeCN(1mL)、乙酸铜(II)(130mg,0.71mmol)、(4-甲氧基-3-(甲氧基羰基)苯基)硼酸(50mg,0.24mmol)及4Å分子筛(300mg)。将反应混合物在23℃搅拌12h(露天),过滤,在减压下浓缩且经由制备型RP-HPLC纯化,得到125-3(37mg,0.12mmol,50%产率)。LC-MS RT=0.72min;MS(ESI)m/z=309.1(M+H)$^+$;方法A。

[0251] 中间体125-4:向反应容器中添加125-3(37mg,0.12mmol)、THF(1mL)、水(0.5mL)及单水合氢氧化锂(34.4mg,0.820mmol)。将反应混合物在23℃搅拌2.5h,用EtOAc(10mL)稀释

且用10mL含有0.82mmol HCl的饱和NH_4Cl洗涤。将有机相经Na_2SO_4干燥且在减压下浓缩,得到125-4(35.3mg,0.120mmol,100%产率),其不经进一步纯化即使用。LC-MS RT=0.62min;MS(ESI)m/z=295.0$(M+H)^+$;方法A。

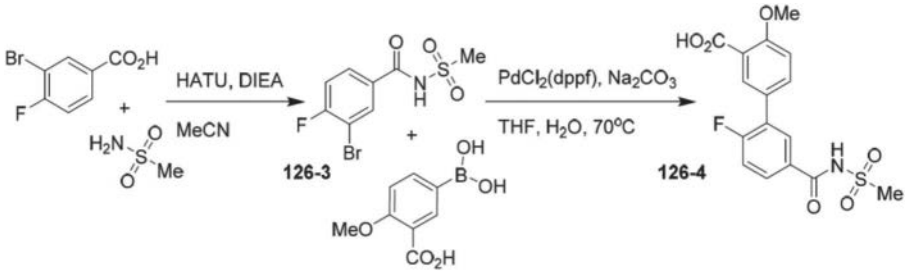
[0252] 针对实施例125的程序:实施例125为根据针对实施例108所描述的方法,采用125-4,由125-2制备。^1H NMR(500MHz,$CDCl_3$)δ9.63(br d,J=7.7Hz,1H),7.96-7.84(m,3H),7.59(dt,J=8.8,3.4Hz,1H),7.33(d,J=4.1Hz,4H),7.29(dd,J=8.9,3.2Hz,1H),7.25-7.20(m,1H),7.10(t,J=9.4Hz,1H),6.95(d,J=9.1Hz,1H),6.33(s,1H),4.89-4.80(m,1H),3.99(s,3H),3.75(s,3H),3.74-3.69(m,4H),3.49(t,J=3.3Hz,1H),3.23-3.14(m,5H),2.89(m,1H),2.27-2.19(m,1H),1.97-1.87(m,1H),1.75-1.66(m,2H)。LC-MS RT:1.16min;MS(ESI)m/z=681.3(M+H)+;方法A。

[0253] 实施例126



中间体126-1:向含有IV-6(125mg,0.25mmol)的反应容器中添加4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)异噁唑(125mg,0.610mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(50.7mg,0.0620mmol)及Na_2CO_3(1.5mL,3.0mmol)。通过使氮气鼓泡使反应混合物脱气3min,密封,且在60℃搅拌2h。在冷却至23℃之后,用EtOAc萃取反应混合物,将合并的有机部分经Na_2SO_4干燥,过滤,在减压下浓缩,且经由硅胶色谱纯化,得到126-1(101mg,0.210mmol,83.0%产率)。LC-MS RT=1.07min;MS(ESI)m/z=492.1$(M+H)^+$;方法A。

[0254] 中间体126-2:中间体126-2为以与中间体IV-7相同的方式由126-1制备(67mg,0.16mmol,100%产率)。RT=0.76min;MS(ESI)m/z=396.0$(M+H)^+$;方法A。



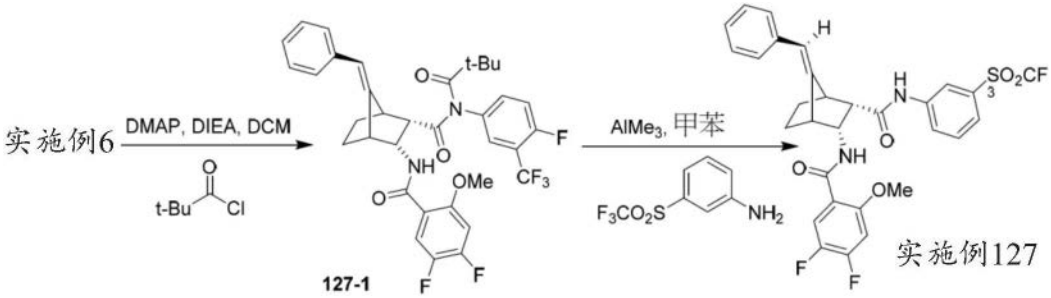
[0255] 中间体126-3:向反应容器中添加甲磺酰胺(521mg,5.48mmol)、3-溴-4-氟苯甲酸(400mg,1.83mmol)、MeCN(3.7mL)、DIEA(1.1mL,6.40mmol)及HATU(833mg,2.19mmol)。将反

应混合物在40℃搅拌12h,使其冷却,在减压下浓缩,且进行制备型RP-HPLC纯化,得到126-3(450mg,1.52mmol,83%产率)。LC-MS RT=0.76min;(M+H)=297.7;方法A

[0256] 中间体126-4:向含有126-3(200mg,0.68mmol)的反应容器中添加5-溴-2-甲氧基苯甲酸(199mg,1.01mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(83mg,0.10mmol)、THF(6.7mL)及1M Na_2CO_3(4.0mL,4.1mmol)。通过使氮气鼓泡使反应混合物脱气10min,密封,且在70℃搅拌2h。在冷却至23℃之后,在减压下浓缩反应混合物且经由制备型RP-HPLC纯化,得到126-4(158mg,0.430mmol,64.0%产率)。LC-MS RT=0.70min;MS(ESI)m/z=368.1(M+H)+;方法A。

[0257] 针对实施例126的程序:实施例126为根据针对实施例108所描述的方法,采用126-4,由126-2制备。^{1}H NMR(500MHz,$CDCl_3$)δ10.32(br s,1H),9.86(br d,J=7.7Hz,1H),8.41(s,1H),8.34(s,1H),8.25(d,J=1.7Hz,1H),8.10(br s,1H),8.04(dd,J=6.1,2.5Hz,1H),7.98(dd,J=7.3,2.1Hz,1H),7.89(ddd,J=8.5,4.5,2.2Hz,1H),7.68(br d,J=8.8Hz,1H),7.58(dt,J=8.6,3.5Hz,1H),7.19-7.06(m,3H),5.95(s,1H),4.72-4.63(m,1H),4.08(s,3H),3.45(s,3H),3.25-3.20(m,1H),3.15(dd,J=10.7,4.1Hz,1H),2.89-2.84(m,1H),2.28-2.23(m,1H),2.01-1.96(m,1H),1.71-1.62(m,2H)。LC-MS RT:1.09min;MS(ESI)m/z=745.2(M+H)+;方法A。

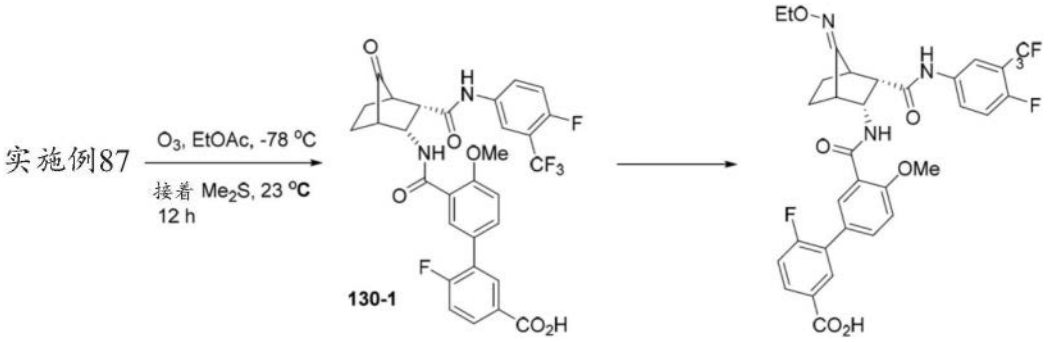
[0258] 实施例127



中间体127-1:向反应容器中添加实施例6(10mg,0.017mmol)、DCM(1mL)、DIEA(0.015mL,0.087mmol)及DMAP(1.06mg,8.70μmol)。在23℃搅拌12h之后,经由硅胶色谱纯化残余物,得到127-1(10.5mg,0.0160mmol,92.0%产率)。LC-MS RT=1.31min;MS(ESI)m/z=659.3$(M+H)^+$;方法A。

[0259] 针对实施例127的程序:向反应容器中添加3-((三氟甲基)磺酰基)苯胺(24mg,0.11mmol)、甲苯(0.5mL)及三甲基铝(0.05mL,0.11mmol)。在23℃搅拌15min之后,添加含中间体127-1(5mg,7.6μmol)的甲苯(0.5mL)。将反应物在23℃搅拌1h,用饱和罗谢尔盐淬灭且用EtOAc萃取。将有机相经Na_2SO_4干燥,浓缩且经由制备型RP-HPLC纯化,得到实施例127(3.6mg,5.80μmol,76%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.56(br d,J=7.7Hz,1H),8.56-8.47(m,1H),8.06-7.98(m,2H),7.78-7.71(m,2H),7.58(t,J=8.0Hz,1H),7.37-7.30(m,4H),7.25-7.21(m,1H),6.79(dd,J=11.7,6.2Hz,1H),6.33(s,1H),4.88-4.81(m,1H),4.03(s,3H),3.52-3.47(m,1H),3.20(dd,J=10.7,3.9Hz,1H),2.91-2.87(m,1H),2.26-2.18(m,1H),1.95-1.88(m,1H),1.74-1.70(m,2H)。LC-MS RT:1.25min;MS(ESI)m/z=621.2(M+H)+;方法A。

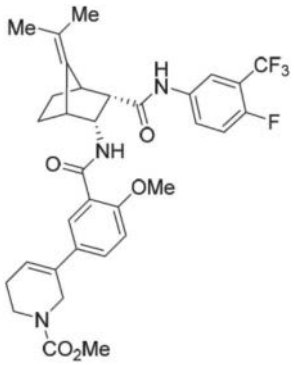
[0260] 实施例130



中间体130-1:中间体130-1为以与如针对77-1所描述的相同方式由实施例87制备(19mg,0.030mmol,100％产率)。LC-MS RT＝1.06min;MS(ESI)m/z＝603.1(M+H)$^+$;方法A。

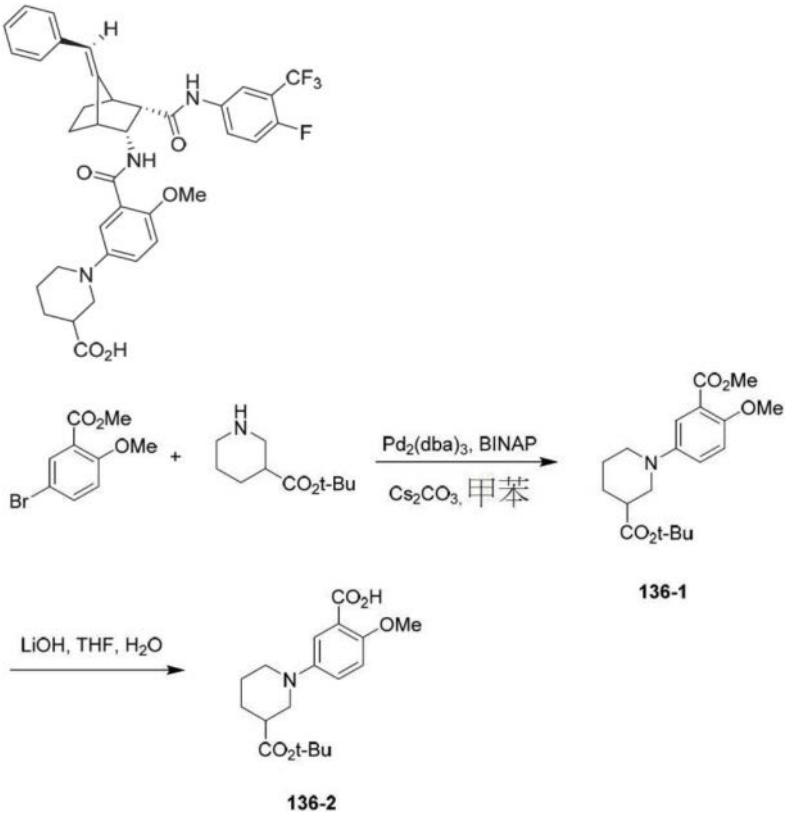
[0261] 针对实施例130的程序:向含有130-1(17mg,0.03mmol)的反应容器中添加DCE(1.5mL)、DIEA(0.09mL,0.51mmol)及O-乙基羟胺HCl(41.3mg,0.42mmol)。将混合物在23℃搅拌24h,在减压下浓缩,且进行制备型RP-HPLC纯化,得到呈Z/E异构体的混合物形式的例子130(15mg,0.023mmol,82％产率)。LC-MS RT:1.13min;MS(ESI)m/z＝464.2(M+H)+;方法A。

[0262] 实施例134



针对实施例134的程序:向反应容器中添加实施例140(6mg,10μmol)、DCM(1mL)、DIEA(6μl,0.03mmol)及氯甲酸甲酯(2μl,0.02mmol)。在23℃搅拌30min之后,在减压下浓缩反应混合物且经由制备型RP-HPLC纯化,得到实施例134(3.5mg,5.4μmol,51％产率)。1H NMR(500MHz,$CDCl_3$)δ9.42-9.17(m,1H),8.25-8.02(m,2H),7.87(dd,J＝6.1,2.4Hz,1H),7.62-7.53(m,1H),7.43(br s,1H),7.07(t,J＝9.5Hz,1H),6.92(br d,J＝8.6Hz,1H),6.17(br s,1H),4.78-4.66(m,1H),4.38-4.23(m,2H),3.98(s,3H),3.75(s,3H),3.66-3.52(m,2H),3.08-2.97(m,3H),2.37-2.26(m,2H),2.23-2.11(m,1H),1.83-1.75(m,1H),1.74-1.72(m,3H),1.72(s,3H),1.62-1.53(m,2H)。LC-MS RT:1.25min;MS(ESI)m/z＝630.3(M+H)+;方法B。

[0263] 实施例136

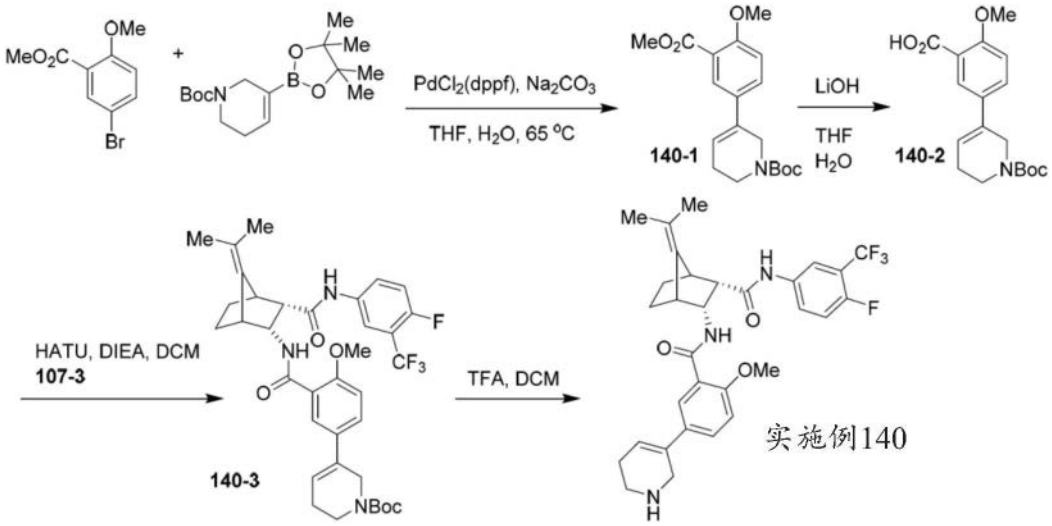


中间体136-1:向反应容器中添加5-溴-2-甲氧基苯甲酸甲酯(33.1mg,0.135mmol)、哌啶-3-甲酸叔丁酯(25mg,0.14mmol)、甲苯(1mL)、哌啶-3-甲酸叔丁酯(25mg,0.14mmol)、BINAP(10.5mg,0.0200mmol)及Pd2(dba)$_3$(6mg,0.01mmol)。将反应混合物用氮气脱气3min且在100℃搅拌12h,使其冷却至23℃,用EtOAc稀释,且用饱和$NaHCO_3$(2×10mL)洗涤溶液。将有机层经Na_2SO_4干燥,过滤,在减压下浓缩,且经由制备型RP-HPLC纯化,得到136-1(39mg,0.084mmol,62%产率)。LC-MS RT=0.82min;MS(ESI)m/z=350.1$(M+H)^+$;方法A。

[0264] 中间体136-2:向反应容器中添加136-1(26mg,0.060mmol)、THF(1mL)、水(0.5mL)及单水合氢氧化锂(19.1mg,0.460mmol)。将反应混合物在23℃搅拌3h,用EtOAc(10mL)稀释且用10mL含有0.5mmol HCl的饱和NH_4Cl洗涤。将有机相经Na_2SO_4干燥且在减压下浓缩,得到136-2(19mg,0.060mmol,100%产率),其不经进一步纯化即使用。LC-MS RT=0.74min;MS(ESI)m/z=336.1$(M+H)^+$;方法A。

[0265] 针对实施例136的程序:实施例136为根据针对实施例108所描述的方法,采用外消旋136-2,由125-2制备。与制备实施例120的程序中一样实现叔丁酯之后续移除。经由SFC色谱将实施例136(峰1)与其非镜像异构体(峰2)实施例138分离。峰1,RT=8.80min,>99.5%ee;峰2,RT=9.97min,>99.5%ee。制备型色谱条件:仪器:Berger MG II;柱:Chiralpak IA,30×250mm,5微米;移动相:25%EtOH/75%CO_2;流动条件:70mL/min,150巴,40℃;检测器波长:220nm;注射详情:0.5mL~3mg/mL于CAN中。分析型色谱条件:仪器:BergerAnalytical SFC;柱:Chiralpak IA,4.6×250mm,5微米;移动相:25%EtOH/75%CO_2;流动条件:2.0mL/min,150巴,40℃;检测器波长:220nm;注射详情:10μL浓缩样本于EtOH中。LC-MS RT:1.07min;MS(ESI)m/z=666.3(M+H)+;方法A。

[0266] 实施例140



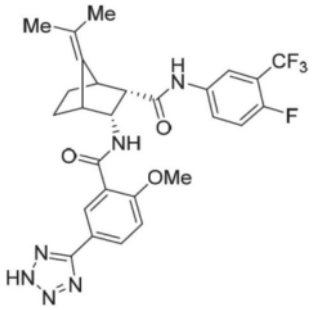
中间体140-1:向含有5-溴-2-甲氧基苯甲酸甲酯(47.6mg,0.190mmol)的反应容器中添加3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)-5,6-二氢吡啶-1(2H)-甲酸叔丁酯(50mg,0.16mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(19.8mg,0.0240mmol)及Na_2CO_3(1mL,2mmol)。通过使氮气鼓泡使反应混合物脱气3min,密封,且在65℃搅拌2h。在冷却至23℃之后,用EtOAc萃取反应混合物。将有机相经Na_2SO_4干燥,过滤,在减压下浓缩,且经由硅胶色谱纯化,得到140-1(57.4mg,0.17mmol,100%产率)。LC-MS RT=1.04min;MS(ESI)m/z=348.0$(M+H)^+$;方法A。

[0267] 中间体140-2:向反应容器中添加140-1(28mg,0.081mmol)、THF(1mL)、水(0.5mL)及单水合氢氧化锂(16.9mg,0.400mmol)。将反应混合物在23℃搅拌1h,用EtOAc(10mL)稀释且用10mL含有0.5mmol HCl的饱和NH_4Cl洗涤所得溶液。将有机相经Na_2SO_4干燥且在减压下浓缩,得到140-2(25mg,0.080mmol,93%产率),其不经进-步纯化即使用。

[0268] 中间体140-3:中间体140-3为使用实施例108中所采用的通用酰胺偶合程序,由140-2及107-3制备(67mg,0.16mmol,100%产率)。RT=1.32min;MS(ESI)m/z=672.3$(M+H)^+$;方法A。

[0269] 针对实施例140的程序:向反应容器中添加140-3(11.4mg,0.02mmol)、DCM(1mL)及TFA(0.1mL,1.30mmol)。在23℃搅拌3h之后,在减压下浓缩反应内容物,得到实施例140(3.7mg,5.13μmol,30%产率)。^1H NMR(500MHz,$CDCl_3$)δ9.29(br d,J=7.9Hz,1H),8.59(br s,1H),8.08(d,J=2.3Hz,1H),7.94(br d,J=4.5Hz,1H),7.67-7.57(m,1H),7.18(br d,J=8.3Hz,1H),7.06(t,J=9.4Hz,1H),6.82(d,J=8.6Hz,1H),6.16(br s,1H),4.75-4.60(m,1H),3.97(s,3H),3.79-3.59(m,2H),3.20-3.12(m,1H),3.11-3.05(m,2H),3.04-3.00(m,1H),2.98-2.95(m,1H),2.46-2.34(m,2H),2.22(br t,J=8.7Hz,1H),1.77(br t,J=8.7Hz,1H),1.72(s,3H),1.71(s,3H),1.60-1.53(m,2H)。LC-MS RT:0.98min;MS(ESI)m/z=572.4(M+H)+;方法B。

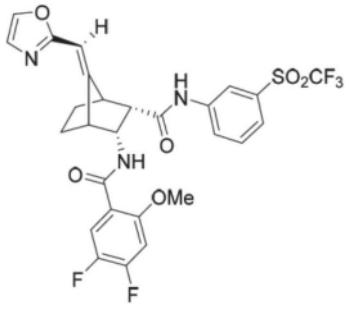
[0270] 实施例144



针对实施例144的程序:向反应容器中添加实施例114(3.4mg,6.6μmol)、叠氮化钠(12.9mg,0.198mmol)、氯化铵(10.6mg,0.198mmol)及DMF。在105℃搅拌反应混合物4h,使其冷却至23℃,用MeOH稀释,过滤,且经由制备型RP-HPLC纯化,得到实施例144(2.3mg,4.0μmol,60%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ10.01(d,J=9.4Hz,1H),9.30(d,J=2.5Hz,1H),8.51(dd,J=8.8,2.5Hz,1H),8.44(s,1H),8.11(dd,J=6.3,2.8Hz,1H),7.41(dt,J=8.7,3.3Hz,1H),7.25-7.22(m,1H),7.08-6.99(m,1H),4.96(td,J=9.8,4.3Hz,1H),4.21(s,3H),3.31(dd,J=10.7,3.9Hz,1H),3.04(t,J=3.7Hz,1H),2.88(t,J=4.0Hz,1H),2.51-2.44(m,1H),1.87-1.80(m,2H),1.67(s,3H),1.60-1.50(m,2H),1.48(s,3H)。LC-MS RT:1.11min;MS(ESI)m/z=559.1(M+H)+;方法A。

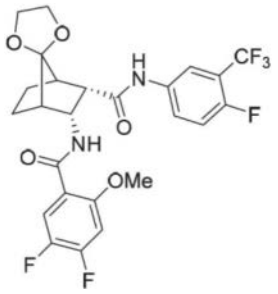
[0271]

实施例145



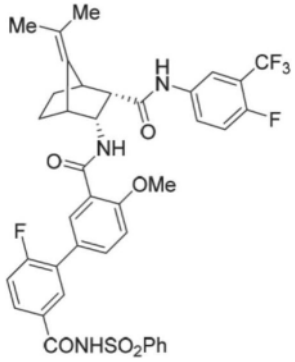
针对实施例145的程序:实施例145为采用2-甲基噁唑,由5-6制备。向反应容器中添加2-甲基噁唑(24.9mg,0.300mmol)及THF(1mL)。在使反应混合物冷却至-78℃之后,添加KHMDS(0.30mL,0.30mmol)。在-78℃搅拌混合物10min且再添加2-甲基噁唑(24.9mg,0.300mmol)。使混合物升温至23℃,在23℃搅拌3h,且通过添加饱和Na_2CO_3淬灭。将有机相经Na_2SO_4干燥,过滤,浓缩,且经由硅胶色谱纯化,得到中间体醇(17mg,0.029mmol,97%产率)。根据实施例33中所描述的方法使中间体醇脱水。^{1}H NMR(500MHz,$CDCl_3$)δ9.53(br d,J=7.4Hz,1H),8.06-7.99(m,2H),7.97(dd,J=6.2,2.6Hz,1H),7.63(s,1H),7.53(dt,J=8.9,3.4Hz,1H),7.18-7.09(m,2H),6.80(dd,J=11.6,6.1Hz,1H),6.28(s,1H),4.88-4.80(m,1H),4.00(s,3H),3.93(t,J=4.0Hz,1H),3.19(dd,J=10.9,3.7Hz,1H),2.99-2.92(m,1H),2.35-2.27(m,1H),2.02-1.94(m,1H),1.78-1.71(m,2H)。LC-MS RT:1.17min;MS(ESI)m/z=566.0(M+H)+;方法A。

[0272] 实施例147



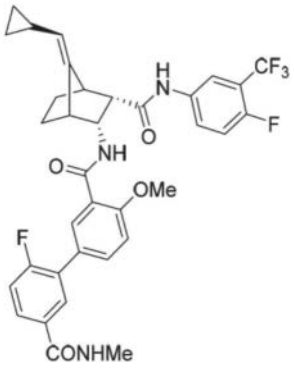
针对实施例147的程序:向反应容器中添加5-6(10mg,0.020mmol)、苯(1mL)、乙烷-1,2-二醇(24.81mg,0.4000mmol)、$MgSO_4$(200mg,1.66mmol)及pTsOH单水合物(3.8mg,0.020mmol)。在50℃搅拌12h之后,过滤反应混合物,在减压下浓缩且经由制备型RP-HPLC纯化,得到实施例147(2.1mg,3.8μmol,19%产率)。1H NMR(500MHz,$CDCl_3$)δ9.35(br d,J=7.8Hz,1H),8.04(dd,J=11.4,9.4Hz,1H),7.93(dd,J=6.3,2.6Hz,1H),7.77(s,1H),7.52(dt,J=8.7,3.6Hz,1H),7.12(t,J=9.4Hz,1H),6.79(dd,J=11.6,6.1Hz,1H),5.05-4.97(m,1H),4.08-4.01(m,4H),3.99(s,3H),3.49-3.41(m,1H),2.23(t,J=4.0Hz,1H),2.20-2.11(m,2H),1.93-1.81(m,2H),1.75-1.67(m,1H)。LC-MS RT:1.14min;MS(ESI)m/z=545.1(M+H)+;方法C。

[0273] 实施例150



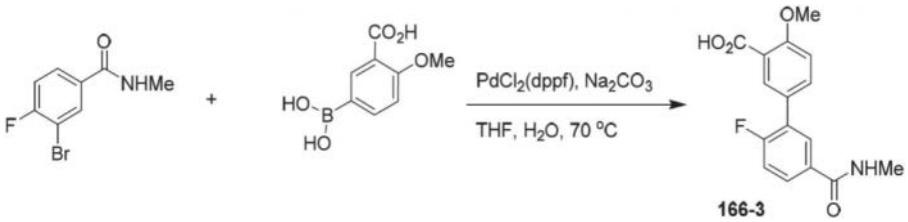
针对实施例150的程序:向反应容器中添加实施例87(5mg,8μmol)、苯磺酰胺(3.8mg,0.020mmol)、MeCN(1mL)、DIEA(5μl,0.03mmol)及BOP-Cl(6.0mg,0.024mrnol)。将反应混合物在40℃搅拌12h,在减压下浓缩且经由制备型RP-HPLC纯化,得到实施例150(2.2mg,2.7μmol,34%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.65(br d,J=8.0Hz,1H),8.41(d,J=2.2Hz,1H),7.96(dd,J=7.2,2.2Hz,2H),7.90-7.84(m,2H),7.73(dt,J=8.5,2.2Hz,1H),7.56(dt,J=8.7,3.5Hz,1H),7.25(dd,J=9.9,8.8Hz,1H),7.16-7.03(m,2H),4.75-4.68(m,1H),4.08(s,3H),3.06(br d,J=8.8Hz,3H),2.21-2.14(m,1H),1.87-1.81(m,1H),1.76(s,3H),1.75(s,3H),1.63-1.56(m,2H)。LC-MS RT:1.4min;MS(ESI)m/z=768.2(M+H)+;方法C。

[0274] 实施例166



中间体166-1:中间体166-1为以与中间体126-1相同的方式由IV-6制备(5.1mg,0.010mmol,23%产率)。RT=1.21min;MS(ESI)m/z=465.1(M+H)$^+$;方法A。

[0275] 中间体166-2:中间体166-2为以与中间体IV-7相同的方式由166-1制备(4.0mg,0.010mmol,100%产率)。RT=0.84min;MS(ESI)m/z=369.1(M+H)$^+$;方法A。

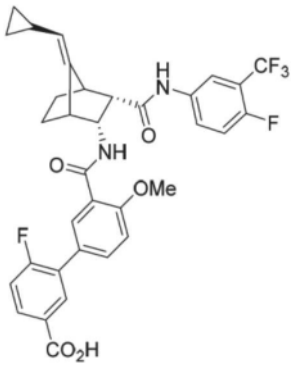


166-3

[0276] 中间体166-3:中间体166-3为以与中间体140-1相同的方式,由3-溴-4-氟-N-甲基苯甲酰胺及5-溴-2-甲氧基苯甲酸制备(28mg,0.080mmol,41%产率)。LC-MSRT=0.99min;MS(ESI)m/z=304.9(M+H)$^+$;方法A。

[0277] 针对实施例166的程序:实施例166为根据针对实施例108所描述的方法,采用166-3,由166-2制备。^{1}H NMR(500MHz,$CDCl_3$)δ9.73(br d,J=7.7Hz,1H),8.39(d,J=1.9Hz,1H),7.97(dd,J=6.2,2.3Hz,1H),7.90(s,1H),7.85(dd,J=7.4,2.2Hz,1H),7.81(ddd,J=8.5,4.7,2.2Hz,1H),7.72(dt,J=8.8,2.2Hz,1H),7.56(dt,J=8.7,3.4Hz,1H),7.24-7.19(m,1H),7.15-7.10(m,1H),7.08(d,J=8.8Hz,1H),6.47(br s,1H),4.85-4.76(m,1H),4.66(d,J=9.6Hz,1H),4.09(s,3H),3.22(t,J=3.7Hz,1H),3.10(dd,J=10.7,3.3Hz,1H),3.05(d,J=4.7Hz,3H),2.77-2.67(m,1H),2.19-2.12(m,1H),1.94-1.86(m,1H),1.71-1.61(m,2H),1.53-1.46(m,1H),0.81-0.71(m,2H),0.41-0.30(m,2H)。LC-MS RT:1.18min;MS(ESI)m/z=654.2(M+H)+;方法A。

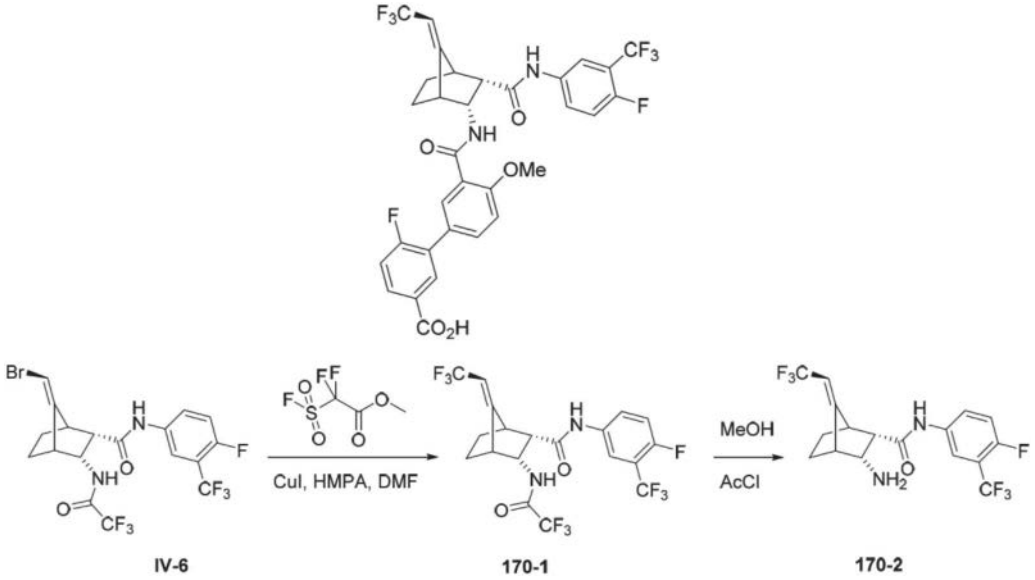
[0278] 实施例168



针对实施例168的程序:实施例168为根据针对实施例108所描述的方法,采用120-

6,由166-2制备。在DCM(1mL)中实现叔丁酯的裂解且在23℃与$ZnBr_2$(20equiv.)一起搅拌12h。在通过添加HCl(1.0M)淬灭反应物且用乙酸乙酯萃取所得溶液之后,将有机相经Na_2SO_4干燥,过滤,在减压下浓缩,且经由制备型RP-HPLC纯化残余物,得到实施例168。实施例168的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.42(br d,J=7.7Hz,1H),8.43(br s,1H),8.30-8.21(m,1H),8.12-8.02(m,1H),7.96(br s,2H),7.71(dt,J=8.7,2.0Hz,1H),7.54-7.47(m,1H),7.26-7.21(m,1H),7.13-7.06(m,2H),4.95-4.85(m,1H),4.66(d,J=9.6Hz,1H),4.07(s,3H),3.27-3.19(m,1H),3.14(br dd,J=10.9,3.2Hz,1H),2.75(t,J=3.9Hz,1H),2.32-2.23(m,1H),1.94-1.87(m,1H),1.74-1.63(m,2H),1.54-1.48(m,1H),0.76(m,2H),0.36(m,2H)。LC-MS RT:1.19min;MS(ESI)m/z=641.1(M+H)+;方法A。

[0279] 实施例170



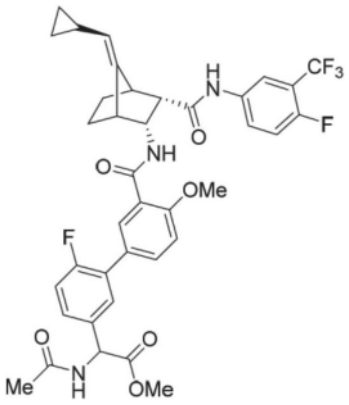
中间体170-1:在氮气氛围下,在75℃经由注射器向装有含2,2-二氟-2-(氟磺酰基)乙酸甲酯(体积?,0.15mmol)的无水DMF(0.5mL)的20mL小瓶中逐滴添加IV-6及CuI(质量?,0.07mmol)于无水DMF(1mL)及HMPA(0.5mL)中的悬浮液持续30min。在相同温度下搅拌所得混合物12h。使反应混合物冷却且经由HPLC过滤器过滤且通过RP-HPLC纯化,得到170-1(24mg,81%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.38(br d,J=6.1Hz,1H),7.77-7.69(m,2H),7.46(s,1H),7.24(t,J=9.1Hz,1H),5.62(q,J=7.2Hz,1H),4.50(dt,J=10.5,5.3Hz,1H),3.50-3.42(m,1H),3.13-3.04(m,1H),2.89(t,J=4.0Hz,1H),2.02-1.90(m,2H),1.76-1.60(m,2H)。

[0280] 中间体170-2:中间体170-2为由170-1制备。将MeOH(1.5mL)及乙酰氯(2.1mmol)装入2打兰小瓶中且在23℃搅拌5min。向反应小瓶中添加170-1且将内容物加热至40℃持续24h。用氮气流浓缩反应混合物,得到呈HCl盐形式的170-2,其不经进一步纯化即使用。LC-MS RT=0.75min;MS(ESI)m/z=397.1$(M+H)^+$;方法A。

[0281] 针对实施例170的程序:实施例170为根据针对实施例120所描述的方法,采用120-6,由170-2制备。实施例170的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.28(br d,J=6.6Hz,1H),8.41(br s,1H),8.37(br s,1H),8.27(br d,J=6.1Hz,1H),8.08(br s,1H),7.92(br s,1H),7.80-7.70(m,1H),7.47(dt,J=8.6,3.7Hz,1H),7.27-7.20(m,1H),7.13-7.02(m,2H),5.60(q,J=7.3Hz,1H),5.05-4.92(m,1H),4.06(s,3H),3.42(br s,1H),3.25(br dd,J=

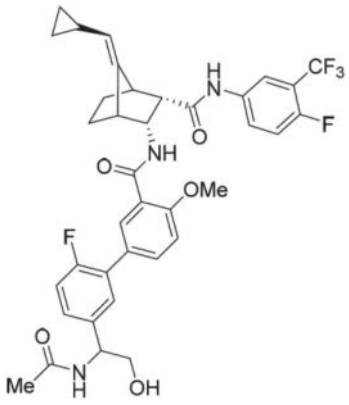
10.6,3.4Hz,1H),2.95(t,J＝4.0Hz,1H),2.61-2.50(m,1H),2.05-1.97(m,1H),1.82-1.72(m,2H)。LC-MS RT:1.15min;MS(ESI)m/z＝669.2(M+H)+;方法A。

[0282] 实施例171



针对实施例171的程序:实施例171为由实施例186制备。向装有实施例186(0.008mmol)、DCM(0.3mL)及MeOH(0.1mL)的1打兰小瓶中添加TMS-重氮甲烷(0.5M于DCM中,0.34mL,0.17mmol,20equiv.),且在23℃搅拌反应混合物1h。在减压下浓缩反应混合物且经由硅胶正相色谱纯化,得到6.1mg实施例171。实施例171的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.45(br d,J＝8.0Hz,1H),8.38-8.35(m,1H),8.00-7.92(m,2H),7.64(dt,J＝8.7,2.0Hz,1H),7.54(dt,J＝8.7,3.5Hz,1H),7.43(dd,J＝7.3,2.3Hz,1H),7.32(ddd,J＝8.4,4.5,2.5Hz,1H),7.17-7.03(m,3H),6.59(br d,J＝6.9Hz,1H),5.61(d,J＝6.9Hz,1H),4.89-4.81(m,1H),4.65(d,J＝9.6Hz,1H),4.06(s,3H),3.77(s,3H),3.21(t,J＝4.1Hz,1H),3.15-3.08(m,1H),2.73(t,J＝4.0Hz,1H),2.24-2.16(m,1H),2.08(s,3H),1.95-1.86(m,1H),1.72-1.63(m,2H),1.54-1.45(m,1H),0.79-0.72(m,2H),0.39-0.32(m,2H)。LC-MS RT:1.15min;MS(ESI)m/z＝726.3(M+H)+;方法A。

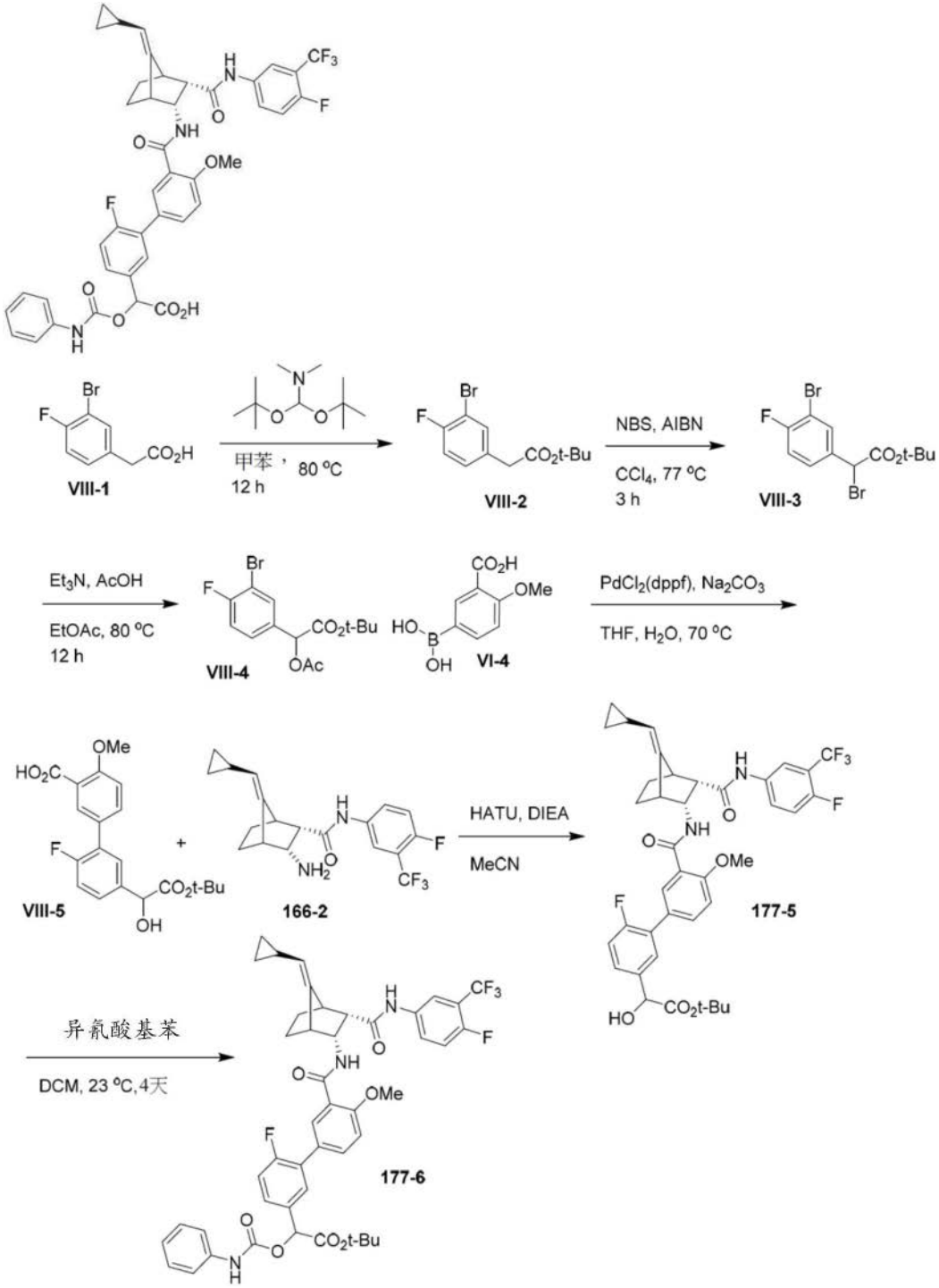
[0283] 实施例172



针对实施例172的程序:实施例172为由实施例171制备。向装有实施例171(0.009mmol)及THF(0.5mL)的经冰浴冷却的1打兰小瓶中添加$LiBH_4$(0.027mmol,3.0quiv.)。在0℃搅拌反应混合物5min,且随后升温至23℃且再搅拌30min用乙酸乙酯(10mL)稀释反应混合物。用饱和氯化铵水溶液(20mL)洗涤溶液。用EtOAc萃取水相,将合并的有机部分经Na_2SO_4干燥,过滤且在减压下浓缩,且经由制备型RP-HPLC纯化残余物,得到实施例172。实施例172的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.54(d,J＝8.0Hz,1H),8.29(d,J＝1.7Hz,1H),8.21(s,1H),7.96(dd,J＝6.1,2.5Hz,1H),7.57-7.47(m,2H),7.32-7.29(m,

1H),7.23(ddd,J＝8.3,4.6,2.5Hz,1H),7.12-7.00(m,3H),6.45(br d,J＝6.9Hz,1H),5.10-5.03(m,1H),4.85-4.76(m,1H),4.62(d,J＝9.4Hz,1H),4.08(s,3H),3.93-3.86(m,2H),3.18(t,J＝4.1Hz,1H),3.13-3.06(m,1H),2.71(t,J＝4.0Hz,1H),2.26-2.18(m,1H),2.08(s,3H),1.95-1.87(m,1H),1.70-1.62(m,2H),1.51-1.43(m,1H),0.77-0.72(m,2H),0.37-0.30(m,2H)。LC-MS RT:1.08min;MS(ESI)m/z＝698.4(M+H)+;方法A。

[0284] 实施例177



中间体VIII-2:除了将反应温度维持在80℃持续12h之外,间物VIII-2为采用关于类似底物的已知条件(Ludwig,J.;Lehr,M.Syn.Comm.2004,34,3691-3695)制备。^{1}H NMR

(500MHz,$CDCl_3$)δ7.49(dd,J＝6.6,2.2Hz,1H),7.20(ddd,J＝8.3,4.6,2.2Hz,1H),7.13-7.03(m,1H),3.49(s,2H),1.46(s,9H)。

[0285] 中间体VIII-3:向装有中间体VIII-2(266mg,0.920mmol)的20mL反应小瓶中添加NBS(196mg,1.10mmol)、四氯化碳(10mL)及AIBN(15mg,0.090mmol)。在77℃搅拌溶液3h在减压下浓缩溶液且通过正相硅胶色谱纯化,得到中间体VIII-3(308mg,0.840mmol,91.0%产率)。

[0286] 中间体VIII-4:向装有中间体VIII-3的2打兰小瓶中添加乙酸乙酯(2mL)、三乙胺(0.27mL,2.0mmol)及乙酸(0.1mL,2mmol)。在80℃搅拌反应混合物12h。在减压下浓缩反应混合物且通过正相硅胶色谱纯化,得到中间体VIII-4。^{1}H NMR(500MHz,$CDCl_3$)δ7.70(dd,J＝6.6,2.2Hz,1H),7.41(ddd,J＝8.4,4.7,2.1Hz,1H),7.15(t,J＝8.4Hz,1H),5.77(s,1H),2.22(s,3H),1.43(s,9H)。

[0287] 中间体VIII-5:中间体VIII-5为以用于中间体140-1的相同条件,采用5-溴-2-甲氧基苯甲酸,由中间体VIII-4制备。分离出呈O-乙酸酯形式之一半物质(85mg,0.60mmol,34%);^{1}H NMR(500MHz,$CDCl_3$)δ8.43-8.36(m,1H),7.81(dt,J＝8.7,2.0Hz,1H),7.56(dd,J＝7.3,2.3Hz,1H),7.45(ddd,J＝8.5,4.6,2.3Hz,1H),7.23-7.16(m,2H),5.84(s,1H),4.17(s,3H),2.23(s,3H),1.45(s,9H)同时分离出呈游离醇形式的另一半(70mg,0.19mmol,31%);^{1}H NMR(500MHz,$CDCl_3$)δ8.40(d,J＝2.2Hz,1H),7.82(dt,J＝8.6,2.2Hz,1H),7.54(dd,J＝7.4,2.5Hz,1H),7.41(ddd,J＝8.4,4.8,2.2Hz,1H),7.19-7.14(m,2H),5.09(s,1H),4.16(s,3H),1.47(s,9H)。使用手性SFC将外消旋VIII-5分离成个别镜像异构体。制备型色谱条件:仪器:Berger MG II;柱:Chiralpak ID,21×250mm,5微米;移动相:25%IPA/75%CO_2;流动条件:45mL/min,120巴,40℃;检测器波长:220nm;注射详情:注射8次0.36mL～20mg/mL于IPA中。分析型色谱条件:仪器:Waters UPC2分析型SFC;柱:Chiralpak ID 4.6×100mm,3微米;移动相:25%IPA/75%CO_2;流动条件:2mL/min,150巴,40℃;检测器波长:220nm。峰1,RT＝3.89min,>99.5%ee;峰2,RT＝5.44min,>99.5%ee。收集中间体VIII-5产物峰#2且继续使用以产生手性中间体177-5。

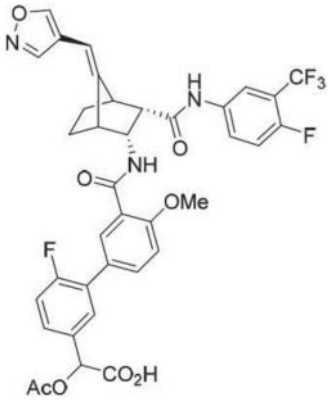
[0288] 中间体177-5:中间体177-5为根据针对实施例108所描述的方法,由VIII-5峰2制备。中间体177-5(14.2mg,0.0200mmol,79.0%产率)。LC-MS RT＝1.22min;MS(ESI)m/z＝727.1$(M+H)^+$;方法A。

[0289] 中间体177-6:向装有177-5的1打兰小瓶中添加DCM(1mL)及异氰酸苯酯(82mg,0.69mmol)。将溶液在23℃搅拌4天,在减压下浓缩且通过RP-HPLC纯化,得到中间体177-6(6.2mg,0.0070mmol,53%产率)。

[0290] 针对实施例177的程序:实施例177为通过采用针对实施例168所描述的叔丁酯裂解方法,由177-6制备。实施例177的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.74(br d,J＝8.0Hz,1H),8.22(d,J＝2.2Hz,1H),8.06-7.97(m,2H),7.73(br s,1H),7.65(td,J＝8.7,2.1Hz,2H),7.46(dt,J＝8.8,3.4Hz,1H),7.41-7.33(m,3H),7.24(t,J＝7.8Hz,2H),7.09-6.98(m,4H),6.15(s,1H),4.84-4.74(m,1H),4.59(d,J＝9.6Hz,1H),4.04(s,3H),3.16(t,J＝4.0Hz,1H),3.09(br dd,J＝10.6,3.7Hz,1H),2.67(br t,J＝3.7Hz,1H),2.21-2.14(m,1H),1.91-1.82(m,1H),1.68-1.52(m,2H),1.51-1.41(m,1H),0.79-0.69(m,2H),0.36-0.29(m,2H)。LC-MS RT:1.26min;MS(ESI)m/z＝790.4(M+H)+;方法A。

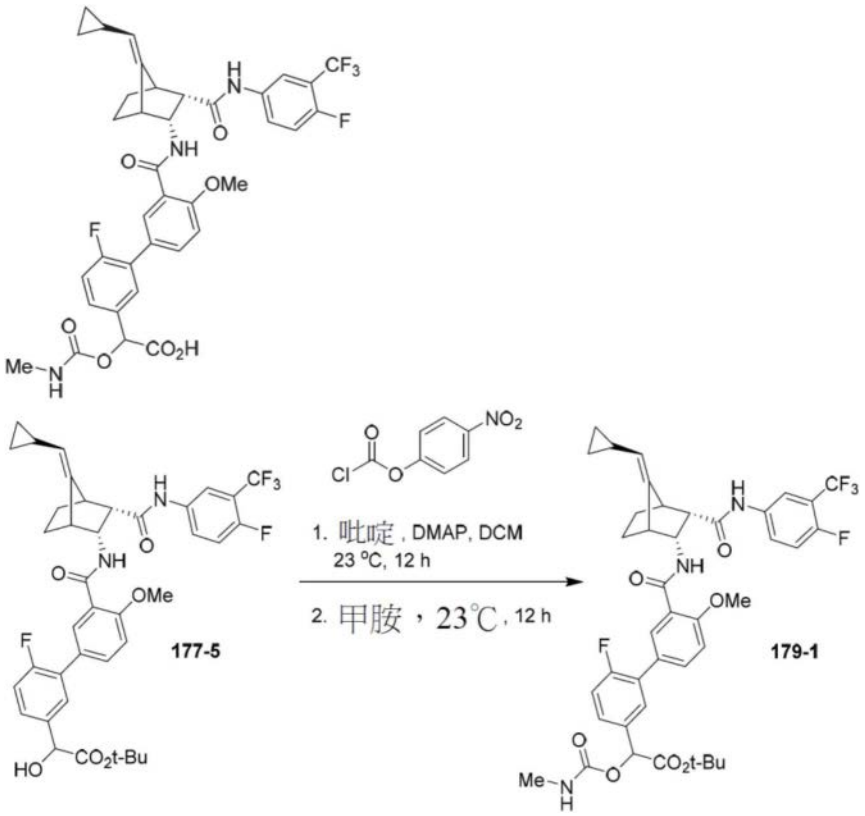
[0291]

实施例178



针对实施例178的程序:实施例178为由34-1制备。向装有34-1、DCM(1.5mL)及DIEA(0.12mL,0.70mmol,30equiv.)的2打兰小瓶中添加乙酰氯(0.03,0.5mmol,20equiv.)且在23℃搅拌1h。通过添加MeOH(1mL)淬灭反应物且根据针对实施例168所描述的方法移除叔丁酯。实施例178的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.82(d,J=8.3Hz,1H),8.45(s,1H),8.36(s,1H),8.29(s,1H),8.26(d,J=2.5Hz,1H),8.00(dd,J=6.3,2.5Hz,1H),7.70(dt,J=8.5,2.2Hz,1H),7.62(dd,J=7.4,2.2Hz,1H),7.46(ddd,J=8.5,4.3,2.6Hz,2H),7.14(dd,J=10.0,8.7Hz,1H),7.08-7.00(m,2H),5.98(s,1H),5.98(s,1H),4.88-4.79(m,1H),4.06(s,3H),3.25-3.19(m,2H),2.91-2.86(m,1H),2.40-2.33(m,1H),2.19(s,3H),2.00-1.93(m,1H),1.72-1.60(m,2H)。LC-MS RT:1.11min;MS(ESI)m/z=740.1(M+H)+;方法A。

[0292] 实施例179

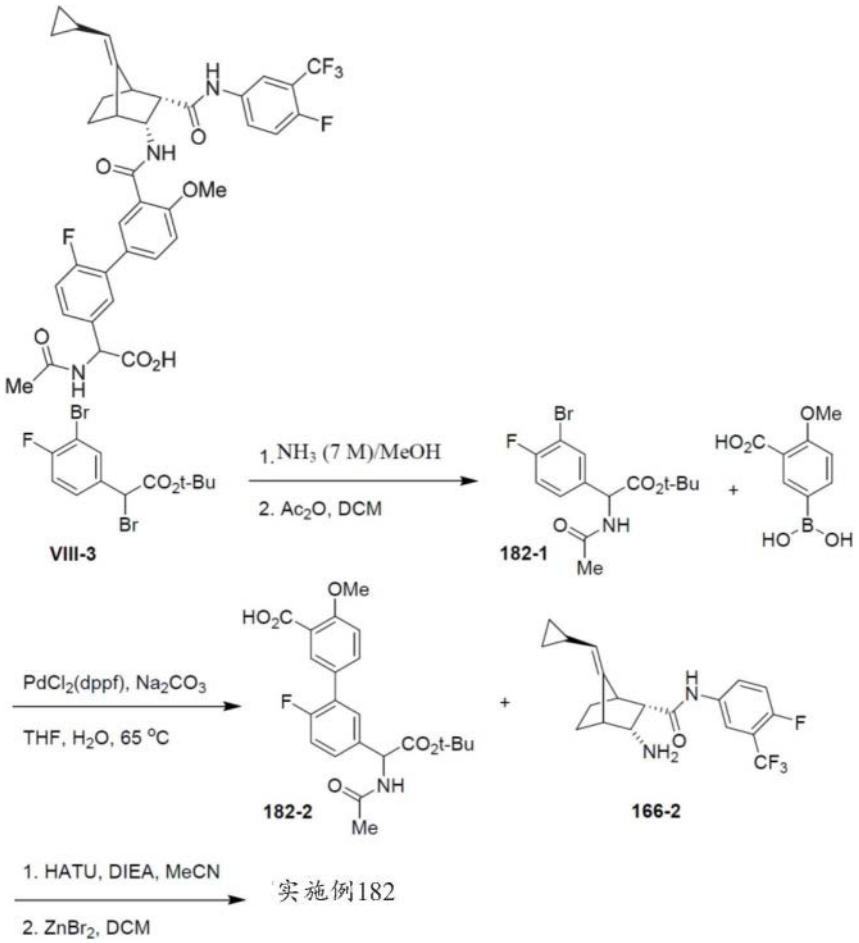


中间体179-1:向装有177-5的20mL小瓶中添加DCM(4mL)、氯甲酸4-硝基苯酯(体积

或质量,0.43mmol)及DMAP(质量,0.04mmol)。在23℃搅拌反应溶液12h。添加甲胺(0.85mmol)且再搅拌反应溶液1h。在减压下浓缩反应溶液且通过RP-HPLC纯化,得到中间体179-1(65mg,0.083mmol,97%)。LC-MS RT=1.24min;MS(ESI)m/z=784.4(M+H)$^+$;方法A。

[0293] 针对实施例179的程序:实施例179为根据如实施例168中针对叔丁酯裂解所描述的方法由179-1制备。实施例179的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.70(br d,J=8.0Hz,1H),8.28(d,J=1.9Hz,1H),8.19(s,1H),8.01(dd,J=6.2,2.6Hz,1H),7.68(dt,J=8.6,2.2Hz,1H),7.60(br d,J=5.5Hz,1H),7.52-7.45(m,1H),7.45-7.37(m,1H),7.15-7.00(m,3H),6.05(s,1H),5.38-5.28(m,1H),4.82-4.75(m,1H),4.60(d,J=9.4Hz,1H),4.07(s,3H),3.16(t,J=4.1Hz,1H),3.10(dd,J=10.5,3.3Hz,1H),2.85(br d,J=3.3Hz,3H),2.71-2.67(m,1H),2.25-2.20(m,1H),1.92-1.86(m,1H),1.68-1.53(m,2H),1.49-1.42(m,1H),0.78-0.69(m,2H),0.36-0.30(m,2H)。LC-MS RT:1.13min;MS(ESI)m/z=728.3(M+H)+;方法A。

[0294] 实施例182



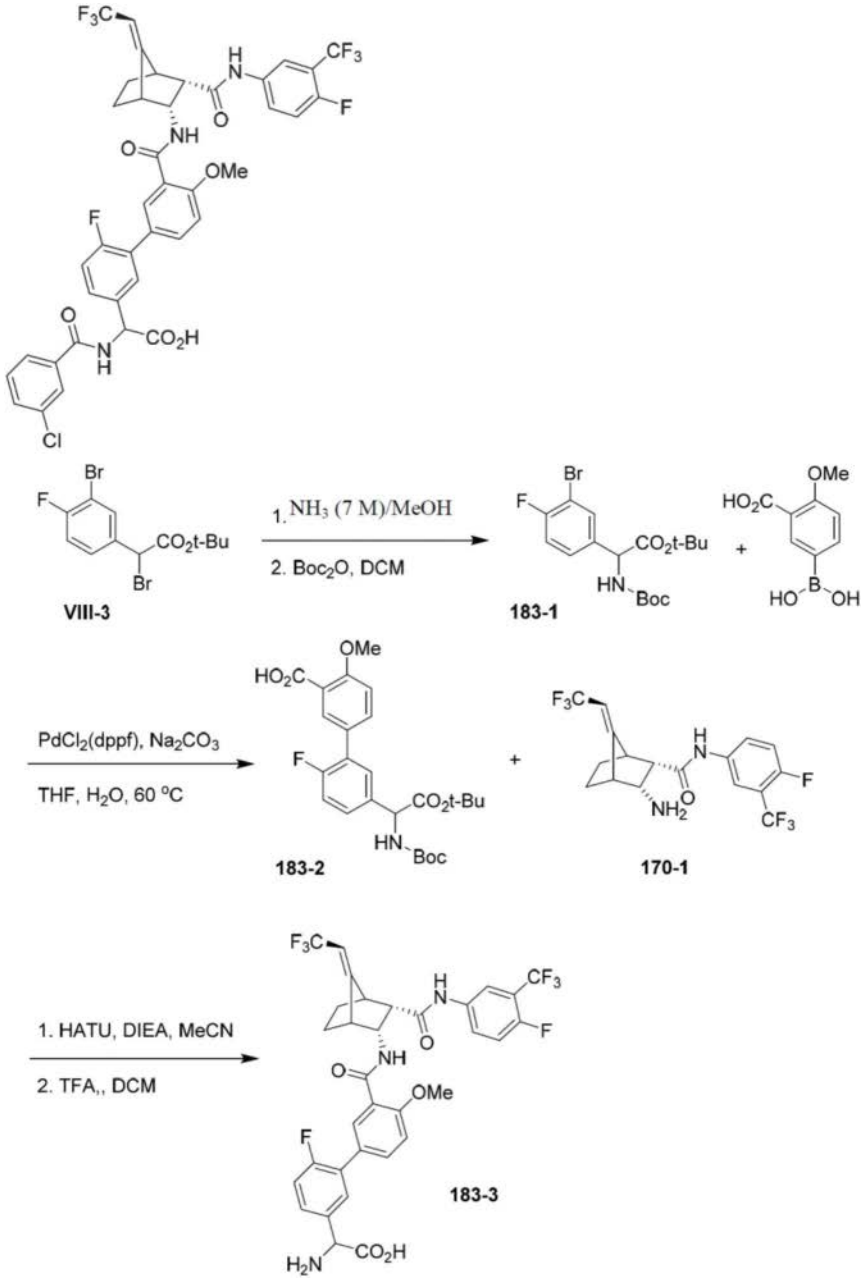
中间体182-1:向装有中间体VIII-3的1打兰小瓶中添加氨(0.5mL,4mmol,7M于MeOH中)。在23℃搅拌溶液12h。在减压下浓缩溶液且用含乙酸酐(7.2μL,0.076mmol)的DCM(1mL)处理残余物且在23℃搅拌1h。通过正相硅胶色谱纯化所得残余物,得到中间体182-1(26mg,0.074mmol,97%产率)。LC-MS RT=0.92min;MS(ESI)m/z=346.1(M+H)$^+$;方法A。

[0295] 中间体182-2:除了在65℃的温度下持续18h以外,中间体182-2为采用针对中间体140-1所描述的类似条件来制备。^{1}H NMR(500MHz,CDCl3)δ8.37(d,J=1.9Hz,1H),7.81(dt,

J＝8.5,2.1Hz,1H),7.45(dd,J＝7.3,2.3Hz,1H),7.35(ddd,J＝8.5,4.6,2.3Hz,1H),7.21-7.13(m,2H),6.74(brd,J＝6.9Hz,1H),5.51(d,J＝6.9Hz,1H),4.17(s,3H),2.12(s,3H),1.45(s,9H)。外消旋182-2为使用手性SFC分离成其镜像异构体。制备型色谱条件:仪器:Berger MG II;柱:Chiralpak ID,21×250mm,5微米;移动相:20％IPA/80％CO_2;流动条件:45mL/min,120巴,40℃;检测器波长:215nm;注射详情:注射3次15mg/mL于MeOH中。分析型色谱条件:仪器:Aurora Infinity分析型SFC;柱:Chiralpak AD-H,4.6×100mm,3微米;移动相:20％IPA/80％Co_2;流动条件:2mL/min,150巴,40℃;检测器波长:220nm。峰1,RT＝3.49min,>99.5％ee;峰2,RT＝4.43min,>99.5％ee。收集中间体182-2产物峰#2且继续使用以产生实施例182。

[0296] 针对实施例182的程序:实施例182为根据针对实施例108所描述的方法,采用182-2(峰2,异构体2),由166-2制备。与制备实施例168的程序中一样实现叔丁酯之后续移除。实施例182(异构体1)的分析资料:^{1}H NMR(500MHz,$CDCl_3$)δ10.14(d,J＝7.7Hz,1H),8.72(brd,J＝9.1Hz,1H),8.46(d,J＝2.5Hz,1H),8.00(dd,J＝6.1,2.8Hz,1H),7.80-7.70(m,2H),7.61(s,1H),7.46-7.38(m,2H),7.11-7.01(m,2H),6.98(d,J＝8.8Hz,1H),5.96(d,J＝9.1Hz,1H),4.73-4.65(m,2H),4.04(s,3H),3.18(br t,J＝3.7Hz,1H),3.03(dd,J＝10.6,4.0Hz,1H),2.69(br t,J＝3.7Hz,1H),2.13(s,3H),2.06-1.98(m,1H),1.88-1.80(m,1H),1.64-1.49(m,3H),0.89-0.76(m,2H),0.44-0.34(m,2H)。LC-MS RT:1.11min;MS(ESI)m/z＝712.2(M+H)+;方法A。

[0297] 实施例183



中间体183-1:中间体183-1为根据针对中间体182-1所描述的方法,用Boc_2O置换Ac_2O,由VIII-3来制备。LC-MS RT＝1.14min;MS(ESI)m/z＝406.0$(M+H)^+$;方法A。

[0298] 中间体183-2:除了在60℃的温度下持续18h以外,中间体183-2为采用用于中间体140-1的相同条件来制备。^1H NMR(500MHz,$CDCl_3$)δ8.38(d,J＝1.9Hz,1H),7.80(dt,J＝8.7,2.0Hz,1H),7.46(dd,J＝7.4,2.5Hz,1H),7.36(dddd,J＝8.8,4.4,2.2,1.1Hz,1H),7.19-7.13(m,2H),5.67(br d,J＝5.2Hz,1H),5.25(br d,J＝6.3Hz,1H),4.16(s,3H),1.46(br s,9H),1.44(s,9H)。使用手性SFC将外消旋183-2分离成个别镜像异构体。制备型色谱条件:仪器:Berger MG II;柱:Chiralpak ID,21×250mm,5微米;移动相:20%MeOH/80%CO_2;流动条件:45mL/min,120巴,40℃;检测器波长:209nm;注射详情:注射49次于MeOH中。分析型色谱条件:仪器:Waters UPC2分析型SFC;柱:Chiralpak IC,4.6×100mm,3微米;移动相:25%MeOH/75%CO_2;流动条件:2mL/min,150巴,40℃;检测器波长:220nm。峰1,RT＝4.22min,95.7%ee;峰2,RT＝5.11min,>99%ee。收集中间体183-2产物峰#2且继续使用以

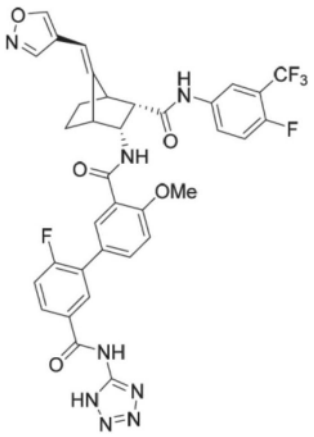
产生中间体183-3。

[0299] 中间体183-3:中间体183-3为根据针对实施例108所描述的方法,由183-2制备。与制备实施例120的程序中一样实现叔丁酯之后续移除。LC-MS RT＝0.99min;MS(ESI)m/z＝698.3(M+H)$^+$;方法A。

[0300] 针对实施例183的程序:实施例183为由183-3制备。向2打兰小瓶中装入183-3、DIEA(0.06mmol,5equiv.)及4-氯苯甲酰氯(0.035mmol,3.0equiv.)。将溶液在23℃搅拌30min且随后用MeOH淬灭。在减压下浓缩反应内容物得到粗产物,该粗产物经由制备型RP-HPLC纯化,得到实施例183。实施例183的分析数据:^{1}H NMR(500MHz,$CDCl_3$)δ9.98(br d,J＝8.0Hz,1H),8.77-8.68(m,1H),8.49(d,J＝2.5Hz,1H),7.96(dd,J＝6.3,2.5Hz,1H),7.91-7.84(m,2H),7.77-7.71(m,1H),7.69(t,J＝1.7Hz,1H),7.60(d,J＝8.0Hz,1H),7.55(ddd,J＝8.3,4.3,2.2Hz,1H),7.43-7.39(m,1H),7.37-7.31(m,1H),7.27-7.24(m,1H),7.08(dd,J＝10.6,8.7Hz,1H),7.01-6.95(m,2H),6.21(d,J＝8.5Hz,1H),5.61(q,J＝7.4Hz,1H),4.83-4.74(m,1H),4.04(s,3H),3.41(br s,1H),3.14(dd,J＝10.5,4.1Hz,1H),2.88(t,J＝3.9Hz,1H),2.30-2.22(m,1H),2.01-1.95(m,1H),1.73-1.62(m,2H)。LC-MS RT:1.21min;MS(ESI)m/z＝836.3(M+H)+;方法A。

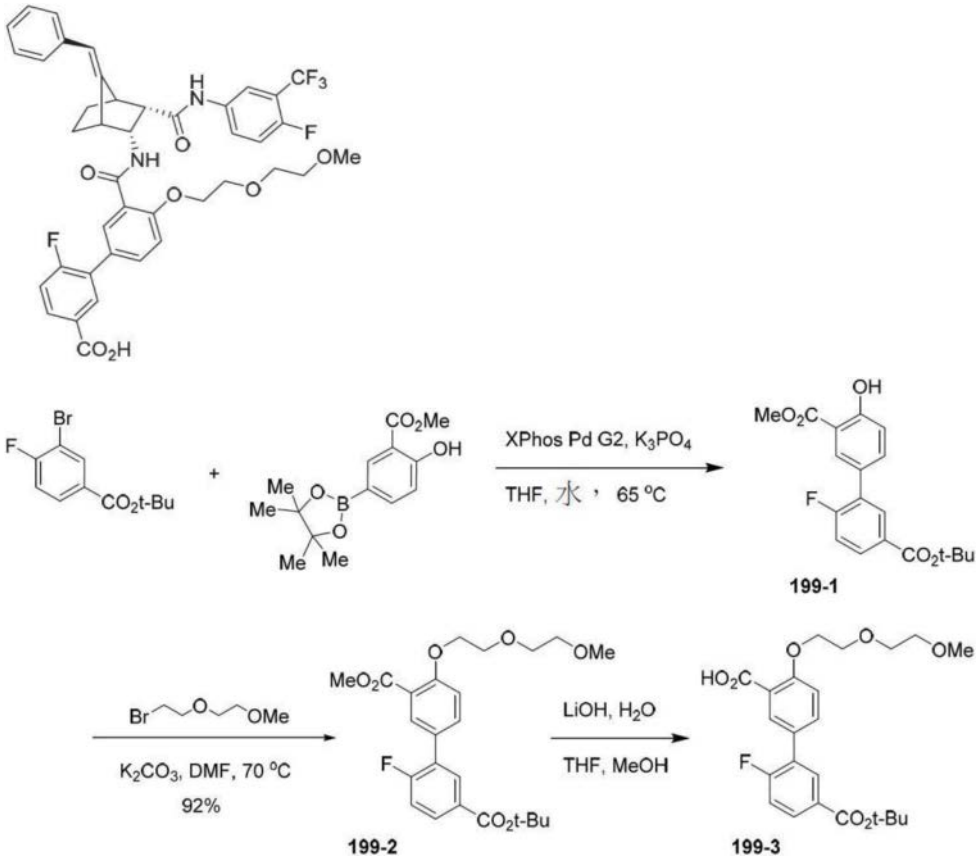
[0301]

实施例192



针对实施例192的程序:实施例192为采用BHFFT作为偶合剂,由实施例120制备。向装有实施例120(0.043mmol,1.3equiv.)的2打兰额定压力小瓶中添加BHFFT(0.049mmol,2.0equiv.),随后添加DCM(1mL)及DIEA(0.15mmol,4.5equiv.)。将反应混合物在23℃搅拌30min,随后加热至80℃持续18h。使反应混合物冷却至23℃,将小瓶内容物溶解于DMF(1.5mL)中,且通过RP-HPLC纯化残余物。实施例192的分析数据:LC-MS RT:2.41min;MS(ESI)m/z＝735.1(M+H)+;方法C。

[0302] 实施例199



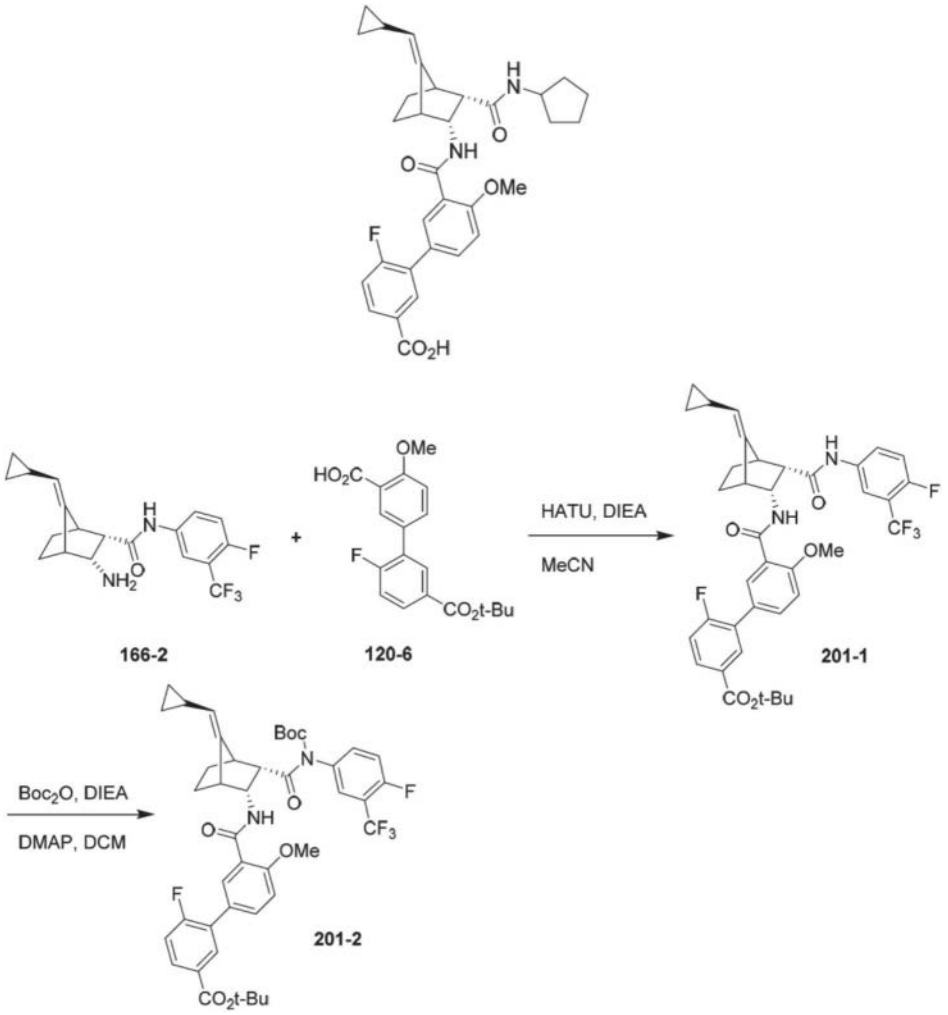
中间体199-1:除了在65℃的温度下持续18h以外,中间体199-1为采用用于中间体140-1的相同条件来制备。^{1}H NMR(500MHz,$CDCl_3$)δ10.87(s,1H),8.11-8.04(m,2H),7.95(ddd,J=8.5,4.8,2.3Hz,1H),7.68(dt,J=8.5,1.9Hz,1H),7.18(dd,J=10.0,8.7Hz,1H),7.09(d,J=8.5Hz,1H),3.99(s,3H),1.66-1.59(m,9H)。LC-MS RT=1.20min;MS(ESI)m/z=347.1(M+H)$^+$

[0303] 中间体199-2:向装有中间体199-1的1打兰小瓶中添加碳酸钾(53.5mg,0.39mmol)、DMF(0.4mL)及1-溴-2-(2-甲氧基乙氧基)乙烷(70.8mg,0.39mmol)。将反应混合物在23℃搅拌18h,随后加热至40℃再持续18h。用氮气流浓缩反应混合物,用乙酸乙酯及水稀释残余物且用乙酸乙酯(3×10mL)萃取所得溶液。将合并的有机部分经硫酸钠干燥,过滤,且在减压下浓缩,得到199-2(80mg,0.18mmol,92%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ8.08(dd,J=7.7,2.2Hz,1H),8.00(dd,J=2.2,1.1Hz,1H),7.94(ddd,J=8.5,4.8,2.3Hz,1H),7.66(dt,J=8.7,2.0Hz,1H),7.17(dd,J=10.0,8.7Hz,1H),7.09(d,J=8.8Hz,1H),4.28(t,J=5.1Hz,2H),3.97-3.93(m,2H),3.91(s,3H),3.81-3.77(m,2H),3.61-3.57(m,2H),3.44-3.39(m,3H),1.61(s,9H)。LC-MS RT=1.11min;MS(ESI)m/z=449.1(M+H)$^+$;方法A。

[0304] 中间体199-3:中间体199-3为以与中间体3-3类似的方式,通过中间体199-2的氢氧化锂水解来制备。LC-MS RT=1.02min;MS(ESI)m/z=348.1(M+H)$^+$;方法A。

[0305] 针对实施例199的程序:实施例199为根据针对实施例108所描述的方法,采用199-3,由125-2制备。与制备实施例120的程序中一样实现叔丁酯之后续移除。实施例199的分析数据:LC-MS RT:1.15min;MS(ESI)m/z=765.2(M+H)+;方法A。

[0306] 实施例201



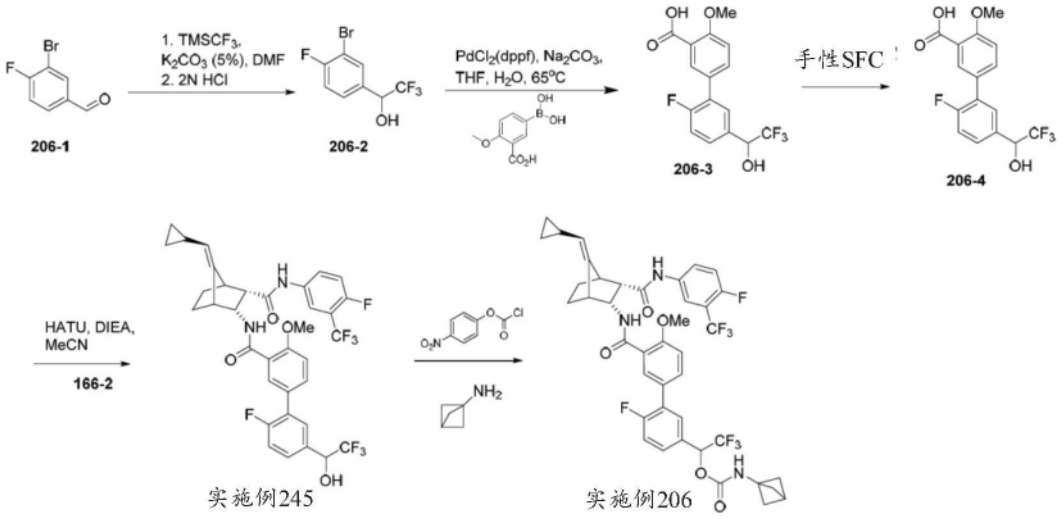
中间体201-1:中间体201-1为根据针对实施例108所描述的方法,采用120-6,由166-2制备。^{1}H NMR(500MHz,$CDCl_3$)δ9.40(br d,J=8.0Hz,1H),8.40(d,J=1.1Hz,1H),8.08(dd,J=7.7,2.2Hz,1H),8.02-7.93(m,3H),7.64(dt,J=8.6,1.9Hz,1H),7.49(dt,J=8.6,3.5Hz,1H),7.18(dd,J=10.0,8.7Hz,1H),7.12-7.03(m,2H),4.89-4.81(m,1H),4.63(d,J=9.4Hz,1H),4.05(s,3H),3.20(t,J=3.9Hz,1H),3.10(dd,J=10.6,3.2Hz,1H),2.72(t,J=3.9Hz,1H),2.24-2.16(m,1H),1.93-1.85(m,1H),1.71-1.63(m,2H),1.61(s,9H),1.53-1.41(m,1H),0.74(dt,J=7.8,3.7Hz,2H),0.41-0.30(m,2H)。LC-MS RT=1.30min;MS(ESI)m/z=697.3$(M+H)^+$;方法A。

[0307] 中间体201-2:向装有中间体201-1(88mg,0.126mmol)的2打兰小瓶中添加DCM(1.25mL),随后添加Boc_2O(0.51mmol)、DMAP(0.06mmol)及DIEA(0.51mmol)。将溶液在23℃搅拌18h,且随后在减压下浓缩。通过正相硅胶色谱纯化所得粗物质,得到中间体201-2(94mg,0.12mmol,93%产率)。LC-MS RT=1.34min;MS(ESI)m/z=797.5$(M+H)^+$;方法A。

[0308] 针对实施例201的程序:实施例201为由201-2制备。向装有201-2(0.013mmol)的1打兰小瓶中添加DCM(0.3mL)及环戊基胺(0.125mmol,10equiv.)。将溶液在23℃搅拌18h且在减压下浓缩,得到粗中间体。与制备实施例120的程序中一样实现叔丁酯之后续移除。实施例201的分析数据:^{1}H NMR(500MHz,DMSO-d6)δ9.78(br d,J=7.0Hz,1H),7.85-7.75(m,3H),7.74-7.67(m,1H),7.48(br d,J=8.5Hz,1H),7.16(br t,J=9.5Hz,1H),7.05(d,J=

8.9Hz,1H),4.36(d,J=9.5Hz,1H),4.04(dt,J=10.0,5.2Hz,1H),3.81-3.73(m,4H),2.83-2.76(m,1H),2.66-2.60(m,1H),1.69-1.45(m,4H),1.40-1.29(m,2H),1.28-1.16(m,3H),1.15-1.01(m,4H),0.53-0.39(m,2H),0.06(br d,J=3.1Hz,2H)。LC-MS RT:2.33min;MS(ESI)m/z=547.4(M+H)+;方法C。

[0309] 实施例206



中间体206-2:向反应容器中添加3-溴-4-氟苯甲醛(206-1,235mg,1.15mmol)、DMF(3.5mL)、(三氟甲基)三甲基硅烷(0.34mL,2.3mmol)及K_2CO_3(8.0mg,0.058mmol)。在室温下搅拌反应混合物60min且添加2N HCl(3mL)。在室温下再搅拌1h之后,用EtOAc(15mL)稀释反应混合物,且用饱和NH_4Cl洗涤溶液。通过添加EtOAc(10mL×2)萃取水相。将合并的有机部分经Na_2SO_4干燥,过滤,浓缩,且通过硅胶色谱纯化,得到206-2(205mg,0.751mmol,64.9%产率)。^1H NMR(500MHz,$CDCl_3$)d 7.74(dd,J=6.5,2.1Hz,1H),7.43(ddd,J=8.4,4.8,2.2Hz,1H),7.19(t,J=8.4Hz,1H),5.11-4.98(m,1H),2.69(d,J=4.4Hz,1H)。

[0310] 中间体206-3:向含有206-2(100mg,0.366mmol)的反应容器中添加5-溴-2-甲氧基苯甲酸(93mg,0.48mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(45mg,0.055mmol)、Na_2CO_3(155mg,1.46mmol)及H_2O(1mL)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在65℃搅拌3h。在冷却至室温之后,通过添加1N HCl淬灭反应混合物,将溶液用EtOAc萃取,经Na_2SO_4干燥,过滤,浓缩且通过HPLC纯化,得到206-3(50.5mg,0.147mmol,40.1%产率)。^1H NMR(500MHz,$CDCl_3$)δ8.39(d,J=1.9Hz,1H),7.83(dt,J=8.7,2.1Hz,1H),7.59(dd,J=7.3,2.1Hz,1H),7.53-7.45(m,1H),7.23(dd,J=10.2,8.8Hz,1H),7.18(d,J=8.5Hz,1H),5.11(q,J=6.6Hz,1H),4.17(s,3H)。

[0311] 中间体206-4:使用手性SFC将外消旋206-3分离成个别镜像异构体。制备型色谱条件:仪器:Berger MG II;柱:Kromasil 5-CelluCoat,21×250mm,5微米;移动相:15%IPA-ACN(0.1%DEA)/85%CO_2;流动条件:45mL/min,120巴,40℃;检测器波长:220nm;注射详情:0.4mL~15mg/mL于ACN-IPA(1:1)中。收集峰#2,得到中间体206-4。分析型色谱条件:仪器:Aurora Infinity Analytical SFC;柱:Kromasil 5-CelluCoat,4.6×250mm,5微米;移动相:20%IPA-ACN(0.1%DEA)/80%CO_2;流动条件:2mL/min,150巴,40℃;检测器波长:220nm。峰1,RT=9.12min,99%ee;峰2,RT=10.19min,98%ee。

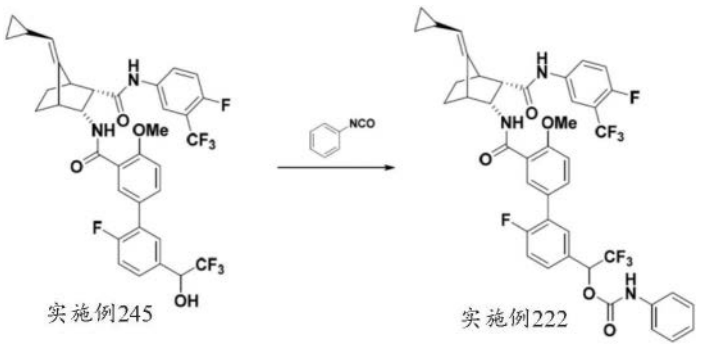
[0312] 实施例245:向反应容器中添加中间体166-2(7.0mg,0.017mmol)、中间体206-4

(6.2mg,0.018mmol)、MeCN(1mL)、DIEA(9.1μl,0.052mmol)及HATU(7.2mg,0.019mmol)。将反应混合物在室温下搅拌12h,在减压下浓缩,且进行制备型HPLC纯化,得到实施例245(9.5mg,0.014mmol,78%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.57(d,J=7.7Hz,1H),8.33(dd,J=2.2,0.8Hz,1H),8.05(s,1H),7.99(dd,J=6.3,2.5Hz,1H),7.66(dt,J=8.7,2.0Hz,1H),7.57(dd,J=7.3,2.1Hz,1H),7.56-7.52(m,1H),7.45-7.40(m,1H),7.17(dd,J=10.2,8.5Hz,1H),7.11-7.04(m,2H),5.11-5.04(m,1H),4.77-4.70(m,1H),4.57(d,J=9.4Hz,1H),4.06(s,3H),3.42(br s,1H),3.19(t,J=4.1Hz,1H),3.08(ddd,J=10.7,4.1,1.2Hz,1H),2.67(t,J=4.0Hz,1H),2.18-2.07(m,1H),1.92-1.82(m,1H),1.67-1.58(m,2H),1.53-1.45(m,1H),0.79-0.68(m,2H),0.38-0.27(m,2H)。LC-MS RT:1.38min;MS(ESI)m/z695.3(M+H)$^+$;方法A。

[0313] 实施例246:遵循合成实施例246的程序,由中间体166-2及206-4的镜像异构体(来自手性SFC纯化的峰1)制备。^{1}H NMR(500MHz,$CDCl_3$)δ9.53(d,J=7.7Hz,1H),8.34(dd,J=2.5,0.8Hz,1H),8.01(s,1H),7.97(dd,J=6.2,2.6Hz,1H),7.66(dt,J=8.7,2.0Hz,1H),7.57-7.50(m,2H),7.48-7.40(m,1H),7.18(dd,J=10.2,8.5Hz,1H),7.12-7.02(m,2H),5.13-5.03(m,1H),4.81-4.71(m,1H),4.60(d,J=9.6Hz,1H),4.06(s,3H),3.19(t,J=3.7Hz,2H),3.09(ddd,J=10.8,4.1,1.1Hz,1H),2.70(t,J=4.0Hz,1H),2.19-2.11(m,1H),1.92-1.84(m,1H),1.70-1.60(m,2H),1.51-1.42(m,1H),0.77-0.70(m,2H),0.36-0.30(m,2H)。LC-MS RT:1.38min;MS(ESI)m/z 695.3(M+H)$^+$;方法A。

[0314] 实施例206:向反应容器中添加实施例245(6.0mg,8.6μmol)、DCM(1mL)、吡啶(7.0μl,0.086mmol)、氯甲酸4-硝基苯酯(8.7mg,0.043mmol)及DMAP(1.0mg,8.6μmol)。在室温下搅拌2h之后,添加双环[1.1.1]戊-1-胺(7.2mg,0.086mmol)。将反应混合物在室温下搅拌1h,在减压下浓缩且进行制备型HPLC纯化,得到双环[1.1.1]戊烷-1-基氨基甲酸1-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)-2,2,2-三氟乙酯(实施例206,3.8mg,4.7μmol,54%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.95(br d,J=6.3Hz,1H),8.55(br s,1H),8.24(br d,J=4.2Hz,1H),8.13(br s,1H),7.86-7.75(m,1H),7.69(br t,J=9.4Hz,2H),7.58-7.38(m,3H),7.33(d,J=8.8Hz,1H),6.43-6.30(m,1H),4.69(d,J=9.6Hz,1H),4.51-4.41(m,1H),4.06(s,3H),3.16(br dd,J=10.1,3.8Hz,1H),3.11(br s,1H),2.72(br s,1H),2.39-2.34(m,1H),2.02-1.89(m,6H),1.88-1.77(m,2H),1.54-1.47(m,1H),1.45-1.36(m,2H),0.79-0.69(m,2H),0.35(br s,2H)。LC-MS RT:1.27min;MS(ESI)m/z 804.5(M+H)$^+$;方法A。

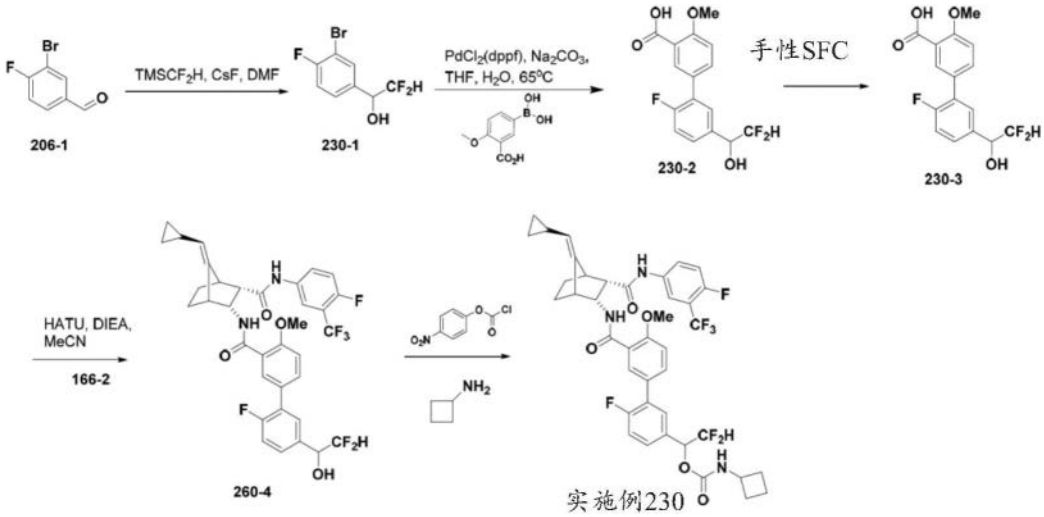
[0315] 实施例222



实施例222:向反应容器中添加实施例246(11mg,0.017mmol)、DCM(1mL)、吡啶(8.0μl,0.099mmol)及异氰酸基苯(9.9mg,0.083mmol)。在室温下搅拌12h之后,将反应混合物浓缩且进行制备型HPLC纯化,得到苯基氨基甲酸1-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)乙酯(实施例222,11.8mg,0.0160mmol,94.0%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.52(s,1H),9.92(br d,J=7.3Hz,1H),9.72(br s,1H),8.22(br d,J=4.9Hz,1H),8.14(s,1H),7.81-7.75(m,1H),7.70(br d,J=8.2Hz,1H),7.54(br d,J=6.7Hz,1H),7.50-7.38(m,4H),7.35-7.27(m,2H),7.25(br t,J=7.8Hz,2H),6.96(t,J=7.5Hz,1H),5.89-5.80(m,1H),4.69(d,J=9.5Hz,1H),4.49-4.41(m,1H),4.05(s,3H),3.16(br dd,J=10.8,3.5Hz,1H),3.11(br s,1H),2.72(br s,1H),1.92-1.74(m,2H),1.56(br d,J=6.1Hz,3H),1.53-1.47(m,1H),1.45-1.35(m,2H),0.82-0.66(m,2H),0.39-0.29(m,2H)。LC-MS RT:1.26min;MS(ESI)m/z 760.5(M+H)$^+$;方法A。

[0316]

实施例230



中间体230-1:向反应容器中添加206-1(577mg,2.84mmol)、DMF(15mL)、(二氟甲基)三甲基硅烷(530mg,4.26mmol)及CsF(216mg,1.42mmol)。在50℃搅拌12h之后,用EtOAc(15mL)稀释反应混合物,且用饱和NH_4Cl洗涤溶液。再用EtOAc(10mL×2)萃取水相。将合并的有机部分经Na_2SO_4干燥,过滤,浓缩,且通过硅胶色谱纯化,得到1-(3-溴-4-氟苯基)-2,2-二氟乙-1-醇(230-1,98mg,0.38mmol,13%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.67(dd,J=6.6,2.1Hz,1H),7.36(ddd,J=8.4,4.6,2.1Hz,1H),7.16(t,J=8.4Hz,1H),5.87-5.57(m,1H),4.86-4.78(m,1H),2.50(br s,1H)。

[0317] 中间体230-2:向含有230-1(220mg,0.863mmol)的反应容器中添加5-溴-2-甲氧基苯甲酸(220mg,1.12mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(106mg,0.129mmol、Na_2CO_3(366mg,3.45mmol)及H_2O(3.5mL)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在65℃搅拌3h。在冷却至室温之后,通过添加1N HCl淬灭反应混合物,将所得溶液用EtOAc萃取,经Na_2SO_4干燥,过滤,浓缩且进行制备型HPLC纯化,得到5′-(2,2-二氟-1-羟基乙基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酸(230-2,186mg,0.570mmol,66.1%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ8.37(d,J=1.8Hz,1H),7.82(dt,J=8.7,2.0Hz,1H),7.53(dd,J=7.4,2.1Hz,1H),7.45-7.39

(m,1H),7.24-7.14(m,2H),6.01-5.59(m,1H),4.89(td,J＝10.1,4.7Hz,1H),4.15(s,3H)。

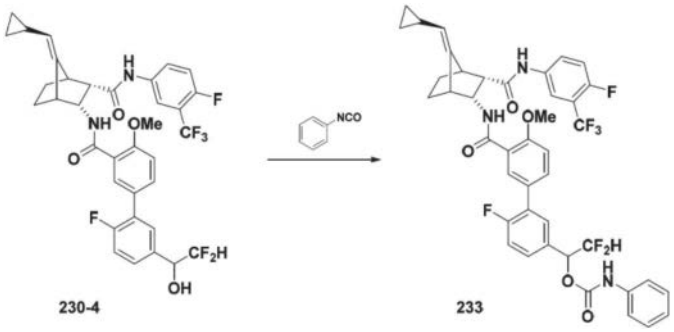
[0318] 中间体230-3:使用手性SFC将外消旋230-2分离成个别镜像异构体。制备型色谱条件:仪器:PIC Solution SFC Pre_p-200;柱:$Chiral_p$ak IC,30×250mm,5微米;移动相:10％MeOH/90％CO_2;流动条件:85mL/min,150巴,40℃;检测器波长:220nm;注射详情:10μL～1mg/mL于MeOH中。收集峰#2,得到中间体230-3。分析型色谱条件:仪器:AuroraInfinity分析型SFC;柱:ChiralpakID,4.6×250mm,5微米;移动相:10％MeOH/90％CO_2;流动条件:2mL/min,150巴,40℃;检测器波长:220nm。峰1,RT＝11.85min,96％ee;峰2,RT＝13.65min,>99.5％ee。

[0319] 中间体230-4:向反应容器中添加中间体166-2(20mg,0.054mmol)、中间体230-3(18mg,0.057mmol)、MeCN(1mL)、DIEA(0.028mL,0.16mmol)及HATU(23mg,0.060mmol)。将反应混合物在室温下搅拌12h,在减压下浓缩且进行硅胶色谱纯化,得到(1R,2S,3R,4R,X)-7-(环丙基亚甲基)-3-(5′-(2,2-二氟-1-羟基乙基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酰胺基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺(230-4,25mg,0.037mmol,68％产率)。^{1}H NMR(400MHz,$CDCl_3$)δ9.49(br d,J＝7.7Hz,1H),8.40-8.33(m,1H),8.01(s,1H),7.98-7.91(m,1H),7.66(dt,J＝8.7,2.0Hz,1H),7.57-7.48(m,2H),7.38(dq,J＝6.4,4.2Hz,1H),7.18(ddd,J＝10.2,8.6,1.2Hz,1H),7.11-7.01(m,2H),6.03-5.59(m,1H),4.91-4.83(m,1H),4.81-4.73(m,1H),4.61(d,J＝9.5Hz,1H),4.06(s,3H),3.19(t,J＝3.7Hz,1H),3.09(dd,J＝10.8,3.3Hz,1H),2.82(br d,J＝12.5Hz,1H),2.70(t,J＝3.9Hz,1H),2.22-2.12(m,1H),1.95-1.85(m,1H),1.72-1.61(m,2H),1.50-1.41(m,1H),0.79-0.69(m,2H),0.39-0.28(m,2H)。

[0320] 实施例230:向反应容器中添加中间体230-4(6.0mg,8.9μmol)、DCM(1mL)、吡啶(7.2μl,0.089mmol)、氯甲酸4-硝基苯酯(8.9mg,0.044mmol)及DMAP(1.1mg,8.9μmol)。在室温下搅拌2h之后,添加环丁胺(6.3mg,0.089mmol)。将反应混合物在室温下搅拌1h,在减压下浓缩且进行制备型HPLC纯化,得到环丁基氨基甲酸1-(3′-(((1R,2R,3S,4R,X)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)-2,2-二氟乙酯(实施例230,4.5mg,5.8μmol,66％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.94(br d,J＝7.2Hz,1H),8.19(br d,J＝5.1Hz,1H),8.09(s,1H),7.94(br d,J＝7.8Hz,1H),7.80-7.71(m,1H),7.68(br d,J＝8.8Hz,1H),7.53(br d,J＝6.7Hz,1H),7.48-7.39(m,2H),7.38-7.27(m,2H),6.49-6.13(m,1H),5.93-5.81(m,1H),4.67(d,J＝9.6Hz,1H),4.48-4.38(m,1H),4.03(s,3H),3.94-3.85(m,1H),3.19-3.11(m,1H),3.08(br s,1H),2.70(br s,1H),2.15-2.01(m,2H),1.92-1.73(m,4H),1.58-1.45(m,3H),1.43-1.35(m,2H),0.77-0.66(m,2H),0.37-0.28(m,2H)。LC-MS RT:1.22min;MS(ESI)m/z 774.3$(M+H)^+$;方法A。

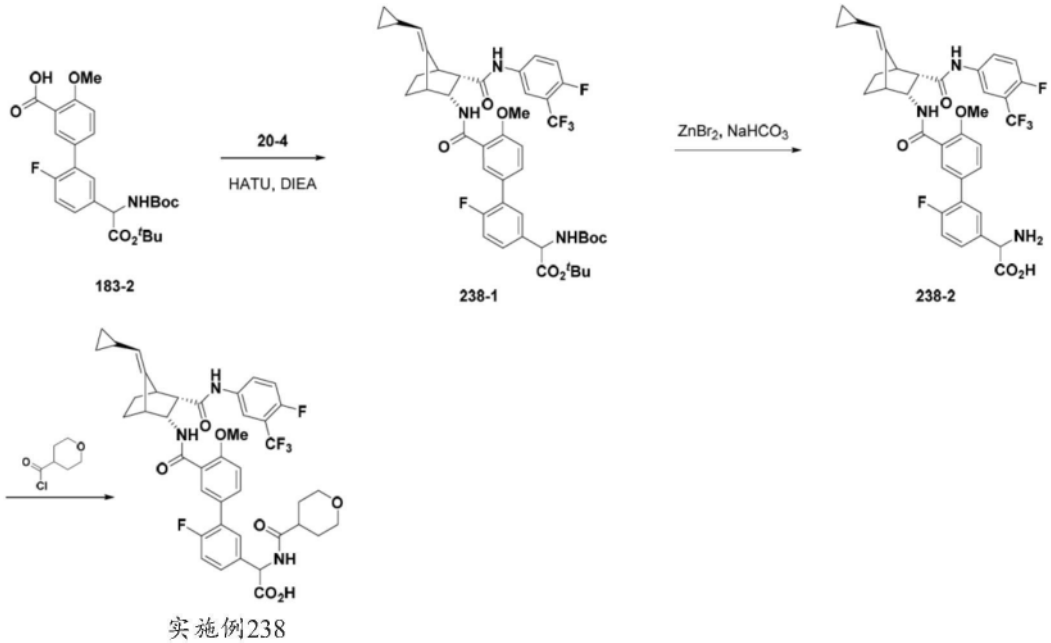
[0321]

实施例233



实施例233:向反应容器中添加230-4(6.0mg,8.9μmol)、DCM(1mL)、吡啶(0.014mL,0.17mmol)及异氰酸基苯(5.3mg,0.044mmol)。在室温下搅拌12h之后,在减压下浓缩混合物且进行制备型HPLC纯化,得到苯基氨基甲酸1-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)-2,2-二氟乙酯(实施例233,4.9mg,5.9μmol,67%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),10.07(br s,1H),9.93(br d,J=7.0Hz,1H),8.17(br d,J=4.6Hz,1H),8.10(s,1H),7.79-7.59(m,3H),7.50(br s,1H),7.47-7.34(m,4H),7.34-7.24(m,3H),7.01(br t,J=7.2Hz,1H),6.55-6.25(m,1H),6.08-5.98(m,1H),4.68(d,J=9.5Hz,1H),4.48-4.39(m,1H),4.02(s,3H),3.19-3.10(m,1H),3.08(br s,1H),2.72-2.67(m,1H),1.87-1.72(m,2H),1.53-1.45(m,1H),1.44-1.34(m,2H),0.77-0.65(m,2H),0.37-0.26(m,2H)。LC-MS RT:1.23min;MS(ESI)m/z 796.2(M+H)$^+$;方法A。

[0322] 实施例238:



实施例238

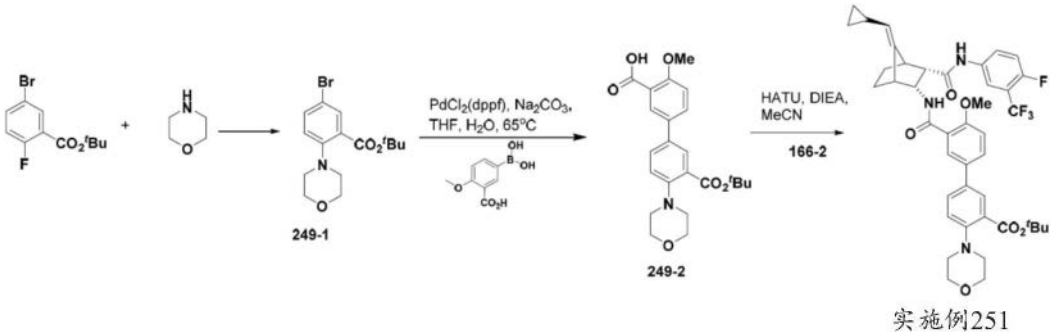
中间体238-1:向反应容器中添加166-2(75mg,0.19mmol)、183-2(92mg,0.20mmol)、MeCN(5mL)、DIEA(0.097mL,0.56mmol)及HATU(77mg,0.200mmol)。将反应混合物在室温下搅拌12h,在减压下浓缩且对残余物进行硅胶色谱纯化,得到2-((叔丁氧基羰基)氨基)-2-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)乙酸叔丁酯(238-1,147mg,0.178mmol,96.0%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ9.42(brd,J=7.9Hz,

1H),8.41(dd,J=2.2,1.3Hz,1H),8.09-8.04(m,1H),8.06(s,1H),8.00(dd,J=6.3,2.5Hz,1H),7.67-7.61(m,1H),7.55-7.48(m,1H),7.44(dd,J=7.3,2.4Hz,1H),7.36-7.31(m,1H),7.20-7.04(m,3H),5.66(br d,J=6.6Hz,1H),5.24(br d,J=7.0Hz,1H),4.92-4.82(m,1H),4.65(d,J=9.5Hz,1H),4.07(s,3H),3.22(t,J=3.9Hz,1H),3.13(dd,J=10.5,3.6Hz,1H),2.74(t,J=3.7Hz,1H),2.27-2.16(m,1H),1.95-1.86(m,1H),1.74-1.66(m,2H),1.46(br s,9H),1.43(s,9H),1.39-1.34(m,1H),0.81-0.72(m,2H),0.43-0.33(m,2H)。

[0323] 中间体238-2:向反应容器中添加238-1(147mg,0.178mrnol)、DCM(10mL)、碳酸氢钠(112mg,1.33mmol)及溴化锌(1200mg,5.34mmol)。在搅拌24h之后,通过添加1N HCl淬灭反应混合物且用EtOAc萃取溶液。将合并的有机部分经Na_2SO_4干燥,过滤,浓缩,且进行制备型HPLC纯化,得到2-氨基-2-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)乙酸TFA(238-2,62mg,0.079mmol,44%产率)。MS(ESI)m/z670.4(M+H)。

[0324] 实施例238:向反应容器中添加238-2(9mg,0.01mmol)、MeCN(1mL)、吡啶(2.8μl,0.034mmol)及四氢-2H-哌喃-4-碳酰氯(1.7mg,0.012mmol)。在室温下搅拌30min之后,通过添加MeOH来淬灭反应混合物,在减压下浓缩,且对残余物进行制备型HPLC纯化,得到2-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)-2-(四氢-2H-哌喃-4-甲酰胺基)乙酸(实施例238,8.9mg,0.011mmol,99%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.89(br d,J=7.7Hz,1H),8.26(d,J=2.2Hz,1H),7.99(dd,J=6.2,2.3Hz,1H),7.84(s,1H),7.74-7.62(m,2H),7.54(dd,J=7.3,2.3Hz,1H),7.49-7.42(m,1H),7.37-7.31(m,1H),7.12-7.05(m,1H),7.02-6.94(m,2H),5.80(d,J=8.0Hz,1H),4.77-4.69(m,1H),4.64(d,J=9.4Hz,1H),4.06(s,3H),4.03-3.90(m,2H),3.49-3.36(m,2H),3.14-3.09(m,1H),3.06(dd,J=10.6,4.0Hz,1H),2.73-2.66(m,1H),2.57-2.48(m,1H),2.16-2.10(m,1H),1.92-1.84(m,2H),1.82-1.74(m,4H),1.67-1.54(m,2H),1.54-1.46(m,1H),0.86-0.74(m,2H),0.41-0.32(m,2H)。LC-MS RT:1.26min;MS(ESI)m/z 782.5$(M+H)^+$;方法A。

[0325] 实施例249:



实施例251

中间体249-1:向反应容器中添加5-溴-2-氟苯甲酸叔丁酯(120mg,0.436mmol)、吗啉(0.19mL,2.2mmol)及甲苯(2mL)。在90℃搅拌12h之后,在减压下浓缩反应混合物且对残余物进行硅胶色谱纯化,得到5-溴-2-N-吗啉基苯甲酸叔丁酯(249-1,117mg,0.342mmol,78.0%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.69(d,J=2.4Hz,1H),7.49(dd,J=8.7,2.5Hz,1H),6.91(d,J=8.8Hz,1H),3.89-3.85(m,4H),3.07-3.03(m,4H),1.62(s,9H)。

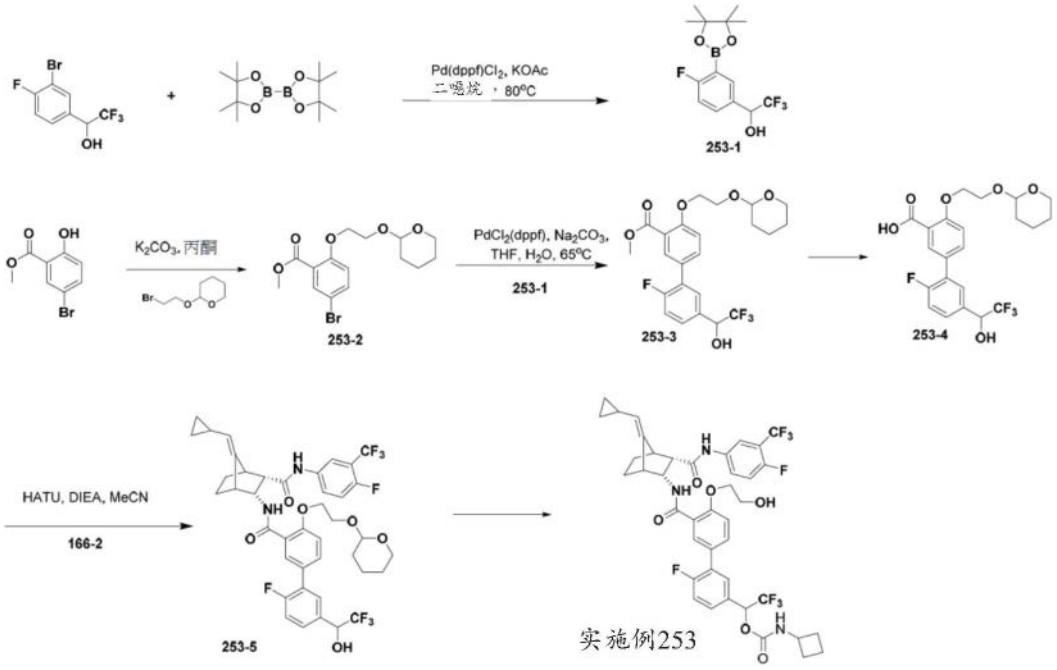
[0326] 中间体249-2:向含有249-1(30mg,0.088mmol)的反应容器中添加5-溴-2-甲氧基

苯甲酸(25.8mg,0.131mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(14mg,0.018mmol)及Na_2CO_3(46mg,0.44mmol)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在65℃搅拌2h。在冷却至室温之后,在减压下浓缩反应混合物,且对残余物进行制备型HPLC纯化,得到3′-(叔丁氧基羰基)-4-甲氧基-4′-N-吗啉基-[1,1′-联苯]-3-甲酸(249-2,40mg,0.097mmol,110%产率)。MS(ESI)m/z 414.0(M+H)。

[0327] 实施例251:向反应容器中添加中间体166-2(15mg,0.037mmol)、249-2(20mg,0.048mmol)、MeCN(1mL)、DIEA(0.02mL,0.1mmol)及HATU(18mg,0.048mmol)。将反应混合物在室温下搅拌12h,在减压下浓缩,且对残余物进行硅胶色谱纯化,得到3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-甲氧基-4-N-吗啉基-[1,1′-联苯]-3-甲酸叔丁酯(实施例251,12mg,0.016mmol,42%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.87(br d,J=7.7Hz,1H),8.31(d,J=2.2Hz,1H),8.22(s,1H),8.04(dd,J=6.3,2.5Hz,1H),7.94(d,J=2.2Hz,1H),7.76(br dd,J=8.3,1.9Hz,1H),7.60(dd,J=8.7,2.3Hz,1H),7.56(dt,J=8.7,3.4Hz,1H),7.47(br d,J=8.0Hz,1H),7.11(t,J=9.4Hz,1H),7.03(d,J=8.8Hz,1H),4.62(d,J=9.6Hz,2H),4.07(s,3H),4.07-4.04(m,4H),3.50-3.38(m,4H),3.17(t,J=3.9Hz,1H),2.97(dd,J=10.7,3.9Hz,1H),2.69(t,J=3.9Hz,1H),2.12-2.05(m,1H),1.90-1.81(m,1H),1.62(s,9H),1.61-1.54(m,2H),1.50-1.43(m,1H),0.78-0.69(m,2H),0.37-0.28(m,2H)。LC-MS RT:1.23min;MS(ESI)m/z 764.3$(M+H)^+$;方法A。

[0328] 实施例249:向反应容器中添加实施例251(12mg,0.016mmol)、CH_2Cl_2(2mL)、碳酸氢钠(13.2mg,0.157mmol)及溴化锌(142mg,0.628mmol)。在35℃搅拌3h之后,通过添加1N HCl淬灭反应混合物且用EtOAc萃取溶液。将合并的有机部分经Na_2SO_4干燥,过滤,浓缩,且进行制备型HPLC纯化,得到3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-甲氧基-4-N-吗啉基-[1,1′-联苯]-3-甲酸TFA(实施例249,5.2mg,6.2μmol,40%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.71(br d,J=7.7Hz,1H),8.53(d,J=2.2Hz,1H),8.41(d,J=2.5Hz,1H),7.96(dd,J=6.1,2.5Hz,1H),7.91-7.84(m,2H),7.76(dd,J=8.7,2.6Hz,1H),7.59(dt,J=8.7,3.5Hz,1H),7.54(d,J=8.3Hz,1H),7.13(t,J=9.4Hz,1H),7.09(d,J=8.8Hz,1H),4.83-4.74(m,1H),4.67(d,J=9.6Hz,1H),4.09(s,3H),4.02(br s,4H),3.23(br t,J=4.0Hz,1H),3.17(br s,4H),3.10(br dd,J=10.9,3.4Hz,1H),2.74(t,J=3.9Hz,1H),2.22-2.15(m,1H),1.93-1.86(m,1H),1.73-1.59(m,2H),1.55-1.47(m,1H),0.80-0.73(m,2H),0.39-0.34(m,2H)。LC-MS RT:1.15min;MS(ESI)m/z 708.4$(M+H)^+$;方法A。

[0329] 实施例253:



中间体253-1:向反应容器中添加1-(3-溴-4-氟苯基)-2,2,2-三氟乙-1-醇(100mg,0.366mmol)、4,4,4′,4′,5,5,5′,5′-八甲基-2,2′-二(1,3,2-二氧杂硼杂环戊烷)(126mg,0.494mmol)及1,4-二噁烷(3mL)。随后添加$PdCl_2$(dppf)-CH_2Cl_2加合物(29.9mg,0.037mmol)及乙酸钾(90mg,0.91mmol),且通过使N_2鼓泡使反应混合物脱气10min。在65℃搅拌反应混合物5h,使其冷却至室温且用EtOAc萃取溶液。将合并的有机部分经Na_2SO_4干燥,过滤且浓缩。所得物质(253-1)不经进一步纯化即用于下一步骤。

[0330] 中间体253-2:向反应容器中添加5-溴-2-羟基苯甲酸甲酯(200mg,0.866mmol)、2-(2-溴乙氧基)四氢-2H-哌喃(217mg,1.039mmol)、丙酮(3mL)及K_2CO_3(239mg,1.73mmol)。在50℃搅拌12h之后,在减压下浓缩反应混合物且对残余物进行硅胶色谱纯化,得到5-溴-2-(2-((四氢-2H-哌喃-2-基)氧基)乙氧基)苯甲酸甲酯(253-2,112mg,0.312mmol,36.0%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.90(d,J=2.6Hz,1H),7.55(dd,J=8.9,2.6Hz,1H),6.94(d,J=8.9Hz,1H),4.76(t,J=3.5Hz,1H),4.30-4.16(m,2H),4.08(dt,J=11.5,4.6Hz,1H),3.94-3.84(m,5H),3.59-3.52(m,1H),1.88-1.79(m,1H),1.79-1.71(m,1H),1.67-1.60(m,2H),1.58-1.50(m,2H)。

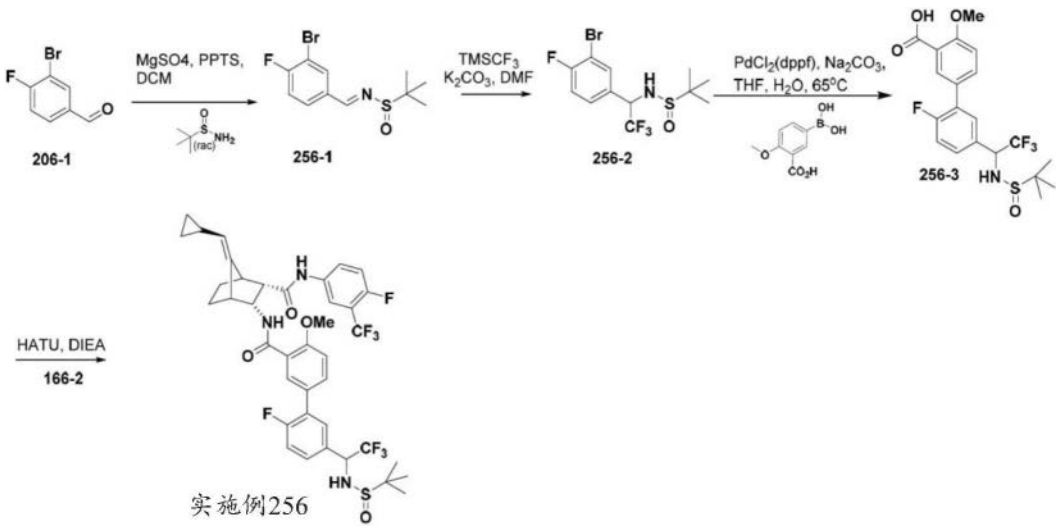
[0331] 中间体253-3:向含有253-2(80mg,0.22mmol)的反应容器中添加253-1(93mg,0.29mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(27mg,0.033mmol)、Na_2CO_3(94mg,0.89mmol)及H_2O(0.5mL)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在65℃搅拌3h。在冷却至室温之后,通过添加水来淬灭反应混合物,且用EtOAc萃取溶液。将合并的EtOAc部分经Na_2SO_4干燥,过滤,浓缩且进行硅胶色谱纯化,得到2′-氟-4-(2-((四氢-2H-哌喃-2-基)氧基)乙氧基)-5′-(2,2,2-三氟-1-羟基乙基)-[1,1′-联苯]-3-甲酸甲酯(253-3,66mg,0.14mmol,62%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.95(dd,J=2.4,1.0Hz,1H),7.64(dt,J=8.7,1.8Hz,1H),7.52(dd,J=7.3,2.1Hz,1H),7.47-7.40(m,1H),7.19(dd,J=10.2,8.5Hz,1H),7.09(d,J=8.7Hz,1H),5.10-5.03(m,1H),4.77(t,J=3.5Hz,1H),4.31-4.25(m,2H),4.15-4.08(m,1H),3.95-3.87(m,5H),3.60-3.52(m,1H),2.98(br d,J=3.5Hz,1H),1.89-1.81(m,1H),1.79-1.71(m,1H),1.67-1.61(m,2H),1.59-1.51(m,2H)。

[0332] 中间体253-4:将253-3(66mg,0.14mmol)溶解于THF(4mL)中且添加单水合氢氧化锂(31.7mg,0.754mmol)于水(2mL)中的溶液。在室温下搅拌反应混合物12h,用EtOAc(10mL)稀释,且通过添加1.0eq的1N HCl淬灭。将有机相经Na_2SO_4干燥,过滤且在减压下浓缩,得到2′-氟-4-(2-((四氢-2H-哌喃-2-基)氧基)乙氧基)-5′-(2,2,2-三氟-1-羟基乙基)-[1,1′-联苯]-3-甲酸(253-4,64mg,0.14mmol,100%产率),其不经进一步纯化即用于下一步骤。

[0333] 中间体253-5:向反应容器中添加中间体166-2(25mg,0.068mmol)、253-4(31mg,0.068mmol)、MeCN(1mL)、DIEA(0.036mL,0.20mmol)及HATU(28.4mg,0.0750mmol)。在室温下搅拌反应混合物12h,在减压下浓缩且对残余物进行制备型HPLC纯化,得到(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2′-氟-4-(2-((四氢-2H-哌喃-2-基)氧基)乙氧基)-5′-(2,2,2-三氟-1-羟基乙基)-[1,1′-联苯]-3-甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(253-5,39mg,0.049mmol,72%产率)。MS(ESI)m/z809.2(M+H)。

[0334] 实施例253:向反应容器中添加253-5(15mg,0.019mmol)、DCM(1mL)、吡啶(0.015mL,0.19mmol)、氯甲酸4-硝基苯酯(19mg,0.093mmol)及DMAP(2.3mg,0.019mmol)。在室温下搅拌2h之后,添加环丁胺(13.2mg,0.185mmol)。在室温下搅拌反应混合物1h且在减压下浓缩。对残余物进行制备型HPLC纯化,产生相应氨基甲酸酯。此产物由于存在TFA而不稳定。在室温下静置12h,随后浓缩且进行制备型HPLC纯化,得到环丁基氨基甲酸1-(3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-(2-羟基乙氧基)-[1,1′-联苯]-3-基)-2,2,2-三氟乙酯(实施例253,11.0mg,0.0130mmol,70.0%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.54(br d,J=8.5Hz,1H),8.29(d,J=2.0Hz,1H),7.76-7.67(m,2H),7.57-7.47(m,3H),7.43-7.36(m,1H),7.21-7.14(m,2H),7.10(br d,J=8.9Hz,1H),6.11-6.05(m,1H),5.32(br d,J=8.2Hz,1H),4.93-4.85(m,1H),4.69(d,J=9.6Hz,1H),4.49-4.43(m,1H),4.32-4.24(m,2H),4.17-4.09(m,2H),3.17(t,J=4.1Hz,1H),3.13(dd,J=10.5,3.8Hz,1H),2.75(t,J=4.0Hz,1H),2.42-2.24(m,2H),2.20-2.14(m,1H),1.98-1.85(m,3H),1.80-1.61(m,4H),1.53-1.46(m,1H),0.82-0.73(m,2H),0.40-0.33(m,2H)。LC-MS RT:1.33min;MS(ESI)m/z 822.1(M+H)$^+$;方法A。

[0335] 实施例256:



中间体256-1:向反应容器中添加3-溴-4-氟苯甲醛(1670mg,8.25mmol)、2-甲基丙

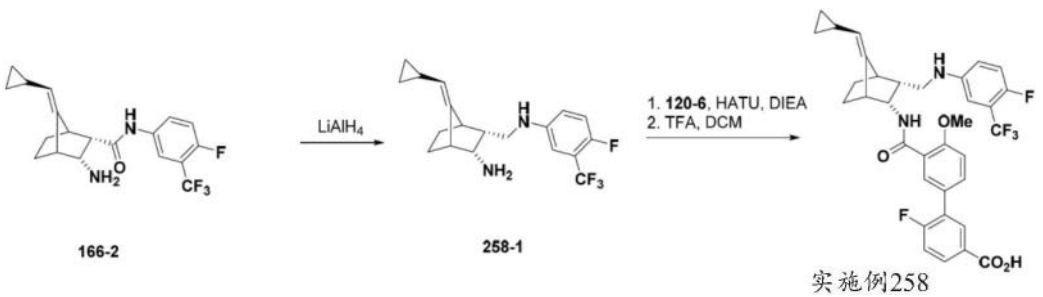
烷-2-亚磺酰胺(500mg,4.13mmol)、DCM(2mL)、$MgSO_4$(2483mg,20.63mmol)及PPTS(52mg,0.21mmol)。在室温下搅拌反应混合物24h,装载至二氧化硅滤筒,且对其进行硅胶色谱纯化,得到(E)-N-(3-溴-4-氟苯亚甲基)-2-甲基丙烷-2-亚磺酰胺(256-1,1220mg,3.98mmol,97%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ8.51(s,1H),8.11(dd,J=6.6,2.2Hz,1H),7.77(ddd,J=8.5,4.7,1.9Hz,1H),7.24(t,J=8.4Hz,1H),1.28(s,9H)。

[0336] 中间体256-2:向反应容器中添加256-1(200mg,0.653mmol)、DMF(3mL)、(三氟甲基)三甲基硅烷(0.19mL,1.3mmol)及K_2CO_3(45mg,0.33mmol)。在室温下搅拌反应混合物60min且添加2N HCl(15mL)。在室温下搅拌1h之后,用EtOAc(30mL)稀释反应混合物,且用饱和NH_4Cl洗涤有机部分。通过添加EtOAc(10mL×2)萃取水相。将合并的有机部分经Na_2SO_4干燥,浓缩,过滤且通过硅胶色谱纯化,得到N-(1-(3-溴-4-氟苯基)-2,2,2-三氟乙基)-2-甲基丙烷-2-亚磺酰胺(256-2,163mg,0.433mmol,66%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.65(dd,J=6.3,2.1Hz,1H),7.42-7.37(m,1H),7.18(t,J=8.4Hz,1H),4.81(quin,J=7.1Hz,1H),3.58(br d,J=6.6Hz,1H),1.27(s,9H)。

[0337] 中间体256-3:向含有256-2(50.mg,0.13mmol)的反应容器中添加5-溴-2-甲氧基苯甲酸(31mg,0.16mmol)、$PdCl_2$(dppf)-CH_2Cl_2加合物(16mg,0.020mmol)、Na_2CO_3(56mg,0.53mmol)及H_2O(0.5mL)。通过使N_2鼓泡使反应混合物脱气10min,密封,且在65℃搅拌3h。在冷却至室温之后,通过添加1N HCl淬灭反应混合物,用EtOAc萃取溶液,将合并的有机部分经Na_2SO_4干燥,过滤,浓缩且进行制备型HPLC纯化,得到5′-(1-((叔丁基亚磺酰基)氨基)-2,2,2-三氟乙基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酸(256-3,47mg,0.10mmol,79%产率)。MS(ESI)m/z 448.1(M+H)。

[0338] 实施例256:向反应容器中添加166-2(10mg,0.027mmol)、256-3(12mg,0.027mmol)、MeCN(1mL)、DIEA(0.014mL,0.081mmol)及HATU(11mg,0.030mmol)。在室温下搅拌反应混合物12h,在减压下浓缩且对残余物进行制备型HPLC纯化,得到(1R,2S,3R,4R,Z)-3-(5′-(1-((叔丁基亚磺酰基)氨基)-2,2,2-三氟乙基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酰胺基)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺(实施例256,7.5mg,9.3μmol,34%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.95(brt,J=6.4Hz,1H),8.27-8.19(m,1H),8.16(s,1H),7.87-7.74(m,2H),7.70(brd,J=8.8Hz,1H),7.66-7.58(m,1H),7.48(br t,J=9.7Hz,1H),7.40-7.29(m,2H),6.51(d,J=9.6Hz,1H),5.39-5.27(m,1H),4.68(d,J=9.7Hz,1H),4.51-4.41(m,1H),4.05(s,3H),3.19-3.14(m,1H),3.11(br s,1H),1.88-1.75(m,2H),1.56-1.46(m,1H),1.44-1.35(m,2H),1.14(s,9H),0.79-0.68(m,2H),0.39-0.30(m,2H)。LC-MS RT:1.25min;MS(ESI)m/z798.1(M+H)$^+$;方法A。

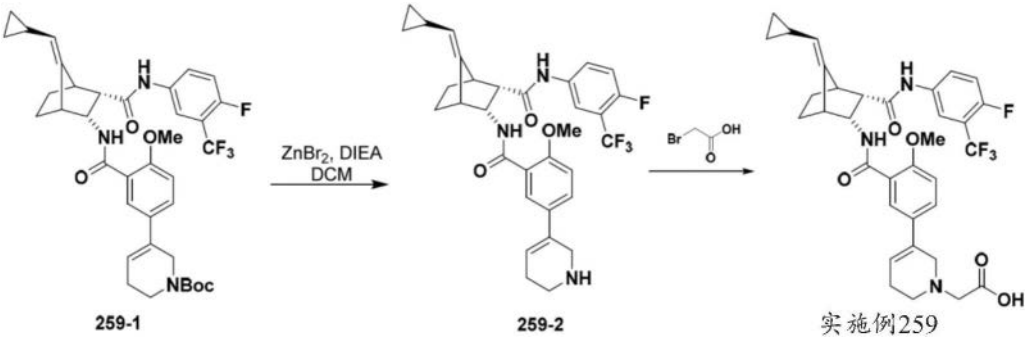
[0339] 实施例258:



中间体258-1:向反应容器中添加中间体166-2(15mg,0.041mmol)及THF(1mL)。在冷却至0℃之后,添加$LiAlH_4$(0.5mL,0.500mmol)。在0℃搅拌5min之后,使反应混合物升温至室温且在室温下搅拌20min。用EtOAc稀释反应混合物。在用饱和$NaHCO_3$洗涤有机溶液之后,经Na_2SO_4干燥有机相且在减压下浓缩,得到(1R,2R,3R,4R,Z)-7-(环丙基亚甲基)-3-(((4-氟-3-(三氟甲基)苯基)氨基)甲基)双环[2.2.1]庚烷-2-胺(258-1,7.0mg,0.020mmol,49%产率)。此物质不经进一步纯化即用于下一步骤。MS(ESI)m/z 355.3(M+H)。

[0340] 实施例258:向反应容器中添加258-1(7.0mg,0.020mmol)、120-6(6.5mg,0.019mmol)、MeCN(1mL)、DIEA(9.4μl,0.054mmol)及HATU(7.5mg,0.020mmol)。在室温下搅拌反应混合物12h,在减压下浓缩且对残余物进行硅胶色谱纯化,得到残余物,将其在室温下用2:1DCM/TFA处理30min。浓缩所得溶液且通过HPLC纯化残余物,得到3′-(((1R,2R,3R,4R,Z)-7-(环丙基亚甲基)-3-(((4-氟-3-(三氟甲基)苯基)氨基)甲基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-甲酸(实施例258,6.5mg,8.4μmol,47%产率)。^1H NMR(500MHz,$CDCl_3$)δ8.59(br d,J=7.4Hz,1H),8.41(d,J=1.4Hz,1H),8.23(dd,J=7.6,2.1Hz,1H),8.09(ddd,J=8.5,4.6,2.1Hz,1H),7.71(br d,J=8.8Hz,1H),7.26-7.22(m,1H),7.08-7.02(m,2H),6.99-6.94(m,2H),4.65(d,J=9.6Hz,1H),4.63-4.57(m,1H),4.03(s,3H),3.32(dd,J=11.4,2.9Hz,1H),3.09(t,J=4.1Hz,1H),3.04-2.97(m,1H),2.59-2.52(m,2H),1.83-1.74(m,1H),1.73-1.67(m,1H),1.64-1.55(m,2H),1.47-1.39(m,1H),0.76-0.69(m,2H),0.41-0.31(m,2H)。LC-MS RT:1.31min;MS(ESI)m/z683.5$(M+H)^+$;方法A。

[0341] 实施例259



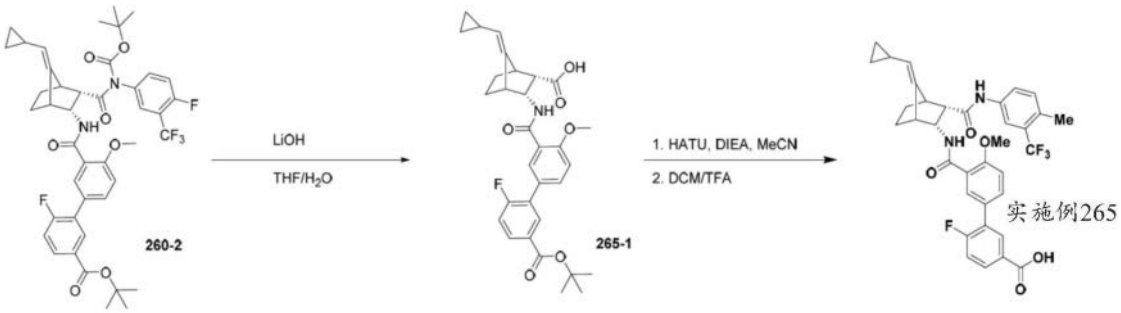
中间体259-1:259-1为遵循针对实施例168所描述的程序由中间体166-2及140-2制备。^1H NMR(500MHz,$CDCl_3$)δ9.58-9.15(br.s,1H),8.20(d,J=2.2Hz,1H),8.17-7.93(m,1H),7.90(dd,J=6.1,2.5Hz,1H),7.56(dt,J=8.9,3.4Hz,1H),7.41(dd,J=8.5,2.5Hz,1H),7.08(t,J=9.4Hz,1H),6.92(br d,J=7.7Hz,1H),6.16(dt,J=4.0,2.1Hz,1H),4.87-4.79(m,1H),4.63(d,J=9.6Hz,1H),4.32-4.18(m,2H),3.99(s,3H),3.55(br s,2H),3.18(t,J=3.7Hz,1H),3.11-3.06(m,1H),2.71(t,J=3.7Hz,1H),2.31(br d,J=2.8Hz,2H),2.23-2.12(m,1H),1.91-1.80(m,1H),1.71-1.61(m,2H),1.50(s,9H),1.49-1.42(m,1H),0.77-0.70(m,2H),0.40-0.30(m,2H)。

[0342] 中间体259-2:向反应容器中添加259-1(13mg,0.019mmol)、DCM(1.5mL)、DIEA(0.012mL,0.067mmol)及溴化锌(150mg,0.665mmol)。在搅拌12h之后,通过添加饱和$NaHCO_3$淬灭反应混合物且用EtOAc萃取溶液。将合并的有机部分经Na_2SO_4干燥,过滤且浓缩,得到(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(1,

2,5,6-四氢吡啶-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(259-2,12mg,0.021mmol,110%产率)。此中间体不经进一步纯化即用于下一步骤中。MS(ESI)m/z 584.4(M+H)。

[0343] 实施例259:向反应容器中添加259-2(11mg,0.019mmol)、MeCN(1mL)、2-溴乙酸(1.5mg,0.011mmol)及DIEA(9.9μl、0.057mmol)。在室温下搅拌反应混合物1h且在减压下浓缩。对所得残余物进行制备型HPLC,随后进行SFC纯化,得到2-(5-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-3,6-二氢吡啶-1(2H)-基)乙酸(实施例259,4.1mg,5.4μmol,28%产率)。^{1}H NMR(500MHz,CD_3OD)δ10.31(br d,J=7.2Hz,1H),10.12(s,1H),8.15(dd,J=6.2,2.6Hz,1H),8.05(d,J=2.5Hz,1H),7.78-7.68(m,1H),7.59(dd,J=8.8,2.5Hz,1H),7.28(t,J=9.6Hz,1H),7.23-7.17(m,1H),6.38-6.32(m,1H),4.74(d,J=9.4Hz,1H),4.60-4.52(m,1H),4.25(br s,4H),4.09(s,3H),3.25-3.19(m,1H),3.17-3.11(m,1H),2.77-2.68(m,3H),2.01-1.89(m,2H),1.59-1.47(m,3H),0.80-0.71(m,2H),0.41-0.29(m,2H)。LC-MS RT:0.94min;MS(ESI)m/z 642.3$(M+H)^+$;方法A。

[0344] 实施例265

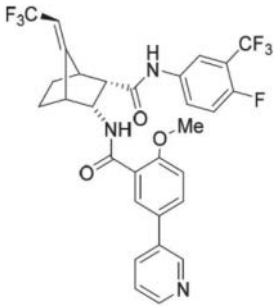


中间体265-1:向含有含260-2(10mg,0.013mmol)的THF(1.3mL)的小瓶中添加呈1M水溶液形式的LiOH(63μl,0.063mmol)。在室温下搅拌反应混合物18h,接着用1N HCl稀释。用EtOAc(3×5mL)萃取所得混合物。将合并的有机物经Na_2SO_4干燥,过滤且浓缩,得到(1R,2S,3R,4R,Z)-3-(5′-(叔丁氧基羰基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酰胺基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酸(7.0mg,0.013mmol,100%产率),其不经进一步纯化即使用。^{1}H-NMR(500MHz,DMSO-d6)δ10.05(br s,1H),8.12(s,1H),8.01-7.97(m,1H),7.96-7.92(m,1H),7.74(d,J=8.9Hz,1H),7.45(t,J=9.5Hz,1H),7.33(d,J=8.9Hz,1H),4.66(d,J=9.5Hz,1H),4.34-4.25(m,1H),4.04(s,3H),3.15-3.09(m,1H),2.99(dd,J=10.8,3.8Hz,1H),2.68-2.61(m,1H),1.76-1.63(m,2H),1.56(s,9H),1.47(dt,J=8.7,4.2Hz,1H),1.42(s,2H),0.84-0.60(m,2H),0.44-0.23(m,2H)。LC-MS RT:1.17min;MS(ESI)m/z 536$(M+H)^+$;方法D。

[0345] 实施例265:向反应容器中添加265-1(4.0mg,0.022mmol)、MeCN(1mL)、DIEA(10μl,0.060mmol)及HATU(6.8mg,0.018mmol)。在室温下搅拌反应混合物12h,随后在减压下浓缩且将残余物溶解于1:2TFA/DCM中且搅拌30min。将反应混合物在减压下浓缩,溶解于DMSO中,且通过HPLC纯化,得到3′-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-甲基-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-甲酸(3.4mg,5.3μmol,35%产率)。1H-NMR(500MHz,DMSO-d6)δ10.41(s,1H),9.98(d,J=6.7Hz,1H),8.21-8.09(m,2H),8.05-7.99(m,1H),7.99-7.90(m,1H),7.77-7.70(m,1H),

7.64(dd,J＝7.8,1.1Hz,1H),7.45-7.36(m,2H),7.33(d,J＝8.5Hz,1H),4.69(d,J＝9.5Hz,1H),4.55-4.36(m,1H),4.06(s,3H),3.19-3.13(m,1H),3.13-3.08(m,1H),2.78-2.66(m,1H),2.37(s,3H),1.90-1.84(m,1H),1.83-1.76(m,1H),1.55-1.47(m,1H),1.47-1.37(m,2H),0.84-0.60(m,2H),0.42-0.23(m,2H)。LC-MS RT:2.21min;MS(ESI)m/z 653(M+H)$^+$;方法A。

[0346] 实施例310



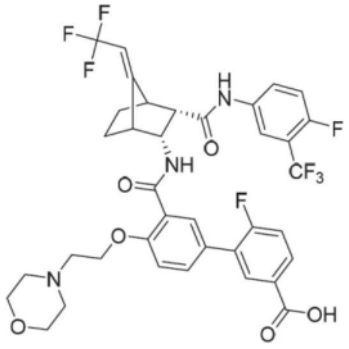
中间体310-1

用四甲基乙二醇(0.121g,1.02mmol)处理5-溴-2-甲氧基苯甲酸(0.200g,1.02mmol)于EtOAc(10ml)中的溶液且在室温下搅拌所得溶液过夜。接着浓缩反应混合物且呈2-甲氧基-5-(4,4,5,5-四甲基-1,3,2-二氧硼杂环己烷-2-基)苯甲酸(0.284g,1.02mmol,100％产率)形式的所得固体不经进一步操作即使用。此固体为根据与实施例108相同的程序与中间体170-2偶合,得到中间体310-1。

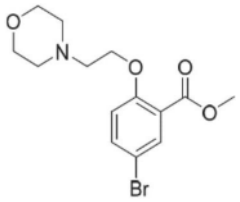
[0347] 将310-1(50mg,0.076mmol)、$PdCl_2$(dppf)(5.6mg,7.6μmol)、3-溴吡啶(0.1mL)及K_3PO_4(48.5mg,0.229mmol)的反应混合物加热至80℃。使反应混合物冷却至室温且分配于水与EtOAc之间。浓缩有机层且通过反相HPLC纯化残余物,得到(1R,2S,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(吡啶-3-基)苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺(11.4mg,0.019mmol,24％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.68(s,1H),9.99(br d,J＝6.8Hz,1H),8.85(s,1H),8.55(br d,J＝3.4Hz,1H),8.24(br d,J＝2.3Hz,2H),8.07-8.00(m,1H),7.90(dd,J＝8.6,2.4Hz,1H),7.83-7.73(m,1H),7.56-7.45(m,2H),7.34(d,J＝8.8Hz,1H),6.05-5.92(m,1H),4.60-4.51(m,1H),4.06(s,3H),3.47(s,1H),3.00(br s,1H),2.74(s,1H),2.02-1.95(m,1H),1.94-1.87(m,1H),1.51(br d,J＝6.6Hz,2H)。LC-MS RT 2.47min;MS(ESI)m/z＝608.3(M+H)+;方法C。

[0348] 实施例320为经由以下中间体,以类似于实施例253的方式制备。

[0349] 实施例320

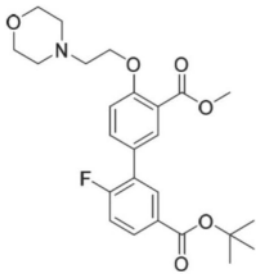


中间体320-1



向5-溴-2-羟基苯甲酸甲酯(750mg,3.25mmol)及4-(2-溴乙基)吗啉(756mg,3.90mmol)于DMF(12mL)中的溶液中添加K_2CO_3(1346mg,9.74mmol),在70℃加热4h。用EtOAc稀释反应混合物,且用水及盐水溶液洗涤溶液。使所分离的有机层经Na_2SO_4干燥,过滤且在减压下浓缩。通过二氧化硅柱纯化残余物,得到5-溴-2-(2-N-吗啉基乙氧基)苯甲酸甲酯(320-1,0.800g,2.32mmol,71.6%产率)。MS,m/z:343.9(M+2H)。

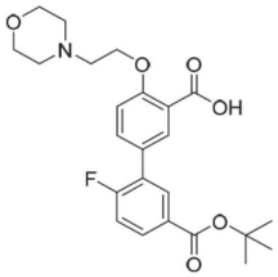
[0350] 中间体320-2



向320-1(300mg,0.872mmol)及4-氟-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)苯甲酸叔丁酯(309mg,0.959mmol)于1,4-二噁烷(10mL)及水(1mL)中的溶液中添加磷酸三钾(555mg,2.61mmol),且用氮气吹扫所得混合物5min。添加$PdCl_2$(dppf)-CH_2Cl_2加合物(71mg,0.087mmol)且用氮气吹扫反应混合物2min,随后在密封管中在85℃加热16h。经由硅藻土过滤反应混合物。用EtOAc稀释滤液且用水及盐水溶液洗涤有机相。使有机层经Na_2SO_4干燥,过滤且在减压下浓缩。通过二氧化硅柱色谱纯化残余物,得到6′-氟-4-(2-N-吗啉基乙氧基)-[1,1′-联苯]-3,3′-二甲酸3′-(叔丁酯)3-甲酯(320-2,0.310g,0.675mmol,77%产率)。MS,m/z:460.2(M+H)。

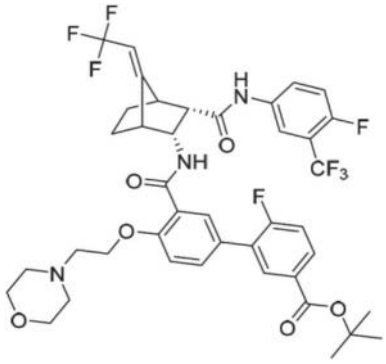
[0351]

中间体320-3



向320-2(100mg,0.218mmol)于THF(2mL)中的溶液中添加NaOH(0.87mL,2.2mmol)溶液且在50℃搅拌30min。在真空下移除THF,添加1ml水且用1.5N HCl酸化至pH 4。用EtOAc(2×20ml)萃取水层。将合并的有机层用水及盐水溶液洗涤,经Na_2SO_4干燥,过滤且在减压下浓缩,得到5′-(叔丁氧基羰基)-2′-氟-4-(2-N-吗啉基乙氧基)-[1,1′-联苯]-3-甲酸(40mg,0.090mmol,41%产率)。MS,m/z:446.2(M+H)。

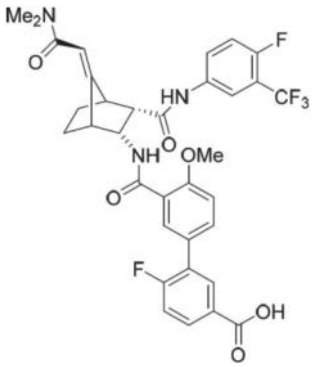
[0352] 中间体320-4



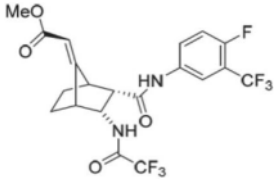
向320-3(30mg,0.076mmol)及170-2(334mg,0.0760mmol)于DMF(2mL)中的溶液中添加DIPEA(0.07mL,0.4mmol)及HATU(57.6mg,0.151mmol),且在室温下搅拌12h。将反应混合物用EtOAc稀释,用水及盐水溶液洗涤。使经分离的有机层经Na_2SO_4干燥,过滤且浓缩。通过硅胶色谱纯化残余物产物,得到6-氟-3′-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-(2-N-吗啉基乙氧基)-[1,1′-联苯]-3-甲酸叔丁酯(320-4,50mg,0.061mmol,80%产率)。MS,m/z:824.3(M+H)。

[0353] 在0℃向320-4(50mg,0.061mmol)于DCM(2mL)中的溶液中添加TFA(0.094mL,1.2mmol),在室温下搅拌4h。在减压下浓缩反应混合物且通过反相HPLC纯化残余物,得到呈白色固体的6-氟-3′-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-(2-N-吗啉基乙氧基)-[1,1′-联苯]-3-甲酸(20mg,0.025mmol,42%产率)。^{1}H NMR(400MHz,DMSO-d6)δppm 13.27-13.08(m,1H),10.47-10.37(m,1H),10.02-9.81(m,1H),8.91-8.75(m,1H),8.16-7.94(m,3H),7.89-7.79(m,1H),7.76-7.60(m,2H),5.82-5.67(m,1H),4.68-4.61(m,1H),4.61-4.43(m,1H),4.01-3.83(m,2H),3.75-3.61(m,2H),3.58-3.48(m,3H),2.84-2.78(m,2H),2.70-2.63(m,5H),2.02-1.85(m,2H),1.81-1.65(m,2H),1.62-1.45(m,2H)。MS,m/z:768.2(M+H)。

[0354] 实施例323



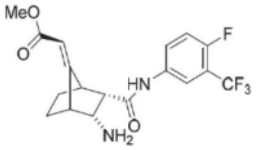
中间体323-1



将溶解于MeOH(0.5mL)及THF(0.5mL)中的120-4(0.05g,0.1mmol)中添加Hunig碱

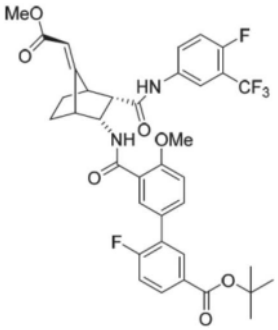
(0.021mL,0.12mmol)、三苯基膦(0.8mg,3μmol)及双(三苯基膦)氯化钯(II)(2mg,3μmol)。在60psi下用一氧化碳加压容器且在70℃加热36h。将反应溶液在真空下浓缩且经由急骤色谱纯化,得到(Z)-2-((1R,2S,3R,4R)-2-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-3-(2,2,2-三氟乙酰胺基)双环[2.2.1]庚烷-7-亚基)乙酸甲酯323-1。^{1}H NMR(500MHz,$CDCl_3$)δ9.49(brd,J=6.9Hz,1H),7.96(s,1H),7.86-7.72(m,2H),7.23(t,J=9.4Hz,1H),5.76(s,1H),4.51(dt,J=10.5,5.3Hz,1H),3.93(t,J=4.1Hz,1H),3.86-3.75(m,3H),3.18-3.05(m,1H),2.89(t,J=4.0Hz,1H),2.06-1.87(m,2H),1.78-1.64(m,2H)。

[0355] 中间体323-2



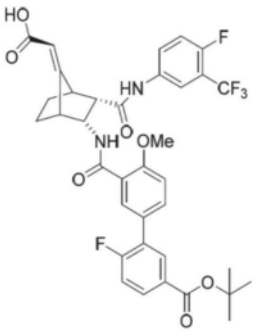
向MeOH(0.8mL)中添加AcCl(0.080mL,1.1mmol)且搅拌5分钟,并添加323-1(0.029g,0.060mmol),且搅拌反应混合物32h。在真空下浓缩反应混合物,得到(Z)-2-((1R,2R,3S,4R)-2-氨基-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-7-亚基)乙酸甲酯氯化氢盐(323-2,0.025g,0.060mmol,100%产率),其不经进一步纯化即使用。MS(ESI)m/z 387.0(M+H)。

[0356] 中间体323-3



向溶解于MeCN(0.6mL)中的323-2及120-6(0.025g,0.072mmol)中添加DIEA(0.03mL,0.2mmol),随后添加HATU(0.034g,0.090mmol)。将反应混合物搅拌16h,在真空下浓缩且经由急骤色谱纯化,得到6-氟-3′-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2-甲氧基-2-氧代亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-甲氧基-[1,1′-联苯]-3-甲酸叔丁酯(323-3,0.028g,0.039mmol,65%产率)。MS(ESI)m/z 715.3(M+H)。

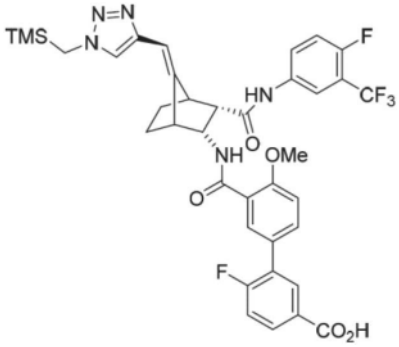
[0357] 中间体323-4



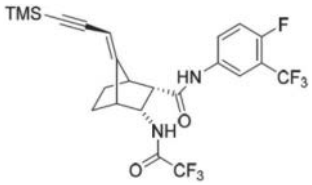
向溶解于THF(1mL)中的323-3(0.028g,0.040mmol)中添加水(0.5mL)及单水合氢氧化锂(2mg,0.05mmol)且搅拌16h。将反应混合物用水稀释,用1MHCl中和且萃取至EtOAc中。分离有机层且经Na_2SO_4干燥且在减压下浓缩,得到(Z)-2-((1R,2R,3S,4R)-2-(5′-(叔丁氧基羰基)-2′-氟-4-甲氧基-[1,1′-联苯]-3-甲酰胺基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-7-亚基)乙酸(323-4,0.025g,0.036mmol,90%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ8.43(s,1H),8.30-8.18(m,1H),8.16-8.06(m,1H),8.02-7.94(m,1H),7.71(br d,J=8.5Hz,1H),7.25-7.13(m,2H),7.00(br d,J=8.8Hz,1H),5.82(s,1H),4.85-4.65(m,1H),4.29(br s,1H),3.97(s,3H),3.16-2.96(m,2H),2.22-2.09(m,1H),2.04-1.86(m,2H),1.75-1.58(m,9H)MS(ESI)m/z 701.3(M+H)。

[0358] 实施例323为通过首先根据实施例34的程序制造酰胺,随后根据实施例120的程序移除叔丁基,由中间体323-4来制备。^{1}H NMR(500MHz,DMSO-d6)δ10.67(s,1H),9.85(br d,J=7.0Hz,1H),8.24(br d,J=4.3Hz,1H),8.11(br s,1H),8.01(br d,J=7.0Hz,1H),7.93(br s,1H),7.80(br d,J=8.2Hz,1H),7.72(br d,J=8.2Hz,1H),7.48(br t,J=9.5Hz,1H),7.37(br t,J=9.5Hz,1H),7.31(br d,J=8.9Hz,1H),6.14(s,1H),4.58-4.44(m,1H),4.06(s,3H),3.54(br s,1H),3.05(s,3H),2.99(s,1H),2.88(s,4H),2.03-1.95(m,1H),1.90-1.73(m,1H),1.45(br s,2H)。LC-MS RT:2.19min;MS(ESI)m/z=627.14(M-H)+;方法C。

[0359] 实施例325



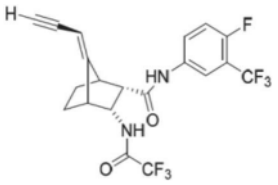
中间体325-1



向在三乙胺(0.2mL)中制成浆液的120-4(0.05g,0.1mmol)中添加乙炔基三甲基硅烷(0.02mL,0.1mmol)、双(三苯基膦)氯化钯(II)(3mg,5μmol)及碘化铜(I)(2mg,10μmol)。在90℃加热反应混合物16h。使反应混合物分配于EtOAc与pH 7.4缓冲液之间且萃取至EtOAc中。分离有机层且经Na_2SO_4干燥,倾析且在真空下浓缩,且经由急骤色谱纯化残余物,得到(1R,2S,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-3-(2,2,2-三氟乙酰胺基)-7-(3-(三甲基硅基)丙-2-炔-1-亚基)双环[2.2.1]庚烷-2-甲酰胺(325-1,40mg,0.077mmol,77%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ9.39(br d,J-6.9Hz,1H),7.78-7.67(m,2H),7.33(s,1H),7.26-7.18(m,1H),5.45(s,1H),4.60-4.41(m,1H),3.32(t,J=4.1Hz,1H),3.05(ddd,J=

10.5,4.4,1.4Hz,1H),2.81(t,J＝4.1Hz,1H),1.98-1.90(m,1H),1.90-1.81(m,1H),1.76-1.59(m,2H),0.31-0.17(m,9H)。MS(ESI)m/z 521.0(M+H)。

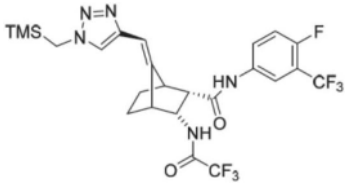
[0360] 中间体325-2



向溶解于THF(0.8mL)中的325-1(40mg,0.077mmol)中添加1M TBAF/THF(0.2mL,0.2mmol)且搅拌反应物16h。在减压下浓缩反应混合物且经由急骤色谱纯化,得到(1R,2S,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-7-(丙-2-炔-1-亚基)-3-(2,2,2-三氟乙酰胺基)双环[2.2.1]庚烷-2-甲酰胺(325-2,38mg,0.084mmol,定量产率)。MS(ESI)m/z 499.0(M+H)。

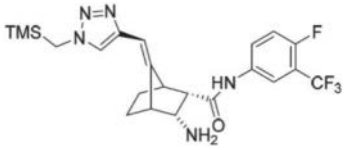
[0361]

中间体325-3



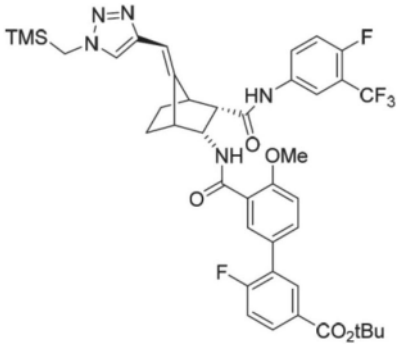
向325-2(0.017g,0.038mmol)、(叠氮基甲基)三甲基硅烷(0.011mL,0.076mmol)溶解于DMF(0.3mL)及水(0.1mL)中的溶液中添加五水合硫酸铜(II)(7mg,0.03mmol)及抗坏血酸钠(8mg,0.04mmol)且搅拌3h。使反应混合物分配于EtOAc与水之间,且将有机层用EtOAc洗涤2次,经$MgSO_4$干燥,过滤且真空浓缩,得到(1R,2S,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-3-(2,2,2-三氟乙酰胺基)-7-((1-((三甲基硅基)甲基)-1H-1,2,3-三唑-4-基)亚甲基)双环[2.2.1]庚烷-2-甲酰胺325-3,其不经进一步纯化即使用。MS(ESI)m/z 578.1(M+H)。

[0362] 中间体325-4



向MeOH(0.5ml)中添加AcCl(0.050ml,0.70mmol)且搅拌反应混合物5min。添加325-3(0.022g,0.038mmol)且在40℃搅拌反应混合物48h。在减压下浓缩反应混合物且在高真空下移除残余溶剂,以产生(1R,2S,3R,4R,Z)-3-氨基-N-(4-氟-3-(三氟甲基)苯基)-7-((1-((三甲基硅基)甲基)-1H-1,2,3-三唑-4-基)亚甲基)双环[2.2.1]庚烷-2-甲酰胺(325-4,0.018g,0.038mmol,100％产率),其不经进一步纯化即使用。MS(ESI)m/z 482.2(M+H)。

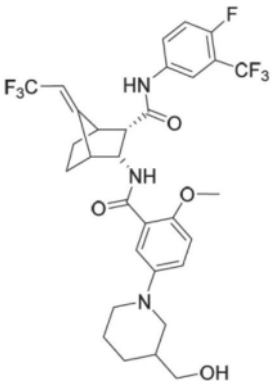
[0363] 中间体325-5



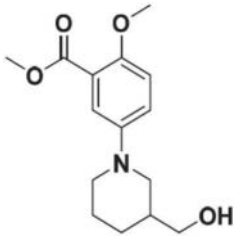
中间体325-5为根据实施例108的程序由325-4及120-6制备。

[0364] 实施例325为根据实施例120的程序由325-5制备。^{1}H NMR(500MHz,DMSO-d6)δ 10.53(s,1H),9.85(br d,J=7.0Hz,1H),8.15(br d,J=4.6Hz,1H),8.05(br s,1H),7.99-7.81(m,3H),7.71(br s,1H),7.65(br d,J=8.2Hz,1H),7.40(br t,J=9.6Hz,1H),7.33(br t,J=9.6Hz,1H),7.24(br d,J=8.5Hz,1H),6.18(s,1H),4.44(br s,1H),3.98(s,3H),3.90(s,2H),3.48(br s,1H),3.27-3.09(m,1H),2.83(br s,1H),1.96-1.72(m,2H),1.41(br d,J=5.8Hz,2H),0.00(s,9H)。LC-MS RT:2.54min;MS(ESI)m/z=754.36(M-H)+;方法C。

[0365] 实施例329

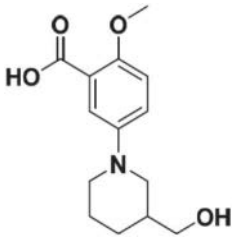


中间体329-1



向5-碘-2-甲氧基苯甲酸甲酯(500mg,1.71mrnol)及哌啶-3-基甲醇(394mg,3.42mmol)于DMSO(10mL)中的溶液中添加K_2CO_3(710mg,5.14mmol)、CuI(98mg,0.51mmol)及L-脯氨酸(59mg,0.51mmol)。将所得溶液用N_2脱气10min,随后在90℃加热12h。将反应混合物用乙酸乙酯稀释,用水、盐水洗涤,经Na_2SO_4干燥且在减压下浓缩。通过硅胶色谱纯化残余物,得到5-(3-(羟基甲基)哌啶-1-基)-2-甲氧基苯甲酸甲酯(329-1,350mg,1.25mmol,73.2%产率)。MS(ESI)m/z 280.2(M+H)。

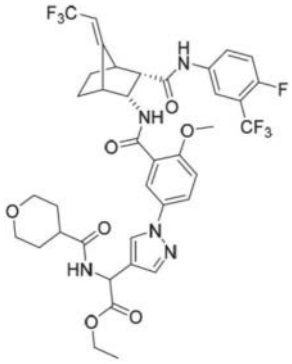
[0366] 中间体329-2



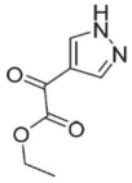
向329-1(350mg,1.253mmol)于MeOH(5mL)、THF(5mL)及水(3mL)中的溶液中添加LiOH(150mg,6.26mmol)且在室温下搅拌3h。在减压下浓缩反应物质,用HCl将水层酸化至pH约4-5,且过滤所得沉淀物且干燥,得到呈白色固体的5-(3-(羟基甲基)哌啶-1-基)-2-甲氧基苯甲酸(300mg,1.13mmol,90%产率)。MS(ESI)m/z 266.2(M+H)。

[0367] 实施例329为根据实施例108的程序,由中间体166-2及329-2制备。通过制备型HPLC柱Chiralcel OD-H(250×4.6)mm,5u分离立体异构体,得到(1R,2R,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(3-(羟基甲基)哌啶-1-基)-2-甲氧基苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺(2.1mg,3.231μmol,3.51%产率)。MS(ESI)m/z 644.2(M+H)。^{1}H NMR(400MHz,DMSO-d6)δppm 10.43(s,1H),8.41(d,J=6.5Hz,1H),8.12(dd,J=2.5,6.5Hz,1H),7.88-7.75(m,1H),7.48(t,J=9.8Hz,1H),7.20(d,J=2.5Hz,1H),7.11-6.95(m,2H),5.82-5.64(m,1H),4.65-4.56(m,1H),4.52(t,J=5.3Hz,1H),3.83(s,3H),3.51(br s,1H),3.44-3.41(m,1H),3.25-3.20(m,2H),2.78(d,J=4.0Hz,1H),2.58-2.55(m,3H),2.32-2.27(m,1H),1.92(td,J=4.7,12.2Hz,1H),1.80-1.65(m,6H),1.56(br s,2H),1.09-0.94(m,1H)。

[0368] 实施例346

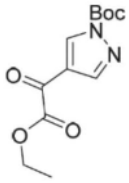


中间体346-1



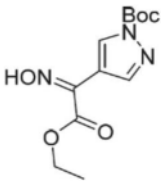
在-78℃向4-溴-1H-吡唑(2.00g,13.6mmol)于THF(100mL)中的溶液中逐滴添加正丁基锂(25.5mL,40.8mmol)。添加完成后,使反应混合物升高至室温且在室温下搅拌1.5小时。随后将混合物冷却回至-78℃且添加草酸二乙酯(2.8mL,20mmol)于THF(2.5mL)中的溶液且搅拌20分钟。通过添加饱和氯化铵淬灭反应混合物且用乙酸乙酯萃取溶液。合并有机层,在减压下浓缩且使用硅胶色谱纯化,得到346-1(496mg,20.6%)。MS(ESI)m/z:168.9(M+H)。

[0369] 中间体346-2



向346-1(150mg,0.892mmol)于乙腈(5mL)中的溶液中添加DMAP(10.90mg,0.089mmol)、二碳酸二-叔丁酯(0.249mL,1.07mmol),随后添加TEA(0.149mL,1.07mmol)。随后在室温下搅拌反应混合物18h。随后在减压下浓缩反应混合物且使用硅胶色谱纯化,得到346-2(185mg,73.4%)。MS(ESI)m/z:269.1(M+H)。

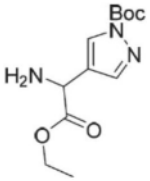
[0370] 中间体346-3



在回流下加热346-2(185mg,0.690mmol)、乙酸钠(62.2mg,0.759mmol)及羟胺盐酸盐(86mg,1.241mmol)于乙醇(3mL)中的溶液1小时。随后在真空下浓缩反应混合物且用乙酸乙酯稀释。将有机层用5%HCl溶液洗涤,得到346-3(190mg,88%),其不经进一步纯化即使用。MS(ESI)m/z:183.9(M+H-Boc)。

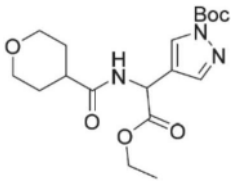
[0371]

中间体346-3



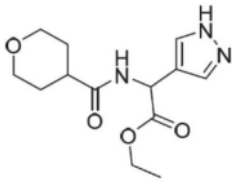
向346-3(190mg,0.671mmol)于乙醇(5mL)中的经脱气溶液中添加钯/碳(143mg,0.134mmol)且用氮气脱气。在氢气球下搅拌反应混合物1.5小时。经硅藻土垫过滤反应混合物,得到346-4(181mg,100%)。MS(ESI)m/z:270.1(M+H)。

[0372] 中间体346-5



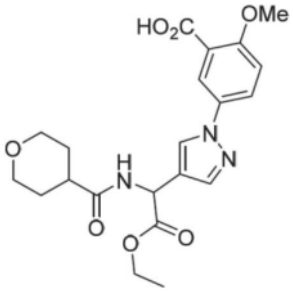
向346-4(181mg,0.672mmol)及四氢-2H-哌喃-4-甲酸(87mg,0.672mmol)于无水DMF(2mL)中的溶液中添加DIEA(0.587mL,3.36mmol),随后添加BOP(327mg,0.739mmol)。在室温下搅拌反应混合物1小时且过滤。在减压下浓缩残余物且使用硅胶色谱纯化,得到346-5(120mg,44.5%)。MS(ESI)m/z:382.3(M+H)。

[0373] 中间体346-6



向346-5(120mg,0.315mmol)于DCM(4mL)中的溶液中添加TFA(1.5mL,19.47mmol),且在室温下搅拌反应混合物1小时。在减压下浓缩反应混合物,得到346-6(125mg,90%)。MS(ESI)m/z:282.2(M+H)。

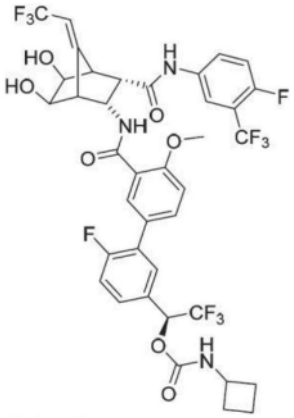
[0374] 中间体346-7



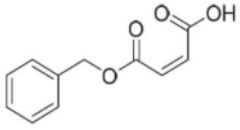
向5-溴-2-甲氧基苯甲酸(87mg,0.444mmol)、346-6(125mg,0.444mmol)及硼酸(boric acid)(82mg,1.3mmol)的经N_2脱气溶液中添加乙酸铜(II)(81mg,0.44mmol),且在室温下搅拌反应混合物18h。在减压下浓缩反应混合物且使用硅胶色谱纯化。MS(ESI)m/z:432.3(M+H)。

[0375] 实施例346为以与实施例108类似的方式由170-2及346-7制备。^{1}H NMR(500MHz,DMSO-d_6)δ10.66(s,1H),10.03(d,J=6.7Hz,1H),8.59-8.51(m,1H),8.46(br.s.,1H),8.32(br.s.,1H),8.24(d,J=4.6Hz,1H),7.98-7.88(m,1H),7.79(br.s.,1H),7.72(s,1H),7.50(t,J=9.8Hz,1H),7.33(d,J=8.8Hz,1H),6.00-5.88(m,1H),5.38(d,J=6.4Hz,1H),4.54(br.s.,1H),4.17-4.09(m,2H),4.05(s,3H),3.36-3.20(m,2H),3.00(br.s.,1H),2.01-1.82(m,2H),1.69-1.55(m,5H),1.50(d,J=6.1Hz,2H),1.17(t,J=7.0Hz,3H);LC-MS(M+H)=810.1;HPLC RT=2.44min;方法B。

[0376] 实施例348

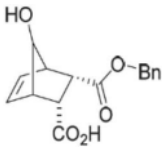


中间体348-1:



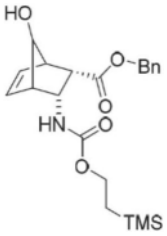
将呋喃-2,5-二酮(10g,102mmol)及苯甲醇(31.7mL,306mmol)于甲苯(50mL)中的混合物加热至80℃持续24小时。随后在减压下浓缩反应混合物且使用硅胶色谱纯化,得到348-1(15.5g,73%)。MS(ESI)m/z:206.9(M+H)。

[0377] 中间体348-2



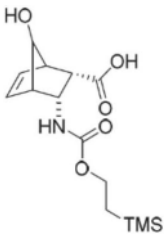
向348-1(3.6g,17mmol)于MeCN(40mL)及水(0.400mL)中的溶液中添加六氟磷酸二茂铁(11.6g,34.9mmol)且在开放氛围中搅拌18小时。在减压下浓缩反应混合物且用DCM稀释。用1N HCl(40mL)处理反应混合物30分钟。接着分离有机层且用DCM洗涤水层且分离。合并有机层且用盐水洗涤。在减压下浓缩有机层且使用硅胶色谱纯化,得到348-2(1.8g,35%)。MS(ESI)m/z:289.1(M+H)。

[0378] 中间体348-3



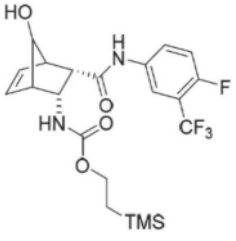
向3颈圆底烧瓶中添加348-2(1.99g,6.90mmol)及甲苯(45mL),随后添加TEA(2.1mL,15mmol)及二苯基磷酰基叠氮化物(1.26mL,5.87mmol)。在室温下搅拌反应混合物2.5小时。向此反应混合物中添加2-(三甲基硅基)乙-1-醇(3.94mL,28.3mmol)且在80℃加热所得反应混合物28小时。使反应混合物冷却至室温,在减压下浓缩且使用硅胶色谱纯化,得到348-3(1.52g,51.8%)。MS(ESI)m/z:403.9(M+H)。

[0379] 中间体348-4



向348-3(1.52g,3.77mmol)于THF(24mL)及水(8.0mL)中的溶液中添加LiOH(5.65mL,11.3mmol)且在室温下搅拌溶液1小时。将反应混合物酸化且用乙酸乙酯萃取。合并有机层且在减压下浓缩,得到348-4(1.1g,92%)。MS(ESI)m/z:313.9(M+H)。

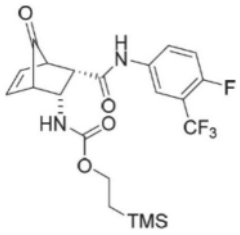
[0380] 中间体348-5



向348-4(680mg,2.17mmol)于无水DMF(12mL)中的溶液中添加4-氟-3-(三氟甲基)苯胺(0.28mL,2.2mmol)、1-羟基苯并三唑水合物(515mg,3.36mmol)及1-(3-二甲基氨基丙基)-3-乙基碳化二亚胺盐酸盐(624mg,3.25mmol)。在室温下搅拌反应混合物18h且在减压下浓缩。使用硅胶色谱纯化残余物,得到348-5(260mg,25%)。MS(ESI)m/z:474.9(M+H)。

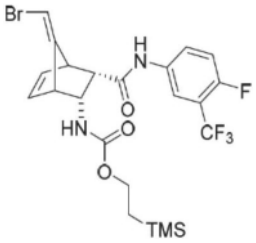
[0381]

中间体348-6



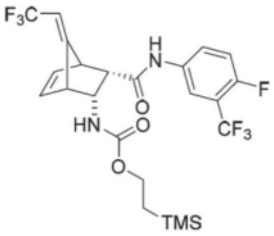
在0℃在N_2下向烧瓶中添加DMSO(4mL)及吡啶三氧化硫(279mg,1.75mmol)、至348-5(260mg,0.548mmol)及TEA(0.61mL,4.4mmol)于DMSO(4mL)中的溶液。搅拌反应混合物1小时且用EtOAc稀释且用盐水洗涤有机相。在减压下浓缩有机层且使用硅胶色谱纯化残余物,得到348-6(280mg,100%)。MS(ESI)m/z:473.0(M+H)。

[0382] 中间体348-7



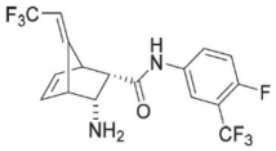
向圆底烧瓶中添加溴化(溴甲基)三苯基鏻(388mg,0.889mmol)及THF(5.0mL)。使反应混合物冷却至-78℃,且接着经2分钟逐滴添加1MNaHMDS(0.89mL,0.89mmol)于THF中的溶液,同时保持内部温度低于-70℃。在-78℃搅拌所得亮黄色悬浮液1小时。向此反应混合物中添加348-6(280mg,0.593mmol)于无水THF(1.0mL)中的溶液,先前经2分钟用NaHMDS(1.12mL,1.12mmol)处理该溶液,同时保持内部温度低于-70℃。在-78℃搅拌所得反应混合物3小时。随后通过缓慢添加水(6mL),接着添加乙酸乙酯(6mL)来淬灭反应混合物。将所得反应混合物搅拌5分钟且接着用EtOAc稀释。用盐水洗涤合并的有机部分且使用硅胶色谱纯化。使用以下对残余物进行手性分离:Chiralcel OD-H,21×250mm,5微米柱,移动相5% MeOH/CAN/95%CO_2,流动速率45mL/min及150巴。在40℃进行分离且在240nm的波长下量测。手性分离产生四个峰,保留时间为9.29min(>99.9%ee),11.16min(>99.9%ee),13.98min(>99.9%ee)及15.30min(>81.0%ee)。在11.16min发现所需产物且其ee>99.9%(来自手性SFC的峰2),其通过2D NMR分析确认,得到348-7(82mg,25.16%)。MS(ESI)m/z:473.1(M+H)。

[0383] 中间体348-8



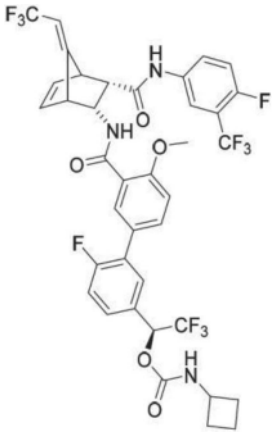
在75℃在N_2下,经10min的时段向348-7(83mg,0.15mmol)及CuI(43.2mg,0.227mmol)于无水DMF(1mL)及HMPA(1.2mL,7.0mmol)中的悬浮液中逐滴添加含2,2-二氟-2-(氟磺酰基)乙酸甲酯(0.048mL,0.38mmol)的无水DMF(0.5mL)。在75℃在氮气下搅拌所得悬浮液12小时。使反应混合物冷却至室温,通过添加$NaHCO_3$(20mL)及溶液淬灭,用EtOAc萃取。将有机层浓缩且进行硅胶色谱,得到348-8(52mg,61%)。MS(ESI)m/z:539.1(M+H)。

[0384] 中间体348-9



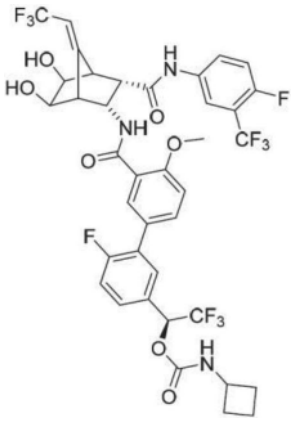
向348-8(52mg,0.097mmol)于1,4-二噁烷(1.5mL)中的溶液中添加DCM(1.6mL)及TFA(0.4mL)。在室温下搅拌反应混合物30分钟且在减压下浓缩,得到348-9,其不经进一步纯化即使用(49mg,95%)。MS(ESI)m/z:394.9(M+H)。

[0385] 中间体348-10



348-10为根据实施例230的程序制备。MS(ESI)m/z:818.2(M+H)。

[0386] 实施例348

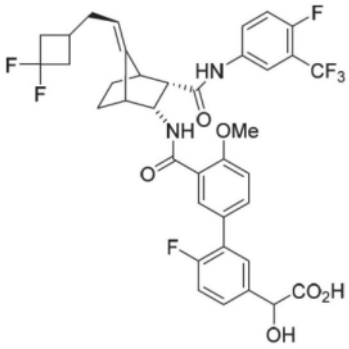


向348-10(35mg,0.043mmol)于丙酮(1mL)中的溶液中添加N-甲基吗啉N-氧化物(10mg,0.086mmol),随后添加含OsO_4的叔丁醇(0.054mL,4.2μmol)。在室温下搅拌反应混合物18h。用EtOAc稀释反应混合物且用硫代硫酸钠洗涤溶液。分离有机层且在减压下浓缩,且使用制备型反相HPLC纯化残余物,得到实施例348(14.6mg,38.0%)。^1H NMR(400MHz,CD_3OD)δ10.41(s,1H),10.15(d,J=7.3Hz,1H),8.27(d,J=1.3Hz,1H),8.19(dd,J=6.3,2.5Hz,

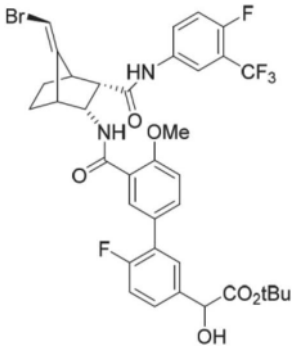
1H),7.84-7.72(m,2H),7.69-7.61(m,1H),7.56-7.48(m,1H),7.38-7.24(m,3H),6.18(q,J＝7.0Hz,1H),5.94(q,J＝7.5Hz,1H),4.70(ddd,J＝10.9,7.1,4.2Hz,1H),4.55(d,J＝6.4Hz,1H),4.45(d,J＝6.4Hz,1H),4.13(s,3H),4.12-3.99(m,1H),3.42(d,J＝1.5Hz,1H),3.38(s,1H),2.90(d,J＝4.0Hz,1H),2.39-2.19(m,2H),2.09-1.90(m,2H),1.78-1.63(m,2H);LC-MS(M+H)＝852.1;HPLC RT＝11.48min;方法C.

[0387] 在环境温度下搅拌351-5(120mg,0.176mmol)及LiOH(21.05mg,0.879mmol)于MeOH(2mL)、THF(2mL)及水(1mL)中的溶液12h。浓缩反应物质且用1.5N HCl酸化。用DCM萃取反应物且浓缩有机层。通过制备型反相HPLC纯化残余物,得到4-氟-3′-(1R,2R,3R,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4′-甲氧基-[1,1′-联苯]-3-甲酸(11.5mg,0.016mmol,9%产率)。^{1}H NMR.MS(E-)m/z:669.2(M+H)。

[0388] 实施例352



中间体352-1

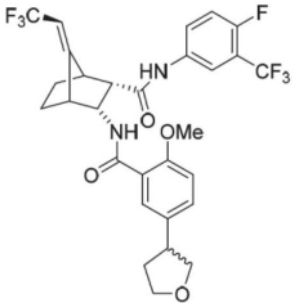


中间体352-1为根据针对实施例108所描述的方法由120-5及177-4制备。LC-MS(M+H)＝767.1;HPLC RT＝1.25min;方法A。

[0389] 将352-1(0.038g,0.050mmol)、Na_2CO_3(5.30mg,0.0500mmol)、(4,4′-二-叔丁基-2,2′-联吡啶)双[3,5-二氟-2-[5-三氟甲基-2-吡啶基-κ_N)苯基-κ_C]铱(III)PF_6(0.515mg,0.500μmol)、$NiCl_2$-乙二醇二甲醚复合物(0.549mg,2.50μmol)、4,4′-二-叔丁基-2,2′-联吡啶(0.551mg,2.50μmol)、$(TMS)_3SiH$(0.03mL)及3-(溴甲基)-1,1-二氟环丁烷(0.019g,0.10mmol)于DME中的浆液用N_2脱气,且用蓝色LED照射96小时。将反应混合物用EtOAc稀释,经由硅胶过滤且在减压下浓缩。将残余物溶解于DCM(0.4mL)中,用TFA(0.08mL)处理。15min之后,用甲苯稀释溶液且在减压下浓缩。通过制备型反相HPLC纯化残余物,得到2-(3′-(((1R,2R,3S,4R,Z)-7-(2-(3,3-二氟环丁基)亚乙基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-6-氟-4′-甲氧基-[1,1′-联苯]-3-基)-2-羟基乙

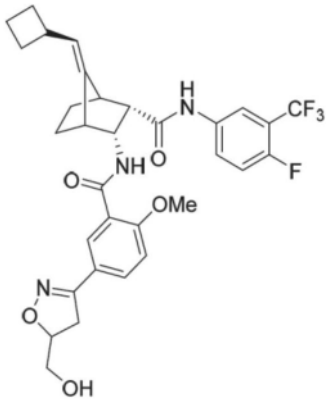
酸(2.6mg,3.2μmol,6.5%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.56(br s,1H),9.92(brdd,J=15.4,7.2Hz,1H),8.18(br t,J=4.9Hz,1H),8.08(br d,J=11.0Hz,1H),7.81-7.61(m,2H),7.52-7.35(m,3H),7.32-7.13(m,2H),5.26-5.13(m,1H),4.92(br d,J=1.8Hz,1H),4.38(br d,J=4.3Hz,1H),4.02(s,1H),3.89-3.71(m,3H),3.19-3.09(m,1H),2.88(s,1H),2.72(s,2H),2.64(br s,2H),2.32-2.06(m,5H),1.89-1.66(m,2H),1.38(br s,2H)。LC-MS(M+H)=734.24;HPLC RT=2.48min;方法C。

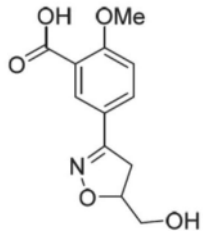
[0390] 实施例360



使实施例292(0.025g,0.041mmol)、Na_2CO_3(4.35mg,0.0410mmol)、(4,4′-二-叔丁基-2,2′-联吡啶)双[3,5-二氟-2-[5-三氟甲基-2-吡啶基-k_N)苯基-k_C]Ir(III)PF_6(0.423mg,0.410μmol)、$NiCl_2$乙二醇二甲醚复合物(0.451mg,2.05μmol)、4,4′-二-叔丁基-2,2′-联吡啶(0.551mg,2.50μmol)、$(TMS)_3SiH$(0.03mL)及3-溴四氢呋喃(0.012g,0.082mmol)于DME(1.641ml)中的浆液脱气,掩盖于N_2下且用蓝色LED照射。96h之后,将反应混合物用EtOAc稀释,经由硅胶过滤且在减压下浓缩。通过制备型反相HPLC纯化残余物,得到呈非镜像异构体混合物形式的(1R,2S,3R,4R,Z)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(四氢呋喃-3-基)苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺(3.5mg,5.5μmol,13%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.78(br d,J=5.8Hz,1H),8.14(br d,J=4.6Hz,1H),7.81-7.65(m,2H),7.49-7.28(m,2H),7.04(br d,J=8.5Hz,1H),5.84(q,J=7.9Hz,1H),4.43(br s,1H),3.95-3.78(m,5H),3.74-3.64(m,1H),3.37-3.07(m,2H),2.89(br s,1H),2.81(s,1H),2.71-2.62(m,1H),2.24-2.11(m,1H),1.99-1.87(m,1H),1.83-1.71(m,2H),1.50-1.26(m,2H)。LC-MS(M+H)=601.16;HPLC RT=2.58min;方法C。

[0391] 实施例378





中间体378-1:制备(E)-5-((羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯。将市售5-甲酰基-2-甲氧基苯甲酸酯(1.16g,5.97mmol)溶解于DCM(5mL)中,且向此溶液中添加羟胺.HCl(415mg,5.97mmol),随后添加TEA(1mL),且在室温下搅拌反应混合物18h。添加水(100mL)且用EtOAc(2×25mL)萃取溶液,将合并的有机部分干燥($MgSO_4$),过滤且在减压下蒸发,产生378-1,1.19g,95%产率。^{1}H NMR(400MHz,$CDCl_3$)δ8.13(s,1H),8.03(d,J=2.4Hz,1H),7.78-7.67(m,1H),7.03(d,J=8.8Hz,1H),3.97(s,3H),3.93(s,3H)。MS(ESI)m/z=210.1(M+H)。

[0392] 中间体378-2:制备5-(5-(羟基甲基)-4,5-二氢异噁唑-3-基)-2-甲氧基苯甲酸甲酯。将中间体378-1(55mg,0.26mmol)溶解于DMF(2mL)中,且向此溶液中添加NCS(35mg,0.26mmol),且在室温下搅拌反应混合物4h。添加水且用EtOAc(2×25mL)萃取溶液,将合并的有机部分干燥($MgSO_4$),过滤,在减压下浓缩且使残余物立即再溶解于DCM(5mL)中。向溶液中添加烯丙醇(61mg,1.05mmol),随后添加TEA(0.5mL),且在室温下搅拌所得反应混合物18h。添加水(20mL)且用EtOAc(2×20mL)萃取溶液,将合并的有机部分干燥($MgSO_4$),过滤且通过正相色谱,用己烷/EtOAc洗脱来纯化,得到378-2,58mg,85%产率。^{1}H NMR(500MHz,$CDCl_3$)δ8.05(d,J=2.4Hz,1H),7.89(dd,J=8.8,2.4Hz,1H),7.05(d,J=8.9Hz,1H),4.90(dddd,J=10.8,7.7,4.6,3.2Hz,1H),4.08-3.85(ss,6H),3.81-3.68(m,1H),3.46-3.36(m,1H),1.89(br t,J=6.2Hz,1H),1.57(s,2H)。MS(ESI)m/z=266.1(M+H)。

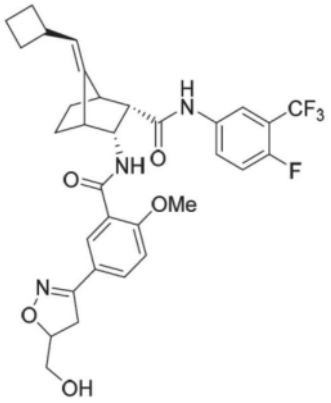
[0393] 中间体378-3:将378-2(58mg,0.22mmol)溶解于THF(2mL)中且向其中添加LiOH(6.3g,0.26mmol),随后添加水(2mL)及甲醇(1mL)且在室温下搅拌4h。用稀释HCl(1N)淬灭至pH 7且用EtOAc(2×25mL)萃取溶液,将合并的有机部分干燥($MgSO_4$),过滤且蒸发成378-3。^{1}H NMR(500MHz,$CDCl_3$)δ8.28(d,J=2.3Hz,1H),8.14(dd,J=8.8,2.4Hz,1H),7.28-7.14(m,1H),4.92(dddd,J=10.8,7.7,4.6,3.1Hz,1H),4.16(s,3H),4.09-3.89(m,1H),3.72(dd,J=12.4,4.6Hz,1H),3.48-3.39(m,1H),3.38-3.29(m,1H),1.94-1.72(m,1H),1.60(br s,1H)。MS(ESI)m/z=252.3(M+H)。

[0394] 中间体378-4及378-5.根据以下制备型方法对378-3进行手性SFC分离:仪器:

Berger MG II,柱:Chiralpak IC,21×250mm,5微米,移动相:20%甲醇/80%CO_2,流动条件:2mL/min,150巴,40℃检测器波长:220nm,注射详情:0.7mL～35mg/mL于MeOH中,得到378-4(峰1,>99%de,分析型RT=5.6min)and378-5(峰2,99%de,分析型RT=6.6min),分析型色谱条件:仪器:ShimadzuNexera SFC(CTR-L410-SFC3),柱:Chiralpak IC,4.6×100mm,3微米,移动相:20%甲醇/80%CO_2,流动条件:2.0mL/min,150巴,40℃,检测器波长:220nm,注射详情:5μL～1mg/mL于MeOH中

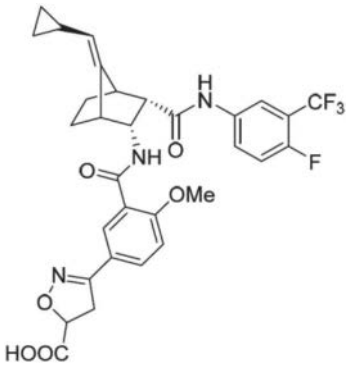
[0395] 通过使中间体378-3(4.6mg,0.018mmol)与环丁基降冰片烷基中间体369-1(7mg,0.02mmol)、BOP试剂(8.1mg,0.018mmol)及Hunig碱(0.05ml)在DMF中偶合来制备(1R,2S,3R,4R,Z)-7-(环丁基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(羟基甲基)-4,5-二氢异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺378(非镜像异构混合物)。经由反相HPLC纯化得到呈固体的378(5mg,44%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.89(dd,J=7.1,2.8Hz,1H),8.26-8.17(m,2H),7.84-7.73(m,2H),7.48(br t,J=9.7Hz,1H),7.26(d,J=8.8Hz,1H),5.37(d,J=8.4Hz,1H),4.78-4.65(m,1H),4.35(br s,1H),4.03(s,3H),3.63(br s,1H),3.22-3.05(m,3H),2.96(br s,1H),2.70(br s,1H),2.23-2.06(m,3H),1.91-1.70(m,7H),1.43-1.22(m,2H)。MS(ESI)m/z=616.1(M+H)。HPLC纯度:100%;保留时间:2.54min;方法C。

[0396] 实施例379

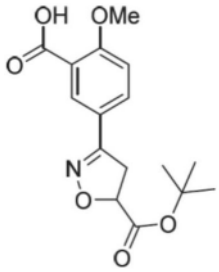


实施例379.通过针对实施例378所描述的偶合方法,使用环丁基降冰片烷基中间体369-1及中间体378-5来制备(1R,2S,3R,4R,Z)-7-(环丁基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(羟基甲基)-4,5-二氢异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(同手性异构体-2)(49%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.88(br d,J=7.0Hz,1H),8.22(s,1H),8.23(d,J=7.0Hz,1H),7.79(br d,J=8.2Hz,2H),7.49(br t,J=9.6Hz,1H),7.27(d,J=8.5Hz,1H),5.38(br d,J=8.5Hz,1H),4.70(br d,J=3.1Hz,2H),4.36(br s,1H),4.04(s,3H),3.51(br s,1H),3.37(br s,2H),3.22-3.04(m,2H),2.97(br s,1H),2.71(br s,1H),2.19(br d,J=5.8Hz,1H),2.14(br s,1H),1.92-1.71(m,6H),1.37(br s,2H)。MS(ESI)m/z=616.1(M+H)。HPLC纯度:100%;保留时间:2.54min;方法C。

[0397] 实施例384



中间体384-1(外消旋体)及384-2(同手性峰-1)及384-3(同手性峰-2)

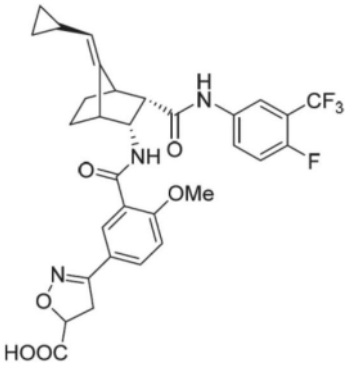


中间体384-1:中间体5-(5-(叔丁氧基羰基)-4,5-二氢异噁唑-3-基)-2-甲氧基苯甲酸为如针对378-2所描述经由水解酯且用NCS/DMF处理由来自378-1的产物制备,得到5-(氯(羟基亚氨基)甲基)-2-甲氧基苯甲酸,在用过量丙烯酸叔丁酯处理后得到所需中间体5-(5-(叔丁氧基羰基)-4,5-二氢异噁唑-3-基)-2-甲氧基苯甲酸(384-1),产率为76%。^{1}H NMR(500MHz,$CDCl_3$)δ8.25(d,J=2.3Hz,1H),8.19(dd,J=8.8,2.4Hz,1H),7.16(d,J=8.9Hz,1H),5.10(dd,J=9.9,8.7Hz,1H),4.16(s,3H),3.67-3.60(m,2H),1.74-1.51(m,9H)。MS(ESI)m/z=322.1(M+H)。

[0398] 中间体384-2及384-3:通过手性SFC,通过以下制备型色谱方法分离384-1手性中间体:仪器:Berger MG II,柱:Chiralpak IC,21×250mm,5微米,移动相:20%甲醇/80%Co_2,流动条件:2mL/min,150巴,40℃,检测器波长:220nm,注射详情:0.7mL~35mg/mL于MeOH中,得到384-2(峰1,>99%de,分析型RT=7.93min)及384-3(峰2,>99%de,分析型RT=9.65min)。分析型色谱条件:仪器:Shimadzu Nexera SFC(CTR-L410-SFC3),柱:ChiralpakIC,4.6×100mm,3微米,移动相:20%甲醇/80%CO_2,流动条件:2.0mL/min,150巴,40℃,检测器波长:220nm,注射详情:5μL~1mg/mL于甲醇中。

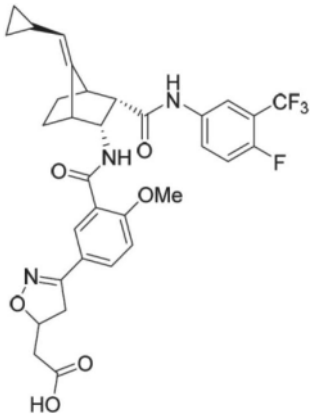
[0399] 通过针对实施例378所描述的偶合方法,使用降冰片烷基中间体166-2及中间体384-1来制备3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-4,5-二氢异噁唑-5-甲酸(℃镜像异构混合物)(7%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.56(s,1H),9.92(d,J=7.0Hz,1H),8.32-8.20(m,2H),7.87-7.75(m,2H),7.49(t,J=9.8Hz,1H),7.34-7.22(m,1H),5.15(dd,J=11.6,6.7Hz,1H),4.70(d,J=9.5Hz,1H),4.45(br s,1H),4.05(s,3H),3.74(dd,J=17.1,11.6Hz,1H),3.23-3.13(m,2H),3.11(br s,2H),2.86-2.64(m,1H),1.88-1.68(m,2H),1.62-1.46(m,1H),1.42(br s,2H),0.88-0.68(m,2H),0.36(br s,2H)。MS(ESI)m/z=616.3(M+H)。HPLC纯度:100%;保留时间:2.38min。方法C。

[0400] 实施例385

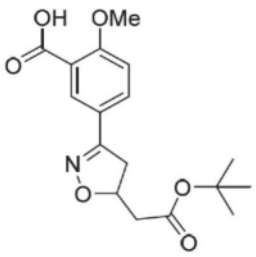


通过使中间体384-2(13.9mg,0.04mmol)与中间体166-2(16mg,0.04mmol)在DMF中在BOP试剂(19mg,0.04mmol)及Hunig碱(0.05mL)存在下偶合来制备3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-4,5-二氢异噁唑-5-甲酸同手性异构体-1。在减压下浓缩反应混合物且添加水(25mL),且用EtOAc(2×25mL)萃取溶液,将合并的有机部分干燥($MgSO_4$),过滤且在减压下浓缩。将残余物溶解于DCM(1ml)中且向其中添加TFA(0.2mL)且在室温下搅拌15min。将溶液在减压下浓缩且用DMF(1mL)使其再溶解且经由反相HPLC纯化,得到385,即呈固体的3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-4,5-二氢异噁唑-5-甲酸(同手性)(12mg,99%产率)。^{1}H NMR(500MHz,DMSO-d_6)δ10.62(s,1H),9.92(br d,J=7.0Hz,1H),8.24(br s,2H),7.88-7.76(m,2H),7.49(br t,J=9.5Hz,1H),7.27(d,J=8.9Hz,1H),5.01-4.84(m,1H),4.69(d,J=9.5Hz,1H),4.45(br s,1H),4.05(s,3H),3.67-3.43(m,1H),3.18(br d,J=7.3Hz,1H),3.12(br s,1H),2.73(br s,1H),1.92(s,1H),1.88-1.66(m,2H),1.51(br d,J=4.3Hz,1H),1.42(br s,2H),0.89-0.68(m,2H),0.35(br s,2H)。HPLC纯度100%。分析型LC-MS:2.33min;(ESI)m/z=616.28(M+H)+,方法C。

[0401] 实施例390



中间体390-1

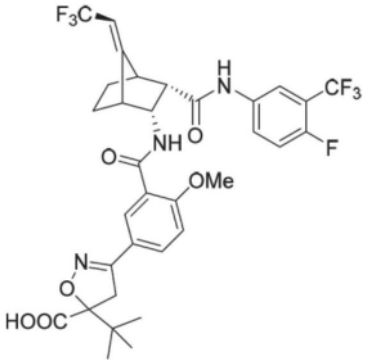


中间体390-1为以针对中间体378-3所描述的相同方式制备(71％产率),在此情况下为通过用丁-3-炔酸叔丁酯取代烯丙醇来制备。^{1}H NMR(400MHz,$CDCl_3$)δ10.40(br s,1H),8.29-8.25(m,1H),8.18(dd,J＝8.8,2.4Hz,1H),7.16(d,J＝8.8Hz,1H),5.21-5.09(m,1H),4.23-4.12(m,3H),3.58(dd,J＝16.8,10.5Hz,1H),3.17(dd,J＝16.7,7.5Hz,1H),2.82(dd,J＝15.8,5.9Hz,1H),2.61(dd,J＝15.8,7.5Hz,1H),1.52-1.43(m,9H)。MS(ESI)m/z＝336.1(M+H)。

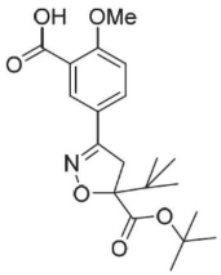
[0402] 中间体390-2及390-3:通过手性SFC,通过以下制备型色谱方法分离390-1的手性中间体:仪器:PIC Solution SFC Prep-200,柱:Chiralpak IC,30×250mm,5微米,移动相:15％MeOH/85％CO_2,流动条件:85mL/min,150巴,40℃,检测器波长:227nm,注射详情:0.5mL～53mg/mL于MeOH中,得到390-2(峰1,100％de,分析型RT＝11.3min)及390-3(峰2,93.8％de,分析型RT＝12.6min)。分析型色谱条件:仪器:Aurora Infinity SFC。柱:Chiralpak IC,4.6×250mm,3微米,移动相:20％MeOH/80％CO_2,流动条件:2.0mL/min,150巴,40℃,检测器波长:220nm,注射详情:5μL～1mg/mL于MeOH中。

[0403] 通过针对实施例378所描述的偶合方法,使用环丙基降冰片烷基中间体166-2及中间体390-3,随后用TFA脱除保护基来制备2-(3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-4,5-二氢异噁唑-5-基)乙酸同手性异构体-2390(47％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.92(br d,J＝7.2Hz,1H),8.26-8.19(m,2H),7.84-7.77(m,2H),7.49(t,J＝9.6Hz,1H),7.28(d,J＝8.9Hz,1H),5.04-4.90(m,1H),4.70(d,J＝9.5Hz,1H),4.46(br s,1H),4.05(s,3H),3.22-3.09(m,2H),2.73(br s,1H),2.70-2.59(m,2H),2.55(s,2H),1.89-1.71(m,2H),1.51(br d,J＝4.9Hz,1H),1.42(br s,2H),0.87-0.69(m,2H),0.36(br s,2H)。MS(ESI)m/z＝630.3(M+H)。HPLC纯度:100％;保留时间:2min。方法B。

[0404] 实施例397



中间体397-1

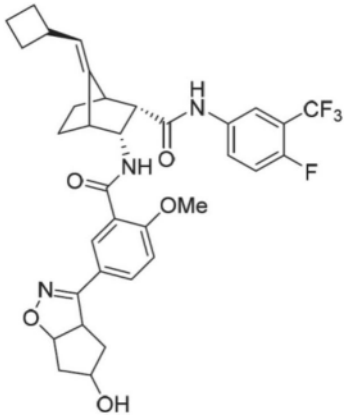


中间体397-1为以针对中间体378-3所描述的相同方式制备(81％产率),在此情况

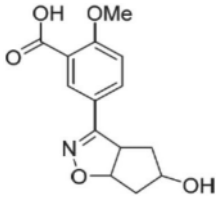
下为通过用3,3-二甲基-2-亚甲基丁酸叔丁酯取代烯丙醇来制备。^{1}H NMR(500MHz,CD_3OD)δ 8.12(d,J＝2.3Hz,1H),7.88(d,J＝8.5Hz,1H),7.22(d,J＝8.9Hz,1H),4.06-3.88(s,3H),3.62(q,J＝18.0Hz,2H),1.61-1.39(m,9H)。MS(ESI)m/z＝378.3(M+H)。

[0405] 通过针对实施例378所描述的偶合方法,使用三氟甲基降冰片烷基中间体170-2及中间体397-1,随后用TFA处理来制备5-(叔丁基)-3-(3-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-4,5-二氢异噁唑-5-甲酸非镜像异构混合物397(54％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.74-10.63(m,1H),9.98-9.88(m,1H),8.21(br d,J＝5.2Hz,1H),7.79(br s,1H),7.50(br t,J＝9.2Hz,1H),7.26(br s,1H),7.08(br s,1H),5.99-5.86(m,1H),4.50(br s,1H),4.03(s,3H),3.51(br s,3H),3.24(br s,1H),2.99(s,1H),2.11-1.90(m,1H),1.86(br s,1H),1.49(br s,1H),0.99(br s,9H)。MS(ESI)m/z＝700.3(M+H)。HPLC纯度:98.8％;保留时间:2.07min。方法B。

[0406] 实施例406



中间体406-1



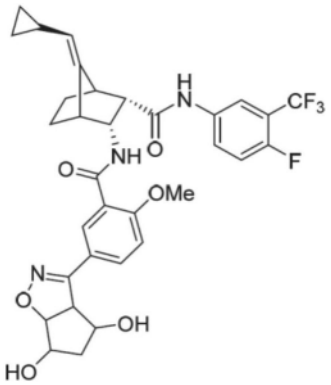
中间体406-1为以针对中间体378-3所描述的相同方式制备(31％产率),在此情况下为以非镜像异构体的混合物形式,通过用环戊-3-烯-1-基醇取代烯丙醇来制备。^{1}H NMR(600MHz,$CDCl_3$)δ8.04(d,J＝2.3Hz,1H),7.85(dd,J＝8.8,2.3Hz,1H),7.03(d,J＝8.8Hz,1H),5.30(ddd,J＝9.4,6.2,2.9Hz,1H),4.50(quin,J＝5.9Hz,1H),4.19(td,J＝9.3,4.7Hz,1H),3.92(s,3H),2.33-2.27(m,1H),2.18-2.06(m,3H)。MS(ESI)m/z＝292.0(M+H)。

[0407] 中间体406-2至406-5(手性).通过手性SFC,通过以下制备型色谱方法分离406-1的手性中间体:仪器:Berger SFC(LVL-L4021Lab)柱:IC 25×3cm ID,5μm,温度:40℃,流动速率:85mL/min,移动相:梯度75/25CO_2/MeOH,持续12min,接着达到45％MeOH,检测器波长:235nm,注射量:1000μL,得到手性406-2峰-1,>99％de,分析型RT＝8.80min)、手性406-3(峰-2,>95％de,分析型RT＝9.86min)、手性406-4(峰-3,>99％de,分析型RT＝13.53min)、手性406-5(峰-4,>99％de,分析型RT＝16.67min)。分析型色谱条件:仪器:Agilent SFC(LVL-L4021Lab),柱:IC 250×4.6mm ID,5μm,温度:环境温度,流动速率:2.0mL/min,移动

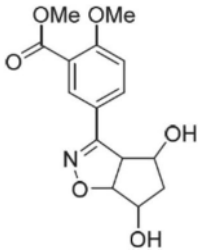
相:梯度75/25CO_2/MeOH 12min,接着达到45%MeOH。

[0408] 通过针对实施例378所描述的偶合方法,使用环丁基降冰片烷基中间体369-1及中间体406-1来制备(1R,2S,3R,4R,Z)-7-(环丁基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-羟基-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物406(74%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.56(s,1H),9.89(d,J=7.3Hz,1H),8.21(br s,2H),7.78(br d,J=8.7Hz,2H),7.48(br t,J=9.6Hz,1H),7.26(br d,J=8.8Hz,1H),5.37(d,J=8.3Hz,1H),5.10(br t,J=7.2Hz,1H),4.34(br s,1H),4.15(br s,1H),4.12-4.05(m,1H),4.03(s,3H),3.72-3.56(m,3H),3.20-3.02(m,2H),2.95(br s,1H),2.70(br s,1H),2.16(br s,1H),2.13-2.01(m,2H),1.92-1.70(m,6H),1.36(br s,2H)。MS(ESI)m/z=642.1(M+H)。HPLC纯度:100%;保留时间:2.49min。方法C。

[0409] 实施例413

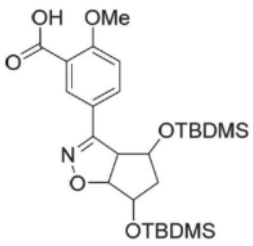


中间体413-1(非镜像异构混合物)



中间413-1为以与针对中间体378-3所描述相同的方式制备(10%产率),在此情况下为呈非镜像异构体的混合物形式,通过用(1R,3S)-环戊-4-烯-1,3-二醇取代烯丙醇来制备。^{1}H NMR(400MHz,$CDCl_3$)δ8.09-7.91(m,1H),7.30(s,1H),7.11-7.01(m,1H),5.46-5.21(m,1H),4.45-4.23(m,1H),4.04-3.88(ss,6H),3.02-2.98(m,1H),2.92(d,J=0.7Hz,1H),2.45-2.35(m,1H),2.02(s,2H)。MS(ESI)m/z=294.1(M+H)。

[0410] 中间体413-2(非镜像异构混合物)

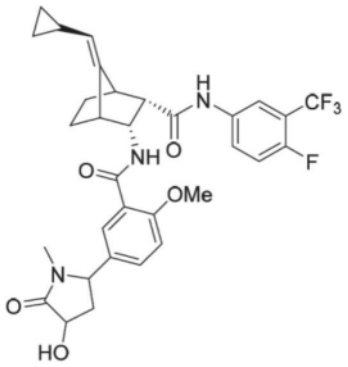


经由两步顺序,通过用过量TBDMS三氟甲磺酸盐(2.64g,9.99mmol)及含2,6-二甲

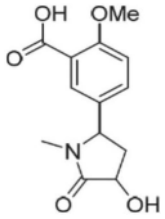
基吡啶(1.61g,14.9mmol)的DCM(5mL)进行保护,随后在THF/MeOH/水(1:1:1,5mL)中用LiOH水解酯以自中间体413-1获得413-2。^{1}H NMR(500MHz,$CDCl_3$)δ8.48-8.46(m,1H),8.04-8.00(m,1H),7.10-7.05(m,1H),5.06-5.02(m,1H),4.33-4.29(m,1H),4.23-4.18(s,3H),4.15-4.13(m,1H),4.12-4.10(m,1H),4.00-3.94(m,1H),1.29-1.24(m,1H),0.93(ss,18H),0.12(s,3H),0.12-0.03(m,3H),0.03(s,1H),0.02(s,3H),-0.05-0.06(m,3H)。MS(ESI)m/z 522.5(M+H)。

[0411] 通过针对实施例378所描述的偶合方法,使用环丙基降冰片烷基中间体166-2及中间体413-2,随后用氟化四丁铵(1M于THF中,1mL)脱除保护基来制备(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(5-(4,6-二羟基-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物413(36%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.90(br d,J=7.3Hz,1H),8.43-8.37(m,1H),8.21(br d,J=6.1Hz,1H),7.89(dd,J=8.7,2.3Hz,1H),7.83-7.66(m,1H),7.48(t,J=9.6Hz,1H),7.29(d,J=8.9Hz,1H),4.96(dd,J=10.2,2.0Hz,1H),4.70(d,J=9.5Hz,1H),4.45(br s,1H),4.05(s,3H),3.54(br s,1H),3.21-3.07(m,2H),3.00(s,1H),2.54(s,1H),2.85-2.64(m,1H),1.92-1.76(m,3H),1.76-1.62(m,1H),1.52(br s,1H),1.42(br s,2H),0.85-0.68(m,2H),0.36(br s,2H)。MS(ESI)m/z=644.4(M+H)。HPLC纯度:100%;保留时间:2.36min。方法C。

[0412] 实施例414



中间体414-3(外消旋体)及手性414-4(手性峰-1)、手性414-5(手性峰-2)、手性414-6(手性峰-3)、手性414-7(手性峰-4)。



中间体414-1:将市售5-甲酰基-2-甲氧基苯甲酸甲酯(948mg,4.88mmol)溶解于EtOH(10mL)中且向此溶液中添加NMeNHOH.HCl(408mg,4.88mmol),随后添加K_2CO_3(675mg,4.88mmol)且在室温下搅拌反应混合物1h。添加水(100mL)且用EtOAc(2×25mL)萃取溶液,将合并的有机部分干燥($MgSO_4$)且在减压下蒸发成固体。将固体转移至小瓶中且添加甲苯(7mL),随后添加丙烯酸甲酯(3mL)且密封小瓶。在95℃加热反应混合物18h。在减压下浓缩经冷却的反应混合物且通过硅胶色谱纯化残余物。分离呈油状物的414-3(200mg,13%)。^{1}H

NMR(400MHz,$CDCl_3$)δ7.96(m,1H),7.88(m,1),7.02(d,J＝8.8Hz,1H),4.01-3.84(mss,8H),3.79-3.71(m,3H),3.17-3.01(m,3H),2.92-2.67(m,1H),2.07-1.81(m,2H)。MS(ESI)m/z＝310.0(M+H)。

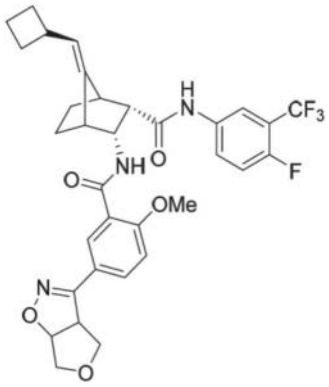
[0413] 中间体414-2:在Parr烧瓶中将产物414-1(49mg,0.158mmol)溶解于甲醇(5mL)中,且向其中添加10％Pd/C(20mg)且在60psi下氢化5h。经硅藻土垫过滤反应混合物且在减压下蒸发,得到呈油状物的5-(4-羟基-1-甲基-5-氧代吡咯烷-2-基)-2-甲氧基苯甲酸甲酯(35mg,79％)。^{1}H NMR(500MHz,CD_3OD)δ7.71(d,J＝2.4Hz,1H),7.50(dd,J＝8.7,2.4Hz,1H),7.18(d,J＝8.7Hz,1H),4.51-4.42(m,1H),4.38(t,J＝8.5Hz,1H),3.90(s,3H),3.86(s,3H),2.84(ddd,J＝13.1,8.4,6.9Hz,1H),2.58(s,3H),1.74(dt,J＝13.0,8.5Hz,1H)。MS(ESI)m/z＝280.2(M+H)。

[0414] 中间体414-3:将产物414-2(30mg)溶解于MeOH(1mL)中,且向此溶液中添加LiOH,随后添加水(1mL),且在室温下搅拌5h。添加稀释HCl,且将所得溶液在减压下浓缩为胶状固体。添加甲醇且过滤反应混合物且在减压下浓缩以产生414-3(20mg,71％产率)。MS m/z＝266.08(M+H)。

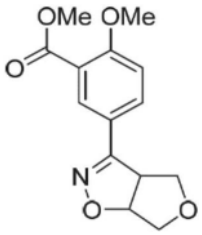
[0415] 手性中间体414-(4-7):在以下制备型条件下通过SFC分离414-3:仪器:Berger SFC(LVL-L4021Lab),柱:IG 25×3cm ID,5μm,温度:40℃,流动速率:85mL/min,移动相:82/18CO_2/MeOH-0.1％DEA,检测器波长:220nm,注射量:1200μL,得到手性414-4(峰-1,>99％de,分析型RT＝15.56min)、手性414-5(峰-2>95％de,分析型RT＝18.09min)、手性414-6(峰-3,>99％de,分析型RT＝26.38min)及手性414-7(峰-4,>95％de,分析型RT＝29.29min)。分析型色谱条件:仪器:Agilent SFC(LVL-L4021Lab),柱:IG 250×4.6mm ID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:80/20CO_2/MeOH-0.1％DEA

[0416] 通过针对实施例378所描述的偶合方法,使用环丙基降冰片烷基中间体166-2及中间体414-4来制备(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(4-羟基-1-甲基-5-氧代吡咯烷-2-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺同手性异构体-1414(48％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.89(d,J＝7.3Hz,1H),8.23(dd,J＝6.6,2.3Hz,1H),7.89(d,J＝2.1Hz,1H),7.84-7.67(m,1H),7.49(t,J＝9.2Hz,1H),7.44(d,J＝8.3Hz,1H),7.24(d,J＝8.5Hz,1H),4.70(d,J＝9.8Hz,1H),4.34(m,1H),4.20(br s,1H),4.02(s,3H),3.16(br dd,J＝10.7,4.0Hz,1H),3.09(br s,1H),2.80-2.63(m,2H),2.50-2.39(m,2H),1.94-1.74(m,2H),1.65-1.45(m,1H),1.45-1.24(m,2H),0.88-0.67(m,2H),0.36(br s,2H)。MS(ESI)m/z＝616.2(M+H)。HPLC纯度:100％;保留时间:2.12min。方法C。

[0417] 实施例416



中间体416-1:(外消旋体)及手性416-2(手性峰-1)、416-3(手性峰-2)。

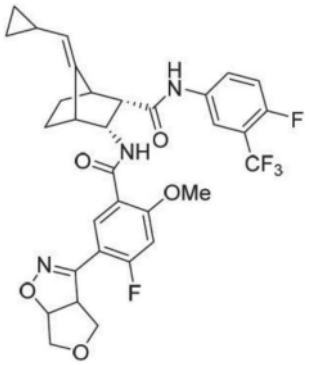


中间体416-1为以与针对中间体378-1所描述相同的方式制备(50%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.98(d,J=2.3Hz,1H),7.86(dd,J=8.8,2.4Hz,1H),7.04(d,J=8.7Hz,1H),5.38(dd,J=9.2,3.9Hz,1H),4.34-4.26(m,2H),4.20-4.09(m,1H),3.96(s,3H),3.91(s,3H),3.83-3.76(m,1H),2.92-2.70(m,1H)。MS(ESI)m/z=278.3(M+H)。

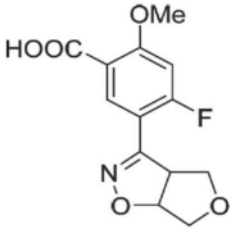
[0418] 416-2及416-3:通过手性SFC,通过以下制备型色谱方法将以下手性中间体与外消旋体DP39-1分离:仪器:Berger MG II柱:Chiralpak IA,21×250mm,5微米,移动相:20%MeOH/80%CO_2,流动条件:45mL/min,150巴,40℃,检测器波长:220nm,得到手性416-2(峰-1,>99%de,分析型RT=3.80min)及手性416-3(峰-2,>98%de,分析型RT=7.43min)。分析型色谱条件:仪器:Shimadzu Nexera SFC,柱:Chiralpak IA,4.6×100mm,3微米,移动相:20%MeOH/80%CO_2,流动条件:2.0mL/min,150巴,40℃,检测器波长:220nm,注射详情:5μL~1mg/mL于MeOH中。

[0419] 通过针对实施例378所描述的方法,使用环丁基降冰片烷基中间体369-1及中间体416-2来制备(1R,2S,3R,4R,Z)-7-(环丁基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺同手性异构体-2416(62%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.56(s,1H),9.93(dd,J=10.8,7.2Hz,1H),8.25-8.20(m,2H),7.84-7.76(m,2H),7.48(t,J=9.8Hz,1H),7.28(d,J=8.9Hz,1H),5.35(dd,J=9.0,3.2Hz,1H),4.70(d,J=9.5Hz,1H),4.54-4.41(m,2H),4.12-4.02(m,3H),3.90(br d,J=9.5Hz,1H),3.84-3.73(m,1H),3.50(br s,1H),3.16(br dd,J=10.8,4.4Hz,1H),3.11(br s,1H),2.73(br s,1H),2.56(s,4H),1.91-1.71(m,2H),1.50(br s,1H),1.42(br s,2H),0.87-0.68(m,2H),0.35(br s,2H)。MS(ESI)m/z=614.2(M+H)。HPLC纯度:100%;保留时间:2.42min。方法C。

[0420] 实施例419



中间体419-5(手性峰-1)及419-6(手性峰-2)



中间体419-1:向含4-氟-5-甲酰基-2-甲氧基苯甲酸甲酯(0.15g,0.68mmol)(Chen,Xiao-Yang,Sorensen,Eric,J.JACS,2018,140,2789-2792中所描述来制备)及NH_2OH HCl(48mg,0.68mmol)的DCM(10mL)中添加DIEA(0.12mL,0.68mmol)。24h之后,用水稀释反应混合物且通过过滤收集(E)-4-氟-5-((羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯白色固体(0.15g,96%),干燥且按原样使用。^{1}H NMR(400MHz,$CDCl_3$)δ8.53-8.37(m,1H),8.33-8.22(m,2H),6.79-6.61(m,1H),3.94(s,3H),3.91(s,3H)。MS(ESI)m/z 228.2$(M+H)^+$。

[0421] 中间体419-2:向中间体419-1(0.15g,0.66mmol)及DMF(1mL)中添加NCS(88mg,0.66mmol)。24h之后,用水(20mL)及乙酸乙酯(50mL)分配反应混合物。用乙酸乙酯(2×20mL)萃取水层。将合并的有机层用盐水(15mL)洗涤且干燥(Na_2SO_4),得到固体。向含固体的DCM(3mL)中添加2,5-二氢呋喃(0.46g,6.6mmol)及TEA(0.1mL,0.66mmol)。24h之后,将反应混合物用水(20mL)淬灭且用DCM(3×30mL)萃取。将合并的有机层用盐水(15mL)洗涤且干燥($MgSO_4$)。经由硅胶色谱,使用己烷/EtOAc作为洗脱剂纯化残余物,得到呈茶色固体的4-氟-2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酸甲酯(0.13g,66%)。MS(ESI)m/z=296.2$(M+H)^+$。

[0422] 手性中间体419-3及419-4:中间体419-2为在具有ChiralpakIA,21×250mm柱的Jasco SFC Prep上,用20%MeOH/80%CO_2洗脱(45mL/min,150巴,40℃,检测器波长267nm)分离,得到419-3(33mg,0.11mmol,17%产率)(峰-1,99%ee,分析型RT=1.693min.);^{1}H NMR(400MHz,$CDCl_3$)δ8.45(d,J=8.8Hz,1H),6.75(d,J=13.2Hz,1H),5.39(dd,J=9.1,3.9Hz,1H),4.40(dt,J=4.6,2.3Hz,1H),4.34(d,J=10.8Hz,1H),4.11(br d,J=9.7Hz,1H),3.97(s,3H),3.91(s,3H),3.86(dd,J=9.7,6.8Hz,1H),3.79(dd,J=10.8,4.0Hz,1H);419-4(32mg,0.11mmol,6%产率)(峰-2,99%ee,分析型RT=5.463min.);^{1}H NMR(400MHz,$CDCl_3$)δ8.45(d,J=8.6Hz,1H),6.75(d,J=13.4Hz,1H),5.39(dd,J=9.5,4.0Hz,1H),4.46-4.38(m,1H),4.34(d,J=11.0Hz,1H),4.16-4.09(m,1H),3.97(s,3H),3.91(s,3H),3.86(dd,J=9.7,6.8Hz,1H),3.79(dd,J=10.8,4.0Hz,1H)。分析型色谱条件:仪器:Shimadzu NexeraSFC,柱:ChiralpakIC,4.6×100mm,3微米,移动相:20%甲醇/80%CO_2,流

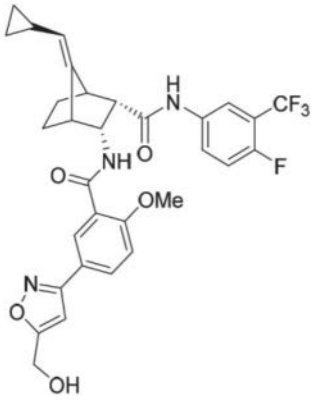
动条件:2.0mL/min,150巴,40℃,检测器波长:220nm

[0423] 中间体419-5:向冷却至0℃的含419-3(33mg,0.11mmol)的THF(2mL)/MeOH(0.1mL)中添加2M LiOH水溶液(0.17ml,0.34mmol)。搅拌18h之后,将反应物用稀释HCl(10mL)淬灭且用EtOAc(3×30mL)萃取。将合并的有机层用盐水(15mL)洗涤,干燥($MgSO_4$),过滤且浓缩,得到呈白色固体的419-5(31mg,0.11mmol,99%产率)。^{1}H NMR(600MHz,DMSO-d6)δ12.90(br s,1H),8.07(d,J=8.7Hz,1H),7.17(d,J=13.8Hz,1H),5.34(dd,J=9.2,3.7Hz,1H),4.49-4.42(m,1H),4.09(d,J=10.7Hz,1H),3.90(br d,J=9.7Hz,1H),3.88(s,3H),3.73(dd,J=9.5,6.9Hz,1H),3.64(dd,J=10.8,3.7Hz,1H)。LCMS(ESI)m/z=282.2(M+H)$^+$。

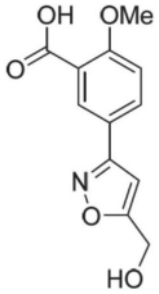
[0424] 中间体419-6:419-6(30mg,0.11mmol,96%产率)为以与419-5类似的方式,以419-3取代419-4来制备。^{1}H NMR(400MHz,$CDCl_3$)δ8.62(d,J=8.6Hz,1H),6.86(d,J=12.5Hz,1H),5.40(dd,J=9.2,4.0Hz,1H),4.55-4.28(m,2H),4.11(s,3H),4.08(s,1H),3.87(dd,J=9.7,6.8Hz,1H),3.79(dd,J=10.8,4.0Hz,1H)。LCMS(ESI)m/z=282.2(M+H)$^+$。

[0425] 实施例419.以与实施例378类似的方式,通过使用环丙基降冰片烷基中间体20-4及中间体419-5来制备(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(4-氟-2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺419(5.9mg,67%产率)。^{1}H NMR(500MHz,DMSO-d_6)δ10.67-10.38(m,1H),9.89(br d,J=7.0Hz,1H),8.33(br d,J=8.9Hz,1H),8.20(br d,J=4.0Hz,1H),7.85-7.71(m,1H),7.48(br t,J=9.8Hz,1H),7.22(br d,J=13.1Hz,1H),5.35(br dd,J=9.5,3.4Hz,1H),4.69(br d,J=9.5Hz,1H),4.52-4.36(m,2H),4.10(br d,J=10.7Hz,1H),4.05(s,3H),3.77-3.66(m,1H),3.66-3.54(m,2H),3.22-3.12(m,1H),3.09(br s,1H),2.72(br s,1H),1.90-1.79(m,1H),1.79-1.66(m,1H),1.50(br dd,J=8.5,4.3Hz,1H),1.45-1.32(m,2H),0.87-0.61(m,2H),0.35(br d,J=2.7Hz,2H)。HPLC纯度98%。分析型LC-MS:2.48min;MS(ESI)m/z=631.9(M+H)$^+$。方法B。

[0426] 实施例423



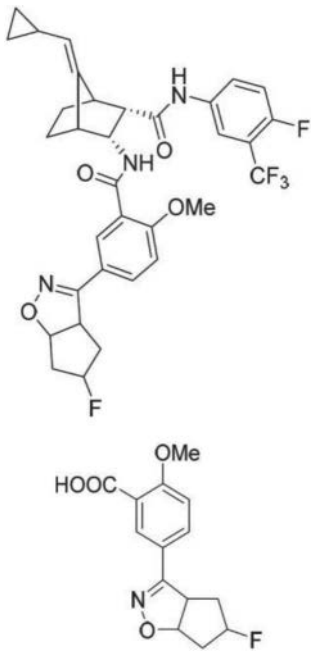
中间体423-1



中间体423-1为以针对中间体378-3所描述的相同方式制备,在此情况下为通过用炔丙醇取代烯丙醇来制备。^{1}H NMR(500MHz,CD_3OD)δ8.28(d,J＝2.3Hz,1H),8.01(dd,J＝8.7,2.3Hz,1H),7.27(d,J＝8.7Hz,1H),6.75(s,1H),4.91-4.82(m,5H),4.73(s,2H),4.00-3.96(m,3H)。MS(ESI)m/z＝250.3(M+H)。

[0427] 通过针对实施例378所描述的偶合方法,使用降冰片烷基中间体20-4及中间体423-1来制备(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(羟基甲基)异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺423(77%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.56(s,1H),9.95(br d,J＝7.0Hz,1H),8.40(d,J＝1.8Hz,1H),8.19(br d,J＝4.3Hz,1H),7.97(dd,J＝8.5,2.1Hz,1H),7.77(br d,J＝8.9Hz,1H),7.46(br t,J＝9.8Hz,1H),7.32(d,J＝8.5Hz,1H),6.84(s,1H),4.69(d,J＝9.8Hz,1H),4.61(d,J＝5.8Hz,2H),4.45(br s,1H),4.05(s,3H),3.21-3.06(m,2H),2.72(br s,1H),1.92-1.73(m,2H),1.62-1.45(m,1H),1.41(br s,2H),0.84-0.67(m,2H),0.35(br d,J＝4.3Hz,2H)。MS(ESI)m/z＝600.1(M+H)。HPLC纯度:100%;保留时间:2.39min;方法B。

[0428] 实施例427



制备5-(5-氟-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯(非镜像异构体混合物)。向含406-1酯(0.1g,0.3mmol)的DCM(2mL)中添加DAST(0.05mL,0.412mmol)。24h之后,在减压下浓缩反应混合物且通过硅胶色谱纯化,得到呈透明膜形式的相应氟化物(66mg,0.23mmol,66%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ8.06(d,J＝2.4Hz,1H),7.88(dd,J＝8.7,2.3Hz,1H),7.06(d,J＝8.8Hz,1H),5.53-5.38(m,1H),4.25(dd,J＝9.5,

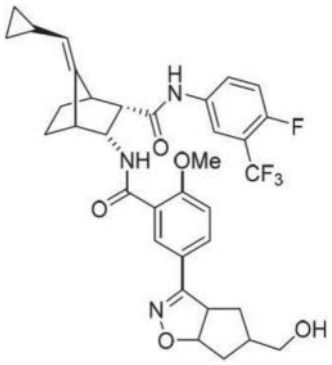
2.0Hz,1H),4.01-3.97(m,4H),3.94-3.92(m,3H),2.76-2.47(m,2H),2.33-2.12(m,1H),2.10-1.90(m,1H)。LCMS(ESI)m/z=294.2(M+H)$^+$。

[0429] 中间体427-2:制备5-(5-氟-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸。向含中间体427-1(14mg,0.048mmol)的THF(1mL)中添加2M LiOH水溶液(72μl,0.14mmol)。24h之后,添加稀释HCl(10mL)且用EtOAc(3×30mL)萃取溶液。将合并的有机层用盐水(15mL)洗涤,干燥($MgSO_4$),过滤,且在减压下浓缩,得到427-2(13mg,0.047mmol,98%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ8.28(d,J=2.2Hz,1H),8.13(dd,J=8.8,2.4Hz,1H),7.20-7.12(m,1H),5.95-5.83(m,1H),5.45(ddd,J=10.0,6.8,4.7Hz,1H),5.38-5.18(m,1H),4.28(td,J=9.4,7.5Hz,1H),4.16(s,3H),2.75-2.55(m,2H),2.32-2.17(m,1H),2.06-1.92(m,1H)。LCMS(ESI)m/z=280.2(M+H)$^+$。

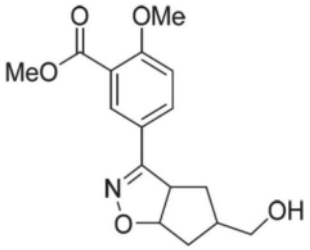
[0430] 通过使用环丙基降冰片烷基中间体20-4及中间体427-2,以与实施例378类似的方式,使用环丙基降冰片烷基中间体20-4来制备(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-氟-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物427(5.7mg,9.1μmol,67%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.69-10.39(m,1H),9.92(br t,J=7.0Hz,1H),8.49-8.08(m,2H),7.91-7.71(m,2H),7.50(br t,J=9.6Hz,1H),7.29(d,J=8.9Hz,1H),5.45-5.26(m,1H),4.71(br d,J==9.2Hz,1H),4.46(br s,1H),4.39-4.30(m,1H),4.06(d,J==2.4Hz,3H),3.41(br s,1H),3.18(br dd,J=10.8,3.5Hz,1H),3.12(br s,1H),2.74(br s,1H),2.51-2.35(m,2H),2.17-2.06(m,1H),2.06-2.00(m,1H),1.92-1.84(m,1H),1.80(br d,J==11.3Hz,1H),1.61-1.50(m,1H),1.49-1.36(m,2H),0.86-0.68(m,2H),0.37(br s,2H)。HPLC纯度100%。分析型LC-MS:2.65min;MS(ESI)m/z=630.3(M+H)$^+$。方法B。

[0431] 428为以与实施例379类似的方式,通过使用环丙基降冰片烷基中间体20-4及中间体428-1来制备(6.1mg,69%产率)。^{1}H NMR。HPLC纯度100%。分析型LC-MS:2.84min;MS(ESI)m/z=638.2(M+H)$^+$。方法B。

[0432] 实施例429

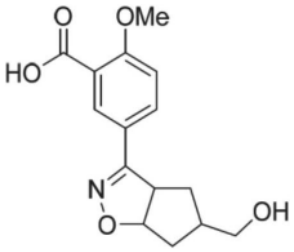


中间体429-1:制备5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯。



中间体429-1为以针对中间体378-3所描述的相同方式制备(75％产率),在此情况下为通过用环戊-3-烯-1-基甲醇取代烯丙醇来制备。

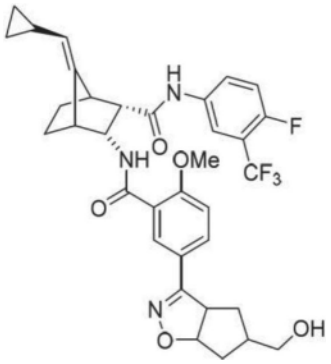
[0433] 中间体429-2:制备5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸。



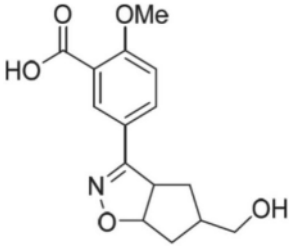
将5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯(58mg,0.22mmol)溶解于THF(1mL)/MeOH(1mL)中,在室温下用含LiOH单水合物(36mg,0.86mmol)的H_2O(1mL)处理。3h之后,用H_2O(5mL)稀释反应混合物且释放有机物。用1M HCl溶液将剩余水层的pH调节至pH 7,用EtOAc(2×25mL)萃取,用盐水洗涤,干燥(Na_2SO_4),过滤且蒸发,得到中间体429-2(62mg,74.2％)。甲酸不经进一步纯化即继续用于下一反应。MS(ESI)m/z＝292.3(M+H)。

[0434] 实施例429为通过使中间体429-2(3.95mg,0.014mmol)与溶解于无水THF(2mL)中的中间体166-2(5mg,0.014mmol)在DIEA(0.012mL,0.068mmol)及BOP(6.60mg,0.015mmol)存在下偶合来制备。3h之后,过滤反应混合物且通过反相制备型HPLC纯化,得到所需产物(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物429(5.1mg,0.0079mmol,58％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.53(s,1H),9.90(br d,J＝6.4Hz,1H),8.23-8.17(m,2H),7.81-7.74(m,2H),7.46(br t,J＝9.8Hz,1H),7.26(d,J＝8.9Hz,1H),5.15-5.07(m,1H),4.68(br d,J＝9.5Hz,1H),4.42(br s,1H),4.20-4.14(m,1H),4.02(s,3H),3.58-3.47(m,2H),3.39-3.18(m,2H),3.17-3.06(m,2H),2.73-2.68(m,1H),1.99-1.73(m,5H),1.66-1.59(m,1H),1.56-1.37(m,4H),0.78-0.68(m,2H),0.38-0.29(m,2H)。HPLC纯度:99.2％。分析型LC-MS:2.53min;MS(ESI)m/z＝642.2(M+H);方法B。

[0435] 实施例430



中间体429-4(手性峰-1)、429-6(手性峰-2)、429-8(手性峰-3)及429-10(手性峰4)



通过非镜像异构混合物中间体429(524.9mg,1.72mmol)的手性SFC获得个别手性非镜像异构体酯中间体429-4A、429-6A、429-8A及429-10A。手性SFC制备型色谱条件:仪器:BergerMGII(SFC);柱:ChiralpakAD-H,21×250mm,5微米;移动相:15%MeOH/85%CO_2;流动条件:45mL/min,150巴,40℃;检测器波长:210nm;注射详情:0.5mL～35mg/mL于MeOH中。分析型色谱条件:仪器:ShimadzuNexera SFC;柱:Chiralpak AD-H,4.6×100mm,3微米;移动相:15%MeOH/85%CO_2;流动条件:2.0mL/min,150巴,40℃;检测器波长:220nm;注射详情:5μL～1mg/mL于MeOH中。

[0436] 获得呈膜形式的中间体429-4A(峰-1,>99%de,分析型RT=4.02min)(152.8mg,29.1%)。^{1}H NMR(600MHz,$CDCl_3$)δ8.04(d,J=2.3Hz,1H),7.87(dd,J=8.7,2.3Hz,1H),7.01(d,J=8.8Hz,1H),5.23(dd,J=8.8,5.1Hz,1H),4.10(t,J=8.7Hz,1H),3.94(s,3H),3.90(s,3H),3.72-3.66(m,1H),3.61(dt,J=10.5,5.2Hz,1H),2.30-2.16(m,2H),2.05(dd,J=13.0,6.1Hz,1H),1.76(ddd,J=12.9,11.5,9.4Hz,1H),1.68-1.62(m,1H),1.39(br t,J=4.8Hz,1H)。

[0437] 中间体429-4(104.4mg,78%)为以与中间体429-2类似的方式,通过水解中间体429-4A来制备。MS(ESI)m/z=292.3(M+H)。

[0438] 获得呈膜形式的中间体429-6A(峰-2,>99%de,分析型RT=4.56min)(33.2mg,6.3%)。^{1}H NMR(600MHz,$CDCl_3$)δ8.05(d,J=2.3Hz,1H),7.87(dd,J=8.8,2.3Hz,1H),7.02(d,J=8.8Hz,1H),5.25(ddd,J=10.1,6.2,4.2Hz,1H),4.04-3.98(m,1H),3.94(s,3H),3.90(s,3H),3.63-3.57(m,1H),3.56-3.50(m,1H),2.38-2.26(m,3H),1.92-1.85(m,1H),1.73-1.66(m,1H),1.51(t,J=5.3Hz,1H)。

[0439] 中间体429-6(20.2mg,92%)为以与中间体429-2类似的方式,通过水解中间体429-6来制备。MS(ESI)m/z=292.3(M+H)。

[0440] 获得呈膜形式的中间体429-8A(峰-3,>99%de,分析型RT=5.67min)(160.8mg,30.6%)。^{1}H NMR:(600MHz,$CDCl_3$)δ8.05-8.03(m,1H),7.86(dd,J=8.7,2.3Hz,1H),7.01(d,

J＝8.8Hz,1H),5.23(dd,J＝8.7,5.2Hz,1H),4.10(t,J＝8.7Hz,1H),3.94(s,3H),3.90(s,3H),3.69(br dd,J＝10.6,5.2Hz,1H),3.63-3.58(m,1H),2.28-2.17(m,2H),2.05(br dd,J＝12.9,6.2Hz,1H),1.76(ddd,J＝13.0,11.5,9.4Hz,1H),1.64-1.60(m,1H),1.49(br s,1H)。

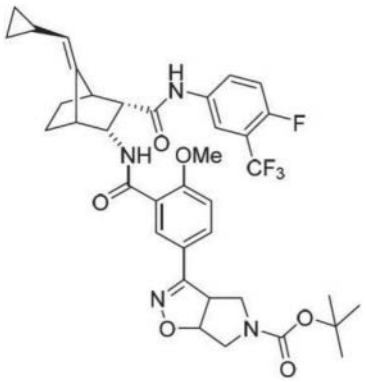
[0441] 中间体429-8(121mg,85％)为以与中间体429-2类似的方式,通过水解中间体429-8a来制备。MS(ESI)m/z＝292.3(M+H)。

[0442] 获得呈膜形式的中间体429-10A(峰-4,>99％de,分析型RT＝9.78min)(47.1mg,9.0％)。^{1}H NMR:(600MHz,$CDCl_3$)δ8.04(d,J＝2.3Hz,1H),7.87(dd,J＝8.7,2.3Hz,1H),7.02(d,J＝8.8Hz,1H),5.24(ddd,J＝10.1,6.2,4.2Hz,1H),4.03-3.98(m,1H),3.94(s,3H),3.90(s,3H),3.63-3.57(m,1H),3.56-3.49(m,1H),2.38-2.25(m,3H),1.91-1.85(m,1H),1.72-1.66(m,1H),1.55(br s,1H)。

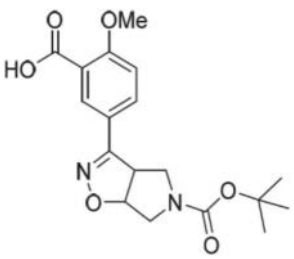
[0443] 中间体429-10(18.2mg,51.6％)为以与中间体429-2类似的方式,通过水解中间体429-10A来制备。MS(ESI)m/z＝292.3(M+H)。

[0444] 实施例430为以与实施例429类似的方式,用中间体429-4(来自SFC的峰-1)来制备。(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺同手性异构体-1(10.5mg,0.016mmol,60.3％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.53(s,1H),9.90(br d,J＝7.0Hz,1H),8.23-8.18(m,2H),7.81-7.75(m,2H),7.47(br t,J＝9.5Hz,1H),7.26(d,J＝8.5Hz,1H),5.11(br dd,J＝8.2,5.5Hz,1H),4.68(d,J＝9.8Hz,1H),4.46-4.39(m,1H),4.22-4.13(m,1H),4.03(s,3H),3.49-3.28(m,1H),3.19-3.05(m,2H),2.73-2.68(m,1H),1.98(br dd,J＝13.6,5.0Hz,1H),1.93-1.74(m,4H),1.69-1.60(m,1H),1.58-1.36(m,4H),0.77-0.68(m,2H),0.37-0.30(m,2H)。HPLC纯度:100％。分析型LC-MS:2.3min;MS(ESI)m/z＝642.3(M+H);方法B。

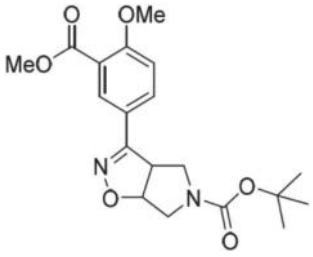
[0445] 实施例434



中间体434-2(非镜像异构混合物)



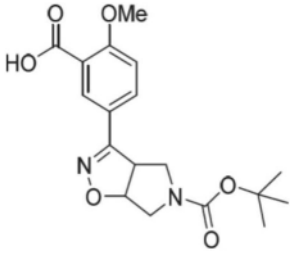
中间体434-1:制备3-(4-甲氧基-3-(甲氧基羰基)苯基)-3a,4,6,6a-四氢-5H-吡咯并[3,4-d]异噁唑-5-甲酸叔丁酯。



[0446] 中间体434-1(499.5mg,46%)为通过针对中间体429-1所描述的方法制备,在此情况下为通过用2,5-二氢-1H-吡咯-1-甲酸叔丁酯取代环戊-3-烯-1-基甲醇来制备。^{1}H NMR:(400MHz,$CDCl_3$)δ7.99(d,J=2.4Hz,1H),7.84(dd,J=8.7,2.3Hz,1H),7.04(d,J=8.8Hz,1H),5.31(ddd,J=9.2,5.4,1.2Hz,1H),4.21(br dd,J=12.4,9.1Hz,1H),3.96(s,3H),3.91(s,3H),3.72-3.61(m,2H),1.43(s,9H)。MS(ESI)m/z=377.4(M+H)。

[0447] 中间体434-2:制备5-(5-(叔丁氧基羰基)-3a,5,6,6a-四氢-4H-吡咯并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酸。434-2(151.4mg,43.7%,经三个步骤)为通过针对中间体429-2所描述的方法,用中间体434-1置换中间体429-1来制备。MS(ESI)m/z=363.4(M+H)。

[0448] 中间体434-4及434-6(同手性)



中间体434-3及434-4为通过非镜像异构混合物中间体434-2(499mg,1.33mmol)的手性SFC获得。手性SFC制备型色谱条件:仪器:Berger MG II(SFC);柱:Regis Whelk-01,21×250mm,5微米;移动相:15%MeOH/85%CO_2;流动条件:45mL/min,150巴,40℃;检测器波长:220nm;注射详情:1.0mL~31mg/mL于MeOH-ACN中。分析型色谱条件:仪器:ShimadzuNexera SFC;柱:Regis Whelk-01,4.6×100mm,3微米;移动相:15%MeOH/85%CO_2;流动条件:2.0mL/min,150巴,40℃;检测器波长:220nm;注射详情:5μL~1mg/mL于乙腈。

[0449] 获得呈白色固体的中间体434-3(峰-1,>99%de,分析型RT=4.02min)(95.9mg,19.2%产率)。^{1}H NMR:(600MHz,$CDCl_3$)δ7.99(d,J=2.3Hz,1H),7.86-7.82(m,1H),7.04(br d,J=8.7Hz,1H),5.31(ddd,J=9.2,5.4,1.3Hz,1H),4.24-4.18(m,1H),4.01-3.93(m,4H),3.91(s,3H),3.83-3.76(m,1H),3.71-3.67(m,1H),3.63(br s,1H),1.43(br s,9H)。

[0450] 中间体434-4.制备5-(5-(叔丁氧基羰基)-3a,5,6,6a-四氢-4H-吡咯并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酸。中间体434-4(52mg,67.5%产率)为以与中间体434-2类似的方式,通过水解中间体434-3来制备。MS(ESI)m/z=363.1(M+H)。

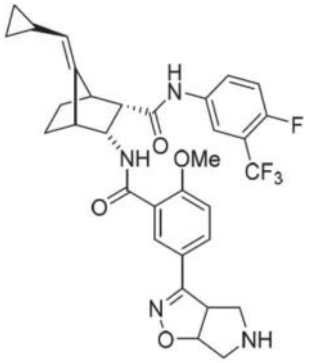
[0451] 获得呈白色固体的中间体434-5(峰-2,99.6%de,分析型RT=4.56min)(96.7mg,19.4%产率)。1H NMR(600MHz,$CDCl_3$)δ7.98(d,J=2.3Hz,1H),7.83(dd,J=8.8,2.2Hz,1H),7.03(d,J=8.7Hz,1H),5.32-5.28(m,1H),4.21(td,J=8.8,4.0Hz,1H),4.01-3.94(m,

1H),3.95(s,3H),3.90(s,3H),3.83-3.73(m,1H),3.68(dd,J＝11.4,8.9Hz,1H),3.65-3.58(m,1H),1.43(s,9H)。

[0452] 中间体434-6.制备5-(5-(叔丁氧基羰基)-3a,5,6,6a-四氢-4H-吡咯并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酸。中间体434-6(48mg,62.3％产率)为以与中间体434-2类似的方式,通过水解中间体434-5来制备。MS(ESI)m/z＝363.1(M+H)。

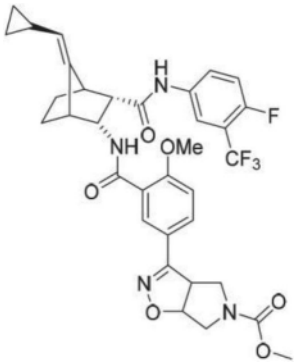
[0453] 实施例434为以与实施例429类似的方式,用中间体434-2置换中间体429-2来制备。3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-3a,4,6,6a-四氢-5H-吡咯并[3,4-d]异噁唑-5-甲酸叔丁酯非镜像异构混合物434(7.1mg,0.0098mmol,72.3％产率,非镜像异构混合物)。^{1}H NMR(500MHz,DMSO-d6)δ10.53(s,1H),9.91(br d,J＝6.7Hz,1H),8.21(br s,2H),7.78(br d,J＝7.0Hz,2H),7.47(br t,J＝9.5Hz,1H),7.28(d,J＝8.5Hz,1H),5.25(br dd,J＝8.9,4.9Hz,1H),4.68(br d,J＝9.5Hz,1H),4.46-4.39(m,2H),4.04(d,J＝3.1Hz,3H),3.80-3.69(m,1H),3.15(br dd,J＝11.0,3.7Hz,1H),3.10(br d,J＝3.4Hz,1H),2.73-2.68(m,1H),1.90(s,1H),1.85-1.74(m,2H),1.55-1.15(m,14H),0.79-0.67(m,2H),0.40-0.24(m,2H)。HPLC纯度:98.5％。分析型LC-MS:2.81min;MS(ESI)m/z＝713.2(M+H);方法B。

[0454] 实施例437



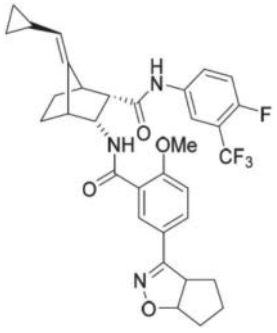
通过使中间体434-2(9.84mg,0.027mmol)与溶解于无水THF(2mL)中的中间体166-2(10mg,0.027mmol)在DIEA(0.024mL,0.136mmol)及BOP(13.21mg,0.030mmol)存在下偶合来制备。1h之后,浓缩反应混合物,溶解于DCM(1mL)中,且用50％TFA/DCM(1mL)处理。1h之后,在减压下浓缩反应混合物且通过反相制备型HPLC纯化,得到437(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(3a,5,6,6a-四氢-4H-吡咯并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物(10.3mg,0.0140mmol,51.5％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.58-10.55(m,1H),9.94(dd,J＝18.8,7.1Hz,1H),8.25(dd,J＝10.2,2.0Hz,1H),8.22-8.17(m,1H),7.83-7.78(m,1H),7.78-7.74(m,1H),7.46(br t,J＝9.5Hz,1H),7.29(d,J＝8.7Hz,1H),5.43(dd,J＝9.3,4.6Hz,1H),4.69-4.64(m,2H),4.44-4.37(m,1H),4.04(d,J＝1.7Hz,3H),3.72-3.65(m,2H),3.46-3.38(m,1H),3.16-3.11(m,1H),3.09-3.05(m,1H),2.73-2.68(m,1H),1.83-1.70(m,2H),1.51-1.34(m,4H),0.76-0.66(m,2H),0.33(br d,J＝3.2Hz,2H)。HPLC纯度:98.6％。分析型LC-MS:2.32min;MS(ESI)m/z＝613.2(M+H);方法C。

[0455] 实施例438

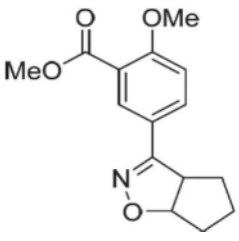


将中间体434-2(9.84mg,0.027mmol)及环丙基降冰片烷基中间体166-2(10mg,0.027mmol)溶解于无水THF(2.0mL)中,接着添加DIEA(0.024mL,0.136mmol)及BOP(13.21mg,0.030mmol)。2h之后,浓缩反应混合物,将所得残余物再溶解于DCM(0.25mL)中,且用50％TFA/DCM(0.25mL)处理。1h之后,将反应混合物浓缩至干燥。将胺溶解于THF(2.0mL)中且在0℃用TEA(0.019mL,0.13mmol)处理,随后用氯甲酸甲酯(2.6mg,0.027mmol)处理。在室温下搅拌2h之后,在减压下浓缩反应混合物且通过制备型RP-HPLC纯化,得到3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-3a,4,6,6a-四氢-5H-吡咯并[3,4-d]异噁唑-5-甲酸甲酯(非镜像异构混合物)438(2.6mg,0.0036mmol,14.2％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.92(br t,J＝6.1Hz,1H),8.18(br s,2H),7.81-7.74(m,2H),7.45(br t,J＝9.8Hz,1H),7.29-7.26(m,1H),5.28(br dd,J＝8.5,4.9Hz,1H),4.68(br d,J＝9.5Hz,1H),4.48-4.38(m,2H),4.03(d,J＝3.1Hz,2H),3.81-3.74(m,1H),3.64-3.48(m,4H),3.17-3.06(m,2H),2.73-2.66(m,1H),1.84-1.72(m,2H),1.52-1.33(m,4H),0.77-0.67(m,2H),0.33(br d,J＝3.4Hz,2H)。HPLC纯度:99.1％。分析型LC-MS:2.48min;MS(ESI)m/z＝671.1(M+H);方法B。

[0456] 实施例439



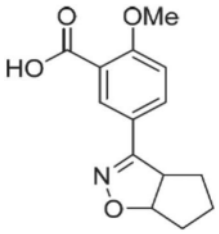
中间体439-1:制备2-甲氧基-5-(3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酸甲酯。



中间体439-1为以针对中间体378-3所描述的相同方式制备(128mg,23％产率),在

此情况下为通过用环戊烯取代烯丙醇来制备。

[0457] 中间体439-2:制备2-甲氧基-5-(3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酸。



中间体439-2(45.2mg,60.3%)为以与中间体429-2类似的方式,通过水解中间体439-1来制备。MS(ESI)m/z=262.2(M+H)。

[0458] 通过非镜像异构混合物中间体439-1(128mg,0.465mmol)的手性SFC获得个别手性非镜像异构体酯中间体439-4A(手性峰-1)及439-6A(手性峰-2)。手性SFC制备型色谱条件:仪器:Jasco SFC Prep;柱:Chiralpak OJ-H,21×250mm,5微米;移动相:5%IPA/95%CO_2;流动条件:45mL/min,150巴,40℃;检测器波长:220nm;注射详情:0.5mL~35mg/mL于IPA-ACN中。分析型色谱条件:仪器:Shimadzu Nexera SFC;柱:Chiralpak OJ-H,4.6×100mm,3微米;移动相:10%IPA/90%CO_2;流动条件:2.0mL/min,150巴,40℃;检测器波长:220nm;注射详情:5μL~1mg/mL于MeOH中。

[0459] 获得呈膜形式的中间体439-4A(峰-1,>99%de,分析型RT=2.84min)(48.8mg,38.1%)。^{1}H NMR:(400MHz,氯仿-d)δ8.06(d,J=2.4Hz,1H),7.86(dd,J=8.8,2.2Hz,1H),7.01(d,J=8.8Hz,1H),5.21(dd,J=8.8,4.6Hz,1H),4.03(td,J=8.4,3.0Hz,1H),3.94(s,3H),3.90(s,3H),2.21-2.14(m,1H),1.94-1.85(m,2H),1.83-1.72(m,2H),1.60-1.47(m,1H)。

[0460] 中间体439-4(41.9mg,90%)为以与中间体429-2类似的方式,通过水解中间体439-4A来制备。MS(ESI)m/z=262.3(M+H)。

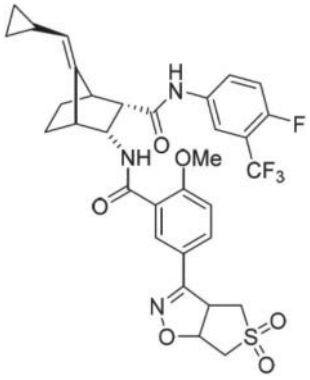
[0461] 获得呈膜形式的中间体439-6A(峰-2,>95%de,分析型RT=3.60min)(51.5mg,40.2%)。^{1}H NMR:(400MHz,$CDCl_3$)δ8.06(d,J=2.4Hz,1H),7.86(dd,J=8.8,2.4Hz,1H),7.01(d,J=8.8Hz,1H),5.21(dd,J=8.8,4.6Hz,1H),4.07-4.00(m,1H),3.94(s,3H),3.90(s,3H),2.21-2.15(m,1H),1.94-1.87(m,2H),1.83-1.71(m,2H),1.60-1.49(m,1H)。

[0462] 中间体439-6(45.3mg,93%)为以与中间体429-2类似的方式,通过水解中间体439-6A来制备。MS(ESI)m/z=262.3(M+H)。

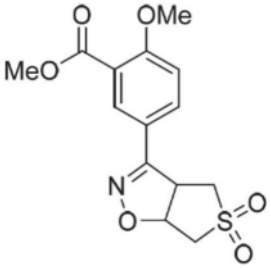
[0463] 实施例439为以与实施例429类似的方式,用中间体439-2置换中间体429-2来制备。(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物439(6.2mg,0.010mmol,74.2%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.57-10.50(m,1H),9.93-9.85(m,1H),8.23-8.17(m,2H),7.80-7.73(m,2H),7.49-7.44(m,1H),7.28-7.24(m,1H),5.16-5.09(m,1H),4.71-4.66(m,1H),4.46-4.37(m,1H),4.18-4.12(m,1H),4.05-3.99(m,3H),3.17-3.06(m,2H),2.73-2.67(m,1H),1.99-1.90(m,1H),1.86-1.63(m,6H),1.52-1.26(m,4H),0.78-0.68(m,2H),0.39-0.29(m,2H)。HPLC纯度:99.4%。分析型LC-MS:2.82min;MS(ESI)m/z 612.2(M+H);方法B。

[0464] 以与实施例429类似的方式,用中间体439-6(来自SFC的峰-2)置换中间体429-2来制备。(1R,2S,3R,4R,X)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺同手性异构体-2,441(10.9mg,0.017mmol,63.1%产率)。^{1}H NMR。HPLC纯度:100%。分析型LC-MS:2.71min;MS(ESI)m/z=612.3(M+H);方法B。

[0465] 实施例442

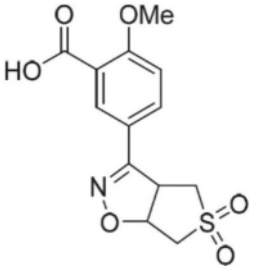


中间体442-1:制备5-(5,5-二氧代-3a,4,6,6a-四氢噻吩并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯。



中间体442-1为以针对中间体378-3所描述的相同方式制备(128mg,23%产率),在此情况下为通过用2,5-二氢噻吩1,1-二氧化物取代烯丙醇来制备。

[0466] 中间体442-2:制备5-(5,5-二氧代-3a,4,6,6a-四氢噻吩并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酸。



中间体442-2(59.0mg,39.6%)为以与中间体429-2类似的方式,通过水解中间体442-1来制备。MS(ESI)m/z=312.2(M+H)。

[0467] 通过非镜像异构混合物中间体441-1的手性SFC获得个别手性非镜像异构体酯中间体442-4A及442-6A(600mg,1.84mmol)。手性SFC制备型色谱条件:仪器:PIC Solution SFC Prep-200;柱:Chiralcel OD-H,21×250mm,5微米;移动相:25%MeOH/75%CO_2;流动条件:45mL/min,150巴,40℃;检测器波长:271nm;注射详情:1.0mL~50mg/mL于MeOH:ACN中。分析型色谱条件:仪器:Shimadzu Nexera SFC;柱:Chiralcel OD-H,4.6×100mm,3微米;移

动相:15％MeOH/85％CO_2;流动条件:2.0mL/min,150巴,40℃;检测器波长:220nm;注射详情:5μL～1mg/mL于MeOH中。

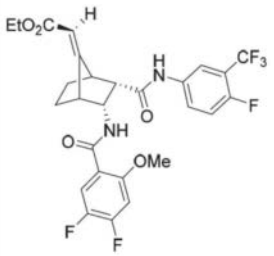
[0468] 获得呈白色固体的中间体442-4A(峰-1,>99％de,分析型RT＝3.74min)(108.1mg,18％)。^{1}H NMR:(400MHz,氯仿-d)δ7.96(d,J＝2.4Hz,1H),7.85(dd,J＝8.8,2.2Hz,1H),7.07(d,J＝9.0Hz,1H),5.43(ddd,J＝10.1,7.2,4.1Hz,1H),4.52-4.44(m,1H),3.97(s,3H),3.92(s,3H),3.66-3.47(m,3H),3.14(dd,J＝13.6,8.1Hz,1H)。

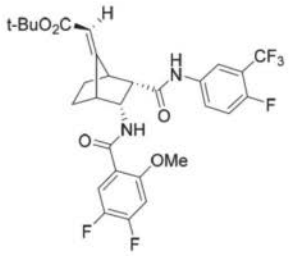
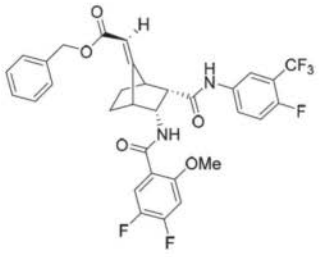
[0469] 中间体442-4(82mg,79％)为以与中间体429-2类似的方式,通过水解中间体442-4A来制备。MS(ESI)m/z＝312.3(M+H)。

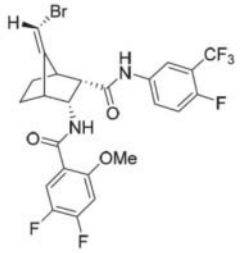
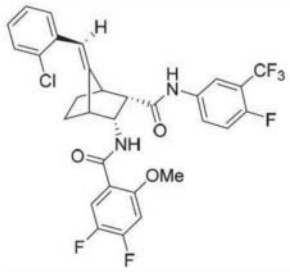
[0470] 获得呈白色固体的中间体442-6A(峰-2,>99％de,分析型RT＝5.44min)(108.8mg,18％)。^{1}H NMR:(400MHz,氯仿-d)δ7.96(d,J＝2.4Hz,1H),7.85(dd,J＝8.8,2.2Hz,1H),7.06(d,J＝8.8Hz,1H),5.42(ddd,J＝10.1,7.2,4.1Hz,1H),4.52-4.44(m,1H),3.97(s,3H),3.91(s,3H),3.66-3.46(m,3H),3.14(dd,J＝13.6,8.4Hz,1H)。

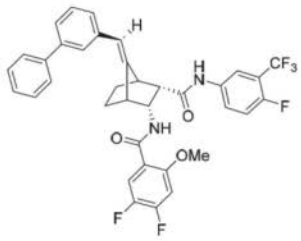
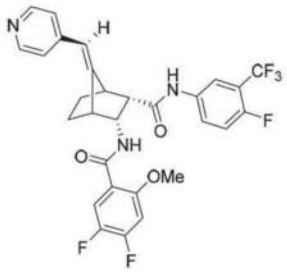
[0471] 中间体442-6(89.6mg,87％)为以与中间体429-2类似的方式,通过水解中间体442-6A来制备。MS(ESI)m/z＝312.3(M+H)。

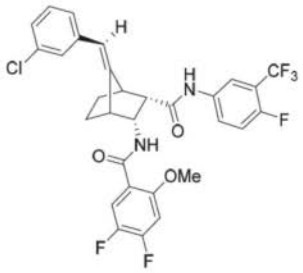
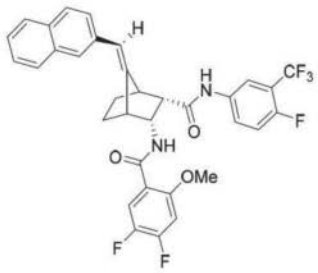
[0472] 实施例442为以与实施例429类似的方式,用中间体442-2置换中间体429-2来制备。(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(5-(5,5-二氧代-3a,4,6,6a-四氢噻吩并[3,4-d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺非镜像异构混合物442(4.8mg,0.0072mmol,53.0％产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.91(br t,J＝8.4Hz,1H),8.26-8.20(m,2H),7.81-7.74(m,2H),7.48(br t,J＝9.9Hz,1H),7.28(d,J＝8.9Hz,1H),5.43-5.38(m,1H),4.78-4.72(m,1H),4.69(br d,J＝9.8Hz,1H),4.43(br s,1H),4.05(s,3H),3.65(br dd,J＝14.3,6.7Hz,1H),3.44-3.33(m,1H),3.18-3.08(m,3H),2.72(br s,1H),1.85-1.74(m,2H),1.52-1.46(m,1H),1.45-1.34(m,2H),0.79-0.68(m,2H),0.34(br s,2H)。HPLC纯度:99.2％。分析型LC-MS:2.33min;MS(ESI)m/z 662.2(M+H);方法B。

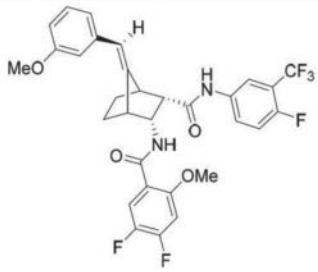
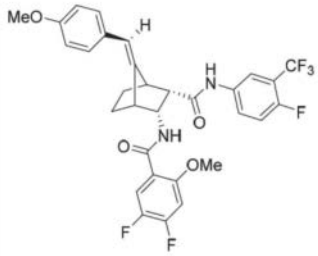
表2					
实施例编号	结构	名称	MS (ESI) (M+H)	1H NMR	LC RT Meth. (min)
7		2-[(2R,3S,7Z)-2-(4,5-二氟-2-甲氧基苯甲酰胺基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-7-亚基]乙酸乙酯	571.1	(400MHz, $CDCl_3$) δ 9.30 (d, J=7.9 Hz, 1H), 8.26 (s, 1H), 7.99 (dd, J=11.2, 9.2 Hz, 1H), 7.92 (dd, J=6.3, 2.5 Hz, 1H), 7.56 (dt, J=8.7, 3.5 Hz, 1H), 7.10 (t, J=9.4 Hz, 1H), 6.78 (dd, J=11.4, 6.2 Hz, 1H), 5.72 (s, 1H), 4.85 - 4.76 (m, 1H), 4.21 (qd, J=7.2, 1.0 Hz, 2H), 3.98 (s, 3H), 3.91 (t, J=4.1 Hz, 1H), 3.14 (dd, J=10.7, 3.0 Hz, 1H), 2.86 (t, J=4.0 Hz, 1H), 2.39 - 2.30 (m, 1H), 1.97 - 1.87 (m, 1H), 1.78 - 1.65 (m, 2H), 1.32 (t, J=7.2 Hz, 3H)	1.20, A

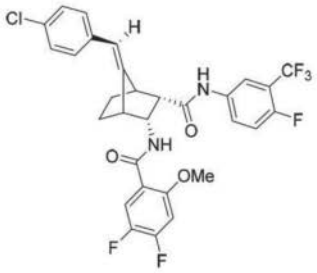
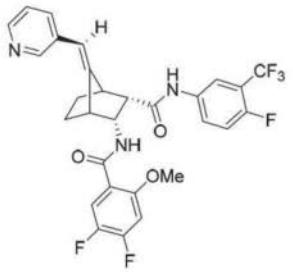
8		2-[(2R,3S,7Z)-2-(4,5-二氟-2-甲氧基苯甲酰胺基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-7-亚基]乙酸叔丁酯	599.1	(500MHz, $CDCl_3$) δ 9.50 (d, J=7.7 Hz, 1H), 8.74 (s, 1H), 8.00 (dd, J=6.3, 2.5 Hz, 1H), 7.97 - 7.92 (m, 1H), 7.66 (dt, J=8.6, 3.5 Hz, 1H), 7.11 (t, J=9.4 Hz, 1H), 6.78 (dd, J=11.6, 6.1 Hz, 1H), 5.64 (s, 1H), 4.78 - 4.68 (m, 1H), 4.00 (s, 3H), 3.86 (t, J=4.1 Hz, 1H), 3.16 (dd, J=10.7, 3.3 Hz, 1H), 2.83 (t, J=4.0 Hz, 1H), 2.33 - 2.25 (m, 1H), 1.98 - 1.92 (m, 1H), 1.74 - 1.59 (m, 3H), 1.50 (s, 9H)	1.25, C
9		2-[(2R,3S,7Z)-2-(4,5-二氟-2-甲氧基苯甲酰胺基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-7-亚基]乙酸苯甲酯	633.2	(500MHz, $CDCl_3$) δ 9.29 (d, J=7.9 Hz, 1H), 8.21 (s, 1H), 8.02 (dd, J=11.3, 9.3 Hz, 1H), 7.93 (dd, J=6.3, 2.6 Hz, 1H), 7.56 (dt, J=8.7, 3.5 Hz, 1H), 7.45 - 7.33 (m, 5H), 7.12 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.4, 6.1 Hz, 1H), 5.78 (s, 1H), 5.27 - 5.18 (m, 2H), 4.90 - 4.79 (m, 1H), 3.99 (s, 3H), 3.99 - 3.96 (m, 1H), 3.19 - 3.11 (m, 1H), 2.87 (t, J=4.0 Hz, 1H), 2.41 - 2.32 (m, 1H), 1.98 - 1.89 (m, 1H), 1.79 - 1.66 (m, 2H)	1.25, B

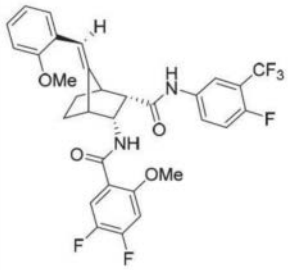
10		(2S,3R,7E)-7-(溴亚甲基)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	578.9	(500MHz, $CDCl_3$) δ 9.65 (d, J=7.4 Hz, 1H), 8.03 - 7.96 (m, 2H), 7.84 (s, 1H), 7.53 (dt, J=8.7, 3.5 Hz, 1H), 7.14 (t, J=9.4 Hz, 1H), 6.79 (dd, J=11.6, 6.1 Hz, 1H), 5.95 (s, 1H), 4.75 - 4.67 (m, 1H), 4.00 (s, 3H), 3.24 (t, J=3.9 Hz, 1H), 3.12 (dd, J=10.7, 4.1 Hz, 1H), 2.98 (t, J=4.0 Hz, 1H), 2.22 - 2.13 (m, 1H), 1.96 - 1.88 (m, 1H), 1.70 - 1.61 (m, 1H)	2.60, B
14		(2S,3R,7Z)-7-[(2-氯苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	609.1	-	1.28, B

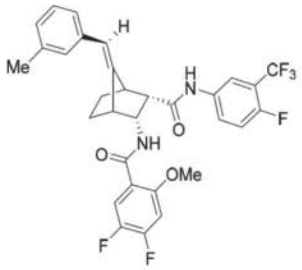
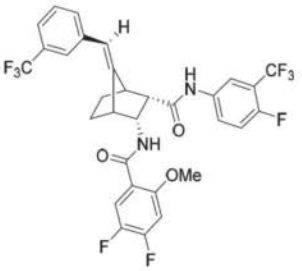
15		(2S,3R,7Z)-7-({[1,1'-联苯]-3-基}亚甲基)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	651.2	(500MHz, $CDCl_3$) δ 9.51 (d, J=7.6 Hz, 1H), 8.04 (dd, J=11.2, 9.4 Hz, 1H), 7.97 (dd, J=6.1, 2.4 Hz, 1H), 7.84 (s, 1H), 7.66 - 7.62 (m, 2H), 7.58 - 7.52 (m, 2H), 7.51 - 7.42 (m, 4H), 7.40 - 7.35 (m, 2H), 7.14 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 6.41 (s, 1H), 4.92 - 4.84 (m, 1H), 4.01 (s, 3H), 3.56 - 3.51 (m, 1H), 3.21 (dd, J=10.7, 4.0 Hz, 1H), 2.92 (br. s., 1H), 2.30 - 2.23 (m, 1H), 1.98 - 1.92 (m, 1H), 1.79 - 1.69 (m, 2H)	1.35, B
16		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(吡啶-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	576.1	(500MHz, $CDCl_3$) δ 9.65 (d, J=7.3 Hz, 1H), 8.58 (br. s., 2H), 8.10 - 7.98 (m, 2H), 7.61 - 7.54 (m, 1H), 7.27 (br. s., 1H) 7.15 (t, J=9.3 Hz, 1H), 6.82 (dd, J=11.6, 6.1 Hz, 1H), 6.27 (s, 1H), 4.83 (t, J=10.8 Hz, 1H), 4.03 (s, 3H), 3.51 (d, J=2.6 Hz, 1H), 3.22 (dd, J=11.0, 4.0 Hz, 1H), 2.94 (br. s., 1H), 2.26 (t, J=9.2 Hz, 1H), 2.00 (t, J=8.7 Hz, 1H), 1.73 (m, 2H)	0.96, C

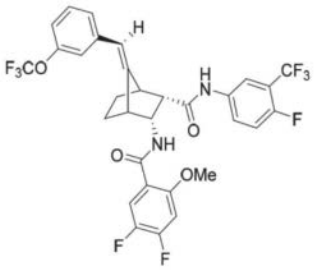
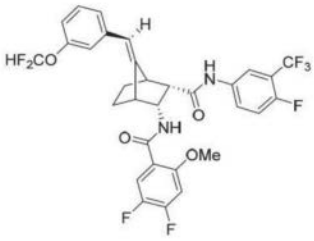
17		(2S,3R,7Z)-7-[(3-氯苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	609.0	(500MHz, $CDCl_3$) δ 9.49 (d, J=7.9 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 7.96 (dd, J=6.1, 2.6 Hz, 1H), 7.77 (s, 1H), 7.59 - 7.52 (m, 1H), 7.33 - 7.27 (m, 2H), 7.26 - 7.22 (m, 2H), 7.15 (t, J=9.4 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 6.29 (s, 1H), 4.89 - 4.81 (m, 1H), 4.02 (s, 3H), 3.49 - 3.41 (m, 1H), 3.19 (dd, J=10.8, 3.8 Hz, 1H), 2.91 (br. s., 1H), 2.28 (t, J=8.9 Hz, 1H), 1.96 (t, J=8.7 Hz, 1H), 1.78 - 1.67 (m, 2H)	1.29, B
18		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(萘-2-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	625.1	(500MHz, $CDCl_3$) δ 9.51 (d, J=7.6 Hz, 1H), 8.06 (dd, J=11.3, 9.3 Hz, 1H), 7.97 (dd, J=6.2, 2.7 Hz, 1H), 7.87 - 7.81 (m, 3H), 7.78 (d, J=13.9 Hz, 2H), 7.59 - 7.52 (m, 2H), 7.51 - 7.43 (m, 2H), 7.15 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.52 (s, 1H), 4.97 - 4.88 (m, 1H), 4.02 (s, 3H), 3.61 (t, J=3.4 Hz, 1H), 3.24 (dd, J=10.8, 3.8 Hz, 1H), 2.96 (br. s., 1H), 2.29 (t, J=8.6 Hz, 1H), 1.97 (t, J=8.6 Hz, 1H), 1.82 - 1.69 (m, 2H)	1.31, B

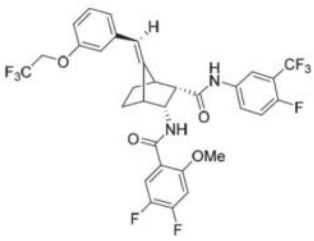
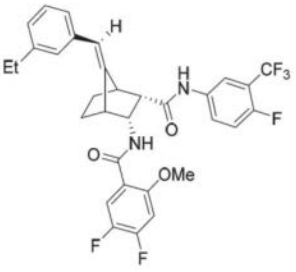
19		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(3-甲氧基苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	605.2	-	1.25, B
20		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(4-甲氧基苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	605.1	(500MHz, $CDCl_3$) δ 9.57 (d, J=7.6 Hz, 1H), 8.04 (dd, J=11.4, 9.4 Hz, 1H), 7.98 (dd, J=6.1, 2.6 Hz, 1H), 7.80 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.31 - 7.29 (m, 1H), 7.14 (t, J=9.3 Hz, 1H), 6.92 - 6.87 (m, 2H), 6.80 (dd, J=11.5, 6.2 Hz, 1H), 6.27 (s, 1H), 4.87 - 4.77 (m, 1H), 4.02 (s, 3H), 3.83 (s, 3H), 3.49 (t, J=3.4 Hz, 1H), 3.16 (dd, J=10.8, 3.8 Hz, 1H), 2.88 - 2.84 (m, 1H), 2.21 (t, J=8.9 Hz, 1H), 1.93 (t, J=8.6 Hz, 1H), 1.73 - 1.64 (m, 2H)	1.26, C

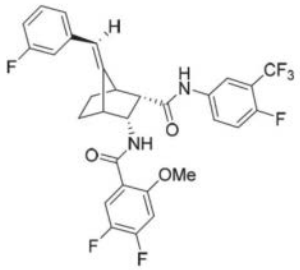
21		(2S,3R,7Z)-7-[(4-氯苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	609.1	(500MHz, $CDCl_3$) δ 9.56 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.4, 9.4 Hz, 1H), 7.97 (dd, J=6.1, 2.6 Hz, 1H), 7.75 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.34 - 7.30 (m, 2H), 7.28 - 7.26 (m, 2H), 7.15 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 6.29 (s, 1H), 4.90 - 4.78 (m, 1H), 4.02 (s, 3H), 3.51 - 3.42 (m, 1H), 3.18 (dd, J=10.8, 4.0 Hz, 1H), 2.90 (br. s., 1H), 2.30 - 2.19 (m, 1H), 1.99 - 1.90 (m, 1H), 1.76 - 1.65 (m, 2H)	1.29, C
22		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(吡啶-3-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	576.0	(500MHz, $CDCl_3$) δ 9.62 (d, J=7.5 Hz, 1H), 8.57 (d, J=2.0 Hz, 1H), 8.49 (dd, J=4.7, 1.5 Hz, 1H), 8.16 (br. s., 1H), 8.06 - 7.99 (m, 2H), 7.74 (dt, J=8.0, 1.8 Hz, 1H), 7.59 (dt, J=8.6, 3.5 Hz, 1H), 7.31 (dd, J=7.8, 4.9 Hz, 1H), 7.16 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 6.33 (s, 1H), 4.88 - 4.76 (m, 1H), 4.03 (s, 3H), 3.46 (t, J=3.6 Hz, 1H), 3.21 (dd, J=10.8, 3.9 Hz, 1H), 2.96 (t, J=3.4 Hz, 1H), 2.28 (t, J=9.0 Hz, 1H), 2.03 - 1.97 (m, 1H), 1.79 - 1.69 (m, 2H)	0.95, B

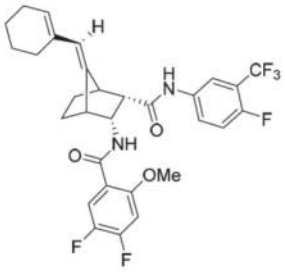
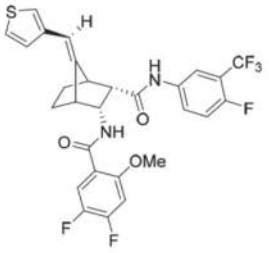
23		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2-甲氧基苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	605.1	(500MHz, $CDCl_3$) δ 9.49 (d, J=7.8 Hz, 1H), 8.04 (dd, J=11.4, 9.4 Hz, 1H), 7.97 (dd, J=6.1, 2.6 Hz, 1H), 7.75 (s, 1H), 7.55 (dt, J=8.8, 3.5 Hz, 1H), 7.33 (dd, J=7.5, 1.5 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.14 (t, J=9.4 Hz, 1H), 7.01 - 6.94 (m, 1H), 6.91 (d, J=8.4 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 6.49 (s, 1H), 4.90 - 4.81 (m, 1H), 4.01 (s, 3H), 3.89 (s, 3H), 3.36 (t, J=3.9 Hz, 1H), 3.22 (dd, J=10.8, 4.0 Hz, 1H), 2.93 (t, J=3.7 Hz, 1H), 2.29 - 2.20 (m, 1H), 1.95 - 1.88 (m, 1H), 1.80 - 1.67 (m, 2H)	1.26, C

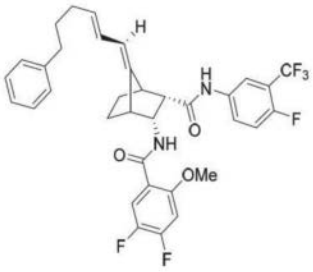
24		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(3-甲基苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	589.2	(500MHz, $CDCl_3$) δ 9.53 (d, J=7.9 Hz, 1H), 8.03 (dd, J=11.3, 9.3 Hz, 1H), 7.97 (dd, J=6.3, 2.6 Hz, 1H), 7.91 (s, 1H), 7.56 (dt, J=8.6, 3.6 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.20 - 7.11 (m, 3H), 7.07 (d, J=7.5 Hz, 1H), 6.80 (dd, J=11.5, 6.2 Hz, 1H), 6.31 (s, 1H), 4.87 - 4.80 (m, 1H), 4.01 (s, 3H), 3.50 (t, J=3.7 Hz, 1H), 3.18 (dd, J=10.5, 3.7 Hz, 1H), 2.87 (t, J=3.7 Hz, 1H), 2.38 (s, 3H), 2.24 (t, J=8.9 Hz, 1H), 1.98 - 1.91 (m, 1H), 1.74 - 1.67 (m, 2H)	1.30, C
25		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-{[3-(三氟甲基)苯基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	643.0	(500MHz, CDCl3) δ 9.53 (d, J=7.8 Hz, 1H), 8.04 (dd, J=11.4, 9.4 Hz, 1H), 7.97 (dd, J=6.2, 2.7 Hz, 1H), 7.83 (s, 1H), 7.59 - 7.46 (m, 5H), 7.15 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 6.37 (s, 1H), 4.89 - 4.81 (m, 1H), 4.02 (s, 3H), 3.43 (t, J=3.4 Hz, 1H), 3.20 (dd, J=10.8, 3.8 Hz, 1H), 2.93 (br. s., 1H), 2.29 (t, J=8.9 Hz, 1H), 1.97 (t, J=8.6 Hz, 1H), 1.80 - 1.65 (m, 2H)	1.29, C

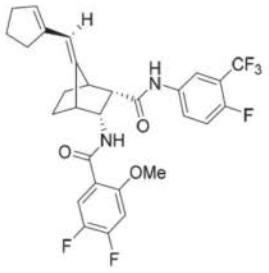
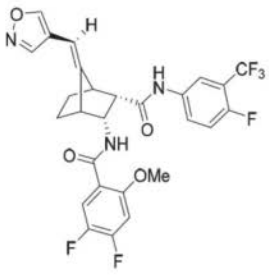
26		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-{[3-(三氟甲氧基)苯基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	659.1	(500MHz, $CDCl_3$) δ 9.51 (d, J=7.6 Hz, 1H), 8.04 (dd, J=11.2, 9.4 Hz, 1H), 7.96 (dd, J=6.2, 2.5 Hz, 1H), 7.85 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.41 - 7.36 (m, 1H), 7.31 (d, J=7.8 Hz, 1H), 7.14 (q, J=9.5 Hz, 3H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.32 (s, 1H), 4.90 - 4.80 (m, 1H), 4.02 (s, 3H), 3.44 (br. s., 1H), 3.19 (dd, J=10.8, 4.0 Hz, 1H), 2.91 (br. s., 1H), 2.28 (t, J=9.0 Hz, 1H), 2.01 - 1.91 (m, 1H), 1.79 - 1.68 (m, 2H)	1.31, C
27		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-{[3-(二氟甲氧基)苯基]亚甲基}-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	641.0	(500MHz, $CDCl_3$) δ 9.55 (d, J=7.8 Hz, 1H), 8.03 (dd, J=11.3, 9.3 Hz, 1H), 7.97 (dd, J=6.1, 2.6 Hz, 1H), 7.87 (s, 1H), 7.56 (dt, J=8.8, 3.4 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.14 (t, J=9.3 Hz, 1H), 7.06 (s, 1H), 7.01 (dd, J=8.0, 1.9 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.74 - 6.41 (m, 1H), 6.31 (s, 1H), 4.89 - 4.76 (m, 1H), 4.02 (s, 3H), 3.45 (br. s., 1H), 3.19 (dd, J=10.8, 4.0 Hz, 1H), 2.90 (br. s., 1H), 2.26 (t, J=8.9 Hz, 1H), 2.01 - 1.90 (m, 1H), 1.77 - 1.67 (m, 2H)	1.27, C

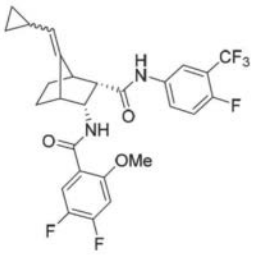
28		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-{[3-(2,2,2-三氟乙氧基)苯基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	673.1	(500MHz, $CDCl_3$) δ 9.56 (d, J=7.8 Hz, 1H), 8.04 (dd, J=11.3, 9.5 Hz, 1H), 7.98 (dd, J=6.1, 2.4 Hz, 1H), 7.79 (s, 1H), 7.60 - 7.53 (m, 1H), 7.34 - 7.29 (m, 1H), 7.15 (t, J=9.3 Hz, 1H), 7.05 (d, J=7.8 Hz, 1H), 6.94 (s, 1H), 6.88 - 6.78 (m, 2H), 6.32 (s, 1H), 4.90 - 4.79 (m, 1H), 4.44 (q, J=8.2 Hz, 2H), 4.02 (s, 3H), 3.48 (br. s., 1H), 3.20 (dd, J=10.7, 4.1 Hz, 1H), 2.91 (br. s., 1H), 2.23 (t, J=9.0 Hz, 1H), 1.95 (t, J=8.8 Hz, 1H), 1.76 - 1.66 (m, 2H)	1.29, B
29		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-[(3-乙基苯基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	603.2	(500MHz, $CDCl_3$) δ 9.50 (d, J=7.8 Hz, 1H), 8.04 (dd, J=11.3, 9.5 Hz, 1H), 7.97 (dd, J=6.2, 2.4 Hz, 1H), 7.88 (s, 1H), 7.56 (dt, J=8.7, 3.3 Hz, 1H), 7.31 - 7.26 (m, 1H), 7.21 (d, J=7.6 Hz, 1H), 7.17 - 7.08 (m, 3H), 6.80 (dd, J=11.4, 6.1 Hz, 1H), 6.33 (s, 1H), 4.91 - 4.82 (m, 1H), 4.01 (s, 3H), 3.53 - 3.46 (m, 1H), 3.19 (dd, J=10.7, 3.8 Hz, 1H), 2.90 - 2.86 (m, 1H), 2.68 (q, J=7.5 Hz, 2H), 2.30 - 2.19 (m, 1H), 1.97 - 1.87 (m, 1H), 1.77 - 1.66 (m, 2H), 1.28 (t, J=7.6 Hz, 3H)	1.34, C

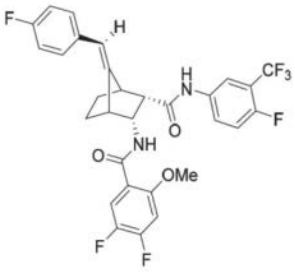
30		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(3-氟苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	593.0	(500MHz, $CDCl_3$) δ 9.52 (d, J=7.6 Hz, 1H), 8.04 (dd, J=11.3, 9.3 Hz, 1H), 7.97 (dd, J=6.3, 2.6 Hz, 1H), 7.84 (s, 1H), 7.55 (dt, J=8.7, 3.4 Hz, 1H), 7.32 (td, J=7.9, 6.1 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.01 (dt, J=10.1, 1.9 Hz, 1H), 6.95 (td, J=8.2, 2.3 Hz, 1H), 6.81 (dd, J=11.5, 6.2 Hz, 1H), 6.30 (s, 1H), 4.89 - 4.78 (m, 1H), 4.02 (s, 3H), 3.47 (t, J=3.6 Hz, 1H), 3.19 (dd, J=10.8, 3.9 Hz, 1H), 2.90 (t, J=3.5 Hz, 1H), 2.27 (t, J=8.9 Hz, 1H), 2.00 - 1.92 (m, 1H), 1.76 - 1.67 (m, 2H)	1.28, C

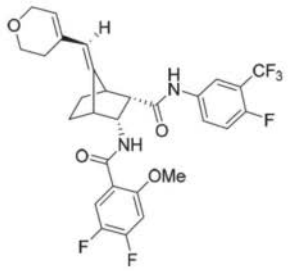
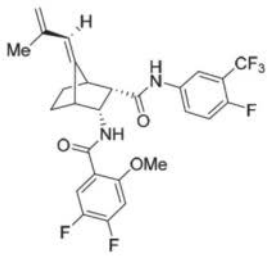
35		(2S,3R,7Z)-7-[(环己-1-烯-1-基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	579.1	(500MHz, $CDCl_3$) δ 9.55 (d, J=7.6 Hz, 1H), 8.06 (dd, J=11.4, 9.4 Hz, 1H), 7.97 (dd, J=6.2, 2.5 Hz, 1H), 7.69 (s, 1H), 7.61 - 7.50 (m, 1H), 7.14 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.5, 6.2 Hz, 1H), 5.84 (s, 1H), 5.74 (br. s., 1H), 4.80 - 4.69 (m, 1H), 4.01 (s, 3H), 3.41 (t, J=3.9 Hz, 1H), 3.06 (dd, J=10.7, 3.5 Hz, 1H), 2.74 (t, J=3.9 Hz, 1H), 2.42 - 2.33 (m, 1H), 2.29 - 2.20 (m, 1H), 2.18 - 2.06 (m, 3H), 1.92 - 1.85 (m, 1H), 1.73 - 1.66 (m, 2H), 1.65 - 1.53 (m, 4H)	1.35, B
36		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(噻吩-3-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	581.0	(500MHz, $CDCl_3$) δ 9.59 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.4, 9.4 Hz, 1H), 7.98 (dd, J=6.1, 2.6 Hz, 1H), 7.74 (s, 1H), 7.56 (dt, J=8.6, 3.5 Hz, 1H), 7.31 (dd, J=4.5, 3.4 Hz, 1H), 7.22 - 7.19 (m, 2H), 7.15 (t, J=9.2 Hz, 1H), 6.81 (dd, J=11.5, 6.2 Hz, 1H), 6.30 (s, 1H), 4.87 - 4.78 (m, 1H), 3.54 - 3.45 (m, 1H), 3.17 (dd, J=10.7, 4.0 Hz, 1H), 2.86 (br. s., 1H), 2.24 - 2.16 (m, 1H), 1.99 - 1.89 (m, 1H), 1.74 - 1.65 (m, 2H)	1.26, B

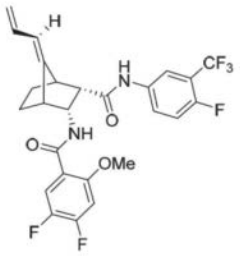
37		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2E)-6-苯基己-2-烯-1-亚基]双环[2.2.1]庚烷-2-甲酰胺	643.3	(500MHz, $CDCl_3$) δ 9.53 (d, J=7.8 Hz, 1H), 8.05 (dd, J=11.4, 9.4 Hz, 1H), 7.96 (dd, J=6.2, 2.5 Hz, 1H), 7.69 (s, 1H), 7.58 - 7.50 (m, 1H), 7.34 - 7.29 (m, 2H), 7.24 - 7.19 (m, 3H), 7.14 (t, J=9.2 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 6.20 (dd, J=15.2, 10.8 Hz, 1H), 5.88 (d, J=10.7 Hz, 1H), 5.76 - 5.67 (m, 1H), 4.76 - 4.68 (m, 1H), 4.01 (s, 3H), 3.23 (br. s., 1H), 3.07 (dd, J=10.7, 4.0 Hz, 1H), 2.77 (br. s., 1H), 2.69 - 2.64 (m, 2H), 2.22 - 2.13 (m, 3H), 1.87 (t, J=8.6 Hz, 1H), 1.77 (quin, J=7.6 Hz, 2H), 1.60 (d, J=8.5 Hz, 4H)	1.33, B

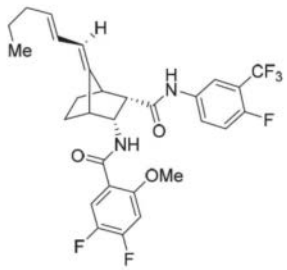
38		(2S,3R,7Z)-7-[(环戊-1-烯-1-基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	565.0	(500MHz, $CDCl_3$) δ 9.53 (d, J=7.6 Hz, 1H), 8.06 (dd, J=11.4, 9.3 Hz, 1H), 7.96 (dd, J=6.2, 2.5 Hz, 1H), 7.68 (s, 1H), 7.58 - 7.52 (m, 1H), 7.14 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 6.11 (s, 1H), 5.74 (s, 1H), 4.79 - 4.70 (m, 1H), 4.01 (s, 3H), 3.38 (t, J=3.9 Hz, 1H), 3.08 (dd, J=10.8, 4.0 Hz, 1H), 2.78 (t, J=3.7 Hz, 1H), 2.73 - 2.66 (m, 1H), 2.60 - 2.53 (m, 1H), 2.44 - 2.38 (m, 2H), 2.16 - 2.10 (m, 1H), 1.98 (quin, J=7.2 Hz, 2H), 1.92 - 1.86 (m, 1H), 1.67 - 1.61 (m, 2H)	1.28, B
39		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	566.2	(500MHz, $CDCl_3$) δ 9.54 (d, J=7.4 Hz, 1H), 8.44 (s, 1H), 8.35 (s, 1H), 8.03 (dd, J=11.3, 9.4 Hz, 1H), 7.94 (dd, J=6.1, 2.5 Hz, 1H), 7.65 (s, 1H), 7.56 - 7.49 (m, 1H), 7.13 (t, J=9.4 Hz, 1H), 6.79 (dd, J=11.6, 6.1 Hz, 1H), 6.02 (s, 1H), 4.83 - 4.74 (m, 1H), 4.03 - 3.97 (m, 3H), 3.26 (br. s., 1H), 3.14 (dd, J=10.7, 4.1 Hz, 1H), 2.88 (br. s., 1H), 2.23 (t, J=8.9 Hz, 1H), 1.95 (t, J=8.7 Hz, 1H), 1.72 - 1.63 (m, 2H)	1.03, A

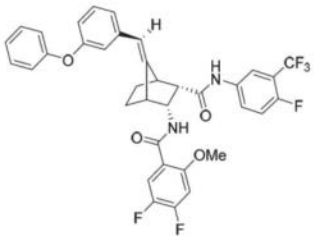
40		(2S,3R)-7-(环丙基亚甲基)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	539.1	(500MHz, $CDCl_3$) δ 9.48 (d, J=7.7 Hz, 1H), 9.38 (d, J=7.7 Hz, 1H), 8.03 (ddd, J=11.4, 9.4, 4.8 Hz, 2H), 7.92 (dt, J=6.1, 2.9 Hz, 2H), 7.78 (s, 1H), 7.70 (s, 1H), 7.58 - 7.47 (m, 2H), 7.11 (t, J=9.4 Hz, 2H), 6.78 (ddd, J=11.6, 6.2, 4.3 Hz, 2H), 4.78 - 4.71 (m, 1H), 4.71 - 4.65 (m, 1H), 4.63 (d, J=3.3 Hz, 1H), 4.61 (d, J=3.3 Hz, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.20 - 3.13 (m, 2H), 3.13 - 3.07 (m, 1H), 3.04 (ddd, J=10.7, 4.1, 1.1 Hz, 1H), 2.72 (t, J=4.3 Hz, 1H), 2.68 (t, J=3.9 Hz, 1H), 2.17 (ddd, J=12.1, 8.8, 3.6 Hz, 1H), 2.13 - 2.06 (m, 1H), 1.87 - 1.81 (m, 1H), 1.80 - 1.74 (m, 1H), 1.68 - 1.53 (m, 2H), 1.51 - 1.40 (m, 2H), 0.76 - 0.66 (m, 4H), 0.40 - 0.29 (m, 4H)	1.23, A

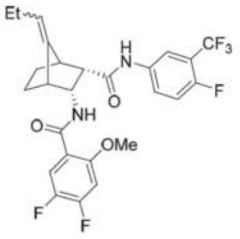
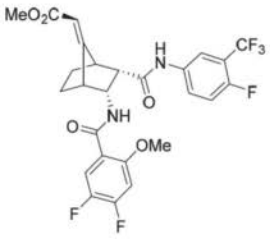
41		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(4-氟苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	593.0	(500MHz, $CDCl_3$) δ 9.56 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.4, 9.4 Hz, 1H), 7.97 (dd, J=6.1, 2.6 Hz, 1H), 7.72 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.15 (t, J=9.3 Hz, 1H), 7.07 - 7.02 (m, 2H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.30 (s, 1H), 4.88 - 4.79 (m, 1H), 4.02 (s, 3H), 3.45 (t, J=3.4 Hz, 1H), 3.18 (dd, J=10.8, 3.7 Hz, 1H), 2.89 (t, J=3.3 Hz, 1H), 2.23 (t, J=8.9 Hz, 1H), 1.98 - 1.90 (m, 1H), 1.76 - 1.65 (m, 2H)	1.29, C

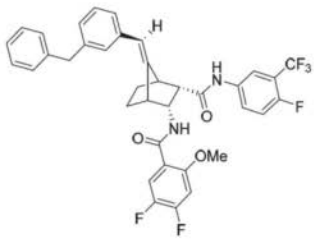
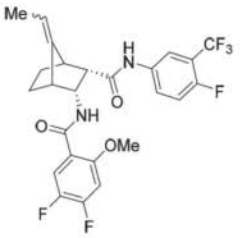
42		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-[(3,6-二氢-2H-哌喃-4-基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	581.2	(500MHz, $CDCl_3$) δ 9.60 (d, J=7.5 Hz, 1H), 8.07 - 7.96 (m, 2H), 7.80 (s, 1H), 7.56 (dt, J=8.7, 3.5 Hz, 1H), 7.15 (t, J=9.4 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 5.85 (s, 1H), 5.72 (d, J=0.8 Hz, 1H), 4.77 - 4.69 (m, 1H), 4.27 (d, J=2.6 Hz, 2H), 4.01 (s, 3H), 3.91 - 3.80 (m, 2H), 3.39 (t, J=3.9 Hz, 1H), 3.08 (dd, J=10.7, 4.3 Hz, 1H), 2.76 (t, J=3.8 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.43 - 2.35 (m, 1H), 2.16 - 2.09 (m, 1H), 1.95 - 1.87 (m, 1H), 1.67 - 1.58 (m, 2H)	1.19, C
43		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2-甲基丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-甲酰胺	539.1	(500MHz, $CDCl_3$) δ 9.53 (d, J=7.5 Hz, 1H), 8.05 (dd, J=11.4, 9.3 Hz, 1H), 7.96 (dd, J=6.3, 2.6 Hz, 1H), 7.72 (s, 1H), 7.54 (dt, J=8.8, 3.5 Hz, 1H), 7.14 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 5.95 (s, 1H), 4.97 (s, 2H), 4.82 - 4.71 (m, 1H), 4.01 (s, 3H), 3.45 (t, J=4.0 Hz, 1H), 3.12 - 3.06 (m, 1H), 2.77 (t, J=3.9 Hz, 1H), 2.18 - 2.11 (m, 1H), 2.01 (s, 3H), 1.94 - 1.87 (m, 1H), 1.70 - 1.61 (m, 2H)	1.25, B

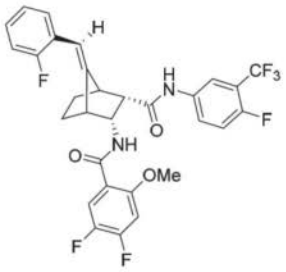
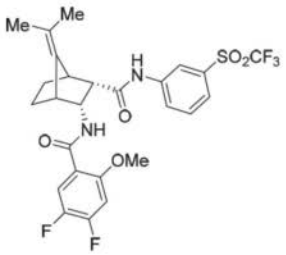
44		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-甲酰胺	525.0	(500MHz, $CDCl_3$) δ 9.51 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.4, 9.4 Hz, 1H), 7.96 (dd, J=6.3, 2.6 Hz, 1H), 7.73 (s, 1H), 7.54 (dt, J=8.8, 3.5 Hz, 1H), 7.14 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.51 (dt, J=16.9, 10.5 Hz, 1H), 5.93 (d, J=10.8 Hz, 1H), 5.22 (dd, J=16.9, 1.4 Hz, 1H), 5.12 (dd, J=10.1, 1.5 Hz, 1H), 4.78 - 4.68 (m, 1H), 4.01 (s, 3H), 3.24 (t, J=3.6 Hz, 1H), 3.08 (dd, J=10.8, 3.9 Hz, 1H), 2.79 (t, J=3.4 Hz, 1H), 2.19 (t, J=8.9 Hz, 1H), 1.95 - 1.85 (m, 1H), 1.68 - 1.60 (m, 2H)	1.21, B

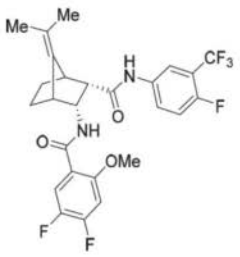
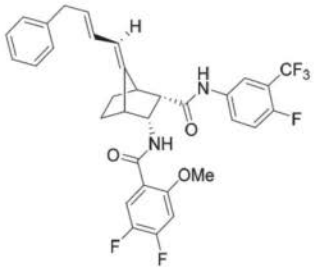
45		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2E)-己-2-烯-1-亚基]双环[2.2.1]庚烷-2-甲酰胺	567.1	(500MHz, $CDCl_3$) δ 9.57 (d, J=7.8 Hz, 1H), 8.06 (dd, J=11.4, 9.4 Hz, 1H), 7.98 (dd, J=6.2, 2.7 Hz, 1H), 7.73 (s, 1H), 7.58 - 7.50 (m, 1H), 7.15 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.19 (dd, J=15.1, 10.8 Hz, 1H), 5.87 (d, J=10.7 Hz, 1H), 5.75 - 5.64 (m, 1H), 4.77 - 4.66 (m, 1H), 4.06 - 3.97 (m, 3H), 3.23 (br. s., 1H), 3.07 (dd, J=10.8, 3.9 Hz, 1H), 2.76 (br. s., 1H), 2.17 - 2.06 (m, 3H), 1.86 (t, J=8.6 Hz, 1H), 1.70 - 1.55 (m, 2H), 1.45 (sxt, J=7.4 Hz, 2H), 0.98 - 0.91 (m, 3H)	1.33, C

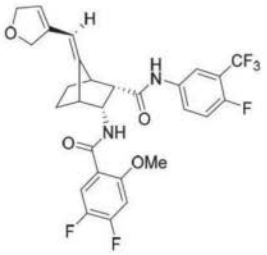
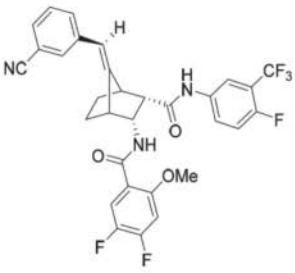
46		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(3-苯氧基苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	667.3	(500MHz, $CDCl_3$) δ 9.43 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 7.95 (dd, J=6.3, 2.6 Hz, 1H), 7.76 (s, 1H), 7.59 - 7.51 (m, 1H), 7.40 - 7.35 (m, 2H), 7.33 - 7.29 (m, 1H), 7.17 - 7.11 (m, 3H), 7.08 - 7.04 (m, 2H), 6.96 (t, J=1.9 Hz, 1H), 6.89 (dd, J=8.2, 1.7 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.30 (s, 1H), 4.88 - 4.80 (m, 1H), 4.01 (s, 3H), 3.47 (br. s., 1H), 3.18 (dd, J=10.8, 3.7 Hz, 1H), 2.91 - 2.87 (m, 1H), 2.27 (t, J=8.7 Hz, 1H), 1.96 - 1.90 (m, 1H), 1.76 - 1.68 (m, 2H)	1.31, B

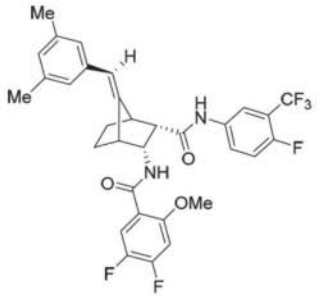
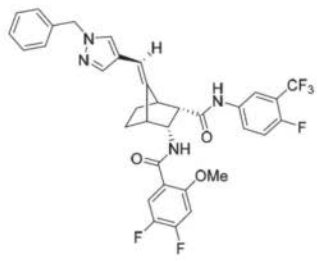
47		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-亚丙基双环[2.2.1]庚烷-2-甲酰胺	527.2	(500MHz, $CDCl_3$) δ 9.45 (d, J=7.7 Hz, 1H), 9.34 (d, J=8.0 Hz, 1H), 8.02 (dd, J=11.3, 9.4 Hz, 2H), 7.96 - 7.88 (m, 2H), 7.77 (s, 1H), 7.68 (s, 1H), 7.52 (tt, J=9.2, 3.6 Hz, 2H), 7.10 (t, J=9.4 Hz, 2H), 6.77 (ddd, J=11.6, 6.3, 3.0 Hz, 2H), 5.23 (t, J=7.3 Hz, 2H), 4.74 - 4.63 (m, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.09 - 2.98 (m, 4H), 2.70 (dt, J=13.1, 3.9 Hz, 2H), 2.21 - 2.03 (m, 6H), 1.84 - 1.74 (m, 2H), 1.63 - 1.53 (m, 4H), 1.00 (m, 6H)	1.24, A
48		2-[(2R,3S,7Z)-2-(4,5-二氟-2-甲氧基苯甲酰胺基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-7-亚基]乙酸甲酯	599.1	(500MHz, $CDCl_3$) δ 9.33 (d, J=7.8 Hz, 1H), 8.21 (s, 1H), 8.02 (dd, J=11.3, 9.3 Hz, 1H), 7.94 (dd, J=6.2, 2.7 Hz, 1H), 7.58 (dt, J=8.5, 3.6 Hz, 1H), 7.12 (t, J=9.4 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 5.75 (s, 1H), 4.89 - 4.77 (m, 1H), 4.01 (s, 3H), 3.93 (t, J=4.2 Hz, 1H), 3.78 (s, 3H), 3.16 (ddd, J=10.8, 4.1, 1.2 Hz, 1H), 2.89 (t, J=4.0 Hz, 1H), 2.42 - 2.32 (m, 1H), 1.99 - 1.90 (m, 1H), 1.81 - 1.65 (m, 2H)	1.25, B

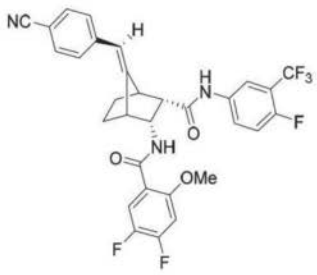
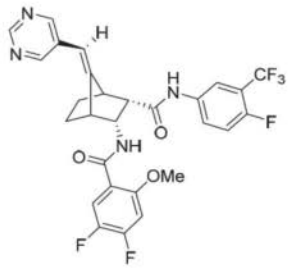
49		(2S,3R,7Z)-7-[(3-苯甲基苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	665.1	(500MHz, $CDCl_3$) δ 9.44 (d, J=7.8 Hz, 1H), 8.06 (dd, J=11.4, 9.4 Hz, 1H), 7.95 (dd, J=6.3, 2.7 Hz, 1H), 7.77 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.34 - 7.29 (m, 3H), 7.26 - 7.19 (m, 4H), 7.16 - 7.07 (m, 3H), 6.81 (dd, J=11.5, 6.2 Hz, 1H), 6.30 (s, 1H), 4.89 - 4.80 (m, 1H), 4.01 (s, 5H), 3.43 (t, J=3.4 Hz, 1H), 3.17 (dd, J=10.9, 3.9 Hz, 1H), 2.87 (br. s., 1H), 2.24 (t, J=8.9 Hz, 1H), 1.95 - 1.86 (m, 1H), 1.75 - 1.64 (m, 2H)	1.33, B
50		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-亚乙基-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	513.1	(500MHz, $CDCl_3$) δ 9.49 (d, J=7.7 Hz, 1H), 9.38 (d, J=8.0 Hz, 1H), 8.02 (ddd, J=11.6, 9.4, 3.0 Hz, 2H), 7.92 (td, J=5.6, 2.8 Hz, 2H), 7.83 (s, 1H), 7.76 (s, 1H), 7.57 - 7.48 (m, 2H), 7.10 (t, J=9.4 Hz, 2H), 6.78 (ddd, J=11.6, 6.1, 3.0 Hz, 2H), 5.25 (q, J=6.8 Hz, 2H), 4.71 - 4.62 (m, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.11 - 3.00 (m, 4H), 2.71 (dt, J=14.9, 3.7 Hz, 2H), 2.20 - 2.07 (m, 2H), 1.84 - 1.73 (m, 2H), 1.69 (d, J=3.0 Hz, 3H), 1.68 (d, J=3.0 Hz, 3H), 1.62 - 1.51 (m, 4H)	1.20, A

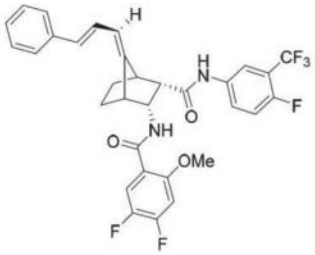
54		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2-氟苯基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	593.0	(500MHz, $CDCl_3$) δ 9.57 (d, J=7.6 Hz, 1H), 8.04 (dd, J=11.4, 9.4 Hz, 1H), 7.99 (dd, J=6.2, 2.5 Hz, 1H), 7.80 (s, 1H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.38 (td, J=7.6, 1.5 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.18 - 7.11 (m, 2H), 7.10 - 7.04 (m, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.39 (s, 1H), 4.88 - 4.79 (m, 1H), 4.02 (s, 3H), 3.35 (t, J=3.6 Hz, 1H), 3.21 (dd, J=10.5, 3.8 Hz, 1H), 2.93 (t, J=3.7 Hz, 1H), 2.31 - 2.20 (m, 1H), 2.00 - 1.91 (m, 1H), 1.79 - 1.68 (m, 2H)	1.30, B
55		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-丙烷-2-亚基)-N-(3-三氟甲磺酰基苯基)双环[2.2.1]庚烷-2-甲酰胺	573.3	(500MHz, $CDCl_3$) δ 9.45 (d, J=7.6 Hz, 1H), 8.48 (s, 1H), 8.13 (br. s., 1H), 8.07 (dd, J=11.4, 9.4 Hz, 1H), 7.80 (dt, J=8.2, 1.0 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 4.74 - 4.63 (m, 1H), 4.04 (s, 3H), 3.11 - 2.99 (m, 3H), 2.18 - 2.07 (m, 1H), 1.84 - 1.77 (m, 1H), 1.75 (s, 3H), 1.75 (s, 3H), 1.66 - 1.52 (m, 2H)	1.21, B

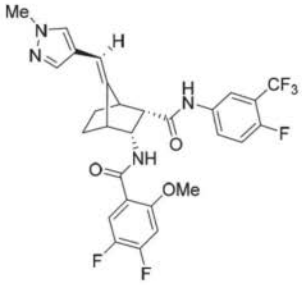
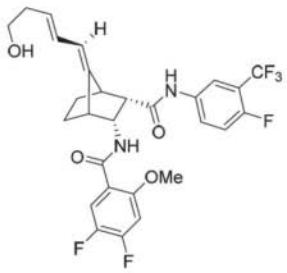
56		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	527.2	(500MHz, $CDCl_3$) δ 9.35 (d, J=7.4 Hz, 1H), 8.03 (dd, J=11.6, 9.4 Hz, 1H), 7.91 (dd, J=6.2, 2.6 Hz, 1H), 7.75 (s, 1H), 7.57 - 7.50 (m, 1H), 7.10 (t, J=9.4 Hz, 1H), 6.77 (dd, J=11.6, 6.1 Hz, 1H), 4.65 (d, J=4.4 Hz, 1H), 3.97 (s, 3H), 3.03 - 2.95 (m, 3H), 2.14 - 2.08 (m, 1H), 1.79 - 1.73 (m, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.57 - 1.53 (m, 2H)	1.24, A
57		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2-苯基亚乙基)双环[2.2.1]庚烷-2-甲酰胺	589.0	(500MHz, $CDCl_3$) δ 9.52 (d, J=7.5 Hz, 1H), 8.10 - 8.02 (m, 1H), 7.98 - 7.93 (m, 1H), 7.69 (br. s., 1H), 7.57 - 7.50 (m, 1H), 7.37 - 7.30 (m, 2H), 7.25 - 7.18 (m, 3H), 7.13 (t, J=9.2 Hz, 1H), 6.81 (dd, J=11.5, 6.2 Hz, 1H), 5.43 (t, J=7.5 Hz, 1H), 4.77 (t, J=10.9 Hz, 1H), 4.01 (s, 3H), 3.45 (m, 2H), 3.22 (br. s., 1H), 3.10 (dd, J=10.6, 3.7 Hz, 1H), 2.76 (br. s., 1H), 2.21 - 2.13 (m, 1H), 1.94 - 1.87 (m, 1H), 1.64 (d, J=8.5 Hz, 2H)	1.26, A

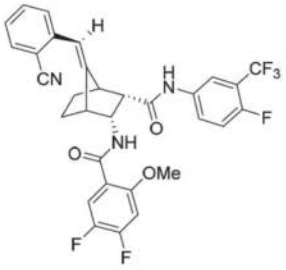
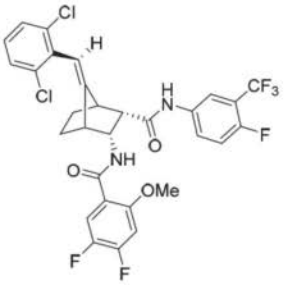
58		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-[(2,5-二氢呋喃-3-基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	567.0	(500MHz, $CDCl_3$) δ 9.48 (d, J=7.7 Hz, 1H), 8.00 (dd, J=11.3, 9.4 Hz, 1H), 7.93 (dd, J=6.2, 2.6 Hz, 1H), 7.85 (s, 1H), 7.52 (dt, J=8.9, 3.4 Hz, 1H), 7.11 (t, J=9.2 Hz, 1H), 6.78 (dd, J=11.6, 6.3 Hz, 1H), 6.05 (s, 1H), 5.83 (t, J=1.8 Hz, 1H), 4.92 - 4.85 (m, 1H), 4.81 - 4.74 (m, 1H), 4.73 - 4.66 (m, 3H), 3.98 (s, 3H), 3.08 (dd, J=10.7, 3.9 Hz, 1H), 2.97 (t, J=3.4 Hz, 1H), 2.79 (t, J=3.3 Hz, 1H), 2.19 - 2.14 (m, 1H), 1.89 (t, J=8.7 Hz, 1H), 1.65 - 1.59 (m, 2H)	1.18, B
59		(2S,3R,7Z)-7-[(3-氰基苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	600.1	(500MHz, $CDCl_3$) δ 9.59 (d, J=7.6 Hz, 1H), 8.05 - 7.96 (m, 2H), 7.86 (s, 1H), 7.60 - 7.52 (m, 4H), 7.51 - 7.44 (m, 1H), 7.16 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 6.29 (s, 1H), 4.86 - 4.77 (m, 1H), 4.01 (s, 3H), 3.42 (br. s., 1H), 3.23 (dd, J=10.8, 4.1 Hz, 1H), 2.95 (br. s., 1H), 2.31 - 2.22 (m, 1H), 1.99 (t, J=8.7 Hz, 1H), 1.77 - 1.67 (m, 2H)	1.29, B

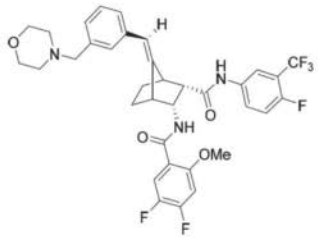
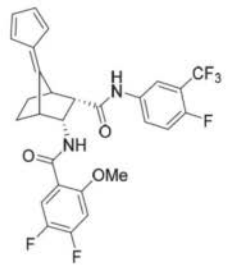
60		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-[(3,5-二甲基苯基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	603.1	(500MHz, $CDCl_3$) δ 9.42 (d, J=7.8 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 7.94 (dd, J=6.2, 2.5 Hz, 1H), 7.80 (s, 1H), 7.60 - 7.52 (m, 1H), 7.13 (t, J=9.4 Hz, 1H), 6.97 (s, 2H), 6.91 (s, 1H), 6.84 - 6.76 (m, 1H), 6.29 (s, 1H), 4.90 - 4.83 (m, 1H), 4.03 - 3.99 (m, 3H), 3.51 - 3.47 (m, 1H), 3.18 (dd, J=10.9, 3.9 Hz, 1H), 2.88 (t, J=3.6 Hz, 1H), 2.34 (s, 6H), 2.29 - 2.23 (m, 1H), 1.96 - 1.89 (m, 1H), 1.77 - 1.68 (m, 2H)	1.35, B
61		(2S,3R,7Z)-7-[(1-苯甲基-1H-吡唑-4-基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	655.1	(500MHz, $CDCl_3$) δ 9.60 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.3, 9.5 Hz, 1H), 7.98 (dd, J=6.1, 2.4 Hz, 1H), 7.87 (s, 1H), 7.60 (s, 1H), 7.57 - 7.52 (m, 1H), 7.49 (s, 1H), 7.40 - 7.31 (m, 4H), 7.27 - 7.23 (m, 2H), 7.14 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 6.07 (s, 1H), 5.38 - 5.28 (m, 2H), 4.82 - 4.74 (m, 1H), 4.06 - 3.98 (m, 3H), 3.33 (br. s., 1H), 3.12 (dd, J=10.8, 3.9 Hz, 1H), 2.83 (br. s., 1H), 2.18 (t, J=8.9 Hz, 1H), 1.96 - 1.88 (m, 1H), 1.71 - 1.62 (m, 2H)	1.23, C

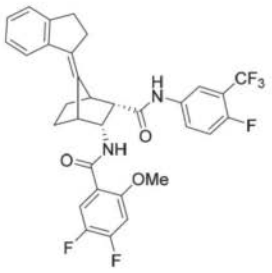
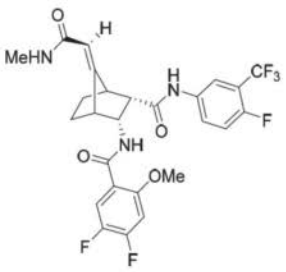
62		(2S,3R,7Z)-7-[(4-氰基苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	600.0	(500MHz, $CDCl_3$) δ 9.61 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 7.98 (dd, J=6.3, 2.6 Hz, 1H), 7.71 (s, 1H), 7.66 - 7.66 (m, 1H), 7.67 - 7.61 (m, 2H), 7.55 (dt, J=8.8, 3.5 Hz, 1H), 7.44 (d, J=8.1 Hz, 2H), 7.16 (t, J=9.3 Hz, 1H), 6.82 (dd, J=11.4, 6.1 Hz, 1H), 6.36 (s, 1H), 4.89 - 4.78 (m, 1H), 4.03 (s, 3H), 3.46 (t, J=3.4 Hz, 1H), 3.19 (dd, J=10.7, 4.0 Hz, 1H), 2.97 - 2.89 (m, 1H), 2.31 - 2.20 (m, 1H), 2.06 - 1.94 (m, 1H), 1.78 - 1.67 (m, 2H)	1.29, B
63		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(嘧啶-5-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	577.1	(500MHz, $CDCl_3$) δ 9.52 (d, J=7.5 Hz, 1H), 9.11 (br. s., 1H), 8.72 (br. s., 2H), 8.02 (dd, J=11.2, 9.4 Hz, 1H), 7.97 (dd, J=6.1, 2.4 Hz, 1H), 7.86 (s, 1H), 7.56 (dt, J=8.7, 3.4 Hz, 1H), 7.16 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.6, 6.1 Hz, 1H), 6.25 (s, 1H), 4.89 - 4.79 (m, 1H), 4.02 (s, 3H), 3.38 (br. s., 1H), 3.21 (dd, J=10.8, 4.0 Hz, 1H), 2.98 (br. s., 1H), 2.33 (t, J=9.1 Hz, 1H), 2.02 (t, J=8.7 Hz, 1H), 1.79 - 1.71 (m, 2H)	1.14, B

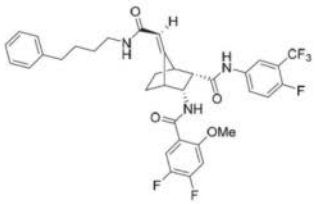
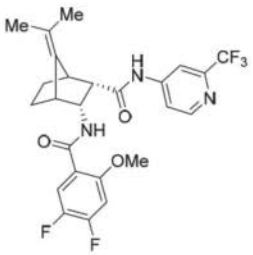
64		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2E)-3-苯基丙-2-烯-1-亚基]双环[2.2.1]庚烷-2-甲酰胺	601.1	(500MHz, $CDCl_3$) δ 9.59 (d, J=7.6 Hz, 1H), 8.07 (dd, J=11.4, 9.4 Hz, 1H), 7.98 (dd, J=6.2, 2.5 Hz, 1H), 7.69 (s, 1H), 7.58 - 7.52 (m, 1H), 7.44 (d, J=7.5 Hz, 2H), 7.38 - 7.31 (m, 3H), 7.27 - 7.22 (m, 1H), 7.15 (t, J=9.4 Hz, 1H), 6.93 (dd, J=15.6, 10.8 Hz, 1H), 6.82 (dd, J=11.5, 6.0 Hz, 1H), 6.56 (d, J=15.6 Hz, 1H), 6.10 (d, J=10.8 Hz, 1H), 4.81 - 4.74 (m, 1H), 4.02 (s, 3H), 3.38 (br. s., 1H), 3.12 (dd, J=10.8, 4.0 Hz, 1H), 2.85 (br. s., 1H), 2.21 (t, J=8.6 Hz, 1H), 1.96 - 1.90 (m, 1H), 1.65 (d, J=6.6 Hz, 2H)	1.35, C

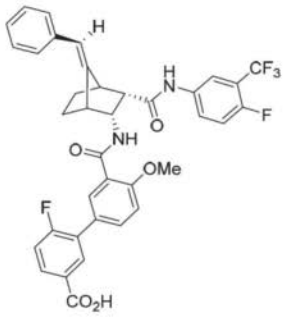
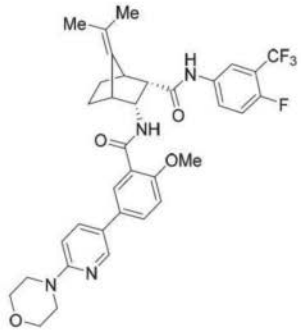
66		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(1-甲基-1H-吡唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	579.1	(500MHz, $CDCl_3$) δ 9.66 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 8.02 - 7.98 (m, 1H), 7.86 (s, 1H), 7.56 (dt, J=8.7, 3.5 Hz, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 7.16 (t, J=9.2 Hz, 1H), 6.82 (dd, J=11.6, 6.1 Hz, 1H), 6.08 (s, 1H), 4.80 - 4.71 (m, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.37 - 3.33 (m, 1H), 3.17 - 3.08 (m, 1H), 2.84 (br. s., 1H), 2.17 (t, J=8.9 Hz, 1H), 1.97 - 1.87 (m, 1H), 1.71 - 1.65 (m, 2H)	1.14, C
67		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2E)-5-羟基戊-2-烯-1-亚基]双环[2.2.1]庚烷-2-甲酰胺	569.2	(500MHz, $CDCl_3$) δ 9.66 (d, J=7.6 Hz, 1H), 8.05 (dd, J=11.3, 9.3 Hz, 1H), 8.02 - 7.98 (m, 1H), 7.86 (s, 1H), 7.56 (dt, J=8.7, 3.5 Hz, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 7.16 (t, J=9.2 Hz, 1H), 6.82 (dd, J=11.6, 6.1 Hz, 1H), 6.08 (s, 1H), 4.80 - 4.71 (m, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.37 - 3.33 (m, 1H), 3.17 - 3.08 (m, 1H), 2.84 (br. s., 1H), 2.17 (t, J=8.9 Hz, 1H), 1.97 - 1.87 (m, 1H), 1.71 - 1.65 (m, 2H)	1.13, C

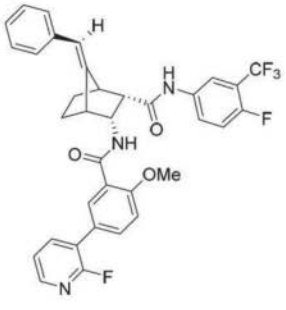
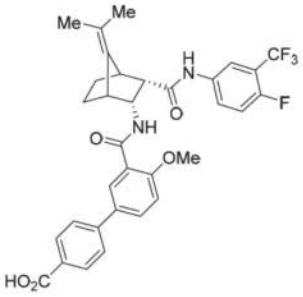
68		(2S,3R,7Z)-7-[(2-氰基苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	600.0	(500MHz, $CDCl_3$) δ 9.81 (d, J=7.5 Hz, 1H), 8.13 - 8.05 (m, 2H), 8.01 (dd, J=11.4, 9.4 Hz, 1H), 7.67 (d, J=7.6 Hz, 1H), 7.60 - 7.52 (m, 3H), 7.38 - 7.31 (m, 1H), 7.18 (t, J=9.3 Hz, 1H), 6.82 (dd, J=11.6, 6.1 Hz, 1H), 6.62 (s, 1H), 4.84 - 4.75 (m, 1H), 4.04 (s, 3H), 3.40 (t, J=3.7 Hz, 1H), 3.26 (dd, J=10.7, 3.8 Hz, 1H), 2.96 (t, J=3.7 Hz, 1H), 2.25 - 2.17 (m, 1H), 2.07 - 1.98 (m, 1H), 1.78 - 1.67 (m, 2H)	1.29, B
69		(2S,3R,7Z)-7-[(2,6-二氯苯基)亚甲基]-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	643.0	(500MHz, $CDCl_3$) δ 9.81 (d, J=7.5 Hz, 1H), 8.13 - 8.05 (m, 2H), 8.01 (dd, J=11.4, 9.4 Hz, 1H), 7.67 (d, J=7.6 Hz, 1H), 7.60 - 7.52 (m, 3H), 7.38 - 7.31 (m, 1H), 7.18 (t, J=9.3 Hz, 1H), 6.82 (dd, J=11.6, 6.1 Hz, 1H), 6.62 (s, 1H), 4.84 - 4.75 (m, 1H), 4.04 (s, 3H), 3.40 (t, J=3.7 Hz, 1H), 3.26 (dd, J=10.7, 3.8 Hz, 1H), 2.96 (t, J=3.7 Hz, 1H), 2.25 - 2.17 (m, 1H), 2.07 - 1.98 (m, 1H), 1.78 - 1.67 (m, 2H)	1.29, B

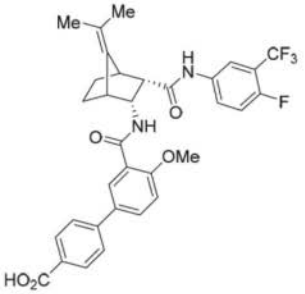
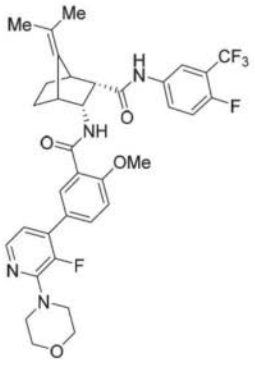
70		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-({3-[(吗啉-4-基)甲基]苯基}亚甲基)双环[2.2.1]庚烷-2-甲酰胺	674.2	(500MHz, DMSO-d6) δ 1H NMR (500MHz, CDCl3) d 9.65 (br. s., 1H), 8.02 (t, J=10.2 Hz, 2H), 7.63 - 7.54 (m, 1H), 7.31 (br. s., 3H), 7.21 (br. s., 1H), 7.15 (t, J=9.3 Hz, 1H), 6.80 (dd, J=11.5, 6.2 Hz, 1H), 6.33 (s, 1H), 4.80 (br. s., 1H), 4.02 (s, 3H), 3.80 (br. s., 4H), 3.65 (br. s., 2H), 3.47 (br. s., 1H), 3.21 (dd, J=10.7, 4.0 Hz, 1H), 2.89 (br. s., 1H), 2.64 (br. s., 2H), 2.26 - 2.15 (m, 1H), 2.00 - 1.91 (m, 1H), 1.69 (br. s., 3H)	1.02, B
71		(2S,3R)-7-(环戊-2,4-二烯-1-亚基)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	567.0	(500MHz, $CDCl_3$) δ 9.39 (d, J=7.7 Hz, 1H), 7.85 (dd, J=11.3, 9.4 Hz, 1H), 7.79 (dd, J=6.2, 2.6 Hz, 1H), 7.61 (s, 1H), 7.37 (dt, J=8.7, 3.5 Hz, 1H), 6.97 (t, J=9.4 Hz, 1H), 6.62 (dd, J=11.6, 6.3 Hz, 1H), 6.44 - 6.39 (m, 2H), 6.30 - 6.26 (m, 1H), 6.21 (dt, J=4.3, 2.1 Hz, 1H), 4.70 - 4.60 (m, 1H), 3.83 (s, 3H), 3.20 (t, J=3.9 Hz, 1H), 3.14 (t, J=3.7 Hz, 1H), 2.99 (dd, J=10.9, 4.0 Hz, 1H), 2.23 - 2.15 (m, 1H), 1.86 - 1.79 (m, 1H), 1.60 - 1.51 (m, 2H)	1.19, A

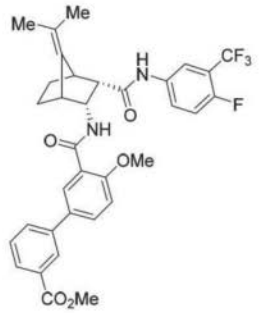
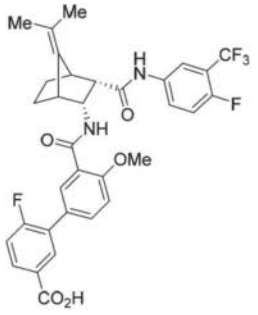
72		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-[(1Z)-2,3-二氢-1H-茚-1-亚基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	601.1	(400MHz, $CDCl_3$) δ 9.48 (d, J=7.5 Hz, 1H), 8.06 (dd, J=11.4, 9.2 Hz, 1H), 7.94 (dd, J=6.2, 2.6 Hz, 1H), 7.80 (s, 1H), 7.71 - 7.63 (m, 1H), 7.59 - 7.51 (m, 1H), 7.31 - 7.24 (m, 2H), 7.22 - 7.17 (m, 2H), 7.12 (t, J=9.5 Hz, 1H), 6.79 (dd, J=11.7, 6.2 Hz, 1H), 4.86 - 4.77 (m, 1H), 4.00 (s, 3H), 3.71 (t, J=4.2 Hz, 1H), 3.12 (dd, J=10.1, 3.5 Hz, 1H), 3.06 (t, J=3.9 Hz, 1H), 3.03 - 2.96 (m, 2H), 2.84 - 2.75 (m, 2H), 2.26 - 2.16 (m, 1H), 1.97 - 1.89 (m, 1H), 1.75 - 1.66 (m, 2H)	1.34, A
73		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(甲基胺甲酰基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	556.1	(500MHz, $CDCl_3$) δ 10.00 (br. s., 1H), 9.75 (br. s., 1H), 8.16 (dd, J=6.2, 2.4 Hz, 1H), 7.92 (t, J=10.2 Hz, 1H), 7.73 - 7.61 (m, 1H), 7.14 - 7.05 (m, 1H), 6.79 (dd, J=11.4, 6.1 Hz, 1H), 6.38 (br. s., 1H), 5.73 (s, 1H), 4.62 (br. s., 1H), 4.03 (s, 3H), 3.81 (br. s., 1H), 3.26 (dd, J=10.8, 3.7 Hz, 1H), 2.86 (br. s., 3H), 2.22 - 2.09 (m, 1H), 2.03 - 1.94 (m, 1H), 1.70 - 1.51 (m, 2H)	1.04, C

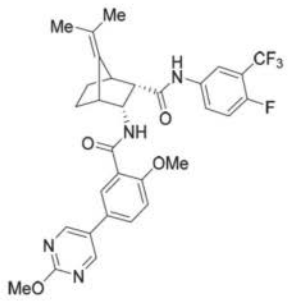
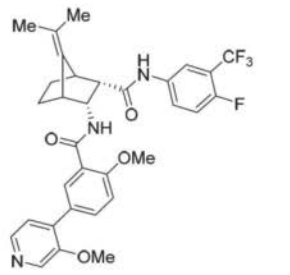
74		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-{[(4-苯基丁基)胺甲酰基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	674.1	(500MHz, $CDCl_3$) δ 9.75 (br. s., 1H), 9.44 (br. s., 1H), 8.11 (d, J=4.0 Hz, 1H), 7.93 (t, J=10.2 Hz, 1H), 7.73 - 7.60 (m, 1H), 7.26 (d, J=7.6 Hz, 2H), 7.21 - 7.16 (m, 1H), 7.15 - 7.06 (m, 3H), 6.76 (dd, J=11.5, 6.0 Hz, 1H), 5.97 (br. s., 1H), 5.68 (s, 1H), 4.67 (br. s., 1H), 3.99 (s, 3H), 3.85 (br. s., 1H), 3.30 (br. s., 2H), 3.24 (dd, J=10.7, 3.8 Hz, 1H), 2.83 (br. s., 1H), 2.61 - 2.54 (m, 2H), 2.22 (t, J=9.4 Hz, 1H), 1.99 - 1.90 (m, 1H), 1.85 (m, 2H), 1.59 (d, J=16.6 Hz, 4H)	1.20, B
75		(2S,3R)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-丙烷-2-亚基)-N-[2-(三氟甲基)吡啶-4-基]双环[2.2.1]庚烷-2-甲酰胺	510.3	(500MHz, $CDCl_3$) δ 9.20 (d, J=7.9 Hz, 1H), 8.55 (d, J=5.5 Hz, 1H), 8.47 (s, 1H), 8.05 (dd, J=11.2, 9.4 Hz, 1H), 8.00 (d, J=1.8 Hz, 1H), 7.54 (dd, J=5.5, 2.0 Hz, 1H), 6.80 (dd, J=11.4, 6.1 Hz, 1H), 4.74 - 4.68 (m, 1H), 4.01 (s, 3H), 3.14 - 3.00 (m, 3H), 2.17 - 2.07 (m, 1H), 1.80 - 1.71 (m, 7H), 1.68 - 1.56 (m, 2H)	1.18, B

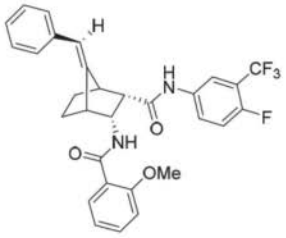
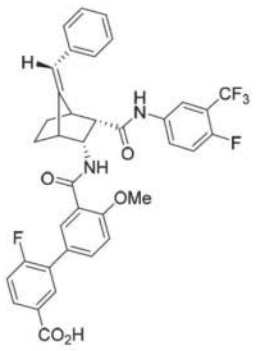
80		6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	677.4	(500MHz, DMSO-d6) δ 10.65 (s, 1H), 10.04 (d, J=6.7 Hz, 1H), 8.25 (d, J=4.3 Hz, 1H), 8.14 (s, 1H), 8.02 (d, J=7.6 Hz, 1H), 7.94 (br. s., 1H), 7.81 (br. s., 1H), 7.74 (d, J=8.2 Hz, 1H), 7.49 (t, J=9.6 Hz, 1H), 7.43 - 7.35 (m, 5H), 7.33 (d, J=8.5 Hz, 1H), 7.29 - 7.20 (m, 1H), 6.38 (s, 1H), 4.53 (br. s., 1H), 4.07 (s, 3H), 3.45 (br. s., 1H), 3.36 - 3.24 (m, 1H), 2.97 - 2.88 (m, 1H), 1.91 (dd, J=20.0, 10.8 Hz, 2H), 1.53 (br. s., 2H)	2.18, B
81		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(吗啉-4-基)吡啶-3-基]苯甲酰胺基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	652.9	(500MHz, DMSO-d6) δ 10.52 (s, 1H), 9.87 (d, J=7.0 Hz, 1H), 8.38 (s, 1H), 8.20 (d, J=4.3 Hz, 1H), 8.13 - 8.07 (m, 1H), 7.84 - 7.76 (m, 2H), 7.76 - 7.69 (m, 1H), 7.52 - 7.41 (m, 1H), 7.23 (d, J=8.5 Hz, 1H), 6.90 (d, J=8.9 Hz, 1H), 4.36 (br. s., 1H), 4.00 (s, 3H), 3.75 - 3.64 (m, 4H), 3.51 (d, J=7.0 Hz, 1H), 3.49 - 3.41 (m, 2H), 3.16 (d, J=4.6 Hz, 1H), 3.10 (dd, J=10.7, 4.0 Hz, 1H), 3.02 (br. s., 1H), 2.93 (br. s., 1H), 1.83 (s, 1H), 1.72 (d, J=9.5 Hz, 7H), 1.34 (d, J=5.8 Hz, 2H)	2.19, C

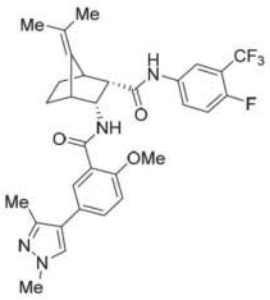
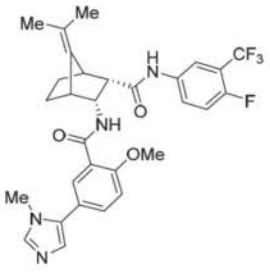
82		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[5-(2-氟吡啶-3-基)-2-甲氧基苯甲酰胺基]-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	634.2	(500MHz, DMSO-d6) δ 10.70 - 10.59 (m, 1H), 10.05 (d, J=6.3 Hz, 1H), 8.26 (br. s., 1H), 8.18 (s, 1H), 8.22 (s, 1H), 8.11 (t, J=8.2 Hz, 1H), 7.88 - 7.72 (m, 2H), 7.55 - 7.43 (m, 2H), 7.43 - 7.30 (m, 5H), 7.26 (d, J=4.5 Hz, 1H), 6.43 - 6.34 (m, 1H), 4.53 (br. s., 1H), 4.07 (s, 3H), 3.29 (br. s., 1H), 2.94 (br. s., 1H), 1.99 - 1.82 (m, 2H), 1.53 (br. s., 2H)。	2.72, B
83		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	611.3	(500MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.26 (s, 1H), 8.21 (d, J=4.9 Hz, 1H), 8.00 (d, J=7.9 Hz, 2H), 7.88 (d, J=8.5 Hz, 1H), 7.84 - 7.68 (m, 3H), 7.47 (t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.38 (br. s., 1H), 4.04 (s, 3H), 3.11 (d, J=10.7 Hz, 1H), 3.03 (br. s., 1H), 2.98 (s, 1H), 2.95 (br. s., 1H), 1.88 - 1.79 (m, 1H), 1.72 (d, J=9.2 Hz, 7H), 1.35 (d, J=5.5 Hz, 2H)	2.54, C

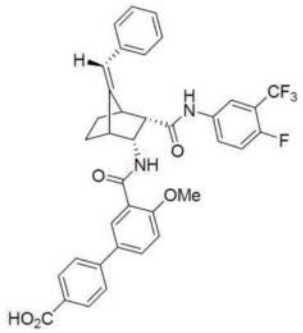
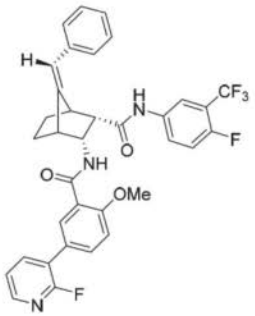
84		2-氟-3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	629.5	(500 MHz, DMSO-d6) δ 10.66 - 10.45 (m, 1H), 10.00 - 9.83 (m, 1H), 8.25 - 8.18 (m, 1H), 8.18 - 8.12 (m, 1H), 7.88 - 7.67 (m, 4H), 7.68 - 7.59 (m, 1H), 7.54 - 7.42 (m, 1H), 7.34 - 7.25 (m, 1H), 4.45 - 4.28 (m, 1H), 4.11 - 3.92 (m, 3H), 3.14 - 3.06 (m, 1H), 3.06 - 2.98 (m, 1H), 2.97 - 2.85 (m, 1H), 1.90 - 1.75 (m, 2H), 1.80 - 1.58 (m, 7H), 1.41 - 1.25 (m, 2H)	2.07, B
85		(1R,2S,3R,4R)-3-{5-[3-氟-2-(吗啉-4-基)吡啶-4-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	671.4	(500MHz, DMSO-d6) δ 10.54 (s, 1H), 9.90 (d, J=7.0 Hz, 1H), 8.19 (d, J=4.3 Hz, 1H), 8.15 (s, 1H), 8.03 (d, J=5.2 Hz, 1H), 7.83 - 7.68 (m, 2H), 7.46 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 6.99 (t, J=5.0 Hz, 1H), 4.34 (br. s., 1H), 4.03 (s, 3H), 3.76 - 3.67 (m, 3H), 3.60 - 3.51 (m, 5H), 3.10 (dd, J=10.5, 3.8 Hz, 1H), 3.02 (br. s., 1H), 2.93 (br. s., 1H), 1.85 - 1.77 (m, 1H), 1.70 (s, 4H), 1.72 (s, 3H), 1.34 (d, J=5.5 Hz, 2H)	2.78, C

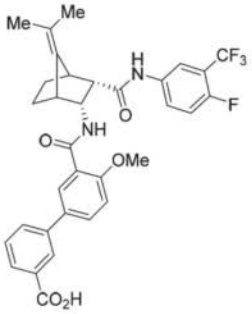
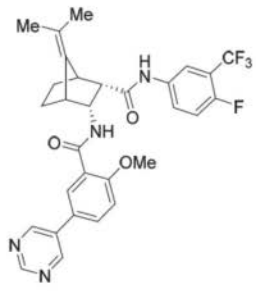
86		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸甲酯	625.4	(500MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (d, J=7.3 Hz, 1H), 8.26 - 8.16 (m, 2H), 8.13 (s, 1H), 7.91 (t, J=7.0 Hz, 2H), 7.85 (dd, J=8.5, 2.1 Hz, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.61 (t, J=7.8 Hz, 1H), 7.46 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.37 (br. s., 1H), 4.03 (s, 3H), 3.88 (s, 3H), 3.14 - 3.07 (m, 1H), 3.03 (br. s., 1H), 2.95 (br. s., 1H), 1.88 - 1.78 (m, 1H), 1.72 (d, J=8.9 Hz, 7H), 1.35 (d, J=6.1 Hz, 2H)	2.84, B
87		6-氟-3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	629.4	(500MHz, DMSO-d6) δ 10.53 (br. s., 1H), 9.92 (br. s., 1H), 8.22 (br. s., 1H), 8.13 (br. s., 1H), 8.02 (d, J=5.8 Hz, 1H), 7.96 (br. s., 1H), 7.80 (br. s., 1H), 7.73 (d, J=7.9 Hz, 1H), 7.52 - 7.38 (m, 2H), 7.31 (d, J=8.2 Hz, 1H), 4.37 (br. s., 1H), 4.05 (br. s., 3H), 3.11 (d, J=10.4 Hz, 1H), 3.04 (br. s., 1H), 2.95 (br. s., 1H), 1.84 (br. s., 1H), 1.71 (s, 3H), 1.73 (s, 4H), 1.35 (br. s., 2H)	2.09, B

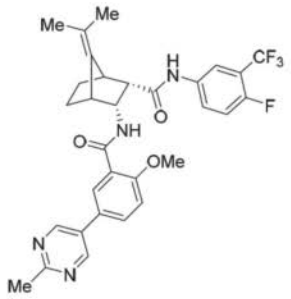
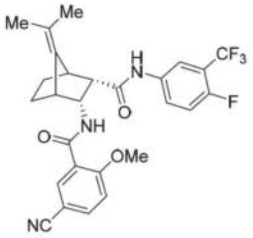
88		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-甲氧基嘧啶-5-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	599.1	(500MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (d, J=7.0 Hz, 1H), 8.86 (s, 2H), 8.22 (d, J=4.3 Hz, 1H), 8.19 - 8.13 (m, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.84 (d, J=8.5 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 4.37 (br. s., 1H), 4.03 (s, 3H), 3.95 (s, 3H), 3.15 - 3.07 (m, 1H), 3.04 (br. s., 1H), 2.94 (br. s., 1H), 1.89 - 1.78 (m, 1H), 1.72 (s, 4H), 1.74 (s, 3H), 1.35 (d, J=6.1 Hz, 2H)	2.59, B
89		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(3-甲氧基吡啶-4-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	598.2	(500MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (d, J=7.3 Hz, 1H), 8.41 (br. s., 1H), 8.23 (br. s., 1H), 8.19 (d, J=4.3 Hz, 1H), 8.14 (d, J=2.1 Hz, 1H), 7.78 (d, J=8.5 Hz, 1H), 7.72 (dd, J=8.5, 2.1 Hz, 1H), 7.45 (t, J=9.8 Hz, 1H), 7.32 (d, J=4.6 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 4.34 (br. s., 1H), 4.02 (s, 3H), 3.86 (s, 3H), 3.16 (s, 1H), 3.09 (dd, J=10.7, 4.0 Hz, 1H), 3.02 (br. s., 1H), 2.92 (br. s., 1H), 1.87 - 1.78 (m, 1H), 1.70 (s, 4H), 1.72 (s, 4H), 1.34 (d, J=5.8 Hz, 2H)	2.53, B

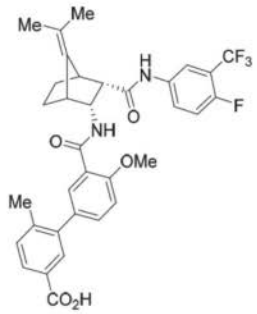
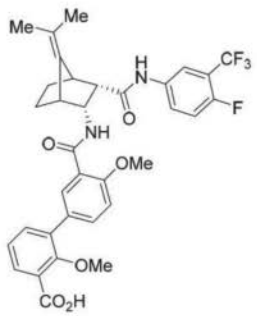
90		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基苯甲酰胺基)-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	539.4	(500MHz, DMSO-d6) δ 9.95 (d, J=7.0 Hz, 1H), 8.26 (d, J=4.3 Hz, 1H), 7.94 (d, J=6.7 Hz, 1H), 7.81 (br. s., 1H), 7.50 (t, J=8.2 Hz, 3H), 7.44 - 7.32 (m, 6H), 7.25 (br. s., 2H), 7.18 (d, J=8.2 Hz, 1H), 7.04 (t, J=7.5 Hz, 1H), 6.39 (s, 1H), 4.52 (br. s., 1H), 3.28 (br. s., 1H), 2.93 (br. s., 1H), 2.02 - 1.79 (m, 3H), 1.53 (br. s., 3H)	2.64, C
91		6-氟-3'-{[(1R,2R,3S,4R,7E)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	677.5	(500MHz, DMSO-d6) δ 10.62 (s, 1H), 10.00 (d, J=7.0 Hz, 1H), 8.21 (d, J=4.3 Hz, 1H), 8.14 (s, 1H), 8.02 (d, J=7.6 Hz, 1H), 7.95 (br. s., 1H), 7.80 (br. s., 1H), 7.73 (d, J=8.5 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.44 - 7.28 (m, 6H), 7.25 (t, J=7.0 Hz, 1H), 6.36 (s, 1H), 4.52 (br. s., 1H), 4.07 (s, 3H), 3.45 (d, J=15.3 Hz, 1H), 3.35 - 3.22 (m, 1H), 2.85 (br. s., 1H), 2.02 - 1.94 (m, 1H), 1.89 - 1.79 (m, 1H), 1.54 (t, J=14.2 Hz, 2H)	2.21, B

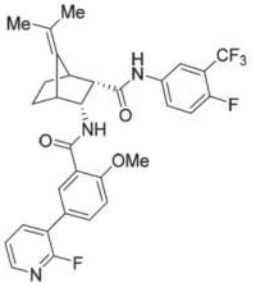
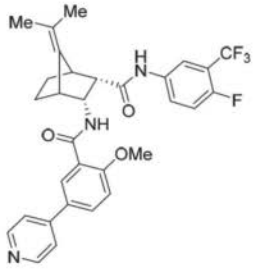
92		(1R,2S,3R,4R)-3-[5-(1,3-二甲基-1H-吡唑-4-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	585.2	(500MHz, DMSO-d6) δ 10.51 (s, 1H), 9.85 (d, J=7.3 Hz, 1H), 8.21 (d, J=4.3 Hz, 1H), 7.97 (d, J=2.1 Hz, 1H), 7.85 - 7.74 (m, 2H), 7.55 - 7.41 (m, 2H), 7.18 (d, J=8.5 Hz, 1H), 4.36 (br. s., 1H), 3.99 (s, 3H), 3.76 (s, 3H), 3.47 - 3.35 (m, 2H), 3.10 (dd, J=10.5, 3.8 Hz, 1H), 3.03 (br. s., 1H), 2.93 (br. s., 1H), 2.24 (s, 3H), 1.89 - 1.79 (m, 1H), 1.71 (s, 3H), 1.73 (s, 4H), 1.35 (d, J=6.1 Hz, 2H)	2.51, B
93		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(1-甲基-1H-咪唑-5-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	571.2	(500MHz, DMSO-d6) δ 10.58 (s, 1H), 9.93 (d, J=7.0 Hz, 1H), 8.78 (br. s., 1H), 8.21 (d, J=4.3 Hz, 1H), 8.05 (s, 1H), 7.79 (d, J=8.5 Hz, 1H), 7.70 (d, J=8.5 Hz, 1H), 7.63 (br. s., 1H), 7.48 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.9 Hz, 1H), 4.34 (br. s., 1H), 4.05 (s, 3H), 3.74 (s, 3H), 3.52 (br. s., 1H), 3.11 (dd, J=10.7, 4.0 Hz, 1H), 3.04 (br. s., 1H), 2.93 (br. s., 1H), 1.81 (t, J=8.7 Hz, 1H), 1.70 (s, 4H), 1.73 (s, 3H), 1.35 (d, J=6.4 Hz, 2H)	2.37, B

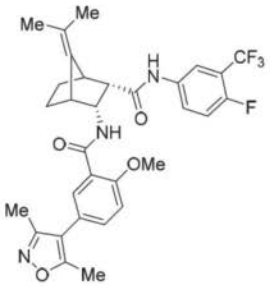
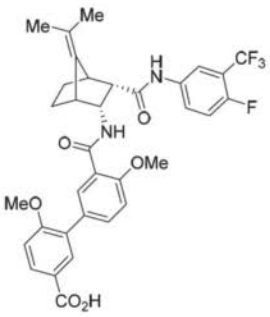
94		3'-{[(1R,2R,3S,4R,7E)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	659.2	(500MHz, DMSO-d6) δ 10.62 (s, 1H), 9.98 (d, J=7.0 Hz, 1H), 8.27 (s, 1H), 8.22 (d, J=4.6 Hz, 1H), 8.03 - 7.97 (m, J=8.2 Hz, 2H), 7.88 (d, J=8.5 Hz, 1H), 7.80 (br. s., 1H), 7.78 - 7.68 (m, J=8.2 Hz, 2H), 7.48 (t, J=9.8 Hz, 1H), 7.44 - 7.35 (m, 4H), 7.32 (d, J=8.5 Hz, 1H), 7.29 - 7.20 (m, 1H), 6.37 (s, 1H), 4.54 (br. s., 1H), 4.06 (s, 3H), 3.29 (d, J=7.3 Hz, 1H), 2.86 (br. s., 1H), 2.03 - 1.94 (m, 1H), 1.84 (br. s., 1H), 1.55 (t, J=13.7 Hz, 2H)	2.69, C
95		(1R,2S,3R,4R,7E)-N-[4-氟-3-(三氟甲基)苯基]-3-[5-(2-氟吡啶-3-基)-2-甲氧基苯甲酰胺基]-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	634.5	(500MHz, DMSO-d6) δ 10.61 (s, 1H), 9.99 (d, J=7.0 Hz, 1H), 8.21 (d, J=4.6 Hz, 2H), 8.18 (s, 1H), 8.10 (t, J=8.2 Hz, 1H), 7.85 - 7.72 (m, 2H), 7.51 - 7.43 (m, 2H), 7.43 - 7.30 (m, 5H), 7.25 (t, J=7.2 Hz, 1H), 6.37 (s, 1H), 4.52 (br. s., 1H), 4.07 (s, 3H), 3.46 - 3.36 (m, 2H), 3.32 - 3.24 (m, 1H), 2.85 (br. s., 1H), 1.97 (d, J=9.2 Hz, 1H), 1.89 - 1.78 (m, 1H), 1.65 - 1.46 (m, 2H)	2.69, B

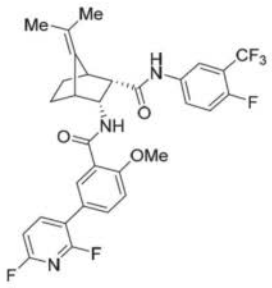
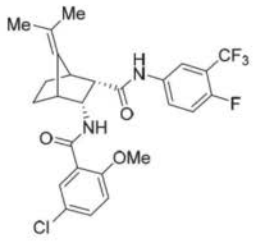
96		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	611.3	(500MHz, DMSO-d6) δ 10.63 (s, 1H), 9.91 (d, J=7.3 Hz, 1H), 8.23 (br. s., 2H), 8.13 (br. s., 1H), 7.90 - 7.75 (m, 3H), 7.69 (d, J=7.6 Hz, 1H), 7.53 - 7.40 (m, 2H), 7.28 (d, J=8.9 Hz, 1H), 4.39 (br. s., 1H), 4.04 (s, 3H), 3.17 - 3.11 (m, 1H), 3.04 (br. s., 1H), 2.99 (s, 1H), 2.96 (br. s., 1H), 1.72 (d, J=6.1 Hz, 6H), 1.35 (d, J=5.8 Hz, 2H), 1.22 (s, 3H), 1.15 (d, J=7.0 Hz, 1H), 0.92 - 0.79 (m, 1H)	2.61, C
97		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(嘧啶-5-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	569.3	(500MHz, DMSO-d6) δ 10.54 (s, 1H), 9.90 (d, J=7.0 Hz, 1H), 9.13 (s, 1H), 9.06 (s, 2H), 8.24 (d, J=1.8 Hz, 1H), 8.19 (d, J=4.3 Hz, 1H), 7.97 - 7.89 (m, 1H), 7.78 (br. s., 1H), 7.46 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.9 Hz, 1H), 4.36 (br. s., 1H), 4.03 (s, 3H), 3.10 (dd, J=10.7, 4.0 Hz, 1H), 3.03 (br. s., 1H), 2.94 (br. s., 1H), 1.88 - 1.76 (m, 1H), 1.71 (d, J=9.8 Hz, 7H), 1.35 (d, J=6.1 Hz, 2H)	2.42, B

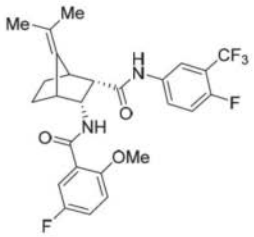
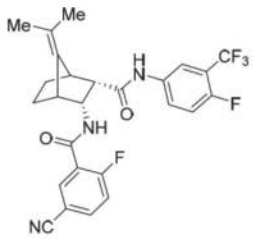
98		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-甲基嘧啶-5-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	583.2	(500MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.90 (s, 2H), 8.22 - 8.11 (m, 2H), 7.87 (d, J=8.5 Hz, 1H), 7.74 (br. s., 1H), 7.43 (t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.33 (br. s., 1H), 4.00 (s, 2H), 3.08 (d, J=10.7 Hz, 1H), 3.00 (br. s., 1H), 2.92 (br. s., 1H), 2.62 (s, 3H), 1.69 (d, J=8.5 Hz, 7H), 1.33 (d, J=6.1 Hz, 2H), 1.17 (br. s., 1H)	2.50, B
99		(1R,2S,3R,4R)-3-(5-氰基-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	516.2	(500MHz, DMSO-d6) δ 10.56 (s, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.25 - 8.13 (m, 2H), 7.97 (d, J=8.5 Hz, 1H), 7.79 (d, J=8.9 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.37 (d, J=8.9 Hz, 1H), 4.32 (br. s., 1H), 4.07 (s, 3H), 3.49 - 3.38 (m, 1H), 3.10 (dd, J=10.7, 4.0 Hz, 1H), 3.03 (br. s., 1H), 2.93 (br. s., 1H), 1.79 (d, J=9.5 Hz, 1H), 1.78 - 1.65 (m, 8H), 1.34 (d, J=5.5 Hz, 2H)	2.59, B

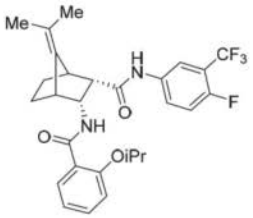
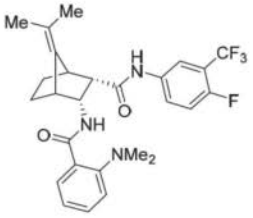
100		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-6-甲基-[1,1'-联苯]-3-甲酸	625.5	(500 MHz, DMSO-d6) δ 10.63 - 10.51 (m, 1H), 9.98 - 9.86 (m, 1H), 8.30 - 8.17 (m, 1H), 7.95 - 7.86 (m, 1H), 7.86 - 7.77 (m, 2H), 7.77 - 7.64 (m, 1H), 7.56 - 7.44 (m, 2H), 7.44 - 7.34 (m, 1H), 7.33 - 7.17 (m, 1H), 4.44 - 4.29 (m, 1H), 4.10 - 3.98 (m, 3H), 3.15 - 3.08 (m, 1H), 3.08 - 2.99 (m, 1H), 2.97 - 2.83 (m, 2H), 2.32 - 2.21 (m, 2H), 1.95 - 1.81 (m, 2H), 1.80 - 1.61 (m, 7H), 1.41 - 1.29 (m, 2H), 1.21 - 1.10 (m, 1H)	2.19, B
101		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-2,4'-二甲氧基-[1,1'-联苯]-3-甲酸	641.2	(500MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.19 (d, J=4.6 Hz, 1H), 8.07 (s, 1H), 7.92 (s, 1H), 7.77 (br. s., 1H), 7.64 (d, J=8.8 Hz, 1H), 7.53 (br. s., 1H), 7.45 (t, J=9.8 Hz, 1H), 7.39 (d, J=7.0 Hz, 1H), 7.29 - 7.15 (m, 2H), 4.35 (br. s., 1H), 4.02 (s, 3H), 3.39 (s, 3H), 3.09 (d, J=10.4 Hz, 1H), 3.01 (br. s., 1H), 2.92 (br. s., 1H), 1.88 - 1.79 (m, 1H), 1.70 (d, J=9.5 Hz, 7H), 1.39 - 1.29 (m, 2H)	2.04, B

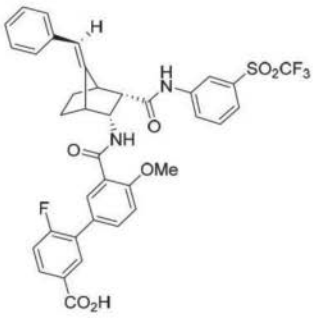
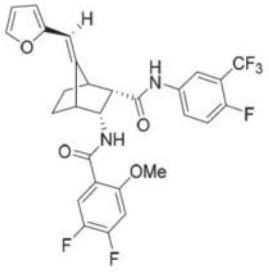
102		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[5-(2-氟吡啶-3-基)-2-甲氧基苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	586.3	(500MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 (d, J=7.3 Hz, 1H), 8.20 - 8.13 (m, 2H), 8.11 (br. s., 1H), 8.04 (t, J=8.7 Hz, 1H), 7.79 - 7.69 (m, 2H), 7.47 - 7.38 (m, 2H), 7.30 (d, J=8.9 Hz, 1H), 4.33 (br. s., 1H), 4.01 (s, 3H), 3.12 - 3.04 (m, 1H), 3.00 (br. s., 1H), 2.92 (br. s., 1H), 1.80 (t, J=8.7 Hz, 1H), 1.69 (d, J=8.9 Hz, 6H), 1.33 (d, J=6.4 Hz, 2H), 1.17 (br. s., 1H)	2.71, B
103		(1R,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(吡啶-4-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	568.2	(500MHz, DMSO-d6) δ 10.59 (s, 1H), 9.93 (d, J=6.7 Hz, 1H), 8.80 (br. s., 2H), 8.45 (s, 1H), 8.22 (d, J=4.6 Hz, 1H), 8.12 (d, J=6.1 Hz, 3H), 7.80 (br. s., 1H), 7.48 (t, J=9.8 Hz, 1H), 7.40 (d, J=8.9 Hz, 1H), 4.37 (br. s., 1H), 4.08 (s, 3H), 3.51 (br. s., 1H), 3.16 (s, 1H), 3.12 (dd, J=10.4, 4.0 Hz, 1H), 3.05 (br. s., 1H), 2.95 (br. s., 1H), 1.87 - 1.77 (m, 1H), 1.72 (d, J=9.8 Hz, 7H), 1.36 (d, J=5.8 Hz, 2H)	2.12, C

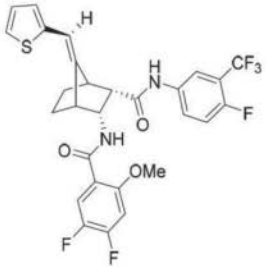
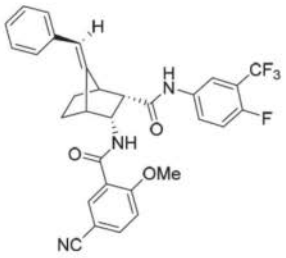
104		(1R,2S,3R,4R)-3-[5-(3,5-二甲基-1,2-噁唑-4-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	586.3	(500MHz, DMSO-d6) δ 10.57 (br. s., 1H), 9.90 (d, J=6.3 Hz, 1H), 8.23 (d, J=5.0 Hz, 1H), 7.86 (d, J=2.0 Hz, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.55 - 7.44 (m, 2H), 7.27 (d, J=8.6 Hz, 1H), 4.35 (br. s., 1H), 4.03 (s, 3H), 3.46 (br. s., 5H), 3.10 (dd, J=10.6, 4.0 Hz, 1H), 3.03 (br. s., 1H), 2.93 (br. s., 1H), 2.35 (s, 3H), 2.17 (s, 3H), 1.83 (t, J=9.0 Hz, 1H), 1.70 (s, 3H), 1.73 (s, 4H), 1.35 (d, J=6.0 Hz, 2H)	2.69, B
105		3'-{[(1R,2R,3S,4R)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4',6-二甲氧基-[1,1'-联苯]-3-甲酸	641.2	(500 MHz, DMSO-d6) δ 10.63 - 10.50 (m, 1H), 9.98 - 9.85 (m, 1H), 8.26 - 8.16 (m, 1H), 8.09 - 8.00 (m, 1H), 8.00 - 7.86 (m, 1H), 7.86 - 7.71 (m, 2H), 7.71 - 7.59 (m, 1H), 7.51 - 7.40 (m, 1H), 7.27 - 7.10 (m, 2H), 4.41 - 4.28 (m, 1H), 4.10 - 3.97 (m, 3H), 3.88 - 3.73 (m, 2H), 3.72 - 3.61 (m, 1H), 3.19 - 3.14 (m, 1H), 3.13 - 3.05 (m, 1H), 3.05 - 2.98 (m, 1H), 2.98 - 2.85 (m, 1H), 1.87 - 1.79 (m, 1H), 1.79 - 1.64 (m, 7H), 1.44 - 1.27 (m, 2H)	2.24, B

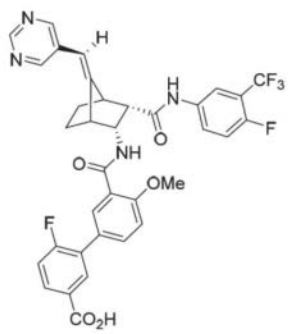
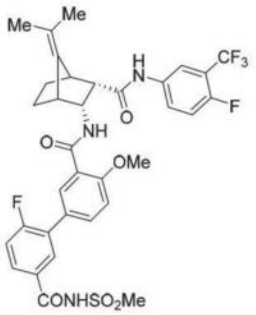
106		(1R,2S,3R,4R)-3-[5-(2,6-二氟吡啶-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	604.3	(500MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.3 Hz, 1H), 8.31 - 8.22 (m, 1H), 8.19 (d, J=4.6 Hz, 1H), 8.11 (s, 1H), 7.77 (br. s., 1H), 7.72 (d, J=8.8 Hz, 1H), 7.46 (t, J=9.6 Hz, 1H), 7.31 (d, J=8.5 Hz, 1H), 7.24 (d, J=6.7 Hz, 1H), 4.35 (br. s., 1H), 4.03 (s, 3H), 3.10 (dd, J=10.8, 3.8 Hz, 1H), 3.02 (br. s., 1H), 2.93 (br. s., 1H), 1.87 - 1.77 (m, 1H), 1.70 (s, 4H), 1.72 (s, 3H), 1.34 (d, J=6.4 Hz, 2H)	2.77, B
109		(2S,3R)-3-(5-氯-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	525.2	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.90 (br d, J=7.0 Hz, 1H), 8.17 (br d, J=4.0 Hz, 1H), 7.83 (d, J=2.4 Hz, 1H), 7.80 - 7.71 (m, 1H), 7.52 (dd, J=8.9, 2.4 Hz, 1H), 7.45 (br t, J=9.6 Hz, 1H), 7.20 (d, J=8.9 Hz, 1H), 4.35 - 4.25 (m, 1H), 3.97 (s, 3H), 3.08 (br dd, J=10.7, 4.0 Hz, 1H), 3.03 - 2.98 (m, 1H), 2.93 - 2.88 (m, 1H), 1.82 - 1.75 (m, 1H), 1.73 - 1.65 (m, 7H), 1.40 - 1.25 (m, 2H)	2.60, B

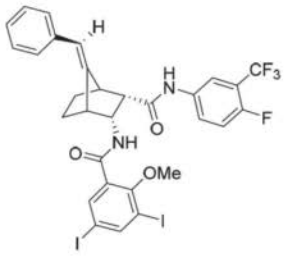
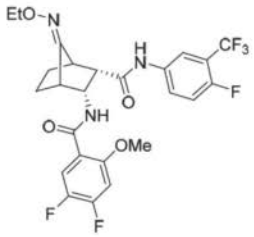
111		(2S,3R)-3-(5-氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	509.0	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.94 (d, J=7.0 Hz, 1H), 8.19 (d, J=4.3 Hz, 1H), 7.84 - 7.72 (m, 1H), 7.63 (dd, J=9.5, 3.1 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.20 (dd, J=9.2, 4.3 Hz, 1H), 4.42 - 4.24 (m, 1H), 3.97 (s, 3H), 3.09 (dd, J=10.7, 4.0 Hz, 1H), 3.05 - 2.99 (m, 1H), 2.95 - 2.88 (m, 1H), 1.81 (t, J=8.7 Hz, 1H), 1.75 - 1.63 (m, 7H), 1.40 - 1.26 (m, 2H)	2.64, B
114		(2S,3R)-3-(5-氰基-2-氟苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	504.1	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.34 (br t, J=6.0 Hz, 1H), 8.14 - 8.10 (m, 1H), 8.07 - 8.02 (m, 1H), 8.02 - 7.99 (m, 1H), 7.83 - 7.76 (m, 1H), 7.56 (t, J=9.6 Hz, 1H), 7.46 (t, J=9.8 Hz, 1H), 4.36 - 4.27 (m, 1H), 3.09 (dd, J=10.4, 4.0 Hz, 1H), 3.06 - 3.01 (m, 1H), 2.95 - 2.90 (m, 1H), 1.80 - 1.74 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.41 - 1.32 (m, 2H)	2.53, C

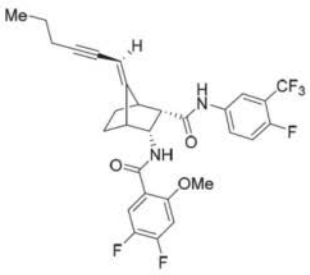
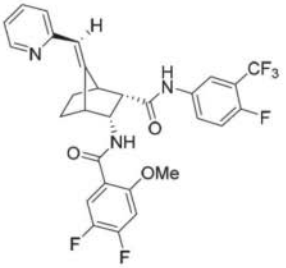
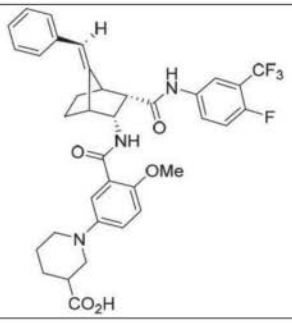
115		(2S,3R)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)-3-[2-丙烷-2-基氧基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	519.4	(500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.54 (d, J=7.9 Hz, 1H), 8.26 (d, J=4.3 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.47 - 7.37 (m, 2H), 7.15 (d, J=8.2 Hz, 1H), 6.96 (t, J=7.5 Hz, 1H), 4.87 (dt, J=11.9, 6.0 Hz, 1H), 4.48 - 4.38 (m, 1H), 3.05 (dd, J=10.7, 3.7 Hz, 1H), 3.02 - 2.98 (m, 1H), 2.89 - 2.84 (m, 1H), 1.86 (dd, J=15.6, 9.2 Hz, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.46 (d, J=5.8 Hz, 3H), 1.41 (d, J=6.1 Hz, 3H), 1.39 - 1.34 (m, 2H)	2.75, C
119		(2S,3R)-3-[2-(二甲基氨基)苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	504.3	(500 MHz, DMSO-d6) δ 10.52 (br d, J=7.4 Hz, 1H), 10.47 (br s, 1H), 8.21 (d, J=5.1 Hz, 1H), 7.77 (d, J=7.7 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.50 - 7.36 (m, 2H), 7.26 (d, J=8.0 Hz, 1H), 7.09 (t, J=7.4 Hz, 1H), 4.48 - 4.32 (m, 1H), 3.08 (dd, J=10.8, 4.0 Hz, 1H), 3.03 - 2.97 (m, 1H), 2.93 - 2.87 (m, 1H), 2.63 (s, 6H), 1.90 (t, J=9.2 Hz, 1H), 1.80 - 1.65 (m, 7H), 1.45 - 1.26 (m, 2H)	2.71, B

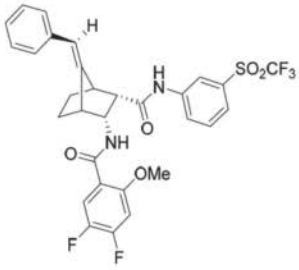
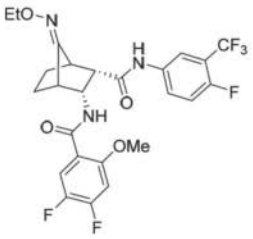
122		6-氟-4'-甲氧基-3'-{[(2R,3S,7Z)-7-(苯基亚甲基)-3-[(3-三氟甲磺酰基苯基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-[1,1'-联苯]-3-甲酸	723.2	(500 MHz, $CDCl_3$) δ 9.94 - 9.64 (m, 1H), 8.61 (br d, J=7.7 Hz, 1H), 8.45 - 7.97 (m, 3H), 7.80 - 7.65 (m, 3H), 7.63 - 7.56 (m, 1H), 7.42 - 7.30 (m, 3H), 7.25 - 7.15 (m, 2H), 7.10 (br d, J=8.3 Hz, 1H), 6.35 (br s, 1H), 4.97 (br s, 1H), 4.15 (br s, 3H), 3.52 (br s, 1H), 3.37 - 3.23 (m, 1H), 2.94 (br s, 1H), 2.40 - 2.33 (m, 1H), 2.02 - 1.96 (m, 1H), 1.80 - 1.68 (m, 2H)	1.21, A
123		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(呋喃-2-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	565.0	(500 MHz, $CDCl_3$) δ 9.43 (br d, J=7.4 Hz, 1H), 8.04 (br t, J=10.3 Hz, 1H), 7.93 (br d, J=4.0 Hz, 1H), 7.88 (br s, 1H), 7.60 - 7.49 (m, 1H), 7.36 (s, 1H), 7.11 (br t, J=9.3 Hz, 1H), 6.79 (br dd, J=11.4, 6.1 Hz, 1H), 6.38 (br s, 1H), 6.25 (d, J=2.9 Hz, 1H), 6.08 (s, 1H), 4.82 (br t, J=11.0 Hz, 1H), 3.74 (br s, 1H), 3.14 (br dd, J=10.6, 3.2 Hz, 1H), 2.85 (br s, 1H), 2.31 - 2.17 (m, 1H), 1.98 - 1.85 (m, 1H), 1.76 - 1.63 (m, 2H)	1.23, C

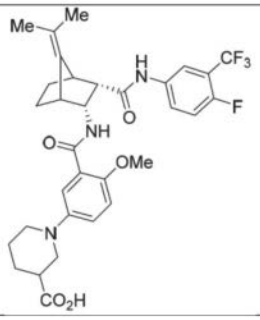
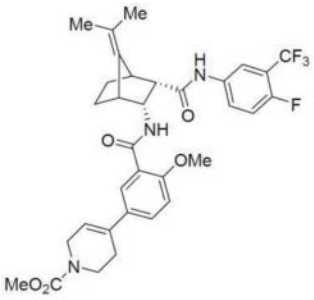
124		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(噻吩-2-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	581.0	(500 MHz, $CDCl_3$) δ 9.49 (br d, J=7.4 Hz, 1H), 8.05 (br t, J=10.3 Hz, 1H), 7.94 (br d, J=5.7 Hz, 1H), 7.84 (br s, 1H), 7.59 - 7.48 (m, 1H), 7.20 (br d, J=4.6 Hz, 1H), 7.12 (br t, J=9.3 Hz, 1H), 7.01 - 6.94 (m, 2H), 6.79 (dd, J=11.4, 6.1 Hz, 1H), 6.43 (s, 1H), 4.84 - 4.77 (m, 1H), 3.66 - 3.60 (m, 1H), 3.19 - 3.12 (m, 1H), 2.89 - 2.83 (m, 1H), 2.26 - 2.18 (m, 1H), 1.96 - 1.87 (m, 1H), 1.75 - 1.63 (m, 2H)	1.25, C
128		(2S,3R,7Z)-3-(5-氰基-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	564.1	(500 MHz, $CDCl_3$) δ 9.67 (br d, J=7.7 Hz, 1H), 8.49 (d, J=2.2 Hz, 1H), 8.01 (dd, J=6.2, 2.6 Hz, 1H), 7.72 (dd, J=8.5, 2.2 Hz, 1H), 7.63 (s, 1H), 7.50 (dt, J=8.5, 3.6 Hz, 1H), 7.34 (d, J=4.4 Hz, 4H), 7.25 - 7.21 (m, 1H), 7.15 (t, J=9.2 Hz, 1H), 7.05 (d, J=8.5 Hz, 1H), 6.33 (s, 1H), 4.85 - 4.79 (m, 1H), 4.10 (s, 3H), 3.55 - 3.50 (m, 1H), 3.16 (dd, J=10.7, 3.9 Hz, 1H), 2.90 - 2.85 (m, 1H), 2.20 - 2.14 (m, 1H), 1.96 - 1.90 (m, 1H), 1.67 - 1.64 (m, 2H)	1.22, A

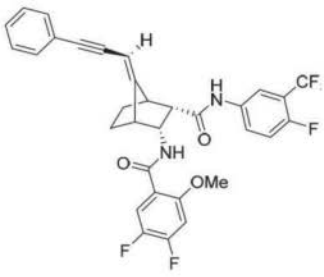
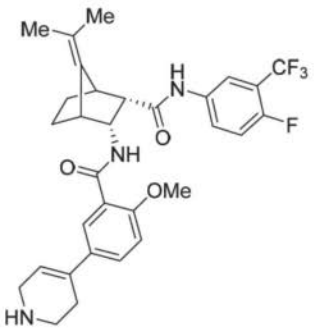
129		6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(嘧啶-5-基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	679.3	-	1.08, A
131		6'-氟-N3-[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]-N3'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	706.3	(500 MHz, $CDCl_3$) δ 10.44 (br s, 1H), 9.77 (d, J=7.7 Hz, 1H), 8.30 (d, J=1.9 Hz, 1H), 8.12 (s, 1H), 8.07 - 7.99 (m, 2H), 7.92 (ddd, J=8.6, 4.5, 2.3 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.61 (dt, J=8.8, 3.4 Hz, 1H), 7.20 (dd, J=9.9, 8.5 Hz, 1H), 7.13 (t, J=9.4 Hz, 1H), 7.07 (d, J=8.8 Hz, 1H), 4.45 - 4.37 (m, 1H), 4.06 (s, 3H), 3.46 (s, 3H), 2.99 - 2.91 (m, 3H), 2.11 - 2.04 (m, 1H), 1.83 - 1.77 (m, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.55 - 1.46 (m, 2H)	1.23, A

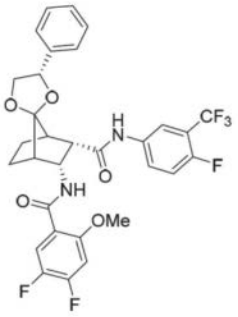
132		(2S,3R,7Z)-3-(3,5-二碘-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	791.0	(500 MHz, $CDCl_3$) δ 9.10 (br d, J=8.0 Hz, 1H), 8.25 (d, J=2.2 Hz, 1H), 8.19 (d, J=2.2 Hz, 1H), 7.83 - 7.72 (m, 2H), 7.66 (dt, J=8.5, 3.6 Hz, 1H), 7.38 - 7.30 (m, 4H), 7.26 - 7.22 (m, 1H), 7.13 (t, J=9.4 Hz, 1H), 6.34 (s, 1H), 4.89 - 4.81 (m, 1H), 3.78 (s, 3H), 3.47 - 3.41 (m, 1H), 3.24 - 3.17 (m, 1H), 2.93 - 2.88 (m, 1H), 2.31 - 2.24 (m, 1H), 1.97 - 1.88 (m, 1H), 1.79 - 1.68 (m, 2H)	1.35, A
133		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-(乙氧基亚氨基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	544.1	(500 MHz, $CDCl_3$) δ 9.49 (br d, J=7.3 Hz, 1H), 8.05 - 7.93 (m, 3H), 7.51 (dt, J=8.8, 3.5 Hz, 1H), 7.13 (t, J=9.3 Hz, 1H), 6.79 (dd, J=11.5, 6.1 Hz, 1H), 4.90 - 4.81 (m, 1H), 4.09 (q, J=7.0 Hz, 2H), 3.99 (s, 3H), 3.50 (t, J=3.9 Hz, 1H), 3.22 (dd, J=10.8, 4.0 Hz, 1H), 2.86 (t, J=3.8 Hz, 1H), 2.38 - 2.26 (m, 1H), 1.98 - 1.87 (m, 1H), 1.81 - 1.70 (m, 2H), 1.27 (t, J=7.1 Hz, 3H)	1.18, B

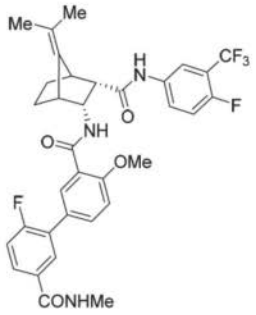
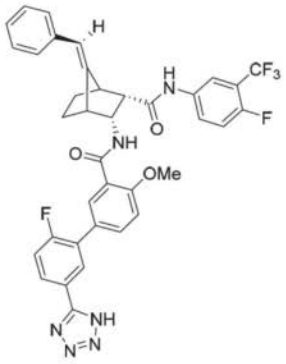
135		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(己-2-炔-1-亚基)双环[2.2.1]庚烷-2-甲酰胺	565.1	(500 MHz, $CDCl_3$) δ 9.32 (br d, J=7.6 Hz, 1H), 8.06 (dd, J=11.3, 9.3 Hz, 1H), 7.91 (dd, J=6.3, 2.6 Hz, 1H), 7.84 (s, 1H), 7.53 (dt, J=8.7, 3.5 Hz, 1H), 7.17 - 7.05 (m, 1H), 6.80 (dd, J=11.6, 6.1 Hz, 1H), 5.37 (t, J=2.0 Hz, 1H), 4.87 - 4.77 (m, 1H), 4.00 (s, 3H), 3.25 (t, J=4.0 Hz, 1H), 3.11 (dd, J=11.3, 3.5 Hz, 1H), 2.82 (t, J=3.8 Hz, 1H), 2.35 - 2.23 (m, 3H), 1.94 - 1.82 (m, 1H), 1.74 - 1.66 (m, 2H), 1.63 - 1.57 (m, 2H), 1.03 (t, J=7.3 Hz, 3H)	1.28, B
137		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(吡啶-2-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	576.0	-	0.96, C
138		1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)哌啶-3-甲酸	666.3	-	1.07, A

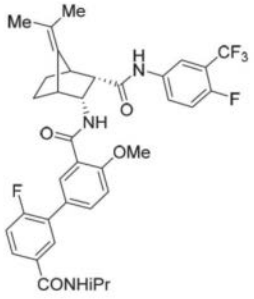
139		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-(3-甲磺酰基苯基)-7-(苯基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	567.1	(500 MHz, $CDCl_3$) δ 9.58 (br d, J=7.7 Hz, 1H), 8.34 (t, J=1.8 Hz, 1H), 8.03 (dd, J=11.6, 9.4 Hz, 1H), 7.91 (s, 1H), 7.68 - 7.61 (m, 2H), 7.53 - 7.44 (m, 1H), 7.34 (d, J=4.4 Hz, 4H), 7.25 - 7.20 (m, 1H), 6.79 (dd, J=11.6, 6.3 Hz, 1H), 6.33 (s, 1H), 4.87 - 4.80 (m, 1H), 4.04 (s, 3H), 3.51 - 3.47 (m, 1H), 3.21 - 3.16 (m, 1H), 3.04 (s, 3H), 2.91 - 2.86 (m, 1H), 2.24 - 2.19 (m, 1H), 1.96 - 1.88 (m, 1H), 1.73 - 1.67 (m, 2H)	1.11, A
141		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-7-(乙氧基亚氨基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	544.1	(500 MHz, $CDCl_3$) δ 9.52 (br d, J=7.6 Hz, 1H), 8.01 (dd, J=11.2, 9.4 Hz, 1H), 7.96 (dd, J=6.2, 2.4 Hz, 1H), 7.83 (br s, 1H), 7.50 (dt, J=8.8, 3.4 Hz, 1H), 7.13 (t, J=9.3 Hz, 1H), 6.78 (dd, J=11.5, 6.1 Hz, 1H), 4.91 - 4.82 (m, 1H), 4.11 (q, J=7.0 Hz, 2H), 4.00 (s, 3H), 3.50 - 3.45 (m, 1H), 3.18 (dd, J=10.6, 4.0 Hz, 1H), 2.92 - 2.87 (m, 1H), 2.33 - 2.23 (m, 1H), 1.98 - 1.86 (m, 1H), 1.81 - 1.70 (m, 2H), 1.28 (t, J=7.1 Hz, 3H)	1.18, B

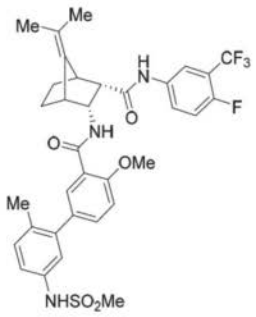
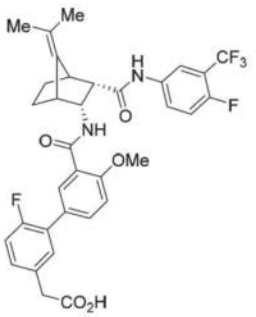
142		1-(3-{[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)哌啶-3-甲酸	618.3	-	0.98, A
143		4-(3-{[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1,2,3,6-四氢吡啶-1-甲酸甲酯	630.4	(500 MHz, $CDCl_3$) δ 9.27 (br d, J=8.2 Hz, 1H), 8.20 (br s, 1H), 8.08 (br s, 1H), 7.83 (dd, J=6.1, 2.5 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.44 (dd, J=8.5, 2.1 Hz, 1H), 7.05 (t, J=9.3 Hz, 1H), 6.92 (d, J=8.7 Hz, 1H), 6.06 - 5.94 (m, 1H), 4.78 - 4.67 (m, 1H), 4.11 (br s, 2H), 3.98 (s, 3H), 3.75 (s, 3H), 3.68 (br s, 2H), 3.09 - 2.99 (m, 3H), 2.51 (br s, 2H), 2.20 - 2.13 (m, 1H), 1.82 - 1.76 (m, 1H), 1.73 (s, 3H), 1.72 (s, 3H), 1.64 - 1.58 (m, 2H)	1.25, C

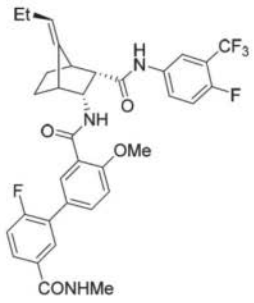
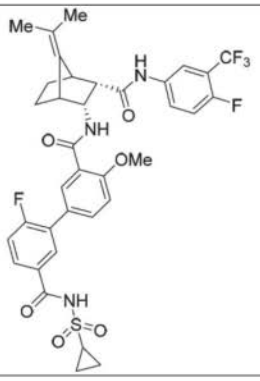
146		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(3-苯基丙-2-炔-1-亚基)双环[2.2.1]庚烷-2-甲酰胺	598.6	(500 MHz, $CDCl_3$) δ 9.34 (br d, J=8.1 Hz, 1H), 8.06 (dd, J=11.4, 9.4 Hz, 1H), 7.92 (dd, J=6.2, 2.7 Hz, 1H), 7.87 (s, 1H), 7.54 (dt, J=9.0, 3.4 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.36 - 7.31 (m, 3H), 7.13 (t, J=9.3 Hz, 1H), 6.81 (dd, J=11.4, 6.1 Hz, 1H), 5.62 (s, 1H), 4.94 - 4.84 (m, 1H), 4.01 (s, 3H), 3.36 (t, J=4.0 Hz, 1H), 3.21 - 3.13 (m, 1H), 2.91 (t, J=3.8 Hz, 1H), 2.38 - 2.30 (m, 1H), 1.96 - 1.88 (m, 1H), 1.80 - 1.66 (m, 2H)	2.84, C
148		(2S,3R)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(1,2,3,6-四氢吡啶-4-基)苯甲酰胺基]-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-甲酰胺	572.4	(500 MHz, $CDCl_3$) δ 9.36 (br d, J=7.7 Hz, 1H), 8.41 (br s, 1H), 8.15 (d, J=2.4 Hz, 1H), 7.91 (dd, J=5.9, 1.9 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.44 (dd, J=8.7, 2.4 Hz, 1H), 7.06 (t, J=9.3 Hz, 1H), 6.93 (d, J=8.7 Hz, 1H), 6.03 (br s, 1H), 4.70 - 4.62 (m, 1H), 3.99 (s, 3H), 3.62 (br d, J=2.4 Hz, 2H), 3.22 (t, J=5.8 Hz, 2H), 3.06 (dd, J=10.8, 3.9 Hz, 1H), 3.01 - 2.95 (m, 2H), 2.57 (br d, J=2.7 Hz, 2H), 2.19 - 2.14 (m, 1H), 1.81 - 1.75 (m, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.59 - 1.52 (m, 2H)	0.98, B

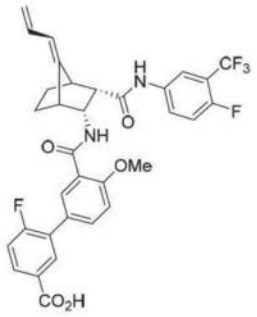
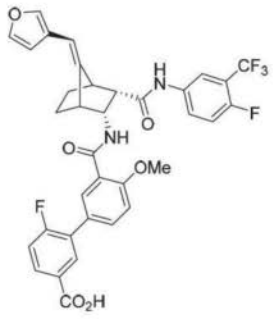
149		6'-氟-N3-((1R,2R,3S,4R)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基)-4-甲氧基-N3'-甲基-[1,1'-联苯]-3,3'-二甲酰胺	621.2	(400 MHz, $CDCl_3$) δ 9.32 (br d, J=8.1 Hz, 1H), 8.02 (dd, J=11.4, 9.5 Hz, 1H), 7.91 (dd, J=6.3, 2.5 Hz, 1H), 7.81 (s, 1H), 7.54 - 7.47 (m, 1H), 7.42 - 7.34 (m, 5H), 7.09 (t, J=9.2 Hz, 1H), 6.78 (dd, J=11.6, 6.1 Hz, 1H), 5.16 (t, J=6.8 Hz, 1H), 5.09 - 4.98 (m, 1H), 4.34 (dd, J=8.1, 6.4 Hz, 1H), 3.98 (s, 3H), 3.83 (t, J=7.8 Hz, 1H), 3.55 (dd, J=10.6, 3.7 Hz, 1H), 2.36 - 2.31 (m, 1H), 2.31 - 2.26 (m, 1H), 2.23 - 2.17 (m, 1H), 1.96 - 1.83 (m, 2H), 1.78 - 1.68 (m, 1H)	1.24, A

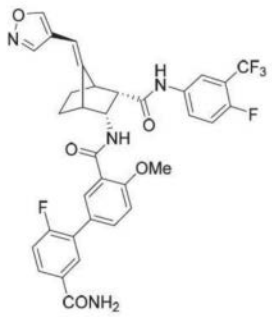
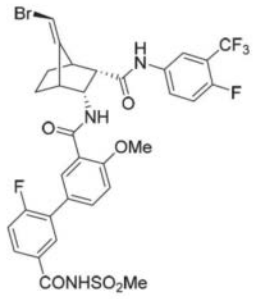
151		6'-氟-N3-((1R,2R,3S,4R)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基)-4-甲氧基-N3'-甲基-[1,1'-联苯]-3,3'-二甲酰胺	642.2	(500 MHz, $CDCl_3$) δ 9.41 (d, J=7.9 Hz, 1H), 8.36 (d, J=1.8 Hz, 1H), 8.14 (s, 1H), 7.94 (dd, J=6.2, 2.5 Hz, 1H), 7.81 (dd, J=7.3, 2.2 Hz, 1H), 7.76 (ddd, J=8.4, 4.6, 2.3 Hz, 1H), 7.66 (dt, J=8.6, 1.9 Hz, 1H), 7.56 (dt, J=8.7, 3.4 Hz, 1H), 7.19 (dd, J=10.0, 8.7 Hz, 1H), 7.08 (t, J=9.3 Hz, 1H), 7.04 (d, J=8.6 Hz, 1H), 6.29 (br d, J=4.3 Hz, 1H), 4.74 - 4.64 (m, 1H), 4.04 (s, 3H), 3.07 - 3.00 (m, 6H), 2.18 - 2.11 (m, 1H), 1.84 - 1.78 (m, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.60 - 1.53 (m, 2H)	1.18, B
152		2'-氟-N-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]-4-甲氧基-5'-(1H-1,2,3,4-四唑-5-基)-[1,1'-联苯]-3-甲酰胺	701.2	(500 MHz, DMSO-d6) δ 10.64 (s, 1H), 10.07 (br d, J=7.0 Hz, 1H), 8.27 (d, J=4.3 Hz, 1H), 8.23 (br s, 1H), 8.20 - 8.15 (m, 1H), 8.10 - 8.00 (m, 1H), 7.87 - 7.76 (m, 2H), 7.58 - 7.46 (m, 2H), 7.42 - 7.34 (m, 5H), 7.29 - 7.23 (m, 1H), 6.39 (s, 1H), 4.64 - 4.47 (m, 1H), 4.08 (s, 3H), 3.31 (br dd, J=10.1, 4.0 Hz, 1H), 3.16 (s, 1H), 2.97 - 2.91 (m, 1H), 1.91 (dd, J=17.5, 8.7 Hz, 2H), 1.64 - 1.44 (m, 2H)	2.26, B

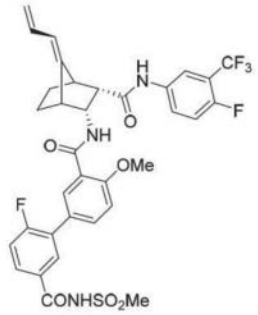
153		6'-氟-N3-[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N3'-丙烷-2-基)-[1,1'-联苯]-3,3'-二甲酰胺	670.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, J=7.3 Hz, 1H), 8.34 (d, J=7.6 Hz, 1H), 8.22 (d, J=4.0 Hz, 1H), 8.15 (s, 1H), 8.01 - 7.94 (m, 1H), 7.90 - 7.84 (m, 1H), 7.83 - 7.78 (m, 1H), 7.74 (d, J=8.5 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.37 (t, J=9.5 Hz, 1H), 7.32 (d, J=8.9 Hz, 1H), 4.41 - 4.33 (m, 1H), 4.14 - 4.07 (m, 1H), 4.05 (s, 3H), 3.11 (dd, J=10.5, 3.8 Hz, 1H), 3.06 - 3.01 (m, 1H), 2.98 - 2.92 (m, 1H), 1.88 - 1.80 (m, 1H), 1.78 - 1.67 (m, 7H), 1.41 - 1.31 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H)	2.69, C

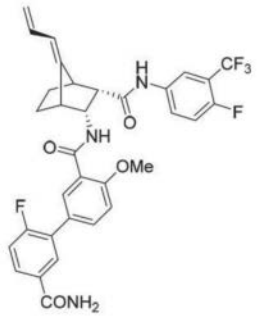
154		N-[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]-5'-甲磺酰胺基-4-甲氧基-2'-甲基-[1,1'-联苯]-3-甲酰胺	674.4	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.22 (d, J=4.0 Hz, 1H), 7.86 (d, J=2.1 Hz, 1H), 7.83 - 7.75 (m, 1H), 7.54 - 7.43 (m, 2H), 7.25 (dd, J=8.5, 1.5 Hz, 2H), 7.12 (dd, J=8.2, 2.1 Hz, 1H), 7.02 (d, J=1.8 Hz, 1H), 4.44 - 4.30 (m, 1H), 4.03 (s, 3H), 3.10 (dd, J=10.7, 4.0 Hz, 1H), 3.05 - 3.00 (m, 1H), 2.99 - 2.90 (m, 4H), 2.14 (s, 3H), 1.90 - 1.81 (m, 1H), 1.79 - 1.65 (m, 7H), 1.43 - 1.28 (m, 2H)	2.66, C
155		2-(6-氟-3'-{[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	643.1	(500 MHz, $CDCl_3$) δ 10.01 (br d, J=8.0 Hz, 1H), 8.53 (br s, 1H), 8.24 (d, J=2.2 Hz, 1H), 7.92 (dd, J=6.3, 2.5 Hz, 1H), 7.84 (s, 1H), 7.71 (dt, J=8.7, 2.0 Hz, 1H), 7.49 (dt, J=8.6, 3.5 Hz, 1H), 7.36 (dd, J=7.4, 2.2 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.15 - 7.05 (m, 3H), 4.72 - 4.64 (m, 1H), 4.08 (s, 3H), 3.73 (s, 2H), 3.11 - 2.98 (m, 3H), 2.20 - 2.13 (m, 1H), 1.87 - 1.80 (m, 1H), 1.76 (s, 3H), 1.75 (s, 3H), 1.59 - 1.54 (m, 2H)	1.19, A

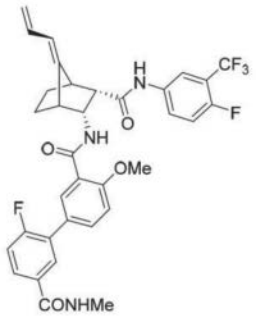
156		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-亚丙基双环[2.2.1]庚烷-2-基]-4-甲氧基-N3'-甲基-[1,1'-联苯]-3,3'-二甲酰胺	642.2	(500 MHz, $CDCl_3$) δ 10.02 (br d, J=7.4 Hz, 1H), 8.40 (d, J=2.2 Hz, 1H), 8.00 (dd, J=6.2, 2.6 Hz, 1H), 7.89 - 7.83 (m, 2H), 7.80 - 7.75 (m, 2H), 7.55 (dt, J=8.7, 3.5 Hz, 1H), 7.22 (dd, J=10.3, 8.4 Hz, 1H), 7.14 (t, J=9.4 Hz, 1H), 7.09 (d, J=8.8 Hz, 1H), 6.82 (br d, J=3.3 Hz, 1H), 5.27 (t, J=7.3 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.11 (s, 3H), 3.13 - 3.07 (m, 2H), 3.06 (d, J=5.0 Hz, 3H), 2.73 (t, J=3.7 Hz, 1H), 2.16 - 2.08 (m, 3H), 1.91 - 1.84 (m, 1H), 1.68 - 1.53 (m, 2H), 1.04 (t, J=7.6 Hz, 3H)	1.20, A
157		N3'-(环丙烷磺酰基)-6'-氟-N3-[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	732.2	-	1.18, B

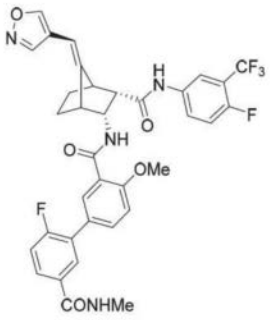
158		6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	627.2	(500 MHz, $CDCl_3$) δ 9.43 (br d, J=8.3 Hz, 1H), 8.43 (br s, 1H), 8.25 (br d, J=6.6 Hz, 1H), 8.11 - 7.94 (m, 3H), 7.72 (br d, J=8.8 Hz, 1H), 7.51 (br d, J=8.3 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.10 - 7.03 (m, 2H), 6.59 - 6.45 (m, 1H), 5.95 (br d, J=10.7 Hz, 1H), 5.23 (br d, J=16.5 Hz, 1H), 5.12 (br d, J=9.1 Hz, 1H), 4.92 - 4.83 (m, 1H), 4.07 (s, 3H), 3.31 - 3.23 (m, 1H), 3.19 - 3.13 (m, 1H), 2.87 - 2.80 (m, 1H), 2.40 - 2.33 (m, 1H), 1.96 - 1.90 (m, 1H), 1.71 - 1.64 (m, 2H)	1.15, A
159		6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(呋喃-3-基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	667.2	-	1.17, A

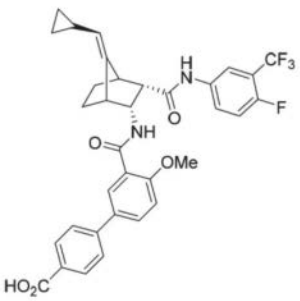
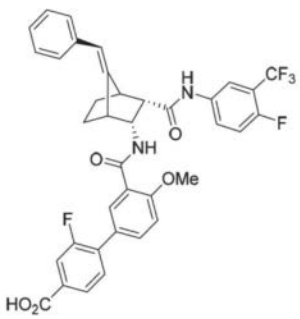
160		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	667.2	(500 MHz, $CDCl_3$) δ 9.68 (br d, J=7.4 Hz, 1H), 8.47 (s, 1H), 8.42 - 8.33 (m, 2H), 8.00 (br d, J=3.6 Hz, 1H), 7.94 (br dd, J=7.3, 2.1 Hz, 2H), 7.87 - 7.78 (m, 1H), 7.71 (br d, J=8.5 Hz, 1H), 7.60 - 7.52 (m, 1H), 7.27 - 7.20 (m, 1H), 7.14 (t, J=9.2 Hz, 1H), 7.09 (d, J=8.8 Hz, 1H), 6.04 (s, 1H), 4.90 - 4.80 (m, 1H), 4.10 (s, 3H), 3.33 - 3.27 (m, 1H), 3.20 (dd, J=10.7, 3.9 Hz, 1H), 2.96 - 2.89 (m, 1H), 2.33 - 2.24 (m, 1H), 2.05 - 1.95 (m, 1H), 1.76 - 1.66 (m, 2H)	1.08, A
161		N3-[(2R,3S,7Z)-7-(溴亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-6'-氟-N3'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	756.1	(400 MHz, $CDCl_3$) δ 10.85 - 10.61 (m, 1H), 9.93 (d, J=7.7 Hz, 1H), 8.43 (s, 1H), 8.34 (d, J=1.3 Hz, 1H), 8.15 (dd, J=6.2, 2.4 Hz, 1H), 8.09 (dd, J=7.3, 2.2 Hz, 1H), 7.91 (ddd, J=8.5, 4.5, 2.2 Hz, 1H), 7.76 (br d, J=8.8 Hz, 1H), 7.61 (dt, J=8.6, 3.5 Hz, 1H), 7.25 - 7.15 (m, 2H), 7.11 (d, J=8.8 Hz, 1H), 5.74 (s, 1H), 4.47 - 4.33 (m, 1H), 4.10 (s, 3H), 3.49 (s, 3H), 3.18 (br s, 1H), 3.09 (dd, J=10.8, 4.0 Hz, 1H), 2.83 (br s, 1H), 2.15 - 2.10 (m, 1H), 1.95 - 1.83 (m, 1H), 1.68 - 1.55 (m, 2H)	1.14, A

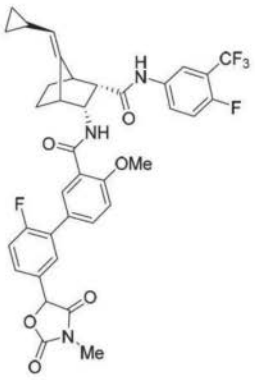
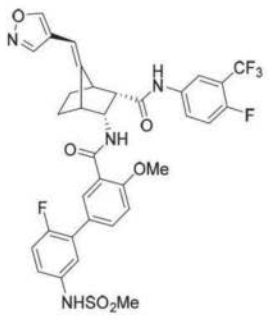
162		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-基]-N3'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	704.3	(400 MHz, $CDCl_3$) δ 10.41 (br s, 1H), 10.00 (br d, J=7.7 Hz, 1H), 8.36 (d, J=1.5 Hz, 1H), 8.16 (s, 1H), 8.11 (dd, J=6.1, 2.1 Hz, 1H), 8.05 (dd, J=7.2, 1.9 Hz, 1H), 7.92 (ddd, J=6.3, 4.3, 2.1 Hz, 1H), 7.75 (br d, J=8.6 Hz, 1H), 7.63 - 7.58 (m, 1H), 7.27 - 7.13 (m, 2H), 7.11 (d, J=8.8 Hz, 1H), 6.42 (dt, J=16.9, 10.5 Hz, 1H), 5.77 (d, J=10.8 Hz, 1H), 5.24 - 5.11 (m, 2H), 4.48 - 4.38 (m, 1H), 4.11 (s, 3H), 3.48 (s, 3H), 3.20 - 3.12 (m, 1H), 3.06 (br dd, J=10.5, 4.1 Hz, 1H), 2.74 - 2.70 (m, 1H), 2.15 - 2.10 (m, 1H), 1.94 - 1.86 (m, 1H), 1.64 - 1.51 (m, 2H)	1.16, A

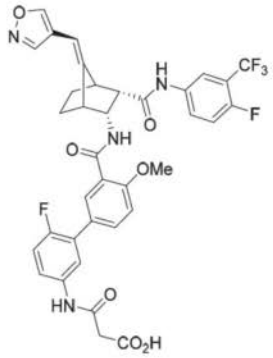
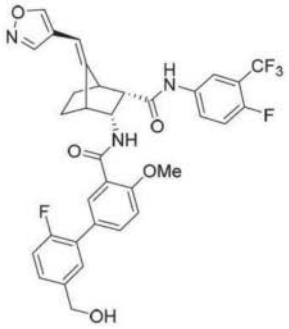
163		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-基]-4-甲氧基-[1,1'-联苯]-3,3'-二甲酰胺	626.3	(400 MHz, $CDCl_3$) δ 9.61 (br d, J=7.7 Hz, 1H), 8.41 (d, J=1.8 Hz, 1H), 8.02 - 7.90 (m, 3H), 7.86 (ddd, J=8.4, 4.7, 2.3 Hz, 1H), 7.73 (dt, J=8.5, 2.1 Hz, 1H), 7.56 (dt, J=8.3, 3.6 Hz, 1H), 7.26 (dd, J=10.0, 8.5 Hz, 1H), 7.17 - 7.07 (m, 2H), 6.53 (dt, J=16.9, 10.6 Hz, 1H), 5.95 (d, J=10.8 Hz, 1H), 5.24 (dd, J=16.8, 1.2 Hz, 1H), 5.17 - 5.11 (m, 1H), 4.85 - 4.73 (m, 1H), 4.10 (s, 3H), 3.31 - 3.23 (m, 1H), 3.13 (dd, J=10.8, 3.7 Hz, 1H), 2.85 - 2.80 (m, 1H), 2.31 - 2.21 (m, 1H), 1.99 - 1.93 (m, 1H), 1.72 - 1.63 (m, 2H)	1.15, A

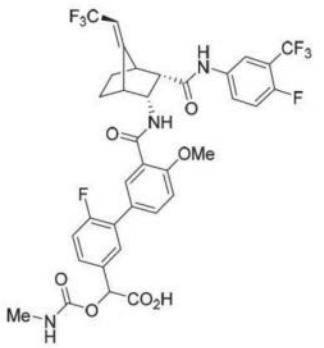
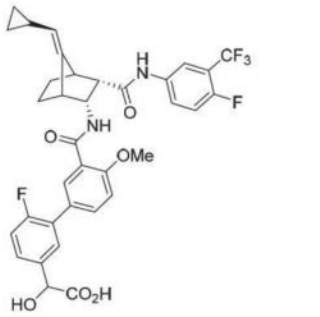
164		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(丙-2-烯-1-亚基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N3'-甲基-[1,1'-联苯]-3,3'-二甲酰胺	640.2	(400 MHz, $CDCl_3$) δ 9.84 (br d, J=7.7 Hz, 1H), 8.40 (d, J=2.2 Hz, 1H), 8.00 (dd, J=6.2, 2.4 Hz, 1H), 7.91 - 7.81 (m, 3H), 7.75 (dt, J=8.6, 2.2 Hz, 1H), 7.57 (dt, J=8.6, 3.2 Hz, 1H), 7.23 (dd, J=10.2, 8.5 Hz, 1H), 7.15 (t, J=9.4 Hz, 1H), 7.10 (d, J=8.6 Hz, 1H), 6.65 - 6.47 (m, 2H), 5.95 (d, J=10.8 Hz, 1H), 5.25 (dd, J=16.8, 1.2 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.81 - 4.70 (m, 1H), 4.11 (s, 3H), 3.31 - 3.25 (m, 1H), 3.16 - 3.09 (m, 1H), 3.06 (d, J=4.8 Hz, 3H), 2.85 - 2.81 (m, 1H), 2.21 - 2.16 (m, 1H), 1.98 - 1.91 (m, 1H), 1.72 - 1.61 (m, 2H)	1.17, A

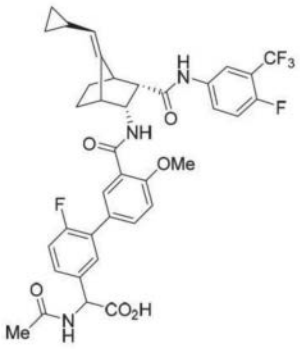
165		6'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]-4-甲氧基-N3'-甲基-[1,1'-联苯]-3,3'-二甲酰胺	681.2	(500 MHz, $CDCl_3$) δ 9.93 (br d, J=7.2 Hz, 1H), 8.46 (s, 1H), 8.38 (br s, 2H), 8.15 - 7.98 (m, 2H), 7.86 (dd, J=7.3, 2.3 Hz, 1H), 7.80 (ddd, J=8.5, 4.6, 2.3 Hz, 1H), 7.72 (br d, J=8.3 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.23 - 7.11 (m, 2H), 7.08 (br d, J=9.1 Hz, 1H), 6.59 (br s, 1H), 6.02 (s, 1H), 4.86 - 4.69 (m, 1H), 4.46 - 4.46 (m, 1H), 4.10 (s, 3H), 3.33 - 3.27 (m, 1H), 3.19 (dd, J=10.7, 4.1 Hz, 1H), 3.04 (br d, J=4.1 Hz, 3H), 2.91 (br s, 1H), 2.23 (br t, J=8.4 Hz, 1H), 2.01 (br t, J=8.8 Hz, 1H), 1.73 - 1.64 (m, 2H)	1.12, A

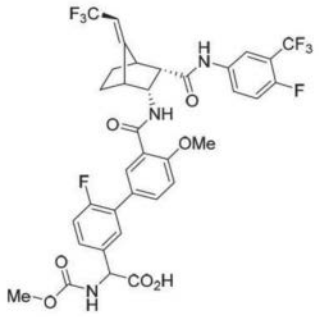
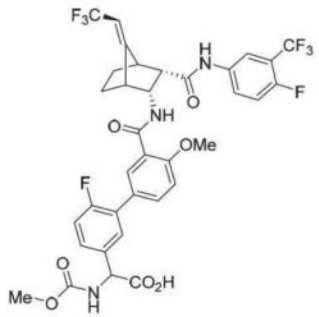
167		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	623.2	(500 MHz, $CDCl_3$) δ 9.51 (d, J=8.3 Hz, 1H), 8.52 (d, J=2.5 Hz, 1H), 8.17 (d, J=8.5 Hz, 2H), 7.94 (dd, J=6.2, 2.6 Hz, 1H), 7.84 (s, 1H), 7.75 (dd, J=8.5, 2.5 Hz, 1H), 7.71 (d, J=8.3 Hz, 2H), 7.56 (dt, J=8.7, 3.3 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 4.92 - 4.83 (m, 1H), 4.67 (d, J=9.6 Hz, 1H), 4.08 (s, 3H), 3.24 (t, J=4.0 Hz, 1H), 3.12 (dd, J=10.7, 3.0 Hz, 1H), 2.74 (t, J=3.9 Hz, 1H), 2.25 - 2.18 (m, 1H), 1.94 - 1.87 (m, 1H), 1.74 - 1.60 (m, 2H), 1.56 - 1.47 (m, 1H), 0.81 - 0.71 (m, 2H), 0.37 (dt, J=2.9, 1.6 Hz, 2H)	1.17, A
169		2-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	677.1	(500 MHz, DMSO-d6) δ 10.69 (s, 1H), 10.06 (br d, J=6.7 Hz, 1H), 8.28 (br d, J=4.6 Hz, 1H), 8.20 (s, 1H), 7.85 (br d, J=7.6 Hz, 2H), 7.82 - 7.72 (m, 2H), 7.63 (br t, J=7.9 Hz, 1H), 7.52 (br t, J=9.8 Hz, 1H), 7.44 - 7.34 (m, 5H), 7.29 (br d, J=4.3 Hz, 1H), 6.41 (s, 1H), 4.56 (br s, 1H), 4.09 (s, 3H), 3.57 (br s, 1H), 3.42 (br s, 1H), 3.38 - 3.27 (m, 1H), 3.20 (s, 1H), 2.96 (br s, 1H), 2.59 - 2.56 (m, 6H), 2.02 - 1.84 (m, 2H), 1.56 (br s, 2H), 1.24 (s, 1H)	2.59, C

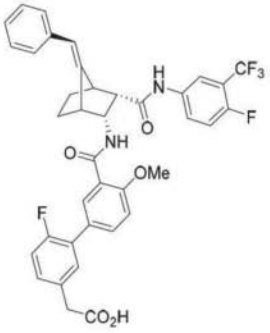
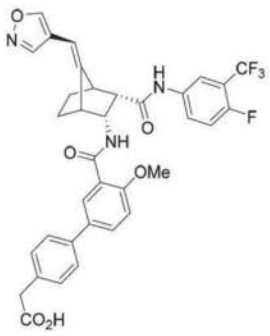
173		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(3-甲基-2,4-二氧代-1,3-噁唑啶-5-基)-[1,1'-联苯]-3-甲酰胺	710.4	(500 MHz, $CDCl_3$) δ 9.45 (br d, J=8.0 Hz, 1H), 8.38 (d, J=1.4 Hz, 1H), 7.97 (dd, J=6.2, 2.6 Hz, 1H), 7.86 (s, 1H), 7.66 (dt, J=8.5, 2.1 Hz, 1H), 7.53 (dd, J=6.9, 2.5 Hz, 2H), 7.40 (ddd, J=8.4, 4.3, 2.2 Hz, 1H), 7.25 (dd, J=9.9, 8.8 Hz, 1H), 7.14 - 7.05 (m, 2H), 5.79 (s, 1H), 4.91 - 4.81 (m, 1H), 4.66 (d, J=9.4 Hz, 1H), 4.07 (s, 3H), 3.22 (t, J=4.1 Hz, 1H), 3.18 (s, 3H), 3.11 (dd, J=10.5, 3.3 Hz, 1H), 2.74 (t, J=3.9 Hz, 1H), 2.25 - 2.18 (m, 1H), 1.94 - 1.86 (m, 1H), 1.55 - 1.49 (m, 1H)	1.20, A
174		2'-氟-N-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]-5'-甲磺酰胺基-4-甲氧基-[1,1'-联苯]-3-甲酰胺	717.1	(500 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.89 (br d, J=7.2 Hz, 1H), 8.96 (s, 1H), 8.69 (s, 1H), 8.21 - 8.14 (m, 1H), 8.11 (s, 1H), 7.86 - 7.75 (m, 1H), 7.67 (br dd, J=9.4, 1.1 Hz, 1H), 7.45 (t, J=9.8 Hz, 1H), 7.34 - 7.20 (m, 4H), 6.13 (s, 1H), 4.58 - 4.42 (m, 1H), 4.05 (s, 3H), 3.87 (s, 1H), 3.18 (d, J=5.2 Hz, 1H), 2.98 (s, 3H), 2.93 (br s, 1H), 2.02 - 1.84 (m, 2H), 1.64 - 1.45 (m, 2H)	2.40, C

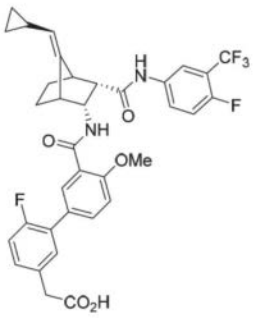
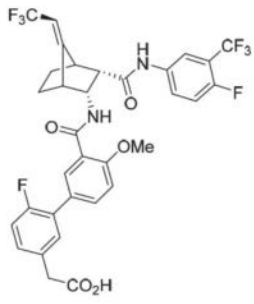
175		2-[(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)胺甲酰基]乙酸	725.3	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.90 (d, J=7.2 Hz, 1H), 8.98 (s, 1H), 8.71 (s, 1H), 8.20 (br d, J=5.0 Hz, 1H), 8.14 (s, 1H), 7.83 (br s, 1H), 7.75 (br d, J=5.0 Hz, 1H), 7.68 (br d, J=8.6 Hz, 1H), 7.54 (br d, J=8.5 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.32 (d, J=8.7 Hz, 1H), 7.23 (t, J=9.7 Hz, 1H), 6.14 (s, 1H), 4.55 (br s, 1H), 4.07 (s, 3H), 3.34 - 3.23 (m, 1H), 3.19 (s, 2H), 2.94 (br s, 1H), 2.57 - 2.53 (m, 10H), 2.00 (br t, J=10.2 Hz, 1H), 1.92 (s, 2H), 1.63 - 1.47 (m, 2H), 1.18 (s, 1H)	2.29, C
176		2'-氟-N-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]-5'-(羟基甲基)-4-甲氧基-[1,1'-联苯]-3-甲酰胺	654.3	(500 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.90 (br d, J=7.2 Hz, 1H), 8.97 (s, 1H), 8.70 (s, 1H), 8.23 - 8.13 (m, 2H), 8.00 - 7.79 (m, 1H), 7.70 (br d, J=8.7 Hz, 1H), 7.53 - 7.38 (m, 2H), 7.35 - 7.28 (m, 2H), 7.23 (dd, J=10.8, 8.5 Hz, 1H), 6.15 (s, 1H), 4.54 (br d, J=4.0 Hz, 3H), 4.07 (s, 3H), 3.19 (br s, 2H), 2.94 (br s, 1H), 2.58 - 2.53 (m, 8H), 2.07 - 1.96 (m, 1H), 1.96 - 1.86 (m, 2H), 1.55 (br t, J=13.9 Hz, 2H)	2.41, C

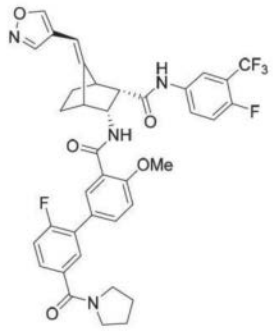
180		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(甲基胺甲酰基)氧基]乙酸	756.3	-	1.11, A
181		2-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	671.2	-	1.14, A

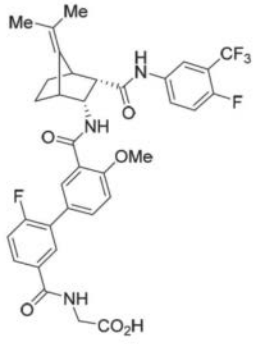
184		2-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-乙酰胺基乙酸	712.2	(500 MHz, $CDCl_3$) δ 10.11 (d, J=7.4 Hz, 1H), 8.66 (br d, J=8.8 Hz, 1H), 8.48 (d, J=2.2 Hz, 1H), 7.99 (dd, J=6.1, 2.5 Hz, 1H), 7.82 (dt, J=8.5, 2.5 Hz, 1H), 7.74 (dd, J=7.4, 2.2 Hz, 1H), 7.65 (s, 1H), 7.53 (dt, J=8.8, 3.4 Hz, 1H), 7.42 (ddd, J=8.3, 4.4, 2.2 Hz, 1H), 7.13 (t, J=9.4 Hz, 1H), 7.08 (dd, J=10.7, 8.3 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H), 5.97 (d, J=9.4 Hz, 1H), 4.70 - 4.62 (m, 2H), 4.08 (s, 3H), 3.14 - 3.10 (m, 1H), 3.04 (dd, J=10.7, 4.1 Hz, 1H), 2.69 (br s, 1H), 2.09 (s, 3H), 2.05 - 2.00 (m, 1H), 1.85 - 1.79 (m, 1H), 1.61 - 1.47 (m, 3H), 0.90 - 0.78 (m, 2H), 0.43 - 0.35 (m, 2H)	1.10, A

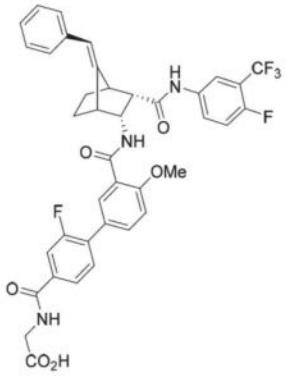
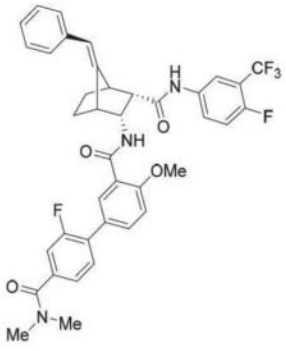
185		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(甲氧基羰基)氨基]乙酸	756.3	(500 MHz, $CDCl_3$) δ 9.75 (br d, J=8.0 Hz, 1H), 8.40 (br s, 1H), 8.08 (br s, 1H), 7.98 (dd, J=6.1, 2.2 Hz, 1H), 7.76 (br d, J=8.5 Hz, 1H), 7.67 (br d, J=5.8 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.15 - 7.05 (m, 2H), 7.05 - 6.94 (m, 2H), 5.63 - 5.53 (m, 2H), 4.86 - 4.76 (m, 1H), 4.06 (s, 3H), 3.67 (s, 3H), 3.34 (br s, 1H), 3.15 (dd, J=10.7, 4.1 Hz, 1H), 2.89 (br s, 1H), 2.36 (br d, J=11.3 Hz, 1H), 2.00 - 1.89 (m, 1H), 1.70 - 1.60 (m, 2H)	1.10, A
186		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(甲氧基羰基)氨基]乙酸	756.3	-	1.11, A

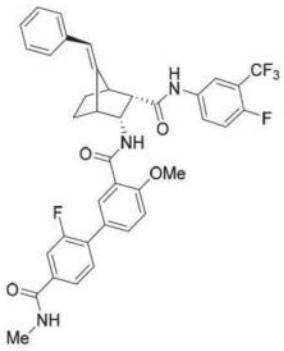
187		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	691.3	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.93 (d, J=7.1 Hz, 1H), 8.22 (dd, J=6.3, 2.2 Hz, 1H), 8.14 (s, 1H), 7.89 - 7.80 (m, 1H), 7.69 (br d, J=8.5 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.43 - 7.36 (m, 5H), 7.34 - 7.19 (m, 4H), 6.40 (s, 1H), 4.62 - 4.52 (m, 1H), 4.07 (s, 3H), 3.62 - 3.56 (m, 1H), 3.46 - 3.38 (m, 1H), 2.98 - 2.92 (m, 1H), 2.07 - 1.87 (m, 2H), 1.63 - 1.49 (m, 2H)	2.64, C
188		2-(3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-基)乙酸	664.2	(500 MHz, DMSO-d6) δ 10.46 (br s, 1H), 9.87 (br d, J=6.7 Hz, 1H), 8.98 (s, 1H), 8.71 (s, 1H), 8.27 - 8.18 (m, 2H), 7.88 - 7.77 (m, 2H), 7.57 (br d, J=7.5 Hz, 2H), 7.47 (br t, J=9.6 Hz, 1H), 7.35 (br d, J=7.5 Hz, 2H), 7.29 (br d, J=8.5 Hz, 1H), 6.15 (s, 1H), 4.56 (br s, 1H), 4.06 (s, 3H), 3.60 (s, 2H), 3.29 (br s, 1H), 2.95 (br s, 1H), 2.06 - 1.97 (m, 1H), 1.97 - 1.87 (m, 1H), 1.65 - 1.47 (m, 2H)	1.09, A

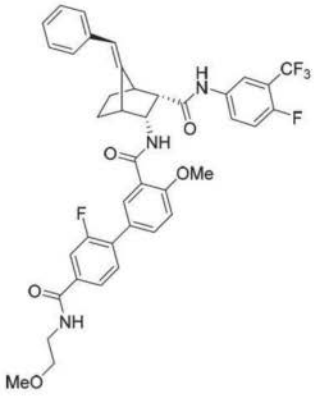
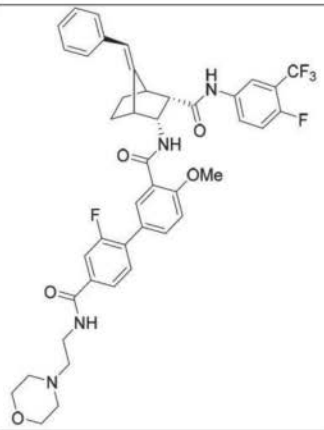
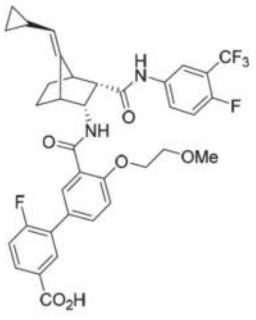
189		2-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	655.2	(500 MHz, $CDCl_3$) δ 9.55 (d, J=8.0 Hz, 1H), 8.33 (d, J=1.9 Hz, 1H), 8.03 (s, 1H), 7.97 (dd, J=6.2, 2.6 Hz, 1H), 7.68 (dt, J=8.7, 2.0 Hz, 1H), 7.55 - 7.47 (m, 1H), 7.38 (dd, J=7.3, 2.3 Hz, 1H), 7.24 (ddd, J=8.2, 4.6, 2.3 Hz, 1H), 7.15 - 7.03 (m, 3H), 4.86 - 4.79 (m, 1H), 4.64 (d, J=9.4 Hz, 1H), 4.06 (s, 3H), 3.70 (s, 2H), 3.22 - 3.18 (m, 1H), 3.13 - 3.07 (m, 1H), 2.74 - 2.71 (m, 1H), 2.26 - 2.19 (m, 1H), 1.93 - 1.86 (m, 1H), 1.73 - 1.58 (m, 2H), 1.53 - 1.44 (m, 1H), 0.79 - 0.71 (m, 2H), 0.39 - 0.32 (m, 2H)	1.17
190		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	655.2	(500 MHz, $CDCl_3$) δ 9.41 (br d, J=8.3 Hz, 1H), 8.37 (s, 1H), 8.30 (d, J=1.9 Hz, 1H), 7.95 (dd, J=6.2, 2.6 Hz, 1H), 7.67 (dt, J=8.5, 2.1 Hz, 1H), 7.45 (dt, J=8.7, 3.3 Hz, 1H), 7.34 (dd, J=7.4, 2.2 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.10 (dd, J=10.3, 8.4 Hz, 1H), 7.06 - 6.99 (m, 2H), 5.57 (q, J=7.4 Hz, 1H), 4.94 - 4.85 (m, 1H), 4.05 (s, 3H), 3.69 (s, 2H), 3.39 (br s, 1H), 3.18 (dd, J=10.6, 3.4 Hz, 1H), 2.91 (br t, J=3.9 Hz, 1H), 2.49 - 2.42 (m, 1H), 2.02 - 1.95 (m, 1H), 1.79 - 1.67 (m, 2H)	1.17, A

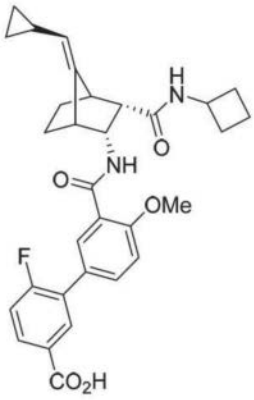
191		2'-氟-N-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]-4-甲氧基-5'-(吡咯烷-1-羰基)-[1,1'-联苯]-3-甲酰胺	721.1	(500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.89 (br d, J=7.2 Hz, 1H), 8.97 (s, 1H), 8.70 (s, 1H), 8.20 (d, J=6.7 Hz, 1H), 8.16 (s, 1H), 7.83 (br d, J=8.5 Hz, 1H), 7.73 (br d, J=8.5 Hz, 1H), 7.62 (br d, J=7.7 Hz, 1H), 7.55 (t, J=6.8 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.40 - 7.27 (m, 2H), 6.14 (s, 1H), 4.54 (br s, 1H), 4.07 (s, 3H), 3.48 (br s, 3H), 3.19 (s, 1H), 2.94 (br s, 1H), 2.58 - 2.53 (m, 5H), 2.07 - 1.96 (m, 1H), 1.95 - 1.89 (m, 2H), 1.86 (br s, 4H), 1.55 (br t, J=14.2 Hz, 2H)	2.38

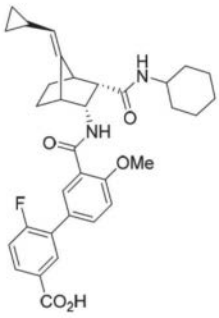
193		2-[(6-氟-3'-{[(2R,3S)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-丙烷-2-亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)甲酰胺基]乙酸	686.1	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 8.97 (br s, 1H), 8.31 - 8.14 (m, 2H), 8.05 (br d, J=7.0 Hz, 1H), 7.91 (br s, 1H), 7.83 (br d, J=7.9 Hz, 1H), 7.77 (br d, J=8.5 Hz, 1H), 7.50 (t, J=9.0 Hz, 1H), 7.44 (t, J=9.0 Hz, 1H), 7.34 (d, J=8.5 Hz, 1H), 4.40 (br s, 1H), 4.07 (s, 3H), 3.99 - 3.88 (m, 2H), 3.19 - 3.10 (m, 1H), 3.06 (br s, 1H), 2.97 (br s, 1H), 2.57 - 2.54 (m, 6H), 1.86 (br t, J=9.2 Hz, 1H), 1.75 (br d, J=11.3 Hz, 6H), 1.38 (br d, J=5.8 Hz, 2H)	2.37, C

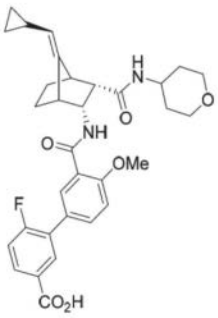
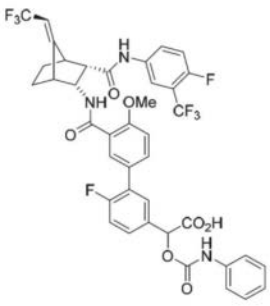
194		2-[(2-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-基)甲酰胺基]乙酸	734.1	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.94 (br d, J=7.1 Hz, 1H), 8.28 (br s, 1H), 8.26 - 8.05 (m, 2H), 7.85 (br s, 2H), 7.80 - 7.70 (m, 3H), 7.62 (br t, J=8.1 Hz, 1H), 7.48 (br t, J=9.6 Hz, 1H), 7.39 (d, J=4.1 Hz, 3H), 7.33 (d, J=8.7 Hz, 1H), 7.30 - 7.18 (m, 1H), 6.40 (s, 1H), 4.58 (br s, 1H), 4.08 (s, 3H), 3.90 (s, 1H), 3.72 (br s, 2H), 3.43 (br s, 1H), 2.96 (br s, 1H), 2.70 - 2.54 (m, 1H), 2.00 (br d, J=10.0 Hz, 1H), 1.97 - 1.76 (m, 2H), 1.56 (br s, 2H), 1.25 (br s, 2H), 0.87 (br s, 1H)	2.53, C
195		2'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N4',N4'-二甲基-[1,1'-联苯]-3,4'-二甲酰胺	704.1	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.90 (br d, J=7.1 Hz, 1H), 8.21 - 8.10 (m, 2H), 7.79 (br s, 1H), 7.72 (br d, J=8.7 Hz, 1H), 7.55 (t, J=7.9 Hz, 1H), 7.49 - 7.40 (m, 1H), 7.37 (d, J=4.2 Hz, 4H), 7.34 - 7.23 (m, 4H), 6.38 (s, 1H), 4.55 (br s, 1H), 4.05 (s, 3H), 3.86 (s, 1H), 3.62 - 3.49 (m, 12H), 3.38 (br s, 1H), 3.29 (br dd, J=10.6, 3.9 Hz, 1H), 2.97 (br s, 5H), 2.93 (br s, 1H), 2.56 - 2.54 (m, 1H), 1.98 (br d, J=10.0 Hz, 1H), 1.90 (br d, J=10.1 Hz, 1H), 1.54 (br s, 2H), 1.22 (s, 1H)	2.58, C

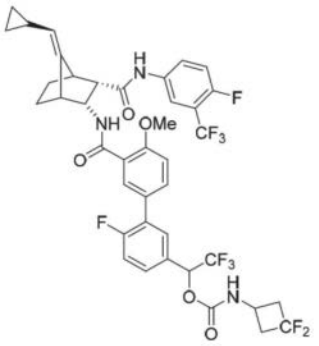
196		2'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N4'-甲基-[1,1'-联苯]-3,4'-二甲酰胺	690.1	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.9 Hz, 1H), 8.48 (br d, J=4.4 Hz, 1H), 8.24 (br d, J=4.5 Hz, 1H), 8.19 (s, 1H), 7.97 - 7.82 (m, 1H), 7.80 - 7.71 (m, 3H), 7.62 (t, J=8.0 Hz, 1H), 7.50 - 7.37 (m, 5H), 7.33 (d, J=8.4 Hz, 1H), 7.27 (d, J=7.4 Hz, 1H), 6.40 (s, 1H), 4.57 (br s, 1H), 4.08 (s, 3H), 3.42 (br s, 1H), 3.35 (br dd, J=10.7, 4.3 Hz, 1H), 2.96 (br s, 1H), 2.83 (d, J=4.5 Hz, 3H), 2.65 - 2.54 (m, 1H), 2.00 (br d, J=9.9 Hz, 1H), 1.93 (br d, J=10.4 Hz, 1H), 1.72 (br s, 2H), 1.56 (br s, 2H), 1.25 (br s, 1H)	2.76, C

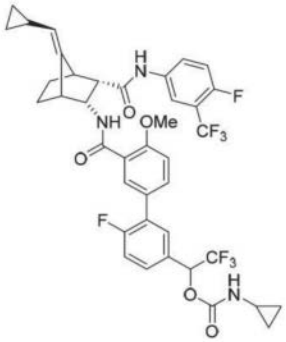
197		2'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N4'-(2-甲氧基乙基)-[1,1'-联苯]-3,4'-二甲酰胺	734.1	(500 MHz, DMSO-d6) δ 9.94 (br d, J=7.0 Hz, 1H), 8.59 - 8.48 (m, 1H), 8.23 (d, J=6.9 Hz, 1H), 8.19 (s, 1H), 7.85 (br d, J=8.6 Hz, 1H), 7.81 - 7.73 (m, 3H), 7.62 (t, J=8.0 Hz, 1H), 7.48 (br t, J=9.8 Hz, 1H), 7.39 (d, J=4.2 Hz, 4H), 7.33 (d, J=8.7 Hz, 1H), 7.30 - 7.23 (m, 1H), 6.40 (s, 1H), 4.57 (br s, 1H), 4.08 (s, 3H), 3.55 - 3.39 (m, 4H), 3.38 - 3.25 (m, 1H), 2.96 (br s, 1H), 2.00 (br d, J=9.9 Hz, 1H), 1.97 - 1.88 (m, 1H), 1.56 (br s, 2H)	2.55, C
198		2'-氟-N3-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]-4-甲氧基-N4'-[2-(吗啉-4-基)乙基]-[1,1'-联苯]-3,4'-二甲酰胺	789.1	-	2.90, C
200		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-(2-甲氧基乙氧基)-[1,1'-联苯]-3-甲酸	685.1	-	1.14, A

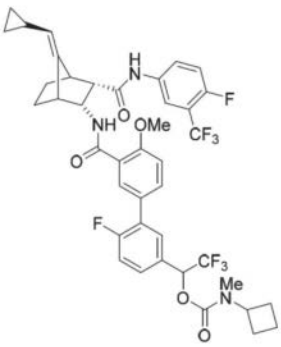
202		3'-{[(2R,3S,7Z)-3-(环丁基胺甲酰基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	533.1	(500 MHz, DMSO-d6) δ 9.74 (br d, J=7.0 Hz, 1H), 8.10 (br d, J=7.6 Hz, 1H), 7.81 (s, 1H), 7.76 (br d, J=7.3 Hz, 1H), 7.69 (br d, J=18.3 Hz, 1H), 7.47 (br d, J=8.5 Hz, 1H), 7.16 (br t, J=9.5 Hz, 1H), 7.04 (d, J=8.9 Hz, 1H), 4.36 (d, J=9.8 Hz, 1H), 4.03 (br s, 1H), 3.98 - 3.92 (m, 1H), 3.76 (s, 2H), 2.79 (br s, 1H), 2.64 - 2.59 (m, 1H), 2.48 (s, 1H), 2.28 (br d, J=18.9 Hz, 9H), 1.90 (br s, 2H), 1.66 - 1.53 (m, 3H), 1.51 - 1.45 (m, 1H), 1.39 - 1.32 (m, 2H), 1.23 - 1.17 (m, 1H), 1.08 (br t, J=12.5 Hz, 2H), 0.45 (br t, J=8.1 Hz, 2H), 0.08 - 0.02 (m, 2H)	2.29, C

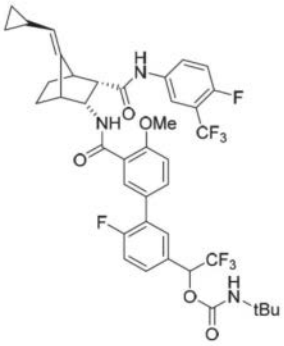
203		3'-{[(2R,3S,7Z)-3-(环己基胺甲酰基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	561.2	(500 MHz, DMSO-d6) δ 10.00 (br d, J=6.7 Hz, 1H), 8.09 (s, 1H), 8.06 - 8.02 (m, 1H), 8.00 - 7.92 (m, 2H), 7.74 (br d, J=8.9 Hz, 1H), 7.44 (t, J=9.5 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.35 - 4.26 (m, 1H), 4.03 (s, 3H), 3.65 - 3.53 (m, 1H), 3.05 (br s, 1H), 2.89 (br dd, J=10.8, 3.8 Hz, 1H), 1.89 (br t, J=9.8 Hz, 1H), 1.81 - 1.59 (m, 5H), 1.57 - 1.43 (m, 2H), 1.41 - 1.18 (m, 4H), 1.12 (br d, J=8.9 Hz, 3H), 0.71 (quin, J=9.5 Hz, 2H), 0.32 (br d, J=2.1 Hz, 2H)	2.38, C

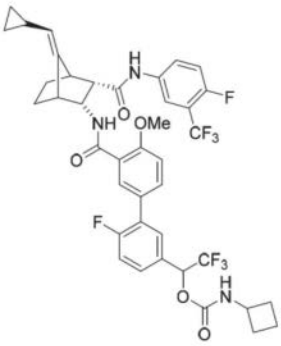
204		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(噁烷-4-基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	563.4	(500 MHz, DMSO-d6) δ 9.99 (br d, J=7.0 Hz, 1H), 8.12 - 8.06 (m, 2H), 8.06 - 8.01 (m, 1H), 8.00 - 7.94 (m, 1H), 7.74 (br d, J=8.5 Hz, 1H), 7.44 (t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.62 (d, J=9.8 Hz, 1H), 4.32 (br s, 1H), 4.03 (s, 3H), 3.79 (br t, J=10.2 Hz, 3H), 3.40 - 3.27 (m, 2H), 3.05 (br s, 1H), 2.90 (br dd, J=10.8, 3.8 Hz, 1H), 1.90 - 1.82 (m, 1H), 1.81 - 1.73 (m, 1H), 1.73 - 1.62 (m, 2H), 1.52 - 1.43 (m, 1H), 1.42 - 1.28 (m, 4H), 0.71 (quin, J=9.3 Hz, 2H), 0.32 (br d, J=2.4 Hz, 2H)	2.02, C
205		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(苯基胺甲酰基)氧基]乙酸	818.6	(500 MHz, $CDCl_3$) δ 9.58 (br d, *J*=8.5 Hz, 1H), 8.37 (br s, 1H), 8.26 (br s, 1H), 7.98 (dd, *J*=5.9, 2.3 Hz, 1H), 7.68 (br d, *J*=8.5 Hz, 1H), 7.62 (br d, *J*=5.5 Hz, 1H), 7.48 - 7.36 (m, 5H), 7.31 - 7.26 (m, 2H), 7.12 - 7.01 (m, 4H), 6.10 (s, 1H), 5.43 (q, *J*=7.3 Hz, 1H), 4.92 - 4.83 (m, 1H), 4.05 (s, 3H), 3.33 (br s, 1H), 3.15 (br dd, *J*=10.6, 3.4 Hz, 1H), 2.81 (br s, 1H), 2.50 - 2.43 (m, 1H), 2.01 - 1.95 (m, 2H), 1.73 - 1.62 (m, 2H)	1.13, A

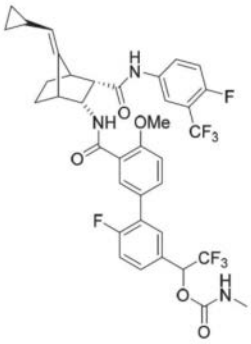
207		N-(3,3-二氟环丁基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	828.5	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.94 (br d, J=7.4 Hz, 1H), 8.40 (br d, J=6.7 Hz, 1H), 8.21 (br d, J=3.2 Hz, 1H), 8.10 (br s, 1H), 7.77 (br dd, J=4.5, 2.9 Hz, 1H), 7.68 (br t, J=10.3 Hz, 2H), 7.53 (br d, J=4.4 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.32 (d, J=8.8 Hz, 1H), 6.47 - 6.29 (m, 1H), 4.68 (d, J=9.7 Hz, 1H), 4.43 (br d, J=5.6 Hz, 1H), 4.04 (s, 3H), 3.91 - 3.81 (m, 1H), 3.19 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.94 - 2.78 (m, 2H), 2.71 (br s, 1H), 2.63 - 2.54 (m, 2H), 1.89 - 1.72 (m, 2H), 1.55 - 1.32 (m, 3H), 0.79 - 0.65 (m, 2H), 0.40 - 0.27 (m, 2H)	1.24, A

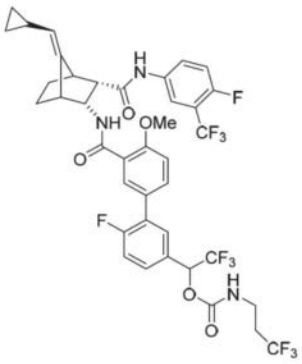
208		N-环丙基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	778.4	(400 MHz, CDCl3) δ 9.66 (br d, J=7.7 Hz, 1H), 8.38 (d, J=1.5 Hz, 1H), 7.97 (dd, J=6.2, 2.6 Hz, 1H), 7.81 (s, 1H), 7.70 (br d, J=8.6 Hz, 1H), 7.61 - 7.50 (m, 2H), 7.46 - 7.37 (m, 1H), 7.21 (br t, J=9.6 Hz, 1H), 7.15 - 7.06 (m, 2H), 6.18 - 6.08 (m, 1H), 5.30 (br s, 1H), 4.88 - 4.80 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.09 (s, 3H), 3.27 - 3.21 (m, 1H), 3.11 (dd, J=10.7, 3.9 Hz, 1H), 2.78 - 2.71 (m, 1H), 2.65 (br d, J=1.8 Hz, 1H), 1.97 - 1.86 (m, 1H), 1.75 - 1.60 (m, 2H), 1.56 - 1.46 (m, 1H), 0.82 - 0.72 (m, 4H), 0.67 - 0.55 (m, 2H), 0.41 - 0.32 (m, 2H)	1.23, A

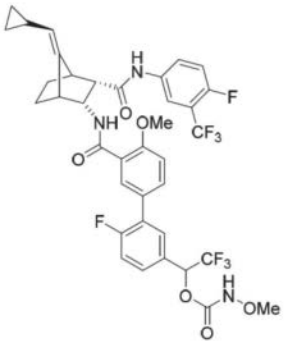
209		N-环丁基-N-甲基氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	806.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.22 (dd, J=6.4, 2.7 Hz, 1H), 8.12 (s, 1H), 7.82 - 7.75 (m, 1H), 7.69 (br d, J=7.9 Hz, 2H), 7.55 (br s, 1H), 7.50 - 7.36 (m, 2H), 7.32 (d, J=8.9 Hz, 1H), 6.47 - 6.35 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.50 - 4.34 (m, 2H), 4.05 (s, 3H), 3.16 (br dd, J=10.2, 3.8 Hz, 1H), 3.10 (br s, 1H), 2.97 - 2.76 (m, 3H), 2.72 (br s, 1H), 2.21 - 2.01 (m, 4H), 1.89 - 1.75 (m, 2H), 1.67 - 1.54 (m, 2H), 1.53 - 1.45 (m, 1H), 1.44 - 1.35 (m, 2H), 0.77 - 0.66 (m, 2H), 0.38 - 0.30 (m, 2H)	1.31, A

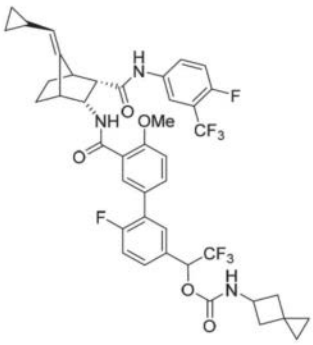
210		N-叔丁基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	794.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.22 (dd, J=6.4, 2.4 Hz, 1H), 8.12 (s, 1H), 7.81 - 7.75 (m, 1H), 7.72 - 7.66 (m, 2H), 7.59 (br s, 1H), 7.57 - 7.53 (m, 1H), 7.50 - 7.44 (m, 1H), 7.41 (br t, J=9.6 Hz, 1H), 7.33 (d, J=8.5 Hz, 1H), 6.37 - 6.27 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.49 - 4.41 (m, 1H), 4.05 (s, 3H), 3.16 (br dd, J=11.0, 4.3 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.89 - 1.75 (m, 2H), 1.54 - 1.46 (m, 1H), 1.45 - 1.35 (m, 2H), 1.20 (s, 9H), 0.78 - 0.67 (m, 2H), 0.38 - 0.30 (m, 2H)	1.28, A

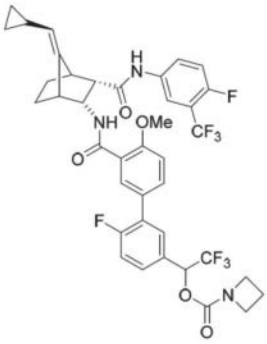
211		N-环丁基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	792.5	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (br d, J=6.7 Hz, 1H), 8.24 - 8.17 (m, 1H), 8.14 - 8.07 (m, 2H), 7.81 - 7.74 (m, 1H), 7.70 - 7.62 (m, 2H), 7.52 (br s, 1H), 7.48 - 7.37 (m, 2H), 7.32 (d, J=8.5 Hz, 1H), 6.35 - 6.28 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.04 (s, 3H), 3.95 - 3.86 (m, 1H), 3.19 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 2.17 - 2.04 (m, 2H), 1.96 - 1.74 (m, 4H), 1.62 - 1.52 (m, 2H), 1.52 - 1.46 (m, 1H), 1.44 - 1.34 (m, 2H), 0.78 - 0.65 (m, 2H), 0.39 - 0.27 (m, 2H)	1.25, A

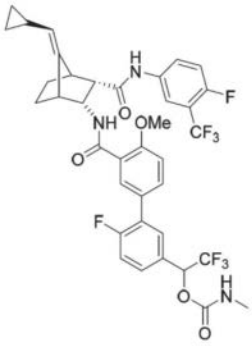
212		N-甲基氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	752.4	(500 MHz, CDCl3) δ 9.92 (br d, J=8.0 Hz, 1H), 8.33 (d, J=1.9 Hz, 1H), 7.97 (dd, J=6.1, 2.5 Hz, 1H), 7.76 - 7.71 (m, 1H), 7.69 (s, 1H), 7.62 - 7.57 (m, 1H), 7.54 - 7.49 (m, 1H), 7.43 - 7.38 (m, 1H), 7.19 (dd, J=10.2, 8.5 Hz, 1H), 7.15 - 7.08 (m, 2H), 6.13 (q, J=6.8 Hz, 1H), 5.19 - 5.13 (m, 1H), 4.84 - 4.77 (m, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.10 (s, 3H), 3.24 (t, J=4.0 Hz, 1H), 3.13 - 3.07 (m, 1H), 2.86 (d, J=4.7 Hz, 3H), 2.74 (t, J=4.1 Hz, 1H), 2.20 - 2.14 (m, 1H), 1.95 - 1.87 (m, 1H), 1.72 - 1.58 (m, 2H), 1.56 - 1.49 (m, 1H), 0.83 - 0.73 (m, 2H), 0.40 - 0.33 (m, 2H)	1.23, A

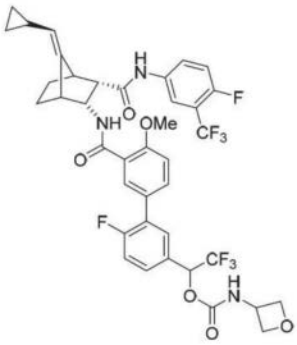
213		N-(3,3,3-三氟丙基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	834.5	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.94 (br d, J=7.2 Hz, 1H), 8.27 - 8.17 (m, 1H), 8.10 (s, 1H), 8.06 (br t, J=5.6 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.67 (br dd, J=13.8, 7.8 Hz, 2H), 7.54 (br d, J=4.5 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.32 (d, J=8.6 Hz, 1H), 6.42 - 6.31 (m, 1H), 4.68 (d, J=9.7 Hz, 1H), 4.49 - 4.37 (m, 1H), 4.04 (s, 3H), 3.34 - 3.19 (m, 2H), 3.18 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 2.46 - 2.33 (m, 2H), 1.89 - 1.74 (m, 2H), 1.53 - 1.45 (m, 1H), 1.40 (br t, J=9.2 Hz, 2H), 0.78 - 0.66 (m, 2H), 0.40 - 0.26 (m, 2H)	1.24, A

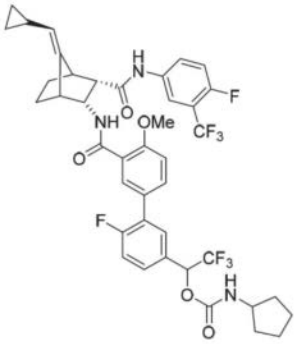
214		N-甲氧基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	768.3	(500 MHz, $CDCl_3$) δ 9.63 - 9.55 (m, 1H), 8.37 (dd, J=5.1, 1.8 Hz, 1H), 7.97 (ddd, J=9.5, 6.5, 2.8 Hz, 1H), 7.90 - 7.76 (m, 2H), 7.72 - 7.66 (m, 1H), 7.61 - 7.55 (m, 1H), 7.53 (dt, J=4.7, 2.1 Hz, 1H), 7.46 - 7.38 (m, 1H), 7.25 - 7.18 (m, 1H), 7.14 - 7.06 (m, 2H), 6.15 (qd, J=6.6, 3.0 Hz, 1H), 4.89 - 4.80 (m, 1H), 4.66 (d, J=9.6 Hz, 1H), 4.08 (d, J=2.2 Hz, 3H), 3.80 (s, 3H), 3.23 (t, J=4.0 Hz, 1H), 3.11 (dd, J=10.6, 3.2 Hz, 1H), 2.74 (t, J=3.9 Hz, 1H), 2.23 - 2.16 (m, 1H), 1.95 - 1.87 (m, 1H), 1.73 - 1.59 (m, 2H), 1.56 - 1.46 (m, 1H), 0.80 - 0.73 (m, 2H), 0.39 - 0.33 (m, 2H)	1.27, A

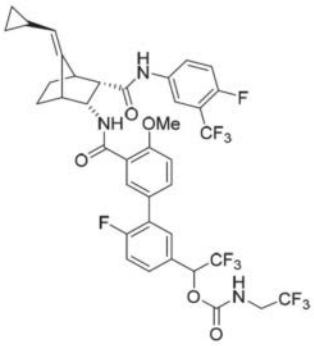
215		N-{螺[2.3]己烷-5-基}氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	818.5	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.95 (br d, J=7.1 Hz, 1H), 8.28 - 8.17 (m, 2H), 8.10 (br s, 1H), 7.82 - 7.74 (m, 1H), 7.70 - 7.63 (m, 2H), 7.53 (br d, J=4.1 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.32 (br d, J=8.7 Hz, 1H), 6.47 - 6.24 (m, 1H), 4.68 (br d, J=9.7 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.17 - 4.07 (m, 1H), 4.04 (s, 3H), 3.19 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 2.27 - 2.03 (m, 4H), 1.88 - 1.74 (m, 2H), 1.54 - 1.45 (m, 1H), 1.44 - 1.32 (m, 2H), 0.78 - 0.67 (m, 2H), 0.45 - 0.37 (m, 2H), 0.34 (br s, 4H)	1.27, A

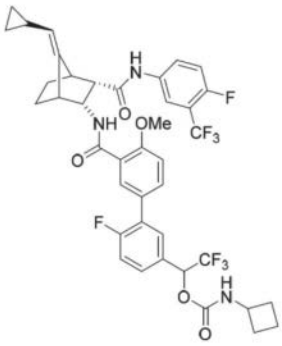
216		氮杂环丁烷-1-甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	778.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.92 (d, J=7.3 Hz, 1H), 8.23 (dd, J=6.4, 2.4 Hz, 1H), 8.13 (d, J=1.2 Hz, 1H), 7.79 (br dd, J=8.5, 4.0 Hz, 1H), 7.73 - 7.63 (m, 2H), 7.61 - 7.52 (m, 1H), 7.50 - 7.36 (m, 2H), 7.33 (d, J=8.5 Hz, 1H), 6.41 - 6.33 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.54 - 4.41 (m, 1H), 4.17 - 4.08 (m, 2H), 4.06 (s, 3H), 3.97 - 3.86 (m, 2H), 3.21 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.72 (br d, J=2.7 Hz, 1H), 2.22 (br dd, J=7.5, 5.6 Hz, 2H), 1.89 - 1.75 (m, 2H), 1.55 - 1.47 (m, 1H), 1.47 - 1.34 (m, 2H), 0.79 - 0.67 (m, 2H), 0.40 - 0.29 (m, 2H)	1.26, A

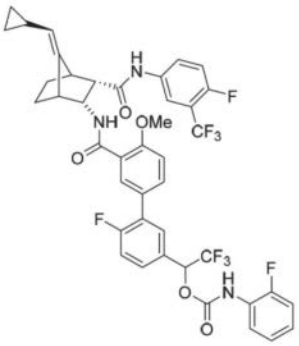
217		N-甲基氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	752.3	(500 MHz, $CDCl_3$) δ 9.92 (br d, J=7.4 Hz, 1H), 8.33 (t, J=2.5 Hz, 1H), 8.02 - 7.94 (m, 1H), 7.73 (br d, J=8.8 Hz, 2H), 7.59 (br d, J=7.2 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.44 - 7.37 (m, 1H), 7.19 (t, J=8.9 Hz, 1H), 7.15 - 7.07 (m, 2H), 6.13 (q, J=6.8 Hz, 1H), 5.22 - 5.14 (m, 1H), 4.83 - 4.75 (m, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.10 (d, J=3.3 Hz, 3H), 3.24 (br d, J=3.0 Hz, 1H), 3.10 (dd, J=10.7, 3.3 Hz, 1H), 2.86 (d, J=4.7 Hz, 3H), 2.73 (t, J=3.9 Hz, 1H), 2.20 - 2.14 (m, 1H), 1.95 - 1.84 (m, 1H), 1.75 - 1.58 (m, 2H), 1.55 - 1.47 (m, 1H), 0.82 - 0.74 (m, 2H), 0.44 - 0.32 (m, 2H)	1.27, A

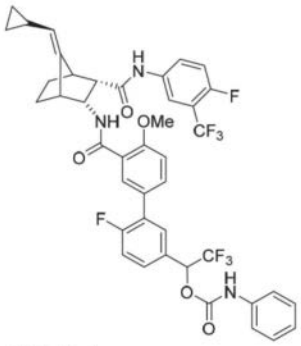
218		N-(氧杂环丁烷-3-基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	794.5	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.95 (br d, J=7.2 Hz, 1H), 8.69 (br d, J=6.5 Hz, 1H), 8.26 - 8.18 (m, 1H), 8.11 (br s, 1H), 7.81 - 7.74 (m, 1H), 7.72 - 7.65 (m, 2H), 7.58 - 7.52 (m, 1H), 7.50 - 7.38 (m, 2H), 7.33 (d, J=8.8 Hz, 1H), 6.43 - 6.32 (m, 1H), 4.71 - 4.65 (m, 2H), 4.65 - 4.58 (m, 2H), 4.49 - 4.37 (m, 3H), 4.05 (s, 3H), 3.15 (br dd, J=8.8, 4.5 Hz, 1H), 3.10 (br s, 1H), 2.75 - 2.67 (m, 1H), 1.87 - 1.74 (m, 2H), 1.53 - 1.47 (m, 1H), 1.45 - 1.36 (m, 2H), 0.78 - 0.66 (m, 2H), 0.39 - 0.26 (m, 2H)	1.19, A

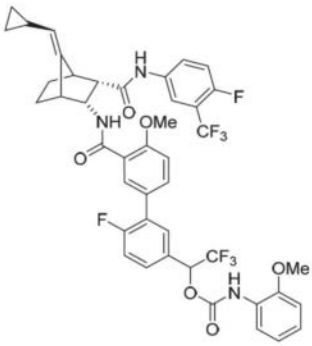
219		N-环戊基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	806.5	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.19 (br d, J=6.1 Hz, 1H), 8.09 (s, 1H), 7.82 (br d, J=7.0 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.67 (br dd, J=14.2, 8.1 Hz, 2H), 7.53 (br d, J=1.8 Hz, 1H), 7.49 - 7.35 (m, 2H), 7.31 (d, J=8.9 Hz, 1H), 6.37 - 6.24 (m, 1H), 4.68 (d, J=9.8 Hz, 1H), 4.48 - 4.39 (m, 1H), 4.03 (s, 3H), 3.81 - 3.67 (m, 1H), 3.14 (br dd, J=11.0, 4.0 Hz, 1H), 3.09 (br s, 1H), 2.70 (br s, 1H), 1.87 - 1.67 (m, 4H), 1.65 - 1.52 (m, 2H), 1.52 - 1.28 (m, 7H), 0.76 - 0.66 (m, 2H), 0.38 - 0.26 (m, 2H)	1.27, A

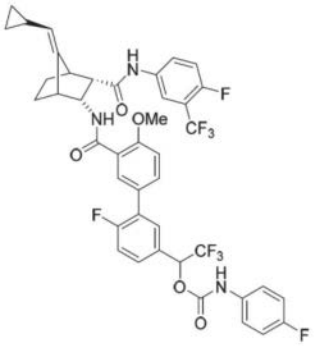
220		N-(2,2,2-三氟乙基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	820.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (br d, J=6.7 Hz, 1H), 8.65 (br t, J=6.4 Hz, 1H), 8.19 (br d, J=5.8 Hz, 1H), 8.10 (s, 1H), 7.80 - 7.72 (m, 1H), 7.68 (br d, J=7.9 Hz, 2H), 7.55 (br d, J=4.6 Hz, 1H), 7.43 (dt, J=19.1, 9.5 Hz, 2H), 7.32 (d, J=8.9 Hz, 1H), 6.51 - 6.35 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.43 (br s, 1H), 4.03 (s, 3H), 3.90 - 3.68 (m, 2H), 3.18 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.70 (br s, 1H), 1.89 - 1.74 (m, 2H), 1.53 - 1.45 (m, 1H), 1.43 - 1.34 (m, 2H), 0.79 - 0.65 (m, 2H), 0.38 - 0.28 (m, 2H)	1.23, A

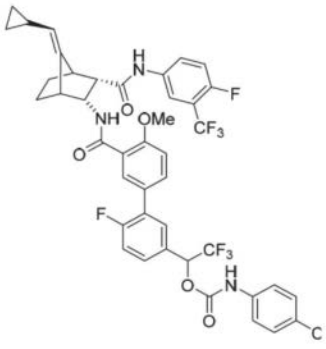
221		N-环丁基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	792.4	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.94 (br d, J=7.2 Hz, 1H), 8.20 (dd, J=5.9, 2.0 Hz, 1H), 8.14 (br d, J=7.9 Hz, 1H), 8.09 (s, 1H), 7.81 - 7.74 (m, 1H), 7.66 (br dd, J=19.9, 8.2 Hz, 2H), 7.52 (br d, J=1.7 Hz, 1H), 7.48 - 7.36 (m, 2H), 7.32 (d, J=8.8 Hz, 1H), 6.37 - 6.25 (m, 1H), 4.67 (d, J=9.5 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.04 (s, 2H), 3.94 - 3.86 (m, 1H), 3.14 (br dd, J=10.2, 4.0 Hz, 1H), 3.08 (br s, 1H), 2.71 (br s, 1H), 2.18 - 2.04 (m, 2H), 1.95 - 1.75 (m, 4H), 1.59 - 1.43 (m, 3H), 1.43 - 1.32 (m, 2H), 0.76 - 0.64 (m, 2H), 0.41 - 0.27 (m, 2H)	1.26, A

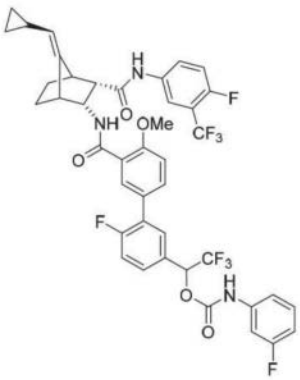
223		N-(2-氟苯基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	832.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 10.14 - 9.99 (m, 1H), 9.95 (br d, J=7.2 Hz, 1H), 8.22 (br d, J=4.4 Hz, 1H), 8.14 (br s, 1H), 7.82 - 7.74 (m, 2H), 7.70 (br d, J=7.7 Hz, 1H), 7.65 - 7.52 (m, 2H), 7.51 - 7.40 (m, 2H), 7.33 (d, J=8.8 Hz, 1H), 7.27 - 7.11 (m, 3H), 6.54 (br d, J=6.1 Hz, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.45 (br t, J=10.6 Hz, 1H), 4.05 (s, 3H), 3.15 (br dd, J=7.9, 4.6 Hz, 1H), 3.10 (br s, 1H), 2.71 (br s, 1H), 1.91 - 1.74 (m, 2H), 1.54 - 1.47 (m, 1H), 1.45 - 1.34 (m, 2H), 0.78 - 0.66 (m, 2H), 0.40 - 0.28 (m, 2H)	1.27, A

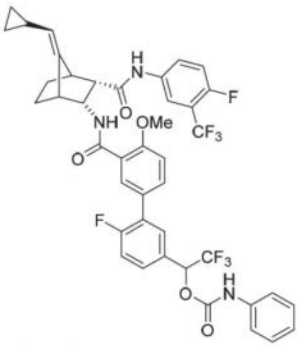
224	 异构体1	N-苯基氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	814.5	(500 MHz, $CDCl_3$) δ 9.62 (br d, J=7.7 Hz, 1H), 8.39 (d, J=1.9 Hz, 1H), 7.97 (dd, J=6.2, 2.6 Hz, 1H), 7.79 (s, 1H), 7.74 - 7.67 (m, 1H), 7.63 (br d, J=5.8 Hz, 1H), 7.53 (dt, J=8.6, 3.5 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.42 (br d, J=8.0 Hz, 2H), 7.37 - 7.32 (m, 2H), 7.22 (dd, J=10.2, 8.5 Hz, 1H), 7.16 - 7.05 (m, 3H), 7.02 (br s, 1H), 6.20 (q, J=6.8 Hz, 1H), 4.88 - 4.81 (m, 1H), 4.67 (d, J=9.6 Hz, 1H), 4.08 (s, 3H), 3.23 (t, J=4.0 Hz, 1H), 3.15 - 3.07 (m, 1H), 2.74 (t, J=3.9 Hz, 1H), 2.23 - 2.14 (m, 1H), 1.95 - 1.85 (m, 1H), 1.72 - 1.59 (m, 2H), 1.55 - 1.47 (m, 1H), 0.82 - 0.72 (m, 2H), 0.40 - 0.33 (m, 2H)	1.28, A

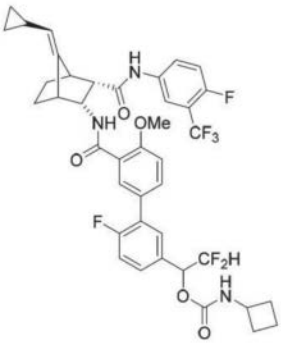
225		N-(2-甲氧基苯基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	844.2	(500 MHz, $CDCl_3$) δ 9.88 (br d, J=7.9 Hz, 1H), 8.32 (d, J=1.7 Hz, 1H), 8.03 (br d, J=6.7 Hz, 1H), 7.96 (dd, J=6.3, 2.6 Hz, 1H), 7.74 (s, 1H), 7.72 - 7.68 (m, 1H), 7.64 - 7.60 (m, 1H), 7.56 (br s, 1H), 7.52 - 7.47 (m, 2H), 7.22 (dd, J=10.1, 8.5 Hz, 1H), 7.14 - 7.08 (m, 2H), 7.07 - 7.02 (m, 1H), 6.96 (td, J=7.8, 1.1 Hz, 1H), 6.89 (dd, J=8.2, 1.1 Hz, 1H), 6.21 (q, J=6.8 Hz, 1H), 4.86 - 4.77 (m, 1H), 4.67 (d, J=9.6 Hz, 1H), 4.09 (s, 3H), 3.91 (s, 3H), 3.24 (t, J=4.1 Hz, 1H), 3.14 - 3.05 (m, 1H), 2.73 (t, J=4.0 Hz, 1H), 2.23 - 2.15 (m, 1H), 1.93 - 1.86 (m, 1H), 1.74 - 1.57 (m, 2H), 1.55 - 1.48 (m, 1H), 0.83 - 0.73 (m, 2H), 0.41 - 0.32 (m, 2H)	1.36, A

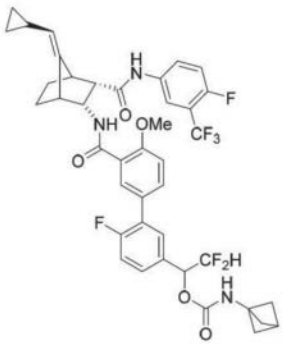
226		N-(4-氟苯基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酯	778.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (br d, J=6.7 Hz, 1H), 9.76 (br s, 1H), 8.21 (br d, J=4.9 Hz, 1H), 8.12 (s, 1H), 7.81 - 7.74 (m, 1H), 7.69 (br d, J=8.9 Hz, 1H), 7.53 (br s, 1H), 7.49 - 7.36 (m, 4H), 7.34 - 7.27 (m, 2H), 7.08 (br t, J=8.7 Hz, 2H), 5.87 - 5.81 (m, 1H), 4.68 (d, J=9.8 Hz, 1H), 4.44 (br d, J=7.0 Hz, 1H), 4.04 (s, 3H), 3.15 (br dd, J=10.5, 3.2 Hz, 1H), 3.10 (br s, 1H), 2.71 (br s, 1H), 1.89 - 1.74 (m, 2H), 1.55 (br d, J=6.7 Hz, 3H), 1.50 - 1.43 (m, 1H), 1.43 - 1.34 (m, 2H), 0.78 - 0.67 (m, 2H), 0.40 - 0.29 (m, 2H)	1.30, A

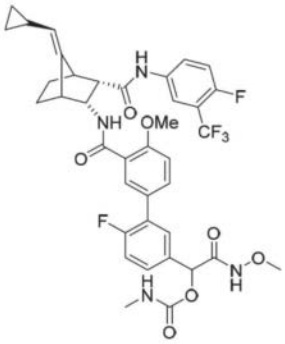
227		N-(4-氯苯基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	848.5	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 10.44 (br s, 1H), 9.94 (br d, J=7.3 Hz, 1H), 8.22 (br d, J=4.6 Hz, 1H), 8.13 (s, 1H), 7.83 - 7.75 (m, 2H), 7.71 (br d, J=7.6 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.52 - 7.39 (m, 4H), 7.36 - 7.29 (m, 3H), 6.62 - 6.50 (m, 1H), 4.69 (br d, J=9.5 Hz, 1H), 4.51 - 4.42 (m, 1H), 4.05 (s, 3H), 3.18 - 3.14 (m, 1H), 3.10 (br d, J=1.2 Hz, 1H), 2.72 (br d, J=2.4 Hz, 1H), 1.90 - 1.78 (m, 2H), 1.55 - 1.49 (m, 1H), 1.45 - 1.36 (m, 2H), 0.79 - 0.68 (m, 2H), 0.35 (br s, 2H)	1.30, A

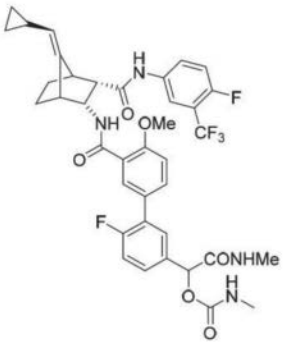
228		N-(3-氟苯基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	832.4	(500 MHz, DMSO-d6) δ 10.53 (br s, 2H), 9.94 (br d, J=7.0 Hz, 1H), 8.21 (br d, J=4.9 Hz, 1H), 8.13 (s, 1H), 7.82 - 7.73 (m, 2H), 7.70 (br d, J=8.2 Hz, 1H), 7.61 (br d, J=4.3 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.33 (br d, J=8.9 Hz, 3H), 7.23 (br d, J=8.2 Hz, 1H), 6.86 (br t, J=8.1 Hz, 1H), 6.63 - 6.50 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.45 (br t, J=10.2 Hz, 1H), 4.05 (s, 3H), 3.16 (br dd, J=10.5, 4.1 Hz, 1H), 3.10 (br s, 1H), 2.71 (br s, 1H), 1.90 - 1.73 (m, 2H), 1.56 - 1.44 (m, 1H), 1.44 - 1.34 (m, 2H), 0.80 - 0.66 (m, 2H), 0.34 (br d, J=1.2 Hz, 2H)	1.28, A

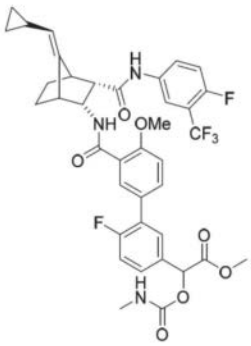
229	 异构体2	N-苯基氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	814.5	1H NMR (500 MHz, 氯仿-d) Shift 9.60 (br d, J=8.0 Hz, 1H), 8.36 (d, J=2.2 Hz, 1H), 7.98 (dd, J=6.2, 2.6 Hz, 1H), 7.83 (s, 1H), 7.74 - 7.66 (m, 1H), 7.64 - 7.58 (m, 1H), 7.51 (dt, J=8.7, 3.5 Hz, 1H), 7.46 - 7.38 (m, 3H), 7.32 (t, J=8.0 Hz, 2H), 7.20 (dd, J=10.2, 8.5 Hz, 1H), 7.14 - 7.04 (m, 4H), 6.18 (q, J=6.9 Hz, 1H), 4.86 - 4.78 (m, 1H), 4.64 (d, J=9.4 Hz, 1H), 4.07 (s, 3H), 3.22 (t, J=4.0 Hz, 1H), 3.09 (ddd, J=10.8, 4.1, 1.1 Hz, 1H), 2.72 (t, J=3.9 Hz, 1H), 2.20 - 2.13 (m, 1H), 1.94 - 1.84 (m, 1H), 1.71 - 1.58 (m, 2H), 1.54 - 1.45 (m, 1H), 0.79 - 0.69 (m, 2H), 0.37 - 0.31 (m, 2H)	1.28, A

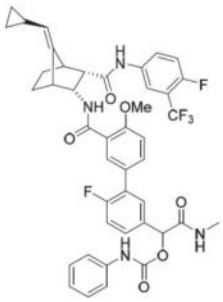
231		N-环丁基氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2-二氟乙酯	774.4	1H NMR (500 MHz, DMSO-d6) Shift 10.52 (s, 1H), 9.98 - 9.87 (m, 1H), 8.23 (br d, J=4.6 Hz, 1H), 8.12 (br s, 1H), 7.95 (br d, J=7.6 Hz, 1H), 7.82 - 7.74 (m, 1H), 7.69 (br d, J=8.2 Hz, 1H), 7.56 (br d, J=7.3 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.40 - 7.26 (m, 2H), 6.49 - 6.19 (m, 1H), 5.91 (br t, J=12.5 Hz, 1H), 4.69 (d, J=9.8 Hz, 1H), 4.49 - 4.41 (m, 1H), 4.05 (s, 3H), 3.97 - 3.86 (m, 1H), 3.20 - 3.13 (m, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.17 - 2.03 (m, 2H), 1.95 - 1.77 (m, 4H), 1.62 - 1.46 (m, 3H), 1.46 - 1.34 (m, 2H), 0.78 - 0.67 (m, 2H), 0.38 - 0.30 (m, 2H)	1.22, A

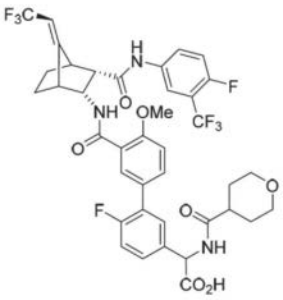
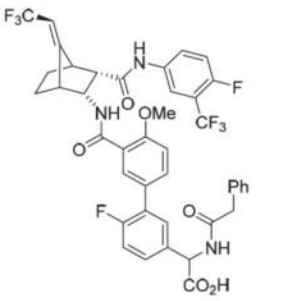
232		N-{双环[1.1.1]戊烷-1-基}氨基甲酸 1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2-二氟乙酯	786.3	1H NMR (500 MHz, DMSO-d6) Shift 10.55 (s, 1H), 9.95 (br d, J=6.3 Hz, 1H), 8.37 (br s, 1H), 8.24 (br d, J=4.2 Hz, 1H), 8.13 (br s, 1H), 7.85 - 7.76 (m, 1H), 7.70 (br d, J=8.5 Hz, 1H), 7.57 (br d, J=5.7 Hz, 1H), 7.52 - 7.30 (m, 4H), 6.56 - 6.17 (m, 1H), 6.02 - 5.84 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.51 - 4.39 (m, 1H), 4.05 (s, 3H), 3.16 (br dd, J=10.1, 4.3 Hz, 1H), 3.11 (br s, 1H), 2.72 (br s, 1H), 2.36 (s, 1H), 1.90 (br s, 6H), 1.88 - 1.76 (m, 2H), 1.56 - 1.47 (m, 1H), 1.46 - 1.35 (m, 2H), 0.79 - 0.68 (m, 2H), 0.40 - 0.30 (m, 2H)	1.23, A

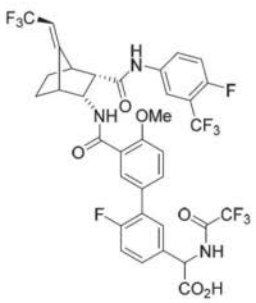
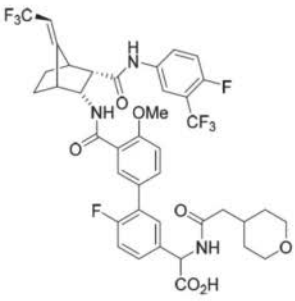
234		N-甲基氨基甲酸(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)(甲氧基胺甲酰基)甲酯	757.3	(500 MHz, $CDCl_3$) δ 9.84 - 9.58 (m, 2H), 8.30 (br s, 1H), 8.11 (br s, 1H), 8.01 (br d, *J*=3.9 Hz, 1H), 7.63 (br d, *J*=8.8 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.47 - 7.39 (m, 1H), 7.17 - 7.07 (m, 2H), 7.04 (d, *J*=8.5 Hz, 1H), 6.06 (br s, 1H), 5.25 (br s, 1H), 4.78 (br s, 1H), 4.62 (d, *J*=9.6 Hz, 1H), 4.09 (s, 3H), 3.77 (s, 3H), 3.20 (t, *J*=4.0 Hz, 1H), 3.10 (dd, *J*=10.5, 3.6 Hz, 1H), 2.81 (br d, *J*=2.8 Hz, 3H), 2.71 (br s, 1H), 2.20 - 2.13 (m, 1H), 1.94 - 1.86 (m, 1H), 1.71 - 1.55 (m, 2H), 1.52 - 1.42 (m, 1H), 0.74 (dd, *J*=8.0, 1.7 Hz, 2H), 0.39 - 0.27 (m, 2H)	1.17, A

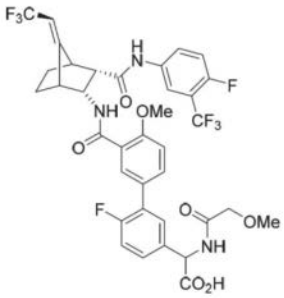
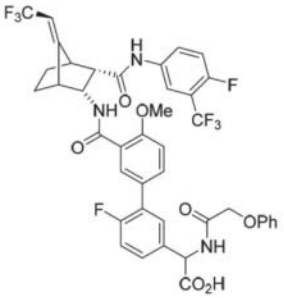
235		N-甲基氨基甲酸(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)(甲基胺甲酰基)甲酯	741.5	(500 MHz, CDCl3) δ 9.53 (br d, J=7.3 Hz, 1H), 8.36 - 8.31 (m, 1H), 8.09 (br s, 1H), 7.99 (dd, J=6.0, 2.5 Hz, 1H), 7.64 (dt, J=8.5, 2.0 Hz, 1H), 7.53 (dt, J=8.4, 3.4 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.37 (m, 1H), 7.17 - 7.02 (m, 3H), 6.51 - 6.43 (m, 1H), 6.08 (s, 1H), 5.13 - 5.05 (m, 1H), 4.87 - 4.77 (m, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.07 (s, 3H), 3.19 (t, J=3.8 Hz, 1H), 3.10 (dd, J=10.2, 3.5 Hz, 1H), 2.87 (d, J=4.9 Hz, 3H), 2.82 (d, J=4.9 Hz, 3H), 2.72 (t, J=3.7 Hz, 1H), 2.22 - 2.14 (m, 1H), 1.94 - 1.86 (m, 1H), 1.71 - 1.62 (m, 2H), 1.51 - 1.47 (m, 1H), 0.78 - 0.71 (m, 2H), 0.38 - 0.30 (m, 2H)	1.11, A

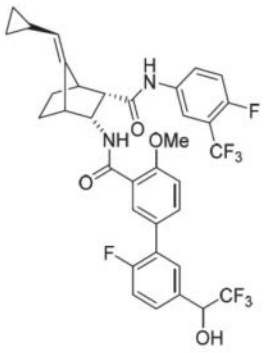
236		2-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(甲基胺甲酰基)氧基]乙酸甲酯	741.5	(500 MHz, $CDCl_3$) δ 9.41 (br d, *J*=7.7 Hz, 1H), 8.40 (d, *J*=1.7 Hz, 1H), 7.97 (dd, *J*=6.1, 2.5 Hz, 1H), 7.90 (s, 1H), 7.66 (dt, *J*=8.5, 2.1 Hz, 1H), 7.58 - 7.50 (m, 2H), 7.45 - 7.37 (m, 1H), 7.18 (dd, *J*=10.0, 8.7 Hz, 1H), 7.13 - 7.03 (m, 2H), 5.98 (s, 1H), 4.97 (br d, *J*=4.1 Hz, 1H), 4.90 - 4.82 (m, 1H), 4.66 (d, *J*=9.4 Hz, 1H), 4.07 (s, 3H), 3.77 (s, 3H), 3.22 (t, *J*=4.0 Hz, 1H), 3.14 - 3.07 (m, 1H), 2.87 (d, *J*=5.0 Hz, 3H), 2.74 (t, *J*=3.9 Hz, 1H), 2.25 - 2.17 (m, 1H), 1.93 - 1.85 (m, 1H), 1.73 - 1.62 (m, 2H), 1.55 - 1.47 (m, 1H), 0.80 - 0.73 (m, 2H), 0.40 - 0.33 (m, 2H)	1.23, A

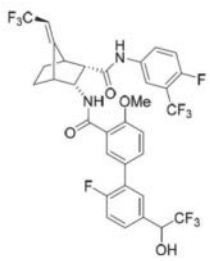
237		N-苯基氨基甲酸(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)(甲基胺甲酰基)甲酯	803.3	(500 MHz, $CDCl_3$) δ 9.64 (br d, J=7.9 Hz, 1H), 8.37 (d, J=2.3 Hz, 1H), 7.99 (dd, J=6.0, 2.2 Hz, 1H), 7.96 - 7.90 (m, 1H), 7.74 - 7.66 (m, 1H), 7.59 - 7.52 (m, 3H), 7.50 - 7.46 (m, 1H), 7.43 - 7.43 (m, 1H), 7.43 - 7.39 (m, 1H), 7.35 - 7.29 (m, 3H), 7.20 - 7.04 (m, 5H), 6.45 - 6.37 (m, 1H), 6.15 (s, 1H), 4.86 - 4.77 (m, 1H), 4.63 (d, J=9.6 Hz, 1H), 4.08 (s, 3H), 3.21 (t, J=3.9 Hz, 1H), 3.09 (br dd, J=10.5, 3.1 Hz, 1H), 2.88 (d, J=4.7 Hz, 3H), 2.77 - 2.70 (m, 1H), 2.22 - 2.13 (m, 1H), 1.97 - 1.87 (m, 1H), 1.65 - 1.59 (m, 2H), 1.50 - 1.45 (m, 1H), 1.54 - 1.43 (m, 2H), 0.78 - 0.71 (m, 2H), 0.79 - 0.69 (m, 3H), 0.38 - 0.29 (m, 2H)	1.17, A

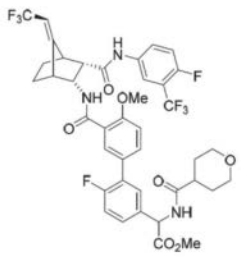
239		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	810.4	(500 MHz, $CDCl_3$) δ 10.00 (br d, J=7.7 Hz, 1H), 8.24 (br s, 1H), 8.14 (s, 1H), 7.98 (dd, J=6.1, 2.5 Hz, 1H), 7.67 (br d, J=8.3 Hz, 1H), 7.52 - 7.39 (m, 3H), 7.09 (br t, J=9.4 Hz, 1H), 7.05 - 6.96 (m, 2H), 5.63 (br d, J=7.2 Hz, 1H), 5.57 (q, J=7.3 Hz, 1H), 4.81 - 4.72 (m, 1H), 4.08 (s, 3H), 4.07 - 4.00 (m, 2H), 3.50 - 3.42 (m, 2H), 3.32 (br s, 1H), 3.16 (dd, J=10.6, 4.0 Hz, 1H), 2.88 (br s, 1H), 2.62 - 2.54 (m, 1H), 2.35 - 2.28 (m, 1H), 2.02 - 1.96 (m, 1H), 1.88 - 1.74 (m, 4H), 1.73 - 1.60 (m, 2H)	1.07, A
240		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-(2-苯基乙酰胺基)乙酸	816.5	(500 MHz, $CDCl_3$) δ fin9.71 (br d, J=8.5 Hz, 1H), 8.24 (d, J=2.5 Hz, 1H), 8.11 (br s, 1H), 8.02 - 7.93 (m, 1H), 7.67 - 7.59 (m, 1H), 7.48 - 7.42 (m, 2H), 7.32 (s, 1H), 7.26 - 7.18 (m, 5H), 7.05 - 6.94 (m, 4H), 5.73 (d, J=7.4 Hz, 1H), 5.61 - 5.54 (m, 1H), 4.87 - 4.75 (m, 1H), 4.05 (s, 3H), 3.64 (s, 2H), 3.40 (br s, 1H), 3.19 - 3.11 (m, 1H), 2.90 - 2.84 (m, 1H), 2.43 - 2.32 (m, 1H), 2.03 - 1.97 (m, 1H), 1.73 - 1.57 (m, 2H)	1.11, A

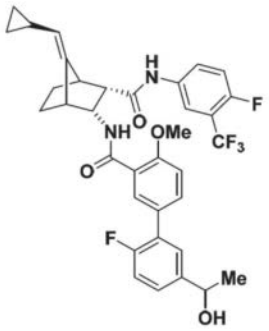
241		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-(2,2,2-三氟乙酰胺基)乙酸	794.3	(500 MHz, $CDCl_3$) δ 10.02 (br d, J=7.7 Hz, 1H), 9.14 (br d, J=8.0 Hz, 1H), 8.42 (d, J=2.5 Hz, 1H), 7.98 (dd, J=6.2, 2.6 Hz, 1H), 7.82 - 7.73 (m, 2H), 7.61 (s, 1H), 7.54 - 7.47 (m, 1H), 7.45 - 7.37 (m, 1H), 7.12 (dd, J=10.6, 8.4 Hz, 1H), 7.08 - 7.03 (m, 1H), 7.01 (d, J=8.8 Hz, 1H), 5.92 (d, J=8.5 Hz, 1H), 5.60 (q, J=7.3 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.05 (s, 3H), 3.40 (br s, 1H), 3.09 (dd, J=10.7, 4.1 Hz, 1H), 2.90 - 2.84 (m, 1H), 2.28 - 2.22 (m, 1H), 2.03 - 1.92 (m, 1H), 1.73 - 1.62 (m, 2H)	1.12, A
242		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[2-(噁烷-4-基)乙酰胺基]乙酸	824.3	(500 MHz, $CDCl_3$) δ 9.78 - 9.41 (m, 1H), 8.22 - 8.04 (m, 1H), 7.91 (br d, J=5.3 Hz, 1H), 7.63 - 7.31 (m, 4H), 7.23 - 7.17 (m, 1H), 7.04 - 6.80 (m, 3H), 5.65 - 5.45 (m, 2H), 4.80 - 4.68 (m, 1H), 4.01 (s, 3H), 3.88 - 3.72 (m, 2H), 3.33 - 3.19 (m, 3H), 3.18 - 3.10 (m, 1H), 2.82 (br s, 1H), 2.44 - 2.32 (m, 1H), 2.21 - 2.09 (m, 2H), 2.03 - 1.91 (m, 2H), 1.70 - 1.58 (m, 2H), 1.57 - 1.45 (m, 2H), 1.32 - 1.18 (m, 2H)	1.07, A

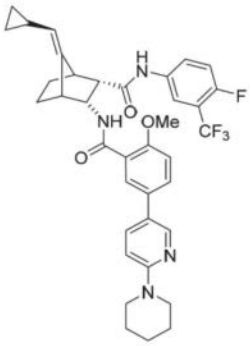
243		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-(2-甲氧基乙酰胺基)乙酸	770.4	(500 MHz, $CDCl_3$) δ 9.51 - 9.36 (m, 1H), 8.59 - 8.30 (m, 1H), 8.21 (br s, 1H), 8.00 - 7.90 (m, 1H), 7.67 - 7.53 (m, 2H), 7.51 - 7.36 (m, 2H), 7.37 - 7.30 (m, 1H), 7.11 - 6.92 (m, 3H), 5.73 - 5.61 (m, 1H), 5.53 (q, J=7.4 Hz, 1H), 4.84 (br s, 1H), 4.04 (s, 3H), 3.93 (br s, 2H), 3.41 (br s, 3H), 3.34 (br s, 1H), 3.21 - 3.13 (m, 1H), 2.87 (br s, 1H), 2.52 - 2.42 (m, 1H), 2.05 - 1.94 (m, 1H), 1.77 - 1.59 (m, 2H)	1.09, A
244		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-(2-苯氧基乙酰胺基)乙酸	832.2	(500 MHz, $CDCl_3$) δ 9.57 (br d, J=7.8 Hz, 1H), 8.26 (br s, 1H), 8.21 (br s, 1H), 8.02 - 7.91 (m, 2H), 7.60 (br d, J=8.3 Hz, 1H), 7.50 (br d, J=5.9 Hz, 1H), 7.42 - 7.35 (m, 1H), 7.32 (br d, J=0.9 Hz, 1H), 7.21 (br t, J=7.8 Hz, 2H), 7.05 - 6.92 (m, 4H), 6.89 (br d, J=8.0 Hz, 2H), 5.74 (br d, J=6.7 Hz, 1H), 5.53 (q, J=7.1 Hz, 1H), 4.86 - 4.76 (m, 1H), 4.51 (q, J=15.0 Hz, 2H), 4.03 (s, 3H), 3.36 (br s, 1H), 3.14 (br dd, J=10.5, 3.9 Hz, 1H), 2.84 (br s, 1H), 2.44 - 2.36 (m, 1H), 2.06 - 1.97 (m, 1H), 1.78 - 1.60 (m, 2H)	1.22, A

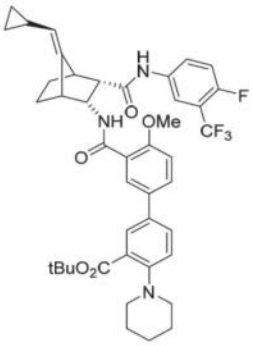
245		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(2,2,2-三氟-1-羟基乙基)-[1,1'-联苯]-3-甲酰胺	695.3	(500 MHz, $CDCl_3$) δ 9.57 (d, J=7.7 Hz, 1H), 8.33 (dd, J=2.2, 0.8 Hz, 1H), 8.05 (s, 1H), 7.99 (dd, J=6.3, 2.5 Hz, 1H), 7.66 (dt, J=8.7, 2.0 Hz, 1H), 7.57 (dd, J=7.3, 2.1 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.45 - 7.40 (m, 1H), 7.17 (dd, J=10.2, 8.5 Hz, 1H), 7.11 - 7.04 (m, 2H), 5.11 - 5.04 (m, 1H), 4.77 - 4.70 (m, 1H), 4.57 (d, J=9.4 Hz, 1H), 4.06 (s, 3H), 3.42 (br s, 1H), 3.19 (t, J=4.1 Hz, 1H), 3.08 (ddd, J=10.7, 4.1, 1.2 Hz, 1H), 2.67 (t, J=4.0 Hz, 1H), 2.18 - 2.07 (m, 1H), 1.92 - 1.82 (m, 1H), 1.67 - 1.58 (m, 2H), 1.53 - 1.45 (m, 1H), 0.79 - 0.68 (m, 2H), 0.38 - 0.27 (m, 2H)	1.38, A

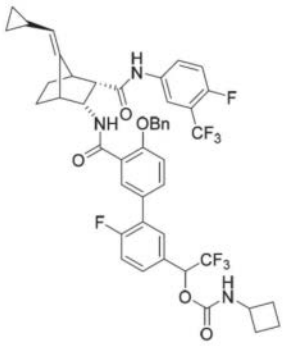
246		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(2,2,2-三氟-1-羟基乙基)-[1,1'-联苯]-3-甲酰胺	695.3	(500 MHz, $CDCl_3$) δ 9.53 (d, J=7.7 Hz, 1H), 8.34 (dd, J=2.5, 0.8 Hz, 1H), 8.01 (s, 1H), 7.97 (dd, J=6.2, 2.6 Hz, 1H), 7.66 (dt, J=8.7, 2.0 Hz, 1H), 7.57 - 7.50 (m, 2H), 7.48 - 7.40 (m, 1H), 7.18 (dd, J=10.2, 8.5 Hz, 1H), 7.12 - 7.02 (m, 2H), 5.13 - 5.03 (m, 1H), 4.81 - 4.71 (m, 1H), 4.60 (d, J=9.6 Hz, 1H), 4.06 (s, 3H), 3.19 (t, J=3.7 Hz, 2H), 3.09 (ddd, J=10.8, 4.1, 1.1 Hz, 1H), 2.70 (t, J=4.0 Hz, 1H), 2.19 - 2.11 (m, 1H), 1.92 - 1.84 (m, 1H), 1.70 - 1.60 (m, 2H), 1.51 - 1.42 (m, 1H), 0.77 - 0.70 (m, 2H), 0.36 - 0.30 (m, 2H)	1.38, A

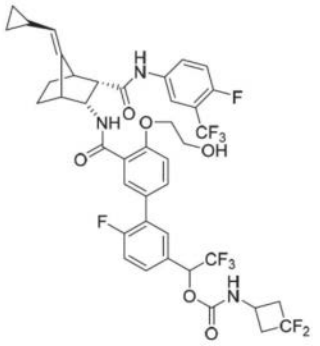
247		2-(6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸甲酯	824.4	(500 MHz, $CDCl_3$) δ 9.25 (br d, J=8.0 Hz, 1H), 8.40 - 8.33 (m, 1H), 8.11 (s, 1H), 7.89 (dd, J=6.3, 2.5 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.51 (dt, J=8.5, 3.6 Hz, 1H), 7.40 (dd, J=7.2, 2.2 Hz, 1H), 7.31 (ddd, J=8.4, 4.4, 2.3 Hz, 1H), 7.15 (dd, J=10.2, 8.5 Hz, 1H), 7.09 - 7.01 (m, 2H), 6.56 (br d, J=6.6 Hz, 1H), 5.62 - 5.53 (m, 2H), 4.96 - 4.88 (m, 1H), 4.04 (s, 3H), 4.03 - 3.99 (m, 2H), 3.76 (s, 3H), 3.47 - 3.39 (m, 3H), 3.17 (dd, J=10.9, 2.9 Hz, 1H), 2.93 (t, J=3.7 Hz, 1H), 2.49 - 2.39 (m, 2H), 2.01 - 1.94 (m, 1H), 1.87 - 1.80 (m, 3H), 1.79 - 1.72 (m, 3H)。	1.17, A

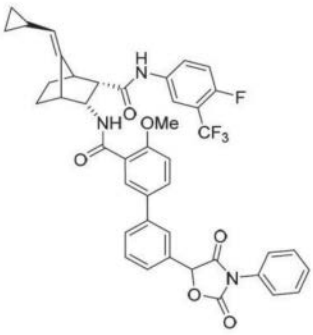
248		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-(1-羟基乙基)-4-甲氧基-[1,1'-联苯]-3-甲酰胺	641.4	(500 MHz, $CDCl_3$) δ 9.43 (br d, *J*=7.7 Hz, 1H), 8.38 (dd, *J*=2.5, 0.8 Hz, 1H), 8.02 (s, 1H), 7.96 (dt, *J*=6.1, 3.0 Hz, 1H), 7.67 (dt, *J*=8.7, 2.0 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.44 (dt, *J*=7.4, 1.9 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.16 - 7.02 (m, 3H), 4.94 (q, *J*=6.3 Hz, 1H), 4.85 - 4.76 (m, 1H), 4.62 (d, *J*=9.4 Hz, 1H), 4.05 (s, 3H), 3.20 (t, *J*=4.0 Hz, 1H), 3.10 (ddd, *J*=10.8, 4.1, 1.1 Hz, 1H), 2.71 (t, *J*=4.0 Hz, 1H), 2.22 - 2.14 (m, 1H), 1.92 - 1.86 (m, 1H), 1.70 - 1.56 (m, 2H), 1.53 (d, *J*=6.3 Hz, 3H), 1.51 - 1.44 (m, 1H), 0.76 - 0.69 (m, 2H), 0.37 - 0.30 (m, 2H)	1.18, A

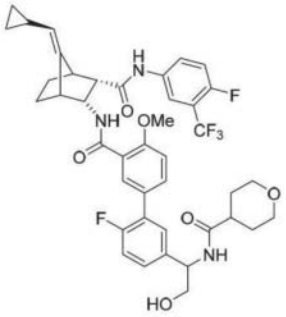
250		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(吗啉-4-基)吡啶-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	665.3	(500 MHz, $CDCl_3$) δ 9.73 (d, J=7.4 Hz, 1H), 8.55 - 8.46 (m, 2H), 8.24 (d, J=2.5 Hz, 1H), 8.15 (dd, J=9.4, 2.2 Hz, 1H), 8.10 (dd, J=6.3, 2.5 Hz, 1H), 7.64 (dt, J=8.7, 3.5 Hz, 1H), 7.54 (dd, J=8.5, 2.5 Hz, 1H), 7.13 (t, J=9.4 Hz, 1H), 7.06 (d, J=9.6 Hz, 1H), 6.93 (d, J=8.8 Hz, 1H), 4.65 (d, J=9.4 Hz, 1H), 4.58 - 4.49 (m, 1H), 4.04 (s, 3H), 3.95 - 3.90 (m, 4H), 3.79 - 3.73 (m, 4H), 3.14 (t, J=3.7 Hz, 1H), 3.06 (dd, J=10.7, 4.1 Hz, 1H), 2.74 - 2.68 (m, 1H), 2.11 - 2.04 (m, 1H), 1.88 - 1.81 (m, 1H), 1.63 - 1.52 (m, 2H), 1.51 - 1.42 (m, 1H), 0.77 - 0.70 (m, 2H), 0.38 - 0.32 (m, 2H)	1.00, A

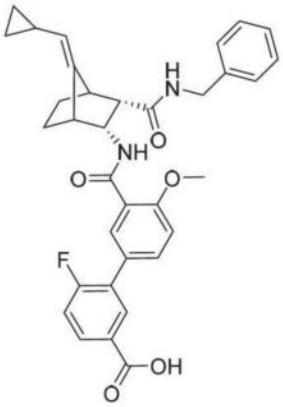
251		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-4-(吗啉-4-基)-[1,1'-联苯]-3-甲酸叔丁酯	764.3	(500 MHz, $CDCl_3$) δ 9.87 (br d, J=7.7 Hz, 1H), 8.31 (d, J=2.2 Hz, 1H), 8.22 (s, 1H), 8.04 (dd, J=6.3, 2.5 Hz, 1H), 7.94 (d, J=2.2 Hz, 1H), 7.76 (br dd, J=8.3, 1.9 Hz, 1H), 7.60 (dd, J=8.7, 2.3 Hz, 1H), 7.56 (dt, J=8.7, 3.4 Hz, 1H), 7.47 (br d, J=8.0 Hz, 1H), 7.11 (t, J=9.4 Hz, 1H), 7.03 (d, J=8.8 Hz, 1H), 4.62 (d, J=9.6 Hz, 2H), 4.07 (s, 3H), 4.07 - 4.04 (m, 4H), 3.50 - 3.38 (m, 4H), 3.17 (t, J=3.9 Hz, 1H), 2.97 (dd, J=10.7, 3.9 Hz, 1H), 2.69 (t, J=3.9 Hz, 1H), 2.12 - 2.05 (m, 1H), 1.90 - 1.81 (m, 1H), 1.62 (s, 9H), 1.61 - 1.54 (m, 2H), 1.50 - 1.43 (m, 1H), 0.78 - 0.69 (m, 2H), 0.37 - 0.28 (m, 2H)	1.23, A

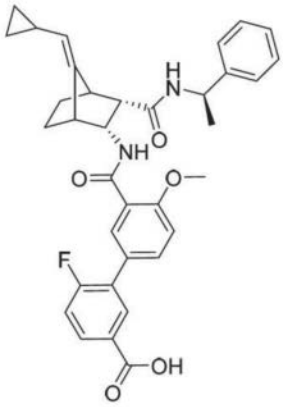
252		N-环丁基氨基甲酸1-[4'-(苯甲基氧基)-3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-[1,1'-联苯]-3-基]-2,2,2-三氟乙酯	868.2	(500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.88 - 9.81 (m, 1H), 8.14 - 8.08 (m, 2H), 8.06 (s, 1H), 7.75 - 7.69 (m, 1H), 7.64 (br d, J=7.0 Hz, 1H), 7.59 (br d, J=8.5 Hz, 1H), 7.54 (br d, J=7.3 Hz, 3H), 7.43 - 7.36 (m, 2H), 7.30 (td, J=13.5, 7.8 Hz, 4H), 6.38 - 6.30 (m, 1H), 5.50 (s, 2H), 4.67 (d, J=9.8 Hz, 1H), 4.54 - 4.42 (m, 1H), 3.98 - 3.86 (m, 1H), 3.15 (br dd, J=10.8, 3.8 Hz, 1H), 3.05 (br s, 1H), 2.69 (br s, 1H), 2.17 - 2.03 (m, 2H), 1.95 - 1.81 (m, 2H), 1.76 - 1.65 (m, 2H), 1.60 - 1.52 (m, 2H), 1.51 - 1.44 (m, 1H), 1.36 - 1.28 (m, 2H), 0.79 - 0.67 (m, 2H), 0.39 - 0.28 (m, 2H)	1.34, A

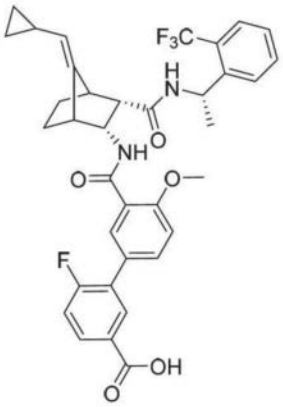
254		N-(3,3-二氟环丁基)氨基甲酸1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-(2-羟基乙氧基)-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	858.0	(500 MHz, $CDCl_3$) δ 9.55 (br d, J=8.4 Hz, 1H), 8.30 (d, J=2.3 Hz, 1H), 7.73 (br d, J=8.7 Hz, 1H), 7.65 (s, 1H), 7.59 - 7.51 (m, 3H), 7.42 - 7.35 (m, 1H), 7.21 - 7.14 (m, 2H), 7.11 (d, J=8.7 Hz, 1H), 6.08 (q, J=6.7 Hz, 1H), 5.51 (br d, J=7.0 Hz, 1H), 4.92 - 4.83 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.51 - 4.42 (m, 1H), 4.29 - 4.21 (m, 2H), 4.13 - 4.03 (m, 2H), 3.18 (t, J=4.0 Hz, 1H), 3.12 (dd, J=10.9, 3.9 Hz, 1H), 3.07 - 2.89 (m, 2H), 2.75 (t, J=4.0 Hz, 1H), 2.63 - 2.48 (m, 2H), 2.20 - 2.13 (m, 1H), 1.95 - 1.87 (m, 1H), 1.79 - 1.70 (m, 1H), 1.68 - 1.58 (m, 1H), 1.54 - 1.45 (m, 1H), 0.84 - 0.74 (m, 2H), 0.41 - 0.32 (m, 2H)	1.31, A

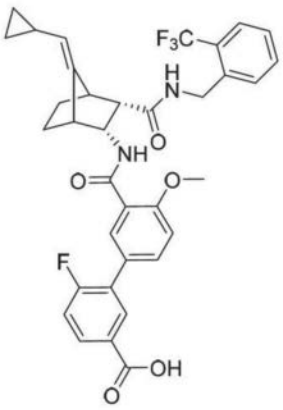
255		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-5'-(2,4-二氧代-3-苯基-1,3-噁唑啶-5-基)-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	772.3	(500 MHz, $CDCl_3$) δ 9.48 (dd, *J*=7.9, 2.4 Hz, 1H), 8.44 - 8.37 (m, 1H), 8.03 - 7.94 (m, 1H), 7.86 (s, 1H), 7.68 (dt, *J*=8.6, 1.8 Hz, 1H), 7.64 - 7.59 (m, 1H), 7.56 - 7.43 (m, 7H), 7.15 - 7.07 (m, 2H), 5.96 (s, 1H), 4.89 - 4.81 (m, 1H), 4.66 (d, *J*=9.5 Hz, 1H), 4.08 (s, 3H), 3.22 (t, *J*=4.2 Hz, 1H), 3.14 - 3.06 (m, 1H), 2.74 (t, *J*=4.0 Hz, 1H), 2.25 - 2.16 (m, 1H), 1.94 - 1.87 (m, 1H), 1.71 - 1.61 (m, 2H), 1.55 - 1.48 (m, 1H), 0.80 - 0.72 (m, 2H), 0.36 (td, *J*=4.0, 2.4 Hz, 2H)	1.20, A

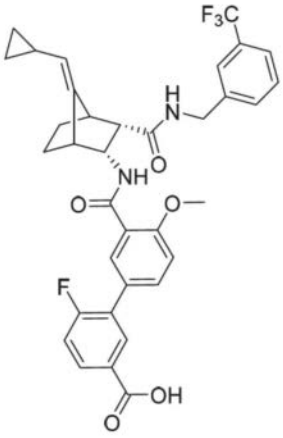
257		N-[1-(3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙基]噁烷-4-甲酰胺	768.6	(500 MHz, $CDCl_3$) δ 9.55 (br d, *J*=7.7 Hz, 1H), 8.32 (s, 1H), 8.01 - 7.89 (m, 2H), 7.59 (br d, *J*=8.5 Hz, 1H), 7.55 - 7.48 (m, 1H), 7.35 - 7.30 (m, 1H), 7.24 - 7.19 (m, 1H), 7.15 - 7.02 (m, 2H), 6.40 - 6.24 (m, 1H), 5.12 - 5.04 (m, 1H), 4.84 - 4.75 (m, 1H), 4.63 (d, *J*=9.6 Hz, 1H), 4.06 (s, 3H), 4.04 - 3.97 (m, 2H), 3.91 (br d, *J*=4.4 Hz, 2H), 3.42 (tt, *J*=11.5, 3.2 Hz, 2H), 3.19 (br t, *J*=3.9 Hz, 1H), 3.08 (br dd, *J*=10.5, 3.0 Hz, 1H), 2.71 (t, *J*=3.9 Hz, 1H), 2.48 - 2.41 (m, 1H), 2.21 - 2.17 (m, 1H), 1.92 - 1.76 (m, 4H), 1.70 - 1.59 (m, 2H), 1.51 - 1.44 (m, 1H), 0.78 - 0.71 (m, 2H), 0.37 - 0.30 (m, 2H)	1.10, A

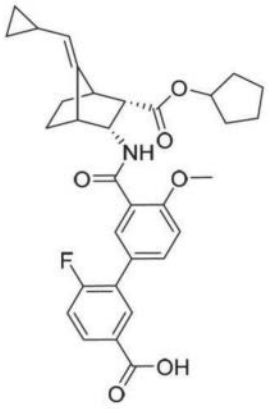
260		3'-{[(2R,3S,7Z)-3-(苯甲基胺甲酰基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	569.0	(500 MHz, $CDCl_3$) 9.71 (d, J=6.9 Hz, 1H), 8.37 (s, 1H), 8.22 (dd, J=5.1, 1.9 Hz, 1H), 8.02 - 7.89 (m, 1H), 7.66 - 7.56 (m, 1H), 7.23 - 7.15 (m, 5H), 7.14 - 7.06 (m, 1H), 6.99 (d, J=7.5 Hz, 1H), 6.12 - 5.79 (m, 1H), 4.75 - 4.64 (m, 1H), 4.57 (d, J=9.0 Hz, 1H), 4.39 (d, J=5.6 Hz, 2H), 4.00 (s, 3H), 3.27 - 3.14 (m, 1H), 2.87 (br dd, J=10.6, 3.0 Hz, 1H), 2.57 - 2.49 (m, 1H), 2.20 - 2.08 (m, 1H), 1.99 - 1.85 (m, 1H), 1.61 - 1.39 (m, 3H), 0.75 - 0.60 (m, 2H), 0.35 - 0.18 (m, 2H)	1.91, A

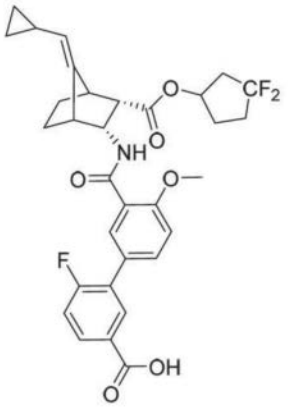
261		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[(1R)-1-苯基乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	582.9	(500 MHz, $CDCl_3$) δ 9.72 (br d, J=7.5 Hz, 1H), 8.42 (d, J=1.8 Hz, 1H), 8.26 (dd, J=7.5, 1.7 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.69 - 7.64 (m, 1H), 7.34 - 7.21 (m, 6H), 7.18 (t, J=9.3 Hz, 1H), 7.07 (d, J=8.6 Hz, 1H), 5.82 (br d, J=7.6 Hz, 1H), 5.07 (quin, J=7.1 Hz, 1H), 4.74 - 4.67 (m, 1H), 4.58 (d, J=9.2 Hz, 1H), 4.09 (s, 2H), 3.71 (s, 1H), 3.21 (t, J=4.1 Hz, 1H), 2.92 - 2.80 (m, 1H), 2.60 (s, 1H), 2.51 (t, J=4.1 Hz, 1H), 2.08 - 1.99 (m, 1H), 1.92 - 1.84 (m, 1H), 1.57 - 1.42 (m, 3H), 1.39 (d, J=6.9 Hz, 3H), 0.75 - 0.64 (m, 2H), 0.28 (dd, J=4.5, 2.0 Hz, 2H)	1.94, A

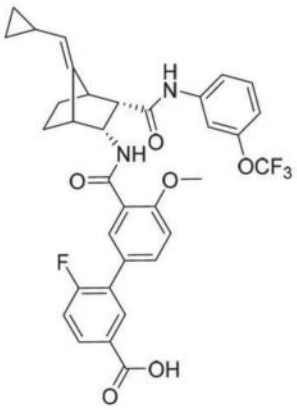
262		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[(1S)-1-[2-(三氟甲基)苯基]乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	651.48	(500 MHz, DMSO-d6) δ 9.82 (br d, J=6.8 Hz, 1H), 8.39 (br d, J=6.6 Hz, 1H), 7.89 (s, 1H), 7.83 - 7.76 (m, 1H), 7.71 (ddd, J=8.3, 4.9, 2.1 Hz, 1H), 7.47 (br d, J=8.4 Hz, 1H), 7.44 - 7.38 (m, 3H), 7.20 (br dt, J=8.0, 4.2 Hz, 1H), 7.14 (br dd, J=10.4, 8.7 Hz, 1H), 7.05 (d, J=8.7 Hz, 1H), 5.08 - 4.91 (m, 1H), 4.42 (d, J=9.2 Hz, 1H), 4.09 (dt, J=9.9, 4.8 Hz, 1H), 3.76 (s, 3H), 2.82 (br t, J=3.7 Hz, 1H), 2.80 - 2.77 (m, 1H), 2.37 (br t, J=4.0 Hz, 1H), 1.45 - 1.32 (m, 1H), 1.22 (td, J=8.7, 4.0 Hz, 1H), 1.19 - 1.14 (m, 1H), 1.09 (br d, J=6.8 Hz, 3H), 1.06 - 0.99 (m, 1H), 0.97 - 0.87 (m, 1H), 0.55 - 0.39 (m, 2H), 0.08 (br d, J=4.5 Hz, 2H)	2.05, B

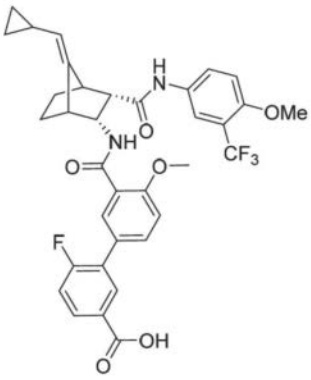
263		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({[2-(三氟甲基)苯基]甲基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	637.15	(500 MHz, CDCl3) δ 9.69 (br d, J=6.9 Hz, 1H), 8.36 (br s, 1H), 8.22 (br d, J=6.0 Hz, 1H), 8.03 - 7.90 (m, 1H), 7.63 (br d, J=7.2 Hz, 1H), 7.57 (br d, J=7.7 Hz, 1H), 7.42 (br d, J=7.7 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.27 (br d, J=7.9 Hz, 1H), 7.19 - 7.08 (m, 1H), 7.01 (br d, J=8.3 Hz, 1H), 6.07 - 5.95 (m, 1H), 4.75 - 4.66 (m, 1H), 4.66 - 4.53 (m, 3H), 4.01 (s, 3H), 3.20 (br s, 1H), 2.90 (br dd, J=10.6, 3.5 Hz, 1H), 2.54 (br t, J=3.7 Hz, 1H), 2.09 (br t, J=9.8 Hz, 1H), 1.97 - 1.84 (m, 1H), 1.60 - 1.41 (m, 3H), 0.75 - 0.58 (m, 2H), 0.36 - 0.19 (m, 2H)	2.09, A

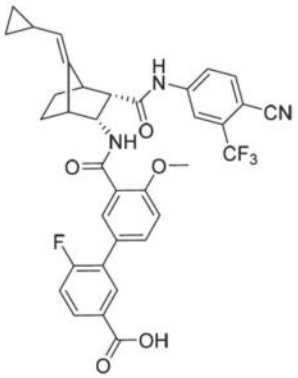
264		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({[3-(三氟甲基)苯基]甲基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	637.27	(400 MHz, CDCl3) δ 9.76 (br d, J=7.4 Hz, 1H), 8.42 (s, 1H), 8.36 - 8.24 (m, 1H), 8.09 - 7.94 (m, 1H), 7.77 - 7.67 (m, 1H), 7.53 - 7.48 (m, 1H), 7.47 - 7.36 (m, 2H), 7.34 - 7.28 (m, 1H), 7.21 (t, J=9.5 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.45 - 6.14 (m, 1H), 4.86 - 4.69 (m, 1H), 4.60 (d, J=9.6 Hz, 1H), 4.54 - 4.38 (m, 2H), 4.11 - 3.92 (m, 3H), 3.23 (d, J=3.7 Hz, 1H), 2.99 (dd, J=10.3, 4.2 Hz, 1H), 2.70 - 2.51 (m, 1H), 2.16 (t, J=8.4 Hz, 1H), 2.02 - 1.80 (m, 1H), 1.73 - 1.41 (m, 3H), 0.81 - 0.62 (m, 2H), 0.42 - 0.19 (m, 2H)	1.88, A

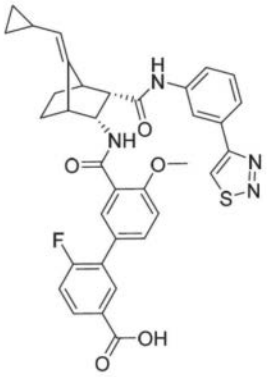
266		3'-{[(2R,3S,7Z)-3-[(环戊基氧基)羰基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	582.9	(500 MHz, $CDCl_3$) δ 9.72 (br d, J=7.5 Hz, 1H), 8.42 (d, J=1.8 Hz, 1H), 8.26 (dd, J=7.5, 1.7 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.69 - 7.64 (m, 1H), 7.34 - 7.21 (m, 6H), 7.18 (t, J=9.3 Hz, 1H), 7.07 (d, J=8.6 Hz, 1H), 5.82 (br d, J=7.6 Hz, 1H), 5.07 (quin, J=7.1 Hz, 1H), 4.74 - 4.67 (m, 1H), 4.58 (d, J=9.2 Hz, 1H), 4.09 (s, 2H), 3.71 (s, 1H), 3.21 (t, J=4.1 Hz, 1H), 2.92 - 2.80 (m, 1H), 2.60 (s, 1H), 2.51 (t, J=4.1 Hz, 1H), 2.08 - 1.99 (m, 1H), 1.92 - 1.84 (m, 1H), 1.57 - 1.42 (m, 3H), 1.39 (d, J=6.9 Hz, 3H), 0.75 - 0.64 (m, 2H), 0.28 (dd, J=4.5, 2.0 Hz, 2H)	2.19, B

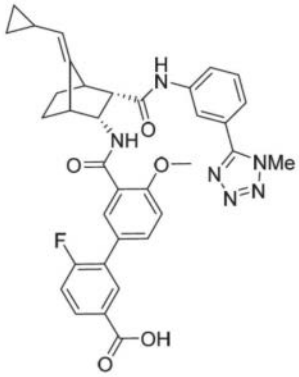
267		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(3,3-二氟环戊基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	651.48	(500 MHz, DMSO-d6) δ 9.82 (br d, J=6.8 Hz, 1H), 8.39 (br d, J=6.6 Hz, 1H), 7.89 (s, 1H), 7.83 - 7.76 (m, 1H), 7.71 (ddd, J=8.3, 4.9, 2.1 Hz, 1H), 7.47 (br d, J=8.4 Hz, 1H), 7.44 - 7.38 (m, 3H), 7.20 (br dt, J=8.0, 4.2 Hz, 1H), 7.14 (br dd, J=10.4, 8.7 Hz, 1H), 7.05 (d, J=8.7 Hz, 1H), 5.08 - 4.91 (m, 1H), 4.42 (d, J=9.2 Hz, 1H), 4.09 (dt, J=9.9, 4.8 Hz, 1H), 3.76 (s, 3H), 2.82 (br t, J=3.7 Hz, 1H), 2.80 - 2.77 (m, 1H), 2.37 (br t, J=4.0 Hz, 1H), 1.45 - 1.32 (m, 1H), 1.22 (td, J=8.7, 4.0 Hz, 1H), 1.19 - 1.14 (m, 1H), 1.09 (br d, J=6.8 Hz, 3H), 1.06 - 0.99 (m, 1H), 0.97 - 0.87 (m, 1H), 0.55 - 0.39 (m, 2H), 0.08 (br d, J=4.5 Hz, 2H)	2.2, A

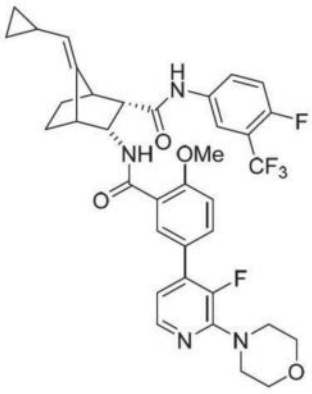
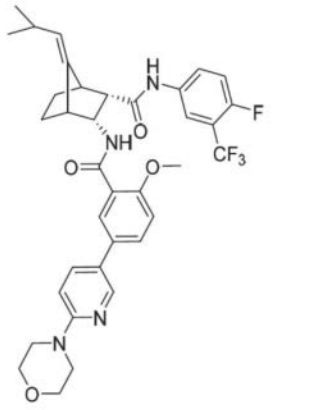
268		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[3-(三氟甲氧基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	637.15	(500 MHz, $CDCl_3$) δ 9.69 (br d, J=6.9 Hz, 1H), 8.36 (br s, 1H), 8.22 (br d, J=6.0 Hz, 1H), 8.03 - 7.90 (m, 1H), 7.63 (br d, J=7.2 Hz, 1H), 7.57 (br d, J=7.7 Hz, 1H), 7.42 (br d, J=7.7 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.27 (br d, J=7.9 Hz, 1H), 7.19 - 7.08 (m, 1H), 7.01 (br d, J=8.3 Hz, 1H), 6.07 - 5.95 (m, 1H), 4.75 - 4.66 (m, 1H), 4.66 - 4.53 (m, 3H), 4.01 (s, 3H), 3.20 (br s, 1H), 2.90 (br dd, J=10.6, 3.5 Hz, 1H), 2.54 (br t, J=3.7 Hz, 1H), 2.09 (br t, J=9.8 Hz, 1H), 1.97 - 1.84 (m, 1H), 1.60 - 1.41 (m, 3H), 0.75 - 0.58 (m, 2H), 0.36 - 0.19 (m, 2H)	2.61, A

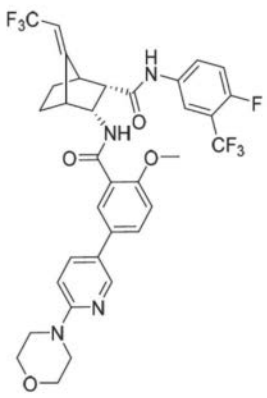
269		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-甲氧基-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	637.27	(400 MHz, $CDCl_3$) δ 9.76 (br d, J=7.4 Hz, 1H), 8.42 (s, 1H), 8.36 - 8.24 (m, 1H), 8.09 - 7.94 (m, 1H), 7.77 - 7.67 (m, 1H), 7.53 - 7.48 (m, 1H), 7.47 - 7.36 (m, 2H), 7.34 - 7.28 (m, 1H), 7.21 (t, J=9.5 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.45 - 6.14 (m, 1H), 4.86 - 4.69 (m, 1H), 4.60 (d, J=9.6 Hz, 1H), 4.54 - 4.38 (m, 2H), 4.11 - 3.92 (m, 3H), 3.23 (d, J=3.7 Hz, 1H), 2.99 (dd, J=10.3, 4.2 Hz, 1H), 2.70 - 2.51 (m, 1H), 2.16 (t, J=8.4 Hz, 1H), 2.02 - 1.80 (m, 1H), 1.73 - 1.41 (m, 3H), 0.81 - 0.62 (m, 2H), 0.42 - 0.19 (m, 2H)	2.48, B

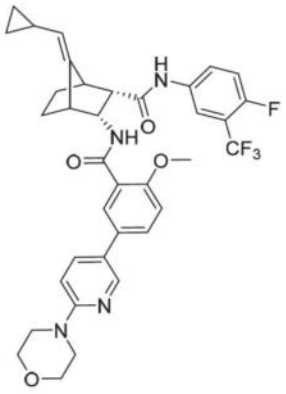
270		3'-{[(2R,3S,7Z)-3-{[4-氰基-3-(三氟甲基)苯基]胺甲酰基}-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	648.18	(500 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.84 (br d, J=7.0 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.08 (d, J=8.5 Hz, 1H), 8.03 - 7.97 (m, 1H), 7.97 - 7.93 (m, 1H), 7.93 - 7.88 (m, 1H), 7.78 - 7.64 (m, 1H), 7.41 - 7.22 (m, 2H), 4.69 (d, J=9.5 Hz, 1H), 4.55 - 4.38 (m, 1H), 4.07 (s, 3H), 3.22 (dd, J=10.8, 3.8 Hz, 1H), 3.13 - 3.08 (m, 1H), 2.80 - 2.67 (m, 1H), 1.90 (s, 1H), 1.86 - 1.73 (m, 2H), 1.62 - 1.46 (m, 1H), 1.46 - 1.33 (m, 2H), 0.86 - 0.60 (m, 2H), 0.42 - 0.23 (m, 2H)	1.95, A

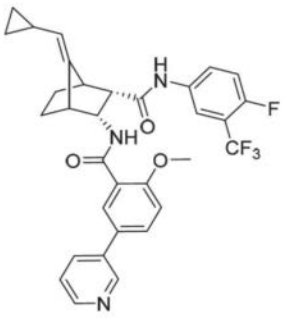
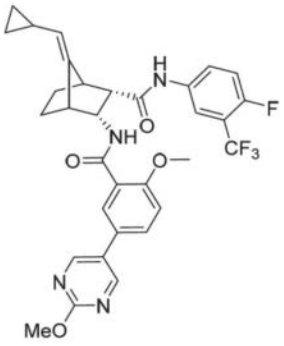
271		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[3-(1,2,3-噻二唑-4-基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	639.3	(500 MHz, DMSO-d6) δ 10.37 (s, 1H), 10.02 (br d, J=7.0 Hz, 1H), 9.50 (s, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 8.01 (d, J=7.0 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.74 (dd, J=18.6, 7.9 Hz, 2H), 7.66 (d, J=7.9 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.40 (t, J=9.5 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.69 (d, J=9.8 Hz, 1H), 4.52 - 4.40 (m, 1H), 4.08 (s, 3H), 3.24 - 3.18 (m, 1H), 3.15 - 3.09 (m, 1H), 2.77 - 2.70 (m, 1H), 1.96 - 1.88 (m, 1H), 1.86 - 1.78 (m, 1H), 1.55 - 1.47 (m, 1H), 1.47 - 1.34 (m, 2H), 0.80 - 0.66 (m, 2H), 0.41 - 0.28 (m, 2H)	2.35, B

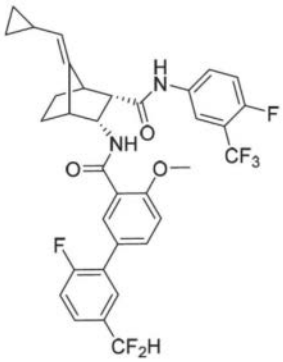
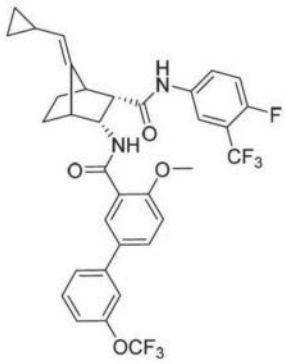
272		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[3-(1-甲基-1H-1,2,3,4-四唑-5-基)苯氧基]羰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	638.16	(500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.97 (br d, J=7.0 Hz, 1H), 8.21 (s, 1H), 8.14 (s, 1H), 8.05 - 7.98 (m, 1H), 7.98 - 7.92 (m, 1H), 7.82 (d, J=7.6 Hz, 1H), 7.74 (d, J=8.2 Hz, 1H), 7.61 - 7.53 (m, 2H), 7.42 (t, J=9.3 Hz, 1H), 7.32 (d, J=8.5 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.54 - 4.40 (m, 1H), 4.17 (s, 3H), 4.07 (s, 3H), 3.20 (dd, J=10.4, 3.4 Hz, 1H), 3.15 - 3.07 (m, 1H), 2.73 (br d, J=3.1 Hz, 1H), 1.96 - 1.87 (m, 1H), 1.86 - 1.79 (m, 1H), 1.57 - 1.48 (m, 1H), 1.47 - 1.35 (m, 2H), 0.79 - 0.66 (m, 2H), 0.45 - 0.25 (m, 2H)	1.57, A

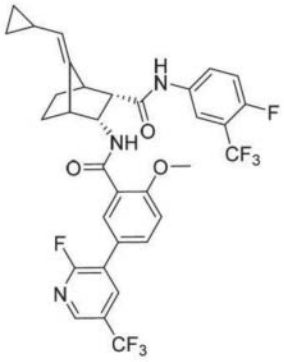
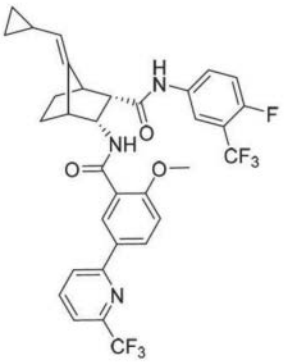
274		(2S,3R,7Z)-7-(环丙基亚甲基)-3-{5-[3-氟-2-(吗啉-4-基)吡啶-4-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	683.0	(500 MHz, $CDCl_3$) δ 9.47 (br d, J=7.5 Hz, 1H), 8.42 (s, 1H), 8.04 (d, J=4.9 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.86 (s, 1H), 7.73 - 7.64 (m, 1H), 7.59 - 7.46 (m, 1H), 7.13 - 7.02 (m, 2H), 6.88 (t, J=4.8 Hz, 1H), 4.90 - 4.76 (m, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.07 (s, 3H), 3.95 - 3.82 (m, 4H), 3.58 - 3.44 (m, J=4.1 Hz, 4H), 3.24 - 3.16 (m, 1H), 3.09 (dd, J=10.7, 3.1 Hz, 1H), 2.78 - 2.65 (m, 1H), 2.25 - 2.09 (m, 1H), 1.97 - 1.81 (m, 1H), 1.74 - 1.61 (m, 2H), 1.54 - 1.41 (m, 1H), 0.82 - 0.65 (m, 2H), 0.45 - 0.26 (m, 2H)	2.52, A
275		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(吗啉-4-基)吡啶-3-基]苯甲酰胺基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-甲酰胺	667.1	(500 MHz, $CDCl_3$) δ 9.40 (br d, J=7.7 Hz, 1H), 8.43 (d, J=2.1 Hz, 1H), 8.36 (d, J=2.3 Hz, 1H), 7.97 - 7.89 (m, 2H), 7.73 (dd, J=8.7, 2.4 Hz, 1H), 7.60 (dd, J=8.5, 2.4 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.12 - 6.97 (m, 2H), 6.71 (d, J=8.7 Hz, 1H), 5.07 (d, J=9.1 Hz, 1H), 4.80 - 4.70 (m, 1H), 4.03 (s, 3H), 3.90 - 3.83 (m, 4H), 3.64 - 3.50 (m, 4H), 3.13 - 3.03 (m, 2H), 2.73 - 2.66 (m, 1H), 2.59 - 2.43 (m, 1H), 2.25 - 2.10 (m, 1H), 1.92 - 1.78 (m, 1H), 1.01 (dd, J=15.1, 6.6 Hz, 6H)	2.21, C

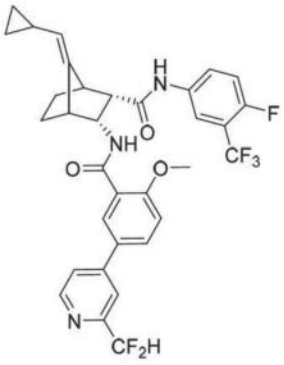
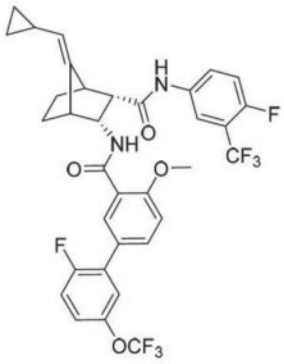
276		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(吗啉-4-基)吡啶-3-基]苯甲酰胺基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	693.3	(500 MHz, $CDCl_3$) δ 9.29 (d, J=8.0 Hz, 1H), 8.42 (d, J=2.3 Hz, 1H), 8.33 (d, J=2.5 Hz, 1H), 8.21 (s, 1H), 7.89 (dd, J=6.2, 2.6 Hz, 1H), 7.70 (dd, J=8.8, 2.6 Hz, 1H), 7.61 (dd, J=8.5, 2.6 Hz, 1H), 7.53 (dt, J=8.8, 3.5 Hz, 1H), 7.08 - 6.98 (m, 2H), 6.71 (d, J=8.8 Hz, 1H), 5.58 (q, J=7.4 Hz, 1H), 4.96 - 4.84 (m, 1H), 3.89 - 3.82 (m, 3H), 3.60 - 3.52 (m, 4H), 3.44 - 3.37 (m, 1H), 3.18 (dd, J=10.9, 3.9 Hz, 1H), 2.92 (t, J=3.9 Hz, 1H), 2.63 (s, 1H), 2.46 - 2.36 (m, 1H), 2.02 - 1.94 (m, 1H), 1.81 - 1.66 (m, 2H), 1.59 (s, 3H)	2.08, C

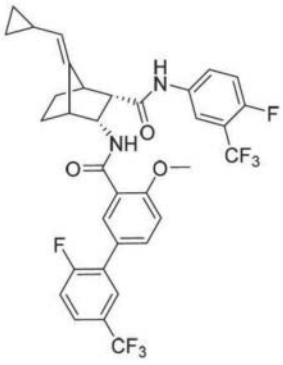
277		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(吗啉-4-基)吡啶-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	366.1	(500 MHz, $CDCl_3$) δ 9.57 (br d, J=7.7 Hz, 1H), 8.52 (d, J=1.9 Hz, 1H), 8.30 (d, J=2.5 Hz, 1H), 8.26 (br s, 1H), 8.09 (dd, J=9.1, 2.2 Hz, 1H), 8.04 (dd, J=5.9, 2.3 Hz, 1H), 7.70 - 7.61 (m, 1H), 7.57 (dd, J=8.8, 2.5 Hz, 1H), 7.13 (t, J=9.4 Hz, 1H), 7.03 - 6.96 (m, 2H), 4.67 (d, J=9.4 Hz, 2H), 4.06 (s, 3H), 3.98 - 3.88 (m, 4H), 3.83 - 3.70 (m, 4H), 3.18 (t, J=4.0 Hz, 1H), 3.11 (dd, J=10.9, 4.0 Hz, 1H), 2.73 (t, J=3.6 Hz, 1H), 1.91 - 1.84 (m, 2H), 1.69 - 1.57 (m, 2H), 1.50 (tt, J=12.9, 4.7 Hz, 1H), 0.82 - 0.71 (m, 2H), 0.43 - 0.29 (m, 2H)	0.70, A

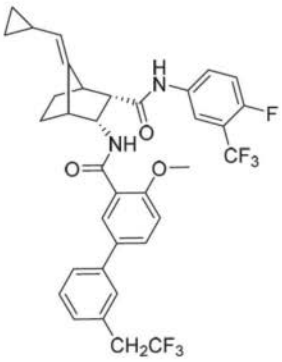
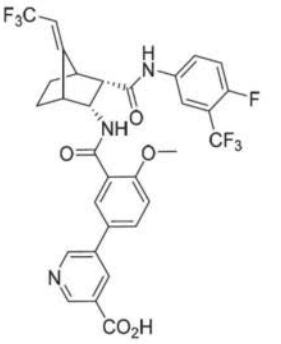
278		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(吡啶-3-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	580.3	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.87 (br d, J=7.0 Hz, 1H), 8.78 (s, 1H), 8.49 (d, J=3.7 Hz, 1H), 8.21 - 8.09 (m, 2H), 7.98 (d, J=7.3 Hz, 1H), 7.83 (dd, J=8.9, 1.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.50 - 7.37 (m, 2H), 7.28 (d, J=8.5 Hz, 1H), 4.64 (d, J=9.8 Hz, 1H), 4.48 - 4.36 (m, 1H), 4.00 (s, 2H), 3.60 - 3.46 (m, 1H), 3.11 (dd, J=10.5, 4.1 Hz, 1H), 3.08 - 3.03 (m, 1H), 2.71 - 2.63 (m, 1H), 1.89 - 1.66 (m, 2H), 1.55 - 1.27 (m, 3H), 0.69 (br dd, J=11.4, 9.0 Hz, 2H), 0.37 - 0.21 (m, 2H)	2.05, C
279		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-甲氧基嘧啶-5-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	611.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (br d, J=7.3 Hz, 1H), 8.84 (s, 2H), 8.19 (dd, J=6.6, 2.0 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 7.83 (dd, J=8.2, 2.4 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.46 (t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.02 (s, 3H), 3.94 (s, 3H), 3.14 (dd, J=10.8, 3.2 Hz, 1H), 3.11 - 3.07 (m, 1H), 2.76 - 2.65 (m, 1H), 1.90 - 1.72 (m, 2H), 1.56 - 1.33 (m, 4H), 0.82 - 0.61 (m, 3H), 0.42 - 0.24 (m, 2H)	2.54, C

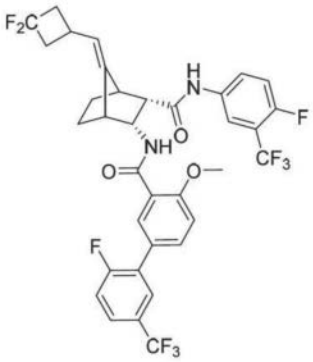
280		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-5'-(二氟甲基)-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	647.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (d, J=7.3 Hz, 1H), 8.19 (dd, J=6.3, 2.3 Hz, 1H), 8.12 (s, 1H), 7.82 - 7.67 (m, 3H), 7.61 (br d, J=8.9 Hz, 1H), 7.45 (t, J=9.6 Hz, 2H), 7.31 (d, J=8.9 Hz, 1H), 7.21 - 6.90 (m, 1H), 4.67 (d, J=9.8 Hz, 1H), 4.49 - 4.39 (m, 1H), 4.04 (s, 3H), 3.20 - 3.11 (m, 1H), 3.11 - 3.05 (m, 1H), 2.74 - 2.66 (m, 1H), 1.90 - 1.81 (m, 1H), 1.81 - 1.72 (m, 1H), 1.55 - 1.45 (m, 1H), 1.44 - 1.34 (m, 2H), 0.72 (quin, J=9.5 Hz, 2H), 0.39 - 0.27 (m, 2H)	2.78, C
281		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-4-甲氧基-3'-(三氟甲氧基)-[1,1'-联苯]-3-甲酰胺	663.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (d, J=7.2 Hz, 1H), 8.28 - 8.17 (m, 2H), 7.88 (dd, J=8.6, 2.4 Hz, 1H), 7.82 - 7.76 (m, 1H), 7.68 (d, J=8.1 Hz, 1H), 7.63 - 7.55 (m, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.4 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.55 - 4.41 (m, 1H), 4.05 (s, 3H), 3.24 - 3.14 (m, 1H), 3.14 - 3.05 (m, 1H), 2.78 - 2.68 (m, 1H), 1.96 - 1.71 (m, 2H), 1.58 - 1.46 (m, 1H), 1.46 - 1.31 (m, 2H), 0.87 - 0.62 (m, 2H), 0.44 - 0.29 (m, 2H)	2.92, C

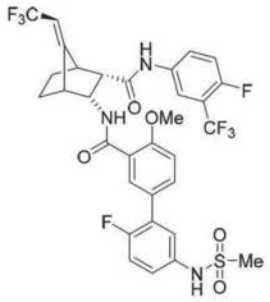
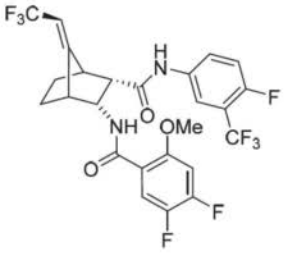
282		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[2-氟-5-(三氟甲基)吡啶-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	666.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.3 Hz, 1H), 8.66 (s, 1H), 8.53 - 8.44 (m, 1H), 8.24 - 8.19 (m, 2H), 7.85 (d, J=9.2 Hz, 1H), 7.81 - 7.72 (m, 1H), 7.47 (t, J=9.6 Hz, 1H), 7.35 (d, J=8.9 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.06 (s, 3H), 3.16 (dd, J=10.7, 3.7 Hz, 1H), 3.13 - 3.07 (m, 1H), 2.75 - 2.68 (m, 1H), 1.90 - 1.75 (m, 2H), 1.57 - 1.45 (m, 1H), 1.45 - 1.34 (m, 2H), 0.73 (quin, J=9.6 Hz, 2H), 0.41 - 0.28 (m, 2H)	2.83, C
283		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[6-(三氟甲基)吡啶-2-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	647.9	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (br d, J=6.8 Hz, 1H), 8.73 (d, J=2.1 Hz, 1H), 8.31 - 8.19 (m, 3H), 8.14 (t, J=7.8 Hz, 1H), 7.81 (d, J=7.9 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 4.69 (d, J=9.4 Hz, 1H), 4.53 - 4.41 (m, 1H), 4.07 (s, 3H), 3.23 - 3.14 (m, 1H), 3.14 - 3.10 (m, 1H), 2.75 - 2.70 (m, 1H), 1.88 - 1.71 (m, 2H), 1.59 - 1.47 (m, 1H), 1.47 - 1.34 (m, 2H), 0.82 - 0.64 (m, 2H), 0.43 - 0.28 (m, 2H)	2.85, C

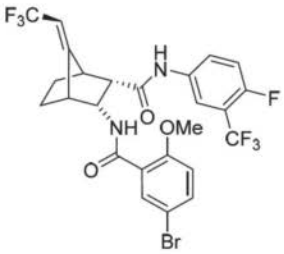
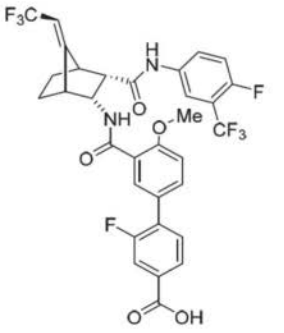
284		(2S,3R,7Z)-7-(环丙基亚甲基)-3-{5-[2-(二氟甲基)吡啶-4-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	630.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (d, J=7.0 Hz, 1H), 8.72 (d, J=2.4 Hz, 1H), 8.28 - 8.17 (m, 2H), 8.16 - 8.00 (m, 2H), 7.82 - 7.76 (m, 1H), 7.62 (d, J=7.3 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.9 Hz, 1H), 7.18 - 6.83 (m, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.55 - 4.39 (m, 1H), 4.07 (s, 3H), 3.17 (br dd, J=10.7, 4.0 Hz, 1H), 3.15 - 3.11 (m, 1H), 2.76 - 2.70 (m, 1H), 1.95 - 1.72 (m, 2H), 1.61 - 1.47 (m, 1H), 1.47 - 1.32 (m, 2H), 0.85 - 0.64 (m, 2H), 0.47 - 0.25 (m, 2H)	2.77, C
285		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(三氟甲氧基)-[1,1'-联苯]-3-甲酰胺	681.3	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.87 (d, J=7.1 Hz, 1H), 8.20 - 8.11 (m, 1H), 8.11 - 8.01 (m, 1H), 7.78 - 7.64 (m, 2H), 7.50 - 7.33 (m, 4H), 7.27 (d, J=8.8 Hz, 1H), 4.63 (d, J=9.6 Hz, 1H), 4.47 - 4.31 (m, 1H), 3.99 (s, 3H), 3.14 - 3.07 (m, 1H), 3.04 (br s, 1H), 2.66 (br d, J=19.2 Hz, 1H), 1.87 - 1.76 (m, 1H), 1.76 - 1.67 (m, 1H), 1.50 - 1.41 (m, 1H), 1.40 - 1.29 (m, 2H), 0.76 - 0.58 (m, 2H), 0.36 - 0.24 (m, 2H)	2.99, C

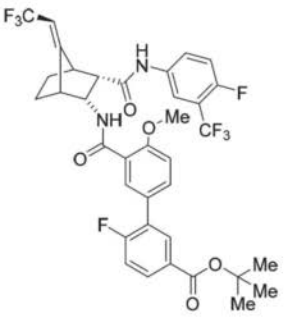
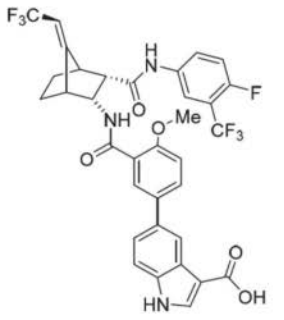
286		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(三氟甲基)-[1,1'-联苯]-3-甲酰胺	665.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.90 (br d, J=7.0 Hz, 1H), 8.22 - 8.16 (m, 1H), 8.12 (s, 1H), 7.82 (d, J=7.0 Hz, 1H), 7.80 - 7.72 (m, 3H), 7.54 (t, J=9.3 Hz, 1H), 7.45 (t, J=9.8 Hz, 1H), 7.32 (d, J=8.5 Hz, 1H), 4.68 (d, J=9.8 Hz, 1H), 4.49 - 4.39 (m, 1H), 4.04 (s, 3H), 3.14 (dd, J=10.8, 4.4 Hz, 1H), 3.11 - 3.05 (m, 1H), 2.77 - 2.65 (m, 1H), 1.88 - 1.82 (m, 1H), 1.81 - 1.72 (m, 1H), 1.54 - 1.45 (m, 1H), 1.44 - 1.35 (m, 2H), 0.83 - 0.63 (m, 2H), 0.40 - 0.25 (m, 2H)	2.88, C

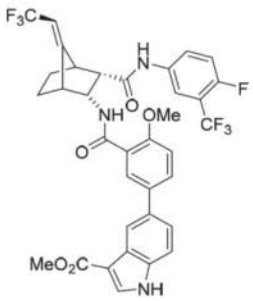
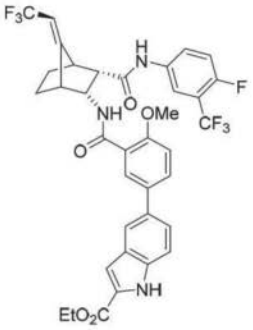
287		N-[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-4-甲氧基-3'-(2,2,2-三氟乙基)-[1,1'-联苯]-3-甲酰胺	661.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.94 (d, J=7.1 Hz, 1H), 8.28 - 8.20 (m, 2H), 7.85 - 7.74 (m, 2H), 7.67 - 7.57 (m, 2H), 7.53 - 7.43 (m, 2H), 7.32 (dd, J=16.3, 8.0 Hz, 2H), 4.70 (d, J=9.6 Hz, 1H), 4.56 - 4.39 (m, 1H), 4.05 (s, 3H), 3.80 - 3.65 (m, 2H), 3.17 (dd, J=10.4, 4.1 Hz, 1H), 3.14 - 3.08 (m, 1H), 2.78 - 2.68 (m, 1H), 1.92 - 1.73 (m, 2H), 1.55 - 1.48 (m, 1H), 1.47 - 1.35 (m, 2H), 0.81 - 0.66 (m, 2H), 0.42 - 0.30 (m, 2H)	2.86, C
288		5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡啶-3-甲酸	652.0	(500 MHz, $CDCl_3$) δ 10.32 - 9.84 (m, 2H), 9.73 (br s, 1H), 9.27 (br s, 1H), 9.14 (s, 1H), 8.72 (br d, J=2.1 Hz, 2H), 7.81 - 7.68 (m, 1H), 7.54 - 7.41 (m, 1H), 7.28 - 7.23 (m, 1H), 6.71 - 6.51 (m, 1H), 5.63 (q, J=7.4 Hz, 1H), 4.44 - 4.25 (m, 1H), 4.06 (s, 3H), 3.39 (br dd, J=10.6, 4.0 Hz, 1H), 3.19 (br s, 1H), 2.93 (br s, 1H), 2.40 - 2.28 (m, 1H), 1.92 - 1.80 (m, 1H), 1.70 - 1.53 (m, 2H)	1.19, D

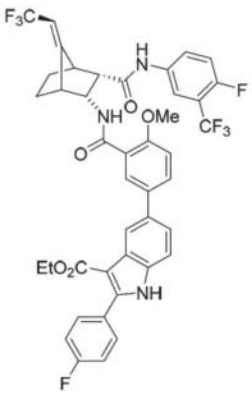
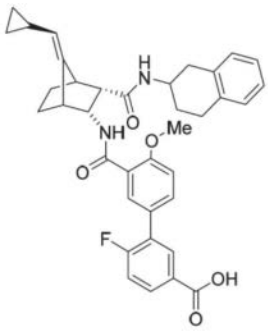
289		N-[(2R,3S,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-(三氟甲基)-[1,1'-联苯]-3-甲酰胺	715.0	(500 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.87 (br d, J=6.3 Hz, 1H), 8.50 (dd, J=2.4, 1.0 Hz, 1H), 8.13 (dd, J=6.3, 2.7 Hz, 1H), 7.87 (dt, J=8.5, 3.8 Hz, 1H), 7.80 - 7.74 (m, 2H), 7.68 - 7.62 (m, 1H), 7.35 - 7.30 (m, 1H), 7.19 (d, J=8.7 Hz, 1H), 7.16 (t, J=9.5 Hz, 1H), 5.41 (d, J=8.7 Hz, 1H), 4.41 - 4.31 (m, 1H), 4.15 (s, 3H), 3.26 (d, J=4.9 Hz, 1H), 2.99 (t, J=3.8 Hz, 1H), 2.92 - 2.82 (m, 1H), 2.81 - 2.68 (m, 2H), 1.98 - 1.89 (m, 1H), 1.86 - 1.72 (m, 2H), 1.53 (ddd, J=12.3, 8.9, 5.6 Hz, 1H), 1.29 - 1.27 (m, 2H), 0.97 - 0.77 (m, 2H)	1.21, D

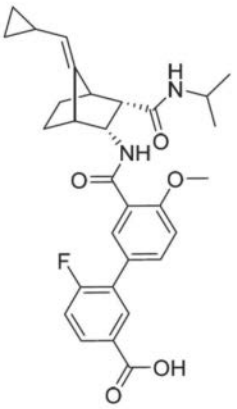
290		2'-氟-N-[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]-5'-甲磺酰胺基-4-甲氧基-[1,1'-联苯]-3-甲酰胺	718.0	(500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 9.97 (br d, *J*=6.7 Hz, 1H), 8.23 (br d, *J*=4.6 Hz, 1H), 8.11 (br s, 1H), 7.80 (br s, 1H), 7.67 (br d, *J*=8.2 Hz, 1H), 7.50 (br t, *J*=9.5 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.23 (br s, 1H), 5.93 (br d, *J*=7.9 Hz, 1H), 4.53 (br s, 1H), 4.05 (s, 2H), 3.30 (br s, 2H), 2.99 (s, 3H), 2.55 - 2.51 (m, 10H), 1.97 (br d, *J*=8.9 Hz, 1H), 1.90 (br s, 1H), 1.49 (br d, *J*=6.1 Hz, 2H)	2.56, C
291		(2S,3R,7Z)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	567.0	(500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.97 (br d, J=6.4 Hz, 1H), 8.23 (br d, J=4.6 Hz, 1H), 7.86 (br t, J=10.4 Hz, 1H), 7.77 (br s, 1H), 7.50 (br t, J=9.8 Hz, 1H), 7.39 (br dd, J=12.5, 6.4 Hz, 1H), 5.94 (q, J=7.9 Hz, 1H), 4.49 (br s, 1H), 4.01 (s, 3H), 3.29 - 3.21 (m, 1H), 2.99 (br s, 1H), 2.55 - 2.53 (m, 1H), 1.96 - 1.91 (m, 1H), 1.87 - 1.82 (m, 1H), 1.49 (br d, J=6.4 Hz, 2H)	2.60, C

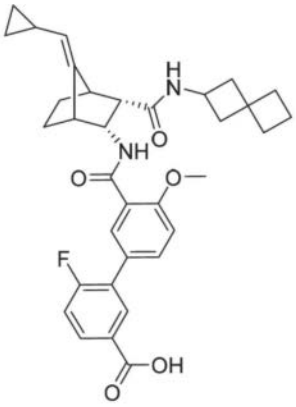
292		(2S,3R,7Z)-3-(5-溴-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	609.0	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.82 (br d, J=6.9 Hz, 1H), 8.16 (br d, J=5.7 Hz, 1H), 7.98 (d, J=1.9 Hz, 1H), 7.85 - 7.72 (m, 1H), 7.65 (dd, J=8.8, 2.4 Hz, 1H), 7.46 (t, J=9.7 Hz, 1H), 7.17 (d, J=8.8 Hz, 1H), 5.89 (q, J=7.8 Hz, 1H), 4.58 - 4.45 (m, 1H), 3.99 (s, 3H), 3.49 - 3.34 (m, 3H), 3.28 - 3.18 (m, 1H), 2.99 (br s, 1H), 2.57 - 2.54 (m, 4H), 2.08 - 1.95 (m, 1H), 1.95 - 1.83 (m, 1H), 1.50 (br d, J=6.6 Hz, 2H)	2.78, C
293		2-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-4-甲酸	669.0	(500 MHz, DMSO-d_6) δ 10.57 (s, 1H), 9.85 (br d, *J*=7.1 Hz, 1H), 8.22 - 8.13 (m, 2H), 7.87 - 7.78 (m, 2H), 7.78 - 7.70 (m, 2H), 7.60 (t, *J*=8.0 Hz, 1H), 7.46 (t, *J*=9.7 Hz, 1H), 7.33 (d, *J*=8.7 Hz, 1H), 5.90 (q, *J*=7.7 Hz, 1H), 4.56 (br t, *J*=10.7 Hz, 1H), 4.06 (s, 3H), 3.32 - 3.25 (m, 1H), 3.00 (br d, *J*=6.9 Hz, 1H), 2.58 - 2.53 (m, 6H), 2.05 (br t, *J*=9.2 Hz, 1H), 1.94 (br t, *J*=8.7 Hz, 1H), 1.52 (br d, *J*=6.3 Hz, 2H)	2.55, C

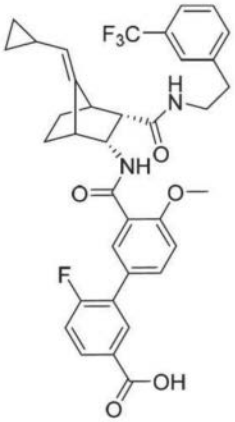
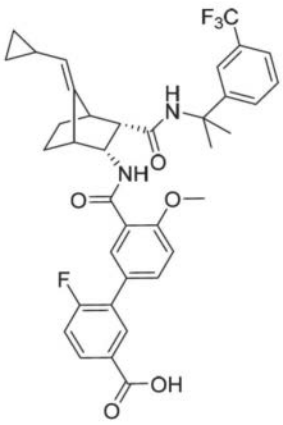
294		6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸叔丁酯	725.0	(500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 9.94 (br d, *J*=7.0 Hz, 1H), 8.22 (br d, *J*=4.3 Hz, 1H), 8.16 (s, 1H), 7.81 - 7.69 (m, 4H), 7.64 (br t, *J*=7.9 Hz, 1H), 7.49 (br t, *J*=9.6 Hz, 1H), 7.33 (d, *J*=8.9 Hz, 1H), 5.93 (q, *J*=7.9 Hz, 1H), 4.53 (br s, 1H), 4.05 (s, 3H), 3.48 - 3.41 (m, 1H), 3.29 - 3.23 (m, 1H), 2.99 (br s, 1H), 1.99 (br t, *J*=9.3 Hz, 1H), 1.90 (br t, *J*=8.7 Hz, 1H), 1.56 (s, 9H), 1.50 (br d, *J*=6.4 Hz, 2H)	3.00, C
295		5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吲哚-3-甲酸	690.0	(500 MHz, DMSO-d_6) δ 10.52 (s, 1H), 9.87 (br d, *J*=7.0 Hz, 1H), 8.30 - 8.18 (m, 3H), 8.01 (d, *J*=2.2 Hz, 1H), 7.89 - 7.74 (m, 2H), 7.55 (d, *J*=8.5 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.29 (d, *J*=8.7 Hz, 1H), 5.92 (q, *J*=7.9 Hz, 1H), 4.71 - 4.53 (m, 1H), 4.06 (s, 3H), 3.31 (br s, 1H), 3.01 (br s, 1H), 2.91 (s, 1H), 2.75 (s, 1H), 2.57 - 2.53 (m, 4H), 2.08 (br t, *J*=9.3 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.53 (br d, *J*=6.5 Hz, 2H)	2.33, C

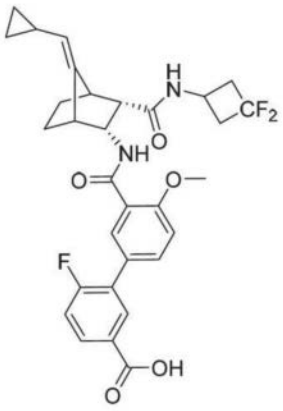
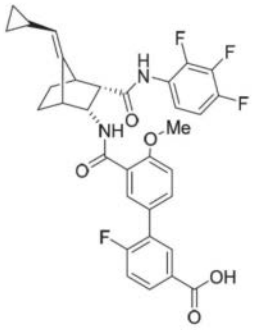
296		6-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吲哚-3-甲酸甲酯	704	(500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.97 (br d, J=7.0 Hz, 1H), 8.27 - 8.22 (m, 2H), 8.11 (s, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.95 (s, 1H), 7.87 - 7.77 (m, 2H), 7.68 (s, 1H), 7.52 - 7.44 (m, 2H), 7.29 (d, J=8.5 Hz, 1H), 5.94 (q, J=7.4 Hz, 1H), 4.55 (br s, 1H), 4.05 (s, 3H), 3.36 (br s, 2H), 3.33 - 3.23 (m, 1H), 3.00 (br s, 1H), 2.89 (s, 2H), 2.73 (s, 2H), 2.56 - 2.53 (m, 1H), 1.99 (br d, J=9.8 Hz, 1H), 1.95 - 1.86 (m, 1H), 1.50 (br d, J=6.1 Hz, 2H), 1.22 (br d, J=7.6 Hz, 3H)	2.63, C
297		5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吲哚-2-甲酸乙酯	718	(500 MHz, DMSO-d6) δ 9.96 (br d, J=6.7 Hz, 1H), 8.24 (br s, 2H), 7.89 (s, 1H), 7.84 - 7.78 (m, 2H), 7.56 - 7.48 (m, 3H), 7.28 (d, J=8.5 Hz, 1H), 7.20 (s, 1H), 5.94 (q, J=7.8 Hz, 1H), 4.56 (br s, 1H), 4.35 (q, J=7.0 Hz, 2H), 4.04 (s, 3H), 3.31 - 3.25 (m, 1H), 3.00 (br s, 1H), 2.56 - 2.53 (m, 6H), 2.02 - 1.96 (m, 1H), 1.96 - 1.88 (m, 1H), 1.50 (br d, J=6.1 Hz, 2H), 1.35 (t, J=7.2 Hz, 3H)	2.78, C

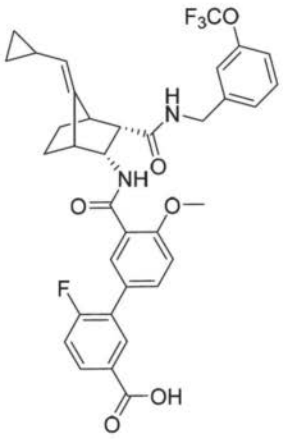
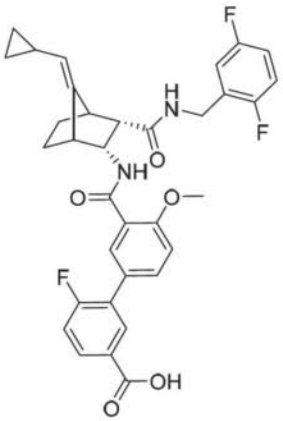
298		5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-2-(4-氟苯基)-1H-吲哚-3-甲酸乙酯	812	(500 MHz, DMSO-d6) δ 9.97 (br d, J=6.7 Hz, 1H), 8.29 - 8.23 (m, 3H), 7.83 - 7.73 (m, 4H), 7.54 - 7.46 (m, 3H), 7.36 - 7.29 (m, 3H), 5.93 (q, J=7.7 Hz, 1H), 4.56 (br s, 1H), 4.20 (q, J=7.0 Hz, 2H), 4.05 (s, 3H), 3.33 - 3.25 (m, 1H), 3.00 (br s, 1H), 2.88 (s, 1H), 2.72 (s, 1H), 2.55 - 2.52 (m, 1H), 2.00 (br d, J=9.2 Hz, 1H), 1.95 - 1.89 (m, 1H), 1.66 (br s, 1H), 1.54 - 1.46 (m, 2H), 1.22 (br t, J=7.0 Hz, 3H)	2.87, C
299		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(1,2,3,4-四氢萘-2-基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	609.0	(500 MHz, DMSO-d_6) δ 10.01 (br d, *J*=6.7 Hz, 1H), 8.17 (br d, *J*=7.3 Hz, 1H), 8.11 (br s, 1H), 8.03 (br d, *J*=7.0 Hz, 1H), 7.94 (br d, *J*=5.8 Hz, 1H), 7.72 (br s, 1H), 7.36 (br t, *J*=9.5 Hz, 1H), 7.29 (d, *J*=8.2 Hz, 1H), 7.06 (br s, 4H), 4.61 (br d, *J*=9.2 Hz, 1H), 4.33 (br s, 1H), 4.06 - 3.98 (m, 4H), 3.06 (br s, 1H), 2.95 (br d, *J*=6.4 Hz, 2H), 2.89 (s, 1H), 2.79 (br s, 2H), 2.73 (s, 1H), 2.61 - 2.57 (m, 1H), 2.56 - 2.52 (m, 8H), 1.90 (s, 9H), 1.79 (br s, 1H), 1.63 (br s, 1H), 1.47 (br s, 1H), 1.36 (br s, 2H), 0.71 (br t, *J*=9.2 Hz, 2H), 0.31 (br s, 2H)	2.52, C

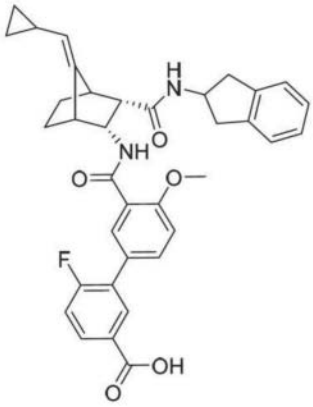
300		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[丙烷-2-基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	521	(500 MHz, DMSO-d6) δ 10.03 (br d, J=7.0 Hz, 1H), 8.09 (s, 1H), 7.97 (br dd, J=15.9, 7.6 Hz, 1H), 7.85 (br t, J=6.9 Hz, 1H), 7.69 (br d, J=8.5 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 7.17 (t, J=8.9 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.30 (br s, 1H), 4.03 (s, 2H), 3.92 - 3.86 (m, 1H), 3.57 - 3.48 (m, 2H), 3.06 (br s, 1H), 2.86 (br dd, J=10.7, 4.0 Hz, 1H), 2.55 (s, 6H), 1.90 (br t, J=9.6 Hz, 1H), 1.78 (s, 2H), 1.48 (br d, J=8.9 Hz, 1H), 1.34 (br t, J=13.4 Hz, 1H), 1.04 (t, J=7.0 Hz, 4H), 0.75 - 0.67 (m, 1H), 0.31 (br s, 1H)	2.28, C

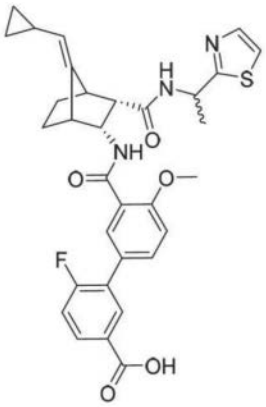
301		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({螺[3.3]庚烷-2-基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	573	(500 MHz, DMSO-d6) d 9.98 (br d, J=6.4 Hz, 1H), 8.24 (br d, J=7.0 Hz, 1H), 8.14 - 7.98 (m, 2H), 7.90 (br s, 1H), 7.70 (br d, J=8.5 Hz, 1H), 7.35 - 7.20 (m, 2H), 4.62 (br d, J=9.5 Hz, 1H), 4.30 (br s, 1H), 4.08 - 3.98 (m, 4H), 3.33 (br s, 1H), 3.05 (br s, 1H), 2.85 (br d, J=6.7 Hz, 1H), 2.65 (br s, 1H), 2.56 - 2.54 (m, 5H), 2.27 (br d, J=7.9 Hz, 2H), 1.98 (br d, J=6.4 Hz, 2H), 1.90 - 1.72 (m, 8H), 1.46 (br s, 1H), 1.34 (br s, 2H), 0.80 - 0.59 (m, 2H), 0.32 (br s, 2H)	2.55, C

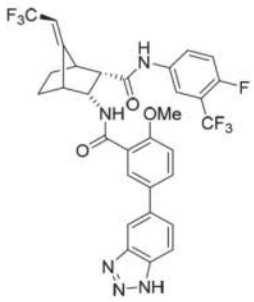
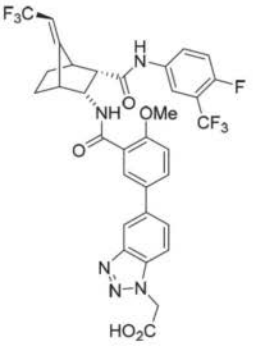
302		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({2-[3-(三氟甲基)苯基]乙基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	651	(500 MHz, DMSO-d6) δ 9.64 (br d, J=6.9 Hz, 1H), 7.86 (s, 1H), 7.80 (br d, J=5.7 Hz, 2H), 7.76 - 7.68 (m, 1H), 7.47 (br d, J=8.5 Hz, 1H), 7.32 - 7.14 (m, 5H), 7.04 (d, J=8.7 Hz, 1H), 4.38 (d, J=9.3 Hz, 1H), 4.06 (br s, 1H), 3.24 (dq, J=13.3, 6.7 Hz, 1H), 2.81 (br s, 1H), 2.68 - 2.56 (m, 3H), 2.53 - 2.43 (m, 1H), 2.33 - 2.22 (m, 9H), 2.18 (br t, J=3.9 Hz, 1H), 1.50 (br t, J=6.2 Hz, 2H), 1.22 (br dd, J=8.6, 4.1 Hz, 1H), 1.10 (br s, 1H), 1.01 (br s, 1H), 0.54 - 0.39 (m, 2H), 0.08 (br d, J=2.7 Hz, 2H)	2.64, C
303		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({2-[3-(三氟甲基)苯基]丙烷-2-基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	664	(500 MHz, DMSO-d6) δ 9.81 (br d, J=6.9 Hz, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.99 (br d, J=6.6 Hz, 1H), 7.92 - 7.75 (m, 1H), 7.74 - 7.55 (m, 3H), 7.54 - 7.31 (m, 2H), 7.29 - 7.13 (m, 2H), 4.69 (d, J=9.3 Hz, 1H), 4.35 (br s, 1H), 3.90 (s, 1H), 3.65 (s, 2H), 3.12 - 2.94 (m, 1H), 2.77 - 2.60 (m, 1H), 2.59 - 2.54 (m, 1H), 2.48 - 2.24 (m, 1H), 2.07 (s, 1H), 1.90 (s, 2H), 1.75 - 1.54 (m, 7H), 1.54 - 1.40 (m, 1H), 1.38 - 1.18 (m, 2H), 1.17 - 0.96 (m, 2H), 0.89 - 0.69 (m, 2H), 0.34 (br s, 2H)	2.22, C

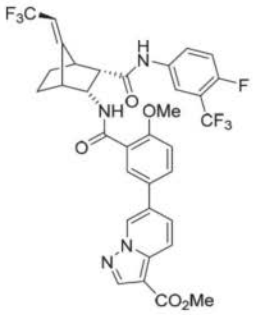
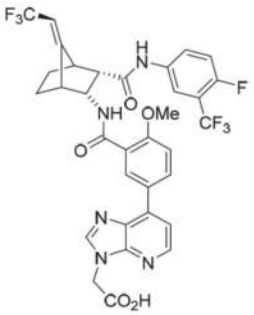
304		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(3,3-二氟环丁基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	569	(500 MHz, DMSO-d6) δ 9.87 (br d, J=7.0 Hz, 1H), 8.47 (br d, J=6.5 Hz, 1H), 8.12 (s, 1H), 8.03 (br d, J=8.8 Hz, 1H), 7.89 (br s, 1H), 7.69 (br d, J=8.8 Hz, 1H), 7.28 (br d, J=8.7 Hz, 1H), 7.22 (br d, J=9.7 Hz, 1H), 4.67 (d, J=9.4 Hz, 1H), 4.37 (br s, 1H), 4.15 - 3.99 (m, 3H), 3.09 (br s, 1H), 3.00 - 2.78 (m, 2H), 2.65 (br s, 1H), 2.59 - 2.54 (m, 3H), 1.87 (br d, J=8.8 Hz, 1H), 1.79 (br s, 1H), 1.50 (br s, 1H), 1.38 (br s, 1H), 1.26 (s, 1H), 0.80 - 0.67 (m, 1H), 0.33 (br s, 2H)	1.84, C
305		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(2,3,4-三氟苯基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	609.0	(500 MHz, DMSO-d_6) δ 9.82 (br d, *J*=7.0 Hz, 1H), 8.13 (s, 1H), 8.02 (br d, *J*=7.3 Hz, 1H), 7.88 (br s, 1H), 7.69 (br d, *J*=8.2 Hz, 1H), 7.53 (br s, 1H), 7.34 - 7.18 (m, 3H), 4.69 (br d, *J*=9.5 Hz, 1H), 4.46 (br s, 1H), 3.96 (s, 3H), 3.35 (br s, 1H), 3.10 (br s, 1H), 2.73 (br s, 1H), 2.56 - 2.53 (m, 8H), 1.88 (br d, *J*=10.1 Hz, 1H), 1.83 - 1.76 (m, 1H), 1.72 (br s, 1H), 1.50 (br s, 1H), 1.42 (br s, 2H), 0.74 (br dd, *J*=13.1, 8.9 Hz, 2H), 0.35 (br s, 2H)	2.49, C

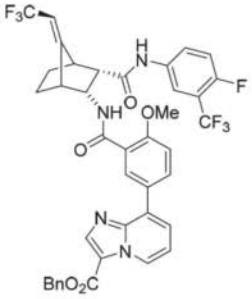
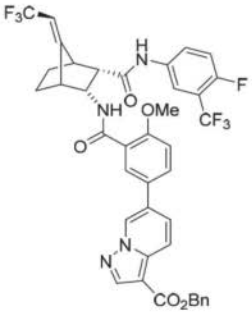
306		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-({[2-(三氟甲氧基)苯基]甲基}胺甲酰基)双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	653	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.7 Hz, 1H), 8.66 (br s, 1H), 8.12 (br s, 1H), 8.04 (br d, J=7.3 Hz, 1H), 7.97 (br s, 1H), 7.73 (br d, J=8.5 Hz, 1H), 7.45 (br t, J=9.5 Hz, 1H), 7.39 - 7.30 (m, 2H), 7.30 - 7.22 (m, 2H), 4.64 (br d, J=9.5 Hz, 1H), 4.37 (br s, 2H), 3.91 (s, 2H), 3.09 - 3.01 (m, 1H), 2.60 (br s, 1H), 2.56 - 2.52 (m, 6H), 1.89 - 1.82 (m, 1H), 1.80 - 1.70 (m, 1H), 1.47 (br s, 1H), 1.35 (br t, J=12.4 Hz, 2H), 0.76 - 0.67 (m, 1H), 0.33 (br s, 1H)	2.5, C
307		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[1-(2,5-二氟苯基)乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	619	(500 MHz, DMSO-d6) δ 8.63 (br dd, J=16.6, 7.5 Hz, 1H), 8.12 - 8.00 (m, 1H), 7.95 (br s, 1H), 7.75 - 7.66 (m, 1H), 7.42 (br t, J=8.1 Hz, 1H), 7.18 - 7.05 (m, 2H), 5.17 - 5.10 (m, 1H), 4.66 - 4.62 (m, 1H), 4.34 (br s, 1H), 4.01 (s, 1H), 3.67 (s, 1H), 3.06 - 2.98 (m, 1H), 2.61 (br s, 1H), 2.55 - 2.52 (m, 5H), 1.70 (br s, 1H), 1.47 (br s, 1H), 1.32 (br d, J=6.7 Hz, 4H), 0.76 - 0.67 (m, 1H), 0.32 (br s, 1H)	2.41, C

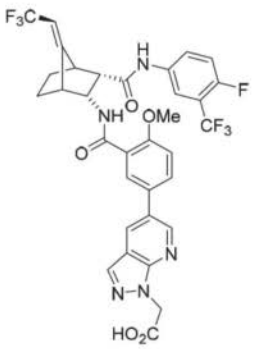
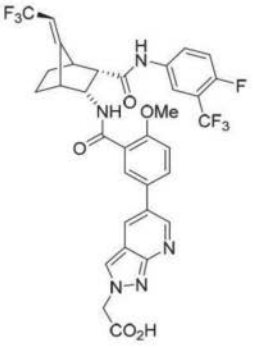
308		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-[(2,3-二氢-1H-茚-2-基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	595	(500 MHz, DMSO-d6) δ 10.04 (br d, J=7.0 Hz, 1H), 8.41 (br d, J=6.7 Hz, 1H), 8.12 (br s, 1H), 8.05 (br d, J=7.6 Hz, 1H), 7.97 (br s, 1H), 7.75 (br d, J=7.6 Hz, 1H), 7.44 (br t, J=9.5 Hz, 1H), 7.32 (br d, J=8.5 Hz, 1H), 7.21 (br d, J=6.4 Hz, 1H), 7.13 (br d, J=7.0 Hz, 3H), 4.60 (br d, J=9.5 Hz, 1H), 4.54 - 4.45 (m, 1H), 4.32 (br s, 1H), 4.07 (s, 3H), 3.24 - 3.10 (m, 1H), 3.06 (br s, 1H), 2.96 - 2.83 (m, 1H), 2.78 - 2.64 (m, 2H), 2.55 - 2.53 (m, 3H), 2.08 - 1.86 (m, 1H), 1.79 (br s, 1H), 1.46 (br s, 1H), 1.36 (br s, 2H), 1.27 - 1.11 (m, 1H), 1.04 (d, J=6.1 Hz, 3H), 0.71 (br t, J=9.2 Hz, 2H), 0.31 (br s, 2H)	2.47, C

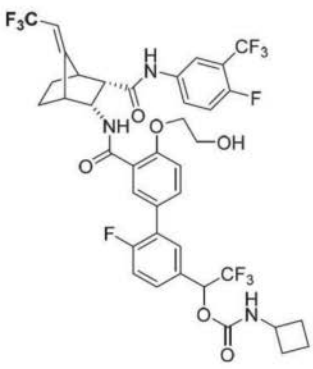
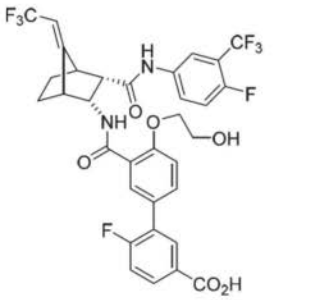
309		3'-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[1-(1,3-噻唑-2-基)乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	590	(500 MHz, DMSO-d6) δ 10.00 (br d, J=7.0 Hz, 1H), 8.90 (t, J=8.4 Hz, 1H), 8.11 (br s, 1H), 8.03 (br d, J=7.0 Hz, 1H), 7.95 (br s, 1H), 7.77 - 7.68 (m, 2H), 7.62 (dd, J=17.7, 3.1 Hz, 1H), 7.46 - 7.38 (m, 1H), 7.30 (br d, J=8.9 Hz, 1H), 5.31 - 5.19 (m, 1H), 4.65 (br t, J=9.2 Hz, 1H), 4.37 (br s, 1H), 4.02 (s, 2H), 3.90 (s, 1H), 3.80 (s, 1H), 3.17 (s, 1H), 3.07 (br s, 1H), 3.05 - 2.97 (m, 1H), 2.89 (s, 1H), 2.73 (s, 1H), 2.63 (br d, J=15.3 Hz, 1H), 2.55 - 2.52 (m, 8H), 1.97 - 1.86 (m, 1H), 1.86 - 1.70 (m, 2H), 1.48 (br d, J=6.4 Hz, 4H), 1.36 (br s, 2H), 0.85 - 0.66 (m, 2H), 0.33 (br s, 2H)	2.04, C

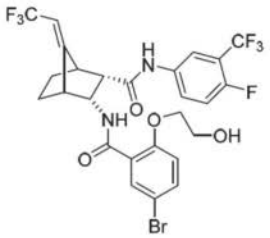
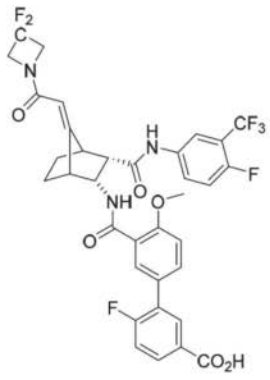
311		(2S,3R,7Z)-3-[5-(1H-1,2,3-苯并三唑-5-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	684.3	(500 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.97 (br d, J=7.0 Hz, 1H), 8.33 - 8.22 (m, 2H), 8.01 (s, 1H), 7.94 - 7.86 (m, 2H), 7.83 - 7.76 (m, 1H), 7.59 (br d, J=8.5 Hz, 1H), 7.52 - 7.44 (m, 1H), 7.31 (d, J=8.5 Hz, 1H), 5.94 (q, J=7.7 Hz, 1H), 4.56 (br s, 1H), 4.06 (s, 3H), 3.36 - 3.24 (m, 2H), 2.99 (s, 2H), 2.10 - 1.90 (m, 2H), 1.50 (br d, J=6.4 Hz, 2H)	2.48, C
312		2-[5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-1,2,3-苯并三唑-1-基]乙酸	706.18	(500 MHz, DMSO-d6) δ 10.68 (br d, J=4.3 Hz, 1H), 9.98 (br s, 1H), 8.39 - 8.18 (m, 2H), 8.08 (br d, J=7.9 Hz, 1H), 7.98 - 7.76 (m, 3H), 7.68 (br d, J=8.9 Hz, 1H), 7.49 (br t, J=9.6 Hz, 1H), 7.32 (br dd, J=8.4, 4.7 Hz, 1H), 5.93 (br d, J=7.9 Hz, 1H), 5.59 - 5.46 (m, 2H), 4.61 - 4.44 (m, 1H), 4.05 (s, 3H), 3.47 - 3.38 (m, 1H), 3.27 (br s, 1H), 2.99 (br s, 1H), 2.06 - 1.85 (m, 2H), 1.55 - 1.45 (m, 2H), 1.22 (s, 1H)	2.35, C

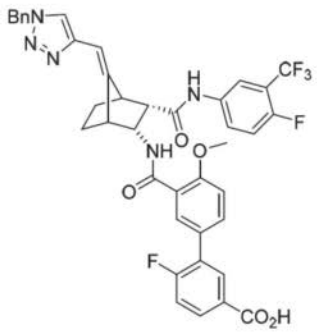
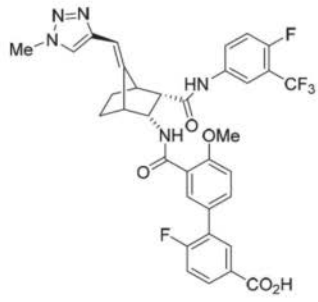
313		6-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡唑并[1,5-a]吡啶-3-甲酸甲酯	705.2	(500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 9.06 (s, 1H), 8.44 (s, 1H), 8.24 (s, 1H), 8.18 (br d, J=5.5 Hz, 1H), 8.11 (br d, J=9.2 Hz, 1H), 7.96 - 7.83 (m, 2H), 7.75 (br s, 1H), 7.45 (br t, J=9.6 Hz, 1H), 7.30 (br d, J=8.5 Hz, 1H), 5.89 (q, J=7.7 Hz, 1H), 4.51 (br s, 1H), 4.02 (s, 3H), 3.82 (s, 1H), 3.65 - 3.59 (m, 3H), 3.24 (br s, 1H), 2.97 (br s, 1H), 2.00 - 1.82 (m, 2H), 1.56 - 1.40 (m, 2H)	2.70, C
314		2-[7-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3H-咪唑并[4,5-b]吡啶-3-基]乙酸	705.9	(500 MHz, DMSO-d6) δ 10.66 (br d, J=4.9 Hz, 1H), 9.97 (br t, J=5.8 Hz, 1H), 8.58 (br d, J=4.6 Hz, 1H), 8.46 (br d, J=4.9 Hz, 1H), 8.30 - 8.19 (m, 3H), 7.90 (br s, 1H), 7.80 (br s, 1H), 7.50 (br d, J=5.8 Hz, 1H), 7.35 - 7.27 (m, 1H), 6.00 - 5.90 (m, 1H), 5.03 (br s, 2H), 4.55 (br s, 1H), 4.05 (br d, J=5.8 Hz, 3H), 3.26 (br s, 1H), 2.99 (br s, 1H), 2.04 - 1.87 (m, 2H), 1.50 (br s, 2H), 1.23 (br d, J=4.6 Hz, 2H)	1.92, C

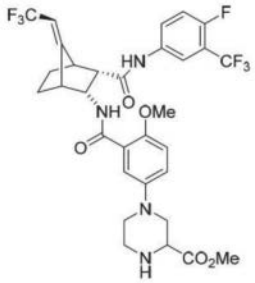
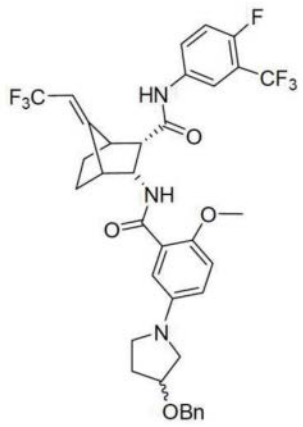
315		8-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)咪唑并[1,2-a]吡啶-3-甲酸苯甲酯	781.1	(500 MHz, DMSO-d6) δ 9.97 (br d, J=6.7 Hz, 1H), 9.23 (br d, J=7.3 Hz, 1H), 8.41 - 8.34 (m, 2H), 8.26 - 8.18 (m, 1H), 8.11 - 8.00 (m, 2H), 7.87 - 7.78 (m, 1H), 7.60 (s, 1H), 7.53 - 7.43 (m, 3H), 7.42 - 7.37 (m, 1H), 7.35 (br t, J=9.0 Hz, 2H), 5.97 - 5.89 (m, 1H), 5.41 (s, 2H), 4.54 (br dd, J=9.9, 4.1 Hz, 1H), 4.06 (s, 3H), 3.43 (br d, J=1.5 Hz, 1H), 3.31 - 3.24 (m, 1H), 3.00 (br s, 1H), 2.53 - 2.51 (m, 1H), 2.00 - 1.87 (m, 2H), 1.80 (br s, 1H), 1.56 - 1.42 (m, 2H)	2.76, C
316		6-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡唑并[1,5-a]吡啶-3-甲酸苯甲酯	781.36	(500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.98 (br d, J=6.8 Hz, 1H), 9.17 (s, 1H), 8.53 (s, 1H), 8.29 (br d, J=2.4 Hz, 2H), 8.12 (d, J=9.3 Hz, 1H), 8.02 - 7.90 (m, 2H), 7.86 - 7.77 (m, 1H), 7.53 - 7.47 (m, 3H), 7.46 - 7.29 (m, 4H), 5.94 (br d, J=7.6 Hz, 1H), 5.37 (s, 2H), 4.60 - 4.49 (m, 1H), 4.06 (s, 3H), 3.33 - 3.23 (m, 1H), 2.94 - 2.89 (m, 2H), 2.01 - 1.85 (m, 2H), 1.50 (br d, J=5.6 Hz, 2H)	2.89, C

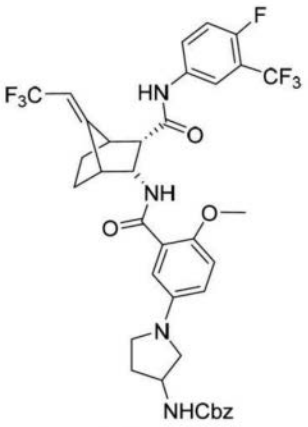
317		2-[5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑并[3,4-b]吡啶-1-基]乙酸	706.29	(500 MHz, DMSO-d6) δ 10.75 - 10.68 (m, 1H), 9.99 (d, J=6.7 Hz, 1H), 8.79 (d, J=1.9 Hz, 1H), 8.45 (d, J=1.9 Hz, 1H), 8.30 - 8.20 (m, 3H), 7.96 - 7.87 (m, 2H), 7.84 - 7.74 (m, 1H), 7.50 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 5.94 (d, J=7.7 Hz, 1H), 5.22 (s, 2H), 4.61 - 4.51 (m, 1H), 4.05 (s, 3H), 3.36 - 3.20 (m, 1H), 2.89 (s, 1H), 2.73 (s, 1H), 2.03 - 1.83 (m, 2H), 1.50 (br d, J=6.7 Hz, 2H)	1.97, C
318		2-[5-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-2H-吡唑并[3,4-b]吡啶-2-基]乙酸	706.18	(500 MHz, DMSO-d6) δ 10.82 - 10.71 (m, 1H), 9.99 (br d, J=6.7 Hz, 1H), 8.82 (s, 1H), 8.36 (d, J=10.4 Hz, 2H), 8.29 - 8.21 (m, 2H), 7.90 (br d, J=10.1 Hz, 1H), 7.84 - 7.76 (m, 1H), 7.50 (t, J=9.6 Hz, 1H), 7.33 (d, J=8.9 Hz, 1H), 6.00 - 5.91 (m, 1H), 4.85 (s, 2H), 4.63 - 4.50 (m, 1H), 4.06 (s, 3H), 3.36 - 3.23 (m, 1H), 3.01 (br s, 1H), 2.07 - 1.86 (m, 3H), 1.51 (br d, J=5.5 Hz, 3H)	1.92, C

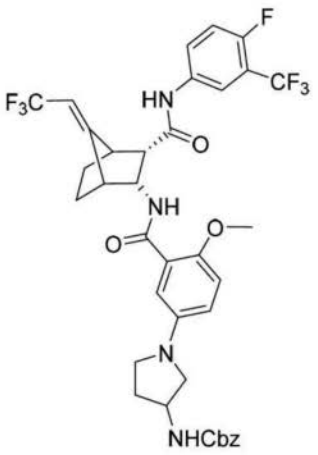
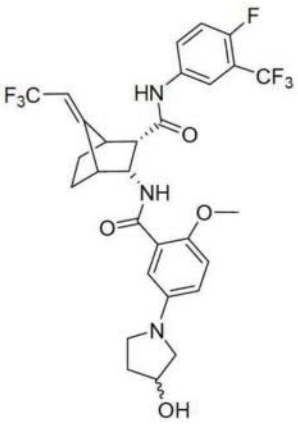
319		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-(2-羟基乙氧基)-[1,1'-联苯]-3-基)乙酯	850.19	(500 MHz, DMSO-d6) δ 10.61 (s, 1H), 9.67 (br d, J=7.3 Hz, 1H), 8.23 - 8.04 (m, 3H), 7.81 - 7.73 (m, 1H), 7.69 (br d, J=7.6 Hz, 2H), 7.56 (br d, J=2.1 Hz, 1H), 7.51 - 7.34 (m, 3H), 6.47 - 6.27 (m, 1H), 5.96 (q, J=8.0 Hz, 1H), 4.90 (t, J=5.5 Hz, 1H), 4.69 - 4.56 (m, 1H), 4.45 - 4.30 (m, 2H), 4.06 - 3.83 (m, 3H), 3.29 (br dd, J=10.8, 4.1 Hz, 1H), 3.23 (br s, 1H), 3.01 (s, 1H), 2.28 - 2.00 (m, 4H), 2.00 - 1.82 (m, 2H), 1.70 - 1.48 (m, 4H)	2.62, C
321		6- 氟 -3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-(2-羟基乙氧基)-[1,1'-联苯]-3-甲酸	699.33	(500 MHz, DMSO-d6) δ 10.61 (s, 1H), 9.63 (br d, J=7.6 Hz, 1H), 8.07 (br s, 2H), 8.04 - 7.91 (m, 2H), 7.78 - 7.68 (m, 2H), 7.52 - 7.32 (m, 3H), 5.93 (q, J=7.7 Hz, 1H), 4.70 - 4.54 (m, 1H), 4.43 - 4.18 (m, 2H), 4.07 - 3.84 (m, 2H), 3.27 (br dd, J=11.0, 4.3 Hz, 1H), 3.23 - 3.15 (m, 1H), 2.99 (br s, 1H), 2.07 (br d, J=7.9 Hz, 2H), 1.53 (br d, J=7.0 Hz, 2H)	2.19, C

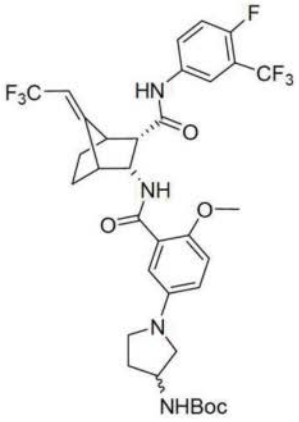
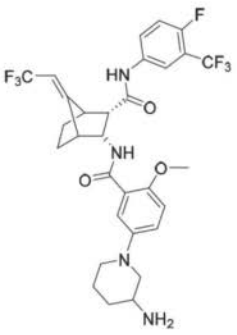
322		(2S,3R,7Z)-3-[5-溴-2-(2-羟基乙氧基)苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	639.22	(500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.60 (br d, J=7.3 Hz, 1H), 8.12 - 8.02 (m, 1H), 7.92 (d, J=2.4 Hz, 1H), 7.74 (br dd, J=8.2, 3.1 Hz, 1H), 7.64 (dd, J=8.9, 2.7 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.22 (d, J=8.9 Hz, 1H), 5.93 (q, J=7.8 Hz, 1H), 4.91 (t, J=5.5 Hz, 1H), 4.64 - 4.49 (m, 1H), 4.35 - 4.20 (m, 2H), 3.98 - 3.80 (m, 2H), 3.25 (br dd, J=10.5, 4.4 Hz, 1H), 3.19 (br s, 1H), 2.98 (br s, 1H), 2.02 (br d, J=7.9 Hz, 2H), 1.51 (br d, J=8.5 Hz, 2H)	2.38, C
324		3'-{[(2R,3S,7Z)-7-[2-(3,3-二氟氮杂环丁烷-1-基)-2-氧代亚乙基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	720.3	(500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.75 (br d, J=7.3 Hz, 1H), 8.15 (br d, J=6.2 Hz, 1H), 8.11 (s, 1H), 8.02 (br d, J=7.2 Hz, 1H), 7.96 (br s, 1H), 7.83 - 7.76 (m, 1H), 7.72 (br d, J=8.7 Hz, 1H), 7.52 - 7.37 (m, 2H), 7.32 (d, J=8.7 Hz, 1H), 5.86 (s, 1H), 4.75 - 4.27 (m, 5H), 4.05 (s, 3H), 3.83 (br s, 1H), 3.24 (br dd, J=10.8, 4.2 Hz, 1H), 2.88 (br s, 1H), 2.13 - 2.01 (m, 1H), 1.90 (br t, J=8.5 Hz, 1H), 1.48 (br d, J=6.7 Hz, 2H)	2.29, C

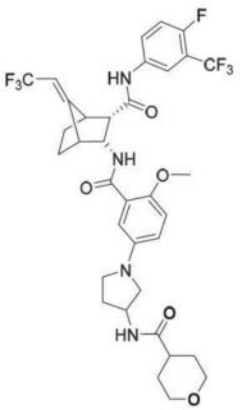
326		3'-{[(2R,3S,7Z)-7-[(1-苯甲基-1H-1,2,3-三唑-4-基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-甲酸	758.1	(500 MHz, DMSO-d6) δ 10.77 (s, 1H), 9.95 (br d, J=7.0 Hz, 1H), 8.34 - 8.22 (m, 2H), 8.16 (br s, 1H), 8.02 (br d, J=7.6 Hz, 1H), 7.95 - 7.79 (m, 2H), 7.73 (br d, J=8.2 Hz, 1H), 7.50 (br t, J=9.8 Hz, 1H), 7.42 - 7.23 (m, 7H), 6.28 (s, 1H), 5.61 (s, 2H), 4.54 (br s, 1H), 3.59 (br s, 3H), 3.31 (br dd, J=10.7, 3.7 Hz, 1H), 2.94 (br s, 1H), 2.07 - 1.81 (m, 3H), 1.60 - 1.43 (m, 2H)	2.47, C
327		6-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-[(1-甲基-1H-1,2,3-三唑-4-基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	682.3	(500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.96 (br d, J=7.0 Hz, 1H), 8.22 (br d, J=4.3 Hz, 1H), 8.13 (br s, 2H), 7.99 (br d, J=7.6 Hz, 1H), 7.89 (br s, 1H), 7.80 (br s, 1H), 7.72 (br d, J=9.5 Hz, 1H), 7.48 (br t, J=9.8 Hz, 1H), 7.38 - 7.21 (m, 2H), 6.29 (s, 1H), 4.59 - 4.45 (m, 1H), 4.05 (br d, J=7.9 Hz, 5H), 3.33 - 3.23 (m, 1H), 2.93 (br s, 1H), 2.03 - 1.84 (m, 2H)	2.33, C

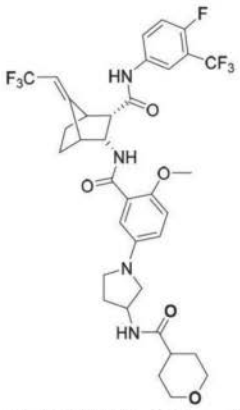
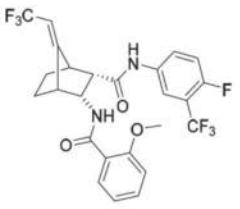
328		4-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)哌嗪-2-甲酸甲酯	659.3	(500 MHz, DMSO-d6) δ 10.60 (s, 1H), 9.89 (br d, J=4.6 Hz, 1H), 8.20 (br d, J=4.9 Hz, 1H), 7.84 - 7.69 (m, 1H), 7.56 - 7.39 (m, 2H), 7.16 - 6.97 (m, 2H), 5.91 (br d, J=7.9 Hz, 1H), 4.54 - 4.40 (m, 1H), 3.96 - 3.86 (m, 3H), 3.86 - 3.76 (m, 1H), 3.68 (s, 2H), 3.32 - 2.92 (m, 4H), 2.92 - 2.78 (m, 2H), 2.00 - 1.91 (m, 1H), 1.88 (s, 1H), 1.84 (br t, J=8.5 Hz, 1H), 1.45 (br d, J=6.4 Hz, 2H)	2.05, B
330		(2S,3R,7Z)-3-{5-[3-(苯甲基氧基)吡咯烷-1-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	706.1	(500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.89 (d, J=7.3 Hz, 1H), 8.24 (dd, J=6.4, 2.4 Hz, 1H), 7.88 - 7.75 (m, 1H), 7.50 (t, J=9.9 Hz, 1H), 7.37 - 7.32 (m, 3H), 7.30 - 7.24 (m, 1H), 7.16 (d, J=3.1 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.72 (dd, J=8.9, 3.1 Hz, 1H), 5.94 (q, J=7.9 Hz, 1H), 4.60 - 4.49 (m, 3H), 4.30 (br s, 1H), 3.96 - 3.82 (m, 3H), 3.51 - 3.39 (m, 1H), 3.33 - 3.20 (m, 2H), 2.99 (br s, 1H), 2.20 (d, J=4.3 Hz, 1H), 2.15 - 2.07 (m, 2H), 2.08 - 1.85 (m, 3H), 1.49 (br d, J=6.7 Hz, 2H), 1.36 (d, J=7.6 Hz, 2H)	2.90, C

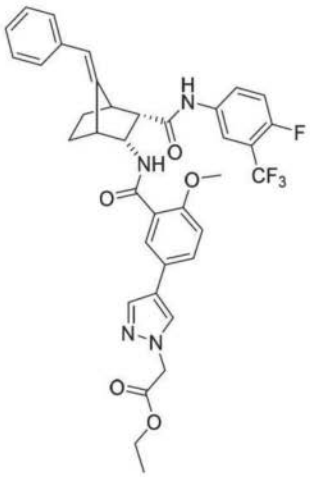
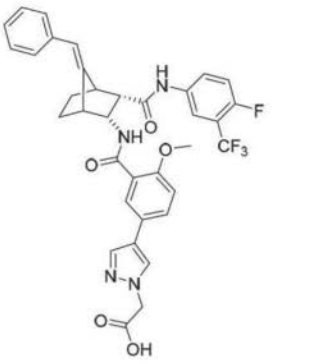
331	 异构体1	N-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-3-基]氨基甲酸苯甲酯	749.1	(500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.29 - 8.21 (m, 1H), 7.96 (s, 1H), 7.88 - 7.74 (m, 1H), 7.64 (br d, J=6.6 Hz, 1H), 7.50 (t, J=9.7 Hz, 1H), 7.42 - 7.29 (m, 4H), 7.15 - 6.96 (m, 2H), 6.69 (br dd, J=9.2, 2.7 Hz, 1H), 5.94 (q, J=7.8 Hz, 1H), 5.03 (s, 2H), 4.61 - 4.47 (m, 1H), 4.25 - 4.13 (m, 1H), 3.97 - 3.87 (m, 3H), 3.37 - 3.15 (m, 2H), 3.12 - 2.97 (m, 2H), 2.90 (s, 2H), 2.74 (s, 2H), 2.26 - 2.17 (m, 1H), 2.04 - 1.79 (m, 2H), 1.57 - 1.44 (m, 2H)	2.65, C

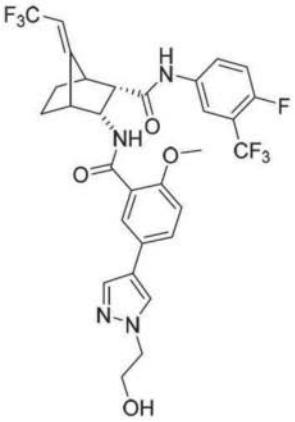
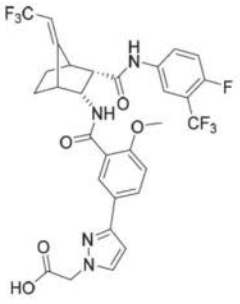
332	 异构体2	N-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-3-基]氨基甲酸苯甲酯	648.9	(500 MHz, DMSO-d6) δ 10.72 (br s, 1H), 9.91 (br d, J=6.8 Hz, 1H), 8.25 (br d, J=4.5 Hz, 1H), 7.96 (s, 1H), 7.86 - 7.74 (m, 1H), 7.65 (br d, J=6.1 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.42 - 7.29 (m, 5H), 7.16 - 6.98 (m, 2H), 6.69 (br d, J=7.7 Hz, 1H), 5.94 (br d, J=8.0 Hz, 1H), 5.03 (s, 2H), 4.52 (br s, 1H), 4.24 - 4.12 (m, 1H), 3.90 (s, 3H), 3.11 - 2.95 (m, 2H), 2.90 (s, 2H), 2.74 (s, 2H), 2.19 (br dd, J=12.5, 5.6 Hz, 1H), 2.06 - 1.84 (m, 3H), 1.49 (br d, J=6.3 Hz, 2H)	2.64, C
333		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[5-(3-羟基吡咯烷-1-基)-2-甲氧基苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	616.03	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.81 (d, J=6.7 Hz, 1H), 8.16 (dd, J=6.4, 2.1 Hz, 1H), 7.78 - 7.64 (m, 1H), 7.43 (br t, J=9.6 Hz, 1H), 7.09 - 6.94 (m, 2H), 6.60 (dd, J=8.9, 3.1 Hz, 1H), 5.94 - 5.82 (m, 1H), 4.51 - 4.43 (m, 1H), 4.32 (br s, 1H), 4.05 - 3.92 (m, 1H), 3.82 (s, 3H), 3.27 - 3.10 (m, 2H), 2.97 - 2.89 (m, 2H), 2.83 (s, 1H), 2.67 (s, 1H), 2.02 - 1.87 (m, 2H), 1.87 - 1.75 (m, 3H), 1.42 (br d, J=6.7 Hz, 2H)	2.33, C

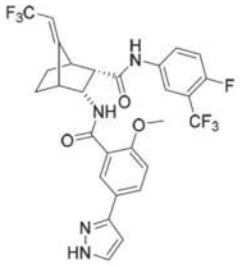
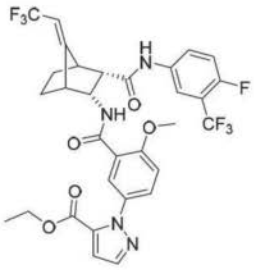
334		N-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-3-基]氨基甲酸叔丁酯	715.29	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.81 (br d, J=7.0 Hz, 1H), 8.22 - 8.09 (m, 1H), 7.81 - 7.65 (m, 1H), 7.43 (t, J=9.8 Hz, 1H), 7.13 - 6.93 (m, 3H), 6.61 (dd, J=9.0, 2.9 Hz, 1H), 5.87 (q, J=7.6 Hz, 1H), 4.45 (ddd, J=10.5, 6.6, 4.0 Hz, 1H), 4.11 - 4.00 (m, 1H), 3.83 (s, 3H), 3.42 - 3.24 (m, 2H), 3.16 (m, 2H), 2.96 - 2.88 (m, 2H), 2.08 (br d, J=6.4 Hz, 1H), 2.00 - 1.90 (m, 1H), 1.88 - 1.77 (m, 2H), 1.41 (br d, J=6.7 Hz, 2H), 1.33 (s, 10H)	2.76, C
335		(2S,3R,7Z)-3-[5-(3-氨基哌啶-1-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	628.9	(500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.93 (d, J=7.0 Hz, 1H), 8.24 (br d, J=4.0 Hz, 1H), 8.00 (br s, 2H), 7.84 - 7.68 (m, 1H), 7.58 (d, J=2.7 Hz, 1H), 7.50 (t, J=9.8 Hz, 1H), 7.19 - 7.06 (m, 3H), 5.93 (q, J=8.0 Hz, 1H), 4.57 - 4.43 (m, 1H), 3.94 (s, 3H), 3.30 - 3.16 (m, 2H), 2.99 (br s, 1H), 2.93 - 2.79 (m, 3H), 2.06 - 1.80 (m, 4H), 1.69 - 1.42 (m, 5H)	2.06, C

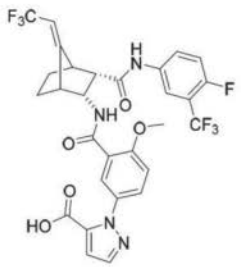
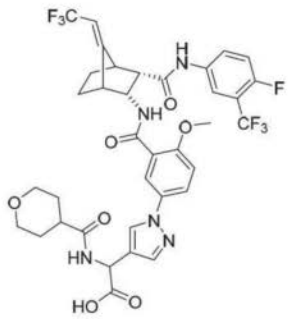
336	 MeOH/80% CO_2；流动条件：340 mL/min，100巴，40 ℃；检测器波长：220 nm。异构体1，RT = 3.427 min，> 95% de	N-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-3-基]噁烷-4-甲酰胺	727.0	(500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.88 (br d, J=7.0 Hz, 1H), 8.29 - 8.16 (m, 1H), 8.07 (br d, J=6.7 Hz, 1H), 7.85 - 7.73 (m, 1H), 7.50 (br t, J=9.8 Hz, 1H), 7.16 - 6.98 (m, 2H), 6.76 - 6.67 (m, 1H), 5.93 (br d, J=7.9 Hz, 1H), 4.56 - 4.45 (m, 1H), 4.39 - 4.26 (m, 1H), 3.89 (s, 5H), 3.48 - 3.38 (m, 3H), 3.34 - 3.16 (m, 4H), 2.99 (br d, J=7.9 Hz, 2H), 2.41 - 2.32 (m, 1H), 2.17 (br s, 1H), 2.07 - 1.80 (m, 3H), 1.63 - 1.46 (m, 6H)。	2.41, C

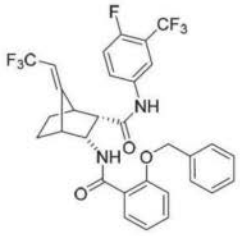
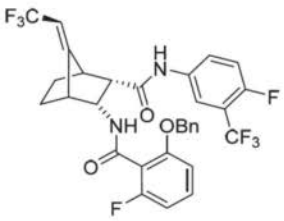
337	 MeOH/80% CO_2；流动条件：340 mL/min，100巴，40 ℃；检测器波长：220 nm。异构体2，RT = 3.820 min，> 95% de	N-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-3-基]噁烷-4-甲酰胺	727.1	(500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.90 (br d, J=6.7 Hz, 1H), 8.24 (br dd, J=6.1, 2.1 Hz, 1H), 8.09 (br d, J=7.0 Hz, 1H), 7.89 - 7.78 (m, 1H), 7.51 (br t, J=9.6 Hz, 1H), 7.14 (d, J=3.1 Hz, 1H), 7.06 (d, J=8.9 Hz, 1H), 6.71 (dd, J=8.9, 2.7 Hz, 1H), 5.94 (q, J=8.1 Hz, 1H), 4.53 (br t, J=10.7 Hz, 1H), 4.39 - 4.31 (m, 1H), 4.02 (br d, J=18.9 Hz, 1H), 3.99 - 3.75 (m, 6H), 3.33 - 3.19 (m, 3H), 3.10 - 2.97 (m, 2H), 2.44 - 2.29 (m, 1H), 2.19 (dq, J=12.9, 6.5 Hz, 1H), 2.11 - 1.96 (m, 1H), 1.94 - 1.83 (m, 2H), 1.69 - 1.38 (m, 8H)	2.43, C
338		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	531.0	(500MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.88 (d, *J*=6.9 Hz, 1H), 8.19 (d, *J*=4.8 Hz, 1H), 7.92 (d, *J*=7.7 Hz, 1H), 7.80 - 7.71 (m, 1H), 7.54 - 7.43 (m, 2H), 7.16 (d, *J*=8.3 Hz, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 5.90 (q, *J*=8.0 Hz, 1H), 4.49 (br. s., 1H), 3.97 (s, 3H), 3.29 - 3.18 (m, 2H), 2.96 (br. s., 1H), 1.97 (t, *J*=9.2 Hz, 1H), 1.89 - 1.80 (m, 1H), 1.47 (d, *J*=6.6 Hz, 2H)	2.48, B

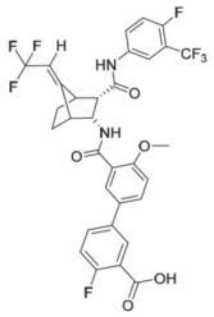
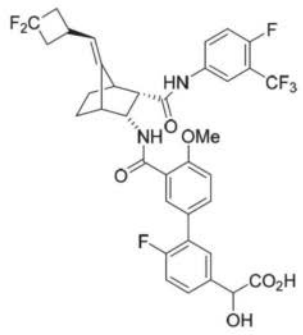
339		2-[4-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-1-基]乙酸乙酯	691.4	(500MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.87 (d, *J*=7.1 Hz, 1H), 8.23 - 8.16 (m, 1H), 8.08 (s, 2H), 7.81 (s, 2H), 7.67 (dd, *J*=8.5, 2.2 Hz, 1H), 7.45 (t, *J*=9.7 Hz, 1H), 7.37 (d, *J*=4.0 Hz, 4H), 7.29 - 7.21 (m, 1H), 7.18 (d, *J*=8.6 Hz, 1H), 6.38 (s, 1H), 5.03 (s, 2H), 4.55 (br. s., 1H), 4.22 - 4.11 (m, 2H), 4.00 (s, 3H), 2.93 (br. s., 1H), 2.02 - 1.84 (m, 2H), 1.53 (br. s., 2H), 1.26 - 1.15 (m, 3H)	2.64, B
340		2-[4-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(苯基亚甲基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-1-基]乙酸	663.2	(500MHz, DMSO-d_6) δ 10.47 (s, 1H), 9.87 (d, *J*=7.2 Hz, 1H), 8.17 (d, *J*=6.4 Hz, 1H), 8.04 (d, *J*=18.2 Hz, 2H), 7.83 - 7.73 (m, 2H), 7.66 (dd, *J*=8.5, 2.0 Hz, 1H), 7.43 (s, 1H), 7.37 (d, *J*=4.2 Hz, 4H), 7.25 (d, *J*=4.3 Hz, 1H), 7.17 (d, *J*=8.7 Hz, 1H), 6.37 (s, 1H), 4.86 (s, 2H), 4.58 - 4.49 (m, 1H), 3.98 (s, 3H), 3.71 - 3.55 (m, 1H), 3.41 - 3.35 (m, 1H), 3.32 - 3.23 (m, 1H), 2.92 (br. s., 1H), 1.96 (d, *J*=9.8 Hz, 1H), 1.89 (d, *J*=13.6 Hz, 1H), 1.53 (br. s., 2H)	2.10, B

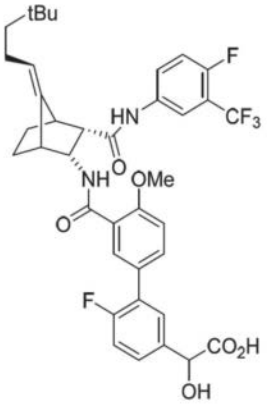
341		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基乙基)-1H-吡唑-4-基]-2-甲氧基苯甲酰胺基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	641.1	(500MHz, DMSO-d_6) δ 9.80 (d, *J*=7.0 Hz, 1H), 8.18 (d, *J*=4.1 Hz, 1H), 8.07 (d, *J*=2.3 Hz, 1H), 8.03 (s, 1H), 7.83 - 7.73 (m, 2H), 7.67 (dd, *J*=8.5, 2.1 Hz, 1H), 7.46 (t, *J*=9.8 Hz, 1H), 7.17 (d, *J*=8.6 Hz, 1H), 5.89 (m, 1H), 4.54 (br. s., 1H), 4.15 (t, *J*=5.6 Hz, 2H), 3.99 (s, 3H), 3.81 - 3.75 (m, 2H), 2.98 (d, *J*=5.0 Hz, 1H), 2.03 (t, *J*=8.9 Hz, 1H), 1.96 - 1.87 (m, 1H), 1.50 (d, *J*=7.3 Hz, 2H)	2.18, B
342		2-[3-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-1-基]乙酸	655.4	(500MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.97 - 9.91 (m, 1H), 8.37 (s, 1H), 8.28 - 8.20 (m, 1H), 7.93 - 7.86 (m, 1H), 7.84 - 7.76 (m, 1H), 7.74 (br. s., 1H), 7.55 - 7.44 (m, 1H), 7.21 (d, *J*=8.5 Hz, 1H), 6.65 (s, 1H), 5.94 (q, *J*=7.8 Hz, 1H), 4.92 (br. s., 2H), 4.53 (br. s., 1H), 4.02 (s, 3H), 2.99 (s, 2H), 2.01 - 1.86 (m, 2H), 1.49 (d, *J*=6.4 Hz, 2H), 1.23 (s, 2H)	1.89, B

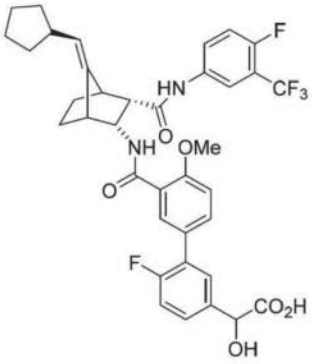
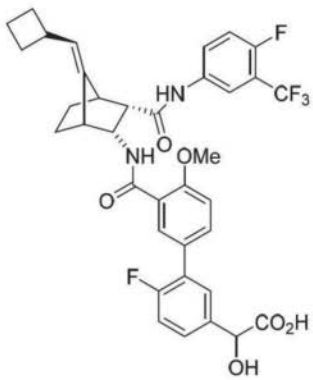
343		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(1H-吡唑-3-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	597.1	(500MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.99 - 9.89 (m, 1H), 8.40 - 8.35 (m, 1H), 8.26 - 8.20 (m, 1H), 7.97 - 7.87 (m, 1H), 7.83 - 7.72 (m, 2H), 7.54 - 7.45 (m, 1H), 7.26 - 7.17 (m, 1H), 6.67 - 6.58 (m, 1H), 5.98 - 5.90 (m, 1H), 4.59 - 4.49 (m, 1H), 3.41 - 3.14 (m, 3H), 3.02 - 2.87 (m, 2H), 2.04 - 1.85 (m, 2H), 1.49 (d, *J*=6.4 Hz, 2H), 1.16 (t, *J*=7.3 Hz, 1H)	2.38, B
344		1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-5-甲酸乙酯	669.1	(500MHz, DMSO-d_6) δ 10.05 (d, *J*=6.7 Hz, 1H), 8.58 (d, *J*=2.1 Hz, 1H), 8.42 (d, *J*=2.4 Hz, 1H), 8.24 (d, *J*=4.0 Hz, 1H), 8.01 (dd, *J*=8.8, 2.4 Hz, 1H), 7.79 (br. s., 1H), 7.50 (t, *J*=9.8 Hz, 1H), 7.37 (d, *J*=8.8 Hz, 1H), 6.98 (d, *J*=1.8 Hz, 1H), 5.94 (q, *J*=7.5 Hz, 1H), 4.54 (br. s., 1H), 4.33 (q, *J*=7.0 Hz, 2H), 4.06 (s, 3H), 3.35 - 3.22 (m, 1H), 3.00 (br. s., 1H), 2.02 - 1.84 (m, 2H), 1.50 (d, *J*=6.7 Hz, 2H), 1.37 - 1.27 (m, 3H)	2.69, B

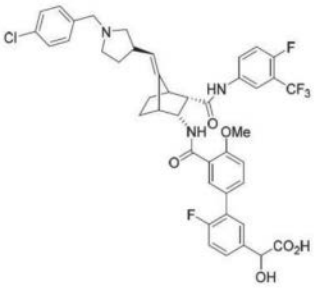
345		1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-5-甲酸	641.1	(500MHz, DMSO-d_6) δ 11.07 (br. s., 1H), 9.94 (d, *J*=6.7 Hz, 1H), 8.36 - 8.22 (m, 3H), 7.98 - 7.79 (m, 2H), 7.49 (t, *J*=9.6 Hz, 1H), 7.25 (d, *J*=9.2 Hz, 1H), 6.73 (s, 1H), 5.90 (q, *J*=7.8 Hz, 1H), 4.45 (br. s., 1H), 4.03 (s, 3H), 3.35 - 3.15 (m, 1H), 2.98 (br. s., 1H), 1.99 (t, *J*=9.2 Hz, 1H), 1.94 - 1.81 (m, 1H), 1.47 (d, *J*=6.7 Hz, 2H)	1.89, B
347		2-[1-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吡唑-4-基]-2-[(噁烷-4-基)甲酰胺基]乙酸	782.4	(400MHz, CD_3OD) δ 10.35 (d, *J*=7.0 Hz, 1H), 10.25 (s, 1H), 8.35 (d, *J*=2.2 Hz, 1H), 8.24 - 8.14 (m, 2H), 7.89 (dd, *J*=8.7, 2.3 Hz, 1H), 7.81 - 7.72 (m, 2H), 7.38 - 7.27 (m, 2H), 5.79 (q, *J*=7.6 Hz, 1H), 5.56 (s, 1H), 4.67 (d, *J*=3.7 Hz, 1H), 4.15 (s, 3H), 4.05 - 3.95 (m, 2H), 3.53 - 3.41 (m, 3H), 3.32 - 3.23 (m, 2H), 2.96 (br. s., 1H), 2.72 - 2.56 (m, 1H), 2.20 (t, *J*=9.4 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.89 - 1.56 (m, 6H), 1.44 - 1.36 (m, 1H)	1.03, D

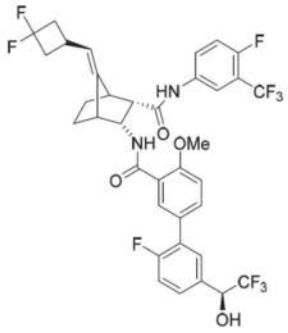
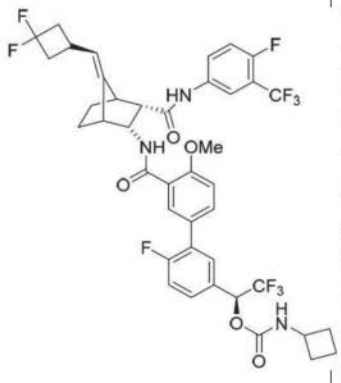
349		(2S,3R,7Z)-3-[2-(苯甲基氧基)苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	625.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 8.88 (d, J=7.5 Hz, 1H), 8.13 - 7.91 (m, 1H), 7.72 (dd, J=7.4, 4.8 Hz, 1H), 7.49 - 7.34 (m, 4H), 7.32 - 7.21 (m, 3H), 7.01 (d, J=8.5 Hz, 1H), 6.83 (t, J=8.7 Hz, 1H), 5.98 - 5.81 (m, 1H), 5.23 - 5.05 (m, 2H), 4.51 (d, J=1.7 Hz, 1H), 3.51 - 3.36 (m, 1H), 3.23 (dd, J=11.1, 3.9 Hz, 1H), 2.94 (t, J=3.9 Hz, 1H), 2.03 - 1.76 (m, 2H), 1.48 - 1.18 (m, 2H)	2.74, B
350		(2S,3R,7Z)-3-[2-(苯甲基氧基)-6-氟苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	625.33	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 8.88 (d, J=7.5 Hz, 1H), 8.13 - 7.91 (m, 1H), 7.72 (dd, J=7.4, 4.8 Hz, 1H), 7.49 - 7.34 (m, 4H), 7.32 - 7.21 (m, 3H), 7.01 (d, J=8.5 Hz, 1H), 6.83 (t, J=8.7 Hz, 1H), 5.98 - 5.81 (m, 1H), 5.23 - 5.05 (m, 2H), 4.51 (d, J=1.7 Hz, 1H), 3.51 - 3.36 (m, 1H), 3.23 (dd, J=11.1, 3.9 Hz, 1H), 2.94 (t, J=3.9 Hz, 1H), 2.03 - 1.76 (m, 2H), 1.48 - 1.18 (m, 2H)	2.33, B

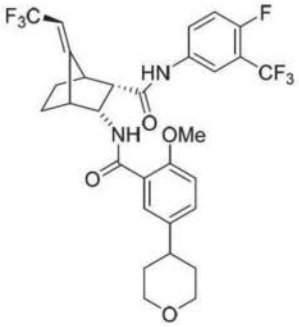
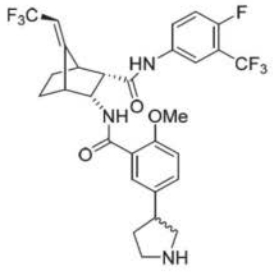
351		4-氟-3'-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-甲酸	669.2	(400 MHz, DMSO-d6) δ ppm 10.46 (s, 1H), 8.50 (d, J = 6.6 Hz, 1H), 8.13 (dd, J = 2.6, 6.5 Hz, 1H), 8.03 (dd, J = 2.6, 7.0 Hz, 1H), 7.91 - 7.70 (m, 4H), 7.47 (t, J = 9.9 Hz, 1H), 7.36 (dd, J = 8.7, 10.4 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 5.74 (q, J = 8.0 Hz, 1H), 4.71 - 4.61 (m, 1H), 3.91 (s, 3H), 3.25 - 3.22 (m, 1H), 2.79 (br s, 1H), 2.60 (d, J = 5.1 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.81 - 1.64 (m, 2H), 1.61 - 1.48 (m, 1H)	1.89, D
353		2-(3'-{[(7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	721.14	(500 MHz, DMSO-d6) δ 10.44 (br s, 1H), 9.85 - 9.70 (m, 1H), 8.07 (br d, J=4.6 Hz, 1H), 7.97 (br d, J=8.2 Hz, 1H), 7.80 (s, 1H), 7.66 (br s, 1H), 7.57 - 7.48 (m, 1H), 7.35 (br dd, J=14.0, 5.2 Hz, 3H), 7.21 - 7.03 (m, 2H), 5.23 (br dd, J=16.0, 8.7 Hz, 1H), 4.71 (s, 1H), 4.26 (br s, 1H), 3.90 (s, 3H), 3.09 - 2.97 (m, 2H), 2.90 - 2.78 (m, 2H), 2.72 - 2.62 (m, 2H), 2.54 (br s, 1H), 2.28 (br d, J=5.8 Hz, 1H), 1.77 (s, 2H), 1.64 (br s, 1H), 1.26 (br s, 2H)	2.44, C

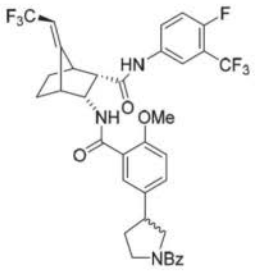
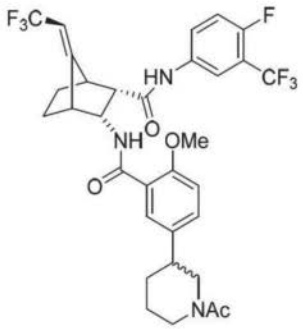
354		2-(3'-{[(7Z)-7-(4,4-二甲基亚戊基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	715.04	(500 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.73 (br d, J=7.0 Hz, 1H), 8.09 (br d, J=4.0 Hz, 1H), 7.95 (s, 1H), 7.68 (br s, 1H), 7.50 (br d, J=8.2 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.22 (br d, J=4.9 Hz, 1H), 7.18 - 7.10 (m, 1H), 6.99 (dd, J=10.4, 8.9 Hz, 1H), 5.10 - 5.03 (m, 1H), 4.34 (s, 1H), 4.27 (br t, J=10.2 Hz, 1H), 3.90 (s, 3H), 3.07 - 3.00 (m, 1H), 2.94 - 2.89 (m, 1H), 2.50 (br s, 1H), 1.90 (br d, J=6.4 Hz, 2H), 1.81 - 1.56 (m, 2H), 1.52 (s, 1H), 1.28 - 1.04 (m, 5H), 0.77 (s, 9H)	2.76, C

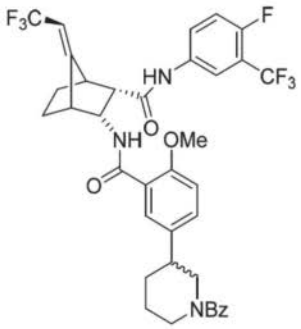
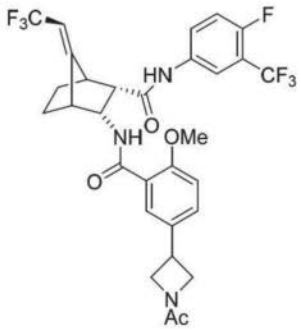
355		2-(3'-{[(7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	699.0	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.19 (br d, J=4.3 Hz, 1H), 8.09 (s, 1H), 7.79 - 7.70 (m, 1H), 7.68 - 7.59 (m, 1H), 7.53 - 7.33 (m, 3H), 7.29 - 7.16 (m, 2H), 5.16 (d, J=8.9 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.01 (s, 3H), 3.59 (br s, 1H), 3.12 (br dd, J=10.8, 4.1 Hz, 1H), 2.97 (br s, 1H), 2.68 (br s, 1H), 2.53 (s, 2H), 1.86 - 1.67 (m, 4H), 1.66 - 1.47 (m, 4H), 1.36 (br d, J=6.1 Hz, 2H), 1.19 (br s, 3H)	2.62, C
356		2-(3'-{[(7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	685.1	(500 MHz, DMSO-d6) δ 10.63 - 10.53 (m, 1H), 9.99 - 9.85 (m, 1H), 8.27 - 8.21 (m, 1H), 8.14 - 8.07 (m, 1H), 7.86 - 7.77 (m, 1H), 7.70 - 7.63 (m, 1H), 7.53 - 7.38 (m, 4H), 7.33 - 7.27 (m, 1H), 7.24 - 7.17 (m, 1H), 5.39 - 5.31 (m, 1H), 4.82 (s, 1H), 4.43 - 4.34 (m, 1H), 4.05 (s, 3H), 3.57 (br d, J=2.2 Hz, 1H), 3.21 - 3.06 (m, 1H), 2.21 - 2.05 (m, 3H), 1.92 - 1.66 (m, 8H), 1.37 (br s, 2H)	2.25, C

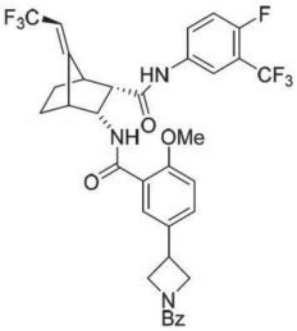
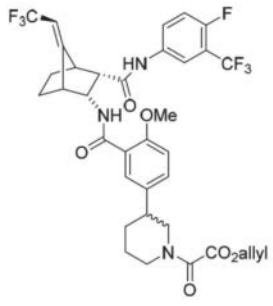
357		2-(3'-{[(7Z)-7-({1-[(4-氯苯基)甲基]吡咯烷-3-基}亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-羟基乙酸	824.2	(500 MHz, DMSO-d6) δ 10.65 - 10.54 (m, 1H), 9.91 (br d, J=6.7 Hz, 1H), 8.25 (br d, J=5.8 Hz, 1H), 8.17 - 8.09 (m, 1H), 7.86 - 7.78 (m, 1H), 7.68 (br d, J=8.2 Hz, 1H), 7.57 - 7.46 (m, 2H), 7.45 - 7.35 (m, 5H), 7.33 - 7.19 (m, 2H), 5.25 (br d, J=8.5 Hz, 1H), 4.93 (br s, 1H), 4.41 (dt, J=7.3, 3.4 Hz, 1H), 4.05 (s, 3H), 3.74 - 3.66 (m, 1H), 3.23 - 3.12 (m, 1H), 3.04 - 2.94 (m, 2H), 2.82 (br t, J=8.5 Hz, 1H), 2.76 - 2.60 (m, 3H), 2.55 - 2.52 (m, 2H), 2.38 - 2.28 (m, 1H), 2.23 - 2.02 (m, 1H), 1.90 - 1.84 (m, 1H), 1.80 - 1.71 (m, 1H), 1.67 - 1.54 (m, 1H), 1.44 - 1.31 (m, 2H)	2.07, C

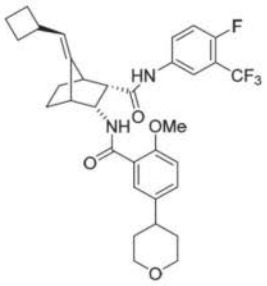
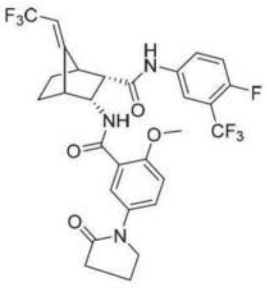
358		N-[(7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-[(1S)-2,2,2-三氟-1-羟基乙基]-[1,1'-联苯]-3-甲酰胺	745.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.94 (br d, J=7.1 Hz, 1H), 8.24 (br d, J=4.1 Hz, 1H), 8.13 (d, J=0.9 Hz, 1H), 7.89 - 7.78 (m, 1H), 7.70 (br d, J=8.4 Hz, 1H), 7.63 (br d, J=7.1 Hz, 1H), 7.57 - 7.44 (m, 2H), 7.39 - 7.29 (m, 2H), 5.40 (d, J=8.6 Hz, 1H), 5.28 (br d, J=6.8 Hz, 1H), 4.44 - 4.37 (m, 1H), 4.06 (s, 3H), 3.69 - 3.55 (m, 1H), 3.25 - 3.09 (m, 1H), 3.01 (br s, 1H), 2.98 - 2.79 (m, 3H), 2.77 (br s, 1H), 2.43 (br s, 2H), 1.87 (br s, 2H), 1.40 (br s, 2H)	2.75, C
359		N-环丁基氨基甲酸(1S)-1-(3'-{[(2R,3S,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	842.2	(400 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 8.25 (dd, J=6.3, 2.3 Hz, 1H), 8.18 - 8.08 (m, 2H), 7.87 - 7.78 (m, 1H), 7.74 - 7.66 (m, 2H), 7.58 - 7.29 (m, 5H), 6.39 (q, J=7.3 Hz, 1H), 5.45 - 5.34 (m, 1H), 4.49 - 4.36 (m, 1H), 4.08 (s, 3H), 3.95 (br d, J=7.9 Hz, 1H), 3.24 - 2.68 (m, 7H), 2.47 (br d, J=2.0 Hz, 2H), 1.98 - 1.84 (m, 4H), 1.65 - 1.53 (m, 2H), 1.46 - 1.36 (m, 2H)	1.25, A

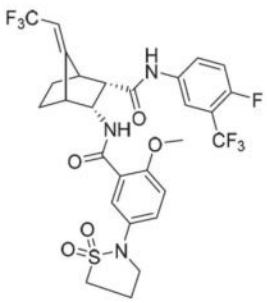
361		(7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(噁烷-4-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	615.14	(500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.86 (br d, J=7.0 Hz, 1H), 8.24 (br d, J=5.5 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.56 - 7.44 (m, 1H), 7.42 - 7.31 (m, 1H), 7.13 (br d, J=8.5 Hz, 1H), 5.94 (br d, J=7.6 Hz, 1H), 4.60 - 4.46 (m, 1H), 4.07 - 3.86 (m, 5H), 3.23 (br s, 1H), 2.99 (br s, 1H), 2.78 - 2.67 (m, 1H), 2.51 - 2.34 (m, 3H), 2.09 - 1.80 (m, 2H), 1.72 - 1.56 (m, 4H), 1.49 (br d, J=6.7 Hz, 2H)	2.64, C
362		(7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(吡咯烷-3-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	600.1	(500 MHz, DMSO-d6) δ 9.89 (br d, J=6.4 Hz, 1H), 8.21 (br d, J=6.1 Hz, 1H), 7.85 (s, 1H), 7.81 - 7.71 (m, 1H), 7.55 - 7.40 (m, 2H), 7.15 (br d, J=8.5 Hz, 1H), 5.92 (q, J=8.2 Hz, 1H), 4.55 - 4.45 (m, 1H), 3.97 (s, 3H), 3.57 (br d, J=5.5 Hz, 2H), 3.46 - 3.38 (m, 1H), 3.31 - 3.19 (m, 3H), 3.12 - 3.03 (m, 1H), 2.98 (br s, 1H), 2.85 - 2.78 (m, 1H), 2.23 (br dd, J=7.2, 4.1 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.87 - 1.72 (m, 3H), 1.54 - 1.43 (m, 2H)	2.09, C

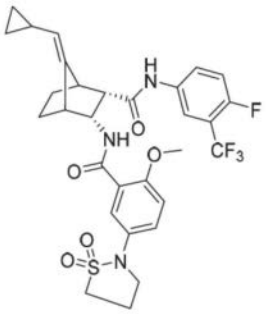
363		(7Z)-3-[5-(1-苯甲酰基吡咯烷-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	704.4	(500 MHz, DMSO-d6) δ 9.87 (br dd, J=15.6, 6.7 Hz, 1H), 8.21 (br s, 1H), 7.80 - 7.76 (m, 1H), 7.58 - 7.39 (m, 7H), 7.19 - 7.07 (m, 1H), 5.96 - 5.87 (m, 1H), 4.56 - 4.43 (m, 1H), 3.97 (br d, J=16.2 Hz, 3H), 3.68 (br d, J=2.7 Hz, 1H), 3.47 (br s, 4H), 3.30 - 3.13 (m, 2H), 2.97 (br s, 1H), 2.73 (s, 1H), 2.27 (br d, J=5.5 Hz, 1H), 2.07 - 1.71 (m, 4H), 1.48 (br s, 2H)	2.56, C
364		(7Z)-3-[5-(1-乙酰基哌啶-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	656.19	(500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.87 (br d, J=5.8 Hz, 1H), 8.23 (br d, J=6.1 Hz, 1H), 7.87 - 7.72 (m, 2H), 7.50 (br t, J=9.5 Hz, 1H), 7.39 (br d, J=8.5 Hz, 1H), 7.12 (br d, J=8.9 Hz, 1H), 5.94 (q, J=8.0 Hz, 1H), 4.51 (br d, J=11.3 Hz, 2H), 4.00 - 3.81 (m, 4H), 3.40 - 3.30 (m, 2H), 3.29 - 3.06 (m, 2H), 2.98 (br s, 1H), 2.82 - 2.72 (m, 1H), 2.66 - 2.54 (m, 1H), 2.09 - 1.96 (m, 4H), 1.91 - 1.83 (m, 1H), 1.80 - 1.68 (m, 2H), 1.63 - 1.46 (m, 3H)	2.34, C

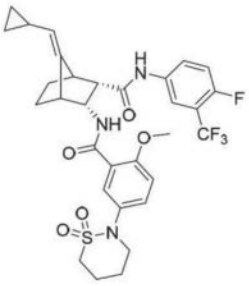
365		(7Z)-3-[5-(1-苯甲酰基哌啶-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	718.44	(500 MHz, DMSO-d6) δ 10.63 (br s, 1H), 9.87 (br d, J=7.0 Hz, 1H), 8.27 - 8.17 (m, 1H), 7.89 - 7.72 (m, 2H), 7.55 - 7.36 (m, 7H), 7.12 (br d, J=8.5 Hz, 1H), 5.93 (br d, J=7.9 Hz, 1H), 4.57 - 4.45 (m, 1H), 3.97 (s, 3H), 3.48 - 3.38 (m, 2H), 3.29 - 3.18 (m, 1H), 2.98 (br s, 2H), 2.85 - 2.69 (m, 2H), 2.55 (s, 1H), 2.01 - 1.76 (m, 3H), 1.78 - 1.64 (m, 1H), 1.62 - 1.41 (m, 4H)	2.65, C
366		(7Z)-3-[5-(1-乙酰基氮杂环丁烷-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	628.18	(500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.98 - 9.86 (m, 1H), 8.23 (br d, J=4.6 Hz, 1H), 8.00 - 7.87 (m, 1H), 7.85 - 7.74 (m, 1H), 7.57 - 7.44 (m, 2H), 7.18 (br d, J=8.9 Hz, 1H), 6.00 - 5.87 (m, 1H), 4.58 - 4.43 (m, 2H), 4.22 (t, J=9.0 Hz, 1H), 4.10 - 4.03 (m, 1H), 3.99 (s, 3H), 3.87 - 3.69 (m, 2H), 3.39 - 3.18 (m, 1H), 3.01 - 2.87 (m, 2H), 2.02 - 1.84 (m, 2H), 1.80 (d, J=2.1 Hz, 3H), 1.56 - 1.44 (m, 2H)	2.20, C

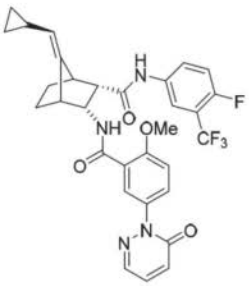
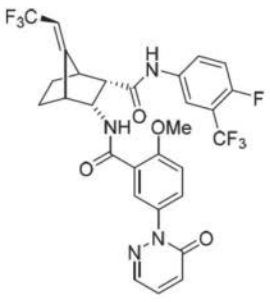
367		(7Z)-3-[5-(1-苯甲酰基氮杂环丁烷-3-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	690.21	(500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.92 (br d, J=6.4 Hz, 1H), 8.23 (br d, J=5.5 Hz, 1H), 7.95 (br s, 1H), 7.81 - 7.72 (m, 2H), 7.69 (br d, J=7.3 Hz, 1H), 7.58 - 7.37 (m, 6H), 7.25 - 7.14 (m, 1H), 5.94 (q, J=7.8 Hz, 1H), 4.68 (br t, J=8.7 Hz, 1H), 4.54 - 4.42 (m, 2H), 4.34 - 4.24 (m, 1H), 4.00 (s, 4H), 3.23 (br d, J=1.8 Hz, 1H), 3.01 - 2.98 (m, 1H), 2.50 - 2.39 (m, 1H), 2.01 - 1.96 (m, 1H), 1.90 - 1.85 (m, 1H), 1.58 - 1.45 (m, 2H)	2.45, C
368		2-[3-(3-{[(7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)哌啶-1-基]-2-氧代乙酸	686.2	(500 MHz, DMSO-d6) δ 10.80 - 10.58 (m, 1H), 9.94 - 9.74 (m, 1H), 8.24 (br d, J=6.4 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.50 (br t, J=9.8 Hz, 1H), 7.36 (br d, J=5.8 Hz, 1H), 7.17 - 7.05 (m, 1H), 5.98 - 5.86 (m, 1H), 4.52 (br d, J=4.9 Hz, 1H), 4.38 - 4.20 (m, 1H), 4.00 - 3.94 (m, 3H), 3.82 - 3.70 (m, 1H), 3.22 (br s, 1H), 3.07 - 2.93 (m, 2H), 2.64 - 2.53 (m, 1H), 2.07 - 1.94 (m, 1H), 1.89 (br d, J=9.2 Hz, 2H), 1.76 - 1.59 (m, 2H), 1.51 - 1.31 (m, 4H), 1.19 - 0.93 (m, 1H)。	1.81, C

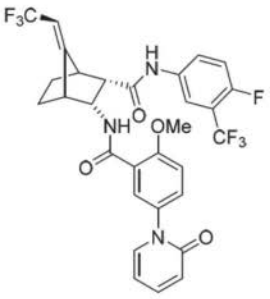
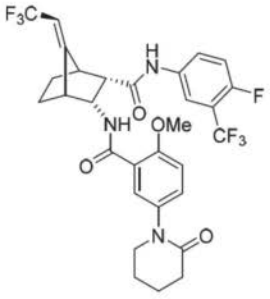
369		(7Z)-7-(环丁基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(噁烷-4-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	601.3	(500 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.67 (br d, J=7.3 Hz, 1H), 8.08 (br d, J=5.2 Hz, 1H), 7.71 - 7.59 (m, 2H), 7.41 - 7.20 (m, 2H), 6.99 (br d, J=8.5 Hz, 1H), 5.24 (br d, J=8.2 Hz, 1H), 4.29 - 4.20 (m, 1H), 3.91 - 3.74 (m, 4H), 3.61 - 3.44 (m, 1H), 3.30 (br t, J=11.7 Hz, 2H), 3.12 - 2.88 (m, 2H), 2.81 (br s, 1H), 2.70 - 2.55 (m, 2H), 2.11 - 1.96 (m, 2H), 1.83 - 1.64 (m, 5H), 1.57 - 1.42 (m, 5H), 1.33 - 1.18 (m, 2H)	2.87, C
370		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-氧代吡咯烷-1-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	614.2	(500 MHz, DMSO-d_6) δ 10.65 (s, 1H), 9.91 (d, *J*=7.0 Hz, 1H), 8.25 - 8.11 (m, 1H), 8.09 (d, *J*=2.8 Hz, 1H), 7.75 (br dd, *J*=8.8, 2.7 Hz, 2H), 7.46 (t, *J*=9.7 Hz, 1H), 7.18 (d, *J*=9.1 Hz, 1H), 5.88 (q, *J*=7.7 Hz, 1H), 4.59 - 4.38 (m, 1H), 3.96 (s, 3H), 3.29 - 3.16 (m, 2H), 2.99 - 2.93 (m, 1H), 2.45 (t, *J*=8.0 Hz, 2H), 2.12 - 2.02 (m, 2H), 1.97 - 1.91 (m, 1H), 1.88 - 1.79 (m, 1H), 1.47 (br d, *J*=6.9 Hz, 2H)	2.36, C

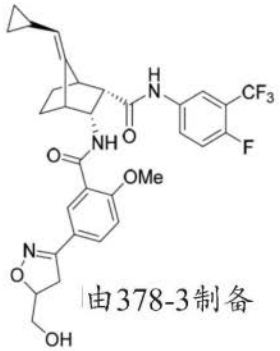
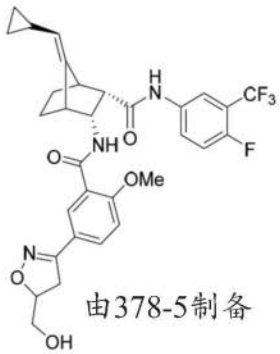
371		(2S,3R,7Z)-3-[5-(1,1-二氧代-1λ⁶,2-噻唑啶-2-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	650.2	(500 MHz, DMSO-d_6) δ 10.68 (s, 1H), 9.97 (br d, *J*=6.7 Hz, 1H), 8.20 (br d, *J*=4.0 Hz, 1H), 7.83 (d, *J*=2.7 Hz, 1H), 7.78 (br d, *J*=7.9 Hz, 1H), 7.48 (br t, *J*=9.8 Hz, 1H), 7.43 - 7.35 (m, 1H), 7.23 (d, *J*=9.2 Hz, 1H), 5.91 (q, *J*=7.9 Hz, 1H), 4.54 - 4.46 (m, 1H), 3.98 (s, 3H), 3.45 (t, *J*=7.6 Hz, 1H), 3.30 - 3.17 (m, 2H), 2.98 (br s, 1H), 2.40 (quin, *J*=6.9 Hz, 2H), 2.06 - 1.93 (m, 1H), 1.89 - 1.79 (m, 1H), 1.62 - 1.41 (m, 2H), 1.28 - 1.10 (m, 1H)	2.40, C

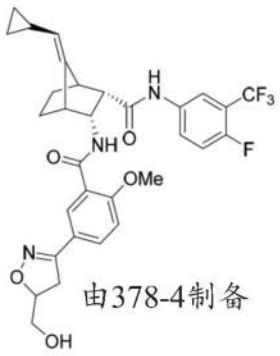
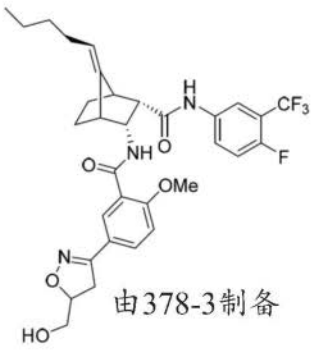
372		(2S,3R,7Z)-7-(环丙基亚甲基)-3-[5-(1,1-二氧代-1λ⁶,2-噻唑啶-2-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	622.1	(500 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.94 (br d, *J*=7.0 Hz, 1H), 8.24 (br d, *J*=4.6 Hz, 1H), 7.86 (d, *J*=3.1 Hz, 1H), 7.83 - 7.76 (m, 1H), 7.50 (br t, *J*=9.6 Hz, 1H), 7.37 (dd, *J*=8.7, 2.9 Hz, 1H), 7.24 (d, *J*=8.9 Hz, 1H), 4.70 (d, *J*=9.8 Hz, 1H), 4.45 (br t, *J*=10.4 Hz, 1H), 4.00 (s, 3H), 3.71 (br t, *J*=6.7 Hz, 1H), 3.60 - 3.41 (m, 1H), 3.45 - 3.29 (m, 1H), 3.17 (br dd, *J*=10.8, 3.8 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.41 (quin, *J*=6.9 Hz, 2H), 1.94 - 1.81 (m, 1H), 1.82 - 1.73 (m, 1H), 1.60 - 1.47 (m, 1H), 1.46 - 1.32 (m, 2H), 0.90 - 0.63 (m, 2H), 0.37 (br s, 2H)	2.44, B

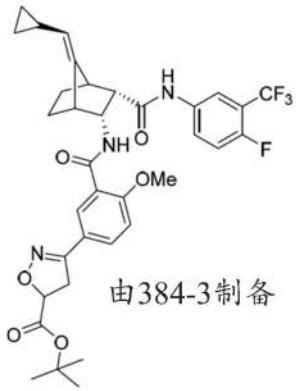
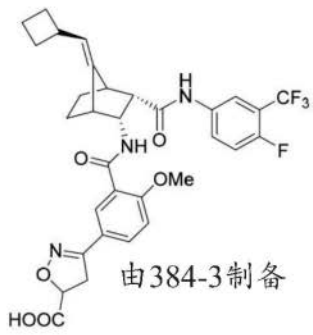
373		(2S,3R,7Z)-7-(环丙基亚甲基)-3-[5-(1,1-二氧代-1λ⁶,2-噻嗪烷-2-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	636.3	(500 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.91 (d, *J*=7.0 Hz, 1H), 8.30 - 8.14 (m, 1H), 7.85 (d, *J*=2.7 Hz, 1H), 7.77 (br dd, *J*=8.4, 3.4 Hz, 1H), 7.47 (t, *J*=9.7 Hz, 1H), 7.43 (dd, *J*=8.8, 2.9 Hz, 1H), 7.19 (d, *J*=8.9 Hz, 1H), 4.68 (d, *J*=9.5 Hz, 1H), 4.50 - 4.31 (m, 1H), 4.00 (s, 3H), 3.79 - 3.64 (m, 2H), 3.34 - 3.22 (m, 2H), 3.14 (br dd, *J*=10.6, 4.1 Hz, 1H), 3.08 (br s, 1H), 2.71 (br s, 1H), 2.25 - 2.05 (m, 2H), 1.88 - 1.67 (m, 4H), 1.62 - 1.44 (m, 1H), 1.44 - 1.31 (m, 2H), 0.84 - 0.58 (m, 2H), 0.34 (br d, *J*=3.1 Hz, 2H)	2.51, B

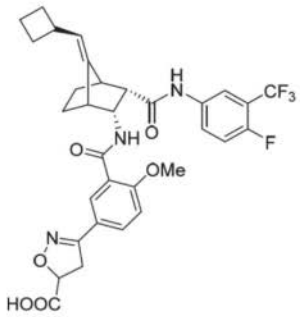
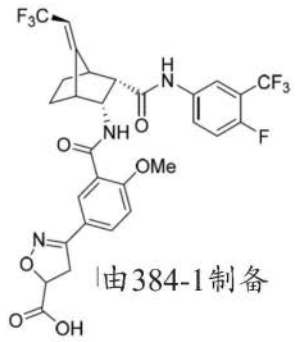
374		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(6-氧代-1,6-二氢哒嗪-1-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	662.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.95 (br d, *J*=7.0 Hz, 1H), 8.20 (br d, *J*=4.6 Hz, 1H), 8.05 (dd, *J*=13.1, 2.4 Hz, 2H), 7.79 - 7.76 (m, 1H), 7.69 (dd, *J*=8.9, 2.7 Hz, 1H), 7.49 - 7.45 (m, 2H), 7.29 (d, *J*=8.9 Hz, 1H), 7.05 (dd, *J*=9.5, 1.2 Hz, 1H), 4.68 (d, *J*=9.8 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.04 (s, 3H), 3.18 - 3.15 (m, 1H), 3.12 - 3.05 (m, 1H), 2.76 - 2.66 (m, 1H), 1.86 - 1.75 (m, 2H), 1.52 - 1.46 (m, 1H), 1.40 (br t, *J*=9.5 Hz, 2H), 0.77 - 0.68 (m, 2H), 0.36 - 0.29 (m, 2H)	2.38, C
375		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(6-氧代-1,6-二氢哒嗪-1-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	625.4	(500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.98 (br d, *J*=6.7 Hz, 1H), 8.21 (br d, *J*=4.3 Hz, 1H), 8.05 (dd, *J*=13.6, 2.6 Hz, 2H), 7.81 - 7.76 (m, 1H), 7.70 (dd, J=8.7, 2.6 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.30 (d, *J*=8.9 Hz, 1H), 7.05 (br d, *J*=9.5 Hz, 1H), 5.92 (q, *J*=7.9 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.05 (s, 3H), 3.29 - 3.23 (m, 1H), 3.01 - 2.93 (m, 1H), 1.97 - 1.83 (m, 3H), 1.52 - 1.44 (m, 2H)	2.42, B

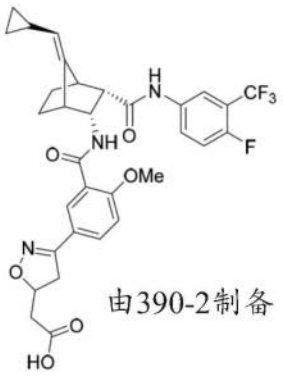
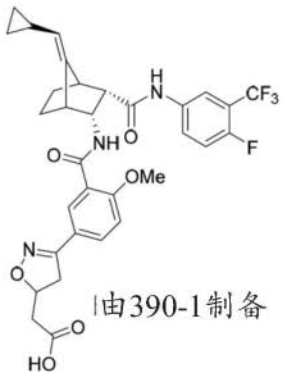
376		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-氧代-1,2-二氢吡啶-1-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	624.1	(500 MHz, DMSO-d6) δ 10.67 (s, 1H), 10.00 (br d, *J*=6.7 Hz, 1H), 8.21 (br d, *J*=4.3 Hz, 1H), 7.85 (d, *J*=2.4 Hz, 1H), 7.79 (br d, *J*=8.5 Hz, 1H), 7.60 (br d, *J*=5.5 Hz, 1H), 7.55 - 7.46 (m, 3H), 7.31 (d, *J*=8.9 Hz, 1H), 6.47 (d, *J*=9.5 Hz, 1H), 6.32 (t, *J*=6.7 Hz, 1H), 5.92 (q, *J*=7.8 Hz, 1H), 4.50 (br t, *J*=10.7 Hz, 1H), 4.05 (s, 3H), 3.29 - 3.20 (m, 2H), 3.02 - 2.94 (m, 1H), 1.96 (br t, *J*=9.3 Hz, 1H), 1.90 - 1.84 (m, 1H), 1.52 - 1.44 (m, 2H)	2.40, B
377		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-氧代哌啶-1-基)苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	628.1	(500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.90 (br d, *J*=7.3 Hz, 1H), 8.18 (br d, *J*=4.3 Hz, 1H), 7.79 - 7.72 (m, 2H), 7.47 (br t, *J*=9.8 Hz, 1H), 7.37 (dd, *J*=8.9, 2.4 Hz, 1H), 7.17 (d, *J*=8.9 Hz, 1H), 5.89 (q, *J*=7.9 Hz, 1H), 4.51 - 4.45 (m, 1H), 3.97 (s, 3H), 3.55 - 3.48 (m, 1H), 3.25 - 3.15 (m, 2H), 3.00 - 2.94 (m, 1H), 2.35 (br t, *J*=6.0 Hz, 2H), 2.00 - 1.93 (m, 1H), 1.87 - 1.78 (m, 5H), 1.51 - 1.42 (m, 2H)	2.40, B

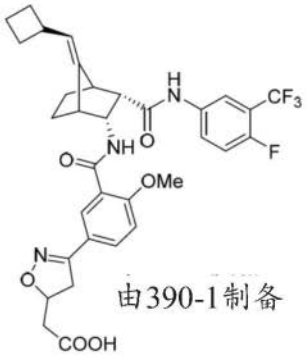
380	 由378-3制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	602.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (dd, *J*=6.9, 3.8 Hz, 1H), 8.22 (s, 1H), 8.23 (d, *J*=6.4 Hz, 1H), 7.82 - 7.76 (m, 2H), 7.49 (t, *J*=9.8 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 5.09 - 4.97 (m, 1H), 4.75 - 4.64 (m, 2H), 4.44 (br s, 1H), 4.04 (s, 3H), 3.58 - 3.43 (m, 3H), 3.22 - 3.13 (m, 2H), 2.72 (br s, 1H), 1.92 - 1.73 (m, 2H), 1.61 - 1.46 (m, 1H), 1.41 (br s, 2H), 0.85 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.32, C
381	 由378-5制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	602.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, *J*=7.3 Hz, 1H), 8.23 (s, 1H), 8.24 (d, *J*=6.5 Hz, 1H), 7.80 (br d, *J*=6.4 Hz, 2H), 7.50 (t, *J*=9.8 Hz, 1H), 7.34 - 7.21 (m, 1H), 4.70 (br d, *J*=9.5 Hz, 2H), 4.46 (br s, 1H), 4.05 (s, 3H), 3.51 (br s, 1H), 3.35 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.93 - 1.74 (m, 3H), 1.51 (br s, 1H), 1.42 (br s, 2H), 1.17 (br t, *J*=7.5 Hz, 2H), 0.88 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.38, C

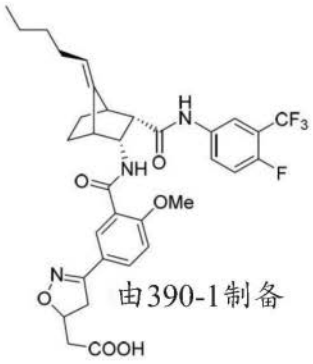
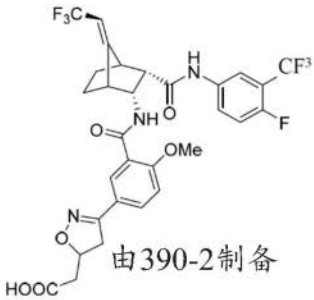
382		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	602.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.91 (br d, *J*=7.3 Hz, 1H), 8.23 (br s, 2H), 7.89 - 7.75 (m, 2H), 7.49 (br t, *J*=9.9 Hz, 1H), 7.34 - 7.19 (m, 1H), 4.70 (br d, *J*=9.5 Hz, 2H), 4.46 (br s, 1H), 4.05 (s, 3H), 3.51 (br s, 1H), 3.33 - 3.14 (m, 2H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.91 - 1.72 (m, 3H), 1.51 (br s, 1H), 1.42 (br s, 2H), 1.17 (s, 1H), 0.88 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.37, C
383		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-亚戊基双环[2.2.1]庚烷-2-甲酰胺	618.1	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.91 (dd, *J*=6.8, 3.7 Hz, 1H), 8.26 - 8.20 (m, 2H), 7.79 (br d, *J*=8.6 Hz, 2H), 7.49 (t, *J*=9.8 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 5.23 (t, *J*=7.4 Hz, 1H), 4.77 - 4.66 (m, 1H), 4.39 (br s, 1H), 4.04 (s, 3H), 3.66 - 3.45 (m, 2H), 3.18 (br dd, *J*=16.5, 8.1 Hz, 2H), 2.97 (br s, 1H), 2.73 (br s, 1H), 2.14 - 2.01 (m, 2H), 1.93 - 1.80 (m, 1H), 1.80 - 1.61 (m, 1H), 1.44 - 1.29 (m, 6H), 0.99 - 0.83 (m, 3H)	2.62, B

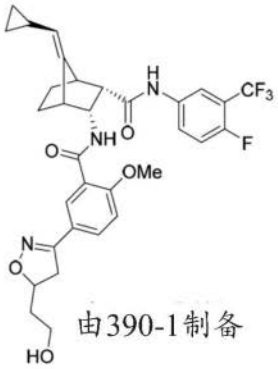
386	 由384-3制备	3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-甲酸叔丁酯	672.1	(500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.68 (d, *J*=7.1 Hz, 1H), 8.01 - 7.95 (m, 2H), 7.62 - 7.52 (m, 2H), 7.24 (br t, *J*=9.8 Hz, 1H), 7.04 (d, *J*=8.8 Hz, 1H), 4.85 (dd, *J*=11.7, 6.7 Hz, 1H), 4.44 (d, *J*=9.6 Hz, 1H), 4.19 (br s, 1H), 3.80 (s, 3H), 3.49 (br dd, *J*=17.2, 12.1 Hz, 1H), 3.35 - 3.23 (m, 3H), 2.97 - 2.88 (m, 1H), 2.86 (br s, 1H), 2.30 (s, 3H), 1.62 - 1.47 (m, 2H), 1.26 - 1.12 (m, 9H), 0.57 - 0.42 (m, 2H), 0.10 (br s, 2H)	2.71, B
387	 由384-3制备	3-(3-{[(2R,3S,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-甲酸	630.3	(500 MHz, DMSO-d6) δ 10.75 - 10.65 (m, 1H), 9.95 - 9.89 (m, 1H), 8.31 - 8.21 (m, 2H), 7.88 - 7.73 (m, 2H), 7.54 - 7.44 (m, 1H), 7.31 - 7.26 (m, 1H), 5.42 - 5.34 (m, 1H), 4.90 - 4.76 (m, 1H), 4.44 - 4.32 (m, 1H), 4.07 (s, 3H), 3.23 - 3.06 (m, 2H), 3.01 - 2.93 (m, 1H), 2.78 - 2.67 (m, 1H), 2.23 - 2.11 (m, 2H), 2.25 - 2.08 (m, 3H), 1.96 - 1.66 (m, 5H), 1.44 - 1.30 (m, 2H)	2.09, B

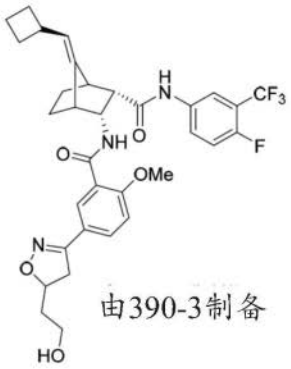
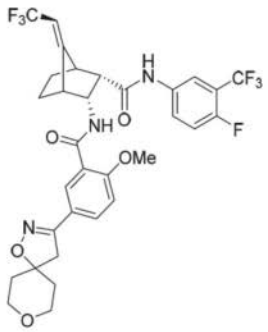
388		3-(3-{[(2R,3S,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-甲酸	630.1	(500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.91 (br s, 1H), 8.26 (br s, 1H), 7.82 (br s, 2H), 7.57 - 7.44 (m, 1H), 7.31 (s, 1H), 5.40 (br d, *J*=8.5 Hz, 1H), 5.22 - 5.06 (m, 1H), 4.43 - 4.33 (m, 1H), 4.06 (s, 3H), 3.92 (s, 1H), 3.60 - 3.37 (m, 3H), 3.19 (br s, 2H), 2.73 (br s, 1H), 2.09 (s, 2H), 1.86 (br dd, *J*=17.4, 7.6 Hz, 5H), 1.39 (br s, 2H)	2.12, C
389		3-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-甲酸	644.1	(500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.97 (br d, *J*=6.7 Hz, 1H), 8.24 (s, 1H), 8.23 (d, *J*=5.8 Hz, 1H), 7.88 - 7.71 (m, 2H), 7.51 (t, *J*=9.6 Hz, 1H), 7.29 (d, *J*=8.9 Hz, 1H), 5.94 (q, *J*=7.6 Hz, 1H), 5.13 (br dd, *J*=11.3, 6.7 Hz, 1H), 4.52 (br s, 1H), 4.06 (s, 3H), 3.72 (br dd, *J*=16.8, 11.9 Hz, 1H), 3.32 - 3.13 (m, 1H), 3.00 (s, 1H), 2.02 - 1.82 (m, 2H), 1.50 (br d, *J*=5.5 Hz, 2H)	2.21, C

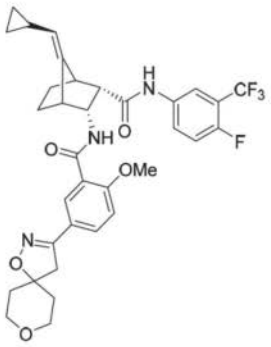
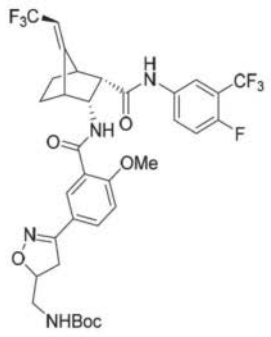
391	 由390-2制备	2-[3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]乙酸	630.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.93 (br d, *J*=7.0 Hz, 1H), 8.24 (br s, 2H), 7.87 - 7.76 (m, 2H), 7.51 (br t, *J*=9.6 Hz, 1H), 7.30 (br d, *J*=8.9 Hz, 1H), 5.04 - 4.89 (m, 1H), 4.72 (br d, *J*=9.8 Hz, 1H), 4.47 (br s, 1H), 4.07 (s, 3H), 3.19 (br d, *J*=9.2 Hz, 2H), 3.13 (br s, 1H), 2.75 (br s, 1H), 2.71 - 2.61 (m, 2H), 2.58 - 2.55 (m, 2H), 1.94 - 1.73 (m, 2H), 1.52 (br s, 1H), 1.43 (br s, 2H), 0.84 - 0.66 (m, 2H), 0.38 (br s, 2H)	2.39, C
392	 由390-1制备	2-[3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]乙酸	630.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (br d, *J*=7.0 Hz, 1H), 8.27 - 8.19 (m, 2H), 7.80 (br d, *J*=9.2 Hz, 2H), 7.49 (t, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 5.06 - 4.89 (m, 1H), 4.70 (d, *J*=9.8 Hz, 1H), 4.46 (br s, 1H), 4.05 (s, 3H), 3.55 (br dd, *J*=16.9, 10.5 Hz, 1H), 3.21 - 3.06 (m, 2H), 2.73 (br s, 1H), 2.68 - 2.59 (m, 2H), 2.49 - 2.28 (m, 1H), 1.92 - 1.72 (m, 2H), 1.63 - 1.46 (m, 1H), 1.46 - 1.35 (m, 2H), 0.87 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.37, C

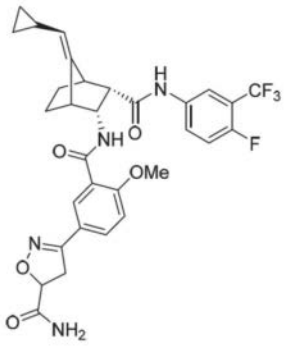
393		2-[3-(3-{[(2R,3S,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]乙酸	644.2	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.89 (d, *J*=6.7 Hz, 1H), 8.24 - 8.18 (m, 2H), 7.78 (br d, *J*=8.4 Hz, 2H), 7.48 (t, *J*=9.7 Hz, 1H), 7.26 (d, *J*=8.8 Hz, 1H), 5.36 (d, *J*=8.3 Hz, 1H), 5.08 - 4.91 (m, 1H), 4.35 (br s, 1H), 4.03 (s, 3H), 3.58 (br s, 1H), 3.21 - 3.04 (m, 3H), 2.96 (br s, 1H), 2.70 (br s, 1H), 2.56 (s, 2H), 2.22 - 2.05 (m, 2H), 1.91 - 1.70 (m, 6H), 1.42 - 1.22 (m, 2H)	2.50, C
394		2-[3-(3-{[(2R,3S,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]乙酸	644.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (br d, *J*=7.0 Hz, 1H), 8.25 - 8.19 (m, 2H), 7.79 (br d, *J*=8.9 Hz, 2H), 7.49 (t, *J*=9.9 Hz, 1H), 7.27 (d, *J*=8.9 Hz, 1H), 5.38 (d, *J*=8.5 Hz, 1H), 5.09 - 4.93 (m, 1H), 4.36 (br s, 1H), 4.04 (s, 3H), 3.55 (br dd, *J*=17.1, 10.4 Hz, 1H), 3.24 - 3.04 (m, 2H), 2.97 (br s, 1H), 2.77 - 2.57 (m, 3H), 2.55 (bs, 2H), 2.16 (br d, *J*=19.8 Hz, 2H), 1.92 - 1.71 (m, 4H), 1.48 - 1.27 (m, 2H)	2.55, C

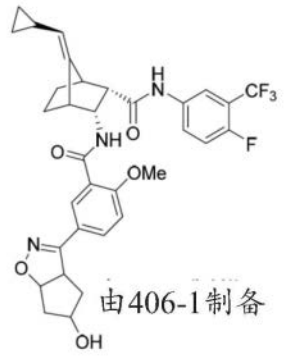
395		2-[3-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-亚戊基双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基] 乙酸	646.3	(500 MHz, DMSO-d6) δ 10.60 (s, 1H), 9.91 (br d, *J*=7.1 Hz, 1H), 8.28 - 8.20 (m, 2H), 7.84 - 7.77 (m, 2H), 7.50 (t, *J*=9.8 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 5.23 (t, *J*=7.4 Hz, 1H), 5.08 - 4.90 (m, 1H), 4.46 - 4.35 (m, 1H), 4.05 (s, 3H), 3.54 (br dd, *J*=16.6, 9.6 Hz, 1H), 3.23 - 3.11 (m, 2H), 2.98 (br s, 1H), 2.73 (br s, 1H), 2.61 (br d, *J*=5.6 Hz, 2H), 2.13 - 2.01 (m, 3H), 1.92 - 1.80 (m, 1H), 1.80 - 1.64 (m, 1H), 1.43 - 1.24 (m, 6H), 0.91 (t, *J*=7.0 Hz, 3H)	2.30, B
396		2-[3-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]乙酸	658.2	(500 MHz, DMSO-d6) δ 10.81 (br s, 1H), 10.10 (br s, 1H), 8.35 (br d, *J*=12.8 Hz, 1H), 7.95 (br s, 1H), 7.65 (br d, *J*=8.5 Hz, 1H), 7.53 - 7.37 (m, 1H), 6.07 (br d, *J*=6.7 Hz, 1H), 5.11 (br s, 1H), 4.66 (br s, 2H), 4.18 (br s, 3H), 3.81 (br s, 1H), 3.38 (br s, 1H), 3.31 (br s, 1H), 3.13 (br s, 1H), 2.78 (br s, 2H), 2.09 (br s, 1H), 2.01 (br s, 1H), 1.64 (br s, 2H)	2.27, C

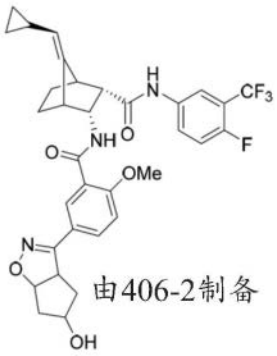
398	 由390-1制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (d, *J*=7.0 Hz, 1H), 8.22 (s, 2H), 7.80 (br dd, *J*=8.5, 2.1 Hz, 2H), 7.49 (t, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 4.80 - 4.67 (m, 2H), 4.63 (t, *J*=5.0 Hz, 1H), 4.46 (br s, 1H), 4.05 (s, 3H), 3.64 - 3.48 (m, 1H), 3.42 (br s, 1H), 3.20 - 3.01 (m, 3H), 2.91 (s, 1H), 2.79 - 2.68 (m, 2H), 2.58 - 2.54 (m, 2H), 1.89 - 1.69 (m, 4H), 1.60 - 1.46 (m, 1H), 1.42 (br s, 2H), 0.75 (br dd, *J*=11.6, 8.5 Hz, 2H), 0.36 (br s, 2H)	2.35, C
399	 由390-2制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (br d, *J*=7.0 Hz, 1H), 8.25 - 8.19 (m, 2H), 7.79 (br dd, *J*=8.7, 2.0 Hz, 2H), 7.49 (t, *J*=9.9 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 4.80 - 4.68 (m, 2H), 4.45 (br s, 1H), 4.05 (s, 3H), 3.55 (br t, *J*=6.1 Hz, 1H), 3.21 - 3.01 (m, 3H), 2.73 (br s, 1H), 2.56 (s, 1H), 1.92 - 1.70 (m, 5H), 1.51 (br d, *J*=4.3 Hz, 1H), 1.42 (br s, 2H), 0.86 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.33, C

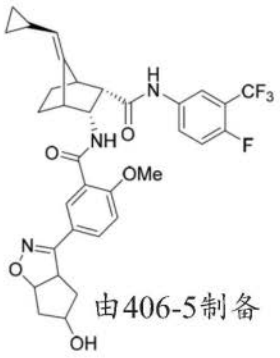
400	 由390-3制备	(2S,3R,7Z)-7-(环丁基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.88 (d, *J*=7.2 Hz, 1H), 8.24 - 8.19 (m, 2H), 7.78 (br d, *J*=8.4 Hz, 2H), 7.48 (br t, *J*=9.9 Hz, 1H), 7.26 (d, *J*=8.8 Hz, 1H), 5.37 (d, *J*=8.4 Hz, 1H), 4.79 - 4.72 (m, 1H), 4.35 (br s, 1H), 4.03 (s, 3H), 3.53 (br s, 5H), 3.18 - 3.05 (m, 3H), 2.95 (br s, 1H), 2.70 (br s, 1H), 2.20 - 2.07 (m, 2H), 1.92 - 1.79 (m, 4H), 1.79 - 1.69 (m, 3H), 1.41 - 1.30 (m, 2H)	2.52, C
401		(2S,3R,7Z)-3-(5-{1,8-二氧杂-2-氮杂螺[4.5]癸-2-烯-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	670.1	(500 MHz, DMSO-d6) δ 9.96 (br d, *J*=6.7 Hz, 1H), 8.28 - 8.19 (m, 2H), 7.82 (br dd, *J*=8.5, 2.4 Hz, 2H), 7.52 (br t, *J*=9.6 Hz, 1H), 7.29 (d, *J*=8.5 Hz, 1H), 5.95 (q, *J*=8.1 Hz, 1H), 4.53 (br s, 1H), 4.05 (s, 3H), 3.85 - 3.70 (m, 1H), 3.61 (br d, *J*=6.1 Hz, 1H), 3.47 (br s, 1H), 3.32 - 3.18 (m, 2H), 3.01 (br s, 1H), 2.03 - 1.92 (m, 1H), 1.92 - 1.82 (m, 1H), 1.77 (br s, 5H), 1.51 (br d, *J*=6.1 Hz, 3H)	2.48, C

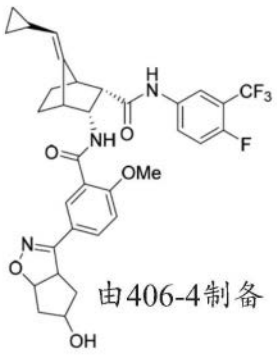
402		(2S,3R,7Z)-7-(环丙基亚甲基)-3-(5-{1,8-二氧杂-2-氮杂螺[4.5]癸-2-烯-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.90 (br d, *J*=7.0 Hz, 1H), 8.22 (br d, *J*=2.1 Hz, 2H), 7.80 (br dd, *J*=8.5, 2.1 Hz, 2H), 7.49 (t, *J*=9.9 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 4.70 (d, *J*=9.5 Hz, 1H), 4.45 (br s, 1H), 4.05 (s, 3H), 3.91 - 3.71 (m, 2H), 3.60 (br d, *J*=4.9 Hz, 1H), 3.46 (br s, 1H), 3.25 (s, 1H), 3.17 (br dd, *J*=10.5, 4.1 Hz, 1H), 2.73 (br s, 1H), 2.56 (bs, 2H), 2.01 - 1.80 (m, 2H), 1.77 (br s, 4H), 1.51 (br d, *J*=4.9 Hz, 1H), 1.42 (br s, 2H), 0.88 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.44, C
403		N-{[3-(3-{[(2R,3S,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-基]甲基}氨基甲酸叔丁酯	729.3	(500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.97 (br d, *J*=6.7 Hz, 1H), 8.32 - 8.13 (m, 2H), 7.81 (br d, *J*=5.8 Hz, 2H), 7.51 (t, *J*=9.6 Hz, 1H), 7.29 (d, *J*=8.9 Hz, 1H), 7.05 (br s, 1H), 5.95 (q, *J*=7.8 Hz, 1H), 4.86 - 4.66 (m, 1H), 4.53 (br s, 1H), 4.05 (s, 3H), 3.48 - 3.36 (m, 1H), 3.33 - 3.12 (m, 3H), 2.02 - 1.80 (m, 2H), 1.50 (br d, *J*=6.7 Hz, 2H), 1.36 (s, 9H)	2.72, C

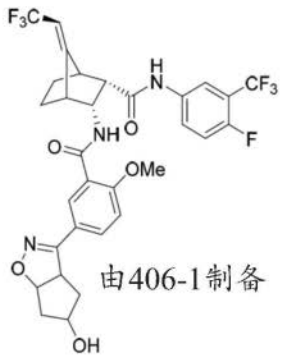
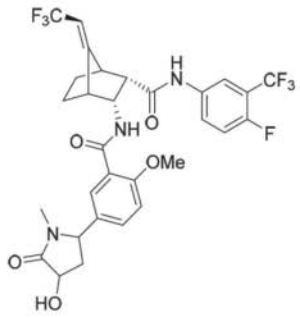
404		3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-4,5-二氢-1,2-噁唑-5-甲酰胺	615.2	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.93 (br d, *J*=7.0 Hz, 1H), 8.36 - 8.18 (m, 2H), 7.81 (br d, *J*=8.5 Hz, 2H), 7.66 (br s, 1H), 7.47 (br t, *J*=9.8 Hz, 1H), 7.40 (br s, 1H), 7.28 (d, *J*=8.5 Hz, 1H), 5.04 (dd, *J*=11.6, 6.4 Hz, 1H), 4.69 (d, *J*=9.5 Hz, 1H), 4.43 (br s, 1H), 4.04 (s, 3H), 3.51 (br d, *J*=7.0 Hz, 1H), 3.25 - 3.07 (m, 2H), 2.72 (br s, 1H), 2.05 (s, 1H), 1.93 - 1.72 (m, 2H), 1.69 (br s, 1H), 1.50 (br s, 1H), 1.41 (br s, 2H), 0.80 - 0.66 (m, 2H), 0.35 (br d, *J*=4.6 Hz, 2H)	2.24, B

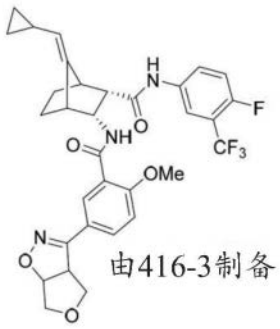
407		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[(5R)-5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	628.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.92 (br d, *J*=6.7 Hz, 1H), 8.25 (s, 1H), 8.25 (d, *J*=5.2 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.50 (t, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.5 Hz, 1H), 5.12 (br t, *J*=7.2 Hz, 1H), 4.71 (d, *J*=9.5 Hz, 1H), 4.46 (br d, *J*=3.1 Hz, 2H), 4.18 - 4.02 (m, 4H), 3.29 - 3.14 (m, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 2.18 - 2.02 (m, 2H), 1.94 - 1.72 (m, 4H), 1.52 (br d, *J*=9.5 Hz, 1H), 1.43 (br s, 2H), 0.90 - 0.69 (m, 2H), 0.37 (br s, 2H)	2.34, C

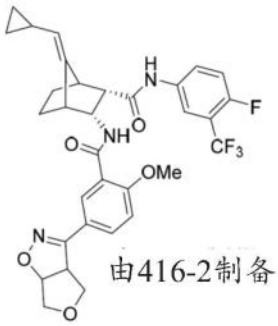
408		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.92 (d, *J*=7.0 Hz, 1H), 8.27 - 8.21 (m, 2H), 7.84 - 7.77 (m, 2H), 7.49 (t, *J*=9.8 Hz, 1H), 7.28 (d, *J*=8.5 Hz, 1H), 5.23 - 5.07 (m, 1H), 4.70 (d, *J*=9.8 Hz, 1H), 4.45 (br s, 1H), 4.22 (td, *J*=9.4, 4.1 Hz, 1H), 4.12 - 4.02 (m, 3H), 3.17 (br dd, *J*=10.5, 3.8 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.01 - 1.97 (m, 1H), 1.96 - 1.89 (m, 2H), 1.87 - 1.77 (m, 3H), 1.64 - 1.46 (m, 1H), 1.42 (br s, 2H), 0.87 - 0.69 (m, 2H), 0.37 (br s, 2H)	2.23, C

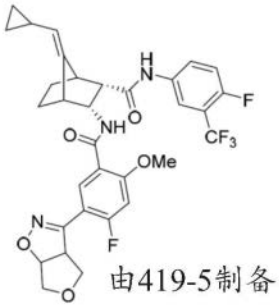
409		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2. 2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.92 (br d, *J*=6.7 Hz, 1H), 8.25 (s, 1H), 8.25 (d, *J*=5.2 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.50 (t, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.5 Hz, 1H), 5.12 (br t, *J*=7.2 Hz, 1H), 4.71 (d, *J*=9.5 Hz, 1H), 4.46 (br d, *J*=3.1 Hz, 2H), 4.18 - 4.02 (m, 4H), 3.29 - 3.14 (m, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 2.18 - 2.02 (m, 2H), 1.94 - 1.72 (m, 4H), 1.52 (br d, *J*=9.5 Hz, 1H), 1.43 (br s, 2H), 0.90 - 0.69 (m, 2H), 0.37 (br s, 2H)	2.38, B
410		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.1	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (d, *J*=7.0 Hz, 1H), 8.28 - 8.20 (m, 2H), 7.84 - 7.77 (m, 2H), 7.50 (t, *J*=9.8 Hz, 1H), 7.29 (d, *J*=8.5 Hz, 1H), 5.25 - 5.07 (m, 1H), 4.89 (d, *J*=4.0 Hz, 1H), 4.71 (d, *J*=9.5 Hz, 1H), 4.46 (br s, 1H), 4.35 - 4.17 (m, 1H), 4.11 (br d, *J*=5.2 Hz, 1H), 4.06 (s, 3H), 3.23 - 3.04 (m, 2H), 2.74 (br s, 1H), 2.01 - 1.78 (m, 5H), 1.53 (br d, *J*=4.6 Hz, 1H), 1.43 (br s, 2H), 0.90 - 0.69 (m, 2H), 0.37 (br s, 2H)	2.40, B

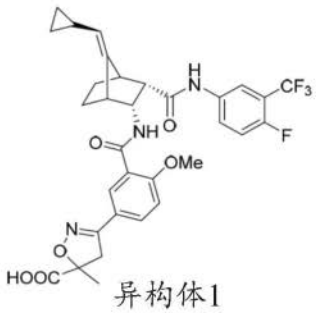
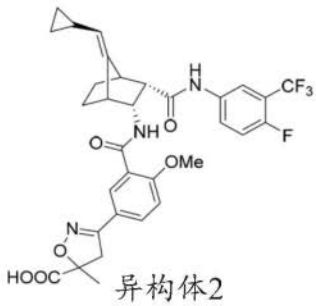
411		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 9.94 (br d, *J*=7.0 Hz, 1H), 8.24 (br d, *J*=2.1 Hz, 2H), 7.79 (br t, *J*=7.0 Hz, 2H), 7.49 (t, *J*=9.6 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 5.11 (br t, *J*=7.4 Hz, 1H), 4.69 (d, *J*=9.6 Hz, 1H), 4.44 (br s, 1H), 4.03 (s, 3H), 3.57 - 3.47 (m, 2H), 3.29 - 3.13 (m, 1H), 3.11 (br s, 1H), 3.00 (s, 1H), 2.73 (br s, 1H), 2.09 (br dd, *J*=13.6, 5.5 Hz, 2H), 1.92 - 1.71 (m, 4H), 1.51 (br dd, *J*=8.8, 3.4 Hz, 1H), 1.42 (br s, 2H), 0.87 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.32, C

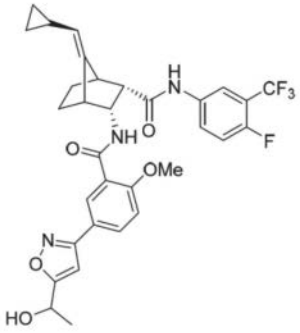
412		(2S,3R,7Z)-3-{5-[(3aS,5S,6aS)-5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	656.0	(500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.98 (br d, *J*=6.3 Hz, 1H), 8.26 - 8.20 (m, 1H), 7.84 - 7.77 (m, 2H), 7.51 (t, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.8 Hz, 1H), 5.95 (q, *J*=8.0 Hz, 1H), 5.20 - 5.09 (m, 1H), 4.95 (s, 1H), 4.52 (br s, 1H), 4.21 (dt, *J*=9.2, 4.8 Hz, 1H), 4.03 (m, 3H), 3.47 (br s, 2H), 3.45 - 3.39 (m, 1H), 3.31 - 3.22 (m, 1H), 3.00 (br s, 1H), 2.02 - 1.85 (m, 2H), 1.79 (br d, *J*=12.0 Hz, 1H), 1.50 (br d, *J*=6.1 Hz, 2H)	2.29, C
415		(2S,3R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-[5-(4-羟基-1-甲基-5-氧代吡咯烷-2-基)-2-甲氧基苯甲酰胺基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	644.0	(500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.94 (t, *J*=6.1 Hz, 1H), 8.32 - 8.11 (m, 1H), 7.89 (t, *J*=2.6 Hz, 1H), 7.84 - 7.67 (m, 1H), 7.50 (t, *J*=9.2 Hz, 1H), 7.45 (d, *J*=8.3 Hz, 1H), 7.23 (d, *J*=9.0 Hz, 1H), 5.93 (q, *J*=7.5 Hz, 1H), 4.52 (br s, 1H), 4.41 (t, *J*=7.5 Hz, 1H), 4.20 (t, *J*=8.4 Hz, 1H), 4.06 (s, 3H), 3.32 - 3.13 (m, 1H), 2.99 (br s, 1H), 2.81 - 2.63 (m, 1H), 2.50 - 2.36 (m, 2H), 1.99 (br t, *J*=9.3 Hz, 1H), 1.94 - 1.74 (m, 1H), 1.60 - 1.42 (m, 2H)	2.21, B

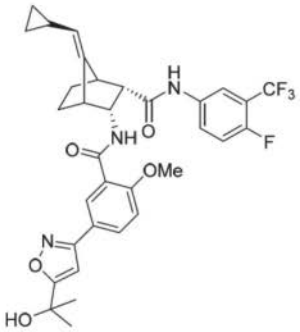
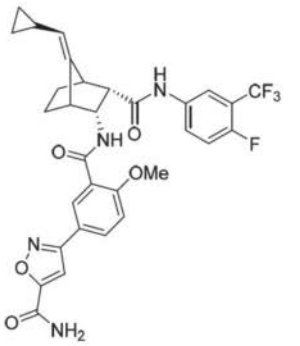
417	 由416-3制备	(2S,3R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	614.2	(500 MHz, DMSO-d_6) δ 10.70 - 10.42 (m, 1H), 9.93 (br d, *J*=7.3 Hz, 1H), 8.30 - 8.11 (m, 2H), 7.92 - 7.72 (m, 2H), 7.47 (br t, *J*=9.5 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 1H), 5.35 (br dd, *J*=9.0, 3.2 Hz, 1H), 4.70 (br d, *J*=9.8 Hz, 1H), 4.48 (br t, *J*=7.9 Hz, 1H), 4.45 - 4.36 (m, 1H), 4.10 (br d, *J*=11.0 Hz, 1H), 4.04 (s, 3H), 3.89 (s, 1H), 3.71 (m, 3H), 3.24 - 3.06 (m, 2H), 2.72 (br d, *J*=3.7 Hz, 1H), 1.87 - 1.81 (m, 1H), 1.80 - 1.70 (m, 1H), 1.57 - 1.47 (m, 1H), 1.43 - 1.30 (m, 1H), 0.85 - 0.65 (m, 2H), 0.35 (br d, *J*=4.3 Hz, 2H)	2.50, B

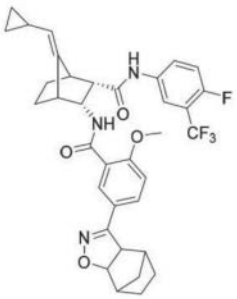
418	 由416-2制备	(2S,3R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	614.3	(500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.94 (br d, *J*=7.0 Hz, 1H), 8.43 - 8.15 (m, 2H), 8.03 - 7.73 (m, 2H), 7.49 (br t, *J*=9.8 Hz, 1H), 7.29 (d, *J*=8.5 Hz, 1H), 5.36 (dd, *J*=9.2, 3.4 Hz, 1H), 4.71 (br d, *J*=9.8 Hz, 1H), 4.55 - 4.32 (m, 2H), 4.11 (br d, *J*=11.0 Hz, 1H), 4.06 (s, 3H), 3.91 (br d, *J*=9.5 Hz, 1H), 3.84 - 3.63 (m, 1H), 3.51 (br d, *J*=3.1 Hz, 1H), 3.30 - 3.14 (m, 1H), 3.12 (br s, 1H), 2.73 (br s, 1H), 1.88 - 1.67 (m, 2H), 1.59 - 1.48 (m, 1H), 1.47 - 1.36 (m, 2H), 0.84 - 0.65 (m, 2H), 0.36 (br d, *J*=2.1 Hz, 2H)	2.38, C

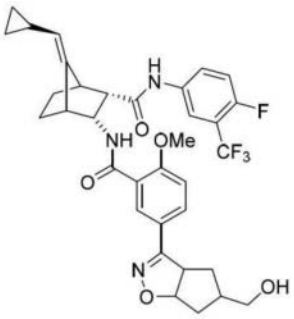
420	 由419-5制备	(2S,3R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-4-氟-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.3	(500 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.88 (br d, *J*=6.7 Hz, 1H), 8.35 (d, *J*=8.9 Hz, 1H), 8.27 - 8.20 (m, 1H), 7.89 - 7.75 (m, 1H), 7.50 (br t, *J*=9.8 Hz, 1H), 7.25 (d, *J*=13.1 Hz, 1H), 5.35 (dd, *J*=9.2, 3.4 Hz, 1H), 4.71 (d, *J*=9.8 Hz, 1H), 4.53 - 4.39 (m, 2H), 4.12 (br d, *J*=10.7 Hz, 1H), 4.07 (s, 3H), 3.91 (br d, *J*=9.2 Hz, 1H), 3.75 (dd, *J*=9.2, 7.0 Hz, 1H), 3.66 (dd, *J*=10.7, 3.4 Hz, 1H), 3.23 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.74 (br s, 1H), 1.91 - 1.81 (m, 1H), 1.80 - 1.72 (m, 1H), 1.51 (ddd, *J*=12.8, 8.4, 4.4 Hz, 1H), 1.46 - 1.34 (m, 2H), 0.85 - 0.64 (m, 2H), 0.36 (br s, 2H)	2.55, B

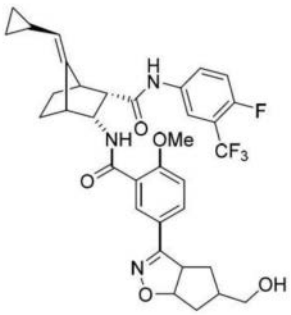
421	 异构体1	3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-5-甲基-4,5-二氢-1,2-噁唑-5-甲酸	630.2	(500 MHz, DMSO-d6) δ 10.61 - 10.56 (m, 1H), 9.95 - 9.87 (m, 1H), 8.26 - 8.20 (m, 2H), 7.86 - 7.74 (m, 3H), 7.54 - 7.44 (m, 2H), 7.32 - 7.23 (m, 1H), 4.73 - 4.69 (m, 1H), 4.50 - 4.41 (m, 1H), 4.05 (s, 3H), 3.80 - 3.70 (m, 2H), 3.21 - 3.09 (m, 2H), 3.03 - 3.02 (m, 1H), 2.77 - 2.70 (m, 1H), 1.87 - 1.71 (m, 2H), 1.51 (br s, 2H), 1.46 - 1.20 (m, 3H), 0.84 - 0.68 (m, 2H), 0.39 - 0.33 (m, 2H)	1.9, B
422	 异构体2	3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-5-甲基-4,5-二氢-1,2-噁唑-5-甲酸	630.2	(500 MHz, DMSO-d_6) δ 10.61 - 10.56 (m, 1H), 9.95 - 9.87 (m, 1H), 8.26 - 8.20 (m, 2H), 7.86 - 7.74 (m, 3H), 7.54 - 7.44 (m, 2H), 7.32 - 7.23 (m, 1H), 4.73 - 4.69 (m, 1H), 4.50 - 4.41 (m, 1H), 4.05 (s, 3H), 3.80 - 3.70 (m, 2H), 3.21 - 3.09 (m, 2H), 3.03 - 3.02 (m, 1H), 2.77 - 2.70 (m, 1H), 1.87 - 1.71 (m, 3H), 1.51 (br s, 1H), 1.46 - 1.20 (m, 3H), 0.84 - 0.68 (m, 2H), 0.39 - 0.33 (m, 2H)	2.0, B

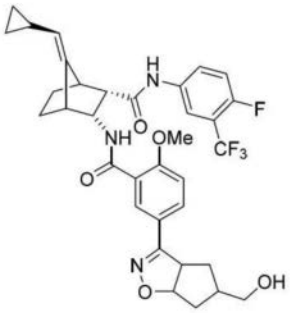
424		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	614.1	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.94 (br d, *J*=7.0 Hz, 1H), 8.44 (d, *J*=2.1 Hz, 1H), 8.24 (br d, *J*=4.3 Hz, 1H), 8.00 (dd, *J*=8.5, 2.1 Hz, 1H), 7.81 (br d, *J*=8.5 Hz, 1H), 7.50 (br t, *J*=9.8 Hz, 1H), 7.34 (d, *J*=8.5 Hz, 1H), 6.86 (s, 1H), 5.05 - 4.84 (m, 1H), 4.71 (d, *J*=9.5 Hz, 1H), 4.48 (br s, 1H), 4.08 (s, 3H), 3.37 (br s, 1H), 3.27 - 3.15 (m, 1H), 3.13 (br s, 1H), 3.01 (s, 1H), 2.74 (br s, 1H), 1.97 - 1.75 (m, 2H), 1.57 - 1.37 (d, 3H), 1.25 (br s, 1H), 0.88 - 0.68 (m, 2H), 0.37 (br s, 2H)	2.6, B

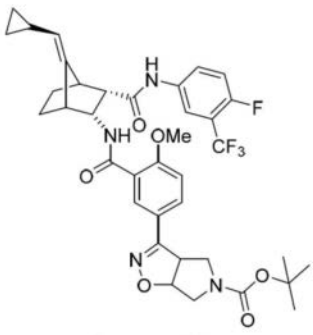
425		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	628.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.93 (d, *J*=7.0 Hz, 1H), 8.42 (d, *J*=1.5 Hz, 1H), 8.22 (br d, *J*=4.3 Hz, 1H), 7.98 (dd, *J*=8.5, 1.7 Hz, 1H), 7.79 (br d, *J*=8.1 Hz, 1H), 7.48 (br t, *J*=9.7 Hz, 1H), 7.32 (d, *J*=8.6 Hz, 1H), 6.83 - 6.77 (m, 1H), 4.70 (d, *J*=9.5 Hz, 1H), 4.46 (br s, 1H), 4.06 (s, 3H), , 3.47 - 3.43 (m, 1H), 3.20 - 3.09 (m, 2H), 2.72 (br s, 1H), 1.92 - 1.74 (m, 2H), 1.51 (s, 6H), 1.42 (br s, 2H), 0.85 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.66, B
426		3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1,2-噁唑-5-甲酰胺	612.9	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.95 (br d, *J*=7.3 Hz, 1H), 8.48 - 8.39 (m, 2H), 8.19 (br d, *J*=4.3 Hz, 1H), 8.02 (br d, *J*=8.5 Hz, 1H), 8.00 (br d, *J*=7.9 Hz, 1H), 7.76 (br s, 1H), 7.57 - 7.42 (m, 2H), 7.35 (d, *J*=8.9 Hz, 1H), 4.69 (br d, *J*=9.5 Hz, 1H), 4.45 (br s, 1H), 4.06 (s, 3H), 3.22 - 3.05 (m, 2H), 2.72 (br s, 1H), 1.88 - 1.70 (m, 2H), 1.50 (br s, 2H), 1.42 (br s, 2H), 1.21 (br s, 1H), 0.86 - 0.65 (m, 2H), 0.35 (br d, *J*=4.3 Hz, 2H)	2.37, C

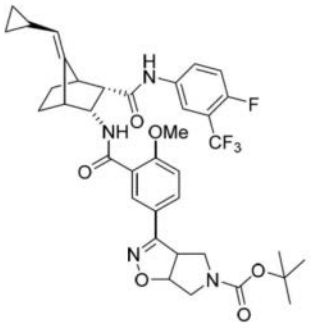
428		(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-*N*-(4-氟-3-(三氟甲基)苯基)-3-(5-(3a,4,5,6,7,7a-六氢-4,7-甲桥苯并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	638.2	(500 MHz, DMSO-d_6) δ 10.44 - 10.20 (m, 1H), 9.68 (br t, *J*=7.3 Hz, 1H), 8.34 - 7.88 (m, 2H), 7.80 - 7.45 (m, 2H), 7.26 (br t, *J*=9.8 Hz, 1H), 7.04 (d, *J*=8.9 Hz, 1H), 4.47 (br d, *J*=9.8 Hz, 1H), 4.35 (br d, *J*=8.2 Hz, 1H), 4.21 (br s, 1H), 3.82 (d, *J*=1.8 Hz, 3H), 3.43 (br dd, *J*=7.6, 4.6 Hz, 1H), 3.25 - 3.08 (m, 1H), 2.93 (br dd, *J*=11.0, 4.3 Hz, 1H), 2.88 (br s, 1H), 2.50 (br s, 1H), 2.13 (br d, *J*=8.5 Hz, 1H), 1.70 - 1.59 (m, 1H), 1.57 - 1.43 (m, 1H), 1.39 - 1.22 (m, 3H), 1.22 - 1.08 (m, 3H), 1.03 (br d, *J*=10.4 Hz, 1H), 0.90 (br d, *J*=10.1 Hz, 2H), 0.62 - 0.36 (m, 2H), 0.13 (br s, 2H)	2.84, B

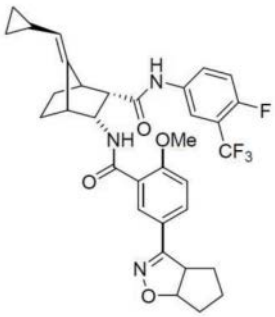
431	 由429-8制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (d, *J*=7.2 Hz, 1H), 8.21 (d, *J*=2.3 Hz, 1H), 8.19 (dd, *J*=6.4, 2.4 Hz, 1H), 7.80 - 7.74 (m, 2H), 7.45 (t, *J*=9.7 Hz, 1H), 7.26 (d, *J*=8.8 Hz, 1H), 5.15 - 5.10 (m, 1H), 4.67 (d, *J*=9.7 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.07 (td, *J*=9.6, 6.2 Hz, 1H), 4.02 (s, 3H), 3.28 (dt, *J*=10.6, 5.3 Hz, 1H), 3.23 - 3.18 (m, 1H), 3.13 (br dd, *J*=10.8, 4.1 Hz, 1H), 3.10 - 3.03 (m, 1H), 2.73 - 2.67 (m, 1H), 2.22 - 2.08 (m, 3H), 1.85 - 1.73 (m, 2H), 1.64 - 1.57 (m, 1H), 1.52 - 1.36 (m, 4H), 0.77 - 0.67 (m, 2H), 0.38 - 0.29 (m, 2H)	2.5, B

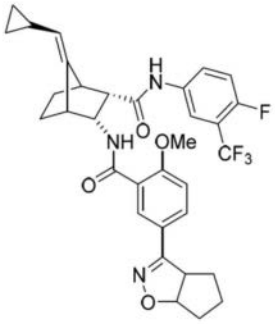
432	 由429-8制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.4	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (br d, *J*=7.0 Hz, 1H), 8.24 - 8.21 (m, 1H), 8.21 - 8.17 (m, 1H), 7.80 - 7.75 (m, 2H), 7.46 (t, *J*=9.8 Hz, 1H), 7.26 (d, *J*=8.5 Hz, 1H), 5.15 - 5.10 (m, 1H), 4.68 (d, *J*=9.8 Hz, 1H), 4.42 (br t, *J*=10.1 Hz, 1H), 4.12 - 4.05 (m, 1H), 4.02 (s, 3H), 3.30 - 3.25 (m, 1H), 3.20 (dt, *J*=10.5, 5.4 Hz, 1H), 3.14 (br dd, *J*=11.0, 4.0 Hz, 1H), 3.11 - 3.03 (m, 1H), 2.73 - 2.66 (m, 1H), 2.22 - 2.09 (m, 3H), 1.84 - 1.73 (m, 2H), 1.65 - 1.58 (m, 1H), 1.51 - 1.36 (m, 4H), 0.77 - 0.68 (m, 2H), 0.37 - 0.30 (m, 2H)	2.41, B

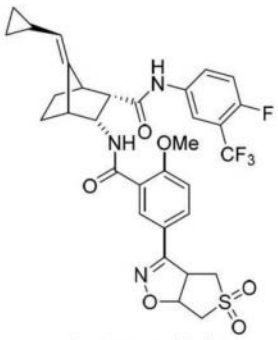
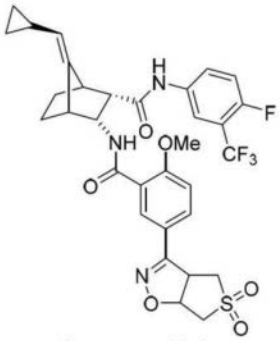
433	 由429-10制备	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, *J*=7.2 Hz, 1H), 8.24 - 8.18 (m, 2H), 7.81 - 7.75 (m, 2H), 7.47 (t, *J*=9.7 Hz, 1H), 7.26 (d, *J*=8.8 Hz, 1H), 5.11 (dd, J=8.8, 5.1 Hz, 1H), 4.68 (d, *J*=9.5 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.20 - 4.15 (m, 1H), 4.03 (s, 3H), 3.40 - 3.29 (m, 1H), 3.14 (dd, *J*=10.7, 4.1 Hz, 1H), 3.11 - 3.06 (m, 1H), 2.74 - 2.68 (m, 1H), 1.97 (br dd, *J*=13.6, 5.9 Hz, 1H), 1.93 - 1.71 (m, 5H), 1.68 - 1.60 (m, 1H), 1.57 - 1.46 (m, 2H), 1.45 - 1.37 (m, 2H), 0.78 - 0.68 (m, 2H), 0.38 - 0.30 (m, 2H)	2.42, B

435	 由434-4制备	3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-5-甲酸叔丁酯	713.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (br d, *J*=6.6 Hz, 1H), 8.22 - 8.18 (m, 2H), 7.80 - 7.75 (m, 2H), 7.46 (t, *J*=9.8 Hz, 1H), 7.29 (d, *J*=8.8 Hz, 1H), 5.25 (dd, *J*=9.2, 4.8 Hz, 1H), 4.68 (d, *J*=9.6 Hz, 1H), 4.46 - 4.39 (m, 2H), 4.04 (s, 3H), 3.80 - 3.70 (m, 1H), 3.18 - 3.12 (m, 1H), 3.11 - 3.07 (m, 1H), 2.74 - 2.69 (m, 1H), 1.86 - 1.74 (m, 2H), 1.50 (td, *J*=8.7, 4.4 Hz, 1H), 1.43 - 1.22 (m, 12H), 0.77 - 0.68 (m, 2H), 0.37 - 0.31 (m, 2H)	2.8, C

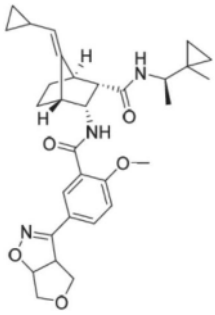
436	 由434-6制备	3-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-5-甲酸叔丁酯	713.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (d, J=7.1 Hz, 1H), 8.22 - 8.19 (m, 2H), 7.80 - 7.75 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.29 (d, J=8.9 Hz, 1H), 5.25 (dd, J=9.2, 4.8 Hz, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.43 (br t, J=10.3 Hz, 2H), 4.04 (s, 3H), 3.75 (br d, J=12.8 Hz, 1H), 3.15 (dd, J=10.6, 4.1 Hz, 1H), 3.10 - 3.08 (m, 1H), 2.71 (m, 1H), 1.84 - 1.74 (m, 2H), 1.49 (ddd, J=12.9, 8.3, 4.4 Hz, 1H), 1.42 - 1.25 (m, 12H), 0.77 - 0.69 (m, 2H), 0.37 - 0.31 (m, 2H)	2.67, C

440	 由439-4制备	(2S,3R,7Z)-3-(5-{3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	612.4	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.88 (br d, *J*=7.0 Hz, 1H), 8.22 - 8.18 (m, 2H), 7.80 - 7.75 (m, 2H), 7.46 (br t, *J*=9.6 Hz, 1H), 7.25 (d, *J*=8.5 Hz, 1H), 5.12 (br dd, *J*=8.4, 4.7 Hz, 1H), 4.68 (d, *J*=9.5 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.14 (br t, *J*=8.4 Hz, 1H), 4.02 (s, 3H), 3.14 (br dd, *J*=10.8, 4.1 Hz, 1H), 3.11 - 3.06 (m, 1H), 2.73 - 2.68 (m, 1H), 1.94 (br dd, *J*=13.3, 6.3 Hz, 1H), 1.88 - 1.81 (m, 2H), 1.78 - 1.72 (m, 2H), 1.67 (ddd, *J*=19.4, 13.0, 6.1 Hz, 2H), 1.49 (dt, *J*=8.4, 4.0 Hz, 1H), 1.43 - 1.34 (m, 2H), 1.32 - 1.24 (m, 1H), 0.77 - 0.69 (m, 2H), 0.37 - 0.30 (m, 2H)	2.72, B

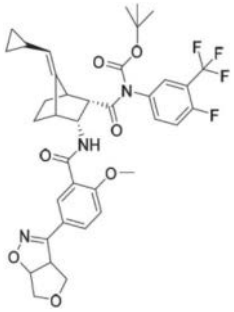
441	 由439-6制备	(2S,3R,7Z)-3-(5-{3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	612.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (br d, *J*=7.0 Hz, 1H), 8.23 - 8.18 (m, 2H), 7.80 - 7.75 (m, 2H), 7.46 (br t, *J*=9.8 Hz, 1H), 7.25 (d, *J*=8.5 Hz, 1H), 5.12 (br dd, *J*=8.4, 4.7 Hz, 1H), 4.68 (br d, *J*=9.5 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.14 (br t, *J*=9.0 Hz, 1H), 4.03 (s, 3H), 3.14 (br dd, *J*=10.8, 3.8 Hz, 1H), 3.10 - 3.08 (m, 1H), 2.73 - 2.68 (m, 1H), 1.94 (br dd, *J*=13.3, 6.0 Hz, 1H), 1.88 - 1.80 (m, 2H), 1.79 - 1.63 (m, 4H), 1.53 - 1.46 (m, 1H), 1.44 - 1.36 (m, 2H), 1.30 (qd, *J*=11.9, 5.5 Hz, 1H), 0.77 - 0.69 (m, 2H), 0.37 - 0.30 (m, 2H)	2.71, B

443	 由442-4制备	(2S,3R,7Z)-7-(环丙基亚甲基)-3-(5-{5,5-二氧代-3aH,4H,6H,6aH-5λ⁶-噻吩并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	662.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (br d, *J*=7.0 Hz, 1H), 8.23 - 8.18 (m, 2H), 7.79 - 7.74 (m, 2H), 7.46 (br t, *J*=9.8 Hz, 1H), 7.27 (d, *J*=8.9 Hz, 1H), 5.43 - 5.38 (m, 1H), 4.77 - 4.72 (m, 1H), 4.68 (d, *J*=9.5 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.04 (s, 3H), 3.67 - 3.61 (m, 1H), 3.53 - 3.45 (m, 1H), 3.16 - 3.08 (m, 3H), 2.73 - 2.68 (m, 1H), 1.84 - 1.73 (m, 2H), 1.51 - 1.45 (m, 1H), 1.43 - 1.35 (m, 2H), 0.77 - 0.68 (m, 2H), 0.38 - 0.30 (m, 2H)	2.38, C
444	 由442-6制备	(2S,3R,7Z)-7-(环丙基亚甲基)-3-(5-{5,5-二氧代-3aH,4H,6H,6aH-5λ⁶-噻吩并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	662.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (br d, *J*=7.3 Hz, 1H), 8.25 - 8.20 (m, 2H), 7.76 (br dd, *J*=8.4, 2.0 Hz, 2H), 7.47 (br t, *J*=9.8 Hz, 1H), 7.27 (d, *J*=8.9 Hz, 1H), 5.40 (br dd, *J*=8.9, 6.7 Hz, 1H), 4.75 (td, *J*=10.1, 3.5 Hz, 1H), 4.68 (d, *J*=9.5 Hz, 1H), 4.46 - 4.40 (m, 1H), 4.04 (s, 3H), 3.68 - 3.62 (m, 1H), 3.48 - 3.37 (m, 1H), 3.18 - 3.13 (m, 2H), 3.11 - 3.07 (m, 1H), 2.74 - 2.68 (m, 1H), 1.85 - 1.75 (m, 2H), 1.53 - 1.45 (m, 1H), 1.44 - 1.36 (m, 2H), 0.78 - 0.68 (m, 2H), 0.34 (br s, 2H)	2.38, C

[0001] 实施例447

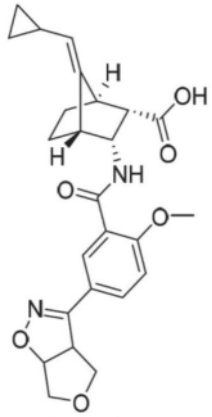


中间体447-1：



向(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(250mg,0.407mmol,实施例417)于DCM(4.1mL)中的溶液中添加Boc_2O(0.38mL,1.6mmol)、Hunig碱(0.28μl、1.6mmol)及DMAP(25mg,0.20mmol)。搅拌反应混合物14h,随后真空浓缩。经由硅胶色谱纯化残余物,得到((1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-羰基)(4-氟-3-(三氟甲基)苯基)氨基甲酸叔丁酯(242mg,0.339mmol,83.0%产率)。LC-MS RT:1.20min;MS(ESI)m/z 736$(M+Na)^+$;方法E。

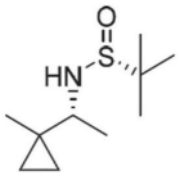
[0002] 中间体447-2：



向中间体447-1(533mg,0.747mmol)于THF(14mL)中的溶液中添加LiOH(1M水溶液)(3.7mL,3.7mmol)。3小时之后,将反应混合物用水稀释且用EtOAc萃取两次。用1M NaOH再萃取有机层,随后用1M HCl将水层酸化至约pH 1。滤出所沉淀的固体,接着用EtOAc萃取滤液两次。将有机洗脱份与固体合并且在减压下浓缩,得到(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酸实施例447-2(294mg,0.650mmol,87.0%产率)。LC-MS RT:0.75min;MS

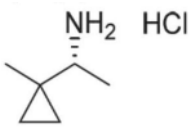
(ESI)m/z 453(M+H)$^+$;方法E。

[0003] 中间体447-3:



在两个40mL压力小瓶中的每一者中,将1-(1-甲基环丙基)乙-1-酮(0.500g,5.09mmol)溶解于THF(10ml)中。向此溶液中添加乙醇钛(IV)(2.1ml,10mmol)及(R)-2-甲基丙烷-2-亚磺酰胺(0.617g,5.09mmol)。将反应混合物加热至65℃持续14h,随后使其冷却至室温。将硼氢化钠(1.54g,40.8mmol)于7mL THF中的悬浮液冷却至-50℃。将含有反应溶液的小瓶冷却至-50℃。将反应溶液转移至硼氢化钠溶液中。在两小时之后,用MeOH淬灭反应混合物。在气体逸出停止之后,将反应混合物随着搅拌倒入盐水中。经由硅藻土过滤悬浮液,用EtOAc冲洗。在减压下浓缩滤液。经由硅胶色谱纯化残余物,得到中间体447-3(982mg,47%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ3.22(br s,1H),2.61(qd,J=6.5,3.2Hz,1H),1.26-1.21(m,12H),1.01(s,3H),0.54-0.46(m,1H),0.42-0.32(m,3H)。

[0004] 中间体447-4:

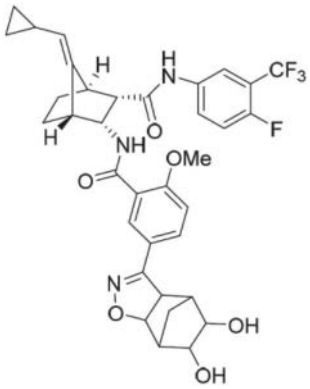


向中间体447-3(100mg,0.492mmol)于甲醇(0.49mL)中的溶液中添加HCl(4M于二噁烷中)(0.12mL,0.49mmol)。2.75小时之后,真空浓缩反应混合物。将残余物用Et_2O进行音波处理且过滤。干燥固体,得到(R)-1-(1-甲基环丙基)乙-1-胺HCl(60mg,0.44mmol,90%产率)。^{1}H NMR(400MHz,CD_3OD)δ2.66-2.52(m,1H),1.38-1.27(m,3H),1.09(s,3H),0.65-0.55(m,1H),0.55-0.41(m,3H)。

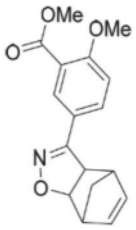
[0005] 实施例447:

向中间体447-2(20mg,0.044mmol)于DMF(0.5mL)中的溶液中添加中间体447-4(24mg,0.18mmol)、HATU(22mg,0.057mmol)及Hunig碱(0.046mL,0.27mmol)。1.5小时之后,用MeOH淬灭反应混合物。经由制备型HPLC纯化残余物,得到实施例447(15.2mg,64.0%产率)。^{1}H NMR(400MHz,DMSO-d_6)δ10.07(br d,J=6.7Hz,1H),8.15(d,J=2.4Hz,1H),7.92(d,J=8.6Hz,1H),7.78(dd,J=8.6,2.4Hz,1H),7.23(d,J=8.8Hz,1H),5.34(dd,J=9.4,3.5Hz,1H),4.63(d,J=9.4Hz,1H),4.54-4.47(m,1H),4.31-4.23(m,1H),4.09(d,J=10.9Hz,1H),4.00(s,3H),3.90(d,J=10.0Hz,1H),3.77(dd,J=9.3,6.7Hz,1H),3.65(dd,J=10.7,3.6Hz,1H),3.50-3.42(m,1H),3.07-3.02(m,1H),2.94(dd,J=11.0,4.0Hz,1H),1.91-1.81(m,1H),1.78-1.68(m,1H),1.52-1.43(m,1H),1.40-1.30(m,2H),1.05-0.99(m,3H),0.99-0.94(m,3H),0.77-0.66(m,2H),0.58-0.47(m,1H),0.36-0.27(m,2H),0.17(br t,J=6.6Hz,2H)。LC-MS RT:2.26min;MS(ESI)m/z 534.3(M+H)$^+$;方法B。

[0006] 实施例448

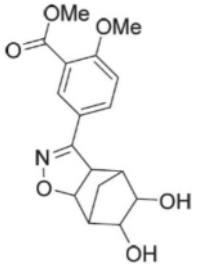


中间体448-1：



将(Z)-5-(氯(羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯(200mg,0.821mmol)及双环[2.2.1庚-2,5-二烯(756mg,8.21mmol)溶解于DCM(5mL)中。向溶液中添加TEA(1mL)且在室温下搅拌14h。将反应混合物用水(50mL)淬灭且用EtOAc(2×25mL)萃取,接着干燥($MgSO_4$),过滤且真空浓缩成油状物。经由硅胶色谱法纯化残余物且用己烷/EtOAc洗脱。分离含有纯产物的洗脱份且在减压下浓缩成2-甲氧基-5-(3a,4,7,7a-四氢-4,7-甲桥苯并[d]异噁唑-3-基)苯甲酸甲酯448-1(240mg,98%产率)。^1H NMR(500MHz,$CDCl_3$)δ8.09(d,J=2.3Hz,1H),7.88(dd,J=8.9,2.3Hz,1H),7.02(d,J=8.7Hz,1H),6.36(dd,J=5.7,3.0Hz,1H),6.10(dd,J=5.8,3.2Hz,1H),4.97(dt,J=8.2,1.2Hz,1H),3.94(s,3H),3.91(s,3H),3.29-3.25(m,1H),1.71(d,J=9.5Hz,1H),1.62(dt,J=9.4,1.5Hz,1H)。LCMS m/z=300.2$(M+H)^+$。

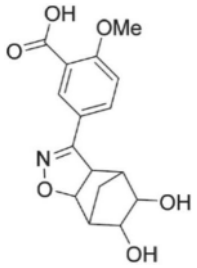
[0007] 制备中间体同手性异构体448-2及448-3。



将中间体448-1(180mg,0.60mmol)搅拌成于t-BuOH(3mL)中的浆液,且向溶液中添加N-甲基吗啉氧化物(146mg,1.20mmol),随后添加OsO_4(380mg,0.060mmol)。反应物立即变成黑色且在室温下搅拌14h。将反应混合物用饱和亚硫酸钠溶液(20mL)淬灭,搅拌5min且用EtOAc(2×25mL)萃取,干燥($MgSO_4$),过滤且在减压下蒸发成呈泡沫的5-(5,6-二羟基-3a,4,5,6,7,7a-六氢-4,7-甲桥苯并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯(220mg)。经由手性SFC将化合物分离成两种同手性异构体448-2及448-3。制备型色谱条件:仪器:Berger MG II(CTR-L409-PSFC1)柱:Chiralpak IF,21×250mm,5微米,移动相:30%MeOH/70%CO_2,流动条件:45mL/min,150巴,40℃,检测器波长:220nm。注射详情:1.0mL～200mg/3mL于MeOH-

CAN中。分析型色谱条件:仪器:Shimadzu Nexera SFC(CTR-L410-SFC3)柱:Chiralpak IF,4.6×100mm,3微米。移动相:30%MeOH/70%CO_2。流动条件:2.0mL/min,150巴,40℃。检测器波长:220nm。注射详情:5μL～1mg/mL于MeOH中。将两种同手性异构体分离成448-2异构体-1>99%ee,RT=2.89min(84mg,49%产率)及448-3异构体-2>99%ee,RT=6.03min(78mg,46%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ8.07-8.04(m,1H),7.89-7.87(m,1H),7.05-7.00(m,1H),4.67-4.59(m,1H),3.96(s,3H),3.93(s,3H),3.91-3.83(m,1H),3.52-3.41(m,1H),2.64-2.58(m,1H),2.52-2.49(m,1H),1.89-1.82(m,1H),1.50-1.44(m,1H)。LCMS m/z=334.2$(M+H)^+$。

[0008] 制备中间体448-4。

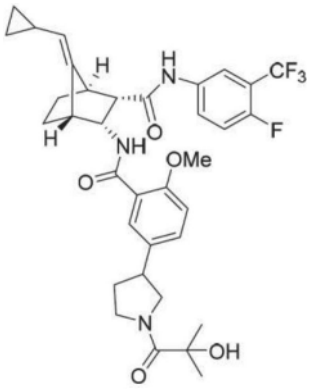


将5-(5,6-二羟基-3a,4,5,6,7,7a-六氢-4,7-甲桥苯并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯448-3(>99%ee)溶解于甲醇(3mL)中,且向溶液中添加LiOH(20mg,0.47mmol),随后添加水(2mL)。在室温下搅拌反应混合物14h,接着用水(25mL)淬灭。将有机物用EtOAc(2×25mL)萃取,干燥($MgSO_4$)且真空蒸发,得到5-(5,6-二羟基-3a,4,5,6,7,7a-六氢-4,7-甲桥苯并[d]异噁唑-3-基)-2-甲氧基苯甲酸448-4(63mg,84%产率)。LCMS m/z=320.3(M+H)。^{1}H NMR(500MHz,CD_3OD)δ8.17-8.12(m,1H),7.90(dd,J=8.7,2.3Hz,1H),7.23(d,J=8.9Hz,1H),4.81-4.61(m,1H),3.97(s,3H),3.92(m.1H),3.78-3.75(m,1H),3.71-3.58(m,1H),2.45(s,1H),2.35(s,1H),1.84(br d,J=11.1Hz,1H),1.36-1.15(m,1H)。

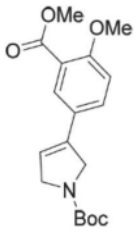
[0009] 实施例448.中间体448-4(17mg,0.050mmol)为使用针对实施例378所描述的得到(1R,2S,3R,4R,Z)-3-氨基-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺中间体166-2(15mg,0.050mmol)的通用程序,使用BOP(10mg,0.050mmol)试剂及Hunig碱(0.1mL)来制备。经由HPLC纯化分离呈固体的例子448(18mg,58%产率)。HPLC纯度:98.3%;RT=2.35min,[方法D]。LCMS m/z=670.3$(M+H)^+$。^{1}H NMR(500MHz,CD_3OD)δ8.41-8.36(m,1H),8.16(dd,J=6.6,2.4Hz,1H),7.91(dd,J=8.7,2.4Hz,1H),7.84-7.74(m,1H),7.32-7.22(m,2H),4.85-4.82(m,1H),4.79-4.70(m,1H),4.67-4.51(m,1H),4.14(s,3H),3.92(br d,J=6.9Hz,1H),3.76(d,J=5.6Hz,1H),3.65(d,J=8.1Hz,1H),3.56-3.42(m,1H),3.31-3.22(m,2H),3.21-3.06(m,2H),2.73(br d,J=4.3Hz,1H),2.45(s,1H),2.35(s,1H),2.06-1.97(m,1H),1.97-1.91(m,1H),1.83(br d,J=11.1Hz,1H),1.62-1.48(m,2H),1.38-1.21(m,1H),0.77(br d,J=4.4Hz,2H),0.37(br s,2H)。

[0010]

实施例449

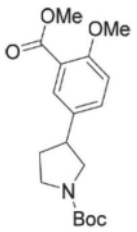


中间体449-1：



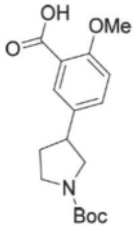
将含5-溴-2-甲氧基苯甲酸甲酯(2.0g,8.2mmol)及3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)-2,5-二氢-1H-吡咯1-甲酸叔丁酯(2.65g,8.98mmol)的二噁烷(55mL)/水(10mL)再次脱气5min,接着添加$PdCl_2$(dppf)-CH_2Cl_2加合物(0.666g,0.816mmol)及K_3PO_4(5.64g,24.5mmol),且再次使反应混合物脱气5min,接着在密封管中在100℃搅拌浆液4h。用EtOAc稀释反应混合物,过滤固体,用过量EtOAc洗涤且收集滤液且在减压下浓缩。通过硅胶色谱纯化残余物,得到呈淡棕色固体的3-(4-甲氧基-3-(甲氧基羰基)苯基)-2,5-二氢-1H-吡咯-1-甲酸叔丁酯(2.2g,6.60mmol,81％产率)化合物。MS(ES):m/z＝234.2[M+H-Boc]。

[0011] 中间体449-2



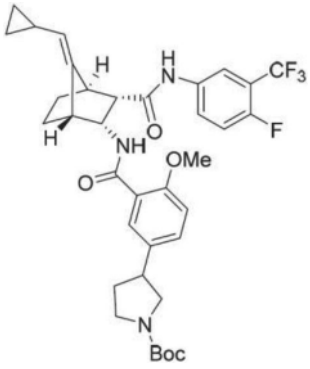
在室温下向449-1(2.2g,6.6mmol)于MeOH(100mL)中的溶液中添加Pd-C(1.756g,16.50mmol),且在氢气氛围下搅拌浆液12h。经由硅藻土过滤反应混合物,用过量甲醇及THF洗涤硅藻土,收集滤液且在减压下浓缩,得到呈淡棕色半固体的3-(4-甲氧基-3-(甲氧基羰基)苯基)吡咯烷-1-甲酸叔丁酯(1.7g,5.1mmol,77％产率)。MS(ES):m/z＝353.2[M+H_2O]。

[0012] 中间体449-3



将含LiOH(1.43g,59.6mmol)的水(5.0mL)添加至449-2(2.0g,6.0mmol)于甲醇(10mL)、THF(10mL)中的溶液中,在室温下搅拌所得反应混合物5h。真空蒸发挥发物且在高真空下干燥。用冰水(10mL)稀释残余物,接着使用0.1M HCl酸化。形成固体且过滤,用水洗涤且在真空下干燥,得到呈白色固体的5-(1-(叔丁氧基羰基)吡咯烷-3-基)-2-甲氧基苯甲酸(1.5g,4.7mmol,78%产率)化合物。MS(ES):m/z=320.2[M-H]。

[0013] 中间体449-4



在室温下将HATU(206mg,0.543mmol)及TEA(0.38mL,2.7mmol)添加至449-2(349mg,1.09mmol)及166-2(200mg,0.543mmol)于DMF(30mL)中的溶液中,搅拌反应混合物3h。在减压下移除挥发物且通过硅胶色谱纯化残余物,得到呈灰白色固体的3-(3-(((1R,2R,3R,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)吡咯烷-1-甲酸叔丁酯(190mg)。对固体进行SFC纯化:柱名称:Welk-01(R,R)(250*4.6)mm.5μ,助溶剂;20%小瓶N°;LA8助溶剂名称:0.2%氨/甲醇;注射量:30μl,流动速率:4ml/min,出口压力:100巴,温度:35℃,以分离非镜像异构体。

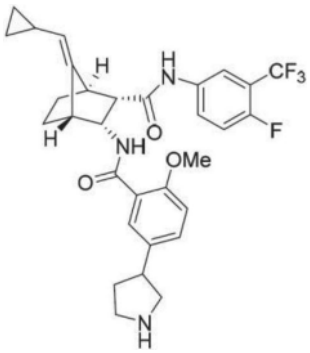
[0014] 在SFC纯化之后,收集洗脱份,在减压下浓缩且冻干,以产生3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)吡咯烷-1-甲酸叔丁酯。

[0015] 峰-1,449-4,(55mg,0.082mmol,14%产率),手性SFC RT-9.9min,^{1}H NMR(400MHz,DMSO-d6)δppm 10.50(s,1H),9.82(d,J=7.0Hz,1H),8.22(dd,J=2.5,6.0Hz,1H),7.82(d,J=2.5Hz,2H),7.48(t,J=10.0Hz,1H),7.43(dd,J=2.5,8.5Hz,1H),7.14(d,J=8.5Hz,1H),6.88(s,1H),4.69(d,J=10.0Hz,1H),3.97(s,3H),3.68(dd,J=7.5,10.0Hz,1H),3.49-3.36(m,5H),3.31-3.21(m,5H),3.20-3.05(m,4H),2.73-2.69(m,1H),2.19(s,3H),1.86(br d,J=10.5Hz,3H),1.46-1.33(m,20H),0.74(br t,J=8.3Hz,2H),0.35(br d,J=2.5Hz,2H);LCMS:RT=1.565min,MS(ES):m/z=616.4[M+H-tBu]方法B;呈白色固体的3-(3-(((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)吡咯烷-1-甲酸叔丁酯(55mg,0.082mmol,15%产率)。

[0016] 峰-2,(60mg,0.089mmol,16%产率),手性SFCRT-10.98min,^{1}H NMR(400MHz,DMSO-d6)δppm 10.49(s,1H),9.81(d,J=7.0Hz,1H),8.22(dd,J=2.5,6.5Hz,1H),7.82(d,J=2.5Hz,1H),7.76(br s,1H),7.48(t,J=9.8Hz,1H),7.42(dd,J=2.5,8.5Hz,1H),7.13(d,J=8.5Hz,1H),4.68(d,J=9.5Hz,1H),4.44(br s,1H),3.97(s,3H),3.67(dd,J=7.5,10.0Hz,1H),3.49-3.34(m,2H),3.29-3.06(m,4H),2.72-2.67(m,1H),2.56-2.52(m,2H),

2.18(s,2H),1.86(br t,J＝9.3Hz,2H),1.76(br s,1H),1.50(br d,J＝4.5Hz,1H),1.45-1.33(m,17H),0.74(br t,J＝9.0Hz,2H),0.34(br s,2H);LCMS:RT＝1.716min,MS(ES):m/z＝616.3[M+H-tBu]方法B。

[0017] 中间体449-5:

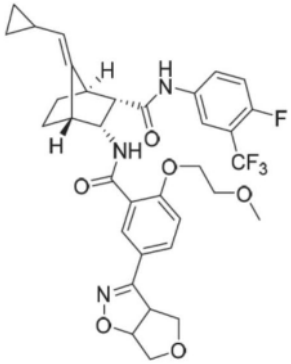


在0℃将TFA(0.16mL,2.0mmol)添加至449-4(55mg,0.082mmol)于DCM(5.0mL)中的溶液中,随后在室温下搅拌反应混合物2h。在减压下移除挥发物且在真空下干燥残余物,得到呈淡棕色半固体的(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(吡咯烷-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(35mg),其不经进一步纯化即用于下一步骤。MS(ES):m/z＝572.2[M+H]。

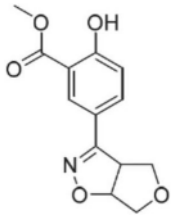
[0018] 实施例449

在室温下将HATU(13mg,0.035mmol)、DIPEA(0.06mL,0.04mmol)添加至含449-5(20mg,0.035mmol)及2-羟基-2-甲基丙酸(3.6mg,0.035mmol)的DMF(2.0mL)中。将反应混合物搅拌15h且通过制备型反相HPLC纯化,得到呈白色固体的(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(1-(2-羟基-2-甲基丙酰基)吡咯烷-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(13mg,49%)。^{1}H NMR(400MHz,DMSO-d6)δ ppm 10.48(s,1H),9.83(dd,J＝3.3,6.7Hz,1H),8.25-8.17(m,1H),7.85(br s,1H),7.77(td,J＝3.6,8.7Hz,1H),7.48(t,J＝9.9Hz,1H),7.43(dd,J＝2.2,8.6Hz,1H),7.14(dd,J＝1.8,7.9Hz,1H),5.19-5.12(m,1H),4.68(d,J＝9.5Hz,1H),4.48-4.40(m,1H),4.27(br d,J＝0.7Hz,1H),4.08(q,J＝5.5Hz,1H),3.97(s,4H),3.78-3.65(m,1H),3.58-3.47(m,1H),3.24-3.06(m,4H),2.74-2.68(m,1H),2.13(br d,J＝0.7Hz,1H),1.93-1.72(m,3H),1.53-1.36(m,3H),1.32-1.26(m,7H),0.80-0.65(m,2H),0.35(dd,J＝1.8,4.8Hz,2H)。LCMS:RT＝2.465min,MS(ES):m/z＝658.3[M+H$^+$]方法B。

[0019] 实施例452

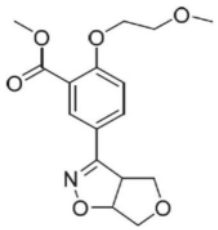


中间体452-1



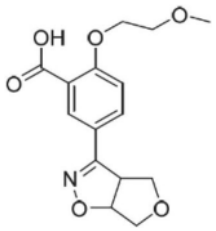
452-1(0.13g,0.49mmol,49%产率)为以与实施例416类似的方式,以5-甲酰基-2-甲氧基苯甲酸甲酯取代5-甲酰基-2-羟基苯甲酸甲酯来制备。^{1}H NMR(400MHz,$CDCl_3$)δ10.98(s,1H),8.04(d,J=2.2Hz,1H),7.82(dd,J=8.8,2.2Hz,1H),7.04(d,J=8.8Hz,1H),5.38(dd,J=9.1,3.9Hz,1H),4.36-4.30(m,1H),4.30-4.25(m,1H),4.14(dd,J=9.2,1.3Hz,1H),3.99(s,3H),3.89(dd,J=9.4,6.7Hz,1H),3.79(dd,J=10.8,3.7Hz,1H)。LCMS(ESI)m/z:264$(M+H)^+$。

[0020] 中间体452-2



向含452-1(0.1g,0.4mmol)的DMF(2mL)中添加1-氯-2-甲氧基乙烷(72mg,0.80mmol)、K_2CO_3(0.16g,1.1mmol)、KI(63mg,0.38mmol)且在60℃加热反应混合物24h。用水(10mL)及EtOAc(20mL)分配反应混合物。用EtOAc(2×20mL)萃取水层,将合并的有机层用盐水(15mL)洗涤且干燥($MgSO_4$),过滤且在减压下浓缩。通过正相硅胶色谱纯化残余物,得到呈澄清油状物的452-2(62mg,0.20mmol,51%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.99(d,J=2.3Hz,1H),7.87(dd,J=8.8,2.4Hz,1H),7.07(d,J=8.7Hz,1H),5.39(dd,J=9.2,3.9Hz,1H),4.37-4.32(m,1H),4.32-4.28(m,1H),4.28-4.24(m,2H),4.16(dd,J=9.4,1.3Hz,1H),3.93-3.92(m,3H),3.91-3.87(m,1H),3.84(dd,J=5.3,4.3Hz,2H),3.80(dd,J=10.8,3.9Hz,1H),3.50(s,3H)。LCMS(ESI)m/z:322$(M+H)^+$。

[0021] 中间体452-3

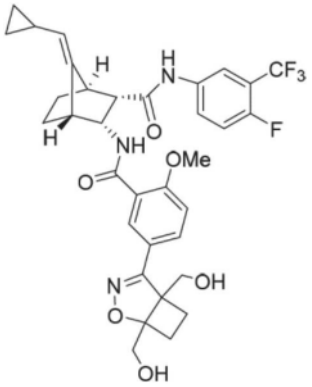


452-3(41mg,0.13mmol,72%产率)为通过如378-3中所描述水解452-2来制备。^{1}H NMR(500MHz,$CDCl_3$)δ8.23-8.07(m,2H),7.20-7.07(m,1H),5.42(dd,J=9.2,3.9Hz,1H),5.32(s,1H),4.46-4.39(m,2H),4.36-4.30(m,2H),4.14(d,J=9.5Hz,1H),3.93-3.88(m,1H),3.85-3.82(m,2H),3.78(dd,J=10.9,3.9Hz,1H),3.49(s,3H)。

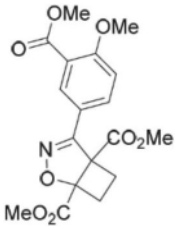
[0022] 实施例452.异构体混合物为通过如实施例378中所描述的BOP偶合,以中间体378-3及环丁基降冰片烷基中间体369-1取代环丙基降冰片烷基中间体166-2及中间体452-3来

制备。使用手性SFC色谱分离异构混合物。制备型色谱条件:仪器:Waters 100Prep SFC柱:Chiral OD,30×250mm,5微米,移动相:25%MeOH/75%CO_2(具有0.1%DEA),流动条件:100mL/min,检测器波长:220nm:分析方法:仪器:ShimadzuNexera SFC,柱Chiral OD,4.6×100mm,5微米,移动相:25%MeOH/75%CO_2(具有0.1%DEA),流动条件:2mL/min,检测器波长:220nm,得到手性峰-1,实施例452(9.3mg,14μmol,23%产率),RT=2.92min.,>95%de及峰-2(9.3mg,14μmol,23%产率),RT=3.6min,>95%de。对于实施例452:^{1}H NMR(500MHz,DMSO-d6)δ10.49(s,1H),9.60(br d,J=7.9Hz,1H),8.37-8.10(m,2H),7.86-7.68(m,2H),7.47(t,J=9.9Hz,1H),7.32(d,J=8.9Hz,1H),5.35(dd,J=9.2,3.7Hz,1H),4.71(d,J=9.5Hz,1H),4.61-4.47(m,2H),4.43(br d,J=4.0Hz,2H),4.11(d,J=10.7Hz,1H),4.07-3.98(m,1H),3.95-3.86(m,1H),3.83-3.74(m,1H),3.66(dd,J=10.7,3.4Hz,1H),3.28(s,1H),3.21-3.13(m,1H),3.09-2.99(m,1H),2.74(br s,1H),2.52(br s,3H),2.03-1.84(m,2H),1.63-1.51(m,1H),1.48-1.31(m,1H),0.89-0.67(m,2H),0.46-0.27(m,2H)。LCMS(ESI)m/z:658.15$(M+H)^+$。HPLC纯度100%,保留时间2.42min。[方法C]

[0023] 实施例461

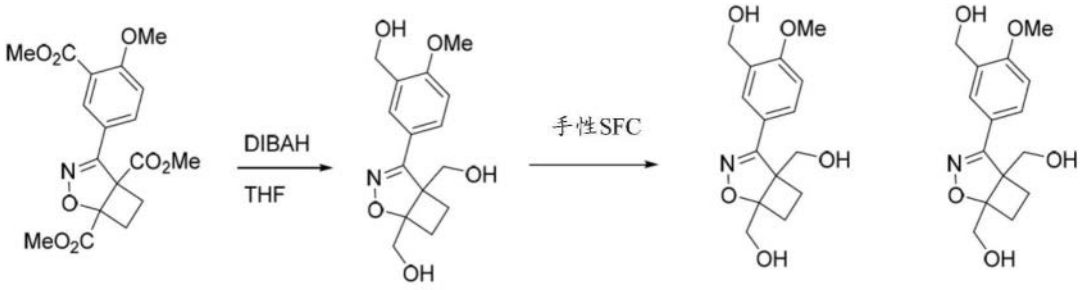


制备非镜像异构中间体461-1。



非镜像异构中间体461-1(200mg,80%)为以如针对实施例378所描述的类似方式,通过使环丁-1-烯-1,2-二甲酸二甲酯与(Z)-5-(氯(羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯发生环化加成来制备。LCMSm/z=378.2(M+H)。^{1}H NMR(500MHz,$CDCl_3$)δ8.12(d,J=2.4Hz,1H),7.75(dd,J=8.9,2.4Hz,1H),7.00(d,J=8.9Hz,1H),3.96(s,3H),3.92(s,3H),3.87(s,3H),3.68(s,3H),3.21-3.09(m,1H),2.79-2.67(m,1H),2.62-2.52(m,2H)。

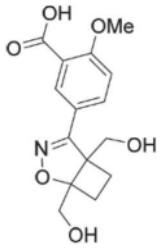
[0024] 制备同手性中间体461-3及461-4。



461-1 非镜像异构混合物 | 461-2 非镜像异构混合物 | 461-3 同手性峰-1 | 461-4 同手性峰-2

将非镜像异构中间体461-1(112mg,0.29mmol)溶解于THF(10mL)中且向其中添加DIBAH(1M,2.08mL,2.08mmol)溶液。在室温下搅拌反应混合物14h且随后用稀释HCl(5mL)淬灭,接着用EtOAc(2×25mL)萃取有机物质。将合并的有机层干燥($MgSO_4$),过滤且在减压下浓缩,得到呈油状物的非镜像异构体(4-(3-(羟基甲基)-4-甲氧基苯基)-2-氧杂-3-氮杂双环[3.2.0]庚-3-烯-1,5-二基)二甲醇461-2(100mg,100%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.69-7.49(m,2H),6.92-6.86(m,1H),4.73-4.60(m,2H),3.90(s,3H),3.88(s,3H),3.74-3.65(m,1H),3.05-2.82(m,1H),2.54-2.32(m,2H),2.19-1.97(m,2H),1.95-1.37(m,1H),1.33-0.84(m,1H)。LCMS m/z=294.2$(M+H)^+$。经由手性SFC条件以手性方式分离中间体461-2,得到同手性中间体461-3(峰-1)及461-4(峰-2)。制备型色谱条件:仪器:Berger MG II柱:Chiralpak IC,21×250mm,5微米,移动相:30%甲醇/70%CO_2,流动条件:45mL/min,150巴,40℃。检测器波长:220nm,注射详情:0.5mL~55mg/mL于甲醇中。分析型色谱条件:仪器:Shimadzu Nexera SFC柱:Chiralpak IC,4.6×100mm,3微米,移动相:30%甲醇/70%CO_2,流动条件:2.0mL/min,150巴,40℃。检测器波长:220nm,注射详情:5μL~1mg/mL于甲醇中。461-3同手性峰-1(57mg,15%产率,>99%ee,RT=2.98min)的分析资料;^{1}H NMR(500MHz,$CDCl_3$)δ7.64(s,1H),7.60(d,J=8.4Hz,1H),6.91(d,J=8.7Hz,1H),4.69(br s,2H),4.05(m,2H),3.91(s,3H),3.81(br s,1H),3.50(s,1H),3.33(br s,1H),2.56(br s,1H),2.50-2.39(m,2H),2.20-1.99(m,2H),1.70(br s,1)。461-4同手性峰-2(60mg,60%产率,>99%ee,RT=5.72min)的分析资料。^{1}H NMR(500MHz,$CDCl_3$)δ7.64(s,1H),7.60(d,J=8.4Hz,1H),6.91(d,J=8.5Hz,1H),4.69(d,J=6.3Hz,2H),4.08(m,2H),3.91(s,3H),3.84-3.76(m,1H),3.50(d,J=4.7Hz,2H),3.33(br s,1H),2.56(br t,J=6.5Hz,1H),2.50-2.39(m,2H),2.20-1.99(m,2H),1.70(s,1H)。

[0025] 制备同手性异构体-1中间体461-4。

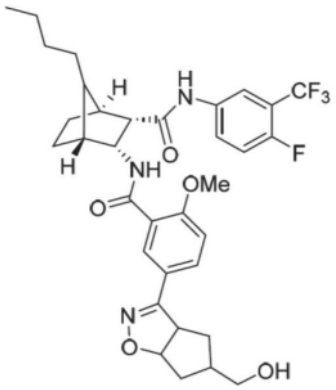


将同手性异构体-1中间体461-2(4-(3-(羟基甲基)-4-甲氧基苯基)-2-氧杂-3-氮杂双环[3.2.0]庚-3-烯-1,5-二基)二甲醇(57mg,0.19mmol)溶解于无水DCM(10mL)中且向溶液中添加经活化MnO_2(847mg,9.72mmol)。在室温下搅拌反应混合物14h。过滤反应混合物

且真空浓缩成油状物。将油状物再溶解于tBuOH(5mL)中且向溶液中添加$NaClO_2$(37mg,0.41mmol),随后添加NaH_2PO_4水溶液(5mL)以使pH约3且添加2-甲基丁烯(10mmol)。在室温下搅拌反应混合物6h,接着用水(100mL)淬灭且用EtOAc(2×25mL)萃取。将合并的有机部分干燥($MgSO_4$),过滤且真空蒸发,得到呈油状物的异构体-1中间体461-4(50mg,55%产率)。^{1}H NMR(500MHz,CD_3OD)δ8.15(d,J=2.3Hz,1H),7.88(dd,J=8.8,2.4Hz,1H),7.17(d,J=8.9Hz,1H),4.79-4.58(m,4H),3.97(s,3H),3.95-3.88(m,2H),3.51-3.34(m,2H),2.63-1.96(m,2H)。LCMS m/z=308.2$(M+H)^+$。

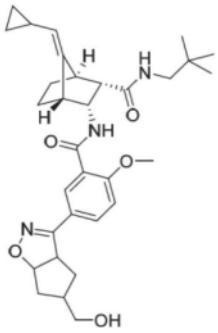
[0026] 实施例461.如针对实施例378所描述,使用BOP(6mg,0.02mmol)试剂及Hunig碱(0.1mL)使同手性异构体-1中间体461-4(4.3mg,0.02mmol)与中间体166-2(5.2mg,0.02mmol)偶合。在通过反相HPLC纯化之后,以固体形式分离实施例461(4.3mg,45%产率)。HPLC纯度:100%;RT=2.43min[方法D]。LCMS m/z=658.33$(M+H)^+$。^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.93(br d,J=7.0Hz,1H),8.30-8.21(m,2H),7.85-7.75(m,2H),7.50(br t,J=9.8Hz,1H),7.27(br d,J=8.9Hz,1H),5.38(br t,J=5.3Hz,1H),4.85-4.67(m,2H),4.45(br s,1H),4.06(s,3H),3.92-3.78(m,3H),3.71(br dd,J=11.9,7.0Hz,1H),3.38(br s,1H),3.17(br d,J=7.3Hz,1H),3.12(br s,1H),2.74(br s,1H),2.33-2.19(m,1H),2.15(br s,3H),2.09(s,1H),1.93(s,1H),1.89-1.68(m,2H),1.52(br d,J=8.5Hz,1H),1.42(br s,2H),0.87-0.67(m,2H),0.36(br s,2H)

[0027] 实施例467

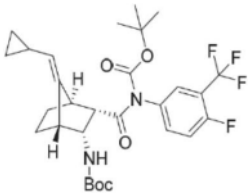


化合物467为如针对实施例378所描述,通过用催化性Pd/C(10%)还原166-2(6mg,0.02mmol),随后使所得(1S,2S,3R,4R)-3-氨基-7-丁基-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺与429-8(4.72mg,0.0200mmol)及BOP(7.16g,0.0200mmol)以及Hunig碱(0.1mL)在DMF中偶合来制备。经由HPLC纯化来纯化残余物,以产生呈固体的467(0.7mg,7%产率)。HPLC纯度:100%;RT=2.72min[方法C]。LCMS m/z=645.94(M+H)+。^{1}H NMR(500MHz,DMSO-d_6)δ10.64(s,1H),8.37(br d,J=7.3Hz,1H),8.13(br d,J=4.0Hz,1H),7.94(d,J=2.4Hz,1H),7.87(br s,1H),7.77(br d,J=8.9Hz,1H),7.50(br t,J=9.6Hz,1H),7.25(d,J=8.9Hz,1H),5.23-5.05(m,1H),4.84(br s,1H),4.23(br t,J=9.2Hz,1H),3.93(s,3H),3.35(br s,1H),2.77-2.54(m,2H),2.43-2.27(m,2H),2.17-1.95(m,2H),1.95-1.86(m,1H),1.80(br d,J=12.8Hz,1H),1.74-1.63(m,3H),1.58(br d,J=8.2Hz,1H),1.54-1.44(m,2H),1.36(br d,J=6.7Hz,2H),1.30-1.13(m,4H),0.94-0.72(m,3H)

[0028] 实施例453

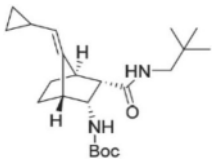


中间体453-1：



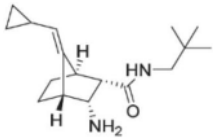
向(1R,2S,3R,4R,Z)-3-氨基-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺IV-2a(33mg,0.090mmol)于DCM(0.9mL)中的溶液中添加Boc_2O(0.10mL,0.45mmol)、Hunig碱(78μl,0.45mrnol)及DMAP(5.5mg,0.045mmol)。搅拌反应混合物14h,接着在减压下浓缩且经由硅胶色谱纯化,得到((1R,2S,3R,4R,Z)-3-((叔丁氧基羰基)氨基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-羰基)(4-氟-3-(三氟甲基)苯基)氨基甲酸叔丁酯中间体453-1(43mg,0.076mmol,84％产率)。LC-MS RT:1.37min;MS(ESI)m/z 591 $(M+Na)^+$;方法A。

[0029] 中间体453-2：



向((1R,2S,3R,4R,Z)-3-((叔丁氧基羰基)氨基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-羰基)(4-氟-3-(三氟甲基)苯基)氨基甲酸叔丁酯中间体453-1(43mg,0.076mmol)的溶液中添加2,2-二甲基丙烷-1-胺(26.4mg,0.302mmol)。搅拌反应混合物两天,随后真空浓缩且经由硅胶色谱纯化,得到((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-(新戊基胺甲酰基)双环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯中间体453-2(20mg,0.053mmol,70％产率)。LC-MS RT:1.19min;MS(ESI)m/z 377$(M+H)^+$;方法A。

[0030] 中间体453-3：

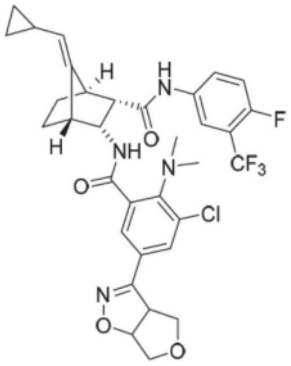


将((1R,2R,3S,4R,Z)-7-(环丙基亚甲基)-3-(新戊基胺甲酰基)双环[2.2.1]庚烷-2-基)氨基甲酸叔丁酯(20mg,0.053mmol)453-2溶解于THF(0.4mL)中。添加HCl(4M于二噁烷中)(0.13mL,0.53mmol)。在1小时之后,再添加0.3mL 4M HCl/二噁烷。在2小时之后,真空浓缩反应混合物,随后与DCM/己烷共沸,得到(1R,2S,3R,4R,Z)-3-氨基-7-(环丙基亚甲基)-N-新戊基双环[2.2.1]庚烷-2-甲酰胺HCl中间体453-3(20mg,0.064mmol,120％产率)。

LC-MS RT:0.80min;MS(ESI)m/z 277(M+H)$^+$;方法A。

[0031] 实施例453:向429-8(7.87mg,0.0270mmol)及中间体453-3(8.45mg,0.0270mmol)于DMF(0.4mL)中的溶液中添加BOP(13mg,0.030mmol)及Hunig碱(0.024mL,0.14mmol)。4小时之后,用MeOH稀释反应混合物,经由针筒过滤器过滤且经由制备型反相HPLC纯化,得到实施例453(7.4mg,49%产率)。^{1}H NMR(500MHz,DMSO-d_6)δ9.96(d,J=6.8Hz,1H),8.16(d,J=2.3Hz,1H),7.96(br t,J=6.2Hz,1H),7.77(dd,J=8.7,2.3Hz,1H),7.22(d,J=8.7Hz,1H),5.11(dd,J=8.7,5.2Hz,1H),4.62(d,J=9.5Hz,1H),4.53-4.48(m,1H),4.34-4.25(m,1H),4.19(br t,J=8.6Hz,1H),3.99(s,3H),3.06-2.97(m,3H),2.79(dd,J=13.0,5.7Hz,1H),2.02-1.40(m,10H),1.39-1.25(m,2H),0.81(s,9H),0.74-0.64(m,2H),0.36-0.25(m,2H)。LC-MS RT:2.23min;MS(ESI)m/z 550.1(M+H)$^+$;方法B。

[0032] 实施例475



中间体475-1:制备2-(二甲基氨基)-5-甲酰基苯甲酸甲酯:

向2-氟-5-甲基苯甲酸甲酯(3.00g,17.8mmol)于CCl_4(100mL)中的溶液中添加N-溴代丁二酰亚胺(6.99g,39.2mmol)及过氧化苯甲酰(0.475g,1.96mmol)。在回流下加热反应混合物14h。使反应混合物冷却至室温且通过过滤移除丁二酰亚胺。在减压下浓缩滤液,得到黄色液体,将其添加至二甲胺(40%水溶液)(90mL,711mmol)中,且将内容物缓慢加热至56℃持续15min,且接着排出热量。将深橙色溶液倒入DCM(2×75mL)中且分离各层。浓缩有机层且使用硅胶色谱来纯化,得到中间体465-1(2.2g,56%产率)。MS(ESI)m/z:208.2(M+H)。

[0033] 中间体475-2:制备(E)-3-氯-2-(二甲基氨基)-5-(羟基亚氨基)甲基)苯甲酸甲酯:

向中间体475-1(2200mg,10.62mmol)于DCM(25mL)中的溶液中添加TEA(1.48mL,10.6mmol)。随后向此溶液中添加羟胺盐酸盐(885mg,12.7mmol)且在室温下搅拌反应混合物过夜。随后将反应混合物浓缩成固体且溶解于EtOAc中且用水洗涤。接着将有机层经$MgSO_4$干燥且在真空下浓缩,得到中间体475-2(2.1g,73%产率)。MS(ESI)m/z:257.1(M+H)。

[0034] 中间体475-3:制备(Z)-3-氯-5-(氯(羟基亚氨基)甲基)-2-(二甲基氨基)苯甲酸甲酯:向含中间体475-2(770mg,3.00mmol)的DMF(15mL)中添加N-氯代丁二酰亚胺(441mg,3.30mmol)。在用水淬灭反应混合物之后,通过过滤收集灰白色固体,将其真空干燥,得到中间体475-3(480mg,52%产率)。MS(ESI)m/z:291.0(M+H)。

[0035] 475-4:制备3-氯-2-(二甲基氨基)-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酸甲酯:向含中间体475-3(1.13g,3.88mmol)及2,5-二氢呋喃(2.72g,38.8mmol)的

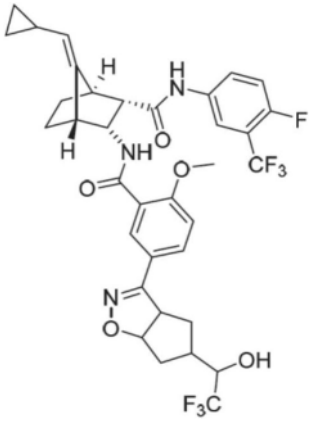
DCM(12mL)中添加TEA(1.62mL,11.6mmol)。在室温下搅拌反应混合物14h,在真空下浓缩,且使用硅胶色谱纯化残余物,得到中间体475-4(440mg,35%产率)。MS(ESI)m/z:325.2(M+H)。

[0036] 475-5:制备3-氯-2-(二甲基氨基)-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酸:

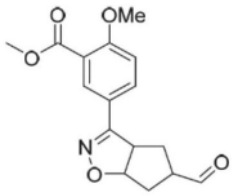
向中间体475-4(100mg,0.308mmol)于THF(3mL)及水(1.000mL)中的溶液中添加LiOH(0.462mL,0.924mmol)且在室温下搅拌反应混合物2h。在真空下浓缩反应混合物且不经进一步操作即用于下一步骤中。MS(ESI)m/z:311.1(M+H)。

[0037] 实施例475:(1R,2S,3R,4R,Z)-3-(3-氯-2-(二甲基氨基)-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)-N-(4-氟-3-(三氟甲基)苯基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺475为使用针对378所描述的通用程序,通过使用环丙基降冰片烷基中间体166-2(75mg,0.15mmol)及中间体475-5来制备,得到实施例475(经由反相HPLC的第一洗脱立体异构体,55mg,17%产率)。^{1}H NMR(500MHz,DMSO-d_6)δ10.45(br d,J=5.2Hz,1H),9.88(br d,J=7.3Hz,1H),8.12(br d,J=4.6Hz,1H),7.87(s,1H),7.85-7.80(m,1H),7.77(br d,J=4.3Hz,2H),7.45(br t,J=9.8Hz,1H),5.42-5.29(m,1H),4.67(br d,J=9.5Hz,1H),4.55-4.37(m,2H),4.09(br dd,J=10.8,5.0Hz,1H),3.91(br d,J=9.8Hz,1H),3.70-3.57(m,2H),3.15(br d,J=11.0Hz,1H),3.07(br s,1H),2.82(s,6H),2.72(br s,1H),1.92(br d,J=7.3Hz,2H),1.60-1.47(m,1H),1.42(br d,J=18.3Hz,2H),0.82-0.65(m,2H),0.34(br s,2H)。MS(ESI)m/z=661.0(M+H)。HPLC纯度:99%;保留时间:2.96min;方法B。

[0038] 实施例489及530



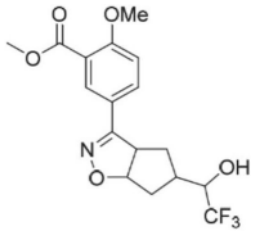
中间体489-1:



将戴斯-马丁高碘烷(417mg,0.983mmol)添加至5-(5-(羟基甲基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯429-8(2.75grams、9.01mmol)于DCM(90mL)中的溶液。在3h之后,将反应溶液转移至分液漏斗中且依次用NH_4Cl溶液及盐水洗涤,经硫酸钠干燥,过滤且在减压下浓缩。通过硅胶色谱纯化残余物,得到呈白色固体的5-

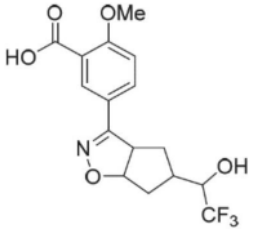
(5-甲酰基-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酸甲酯489-1(1.46公克,53%)。LC-MS RT＝0.97min;(M+H)＝304.1;方法A。

[0039] 中间体489-2:



在氮气氛围下,向489-1(100mg,0.330mmol)于THF(3.3mL)中的溶液中添加三甲基(三氟甲基)硅烷(188mg,1.32mmol)。将溶液冷却至0℃且添加TBAF(0.40mL,0.40mmol)。10min之后,使反应混合物升温至室温且搅拌14h。将反应物用MeOH淬灭,在减压下浓缩于Celite®上,且通过硅胶色谱纯化,得到2-甲氧基-5-(5-(2,2,2-三氟-1-羟基乙基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酸甲酯489-2(82.2mg,66.8%)。^{1}H NMR(500MHz,$CDCl_3$)δ8.05-8.01(m,1H),7.84(ddd,J＝8.8,4.7,2.3Hz,1H),7.04-6.98(m,1H),5.24-5.17(m,1H),4.08(t,J＝8.8Hz,1H),3.94(d,J＝2.4Hz,3H),3.89(d,J＝1.8Hz,3H),2.38-2.23(m,2H),2.10-1.96(m,2H),1.89-1.81(m,1H)。LC-MS RT＝0.834min;(M+H)＝374;方法C。

[0040] 中间体489-3:



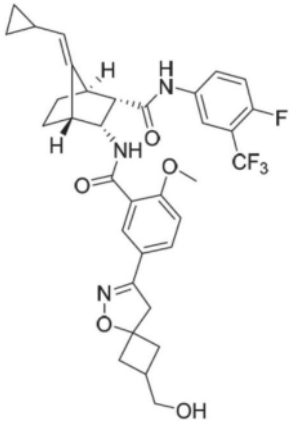
将LiOH单水合物(27.0mg,0.643mmol)于H_2O(0.5mL)中的溶液添加至含489-2(80mg,0.214mmol)的THF(2.1mL)/MeOH(2.1mL)。3h之后,在减压下浓缩反应混合物。将残余物悬浮于水中,用1.0MHCl溶液酸化,用EtOAc萃取,将萃取物用盐水洗涤,经硫酸钠干燥,过滤且在减压下浓缩。中间体489-3(71.7mg,93%)不经进一步操作即继续用于下一反应。LC-MS RT＝0.759min;(M+H)＝360.0;方法C。

[0041] 实施例489为通过使用DIEA(0.012mL,0.068mmol)及BOP(6.60mg,0.015mmol)使中间体489-3(3.95mg,0.014mmol)及溶解于无水DMF(2mL)中的中间体166-2(5mg,0.014mmol)偶合来制备。3h之后,将反应混合物过滤且通过反相制备型HPLC纯化,得到(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(2-甲氧基-5-(5-(2,2,2-三氟-1-羟基乙基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺实施例489(52mg,35%)作为第一洗脱峰(RT＝10.87min)。^{1}H NMR:(500MHz,$DMSO-d_6$)δ10.53-10.49(m,1H),9.93-9.89(m,1H),8.25-8.20(m,2H),7.83-7.76(m,2H),7.48(t,J＝9.8Hz,1H),7.27(d,J＝8.9Hz,1H),5.16-5.09(m,1H),4.69(d,J＝9.5Hz,1H),4.47-4.40(m,1H),4.28-4.21(m,1H),4.04(s,3H),3.99-3.92(m,1H),3.15(dd,J＝10.7,4.1Hz,1H),3.10(br s,1H),2.74-2.68(m,1H),2.06-1.96(m,2H),1.94-1.87(m,1H),1.86-1.72(m,4H),1.54-1.35(m,3H),0.78-0.69(m,2H),0.38-0.31(m,2H)。LC-MS RT＝2.379min;(M+

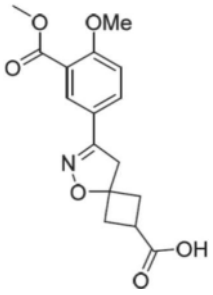
H)＝710.4;方法C。

[0042] 通过实施例489的反相制备型HPLC分离实施例530(25mg,17%)作为第二洗脱峰(11.52min)。^{1}H NMR:(500MHz,DMSO-d6)δ10.53(s,1H),9.92(d,J＝7.0Hz,1H),8.27-8.21(m,2H),7.84-7.77(m,2H),7.49(t,J＝9.8Hz,1H),7.28(d,J＝8.9Hz,1H),5.15(dd,J＝8.9,5.0Hz,1H),4.70(d,J＝9.5Hz,1H),4.45(ddd,J＝10.3,6.4,4.2Hz,1H),4.25(t,J＝8.9Hz,1H),4.05(s,3H),3.99-3.92(m,1H),3.17(dd,J＝10.8,4.2Hz,1H),3.11(t,J＝3.5Hz,1H),2.73(t,J＝4.1Hz,1H),2.04-1.89(m,3H),1.86-1.76(m,4H),1.54-1.47(m,1H),1.45-1.38(m,2H),0.79-0.70(m,2H),0.39-0.33(m,2H)。LC-MS RT＝2.382min;(M+H)＝710.4;方法C。

[0043] 实施例511



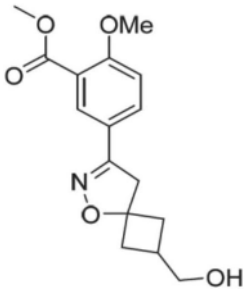
中间体511-1:



7-(4-甲氧基-3-(甲氧基羰基)苯基)-5-氧杂-6-氮杂螺[3.4]辛-6-烯-2-甲酸

511-1为如针对中间体378-2所描述,以烯丙醇取代3-亚甲基环丁烷-1-甲酸来制备,得到呈茶色固体的中间体511-1(1g,3mmol,200%产率),其不经纯化即继续用于下一步骤。LCMS(ESI)m/z:320(M+H)$^+$。

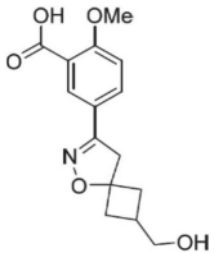
[0044] 中间体511-2:



向含中间体511-1(0.6g,2mmol)的THF(15mL)中添加$BH_3.Me_2S$(1.4mL,2.9mmol)。在

24h之后,再添加一当量的$BH_3.Me_2S$,且再过6h之后,用冰及1N HCl(10mL)淬灭反应混合物,且用乙酸乙酯(3×30mL)萃取水溶液。将合并的有机层用盐水(15mL)洗涤且干燥($MgSO_4$),过滤且在减压下浓缩。通过正相硅胶色谱,用己烷/EtOAc洗脱来纯化残余物,得到呈白色固体的中间体511-2(170mg,0.56mmol,27%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ8.05-7.93(m,1H),7.90-7.82(m,1H),7.06-6.97(m,1H),3.97-3.93(m,3H),3.90(s,3H),3.70(d,J=6.4Hz,2H),2.73-2.65(m,2H),2.62-2.54(m,1H),2.52-2.44(m,1H),2.40-2.31(m,1H),2.22-2.14(m,2H),1.87(t,J=7.2Hz,1H)。LCMS(ESI)m/z:306.1$(M+H)^+$。

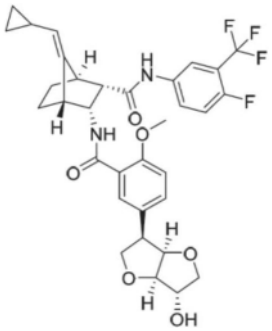
[0045] 中间体511-3:



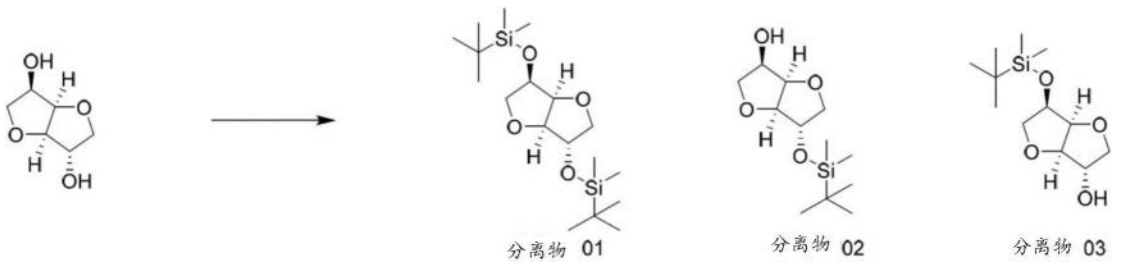
制备5-(2-(羟基甲基)-5-氧杂-6-氮杂螺[3.4]辛-6-烯-7-基)-2-甲氧基苯甲酸。中间体511-3(135mg,0.460mmol,83.0%产率)为通过如378-3中所描述水解511-2来制备。^{1}H NMR(500MHz,$CDCl_3$)δ8.22(dd,J=5.2,2.3Hz,1H),8.18-8.12(m,1H),7.14(dd,J=8.8,3.6Hz,1H),4.15(d,J=1.8Hz,3H),3.73(d,J=6.3Hz,2H),3.48(s,1H),3.42(s,1H),2.55-2.42(m,1H),2.43-2.33(m,3H),2.27-2.15(m,3H)。LCMS(ESI)m/z:291.2$(M+H)^+$。

[0046] 实施例511(7.0mg,11μmol,40%产率)为通过针对实施例452所描述的程序,以中间体452-3取代中间体511-3来制备。^{1}H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.91(br d,J=7.0Hz,1H),8.36-8.15(m,2H),7.86-7.73(m,2H),7.50(t,J=9.8Hz,1H),7.35-7.23(m,1H),4.71(d,J=9.5Hz,1H),4.53-4.36(m,1H),4.05(s,3H),3.52(s,1H),3.49-3.42(m,1H),3.18(br dd,J=10.7,3.4Hz,1H),3.12(br s,1H),2.74(br s,1H),2.49-2.40(m,1H),2.38-2.31(m,1H),2.30-2.21(m,1H),2.15-2.09(m,2H),2.08(br s,1H),1.94-1.83(m,1H),1.83-1.73(m,1H),1.62-1.48(m,1H),1.47-1.33(m,2H),0.85-0.65(m,2H),0.37(br s,2H)。LCMS(ESI)m/z:642.91$(M+H)^+$。HPLC纯度100%,保留时间2.42min。[方法B]

[0047] 实施例536



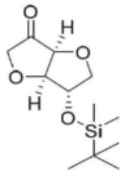
中间体536-1



向二脱水-D-葡萄糖醇(3.0g,21mmol)溶解于DCM(80mL)中的溶液中添加咪唑(2.8g,41mmol)且冷却至0℃。向此混合物中添加TBSCl(3.9g,26mmol)且使反应混合物升温至室温持续14h。用水洗涤反应混合物且在减压下浓缩有机部分,接着通过硅胶色谱,利用直列光散射检测来纯化,得到中间体536-1、分离物02、(3R,3aR,6S,6aS)-6-((叔丁基二甲基硅基)氧基)六氢呋喃并[3,2-b]呋喃-3-醇(1.8g,7.0mmol,34%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ4.70-4.58(m,1H),4.39-4.23(m,3H),3.97-3.82(m,3H),3.55(dd,J=9.4,6.1Hz,1H),2.69(d,J=7.7Hz,1H),0.97-0.84(m,9H),0.13(d,J=2.0Hz,6H)

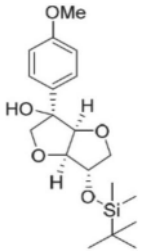
[0048] 峰3,(3S,3aR,6R,6aS)-6-((叔丁基二甲基硅基)氧基)六氢呋喃并[3,2-b]呋喃-3-醇(0.92g,3.5mmol,17%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ4.56(t,J=4.7Hz,1H),4.41(d,J=4.4Hz,1H),4.37-4.29(m,2H),4.04-3.96(m,1H),3.95-3.88(m,1H),3.80(dd,J=8.6,5.9Hz,1H),3.57(dd,J=8.8,6.8Hz,1H),1.83(d,J=5.3Hz,1H),0.99-0.87(m,9H),0.15(d,J=5.7Hz,6H)。

[0049] 中间体536-2



向536-1(1.9g,7.1mmol)溶解于DCM(24mL)中的溶液中添加戴斯-马丁高碘烷(6.1g,14mmol)且搅拌反应混合物14h。使反应混合物分配于DCM与pH 7.4缓冲水溶液之间,且用DCM萃取。在减压下浓缩合并的有机部分,随后通过硅胶色谱,利用直列光散射检测来纯化,得到(3aS,6S,6aS)-6-((叔丁基二甲基硅基)氧基)四氢呋喃并[3,2-b]呋喃-3(2H)-酮(1.4g,5.4mmol,75%产率)。^{1}H NMR(500MHz,$CDCL_3$)δ4.63(d,J=4.0Hz,1H),4.46(d,J=3.2Hz,1H),4.31(d,J=4.0Hz,1H),4.12(d,J=17.4Hz,1H),4.02(dd,J=9.5,3.4Hz,1H),3.95-3.89(m,2H),0.94-0.88(m,9H),0.12(d,J=4.4Hz,6H)。

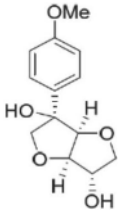
[0050] 中间体536-3



将536-2(1.4g,5.4mmol)溶解于THF(5.4mL)中的溶液冷却至0℃,添加(4-甲氧基苯基)溴化镁(11mL,5.4mmol)且搅拌反应混合物48h。将反应混合物用饱和NH_4Cl分配且用EtOAc萃取。在减压下浓缩合并的有机层,接着经由硅胶色谱纯化,得到(3R,3aS,6S,6aS)-

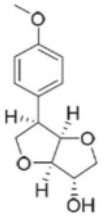
6-((叔丁基二甲基硅基)氧基)-3-(4-甲氧基苯基)六氢呋喃并[3,2-b]呋喃-3-醇(1.5g,4.1mmol,76%产率):^{1}H NMR(500MHz,$CDCl_3$)δ7.49(d,J=8.9Hz,2H),6.93(d,J=8.9Hz,2H),4.45-4.38(m,3H),4.12(d,J=9.3Hz,1H),4.05-4.00(m,1H),3.98-3.93(m,1H),3.83(s,3H),3.79(d,J=9.3Hz,1H),3.48(s,1H),0.91-0.85(m,9H),0.11(d,J=3.1Hz,6H)。

[0051] 中间体536-4



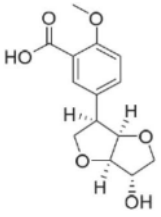
向536-3(0.50g,1.4mmol)中添加1M TBAF/THF(1.4mL,1.4mmol)且搅拌反应混合物14h。将反应混合物用EtOAc稀释,且依次用水及盐水洗涤。将有机部分经Na_2SO_4干燥,过滤且在减压下浓缩,接着通过硅胶色谱纯化,得到(3R,3aS,6S,6aR)-3-(4-甲氧基苯基)六氢呋喃并[3,2-b]呋喃-3,6-二醇(0.23g,0.92mmol,67%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.53-7.43(m,2H),6.99-6.89(m,2H),4.55(d,J=4.1Hz,1H),4.52-4.45(m,2H),4.14-4.01(m,3H),3.88-3.78(m,4H),3.40(s,1H)。

[0052] 中间体536-5



向536-4(0.080g,0.32mmol)溶解于DCM(1mL)中的溶液中添加三乙基硅烷(0.15mL,0.95mmol)及TFA(1mL),且搅拌反应混合物14h。在减压下浓缩反应混合物,接着通过硅胶色谱纯化,得到(3S,3aR,6R,6aR)-6-(4-甲氧基苯基)六氢呋喃并[3,2-b]呋喃-3-醇(0.050g,0.21mmol,67%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.25(d,J=8.4Hz,2H),6.90(d,J=8.7Hz,2H),4.84(t,J=3.8Hz,1H),4.60(d,J=3.7Hz,1H),4.43-4.38(m,1H),4.23(t,J=8.1Hz,1H),4.02(dd,J=10.1,3.8Hz,1H),3.91-3.83(m,2H),3.82(s,3H),3.41(ddd,J=11.6,7.8,4.0Hz,1H)

[0053] 中间体536-6



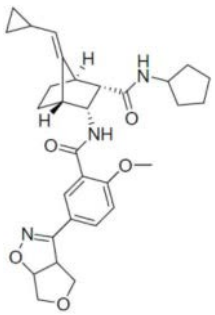
向536-5(0.050g,0.21mmol)溶解于丙酮(2.1mL)中的溶液中添加NBS(0.040g,0.22mmol),随后添加1滴1N HCl且搅拌14h。将反应混合物用EtOAc稀释且用1M pH 7.4磷酸盐缓冲液洗涤。在减压下浓缩有机部分,接着通过硅胶色谱纯化,得到(3S,3aR,6R,6aR)-6-(3-溴-4-甲氧基苯基)六氢呋喃并[3,2-b]呋喃-3-醇(定量),其不经进一步操作即用于下一步骤中。

[0054] 向(3S,3aR,6R,6aR)-6-(3-溴-4-甲氧基苯基)六氢呋喃并[3,2-b]呋喃-3-醇(0.090g,0.21mmol)溶解于DMF(2.6mL)中的浆液中添加$Pd(OAc)_2$(0.019g,0.085mmol)、1,3-双(二苯基膦基)丙烷(0.035g,0.085mmol)、TEA(0.12mL,0.85mmol)及水(0.29mL)。将反应混合物掩盖于CO(100psi)下且加热至100℃持续14h。将反应混合物用EtOAc稀释,用1N HCl分配且用EtOAc萃取。在减压下浓缩经合并的有机部分,接着不经进一步操作即以5-((3R,3aR,6S,6aR)-6-羟基六氢呋喃并[3,2-b]呋喃-3-基)-2-甲氧基苯甲酸(0.046g,0.16mmol,785产率,两个步骤)用于下一步骤中。

[0055] 实施例536

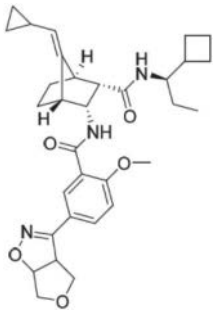
向166-2(0.060g,0.16mmol)溶解于ACN(3.3mL)中的溶液中添加536-6(0.046g,0.16mmol)、DIEA(0.085mL,0.49mmol)及HATU(0.062g,0.16mmol)且搅拌反应混合物30min。将反应混合物用甲醇稀释且通过制备型反相HPLC纯化,得到(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-((3R,3aR,6S,6aR)-6-羟基六氢呋喃并[3,2-b]呋喃-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺(13mg,0.021mmol,13%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.53(s,1H),9.84(br d,J=7.0Hz,1H),8.24(br d,J=4.9Hz,1H),7.88(s,1H),7.83-7.71(m,1H),7.50(br t,J=9.5Hz,1H),7.43(br d,J=8.2Hz,1H),7.12(d,J=8.5Hz,1H),5.26(d,J=3.4Hz,1H),4.76-4.61(m,2H),4.52-4.39(m,2H),4.17-4.06(m,2H),3.99(s,3H),3.81(br dd,J=9.2,3.1Hz,1H),3.73-3.60(m,2H),3.17(br dd,J=10.8,4.1Hz,1H),3.10(br s,1H),2.73(br s,1H),1.91-1.84(m,1H),1.83-1.71(m,1H),1.51(br dd,J=8.2,4.6Hz,1H),1.47-1.31(m,2H),0.82-0.67(m,2H),0.37(br s,2H)。LC-MS RT:2.34min;MS(ESI)m/z 631.2$(M+H)^+$;方法A。

[0056] 实施例565

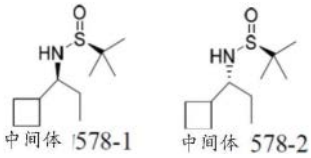


向中间体447-1(20mg,0.028mmol)于DCM(0.5mL)中的溶液中添加环戊胺(24mg,0.28mmol)。搅拌反应混合物14h,随后在减压下浓缩,溶解于MeOH中,且经由针筒过滤器过滤。经由制备型反相HPLC纯化残余物,得到实施例565(12.2mg,84%)。^{1}H NMR(400MHz,$DMSO-d_6$)δ10.01(d,J=6.8Hz,1H),8.15(d,J=2.4Hz,1H),8.02(d,J=7.6Hz,1H),7.79(dd,J=8.6,2.4Hz,1H),7.24(d,J=8.7Hz,1H),5.34(dd,J=9.6,3.2Hz,1H),4.61(d,J=9.7Hz,1H),4.50(dd,J=8.3,6.6Hz,1H),4.34-4.22(m,1H),4.09(d,J=10.8Hz,1H),4.02(s,4H),3.90(d,J=9.3Hz,1H),3.81-3.72(m,1H),3.66(dd,J=10.6,3.9Hz,1H),3.09-3.01(m,1H),2.88(dd,J=11.1,4.4Hz,1H),1.88-1.70(m,4H),1.65-1.54(m,2H),1.53-1.40(m,3H),1.39-1.26(m,4H),0.76-0.64(m,2H),0.32(br d,J=3.5Hz,2H)。可能由于与溶剂峰重叠,一个质子在NMR中不可见。LC-MS RT:2.14min;MS(ESI)m/z 520.4$(M+H)^+$;方法B。

[0057] 实施例578



中间体578-1及578-2：

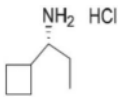


在干冰/丙酮浴中冷却(S,E)-N-(环丁基亚甲基)-2-甲基丙烷-2-亚磺酰胺(0.500g,2.67mmol)的溶液。逐滴添加溴化乙基镁(3.6M于2Me-THF中)(1.48mL,5.34mmol),且使反应混合物升温至室温持续14h。将反应混合物用饱和氯化铵溶液淬灭且用DCM萃取两次。在减压下浓缩有机层。经由硅胶色谱纯化残余物,得到533mg非镜像异构体的混合物。经由制备型SFC在以下条件下分离非镜像异构体:仪器:PIC Solution SFC Prep-200;柱:ChiralpakAD-H,21×250mm,5微米;移动相15%异丙醇-乙腈,85%CO_2;流动速率:45mL/min,150巴;柱温度:40℃。

[0058] (S)-N-((S)-1-环丁基丙基)-2-甲基丙烷-2-亚磺酰胺中间体578-1峰1RT:6min(70mg,0.32mmol,12%产率)。分析型SFC条件:仪器:ShimadzuNexera SFC;柱:Chiralpak AD-H,4.6×100mm,3微米;移动相10%异丙醇-乙腈,90%CO_2;流动速率:42mL/min,150巴;柱温度:40℃。RT:2.09min MS(ESI)m/z 218$(M+H)^+$

[0059] (S)-N-((R)-1-环丁基丙基)-2-甲基丙烷-2-亚磺酰胺中间体578-2峰2RT:8.7min。(350mg,1.61mmol,60.3%产率)。分析型SFC条件:仪器:ShimadzuNexera SFC;柱:ChiralpakAD-H,4.6×100mm,3微米;移动相10%异丙醇-乙腈,90%CO_2;流动速率:42mL/min,150巴;柱温度:40℃。RT:2.26min MS(ESI)m/z 218$(M+H)^+$。

[0060] 中间体578-3：



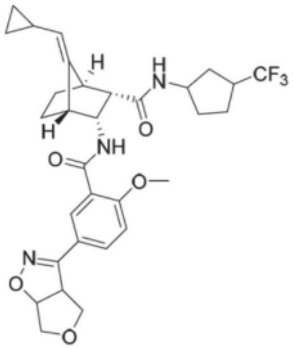
向578-2(350mg,1.61mmol)于MeOH(0.8mL)中的溶液中添加HCl(4M于二噁烷中)(0.81mL,3.2mmol)。45分钟之后,真空浓缩反应混合物。添加Et_2O,接着滤出固体且用Et_2O/己烷洗涤。收集固体且在真空下干燥,得到(R)-1-环丁基丙烷-1-胺578-3(175mg,1.55mmol,96%产率)。^1H NMR(400MHz,CD_3OD)δ3.06-2.97(m,1H),2.55-2.41(m,1H),2.17-2.04(m,2H),2.03-1.80(m,4H),1.73-1.59(m,1H),1.55-1.42(m,1H),0.99(t,J=7.6Hz,3H)。

[0061] 实施例578

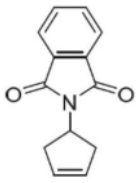
实施例578(4.8mg,49%)为遵循针对实施例378所给出的程序由578-3制备。^1H

NMR(500MHz,DMSO-d_6)δ10.04(d,J=6.8Hz,1H),8.15(d,J=2.4Hz,1H),7.78(dd,J=8.6,2.4Hz,1H),7.70(br d,J=9.1Hz,1H),7.23(d,J=8.8Hz,1H),5.33(dd,J=9.2,3.5Hz,1H),4.62(d,J=9.6Hz,1H),4.49(br t,J=7.9Hz,1H),4.33-4.24(m,1H),4.09(d,J=10.7Hz,1H),4.00(s,3H),3.92-3.87(m,1H),3.77(dd,J=9.2,6.7Hz,1H),3.71-3.59(m,2H),3.09-3.01(m,1H),2.98-2.88(m,1H),2.33-2.19(m,1H),1.95-1.60(m,8H),1.51-1.41(m,1H),1.40-1.25(m,3H),1.19-1.03(m,1H),0.82-0.62(m,5H),0.31(dd,J=4.5,2.2Hz,2H)。可能由于与溶剂峰重叠,一个质子在NMR中不可见。LC-MS RT:2.58min;MS(ESI)m/z 548.2(M+H)$^+$;方法B。

[0062] 实施例589及629:

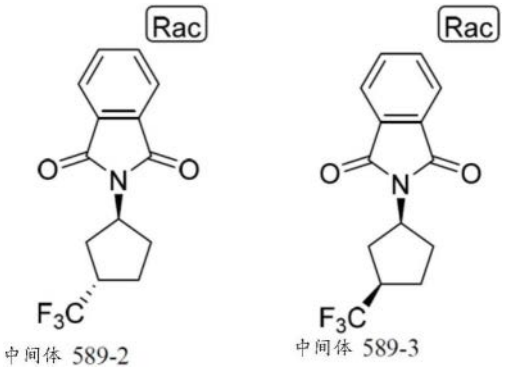


中间体589-1:



向异苯并呋喃-1,3-二酮(372mg,2.51mmol)及环戊-3-烯-1-胺HCl(300mg,2.51mmol)于甲苯(25mL)中的悬浮液中添加Hunig碱(0.44mL,2.5mmol)。将反应混合物加热至120℃。大约5.5小时之后,在减压下浓缩反应混合物。经由硅胶色谱纯化残余物,得到中间体589-1(369mg,69%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.88-7.80(m,2H),7.76-7.67(m,2H),5.81(s,2H),5.02(tt,J=9.6,7.4Hz,1H),2.93-2.82(m,2H),2.74-2.63(m,2H)。

[0063] 中间体589-2及589-3:



中间体 589-2　　中间体 589-3

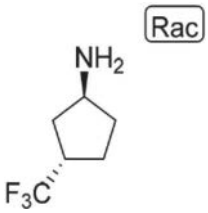
在四个压力小瓶中的每一者中,使三氟甲烷亚磺酸钠(234mg,1.50mmol)、9-均三甲苯基-10-甲基吖啶-10-鎓四氟硼酸盐(15mg,0.038mmol)及rac-2-((1R,3R)-3-(三氟甲基)环戊基)异吲哚啉-1,3-二酮(273mg,0.964mmol)悬浮于$CHCl_3$(3.4mL)及三氟乙醇

(0.38mL)中。使氮气鼓泡通过溶液,接着添加2-巯基苯甲酸甲酯(25mg,0.15mmol),且使氮气短暂鼓泡通过溶液。密封小瓶且用KSH 150B蓝色Kessil生长灯(34W,λ最大值461nm)照射48h。将反应混合物自光反应器移除且倒入.$NaHCO_3$饱和水溶液中。用DCM萃取反应混合物三次。将有机层经硫酸钠干燥且真空浓缩。经由硅胶色谱纯化残余物。

[0064] 第一洗脱峰为反式产物rac-2-((1R,3R)-3-(三氟甲基)环戊基)异吲哚啉-1,3-二酮中间体589-2(273mg,0.964mmol,32.1%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.84(dd,J=5.4,3.1Hz,2H),7.77-7.68(m,2H),4.88-4.72(m,1H),3.22-3.06(m,1H),2.37(ddd,J=14.0,9.6,6.9Hz,1H),2.29-2.05(m,4H),1.85-1.70(m,1H)

[0065] 第二洗脱峰为顺式产物中间体589-3rac-2-((1R,3S)-3-(三氟甲基)环戊基)异吲哚啉-1,3-二酮(38mg,0.134mmol,4.47%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.90-7.79(m,2H),7.77-7.65(m,2H),4.73-4.58(m,1H),2.83-2.59(m,1H),2.55-2.30(m,2H),2.22-2.08(m,2H),2.06-1.84(m,2H)。

[0066] 中间体589-4:



向中间体589-2于EtOH(1.8mL)中的悬浮液中添加水合肼(29μl,0.39mmol)。将反应混合物加热至75℃。大约30分钟之后,添加1mL EtOH。在2.5小时之后,使反应混合物冷却,用EtOH稀释且过滤。90μL含4M HCl的二噁烷添加至滤液中且真空浓缩溶液。所得残余物含有约0.25equiv的酞嗪酮。使残余物悬浮于EtOH中且过滤。在减压下浓缩滤液,得到中间体589-4rac-(1R,3R)-3-(三氟甲基)环戊-1-胺HCl(83mg,0.44mmol,120%产率),其含有约0.1当量的酞嗪酮。^{1}H NMR(400MHz,CD_3OD)δ3.74-3.65(m,1H),3.06-2.91(m,1H),2.29-2.09(m,3H),2.00-1.87(m,1H),1.85-1.64(m,2H)。

[0067] 实施例629及589:

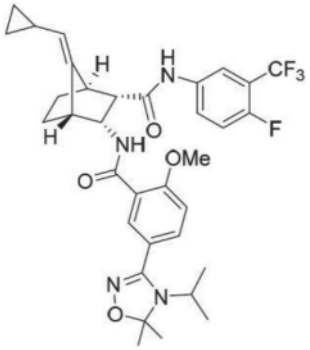
根据针对实施例565所给出的程序制备实施例629及589的非镜像异构混合物。非镜像异构体为经由制备型SFC在以下条件下分离:柱:ChiralOD,30×250mm,5微米;移动相:80%CO_2/20%IPA(具有0.1%DEA);流动速率:100mL/min,120巴;柱温度:40℃。

[0068] 第一洗脱峰(RT=13.5min)为实施例629(0.8mg,3.7%)。^{1}H NMR(500MHz,DMSO-d_6)δ9.95(br d,J=7.0Hz,1H),8.17(br d,J=2.1Hz,2H),7.79(br d,J=8.2Hz,1H),7.29-7.20(m,1H),5.34(br dd,J=9.2,3.1Hz,1H),4.62(br d,J=9.5Hz,1H),4.50(br t,J=7.8Hz,1H),4.35-4.25(m,1H),4.18-4.07(m,2H),4.02(s,3H),3.94-3.86(m,1H),3.82-3.72(m,1H),3.69-3.61(m,1H),3.05(br s,1H),2.98-2.82(m,2H),2.04-1.40(m,9H),1.39-1.26(m,2H),0.76-0.65(m,2H),0.32(br d,J=2.4Hz,2H)。可能由于与经抑制的水峰重叠,一个质子在NMR中不可见。LC-MS RT:2.30min;MS(ESI)m/z588.3$(M+H)^+$;方法B。

[0069] 第二洗脱峰(RT=16.0min)为实施例589(0.7mg,3.4%)。^{1}H NMR(500MHz,DMSO—d_6)δ9.95(br d,J=7.3Hz,1H),8.17(br d,J=8.5Hz,2H),7.79(br d,J=8.5Hz,1H),7.29-7.18(m,1H),5.40-5.27(m,1H),4.62(br d,J=9.5Hz,1H),4.54-4.45(m,1H),4.35-

4.25(m,1H),4.16-4.06(m,2H),4.02(s,3H),3.90(br d,J＝5.8Hz,1H),3.82-3.74(m,1H),3.66(br dd,J＝7.0,3.4Hz,1H),3.08-3.02(m,1H),2.98-2.83(m,2H),2.02-1.41(m,9H),1.40-1.26(m,2H),0.76-0.66(m,2H),0.32(br d,J＝3.7Hz,2H)。LC-MS RT:2.23min;MS(ESI)m/z 588.5$(M+H)^+$;方法B。

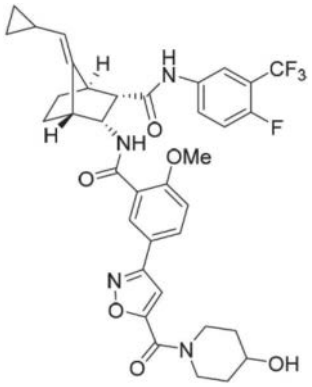
[0070] 实施例591



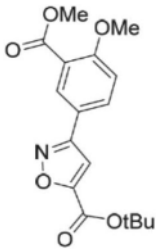
制备中间体591-1。5-(4-异丙基-5,5-二甲基-4,5-二氢-1,2,4-噁二唑-3-基)-2-甲氧基苯甲酸。通过添加nBuLi(2.7M,2.3mL,6.3mmol)至冷却至-78℃的二异丙胺(0.64g,6.33mmol)的THF(15mL)溶液来产生LDA。冷搅拌反应混合物0.5h且添加甲基-3-环戊烯甲酸盐(0.4g,3.0mmol),随后添加碘甲烷(0.2mL,3.0mmol)。将反应混合物低温搅拌4h且逐渐使其升温至室温持续14h。接着向反应混合物中添加(E)-5-(氯(羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯(1.05g,4.32mmol),随后添加TEA(1.4mL,9.1mmol)且在室温下搅拌所得溶液14h。通过添加稀释HCl(1N,10ml)淬灭反应物且用EtOAc(2×25mL)萃取。将合并的有机部分干燥($MgSO_4$),过滤且在减压下浓缩为油状物。经由硅胶色谱,使用己烷/EtOAc作为洗脱剂纯化该油状物,得到呈固体的5-(4-异丙基-5,5-二甲基-4,5-二氢-1,2,4-噁二唑-3-基)-2-甲氧基苯甲酸甲酯中间体副产物(75mg,8％产率)。将固体溶解于MeOH(2mL)中且向该溶液中添加LiOH(10mg.0.24mmol)及水(2mL)。在室温下搅拌反应混合物14h,接着在减压下浓缩且用稀释HCl(1N,5mL)淬灭。将溶液转移至分液漏斗中且用EtOAc(2×25mL)萃取,将有机部分干燥($MgSO_4$),过滤且在减压下浓缩为固体591-1(60mg,85％产率),其不经进一步操作即使用。^1H NMR(500MHz,$CDCl_3$)δ8.29-8.19(m,1H),7.76(dd,J＝8.5,2.3Hz,1H),7.14(d,J＝8.3Hz,1H),4.12(s,3H),3.61(spt,J＝7.0Hz,1H),1.63(s,6H),1.84-0.82(d,6H)。LCMS m/z＝293.3$(M+H)^+$。

[0071] 实施例591.如针对实施例378中所描述使用BOP(13.62mg,0.03mmol)试剂及Hunig碱(0.1mL)使中间体591-1(9mg,0.03mmol)与166-2(11.34mg,0.03mmol)偶合,以在通过制备型反相HPLC纯化之后得到呈固体的例子591(8.4mg,41％产率)。HPLC纯度:96.5％;RT＝2.67min[方法B]。LCMS m/z＝643.18$(M+H)^+$.^1H NMR(500MHz,DMSO-d6)δ10.54(s,1H),9.96(br d,J＝6.7Hz,1H),8.23(br d,J＝4.0Hz,1H),8.03(d,J＝2.1Hz,1H),7.79(br d,J＝8.9Hz,1H),7.61(dd,J＝8.5,2.1Hz,1H),7.49(br t,J＝9.8Hz,1H),7.31(d,J＝8.5Hz,1H),4.70(d,J＝9.5Hz,1H),4.46(br s,1H),4.07(s,3H),3.68-3.48(m,1H),3.41(br s,1H),3.28-3.13(m,1H),3.11(br s,1H),2.73(br s,1H),1.92-1.75(m,2H),1.51(s,6H),1.43(br t,J＝10.7Hz,2H),1.06(br d,J＝6.7Hz,6H),0.86-0.66(m,2H),0.36(br s,2H)

[0072] 实施例594

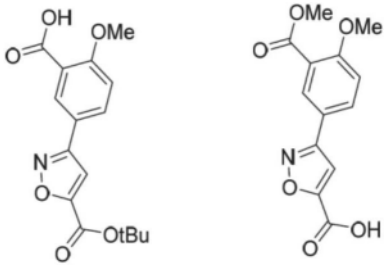


制备中间体594-1。



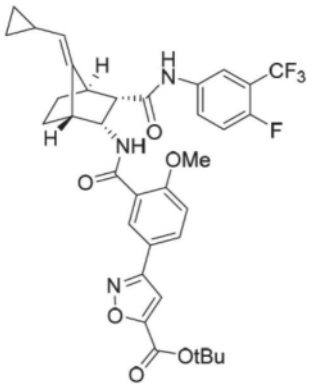
中间体594-1(434mg,60.0%产率)为以如针对实施例378所描述的类似方式,通过如先前所描述将(Z)-5-(氯(羟基亚氨基)甲基)-2-甲氧基苯甲酸甲酯(530mg,2.18mol)与丙炔酸叔丁酯(274mg,2.17mmol)及TEA(2mL)在DCM中进行环化加成来制备。LCMS m/z＝334.3(M+H)$^+$。

[0073] 制备中间体594-2。



如实施例378中先前所描述,使中间体594-1(100mg,0.30mmol)与LiOH(12mg,0.35mmol)一起在甲醇/水中水解,得到呈两种产物的混合物形式的594-2(75mg)。对于所需产物,LCMS m/z＝278.2(M+H)。另一副产物为叔丁酯裂解为酸产物。粗混合物不经进一步操作即继续用于下一步骤中。

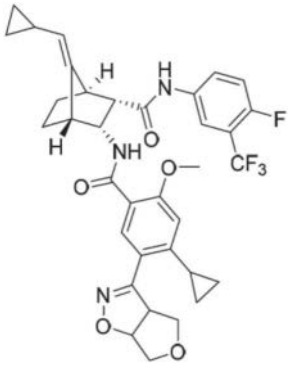
[0074] 制备中间体594-3。



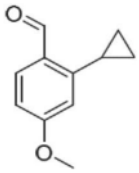
使中间体594-2(60mg,0.22mmol,作为混合物的部分)溶解于DMF(1mL)中,且向其中添加4-OH-哌啶(22mg,0.22mmol),随后添加BOP(6mg,0.22mmol)试剂及Hunig碱(0.1mL)。在室温下搅拌反应混合物14h,用水(25mL)淬灭且用EtOAc(2×25mL)萃取。将合并的有机部分经燥且真空浓缩为油状物。LCMS m/z=361.2(M+H)。将所得油状物溶解于甲醇(1mL)中且向其中添加LiOH(10mg,0.2mmol),随后添加水(1mL),且搅拌反应混合物14h。将反应混合物用水(25mL)稀释且用EtOAc(2×25mL)萃取。将合并的有机部分干燥($MgSO_4$)且真空浓缩,得到呈油状物的594-3(LCMS m/z=347.3(M+H)),其不经进一步纯化即用于下一步骤中。

[0075] 实施例594.使用BOP(10mg,0.02mmol)试剂及Hunig碱(0.1mL)使中间体594-3(8mg,0.02mmol)与166-2(8.5mg,0.020mmol)偶合,以在以下条件下通过制备型LC/MS纯化之后得到呈固体的例子594(3.6mg,22%产率):柱:XBridge C18,200mm×19mm,5-μm粒子;移动相A:5:95乙腈:水(具有0.05%三氟乙酸);移动相B:95:5乙腈:水(具有0.05%三氟乙酸)。HPLC纯度:98.1%;RT=2.30min[方法B]。LCMS m/z=697.01$(M+H)^+$.^{1}H NMR(500MHz,DMSO-d6)δ10.55(s,1H),9.94(br d,J=6.4Hz,1H),9.26-9.19(m,1H),8.27(d,J=2.3Hz,1H),8.22(br d,J=4.6Hz,1H),7.80(br dd,J=8.6,2.1Hz,2H),7.48(br t,J=9.7Hz,1H),7.35(d,J=8.8Hz,1H),7.27-7.21(bs,1H),7.17-7.13(bs,1H),7.09(bs,1H)4.69(d,J=9.5Hz,1H),4.44(br s,1H),4.06(s,3H),3.67(br s,1H),3.51(m,2H),3.34-3.13(m,1H),3.10(br s,1H),2.80-2.63(m,1H),1.83(br d,J=9.8Hz,1H),1.77(br s,2H),1.50(br s,1H),1.45(br s,1H),1.41(br s,2H),1.16(t,J=7.3Hz,1H),1.10(br s,1H),0.86-0.68(m,2H),0.35(br s,2H)

[0076] 实施例626

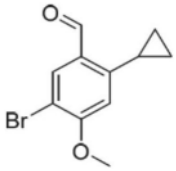


中间体626-1



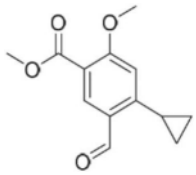
制备2-环丙基-4-甲氧基苯甲醛。中间体626-1(0.30g,1.9mmol,84%产率)为以针对实施例12描述的方式,以实施例11及呋喃-3-基硼酸(boronic acid)取代2-溴-4-甲氧基苯甲醛及环丙基硼酸且以THF取代二噁烷来制备。^{1}H NMR(400MHz,$CDCl_3$)δ10.46(s,1H),7.83(d,J=8.6Hz,1H),6.84(dd,J=8.7,2.5Hz,1H),6.62(d,J=2.4Hz,1H),3.89(s,3H),2.70(tt,J=8.5,5.4Hz,1H),1.15-1.07(m,2H),0.86-0.76(m,2H)。LCMS(ESI)m/z:177.1$(M+H)^+$。

[0077] 中间体626-2



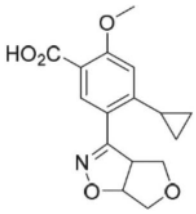
制备5-溴-2-环丙基-4-甲氧基苯甲醛。向冷却至0℃的含626-1(0.30g,1.9mmol)的MeOH(10mL)中添加过溴化氢溴酸吡啶(0.60g,1.9mmol)。24h之后,真空移除溶剂且通过正相硅胶色谱,用己烷/EtOAc洗脱来纯化残余物,得到呈白色固体的中间体626-2(0.31g,1.2mmol,65%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ10.45(s,1H),8.04(s,1H),6.63(s,1H),3.98(s,3H),2.68-2.55(m,1H),1.20-1.11(m,2H),0.88-0.78(m,2H)。

[0078] 中间体626-3:



制备4-环丙基-5-甲酰基-2-甲氧基苯甲酸甲酯。除使用$PdOAc_2$、dppf及DMSO/MeOH之外,中间体626-3(0.16g,0.70mmol,58%产率)为以与中间体323-1类似的方式制备。^{1}H NMR(400MHz,$CDCl_3$)δ10.40(s,1H),8.33(s,1H),6.64(s,1H),3.99(s,3H),3.93(s,3H),2.96-2.71(m,1H),1.25-1.13(m,2H),0.87(dd,J=5.3,1.8Hz,2H)。LCMS(ESI)m/z:235.2(M+H)$^+$。

[0079] 中间体626-4:

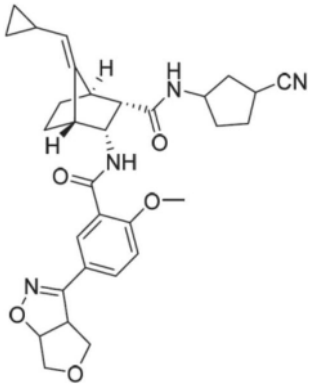


制备4-环丙基-2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酸。遵循针对实施例378及实施例416的通用程序,但以5-甲酰基-2-甲氧基苯甲酸甲酯取代626-3,得到626-4(46mg,0.15mmol,91%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ8.10(s,1H),6.68(s,1H),5.38(dd,J=9.2,3.7Hz,1H),4.48(t,J=7.5Hz,1H),4.37(d,J=10.6Hz,1H),4.12(s,3H),4.03(d,J=9.5Hz,1H),3.86-3.75(m,2H),2.77-2.63(m,1H),1.28-1.20(m,1H),1.18-1.10(m,1H),0.85-0.72(m,2H)。LCMS(ESI)m/z:304.3(M+H)$^+$。

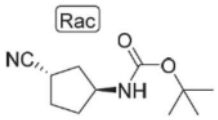
[0080] 实施例626.非镜像异构体的混合物为通过如实施例378中所描述的BOP偶合,以中间体378-3及环丁基降冰片烷基中间体369-1取代环丙基降冰片烷基中间体166-2及中间体626-4来制备。使用以下将非镜像异构体的混合物分离成个别异构体:手性SFC仪器:Waters 100Prep SFC柱:Chiral AD,30×250mm,5微米,移动相:25%MeOH/75%CO_2(具有0.1%DEA),流动条件:100mL/min,检测器波长:220nm;分析方法:仪器:Shimadzu Nexera SFC,柱Chiral AD,4.6×100mm,5微米,移动相:25%MeOH/75%CO_2(具有0.1%DEA),流动条件:2mL/min,检测器波长:220nm,得到手性峰-1(实施例626)(8.2mg,12μmol,16%产率),RT=2.6min.,>95%de及手性峰-2(8.1mg,12μmol,16%产率),RT=3.3min.,>95%de。对于实施

例626:^{1}H NMR(500MHz,DMSO-d_6)δ10.53(s,1H),9.85(br d,J=7.0Hz,1H),8.31-8.18(m,1H),7.90(s,1H),7.82-7.74(m,1H),7.48(t,J=9.6Hz,1H),6.68(s,1H),5.32(dd,J=9.0,3.5Hz,1H),4.69(d,J=9.5Hz,1H),4.56(br t,J=7.6Hz,1H),4.47-4.39(m,1H),4.11(br d,J=10.7Hz,1H),4.04(s,3H),3.76(br d,J=8.9Hz,1H),3.65(br dd,J=10.5,4.4Hz,1H),3.48(br s,1H),3.15(br dd,J=10.8,3.2Hz,1H),3.09(br s,1H),2.78-2.67(m,1H),2.41-2.32(m,1H),1.92-1.81(m,1H),1.79-1.72(m,1H),1.56-1.46(m,1H),1.45-1.33(m,2H),1.06(br dd,J=8.7,5.6Hz,1H),1.02-0.94(m,1H),0.93-0.87(m,1H),0.87-0.81(m,1H),0.79-0.67(m,2H),0.35(br s,2H)。LCMS(ESI)m/z:653.93(M+H)$^+$。HPLC纯度95%,保留时间2.65min。[方法C]。

[0081] 实施例664及实施例702

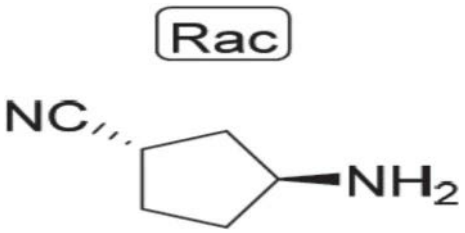


中间体664-1:



将rac-((1R,3S)-3-羟基环戊基)氨基甲酸叔丁酯(260mg,1.29mmol)溶解于DCM(15mL)中。添加Hunig碱(1.13mL,6.46mmol)及MsCl(0.101mL,1.29mmol)。2小时之后,真空浓缩反应混合物。用乙腈(20mL)稀释残余物,且添加氰化四丁基铵(347mg,1.29mmol)。1小时之后,真空浓缩反应混合物。经由硅胶色谱纯化残余物,得到664-1(135mg,50%)。^{1}H NMR(400MHz,$CDCl_3$)δ4.48(br d,J=4.3Hz,1H),4.18-4.05(m,1H),2.99-2.85(m,1H),2.30-2.13(m,3H),2.06-1.85(m,2H),1.58-1.49(m,1H),1.44(s,9H)。

[0082] 中间体664-2:



将rac-((1R,3R)-3-氰基环戊基)氨基甲酸叔丁酯(65mg,0.31mmol)溶解于DCM(1.9mL)中。添加TFA(0.19mL,2.5mmol)。3小时之后,添加TFA(0.19mL,2.5mmol)。再过1.5小时之后,真空浓缩反应混合物,随后与DCM及己烷共沸。获得rac-(1R,3R)-3-氨基环戊烷-1-甲腈TFA(131mg,0.584mmol,189%产率)且不经进一步纯化即继续使用。^{1}H NMR(400MHz,CD_3OD)δ3.99-3.84(m,1H),2.53-2.34(m,3H),2.31-2.19(m,1H),2.11-2.00(m,1H),1.85

(dt,J＝14.1,7.0Hz,1H)。

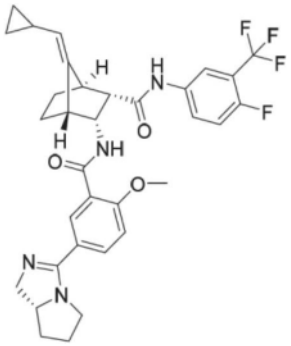
[0083] 实施例642及实施例702:

实施例642与实施例702的混合物为根据针对实施例447所描述的程序由中间体642-2制备。在以下条件下经由制备型反相HPLC纯化所得物质:柱:XBridge C18,200mm×19mm,5-μm粒子;移动相A:5∶95乙腈∶水(具有乙酸铵);移动相B:95∶5乙腈∶水(具有乙酸铵);梯度:在25%B下保持0分钟,在30分钟内25至70%B,随后在100%B下保持0分钟;流动速率:20mL/min;柱温度:25℃。通过MS信号触发洗脱份收集。合并含有所需产物的洗脱份且经由离心蒸发干燥。

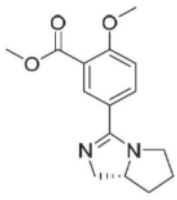
[0084] 峰1为实施例664(6.3mg,41%)。^{1}H NMR(500MHz,DMSO-d_6)δ9.95(br d,J＝7.0Hz,1H),8.21-8.14(m,2H),7.79(dd,J＝8.5,2.1Hz,1H),7.24(d,J＝8.5Hz,1H),5.34(dd,J＝9.0,3.2Hz,1H),4.61(br d,J＝9.5Hz,1H),4.50(br t,J＝7.3Hz,1H),4.27(br dd,J＝6.3,4.1Hz,1H),4.22-4.15(m,1H),4.09(br d,J＝10.7Hz,1H),4.02(s,3H),3.90(br d,J＝9.2Hz,1H),3.77(br dd,J＝9.2,7.0Hz,1H),3.67-3.60(m,1H),3.13-3.01(m,2H),2.86(br dd,J＝11.0,4.3Hz,1H),2.16-2.01(m,2H),2.00-1.92(m,1H),1.87-1.78(m,2H),1.78-1.66(m,2H),1.50-1.40(m,2H),1.39-1.24(m,2H),0.77-0.64(m,2H),0.31(br d,J＝2.4Hz,2H)。可能由于与溶剂峰重叠,一个质子在NMR中不可见。LC-MS RT:2.02min;MS(ESI)m/z 545.2$(M+H)^+$;方法B。

[0085] 峰2为实施例702(5.1,32%)。^{1}H NMR(500MHz,DMSO-d_6)δ9.97(d,J＝6.8Hz,1H),8.20-8.12(m,2H),7.79(dd,J＝8.6,2.3Hz,1H),7.25(d,J＝8.8Hz,1H),5.33(dd,J＝9.2,3.5Hz,1H),4.61(d,J＝9.6Hz,1H),4.49(br t,J＝7.8Hz,1H),4.32-4.24(m,1H),4.23-4.14(m,1H),4.13-4.06(m,1H),4.03(s,3H),3.90(br d,J＝8.9Hz,1H),3.77(dd,J＝9.4,7.0Hz,1H),3.65(dd,J＝10.7,3.5Hz,1H),3.12-3.01(m,2H),2.85(dd,J＝10.9,4.2Hz,1H),2.18-1.95(m,3H),1.88-1.68(m,4H),1.52-1.40(m,2H),1.39-1.24(m,2H),0.70(quin,J＝9.4Hz,2H),0.40-0.21(m,2H)。可能由于与溶剂峰重叠,一个质子在NMR中不可见。LC-MS RT:1.86min;MS(ESI)m/z 545.2$(M+H)^+$;方法B。

[0086] 实施例699

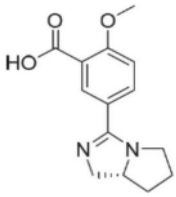


中间体699-1:



在冰浴中冷却(R)-吡咯烷-2-基甲胺2HCl(70.2mg,0.406mrnol)于DCM(1.9mL)中的溶液。添加Hunig碱(0.14mL,0.81mmol)及5-甲酰基-2-甲氧基苯甲酸甲酯(75mg,0.39mmol)。使反应混合物升温至室温。1小时之后,添加NBS(72.2mg,0.406mmol)且搅拌反应混合物14h。在减压下浓缩反应混合物。经由硅胶色谱纯化残余物,得到中间体699-1(49mg,46%)。^{1}H NMR(400MHz,$CDCl_3$)δ8.18(d,J=2.0Hz,1H),7.96(dd,J=8.8,2.0Hz,1H),7.02(d,J=8.7Hz,1H),4.09-4.02(m,2H),3.92(s,3H),3.86(s,3H),3.75(q,J=9.4Hz,1H),3.42-3.27(m,1H),3.24-3.14(m,1H),2.05-1.91(m,1H),1.90-1.72(m,2H),1.52-1.40(m,1H)。

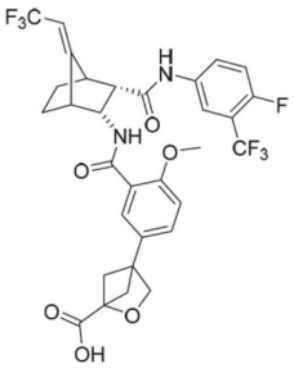
[0087] 中间体699-2:



向中间体699-1(49mg,0.18mmol)于THF(1.9mL)及MeOH(0.37mL)中的溶液中添加LiOH(2M水溶液)(0.27mL,0.54mmol)。在4小时之后,将反应混合物用1M HCl酸化至pH 3且在减压下浓缩,得到(R)-2-甲氧基-5-(5,6,7,7a-四氢-1H-吡咯并[1,2-c]咪唑-3-基)苯甲酸甲酯中间体699-2(49mg,0.18mmol),其不经进一步纯化即使用。

[0088] 实施例699为通过针对实施例378所描述的通用程序由中间体699-2制备(3.8mg,31%)。^{1}H NMR(500MHz,DMSO-d_6)δ10.61(s,1H),9.98(d,J=6.8Hz,1H),8.38(d,J=2.4Hz,1H),8.21(dd,J=6.3,2.2Hz,1H),7.98(dd,J=8.8,2.4Hz,1H),7.83-7.73(m,1H),7.52-7.43(m,2H),4.69(d,J=9.6Hz,1H),4.55-4.39(m,2H),4.13(s,3H),4.08(t,J=11.5Hz,1H),3.81(dd,J=11.9,7.1Hz,1H),3.74-3.64(m,1H),3.17(dd,J=10.2,4.9Hz,1H),3.10(br s,1H),2.73(br s,1H),2.17-2.08(m,1H),2.07-1.96(m,2H),1.88-1.72(m,2H),1.72-1.60(m,1H),1.52-1.35(m,3H),0.79-0.66(m,2H),0.39-0.27(m,2H)。可能由于与经抑制的水峰重叠,一个质子在NMR中不可见。LC-MS RT:2.20min;MS(ESI)m/z611.2$(M+H)^+$;方法B。

[0089] 实施例724



中间体724-1:制备5-溴-2-甲氧基苯甲酸叔丁酯:向5-溴-2-甲氧基苯甲酸(3.67g,15.9mmol)于THF(50mL)中的溶液中添加Boc-酐(7.38mL,31.8mmol)及DMAP(0.194g,1.59mmol)。随后向此混合物中添加t-BuOH(50mL)且随后在75℃加热反应混合物14h。随后在真空下浓缩反应混合物且对残余物进行硅胶色谱,得到中间体724-1(4.1g,81%产率)。^{1}H NMR(500MHz,$CDCl_3$)δ7.81(d,J=2.6Hz,1H),7.52(dd,J=8.9,2.6Hz,1H),

6.85(d,J＝8.9Hz,1H),3.88(s,3H),1.61-1.57(m,9H)

[0090] 中间体724-2:制备5-(3-羟基丙-1-烯-2-基)-2-甲氧基苯甲酸叔丁酯:在氩气下向丙-2-烯-1-醇(1.42mL,20.9mmol)及中间体724-1(1200mg,4.18mmol)于DMSO(3mL)中的溶液中添加TEA(1.05mL,7.52mmol)及1,3-双(二苯基膦基)丙烷(345mg,0.836mmol)。向反应混合物中添加$Pd(OAc)_2$(94mg,0.42mmol)且用氩气吹扫混合物10min。随后将反应混合物密封且在60℃搅拌14h。使反应混合物冷却至室温,用EtOAc稀释且用盐水洗涤有机部分。将有机部分经$MgSO_4$干燥,过滤且使用硅胶色谱纯化,得到中间体724-2(222mg,19.0%产率)。^1H NMR(500MHz,$CDCl_3$)δ7.82(d,J＝2.4Hz,1H),7.53(dd,J＝8.6,2.5Hz,1H),6.95(d,J＝8.7Hz,1H),5.43(d,J＝0.8Hz,1H),5.32(q,J＝1.2Hz,1H),4.53(d,J＝5.3Hz,2H),3.92-3.89(s,3H),1.62-1.59(m,9H)

[0091] 中间体724-3:制备2-((2-(3-(叔丁氧基羰基)-4-甲氧基苯基)烯丙基)氧基)丙二酸二甲酯:向中间体724-2(222mg,0.840mmol)于甲苯(5mL)中的溶液中添加$Rh_2(OAc)_4$(19mg,0.042mmol)。随后用氮气吹扫反应混合物,然后加热至回流。随后经约5分钟向此回流溶液中添加2-重氮丙二酸二甲酯(133mg,0.840mmol)的甲苯(1mL)。在继续回流30分钟之后,使反应混合物冷却至室温且在真空下浓缩。使用硅胶色谱纯化残余物,得到中间体724-3(192mg,58.0%产率)。^1H NMR(500MHz,$CDCl_3$)δ7.85(d,J＝2.4Hz,1H),7.60(dd,J＝8.7,2.4Hz,1H),6.93(d,J＝8.7Hz,1H),5.59-5.56(m,1H),5.34(d,J＝0.9Hz,1H),4.64(s,1H),4.55(d,J＝0.8Hz,2H),3.91(s,3H),3.79(s,6H),1.60(s,9H)。

[0092] 中间体724-4:制备2-((2-(3-(叔丁氧基羰基)-4-甲氧基苯基)烯丙基)氧基)-2-((二甲基氨基)甲基)丙二酸二甲酯:向中间体724-3(192mg,0.487mmol)于DCM(7mL)中的溶液中添加埃申莫瑟氏盐(Eschenmoser's salt)(135mg,0.730mmol),随后添加TEA(0.10mL,0.73mmol)。在室温下搅拌反应混合物14h。使反应混合物冷却至室温且在真空下浓缩。使用硅胶色谱纯化残余物,得到中间体724-4(100mg,45%产率)。MS(ESI)m/z＝452.5(M+H)。

[0093] 中间体724-5:制备2-((2-(3-(叔丁氧基羰基)-4-甲氧基苯基)烯丙基)氧基)-3-甲氧基-2-(甲氧基羰基)-N,N,N-三甲基-3-氧代丙烷-1-铵:向中间体724-4(100mg,0.221mmol)于丙酮(5mL)中的溶液中添加碘甲烷(0.021mL,0.33mmol)且在室温下搅拌反应混合物14h。在真空下浓缩反应混合物,得到中间体724-5,其不经进一步纯化即使用(100mg,87%产率)。MS(ESI)m/z＝466.5(M+H)。

[0094] 中间体724-6:制备2-甲氧基-5-(3-((3-甲氧基-3-氧代丙-1-烯-2-基)氧基)丙-1-烯-2-基)苯甲酸叔丁酯:向中间体724-5(100mg,0.214mmol)于DMSO(4mL)中的溶液中添加NaOH(2M,0.13mL,0.26mmol)且在室温下搅拌反应混合物3h。在真空下浓缩反应混合物且使用硅胶色谱纯化,得到中间体724-6(50mg,64%产率)。MS(ESI)m/z＝349.0(M+H)。

[0095] 中间体724-7:制备4-(3-(叔丁氧基羰基)-4-甲氧基苯基)-2-氧杂双环[2.1.1]己烷-1-甲酸甲酯:向中间体724-6(50mg,0.14mmol)于DMSO(30mL)中的溶液中添加(Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6(1.6mg,1.4μmol)且将反应混合物在N_2下脱气三次。在蓝色LED灯存在下搅拌反应混合物48h。用EtOAc稀释反应混合物且用盐水洗涤有机部分。将有机部分经$MgSO_4$干燥,过滤且使用硅胶色谱纯化,得到中间体724-7(13mg,23%产率)。^1H NMR(500MHz,$CDCl_3$)δ7.75(d,J＝2.4Hz,1H),7.45(dd,J＝8.6,2.5Hz,1H),6.93(d,J＝8.7Hz,1H),5.28(s,1H),5.07(d,J＝0.9Hz,1H),3.90(s,3H),3.86(s,3H),3.04-2.98(m,2H),2.88-2.79(m,

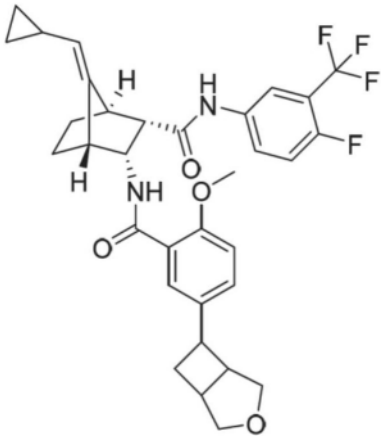
2H),1.62-1.59(m,9H)

[0096] 中间体724-8:制备2-甲氧基-5-(1-(甲氧基羰基)-2-氧杂双环[2.1.1]己烷-4-基)苯甲酸TFA:向中间体724-7(13mg,0.037mmol)于DCM(0.8mL)中的溶液中添加TFA(0.20mL,2.6mmol)且在室温下搅拌反应混合物30min。随后真空浓缩反应混合物,得到中间体724-8,其不经进一步纯化即使用(11mg,95%产率)。MS(ESI)m/z=293.2(M+H)。

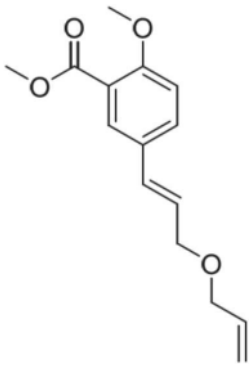
[0097] 中间体724-9:制备4-(3-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-2-氧杂双环[2.1.1]己烷-1-甲酸甲酯:中间体724-9为通过针对378所描述的通用程序,通过使用三氟甲基降冰片烷基中间体170-2(25mg,0.049mmol)及中间体724-8制备,得到中间体724-9(6mg,20%产率)。MS(ESI)m/z=671.1(M+H)。

[0098] 实施例724:通过将中间体724-9(6mg,9μmol)溶解于THF(2mL)及水(0.67mL)中且添加LiOH(2M,0.013mL,0.027mmol)来制备4-(3-(((1R,2R,3S,4R,Z)-3-((4-氟-3-(三氟甲基)苯基)胺甲酰基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基)胺甲酰基)-4-甲氧基苯基)-2-氧杂双环[2.1.1]己烷-1-甲酸724。随后在室温下搅拌反应混合物2h。真空浓缩反应混合物且使用反相制备型HPLC纯化,得到724(4.8mg,75%产率)。^{1}H NMR(500MHz,CD_3OD)δ 10.26-10.17(m,1H),8.14(dd,J=6.3,2.6Hz,1H),8.00-7.92(m,1H),7.80-7.72(m,1H),7.50-7.42(m,1H),7.29(t,J=9.6Hz,1H),7.17(d,J=8.5Hz,1H),5.78-5.71(m,1H),4.67-4.60(m,1H),4.07(s,3H),4.01-3.96(m,2H),3.47-3.41(m,1H),3.40-3.32(m,1H),3.30-3.16(m,2H),2.95-2.91(m,1H),2.76-2.70(m,1H),2.44-2.35(m,2H),2.21-2.13(m,3H),1.63-1.54(m,2H)。MS(ESI)m/z=657.4(M+H)。HPLC纯度:92%;保留时间:1.35min;方法A。

[0099] 实施例725-728

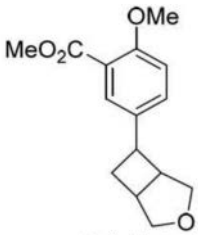


中间体725-1



将含(E)-5-(3-羟基丙-1-烯-1-基)-2-甲氧基苯甲酸甲酯(0.30g,1.3mmol)的DMF(14mL)冷却至0℃且用NaH(60％于矿物油中)(0.059g,1.5mmol)处理。15分钟后,用烯丙基溴(0.13mL,1.5mmol)处理反应混合物且使溶液升温至室温持续14h。用饱和氯化铵溶液稀释反应混合物且用EtOAc(2×)萃取。将有机部分合并,经硫酸钠干燥,过滤且在减压下浓缩。通过硅胶色谱纯化残余物,得到(E)-5-(3-(烯丙氧基)丙-1-烯-1-基)-2-甲氧基苯甲酸甲酯(0.20g,0.76mmol,57％产率)。MS(ESI)m/z 263.0$(M+H)^+$。

[0100] 中间体725-2、726-1至727-1及728-1



四种非镜像异构体

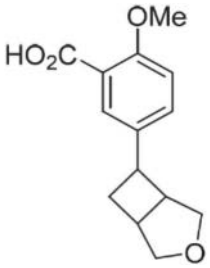
725-2、726-1、727-1及728-1

向溶解于乙腈(75mL)中的中间体725-1(0.20g,0.76mmol)中添加(Ir[dF(CF_3)ppy]$_2$(dtbpy))-PF_6(9mg,8μmol)且用蓝色LED照射溶液60h。在减压下浓缩反应混合物且通过SFC使用两个连续柱纯化残余物。第一柱:(A5-5250×4.6mmID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:85/15CO_2/MeOH),然后是(AD 250×4.6mm ID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:90/10CO_2/MeOH),得到726-2(峰1:33mg,0.13mmol.17％产率)MS(ESI)m/z 263.0$(M+H)^+$,RT=7.2min,AD 250×4.6mmID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:90/10CO_2/MeOH^{1}H NMR(500MHz,$CDCl_3$)δ7.67(d,J=2.3Hz,1H),7.34(dd,J=8.5,2.4Hz,1H),6.94(d,J=8.5Hz,1H),4.02-3.96(m,2H),3.90(s,3H),3.89(s,3H),3.65-3.60(m,1H),3.53-3.50(m,1H),3.23-3.17(m,1H),3.01-2.93(m,2H),2.31-2.22(m,1H),2.21-2.13(m,1H)。

[0101] 727-1(峰2:20mg,0.076mmol.10％产率)MS(ESI)m/z 263.0$(M+H)^+$,RT=13.2min,A5-5250×4.6mmID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:85/15CO_2/MeOH:^{1}H NMR(500MHz,$CDCl_3$)δ7.70(d,J=2.4Hz,1H),7.36(dd,J=8.5,2.4Hz,1H),6.96(d,J=8.7Hz,1H),4.00(dd,J=9.2,7.6Hz,2H),3.93(s,3H),3.91(s,3H),3.63(dd,J=9.2,5.4Hz,1H),3.53(dd,J=9.4,4.0Hz,1H),3.26-3.19(m,1H),3.04-2.95(m,2H),2.33-2.24(m,1H),2.22-2.16(m,1H)。

[0102] 728-1(峰3:5.3mg,0.020mmol.2.7％产率),MS(ESI)m/z 263.0$(M+H)^+$,RT=6.11min,AD 250×4.6mmID,5μm,温度:环境温度,流动速率:2.0mL/min,移动相:90/10CO_2/MeOH^{1}H NMR(500MHz,$CDCl_3$)δ7.58(d,J=2.3Hz,1H),7.40(dd,J=8.5,2.2Hz,1H),6.97(d,J=8.7Hz,1H),3.91(s,3H),3.91(s,3H),3.86(d,J=9.0Hz,1H),3.73-3.64(m,2H),3.44(dd,J=9.0,4.4Hz,1H),3.37(dd,J=10.0,6.6Hz,1H),3.20(q,J=7.5Hz,1H),3.08-2.99(m,1H),2.46(dddd,J=12.3,10.3,8.2,2.3Hz,1H),2.13(ddd,J=12.1,9.6,6.6Hz,1H)

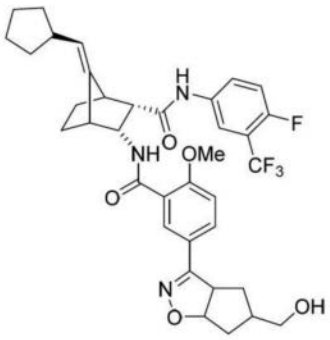
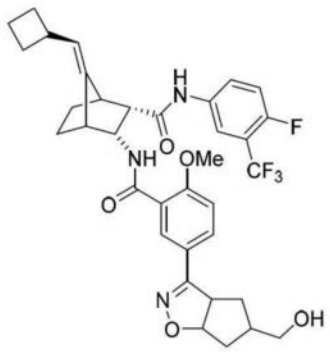
[0103] 中间体725-3

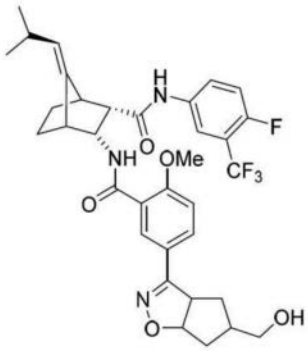
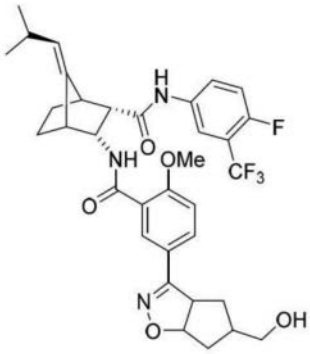


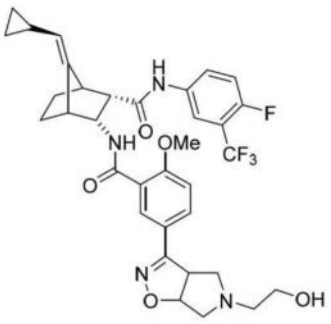
中间体725-3为通过用于中间体4-2的通用程序由725-2制备。LC-MS RT:0.77min;MS(ESI)m/z 249.0(M+H)$^+$;方法A。

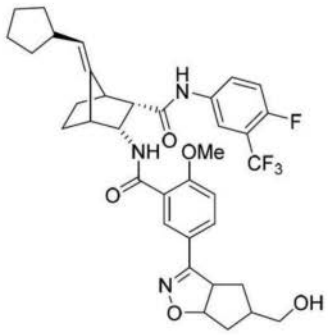
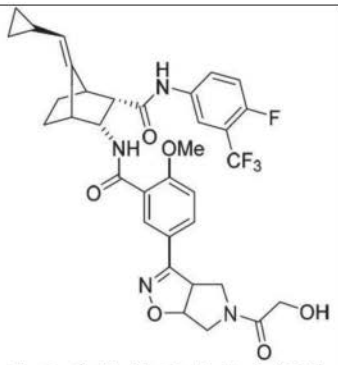
[0104] 实施例725:根据实施例1的通用程序由中间体725-3及IV-2a制备,得到(1R,2S,3R,4R,Z)-3-(5-(3-氧杂双环[3.2.0]庚烷-6-基)-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)双环[2.2.1]庚烷-2-甲酰胺(3.2mg,10%产率)。^{1}H NMR(500MHz,DMSO-d6)δ10.49(s,1H),9.81(d,J=7.2Hz,1H),8.23(dd,J=6.6,2.6Hz,1H),7.84(d,J=2.4Hz,1H),7.78(dt,J=8.5,3.8Hz,1H),7.49(t,J=9.8Hz,1H),7.41(dd,J=8.5,2.4Hz,1H),7.13(d,J=8.7Hz,1H),4.69(d,J=9.6Hz,1H),4.49-4.41(m,1H),3.97(s,3H),3.91-3.84(m,2H),3.48(dd,J=9.2,5.8Hz,1H),3.39(dd,J=9.2,4.7Hz,1H),3.15(dd,J=10.7,4.3Hz,1H),3.13-3.06(m,2H),3.00-2.90(m,1H),2.89-2.83(m,1H),2.72(t,J=3.7Hz,1H),2.16(dt,J=12.3,8.1Hz,1H),2.09-2.01(m,1H),1.87(br t,J=8.7Hz,1H),1.81-1.74(m,1H),1.55-1.47(m,1H),1.46-1.34(m,2H),0.82-0.70(m,2H),0.36(dd,J=4.5,2.5Hz,2H)。LC-MS RT:2.7min;MS(ESI)m/z 599.0(M+H)$^+$;方法A。

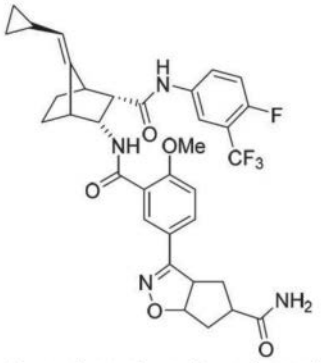
表3

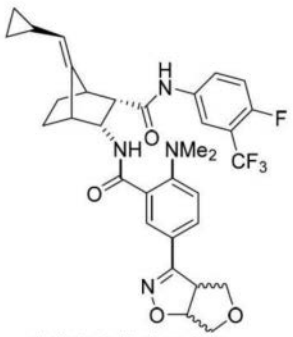
实施例编号	结构	名称	MS (ESI) (M+H)	1H NMR	LC RT Meth. (min)
445	 由429-8制备	(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.6	(400 MHz, CD_3OD) δ 8.35 (d, J=2.2 Hz, 1H), 8.18 (dd, J=6.4, 2.6 Hz, 1H), 7.89 (dd, J=8.8, 2.4 Hz, 1H), 7.81 - 7.73 (m, 1H), 7.30 (t, J=9.6 Hz, 1H), 7.26 (d, J=8.8 Hz, 1H), 5.24 - 5.18 (m, 2H), 4.56 - 4.48 (m, 1H), 4.23 (s, 1H), 4.14 (s, 3H), 3.60 - 3.48 (m, 2H), 3.34 (dt, J=3.3, 1.7 Hz, 2H), 3.16 (dd, J=10.7, 4.3 Hz, 1H), 3.12 (t, J=3.6 Hz, 1H), 2.74 - 2.64 (m, 2H), 2.21 - 2.07 (m, 2H), 2.03 - 1.95 (m, 2H), 1.94 - 1.87 (m, 2H), 1.85 - 1.58 (m, 6H), 1.50 (br d, J=2.9 Hz, 2H), 1.37 - 1.29 (m, 2H)	1.45, A
446	 由429-8制备	(1R,2S,3R,4R,7Z)-7-(环丁基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.0	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.27 - 8.17 (m, 2H), 7.86 - 7.75 (m, 2H), 7.48 (br t, J=9.8 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 5.38 (d, J=8.2 Hz, 1H), 5.13 (br dd, J=8.5, 5.5 Hz, 1H), 4.41 - 4.29 (m, 1H), 4.20 (br t, J=8.9 Hz, 1H), 4.04 (s, 3H), 3.90 (s, 1H), 3.64 - 3.55 (m, 3H), 3.44 - 3.30 (m, 2H), 3.20 - 3.04 (m, 3H), 2.96 (br s, 1H), 2.71 (br s, 1H), 2.23 - 2.08 (m, 2H), 2.00 (br dd, J=14.0, 6.1 Hz, 1H), 1.94 - 1.62 (m, 9H), 1.60 - 1.52 (m, 1H), 1.43 - 1.28 (m, 2H)	2.55, A

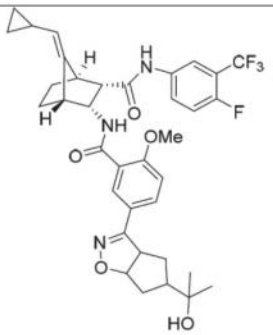
450	 由429-8制备	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-甲酰胺	644.6	(400 MHz, CD_3OD) δ 8.35 (dd, J=2.2, 0.9 Hz, 1H), 8.18 (dd, J=6.4, 2.6 Hz, 1H), 7.89 (dd, J=8.6, 2.2 Hz, 1H), 7.81 - 7.74 (m, 1H), 7.30 (t, J=9.6 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 5.36 - 5.13 (m, 2H), 4.52 (dt, J=10.7, 2.0 Hz, 1H), 4.28 - 4.22 (m, 1H), 4.17 - 4.12 (m, 3H), 3.61 - 3.47 (m, 2H), 3.17 (dt, J=10.6, 3.3 Hz, 1H), 3.14 - 3.09 (m, 1H), 2.72 (dt, J=12.8, 3.9 Hz, 1H), 2.20 - 2.08 (m, 3H), 2.03 - 1.87 (m, 3H), 1.82 - 1.72 (m, 1H), 1.65 (ddd, J=13.3, 11.4, 5.1 Hz, 1H), 1.55 - 1.39 (m, 3H), 1.11 - 0.94 (m, 5H)	1.44, A
454	 由429-10制备	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-甲酰胺	644.6	(400 MHz, CD_3OD) δ 8.36 (dd, J=2.3, 0.8 Hz, 1H), 8.18 (dd, J=6.3, 2.5 Hz, 1H), 7.92 (dd, J=8.8, 2.0 Hz, 1H), 7.78 (dt, J=8.8, 3.4 Hz, 1H), 7.37 - 7.25 (m, 2H), 5.37 - 5.14 (m, 2H), 4.53 (dd, J=10.7, 4.1 Hz, 1H), 4.20 - 4.10 (m, 4H), 3.54 - 3.41 (m, 2H), 3.22 - 3.11 (m, 2H), 2.74 (br dd, J=13.0, 3.7 Hz, 1H), 2.44 - 2.27 (m, 3H), 2.21 - 2.12 (m, 1H), 2.09 - 2.01 (m, 1H), 1.99 - 1.77 (m, 2H), 1.65 (dt, J=12.5, 6.0 Hz, 1H), 1.58 - 1.46 (m, 3H), 1.15 - 0.98 (m, 5H)	1.40, A

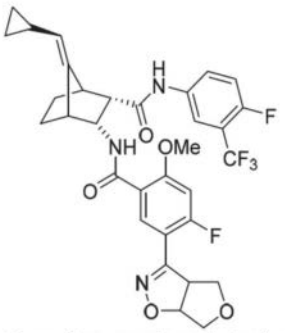
455	 由455-1制备 由同手性苯甲酸酯中间体(峰2；>99%ee；手性分析型RT=8.259 min)制备 制备型手性SFC条件：仪器：Jasco SFC Prep；柱：Regis Whelk-01，21 × 250 mm，5微米；移动相：15% IPA / 85% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~50mg/mL于IPA中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	657.6	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (br d, J=7.0 Hz, 1H), 8.26 (d, J=2.3 Hz, 1H), 8.23 (dd, J=6.5, 2.5 Hz, 1H), 7.83 (dd, J=8.5, 2.1 Hz, 1H), 7.77 (dt, J=8.5, 3.8 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 5.45 (br d, J=4.9 Hz, 1H), 4.78 (br s, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.43 (ddd, J=10.3, 6.5, 4.1 Hz, 1H), 4.05 (s, 3H), 3.98 (br d, J=11.0 Hz, 1H), 3.70 (br d, J=9.6 Hz, 1H), 3.65 (br s, 2H), 3.54 (br s, 2H), 3.23 (br s, 2H), 3.15 (dd, J=10.8, 4.2 Hz, 1H), 3.09 (t, J=3.5 Hz, 1H), 2.72 (t, J=3.6 Hz, 1H), 1.85 - 1.74 (m, 2H), 1.53 - 1.44 (m, 1H), 1.44 - 1.36 (m, 2H), 0.78 - 0.69 (m, 2H), 0.37 - 0.33 (m, 2H)	1.21, A

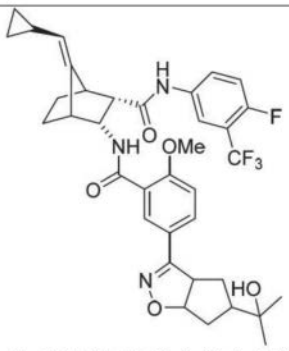
457	 由429-10制备	(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.6	(400 MHz, CD_3OD) δ 8.36 (d, J=2.4 Hz, 1H), 8.19 (dd, J=6.2, 2.4 Hz, 1H), 7.90 (dd, J=8.7, 2.3 Hz, 1H), 7.82 - 7.74 (m, 1H), 7.35 - 7.23 (m, 2H), 5.29 - 5.18 (m, 2H), 4.52 (dd, J=10.6, 3.1 Hz, 1H), 4.15 - 4.13 (m, 4H), 3.54 - 3.40 (m, 2H), 3.22 - 3.10 (m, 2H), 2.76 - 2.67 (m, 2H), 2.43 - 2.25 (m, 3H), 1.94 - 1.80 (m, 4H), 1.76 - 1.59 (m, 5H), 1.50 (br s, 2H), 1.38 - 1.29 (m, 3H)	1.45, A
458	 由同手性苯甲酸酯中间体(峰2；>99%ee；手性分析型RT=5.036 min)制备；制备型手性SFC条件：仪器：Jasco SFC Prep；柱：Regis Whelk-01，21×250 mm，5 微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：0.5 mL ~52mg/mL于MeOH-CAN中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙酰基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	672.0	(400 MHz, CD_3OD) δ 10.38 - 10.31 (m, 1H), 10.22 - 10.13 (m, 1H), 8.33 (dd, J=16.4, 2.1 Hz, 1H), 8.24 - 8.16 (m, 1H), 7.96 - 7.88 (m, 1H), 7.82 - 7.75 (m, 1H), 7.36 - 7.27 (m, 2H), 5.47 - 5.35 (m, 1H), 4.80 - 4.73 (m, 1H), 4.64 - 4.42 (m, 2H), 4.29 - 4.13 (m, 5H), 4.12 - 3.87 (m, 3H), 3.80 - 3.68 (m, 2H), 3.27 - 3.16 (m, 2H), 2.75 (br s, 1H), 2.06 - 1.90 (m, 2H), 1.65 - 1.50 (m, 3H), 0.84 - 0.73 (m, 2H), 0.44 - 0.32 (m, 2H)	2.14, C

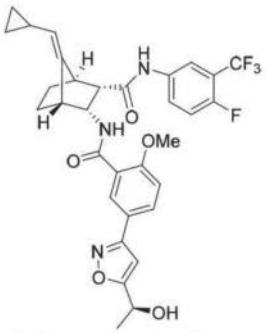
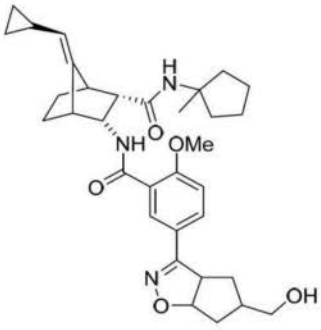
459	 由同手性苯甲酸酯中间体(峰2；>99%ee；手性分析型RT=2.742 min)制备；制备型手性SFC条件：仪器：Jasco SFC Prep：柱：Chiralpak AS-H，30×250 mm，5微米；移动相：30% MeOH / 70% CO_2；流动条件：85 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：1.0 mL ~50mg/mLmg/mL 于MeOH:TFA中	3-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酰胺	655.5	(500 MHz, DMSO-d6) δ 10.55 - 10.51 (m, 1H), 9.92 - 9.88 (m, 1H), 8.31 - 8.26 (m, 1H), 8.25 - 8.20 (m, 1H), 7.84 - 7.77 (m, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.29 - 7.25 (m, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.61 - 4.57 (m, 1H), 4.47 - 4.43 (m, 1H), 4.04 (s, 3H), 3.95 (dd, J=12.0, 4.7 Hz, 1H), 3.86 - 3.81 (m, 2H), 3.59 (d, J=4.7 Hz, 2H), 3.17 (dd, J=10.7, 4.1 Hz, 1H), 3.11 (t, J=3.6 Hz, 1H), 2.73 (t, J=3.4 Hz, 1H), 1.87 - 1.76 (m, 2H), 1.54 - 1.47 (m, 1H), 1.46 - 1.37 (m, 2H), 0.80 - 0.70 (m, 2H), 0.39 - 0.33 (m, 2H)	2.14, A

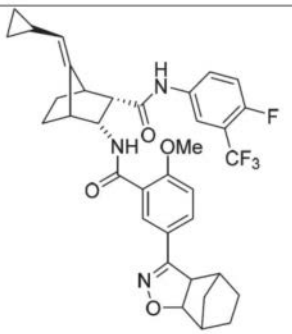
460	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(二甲基氨基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	626.9	(500 MHz, DMSO-d6) δ 10.48 (br d, J=6.1 Hz, 1H), 9.93 (br d, J=7.6 Hz, 1H), 8.19 (br s, 1H), 7.91 (dd, J=16.8, 1.8 Hz, 1H), 7.75 (br s, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.46 (br t, J=9.8 Hz, 1H), 7.20 (t, J=8.5 Hz, 1H), 5.39 - 5.27 (m, 1H), 4.68 (br d, J=9.8 Hz, 1H), 4.52 - 4.38 (m, 2H), 4.13 - 4.01 (m, 1H), 3.96 - 3.82 (m, 1H), 3.80 - 3.67 (m, 1H), 3.63 (br d, J=10.7 Hz, 1H), 3.15 (br d, J=10.1 Hz, 1H), 3.08 (br d, J=4.3 Hz, 1H), 2.72 (s, 6H), 2.56 - 2.52 (m, 1H), 1.93 - 1.73 (m, 2H), 1.50 (br s, 1H), 1.45 (br s, 1H), 1.39 (br d, J=11.3 Hz, 1H), 0.87 - 0.66 (m, 2H), 0.34 (br s, 2H)	2.58, B

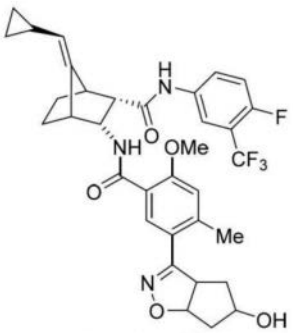
462	 由手性苯甲酸中间体制备。制备型色谱条件：仪器：Berger MG II柱：Chiralpak IC，30 × 250 mm，5微米，移动相：25% 甲醇 /75% CO_2，流动条件：70 mL/min，120巴，40 °C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH中。RT = 5.91 min 峰1	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-(2-羟基丙烷-2-基)-3a,5,6,6a-四氢-4H-环戊并[d]异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	670.4	(500 MHz, CD3OD) δ 8.34 (d, J=2.4 Hz, 1H), 8.19 - 8.14 (m, 1H), 7.87 (d, J=8.5 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.28 (t, J=9.8 Hz, 1H), 7.24 (d, J=8.5 Hz, 1H), 5.17 (dd, J=8.7, 4.9 Hz, 1H), 4.72 (d, J=9.5 Hz, 1H), 4.57 (dd, J=10.6, 3.4 Hz, 1H), 4.13 (s, 3H), 3.33 (dt, J=3.3, 1.6 Hz, 1H), 3.25 - 3.14 (m, 2H), 2.72 (t, J=3.7 Hz, 1H), 2.11 - 2.06 (m, 1H), 2.03 - 1.90 (m, 4H), 1.88 - 1.77 (m, 2H), 1.60 - 1.46 (m, 3H), 1.16 (d, J=11.9 Hz, 6H), 0.82 - 0.68 (m, 2H), 0.42 - 0.28 (m, 2H)	2.53, C

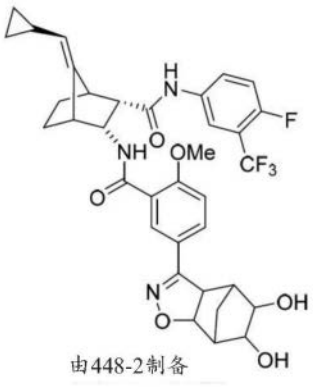
463	 由同手性甲酸酯中间体(峰-2，RT=5.46 min，>99% ee)制备-仪器：Jasco SFC柱：Chiralpak IA，21×250 mm，5微米，移动相：20% MeOH / 80% CO_2，流动条件：45 mL/min，150巴， 40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IA，4.6×100 mm，3微米，移动相：20% MeOH / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=1.69 min.，>99% ee)(峰-2，RT=5.46 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-4-氟-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.88 (br d, J=6.7 Hz, 1H), 8.35 (d, J=8.9 Hz, 1H), 8.27 - 8.20 (m, 1H), 7.89 - 7.75 (m, 1H), 7.50 (br t, J=9.8 Hz, 1H), 7.25 (d, J=13.1 Hz, 1H), 5.35 (dd, J=9.2, 3.4 Hz, 1H), 4.71 (d, J=9.8 Hz, 1H), 4.53 - 4.39 (m, 2H), 4.12 (br d, J=10.7 Hz, 1H), 4.07 (s, 3H), 3.91 (br d, J=9.2 Hz, 1H), 3.75 (dd, J=9.2, 7.0 Hz, 1H), 3.66 (dd, J=10.7, 3.4 Hz, 1H), 3.23 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.74 (br s, 1H), 1.91 - 1.81 (m, 1H), 1.80 - 1.72 (m, 1H), 1.51 (ddd, J=12.8, 8.4, 4.4 Hz, 1H), 1.46 - 1.34 (m, 2H), 0.85 - 0.64 (m, 2H), 0.36 (br s, 2H)	2.55, B

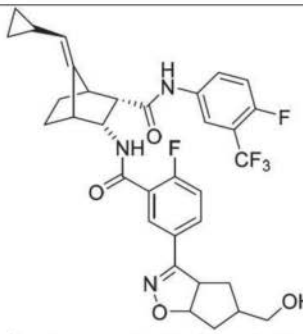
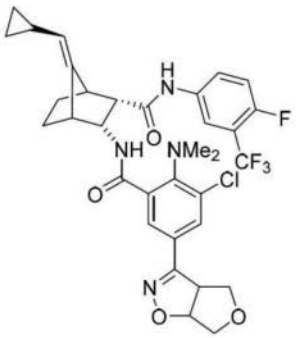
464	 由手性苯甲酸中间体制备。制备型色谱条件：仪器：Berger MG II柱：Chiralpak IC，30 × 250 mm，5微米，移动相：25% 甲醇/75% CO_2，流动条件：70 mL/min，120巴，40 °C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH中。RT = 10.14 min 峰2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.4	(500 MHz, CD_3OD) δ 8.34 (d, J=2.4 Hz, 1H), 8.19 - 8.15 (m, 1H), 7.90 (dd, J=8.7, 2.4 Hz, 1H), 7.76 (d, J=8.3 Hz, 1H), 7.29 (t, J=9.3 Hz, 1H), 7.24 (d, J=8.6 Hz, 1H), 5.18 (dt, J=10.5, 7.0 Hz, 1H), 5.03 - 4.89 (m, 1H), 4.88 - 4.66 (m, 1H), 4.60 - 4.53 (m, 1H), 4.15 - 4.06 (s, 3H), 3.23 (t, J=3.8 Hz, 1H), 3.17 (dd, J=10.7, 4.1 Hz, 1H), 2.72 (t, J=3.8 Hz, 1H), 2.41 - 2.29 (m, 2H), 2.13 (tt, J=12.4, 6.3 Hz, 1H), 2.05 - 1.88 (m, 2H), 1.68 (td, J=12.8, 6.7 Hz, 1H), 1.61 - 1.48 (m, 4H), 1.18 (d, J=2.9 Hz, 6H), 0.81 - 0.71 (m, 2H), 0.40 - 0.31 (m, 2H)。	2.54, B

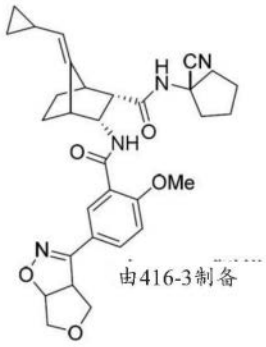
465	 来自(S)-2-丁炔醇	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(4-氟-3-(三氟甲基)苯基)-3-(5-(5-((S)-1-羟基乙基)异噁唑-3-基)-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	614.2	(400 MHz, $CDCl_3$) δ 8.49 (d, J=2.3 Hz, 1H), 8.14 (dd, J=6.5, 2.5 Hz, 1H), 7.99 (dd, J=8.6, 2.3 Hz, 1H), 7.75 (dt, J=8.8, 3.4 Hz, 1H), 7.31 - 7.25 (m, 2H), 6.69 (d, J=0.8 Hz, 1H), 5.00 - 4.93 (m, 1H), 4.83 (ss, 6H), 4.73 (d, J=9.4 Hz, 1H), 4.57 (dd, J=10.7, 3.0 Hz, 1H), 4.14 (s, 3H), 3.26 - 3.12 (m, 2H), 2.73 - 2.69 (m, 1H), 2.05 - 1.87 (m, 2H), 1.62 - 1.47 (d, 3H), 0.80 - 0.70 (m, 2H), 0.39 - 0.30 (m, 2H)	2.46, C
466	 由429-8制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-(1-甲基环戊基)双环[2.2.1]庚烷-2-甲酰胺	562.0	(500 MHz, DMSO-d6) δ 10.16 (d, J=6.6 Hz, 1H), 8.19 (d, J=2.3 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.73 (s, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.11 (dd, J=8.6, 5.3 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.28 - 4.16 (m, 2H), 4.02 (s, 3H), 3.07 - 3.01 (m, 1H), 2.88 (dd, J=10.9, 4.3 Hz, 1H), 2.03 - 1.41 (m, 17H), 1.31 (s, 5H), 0.77 - 0.63 (m, 2H), 0.31 (br d, J=3.6 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.39, B

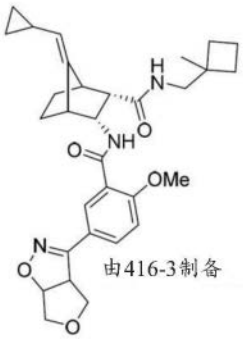
469	 由同手性苯甲酸酯中间体制备。峰 1 酯 (RT=4.42 min.，>99% ee)中间体。仪器：Berger MG II 柱：Chiralcel OD-H，21 × 250 mm，5微米，移动相：7% MeOH / 93% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱 Chiralcel OD-H，4.6 × 100 mm，3微米，移动相：7% MeOH / 93% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=4.42 min.，>99% ee)及手性(峰-2，RT=5.52 min.，>99% dee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂-4-氮杂三环[5.2.1.0^{2,6}]癸-4-烯-5-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	638.0	(500 MHz, DMSO-d6) δ 10.77 - 10.47 (m, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.51 - 8.15 (m, 2H), 8.06 - 7.74 (m, 2H), 7.49 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 4.71 (br d, J=9.5 Hz, 1H), 4.59 (br d, J=8.2 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.05 (s, 3H), 3.52 (br s, 2H), 3.17 (br dd, J=10.5, 4.1 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.47 (br s, 1H), 2.36 (br s, 1H), 1.91 - 1.80 (m, 1H), 1.80 - 1.69 (m, 1H), 1.61 - 1.48 (m, 2H), 1.45 - 1.31 (m, 3H), 1.25 (br s, 1H), 1.14 (br d, J=10.7 Hz, 2H), 0.92 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.84, C

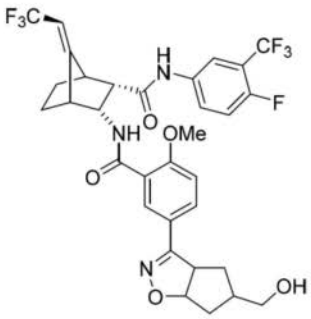
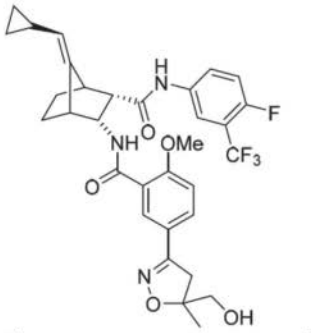
471	 第四洗脱异构体 反相HPLC	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	641.9	(500 MHz, DMSO-d6) δ 10.23 (br d, J=4.3 Hz, 1H), 9.64 (d, J=7.1 Hz, 1H), 7.95 (br d, J=4.8 Hz, 1H), 7.73 (s, 1H), 7.57 - 7.46 (m, 1H), 7.21 (br t, J=9.7 Hz, 1H), 6.90 (s, 1H), 4.91 - 4.75 (m, 1H), 4.43 (d, J=9.5 Hz, 1H), 4.25 - 4.10 (m, 1H), 3.99 (td, J=9.1, 3.0 Hz, 1H), 3.85 - 3.80 (m, 1H), 3.81 - 3.69 (m, 3H), 3.68 - 3.59 (m, 1H), 2.89 (br dd, J=10.6, 3.4 Hz, 1H), 2.83 (br s, 1H), 2.50 - 2.41 (m, 1H), 2.22 (s, 3H), 1.75 (br dd, J=13.9, 3.5 Hz, 1H), 1.68 - 1.55 (m, 3H), 1.52 - 1.47 (m, 1H), 1.46 - 1.35 (m, 1H), 1.30 - 1.19 (m, 1H), 1.18 - 1.05 (m, 2H), 0.59 - 0.35 (m, 2H), 0.25 - 0.01 (m, 2H)	2.52, B

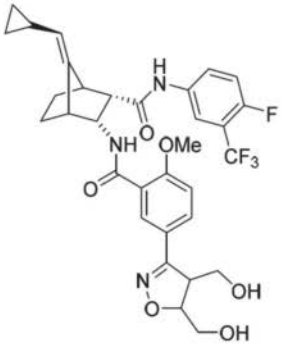
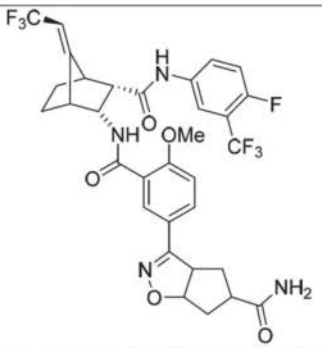
472	 由448-2制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{8,9-二羟基-3-氧杂-4-氮杂三环[5.2.1.0^{2,6}]癸-4-烯-5-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	670.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.36 - 8.21 (m, 2H), 7.99 - 7.77 (m, 2H), 7.49 (br t, J=9.8 Hz, 1H), 7.28 (br d, J=8.9 Hz, 1H), 4.96 - 4.75 (m, 1H), 4.70 (br d, J=9.8 Hz, 1H), 4.58 (br d, J=8.2 Hz, 1H), 4.45 (br s, 1H), 4.08 (s, 3H), 3.80 (br s, 1H), 3.67 (br d, J=4.0 Hz, 1H), 3.63 (br s, 1H), 3.32 (br s, 1H), 3.25 - 3.09 (m, 2H), 2.73 (br s, 1H), 2.31 (s, 1H), 2.17 (br s, 1H), 1.92 (s, 1H), 1.84 (br d, J=10.1 Hz, 1H), 1.78 (br s, 1H), 1.68 (br d, J=10.4 Hz, 1H), 1.52 (br s, 1H), 1.42 (br s, 2H), 1.11 (br d, J=10.1 Hz, 1H), 0.91 - 0.70 (m, 2H), 0.36 (br s, 2H)	2.38, C

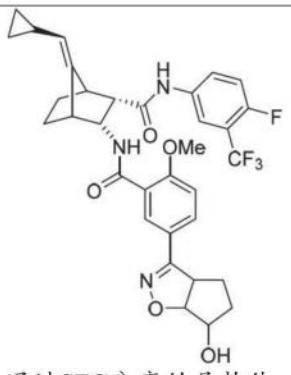
473	 由同手性苯甲酸酯中间体制备(峰3；100%ee；手性分析型RT=4.302 min)；制备型手性SFC条件：仪器：Berger MG II；柱：Chiralpak AD-H，21×250 mm，5微米；移动相：20%MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL~125mg/mL于MeOH:CAN中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.5	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.39 - 9.33 (m, 1H), 8.08 - 8.04 (m, 1H), 8.00 - 7.97 (m, 1H), 7.88 - 7.82 (m, 2H), 7.50 - 7.41 (m, 2H), 5.17 - 5.13 (m, 1H), 4.71 - 4.67 (m, 1H), 4.46 - 4.40 (m, 1H), 4.22 (t, J=8.6 Hz, 1H), 3.40 - 3.30 (m, 2H), 3.16 (dd, J=10.6, 4.2 Hz, 1H), 3.11 (t, J=3.8 Hz, 1H), 2.75 - 2.72 (m, 1H), 1.99 (dd, J=13.6, 5.8 Hz, 1H), 1.92 - 1.72 (m, 4H), 1.67 - 1.37 (m, 5H), 0.79 - 0.69 (m, 2H), 0.39 - 0.31 (m, 2H)	2.22, A
474	 经反相HPLC的第二洗脱非镜像异构体	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氯-2-(二甲基氨基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	661.0	(500 MHz, DMSO-d6) δ 10.46 (s, 1H), 9.79 (br d, J=7.6 Hz, 1H), 8.11 (br d, J=6.9 Hz, 1H), 7.83 (d, J=1.5 Hz, 1H), 7.80 - 7.73 (m, 2H), 7.44 (t, J=9.8 Hz, 1H), 5.35 (dd, J=9.0, 3.5 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.52 - 4.39 (m, 2H), 4.08 (d, J=11.0 Hz, 1H), 3.95 - 3.87 (m, 1H), 3.68 - 3.56 (m, 2H), 3.21 - 3.11 (m, 1H), 3.07 (br s, 1H), 2.82 (s, 6H), 2.71 (br s, 1H), 1.96 - 1.83 (m, 2H), 1.56 - 1.47 (m, 1H), 1.42 (br d, J=19.2 Hz, 2H), 0.79 - 0.67 (m, 2H), 0.34 (br s, 2H)	2.93, B

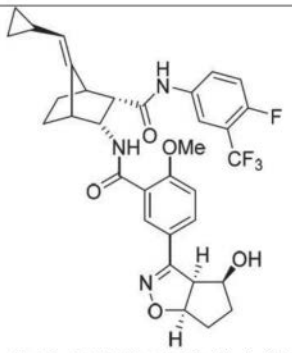
476	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(1-氰基环戊基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	545.1	(500 MHz, DMSO-d6) δ 10.03 (br d, J=6.7 Hz, 1H), 8.69 (s, 1H), 8.20 (d, J=2.1 Hz, 1H), 7.79 (dd, J=8.7, 2.3 Hz, 1H), 7.25 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.3, 3.5 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.6 Hz, 1H), 4.35 - 4.27 (m, 1H), 4.12 - 4.02 (m, 4H), 3.93 - 3.86 (m, 1H), 3.81 - 3.74 (m, 1H), 3.65 (dd, J=10.8, 3.5 Hz, 1H), 3.07 (br s, 1H), 2.96 (br dd, J=10.7, 4.0 Hz, 1H), 2.59 (br s, 1H), 2.16 (br d, J=4.3 Hz, 2H), 2.09 - 1.99 (m, 2H), 1.77 - 1.63 (m, 6H), 1.53 - 1.31 (m, 3H), 0.77 - 0.65 (m, 2H), 0.32 (br d, J=2.4 Hz, 2H)。	2.15, B

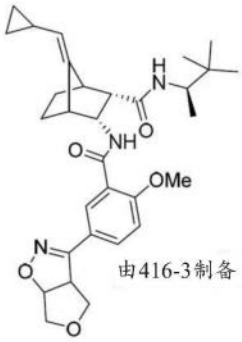
477	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1-甲基环丁基)甲基]双环[2.2.1]庚烷-2-甲酰胺	534.0	(500 MHz, DMSO-d6) δ 9.98 (d, J=7.0 Hz, 1H), 8.16 (d, J=2.3 Hz, 1H), 8.05 (t, J=6.1 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.34 (dd, J=9.2, 3.6 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.9 Hz, 1H), 4.34 - 4.25 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.90 (d, J=9.5 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.65 (dd, J=10.7, 3.6 Hz, 1H), 3.15 (dd, J=13.3, 6.4 Hz, 1H), 3.06 - 2.96 (m, 3H), 1.91 - 1.67 (m, 6H), 1.60 - 1.42 (m, 3H), 1.40 - 1.26 (m, 2H), 1.01 (s, 3H), 0.78 - 0.65 (m, 2H), 0.32 (dd, J=4.6, 2.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子不可见。	2.41, C

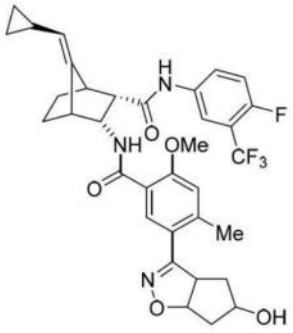
478	 由429-8制备	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	670.3	(400 MHz, CD_3OD) δ 10.32 - 10.26 (m, 1H), 8.34 (d, J=2.2 Hz, 1H), 8.19 (dd, J=6.3, 2.5 Hz, 1H), 7.92 (dd, J=8.7, 2.3 Hz, 1H), 7.82 - 7.75 (m, 1H), 7.39 - 7.26 (m, 2H), 5.80 (q, J=7.5 Hz, 1H), 5.23 (dd, J=8.6, 5.1 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.30 - 4.21 (m, 1H), 4.16 (s, 3H), 3.61 - 3.51 (m, 2H), 3.43 (br s, 1H), 3.28 (br dd, J=10.8, 4.2 Hz, 1H), 2.97 (br s, 1H), 2.23 - 1.96 (m, 6H), 1.83 - 1.73 (m, 1H), 1.71 - 1.59 (m, 3H)	2.20, C
480	 峰 – 2，RT = 3.12 min：制备型SFC条件：柱/尺寸：Chiralpak IC (250 × 30) mm，5u，% CO_2: 50%助溶剂：50% 4M甲醇氨于MEOH中，总流苏：140.0g/min，背压：100巴，温度：40℃，UV：238 nm。	(1R,2S,3R,4R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.89 (d, J=6.8 Hz, 1H), 8.22 (dd, J=6.6, 2.7 Hz, 1H), 8.20 (d, J=2.2 Hz, 1H), 7.84 - 7.77 (m, 1H),7.75 (dd, J=8.7, 2.3 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 5.14 - 5.01 (m, 1H), 4.69 (d, J=9.3 Hz, 1H), 4.49 - 4.38 (m, 1H), 4.03(s, 4H), 3.16 (dd, J=10.6, 4.3 Hz, 2H), 3.12 - 3.07 (m, 1H), 3.02 (d, J=16.6 Hz, 1H), 2.75 - 2.69 (m, 1H), 1.88 - 1.72 (m, 3H), 1.55 - 1.35 (m, 4H),1.31 (s, 3H), 1.23 (s, 1H), 0.80 - 0.66 (m, 2H), 0.35 (dd, J=4.5, 2.3 Hz, 2H)。	2.37, D

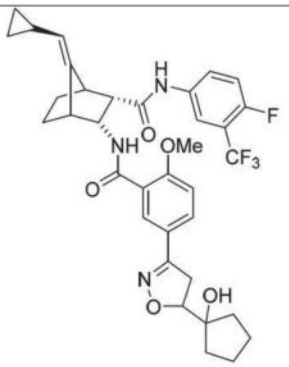
481	 由同手性苯甲酸酯中间体(峰2；>99%ee；手性分析型RT=6.217 min)制备；制备型手性SFC条件：仪器：PIC Solution SFC Prep-200：柱：Chiralpak IF，21×250 mm，5微米：移动相：35% 甲醇/65% CO_2：流动条件：45 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：0.75 mL ~50mg/mL于MeOH-CAN中	(1R,2S,3R,4R,7Z)-3-{5-[4,5-双(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.3	(500 MHz, DMSO-d6) δ 10.55 - 10.51 (m, 1H), 9.92 - 9.88 (m, 1H), 8.31 - 8.26 (m, 1H), 8.25 - 8.20 (m, 1H), 7.84 - 7.77 (m, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.29 - 7.25 (m, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.61 - 4.57 (m, 1H), 4.47 - 4.43 (m, 1H), 4.04 (s, 3H), 3.95 (dd, J=12.0, 4.7 Hz, 1H), 3.86 - 3.81 (m, 2H), 3.59 (d, J=4.7 Hz, 2H), 3.17 (dd, J=10.7, 4.1 Hz, 1H), 3.11 (t, J=3.6 Hz, 1H), 2.73 (t, J=3.4 Hz, 1H), 1.87 - 1.76 (m, 2H), 1.54 - 1.47 (m, 1H), 1.46 - 1.37 (m, 2H), 0.80 - 0.70 (m, 2H), 0.39 - 0.33 (m, 2H)	1.08, A
482	 由同手性苯甲酸酯中间体(峰2；>99%ee；手性分析型RT=2.742 min)制备；制备型手性SFC条件：仪器：Jasco SFC Prep：柱：Chiralpak AS-H，30×250 mm，5微米；移动相：30% MeOH / 70% CO_2；流动条件：85 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：1.0 mL ~50mg/mLmg/mL 于MeOH:TFA中	3-(3-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酰胺	683.3	(500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.97 (d, J=6.9 Hz, 1H), 8.27 - 8.22 (m, 2H), 7.84 - 7.78 (m, 2H), 7.51 (t, J=9.8 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.29 (d, J=8.9 Hz, 1H), 6.81 (br s, 1H), 5.99 - 5.92 (m, 1H), 5.16 (dd, J=8.5, 5.0 Hz, 1H), 4.55 - 4.48 (m, 1H), 4.28 (t, J=8.9 Hz, 1H), 4.05 (s, 3H), 3.31 - 3.23 (m, 2H), 3.02 - 2.97 (m, 1H), 2.58 - 2.53 (m, 1H), 2.13 - 1.85 (m, 6H), 1.50 (br d, J=6.7 Hz, 1H)	1.29

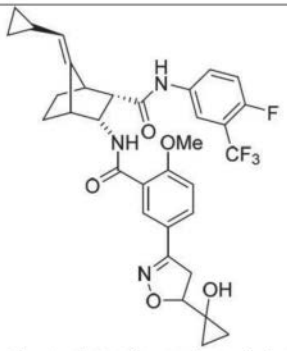
483	 通过SFC分离的异构体，其中实施例483为第四洗脱异构体：仪器：Jasco SFC制备型柱：Chiralpak IA，30×250 mm，5微米，移动相：15% MeOH / 85% CO_2，流动条件：85 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~21mg/mL于甲醇中，分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IA，4.6×100 mm，3微米，移动相：15% MeOH / 85% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中。峰-4 RT 6.83 min > 96.4% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{6-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.91 (br d, J=7.3 Hz, 1H), 8.28 - 8.15 (m, 2H), 7.81 (br d, J=8.5 Hz, 1H), 7.77 (br d, J=9.2 Hz, 1H), 7.47 (br t, J=9.6 Hz, 1H), 7.28 (br d, J=8.9 Hz, 1H), 4.80 (br d, J=8.9 Hz, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.43 (br s, 1H), 4.24 (br t, J=8.5 Hz, 1H), 4.12 (br s, 1H), 4.04 (s, 3H), 3.68 (br s, 2H), 3.26 - 3.07 (m, 2H), 3.00 (s, 1H), 2.72 (br s, 1H), 2.20 (br s, 1H), 1.83 (br d, J=10.1 Hz, 1H), 1.77 (br d, J=9.8 Hz, 1H), 1.70 - 1.58 (m, 2H), 1.50 (br d, J=8.5 Hz, 1H), 1.41 (br s, 3H), 0.84 - 0.69 (m, 2H), 0.35 (br d, J=4.0 Hz, 2H)	2.45

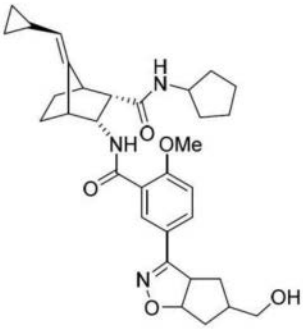
484	 由同手性苯甲酸酯中间体-峰1制备。色谱条件：仪器：Berger MG II 柱：Chiralpak IC，30 × 250 mm，5微米，移动相：25% 甲醇 / 75% CO_2，流动条件：70 mL/min，120巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH中(峰-1，RT 3.40 min.，> 99% ee)	(1R,2S,3R,4R,7Z)-3-{5-[(3aS,4S,6aR)-4-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	628.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (br d, J=6.7 Hz, 1H), 8.23 (s, 1H), 8.23 (d, J=6.2 Hz, 1H), 7.79 (br d, J=8.5 Hz, 2H), 7.49 (br t, J=9.8 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 4.97 (d, J=6.7 Hz, 1H), 4.82 (br dd, J=8.5, 4.6 Hz, 1H), 4.71 (br d, J=9.5 Hz, 1H), 4.45 (br s, 1H), 4.13 (br t, J=9.0 Hz, 1H), 4.05 (s, 3H), 3.47 (br s, 1H), 3.31 - 3.13 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H),1.93 - 1.76 (m, 3H), 1.76 - 1.66 (m, 1H), 1.62 - 1.47 (m, 2H), 1.43 (br s, 2H), 1.40 - 1.19 (m, 2H), 0.86 - 0.68 (m, 2H), 0.36 (br s, 2H)。	2.43

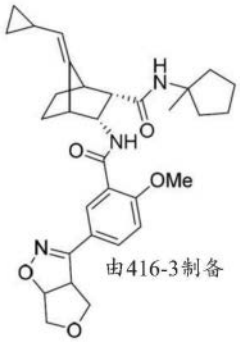
485	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2R)-3,3-二甲基丁烷-2-基]双环[2.2.1]庚烷-2-甲酰胺	536.2	(500 MHz, DMSO-d6) δ 10.04 - 9.95 (m, 1H), 8.12 (d, J=2.1 Hz, 1H), 7.80 - 7.71 (m, 2H), 7.25 - 7.21 (m, 1H), 5.33 (dd, J=9.3, 3.2 Hz, 1H), 4.62 (d, J=9.8 Hz, 1H), 4.48 (br t, J=7.9 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.92 - 3.86 (m, 1H), 3.80 - 3.61 (m, 2H), 3.07 - 3.02 (m, 1H), 3.01 - 2.94 (m, 1H), 1.88 - 1.80 (m, 1H), 1.77 - 1.67 (m, 1H), 1.51 - 1.41 (m, 1H), 1.38 - 1.24 (m, 2H), 0.96 - 0.89 (m, 3H), 0.83 (s, 9H), 0.76 - 0.64 (m, 2H), 0.30 (br d, J=2.7 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR不可见。	2.46

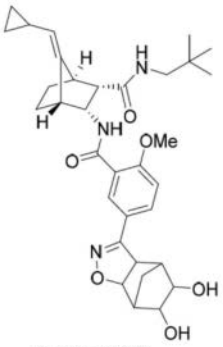
486	 第三洗脱异构体 反相HPLC	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	641.9	(500 MHz, DMSO-d6) δ 10.70 - 10.36 (m, 1H), 10.01 - 9.69 (m, 1H), 8.25 (br d, J=4.3 Hz, 1H), 8.02 (s, 1H), 7.80 (br d, J=8.5 Hz, 1H), 7.50 (br t, J=9.6 Hz, 1H), 7.23 - 7.06 (m, 1H), 5.07 (br t, J=7.8 Hz, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.54 - 4.41 (m, 1H), 4.23 - 4.10 (m, 2H), 4.09 - 3.97 (m, 3H), 3.57 - 3.30 (m, 1H), 3.16 (br dd, J=10.4, 4.0 Hz, 1H), 3.10 (br s, 1H), 2.78 - 2.68 (m, 1H), 2.49 (s, 3H), 2.15 - 2.04 (m, 1H), 2.00 - 1.90 (m, 2H), 1.87 - 1.80 (m, 1H), 1.80 - 1.72 (m, 1H), 1.64 - 1.56 (m, 1H), 1.55 - 1.46 (m, 1H), 1.46 - 1.31 (m, 2H), 0.87 - 0.65 (m, 2H), 0.51 - 0.21 (m, 2H)	2.54

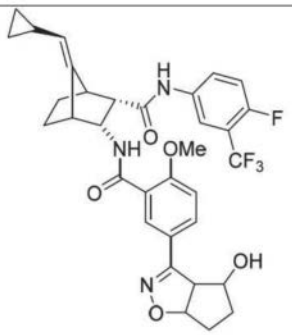
488	 由同手性苯甲酸酯制备。峰1-(RT=3.28 min.，>99% de)-仪器：Berger MG II柱：Chiralpak IC，21×250 mm，5微米，移动相：30% MeOH / 70% CO_2，流动条件：45 mL/min，150巴， 40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱ChiralpakIC，4.6×100 mm，3微米，移动相：30% MeOH / 70% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=3.28 min.，>99% de)及手性(峰-2，RT=3.85 min.，>99% de)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环戊基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.24 (br s, 1H), 8.23 (br s, 1H), 7.80 (br d, J=1.8 Hz, 1H), 7.79 (br d, J=1.8 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.28 (d, J=8.5 Hz, 1H), 4.71 (d, J=9.8 Hz, 1H), 4.60 (dd, J=11.0, 8.9 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.06 (s, 3H), 3.60 - 3.21 (m, 1H), 3.17 (br dd, J=10.5, 4.1 Hz, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 1.90 - 1.77 (m, 2H), 1.73 (br s, 2H), 1.64 - 1.49 (m, 7H), 1.45 - 1.37 (m, 2H), 0.76 (br dd, J=11.9, 8.9 Hz, 2H), 0.37 (br s, 2H)	2.65

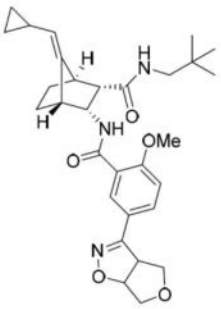
491	 由同手性苯甲酸酯中间体-峰2 (RT=6.88 min.，>97% ee)制备，所用仪器：Berger MG II柱：Chiralpak IF，21 × 250 mm，5微米，移动相：30% MeOH/70% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Aurora Infinity SFC，柱Chiralpak IF，4.6 × 250 mm，3微米，移动相：30% MeOH/70% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=4.78 min.，>99% ee)及手性(峰-2，RT=6.88 min.，>97% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环丙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	628.4	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.92 (d, J=7.2 Hz, 1H), 8.32 - 8.17 (m, 2H), 7.82 - 7.80 (m, 1H), 7.79 (d, J=2.3 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.28 (d, J=8.7 Hz, 1H), 5.74 - 5.37 (m, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.52 - 4.43 (m, 1H), 4.38 - 4.30 (m, 1H), 4.05 (s, 3H), 3.45 - 3.41 (m, 2H), 3.17 (dd, J=11.0, 4.1 Hz, 1H), 3.13 - 3.09 (m, 1H), 2.73 (t, J=3.6 Hz, 1H), 1.90 - 1.81 (m, 1H), 1.80 - 1.72 (m, 1H), 1.56 - 1.47 (m, 1H), 1.44 - 1.32 (m, 2H), 0.83 - 0.74 (m, 1H), 0.70 - 0.65 (m, 1H), 0.62 - 0.51 (m, 3H), 0.44 - 0.32 (m, 2H)	2.41, C

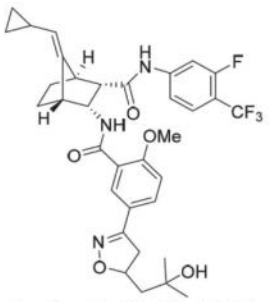
493	 由429-8制备	(1R,2S,3R,4R,7Z)-N-环戊基-7-(环丙基亚甲基)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	548.2	(500 MHz, DMSO-d6) δ 10.01 (br d, J=6.7 Hz, 1H), 8.17 (d, J=1.8 Hz, 1H), 8.02 (br d, J=7.0 Hz, 1H), 7.79 (dd, J=8.5, 2.1 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.11 (br dd, J=8.5, 5.2 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.48 (br t, J=5.0 Hz, 1H), 4.30 - 4.23 (m, 1H), 4.20 (br t, J=8.9 Hz, 1H), 4.07 - 3.97 (m, 4H), 3.04 (br s, 1H), 2.88 (br dd, J=11.0, 4.3 Hz, 1H), 2.02 - 1.41 (m, 15H), 1.38 - 1.26 (m, 4H), 0.71 (quin, J=9.7 Hz, 2H), 0.32 (br s, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.19, B

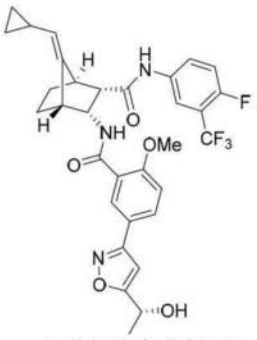
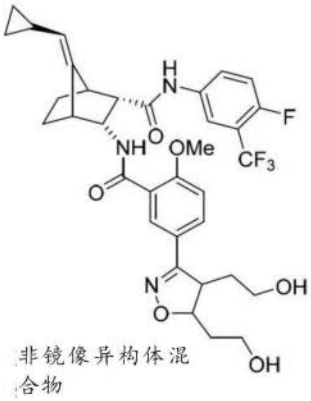
494	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(1-甲基环戊基)双环[2.2.1]庚烷-2-甲酰胺	534.4	(500 MHz, DMSO-d6) δ 10.17 (br d, J=6.7 Hz, 1H), 8.17 (d, J=1.8 Hz, 1H), 7.83 - 7.69 (m, 2H), 7.24 (d, J=8.5 Hz, 1H), 5.33 (br dd, J=9.3, 3.2 Hz, 1H), 4.60 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=7.9 Hz, 1H), 4.30 - 4.20 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.92 - 3.83 (m, 1H), 3.82 - 3.72 (m, 1H), 3.65 (br dd, J=10.8, 3.5 Hz, 1H), 3.03 (br s, 1H), 2.87 (br dd, J=11.1, 4.1 Hz, 1H), 2.02 - 1.87 (m, 2H), 1.86 - 1.76 (m, 1H), 1.74 - 1.64 (m, 1H), 1.63 - 1.39 (m, 7H), 1.30 (s, 5H), 0.77 - 0.60 (m, 2H), 0.30 (br d, J=2.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子不可见。	2.56, B

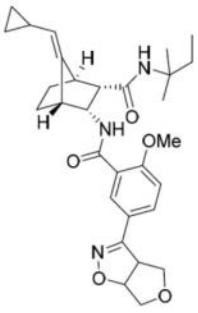
495	 由448-3制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{8,9-二羟基-3-氧杂-4-氮杂三环[5.2.1.0²,⁶]癸-4-烯-5-基}-2-甲氧基苯甲酰胺基)-N-(2,2-二甲基丙基)双环[2.2.1]庚烷-2-甲酰胺	578.6	(500 MHz, DMSO-d6) δ 9.97 (br d, J=7.0 Hz, 1H), 8.17 (d, J=2.1 Hz, 1H), 7.97 (br t, J=6.3 Hz, 1H), 7.80 (dd, J=8.5, 1.8 Hz, 1H), 7.22 (d, J=8.9 Hz, 1H), 4.79 (d, J=5.2 Hz, 1H), 4.62 (br d, J=9.5 Hz, 1H), 4.56 (br d, J=8.9 Hz, 1H), 4.32 - 4.23 (m, 1H), 3.99 (s, 2H), 3.80 - 3.75 (m, 1H), 3.68 - 3.58 (m, 1H), 3.07 - 2.97 (m, 3H), 2.79 (br dd, J=12.8, 5.8 Hz, 1H), 2.29 (s, 1H), 2.15 (s, 1H), 1.88 - 1.82 (m, 1H), 1.77 - 1.69 (m, 1H), 1.66 (br d, J=11.3 Hz, 1H), 1.49 - 1.41 (m, 1H), 1.40 - 1.27 (m, 2H), 1.09 (br d, J=10.4 Hz, 1H), 0.80 (s, 8H), 0.75 - 0.65 (m, 2H), 0.31 (br s, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.12, C

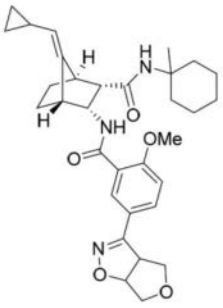
496	 由同手性苯甲酸酯中间体峰3制备：制备型色谱条件：仪器：Berger MG II柱：Chiralpak IC，30×250 mm，5微米，移动相：25%甲醇/75% CO_2，流动条件：70 mL/min，120巴，40℃，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6×100 mm，3微米，移动相：25% MeOH/75% CO_2，流动条件：2.0 mL/min，150巴，40℃，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中（峰-3，RT 4.93 min.，>98% ee)	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{4-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.33 (d, J=2.1 Hz, 1H), 8.23 (br d, J=4.6 Hz, 1H), 7.98 - 7.82 (m, 1H), 7.79 (br d, J=7.9 Hz, 1H), 7.49 (br t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 5.22 (br dd, J=8.2, 4.9 Hz, 1H), 4.71 (d, J=9.5 Hz, 1H), 4.45 (br s, 1H), 4.12 (br s, 1H), 4.06 (s, 3H), 4.01 - 3.83 (m, 1H), 3.57 - 3.39 (m, 1H), 3.24 - 3.08 (m, 2H), 2.85 - 2.63 (m, 1H), 2.15 (dt, J=13.0, 6.6 Hz, 1H), 1.94 (br dd, J=13.4, 6.4 Hz, 1H), 1.88 - 1.74 (m, 2H), 1.65 (br dd, J=13.0, 6.3 Hz, 1H), 1.56 - 1.37 (m, 4H), 0.88 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.48, C

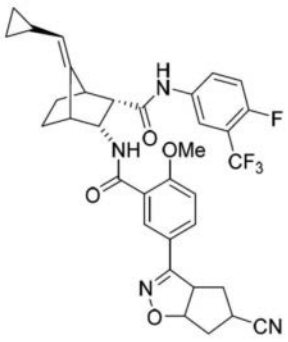
497	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2,2-二甲基丙基)双环[2.2.1]庚烷-2-甲酰胺	534.4	(500 MHz, DMSO-d6) δ 10.17 (br d, J=6.7 Hz, 1H), 8.17 (d, J=1.8 Hz, 1H), 7.83 - 7.69 (m, 2H), 7.24 (d, J=8.5 Hz, 1H), 5.33 (br dd, J=9.3, 3.2 Hz, 1H), 4.60 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=7.9 Hz, 1H), 4.30 - 4.20 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.92 - 3.83 (m, 1H), 3.82 - 3.72 (m, 1H), 3.65 (br dd, J=10.8, 3.5 Hz, 1H), 3.03 (br s, 1H), 2.87 (br dd, J=11.1, 4.1 Hz, 1H), 2.02 - 1.87 (m, 2H), 1.86 - 1.76 (m, 1H), 1.74 - 1.64 (m, 1H), 1.63 - 1.39 (m, 7H), 1.30 (s, 5H), 0.77 - 0.60 (m, 2H), 0.30 (br d, J=2.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子不可见。	2.56, B

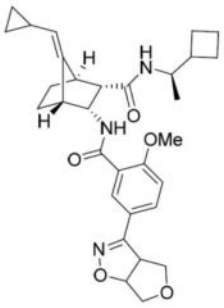
499	 由同手性苯甲酸峰2(RT=7.92 min.，>99% ee)制备。所用仪器：PIC Solution SFC柱：Chiralpak IC，21 × 250 mm，5微米，移动相：40% MeOH / 60% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Aurora Infinity SFC，柱Chiralpak IC，4.6 × 250 mm，3微米，移动相：30% MeOH / 70% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=5.75 min.，>99% ee)及手性(峰-2，RT=7.92 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基-2-甲基丙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.6, 2.6 Hz, 1H), 8.21 (d, J=2.4 Hz, 1H), 7.82 - 7.79 (m, 1H), 7.78 (d, J=2.4 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 4.79 (tt, J=9.8, 6.1 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.45 (ddd, J=10.2, 6.4, 4.1 Hz, 1H), 4.05 (s, 3H), 3.54 (d, J=10.2 Hz, 1H), 3.51 (d, J=10.2 Hz, 1H), 3.17 (dd, J=10.8, 4.2 Hz, 1H), 3.13 - 3.09 (m, 1H), 3.09 - 3.03 (m, 1H), 2.73 (t, J=3.5 Hz, 1H), 1.90 - 1.82 (m, 2H), 1.79 - 1.70 (m, 2H), 1.57 - 1.48 (m, 1H), 1.45 - 1.37 (m, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 0.81 - 0.70 (m, 2H), 0.36 (dd, J=4.4, 2.6 Hz, 2H)	2.47, C

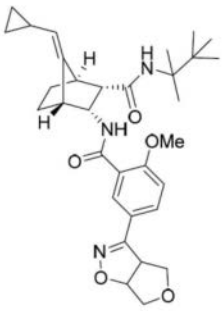
500	 以类似于实施例465的方式制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-[(1R)-1-羟基乙基]-1,2-噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	614.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 8.45 (d, J=1.8 Hz, 1H), 8.24 (br d, J=4.0 Hz, 1H), 8.00 (dd, J=8.4, 2.0 Hz, 1H), 7.81 (br d, J=9.5 Hz, 1H), 7.50 (t, J=9.8 Hz, 1H), 7.34 (d, J=8.9 Hz, 1H), 6.86 (s, 1H), 5.78 (d, J=5.5 Hz, 1H), 4.89 (br t, J=6.3 Hz, 1H), 4.72 (d, J=9.8 Hz, 1H), 4.48 (br s, 1H), 4.08 (s, 3H), 3.18 (br d, J=10.1 Hz, 1H), 3.13 (br s, 1H), 2.74 (br s, 1H), 1.93 - 1.75 (m, 2H), 1.56 - 1.38 (m, 5H), 0.88 - 0.69 (m, 2H), 0.37 (br s, 2H)	2.51, C
501	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-{5-[4,5-双(2-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	660.0	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.90 (t, J=6.9 Hz, 1H), 8.28 - 8.20 (m, 2H), 7.82 - 7.76 (m, 2H), 7.48 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.7 Hz, 1H), 4.72 - 4.58 (m, 3H), 4.48 - 4.42 (m, 1H), 4.04 (d, J=2.0 Hz, 2H), 3.59 (br dd, J=6.8, 3.1 Hz, 1H), 3.54 - 3.46 (m, 5H), 3.18 - 3.09 (m, 2H), 2.75 - 2.69 (m, 1H), 1.86 - 1.56 (m, 6H), 1.55 - 1.46 (m, 2H), 1.45 - 1.36 (m, 2H), 0.79 - 0.69 (m, 2H), 0.39 - 0.31 (m, 2H)	2.12, C

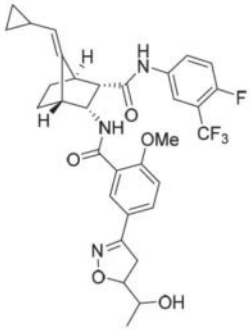
502	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2-甲基丁烷-2-基)双环[2.2.1]庚烷-2-甲酰胺	522.3	(500 MHz, DMSO-d6) δ 10.10 (br d, J=6.7 Hz, 1H), 8.19 (d, J=2.1 Hz, 1H), 7.79 (dd, J=8.5, 2.4 Hz, 1H), 7.48 (s, 1H), 7.24 (d, J=8.9 Hz, 1H), 5.34 (dd, J=8.9, 3.4 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.6 Hz, 1H), 4.30 - 4.20 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.03 (s, 3H), 3.93 - 3.86 (m, 1H), 3.82 - 3.73 (m, 1H), 3.66 (dd, J=10.7, 3.4 Hz, 1H), 3.03 (br s, 1H), 2.92 (br dd, J=10.5, 4.4 Hz, 1H), 1.91 - 1.82 (m, 1H), 1.76 - 1.55 (m, 3H), 1.50 - 1.40 (m, 1H), 1.38 - 1.26 (m, 2H), 1.19 (d, J=15.3 Hz, 6H), 0.78 - 0.64 (m, 5H), 0.31 (br d, J=3.7 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.35, B

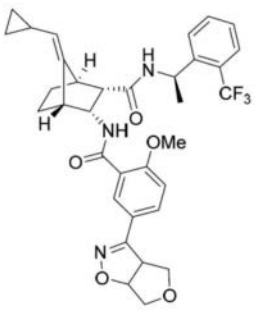
505	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(1-甲基环己基)双环[2.2.1]庚烷-2-甲酰胺	548.2	(500 MHz, DMSO-d6) δ 10.13 (br d, J=6.7 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H), 7.78 (dd, J=8.7, 2.0 Hz, 1H), 7.36 (s, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.9 Hz, 1H), 4.31 - 4.20 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.92 - 3.85 (m, 1H), 3.80 - 3.73 (m, 1H), 3.65 (dd, J=10.8, 3.5 Hz, 1H), 3.03 (br s, 1H), 2.98 (br dd, J=10.8, 3.8 Hz, 1H), 2.12 (br d, J=14.0 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.91 - 1.83 (m, 1H), 1.77 - 1.65 (m, 1H), 1.51 - 1.09 (m, 14H), 0.78 - 0.64 (m, 2H), 0.31 (br d, J=3.7 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.67, B

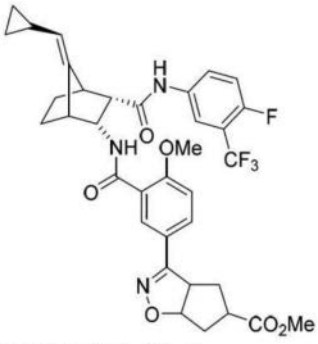
506	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-(5-{5-氟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	637.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 - 9.87 (m, 1H), 8.25 - 8.19 (m, 2H), 7.78 (br d, J=8.9 Hz, 2H), 7.47 (br t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.21 - 5.15 (m, 1H), 4.68 (br d, J=9.5 Hz, 1H), 4.43 (br s, 1H), 4.38 - 4.29 (m, 1H), 4.03 (s, 3H), 3.18 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.81 (tt, J=12.1, 6.4 Hz, 1H), 2.71 (br s, 1H), 2.41 (br dd, J=13.3, 5.6 Hz, 1H), 2.27 - 2.10 (m, 3H), 1.86 - 1.73 (m, 2H), 1.49 (br s, 1H), 1.44 - 1.35 (m, 2H), 0.79 - 0.68 (m, 2H), 0.39 - 0.30 (m, 2H)	.60, B

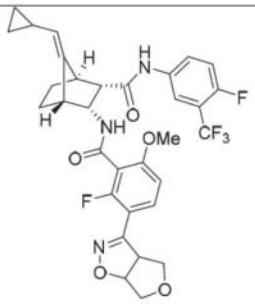
507	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[(1R)-1-环丁基乙基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	534.5	(500 MHz, DMSO-d6) δ 10.06 (d, J=6.8 Hz, 1H), 8.14 (d, J=2.3 Hz, 1H), 7.82 (br d, J=8.6 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.33 (dd, J=9.2, 3.5 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.31 - 4.22 (m, 1H), 4.09 (d, J=10.8 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=9.0 Hz, 1H), 3.85 - 3.73 (m, 2H), 3.65 (dd, J=10.8, 3.6 Hz, 1H), 3.07 - 3.01 (m, 1H), 2.89 (dd, J=10.8, 4.3 Hz, 1H), 2.26 - 2.17 (m, 1H), 1.95 - 1.80 (m, 3H), 1.80 - 1.59 (m, 5H), 1.51 - 1.41 (m, 1H), 1.40 - 1.26 (m, 2H), 0.88 (d, J=6.6 Hz, 3H), 0.78 - 0.64 (m, 2H), 0.31 (dd, J=4.4, 2.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.37, C

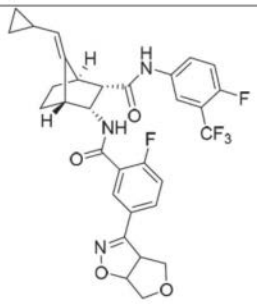
508	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2,3,3-三甲基丁烷-2-基)双环[2.2.1]庚烷-2-甲酰胺	550.0	(500 MHz, DMSO-d6) δ 10.14 (br d, J=6.7 Hz, 1H), 8.19 (d, J=2.1 Hz, 1H), 7.78 (br dd, J=8.7, 2.3 Hz, 1H), 7.23 (br d, J=8.9 Hz, 1H), 7.16 (s, 1H), 5.37 - 5.29 (m, 1H), 4.61 (br d, J=9.5 Hz, 1H), 4.54 - 4.44 (m, 1H), 4.24 (br d, J=5.5 Hz, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=8.5 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.69 - 3.61 (m, 1H), 3.08 - 3.00 (m, 2H), 1.87 (br d, J=10.7 Hz, 1H), 1.74 - 1.64 (m, 1H), 1.50 - 1.41 (m, 1H), 1.32 (s, 5H), 1.25 (s, 3H), 0.89 (s, 9H), 0.76 - 0.64 (m, 2H), 0.30 (br s, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.33, B

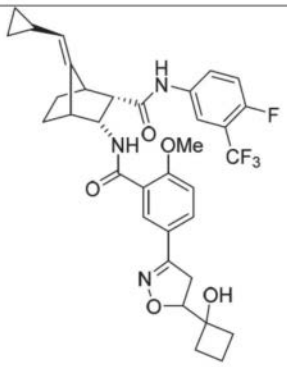
509	 由同手性苯甲酸中间体(峰2；86.6%de；手性分析型RT=9.186 min)制备；手性SFC纯化条件；仪器：Berger MG II；柱：Chiralpak IC，21×250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~35mg/mL于MeOH中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.4	(500 MHz, CD_3OD) δ 10.35 - 10.30 (m, 1H), 10.17 - 10.14 (m, 1H), 8.37 - 8.35 (m, 1H), 8.17 (dd, J=6.2, 2.7 Hz, 1H), 7.91 (dd, J=8.7, 2.4 Hz, 1H), 7.80 - 7.75 (m, 1H), 7.33 - 7.26 (m, 2H), 4.76 (d, J=9.5 Hz, 1H), 4.63 - 4.56 (m, 2H), 4.15 (s, 3H), 3.92 - 3.86 (m, 1H), 3.45 - 3.39 (m, 2H), 3.28 - 3.23 (m, 2H), 3.18 (dd, J=10.6, 3.9 Hz, 1H), 2.76 - 2.72 (m, 1H), 2.05 - 2.00 (m, 1H), 1.97 - 1.91 (m, 1H), 1.65 - 1.58 (m, 1H), 1.57 - 1.51 (m, 2H), 1.35 (t, J=7.3 Hz, 1H), 1.24 (s, 2H), 0.82 - 0.76 (m, 2H), 0.42 - 0.35 (m, 2H)	2.25, A

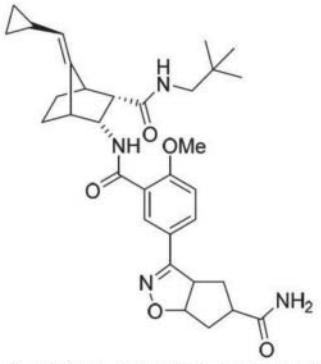
510	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-1-[2-(三氟甲基)苯基]乙基]双环[2.2.1]庚烷-2-甲酰胺	623.9	(500 MHz, DMSO-d6) δ 9.83 (d, J=6.7 Hz, 1H), 8.74 (d, J=7.0 Hz, 1H), 8.14 (d, J=2.3 Hz, 1H), 7.72 (dd, J=8.7, 2.4 Hz, 1H), 7.61 (d, J=8.0 Hz, 2H), 7.49 (br t, J=7.6 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.11 - 7.04 (m, 1H), 5.32 (dd, J=9.2, 3.5 Hz, 1H), 5.28 - 5.17 (m, 1H), 4.65 (d, J=9.5 Hz, 1H), 4.50 - 4.41 (m, 1H), 4.30 - 4.21 (m, 1H), 4.08 (d, J=10.8 Hz, 1H), 3.91 - 3.84 (m, 1H), 3.79 - 3.71 (m, 1H), 3.67 - 3.61 (m, 1H), 3.59 - 3.53 (m, 2H), 3.07 - 2.95 (m, 2H), 2.67 - 2.60 (m, 1H), 1.92 - 1.82 (m, 1H), 1.71 - 1.59 (m, 1H), 1.55 - 1.40 (m, 1H), 1.37 - 1.25 (m, 5H), 0.78 - 0.64 (m, 2H), 0.37 - 0.29 (m, 2H)。	2.43, A

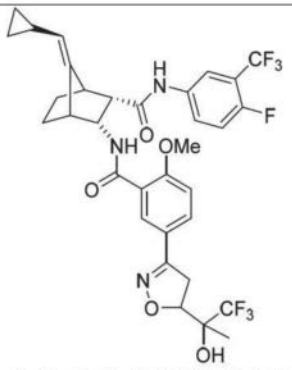
512	 非镜像异构体混合物	3-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酸甲酯	669.9	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (br d, J=5.2 Hz, 1H), 8.27 - 8.20 (m, 2H), 7.80 (br t, J=9.3 Hz, 2H), 7.49 (br t, J=9.9 Hz, 1H), 7.29 (d, J=8.5 Hz, 1H), 5.32 - 5.14 (m, 1H), 4.70 (br d, J=9.2 Hz, 1H), 4.45 (br s, 1H), 4.31 (br s, 1H), 4.05 (s, 6H), 3.59 (s, 1H), 3.47 (br s, 1H), 3.17 (br dd, J=10.4, 4.0 Hz, 1H), 3.11 (br s, 1H), 2.80 - 2.59 (m, 2H), 2.22 (br dd, J=13.6, 6.0 Hz, 1H), 1.89 - 1.72 (m, 2H), 1.52 (br s, 1H), 1.42 (br s, 2H), 0.86 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.60, C

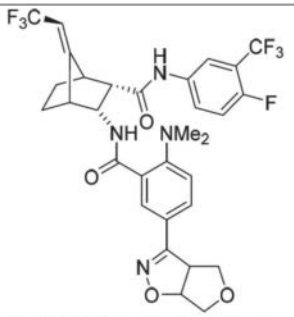
513	 经分离的异构体，其中实施例 513 为峰 1 (RT=6.74 min.，>95% de)：仪器：Waters 100 Prep SFC 柱：Chiral OD, 30 × 250 mm, 5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD, 4.6 × 100 mm，5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰 -1，RT=6.74 min.，>95% de)及手性(峰-2，RT=8.25 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-氟-6-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.2	(500 MHz, DMSO-d6) δ 10.53 - 10.34 (m, 1H), 8.75 (br d, J=7.5 Hz, 1H), 8.07 (br d, J=6.3 Hz, 1H), 7.82 - 7.66 (m, 2H), 7.57 - 7.36 (m, 1H), 7.03 (d, J=9.0 Hz, 1H), 5.31 (dd, J=9.2, 3.4 Hz, 1H), 4.67 (d, J=9.8 Hz, 1H), 4.53 - 4.32 (m, 2H), 4.08 (br d, J=10.8 Hz, 1H), 3.84 (s, 1H), 3.80 - 3.67 (m, 3H), 3.65 - 3.55 (m, 2H), 3.50 - 3.31 (m, 1H), 3.18 - 3.05 (m, 2H), 2.70 (br s, 1H), 2.05 - 1.92 (m, 1H), 1.83 (br t, J=9.9 Hz, 1H), 1.47 - 1.31 (m, 2H), 0.81 - 0.66 (m, 2H), 0.47 - 0.25 (m, 2H)	2.33, B

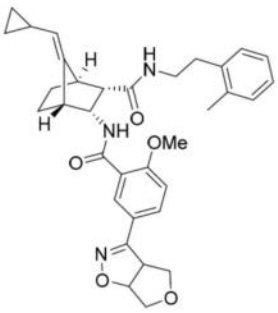
514	 由同手性苯甲酸酯中间体峰2 (RT=7.22 min，>99% ee)制备。所用仪器：Jasco SFC 柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：20% MeOH / 80% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱 Chiralpak AD-H，4.6 × 100 mm，3微米，移动相：20% MeOH / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：240 nm，得到手性（峰-1，RT=1.99 min.，>99% ee)及手性(峰-2，RT=7.22 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-氟苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	602.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.35 (t, J=6.6 Hz, 1H), 8.06 (dd, J=7.1, 2.4 Hz, 1H), 8.02 (dd, J=6.5, 2.5 Hz, 1H), 7.88 (ddd, J=8.5, 4.7, 2.4 Hz, 1H), 7.86 - 7.77 (m, 1H), 7.57 - 7.39 (m, 2H), 5.39 (dd, J=9.2, 3.7 Hz, 1H), 4.71 (d, J=9.6 Hz, 1H), 4.58 - 4.50 (m, 1H), 4.46 - 4.38 (m, 1H), 4.11 (d, J=10.8 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.77 - 3.72 (m, 2H), 3.69 - 3.62 (m, 1H), 3.26 - 3.16 (m, 1H), 3.13 (t, J=3.8 Hz, 1H), 2.75 (t, J=4.0 Hz, 1H), 1.89 - 1.81 (m, 1H), 1.80 - 1.67 (m, 1H), 1.60 - 1.48 (m, 1H), 1.45 - 1.34 (m, 1H), 0.86 - 0.65 (m, 2H), 0.45 - 0.25 (m, 2H)	2.48, C

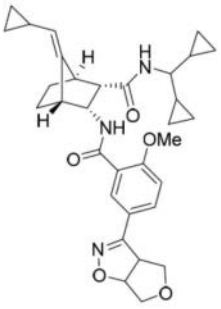
515	 由同手性苯甲酸酯中间体-峰2 (RT=3.85 min, >99% ee)制备。所用仪器: Berger MG II柱: Chiralcel OD-H, 21 × 250 mm, 5微米, 移动相: 30% MeOH / 70% CO_2, 流动条件: 45 mL/min, 150巴, 40°C, 检测器波长: 220 nm; 分析方法: 仪器: Shimadzu Nexera SFC, 柱 Chiralpak IC, 4.6 × 100 mm, 3微米, 移动相: 30% MeOH / 70% CO_2, 流动条件: 2 mL/min, 150巴, 40°C, 检测器波长: 220 nm, 得到手性(峰-1, RT=3.29 min., >99% ee)及手性(峰-2, RT=3.85 min., >99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环丁基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d6) δ 10.53 - 10.34 (m, 1H), 8.75 (br d, J=7.5 Hz, 1H), 8.07 (br d, J=6.3 Hz, 1H), 7.82 - 7.66 (m, 2H), 7.57 - 7.36 (m, 1H), 7.03 (d, J=9.0 Hz, 1H), 5.31 (dd, J=9.2, 3.4 Hz, 1H), 4.67 (d, J=9.8 Hz, 1H), 4.53 - 4.32 (m, 2H), 4.08 (br d, J=10.8 Hz, 1H), 3.84 (s, 1H), 3.80 - 3.67 (m, 3H), 3.65 - 3.55 (m, 2H), 3.50 - 3.31 (m, 1H), 3.18 - 3.05 (m, 2H), 2.70 (br s, 1H), 2.05 - 1.92 (m, 1H), 1.83 (br t, J=9.9 Hz, 1H), 1.47 - 1.31 (m, 2H), 0.81 - 0.66 (m, 2H), 0.47 - 0.25 (m, 2H)	2.67, B

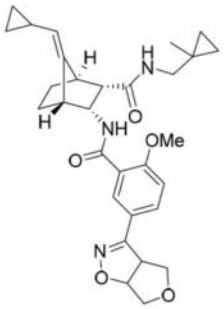
516	 由与实施例459中相同的同手性苯甲酸酯制备	3-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-[(2,2-二甲基丙基)胺甲酰基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酰胺	563.0	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.7 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H), 7.97 (br t, J=6.1 Hz, 1H), 7.77 (dd, J=8.5, 2.1 Hz, 1H), 7.37 (br s, 1H), 7.23 (d, J=8.9 Hz, 1H), 6.80 (br s, 1H), 5.15 (br dd, J=8.5, 4.9 Hz, 1H), 4.63 (d, J=9.2 Hz, 1H), 4.33 - 4.22 (m, 2H), 4.00 (s, 3H), 3.08 - 2.96 (m, 3H), 2.79 (br dd, J=13.0, 5.3 Hz, 1H), 2.13 - 1.83 (m, 5H), 1.77 - 1.68 (m, 1H), 1.53 - 1.41 (m, 1H), 1.39 - 1.27 (m, 2H), 0.81 (s, 9H), 0.75 - 0.63 (m, 2H), 0.32 (br s, 2H)。可能由于与溶剂峰重叠，两个质子在NMR中不可见。	2.09, B

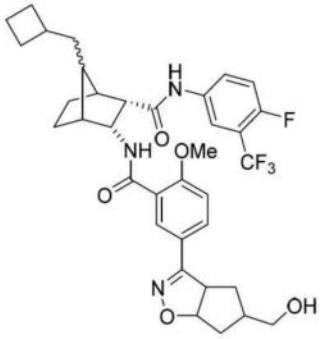
517	 由同手性苯甲酸酯中间体峰2制备。制备型色谱条件：仪器：PIC Solution SFC Prep-200 (CTR-L409-PSFC2)柱：Chiralpak IC，21×250 mm，5微米，移动相：10%甲醇/90% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL~65mg/mL于甲醇中，分析型色谱条件：仪器：Aurora Infinity SFC (CTR-L410-ASFC2)柱：Chiralpak IC，4.6×250 mm，3微米，移动相：10%甲醇/90% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：15 μL ~1mg/mL于MeOH中。峰-2，RT 4.39 min.，>98.5% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(1,1,1-三氟-2-羟基丙烷-2-基)-4,5-二氢-1,2-噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	684.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (d, J=7.1 Hz, 1H), 8.28 - 8.19 (m, 2H), 7.86 - 7.76 (m, 2H), 7.49 (t, J=9.7 Hz, 1H), 7.28 (d, J=8.8 Hz, 1H), 6.47 (s, 1H), 4.83 (dd, J=10.7, 8.4 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.45 (br s, 1H), 4.05 (s, 3H), 3.59 - 3.37 (m, 1H), 3.17 (br dd, J=10.9, 4.0 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.89 - 1.69 (m, 2H), 1.59 - 1.46 (m, 1H), 1.42 (br s, 2H), 1.30 (s, 3H), 0.83 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.61, C

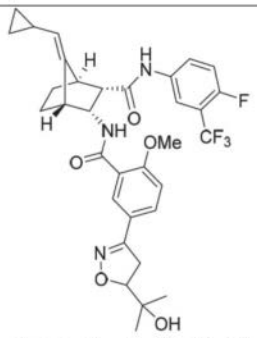
518	 通过SFC分离的异构体，其中实施例518为峰2 (RT=8.63 min，>95% ee)：所用仪器：Waters 100 Prep SFC柱：Chiral AD，30×250 mm，5微米，移动相：20% MeOH / 80% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6 × 100 mm，5微米，移动相：20% MeOH / 80% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=1.5 min.，>95% ee)及手性(峰-2，RT=3.25 min.，>95% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(二甲基氨基)苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	655.0	(500 MHz, DMSO-d6) δ 10.05 (br d, J=7.3 Hz, 1H), 8.21 (br d, J=4.9 Hz, 1H), 7.91 (d, J=1.8 Hz, 1H), 7.76 (br s, 1H), 7.69 (br d, J=8.9 Hz, 1H), 7.48 (br t, J=9.6 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 5.93 (q, J=7.9 Hz, 1H), 5.31 (br dd, J=9.0, 3.2 Hz, 1H), 4.54 (br s, 1H), 4.44 (br t, J=7.8 Hz, 1H), 4.07 (br d, J=10.7 Hz, 1H), 3.88 (br d, J=8.9 Hz, 1H), 3.79 - 3.67 (m, 1H), 3.63 (br dd, J=10.7, 3.4 Hz, 1H), 2.98 (br s, 1H), 2.71 (s, 6H), 2.57 - 2.52 (m, 2H), 2.04 - 1.86 (m, 2H), 1.49 (br s, 1H), 0.84 (br s, 2H)	2.50, B

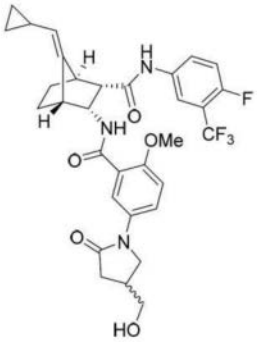
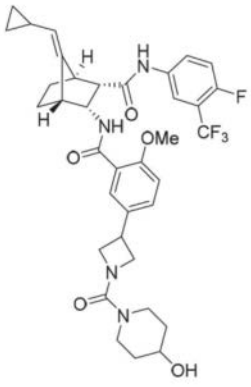
520	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[2-(2-甲基苯基)乙基]双环[2.2.1]庚烷-2-甲酰胺	570.3	(500 MHz, DMSO-d6) δ 10.01 (br d, J=6.7 Hz, 1H), 8.22 (br t, J=5.5 Hz, 1H), 8.17 (d, J=2.1 Hz, 1H), 7.79 (dd, J=8.9, 2.1 Hz, 1H), 7.24 (d, J=8.9 Hz, 1H), 7.14 - 7.00 (m, 4H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.61 (d, J=9.8 Hz, 1H), 4.50 (br t, J=7.8 Hz, 1H), 4.32 - 4.24 (m, 1H), 4.09 (br d, J=11.0 Hz, 1H), 4.03 (s, 3H), 3.93 - 3.86 (m, 1H), 3.77 (dd, J=9.0, 6.9 Hz, 1H), 3.65 (dd, J=10.8, 3.5 Hz, 1H), 3.25 - 3.14 (m, 1H), 3.07 - 3.00 (m, 1H), 2.90 - 2.83 (m, 1H), 2.70 (br t, J=7.3 Hz, 2H), 2.27 (s, 3H), 1.82 - 1.67 (m, 2H), 1.45 (td, J=8.4, 4.0 Hz, 1H), 1.39 - 1.22 (m, 2H), 0.77 - 0.62 (m, 2H), 0.32 (br d, J=3.4 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见	2.49, C

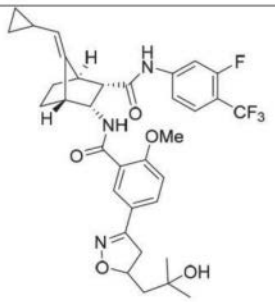
521	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(二环丙基甲基)双环[2.2.1]庚烷-2-甲酰胺	546.0	(500 MHz, DMSO-d6) δ 9.96 (br d, J=7.0 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 7.97 (br d, J=8.9 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.23 (d, J=8.5 Hz, 1H), 5.34 (dd, J=9.0, 3.2 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.9 Hz, 1H), 4.35 - 4.24 (m, 1H), 4.09 (br d, J=10.4 Hz, 1H), 3.97 (s, 3H), 3.93 - 3.85 (m, 1H), 3.82 - 3.74 (m, 1H), 3.65 (dd, J=11.0, 3.7 Hz, 1H), 3.07 - 2.95 (m, 2H), 2.91 (br dd, J=10.7, 4.0 Hz, 1H), 1.91 - 1.80 (m, 1H), 1.77 - 1.68 (m, 1H), 1.54 - 1.41 (m, 1H), 1.33 (br s, 2H), 0.95 - 0.84 (m, 2H), 0.77 - 0.63 (m, 2H), 0.49 - 0.26 (m, 5H), 0.24 - 0.10 (m, 5H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.28, B

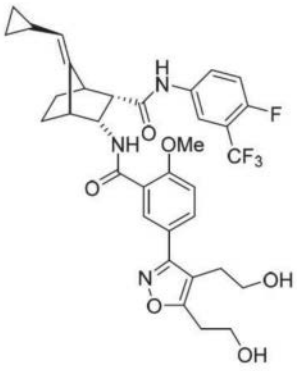
522	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1-甲基环丙基)甲基]双环[2.2.1]庚烷-2-甲酰胺	520.1	(500 MHz, DMSO-d6) δ 9.98 (br d, J=6.7 Hz, 1H), 8.15 (s, 1H), 8.12 - 8.06 (m, 1H), 7.77 (br d, J=8.5 Hz, 1H), 7.26 - 7.21 (m, 1H), 5.33 (br dd, J=9.2, 3.1 Hz, 1H), 4.62 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=7.9 Hz, 1H), 4.32 - 4.22 (m, 1H), 4.08 (br d, J=11.0 Hz, 1H), 4.00 (s, 3H), 3.89 (br d, J=8.9 Hz, 1H), 3.77 (br t, J=8.1 Hz, 1H), 3.67 - 3.59 (m, 1H), 3.09 - 3.00 (m, 2H), 2.97 - 2.85 (m, 2H), 1.89 - 1.80 (m, 1H), 1.77 - 1.68 (m, 1H), 1.45 (br dd, J=8.4, 4.4 Hz, 1H), 1.39 - 1.24 (m, 2H), 0.96 (s, 3H), 0.70 (quin, J=9.7 Hz, 2H), 0.40 - 0.27 (m, 4H), 0.17 (s, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.18, B

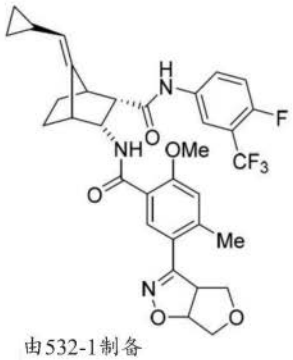
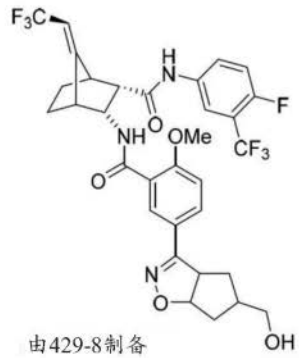
523	 由429-8制备的两种非镜像异构体的混合物	(1S,2S,3R,4R)-7-(环丁基甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.1	(500 MHz, DMSO-d6) δ 10.55 - 10.44 (m, 1H), 9.87 (d, J=7.0 Hz, 1H), 8.22 (br d, J=2.3 Hz, 2H), 7.78 (br dd, J=8.6, 2.4 Hz, 2H), 7.47 (br t, J=9.6 Hz, 1H), 7.26 (d, J=8.7 Hz, 1H), 5.11 (dd, J=8.7, 5.3 Hz, 1H), 4.65 - 4.46 (m, 1H), 4.42 (br s, 1H), 4.20 (br t, J=9.0 Hz, 1H), 4.12 - 3.95 (m, 3H), 3.55 - 3.36 (m, 1H), 3.10 (br dd, J=10.6, 4.1 Hz, 1H), 3.00 (s, 1H), 2.37 - 2.22 (m, 3H), 2.07 (ddd, J=11.5, 7.7, 3.5 Hz, 2H), 1.98 (br dd, J=13.5, 6.0 Hz, 1H), 1.93 - 1.72 (m, 5H), 1.70 - 1.49 (m, 6H), 1.49 - 1.33 (m, 4H)	2.76, C

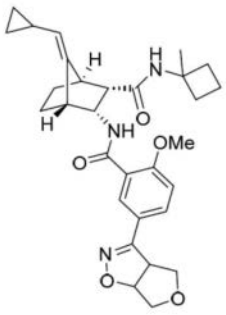
524	 由同手性苯甲酸-峰2(RT=7.7 min.)制备。所用制备型色谱条件:仪器:Berger MG II柱:Chiralpak AD-H,21×250 mm,5微米,移动相:40% MeOH / 60% CO_2,流动条件:45 mL/min,150巴,40°C,检测器波长:220 nm,注射详情:0.5 mL~65mg/mL于甲醇中,分析型色谱条件:仪器:Shimadzu Nexera SFC,柱:Chiralpak AD-H,4.6×100 mm,3微米,移动相:35% MeOH / 65% CO_2,流动条件:2.0 mL/min,150巴,40°C,检测器波长:220 nm,注射详情:5 μL~1mg/mL于MeOH中;保留时间:峰-1=5.51 min,峰-2=7.7 min。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.1	(500 MHz, DMSO-d6) δ 10.70 - 10.46 (m, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.46 - 8.12 (m, 2H), 7.93 - 7.71 (m, 2H), 7.47 (br t, J=9.9 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.52 - 4.25 (m, 2H), 4.03 (s, 2H), 3.71 - 3.54 (m, 4H), 3.37 - 3.22 (m, 1H), 3.15 (br dd, J=10.4, 4.0 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.95 - 1.81 (m, 1H), 1.78 - 1.71 (m, 1H), 1.56 - 1.47 (m, 1H), 1.44 - 1.35 (m, 1H), 1.11 (br s, 3H), 1.10 (br s, 3H), 0.84 - 0.66 (m, 2H), 0.35 (br d, J=4.0 Hz, 2H)	2.46, B

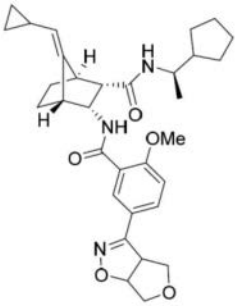
526	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[4-(羟基甲基)-2-氧代吡咯烷-1-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.5	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.88 (dd, J=7.1, 3.6 Hz, 1H), 8.22 (br d, J=3.9 Hz, 1H), 8.18 - 8.06 (m, 1H), 7.87 - 7.70 (m, 2H), 7.48 (br t, J=9.7 Hz, 1H), 7.26 - 7.14 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.54 - 4.35 (m, 1H), 4.04 - 3.93 (m, 3H), 3.92 - 3.81 (m, 1H), 3.65 - 3.53 (m, 1H), 3.51 - 3.41 (m, 1H), 3.15 (br dd, J=11.0, 4.1 Hz, 1H), 3.09 (br s, 1H), 2.77 - 2.66 (m, 1H), 2.64 - 2.52 (m, 1H), 2.28 (dd, J=16.5, 5.1 Hz, 1H), 1.92 - 1.73 (m, 3H), 1.63 - 1.43 (m, 2H), 1.43 - 1.33 (m, 2H), 0.82 - 0.64 (m, 3H), 0.40 - 0.29 (m, 2H)	2.27, B
527		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(4-羟基哌啶-1-羰基)氮杂环丁烷-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	685.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.86 (br d, J=7.0 Hz, 1H), 8.23 (br d, J=4.6 Hz, 1H), 7.92 (d, J=1.8 Hz, 1H), 7.84 - 7.70 (m, 1H), 7.53 - 7.43 (m, 2H), 7.17 (d, J=8.5 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.53 - 4.39 (m, 1H), 4.33 - 4.20 (m, 2H), 3.99 (s, 3H), 3.88 - 3.72 (m, 2H), 3.70 - 3.52 (m, 2H), 3.16 (br dd, J=11.0, 4.0 Hz, 1H), 3.10 (br s, 1H), 2.92 (br t, J=10.1 Hz, 2H), 2.72 (br s, 1H), 1.92 - 1.83 (m, 1H), 1.82 - 1.75 (m, 1H), 1.74 - 1.66 (m, 2H), 1.56 - 1.35 (m, 3H), 1.34 - 1.18 (m, 2H), 0.82 - 0.67 (m, 2H), 0.36 (br s, 2H)	2.32, A

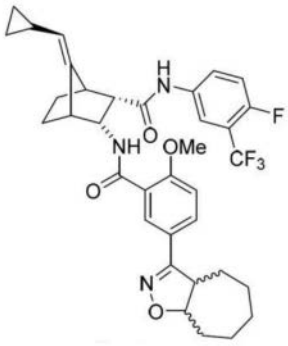
528	 通过SFC分离的异构体，其中实施例528为峰2 (RT=16.4 min，>95% ee)：所用仪器：Waters 100 Prep SFC柱：Chiral OD，30×250 mm，5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD，4.6 × 100 mm，5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=13.9 min.，>95% ee)及手性(峰-2，RT=16.4 min.，>95% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基-2-甲基丙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.0 Hz, 1H), 8.27 - 8.16 (m, 2H), 7.78 (br dd, J=8.6, 2.1 Hz, 2H), 7.48 (t, J=9.7 Hz, 1H), 7.26 (d, J=8.8 Hz, 1H), 4.86 - 4.76 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.52 - 4.39 (m, 2H), 4.04 (s, 3H), 3.22 - 3.13 (m, 1H), 3.11 - 3.00 (m, 2H), 2.72 (br d, J=3.3 Hz, 1H), 1.91 - 1.80 (m, 2H), 1.77 - 1.66 (m, 2H), 1.59 - 1.47 (m, 1H), 1.45 - 1.31 (m, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 0.74 (br dd, J=11.5, 9.0 Hz, 2H), 0.35 (br d, J=1.7 Hz, 2H) 可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.52, B

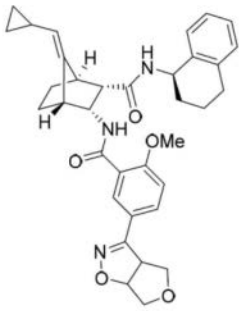
531		(1R,2S,3R,4R,7Z)-3-{5-[4,5-双(2-羟基乙基)-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	658.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (d, J=7.2 Hz, 1H), 8.41 (d, J=2.4 Hz, 1H), 8.23 (dd, J=6.4, 2.6 Hz, 1H), 7.96 (dd, J=8.7, 2.4 Hz, 1H), 7.80 (dt, J=8.4, 3.7 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.35 - 7.30 (m, 1H), 6.83 (s, 1H), 4.73 - 4.68 (m, 1H), 4.47 (ddd, J=10.2, 6.4, 4.2 Hz, 1H), 4.07 (s, 3H), 3.77 (t, J=6.4 Hz, 2H), 3.53 - 3.46 (m, 4H), 3.17 (dd, J=10.7, 4.3 Hz, 1H), 3.12 (t, J=3.7 Hz, 1H), 3.05 (t, J=6.3 Hz, 2H), 2.73 (t, J=3.6 Hz, 1H), 1.88 - 1.78 (m, 2H), 1.55 - 1.48 (m, 1H), 1.47 - 1.38 (m, 2H), 0.80 - 0.71 (m, 2H), 0.40 - 0.33 (m, 2H)	2.25, A

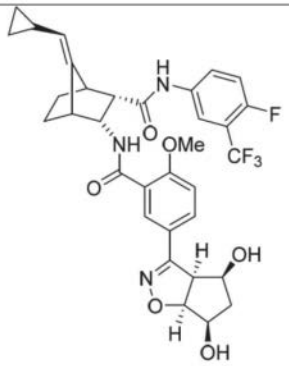
532	 由532-1制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (br d, J=7.0 Hz, 1H), 8.21 (br d, J=5.5 Hz, 1H), 7.95 (s, 1H), 7.85 - 7.68 (m, 1H), 7.48 (br t, J=9.3 Hz, 1H), 7.18 (s, 1H), 5.39 - 5.16 (m, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.52 (br t, J=7.8 Hz, 1H), 4.43 (br s, 1H), 4.18 - 3.94 (m, 3H), 3.91 - 3.87 (m, 1H), 3.80 - 3.74 (m, 1H), 3.73 - 3.69 (m, 1H), 3.61 (s, 1H), 3.58 - 3.55 (m, 1H), 3.21 - 3.12 (m, 1H), 3.09 (br s, 1H), 2.72 (br s, 1H), 2.60 - 2.54 (m, 1H), 1.90 - 1.81 (m, 1H), 1.80 - 1.70 (m, 1H), 1.56 - 1.46 (m, 1H), 1.44 - 1.32 (m, 2H), 0.83 - 0.61 (m, 2H), 0.35 (br s, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.60, C
533	 由429-8制备	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	670.2	(500 MHz, DMSO-d6) δ 9.97 (br d, J=7.0 Hz, 1H), 8.23 (br d, J=2.2 Hz, 2H), 7.81 (br dd, J=8.5, 2.2 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.28 (d, J=8.8 Hz, 1H), 5.97 - 5.91 (m, 1H), 5.16 - 5.11 (m, 1H), 4.53 - 4.49 (m, 1H), 4.14 - 4.07 (m, 1H), 4.04 (s, 3H), 3.43 (s, 3H), 3.31 - 3.20 (m, 2H), 2.23 - 2.10 (m, 3H), 1.98 - 1.85 (m, 2H), 1.78 (br s, 2H), 1.67 - 1.61 (m, 1H), 1.52 - 1.43 (m, 3H)	2.33, C

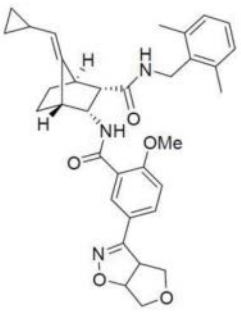
534	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(1-甲基环丁基)双环[2.2.1]庚烷-2-甲酰胺	520.0	(500 MHz, DMSO-d6) δ 10.14 (d, J=6.7 Hz, 1H), 8.19 (d, J=2.4 Hz, 1H), 8.10 (s, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.24 (d, J=8.8 Hz, 1H), 5.34 (dd, J=9.3, 3.6 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.30 - 4.21 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.90 (br d, J=9.2 Hz, 1H), 3.78 (dd, J=9.4, 7.0 Hz, 1H), 3.65 (dd, J=10.9, 3.6 Hz, 1H), 3.04 (br s, 1H), 2.85 (dd, J=10.9, 3.9 Hz, 1H), 2.29 - 2.15 (m, 2H), 1.97 - 1.81 (m, 3H), 1.79 - 1.65 (m, 3H), 1.52 - 1.41 (m, 1H), 1.40 - 1.27 (m, 5H), 0.77 - 0.65 (m, 2H), 0.38 - 0.26 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.33, C

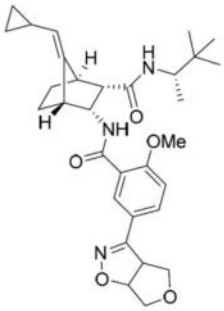
535	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[(1R)-1-环戊基乙基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	548.3	(500 MHz, DMSO-d6) δ 10.06 (d, J=6.7 Hz, 1H), 8.14 (d, J=2.3 Hz, 1H), 7.91 (br d, J=8.7 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.33 (dd, J=9.3, 3.6 Hz, 1H), 4.62 (d, J=9.6 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.31 - 4.23 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.90 (br d, J=10.0 Hz, 1H), 3.77 (dd, J=9.3, 6.9 Hz, 1H), 3.73 - 3.67 (m, 1H), 3.65 (dd, J=10.8, 3.7 Hz, 1H), 3.07 - 3.02 (m, 1H), 2.89 (dd, J=10.7, 4.2 Hz, 1H), 1.90 - 1.69 (m, 3H), 1.68 - 1.39 (m, 7H), 1.36 - 1.27 (m, 2H), 1.23 - 1.08 (m, 2H), 0.99 (d, J=6.6 Hz, 3H), 0.77 - 0.64 (m, 2H), 0.36 - 0.24 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.34, B

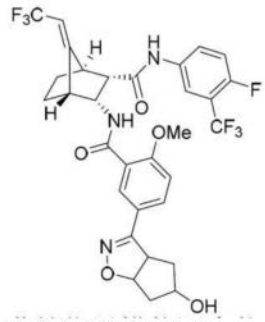
537	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,5H,6H,7H,8H,9H,9aH-环辛并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	654.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.90 (dd, J=7.0, 3.6 Hz, 1H), 8.26 - 8.20 (m, 2H), 7.78 (ddd, J=8.6, 3.6, 2.4 Hz, 2H), 7.48 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.22 - 6.99 (m, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.47 - 4.37 (m, 2H), 4.06 - 4.02 (m, 3H), 3.66 - 3.59 (m, 1H), 2.72 (br s, 1H), 1.98 - 1.76 (m, 4H), 1.72 - 1.60 (m, 4H), 1.56 - 1.45 (m, 3H), 1.45 - 1.24 (m, 6H), 0.78 - 0.69 (m, 2H), 0.38 - 0.32 (m, 2H)	2.92, B

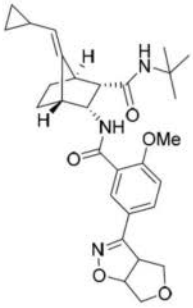
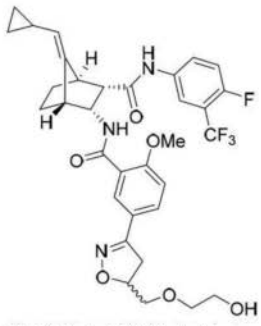
538	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-1,2,3,4-四氢萘-1-基]双环[2.2.1]庚烷-2-甲酰胺	582.1	(500 MHz, DMSO-d6) δ 10.02 (br d, J=7.0 Hz, 1H), 8.46 (br d, J=8.5 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 7.80 (dd, J=8.7, 2.3 Hz, 1H), 7.25 (d, J=8.9 Hz, 1H), 7.17 - 7.04 (m, 4H), 5.34 (br dd, J=9.0, 3.5 Hz, 1H), 5.02 (br d, J=5.5 Hz, 1H), 4.61 (br d, J=9.5 Hz, 1H), 4.50 (br t, J=7.8 Hz, 1H), 4.36 - 4.27 (m, 1H), 4.10 (br d, J=10.4 Hz, 1H), 4.02 (s, 3H), 3.91 (br d, J=9.5 Hz, 1H), 3.78 (br dd, J=9.2, 7.0 Hz, 1H), 3.66 (br dd, J=10.5, 3.5 Hz, 1H), 3.07 (br s, 1H), 2.96 (br dd, J=11.0, 3.7 Hz, 1H), 2.78 - 2.64 (m, 2H), 2.01 (br t, J=8.7 Hz, 1H), 1.91 - 1.77 (m, 3H), 1.74 - 1.57 (m, 2H), 1.53 - 1.34 (m, 3H), 0.71 (br t, J=8.4 Hz, 2H), 0.31 (br d, J=4.0 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.47, B

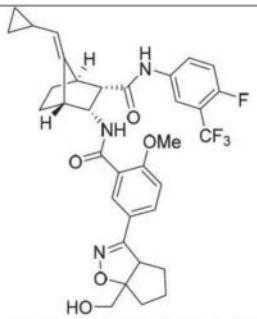
539	 由同手性苯甲酸酯中间体峰3制备。制备型色谱条件：仪器：PIC Solution SFC Prep-200，柱：Chiralpak IC，21×250 mm，5微米，移动相：10%甲醇/90% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~65 mg/mL于甲醇中，分析型色谱条件：仪器：Aurora Infinity SFC，柱：Chiralpak IC，4.6×250 mm，3微米，移动相：10%甲醇/90% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：15 μL~1mg/mL于MeOH中。峰-3，RT 4.83 min.，>99% ee。	(1R,2S,3R,4R,7Z)-3-{5-[(3aS,4S,6R,6aS)-4,6-二羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	644.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.27 (d, J=2.1 Hz, 1H), 8.20 (br d, J=4.0 Hz, 1H), 7.78 (d, J=8.1 Hz, 1H), 7.47 (br t, J=9.8 Hz, 1H), 7.19 (d, J=8.9 Hz, 1H), 4.78 (dd, J=8.4, 4.1 Hz, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.43 (br s, 1H), 4.38 - 4.22 (m, 1H), 4.00 (s, 3H), 3.68 - 3.52 (m, 1H), 3.20 - 3.06 (m, 2H), 3.00 (s, 1H), 2.80 - 2.63 (m, 1H), 2.07 - 1.92 (m, 1H), 1.92 - 1.73 (m, 2H), 1.59 - 1.46 (m, 2H), 1.41 (br s, 2H), 0.86 - 0.68 (m, 2H), 0.35 (br d, J=3.7 Hz, 2H)	2.47, C

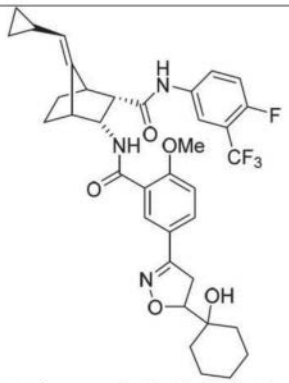
540	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2,6-二甲基苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	570.1	(500 MHz, DMSO-d6) δ 9.97 (d, J=7.1 Hz, 1H), 8.17 (d, J=2.3 Hz, 1H), 8.11 (br t, J=4.8 Hz, 1H), 7.84 - 7.75 (m, 1H), 7.26 (d, J=8.8 Hz, 1H), 7.08 - 7.01 (m, 1H), 7.01 - 6.92 (m, 2H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.58 (d, J=9.7 Hz, 1H), 4.50 (br t, J=7.5 Hz, 1H), 4.32 - 4.25 (m, 3H), 4.10 (d, J=10.6 Hz, 1H), 4.06 (s, 3H), 3.91 (br d, J=9.4 Hz, 1H), 3.78 (dd, J=9.2, 7.0 Hz, 1H), 3.66 (dd, J=10.7, 3.5 Hz, 1H), 3.03 (br t, J=3.9 Hz, 1H), 2.94 (dd, J=10.5, 4.4 Hz, 1H), 2.25 (s, 6H), 1.97 - 1.86 (m, 1H), 1.82 - 1.70 (m, 1H), 1.51 - 1.27 (m, 3H), 0.76 - 0.64 (m, 2H), 0.35 - 0.23 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.40, B

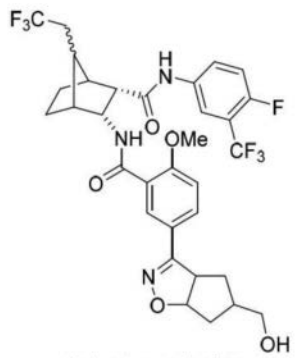
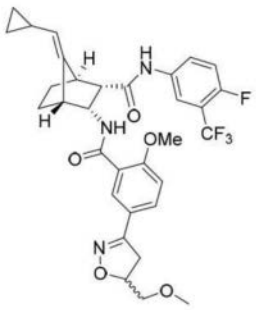
541	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2S)-3,3-二甲基丁烷-2-基]双环[2.2.1]庚烷-2-甲酰胺	536.3	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.7 Hz, 1H), 8.15 (d, J=1.8 Hz, 1H), 7.77 (dd, J=8.5, 2.4 Hz, 1H), 7.70 (br d, J=9.5 Hz, 1H), 7.22 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.5, 3.4 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.48 (br t, J=7.5 Hz, 1H), 4.29 (br d, J=3.1 Hz, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.93 - 3.87 (m, 1H), 3.80 - 3.59 (m, 2H), 3.03 (br s, 1H), 2.97 (br dd, J=10.7, 3.7 Hz, 1H), 1.94 - 1.84 (m, 1H), 1.77 - 1.68 (m, 1H), 1.51 - 1.41 (m, 1H), 1.39 - 1.26 (m, 2H), 0.93 (d, J=6.7 Hz, 3H), 0.76 (s, 9H), 0.73 - 0.64 (m, 2H), 0.31 (br d, J=3.7 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.33, C

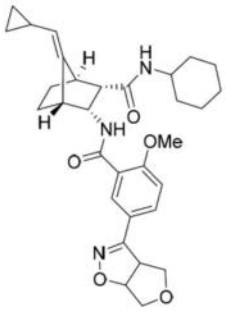
543	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	656.3	(500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.95 (br d, J=6.9 Hz, 1H), 8.20 (br s, 2H), 7.79 (br dd, J=8.5, 2.5 Hz, 2H), 7.50 (br t, J=9.5 Hz, 1H), 7.35 - 7.08 (m, 1H), 6.09 - 5.72 (m, 1H), 5.27 - 5.02 (m, 1H), 4.68 - 4.44 (m, 1H), 4.25 - 4.07 (m, 2H), 4.04 (s, 3H), 3.70 - 3.61 (m, 1H), 3.33 (s, 1H), 3.05 - 2.89 (m, 1H), 2.21 - 2.06 (m, 1H), 2.01 - 1.84 (m, 4H), 1.81 - 1.68 (m, 1H), 1.59 - 1.38 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.30, B

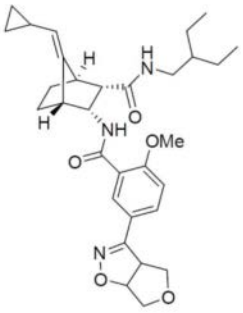
545	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-叔丁基-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	508.3	(500 MHz, DMSO-d6) δ 10.17 (d, J=6.7 Hz, 1H), 8.18 (d, J=2.2 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.65 (s, 1H), 7.24 (d, J=8.8 Hz, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.59 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.7 Hz, 1H), 4.27 - 4.20 (m, 1H), 4.09 (d, J=10.8 Hz, 1H), 4.03 (s, 3H), 3.89 (br d, J=8.7 Hz, 1H), 3.77 (dd, J=9.1, 7.0 Hz, 1H), 3.65 (br dd, J=10.7, 3.8 Hz, 1H), 3.03 (br s, 1H), 2.86 (br dd, J=10.8, 4.1 Hz, 1H), 2.53 (br s, 1H), 1.87 - 1.78 (m, 1H), 1.75 - 1.65 (m, 1H), 1.49 - 1.40 (m, 1H), 1.35 - 1.28 (m, 2H), 1.25 (s, 9H), 0.75 - 0.64 (m, 2H), 0.30 (br d, J=2.6 Hz, 2H)。	2.27, B
546	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-[(2-羟基乙氧基)甲基]-4,5-二氢-1,2-噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	646.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.90 (br d, J=7.2 Hz, 1H), 8.21 (br s, 2H), 7.81 - 7.76 (m, 2H), 7.48 (br t, J=9.7 Hz, 1H), 7.29 - 7.24 (m, 1H), 4.84 - 4.77 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.67 - 4.56 (m, 1H), 4.47 - 4.40 (m, 1H), 4.06 - 4.02 (m, 3H), 3.57 - 3.40 (m, 5H), 3.21 - 3.09 (m, 2H), 2.71 (br s, 1H), 1.86 - 1.74 (m, 2H), 1.53 - 1.37 (m, 3H), 0.79 - 0.68 (m, 2H), 0.41 - 0.29 (m, 2H)	2.39, B

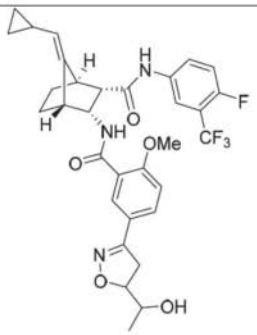
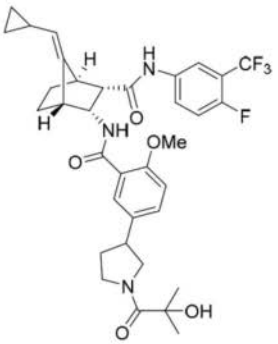
548	 由同手性苯甲酸中间体峰1制备。制备型色谱条件：仪器：PIC Solution SFC Prep-200 (CTR-L409-PSFC2)柱：Chiralpak IC, 21 × 250 mm, 5微米，移动相：10%甲醇/90% CO_2，流动条件：45 mL/min，150巴，40℃，检测器波长：220 nm，注射详情：0.5 mL ~65mg/mL于甲醇中，分析型色谱条件：仪器：Aurora Infinity SFC (CTR-L410-ASFC2) 柱：Chiralpak IC, 4.6 × 250 mm, 3微米，移动相：10%甲醇/90% CO_2，流动条件：2.0 mL/min，150巴，40℃，检测器波长：220 nm，注射详情：15 μL ~1mg/mL于MeOH中。峰-1，RT 4.86 min.，> 99% ee。	(1R,2S,3R,4R,7Z)-3-{5-[6a-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (br d, J=6.7 Hz, 1H), 8.24 (br s, 2H), 7.80 (br d, J=6.7 Hz, 2H), 7.50 (br t, J=10.2 Hz, 1H), 7.28 (br d, J=8.2 Hz, 2H), 5.06 (br s, 1H), 4.71 (br d, J=9.2 Hz, 1H), 4.46 (br s, 1H), 4.06 (s, 3H), 3.98 - 3.84 (m, 1H), 3.63 - 3.48 (m, 1H), 3.18 (br d, J=10.7 Hz, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 1.96 (br s, 1H), 1.89 - 1.77 (m, 4H), 1.73 (br d, J=14.0 Hz, 2H), 1.52 (br s, 2H), 1.43 (br s, 3H), 0.91 - 0.70 (m, 2H), 0.37 (br s, 2H)	2.58, C

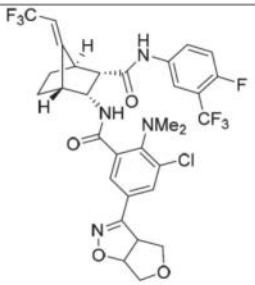
549	 经由SFC分离的异构体，其中实施例549为峰2 (RT=2.72 min.，>99% de)。所用仪器：Berger MG II柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：50% IPA-0.1% DEA/ 50% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak AD-H，4.6 × 100 mm，3微米，移动相：50% IPA0.1% DEA / 50% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=1.15 min.，>99% de)及手性(峰-2，RT=2.72 min.，>99% de)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环己基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.1	(500 MHz, DMSO-d6) δ 10.68 - 10.48 (m, 1H), 9.92 (d, J=7.0 Hz, 1H), 8.32 - 8.04 (m, 2H), 7.90 - 7.72 (m, 2H), 7.49 (t, J=9.7 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.51 - 4.40 (m, 2H), 4.32 (s, 1H), 4.05 (s, 3H), 3.26 - 3.01 (m, 2H), 2.73 (br s, 1H), 1.95 - 1.74 (m, 2H), 1.66 - 1.50 (m, 5H), 1.42 (br d, J=5.2 Hz, 4H), 1.35 - 1.24 (m, 3H), 1.20 - 1.11 (m, 1H), 0.87 (q, J=7.1 Hz, 1H), 0.79 - 0.69 (m, 2H), 0.50 - 0.30 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.74, C

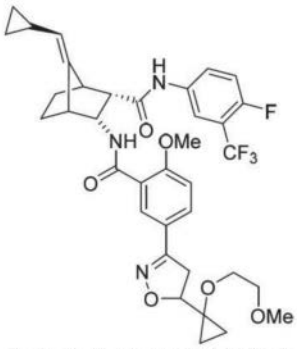
550	 由429-8制备的两种非镜像异构体的混合物	(1S,2S,3R,4R)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2,2,2-三氟乙基)双环[2.2.1]庚烷-2-甲酰胺	672.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (br d, J=6.8 Hz, 1H), 8.29 - 8.18 (m, 2H), 7.86 - 7.74 (m, 2H), 7.49 (br t, J=9.8 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 5.12 (dd, J=8.7, 5.2 Hz, 1H), 4.59 - 4.44 (m, 2H), 4.20 (br t, J=9.0 Hz, 1H), 4.10 - 3.99 (m, 3H), 3.38 - 3.31 (m, 1H), 3.25 - 3.15 (m, 1H), 2.49 - 2.43 (m, 1H), 2.39 (br dd, J=11.7, 6.4 Hz, 2H), 2.18 (br t, J=7.5 Hz, 1H), 1.99 (br dd, J=13.4, 5.6 Hz, 1H), 1.90 (td, J=11.8, 5.6 Hz, 1H), 1.77 (br dd, J=12.7, 6.0 Hz, 1H), 1.73 - 1.61 (m, 3H), 1.59 - 1.46 (m, 3H)	2.32, C
551	 非镜像异构体的混合物	(1R,2S,3R,4R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(甲氧基甲基)-4,5-二氢-1,2-噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(400 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.89 (d, J=6.8 Hz, 1H), 8.22 (dd, J=6.6, 2.7 Hz, 1H), 8.20 (d, J=2.2 Hz, 1H), 7.84 - 7.77 (m, 1H),7.75 (dd, J=8.7, 2.3 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 5.14 - 5.01 (m, 1H), 4.69 (d, J=9.3 Hz, 1H), 4.49 - 4.38 (m, 1H), 4.03(s, 4H), 3.16 (dd, J=10.6, 4.3 Hz, 2H), 3.12 - 3.07 (m, 1H), 3.02 (d, J=16.6 Hz, 1H), 2.75 - 2.69 (m, 1H), 1.88 - 1.72 (m, 3H), 1.55 - 1.35 (m, 4H),1.31 (s, 3H), 1.23 (s, 1H), 0.80 - 0.66 (m, 2H), 0.35 (dd, J=4.5, 2.3 Hz, 2H)。	2.37, D

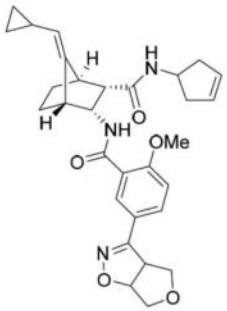
552	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-环己基-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	534.4	(500 MHz, DMSO-d6) δ 9.97 (d, J=7.0 Hz, 1H), 8.20 - 8.08 (m, 1H), 7.98 - 7.90 (m, 1H), 7.85 - 7.76 (m, 1H), 7.23 (s, 1H), 5.34 (dd, J=9.2, 3.5 Hz, 1H), 4.64 - 4.58 (m, 1H), 4.50 (br t, J=8.1 Hz, 1H), 4.32 - 4.24 (m, 1H), 4.12 - 4.06 (m, 1H), 4.00 (s, 3H), 3.90 (br d, J=9.5 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.65 (dd, J=10.9, 3.7 Hz, 1H), 3.60 - 3.52 (m, 1H), 3.08 - 3.00 (m, 1H), 2.88 (br dd, J=10.9, 4.0 Hz, 1H), 1.89 - 1.81 (m, 1H), 1.78 - 1.60 (m, 5H), 1.57 - 1.42 (m, 2H), 1.40 - 1.18 (m, 4H), 1.17 - 1.02 (m, 3H), 0.81 - 0.64 (m, 2H), 0.31 (dd, J=4.4, 2.3 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.38, C

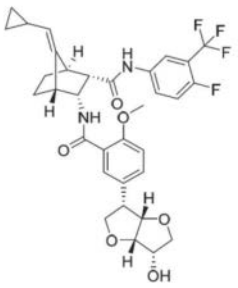
553	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2-乙基丁基)双环[2.2.1]庚烷-2-甲酰胺	536.0	(500 MHz, DMSO-d6) δ 10.01 (d, J=7.0 Hz, 1H), 8.16 (d, J=2.3 Hz, 1H), 8.00 - 7.95 (m, 1H), 7.78 (dd, J=8.6, 2.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.34 (dd, J=9.2, 3.6 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.50 (br t, J=8.3 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=9.1 Hz, 1H), 3.77 (dd, J=9.3, 7.0 Hz, 1H), 3.65 (dd, J=10.7, 3.7 Hz, 1H), 3.12 - 3.02 (m, 2H), 3.00 - 2.89 (m, 2H), 2.53 - 2.51 (m, 1H), 1.90 - 1.81 (m, 1H), 1.78 - 1.69 (m, 1H), 1.46 (tt, J=12.9, 4.7 Hz, 1H), 1.39 - 1.14 (m, 7H), 0.79 (t, J=7.4 Hz, 6H), 0.75 - 0.64 (m, 2H), 0.37 - 0.26 (m, 2H)。	2.43, C

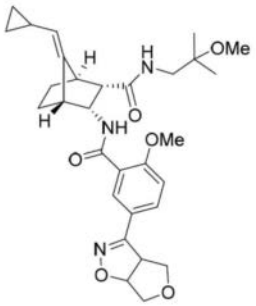
554	 由同手性苯甲酸中间体(峰4；>99%de；手性分析型RT=12.821 min)制备；手性SFC纯化条件；仪器：Berger MG II；柱：Chiralpak IC，21×250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~35mg/mL于MeOH中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.21 (br d, J=2.0 Hz, 2H), 7.78 (dd, J=8.6, 2.2 Hz, 2H), 7.47 (t, J=9.6 Hz, 1H), 7.26 (d, J=8.7 Hz, 1H), 4.94 - 4.88 (m, 1H), 4.68 (d, J=9.7 Hz, 1H), 4.51 (ddd, J=10.9, 8.2, 5.0 Hz, 1H), 4.46 - 4.40 (m, 1H), 4.06 - 4.00 (m, 3H), 3.73 - 3.65 (m, 1H), 3.20 - 3.08 (m, 2H), 2.74 - 2.69 (m, 1H), 1.87 - 1.74 (m, 2H), 1.54 - 1.36 (m, 3H), 1.11 - 1.05 (m, 3H), 0.78 - 0.68 (m, 2H), 0.38 - 0.30 (m, 2H)	2.41, B
555	 由ent-449-4制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙酰基)吡咯烷-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.3	(400MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.82 (d, J=7.1 Hz, 1H), 8.21 (dd, J=2.4, 6.4 Hz, 1H), 7.84 (br s, 1H), 7.81 - 7.69 (m, 1H), 7.47 (t,J=9.8 Hz, 1H), 7.44 - 7.34 (m, 1H), 7.14 (dd, J=2.4, 8.6 Hz, 1H), 5.18 - 5.12 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.32 - 4.04 (m,1H), 3.97 (s, 3H), 3.82 - 3.65 (m, 1H), 3.58 - 3.44 (m, 2H), 3.26 - 3.10 (m, 2H), 3.10 - 3.01 (m, 1H), 2.74 - 2.68 (m, 1H), 2.26 - 2.08 (m, 1H), 1.97 -1.68 (m, 3H), 1.57 - 1.35 (m, 3H), 1.32 - 1.28 (m, 6H), 0.79 - 0.65 (m, 2H), 0.35 (dd, J=1.8, 4.3 Hz, 2H)	2.45, A

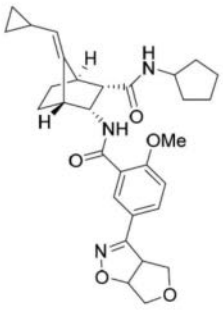
556	 通过SFC分离的异构体，其中实施例556为峰1 (RT=7.99 min，>95% ee)：所用仪器：Waters 100 Prep SFC柱：Chiral AD，30×250 mm，5微米，移动相：15% IPA / 85% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6 × 100 mm，5微米，移动相：15% IPA / 85% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=2.45 min.，>95% ee)及手性(峰-2，RT=3.41 min.，>95% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氯-2-(二甲基氨基)苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	689.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.94 (br d, J=7.6 Hz, 1H), 8.13 (br d, J=4.3 Hz, 1H), 7.84 (d, J=1.5 Hz, 1H), 7.81 - 7.74 (m, 2H), 7.46 (t, J=9.8 Hz, 1H), 5.93 (q, J=7.7 Hz, 1H), 5.35 (dd, J=9.2, 3.4 Hz, 1H), 4.56 (br s, 1H), 4.50 - 4.36 (m, 1H), 4.08 (d, J=11.0 Hz, 1H), 3.95 - 3.85 (m, 1H), 3.69 - 3.57 (m, 2H), 3.25 (br d, J=4.6 Hz, 1H), 3.19 (br s, 1H), 2.98 (br s, 1H), 2.81 (s, 6H), 2.11 - 1.99 (m, 2H), 1.50 (br d, J=9.2 Hz, 2H)	2.87, B

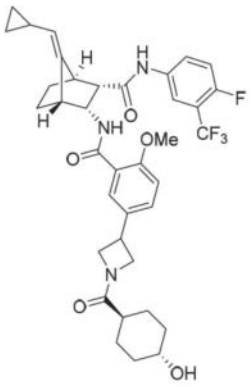
558	 由同手性苯甲酸峰2制备：仪器：Berger MG II柱：Chiralpak IC，21×250 mm，5微米，移动相：25% MeOH / 75% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IC，4.6×250 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到(峰-1，RT=5.02 min.，>99% ee)及手性(峰-2，RT=6.46 min.，>99% ee)	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{5-[1-(2-甲氧基乙氧基)环丙基]-4,5-二氢-1,2-噁唑-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	686.1	(500 MHz, DMSO-d6) δ 10.30 (s, 1H), 9.67 (br d, J=7.0 Hz, 1H), 8.16 - 7.85 (m, 2H), 7.75 - 7.50 (m, 2H), 7.24 (br t, J=9.8 Hz, 1H), 7.04 (d, J=8.9 Hz, 1H), 4.46 (d, J=9.5 Hz, 1H), 4.32 (br t, J=9.6 Hz, 1H), 4.21 (br t, J=10.2 Hz, 1H), 4.00 - 3.62 (m, 3H), 3.52 - 3.41 (m, 2H), 3.39 - 3.33 (m, 2H), 3.30 - 3.21 (m, 1H), 3.18 - 3.11 (m, 1H), 3.07 - 2.98 (m, 1H), 2.92 (br dd, J=10.1, 3.7 Hz, 1H), 2.90 - 2.82 (m, 3H), 2.48 (br s, 1H), 1.66 - 1.59 (m, 1H), 1.57 - 1.48 (m, 1H), 1.38 - 1.23 (m, 1H), 1.21 - 1.03 (m, 2H), 0.82 - 0.62 (m, 1H), 0.60 - 0.50 (m, 2H), 0.50 - 0.29 (m, 3H), 0.11 (br s, 2H)	2.54, C

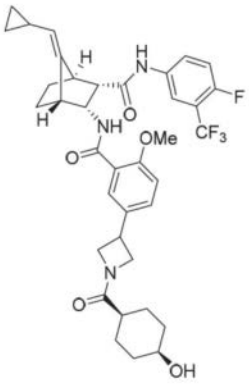
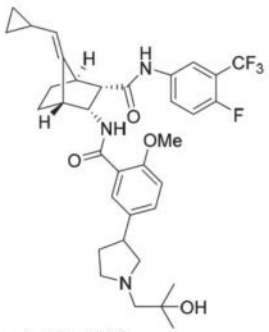
559	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(环戊-3-烯-1-基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	517.9	(500 MHz, DMSO-d6) δ 9.99 (d, J=7.0 Hz, 1H), 8.26 (br d, J=6.8 Hz, 1H), 8.15 (d, J=2.2 Hz, 1H), 7.79 (dd, J=8.7, 2.4 Hz, 1H), 7.24 (d, J=8.6 Hz, 1H), 5.74 - 5.61 (m, 2H), 5.33 (dd, J=9.1, 3.6 Hz, 1H), 4.60 (d, J=9.6 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.35 - 4.20 (m, 2H), 4.09 (d, J=10.5 Hz, 1H), 4.02 (s, 3H), 3.90 (br d, J=9.4 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.65 (dd, J=10.8, 3.6 Hz, 1H), 3.03 (t, J=3.5 Hz, 1H), 2.88 (dd, J=10.8, 4.3 Hz, 1H), 2.67 - 2.56 (m, 2H), 2.11 (dt, J=15.3, 2.1 Hz, 2H), 1.89 - 1.80 (m, 1H), 1.76 - 1.66 (m, 1H), 1.50 - 1.40 (m, 1H), 1.33 (br t, J=10.6 Hz, 2H), 0.77 - 0.63 (m, 2H), 0.31 (br d, J=2.6 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.18, B

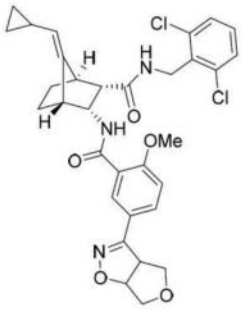
560		(1R,2S,3R,4R,7Z)-3-{5-[(3S,3aS,6S,6aS)-6-羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	631.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.84 (br d, J=7.0 Hz, 1H), 8.24 (br d, J=4.3 Hz, 1H), 7.86 (s, 1H), 7.82 - 7.76 (m, 1H), 7.49 (br t, J=9.8 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.12 (d, J=8.9 Hz, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.57 (br t, J=4.0 Hz, 1H), 4.49 - 4.39 (m, 2H), 4.26 - 4.13 (m, 2H), 3.98 (s, 3H), 3.82 (br dd, J=11.4, 7.8 Hz, 1H), 3.74 (br t, J=7.3 Hz, 1H), 3.16 (br dd, J=10.7, 3.7 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.91 - 1.83 (m, 1H), 1.82 - 1.73 (m, 1H), 1.59 - 1.47 (m, 1H), 1.45 - 1.34 (m, 2H), 0.84 - 0.66 (m, 2H), 0.42 - 0.32 (m, 2H)。	2.46, A

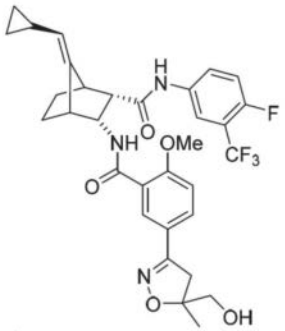
564	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2-甲氧基-2-甲基丙基)双环[2.2.1]庚烷-2-甲酰胺	538.2	(500 MHz, DMSO-d6) δ 9.94 (br d, J=6.7 Hz, 1H), 8.15 (d, J=2.4 Hz, 1H), 7.95 (br t, J=5.8 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.28 - 7.19 (m, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.48 (br t, J=7.5 Hz, 1H), 4.32 - 4.21 (m, 1H), 4.09 (br d, J=11.0 Hz, 1H), 4.00 (s, 3H), 3.89 (br d, J=8.9 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.67 - 3.62 (m, 1H), 3.25 - 3.19 (m, 1H), 3.07 - 2.99 (m, 5H), 1.85 (br t, J=9.5 Hz, 1H), 1.77 - 1.69 (m, 1H), 1.51 - 1.43 (m, 1H), 1.39 - 1.27 (m, 2H), 1.02 (d, J=4.9 Hz, 6H), 0.77 - 0.64 (m, 2H), 0.31 (br s, 2H)。可能由于与经抑制的水峰和/或溶剂峰重叠，两个质子在NMR中不可见	2.07, C

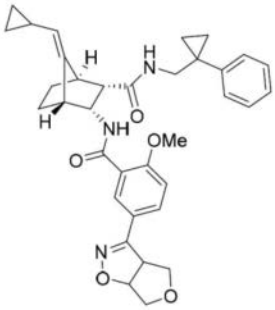
565	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-环戊基-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	520.1	(400 MHz, DMSO-d6) δ 10.01 (d, J=6.8 Hz, 1H), 8.15 (d, J=2.4 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 5.34 (dd, J=9.6, 3.2 Hz, 1H), 4.61 (d, J=9.7 Hz, 1H), 4.50 (dd, J=8.3, 6.6 Hz, 1H), 4.34 - 4.22 (m, 1H), 4.09 (d, J=10.8 Hz, 1H), 4.02 (s, 4H), 3.90 (d, J=9.3 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.66 (dd, J=10.6, 3.9 Hz, 1H), 3.09 - 3.01 (m, 1H), 2.88 (dd, J=11.1, 4.4 Hz, 1H), 1.88 - 1.70 (m, 4H), 1.65 - 1.54 (m, 2H), 1.53 - 1.40 (m, 3H), 1.39 - 1.26 (m, 4H), 0.76 - 0.64 (m, 2H), 0.32 (br d, J=3.5 Hz, 2H) 可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.23, B

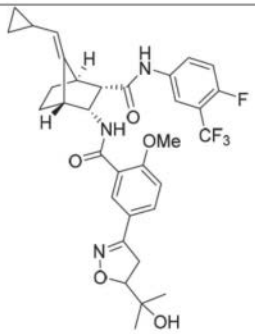
566		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{1-[(1r,4r)-4-羟基环己烷羰基]氮杂环丁烷-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	684.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.87 (br d, J=7.0 Hz, 1H), 8.24 (br d, J=4.6 Hz, 1H), 7.93 (d, J=1.5 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.53 - 7.43 (m, 2H), 7.19 (d, J=8.5 Hz, 1H), 4.71 (br d, J=9.8 Hz, 1H), 4.56 (br t, J=8.5 Hz, 1H), 4.46 (br dd, J=6.6, 3.2 Hz, 1H), 4.30 - 4.20 (m, 1H), 4.14 - 4.05 (m, 1H), 4.01 (s, 3H), 3.87 - 3.79 (m, 1H), 3.78 - 3.66 (m, 1H), 3.17 (br dd, J=10.2, 4.1 Hz, 1H), 3.10 (br s, 1H), 2.73 (br s, 1H), 2.24 - 2.12 (m, 1H), 1.96 - 1.76 (m, 4H), 1.74 - 1.63 (m, 2H), 1.51 (td, J=8.3, 3.5 Hz, 1H), 1.45 - 1.27 (m, 4H), 1.23 - 1.09 (m, 2H), 0.81 - 0.69 (m, 2H), 0.42 - 0.31 (m, 2H)	2.34, A

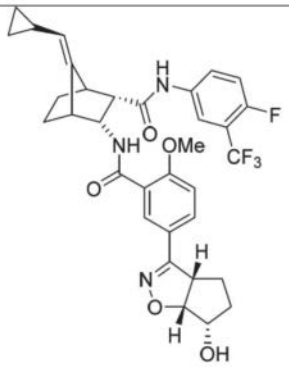
567		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{1-[(1s,4s)-4-羟基环己烷羰基]氮杂环丁烷-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	684.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.86 (br d, J=7.3 Hz, 1H), 8.23 (br d, J=4.0 Hz, 1H), 7.92 (d, J=2.1 Hz, 1H), 7.81 - 7.72 (m, 1H), 7.56 - 7.42 (m, 2H), 7.18 (d, J=8.5 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.55 (br t, J=8.5 Hz, 1H), 4.49 - 4.41 (m, 1H), 4.23 (br t, J=9.3 Hz, 1H), 4.14 - 4.05 (m, 1H), 4.00 (s, 3H), 3.87 - 3.71 (m, 3H), 3.16 (br dd, J=11.1, 3.8 Hz, 1H), 3.10 (br s, 1H), 2.73 (br s, 1H), 2.26 (br t, J=10.8 Hz, 1H), 1.92 - 1.72 (m, 4H), 1.67 (br dd, J=13.0, 2.9 Hz, 2H), 1.56 - 1.29 (m, 7H), 0.82 - 0.64 (m, 2H), 0.36 (br s, 2H)	2.41, A
568	 E由449-4制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙基)吡咯烷-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.4	(400MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.80 (d, J=7.1 Hz, 1H), 8.22 (dd, J=2.6, 6.7 Hz, 1H), 7.87 (d, J=2.4 Hz, 1H), 7.81 - 7.72 (m, 1H),7.47 (t, J=9.8 Hz, 1H), 7.42 (dd, J=2.3, 8.4 Hz, 1H), 7.10 (d, J=8.6 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.50 - 4.35 (m, 1H), 3.96 (s, 4H), 3.18 - 3.12(m, 2H), 3.07 (br t, J=3.3 Hz, 1H), 2.70 (br t, J=3.1 Hz, 2H), 1.85 (br d, J=9.5 Hz, 1H), 1.80 - 1.62 (m, 2H), 1.54 - 1.45 (m, 1H), 1.42 - 1.33 (m,2H), 1.23 (s, 2H), 1.13 (br s, 7H), 0.80 - 0.66 (m, 2H), 0.35 (dd, J=2.1, 4.8 Hz, 2H)	2.32, A

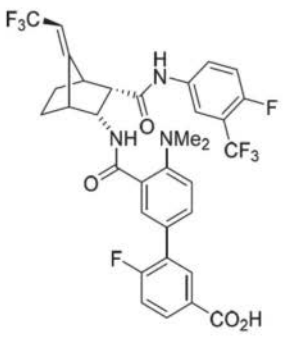
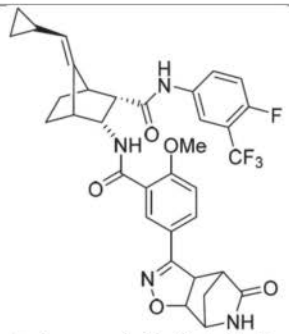
570	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2,6-二氯苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	610.1	(500 MHz, DMSO-d6) δ 9.97 (br d, J=7.0 Hz, 1H), 8.37 - 8.32 (m, 1H), 8.17 (d, J=1.8 Hz, 1H), 7.79 (dd, J=8.7, 2.0 Hz, 1H), 7.44 (d, J=8.2 Hz, 2H), 7.36 - 7.29 (m, 1H), 7.25 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.3, 3.2 Hz, 1H), 4.61 - 4.45 (m, 4H), 4.33 - 4.23 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.04 (s, 3H), 3.91 (br d, J=8.5 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.65 (br dd, J=11.1, 3.2 Hz, 1H), 3.05 - 2.99 (m, 1H), 2.93 (br dd, J=10.8, 3.8 Hz, 1H), 1.88 - 1.79 (m, 1H), 1.76 - 1.68 (m, 1H), 1.49 - 1.40 (m, 1H), 1.38 - 1.21 (m, 2H), 0.74 - 0.63 (m, 2H), 0.29 (br s, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.40, B

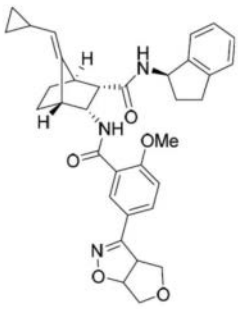
571	 峰1，RT＝2.11 min，制备型SFC条件：柱/尺寸：Chiralpak IC (250 × 30) mm，5u，% CO_2: 50%助溶剂：50% 4M甲醇氨于MEOH中，总流速：140.0g/min，背压：100巴，温度：40℃，UV：238 nm。	(1R,2S,3R,4R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(400 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.89 (d, J=6.8 Hz, 1H), 8.22 (dd, J=6.6, 2.7 Hz, 1H), 8.20 (d, J=2.2 Hz, 1H), 7.84 - 7.77 (m, 1H),7.75 (dd, J=8.7, 2.3 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 5.14 - 5.01 (m, 1H), 4.69 (d, J=9.3 Hz, 1H), 4.49 - 4.38 (m, 1H), 4.03(s, 4H), 3.16 (dd, J=10.6, 4.3 Hz, 2H), 3.12 - 3.07 (m, 1H), 3.02 (d, J=16.6 Hz, 1H), 2.75 - 2.69 (m, 1H), 1.88 - 1.72 (m, 3H), 1.55 - 1.35 (m, 4H),1.31 (s, 3H), 1.23 (s, 1H), 0.80 - 0.66 (m, 2H), 0.35 (dd, J=4.5, 2.3 Hz, 2H)。	2.37, D

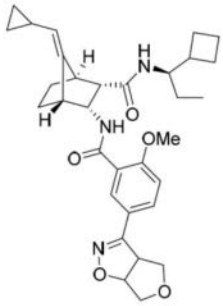
572	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1-苯基环丙基)甲基]双环[2.2.1]庚烷-2-甲酰胺	582.2	(500 MHz, DMSO-d6) δ 9.90 (d, J=6.9 Hz, 1H), 8.15 (d, J=2.4 Hz, 1H), 8.09 (br t, J=5.8 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.29 - 7.20 (m, 3H), 7.19 - 7.13 (m, 2H), 7.09 - 7.01 (m, 1H), 5.33 (dd, J=9.3, 3.4 Hz, 1H), 4.59 (d, J=9.6 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.27 - 4.19 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.92 - 3.86 (m, 1H), 3.77 (dd, J=9.3, 6.8 Hz, 1H), 3.65 (dd, J=10.9, 3.6 Hz, 1H), 3.54 - 3.45 (m, 1H), 3.20 (dd, J=13.6, 5.1 Hz, 1H), 3.00 (t, J=4.0 Hz, 1H), 2.93 - 2.89 (m, 1H), 2.44 - 2.38 (m, 1H), 1.73 - 1.61 (m, 2H), 1.51 - 1.40 (m, 1H), 1.36 - 1.26 (m, 1H), 1.25 - 1.15 (m, 1H), 0.90 - 0.79 (m, 2H), 0.75 - 0.63 (m, 4H), 0.35 - 0.26 (m, 2H)。	2.42, C

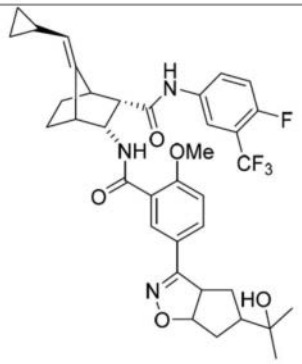
573	 由同手性苯甲酸峰1(RT=5.51 min)制备，制备型色谱条件：仪器：Berger MG II，柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：40% MeOH / 60% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~65mg/mL于甲醇中 分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak AD-H，4.6 × 100 mm，3微米，移动相：35% MeOH / 65% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中，保留时间：峰-1 = 5.51 min，峰-2 = 7.7 min。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.1	(500 MHz, DMSO-d6) δ 10.66 - 10.39 (m, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.33 - 8.10 (m, 2H), 7.79 (br d, J=6.7 Hz, 2H), 7.47 (br t, J=9.8 Hz, 1H), 7.27 (br d, J=8.9 Hz, 1H), 4.69 (br d, J=9.8 Hz, 1H), 4.48 - 4.29 (m, 2H), 4.03 (s, 2H), 3.73 - 3.58 (m, 2H), 3.47 - 3.27 (m, 1H), 3.21 - 3.13 (m, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.88 - 1.81 (m, 1H), 1.79 - 1.70 (m, 1H), 1.60 - 1.48 (m, 1H), 1.46 - 1.29 (m, 2H), 1.25 - 0.90 (m, 6H), 0.83 - 0.65 (m, 2H), 0.49 - 0.20 (m, 2H) 可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.45, B

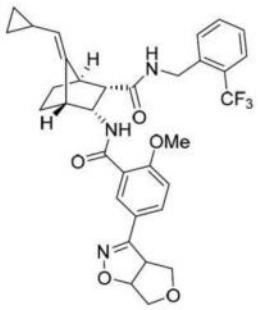
574	 如实施例496中利用来自异构体分离的峰2制备。制备型色谱条件：仪器：Jasco SFC Prep (CTR-L409-PSFC3)柱：Chiralpak IA，30×250 mm，5微米，移动相：15% MeOH / 85% CO_2，流动条件：85 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~21mg/mL于甲醇中，分析型色谱条件：仪器：Shimadzu Nexera SFC (CTR-L410-SFC3) 柱：Chiralpak IA，4.6 × 100 mm，3微米，移动相：15% MeOH / 85% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH中。峰-2 RT 4.97 min > 99% ee。	(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6S,6aS)-6-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.28 - 8.17 (m, 2H), 7.80 (br d, J=8.9 Hz, 2H), 7.47 (br t, J=9.8 Hz, 1H), 7.27 (br d, J=8.5 Hz, 1H), 5.18 (br d, J=3.1 Hz, 1H), 4.80 (br d, J=9.2 Hz, 1H), 4.69 (br d, J=10.1 Hz, 1H), 4.44 (br s, 1H), 4.24 (br t, J=8.9 Hz, 1H), 4.12 (br s, 1H), 4.04 (s, 3H), 3.58 (br d, J=11.0 Hz, 2H), 3.22 - 3.13 (m, 3H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.20 (br s, 1H), 1.92 - 1.72 (m, 2H), 1.64 (br dd, J=11.9, 6.4 Hz, 2H), 1.51 (br s, 1H), 1.42 (br s, 1H), 0.81 - 0.66 (m, 2H), 0.35 (br s, 2H)	2.42, C

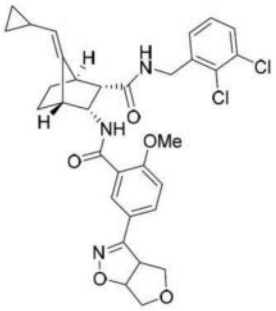
575		4'-(二甲基氨基)-6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-[1,1'-联苯]-3-甲酸	680.0	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 10.42 (br d, J=7.9 Hz, 1H), 8.21 (br d, J=5.5 Hz, 1H), 8.00 (br d, J=7.6 Hz, 1H), 7.97 - 7.88 (m, 2H), 7.73 (br s, 1H), 7.64 (br d, J=7.9 Hz, 1H), 7.49 - 7.33 (m, 3H), 5.98 - 5.88 (m, 1H), 4.58 (br s, 1H), 2.97 (br s, 1H), 2.72 (s, 6H), 2.63 (br s, 1H), 2.14 - 2.02 (m, 1H), 2.00 - 1.86 (m, 1H), 1.50 (br s, 3H), 1.23 (br s, 1H)	2.22, B
576	 经由SFC分离的异构体，其中实施例576为峰1 (RT=3.1 min，>95% de)，所用仪器：Waters 100 Prep SFC柱：Chiral AD，30 × 250 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA），流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6 × 100 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰-1，RT=3.1 min.，>95% de)及手性(峰-2，RT=4.75 min.，>95% de)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{8-氧代-3-氧杂-4,9-二氮杂三环[5.2.1.0^{2,6}]癸-4-烯-5-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	653.1	(500 MHz, DMSO-d6) δ 10.67 - 10.47 (m, 1H), 10.10 - 9.83 (m, 1H), 8.26 (d, J=2.3 Hz, 1H), 8.21 (br dd, J=6.5, 2.4 Hz, 1H), 7.92 - 7.81 (m, 2H), 7.77 (br dd, J=8.1, 4.2 Hz, 1H), 7.47 (br t, J=9.7 Hz, 1H), 7.34 - 7.28 (m, 1H), 4.98 (br d, J=8.2 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.49 - 4.40 (m, 1H), 4.25 (br d, J=8.2 Hz, 1H), 4.09 - 4.01 (m, 3H), 3.99 (br s, 1H), 3.22 - 3.04 (m, 2H), 2.82 - 2.66 (m, 1H), 2.66 - 2.59 (m, 1H), 1.93 - 1.80 (m, 2H), 1.81 - 1.72 (m, 1H), 1.56 - 1.49 (m, 1H), 1.48 - 1.35 (m, 3H), 0.83 - 0.63 (m, 2H), 0.34 (br s, 2H)	2.34, B

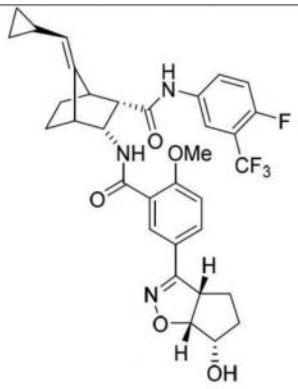
577	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-2,3-二氢-1H-茚-1-基]双环[2.2.1]庚烷-2-甲酰胺	568.3	(500 MHz, DMSO-d6) δ 10.08 (d, J=6.9 Hz, 1H), 8.47 (d, J=8.2 Hz, 1H), 8.17 (d, J=2.3 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.29 - 7.12 (m, 5H), 5.37 - 5.30 (m, 2H), 4.62 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.8 Hz, 1H), 4.36 - 4.26 (m, 1H), 4.09 (d, J=10.9 Hz, 1H), 4.02 (s, 3H), 3.91 (br d, J=9.1 Hz, 1H), 3.78 (dd, J=9.2, 7.0 Hz, 1H), 3.65 (dd, J=10.7, 3.6 Hz, 1H), 3.07 (br s, 1H), 2.96 (br dd, J=10.9, 4.2 Hz, 1H), 2.92 - 2.86 (m, 1H), 2.81 - 2.73 (m, 1H), 2.61 - 2.55 (m, 1H), 2.41 - 2.31 (m, 1H), 2.01 - 1.93 (m, 1H), 1.84 - 1.68 (m, 2H), 1.51 - 1.35 (m, 3H), 0.77 - 0.63 (m, 2H), 0.37 - 0.24 (m, 2H)。	2.39, B

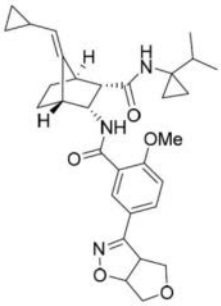
578	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[(1R)-1-环丁基丙基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	548.2	(500 MHz, DMSO-d6) δ 10.04 (d, J=6.8 Hz, 1H), 8.15 (d, J=2.4 Hz, 1H), 7.78 (dd, J=8.6, 2.4 Hz, 1H), 7.70 (br d, J=9.1 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.33 (dd, J=9.2, 3.5 Hz, 1H), 4.62 (d, J=9.6 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.92 - 3.87 (m, 1H), 3.77 (dd, J=9.2, 6.7 Hz, 1H), 3.71 - 3.59 (m, 2H), 3.09 - 3.01 (m, 1H), 2.98 - 2.88 (m, 1H), 2.33 - 2.19 (m, 1H), 1.95 - 1.60 (m, 8H), 1.51 - 1.41 (m, 1H), 1.40 - 1.25 (m, 3H), 1.19 - 1.03 (m, 1H), 0.82 - 0.62 (m, 5H), 0.31 (dd, J=4.5, 2.2 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.58, B

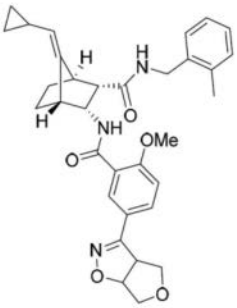
579	 如实施例479中通过在分离中隔离峰4制备。制备型色谱条件：仪器：Berger MG II 柱：Chiralpak IC，30 × 250 mm，5微米，移动相：25% 甲醇/ 75% CO_2，流动条件：70 mL/min，120巴， 40°C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC 柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH 中 (峰-4，RT 11.45 min.，> 99% ee)	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.0	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.27 - 8.18 (m, 2H), 7.95 - 7.75 (m, 2H), 7.48 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 5.18 - 5.06 (m, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.44 (br s, 1H), 4.05 (s, 3H), 3.21 - 3.06 (m, 3H), 2.72 (br s, 1H), 2.20 (br dd, J=12.5, 6.4 Hz, 2H), 1.98 (dt, J=12.3, 5.9 Hz, 1H), 1.90 - 1.71 (m, 2H), 1.65 - 1.46 (m, 2H), 1.46 - 1.33 (m, 3H), 1.11 - 1.00 (m, 6H), 0.87 - 0.68 (m, 2H), 0.35 (br d, J=3.7 Hz, 2H)	2.50, C

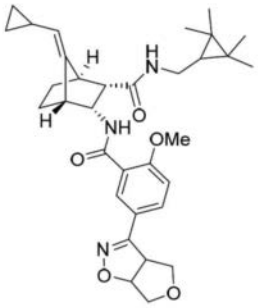
580	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[2-(三氟甲基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	610.2	(500 MHz, DMSO-d6) δ 9.88 (d, J=7.0 Hz, 1H), 8.74 (br t, J=5.7 Hz, 1H), 8.17 (d, J=2.2 Hz, 1H), 7.85 - 7.74 (m, 1H), 7.72 - 7.63 (m, 1H), 7.56 - 7.48 (m, 1H), 7.47 - 7.38 (m, 2H), 7.19 (d, J=8.7 Hz, 1H), 5.33 (dd, J=9.1, 3.5 Hz, 1H), 4.64 (d, J=9.6 Hz, 1H), 4.51 - 4.45 (m, 3H), 4.38 - 4.30 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 3.92 - 3.87 (m, 1H), 3.86 - 3.81 (m, 3H), 3.79 - 3.73 (m, 1H), 3.68 - 3.62 (m, 1H), 3.10 - 3.02 (m, 2H), 2.65 - 2.60 (m, 1H), 1.85 - 1.78 (m, 1H), 1.74 - 1.67 (m, 1H), 1.52 - 1.42 (m, 1H), 1.40 - 1.28 (m, 2H), 0.77 - 0.65 (m, 2H), 0.38 - 0.26 (m, 2H)。	2.37, B

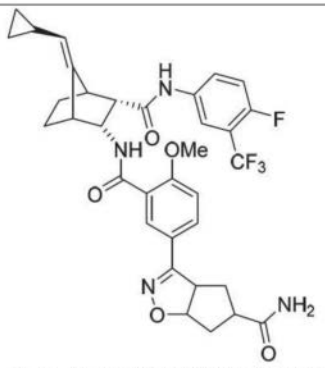
582	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2,3-二氯苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	610.2	(500 MHz, DMSO-d6) δ 9.86 (d, J=7.0 Hz, 1H), 8.72 (br t, J=5.9 Hz, 1H), 8.17 (d, J=2.3 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.50 (br d, J=7.7 Hz, 1H), 7.31 - 7.12 (m, 3H), 5.34 (dd, J=9.1, 3.6 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.7 Hz, 1H), 4.42 - 4.30 (m, 3H), 4.09 (d, J=10.7 Hz, 1H), 3.95 - 3.85 (m, 4H), 3.81 - 3.74 (m, 1H), 3.65 (dd, J=10.7, 3.4 Hz, 1H), 3.11 - 3.00 (m, 2H), 2.64 - 2.60 (m, 1H), 1.85 - 1.78 (m, 1H), 1.76 - 1.68 (m, 1H), 1.53 - 1.43 (m, 1H), 1.40 - 1.29 (m, 2H), 0.78 - 0.65 (m, 2H), 0.37 - 0.27 (m, 2H)。	2.32, B

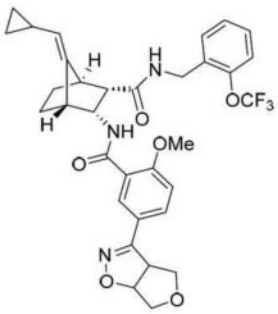
583	 如实施例496中通过隔离峰2制备：制备型色谱条件：仪器：Berger MG II 柱：Chiralpak IC，30×250 mm，5微米，移动相：25%甲醇/75% CO_2，流动条件：70 mL/min，120巴，40℃，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC 柱：Chiralpak IC，4.6×100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40℃，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH 中（峰-2，RT 4.38 min.，>99% ee)	(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6R,6aS)-6-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, J=6.7 Hz, 1H), 8.30 - 8.17 (m, 2H), 7.79 (br d, J=8.5 Hz, 2H), 7.49 (br t, J=9.9 Hz, 1H), 7.28 (br d, J=8.9 Hz, 1H), 4.95 (br d, J=6.7 Hz, 1H), 4.81 (br dd, J=8.2, 4.6 Hz, 1H), 4.70 (br d, J=9.2 Hz, 1H), 4.45 (br s, 1H), 4.12 (br t, J=8.5 Hz, 1H), 4.05 (s, 3H), 3.44 (br d, J=9.8 Hz, 1H), 3.28 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.93 - 1.76 (m, 3H), 1.76 - 1.66 (m, 1H), 1.62 - 1.47 (m, 2H), 1.43 (br s, 1H), 1.40 - 1.24 (m, 1H), 0.84 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.44, C

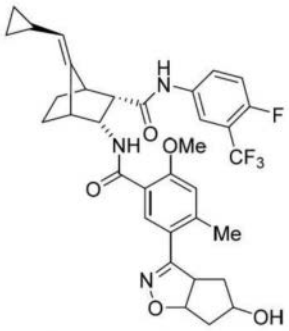
584	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[1-丙烷-2-基)环丙基]双环[2.2.1]庚烷-2-甲酰胺	534.2	(500 MHz, DMSO-d6) δ 10.04 (br d, J=6.7 Hz, 1H), 8.17 (s, 2H), 7.79 (dd, J=8.4, 2.0 Hz, 1H), 7.24 (d, J=8.5 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.60 (d, J=9.8 Hz, 1H), 4.50 (br t, J=7.9 Hz, 1H), 4.31 - 4.18 (m, 1H), 4.09 (br d, J=11.0 Hz, 1H), 4.03 (s, 3H), 3.92 - 3.87 (m, 1H), 3.80 - 3.73 (m, 1H), 3.65 (br dd, J=10.7, 3.7 Hz, 1H), 3.07 - 3.00 (m, 1H), 2.84 (br dd, J=11.0, 4.0 Hz, 1H), 1.86 - 1.76 (m, 1H), 1.74 - 1.65 (m, 1H), 1.50 - 1.39 (m, 2H), 1.32 (br s, 2H), 0.83 (br dd, J=18.6, 6.7 Hz, 6H), 0.75 - 0.64 (m, 2H), 0.63 - 0.45 (m, 4H), 0.31 (br s, 2H)。可能由于与溶剂峰重叠，一个质子不可见。	2.46, B

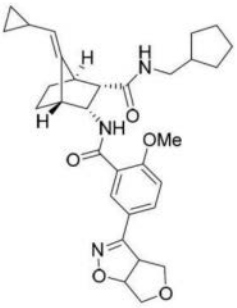
585	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2-甲基苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	556.1	(500 MHz, DMSO-d6) δ 9.94 (br d, J=6.7 Hz, 1H), 8.48 (br t, J=5.8 Hz, 1H), 8.16 (d, J=1.8 Hz, 1H), 7.78 (dd, J=8.9, 2.1 Hz, 1H), 7.21 (d, J=8.9 Hz, 1H), 7.17 - 7.07 (m, 3H), 7.06 - 7.02 (m, 1H), 5.33 (dd, J=9.0, 3.5 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.48 (br t, J=7.6 Hz, 1H), 4.37 - 4.28 (m, 1H), 4.26 (br d, J=5.8 Hz, 2H), 4.09 (br d, J=10.7 Hz, 1H), 3.93 (s, 3H), 3.90 (br d, J=9.5 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.65 (dd, J=10.8, 3.8 Hz, 1H), 3.04 (br s, 1H), 3.00 (br dd, J=11.0, 4.3 Hz, 1H), 2.58 (br s, 1H), 2.23 (s, 3H), 1.92 - 1.81 (m, 1H), 1.78 - 1.69 (m, 1H), 1.53 - 1.42 (m, 1H), 1.40 - 1.27 (m, 2H), 0.77 - 0.64 (m, 2H), 0.32 (br d, J=4.3 Hz, 2H)。	2.38, B

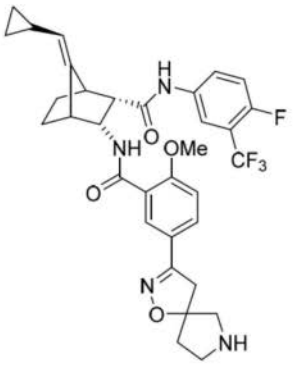
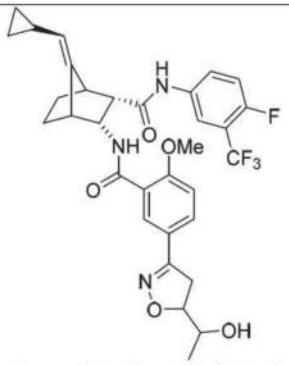
586	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2,2,3,3-四甲基环丙基)甲基]双环[2.2.1]庚烷-2-甲酰胺	562.4	(500 MHz, DMSO-d6) δ 10.00 (br d, J=6.4 Hz, 1H), 8.15 (d, J=2.1 Hz, 1H), 7.98 (br t, J=4.9 Hz, 1H), 7.78 (dd, J=8.5, 2.1 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.0, 3.5 Hz, 1H), 4.63 (br d, J=9.5 Hz, 1H), 4.50 (br t, J=7.6 Hz, 1H), 4.34 - 4.24 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.93 - 3.86 (m, 1H), 3.81 - 3.73 (m, 1H), 3.65 (br dd, J=10.7, 3.4 Hz, 1H), 3.15 - 2.99 (m, 2H), 2.95 (br dd, J=11.0, 3.4 Hz, 1H), 1.91 - 1.82 (m, 1H), 1.79 - 1.71 (m, 1H), 1.52 - 1.41 (m, 1H), 1.41 - 1.26 (m, 2H), 1.00 (d, J=3.4 Hz, 6H), 0.92 (d, J=13.1 Hz, 6H), 0.78 - 0.66 (m, 2H), 0.38 - 0.24 (m, 3H)。可能由于与溶剂峰重叠，一个质子不可见。	2.55, C

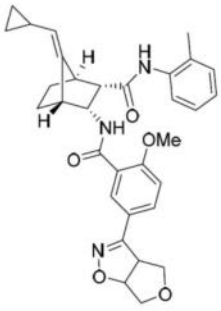
587	 由同手性苯甲酸酯中间体(峰1；100%ee；手性分析型RT=2.071 min)制备；制备型手性SFC条件：仪器：Jasco SFC Prep：柱：Chiralpak AS-H，30×250 mm，5微米；移动相：30% MeOH / 70% CO_2；流动条件：85 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：1.0 mL ~50mg/mLmg/mL 于MeOH:TFA中	3-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酰胺	655.5	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.93 - 9.89 (m, 1H), 8.27 - 8.21 (m, 2H), 7.82 - 7.77 (m, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.35 (br s, 1H), 7.27 (d, J=8.9 Hz, 1H), 6.80 (br s, 1H), 5.15 (dd, J=8.7, 5.0 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.47 - 4.42 (m, 1H), 4.26 (t, J=9.0 Hz, 1H), 4.04 (s, 3H), 3.16 (dd, J=10.8, 4.2 Hz, 1H), 3.11 (t, J=3.7 Hz, 1H), 2.74 - 2.70 (m, 1H), 2.58 - 2.52 (m, 1H), 2.12 - 1.76 (m, 6H), 1.54 - 1.47 (m, 1H), 1.45 - 1.37 (m, 2H), 0.79 - 0.69 (m, 2H), 0.38 - 0.32 (m, 2H)	2.13, A

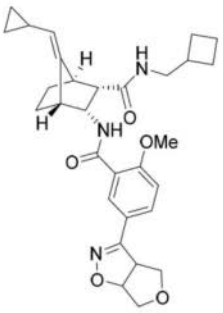
588	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[2-(三氟甲氧基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	626.1	(500 MHz, DMSO-d6) δ 9.91 (br d, J=6.7 Hz, 1H), 8.65 (br t, J=5.2 Hz, 1H), 8.18 (d, J=1.5 Hz, 1H), 7.78 (dd, J=8.5, 1.5 Hz, 1H), 7.38 - 7.30 (m, 3H), 7.28 - 7.23 (m, 1H), 7.20 (d, J=8.9 Hz, 1H), 5.34 (br dd, J=9.2, 3.4 Hz, 1H), 4.64 (br d, J=9.5 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.39 - 4.28 (m, 3H), 4.14 - 4.05 (m, 1H), 3.95 - 3.85 (m, 4H), 3.80 - 3.71 (m, 1H), 3.65 (br dd, J=10.8, 3.5 Hz, 1H), 3.09 - 3.00 (m, 2H), 2.62 - 2.56 (m, 1H), 1.87 - 1.77 (m, 1H), 1.76 - 1.68 (m, 1H), 1.52 - 1.42 (m, 1H), 1.40 - 1.26 (m, 2H), 0.80 - 0.64 (m, 2H), 0.33 (br d, J=4.3 Hz, 2H)。	2.44, B

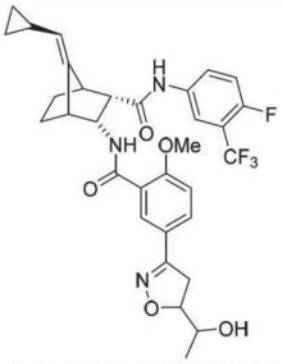
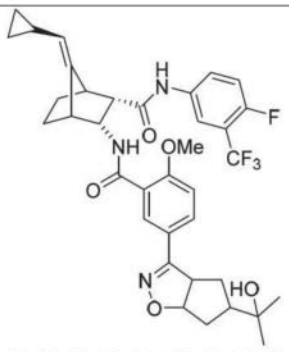
590	 经反相HPLC的第二洗脱非镜像异构体	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	642.1	(500 MHz, DMSO-d6) δ 10.66 - 10.40 (m, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.24 (br d, J=4.3 Hz, 1H), 8.01 (s, 1H), 7.80 (dd, J=5.2, 2.7 Hz, 1H), 7.49 (br t, J=9.6 Hz, 1H), 7.17 (s, 1H), 5.15 - 5.05 (m, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.51 - 4.38 (m, 1H), 4.25 (td, J=9.0, 3.7 Hz, 1H), 4.15 - 4.09 (m, 1H), 4.06 (s, 3H), 3.44 (br s, 1H), 3.16 (br dd, J=10.5, 4.4 Hz, 1H), 3.11 (br s, 1H), 2.77 - 2.68 (m, 1H), 2.50 (s, 3H), 2.07 - 1.98 (m, 1H), 1.94 - 1.82 (m, 3H), 1.82 - 1.75 (m, 1H), 1.75 - 1.65 (m, 1H), 1.57 - 1.48 (m, 1H), 1.45 - 1.31 (m, 2H), 0.75 (quin, J=9.3 Hz, 2H), 0.36 (br s, 2H)	2.52, B

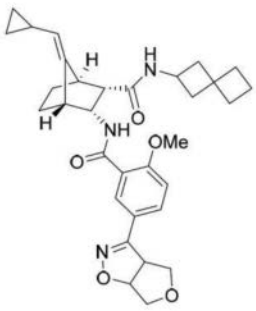
592	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(环戊基甲基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	534.0	(500 MHz, DMSO-d6) δ 9.96 (d, J=6.8 Hz, 1H), 8.14 (d, J=2.2 Hz, 1H), 8.08 (br t, J=5.6 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.33 (dd, J=9.2, 3.6 Hz, 1H), 4.61 (d, J=9.6 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.33 - 4.22 (m, 1H), 4.09 (d, J=10.6 Hz, 1H), 4.00 (s, 3H), 3.89 (br d, J=8.6 Hz, 1H), 3.77 (dd, J=9.2, 7.0 Hz, 1H), 3.65 (br dd, J=10.8, 3.7 Hz, 1H), 3.09 - 3.00 (m, 2H), 3.00 - 2.86 (m, 2H), 1.99 - 1.89 (m, 1H), 1.86 (br t, J=9.9 Hz, 1H), 1.78 - 1.69 (m, 1H), 1.66 - 1.54 (m, 2H), 1.53 - 1.26 (m, 7H), 1.18 - 1.06 (m, 2H), 0.77 - 0.64 (m, 2H), 0.31 (br d, J=2.7 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.29, C

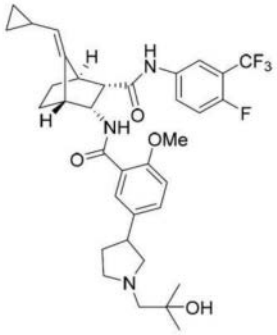
593	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{1-氧杂-2,7-二氮杂螺[4.4]壬-2-烯-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	627.4	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.95 - 9.90 (m, 1H), 8.23 (br d, J=2.4 Hz, 2H), 7.79 (dd, J=8.7, 2.2 Hz, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.8 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.05 (s, 3H), 3.70 - 3.56 (m, 2H), 3.41 (s, 1H), 3.21 - 3.07 (m, 2H), 2.75 - 2.70 (m, 1H), 2.58 - 2.55 (m, 1H), 2.32 - 2.18 (m, 2H), 1.85 - 1.75 (m, 2H), 1.54 - 1.33 (m, 4H), 0.79 - 0.69 (m, 2H), 0.38 - 0.31 (m, 2H)	2.22, B
595	 由同手性苯甲酸中间体(峰1；>99%de；手性分析型RT=7.968 min)制备；手性SFC纯化条件；仪器：Berger MG II；柱：Chiralpak IC，21×250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~35mg/mL于MeOH中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.22 - 8.17 (m, 2H), 7.80 - 7.74 (m, 2H), 7.49 - 7.43 (m, 1H), 7.25 (d, J=8.9 Hz, 1H), 4.72 - 4.63 (m, 1H), 4.50 - 4.40 (m, 2H), 4.02 (s, 3H), 3.55 - 3.44 (m, 2H), 3.34 - 3.22 (m, 1H), 3.17 - 3.10 (m, 1H), 3.10 - 3.05 (m, 1H), 2.73 - 2.67 (m, 1H), 1.84 - 1.73 (m, 2H), 1.50 - 1.37 (m, 3H), 1.07 (d, J=6.1 Hz, 3H), 0.78 - 0.69 (m, 2H), 0.37 - 0.30 (m, 2H)	2.41, B

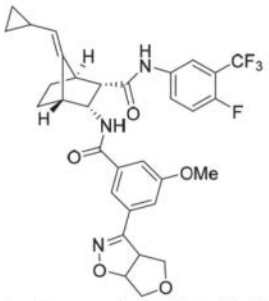
596	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2-甲基苯基)双环[2.2.1]庚烷-2-甲酰胺	542.2	(500 MHz, DMSO-d6) δ 9.94 - 9.86 (m, 1H), 9.53 (s, 1H), 8.18 (d, J=2.2 Hz, 1H), 7.78 (dd, J=8.6, 2.4 Hz, 1H), 7.34 (d, J=7.5 Hz, 1H), 7.27 - 7.21 (m, 2H), 7.19 - 7.15 (m, 1H), 7.14 - 7.09 (m, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.52 - 4.46 (m, 1H), 4.45 - 4.37 (m, 1H), 4.10 (d, J=10.7 Hz, 1H), 3.96 - 3.85 (m, 4H), 3.76 (dd, J=9.2, 7.0 Hz, 1H), 3.65 (dd, J=10.8, 3.8 Hz, 1H), 3.24 (dd, J=10.9, 4.3 Hz, 1H), 3.09 (br s, 1H), 2.74 (br s, 1H), 1.92 (br d, J=9.9 Hz, 1H), 1.81 - 1.72 (m, 1H), 1.52 - 1.45 (m, 4H), 1.45 - 1.36 (m, 2H), 0.78 - 0.66 (m, 2H), 0.39 - 0.29 (m, 2H)。	2.28, C

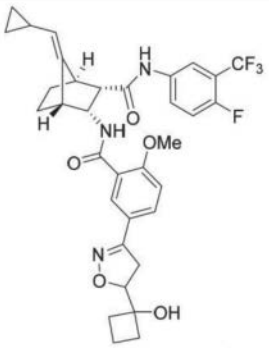
597	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(环丁基甲基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	520.0	(500 MHz, DMSO-d6) δ 9.98 (br d, J=7.0 Hz, 1H), 8.15 (d, J=2.1 Hz, 1H), 8.05 (br t, J=5.5 Hz, 1H), 7.78 (dd, J=8.7, 2.0 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.3, 3.2 Hz, 1H), 4.61 (d, J=9.8 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.32 - 4.21 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=9.5 Hz, 1H), 3.81 - 3.71 (m, 1H), 3.65 (dd, J=10.8, 3.5 Hz, 1H), 3.21 - 3.10 (m, 1H), 3.08 - 3.01 (m, 2H), 2.94 - 2.84 (m, 1H), 2.35 (dt, J=15.0, 7.8 Hz, 1H), 1.97 - 1.79 (m, 3H), 1.78 - 1.68 (m, 3H), 1.67 - 1.54 (m, 2H), 1.46 (dt, J=8.4, 4.0 Hz, 1H), 1.38 - 1.23 (m, 2H), 0.78 - 0.64 (m, 2H), 0.31 (br d, J=1.8 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.20, B

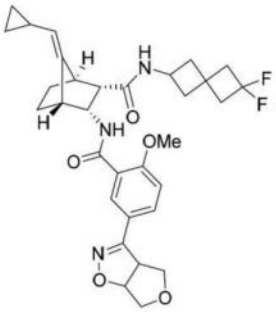
598	 由同手性苯甲酸酯中间体(峰3；94.8%de；手性分析型RT=9.925 min)制备；手性SFC纯化条件；仪器：Berger MG II；柱：Chiralpak IC，21×250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~35mg/mL于MeOH中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.1	(500 MHz, DMSO-d6) δ 10.54 - 10.50 (m, 1H), 9.89 (d, J=7.1 Hz, 1H), 8.22 - 8.17 (m, 2H), 7.80 - 7.75 (m, 2H), 7.46 (br t, J=9.7 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.50 (ddd, J=10.9, 8.3, 5.0 Hz, 1H), 4.42 (br t, J=9.9 Hz, 1H), 4.02 (s, 3H), 3.71 - 3.63 (m, 1H), 3.19 - 3.06 (m, 3H), 2.73 - 2.67 (m, 1H), 2.58 - 2.54 (m, 1H), 1.85 - 1.72 (m, 2H), 1.53 - 1.45 (m, 1H), 1.43 - 1.35 (m, 2H), 1.07 (d, J=6.4 Hz, 3H), 0.77 - 0.67 (m, 2H), 0.34 (br s, 2H)	2.38, C
599	 如实施例479中使用峰2制备：制备型色谱条件：仪器：Berger MG II柱：Chiralpak IC，30×250 mm，5微米，移动相：25%甲醇/ 75% CO_2，流动条件：70 mL/min，120巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6×100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL~1mg/mL于MeOH中(峰-2，RT 7.44 min.，>99% ee)	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基丙烷-2-基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.0	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.27 - 8.18 (m, 2H), 7.95 - 7.75 (m, 2H), 7.48 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 5.18 - 5.06 (m, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.44 (br s, 1H), 4.05 (s, 3H), 3.21 - 3.06 (m, 3H), 2.72 (br s, 1H), 2.20 (br dd, J=12.5, 6.4 Hz, 2H), 1.98 (dt, J=12.3, 5.9 Hz, 1H), 1.90 - 1.71 (m, 2H), 1.65 - 1.46 (m, 2H), 1.46 - 1.33 (m, 3H), 1.11 - 1.00 (m, 6H), 0.87 - 0.68 (m, 2H), 0.35 (br d, J=3.7 Hz, 2H)	2.51, C

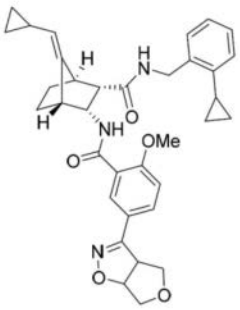
600	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{螺[3.3]庚烷-2-基}双环[2.2.1]庚烷-2-甲酰胺	5456.3	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.7 Hz, 1H), 8.24 (br d, J=7.0 Hz, 1H), 8.14 (d, J=2.1 Hz, 1H), 7.79 (dd, J=8.7, 2.3 Hz, 1H), 7.24 (d, J=8.9 Hz, 1H), 5.34 (br dd, J=9.0, 3.5 Hz, 1H), 4.61 (br d, J=9.2 Hz, 1H), 4.50 (br t, J=7.8 Hz, 1H), 4.29 - 4.21 (m, 1H), 4.13 - 4.07 (m, 1H), 4.06 - 3.99 (m, 3H), 3.92 - 3.86 (m, 2H), 3.81 - 3.73 (m, 1H), 3.68 - 3.62 (m, 1H), 3.03 (br s, 1H), 2.83 (br dd, J=11.6, 3.7 Hz, 1H), 2.31 - 2.19 (m, 2H), 1.98 (br t, J=7.3 Hz, 2H), 1.90 - 1.69 (m, 6H), 1.49 - 1.41 (m, 1H), 1.36 - 1.15 (m, 3H), 0.88 - 0.76 (m, 1H), 0.75 - 0.64 (m, 2H), 0.32 (br d, J=2.1 Hz, 2H)。	2.45, B

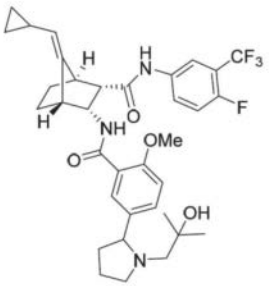
601	 由ent-449-4制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙基)吡咯烷-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.4	(400MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.78 (d, J=6.8 Hz, 1H), 8.21 (dd, J=2.6, 6.0 Hz, 1H), 7.85 (d, J=2.4 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.42 (dd, J=2.2, 8.3 Hz, 1H), 7.10 (d, J=8.3 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.49 - 4.37 (m, 1H), 3.96 (s, 4H), 3.19 - 3.11 (m, 2H), 3.09 - 3.02 (m, 2H), 2.93 - 2.78 (m, 2H), 2.70 (br t, J=3.1 Hz, 2H), 2.29 - 2.14 (m, 1H), 1.93 - 1.82 (m, 3H), 1.80 - 1.61 (m, 2H), 1.55 - 1.30 (m, 3H), 1.13 (s, 8H), 0.80 - 0.63 (m, 2H), 0.35 (dd, J=2.0, 4.6 Hz, 2H)	2.32, A

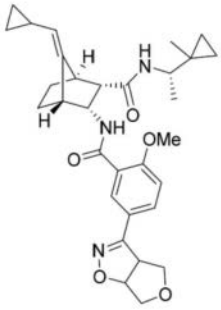
602	 经由SFC分离的异构体，其中实施例602为峰2 (RT=2.76 min.， >99% de)-仪器：PIC Solution SFC柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：30% IPA-0.1% DEA / 70% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Aurora Infinity SFC，柱Chiralpak IC，4.6 × 250 mm，3微米，移动相：20% IPA-0.1% DEA / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性（峰-1，RT=1.81 min.，>99% de)及手性(峰-2，RT=2.76 min.，>99% de)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-5-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	614.2	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.34 (br d, J=6.7 Hz, 1H), 8.18 - 8.05 (m, 1H), 7.84 - 7.78 (m, 1H), 7.60 (s, 1H), 7.50 (br t, J=9.8 Hz, 1H), 7.38 (s, 1H), 7.35 (s, 1H), 5.41 (dd, J=9.0, 3.2 Hz, 1H), 4.71 (d, J=9.2 Hz, 1H), 4.53 (br t, J=7.8 Hz, 1H), 4.45 - 4.36 (m, 1H), 4.13 (br d, J=10.7 Hz, 1H), 4.00 (br d, J=9.5 Hz, 1H), 3.86 (s, 2H), 3.82 - 3.75 (m, 1H), 3.67 (dd, J=10.8, 3.5 Hz, 1H), 3.19 (br dd, J=10.1, 3.4 Hz, 1H), 3.11 (br s, 1H), 2.77 (br s, 1H), 1.89 - 1.82 (m, 1H), 1.80 - 1.73 (m, 1H), 1.60 - 1.50 (m, 1H), 1.45 (br s, 2H), 0.82 - 0.70 (m, 2H), 0.37 (br s, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.51, B

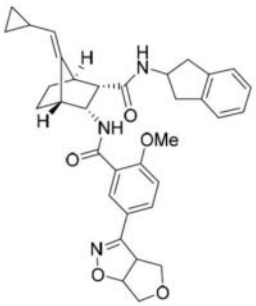
603	 由同手性苯甲酸酯峰1(RT=3.28 min，>99% ee)制备，所用仪器：Berger MG II 柱：Chiralpak IC，21 × 250 mm，5微米，移动相：30% MeOH / 70% CO_2，流动条件：45 mL/min，150巴，40℃，检测器波长：220 nm；分析方法：仪器：Aurora Infinity SFC，柱Chiralpak IC，4.6 × 250 mm，3微米，移动相：30% MeOH / 70% CO_2，流动条件：2 mL/min，150巴，40℃，检测器波长：220 nm，得到手性(峰-1，RT=3.28 min.，>99% ee)及手性(峰-2，RT=3.85 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环丁基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.91 (br d, J=7.3 Hz, 1H), 8.23 (br d, J=2.1 Hz, 2H), 7.84 - 7.74 (m, 2H), 7.49 (t, J=9.6 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 5.26 (s, 1H), 4.79 - 4.65 (m, 2H), 4.50 - 4.39 (m, 1H), 4.05 (s, 3H), 3.38 (m, 1H), 3.22 - 3.15 (m, 1H), 3.13 - 3.08 (m, 1H), 2.73 (br s, 1H), 2.18 - 2.09 (m, 1H), 2.06 (br dd, J=7.8, 3.8 Hz, 1H), 2.02 - 1.90 (m, 2H), 1.88 - 1.83 (m, 1H), 1.81 - 1.77 (m, 1H), 1.75 - 1.66 (m, 1H), 1.64 - 1.57 (m, 1H), 1.55 - 1.47 (m, 1H), 1.47 - 1.31 (m, 2H), 0.75 (br dd, J=11.9, 8.9 Hz, 2H), 0.36 (br s, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.67, B

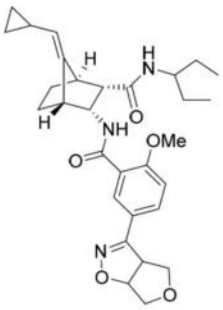
605	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{6,6-二氟螺[3.3]庚烷-2-基}双环[2.2.1]庚烷-2-甲酰胺	582.2	(500 MHz, DMSO-d6) δ 9.94 (br d, J=6.7 Hz, 1H), 8.33 (br d, J=7.3 Hz, 1H), 8.14 (d, J=1.8 Hz, 1H), 7.79 (br d, J=8.5 Hz, 1H), 7.27 - 7.20 (m, 1H), 5.34 (br dd, J=9.2, 3.1 Hz, 1H), 4.61 (br d, J=9.8 Hz, 1H), 4.50 (br t, J=8.1 Hz, 1H), 4.32 - 4.22 (m, 1H), 4.16 - 4.04 (m, 2H), 4.01 (s, 3H), 3.90 (br d, J=9.2 Hz, 1H), 3.77 (br dd, J=8.7, 7.5 Hz, 1H), 3.65 (br dd, J=10.4, 3.4 Hz, 1H), 3.04 (br s, 1H), 2.84 (br dd, J=10.8, 4.1 Hz, 1H), 2.63 (br t, J=12.1 Hz, 2H), 2.42 - 2.28 (m, 2H), 2.06 - 1.91 (m, 2H), 1.81 - 1.67 (m, 2H), 1.51 - 1.40 (m, 1H), 1.38 - 1.22 (m, 2H), 0.78 - 0.64 (m, 2H), 0.31 (br s, 2H)。可能由于与经抑制的水峰和/或溶剂峰重叠，三个质子在NMR中不可见。	2.27, B

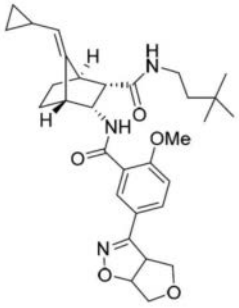
606	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2-环丙基苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	582.2	(500 MHz, DMSO-d6) δ 9.93 (br d, J=7.0 Hz, 1H), 8.53 (br t, J=5.3 Hz, 1H), 8.17 (d, J=2.4 Hz, 1H), 7.78 (dd, J=8.5, 2.1 Hz, 1H), 7.21 (d, J=8.9 Hz, 1H), 7.17 - 7.08 (m, 2H), 7.06 - 7.00 (m, 1H), 6.93 (d, J=7.3 Hz, 1H), 5.34 (dd, J=9.2, 3.1 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.54 - 4.40 (m, 3H), 4.37 - 4.26 (m, 1H), 4.09 (d, J=10.7 Hz, 1H), 3.95 - 3.85 (m, 4H), 3.80 - 3.72 (m, 1H), 3.65 (dd, J=10.7, 3.4 Hz, 1H), 3.08 - 2.98 (m, 2H), 2.62 - 2.57 (m, 1H), 1.97 - 1.84 (m, 2H), 1.79 - 1.69 (m, 1H), 1.52 - 1.41 (m, 1H), 1.39 - 1.26 (m, 2H), 0.82 (br d, J=8.5 Hz, 2H), 0.75 - 0.64 (m, 2H), 0.63 - 0.51 (m, 2H), 0.32 (br d, J=4.3 Hz, 2H)。	2.43, C

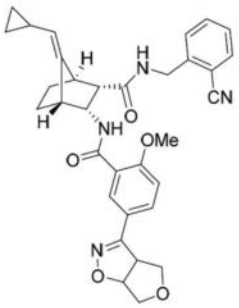
607	 由实施例720制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(400MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.81 (d, J=6.8 Hz, 1H), 8.22 (dd, J=2.4, 6.6 Hz, 1H), 7.93 (d, J=1.7 Hz, 1H), 7.81 - 7.70 (m, 1H), 7.54 - 7.34 (m, 2H), 7.10 (d, J=8.6 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.51 - 4.40 (m, 1H), 4.01 - 3.90 (m, 5H), 3.55 - 3.47 (m, 1H), 3.25 (br t, J=7.9 Hz, 1H), 3.18 - 3.10 (m, 2H), 3.09 - 3.04 (m, 1H), 2.73 - 2.68 (m, 1H), 2.29 - 2.21 (m, 2H), 2.06 - 1.95 (m, 2H), 1.89 - 1.69 (m, 4H), 1.55 - 1.32 (m, 5H), 1.00 (s, 3H), 0.87 (s, 3H), 0.79 - 0.65 (m, 2H), 0.35 (dd, J=2.0, 4.4 Hz, 2H)	2.67, A

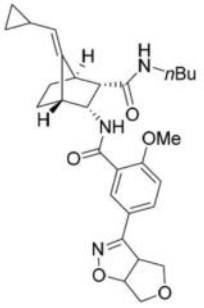
609	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1S)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	534.2	(500 MHz, DMSO-d6) δ 10.07 (d, J=6.9 Hz, 1H), 8.12 (d, J=2.4 Hz, 1H), 7.93 (d, J=8.5 Hz, 1H), 7.77 (dd, J=8.7, 2.4 Hz, 1H), 7.22 (d, J=8.8 Hz, 1H), 5.32 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.46 (br t, J=8.0 Hz, 1H), 4.27 - 4.19 (m, 1H), 4.08 (d, J=10.8 Hz, 1H), 3.97 (s, 3H), 3.88 (br d, J=9.3 Hz, 1H), 3.76 (br dd, J=9.3, 6.8 Hz, 1H), 3.49 - 3.38 (m, 1H), 3.06 - 2.99 (m, 1H), 2.92 (dd, J=10.8, 4.2 Hz, 1H), 1.89 - 1.79 (m, 1H), 1.75 - 1.65 (m, 1H), 1.49 - 1.40 (m, 1H), 1.38 - 1.26 (m, 2H), 0.99 (d, J=6.9 Hz, 3H), 0.95 (s, 3H), 0.76 - 0.64 (m, 2H), 0.54 - 0.46 (m, 1H), 0.37 - 0.24 (m, 3H), 0.21 - 0.10 (m, 2H)。可能由于与经抑制的水峰重叠，一个质子在NMR中不可见。	2.42, C

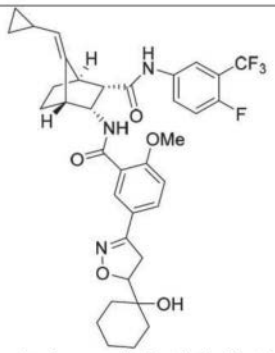
610	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(2,3-二氢-1H-茚-2-基)双环[2.2.1]庚烷-2-甲酰胺	568.0	(500 MHz, DMSO-d6) δ 10.00 (br d, J=6.7 Hz, 1H), 8.41 (br d, J=6.7 Hz, 1H), 8.16 (s, 1H), 7.80 (dd, J=8.7, 1.4 Hz, 1H), 7.26 (d, J=8.9 Hz, 1H), 7.20 (br d, J=6.4 Hz, 1H), 7.17 - 7.08 (m, 3H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.59 (d, J=9.5 Hz, 1H), 4.53 - 4.43 (m, 2H), 4.27 (br d, J=4.0 Hz, 1H), 4.09 (br d, J=11.0 Hz, 1H), 4.04 (s, 3H), 3.90 (br d, J=9.5 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.65 (br dd, J=10.7, 3.4 Hz, 1H), 3.24 - 3.09 (m, 2H), 3.04 (br s, 1H), 2.88 (br dd, J=10.7, 3.7 Hz, 1H), 2.72 (dt, J=15.7, 6.2 Hz, 2H), 1.92 - 1.83 (m, 1H), 1.78 - 1.69 (m, 1H), 1.51 - 1.41 (m, 1H), 1.40 - 1.27 (m, 2H), 0.77 - 0.63 (m, 2H), 0.30 (br d, J=2.4 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.37, B

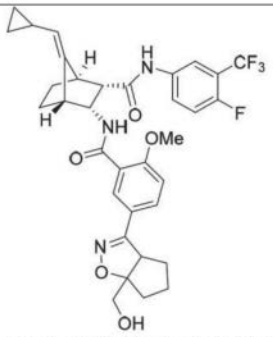
611	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(戊烷-3-基)双环[2.2.1]庚烷-2-甲酰胺	522.0	(500 MHz, DMSO-d6) δ 10.04 (br d, J=6.7 Hz, 1H), 8.15 (d, J=1.5 Hz, 1H), 7.81 - 7.70 (m, 2H), 7.23 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.8 Hz, 1H), 4.28 (br d, J=4.3 Hz, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.93 - 3.85 (m, 1H), 3.80 - 3.72 (m, 1H), 3.69 - 3.54 (m, 2H), 3.05 (br d, J=2.7 Hz, 1H), 2.92 (br dd, J=10.7, 4.0 Hz, 1H), 1.91 - 1.81 (m, 1H), 1.76 - 1.68 (m, 1H), 1.51 - 1.21 (m, 7H), 0.85 - 0.65 (m, 8H), 0.37 - 0.22 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.32, B

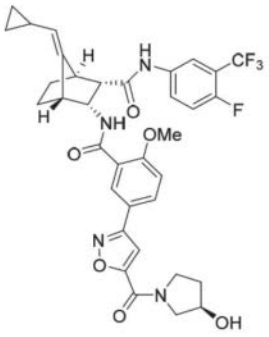
612	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(3,3-二甲基丁基)双环[2.2.1]庚烷-2-甲酰胺	536.3	(500 MHz, DMSO-d6) δ 9.98 (br d, J=7.0 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 8.03 (br t, J=5.3 Hz, 1H), 7.79 (dd, J=8.5, 2.1 Hz, 1H), 7.24 (d, J=8.5 Hz, 1H), 5.34 (dd, J=9.0, 3.2 Hz, 1H), 4.61 (d, J=9.8 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.27 (br t, J=10.8 Hz, 1H), 4.09 (d, J=10.4 Hz, 1H), 4.02 (s, 3H), 3.92 - 3.86 (m, 1H), 3.77 (dd, J=9.0, 7.2 Hz, 1H), 3.65 (dd, J=10.7, 3.4 Hz, 1H), 3.11 - 3.01 (m, 2H), 2.86 (br dd, J=10.8, 3.8 Hz, 1H), 1.86 (br t, J=9.9 Hz, 1H), 1.78 - 1.68 (m, 1H), 1.46 (dtd, J=12.9, 8.4, 4.4 Hz, 1H), 1.39 - 1.24 (m, 4H), 0.86 (s, 9H), 0.75 - 0.63 (m, 2H), 0.32 (br d, J=3.7 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.38, C

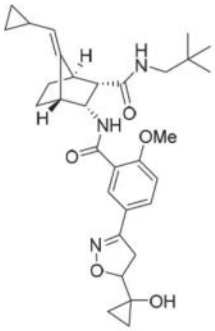
613	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[(2-氰基苯基)甲基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	567.2	(500 MHz, DMSO-d6) δ 9.91 (d, J=7.0 Hz, 1H), 8.83 (br t, J=5.9 Hz, 1H), 8.17 (d, J=2.2 Hz, 1H), 7.84 - 7.73 (m, 2H), 7.57 (t, J=7.9 Hz, 1H), 7.47 - 7.34 (m, 2H), 7.21 (d, J=8.7 Hz, 1H), 5.34 (dd, J=9.2, 3.6 Hz, 1H), 4.64 (d, J=9.6 Hz, 1H), 4.55 - 4.38 (m, 3H), 4.33 (dt, J=10.2, 5.0 Hz, 1H), 4.09 (d, J=10.6 Hz, 1H), 3.90 (d, J=0.7 Hz, 4H), 3.82 - 3.69 (m, 1H), 3.65 (dd, J=10.7, 3.5 Hz, 1H), 3.10 - 2.98 (m, 2H), 2.68 - 2.60 (m, 1H), 1.86 - 1.65 (m, 2H), 1.55 - 1.43 (m, 1H), 1.39 - 1.20 (m, 2H), 0.78 - 0.60 (m, 2H), 0.40 - 0.24 (m, 2H)。	2.14, B

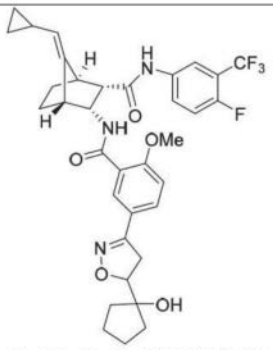
614	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-丁基-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	508.0	(500 MHz, DMSO-d6) δ 9.98 (d, J=6.7 Hz, 1H), 8.15 (d, J=2.2 Hz, 1H), 8.04 (br t, J=5.6 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 5.34 (dd, J=9.2, 3.5 Hz, 1H), 4.61 (d, J=9.5 Hz, 1H), 4.50 (br t, J=7.6 Hz, 1H), 4.32 - 4.23 (m, 1H), 4.09 (d, J=10.8 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=9.3 Hz, 1H), 3.77 (dd, J=9.2, 6.9 Hz, 1H), 3.65 (dd, J=10.8, 3.6 Hz, 1H), 3.12 - 2.99 (m, 3H), 2.89 (dd, J=10.9, 4.2 Hz, 1H), 1.89 - 1.81 (m, 1H), 1.79 - 1.70 (m, 1H), 1.51 - 1.42 (m, 1H), 1.41 - 1.29 (m, 1H), 1.29 - 1.19 (m, 1H), 0.82 (t, J=7.3 Hz, 3H), 0.75 - 0.64 (m, 2H), 0.35 - 0.26 (m, 2H)。可能由于与经抑制的水峰重叠，一个质子在NMR中不可见。	2.23, B

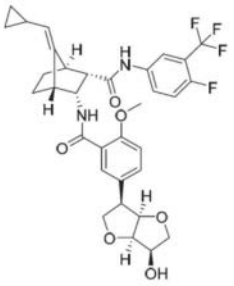
615	 通过SFC分离的异构体，其中实施例615为峰1 (RT=1.15 min，>99% de)，仪器：Berger MG II柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：50% IPA-0.1% DEA/ 50% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak AD-H, 4.6 × 100 mm，3微米，移动相：50% IPA0.1% DEA / 50% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=1.15 min.，>99% de)及手性(峰-2，RT=2.72 min.，>99% de)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环己基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.2	(500 MHz, DMSO-d6) δ 10.30 (s, 1H), 9.67 (br d, J=7.0 Hz, 1H), 8.04 - 7.96 (m, 2H), 7.60 - 7.53 (m, 2H), 7.25 (br t, J=9.9 Hz, 1H), 7.03 (d, J=8.9 Hz, 1H), 4.46 (d, J=9.2 Hz, 1H), 4.28 - 4.15 (m, 2H), 4.08 (s, 1H), 3.91 (br t, J=5.3 Hz, 1H), 3.86 - 3.73 (m, 3H), 2.93 (br dd, J=10.8, 4.4 Hz, 1H), 2.89 - 2.84 (m, 1H), 2.53 - 2.44 (m, 1H), 1.66 - 1.58 (m, 1H), 1.56 - 1.48 (m, 1H), 1.42 - 1.24 (m, 5H), 1.23 - 1.14 (m, 4H), 1.14 - 1.02 (m, 3H), 1.01 - 0.84 (m, 1H), 0.69 - 0.60 (m, 1H), 0.58 - 0.44 (m, 2H), 0.21 - 0.05 (m, 2H)	2.70, B

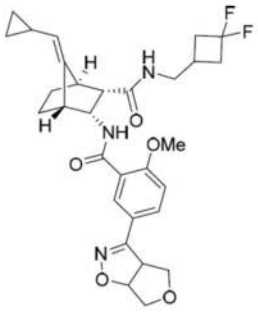
616	 由同手性苯甲酸中间体峰2制备。制备型色谱条件：仪器：Berger MG II (CTR-L409-PSFC1)柱：Chiralpak IC，30 × 250 mm，5微米，移动相：25%甲醇/ 75% CO_2，流动条件：70 mL/min，120巴，40°C，检测器波长：220 nm，注射详情：0.5 mL~75mg/mL于甲醇中，分析型色谱条件：仪器：Shimadzu Nexera SFC (CTR-L410-SFC3)柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 µL~1mg/mL于MeOH中(峰-2，RT 4.97 min.，> 99% ee)	(1R,2S,3R,4R,7Z)-3-{5-[6a-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	642.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (d, J=7.3 Hz, 1H), 8.22 (br d, J=2.2 Hz, 2H), 7.86 - 7.71 (m, 2H), 7.48 (t, J=9.9 Hz, 1H), 7.26 (d, J=8.7 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.44 (br s, 1H), 4.04 (s, 3H), 3.89 (br d, J=6.6 Hz, 1H), 3.56 (br dd, J=11.6, 5.1 Hz, 1H), 3.16 (br dd, J=10.6, 4.0 Hz, 1H), 3.10 (br s, 1H), 2.89 (s, 1H), 2.79 - 2.67 (m, 2H), 1.97 - 1.88 (m, 6H), 1.87 - 1.72 (m, 4H), 1.68 (br s, 2H), 1.55 - 1.35 (m, 4H), 1.04 (d, J=6.1 Hz, 1H), 0.87 - 0.67 (m, 2H), 0.35 (br s, 2H)	2.65, C

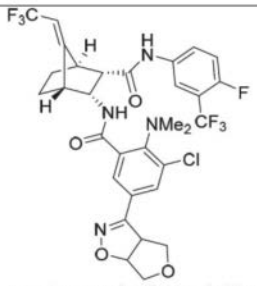
617		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-[(3R)-3-羟基吡咯烷-1-羰基]-1,2-噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	682.9	(500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.67 (br d, J=6.6 Hz, 1H), 9.09 - 9.01 (m, 1H), 8.10 - 8.02 (m, 1H), 7.96 (br d, J=5.1 Hz, 1H), 7.61 - 7.47 (m, 2H), 7.22 (br t, J=9.7 Hz, 1H), 7.06 (dd, J=8.5, 7.0 Hz, 1H), 4.82 (br d, J=12.5 Hz, 1H), 4.43 (d, J=9.6 Hz, 1H), 4.19 (br s, 1H), 4.06 (br s, 1H), 3.95 (br d, J=2.6 Hz, 1H), 3.80 (s, 3H), 3.55 (br s, 1H), 3.37 - 3.25 (m, 2H), 3.19 - 3.08 (m, 1H), 2.97 - 2.87 (m, 1H), 2.85 (br s, 1H), 2.52 - 2.41 (m, 1H), 1.69 - 1.48 (m, 4H), 1.32 - 1.19 (m, 1H), 1.19 - 1.09 (m, 2H), 0.59 - 0.42 (m, 2H), 0.15 - 0.04 (m, 2H)	2.29, B

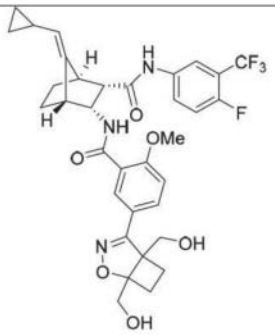
618	 由与实施例491中相同的中间体制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-(2,2-二甲基丙基)-3-{5-[5-(1-羟基环丙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	536.0	(500 MHz, DMSO-d6) δ 9.96 (br d, J=6.7 Hz, 1H), 8.16 (d, J=1.8 Hz, 1H), 7.97 (br t, J=6.1 Hz, 1H), 7.77 (dd, J=8.4, 2.3 Hz, 1H), 7.22 (d, J=8.9 Hz, 1H), 5.62 (s, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.39 - 4.23 (m, 2H), 4.03 - 3.94 (m, 3H), 3.02 (br dd, J=13.1, 7.3 Hz, 3H), 2.79 (br dd, J=12.8, 5.5 Hz, 1H), 1.90 - 1.81 (m, 1H), 1.78 - 1.68 (m, 1H), 1.51 - 1.42 (m, 1H), 1.38 - 1.25 (m, 2H), 0.81 (s, 9H), 0.74 - 0.64 (m, 3H), 0.62 - 0.52 (m, 3H), 0.31 (br d, J=1.8 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.33, B

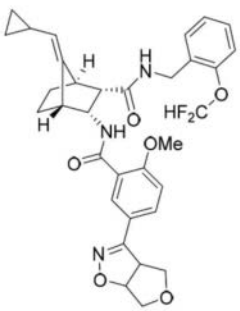
619	 由同手性苯甲酸酯峰2-(RT=3.85 min，>99% ee)制备，仪器：Berger MG II柱：ChiralpakIC-H，21 × 250 mm，5微米，移动相：30% MeOH / 70% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IC，4.6 × 100 mm，3微米，移动相：30% MeOH / 70% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=3.28 min.，>99% ee)及手性(峰-2，RT=3.85 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基环戊基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.23 (br s, 2H), 7.84 - 7.80 (m, 1H), 7.79 (br s, 1H), 7.50 (br t, J=9.9 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 4.71 (d, J=9.5 Hz, 1H), 4.63 - 4.57 (m, 1H), 4.51 - 4.43 (m, 1H), 4.11 - 4.00 (m, 3H), 3.45 - 3.36 (m, 1H), 3.29 (br dd, J=16.6, 8.1 Hz, 1H), 3.17 (br dd, J=10.7, 4.0 Hz, 1H), 3.12 (br s, 1H), 2.73 (br s, 1H), 1.92 - 1.82 (m, 1H), 1.82 - 1.76 (m, 1H), 1.73 (br s, 2H), 1.66 - 1.45 (m, 7H), 1.46 - 1.35 (m, 2H), 0.84 - 0.69 (m, 2H), 0.44 - 0.33 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.65, C

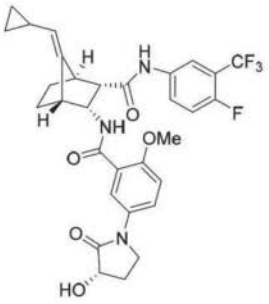
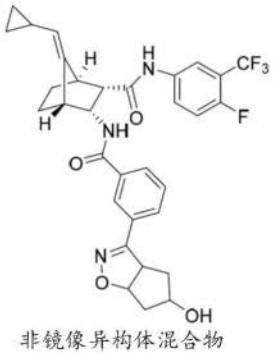
620		(1R,2S,3R,4R,7Z)-3-{5-[(3R,3aR,6R,6aR)-6-羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	631.5	(500 MHz, CD_3OD) δ 8.16 (dd, J=6.4, 2.6 Hz, 1H), 8.00 (d, J=2.4 Hz, 1H), 7.75 (dt, J=8.5, 3.6 Hz, 1H), 7.51 (dd, J=8.5, 2.4 Hz, 1H), 7.29 (t, J=9.8 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 4.74 (d, J=9.3 Hz, 1H), 4.67 - 4.53 (m, 3H), 4.34 (td, J=6.8, 5.0 Hz, 1H), 4.26 (t, J=8.0 Hz, 1H), 4.07 (s, 3H), 4.01 (dd, J=11.6, 8.1 Hz, 1H), 3.87 (dd, J=8.8, 6.5 Hz, 1H), 3.63 (dd, J=8.8, 7.2 Hz, 1H), 3.53 - 3.44 (m, 2H), 3.22 (t, J=4.0 Hz, 1H), 3.19 - 3.11 (m, 1H), 2.72 (t, J=4.0 Hz, 1H), 2.06 - 2.00 (m, 1H), 1.97 - 1.89 (m, 1H), 1.64 - 1.44 (m, 3H), 0.83 - 0.67 (m, 2H), 0.44 - 0.27 (m, 2H)	2.33, B

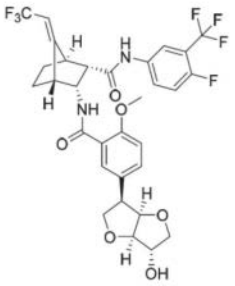
621	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(3,3-二氟环丁基)甲基]双环[2.2.1]庚烷-2-甲酰胺	556.0	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.9 Hz, 1H), 8.24 (br t, J=5.8 Hz, 1H), 8.17 (d, J=2.4 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 5.34 (dd, J=9.2, 3.5 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.50 (br t, J=8.1 Hz, 1H), 4.36 - 4.25 (m, 1H), 4.09 (d, J=10.8 Hz, 1H), 4.01 (s, 3H), 3.90 (br d, J=9.0 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.65 (dd, J=10.6, 3.6 Hz, 1H), 3.24 - 3.12 (m, 1H), 3.05 (br d, J=3.6 Hz, 1H), 2.91 (br dd, J=10.7, 4.1 Hz, 1H), 2.32 - 2.19 (m, 3H), 1.82 (br t, J=9.2 Hz, 1H), 1.77 - 1.68 (m, 1H), 1.46 (ddd, J=12.8, 8.1, 4.5 Hz, 1H), 1.39 - 1.27 (m, 2H), 0.77 - 0.64 (m, 2H), 0.32 (br dd, J=4.2, 1.8 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，四个质子在NMR中不可见。	2.16, B

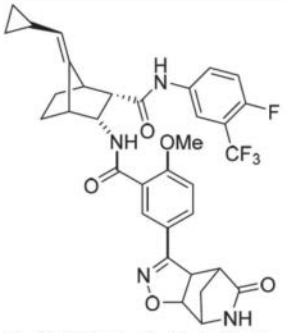
622	 通过SFC分离的异构体，其中实施例622为峰2 (RT=9.99 min.，>95% ee)：所用仪器：Waters 100 Prep SFC柱：Chiral IC, 21 × 250 mm，5微米，移动相：25% MeOH / 75% CO_2 (具有0.1% DEA)，流动条件：60 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral IC，4.6 × 150 mm，5微米，移动相：25% MeOH / 75% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=4.3 min.，>95% ee)及手性(峰-2，RT=5.1 min.，>95% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氯-2-(二甲基氨基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	689.0	(500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 10.02 (br d, *J*=7.6 Hz, 1H), 8.16 (br d, *J*=4.3 Hz, 1H), 7.88 (d, *J*=1.8 Hz, 1H), 7.84 - 7.74 (m, 2H), 7.48 (t, *J*=9.8 Hz, 1H), 5.95 (q, *J*=8.1 Hz, 1H), 5.37 (dd, *J*=9.2, 3.4 Hz, 1H), 4.59 (br s, 1H), 4.43 (br t, *J*=8.1 Hz, 1H), 4.11 (d, *J*=10.7 Hz, 1H), 3.93 (br d, *J*=11.3 Hz, 1H), 3.75 - 3.60 (m, 2H), 3.27 (br d, *J*=10.7 Hz, 1H), 3.21 (br s, 1H), 3.00 (br s, 1H), 2.83 (s, 6H), 2.20 - 2.01 (m, 2H), 1.52 (br s, 2H)	2.87, B

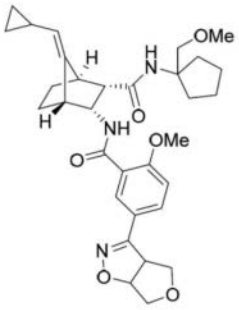
623	 在氧化成苯甲酸峰2之前由三醇制备：制备型色谱条件：仪器：Berger MG II柱：Chiralpak IC，30×250 mm，5微米，移动相：25%甲醇/75% CO_2，流动条件：70 mL/min，120巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~75mg/mL于甲醇中。分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6×100 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL~1mg/mL于MeOH中(峰-2，RT 5.72 min.，>99% ee)	(1R,2S,3R,4R,7Z)-3-{5-[1,5-双(羟基甲基)-2-氧杂-3-氮杂双环[3.2.0]庚-3-烯-4-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	658.1	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.23 (br s, 2H), 7.84 - 7.77 (m, 2H), 7.49 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 4.77 (br s, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.44 (br s, 1H), 4.05 (s, 2H), 3.91 - 3.79 (m, 2H), 3.71 (br dd, J=11.7, 6.9 Hz, 1H), 3.40 (br s, 1H), 3.29 - 3.09 (m, 2H), 2.73 (br s, 1H), 2.42 - 2.20 (m, 1H), 2.18 - 2.11 (m, 2H), 2.08 (s, 1H), 1.94 - 1.73 (m, 2H), 1.52 (br d, J=4.3 Hz, 1H), 1.43 (br s, 2H), 0.92 - 0.70 (m, 2H), 0.36 (br s, 2H)	2.38, C

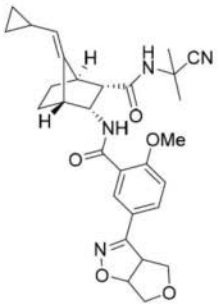
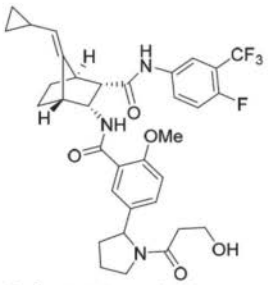
624	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[2-(二氟甲氧基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	608.0	(500 MHz, DMSO-d6) δ 9.92 (d, J=6.9 Hz, 1H), 8.58 (br t, J=5.8 Hz, 1H), 8.16 (d, J=2.3 Hz, 1H), 7.78 (dd, J=8.7, 2.4 Hz, 1H), 7.36 - 7.07 (m, 5H), 7.03 (s, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.48 (br t, J=8.0 Hz, 1H), 4.38 - 4.25 (m, 3H), 4.09 (d, J=10.6 Hz, 1H), 3.89 (s, 4H), 3.77 (dd, J=9.3, 6.9 Hz, 1H), 3.66 - 3.60 (m, 1H), 3.06 - 2.96 (m, 2H), 2.62 - 2.58 (m, 1H), 1.82 (br t, J=9.1 Hz, 1H), 1.77 - 1.67 (m, 1H), 1.52 - 1.43 (m, 1H), 1.39 - 1.28 (m, 2H), 0.78 - 0.65 (m, 2H), 0.38 - 0.27 (m, 2H)。	2.22, C

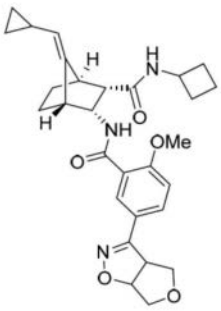
627		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[(3S)-3-羟基-2-氧代吡咯烷-1-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	601.9	(500 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.87 (d, *J*=7.2 Hz, 1H), 8.21 (d, *J*=6.9 Hz, 1H), 8.16 (d, *J*=2.9 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.47 (t, *J*=9.7 Hz, 1H), 7.20 (d, *J*=9.1 Hz, 1H), 4.68 (d, *J*=9.6 Hz, 1H), 4.51 - 4.37 (m, 1H), 4.28 (td, *J*=8.5, 5.9 Hz, 1H), 4.03 - 3.94 (m, 3H), 3.77 - 3.63 (m, 2H), 3.52 - 3.35 (m, 1H), 3.15 (br dd, *J*=10.8, 4.4 Hz, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 2.43 - 2.34 (m, 1H), 1.90 - 1.73 (m, 3H), 1.49 (tt, *J*=8.7, 4.4 Hz, 1H), 1.43 - 1.34 (m, 2H), 0.82 - 0.66 (m, 2H), 0.41 - 0.29 (m, 2H)	2.27, B
628	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(3-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	598.1	(500 MHz, DMSO-d6) δ 10.58 (br s, 1H), 9.51 - 9.26 (m, 1H), 8.10 - 7.99 (m, 2H), 7.96 - 7.78 (m, 3H), 7.68 - 7.58 (m, 1H), 7.50 (td, J=9.7, 4.4 Hz, 1H), 5.25 - 5.13 (m, 1H), 4.72 (br d, J=9.5 Hz, 1H), 4.52 - 4.36 (m, 1H), 4.34 - 4.23 (m, 1H), 4.20 - 4.07 (m, 1H), 3.43 - 3.33 (m, 1H), 3.25 - 3.17 (m, 1H), 3.12 (br s, 1H), 2.78 (br s, 1H), 2.18 - 2.06 (m, 1H), 2.05 - 1.99 (m, 1H), 1.98 - 1.90 (m, 1H), 1.89 - 1.80 (m, 2H), 1.80 - 1.70 (m, 1H), 1.59 - 1.51 (m, 1H), 1.50 - 1.38 (m, 2H), 0.83 - 0.69 (m, 2H), 0.38 (br s, 2H)	2.29, B

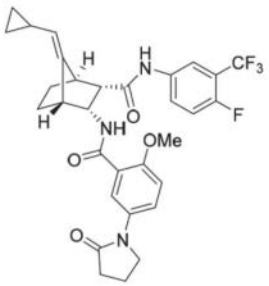
630		(1R,2S,3R,4R,7Z)-3-{5-[(3R,3aR,6S,6aR)-6-羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	259.2	(500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.26 (br d, J=4.6 Hz, 1H), 7.89 (d, J=1.5 Hz, 1H), 7.84 - 7.75 (m, 1H), 7.52 (br t, J=9.8 Hz, 1H), 7.47 - 7.38 (m, 1H), 7.14 (d, J=8.5 Hz, 1H), 5.96 (q, J=7.9 Hz, 1H), 5.23 (d, J=4.0 Hz, 1H), 4.69 (t, J=3.7 Hz, 1H), 4.59 - 4.48 (m, 1H), 4.44 (br d, J=3.4 Hz, 1H), 4.21 - 4.07 (m, 2H), 3.99 (s, 3H), 3.82 (dd, J=9.5, 3.7 Hz, 1H), 3.74 - 3.62 (m, 2H), 3.33 - 3.20 (m, 2H), 3.00 (br s, 1H), 2.06 - 1.96 (m, 1H), 1.94 - 1.84 (m, 1H), 1.51 (br d, J=6.7 Hz, 2H)	2.31, A

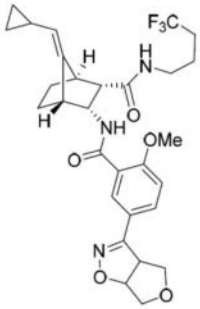
631	 通过SFC分离的异构体，其中实施例631为峰2 (RT=4.7 min.，>95% de)：-仪器：Waters 100 Prep SFC柱：Chiral AD，30×250 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA），流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6×100 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰-1，RT=3.2 min.，>95% de)及手性(峰-2，RT=4.7 min.，>95% de)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{8-氧代-3-氧杂-4,9-二氮杂三环[5.2.1.0²,⁶]癸-4-烯-5-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	653.1	(500 MHz, DMSO-d6) δ 10.65 - 10.48 (m, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.28 (d, J=1.7 Hz, 1H), 8.24 - 8.15 (m, 1H), 7.90 (s, 1H), 7.85 (dd, J=8.6, 2.4 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.48 (br t, J=9.7 Hz, 1H), 7.29 (d, J=8.8 Hz, 1H), 5.10 (br d, J=8.1 Hz, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.27 (br d, J=8.0 Hz, 1H), 4.06 (br s, 1H), 4.04 (s, 3H), 3.20 - 3.13 (m, 1H), 3.10 (br s, 1H), 2.91 (s, 1H), 2.72 (br s, 1H), 1.90 (br d, J=10.4 Hz, 1H), 1.86 - 1.80 (m, 1H), 1.77 (br d, J=10.2 Hz, 1H), 1.59 (br d, J=10.6 Hz, 1H), 1.54 - 1.45 (m, 1H), 1.43 - 1.34 (m, 2H), 0.84 - 0.67 (m, 2H), 0.40 - 0.29 (m, 2H)	2.33, B

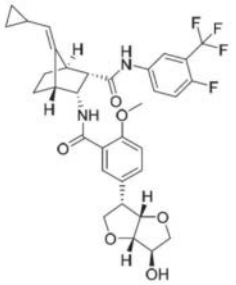
632	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[1-(甲氧基甲基)环戊基]双环[2.2.1]庚烷-2-甲酰胺	564.0	(500 MHz, DMSO-d6) δ 10.08 (br d, J=7.0 Hz, 1H), 8.18 (d, J=1.8 Hz, 1H), 7.78 (dd, J=8.5, 1.8 Hz, 1H), 7.67 (s, 1H), 7.24 (d, J=8.9 Hz, 1H), 5.33 (br dd, J=9.0, 3.2 Hz, 1H), 4.60 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=7.8 Hz, 1H), 4.32 - 4.19 (m, 1H), 4.14 - 4.05 (m, 1H), 4.03 (s, 3H), 3.89 (br d, J=9.2 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.65 (br dd, J=10.8, 3.2 Hz, 1H), 3.16 (s, 3H), 3.02 (br s, 1H), 2.91 (br dd, J=11.0, 4.0 Hz, 1H), 1.91 - 1.79 (m, 3H), 1.75 - 1.66 (m, 1H), 1.64 - 1.40 (m, 7H), 1.38 - 1.22 (m, 2H), 0.78 - 0.62 (m, 2H), 0.30 (br d, J=2.1 Hz, 2H)。可能由于与经抑制的水峰和/或溶剂峰重叠，三个质子在NMR中不可见。	2.36, B

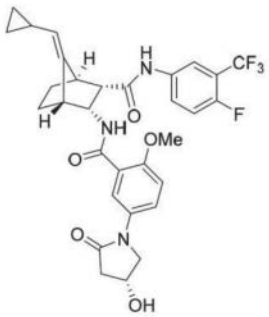
633	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(1-氰基-1-甲基乙基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	519.2	(400 MHz, CD_3OD) δ 8.29 (d, J=2.3 Hz, 1H), 7.91 - 7.84 (m, 1H), 7.26 (d, J=9.0 Hz, 1H), 5.39 - 5.33 (m, 1H), 4.72 - 4.60 (m, 1H), 4.50 - 4.42 (m, 2H), 4.25 - 4.16 (m, 4H), 4.09 - 4.01 (m, 1H), 3.92 - 3.86 (m, 1H), 3.80 - 3.70 (m, 1H), 3.00 - 2.93 (m, 2H), 2.63 - 2.58 (m, 1H), 1.97 - 1.85 (m, 2H), 1.64 (d, J=11.6 Hz, 6H), 1.55 - 1.23 (m, 3H), 0.75 - 0.68 (m, 2H), 0.38 - 0.27 (m,21H)	1.88, C
634	 由实施例715制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(3-羟基丙酰基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(400MHz, DMSO-d6) δ = 9.91 - 9.76 (m, 1H), 8.21 (br d, J=6.6 Hz, 1H), 7.80 - 7.66 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.29 (ddd, J=2.6, 8.6, 19.7 Hz, 1H), 7.20 - 7.00 (m, 1H), 5.13 - 4.94 (m, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.51 (t, J=5.3 Hz, 1H), 4.47 - 4.39 (m, 1H), 4.37 (t, J=5.4 Hz, 1H), 3.99 (s, 2H), 3.96 (s, 1H), 3.75 - 3.60 (m, 2H), 3.57 - 3.40 (m, 2H), 3.18 - 3.11 (m, 1H), 3.10 - 3.04 (m, 1H), 2.71 (br s, 1H), 2.42 - 2.16 (m, 2H), 1.93 - 1.64 (m, 5H), 1.54 - 1.32 (m, 3H), 0.80 - 0.67 (m, 2H), 0.41 - 0.29 (m, 2H)	2.34, A

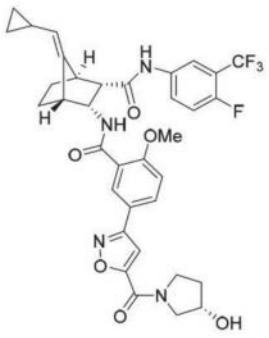
635	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-环丁基-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	506.3	(500 MHz, DMSO-d6) δ 9.98 (br dd, J=14.0, 6.7 Hz, 1H), 8.34 (br dd, J=14.0, 7.6 Hz, 1H), 8.16 (dd, J=14.0, 1.8 Hz, 1H), 7.85 - 7.74 (m, 1H), 7.25 (dd, J=14.0, 8.9 Hz, 1H), 5.40 - 5.28 (m, 1H), 4.62 (br dd, J=13.9, 9.6 Hz, 1H), 4.56 - 4.45 (m, 1H), 4.33 - 4.16 (m, 2H), 4.13 - 4.07 (m, 1H), 4.02 (d, J=14.0 Hz, 2H), 3.95 - 3.87 (m, 1H), 3.83 - 3.74 (m, 1H), 3.70 - 3.61 (m, 1H), 3.09 - 2.98 (m, 1H), 2.90 - 2.80 (m, 1H), 2.21 - 2.07 (m, 2H), 1.91 - 1.68 (m, 4H), 1.66 - 1.55 (m, 2H), 1.46 (ddd, J=12.9, 8.8, 4.3 Hz, 1H), 1.40 - 1.24 (m, 2H), 0.79 - 0.64 (m, 2H), 0.32 (br d, J=13.1 Hz, 2H)。	2.13, B

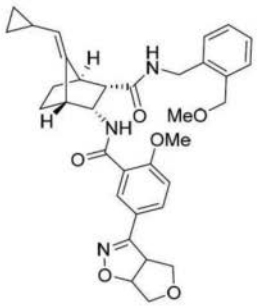
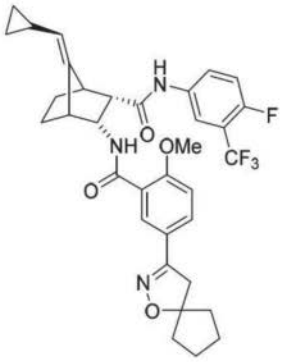
636		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-氧代吡咯烷-1-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	586.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.29 - 8.17 (m, 1H), 8.13 (d, J=3.1 Hz, 1H), 7.79 (br d, J=2.7 Hz, 1H), 7.77 (br d, J=2.7 Hz, 1H), 7.48 (br t, J=9.9 Hz, 1H), 7.20 (d, J=9.2 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.45 (br d, J=6.1 Hz, 1H), 3.99 (s, 3H), 3.85 - 3.71 (m, 1H), 3.59 - 3.43 (m, 1H), 3.16 (br dd, J=11.3, 3.7 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.48 (br t, J=8.1 Hz, 2H), 2.16 - 2.04 (m, 2H), 1.92 - 1.83 (m, 1H), 1.78 (br t, J=8.5 Hz, 1H), 1.59 - 1.50 (m, 1H), 1.46 - 1.33 (m, 2H), 0.87 - 0.67 (m, 2H), 0.36 (br d, J=3.1 Hz, 2H)	2.45, B

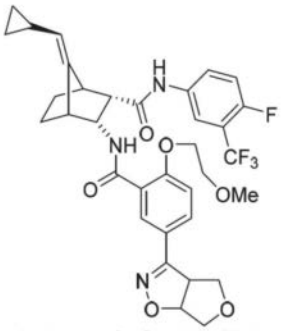
637	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-(4,4,4-三氟丁基)双环[2.2.1]庚烷-2-甲酰胺	506.3	(500 MHz, DMSO-d6) δ 9.98 (br dd, J=14.0, 6.7 Hz, 1H), 8.34 (br dd, J=14.0, 7.6 Hz, 1H), 8.16 (dd, J=14.0, 1.8 Hz, 1H), 7.85 - 7.74 (m, 1H), 7.25 (dd, J=14.0, 8.9 Hz, 1H), 5.40 - 5.28 (m, 1H), 4.62 (br dd, J=13.9, 9.6 Hz, 1H), 4.56 - 4.45 (m, 1H), 4.33 - 4.16 (m, 2H), 4.13 - 4.07 (m, 1H), 4.02 (d, J=14.0 Hz, 2H), 3.95 - 3.87 (m, 1H), 3.83 - 3.74 (m, 1H), 3.70 - 3.61 (m, 1H), 3.09 - 2.98 (m, 1H), 2.90 - 2.80 (m, 1H), 2.21 - 2.07 (m, 2H), 1.91 - 1.68 (m, 4H), 1.66 - 1.55 (m, 2H), 1.46 (ddd, J=12.9, 8.8, 4.3 Hz, 1H), 1.40 - 1.24 (m, 2H), 0.79 - 0.64 (m, 2H), 0.32 (br d, J=13.1 Hz, 2H)。	2.13, B

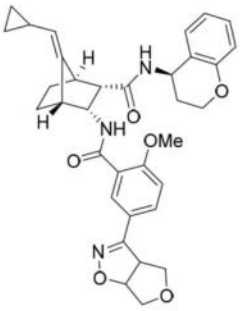
638		(1R,2S,3R,4R,7Z)-3-{5-[(3S,3aS,6R,6aS)-6-羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	631.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.83 (br d, J=7.0 Hz, 1H), 8.24 (br d, J=4.3 Hz, 1H), 7.86 (d, J=1.8 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.49 (br t, J=9.8 Hz, 1H), 7.44 (dd, J=8.4, 1.7 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 4.73 - 4.64 (m, 2H), 4.52 - 4.38 (m, 2H), 4.19 - 4.07 (m, 2H), 3.98 (s, 3H), 3.81 (dd, J=9.5, 3.7 Hz, 1H), 3.74 - 3.60 (m, 2H), 3.16 (br dd, J=10.5, 4.7 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.91 - 1.83 (m, 1H), 1.82 - 1.72 (m, 1H), 1.61 - 1.48 (m, 1H), 1.47 - 1.34 (m, 2H), 0.80 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.45, A

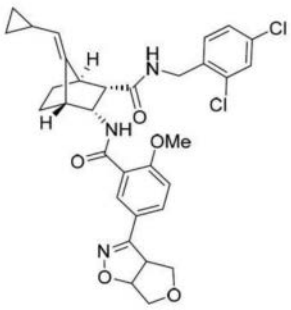
639		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[(4R)-4-羟基-2-氧代吡咯烷-1-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	602.1	(500 MHz, DMSO-d6) δ 10.63 - 10.49 (m, 1H), 9.91 (br d, J=7.3 Hz, 1H), 8.30 - 8.20 (m, 1H), 8.16 (d, J=2.7 Hz, 1H), 7.89 - 7.72 (m, 2H), 7.50 (br t, J=9.6 Hz, 1H), 7.21 (d, J=8.9 Hz, 1H), 4.71 (d, J=9.5 Hz, 1H), 4.46 (br d, J=6.1 Hz, 1H), 4.40 (br s, 1H), 4.07 (dd, J=10.4, 5.2 Hz, 1H), 4.00 (s, 3H), 3.56 (br d, J=10.4 Hz, 1H), 3.17 (br dd, J=10.4, 4.0 Hz, 1H), 3.11 (br s, 1H), 2.80 (br d, J=6.1 Hz, 1H), 2.73 (br s, 1H), 2.35 - 2.26 (m, 1H), 1.98 - 1.84 (m, 2H), 1.82 - 1.70 (m, 1H), 1.60 - 1.49 (m, 1H), 1.47 - 1.34 (m, 2H), 0.89 - 0.65 (m, 2H), 0.37 (br s, 2H)	2.24, B

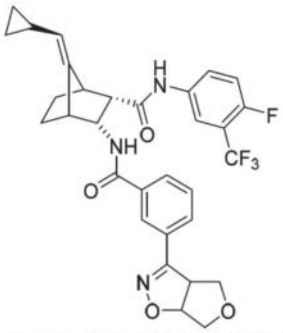
640		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-[(3S)-3-羟基吡咯烷-1-羰基]-1,2-噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	682.9	(500 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.69 (br d, J=6.7 Hz, 1H), 9.10 (d, J=18.9 Hz, 1H), 8.09 (s, 1H), 8.00 (br d, J=5.2 Hz, 1H), 7.63 - 7.52 (m, 2H), 7.33 (s, 1H), 7.25 (br t, J=9.6 Hz, 1H), 7.08 (dd, J=8.4, 6.6 Hz, 1H), 4.52 - 4.39 (m, 1H), 4.22 (br s, 1H), 4.08 (br s, 1H), 3.99 (br s, 1H), 3.83 (s, 3H), 3.67 (s, 1H), 3.35 - 3.12 (m, 1H), 2.97 - 2.83 (m, 2H), 2.54 - 2.45 (m, 1H), 1.73 - 1.50 (m, 4H), 1.42 - 1.24 (m, 2H), 1.24 - 1.06 (m, 2H), 0.58 - 0.40 (m, 2H), 0.12 (br s, 2H), 0.07 (br s, 2H)	2.28, C

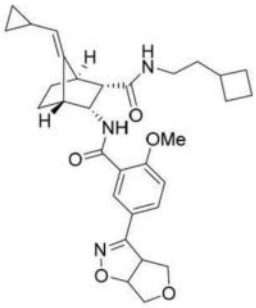
641	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[2-(甲氧基甲基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	586.3	(500 MHz, DMSO-d6) δ 9.93 (br d, J=7.0 Hz, 1H), 8.55 - 8.47 (m, 1H), 8.13 (d, J=2.4 Hz, 1H), 7.77 (dd, J=8.5, 2.1 Hz, 1H), 7.27 (br d, J=6.7 Hz, 1H), 7.23 - 7.10 (m, 4H), 5.32 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.49 - 4.40 (m, 3H), 4.35 - 4.25 (m, 3H), 4.08 (d, J=10.7 Hz, 1H), 3.93 - 3.85 (m, 2H), 3.77 - 3.60 (m, 2H), 3.24 (s, 3H), 3.08 - 3.02 (m, 1H), 2.98 (br dd, J=10.5, 3.8 Hz, 1H), 2.60 - 2.56 (m, 1H), 1.88 - 1.79 (m, 1H), 1.75 - 1.67 (m, 1H), 1.51 - 1.40 (m, 1H), 1.39 - 1.25 (m, 2H), 0.78 - 0.60 (m, 2H), 0.37 - 0.22 (m, 2H)。可能由于与经抑制的水峰重叠，一个质子在NMR中不可见。	2.19, B
642		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{1-氧杂-2-氮杂螺[4.4]壬-2-烯-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	626.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 - 9.86 (m, 1H), 8.24 - 8.17 (m, 2H), 7.80 - 7.74 (m, 2H), 7.51 - 7.45 (m, 1H), 7.28 - 7.23 (m, 1H), 4.68 (d, J=9.7 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.03 (s, 3H), 3.43 - 3.39 (m, 1H), 3.18 - 3.07 (m, 1H), 2.75 - 2.69 (m, 1H), 2.59 - 2.55 (m, 1H), 1.94 - 1.63 (m, 10H), 1.52 - 1.35 (m, 3H), 0.79 - 0.69 (m, 2H), 0.39 - 0.31 (m, 2H)	2.78, B

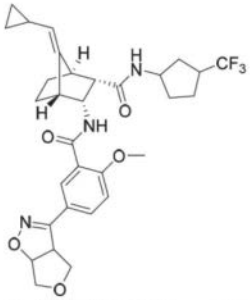
644	 通过SFC分离的异构体，其中实施例644为峰2 (RT=3.6 min，>95% de) -仪器：Waters 100 Prep SFC柱：Chiral OD，30 × 250 mm，5微米，移动相：25% MeOH / 75% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD，4.6 × 100 mm，5微米，移动相：25% MeOH / 75% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=2.92 min.，>95% de)及手性(峰-2，RT=3.6 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(2-甲氧基乙氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	658.2	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.63 (br d, J=7.6 Hz, 1H), 8.22 (d, J=2.4 Hz, 1H), 8.17 (br d, J=4.3 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.48 (t, J=9.8 Hz, 1H), 7.33 (d, J=8.9 Hz, 1H), 5.36 (dd, J=9.2, 3.7 Hz, 1H), 4.76 - 4.68 (m, 1H), 4.58 - 4.48 (m, 2H), 4.48 - 4.40 (m, 2H), 4.12 (br d, J=10.7 Hz, 1H), 4.08 - 4.00 (m, 1H), 3.91 (br d, J=9.2 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.68 (dd, J=10.7, 3.4 Hz, 1H), 3.41 - 3.34 (m, 1H), 3.17 (br dd, J=10.4, 3.7 Hz, 1H), 3.09 (br s, 1H), 2.75 (br s, 1H), 2.57 (s, 3H), 2.02 - 1.85 (m, 2H), 1.60 - 1.51 (m, 1H), 1.51 - 1.41 (m, 2H), 0.82 - 0.70 (m, 2H), 0.38 (br d, J=1.8 Hz, 2H)	2.42, C

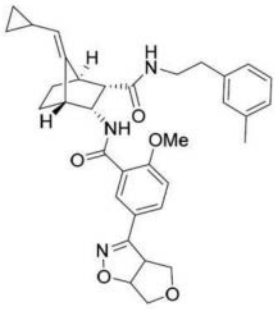
645	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(4R)-3,4-二氢-2H-1-苯并哌喃-4-基]双环[2.2.1]庚烷-2-甲酰胺	584.2	(500 MHz, DMSO-d6) δ 10.00 (br d, J=7.0 Hz, 1H), 8.58 (br d, J=8.2 Hz, 1H), 8.17 (d, J=2.4 Hz, 1H), 7.80 (dd, J=8.9, 2.1 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 7.18 - 7.08 (m, 2H), 6.88 (t, J=7.2 Hz, 1H), 6.76 (d, J=8.2 Hz, 1H), 5.34 (dd, J=9.0, 3.5 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.64 - 4.59 (m, 1H), 4.50 (br t, J=8.1 Hz, 1H), 4.34 - 4.28 (m, 1H), 4.19 - 4.12 (m, 2H), 4.10 (br d, J=10.7 Hz, 1H), 4.03 (s, 3H), 3.95 - 3.87 (m, 1H), 3.78 (dd, J=9.2, 7.0 Hz, 1H), 3.66 (dd, J=10.7, 3.7 Hz, 1H), 3.07 (br s, 1H), 2.95 (br dd, J=10.5, 3.8 Hz, 1H), 2.57 - 2.55 (m, 1H), 2.09 - 1.95 (m, 2H), 1.87 - 1.75 (m, 2H), 1.53 - 1.35 (m, 3H), 0.71 (br t, J=9.0 Hz, 2H), 0.31 (br d, J=4.0 Hz, 2H)。	2.27, C

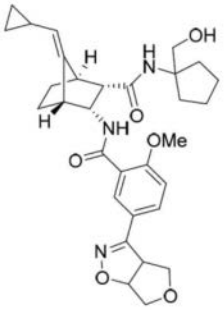
646	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2,4-二氯苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	610.2	(500 MHz, DMSO-d6) δ 9.84 (d, J=7.0 Hz, 1H), 8.68 (t, J=5.8 Hz, 1H), 8.17 (d, J=2.3 Hz, 1H), 7.78 (dd, J=8.6, 2.4 Hz, 1H), 7.56 (d, J=1.9 Hz, 1H), 7.31 - 7.25 (m, 2H), 7.21 - 7.18 (m, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.64 (d, J=9.6 Hz, 1H), 4.48 (br t, J=7.4 Hz, 1H), 4.39 - 4.28 (m, 3H), 4.09 (d, J=10.6 Hz, 1H), 3.92 - 3.87 (m, 4H), 3.77 (dd, J=9.2, 6.8 Hz, 1H), 3.65 (dd, J=10.8, 3.7 Hz, 1H), 3.07 - 3.00 (m, 2H), 2.63 - 2.58 (m, 1H), 1.82 (br t, J=9.1 Hz, 1H), 1.75 - 1.66 (m, 1H), 1.53 - 1.42 (m, 1H), 1.41 - 1.27 (m, 2H), 0.78 - 0.65 (m, 2H), 0.38 - 0.27 (m, 2H)。	2.43, C

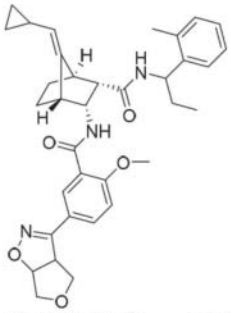
647	 由同手性酸中间体峰2(RT=6.53 min.，>99% ee)制备：所用仪器：Berger MG II 柱：Chiralpak IA，21 × 250 mm，5微米，移动相：20% IPA / 80% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IA，4.6 × 100 mm，3微米，移动相：20% IPA / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=2.55 min.，>99% ee)及手性(峰-2，RT=6.53 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	584.3	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.37 (br d, J=6.7 Hz, 1H), 8.05 (s, 2H), 7.86 (br dd, J=18.9, 7.3 Hz, 3H), 7.63 (t, J=7.8 Hz, 1H), 7.51 (t, J=9.8 Hz, 1H), 5.42 (dd, J=9.3, 3.5 Hz, 1H), 4.73 (d, J=9.8 Hz, 1H), 4.55 (br t, J=7.8 Hz, 1H), 4.48 - 4.39 (m, 1H), 4.15 (d, J=11.0 Hz, 1H), 4.01 (br d, J=9.5 Hz, 1H), 3.80 (dd, J=9.2, 7.0 Hz, 1H), 3.69 (dd, J=10.7, 3.4 Hz, 1H), 3.42 - 3.34 (m, 1H), 3.20 (br dd, J=10.5, 4.1 Hz, 1H), 3.13 (br s, 1H), 2.78 (br s, 1H), 1.91 - 1.85 (m, 1H), 1.80 - 1.74 (m, 1H), 1.54 (td, J=8.3, 3.8 Hz, 1H), 1.46 (br d, J=0.6 Hz, 1H), 0.84 - 0.70 (m, 2H), 0.38 (br d, J=1.5 Hz, 2H)	2.45, B

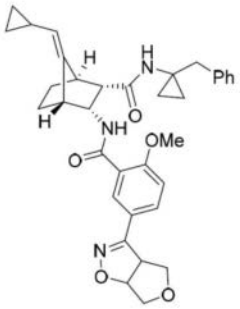
648	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(2-环丁基乙基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	534.2	(500 MHz, DMSO-d6) δ 9.96 (br d, J=6.7 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 8.01 (br t, J=5.3 Hz, 1H), 7.79 (dd, J=8.5, 2.1 Hz, 1H), 7.24 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.2, 3.7 Hz, 1H), 4.61 (br d, J=9.5 Hz, 1H), 4.54 - 4.44 (m, 1H), 4.34 - 4.23 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.89 (br d, J=9.2 Hz, 1H), 3.81 - 3.71 (m, 1H), 3.65 (br dd, J=10.7, 3.7 Hz, 1H), 3.08 - 2.93 (m, 3H), 2.87 (br dd, J=10.8, 4.1 Hz, 1H), 2.22 (quin, J=7.9 Hz, 1H), 2.03 - 1.90 (m, 2H), 1.86 (br t, J=9.2 Hz, 1H), 1.78 - 1.66 (m, 3H), 1.60 - 1.41 (m, 5H), 1.39 - 1.24 (m, 2H), 0.71 (quin, J=9.5 Hz, 2H), 0.31 (br s, 2H)。可能由于与经抑制的水峰重叠，一个质子在NMR中不可见。	2.40, B

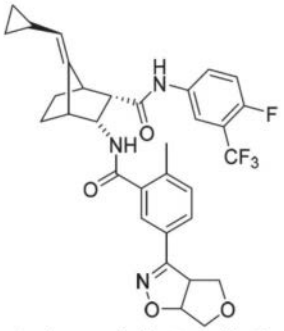
649	 与**实施例589**中一样由**589-3**制备	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)-N-(3-(三氟甲基)环戊基)双环[2.2.1]庚烷-2-甲酰胺	588.4	(400 MHz, CD_3OD) δ 8.26 - 8.21 (m, 1H), 7.88 (dd, *J*=8.7, 2.3 Hz, 1H), 7.25 (d, *J*=8.7 Hz, 1H), 5.36 (dd, *J*=9.2, 3.6 Hz, 1H), 4.67 (d, *J*=9.3 Hz, 1H), 4.50 - 4.41 (m, 2H), 4.22 - 4.14 (m, 2H), 4.11 (s, 3H), 4.06 (d, *J*=9.2 Hz, 1H), 3.90 - 3.84 (m, 1H), 3.75 (dd, *J*=10.6, 3.8 Hz, 1H), 3.19 - 3.15 (m, 1H), 2.94 (dd, *J*=10.6, 4.7 Hz, 1H), 2.82 - 2.68 (m, 1H), 2.58 - 2.52 (m, 1H), 2.33 - 2.18 (m, 1H), 2.05 - 1.79 (m, 5H), 1.62 - 1.42 (m, 5H), 0.73 (br d, *J*=7.9 Hz, 2H), 0.39 - 0.24 (m, 2H)。	2.21, B

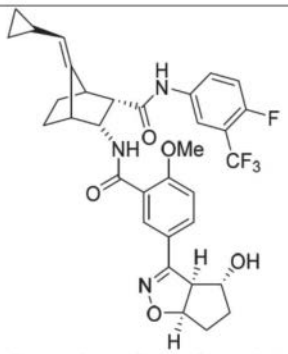
650	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[2-(3-甲基苯基)乙基]双环[2.2.1]庚烷-2-甲酰胺	570.4	(500 MHz, DMSO-d6) δ 9.99 - 9.91 (m, 1H), 8.20 - 8.11 (m, 2H), 7.78 (br dd, J=8.7, 2.0 Hz, 1H), 7.24 (br d, J=8.9 Hz, 1H), 7.17 - 7.06 (m, 1H), 7.01 - 6.90 (m, 3H), 5.33 (br dd, J=9.2, 3.4 Hz, 1H), 4.60 (br d, J=9.5 Hz, 1H), 4.49 (br t, J=7.0 Hz, 1H), 4.27 (br t, J=10.5 Hz, 1H), 4.09 (br d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.89 (br d, J=8.9 Hz, 1H), 3.81 - 3.71 (m, 1H), 3.68 - 3.59 (m, 1H), 3.03 (br s, 1H), 2.91 - 2.82 (m, 1H), 2.65 (br t, J=6.9 Hz, 2H), 2.45 (br s, 1H), 2.22 (s, 3H), 1.80 - 1.65 (m, 2H), 1.53 - 1.40 (m, 1H), 1.37 - 1.18 (m, 2H), 0.77 - 0.61 (m, 2H), 0.31 (br s, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.41, C

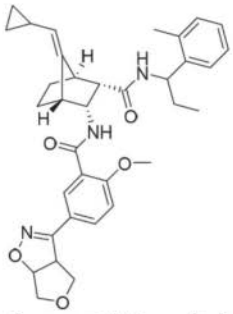
651	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[1-(羟基甲基)环戊基]双环[2.2.1]庚烷-2-甲酰胺	550.3	(500 MHz, DMSO-d6) δ 10.17 - 10.07 (m, 1H), 8.18 (br d, J=2.1 Hz, 1H), 7.79 (br dd, J=8.5, 2.1 Hz, 1H), 7.63 (s, 1H), 7.24 (br d, J=8.9 Hz, 1H), 5.34 (br dd, J=8.5, 2.4 Hz, 1H), 4.60 (br d, J=9.2 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.24 (br s, 1H), 4.09 (br d, J=10.4 Hz, 1H), 4.02 (s, 3H), 3.90 (br d, J=9.5 Hz, 1H), 3.78 (br t, J=8.2 Hz, 1H), 3.65 (br dd, J=10.4, 3.1 Hz, 1H), 3.51 (br d, J=10.7 Hz, 1H), 3.03 (br s, 1H), 2.96 - 2.88 (m, 1H), 1.89 - 1.55 (m, 8H), 1.55 - 1.39 (m, 3H), 1.37 - 1.24 (m, 2H), 0.76 - 0.63 (m, 2H), 0.31 (br s, 2H)。可能由于与经抑制的水峰和/或溶剂峰重叠，两个质子在NMR中不可见。	2.00, B

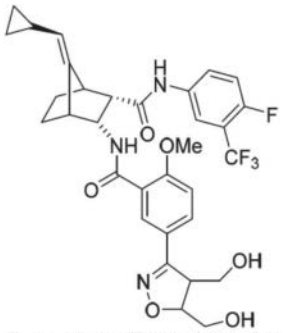
652	 由416-3制备，经由制备型SFC在以下条件下分离非镜像异构体：柱：Chiral OJ，30×250 mm，5微米；移动相85% CO_2/15% MeOH (具有0.1%DEA)；流动速率：120 mL/min，150巴；柱温度：40 °C。 峰1 (RT=7.6 min)为**实施例652**	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)-N-(1-(邻甲苯基)丙基)双环[2.2.1]庚烷-2-甲酰胺	584.0	(500 MHz, DMSO-d_6) δ 10.05 (br d, *J*=6.7 Hz, 1H), 8.49 (br d, *J*=7.9 Hz, 1H), 8.16 (d, *J*=2.1 Hz, 1H), 7.79 (dd, *J*=8.7, 2.3 Hz, 1H), 7.27 - 7.21 (m, 2H), 7.16 - 7.06 (m, 3H), 5.33 (dd, *J*=9.2, 3.4 Hz, 1H), 4.91 - 4.83 (m, 1H), 4.61 (d, *J*=9.5 Hz, 1H), 4.49 (br t, *J*=8.1 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.09 (d, *J*=10.7 Hz, 1H), 4.02 (s, 3H), 3.92 - 3.86 (m, 1H), 3.81 - 3.74 (m, 1H), 3.65 (dd, *J*=10.7, 3.7 Hz, 1H), 3.04 - 2.96 (m, 2H), 2.35 (s, 3H), 1.65 - 1.54 (m, 3H), 1.49 - 1.38 (m, 2H), 1.31 - 1.20 (m, 1H), 1.18 - 1.07 (m, 1H), 0.80 (t, *J*=7.3 Hz, 3H), 0.75 - 0.64 (m, 2H), 0.35 - 0.23 (m, 2H)。可能由于与溶剂峰或经抑制的水峰重叠，一个质子不可见。	2.41, B

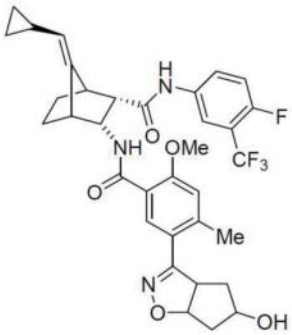
653	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(1-苯甲基环丙基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	582.0	(500 MHz, DMSO-d6) δ 9.98 (br d, J=6.4 Hz, 1H), 8.21 - 8.12 (m, 2H), 7.80 (br dd, J=8.5, 2.4 Hz, 1H), 7.27 (br d, J=8.9 Hz, 1H), 7.24 - 7.19 (m, 2H), 7.18 - 7.10 (m, 3H), 5.36 - 5.31 (m, 1H), 4.56 (br d, J=9.8 Hz, 1H), 4.53 - 4.46 (m, 1H), 4.23 (br s, 1H), 4.13 - 4.06 (m, 4H), 3.93 - 3.87 (m, 1H), 3.81 - 3.74 (m, 1H), 3.66 (br dd, J=10.4, 2.7 Hz, 1H), 3.02 (br s, 1H), 2.94 (br d, J=14.0 Hz, 1H), 2.78 - 2.70 (m, 2H), 2.37 (br s, 1H), 1.97 - 1.88 (m, 1H), 1.80 - 1.70 (m, 1H), 1.48 - 1.40 (m, 1H), 1.40 - 1.26 (m, 2H), 0.77 - 0.65 (m, 4H), 0.64 - 0.51 (m, 2H), 0.30 (br d, J=0.9 Hz, 2H)。	2.30, B

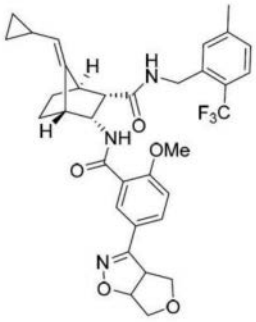
654	 通过SFC分离的异构体，其中实施例654为峰1 (RT=4.74 min.，>95% de)：仪器：Waters 100 Prep SFC 柱：Chiral OD，30 × 250 mm，5微米，移动相：15% MeOH / 85% CO_2（具有0.1% DEA），流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD，4.6 × 100 mm，5微米，移动相：15% MeOH / 85% CO_2（具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰-1，RT=4.74 min.，>95% de)及手性(峰-2，RT=6.75 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	597.9	(500 MHz, DMSO-d6) δ 10.62 - 10.32 (m, 1H), 8.72 (d, J=7.2 Hz, 1H), 8.03 (dd, J=6.3, 2.2 Hz, 1H), 7.81 - 7.76 (m, 1H), 7.64 (dd, J=8.0, 1.5 Hz, 1H), 7.62 (s, 1H), 7.44 (t, J=9.7 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 5.34 (dd, J=9.1, 3.6 Hz, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.48 - 4.37 (m, 3H), 4.09 (d, J=10.8 Hz, 1H), 3.95 (br d, J=9.8 Hz, 1H), 3.66 (dd, J=9.5, 7.0 Hz, 1H), 3.62 (dd, J=10.8, 3.7 Hz, 1H), 3.16 (br dd, J=10.6, 3.9 Hz, 1H), 3.09 (t, J=3.9 Hz, 1H), 2.72 (t, J=3.8 Hz, 1H), 2.01 - 1.88 (m, 1H), 1.86 - 1.73 (m, 1H), 1.59 - 1.51 (m, 1H), 1.48 - 1.44 (m, 1H), 1.42 - 1.36 (m, 1H), 0.78 - 0.69 (m, 3H), 0.35 (br d, J=2.9 Hz, 3H	2.43, B

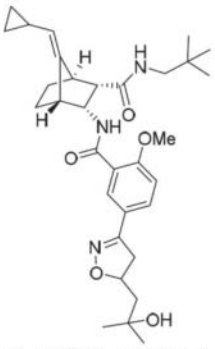
655	 由同手性苯甲酸酯中间体峰1制备：制备型色谱条件：仪器：Jasco SFC Prep (CTR-L409-PSFC3)柱： Chiralpak IA，30 × 250 mm，5微米，移动相：15% MeOH / 85% CO_2，流动条件：85 mL/min，150巴，40°C ，检测器波长：220 nm， 注射详情：0.5 mL ~21mg/mL于甲醇中，分析型色谱条件：仪器：Shimadzu Nexera SFC (CTR-L410-SFC3) 柱： Chiralpak IA，4.6 × 100 mm，3微米，移动相：15% MeOH / 85% CO_2 ，流动条件： 2.0 mL/min，150巴， 40°C ，检测器波长：220 nm，注射详情：5 µL ~1mg/mL于MeOH中。峰-1 RT 3.24 min > 99% ee。	(1R,2S,3R,4R,7Z)-3-{5-[(3aS,4R,6aR)-4-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	627.9	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.36 - 8.28 (m, 1H), 8.22 (br d, J=3.7 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.78 (br d, J=8.5 Hz, 1H), 7.48 (br t, J=9.8 Hz, 1H), 7.29 (d, J=8.9 Hz, 1H), 5.30 (d, J=2.7 Hz, 1H), 5.22 (br dd, J=8.5, 4.9 Hz, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.45 (br s, 1H), 4.12 (br s, 1H), 4.05 (s, 3H), 3.94 (br d, J=8.9 Hz, 1H), 3.69 - 3.50 (m, 2H), 3.20 - 3.09 (m, 3H), 2.73 (br s, 1H), 2.21 - 2.10 (m, 1H), 1.93 (br dd, J=13.4, 6.4 Hz, 1H), 1.88 - 1.73 (m, 2H), 1.66 (br dd, J=12.5, 6.1 Hz, 1H), 1.55 - 1.36 (m, 4H), 0.87 - 0.67 (m, 2H), 0.35 (br s, 2H)	2.44, C

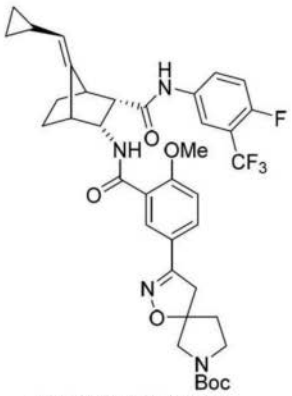
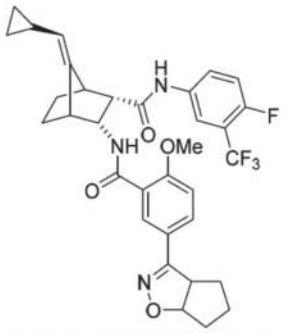
656	 由416-3制备。经由制备型SFC在以下条件下分离非镜像异构体：柱：Chiral OJ，30×250 mm，5微米；移动相85% CO_2 / 15% MeOH (具有0.1%DEA)；流动速率：120 mL/min，150巴；柱温度：40 °C。 峰2 (RT= 12.9 min)为**实施例656**。	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)-N-(1-(邻甲苯基)丙基)双环[2.2.1]庚烷-2-甲酰胺	584.2	(500 MHz, DMSO-d_6) δ 9.96 (d, *J*=6.6 Hz, 1H), 8.49 (d, *J*=8.2 Hz, 1H), 8.10 (d, *J*=2.2 Hz, 1H), 7.73 (dd, *J*=8.7, 2.3 Hz, 1H), 7.23 (br d, *J*=7.2 Hz, 1H), 7.12 (d, *J*=8.8 Hz, 1H), 7.08 - 6.97 (m, 3H), 5.32 (dd, *J*=9.1, 3.6 Hz, 1H), 4.93 (q, *J*=7.5 Hz, 1H), 4.64 (d, *J*=9.5 Hz, 1H), 4.45 (br t, *J*=7.8 Hz, 1H), 4.28 - 4.19 (m, 1H), 4.08 (d, *J*=10.7 Hz, 1H), 3.91 - 3.83 (m, 1H), 3.74 (dd, *J*=9.2, 6.9 Hz, 1H), 3.70 (s, 3H), 3.64 (dd, *J*=10.8, 3.5 Hz, 1H), 3.04 (br s, 1H), 2.98 (dd, *J*=10.9, 4.3 Hz, 1H), 2.62 (br s, 1H), 2.31 (s, 3H), 1.89 - 1.82 (m, 1H), 1.72 - 1.66 (m, 1H), 1.63 - 1.55 (m, 2H), 1.46 (tt, *J*=12.7, 4.7 Hz, 1H), 1.39 - 1.28 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H), 0.76 - 0.65 (m, 2H), 0.32 (dd, *J*=4.3, 2.1 Hz, 2H)。	2.38, B

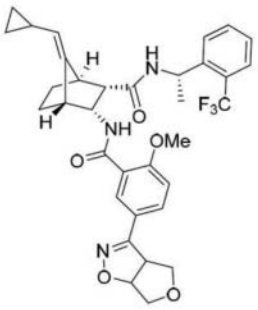
657	 由同手性苯甲酸酯中间体(峰1；>99%ee；手性分析型RT=3.383 min)制备；制备型手性SFC条件：仪器：PIC Solution SFC Prep-200:柱：Chiralpak IF，21 × 250 mm，5微米：移动相：35%甲醇/65% CO_2：流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.75 mL ~50mg/mL 于MeOH-CAN中	(1R,2S,3R,4R,7Z)-3-{5-[4,5-双(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	631.9	(500 MHz, DMSO-d6) δ 10.54 - 10.52 (m, 1H), 9.93 - 9.89 (m, 1H), 8.31 - 8.26 (m, 1H), 8.22 (dd, J=6.3, 2.1 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.51 - 7.44 (m, 1H), 7.28 - 7.21 (m, 1H), 5.00 (t, J=5.6 Hz, 1H), 4.86 - 4.82 (m, 1H), 4.71 - 4.66 (m, 1H), 4.61 - 4.55 (m, 1H), 4.48 - 4.40 (m, 1H), 4.07 - 4.03 (m, 3H), 3.97 - 3.90 (m, 1H), 3.86 - 3.78 (m, 2H), 3.61 - 3.56 (m, 1H), 3.40 - 3.34 (m, 1H), 3.18 - 3.02 (m, 2H), 2.75 - 2.69 (m, 1H), 1.87 - 1.75 (m, 2H), 1.53 - 1.36 (m, 3H), 0.79 - 0.68 (m, 2H), 0.37 - 0.30 (m, 2H)	2.28, C

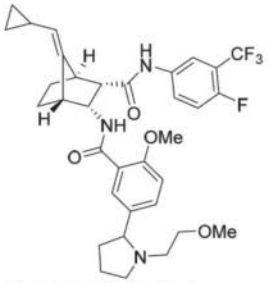
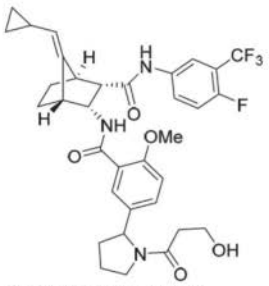
658	 经反相HPLC的第一洗脱非镜像异构体	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	641.9	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 10.11 - 9.82 (m, 1H), 8.27 - 8.17 (m, 1H), 8.00 (s, 1H), 7.82 - 7.72 (m, 1H), 7.48 (br t, J=9.6 Hz, 1H), 7.14 (s, 1H), 5.07 (br t, J=8.2 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.47 - 4.38 (m, 1H), 4.21 - 4.12 (m, 2H), 4.12 - 3.91 (m, 3H), 3.62 - 3.44 (m, 1H), 3.15 (br dd, J=10.8, 3.8 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.48 (s, 2H), 2.14 - 2.02 (m, 1H), 1.99 - 1.90 (m, 2H), 1.88 - 1.82 (m, 1H), 1.80 - 1.74 (m, 1H), 1.62 (br d, J=12.2 Hz, 1H), 1.54 - 1.47 (m, 1H), 1.45 - 1.32 (m, 2H), 0.78 - 0.65 (m, 2H), 0.42 - 0.27 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.47, B

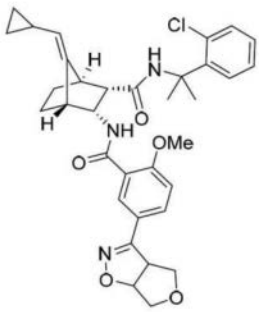
659	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[5-甲基-2-(三氟甲基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	624.2	(500 MHz, DMSO-d6) δ 8.32 (br d, J=7.0 Hz, 2H), 7.86 (d, J=2.2 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.57 (br d, J=7.5 Hz, 1H), 7.30 - 7.19 (m, 3H), 5.34 (br dd, J=8.7, 3.4 Hz, 1H), 4.49 (br d, J=8.9 Hz, 2H), 4.39 (br s, 2H), 4.09 (br d, J=10.9 Hz, 1H), 3.91 (s, 3H), 3.89 - 3.84 (m, 1H), 3.76 (br dd, J=9.2, 6.6 Hz, 1H), 3.65 (br dd, J=10.9, 3.5 Hz, 1H), 3.06 (br d, J=3.2 Hz, 1H), 2.99 (s, 1H), 2.95 - 2.87 (m, 1H), 2.38 - 2.30 (m, 3H), 1.84 - 1.74 (m, 1H), 1.64 - 1.42 (m,3H), 1.16 (t, J=7.2 Hz, 1H), 0.67 (br dd, J=8.2, 5.5 Hz, 2H), 0.25 (br dd, J=2.8, 1.7 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.41, C

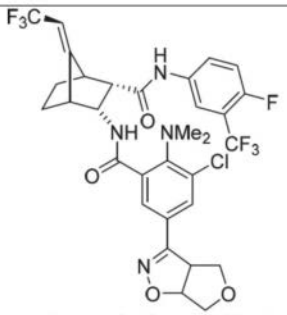
660	 由与实施例499中相同的苯甲酸酯中间体制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-(2,2-二甲基丙基)-3-{5-[5-(2-羟基-2-甲基丙基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	552.5	(500 MHz, DMSO-d6) δ 9.96 (br d, J=7.0 Hz, 1H), 8.14 (d, J=1.8 Hz, 1H), 7.97 (br t, J=6.1 Hz, 1H), 7.76 (dd, J=8.7, 2.0 Hz, 1H), 7.25 - 7.18 (m, 1H), 6.51 (s, 1H), 4.82 - 4.74 (m, 1H), 4.63 (d, J=9.8 Hz, 1H), 4.39 (s, 1H), 4.33 - 4.24 (m, 1H), 4.00 (s, 3H), 3.51 (br dd, J=16.8, 10.1 Hz, 1H), 3.10 - 2.97 (m, 3H), 2.79 (br dd, J=13.0, 5.6 Hz, 1H), 1.86 (br dd, J=13.6, 6.3 Hz, 2H), 1.73 (br dd, J=13.4, 6.4 Hz, 2H), 1.46 (dt, J=8.5, 4.3 Hz, 1H), 1.38 - 1.26 (m, 2H), 1.17 (d, J=6.7 Hz, 6H), 0.81 (s, 9H), 0.75 - 0.64 (m, 2H), 0.35 - 0.26 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.28, C

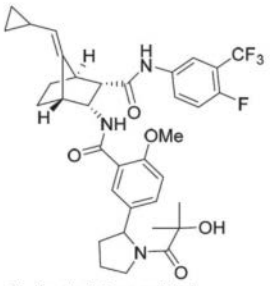
661	 非镜像异构体混合物	3-(3-{[(1R,2R,3S,4R)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1-氧杂-2,7-二氮杂螺[4.4]壬-2-烯-7-甲酸叔丁酯	725.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (br d, J=6.7 Hz, 1H), 8.24 - 8.18 (m, 2H), 7.77 (br d, J=7.3 Hz, 2H), 7.48 (br t, J=9.8 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.47 - 4.40 (m, 1H), 4.04 (s, 3H), 3.54 - 3.44 (m, 1H), 3.10 (br s, 1H), 2.76 - 2.69 (m, 1H), 2.12 (br s, 2H), 1.87 - 1.74 (m, 2H), 1.41 (br d, J=7.0 Hz, 9H), 0.78 - 0.69 (m, 2H), 0.39 - 0.31 (m, 2H)	2.76, B
662	 由同手性苯甲酸酯中间体(峰2；96.5%ee；手性分析型RT=3.602 min)制备；仪器：Jasco SFC Prep柱：Chiralpak OJ-H，21×250 mm，5微米；移动相：5% IPA / 95% CO_2；流动条件：45 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：0.5 mL ~35mg/mL于IPA-CAN中	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	612.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.23 - 8.18 (m, 2H), 7.80 - 7.75 (m, 2H), 7.46 (br t, J=9.8 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 5.12 (br dd, J=8.4, 4.7 Hz, 1H), 4.68 (br d, J=9.5 Hz, 1H), 4.45 - 4.40 (m, 1H), 4.14 (br t, J=9.0 Hz, 1H), 4.03 (s, 3H), 3.14 (br dd, J=10.8, 3.8 Hz, 1H), 3.10 - 3.08 (m, 1H), 2.73 - 2.68 (m, 1H), 1.94 (br dd, J=13.3, 6.0 Hz, 1H), 1.88 - 1.80 (m, 2H), 1.79 - 1.63 (m, 4H), 1.53 - 1.46 (m, 1H), 1.44 - 1.36 (m, 2H), 1.30 (qd, J=11.9, 5.5 Hz, 1H), 0.77 - 0.69 (m, 2H), 0.37 - 0.30 (m, 2H)。	2.71, B

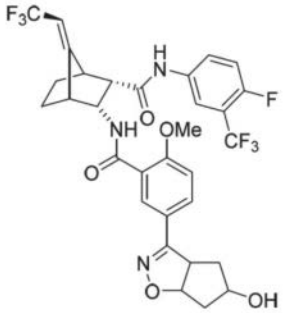
665	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1S)-1-[2-(三氟甲基)苯基]乙基]双环[2.2.1]庚烷-2-甲酰胺	624.2	(500 MHz, DMSO-d6) δ 9.83 (d, J=6.8 Hz, 1H), 8.74 (br d, J=6.6 Hz, 1H), 8.14 (d, J=2.4 Hz, 1H), 7.77 - 7.68 (m, 1H), 7.61 (d, J=8.0 Hz, 2H), 7.48 (t, J=7.7 Hz, 1H), 7.34 - 7.25 (m, 1H), 7.08 (d, J=8.6 Hz, 1H), 5.32 (dd, J=9.2, 3.6 Hz, 1H), 5.27 - 5.15 (m, 1H), 4.65 (d, J=9.4 Hz, 1H), 4.51 - 4.40 (m, 1H), 4.26 (ddd, J=10.5, 6.1, 4.9 Hz, 1H), 4.08 (d, J=10.7 Hz, 1H), 3.90 - 3.84 (m, 1H), 3.75 (dd, J=9.4, 7.1 Hz, 1H), 3.67 - 3.62 (m, 1H), 3.60 - 3.52 (m, 3H), 3.07 - 3.02 (m, 1H), 3.02 - 2.96 (m, 1H), 2.65 - 2.60 (m, 1H), 1.90 - 1.82 (m, 1H), 1.68 - 1.61 (m, 1H), 1.51 - 1.40 (m, 1H), 1.37 - 1.27 (m, 5H), 0.76 - 0.64 (m, 2H), 0.39 - 0.25 (m, 2H)。	2.46, C

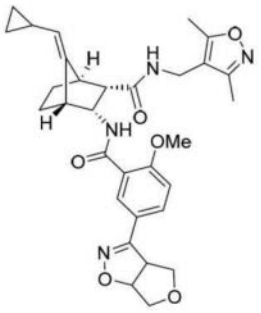
666	 由实施例715制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[1-(2-甲氧基乙基)吡咯烷-2-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.4	(400 MHz, DMSO-d6) δ = 10.49 (s, 1H), 9.90 - 9.72 (m, 1H), 8.22 (dd, J = 2.6, 6.4 Hz, 1H), 7.90 (br s, 1H), 7.77 (td, J = 3.9, 8.1 Hz, 1H), 7.54 - 7.37 (m, 2H), 7.13 (br d, J = 8.1 Hz, 1H), 4.69 (d, J = 9.6 Hz, 1H), 4.45 (tt, J = 3.6, 11.1 Hz, 1H), 4.11 (q, J = 5.2 Hz, 1H), 3.98 (s, 3H), 3.31 - 3.21 (m, 4H), 3.19 - 3.11 (m, 5H), 3.08 (br t, J = 3.8 Hz, 1H), 2.71 (t, J = 3.3 Hz, 1H), 2.29 - 1.99 (m, 3H), 1.94 - 1.67 (m, 4H), 1.58 - 1.33 (m, 4H), 0.82 - 0.65 (m, 2H), 0.35 (dd, J = 2.0, 4.6 Hz, 2H)	2.63, A
667	 由实施例694制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(3-羟基丙酰基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.0	(400 MHz, DMSO-d6) δ = 10.48 (d, J = 1.0 Hz, 1H), 9.85 (dd, J = 7.5, 10.9 Hz, 1H), 8.25 - 8.18 (m, 1H), 7.81 - 7.68 (m, 2H), 7.48 (t, J = 9.9 Hz, 1H), 7.29 (ddd, J = 2.9, 8.6, 20.0 Hz, 1H), 7.20 - 7.03 (m, 1H), 5.14 - 4.96 (m, 2H), 4.68 (d, J = 9.5 Hz, 1H), 4.54 - 4.35 (m, 3H), 3.97 (d, J = 11.7 Hz, 3H), 3.73 - 3.47 (m, 4H), 3.16 - 3.04 (m, 3H), 2.74 - 2.68 (m, 1H), 2.40 - 2.32 (m, 1H), 1.90 - 1.66 (m, 5H), 1.55 - 1.29 (m, 3H), 0.79 - 0.65 (m, 2H), 0.35 (dd, J = 2.0, 4.4 Hz, 2H)。	2.33, A

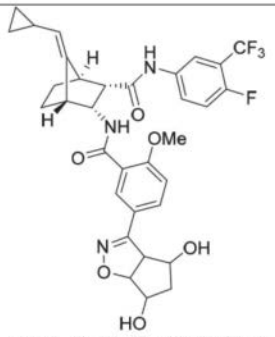
669	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[2-(2-氯苯基)丙烷-2-基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	604.2	(500 MHz, DMSO-d6) δ 9.92 (br d, J=6.6 Hz, 1H), 8.42 (s, 1H), 8.17 (d, J=2.2 Hz, 1H), 7.75 (dd, J=8.7, 2.4 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.15 - 7.11 (m, 3H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.48 (br t, J=7.8 Hz, 1H), 4.28 - 4.19 (m, 1H), 4.09 (d, J=10.9 Hz, 1H), 3.89 (br d, J=9.0 Hz, 1H), 3.77 (dd, J=9.2, 7.0 Hz, 1H), 3.70 - 3.61 (m, 1H), 3.59 (s, 3H), 3.04 - 2.93 (m, 2H), 2.68 - 2.59 (m, 1H), 1.72 - 1.51 (m, 8H), 1.46 - 1.37 (m, 1H), 1.30 - 1.18 (m, 2H), 0.77 - 0.62 (m, 2H), 0.37 - 0.25 (m, 2H)。	2.39, C

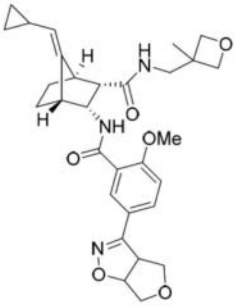
670	 通过SFC分离的异构体，其中实施例670为峰2 (RT=12.15 min，>95% ee)：所用仪器：Waters 100 Prep SFC柱：Chiral AD，30×250 mm，5微米，移动相：15% IPA / 85% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6 × 100 mm，5微米，移动相：15% IPA / 85% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=2.45 min.，>95% ee)及手性(峰-2，RT=3.41 min.，>95% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氯-2-(二甲基氨基)苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	689.0	(500 MHz, DMSO-d_6) δ 10.54 (s, 1H), 10.00 (br d, *J*=7.6 Hz, 1H), 8.14 (br d, *J*=4.3 Hz, 1H), 7.86 (d, *J*=1.8 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.46 (t, *J*=9.8 Hz, 1H), 5.93 (q, *J*=8.1 Hz, 1H), 5.35 (dd, *J*=9.2, 3.4 Hz, 1H), 4.57 (br s, 1H), 4.41 (br t, *J*=8.1 Hz, 1H), 4.09 (d, *J*=10.7 Hz, 1H), 3.91 (br d, *J*=11.3 Hz, 1H), 3.73 - 3.57 (m, 2H), 3.25 (br d, *J*=10.7 Hz, 1H), 3.19 (br s, 1H), 2.98 (br s, 1H), 2.81 (s, 6H), 2.18 - 1.99 (m, 2H), 1.50 (br s, 2H)	2.87, B

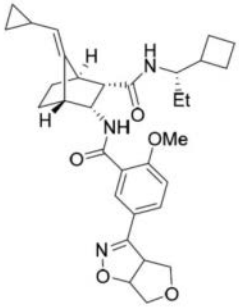
671	 由实施例715制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙酰基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.3	(400MHz, DMSO-d6) δ = 10.47 (s, 1H), 9.81 (br d, J=7.1 Hz, 1H), 8.21 (dd, J=2.6, 6.5 Hz, 1H), 7.77 (td, J=3.7, 8.7 Hz, 1H), 7.73 (d, J=2.2 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 7.25 (dd, J=2.3, 8.7 Hz, 1H), 7.07 (d, J=8.6 Hz, 1H), 5.20 (s, 1H), 4.99 (dd, J=4.2, 7.8 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.47 - 4.36 (m, 1H), 4.08 - 4.01 (m, 1H), 3.93 - 3.85 (m, 1H), 3.60 - 3.48 (m, 1H), 3.10 - 3.10 (m, 1H), 3.20 - 3.02 (m, 1H), 2.70 (brs, 1H), 2.22 - 2.09 (m, 1H), 1.92 - 1.70 (m, 4H), 1.62 - 1.44 (m, 2H), 1.43 - 1.35 (m, 2H), 1.30 (s, 3H), 1.28 - 1.18 (m, 3H), 0.80 - 0.65 (m, 2H), 0.39 - 0.27 (m, 2H)	2.49, A

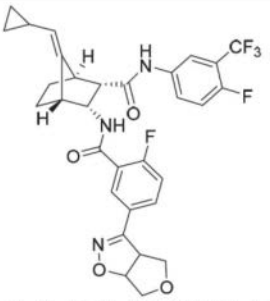
672	 通过反相HPLC与实施例543分离的非镜像异构体对	(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	659.1	(500 MHz, DMSO-d6) δ 10.84 - 10.61 (m, 1H), 10.10 - 9.92 (m, 1H), 8.36 - 8.15 (m, 2H), 7.82 (br d, J=6.7 Hz, 2H), 7.53 (br t, J=9.8 Hz, 1H), 7.30 (br d, J=8.9 Hz, 1H), 6.07 - 5.88 (m, 1H), 5.25 - 5.04 (m, 1H), 4.62 - 4.43 (m, 1H), 4.21 - 4.11 (m, 1H), 4.11 - 3.89 (m, 3H), 3.50 - 3.19 (m, 1H), 3.02 (s, 2H), 2.11 (br dd, J=13.9, 5.6 Hz, 2H), 2.03 - 1.97 (m, 1H), 1.93 (br d, J=12.2 Hz, 2H), 1.87 - 1.81 (m, 1H), 1.81 - 1.72 (m, 1H), 1.62 - 1.44 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.27, B

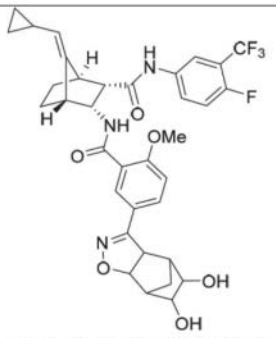
673	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(3,5-二甲基-1,2-噁唑-4-基)甲基]双环[2.2.1]庚烷-2-甲酰胺	561.3	(500 MHz, DMSO-d6) δ 10.00 (d, J=7.0 Hz, 1H), 8.42 (br t, J=5.4 Hz, 1H), 8.16 (d, J=2.2 Hz, 1H), 7.79 (dd, J=8.6, 2.2 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.33 - 4.23 (m, 1H), 4.11 - 3.95 (m, 5H), 3.90 (br d, J=9.2 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.65 (dd, J=10.7, 3.7 Hz, 1H), 3.06 - 3.00 (m, 1H), 2.88 (br dd, J=10.7, 4.3 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 1.79 - 1.68 (m, 2H), 1.45 (ddq, J=13.1, 8.6, 4.3 Hz, 1H), 1.38 - 1.23 (m, 2H), 0.79 - 0.62 (m, 2H), 0.30 (br d, J=3.8 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	1.95, B

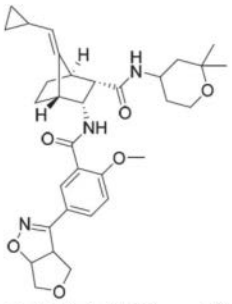
674	 由同手性苯甲酸酯中间体峰1制备。制备型色谱条件：仪器：PIC Solution SFC Prep-200柱：Chiralpak IC，30 × 250 mm，5微米，移动相：20% IPA / 80% CO_2，流动条件：90 mL/min，150巴，40°C，检测器波长：270 nm，注射详情：0.5 mL ~[样本浓度]mg/mL于PA-CAN中，分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：10%异丙醇 / 90% CO2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中。PK-1 RT = 4.69 min.，> 99% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{4,6-二羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	644.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (d, J=7.1 Hz, 1H), 8.41 - 8.35 (m, 1H), 8.21 (d, J=6.8 Hz, 1H), 7.87 (dd, J=8.7, 2.4 Hz, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.47 (t, J=9.9 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 5.26 (br d, J=5.7 Hz, 1H), 5.18 (br d, J=5.2 Hz, 1H), 4.94 (dd, J=10.0, 2.5 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.43 (br s, 1H), 4.03 (s, 3H), 3.61 - 3.48 (bs, 2H), 3.18 - 3.07 (m, 2H), 2.79 - 2.63 (m, 1H), 1.87 - 1.66 (m, 4H), 1.50 (dt, J=8.8, 4.2 Hz, 1H), 1.45 - 1.34 (m, 2H), 0.80 - 0.67 (m, 2H), 0.34 (br s, 2H)	2.34, B

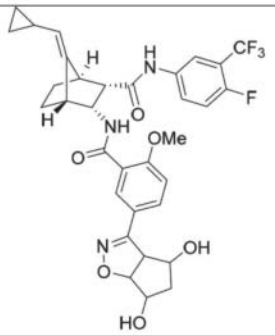
675	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(3-甲基氧杂环丁烷-3-基)甲基]双环[2.2.1]庚烷-2-甲酰胺	536.2	(500 MHz, DMSO-d6) δ 9.94 (br d, J=6.7 Hz, 1H), 8.26 (br t, J=6.0 Hz, 1H), 8.16 (d, J=1.5 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.24 (d, J=8.5 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.33 (br dd, J=10.2, 6.0 Hz, 3H), 4.13 (t, J=5.6 Hz, 2H), 4.09 (br d, J=11.0 Hz, 1H), 4.01 (s, 3H), 3.89 (br d, J=9.2 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.65 (br dd, J=10.4, 3.4 Hz, 1H), 3.05 (br s, 1H), 2.98 (br dd, J=10.5, 3.8 Hz, 1H), 1.87 - 1.80 (m, 1H), 1.76 - 1.71 (m, 1H), 1.52 - 1.42 (m, 1H), 1.41 - 1.29 (m, 2H), 1.16 (s, 3H), 0.71 (quin, J=9.5 Hz, 2H), 0.32 (br s, 2H)。可能由于与经抑制的水峰和/或溶剂峰重叠，三个质子在NMR中不可见。	1.89, C

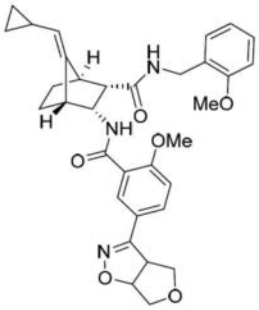
676	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[(1S)-1-环丁基丙基]-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	548.0	(500 MHz, DMSO-d6) δ 10.03 (br d, J=6.7 Hz, 1H), 8.15 (d, J=2.1 Hz, 1H), 7.77 (dd, J=8.5, 2.4 Hz, 1H), 7.71 (br d, J=9.2 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.3, 3.5 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.48 (br t, J=7.8 Hz, 1H), 4.28 (br t, J=10.2 Hz, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.88 (br d, J=8.9 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.71 - 3.62 (m, 1H), 3.49 - 3.39 (m, 1H), 3.04 (br s, 1H), 2.93 (br dd, J=10.8, 4.1 Hz, 1H), 2.27 - 2.19 (m, 1H), 1.92 - 1.80 (m, 2H), 1.78 - 1.57 (m, 6H), 1.49 - 1.27 (m, 4H), 1.16 - 1.09 (m, 1H), 0.77 (t, J=7.5 Hz, 3H), 0.74 - 0.64 (m, 2H), 0.31 (br d, J=2.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.54, B

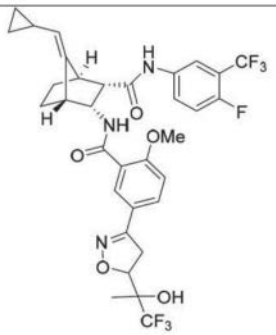
677	 由同手性苯甲酸酯中间体峰1 (RT=1.99 min.，>99% ee)制备；所用仪器：Jasco SFC柱：Chiralpak AD-H，21×250 mm，5微米，移动相：20% MeOH / 80% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak AD-H，4.6 × 100 mm，3微米，移动相：20% MeOH / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：240 nm，得到手性(峰-1，RT=1.99 min.，>99% ee)及手性(峰-2，RT=7.22 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-氟苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	602.3	(500 MHz, DMSO-d6) δ 10.59 - 10.40 (m, 1H), 9.37 (t, J=6.6 Hz, 1H), 8.08 (dd, J=7.1, 2.4 Hz, 1H), 8.02 (dd, J=6.6, 2.6 Hz, 1H), 7.94 - 7.81 (m, 2H), 7.57 - 7.41 (m, 2H), 5.39 (dd, J=9.2, 3.6 Hz, 1H), 4.71 (d, J=9.6 Hz, 1H), 4.56 - 4.50 (m, 1H), 4.47 - 4.37 (m, 1H), 4.12 (d, J=10.8 Hz, 1H), 3.93 (br d, J=9.6 Hz, 2H), 3.76 - 3.71 (m, 1H), 3.66 (dd, J=10.8, 3.7 Hz, 1H), 3.17 (dd, J=10.8, 4.2 Hz, 1H), 3.13 (t, J=3.9 Hz, 1H), 2.75 (t, J=3.9 Hz, 1H), 1.89 - 1.82 (m, 1H), 1.80 - 1.71 (m, 1H), 1.58 - 1.47 (m, 1H), 1.46 - 1.41 (m, 1H), 0.88 - 0.69 (m, 2H), 0.46 - 0.29 (m, 2H)	2.48, C

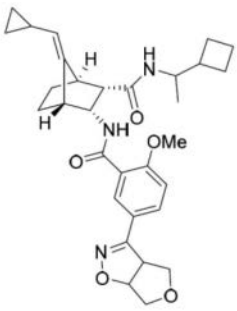
678	 由同手性苯甲酸酯中间体峰1制备。制备型色谱条件：仪器：Berger MG II柱：Chiralpak IF，21 × 250 mm，5微米，移动相：30% MeOH / 70% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：1.0 mL ~200 mg/3mL于MeOH-CAN中，分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IF，4.6 × 100 mm，3微米，移动相：30% MeOH / 70% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中。PK-1，RT = 2.81 min.，100% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{8,9-二羟基-3-氧杂-4-氮杂三环[5.2.1.0^{2,6}]癸-4-烯-5-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	670.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 8.31 - 8.21 (m, 2H), 7.97 - 7.77 (m, 2H), 7.50 (br t, J=9.8 Hz, 1H), 7.29 (d, J=8.5 Hz, 1H), 4.79 (br dd, J=17.7, 4.9 Hz, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.58 (br d, J=8.2 Hz, 1H), 4.46 (br s, 1H), 4.06 (s, 3H), 3.79 (br s, 1H), 3.73 - 3.58 (m, 1H), 3.31 - 3.10 (m, 2H), 2.74 (br s, 1H), 2.31 (s, 1H), 2.17 (s, 1H), 1.95 - 1.74 (m, 2H), 1.68 (br d, J=10.7 Hz, 1H), 1.53 (br d, J=8.5 Hz, 1H), 1.43 (br s, 2H), 1.12 (br d, J=10.7 Hz, 1H), 0.90 - 0.69 (m, 2H), 0.36 (br s, 2H	3.09, C

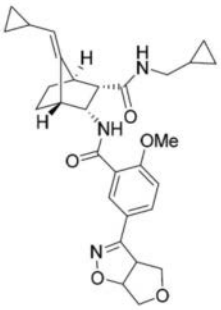
679	 由416-3制备，通过反相HPLC的第二洗脱非镜像异构体	(1R,2S,3R,4R,Z)-7-(环丙基亚甲基)-N-(2,2-二甲基四氢-2H-哌喃-4-基)-3-(2-甲氧基-5-(3a,4,6,6a-四氢呋喃并[3,4-d]异噁唑-3-基)苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	564.0	1H NMR (500 MHz, DMSO-d6) δ 9.96 (br d, J=6.7 Hz, 1H), 8.14 (d, J=2.1 Hz, 1H), 7.99 (br d, J=7.3 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.24 (br d, J=8.5 Hz, 1H), 5.34 (br dd, J=8.9, 3.1 Hz, 1H), 4.61 (br d, J=9.8 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.34 - 4.23 (m, 1H), 4.09 (br d, J=10.4 Hz, 1H), 4.01 (s, 3H), 3.97 - 3.87 (m, 2H), 3.82 - 3.74 (m, 1H), 3.68 - 3.52 (m, 2H), 3.04 (br s, 1H), 2.86 (br dd, J=10.7, 3.4 Hz, 1H), 1.88 - 1.79 (m, 1H), 1.77 - 1.59 (m, 3H), 1.51 - 1.27 (m, 3H), 1.25 - 1.18 (m, 1H), 1.17 (s, 3H), 1.14 - 1.06 (m, 4H), 0.76 - 0.64 (m, 2H), 0.32 (br d, J=2.1 Hz, 2H)。.	2.01, B

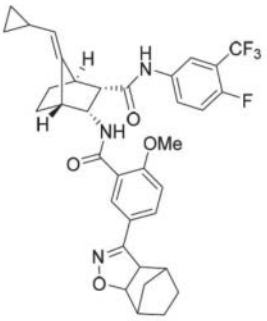
680	 由同手性苯甲酸酯中间体4制备；制备型色谱条件：仪器：PIC Solution SFC Prep-200)柱：Chiralpak IC，21 × 250 mm，5微米，移动相：15% IPA / 85% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：270 nm，注射详情：0.5 mL ~[样本浓度]mg/mL于IPA-CAN中，分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak IC，4.6 × 100 mm，3微米，移动相：10% 异丙醇/ 90% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm 注射详情：5 µL ~1mg/mL于MeOH中。PK-4 RT = 7.18 min.，>99% ee	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{4,6-二羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	644.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.92 (br d, J=7.3 Hz, 1H), 8.25 (s, 1H), 8.20 (br d, J=4.9 Hz, 1H), 7.84 - 7.73 (m, 2H), 7.47 (br t, J=9.6 Hz, 1H), 7.19 (br d, J=8.9 Hz, 1H), 4.79 (br dd, J=8.1, 4.1 Hz, 1H), 4.70 (br d, J=9.8 Hz, 1H), 4.43 (br s, 1H), 4.39 - 4.23 (m, 1H), 4.02 (s, 3H), 3.82 - 3.65 (m, 1H), 3.32 - 3.11 (m, 1H), 3.09 (br s, 1H), 2.72 (br s, 1H), 2.13 - 1.92 (m, 1H), 1.89 - 1.69 (m, 2H), 1.64 - 1.46 (m, 2H), 1.41 (br s, 2H), 0.85 - 0.67 (m, 2H), 0.35 (br d, J=3.7 Hz, 2H)	2.24, B

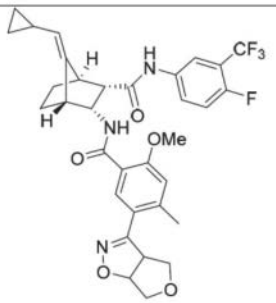
681	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2-甲氧基苯基)甲基]双环[2.2.1]庚烷-2-甲酰胺	572.1	(500 MHz, DMSO-d6) δ 9.94 (br d, J=6.7 Hz, 1H), 8.42 (br t, J=5.6 Hz, 1H), 8.16 (d, J=1.8 Hz, 1H), 7.78 (dd, J=8.7, 2.0 Hz, 1H), 7.24 - 7.16 (m, 2H), 7.12 (br d, J=7.3 Hz, 1H), 6.95 (br d, J=7.9 Hz, 1H), 6.78 (t, J=7.3 Hz, 1H), 5.33 (br dd, J=9.2, 3.1 Hz, 1H), 4.63 (br d, J=9.8 Hz, 1H), 4.49 (br t, J=7.8 Hz, 1H), 4.37 - 4.19 (m, 3H), 4.09 (br d, J=10.7 Hz, 1H), 3.95 - 3.85 (m, 3H), 3.81 - 3.72 (m, 3H), 3.65 (br dd, J=10.8, 3.5 Hz, 1H), 3.10 - 2.97 (m, 2H), 2.62 - 2.56 (m, 1H), 1.92 - 1.81 (m, 1H), 1.77 - 1.66 (m, 1H), 1.52 - 1.43 (m, 1H), 1.41 - 1.26 (m, 2H), 0.79 - 0.62 (m, 2H), 0.32 (br d, J=4.3 Hz, 2H)。可能由于与溶剂峰或经抑制的水峰重叠，两个质子在NMR中不可见。	2.23, B

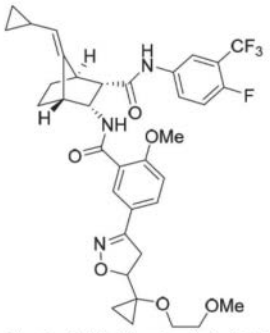
682	 由同手性苯甲酸酯中间体峰1制备。制备型色谱条件：仪器：PIC Solution SFC Prep-200柱：Chiralpak IC，21×250 mm，5微米，移动相：10%甲醇/90% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL~65mg/mL于甲醇中，分析型色谱条件：仪器：Aurora Infinity SFC柱：Chiralpak IC，4.6×250 mm，3微米，移动相：10% 甲醇/90% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：15 μL~1mg/mL于MeOH中。PK-1，RT = 3.07 min.，>99% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(1,1,1-三氟-2-羟基丙烷-2-基)-4,5-二氢-1,2-噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	684.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (d, J=7.0 Hz, 1H), 8.30 - 8.17 (m, 2H), 7.86 - 7.77 (m, 2H), 7.49 (t, J=9.7 Hz, 1H), 7.28 (d, J=8.8 Hz, 1H), 4.88 - 4.78 (m, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.45 (br s, 1H), 4.05 (s, 3H), 3.51 (br t, J=10.0 Hz, 1H), 3.17 (br dd, J=11.2, 4.3 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.89 - 1.69 (m, 2H), 1.50 (br dd, J=9.1, 4.3 Hz, 1H), 1.42 (br s, 2H), 1.30 (s, 3H), 0.81 - 0.66 (m, 2H), 0.36 (br s, 2H)	2.66, C

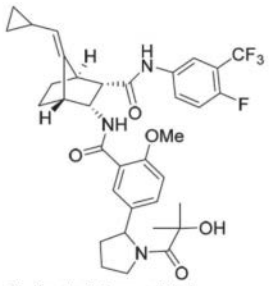
683	 由416-3制备 通过反相HPLC的第二洗脱非镜像异构体	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(1-环丁基乙基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	534.3	(500 MHz, DMSO-d6) δ 9.97 (br d, J=6.7 Hz, 1H), 8.15 (br d, J=2.1 Hz, 1H), 7.85 - 7.73 (m, 2H), 7.23 (br d, J=8.5 Hz, 1H), 5.33 (br dd, J=9.3, 3.2 Hz, 1H), 4.61 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=7.8 Hz, 1H), 4.27 (br d, J=5.2 Hz, 1H), 4.09 (br d, J=11.0 Hz, 1H), 4.01 (s, 3H), 3.88 (br d, J=9.5 Hz, 1H), 3.82 - 3.72 (m, 2H), 3.69 - 3.61 (m, 1H), 3.07 - 2.99 (m, 1H), 2.88 (br dd, J=11.0, 3.7 Hz, 1H), 2.24 - 2.10 (m, 1H), 1.92 - 1.56 (m, 8H), 1.51 - 1.41 (m, 1H), 1.39 - 1.25 (m, 2H), 0.90 (br d, J=6.7 Hz, 3H), 0.77 - 0.61 (m, 2H), 0.36 - 0.24 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.27, B

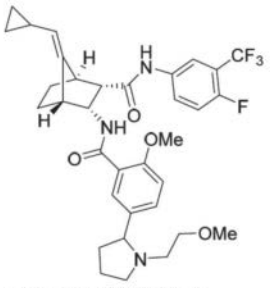
684	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-(环丙基甲基)-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	506.4	(500 MHz, DMSO-d6) δ 9.99 (br d, J=6.7 Hz, 1H), 8.20 - 8.08 (m, 2H), 7.78 (dd, J=8.5, 1.8 Hz, 1H), 7.23 (br d, J=8.5 Hz, 1H), 5.33 (br dd, J=8.9, 3.4 Hz, 1H), 4.62 (br d, J=9.8 Hz, 1H), 4.49 (br t, J=7.6 Hz, 1H), 4.32 - 4.23 (m, 1H), 4.14 - 4.05 (m, 1H), 4.00 (s, 3H), 3.89 (br d, J=8.9 Hz, 1H), 3.77 (br t, J=8.2 Hz, 1H), 3.69 - 3.60 (m, 1H), 3.04 (br s, 1H), 3.00 - 2.94 (m, 2H), 2.94 - 2.86 (m, 1H), 1.87 - 1.80 (m, 1H), 1.76 - 1.68 (m, 1H), 1.52 - 1.41 (m, 1H), 1.40 - 1.27 (m, 2H), 0.91 - 0.81 (m, 1H), 0.76 - 0.64 (m, 2H), 0.40 - 0.28 (m, 4H), 0.12 (br s, 2H)。可能由于与溶剂峰重叠，两个质子不可见。	2.07, C

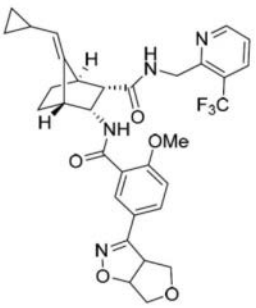
685	 由同手性苯甲酸酯中间体-峰2 (RT=5.52 min, >99% ee)制备：所用仪器：Berger MG II柱：Chiralcel OD-H，21 × 250 mm，5微米，移动相：7% MeOH / 93% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralcel OD-H，4.6 × 100 mm，3微米，移动相：7% MeOH / 93% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=4.42 min.，>99% ee)及手性(峰-2，RT=5.52 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂-4-氮杂三环[5.2.1.0^{2,6}]癸-4-烯-5-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	638.1	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (br d, J=6.7 Hz, 1H), 8.25 (d, J=2.1 Hz, 1H), 8.23 (br d, J=4.6 Hz, 1H), 7.83 (dd, J=8.5, 2.1 Hz, 1H), 7.81 - 7.73 (m, 1H), 7.49 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.59 (br d, J=8.2 Hz, 1H), 4.51 - 4.40 (m, 1H), 4.05 (s, 3H), 3.66 (br d, J=8.2 Hz, 1H), 3.55 - 3.38 (m, 1H), 3.17 (br dd, J=10.7, 3.7 Hz, 1H), 3.12 (br d, J=3.4 Hz, 1H), 2.73 (br s, 1H), 2.47 (br d, J=0.6 Hz, 1H), 2.38 (br d, J=1.2 Hz, 1H), 1.90 - 1.83 (m, 1H), 1.82 - 1.73 (m, 1H), 1.62 - 1.47 (m, 3H), 1.46 - 1.40 (m, 2H), 1.27 (br d, J=10.4 Hz, 1H), 1.14 (br d, J=10.1 Hz, 2H), 0.85 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.85, C

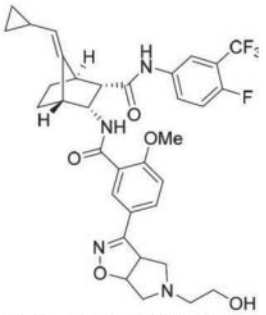
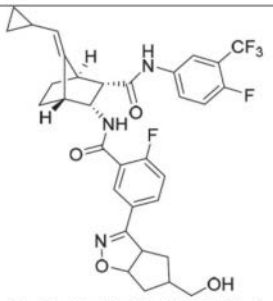
686	 通过SFC分离的异构体，其中实施例686为峰2 (RT=3.2 min.，>95% de)：仪器：Waters 100 Prep SFC柱：Chiral OD，30×250 mm，5微米，移动相：30% MeOH / 70% CO_2（具有0.1% DEA），流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD，4.6×100 mm，5微米，移动相：30% MeOH / 70% CO_2（具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰-1，RT=2.1 min.，>95% de)及手性(峰-2，RT=3.2 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基-4-甲基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d6) δ 10.64 - 10.45 (m, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.22 (br d, J=4.6 Hz, 1H), 7.96 (s, 1H), 7.81 - 7.68 (m, 1H), 7.48 (br t, J=9.9 Hz, 1H), 7.18 (s, 1H), 5.36 - 5.14 (m, 1H), 4.70 (d, J=9.2 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.47 - 4.39 (m, 1H), 4.11 (br d, J=10.4 Hz, 1H), 4.05 (s, 3H), 3.79 (br d, J=9.8 Hz, 1H), 3.74 - 3.68 (m, 1H), 3.64 (br s, 1H), 3.24 - 3.13 (m, 1H), 3.11 - 3.04 (m, 1H), 2.72 (br s, 1H), 2.48 (s, 3H), 1.98 - 1.82 (m, 1H), 1.79 - 1.68 (m, 1H), 1.61 - 1.49 (m, 1H), 1.46 - 1.30 (m, 2H), 0.86 - 0.60 (m, 2H), 0.35 (br d, J=3.1 Hz, 2H)	2.59, C

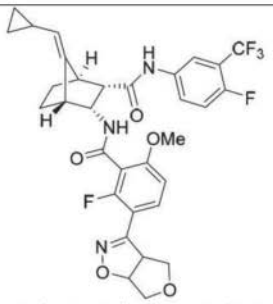
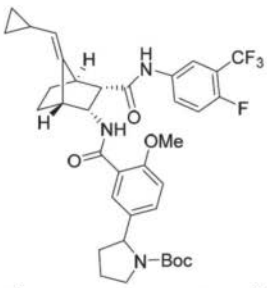
687	 由同手性苯甲酸中间体峰1(RT=5.02 min.，>99% ee)制备-仪器：Berger MG II柱：Chiralpak IC，21×250 mm，5微米，移动相：25% MeOH / 75% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IC，4.6×250 mm，3微米，移动相：25% MeOH / 75% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=5.02 min.，>99% ee)及手性(峰-2，RT=6.46 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{5-[1-(2-甲氧基乙氧基)环丙基]-4,5-二氢-1,2-噁唑-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	686.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.2 Hz, 1H), 8.25 (d, J=2.3 Hz, 1H), 8.22 (dd, J=6.4, 2.3 Hz, 1H), 7.86 - 7.77 (m, 2H), 7.48 (t, J=9.7 Hz, 1H), 7.28 (d, J=8.8 Hz, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.56 (dd, J=10.6, 8.5 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.05 (s, 3H), 3.74 - 3.66 (m, 1H), 3.62 - 3.58 (m, 1H), 3.55 - 3.44 (m, 1H), 3.42 - 3.38 (m, 2H), 3.32 - 3.26 (m, 1H), 3.16 (dd, J=11.4, 4.1 Hz, 1H), 3.13 - 3.06 (m, 3H), 2.77 - 2.69 (m, 1H), 1.89 - 1.81 (m, 1H), 1.80 - 1.72 (m, 1H), 1.59 - 1.48 (m, 1H), 1.45 - 1.35 (m, 2H), 0.96 - 0.85 (m, 1H), 0.82 - 0.71 (m, 3H), 0.71 - 0.65 (m, 2H), 0.42 - 0.27 (m, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.64, C

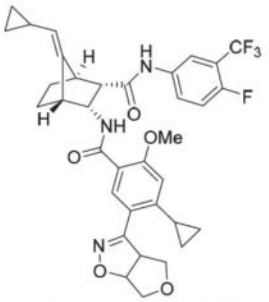
688	 由实施例694制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙酰基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.3	(400 MHz, DMSO-d6) δ = 10.47 (s, 1H), 9.80 (br d, J = 7.6 Hz, 1H), 8.21 (dd, J = 2.4, 6.6 Hz, 1H), 7.83 - 7.74 (m, 1H), 7.74 - 7.64 (m, 1H), 7.48 (d, J = 10.3 Hz, 1H), 7.23 (br d, J = 2.4 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 5.20 (s, 1H), 5.04 - 4.95 (m, 1H), 4.68 (d, J = 9.5 Hz, 1H), 4.49 - 4.37 (m, 1H), 4.07 - 3.99 (m, 1H), 3.96 (s, 3H), 3.91 - 3.82 (m, 1H), 3.58 - 3.49 (m, 1H), 3.20 - 3.10 (m, 2H), 3.07 (t, J = 4.2 Hz, 1H), 2.70 (t, J = 3.4 Hz, 1H), 2.21 - 2.08 (m, 1H), 1.90 - 1.70 (m, 4H), 1.62 - 1.46 (m, 2H), 1.44 - 1.35 (m, 2H), 1.29 (d, J = 14.9 Hz, 6H), 0.80 - 0.56 (m, 2H), 0.35 (dd, J = 2.2, 4.6 Hz, 2H)	2.47, A

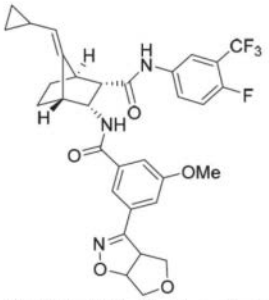
689	 由实施例715制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[1-(2-甲氧基乙基)吡咯烷-2-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.0	(400 MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.85 - 9.73 (m, 1H), 8.21 (dd, J = 2.4, 6.6 Hz, 1H), 7.87 (br d, J = 0.7 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.52 - 7.39 (m, 2H), 7.12 (br d, J = 9.0 Hz, 1H), 4.68 (d, J = 9.5 Hz, 1H), 4.49 - 4.39 (m, 1H), 3.97 (s, 3H), 3.26 - 3.22 (m, 1H), 3.18 - 3.10 (m, 4H), 3.08 (br d, J = 3.9 Hz, 1H), 2.70 (dt, J = 0.7, 3.1 Hz, 1H), 2.61 - 2.53 (m, 1H), 2.27 - 2.12 (m, 2H), 2.07 (s, 1H), 1.93 - 1.70 (m, 4H), 1.54 - 1.33 (m, 5H), 0.81 - 0.67 (m, 2H), 0.35 (dd, J = 2.2, 4.6 Hz, 2H)	2.63, A

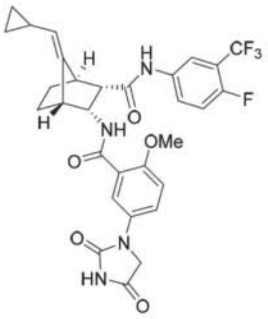
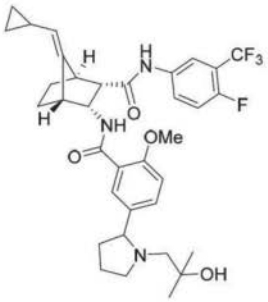
690	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[3-(三氟甲基)吡啶-2-基]甲基}双环[2.2.1]庚烷-2-甲酰胺	611.2	(500 MHz, DMSO-d6) δ 9.90 (br d, J=6.7 Hz, 1H), 8.72 - 8.63 (m, 2H), 8.17 - 8.10 (m, 2H), 7.77 (dd, J=8.5, 1.8 Hz, 1H), 7.47 (br dd, J=6.9, 5.3 Hz, 1H), 7.18 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.63 (d, J=9.8 Hz, 1H), 4.56 (br d, J=4.6 Hz, 2H), 4.48 (br t, J=8.1 Hz, 1H), 4.34 - 4.25 (m, 1H), 4.09 (br d, J=10.7 Hz, 1H), 3.89 (br d, J=9.2 Hz, 1H), 3.83 (s, 3H), 3.77 (br t, J=8.1 Hz, 1H), 3.65 (br dd, J=10.8, 3.2 Hz, 1H), 3.10 - 3.00 (m, 2H), 2.61 (br s, 1H), 1.81 (br t, J=9.3 Hz, 1H), 1.74 - 1.62 (m, 1H), 1.53 - 1.40 (m, 1H), 1.31 (br s, 2H), 0.80 - 0.63 (m, 2H), 0.39 - 0.25 (m, 2H)。	2.14, B

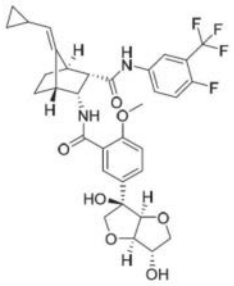
691	 由同手性苯甲酸酯中间体(峰1；>99%ee；手性分析型RT=6.621 min)制备；制备型手性SFC条件：仪器：Jasco SFC Prep；柱：Regis Whelk-01，21 × 250 mm，5微米；移动相：15% IPA / 85% CO_2；流动条件：45 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：0.5 mL ~50mg/mL于IPA中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	657.6	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.97 (d, J=7.0 Hz, 1H), 8.30 (br s, 1H), 8.25 (dd, J=6.5, 2.5 Hz, 1H), 7.85 (dd, J=8.5, 2.0 Hz, 1H), 7.80 - 7.75 (m, 1H), 7.50 (t, J=9.7 Hz, 1H), 7.31 (d, J=8.9 Hz, 1H), 5.49 - 5.42 (m, 1H), 4.78 (br t, J=8.8 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.07 (s, 3H), 3.98 (br d, J=11.9 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.68 - 3.62 (m, 2H), 3.55 (br d, J=1.5 Hz, 2H), 3.23 (br s, 2H), 3.19 - 3.13 (m, 1H), 3.12 - 3.07 (m, 1H), 2.76 - 2.70 (m, 1H), 1.84 - 1.74 (m, 2H), 1.53 - 1.46 (m, 1H), 1.45 - 1.38 (m, 2H), 0.78 - 0.70 (m, 2H), 0.38 - 0.33 (m, 2H)	1.21, A
692	 由同手性苯甲酸酯中间体(峰2；83.4%ee；手性分析型RT=2.155 min)制备；制备型手性SFC条件：仪器：Berger MG II;柱：Chiralpak AD-H，21 × 250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40℃；检测器波长：220 nm；注射详情：0.5 mL ~125mg/mL 于 MeOH:CAN 中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.4	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.37 (t, J=6.9 Hz, 1H), 8.08 - 8.04 (m, 1H), 8.00 (dd, J=6.5, 2.5 Hz, 1H), 7.88 - 7.83 (m, 2H), 7.51 - 7.42 (m, 2H), 5.20 - 5.14 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.10 (td, J=9.7, 6.3 Hz, 1H), 3.31 - 3.25 (m, 1H), 3.23 - 3.11 (m, 3H), 2.75 - 2.72 (m, 1H), 2.20 - 2.06 (m, 3H), 1.87 - 1.74 (m, 2H), 1.66 - 1.59 (m, 1H), 1.55 - 1.39 (m, 4H), 0.78 - 0.69 (m, 2H), 0.38 - 0.32 (m, 2H)	1.34, A

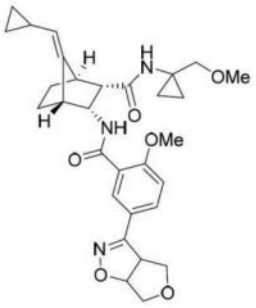
693	 经由SFC分离的异构体，其中实施例693为峰2 (RT=8.3 min.，>95% de)；仪器：Waters 100 Prep SFC柱：Chiral OD，30 × 250 mm，5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral OD，4.6 × 100 mm，5微米，移动相：15% MeOH / 85% CO_2 (具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性(峰-1，RT=6.75 min.，>95% de)及手性(峰-2，RT=8.3 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-氟-6-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.2	(500 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.76 - 8.66 (m, 1H), 8.11 (br d, J=6.1 Hz, 1H), 7.84 - 7.70 (m, 2H), 7.46 (t, J=9.7 Hz, 1H), 7.02 (d, J=9.0 Hz, 1H), 5.30 (dd, J=9.3, 3.6 Hz, 1H), 4.67 (d, J=9.5 Hz, 1H), 4.54 - 4.43 (m, 1H), 4.37 - 4.28 (m, 1H), 4.08 (d, J=10.7 Hz, 1H), 3.92 (br d, J=9.6 Hz, 1H), 3.78 - 3.68 (m, 3H), 3.66 - 3.55 (m, 2H), 3.13 (br dd, J=10.8, 3.7 Hz, 1H), 3.05 (br s, 1H), 2.72 - 2.65 (m, 1H), 2.03 - 1.93 (m, 1H), 1.92 - 1.85 (m, 1H), 1.59 - 1.49 (m, 1H), 1.47 - 1.32 (m, 2H), 0.73 (quin, J=9.4 Hz, 2H), 0.43 - 0.27 (m, 2H)	2.32, B
694	 峰1，RT = 3.54 min，制备型手性SFC纯化条件：仪器详情：品牌/型号：PIC – 175；制备型SFC条件：柱/尺寸：Chiralpak IG (250 × 30)mm，5u，% CO_2: 75%，%助溶剂：25% 4M 甲醇氨于MEOH中，总流速：130.0 g/min，背压：100巴，温度：40°C，UV：240 nm。	2-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-1-甲酸叔丁酯	672.4	(400MHz, CD_3OD) δ ppm 8.21 - 8.05 (m, 1H), 7.88 - 7.81 (m, 1H), 7.76 - 7.69 (m, 1H), 7.35 - 7.22 (m, 2H), 7.16 - 7.08 (m, 1H), 4.80 - 4.74 (m, 1H), 4.74 - 4.67 (m, 1H), 4.60 - 4.49 (m, 1H), 4.08 - 4.01 (m, 3H), 3.68 - 3.49 (m, 3H), 3.23 - 3.09 (m, 2H), 2.74 - 2.64 (m, 1H), 2.44 - 2.22 (m, 1H), 2.09 - 1.96 (m, 1H), 1.96 - 1.73 (m, 4H), 1.63 - 1.38 (m, 7H), 1.15 (br s, 6H), 0.81 - 0.68 (m, 2H), 0.41 - 0.26 (m, 2H)。	1.61, C

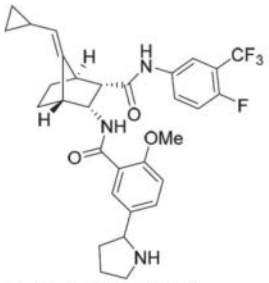
695	 通过SFC分离的异构体，其中实施例695为峰2 (RT=3.3 min.，>95% de)：-仪器：Waters 100 Prep SFC柱：Chiral AD，30×250 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA），流动条件：100 mL/min，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiral AD，4.6×100 mm，5微米，移动相：25% MeOH / 75% CO_2（具有0.1% DEA)，流动条件：2 mL/min，检测器波长：220 nm，得到手性（峰-1，RT=2.6 min.，>95% de)及对掌(峰-2，RT=3.3 min.，>95% de)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-4-环丙基-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	654.0	(500 MHz, DMSO-d6) δ 10.64 - 10.42 (m, 1H), 9.87 (br d, J=6.7 Hz, 1H), 8.33 - 8.11 (m, 1H), 7.92 (s, 1H), 7.83 - 7.72 (m, 1H), 7.48 (br t, J=9.8 Hz, 1H), 6.68 (s, 1H), 5.32 (dd, J=9.0, 3.5 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.56 (br t, J=7.8 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.11 (br d, J=11.0 Hz, 1H), 4.04 (s, 3H), 3.76 (br d, J=9.5 Hz, 1H), 3.70 - 3.61 (m, 1H), 3.51 - 3.42 (m, 1H), 3.15 (br dd, J=10.4, 4.0 Hz, 1H), 3.08 (br s, 1H), 2.72 (br s, 1H), 2.41 - 2.28 (m, 1H), 1.92 - 1.82 (m, 1H), 1.79 - 1.72 (m, 1H), 1.50 (br dd, J=8.4, 3.8 Hz, 1H), 1.41 (br s, 2H), 1.11 - 1.03 (m, 1H), 0.98 (dt, J=8.5, 4.6 Hz, 1H), 0.93 - 0.82 (m, 2H), 0.77 - 0.60 (m, 2H), 0.35 (br s, 2H)	2.63, C

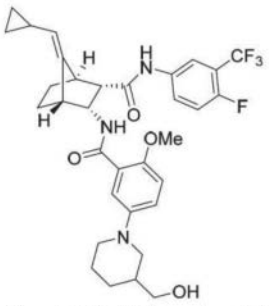
696	 通过SFC分离的异构体，其中实施例696为峰1(RT=1.81 min，>99% de)，-仪器：PIC Solution SFC柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：30% IPA-0.1% DEA / 70% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Aurora Infinity SFC，柱Chiralpak IC，4.6 × 250 mm，3微米，移动相：20% IPA-0.1% DEA / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=1.81 min.，>99% de)及手性(峰-2，RT=2.76 min.，>99% de)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-5-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	614.2	(500 MHz, DMSO-d6) δ 10.69 - 10.53 (m, 1H), 9.39 (br d, J=6.7 Hz, 1H), 8.12 (br d, J=4.6 Hz, 1H), 7.87 - 7.79 (m, 1H), 7.60 (s, 1H), 7.49 (br t, J=9.6 Hz, 1H), 7.38 (s, 1H), 7.37 (s, 1H), 5.42 (dd, J=9.2, 3.1 Hz, 1H), 4.71 (d, J=9.5 Hz, 1H), 4.56 (br t, J=7.8 Hz, 1H), 4.47 - 4.37 (m, 1H), 4.14 (br d, J=10.7 Hz, 1H), 3.95 (br d, J=9.2 Hz, 1H), 3.86 (s, 3H), 3.74 (br dd, J=9.3, 6.9 Hz, 1H), 3.67 (dd, J=10.8, 3.5 Hz, 1H), 3.19 (br dd, J=10.5, 4.1 Hz, 1H), 3.10 (br s, 1H), 2.77 (br s, 1H), 1.91 - 1.83 (m, 1H), 1.79 - 1.73 (m, 1H), 1.59 - 1.49 (m, 1H), 1.45 (br s, 2H), 0.81 - 0.69 (m, 2H), 0.37 (br d, J=1.8 Hz, 2H)可能由于与溶剂峰重叠，一个质子在NMR中不可见	2.51, B

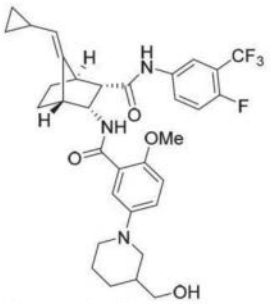
697		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-[5-(2,4-二氧代咪唑啶-1-基)-2-甲氧基苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	601.3	(500 MHz, DMSO-d6) δ 8.28 - 8.15 (m, 1H), 7.90 - 7.76 (m, 1H), 7.69 (br dd, J=8.9, 2.7 Hz, 1H), 7.57 - 7.43 (m, 1H), 7.31 - 7.23 (m, 1H), 7.20 - 7.01 (m, 1H), 4.78 - 4.58 (m, 1H), 4.53 - 4.42 (m, 1H), 4.16 (br d, J=4.6 Hz, 1H), 4.05 - 3.96 (m, 1H), 3.22 - 3.03 (m, 1H), 2.82 (s, 3H), 2.78 - 2.64 (m, 1H), 1.93 - 1.66 (m, 3H), 1.59 - 1.24 (m, 4H), 0.84 - 0.67 (m, 2H), 0.42 - 0.25 (m, 2H)	2.31, B
698	 由实施例703制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙基)吡咯烷-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.0	(400 MHz, DMSO-d6) δ = 10.47 (s, 1H), 0.00 (d, J = 7.6 Hz, 1H), 8.24 - 8.11 (m, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.53 - 7.39 (m, 2H), 7.11 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 9.8 Hz, 1H), 4.48 - 4.39 (m, 1H), 3.99 - 3.91 (m, 4H), 3.55 - 3.47 (m, 1H), 3.26 (s, 1H), 3.13 (dd, J = 4.2, 10.5 Hz, 1H), 3.07 (br t, J = 3.5 Hz, 1H), 2.70 (br s, 1H), 2.31 - 2.21 (m, 2H), 2.08 - 1.96 (m, 2H), 1.88 (s, 1H), 1.83 - 1.66 (m, 3H), 1.55 - 1.36 (m, 4H), 1.02 (s, 3H), 0.88 (s, 3H), 0.79 - 0.68 (m, 2H), 0.35 (dd, J = 2.2, 4.4 Hz, 2H)	2.67, A

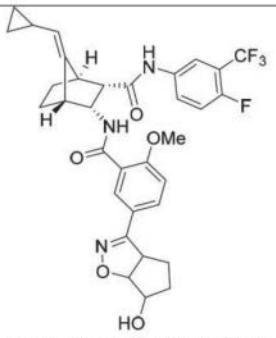
700		(1R,2S,3R,4R,7Z)-3-{5-[(3R,3aS,6S,6aR)-3,6-二羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	647.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.87 (br d, J=7.3 Hz, 1H), 8.23 (br d, J=4.9 Hz, 1H), 8.10 (d, J=2.4 Hz, 1H), 7.84 - 7.75 (m, 1H), 7.61 (dd, J=8.7, 2.3 Hz, 1H), 7.49 (br t, J=9.8 Hz, 1H), 7.19 (d, J=8.5 Hz, 1H), 4.71 (br d, J=9.8 Hz, 1H), 4.52 - 4.41 (m, 1H), 4.32 (br d, J=3.4 Hz, 1H), 4.24 - 4.12 (m, 2H), 4.01 (s, 3H), 3.97 - 3.90 (m, 1H), 3.89 - 3.78 (m, 2H), 3.70 (br d, J=8.9 Hz, 1H), 3.50 (br s, 1H), 3.17 (br dd, J=10.7, 4.0 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.94 - 1.84 (m, 1H), 1.82 - 1.74 (m, 1H), 1.61 - 1.48 (m, 1H), 1.47 - 1.32 (m, 2H), 0.84 - 0.67 (m, 2H), 0.37 (br d, J=2.4 Hz, 2H)	2.28, A

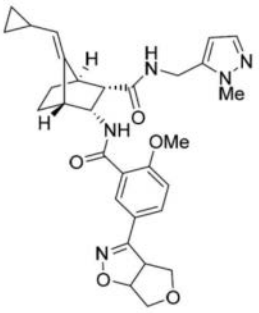
701	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[1-(甲氧基甲基)环丙基]甲基}双环[2.2.1]庚烷-2-甲酰胺	550.3	(500 MHz, DMSO-d6) δ 9.97 (br d, J=7.0 Hz, 1H), 8.14 (s, 1H), 8.05 (br t, J=5.2 Hz, 1H), 7.77 (dd, J=8.2, 1.2 Hz, 1H), 7.23 (d, J=8.5 Hz, 1H), 5.33 (br dd, J=9.3, 3.2 Hz, 1H), 4.62 (br d, J=9.5 Hz, 1H), 4.48 (br t, J=8.1 Hz, 1H), 4.28 (br t, J=10.4 Hz, 1H), 4.08 (br d, J=10.7 Hz, 1H), 4.00 (s, 3H), 3.89 (br d, J=9.2 Hz, 1H), 3.80 - 3.70 (m, 1H), 3.68 - 3.60 (m, 1H), 3.19 - 3.08 (m, 5H), 3.07 - 2.99 (m, 2H), 2.94 (br dd, J=10.5, 4.1 Hz, 1H), 1.87 - 1.80 (m, 1H), 1.77 - 1.69 (m, 1H), 1.50 - 1.41 (m, 1H), 1.38 - 1.26 (m, 2H), 0.76 - 0.64 (m, 2H), 0.46 - 0.35 (m, 2H), 0.30 (br s, 4H)。可能由于与经抑制的水峰重叠，一个质子在NMR中不可见。	2.02, B

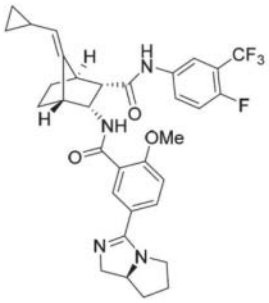
703	 由实施例694制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(吡咯烷-2-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	572.3	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.86 (d, J = 7.3 Hz, 1H), 8.23 (dd, J = 2.4, 6.6 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.80 - 7.72 (m, 1H), 7.56 (dd, J = 2.6, 8.4 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.21 (d, J = 8.6 Hz, 1H), 4.69 (d, J = 9.8 Hz, 1H), 4.49 - 4.40 (m, 1H), 4.39 - 4.32 (m, 1H), 4.00 (s, 3H), 3.20 - 3.11 (m, 4H), 3.08 (br t, J = 3.8 Hz, 1H), 2.74 - 2.69 (m, 1H), 2.29 - 2.17 (m, 1H), 2.02 - 1.72 (m, 6H), 1.55 - 1.33 (m, 4H), 0.83 - 0.62 (m, 2H), 0.35 (dd, J = 2.1, 4.5 Hz, 2H)	2.09, A

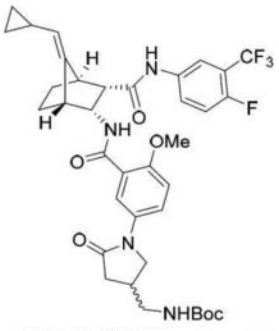
704	 峰 -1/异构体 -1，SFC RT 4.7 min，仪器详情：品牌/型号：Thar SFC-80，制备型SFC条件，柱/尺寸：Chiralcel OD-H (250 × 30)mm，5u，% CO_2: 70%，%助溶剂：30% 4M甲醇氨于MEOH中，总流速：80g/min，背压：100巴，温度：35℃，UV：240，保留时间(min)，峰-1：4.7，峰-2：8.0	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[3-(羟基甲基)哌啶-1-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(400 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.81 (d, J=7.3 Hz, 1H), 8.22 (dd, J=6.4, 2.7 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.55 - 7.42 (m, 2H), 7.10 - 7.02 (m, 2H), 4.68 (d, J=9.3 Hz, 1H), 4.54 (t, J=5.5 Hz, 1H), 4.48 - 4.40 (m, 1H), 3.91 (s, 3H), 3.57 - 3.53 (m, 1H), 3.16 - 3.12 (m, 1H), 3.09 - 3.04 (m, 1H), 2.72 - 2.68 (m, 1H), 2.54 (s, 2H), 2.32 (dd, J=3.9, 2.0 Hz, 1H), 1.90 - 1.84 (m, 1H), 1.81 - 1.65 (m, 4H), 1.60 - 1.45 (m, 3H), 1.44 - 1.35 (m, 2H), 1.27 - 1.21 (m, 3H), 1.05 - 0.95 (m, 1H), 0.85 (br t, J=6.6 Hz, 1H), 0.73 (br t, J=8.6 Hz, 2H), 0.35 (dd, J=4.3, 1.6 Hz, 2H)	2.49, A

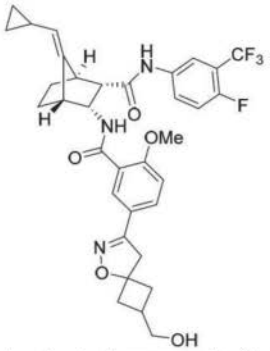
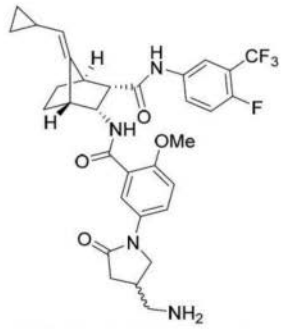
705	 峰 -2/异构体 -2，SFC RT 8.0 min，仪器详情：品牌/型号：Thar SFC-80，制备型SFC条件，柱/尺寸：Chiralcel OD-H (250 × 30)mm,5u，% CO_2: 70%，%助溶剂：30% 4M甲醇氨于MEOH中，总流速：80g/min，背压：100巴，温度：35℃，UV:240，保留时间(min)，峰-1：4.7，峰-2：8.0	(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[3-(羟基甲基)哌啶-1-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(400 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.84 - 9.76 (m, 1H), 8.21 (dd, J=6.2, 2.3 Hz, 1H), 7.83 - 7.71 (m, 1H), 7.52 (d, J=2.9 Hz, 1H), 7.47 (t, J=9.9 Hz, 1H), 7.12 - 6.97 (m, 2H), 4.68 (d, J=9.5 Hz, 1H), 4.54 (t, J=5.1 Hz, 1H), 4.48 - 4.40 (m, 1H), 3.91 (s, 3H), 3.55 - 3.50 (m, 1H), 3.17 - 3.12 (m, 1H), 3.07 (dd, J=4.4, 3.7 Hz, 1H), 2.72 - 2.68 (m, 1H), 2.54 (s, 1H), 2.35 - 2.31 (m, 1H), 1.91 - 1.84 (m, 1H), 1.80 - 1.65 (m, 4H), 1.62 - 1.33 (m, 5H), 1.28 - 1.19 (m, 3H), 1.02 (dt, J=9.3, 1.5 Hz, 1H), 0.79 - 0.68 (m, 2H), 0.42 - 0.26 (m, 2H	2.47, A

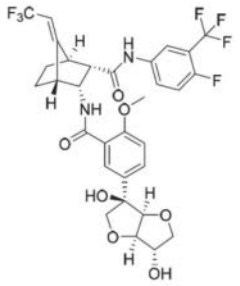
706	 由同手性苯甲酸酯中间体峰4制备。制备型色谱条件：仪器：Berger MG II柱：Chiralpak AD-H，21 × 250 mm，5微米，移动相：12% MeOH / 88% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：0.5 mL ~35mg/mL于甲醇中，分析型色谱条件：仪器：Shimadzu Nexera SFC柱：Chiralpak AD-H，4.6 × 100 mm，3微米，移动相：12% MeOH / 88% CO_2，流动条件：2.0 mL/min，150巴，40°C，检测器波长：220 nm，注射详情：5 μL ~1mg/mL于MeOH中。PK-4，RT = 7.80 min.，> 99% ee。	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{6-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	628.2	(500 MHz, DMSO-d_6) δ 10.70 (br s, 1H), 10.05 (br s, 1H), 8.42 (br s, 1H), 8.37 (br s, 1H), 7.95 (br s, 1H), 7.63 (br s, 1H), 7.35 (br d, *J*=8.2 Hz, 1H), 5.22 (br s, 1H), 4.84 (br d, *J*=9.8 Hz, 1H), 4.57 (br s, 1H), 4.23 (br d, *J*=9.2 Hz, 1H), 4.17 (br s, 3H), 3.75 - 3.67 (m, 1H), 3.64 (br d, *J*=6.4 Hz, 1H), 3.32 (br s, 1H), 3.25 (br s, 1H), 2.87 (br s, 1H), 2.68 (br d, *J*=18.3 Hz, 1H), 1.99 (br s, 2H), 1.93 (br s, 2H), 1.68 (br s, 1H), 1.56 (br s, 2H), 0.89 (br s, 2H), 0.50 (br s, 2H)	2.41, C

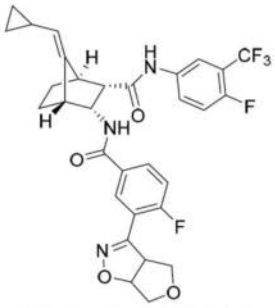
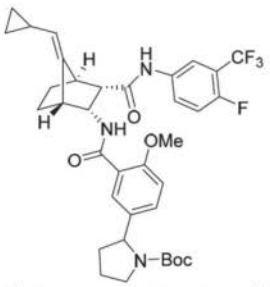
707	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1-甲基-1H-吡唑-5-基)甲基]双环[2.2.1]庚烷-2-甲酰胺	546.3	(500 MHz, DMSO-d6) Â¿ 9.93 (d, J=7.0 Hz, 1H), 8.58 (br t, J=5.5 Hz, 1H), 8.16 (d, J=2.2 Hz, 1H), 7.79 (dd, J=8.6, 2.3 Hz, 1H), 7.24 (dd, J=5.2, 3.5 Hz, 2H), 6.08 (d, J=1.5 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.49 (br t, J=7.9 Hz, 1H), 4.41 - 4.24 (m, 3H), 4.09 (d, J=10.6 Hz, 1H), 4.04 - 3.93 (m, 3H), 3.90 (br d, J=8.8 Hz, 1H), 3.77 (dd, J=9.5, 7.1 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, J=10.7, 3.7 Hz, 1H), 3.09 - 3.01 (m, 1H), 2.96 (br dd, J=10.9, 4.1 Hz, 1H), 2.56 (br d, J=3.6 Hz, 1H), 1.87 - 1.69 (m, 2H), 1.53 - 1.41 (m, 1H), 1.41 - 1.27 (m, 2H), 0.77 - 0.65 (m, 2H), 0.32 (br d, J=4.3 Hz, 2H)。	1.78, B

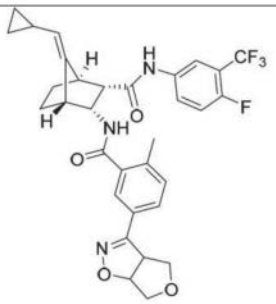
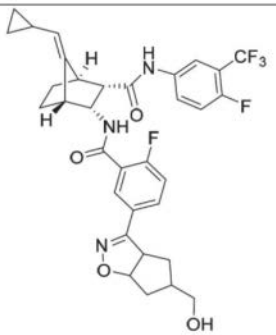
708		(1R,2S,3R,4R,7Z)-3-{5-[(7aS)-1H,5H,6H,7H,7aH-吡咯并[1,2-c]咪唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	611.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.30 (d, J=1.8 Hz, 1H), 8.20 (br d, J=4.3 Hz, 1H), 7.88 - 7.80 (m, 1H), 7.80 - 7.71 (m, 1H), 7.46 (br t, J=9.9 Hz, 1H), 7.24 (d, J=8.9 Hz, 1H), 4.67 (d, J=9.5 Hz, 1H), 4.51 - 4.37 (m, 1H), 4.11 - 4.00 (m, 3H), 3.96 - 3.82 (m, 2H), 3.25 - 3.18 (m, 1H), 3.17 - 3.11 (m, 1H), 3.10 - 2.98 (m, 2H), 2.74 - 2.67 (m, 1H), 1.95 - 1.81 (m, 4H) (与AcOH峰重叠), 1.79 - 1.58 (m, 3H), 1.53 - 1.26 (m, 4H), 0.79 - 0.65 (m, 2H), 0.33 (br s, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.21, B

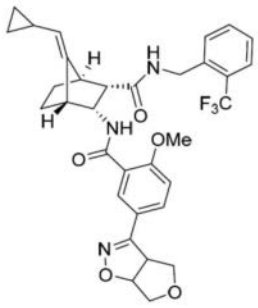
710	 由416-3制备	N-{[1-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-5-氧代吡咯烷-3-基]甲基}氨基甲酸叔丁酯	712.9	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (br dd, J=13.9, 7.2 Hz, 1H), 8.23 (br s, 1H), 8.04 (br d, J=3.1 Hz, 1H), 7.89 - 7.76 (m, 1H), 7.54 (br d, J=8.5 Hz, 1H), 7.49 (br t, J=9.8 Hz, 1H), 7.20 (br d, J=8.5 Hz, 1H), 6.96 (br s, 1H), 4.70 (br d, J=9.8 Hz, 1H), 4.45 (br d, J=4.3 Hz, 1H), 4.25 (br s, 1H), 4.01 (s, 3H), 3.47 (br s, 1H), 3.16 (br dd, J=10.7, 4.0 Hz, 1H), 3.09 (br d, J=3.7 Hz, 1H), 3.00 - 2.88 (m, 1H), 2.72 (br s, 1H), 2.41 - 2.26 (m, 1H), 2.23 - 2.11 (m, 1H), 2.01 - 1.84 (m, 2H), 1.82 - 1.71 (m, 1H), 1.56 - 1.46 (m, 1H), 1.45 - 1.36 (m, 2H), 1.32 (s, 9H), 1.28 - 1.14 (m, 1H), 0.86 - 0.58 (m, 2H), 0.36 (br s, 2H)	2.50, B

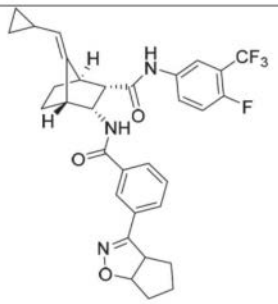
711	 经由反相HPLC自实施例511分离	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[2-(羟基甲基)-5-氧杂-6-氮杂螺[3.4]辛-6-烯-7-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d6) δ 10.48 - 10.22 (m, 1H), 8.36 (br d, J=6.7 Hz, 1H), 8.14 (br d, J=4.0 Hz, 1H), 7.92 - 7.78 (m, 1H), 7.74 (br dd, J=8.5, 2.1 Hz, 1H), 7.47 (br t, J=9.8 Hz, 1H), 7.29 - 7.12 (m, 1H), 4.78 - 4.56 (m, 2H), 4.51 (d, J=9.5 Hz, 1H), 4.19 - 3.72 (m, 3H), 3.54 - 3.25 (m, 3H), 3.16 - 2.96 (m, 1H), 2.56 (br s, 1H), 2.47 - 2.40 (m, 2H), 2.39 - 2.29 (m, 1H), 2.28 - 2.22 (m, 1H), 2.15 - 2.07 (m, 2H), 1.89 - 1.80 (m, 1H), 1.71 - 1.58 (m, 2H), 1.54 - 1.42 (m, 2H), 0.80 - 0.60 (m, 2H), 0.40 - 0.24 (m, 2H)	2.36, B
712	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-{5-[4-(氨基甲基)-2-氧代吡咯烷-1-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	615.3	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 10.04 - 9.79 (m, 1H), 8.41 - 8.17 (m, 1H), 8.12 - 7.96 (m, 1H), 7.99 - 7.83 (m, 1H), 7.88 - 7.74 (m, 1H), 7.61 - 7.42 (m, 2H), 7.35 - 7.08 (m, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.44 (br d, J=2.0 Hz, 2H), 4.23 - 3.89 (m, 3H), 3.22 - 3.11 (m, 1H), 3.12 - 2.99 (m, 1H), 2.94 - 2.77 (m, 2H), 2.79 - 2.67 (m, 1H), 2.63 - 2.54 (m, 2H), 2.46 - 2.37 (m, 1H), 2.35 - 2.25 (m, 1H), 2.04 - 1.92 (m, 1H), 1.90 - 1.70 (m, 2H), 1.57 - 1.45 (m, 1H), 1.44 - 1.34 (m, 2H), 0.80 - 0.66 (m, 2H), 0.44 - 0.19 (m, 2H)	1.95, C

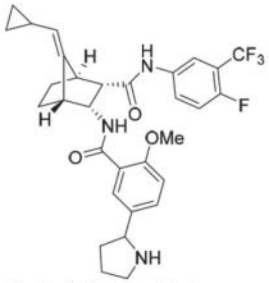
713		(1R,2S,3R,4R,7Z)-3-{5-[(3R,3aS,6S,6aR)-3,6-二羟基-六氢呋喃并[3,2-b]呋喃-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2,2,2-三氟亚乙基)双环[2.2.1]庚烷-2-甲酰胺	674.8	(500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.92 (br d, J=6.7 Hz, 1H), 8.22 (br d, J=4.9 Hz, 1H), 8.08 (d, J=2.1 Hz, 1H), 7.86 - 7.76 (m, 1H), 7.62 (dd, J=8.5, 2.1 Hz, 1H), 7.50 (br t, J=9.9 Hz, 1H), 7.20 (d, J=8.9 Hz, 1H), 5.93 (q, J=8.1 Hz, 1H), 4.59 - 4.46 (m, 1H), 4.31 (br d, J=3.7 Hz, 1H), 4.25 - 4.14 (m, 2H), 4.00 (s, 3H), 3.94 (br dd, J=9.3, 3.2 Hz, 1H), 3.87 - 3.76 (m, 1H), 3.70 - 3.65 (m, 1H), 3.33 - 3.19 (m, 2H), 3.00 (br d, J=4.0 Hz, 1H), 2.00 (br t, J=9.9 Hz, 1H), 1.92 - 1.82 (m, 1H), 1.59 - 1.43 (m, 2H)	2.33, A

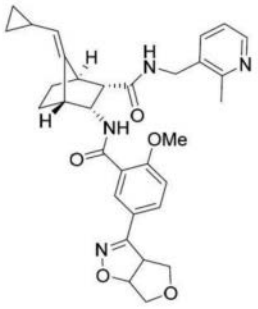
714	 非镜像异构体混合物	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-4-氟苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	602.1	(500 MHz, DMSO-d6) δ 10.64 - 10.37 (m, 1H), 9.33 (dd, J=14.8, 6.9 Hz, 1H), 8.14 (br d, J=5.5 Hz, 1H), 8.01 (br s, 1H), 7.94 - 7.84 (m, 1H), 7.82 (br s, 1H), 7.57 - 7.40 (m, 2H), 5.46 - 5.32 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.56 - 4.46 (m, 1H), 4.41 - 4.32 (m, 1H), 4.12 (br dd, J=10.8, 1.7 Hz, 1H), 3.96 - 3.88 (m, 1H), 3.78 - 3.69 (m, 1H), 3.65 (br dd, J=10.8, 3.6 Hz, 1H), 3.62 (br s, 1H), 3.16 (br dd, J=10.4, 3.4 Hz, 1H), 3.08 (br d, J=2.8 Hz, 1H), 1.91 - 1.80 (m, 1H), 1.79 - 1.63 (m, 1H), 1.53 - 1.32 (m, 3H), 0.73 (quin, J=9.9 Hz, 2H), 0.35 (br s, 2H)	2.50, C
715	 峰2，RT = 5.48 min，制备型手性SFC纯化条件：仪器详情：品牌/型号：PIC – 175；制备型SFC条件：柱/尺寸：Chiralpak IG (250 × 30)mm，5u，% CO_2: 75%，%助溶剂：25% 4M 甲醇氨于 MEOH 中，总流速：130.0 g/min，背压：100巴，温度：40°C，UV：240 nm。	2-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)吡咯烷-1-甲酸叔丁酯	672.4	(400MHz, CD_3OD) δ ppm 8.18 - 8.12 (m, 1H), 7.89 - 7.84 (m, 1H), 7.77 - 7.70 (m, 1H), 7.37 - 7.24 (m, 2H), 7.16 - 7.08 (m, 1H), 4.82 - 4.74 (m, 1H), 4.74 - 4.68 (m, 1H), 4.59 - 4.52 (m, 1H), 4.09 - 4.03 (m, 3H), 3.99 - 3.96 (m, 1H), 3.68 - 3.49 (m, 2H), 3.23 - 3.16 (m, 1H), 3.17 - 3.10 (m, 2H), 2.74 - 2.66 (m, 1H), 2.41 - 2.26 (m, 1H), 2.08 - 1.77 (m, 6H), 1.60 - 1.35 (m, 7H), 1.24 - 1.07 (m, 7H), 0.80 - 0.71 (m, 2H), 0.41 - 0.29 (m, 2H)。	1.58, C

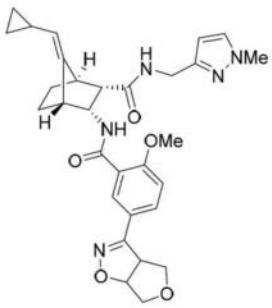
716	 实施例716 (峰2)及实施例654 (峰1)- 仪器: Waters 100 Prep SFC柱: Chiral OD, 30×250 mm, 5微米, 移动相: 15% MeOH / 85% CO_2 (具有0.1% DEA), 流动条件: 100 mL/min, 检测器波长: 220 nm; 分析方法: 仪器: Shimadzu Nexera SFC, 柱 Chiral OD, 4.6 × 100 mm, 5微米, 移动相: 15% MeOH / 85% CO_2 (具有0.1% DEA), 流动条件: 2 mL/min, 检测器波长: 220 nm, 得到手性(峰-1, RT=4.7 min., >95% de)及手性(峰-2, RT=6.7 min., >95% de)。	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	598.2	(500 MHz, DMSO-d6) δ 10.55 - 10.37 (m, 1H), 8.74 (d, J=7.2 Hz, 2H), 8.03 (br d, J=5.8 Hz, 1H), 7.86 - 7.78 (m, 1H), 7.66 - 7.60 (m, 3H), 7.45 (br t, J=9.8 Hz, 1H), 7.34 (d, J=7.9 Hz, 1H), 5.35 (dd, J=9.2, 3.4 Hz, 2H), 4.68 (d, J=9.5 Hz, 2H), 4.49 - 4.35 (m, 3H), 4.10 (d, J=10.6 Hz, 1H), 3.95 (br d, J=9.6 Hz, 1H), 3.74 - 3.59 (m, 2H), 3.15 (br dd, J=10.5, 4.4 Hz, 1H), 1.93 (br d, J=7.5 Hz, 1H), 1.85 - 1.76 (m, 1H), 1.52 (dt, J=8.2, 4.0 Hz, 2H), 1.47 - 1.45 (m, 1H), 1.41 - 1.34 (m, 1H), 0.81 - 0.65 (m, 2H), 0.48 - 0.24 (m, 2H)	2.44, B
717	 由同手性苯甲酸酯中间体(峰1; 100%ee; 手性分析型RT=1.922 min)制备; 制备型手性SFC条件: 仪器: Berger MG II;柱: Chiralpak AD-H, 21 × 250 mm, 5微米; 移动相: 20% MeOH / 80% CO_2; 流动条件: 45 mL/min, 150巴, 40°C; 检测器波长: 220 nm; 注射详情: 0.5 mL ~125mg/mL 于 MeOH:CAN中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.3	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.35 (br t, J=6.7 Hz, 1H), 8.09 - 7.99 (m, 2H), 7.90 - 7.82 (m, 2H), 7.52 - 7.40 (m, 2H), 5.15 (dd, J=8.8, 5.3 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.24 - 4.17 (m, 1H), 3.41 - 3.29 (m, 2H), 3.17 (dd, J=10.7, 4.1 Hz, 1H), 3.12 (t, J=3.7 Hz, 1H), 2.74 (t, J=3.7 Hz, 1H), 2.00 (br dd, J=13.7, 5.9 Hz, 1H), 1.94 - 1.81 (m, 2H), 1.80 - 1.74 (m, 2H), 1.65 - 1.40 (m, 5H), 0.78 - 0.69 (m, 2H), 0.38 - 0.32 (m, 2H)	1.35, A

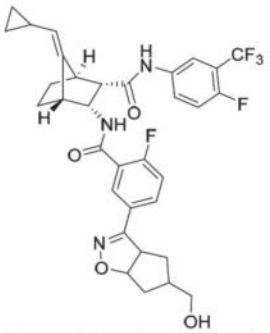
718	 由416-2制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-{[2-(三氟甲基)苯基]甲基}双环[2.2.1]庚烷-2-甲酰胺	610.2	(500 MHz, DMSO-d6) δ 9.89 (d, J=7.0 Hz, 1H), 8.73 (br t, J=5.8 Hz, 1H), 8.18 (br d, J=1.2 Hz, 1H), 7.76 (dd, J=8.7, 2.3 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.54 - 7.46 (m, 1H), 7.46 - 7.36 (m, 2H), 7.18 (d, J=8.7 Hz, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.52 - 4.41 (m, 3H), 4.39 - 4.28 (m, 1H), 4.08 (d, J=10.7 Hz, 1H), 3.92 - 3.87 (m, 1H), 3.86 - 3.79 (m, 3H), 3.78 - 3.72 (m, 1H), 3.66 - 3.61 (m, 1H), 3.09 - 3.01 (m, 2H), 2.67 - 2.60 (m, 1H), 1.86 - 1.77 (m, 1H), 1.75 - 1.64 (m, 1H), 1.55 - 1.42 (m, 1H), 1.39 - 1.27 (m, 2H), 0.75 - 0.63 (m, 2H), 0.41 - 0.22 (m, 2H)。	2.37, C

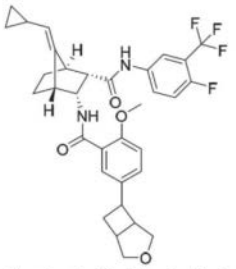
719	 由同手性苯甲酸中间体(峰-1，RT=2.55 min.，>99% ee)制备 –所用仪器：Berger MG II柱：Chiralpak IA，21×250 mm，5微米，移动相：20% IPA / 80% CO_2，流动条件：45 mL/min，150巴，40°C，检测器波长：220 nm；分析方法：仪器：Shimadzu Nexera SFC，柱Chiralpak IA，4.6×100 mm，3微米，移动相：20% IPA / 80% CO_2，流动条件：2 mL/min，150巴，40°C，检测器波长：220 nm，得到手性(峰-1，RT=2.55 min.，>99% ee)及手性(峰-2，RT=6.53 min.，>99% ee)。	(1R,2S,3R,4R,7Z)-3-(3-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	584.1	(500 MHz, DMSO-d6) δ 10.62 - 10.49 (m, 1H), 9.39 (br d, J=6.7 Hz, 1H), 8.15 - 7.97 (m, 2H), 7.91 - 7.74 (m, 3H), 7.61 (t, J=7.8 Hz, 1H), 7.48 (t, J=9.7 Hz, 1H), 5.41 (dd, J=9.3, 3.6 Hz, 1H), 4.87 - 4.67 (m, 1H), 4.59 - 4.51 (m, 1H), 4.46 - 4.37 (m, 1H), 4.13 (d, J=10.6 Hz, 1H), 3.94 (br d, J=9.3 Hz, 1H), 3.78 - 3.64 (m, 2H), 3.48 (br d, J=9.0 Hz, 1H), 3.43 - 3.39 (m, 1H), 3.18 (br dd, J=10.4, 4.0 Hz, 1H), 3.11 (br d, J=3.3 Hz, 1H), 2.76 (br s, 1H), 1.91 - 1.84 (m, 1H), 1.78 - 1.72 (m, 1H), 1.59 - 1.49 (m, 1H), 0.82 - 0.69 (m, 2H), 0.39 - 0.35 (m, 2H)	2.42, B

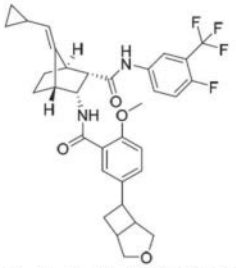
720	 由实施例715制备	(2S,3R)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(吡咯烷-2-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	572.3	(400 MHz, DMSO-d6) δ = 10.54 (s, 1H), 9.91 (d, J = 7.1 Hz, 1H), 9.28 (br d, J = 5.6 Hz, 1H), 8.76 - 8.54 (m, 1H), 8.24 (dd, J = 2.6, 6.7 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H), 7.86 - 7.73 (m, 1H), 7.61 (dd, J = 2.4, 8.6 Hz, 1H), 7.49 (t, J = 9.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 4.69 (d, J = 9.8 Hz, 1H), 4.62 - 4.51 (m, 1H), 4.49 - 4.38 (m, 1H), 4.02 (s, 3H), 3.29 - 3.25 (m, 1H), 3.20 - 3.12 (m, 1H), 3.09 (t, J = 3.9 Hz, 1H), 2.72 (br s, 1H), 2.37 - 2.30 (m, 1H), 2.15 - 1.96 (m, 3H), 1.82 (br d, J = 9.3 Hz, 1H), 1.79 - 1.66 (m, 1H), 1.54 - 1.44 (m, 1H), 1.44 - 1.31 (m, 2H), 0.81 - 0.67 (m, 2H), 0.45 - 0.22 (m, 2H)	2.08, A

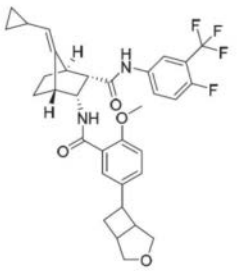
721	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(2-甲基吡啶-3-基)甲基]双环[2.2.1]庚烷-2-甲酰胺	557.3	(500 MHz, DMSO-d6) δ 9.91 (d, J=7.0 Hz, 1H), 8.64 - 8.55 (m, 1H), 8.27 (d, J=4.7 Hz, 1H), 8.17 (d, J=2.2 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.50 (d, J=7.3 Hz, 1H), 7.21 (d, J=8.8 Hz, 1H), 7.08 (dd, J=7.6, 4.9 Hz, 1H), 5.34 (dd, J=9.2, 3.5 Hz, 1H), 4.63 (d, J=9.6 Hz, 1H), 4.49 (br t, J=8.1 Hz, 1H), 4.38 - 4.24 (m, 3H), 4.09 (d, J=10.6 Hz, 1H), 3.96 - 3.86 (m, 4H), 3.80 - 3.74 (m, 1H), 3.69 - 3.61 (m, 1H), 3.07 - 2.97 (m, 2H), 2.62 - 2.56 (m, 1H), 2.43 (s, 3H), 1.87 - 1.78 (m, 1H), 1.76 - 1.69 (m, 1H), 1.52 - 1.42 (m, 1H), 1.40 - 1.27 (m, 2H), 0.77 - 0.65 (m, 2H), 0.38 - 0.25 (m, 2H)。	1.90, B

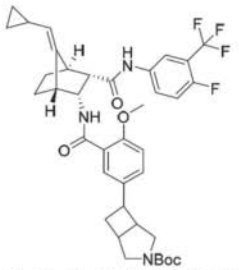
722	 由416-3制备	(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1-甲基-1H-吡唑-3-基)甲基]双环[2.2.1]庚烷-2-甲酰胺	546.0	(500 MHz, DMSO-d6) δ 9.98 (d, J=6.9 Hz, 1H), 8.47 (t, J=5.8 Hz, 1H), 8.15 (d, J=2.2 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.50 (d, J=2.0 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 6.03 (d, J=2.1 Hz, 1H), 5.33 (dd, J=9.2, 3.5 Hz, 1H), 4.61 (d, J=9.6 Hz, 1H), 4.48 (br t, J=8.0 Hz, 1H), 4.32 - 4.26 (m, 1H), 4.25 - 4.16 (m, 2H), 4.09 (d, J=10.8 Hz, 1H), 3.99 (s, 3H), 3.90 (br d, J=9.2 Hz, 1H), 3.77 (dd, J=9.4, 7.0 Hz, 1H), 3.73 (s, 3H), 3.65 (dd, J=10.8, 3.7 Hz, 1H), 3.06 - 3.01 (m, 1H), 2.94 (dd, J=10.7, 4.3 Hz, 1H), 1.91 - 1.80 (m, 1H), 1.78 - 1.67 (m, 1H), 1.52 - 1.41 (m, 1H), 1.39 - 1.25 (m, 2H), 0.78 - 0.63 (m, 2H), 0.38 - 0.22 (m, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	1.78, B

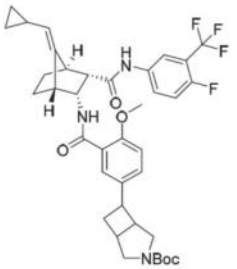
723	 由同手性苯甲酸酯中间体(峰4；100%ee；手性分析型RT=9.061 min)制备；制备型手性SFC条件：仪器：Berger MG II；柱：Chiralpak AD-H，21 × 250 mm，5微米；移动相：20% MeOH / 80% CO_2；流动条件：45 mL/min，150巴，40°C；检测器波长：220 nm；注射详情：0.5 mL ~125mg/mL 于 MeOH:CAN中	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.38 (t, J=6.7 Hz, 1H), 8.08 (dd, J=7.2, 2.3 Hz, 1H), 8.00 (dd, J=6.4, 2.4 Hz, 1H), 7.89 - 7.83 (m, 2H), 7.51 - 7.43 (m, 2H), 5.21 - 5.15 (m, 1H), 4.73 - 4.68 (m, 1H), 4.47 - 4.42 (m, 1H), 4.14 (td, J=9.8, 6.3 Hz, 1H), 3.32 - 3.26 (m, 1H), 3.23 - 3.15 (m, 2H), 3.13 (t, J=3.7 Hz, 1H), 2.77 - 2.73 (m, 1H), 2.24 - 2.09 (m, 3H), 1.86 - 1.80 (m, 1H), 1.79 - 1.73 (m, 1H), 1.68 - 1.61 (m, 1H), 1.53 - 1.41 (m, 4H), 0.79 - 0.70 (m, 2H), 0.38 - 0.32 (m, 2H)	1.35, A

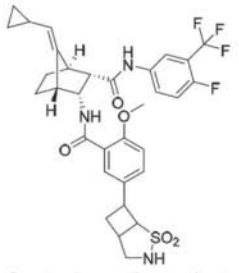
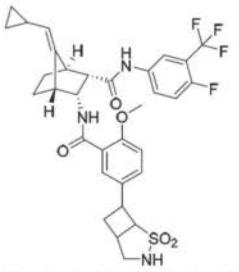
726	 由同手性苯甲酸酯中间体**726-1**制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂双环[3.2.0]庚烷-6-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	599.0	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.81 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.6, 2.6 Hz, 1H), 7.84 (d, J=2.4 Hz, 1H), 7.78 (dt, J=8.5, 3.8 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.41 (dd, J=8.5, 2.4 Hz, 1H), 7.13 (d, J=8.7 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.49 - 4.41 (m, 1H), 3.97 (s, 3H), 3.91 - 3.84 (m, 2H), 3.48 (dd, J=9.2, 5.8 Hz, 1H), 3.39 (dd, J=9.2, 4.7 Hz, 1H), 3.15 (dd, J=10.7, 4.3 Hz, 1H), 3.13 - 3.06 (m, 2H), 3.00 - 2.90 (m, 1H), 2.89 - 2.83 (m, 1H), 2.72 (t, J=3.7 Hz, 1H), 2.16 (dt, J=12.3, 8.1 Hz, 1H), 2.09 - 2.01 (m, 1H), 1.87 (br t, J=8.7 Hz, 1H), 1.81 - 1.74 (m, 1H), 1.55 - 1.47 (m, 1H), 1.46 - 1.34 (m, 2H), 0.82 - 0.70 (m, 2H), 0.36 (dd, J=4.5, 2.5 Hz, 2H)。	2.7, A

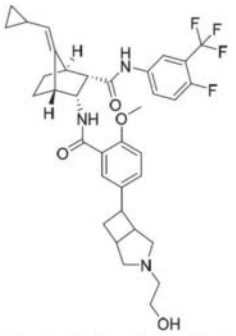
727	 由同手性苯甲酸酯中间体**727-1**制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂双环[3.2.0]庚烷-6-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	599.3	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.81 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.6, 2.6 Hz, 1H), 7.83 (d, J=2.4 Hz, 1H), 7.78 (dt, J=8.5, 3.8 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.41 (dd, J=8.6, 2.4 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.48 - 4.39 (m, 1H), 3.97 (s, 3H), 3.93 - 3.84 (m, 2H), 3.48 (dd, J=9.1, 5.7 Hz, 1H), 3.39 (dd, J=9.2, 4.8 Hz, 1H), 3.15 (dd, J=10.8, 4.3 Hz, 1H), 3.11 - 3.06 (m, 2H), 2.97 - 2.90 (m, 1H), 2.89 - 2.84 (m, 1H), 2.72 (t, J=3.6 Hz, 1H), 2.15 (dt, J=12.3, 8.1 Hz, 1H), 2.09 - 2.00 (m, 1H), 1.87 (br t, J=8.9 Hz, 1H), 1.82 - 1.73 (m, 1H), 1.56 - 1.47 (m, 1H), 1.46 - 1.33 (m, 2H), 0.81 - 0.69 (m, 2H), 0.36 (dd, J=4.5, 2.5 Hz, 2H)	2.7, A

728	 由同手性苯甲酸酯中间体**728-1**制备	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂双环[3.2.0]庚烷-6-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	599.2	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.82 (d, J=7.3 Hz, 1H), 8.23 (dd, J=6.6, 2.4 Hz, 1H), 7.78 (dt, J=8.5, 3.8 Hz, 1H), 7.74 (d, J=2.3 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.30 (dd, J=8.5, 2.3 Hz, 1H), 7.14 (d, J=8.5 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.49 - 4.40 (m, 1H), 3.98 (s, 3H), 3.71 (d, J=9.0 Hz, 1H), 3.69 - 3.62 (m, 1H), 3.41 (d, J=9.9 Hz, 1H), 3.29 (dd, J=9.0, 4.4 Hz, 1H), 3.23 (dd, J=9.7, 6.6 Hz, 1H), 3.20 - 3.12 (m, 2H), 3.09 (t, J=3.9 Hz, 1H), 3.03 - 2.94 (m, 1H), 2.71 (t, J=3.8 Hz, 1H), 2.42 - 2.33 (m, 1H), 1.97 (ddd, J=11.8, 9.8, 6.6 Hz, 1H), 1.91 - 1.84 (m, 1H), 1.83 - 1.75 (m, 1H), 1.57 - 1.47 (m, 1H), 1.46 - 1.33 (m, 2H), 0.81 - 0.68 (m, 2H), 0.40 - 0.32 (m, 2H)。	2.72, A

729	 由同手性苯甲酸酯中间体(峰1；100%ee；手性分析型RT=5.14 min)制备；Chiralpak ID，4.6×100 mm，3微米，移动相：10%异丙醇/90% CO_2，流动条件：2.0 mL/min，150巴，40°C	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{3-氧杂双环[3.2.0]庚烷-6-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	599.0	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.83 (d, J=7.3 Hz, 1H), 8.23 (dd, J=6.5, 2.5 Hz, 1H), 7.78 (dt, J=8.8, 3.5 Hz, 1H), 7.74 (d, J=2.3 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.30 (dd, J=8.5, 2.3 Hz, 1H), 7.14 (d, J=8.5 Hz, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.49 - 4.41 (m, 1H), 3.98 (s, 3H), 3.72 (d, J=9.0 Hz, 1H), 3.66 (q, J=9.6 Hz, 1H), 3.41 (d, J=9.8 Hz, 1H), 3.29 (dd, J=8.9, 4.3 Hz, 1H), 3.23 (dd, J=9.6, 6.6 Hz, 1H), 3.19 - 3.12 (m, 2H), 3.08 (t, J=3.7 Hz, 1H), 3.02 - 2.94 (m, 1H), 2.71 (t, J=3.7 Hz, 1H), 2.38 (dddd, J=12.0, 10.1, 8.3, 2.1 Hz, 1H), 1.97 (ddd, J=11.7, 9.6, 6.8 Hz, 1H), 1.87 (br t, J=9.0 Hz, 1H), 1.82 - 1.77 (m, 1H), 1.55 - 1.46 (m, 1H), 1.45 - 1.34 (m, 2H), 0.82 - 0.67 (m, 2H), 0.36 (dd, J=4.6, 2.3 Hz, 2H)。	2.73, A

730	 由同手性苯甲酸酯中间体(峰2；100%ee；手性分析型RT=7.08 min)制备；Chiralpak ID，4.6×100 mm，3微米，移动相：10%异丙醇/90% CO_2，流动条件：2.0 mL/min，150巴，40°C	6-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3-氮杂双环[3.2.0]庚烷-3-甲酸叔丁酯	698.5	(500 MHz, $CDCl_3$-d) δ 9.41 (br d, J=7.3 Hz, 1H), 8.09 (br s, 1H), 7.98 (br s, 1H), 7.90 - 7.81 (m, 1H), 7.65 - 7.55 (m, 1H), 7.35 - 7.30 (m, 1H), 7.12 - 7.04 (m, 1H), 6.92 (br d, J=8.4 Hz, 1H), 4.89 - 4.80 (m, 1H), 4.65 (d, J=9.5 Hz, 1H), 3.99 (s, 3H), 3.80 - 3.60 (m, 2H), 3.47 (br d, J=7.6 Hz, 1H), 3.33 - 3.24 (m, 2H), 3.20 (t, J=3.9 Hz, 1H), 3.11 (dd, J=10.6, 3.1 Hz, 1H), 2.95 (br s, 2H), 2.74 (t, J=3.7 Hz, 1H), 2.39 - 2.28 (m, 1H), 2.24 - 2.15 (m, 2H), 1.93 - 1.84 (m, 1H), 1.57 - 1.45 (m, 10H), 0.80 - 0.73 (m, 2H), 0.39 - 0.32 (m, 2H)	2.96, A

731	 由同手性苯甲酸酯中间体(峰1；100%ee；手性分析型RT=3.13 min)制备；Chiral AD，4.6×100 mm，5微米，移动相：75% CO_2/25% IPA(具有0.1%DEA)，流动条件：2 mL/min	6-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3-氮杂双环[3.2.0]庚烷-3-甲酸叔丁酯	698.5	(500 MHz, $CDCl_3$-d) δ 9.41 (br d, J=8.1 Hz, 1H), 8.09 (br s, 1H), 7.98 (br s, 1H), 7.89 - 7.83 (m, 1H), 7.63 - 7.56 (m, 1H), 7.34 - 7.29 (m, 1H), 7.12 - 7.04 (m, 1H), 6.92 (d, J=8.4 Hz, 1H), 4.89 - 4.80 (m, 1H), 4.65 (d, J=9.6 Hz, 1H), 3.99 (s, 3H), 3.79 - 3.62 (m, 2H), 3.52 - 3.43 (m, 1H), 3.35 - 3.25 (m, 2H), 3.20 (t, J=3.9 Hz, 1H), 3.11 (dd, J=10.7, 3.4 Hz, 1H), 2.95 (br s, 2H), 2.74 (t, J=3.8 Hz, 1H), 2.36 - 2.28 (m, 1H), 2.23 - 2.14 (m, 2H), 1.91 - 1.84 (m, 1H), 1.56 - 1.44 (m, 10H), 0.79 - 0.73 (m, 2H), 0.40 - 0.32 (m, 2H)	2.96, A
732	 由同手性苯甲酸酯中间体(峰2；100%ee；手性分析型RT=4.10 min)制备；Chiral AD，4.6×100 mm，5微米，移动相：75% CO_2/25% IPA(具有0.1%DEA)，流动条件：2 mL/min	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{2,2-二氧代-2λ⁶-硫杂-3-氮杂双环[3.2.0]庚烷-7-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	648.4	1H NMR (500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.26 (br d, J=4.3 Hz, 1H), 7.90 - 7.74 (m, 2H), 7.57 - 7.39 (m, 3H), 7.21 (br d, J=8.2 Hz, 1H), 4.72 (br d, J=9.8 Hz, 1H), 4.54 - 4.39 (m, 1H), 4.02 (s, 3H), 3.87 - 3.76 (m, 1H), 3.72 (br t, J=6.6 Hz, 1H), 3.26 - 3.14 (m, 2H), 3.12 (br s, 1H), 2.74 (br s, 1H), 2.49 - 2.40 (m, 1H), 2.38 - 2.28 (m, 1H), 1.93 - 1.72 (m, 2H), 1.60 - 1.50 (m, 1H), 1.49 - 1.35 (m, 2H), 0.83 - 0.65 (m, 2H), 0.38 (br s, 2H)	2.47, A

733	 由同手性苯甲酸酯中间体(峰1；100%ee；手性分析型RT=4.32 min)制备；SFC(Chiral IA，4.6×100 mm)，3微米，移动相：15%异丙醇/85% CO_2，流动条件：2.0 mL/min，150巴，40℃	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{2,2-二氧代-2λ⁶-硫杂-3-氮杂双环[3.2.0]庚烷-7-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	648.4	1H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.86 (d, J=7.2 Hz, 1H), 8.22 (dd, J=6.7, 2.4 Hz, 1H), 7.82 (d, J=2.3 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.54 - 7.41 (m, 3H), 7.18 (d, J=8.6 Hz, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.52 - 4.37 (m, 1H), 3.99 (s, 3H), 3.83 - 3.74 (m, 1H), 3.70 (t, J=6.8 Hz, 1H), 3.23 - 3.12 (m, 2H), 3.09 (t, J=3.6 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.45 - 2.37 (m, 1H), 2.36 - 2.26 (m, 1H), 1.89 - 1.82 (m, 1H), 1.81 - 1.72 (m, 1H), 1.58 - 1.46 (m, 1H), 1.45 - 1.32 (m, 2H), 0.85 - 0.64 (m, 2H), 0.41 - 0.28 (m, 2H)	2.47, A

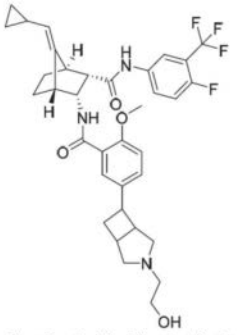
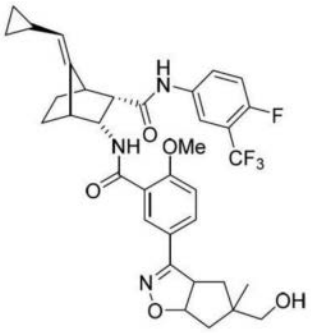
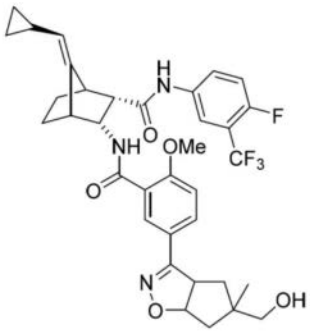
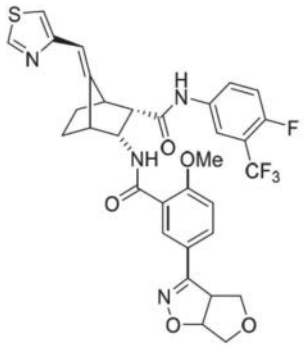
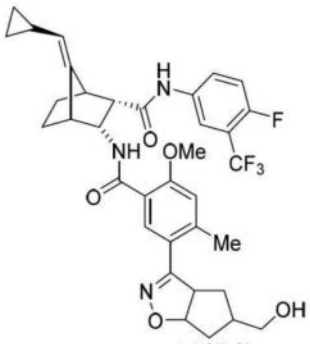
734	 由同手性苯甲酸酯中间体(峰2；100%ee；手性分析型RT=5.90 min)制备；SFC(Chiral IA，4.6×100 mm)，3微米，移动相：15%异丙醇/85% CO_2，流动条件：2.0 mL/min，150巴，40℃	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[3-(3-羟基丙基)-4-氧代-3-氮杂双环[3.2.0]庚烷-6-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	670.2	1H NMR (500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.86 (br d, J=7.3 Hz, 1H), 8.30 - 8.19 (m, 1H), 7.89 (s, 1H), 7.83 - 7.75 (m, 1H), 7.54 - 7.40 (m, 2H), 7.17 (d, J=8.5 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.54 - 4.42 (m, 1H), 4.00 (s, 3H), 3.90 (br s, 1H), 3.69 (ddd, J=14.3, 9.9, 8.1 Hz, 1H), 3.30 - 3.22 (m, 1H), 3.21 - 3.12 (m, 2H), 3.11 (br s, 1H), 3.05 - 2.95 (m, 1H), 2.93 - 2.85 (m, 1H), 2.73 (br s, 1H), 2.43 - 2.29 (m, 2H), 1.94 - 1.85 (m, 1H), 1.80 (br dd, J=15.7, 6.0 Hz, 1H), 1.57 - 1.33 (m, 3H), 1.08 (br d, J=6.1 Hz, 3H), 0.83 - 0.68 (m, 2H), 0.36 (br s, 2H)	2.46, A

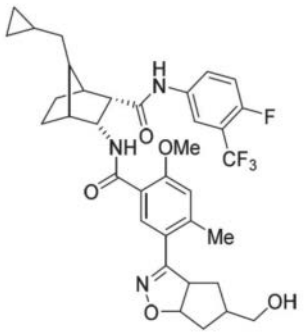
表4

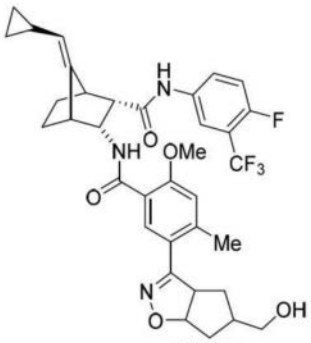
实施例编号	结构	名称	MS (ESI) (M+H)	1H NMR	LC RT Meth. (min)
735	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.92 (d, J = 7.3 Hz, 1H), 8.27 - 8.17 (m, 2H), 7.79 (dd, J = 2.5, 8.8 Hz, 2H), 7.49 (t, J = 9.9 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 5.25 - 5.14 (m, 1H), 4.69 (d, J = 9.5 Hz, 1H), 4.63 - 4.54 (m, 1H), 4.49 - 4.38 (m, 1H), 4.30 - 4.17 (m, 1H), 4.04 (s, 3H), 3.20 - 3.07 (m, 4H), 2.72 (br d, J = 3.0 Hz, 1H), 1.87 - 1.73 (m, 5H), 1.66 (dd, J = 6.5, 13.0 Hz, 1H), 1.54 - 1.45 (m, 1H), 1.44 - 1.37 (m, 2H), 0.95 (s, 3H), 0.80 - 0.68 (m, 2H), 0.41 - 0.28 (m, 2H)	1.96, A

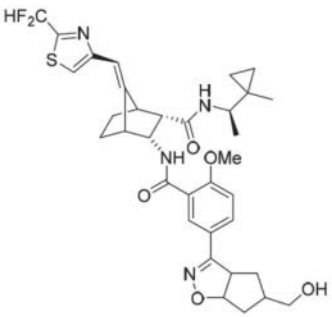
736	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.92 (d, J = 7.3 Hz, 1H), 8.27 - 8.17 (m, 2H), 7.79 (dd, J = 2.5, 8.8 Hz, 2H), 7.49 (t, J = 9.9 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 5.25 - 5.14 (m, 1H), 4.69 (d, J = 9.5 Hz, 1H), 4.63 - 4.54 (m, 1H), 4.49 - 4.38 (m, 1H), 4.30 - 4.17 (m, 1H), 4.04 (s, 3H), 3.20 - 3.07 (m,4H), 2.72 (br d, J = 3.0 Hz, 1H), 1.87 - 1.73 (m, 5H), 1.66 (dd, J = 6.5, 13.0 Hz, 1H), 1.54 - 1.45 (m, 1H), 1.44 - 1.37 (m, 2H), 0.95 (s, 3H), 0.80 - 0.68 (m,2H), 0.41 - 0.28 (m, 2H)	2.38, A

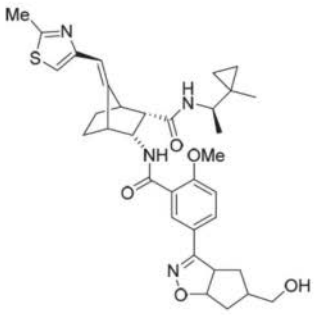
737		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(1,3-噻唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	657.2	(400 MHz, DMSO-d6) δ = 10.60 (s, 1H), 9.90 (d, J = 7.1 Hz, 1H), 9.13 (d, J = 2.0 Hz, 1H), 8.25 (dd, J = 2.6, 6.5 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.87 - 7.74 (m, 2H), 7.58 (d, J = 2.2 Hz, 1H), 7.51 (t, J = 9.7 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 5.35 (dd, J = 3.7, 9.3 Hz, 1H), 4.56 - 4.47 (m, 2H), 4.10 (d, J = 10.8 Hz, 1H), 4.06 (s, 3H), 3.94 (br s, 1H), 3.90 (d, J = 8.3 Hz, 1H), 3.78 (dd, J = 6.8, 9.3 Hz, 1H), 3.66 (dd, J = 3.7, 10.8 Hz, 1H), 3.30 - 3.25 (m, 1H), 2.97 - 2.89 (m, 1H), 1.97 (br t, J = 8.8 Hz, 1H), 1.89 - 1.81 (m, 1H), 1.51 (br d, J = 6.6 Hz, 2H)	2.17.A

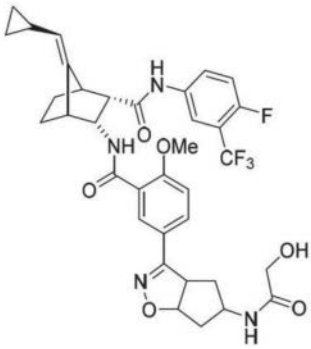
738	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基-4-甲基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(400 MHz, DMSO-d6) δ = 10.50 (s, 1H), 9.86 (d, J = 7.3 Hz, 1H), 8.23 (dd, J = 2.6, 6.4 Hz, 1H), 8.01 (s, 1H), 7.81 - 7.70 (m, 1H), 7.48 (t,J = 9.6 Hz, 1H), 7.15 (s, 1H), 5.06 (dd, J = 5.5, 9.0 Hz, 1H), 4.69 (d, J = 9.8 Hz, 1H), 4.51 - 4.37 (m, 2H), 4.23 (t, J = 9.5 Hz, 1H), 4.04 (s, 3H),3.39 (s, 1H), 3.15 (dd, J = 4.3, 10.8 Hz, 1H), 3.11 - 3.07 (m, 1H), 2.73 - 2.69 (m, 1H), 2.01 - 1.75 (m, 4H), 1.68 - 1.46 (m, 4H), 1.44 - 1.34 (m, 2H),0.73 (br t, J = 8.9 Hz, 2H), 0.35 (dd, J = 1.5, 4.8 Hz, 2H)	2.49, A

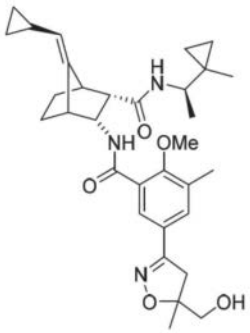
739		(1S,2S,3R,4R)-7-(环丙基甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基-4-甲基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.3	(400 MHz, DMSO-d6) δ = 10.48 (s, 1H), 9.76 (d, J = 7.0 Hz, 1H), 8.22 (dd, J = 2.4, 6.4 Hz, 1H), 8.00 (s, 1H), 7.84 - 7.74 (m, 1H), 7.48 (t,J = 9.8 Hz, 1H), 7.14 (s, 1H), 5.05 (dd, J = 5.5, 9.0 Hz, 1H), 4.68 - 4.56 (m, 1H), 4.47 (t, J = 5.3 Hz, 1H), 4.23 (t, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.39- 3.33 (m, 2H), 3.22 (dd, J = 3.8, 10.8 Hz, 1H), 2.48 (s, 3H), 2.38 (br d, J = 13.0 Hz, 2H), 2.03 - 1.83 (m, 3H), 1.80 - 1.71 (m, 1H), 1.67 - 1.47 (m,5H), 1.43 - 1.27 (m, 3H), 0.86 - 0.75 (m, 1H), 0.53 - 0.41 (m, 2H), 0.23 - 0.10 (m, 2H)	2.44, A

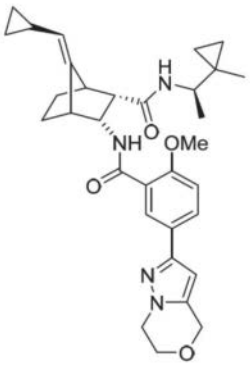
740	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基-4-甲基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(400 MHz, DMSO-d6) δ = 10.50 (s, 1H), 9.85 (s, 1H), 8.23 (br d, J = 6.8 Hz, 1H), 8.04 (s, 1H), 7.82 - 7.72 (m, 1H), 7.53 - 7.42 (m, 1H),7.16 (s, 1H), 5.13 - 5.02 (m, 1H), 4.69 (d, J = 10.0 Hz, 1H), 4.50 - 4.37 (m, 2H), 4.19 - 4.13 (m, 1H), 4.04 (s, 3H), 3.24 - 3.19 (m, 1H), 3.18 - 3.12(m, 1H), 3.12 - 3.05 (m, 1H), 2.71 (br d, J = 3.0 Hz, 1H), 2.17 - 2.04 (m, 2H), 1.86 - 1.80 (m, 1H), 1.80 - 1.71 (m, 1H), 1.66 - 1.58 (m, 1H), 1.54 -1.36 (m, 4H), 0.79 - 0.65 (m, 2H), 0.35 (br d, J = 2.8 Hz, 2H)	2.47, A

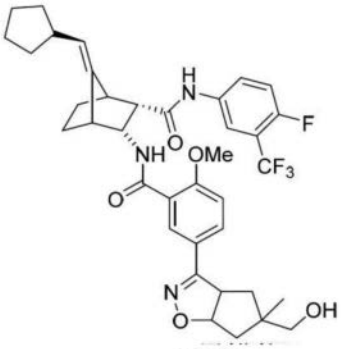
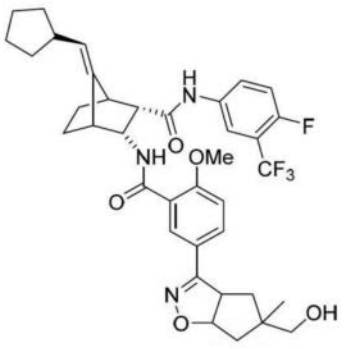
741		(1R,2S,3R,4R,7Z)-7-{[2-(二氟甲基)-1,3-噻唑-4-基]亚甲基}-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	655.3	(400 MHz, DMSO-d6) δ ppm 10.08 (d, J=6.75 Hz, 1 H) 8.16 (d, J=2.50 Hz, 1 H) 8.02 (d, J=8.51 Hz, 1 H) 7.76 - 7.83 (m, 2 H) 7.20 - 7.51 (m, 2 H) 6.39 (s, 1 H) 5.12 (dd, J=8.88, 5.13 Hz, 1 H) 4.48 (t, J=5.25 Hz, 1 H) 4.37 (ddd, J=10.57, 4.25 Hz, 1 H) 4.16 - 4.26 (m, 1 H) 4.01 (s, 3 H) 3.74 (br s, 1 H) 3.46 - 3.53 (m, 1 H) 3.35 - 3.41 (m, 2 H) 3.08 (dd, J=10.88, 4.38 Hz, 1 H) 2.76 (br s, 1 H) 1.74 - 2.04 (m, 5 H) 1.61 - 1.71 (m, 1 H) 1.52 - 1.59 (m, 1 H) 1.46 (br d, J=5.25 Hz, 2 H) 1.04 (d, J=7.00 Hz, 3 H) 1.01 (s, 3 H) 0.51 - 0.59 (m, 1 H) 0.32 - 0.40 (m, 1 H) 0.16 - 0.25 (m, 2 H)	2.08, A

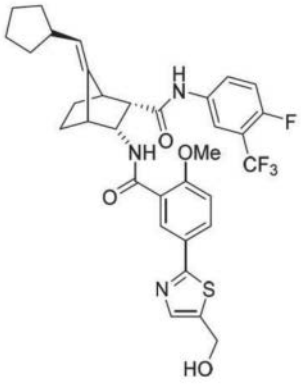
742		(1R,2S,3R,4R,7Z)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(2-甲基-1,3-噻唑-4-基)亚甲基]-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	619.2	(400 MHz, DMSO-d6) δ = 10.06 (d, J = 6.8 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.80 (dd, J = 2.3, 8.8 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.26 (s, 1H), 5.12 (dd, J = 5.3, 8.8 Hz, 1H), 4.48 (t, J = 5.3 Hz, 1H), 4.35 (ddd, J = 4.1, 6.6, 10.8 Hz, 1H), 4.21 (t, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.79 (br s, 1H), 3.49 (dd, J = 7.0, 8.3 Hz, 1H), 3.42 - 3.35 (m, 2H), 3.05 (dd, J = 4.3, 11.0 Hz, 1H), 2.71 (br s, 1H), 2.67 (s, 3H), 2.04 - 1.86 (m, 3H), 1.85 - 1.74 (m, 2H), 1.72 - 1.53 (m, 2H), 1.43 (br d, J = 6.3 Hz, 2H), 1.04 (d, J = 6.8 Hz, 3H), 1.01 (s, 3H), 0.60 - 0.52 (m, 1H), 0.40 - 0.34 (m, 1H), 0.26 - 0.15 (m, 2H)	1.98, A

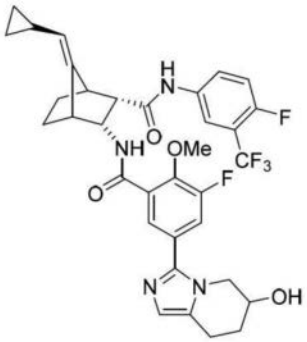
743		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(2-羟基乙酰胺基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	685.3	(400 MHz, DMSO-d6) δ = 10.51 (s, 1H), 9.91 (d, J = 7.0 Hz, 1H), 8.27 - 8.18 (m, 2H), 7.88 - 7.74 (m, 3H), 7.48 (t, J = 9.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 5.42 (br s, 1H), 5.11 (dd, J = 5.5, 9.0 Hz, 1H), 4.69 (d, J = 9.8 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.25 (br t, J = 9.1 Hz, 1H), 4.04 (s, 4H), 3.75 (s, 2H), 3.16 (dd, J = 3.9, 10.6 Hz, 1H), 3.13 - 3.05 (m, 1H), 2.72 (br s, 1H), 2.13 - 2.07 (m, 1H), 2.00 - 1.74 (m, 5H), 1.56 - 1.34 (m, 3H), 0.80 - 0.62 (m, 2H), 0.35 (br d, J = 2.8 Hz, 2H)	2.27, A

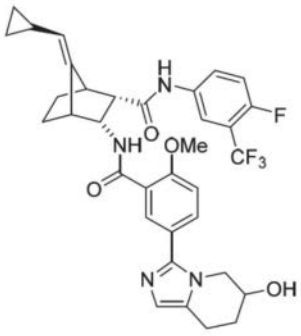
744		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-5-甲基-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	554.3	(400 MHz, DMSO-d6) δ = 9.98 (d, J = 6.9 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.67 (dd, J = 2.2, 12.4 Hz, 1H), 5.09 (t, J = 5.9Hz, 1H), 4.65 (d, J = 9.5 Hz, 1H), 4.35 - 4.26 (m, 1H), 4.05 (d, J = 2.5 Hz, 3H), 3.49 - 3.38 (m, 3H), 3.11 - 3.00 (m, 2H), 2.96 (dd, J = 4.4, 11.0 Hz,1H), 2.55 (br s, 1H), 1.88 - 1.69 (m, 2H), 1.51 - 1.44 (m, 1H), 1.42 - 1.34 (m, 2H), 1.32 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 0.78 - 0.61(m, 2H), 0.57 - 0.48 (m, 1H), 0.33 (br d, J = 3.5 Hz, 3H), 0.21 - 0.11 (m, 2H)	2.25, B

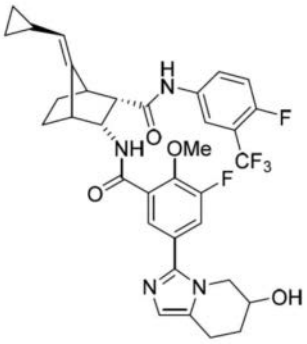
745		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(2-甲氧基-5-{4H,6H,7H-吡唑并[3,2-c][1,4]噁嗪-3-基}苯甲酰胺基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	545.3	(400 MHz, DMSO-d6) δ = 10.02 (d, J = 6.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 2.5 Hz, 1H), 7.78 (s, 1H), 7.48 (dd, J = 2.4, 8.6Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 4.98 (s, 2H), 4.64 (d, J = 9.5 Hz, 1H), 4.34 - 4.23 (m, 1H), 4.18 - 4.14 (m, 2H), 4.14 - 4.04 (m, 2H), 3.96 (s, 3H),3.47 (dd, J = 7.0, 8.4 Hz, 1H), 3.08 - 3.01 (m, 1H), 2.95 (dd, J = 4.4, 11.0 Hz, 1H), 1.93 - 1.84 (m, 1H), 1.81 - 1.72 (m, 1H), 1.54 - 1.44 (m, 1H),1.40 - 1.29 (m, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H), 0.77 - 0.63 (m, 2H), 0.58 - 0.50 (m, 1H), 0.41 - 0.29 (m, 3H), 0.23 - 0.11 (m, 2H)	2.26, B

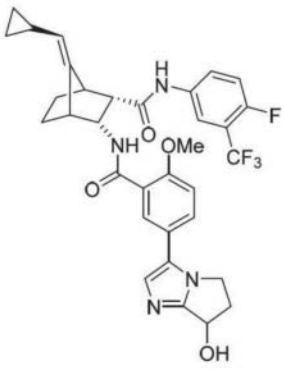
748	 异构体1	(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	684.3	(400 MHz, DMSO-d6) δ = 10.54 (br s, 1H), 9.88 (d, J = 7.1 Hz, 1H), 8.27 - 8.18 (m, 2H), 7.85 - 7.73 (m, 2H), 7.49 (t, J = 9.8 Hz, 1H),7.27 (d, J = 8.8 Hz, 1H), 5.22 - 5.10 (m, 2H), 4.76 (br s, 1H), 4.43 - 4.36 (m, 1H), 4.17 (dt, J = 5.3, 9.5 Hz, 1H), 4.04 (s, 3H), 3.19 - 3.12 (m, 3H),3.00 (br s, 1H), 2.72 (br s, 1H), 2.59 (br d, J = 8.6 Hz, 1H), 2.20 - 2.04 (m, 2H), 1.88 - 1.73 (m, 4H), 1.69 - 1.50 (m, 6H), 1.44 - 1.16 (m, 6H), 0.91(s, 3H)	2.58, B
749	 异构体2	(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	684.2	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.89 (d, J = 7.0 Hz, 1H), 8.26 - 8.17 (m, 2H), 7.86 - 7.74 (m, 2H), 7.49 (t, J = 9.8 Hz, 1H), 7.26(d, J = 8.9 Hz, 1H), 5.27 - 5.13 (m, 2H), 4.59 (br t, J = 5.3 Hz, 1H), 4.39 (ddd, J = 3.8, 6.6, 10.3 Hz, 1H), 4.28 - 4.21 (m, 1H), 4.04 (s, 3H), 3.19 -3.13 (m, 3H), 3.01 (br s, 1H), 2.72 (br s, 1H), 2.63 - 2.55 (m, 2H), 1.87 - 1.72 (m, 8H), 1.69 - 1.49 (m, 7H), 1.43 - 1.13 (m, 5H), 0.96 (s, 3H)	2.58, B

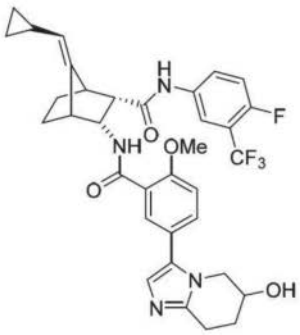
750		(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-1,3-噻唑-2-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.87 (d, J = 7.1 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 2.4, 6.4 Hz, 1H), 8.02 (dd, J =2.4, 8.6 Hz, 1H), 7.83 (s, 1H), 7.82 - 7.71 (m, 1H), 7.49 (t, J = 9.7 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.00 (s, 1H), 5.20 (d, J = 9.0 Hz, 1H), 4.45 -4.32 (m, 1H), 4.03 (s, 3H), 3.16 (dd, J = 3.8, 10.3 Hz, 1H), 3.02 (br s, 1H), 2.72 (br s, 1H), 2.65 - 2.55 (m, 1H), 1.90 - 1.73 (m, 4H), 1.70 - 1.50 (m,10H)	2.54, B

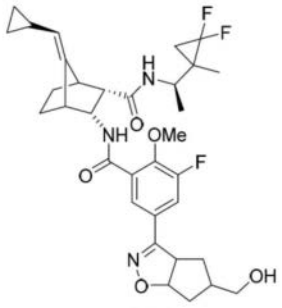
751	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(3-氟-5-{6-羟基-5H,6H,7H,8H-咪唑并[1,2-a]吡啶-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	657.2	(500 MHz, DMSO-d6) δ 10.60 - 10.50 (m, 1H), 9.76 - 9.66 (m, 1H), 8.15 - 8.07 (m, 1H), 7.85 - 7.79 (m, 1H), 7.76 - 7.67 (m, 1H), 7.57 (br d, J=13.1 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.03 (d, J=3.4 Hz, 1H), 5.25 - 5.15 (m, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.52 - 4.42 (m, 1H), 4.21 - 4.14 (m, 1H), 4.09 (br d, J=4.3 Hz, 1H), 4.06 (d, J=1.5 Hz, 3H), 3.81 - 3.72 (m, 1H), 3.20 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.95 - 2.85 (m, 1H), 2.82 - 2.76 (m, 1H), 2.76 - 2.71 (m, 1H), 1.92 (br d, J=7.6 Hz, 2H), 1.87 - 1.78 (m, 2H), 1.55 - 1.38 (m, 3H), 0.80 - 0.69 (m, 2H), 0.36 (br d, J=1.2 Hz, 2H)	2.08, C

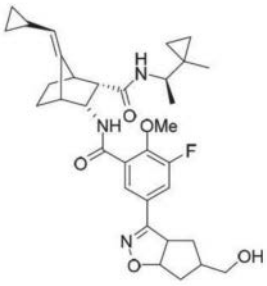
752		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{6-羟基-5H,6H,7H,8H-咪唑并[1,2-a]吡啶-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	639.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (br d, J=7.3 Hz, 1H), 8.24 (br d, J=4.9 Hz, 1H), 7.98 (d, J=2.1 Hz, 1H), 7.83 - 7.76 (m, 1H), 7.57 (dd, J=8.5, 2.1 Hz, 1H), 7.49 (t, J=9.9 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 6.96 (s, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.46 (br s, 1H), 4.15 (br s, 1H), 4.04 (s, 3H), 4.00 (br dd, J=12.2, 3.4 Hz, 1H), 3.73 (br dd, J=12.4, 4.7 Hz, 1H), 3.17 (br dd, J=10.5, 3.8 Hz, 1H), 3.11 (br s, 1H), 2.96 - 2.86 (m, 1H), 2.83 - 2.76 (m, 1H), 2.73 (br s, 1H), 2.01 - 1.90 (m, 2H), 1.89 - 1.75 (m, 2H), 1.59 - 1.48 (m, 1H), 1.47 - 1.34 (m, 2H), 0.80 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.06, C

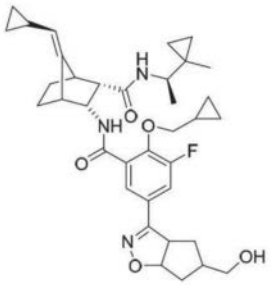
753	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(3-氟-5-{6-羟基-5H,6H,7H,8H-咪唑并[1,2-a]吡啶-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	657.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.74 (br d, J=7.3 Hz, 1H), 8.11 (br d, J=4.9 Hz, 1H), 7.89 - 7.79 (m, 1H), 7.77 (s, 1H), 7.65 (br d, J=11.3 Hz, 1H), 7.48 (br t, J=9.9 Hz, 1H), 7.42 (s, 1H), 4.70 (br d, J=9.8 Hz, 1H), 4.53 - 4.41 (m, 1H), 4.23 (br s, 1H), 4.18 - 4.11 (m, 1H), 4.09 (s, 3H), 3.88 - 3.77 (m, 1H), 3.17 (br dd, J=10.7, 4.3 Hz, 1H), 3.11 (br d, J=3.4 Hz, 1H), 3.05 - 2.88 (m, 2H), 2.74 (br s, 1H), 1.97 (br d, J=4.0 Hz, 2H), 1.88 - 1.76 (m, 2H), 1.58 - 1.35 (m, 3H), 0.74 (quin, J=9.5 Hz, 2H), 0.36 (br d, J=1.8 Hz, 2H)	2.13, C

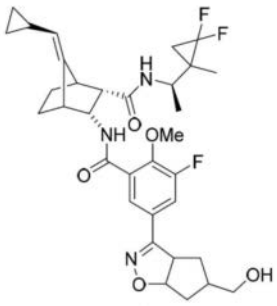
754		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{7-羟基-5H,6H,7H-吡咯并[1,2-a]咪唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	625.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.92 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.4, 2.3 Hz, 1H), 8.11 (d, J=2.4 Hz, 1H), 7.87 - 7.75 (m, 1H), 7.70 (dd, J=8.6, 2.4 Hz, 1H), 7.48 (t, J=9.6 Hz, 1H), 7.30 - 7.18 (m, 2H), 5.61 (d, J=6.0 Hz, 1H), 4.90 (td, J=6.4, 3.2 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.31 - 4.20 (m, 1H), 4.13 - 3.98 (m, 4H), 3.16 (dd, J=10.6, 4.0 Hz, 1H), 3.11 (br s, 1H), 2.85 (dq, J=14.1, 6.9 Hz, 1H), 2.73 (br s, 1H), 2.39 - 2.28 (m, 1H), 1.92 - 1.75 (m, 2H), 1.58 - 1.35 (m, 3H), 0.81 - 0.69 (m, 2H), 0.43 - 0.29 (m, 2H)	2.10, C

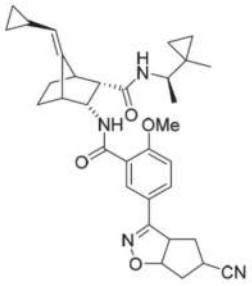
755		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{6-羟基-5H,6H,7H,8H-咪唑并[1,2-a]吡啶-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	639.1	(500 MHz, DMSO-d6) δ 10.58 (br s, 1H), 9.94 (br d, J=7.0 Hz, 1H), 8.29 - 8.21 (m, 1H), 7.99 (d, J=1.8 Hz, 1H), 7.84 - 7.77 (m, 1H), 7.58 (dd, J=8.2, 1.8 Hz, 1H), 7.50 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 6.94 (s, 1H), 4.71 (d, J=9.8 Hz, 1H), 4.52 - 4.41 (m, 1H), 4.17 (br s, 1H), 4.05 (s, 3H), 4.02 (br d, J=3.1 Hz, 1H), 3.71 (br dd, J=12.1, 4.7 Hz, 1H), 3.23 - 3.14 (m, 1H), 3.12 (br d, J=3.7 Hz, 1H), 2.96 - 2.86 (m, 1H), 2.82 - 2.75 (m, 1H), 2.74 (br s, 1H), 2.00 - 1.89 (m, 2H), 1.89 - 1.84 (m, 1H), 1.83 (s, 1H), 1.82 - 1.77 (m, 1H), 1.56 - 1.48 (m, 1H), 1.47 - 1.37 (m, 2H), 0.80 - 0.69 (m, 2H), 0.36 (br s, 2H)。	2.06, C

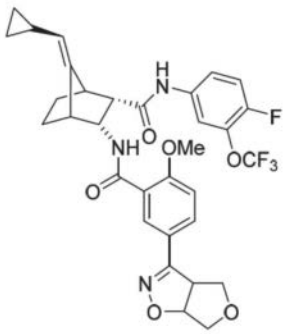
756	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[(1R)-1-(2,2-二氟-1-甲基环丙基)乙基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.3	(500 MHz, DMSO-d6) δ 9.98 (br d, J=6.6 Hz, 1H), 8.09 (br d, J=8.5 Hz, 1H), 7.90 (br s, 1H), 7.68 (br dd, J=12.6, 1.8 Hz, 1H), 5.15 (br dd, J=8.2, 5.3 Hz, 1H), 4.63 (br d, J=9.6 Hz, 1H), 4.31 - 4.22 (m, 1H), 4.19 - 4.15 (m, 1H), 4.07 - 3.99 (m, 3H), 3.84 - 3.72 (m, 1H), 3.42 - 3.29 (m, 2H), 3.04 (br s, 1H), 2.98 - 2.90 (m, 1H), 1.98 (br dd, J=13.9, 5.4 Hz, 1H), 1.92 - 1.82 (m, 1H), 1.80 - 1.69 (m, 3H), 1.68 - 1.59 (m, 1H), 1.59 - 1.50 (m, 1H), 1.49 - 1.41 (m, 1H), 1.40 - 1.23 (m, 3H), 1.18 - 1.01 (m, 7H), 0.75 - 0.61 (m, 2H), 0.30 (br s, 2H)	2.25, C

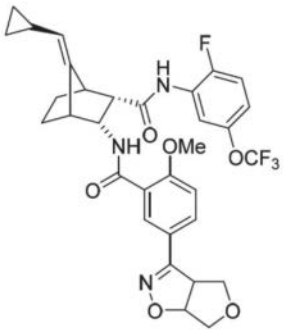
757		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	580.3	(500 MHz, DMSO-d6) δ 9.99 (br d, J=6.7 Hz, 1H), 7.98 (br d, J=8.5 Hz, 1H), 7.90 (s, 1H), 7.70 (dd, J=12.4, 1.7 Hz, 1H), 5.16 (dd, J=8.9, 5.2 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.32 - 4.25 (m, 1H), 4.20 (br t, J=9.2 Hz, 1H), 4.04 (d, J=2.4 Hz, 3H), 3.49 - 3.41 (m, 1H), 3.06 (br s, 1H), 2.97 - 2.89 (m, 1H), 1.99 (br dd, J=13.7, 5.5 Hz, 1H), 1.94 - 1.73 (m, 4H), 1.69 - 1.60 (m, 1H), 1.59 - 1.50 (m, 1H), 1.46 (ddt, J=12.6, 8.5, 4.4 Hz, 1H), 1.41 - 1.29 (m, 2H), 1.01 (d, J=7.0 Hz, 3H), 0.97 (s, 3H), 0.77 - 0.65 (m, 2H), 0.55 - 0.47 (m, 1H), 0.32 (br d, J=3.4 Hz, 3H), 0.21 - 0.10 (m, 2H)	2.39, C

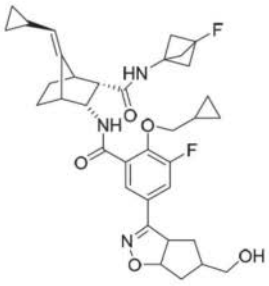
758		(1R,2S,3R,4R,7Z)-3-[2-(环丙基甲氧基)-3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-7-(环丙基亚甲基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	620.3	(500 MHz, DMSO-d6) δ 9.94 - 9.82 (m, 1H), 7.99 (br d, J=8.5 Hz, 1H), 7.84 (s, 1H), 7.67 (br dd, J=12.5, 1.8 Hz, 1H), 5.15 (br dd, J=8.4, 5.0 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.52 (br t, J=5.0 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.20 (br t, J=9.0 Hz, 1H), 4.14 - 4.02 (m, 2H), 3.06 (br s, 1H), 2.94 (br dd, J=10.8, 4.1 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.95 - 1.83 (m, 1H), 1.83 - 1.71 (m, 3H), 1.70 - 1.31 (m, 6H), 1.26 - 1.15 (m, 1H), 0.99 (d, J=7.0 Hz, 3H), 0.95 (s, 3H), 0.77 - 0.63 (m, 2H), 0.57 - 0.44 (m, 3H), 0.33 - 0.21 (m, 4H), 0.20 - 0.07 (m, 2H)	2.02, B

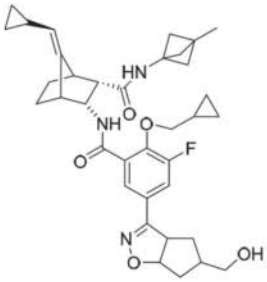
759	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[(1R)-1-(2,2-二氟-1-甲基环丙基)乙基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	616.2	(500 MHz, DMSO-d6) δ 9.94 (d, J=6.8 Hz, 1H), 8.33 (br d, J=8.6 Hz, 1H), 7.91 (s, 1H), 7.74 - 7.66 (m, 1H), 5.16 (dd, J=8.4, 5.3 Hz, 1H), 4.65 (d, J=9.5 Hz, 1H), 4.36 - 4.27 (m, 1H), 4.20 (br t, J=9.1 Hz, 1H), 4.06 - 4.02 (m, 3H), 3.87 (br t, J=7.2 Hz, 1H), 3.06 (br s, 1H), 2.98 (dd, J=10.8, 4.3 Hz, 1H), 2.57 (br d, J=3.0 Hz, 1H), 1.99 (br dd, J=13.5, 5.4 Hz, 1H), 1.88 (td, J=11.5, 5.6 Hz, 1H), 1.81 - 1.70 (m, 3H), 1.69 - 1.61 (m, 1H), 1.58 - 1.44 (m, 3H), 1.43 - 1.33 (m, 2H), 1.23 - 1.15 (m, 1H), 1.13 - 1.05 (m, 6H), 0.72 (quin, J=9.7 Hz, 2H), 0.32 (br s, 2H)	2.43, B

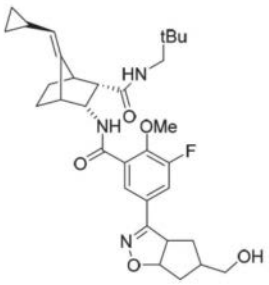
760		(1R,2S,3R,4R,7Z)-3-(5-{5-氰基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	557.4	(500 MHz, DMSO-d6) δ 10.09 - 10.01 (m, 1H), 8.18 - 8.09 (m, 1H), 7.95 - 7.86 (m, 1H), 7.79 - 7.72 (m, 1H), 7.26 - 7.18 (m, 1H), 5.67 - 5.51 (m, 1H), 5.18 (br dd, J=8.3, 5.2 Hz, 1H), 4.63 (d, J=9.4 Hz, 1H), 4.35 (br t, J=8.8 Hz, 1H), 4.27 (dt, J=10.5, 5.3 Hz, 1H), 4.02 - 3.94 (m, 3H), 3.63 (t, J=6.6 Hz, 1H), 3.51 - 3.43 (m, 1H), 3.37 - 3.32 (m, 1H), 3.08 - 3.02 (m, 1H), 2.98 - 2.91 (m, 1H), 2.87 - 2.77 (m, 1H), 2.46 - 2.33 (m, 2H), 2.28 - 2.09 (m, 4H), 1.90 - 1.65 (m, 2H), 1.51 - 1.42 (m, 1H), 1.39 - 1.27 (m, 2H), 1.02 (br d, J=6.9 Hz, 3H), 0.97 (s, 3H), 0.75 - 0.66 (m, 1H), 0.58 - 0.47 (m, 1H), 0.35 - 0.29 (m, 2H), 0.21 - 0.11 (m, 2H)	2.32, C

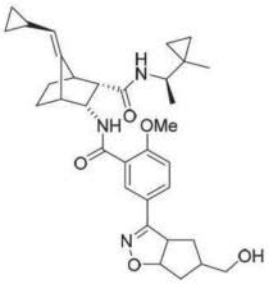
761		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲氧基)苯基]双环[2.2.1]庚烷-2-甲酰胺	629.9	(500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.90 (br d, J=7.0 Hz, 1H), 8.20 (d, J=1.8 Hz, 1H), 8.01 (br d, J=6.1 Hz, 1H), 7.78 (dd, J=8.7, 2.0 Hz, 1H), 7.45 (br d, J=7.3 Hz, 2H), 7.26 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.3, 3.2 Hz, 1H), 4.67 (d, J=9.8 Hz, 1H), 4.50 - 4.44 (m, 1H), 4.43 - 4.37 (m, 1H), 4.08 (br d, J=10.7 Hz, 1H), 4.02 (s, 3H), 3.88 (br d, J=9.2 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.16 - 3.10 (m, 1H), 3.08 (br s, 1H), 2.70 (br s, 1H), 1.85 - 1.72 (m, 2H), 1.53 - 1.34 (m, 3H), 0.78 - 0.66 (m, 2H), 0.33 (br d, J=2.4 Hz, 2H)。可能由于与经抑制的水峰重叠，一个质子不可见。	2.55, B

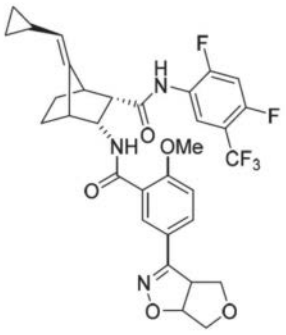
762		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[2-氟-5-(三氟甲氧基)苯基]双环[2.2.1]庚烷-2-甲酰胺	630.1	(500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.81 (br d, J=7.0 Hz, 1H), 8.20 (d, J=2.1 Hz, 1H), 8.03 (br d, J=2.7 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.39 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.9 Hz, 1H), 7.20 - 7.14 (m, 1H), 5.33 (dd, J=9.2, 3.4 Hz, 1H), 4.68 (d, J=9.8 Hz, 1H), 4.51 - 4.44 (m, 1H), 4.44 - 4.36 (m, 1H), 4.08 (br d, J=10.7 Hz, 1H), 3.97 (s, 3H), 3.91 - 3.83 (m, 1H), 3.79 - 3.71 (m, 1H), 3.64 (br dd, J=11.0, 3.7 Hz, 1H), 3.34 (br dd, J=10.5, 3.5 Hz, 1H), 3.07 (br s, 1H), 2.72 (br s, 1H), 1.89 - 1.80 (m, 1H), 1.79 - 1.70 (m, 1H), 1.53 - 1.33 (m, 3H), 0.80 - 0.64 (m, 2H), 0.34 (br d, J=3.1 Hz, 2H)	2.55, C

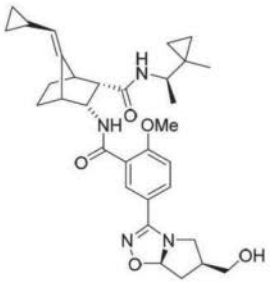
763		(1R,2S,3R,4R,7Z)-3-[2-(环丙基甲氧基)-3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-7-(环丙基亚甲基)-N-{3-氟双环[1.1.1]戊烷-1-基}双环[2.2.1]庚烷-2-甲酰胺	622.2	(500 MHz, DMSO-d6) δ 9.76 (d, J=7.0 Hz, 1H), 8.81 (s, 1H), 7.89 (s, 1H), 7.68 (dd, J=12.4, 1.6 Hz, 1H), 5.15 (dd, J=8.9, 5.0 Hz, 1H), 4.61 (d, J=9.6 Hz, 1H), 4.58 - 4.53 (m, 1H), 4.36 - 4.27 (m, 1H), 4.19 (br t, J=9.1 Hz, 2H), 4.16 - 4.11 (m, 1H), 3.07 - 3.01 (m, 1H), 2.91 - 2.84 (m, 1H), 2.55 (br s, 1H), 2.32 - 2.22 (m, 6H), 2.04 - 1.96 (m, 1H), 1.94 - 1.85 (m, 1H), 1.83 - 1.71 (m, 2H), 1.69 - 1.61 (m, 2H), 1.59 - 1.52 (m, 1H), 1.50 - 1.30 (m, 3H), 1.26 - 1.18 (m, 1H), 0.76 - 0.64 (m, 2H), 0.48 (br d, J=8.1 Hz, 2H), 0.36 - 0.18 (m, 4H)。可能由于与经抑制的水峰重叠，两个质子在NMR中不可见。	2.37, B

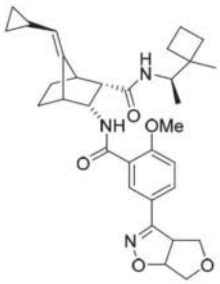
764		(1R,2S,3R,4R,7Z)-3-[2-(环丙基甲氧基)-3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-7-(环丙基亚甲基)-N-{3-甲基双环[1.1.1]戊烷-1-基}双环[2.2.1]庚烷-2-甲酰胺	618.2	(500 MHz, DMSO-d6) δ 9.88 (br d, J=6.7 Hz, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.68 (br d, J=12.2 Hz, 1H), 5.15 (br dd, J=8.7, 5.0 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.51 (br t, J=5.2 Hz, 1H), 4.32 - 4.25 (m, 1H), 4.20 (br t, J=9.2 Hz, 1H), 4.15 (br d, J=7.3 Hz, 2H), 3.04 (br s, 1H), 2.81 (br dd, J=10.8, 4.1 Hz, 1H), 1.99 (br dd, J=13.3, 6.0 Hz, 1H), 1.94 - 1.86 (m, 1H), 1.84 - 1.76 (m, 7H), 1.75 - 1.62 (m, 3H), 1.59 - 1.51 (m, 1H), 1.49 - 1.41 (m, 1H), 1.40 - 1.29 (m, 2H), 1.24 (br d, J=7.9 Hz, 1H), 1.17 (s, 3H), 0.76 - 0.65 (m, 2H), 0.51 - 0.44 (m, 2H), 0.36 - 0.22 (m, 4H)。可能由于与溶剂峰和/或经抑制的水峰重叠，三个质子在NMR中不可见。	2.55, C

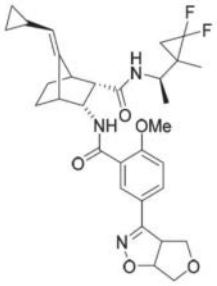
765		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-(2,2-二甲基丙基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	568.3	(500 MHz, DMSO-d6) δ 9.87 (d, J=7.0 Hz, 1H), 8.01 (br t, J=6.1 Hz, 1H), 7.90 (s, 1H), 7.70 (dd, J=12.5, 2.1 Hz, 1H), 5.16 (dd, J=8.5, 5.2 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.36 - 4.27 (m, 1H), 4.20 (br t, J=8.9 Hz, 1H), 4.06 (d, J=2.4 Hz, 3H), 3.09 - 3.00 (m, 2H), 2.74 (dd, J=13.1, 5.5 Hz, 1H), 2.56 (br s, 1H), 1.99 (br dd, J=13.9, 5.6 Hz, 1H), 1.93 - 1.73 (m, 4H), 1.70 - 1.51 (m, 2H), 1.50 - 1.43 (m, 1H), 1.42 - 1.29 (m, 2H), 0.81 (s, 8H), 0.76 - 0.64 (m, 2H), 0.32 (br d, J=2.7 Hz, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，三个质子在NMR中不可见。	2.45, C

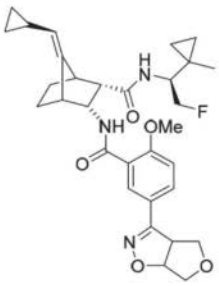
766		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	561.9	(500 MHz, DMSO-d6) δ 10.06 (br d, J=6.4 Hz, 1H), 8.17 (d, J=2.1 Hz, 1H), 7.91 (br d, J=8.5 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 5.13 (br dd, J=9.6, 6.6 Hz, 1H), 4.63 (d, J=9.5 Hz, 1H), 4.49 (t, J=5.2 Hz, 1H), 4.31 - 4.23 (m, 1H), 4.15 - 4.05 (m, 1H), 3.99 (s, 3H), 3.52 - 3.42 (m, 1H), 3.37 - 3.19 (m, 1H), 3.04 (br s, 1H), 2.94 (br dd, J=11.0, 4.0 Hz, 1H), 2.24 - 2.07 (m, 3H), 1.90 - 1.82 (m, 1H), 1.78 - 1.70 (m, 1H), 1.67 - 1.58 (m, 1H), 1.52 - 1.41 (m, 2H), 1.40 - 1.29 (m, 2H), 1.05 - 0.99 (m, 3H), 0.97 (s, 3H), 0.78 - 0.66 (m, 2H), 0.57 - 0.48 (m, 1H), 0.36 - 0.27 (m, 3H), 0.22 - 0.11 (m, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.17, B

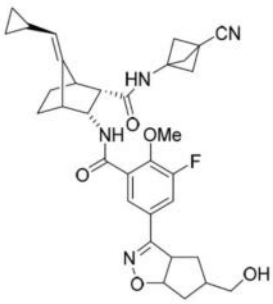
767		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[2,4-二氟-5-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.1	(500 MHz, DMSO-d6) δ 10.24 (s, 1H), 9.78 (br d, J=7.3 Hz, 1H), 8.32 (br t, J=7.9 Hz, 1H), 8.20 (d, J=2.4 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.70 (br t, J=10.5 Hz, 1H), 7.25 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.2, 3.7 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.54 - 4.37 (m, 2H), 4.09 (d, J=10.7 Hz, 1H), 3.97 (s, 3H), 3.91 - 3.83 (m, 1H), 3.80 - 3.72 (m, 1H), 3.65 (dd, J=10.7, 3.7 Hz, 1H), 3.39 (br d, J=1.8 Hz, 1H), 3.08 (br d, J=3.7 Hz, 1H), 2.72 (br s, 1H), 1.87 - 1.80 (m, 1H), 1.79 - 1.71 (m, 1H), 1.53 - 1.34 (m, 3H), 0.81 - 0.64 (m, 2H), 0.34 (br d, J=3.4 Hz, 2H)	2.49, B

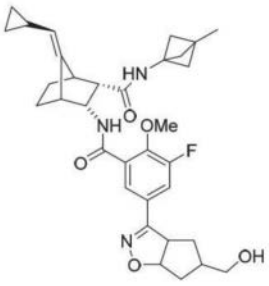
768		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aR)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	563.2	(500 MHz, DMSO-d6) δ 10.18 - 10.02 (m, 1H), 8.19 (br d, J=11.0 Hz, 1H), 7.92 (br d, J=8.5 Hz, 1H), 7.78 (br d, J=8.5 Hz, 1H), 7.26 (br d, J=8.9 Hz, 1H), 5.85 - 5.72 (m, 1H), 4.63 (br d, J=9.5 Hz, 1H), 4.26 (br d, J=3.4 Hz, 1H), 4.01 (br d, J=3.1 Hz, 3H), 3.51 - 3.38 (m, 1H), 3.33 - 3.23 (m, 1H), 3.22 - 3.10 (m, 1H), 3.04 (br d, J=2.7 Hz, 1H), 2.98 - 2.84 (m, 2H), 2.32 - 1.71 (m, 6H), 1.54 - 1.41 (m, 1H), 1.38 - 1.28 (m, 2H), 1.01 (br d, J=6.7 Hz, 3H), 0.97 (s, 3H), 0.77 - 0.62 (m, 2H), 0.52 (br dd, J=6.4, 2.4 Hz, 1H), 0.37 - 0.27 (m, 2H), 0.22 - 0.07 (m, 2H)。可能由于与溶剂峰和/或经抑制的水峰重叠，两个质子在NMR中不可见。	2.22, C

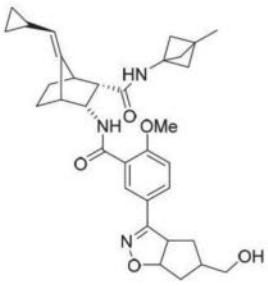
769		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-1-(1-甲基环丁基)乙基]双环[2.2.1]庚烷-2-甲酰胺	548.3	(500 MHz, DMSO-d6) δ 10.05 (br d, J=6.7 Hz, 1H), 8.14 (d, J=2.4 Hz, 1H), 7.78 (dd, J=8.7, 2.0 Hz, 2H), 7.24 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.49 (br t, J=8.1 Hz, 1H), 4.27 (dt, J=10.2, 5.3 Hz, 1H), 4.09 (d, J=10.7 Hz, 1H), 4.01 (s, 3H), 3.99 - 3.92 (m, 1H), 3.90 (br d, J=10.1 Hz, 1H), 3.77 (dd, J=9.2, 7.0 Hz, 1H), 3.65 (dd, J=10.7, 3.7 Hz, 1H), 3.04 (br s, 1H), 2.98 (br dd, J=11.0, 4.3 Hz, 1H), 2.01 - 1.90 (m, 1H), 1.87 - 1.77 (m, 3H), 1.76 - 1.63 (m, 2H), 1.56 - 1.41 (m, 3H), 1.40 - 1.26 (m, 2H), 1.04 (s, 3H), 0.86 (d, J=6.7 Hz, 3H), 0.75 - 0.63 (m, 2H), 0.31 (br d, J=3.1 Hz, 2H)。可能由于与溶剂峰重叠，一个质子在NMR中不可见。	2.40, B

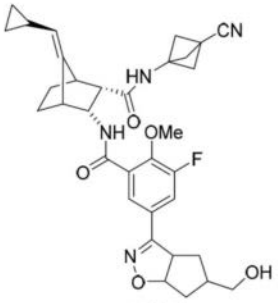
770		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1R)-1-(2,2-二氟-1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	570.2	(500 MHz, DMSO-d6) δ 10.06 (br d, J=6.4 Hz, 1H), 8.29 (br d, J=8.6 Hz, 1H), 8.15 (s, 1H), 7.78 (br d, J=8.5 Hz, 1H), 7.23 (d, J=8.1 Hz, 1H), 5.33 (br d, J=8.5 Hz, 1H), 4.63 (br d, J=9.8 Hz, 1H), 4.48 (br t, J=8.0 Hz, 1H), 4.32 - 4.23 (m, 1H), 4.09 (br d, J=10.5 Hz, 1H), 3.98 (s, 3H), 3.92 - 3.83 (m, 2H), 3.80 - 3.73 (m, 1H), 3.68 - 3.61 (m, 1H), 3.04 (br s, 1H), 2.96 (br dd, J=10.0, 3.2 Hz, 1H), 2.55 (br d, J=1.9 Hz, 1H), 1.79 - 1.65 (m, 2H), 1.57 - 1.44 (m, 2H), 1.34 (br d, J=2.9 Hz, 2H), 1.23 - 1.15 (m, 1H), 1.13 - 1.01 (m, 6H), 0.71 (quin, J=9.4 Hz, 2H), 0.31 (br s, 2H)	2.30, B

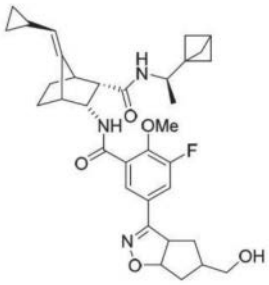
771		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[(1S)-2-氟-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	552.3	(500 MHz, DMSO-d6) δ 10.02 (br d, J=7.0 Hz, 1H), 8.21 (br d, J=8.5 Hz, 1H), 8.14 (d, J=2.4 Hz, 1H), 7.78 (dd, J=8.7, 2.3 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.33 (dd, J=9.2, 3.7 Hz, 1H), 4.64 (d, J=9.5 Hz, 1H), 4.57 - 4.28 (m, 4H), 4.09 (d, J=10.7 Hz, 1H), 3.98 (s, 3H), 3.92 - 3.87 (m, 1H), 3.80 - 3.73 (m, 1H), 3.70 - 3.60 (m, 2H), 3.06 (br s, 1H), 3.01 (br dd, J=11.0, 4.6 Hz, 1H), 2.59 - 2.55 (m, 1H), 1.81 (br d, J=9.5 Hz, 1H), 1.77 - 1.67 (m, 1H), 1.53 - 1.42 (m, 1H), 1.40 - 1.29 (m, 2H), 0.99 (s, 3H), 0.79 - 0.65 (m, 2H), 0.59 - 0.50 (m, 1H), 0.50 - 0.41 (m, 1H), 0.36 - 0.29 (m, 2H), 0.27 (dt, J=9.2, 4.6 Hz, 1H), 0.17 (dt, J=8.6, 4.4 Hz, 1H)	2.16, B

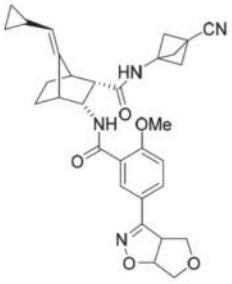
772	 异构体2	(2S,3R,7Z)-N-{3-氰基双环[1.1.1]戊烷-1-基}-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	589.1	(500 MHz, CD_3OD) δ 8.03 (dd, J=2.2, 1.3 Hz, 1H), 7.70 (dd, J=12.8, 2.2 Hz, 1H), 5.25 - 5.19 (m, 1H), 4.68 - 4.63 (m, 1H), 4.44 - 4.39 (m, 1H), 4.21 (d, J=3.2 Hz, 4H), 3.58 - 3.50 (m, 1H), 2.87 - 2.83 (m, 1H), 2.56 - 2.49 (m, 8H), 2.19 - 2.14 (m, 1H), 2.11 - 2.05 (m, 1H), 1.99 - 1.92 (m, 1H), 1.86 - 1.82 (m, 2H), 1.79 - 1.71 (m, 1H), 1.67 - 1.60 (m, 1H), 1.56 - 1.42 (m, 3H), 0.75 - 0.70 (m, 2H), 0.36 - 0.28 (m, 2H)	2.11, C

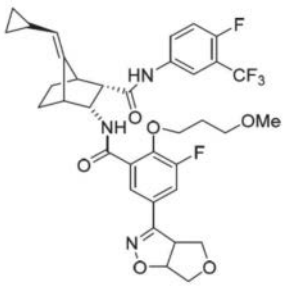
773		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-{3-甲基双环[1.1.1]戊烷-1-基}双环[2.2.1]庚烷-2-甲酰胺	578.2	(500 MHz, DMSO-d6) δ 9.96 (br d, J=6.4 Hz, 1H), 8.55 (s, 1H), 7.94 (s, 1H), 7.71 (dd, J=12.5, 1.8 Hz, 1H), 5.16 (br dd, J=8.4, 5.3 Hz, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.32 - 4.24 (m, 1H), 4.20 (br t, J=9.0 Hz, 1H), 4.08 (d, J=2.4 Hz, 3H), 3.43 - 3.31 (m, 1H), 3.03 (br s, 1H), 2.81 (br dd, J=10.2, 4.1 Hz, 1H), 2.05 - 1.95 (m, 1H), 1.94 - 1.59 (m, 11H), 1.59 - 1.50 (m, 1H), 1.48 - 1.40 (m, 1H), 1.39 - 1.26 (m, 2H), 1.17 (s, 3H), 0.76 - 0.61 (m, 2H), 0.37 - 0.24 (m, 2H)	2.36, B

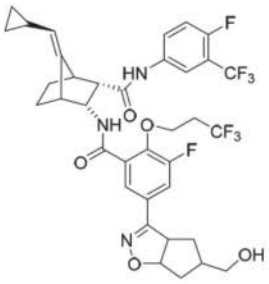
774		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-{3-甲基双环[1.1.1]戊烷-1-基}双环[2.2.1]庚烷-2-甲酰胺	560.3	(500 MHz, DMSO-d6) δ 10.13 (br d, J=6.7 Hz, 1H), 8.50 (s, 1H), 8.20 (d, J=2.1 Hz, 1H), 7.79 (dd, J=8.7, 2.3 Hz, 1H), 7.23 (d, J=8.9 Hz, 1H), 5.11 (dd, J=8.7, 5.3 Hz, 1H), 4.59 (d, J=9.8 Hz, 1H), 4.28 - 4.14 (m, 2H), 4.02 (s, 3H), 3.04 (br s, 1H), 2.80 (br dd, J=10.8, 4.1 Hz, 1H), 1.98 (br dd, J=13.3, 5.6 Hz, 1H), 1.94 - 1.87 (m, 1H), 1.85 (s, 6H), 1.80 - 1.70 (m, 2H), 1.70 - 1.60 (m, 2H), 1.58 - 1.50 (m, 1H), 1.48 - 1.40 (m, 1H), 1.37 - 1.25 (m, 2H), 1.18 (s, 3H), 0.77 - 0.64 (m, 2H), 0.37 - 0.26 (m, 2H)	2.19, C

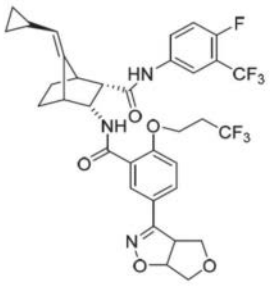
775	 异构体1	(1R,2S,3R,4R,7Z)-N-{3-氰基双环[1.1.1]戊烷-1-基}-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	589.2	(500 MHz, DMSO-d6) δ 9.85 (br d, J=6.7 Hz, 1H), 8.91 (br s, 1H), 7.96 (br s, 1H), 7.70 (br d, J=12.2 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.64 - 4.53 (m, 2H), 4.28 (br s, 1H), 4.09 (br s, 3H), 3.33 - 3.25 (m, 1H), 3.22 (br d, J=5.5 Hz, 1H), 3.03 (br s, 1H), 2.88 - 2.78 (m, 1H), 2.49 - 2.43 (m, 6H), 2.26 - 2.08 (m, 3H), 1.74 - 1.59 (m, 3H), 1.52 - 1.40 (m, 2H), 1.40 - 1.28 (m, 2H), 0.77 - 0.63 (m, 2H), 0.31 (br s, 2H)	2.02, C

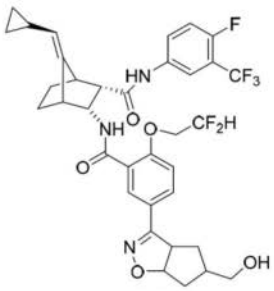
776		(1R,2S,3R,4R,7Z)-N-[(1R)-1-{双环[1.1.1]戊烷-1-基}乙基]-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	592.2	(500 MHz, DMSO-d6) δ 9.69 (br d, J=6.9 Hz, 1H), 7.72 - 7.60 (m, 2H), 7.45 (br dd, J=12.2, 1.3 Hz, 1H), 4.92 (br dd, J=8.7, 5.0 Hz, 1H), 4.39 (br d, J=9.5 Hz, 1H), 4.08 - 4.00 (m, 1H), 3.95 (br t, J=9.0 Hz, 1H), 3.82 - 3.76 (m, 3H), 3.64 - 3.58 (m, 1H), 3.18 - 3.06 (m, 2H), 2.81 (br s, 1H), 2.68 (br dd, J=10.6, 3.9 Hz, 1H), 2.19 (s, 1H), 1.81 - 1.72 (m, 1H), 1.67 - 1.48 (m, 4H), 1.45 - 1.37 (m, 1H), 1.37 - 1.26 (m, 7H), 1.25 - 1.17 (m, 1H), 1.16 - 1.06 (m, 2H), 0.67 (d, J=6.9 Hz, 3H), 0.52 - 0.40 (m, 2H), 0.07 (br d, J=2.4 Hz, 2H)	2.48, B

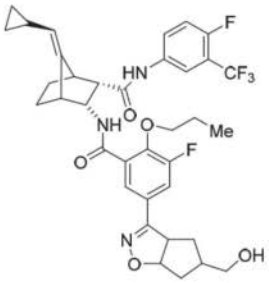
777		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-{3-氰基双环[1.1.1]戊烷-1-基}-7-(环丙基亚甲基)双环[2.2.1]庚烷-2-甲酰胺	543.3	(500 MHz, DMSO-d6) δ 10.05 (br d, J=6.7 Hz, 1H), 8.89 (s, 1H), 8.21 (d, J=2.1 Hz, 1H), 7.81 (dd, J=8.7, 2.3 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 5.35 (dd, J=9.2, 3.4 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 4.51 (br t, J=8.1 Hz, 1H), 4.32 - 4.22 (m, 1H), 4.11 (d, J=10.4 Hz, 1H), 4.06 (s, 3H), 3.91 (br d, J=9.2 Hz, 1H), 3.79 (dd, J=9.3, 7.2 Hz, 1H), 3.67 (dd, J=10.5, 3.5 Hz, 1H), 3.06 (br s, 1H), 2.83 (br dd, J=10.8, 4.1 Hz, 1H), 2.54 (br s, 1H) (部分重叠DMSO), 2.52 - 2.50 (m, 6H) (部分重叠DMSO), 1.76 - 1.62 (m, 2H), 1.52 - 1.41 (m, 1H), 1.34 (br d, J=8.2 Hz, 2H), 0.79 - 0.65 (m, 2H), 0.33 (br d, J=4.3 Hz, 2H)	1.95, B

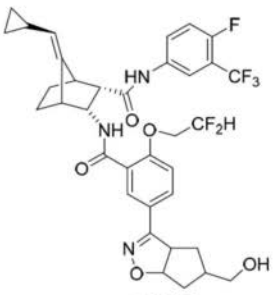
778		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氟-2-(3-甲氧基prop氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	690.3	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.45 (d, J=7.0 Hz, 1H), 8.11 (dd, J=6.3, 2.3 Hz, 1H), 7.86 (s, 1H), 7.79 - 7.75 (m, 1H), 7.73 (dd, J=12.4, 2.0 Hz, 1H), 7.47 (t, J=9.6 Hz, 1H), 5.38 (dd, J=9.3, 3.5 Hz, 1H), 4.71 (d, J=9.5 Hz, 1H), 4.51 - 4.41 (m, 2H), 4.34 - 4.24 (m, 2H), 4.10 (d, J=11.0 Hz, 1H), 3.93 (br d, J=9.8 Hz, 1H), 3.72 (dd, J=9.3, 6.9 Hz, 1H), 3.64 (dd, J=10.8, 3.5 Hz, 1H), 3.47 - 3.30 (m, 1H), 3.17 (s, 2H), 3.12 (br s, 1H), 2.76 - 2.71 (m, 1H), 1.99 (qt, J=13.4, 6.8 Hz, 2H), 1.89 - 1.72 (m, 2H), 1.59 - 1.29 (m, 3H), 0.95 - 0.58 (m, 2H), 0.52 - 0.09 (m, 2H)	2.56, B

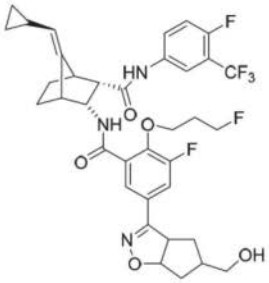
779		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-prop氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	688.3	(500 MHz, DMSO-d6) δ 10.57 - 10.47 (m, 1H), 9.61 - 9.44 (m, 1H), 8.24 - 8.11 (m, 1H), 7.89 (s, 1H), 7.80 - 7.74 (m, 1H), 7.71 - 7.64 (m, 1H), 7.47 (t, J=9.8 Hz, 1H), 5.31 - 5.12 (m, 1H), 4.71 (s, 1H), 4.52 (q, J=5.0 Hz, 1H), 4.46 (br t, J=10.2 Hz, 1H), 4.25 - 4.16 (m, 2H), 4.12 - 4.06 (m, 1H), 3.32 - 3.27 (m, 1H), 3.25 - 3.20 (m, 1H), 3.19 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.25 - 2.09 (m, 2H), 1.83 - 1.79 (m, 2H), 1.78 - 1.71 (m, 2H), 1.67 - 1.60 (m, 1H), 1.53 - 1.37 (m, 4H), 0.87 (t, J=7.4 Hz, 3H), 0.82 - 0.70 (m, 2H), 0.36 (br d, J=2.1 Hz, 2H) 一些质子因水抑制而被遮挡。	2.67, B

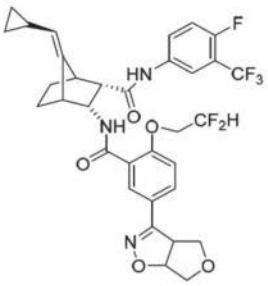
780		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(3,3,3-三氟prop氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	696.0	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.59 (br d, J=7.0 Hz, 1H), 8.20 (d, J=2.1 Hz, 1H), 8.16 (dd, J=6.6, 2.0 Hz, 1H), 7.79 (dd, J=8.9, 2.1 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.46 (t, J=9.9 Hz, 1H), 7.35 (d, J=8.9 Hz, 1H), 5.35 (dd, J=9.2, 3.4 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.61 - 4.39 (m, 4H), 4.10 (br d, J=10.7 Hz, 1H), 3.92 - 3.85 (m, 1H), 3.82 - 3.75 (m, 1H), 3.66 (dd, J=11.0, 3.4 Hz, 1H), 3.35 (br s, 1H), 3.24 - 3.15 (m, 1H), 3.13 - 2.98 (m, 2H), 2.73 (br s, 1H), 1.87 - 1.72 (m, 2H), 1.50 (td, J=8.4, 4.3 Hz, 1H), 1.44 (br s, 2H), 0.84 - 0.66 (m, 2H), 0.36 (br s, 2H)	2.59, B

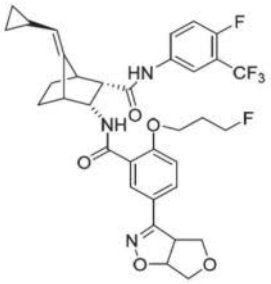
781	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-[2-(2,2-二氟乙氧基)-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	692.3	(500 MHz, DMSO-d6) δ 10.59 - 10.47 (m, 1H), 9.57 (br d, J=7.0 Hz, 1H), 8.20 (d, J=2.1 Hz, 1H), 8.12 (br d, J=4.3 Hz, 1H), 7.79 (dd, J=8.7, 2.0 Hz, 1H), 7.75 - 7.67 (m, 1H), 7.47 (t, J=9.6 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 6.88 - 6.43 (m, 1H), 5.13 (br dd, J=8.5, 5.5 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.68 - 4.61 (m, 2H), 4.53 (t, J=5.2 Hz, 1H), 4.50 - 4.45 (m, 1H), 4.21 (br t, J=9.0 Hz, 1H), 3.49 - 3.31 (m, 1H), 3.16 (br dd, J=11.0, 3.7 Hz, 1H), 3.09 (br s, 1H), 2.73 (br s, 1H), 2.04 - 1.94 (m, 1H), 1.92 - 1.81 (m, 2H), 1.79 - 1.71 (m, 1H), 1.69 - 1.61 (m, 1H), 1.58 - 1.45 (m, 2H), 1.44 - 1.35 (m, 2H), 0.93 - 0.59 (m, 2H), 0.42 - 0.20 (m, 2H)。一些质子因水抑制而被遮挡。	2.48, B

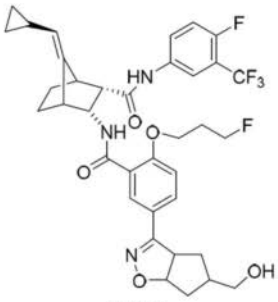
782		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-丙氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	688.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.49 (br d, J=7.6 Hz, 1H), 8.12 (br d, J=6.0 Hz, 1H), 7.87 (s, 1H), 7.77 - 7.71 (m, 1H), 7.68 (br d, J=12.7 Hz, 1H), 7.45 (br t, J=9.7 Hz, 1H), 5.15 (br dd, J=8.5, 5.1 Hz, 1H), 4.69 (br d, J=9.5 Hz, 1H), 4.61 (br d, J=3.2 Hz, 1H), 4.43 (br d, J=5.3 Hz, 1H), 4.27 - 4.11 (m, 3H), 3.41 - 3.28 (m, 1H), 3.18 - 3.14 (m, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.99 (br dd, J=13.0, 5.4 Hz, 1H), 1.93 - 1.85 (m, 1H), 1.81 (br d, J=7.9 Hz, 2H), 1.78 - 1.68 (m, 3H), 1.67 - 1.61 (m, 1H), 1.59 - 1.54 (m, 1H), 1.50 - 1.37 (m, 3H), 0.85 (t, J=7.3 Hz, 3H), 0.77 - 0.67 (m, 2H), 0.34 (br d, J=3.1 Hz, 2H)。一些质子因水抑制而被遮挡。	2.67, B

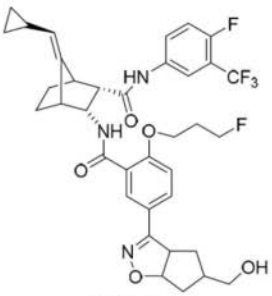
783	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-[2-(2,2-二氟乙氧基)-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	692.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.57 (br d, J=7.2 Hz, 1H), 8.20 (d, J=2.2 Hz, 1H), 8.11 (br d, J=4.4 Hz, 1H), 7.85 - 7.75 (m, 1H), 7.71 (br dd, J=4.3, 3.0 Hz, 1H), 7.45 (br t, J=9.7 Hz, 1H), 7.35 (d, J=8.9 Hz, 1H), 6.62 (br t, J=54.9 Hz, 1H), 5.25 - 5.12 (m, 1H), 4.70 (s, 1H), 4.63 - 4.52 (m, 2H), 4.48 - 4.41 (m, 1H), 4.15 - 4.06 (m, 1H), 3.32 - 3.20 (m, 1H), 3.15 (br dd, J=10.6, 3.3 Hz, 1H), 3.09 (br s, 1H), 2.76 - 2.68 (m, 1H), 2.28 - 2.10 (m, 3H), 1.90 - 1.76 (m, 2H), 1.68 - 1.59 (m, 1H), 1.55 - 1.47 (m, 1H), 1.45 - 1.36 (m, 3H), 0.87 - 0.67 (m, 2H), 0.35 (br d, J=2.6 Hz, 2H)。一些质子因水抑制而被遮挡。	2.41, B

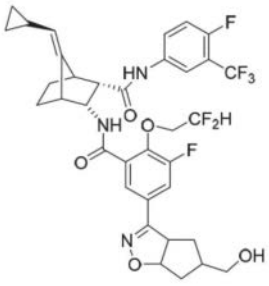
784		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-[3-氟-2-(3-氟prop氧基)-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	706.2	(500 MHz, DMSO-d6) δ 10.58 - 10.44 (m, 1H), 9.48 (d, J=7.1 Hz, 1H), 8.08 (br d, J=5.5 Hz, 1H), 7.85 (s, 1H), 7.78 - 7.72 (m, 1H), 7.71 - 7.67 (m, 1H), 7.45 (t, J=9.6 Hz, 1H), 5.15 (dd, J=8.6, 5.5 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.64 - 4.57 (m, 2H), 4.52 (t, J=5.9 Hz, 1H), 4.43 (br d, J=5.2 Hz, 1H), 4.35 - 4.25 (m, 2H), 4.18 (br t, J=9.3 Hz, 1H), 3.43 - 3.30 (m, 1H), 3.19 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.72 (br s, 1H), 2.25 - 2.14 (m, 1H), 2.15 - 2.09 (m, 1H), 2.04 - 1.96 (m, 1H), 1.93 - 1.84 (m, 1H), 1.81 - 1.73 (m, 3H), 1.68 - 1.61 (m, 1H), 1.59 - 1.54 (m, 1H), 1.53 - 1.48 (m, 1H), 1.46 - 1.38 (m, 1H), 0.81 - 0.65 (m, 2H), 0.47 - 0.30 (m, 2H)。一些质子因水抑制而被遮挡。	2.43, B

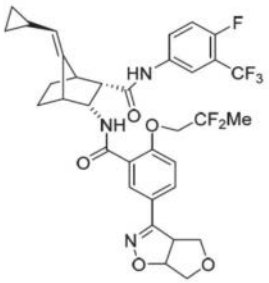
785		(1R,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(2,2-二氟乙氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	664.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.57 (br d, J=7.0 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H), 8.15 - 8.10 (m, 1H), 7.79 (dd, J=8.5, 1.5 Hz, 1H), 7.75 - 7.69 (m, 1H), 7.46 (br t, J=9.8 Hz, 1H), 7.36 (d, J=8.5 Hz, 1H), 6.63 (br t, J=55.2 Hz, 1H), 5.35 (br dd, J=8.9, 3.4 Hz, 1H), 4.70 (br d, J=9.5 Hz, 1H), 4.66 - 4.58 (m, 2H), 4.54 - 4.44 (m, 2H), 4.10 (br d, J=10.4 Hz, 1H), 3.92 - 3.84 (m, 1H), 3.80 - 3.72 (m, 1H), 3.65 (br dd, J=10.7, 3.4 Hz, 1H), 3.16 (br dd, J=10.8, 3.5 Hz, 1H), 3.09 (br s, 1H), 2.73 (br s, 1H), 1.93 - 1.69 (m, 2H), 1.50 (td, J=8.7, 4.6 Hz, 1H), 1.47 - 1.31 (m, 2H), 0.85 - 0.61 (m, 2H), 0.47 - 0.21 (m, 2H)	2.45, B

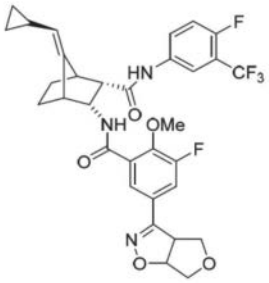
786		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(3-氟丙氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	660.2	(500 MHz, DMSO-d6) δ 10.56 - 10.43 (m, 1H), 9.60 (br d, J=7.3 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H), 8.14 (br d, J=4.6 Hz, 1H), 7.77 (dd, J=8.9, 2.1 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.45 (br t, J=9.8 Hz, 1H), 7.31 (d, J=8.9 Hz, 1H), 5.34 (dd, J=8.9, 3.4 Hz, 1H), 4.76 - 4.67 (m, 2H), 4.65 - 4.57 (m, 1H), 4.53 - 4.46 (m, 2H), 4.42 - 4.35 (m, 1H), 4.09 (br d, J=11.0 Hz, 1H), 3.89 (br d, J=7.6 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.65 (br dd, J=11.0, 3.1 Hz, 1H), 3.56 - 3.44 (m, 1H), 3.19 - 3.13 (m, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.43 - 2.36 (m, 1H), 2.35 - 2.28 (m, 1H), 1.88 - 1.76 (m, 2H), 1.58 - 1.38 (m, 3H), 0.80 - 0.68 (m, 2H), 0.35 (br s, 2H)	2.48, B

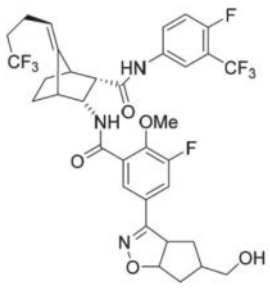
787	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-(3-氟prop氧基)-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	688.4	(500 MHz, DMSO-d6) δ 10.56 - 10.45 (m, 1H), 9.58 (d, J=7.3 Hz, 1H), 8.16 (d, J=2.1 Hz, 1H), 8.12 (dd, J=6.5, 2.1 Hz, 1H), 7.76 (dd, J=8.7, 2.2 Hz, 1H), 7.71 - 7.66 (m, 1H), 7.43 (t, J=9.7 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 5.11 (dd, J=8.7, 5.3 Hz, 1H), 4.72 - 4.67 (m, 2H), 4.63 (br d, J=6.7 Hz, 1H), 4.60 - 4.55 (m, 1H), 4.52 - 4.45 (m, 1H), 4.37 (br t, J=5.5 Hz, 2H), 4.17 (br t, J=8.8 Hz, 1H), 3.40 - 3.35 (m, 1H), 3.34 - 3.29 (m, 1H), 3.17 - 3.11 (m, 1H), 3.10 - 3.05 (m, 1H), 2.71 (br s, 1H), 2.39 - 2.33 (m, 1H), 2.31 - 2.25 (m, 1H), 2.02 - 1.98 (m, 1H), 1.97 - 1.94 (m, 1H), 1.92 - 1.86 (m, 1H), 1.81 (br d, J=7.9 Hz, 2H), 1.76 (br d, J=6.1 Hz, 1H), 1.73 (br s, 1H), 1.68 - 1.61 (m, 1H), 1.58 - 1.54 (m, 1H), 1.50 (br dd, J=10.6, 5.0 Hz, 1H), 0.82 - 0.66 (m, 2H), 0.34 (br d, J=4.0 Hz, 2H)	2.42, B

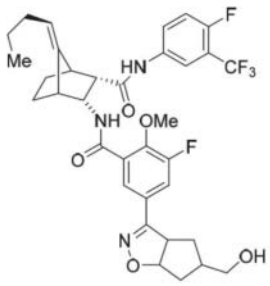
788	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-(3-氟prop氧基)-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	688.2	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.58 (br d, J=7.3 Hz, 1H), 8.20 (s, 1H), 8.14 (br d, J=5.3 Hz, 1H), 7.77 (br d, J=8.6 Hz, 1H), 7.73 (br dd, J=5.7, 3.0 Hz, 1H), 7.46 (t, J=9.9 Hz, 1H), 7.31 (d, J=8.7 Hz, 1H), 5.19 - 5.11 (m, 1H), 4.70 (br d, J=9.0 Hz, 2H), 4.64 - 4.58 (m, 1H), 4.53 - 4.47 (m, 2H), 4.39 (br s, 2H), 4.15 - 4.06 (m, 1H), 3.48 - 3.39 (m, 1H), 3.31 - 3.25 (m, 1H), 3.25 - 3.20 (m, 1H), 3.19 - 3.13 (m, 1H), 3.12 - 3.06 (m, 1H), 2.72 (br s, 1H), 2.42 - 2.36 (m, 1H), 2.35 - 2.29 (m, 1H), 2.22 - 2.08 (m, 3H), 1.88 - 1.79 (m, 2H), 1.67 - 1.60 (m, 1H), 1.55 - 1.49 (m, 1H), 1.47 - 1.41 (m, 2H), 0.83 - 0.69 (m, 2H), 0.36 (br s, 2H)	2.36, B

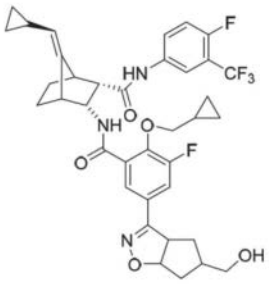
789		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-[2-(2,2-二氟乙氧基)-3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	710.2	(500 MHz, DMSO-d6) δ 10.50 (s, 1H), 9.31 (d, J=7.1 Hz, 1H), 8.05 (br d, J=4.3 Hz, 1H), 7.85 - 7.77 (m, 2H), 7.73 (br d, J=12.3 Hz, 1H), 7.46 (t, J=9.7 Hz, 1H), 6.51 - 6.16 (m, 1H), 5.17 (dd, J=8.6, 5.1 Hz, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.55 - 4.46 (m, 2H), 4.45 - 4.37 (m, 1H), 4.20 (br t, J=8.9 Hz, 1H), 3.43 - 3.37 (m, 1H), 3.16 (br dd, J=10.6, 3.9 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.99 (br dd, J=13.7, 5.6 Hz, 1H), 1.91 - 1.83 (m, 2H), 1.79 - 1.70 (m, 1H), 1.68 - 1.59 (m, 1H), 1.58 - 1.34 (m, 4H), 0.84 - 0.68 (m, 2H), 0.36 (br d, J=1.4 Hz, 2H)。一些质子因水抑制而被遮挡。	2.47, C

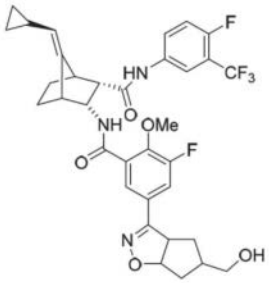
790		(2S,3R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(2,2-二氟prop氧基)苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	678.1	(500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.36 (d, J=7.4 Hz, 1H), 8.14 - 8.07 (m, 1H), 8.04 (d, J=2.3 Hz, 1H), 7.76 (dd, J=8.7, 2.2 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.44 (t, J=9.6 Hz, 1H), 7.36 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.73 - 4.55 (m, 3H), 4.51 - 4.40 (m, 2H), 4.09 (d, J=10.8 Hz, 1H), 3.92 - 3.83 (m, 1H), 3.77 - 3.70 (m, 1H), 3.64 (br dd, J=10.8, 3.6 Hz, 1H), 3.14 (br dd, J=10.5, 3.9 Hz, 1H), 3.08 (br s, 1H), 2.71 (br s, 1H), 1.89 (br d, J=12.7 Hz, 1H), 1.83 - 1.69 (m, 4H), 1.50 (td, J=8.7, 4.3 Hz, 1H), 1.45 - 1.35 (m, 2H), 0.80 - 0.67 (m, 2H), 0.35 (br d, J=1.7 Hz, 2H)	2.43, C

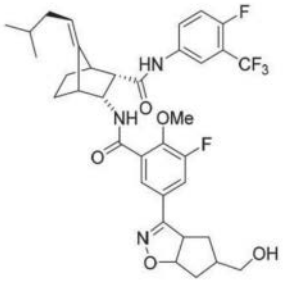
791		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-3-氟-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	632.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.69 (d, J=7.3 Hz, 1H), 8.17 - 8.06 (m, 1H), 7.95 (s, 1H), 7.81 (br dd, J=5.0, 3.6 Hz, 1H), 7.74 (dd, J=12.7, 1.6 Hz, 1H), 7.47 (t, J=9.7 Hz, 1H), 5.38 (dd, J=9.1, 3.5 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.53 - 4.41 (m, 2H), 4.17 - 4.05 (m, 3H), 3.91 (br d, J=9.3 Hz, 1H), 3.73 (dd, J=9.3, 6.6 Hz, 1H), 3.64 (dd, J=10.8, 3.8 Hz, 1H), 3.16 (br dd, J=10.4, 4.1 Hz, 1H), 3.12 - 3.07 (m, 1H), 2.99 (s, 1H), 2.77 - 2.70 (m, 1H), 1.90 - 1.75 (m, 2H), 1.56 - 1.32 (m, 3H), 0.80 - 0.63 (m, 2H), 0.41 - 0.27 (m, 2H)	2.63, C

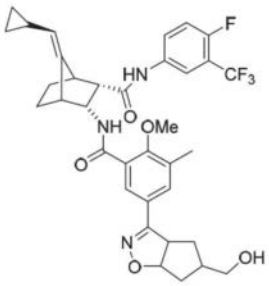
792		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	716.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.70 (br d, J=7.0 Hz, 1H), 8.12 (br d, J=4.3 Hz, 1H), 7.97 (s, 1H), 7.91 - 7.79 (m, 1H), 7.73 (dd, J=12.5, 1.8 Hz, 1H), 7.49 (br t, J=9.8 Hz, 1H), 5.29 (br t, J=7.2 Hz, 1H), 5.17 (br dd, J=8.5, 5.2 Hz, 1H), 4.51 (br t, J=5.0 Hz, 1H), 4.47 - 4.37 (m, 1H), 4.20 (br t, J=9.0 Hz, 1H), 4.09 (d, J=2.1 Hz, 3H), 3.18 (br dd, J=10.7, 4.0 Hz, 1H), 3.01 (br s, 1H), 2.77 (br s, 1H), 2.44 - 2.23 (m, 4H), 2.00 (br dd, J=13.6, 5.0 Hz, 1H), 1.94 - 1.72 (m, 4H), 1.70 - 1.51 (m, 2H), 1.48 - 1.34 (m, 2H)	2.50, C

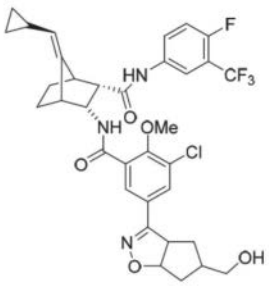
793		(1R,2S,3R,4R,7Z)-7-丁亚基-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	662.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.69 (br d, J=7.0 Hz, 1H), 8.16 - 8.06 (m, 1H), 7.95 (s, 1H), 7.85 - 7.77 (m, 1H), 7.71 (dd, J=12.7, 2.0 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 5.24 (t, J=7.6 Hz, 1H), 5.16 (dd, J=8.7, 5.3 Hz, 1H), 4.60 (br t, J=5.3 Hz, 1H), 4.47 - 4.36 (m, 1H), 4.18 (br t, J=9.2 Hz, 1H), 4.08 (d, J=2.4 Hz, 3H), 3.41 - 3.27 (m, 1H), 3.17 (br dd, J=10.5, 4.1 Hz, 1H), 2.97 (br s, 1H), 2.74 (br s, 1H), 2.11 - 1.96 (m, 3H), 1.94 - 1.72 (m, 4H), 1.70 - 1.48 (m, 2H), 1.47 - 1.34 (m, 4H), 0.90 (t, J=7.3 Hz, 3H)	2.58, C

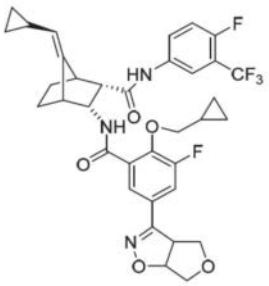
794		(1R,2S,3R,4R,7Z)-3-[2-(环丙基甲氧基)-3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基]-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	700.2	(500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.36 (d, J=7.3 Hz, 1H), 7.90 (dd, J=6.4, 2.1 Hz, 1H), 7.73 (s, 1H), 7.59 - 7.52 (m, 1H), 7.49 (dd, J=12.4, 2.0 Hz, 1H), 7.27 (br t, J=9.8 Hz, 1H), 4.96 (dd, J=8.5, 5.2 Hz, 1H), 4.55 - 4.46 (m, 1H), 4.27 (br t, J=10.5 Hz, 1H), 3.99 (br t, J=9.2 Hz, 1H), 3.93 (br d, J=6.1 Hz, 2H), 3.31 - 3.09 (m, 2H), 2.97 (br dd, J=10.1, 4.0 Hz, 1H), 2.91 (br d, J=4.0 Hz, 1H), 2.56 - 2.50 (m, 1H), 1.80 (br dd, J=13.4, 5.5 Hz, 1H), 1.74 - 1.53 (m, 4H), 1.52 - 1.16 (m, 6H), 1.08 - 0.97 (m, 1H), 0.61 - 0.47 (m, 2H), 0.29 - 0.09 (m, 4H), 0.07 - -0.07 (m, 2H)	2.59, C

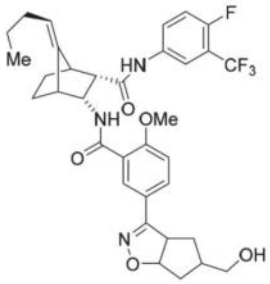
795		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.0	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.71 (d, J=7.1 Hz, 1H), 8.11 (br d, J=4.0 Hz, 1H), 7.97 (s, 1H), 7.88 - 7.77 (m, 1H), 7.72 (br d, J=12.3 Hz, 1H), 7.47 (t, J=9.8 Hz, 1H), 5.16 (dd, J=8.7, 5.1 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.62 - 4.51 (m, 1H), 4.50 - 4.40 (m, 1H), 4.19 (br t, J=9.0 Hz, 1H), 4.09 (d, J=2.4 Hz, 3H), 3.16 (br dd, J=10.4, 4.3 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.99 (br dd, J=13.7, 5.6 Hz, 1H), 1.94 - 1.73 (m, 4H), 1.70 - 1.33 (m, 5H), 0.81 - 0.68 (m, 2H), 0.35 (br d, J=2.5 Hz, 2H)	2.50, C

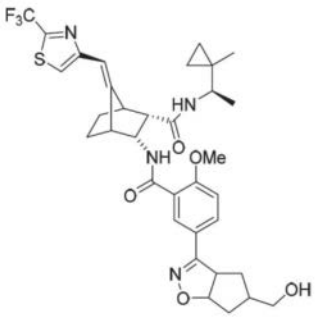
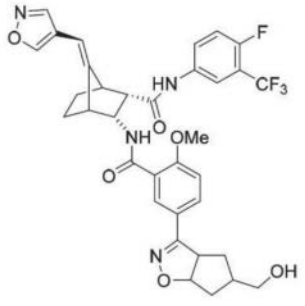
796		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	676.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.69 (d, J=7.3 Hz, 1H), 8.17 - 8.09 (m, 1H), 7.96 (s, 1H), 7.88 - 7.78 (m, 1H), 7.72 (dd, J=12.7, 2.0 Hz, 1H), 7.48 (t, J=9.6 Hz, 1H), 5.25 (t, J=7.6 Hz, 1H), 5.16 (dd, J=8.5, 5.2 Hz, 1H), 4.42 (br t, J=10.7 Hz, 1H), 4.19 (br t, J=9.2 Hz, 1H), 4.08 (d, J=2.4 Hz, 3H), 3.48 - 3.29 (m, 1H), 3.19 (br dd, J=10.5, 3.8 Hz, 1H), 2.96 (br s, 1H), 2.76 (br s, 1H), 2.04 - 1.93 (m, 3H), 1.92 - 1.82 (m, 2H), 1.82 - 1.72 (m, 2H), 1.70 - 1.51 (m, 3H), 1.48 - 1.33 (m, 2H), 0.91 (dd, J=11.0, 6.7 Hz, 6H)	2.67, C

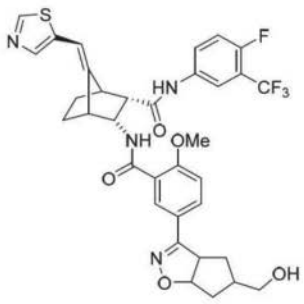
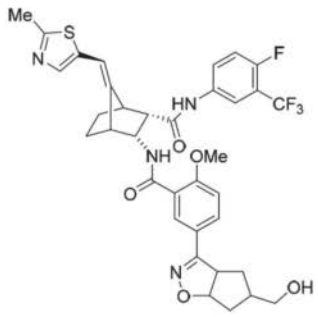
797		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基-3-甲基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.47 (br d, J=7.3 Hz, 1H), 8.05 (br d, J=4.3 Hz, 1H), 7.89 (d, J=1.8 Hz, 1H), 7.85 - 7.77 (m, 1H), 7.69 (s, 1H), 7.47 (t, J=9.9 Hz, 1H), 5.13 (dd, J=8.7, 5.3 Hz, 1H), 4.70 (d, J=9.8 Hz, 1H), 4.58 (t, J=5.2 Hz, 1H), 4.53 - 4.42 (m, 1H), 4.18 (br t, J=9.0 Hz, 1H), 3.74 (s, 3H), 3.42 - 3.25 (m, 1H), 3.16 (br dd, J=11.3, 4.3 Hz, 1H), 3.12 - 3.04 (m, 1H), 2.77 - 2.70 (m, 1H), 2.33 (s, 3H), 1.98 (br dd, J=14.0, 5.8 Hz, 1H), 1.93 - 1.72 (m, 4H), 1.69 - 1.58 (m, 1H), 1.58 - 1.31 (m, 4H), 0.82 - 0.67 (m, 2H), 0.36 (br d, J=3.7 Hz, 2H)	2.49, C

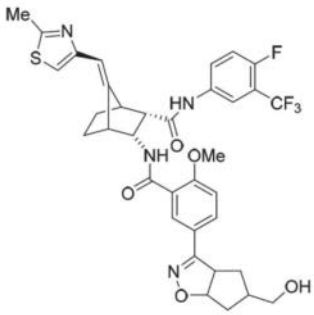
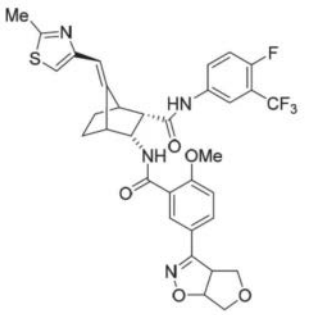
798		(1R,2S,3R,4R,7Z)-3-{3-氯-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	676.4	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.55 (br d, J=7.3 Hz, 1H), 8.10 - 8.02 (m, 1H), 8.01 (d, J=2.1 Hz, 1H), 7.89 (d, J=2.1 Hz, 1H), 7.87 - 7.77 (m, 1H), 7.47 (br t, J=9.8 Hz, 1H), 5.17 (br dd, J=8.9, 5.2 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.59 (br t, J=5.0 Hz, 1H), 4.52 - 4.40 (m, 1H), 4.26 - 4.17 (m, 1H), 3.88 (s, 3H), 3.42 - 3.28 (m, 1H), 3.17 (br dd, J=9.3, 5.0 Hz, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 1.99 (br dd, J=13.1, 5.8 Hz, 1H), 1.93 - 1.73 (m, 4H), 1.69 - 1.35 (m, 5H), 1.04 (d, J=6.1 Hz, 1H), 0.83 - 0.66 (m, 2H), 0.36 (br d, J=2.4 Hz, 2H)	2.60, C

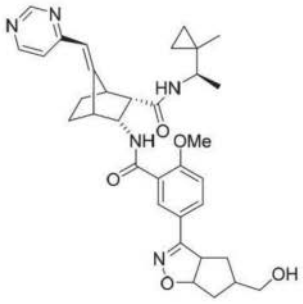
799		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-(环丙基甲氧基)-3-氟苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	672.1	(500 MHz, DMSO-d6) δ 10.30 (s, 1H), 9.32 (br d, J=7.3 Hz, 1H), 7.97 - 7.86 (m, 1H), 7.71 (s, 1H), 7.60 - 7.45 (m, 2H), 7.26 (t, J=9.6 Hz, 1H), 5.17 (dd, J=9.3, 3.5 Hz, 1H), 4.49 (d, J=9.8 Hz, 1H), 4.33 - 4.21 (m, 2H), 3.98 - 3.84 (m, 3H), 3.77 - 3.65 (m, 1H), 3.52 (dd, J=9.5, 7.0 Hz, 1H), 3.43 (dd, J=10.8, 3.5 Hz, 1H), 3.01 - 2.92 (m, 1H), 2.90 (br s, 1H), 2.52 (br s, 1H), 1.70 - 1.56 (m, 2H), 1.38 - 1.16 (m, 3H), 1.09 - 0.97 (m, 1H), 0.61 - 0.47 (m, 2H), 0.23 (ddd, J=16.6, 8.4, 4.9 Hz, 2H), 0.15 (br s, 2H), 0.08 - -0.05 (m, 2H)	2.71, C

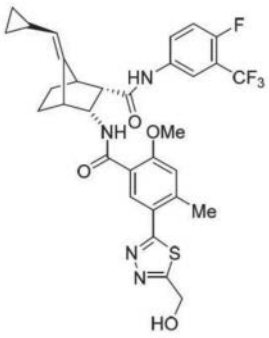
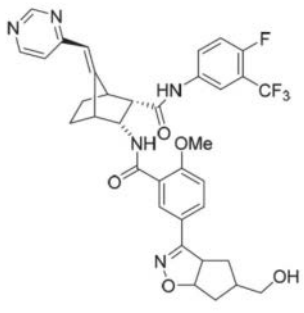
800		(1R,2S,3R,4R,7Z)-7-丁亚基-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.20 (br d, J=2.1 Hz, 2H), 7.83 - 7.74 (m, 2H), 7.46 (t, J=9.6 Hz, 1H), 7.26 (d, J=8.9 Hz, 1H), 5.22 (t, J=7.5 Hz, 1H), 5.12 (dd, J=8.5, 4.9 Hz, 1H), 4.67 (t, J=5.2 Hz, 1H), 4.38 (br s, 1H), 4.18 (br t, J=9.2 Hz, 1H), 4.02 (s, 3H), 3.67 - 3.54 (m, 3H), 3.44 - 3.29 (m, 2H), 3.15 (br dd, J=11.4, 4.1 Hz, 1H), 2.96 (br s, 1H), 2.72 (br s, 1H), 2.09 - 1.94 (m, 2H), 1.93 - 1.80 (m, 1H), 1.80 - 1.71 (m, 1H), 1.70 - 1.48 (m, 2H), 1.44 - 1.31 (m, 4H), 0.89 (t, J=7.3 Hz, 3H)	2.54, C

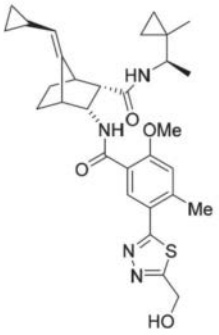
801		(1R,2S,3R,4R,7Z)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-{[2-(三氟甲基)-1,3-噻唑-4-基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	699.2	(400 MHz, DMSO-d6) δ = 10.63 (s, 1H), 10.04 (d, J = 6.8 Hz, 1H), 8.34 - 8.14 (m, 2H), 7.88 - 7.73 (m, 2H), 7.60 (s, 1H), 7.52 (t, J = 9.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.54 (s, 1H), 5.13 (dd, J = 5.1, 8.8 Hz, 1H), 4.56 - 4.43 (m, 2H), 4.27 - 4.17 (m, 1H), 4.06 (s, 3H), 3.31 - 3.26 (m, 1H), 2.95 (br d, J = 3.4 Hz, 1H), 2.66 (s, 3H), 1.99 (dd, J = 5.9, 13.7 Hz, 1H), 1.95 - 1.75 (m, 4H), 1.71 - 1.42 (m, 4H)	2.15, A
802		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(1,2-噁唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	641.2	(400 MHz, DMSO-d6) δ = 10.68 - 10.54 (m, 1H), 9.97 (d, J = 7.3 Hz, 1H), 9.02 (s, 1H), 8.74 (s, 1H), 8.26 - 8.17 (m, 2H), 7.86 - 7.75 (m, 2H), 7.51 (t, J = 9.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.14 (s, 1H), 5.35 (dd, J = 3.5, 9.2 Hz, 1H), 4.50 (br t, J = 7.3 Hz, 2H), 4.10 (d, J = 10.8 Hz, 1H), 4.06 (s, 3H), 3.93 - 3.86 (m, 2H), 3.82 - 3.74 (m, 1H), 3.66 (dd, J = 3.8, 10.9 Hz, 1H), 3.30 - 3.23 (m, 2H), 2.94 (t, J = 3.3 Hz, 1H), 1.99 - 1.79 (m, 2H), 1.62 - 1.43 (m, 2H)	2.12, A

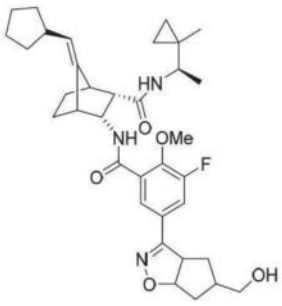
803		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(1,3-噻唑-5-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	685.3	(400 MHz, CD_3OD) δ = 8.86 (s, 1H), 8.17 (d, J = 2.3 Hz, 1H), 8.06 (dd, J = 2.4, 6.4 Hz, 1H), 7.88 (dd, J = 2.3, 8.8 Hz, 1H), 7.83 - 7.76 (m, 2H), 7.32 - 7.21 (m, 2H), 6.51 (s, 1H), 5.19 (dd, J = 5.0, 8.5 Hz, 1H), 4.64 (t, J = 4.0 Hz, 1H), 4.56 (s, 1H), 4.23 (t, J = 8.8 Hz, 1H), 4.07 (s, 3H), 3.57 - 3.48 (m, 3H), 2.91 (d, J = 4.5 Hz, 1H), 2.56 (d, J = 4.8 Hz, 1H), 2.18 - 1.89 (m, 6H), 1.83 - 1.59 (m, 5H)	1.90, B
804		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(2-甲基-1,3-噻唑-5-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	699.2	(400 MHz, DMSO-d6) δ = 10.63 (s, 1H), 10.04 (d, J = 6.8 Hz, 1H), 8.34 - 8.14 (m, 2H), 7.88 - 7.73 (m, 2H), 7.60 (s, 1H), 7.52 (t, J = 9.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.54 (s, 1H), 5.13 (dd, J = 5.1, 8.8 Hz, 1H), 4.56 - 4.43 (m, 2H), 4.27 - 4.17 (m, 1H), 4.06 (s, 3H), 3.31 - 3.26 (m, 1H), 2.95 (br d, J = 3.4 Hz, 1H), 2.66 (s, 3H), 1.99 (dd, J = 5.9, 13.7 Hz, 1H), 1.95 - 1.75 (m, 4H), 1.71 - 1.42 (m, 4H)	2.15, A

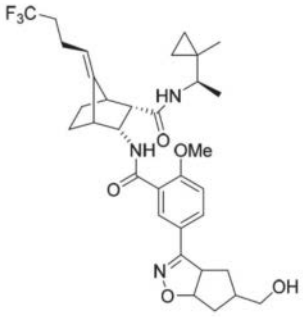
805		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(2-甲基-1,3-噻唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	699.2	(400 MHz, DMSO-d6) δ ppm 10.54 - 10.66 (m, 1 H) 9.80 - 9.90 (m, 1 H) 8.17 - 8.26 (m, 1 H) 7.76 - 7.85 (m, 1 H) 7.45 - 7.54 (m, 1 H) 7.25 - 7.36 (m, 1 H) 6.29 - 6.34 (m, 1 H) 5.05 - 5.17 (m, 1 H) 4.40 - 4.59 (m, 1 H) 4.14 - 4.29 (m, 1 H) 4.01 - 4.09 (m, 1 H) 3.82 - 3.89 (m, 1 H) 2.85 - 2.94 (m, 1 H) 2.62 - 2.72 (m, 2 H) 2.28 - 2.36 (m, 1 H) 1.44 - 2.05 (m, 5 H)	3.42, E
806		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-[(2-甲基-1,3-噻唑-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	671.1	(400 MHz, DMSO-d6) δ = 10.59 (s, 1H), 9.87 (d, J = 7.3 Hz, 1H), 8.24 (dd, J = 2.7, 6.6 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.82 (qd, J = 2.4, 8.7 Hz, 2H), 7.50 (t, J = 9.7 Hz, 1H), 7.34 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.32 (s, 1H), 5.35 (dd, J = 3.5, 9.2 Hz, 1H), 4.58 - 4.44 (m, 2H), 4.10 (d, J = 10.8 Hz, 1H), 4.06 (s, 3H), 3.90 (br d, J = 9.3 Hz, 2H), 3.77 (dd, J = 6.8, 9.3 Hz, 1H), 3.66 (dd, J = 3.7, 10.8 Hz, 1H), 3.27 (dd, J = 4.0, 10.6 Hz, 1H), 2.90 (br s, 1H), 2.68 (s, 3H), 2.02 - 1.93 (m, 1H), 1.90 - 1.81 (m, 1H), 1.58 - 1.44 (m, 2H)	2.25, A

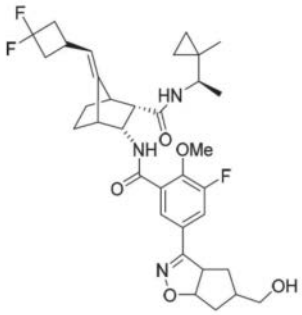
807		(1R,2S,3R,4R,7Z)-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-[(嘧啶-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	600.4	(400 MHz, DMSO-d6) δ 10.13 (d, J = 6.8 Hz, 1H), 9.13 (d, J = 0.8 Hz, 1H), 8.75 (d, J = 5.3 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 2.4, 8.6 Hz, 1H), 7.44 (dd, J = 1.2, 5.2 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H), 6.37 (s, 1H), 5.12 (dd, J = 5.1, 8.9 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 4.44 - 4.35 (m, 1H), 4.21 (t, J = 8.6 Hz, 1H), 4.06 - 3.94 (m, 4H), 3.50 (dd, J = 7.0, 8.4 Hz, 1H), 3.42 - 3.38 (m, 1H), 3.10 (dd, J = 4.2, 10.8 Hz, 1H), 2.81 (br s, 1H), 2.04 - 1.77 (m, 5H), 1.70 - 1.44 (m, 4H), 1.05 (d, J = 6.9 Hz, 3H), 1.01 (s, 3H), 0.63 - 0.52 (m, 1H), 0.43 - 0.32 (m, 1H), 0.26 - 0.15 (m, 2H)。	2.58, A

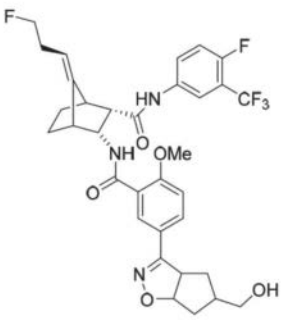
808		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-1,3,4-噻二唑-2-基]-2-甲氧基-4-甲基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	631.1	(400 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.93 (d, J = 7.1 Hz, 1H), 8.28 (s, 1H), 8.25 (dd, J = 2.4, 6.5 Hz, 1H), 7.88 - 7.67 (m, 1H), 7.50 (t, J = 9.8 Hz, 1H), 7.28 (s, 1H), 6.26 (t, J = 6.0 Hz, 1H), 4.90 (d, J = 5.9 Hz, 2H), 4.69 (d, J = 9.6 Hz, 1H), 4.50 - 4.38 (m, 1H), 4.09 (s, 3H), 3.21 - 3.13 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.59 (s, 3H), 1.92 - 1.72 (m, 2H), 1.55 - 1.30 (m, 3H), 0.83 - 0.61 (m, 2H), 0.35 (br d, J = 2.6 Hz, 2H)。	2.45, A
809		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(嘧啶-4-基)亚甲基]双环[2.2.1]庚烷-2-甲酰胺	680.2	(400 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.14 (d, J = 1.0 Hz, 1H), 8.76 (d, J = 5.5 Hz, 1H), 8.33 - 8.13 (m, 2H), 7.87 - 7.75 (m, 2H), 7.56 - 7.43 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 5.12 (dd, J = 5.4,8.9 Hz, 1H), 4.57 (ddd, J = 3.6, 6.6, 10.5 Hz, 1H), 4.48 (t, J = 5.3 Hz, 1H), 4.25 - 4.16 (m, 1H), 4.06 (s, 4H), 3.41 - 3.35 (m, 2H), 3.29 (br d, J = 4.3 Hz, 1H), 3.05 - 2.92 (m, 1H), 2.04 - 1.84 (m, 4H), 1.80 - 1.74 (m, 1H), 1.70 - 1.48 (m, 4H)	1.91, A

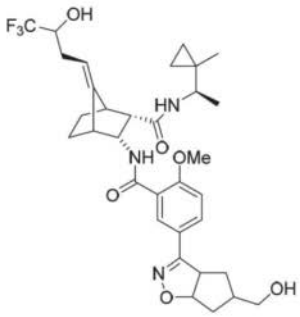
810		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{5-[5-(羟基甲基)-1,3,4-噻二唑-2-基]-2-甲氧基-4-甲基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	551.2	(400 MHz, DMSO-d6) δ 10.11 (d, J = 6.8 Hz, 1H), 8.23 (s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.23 (s, 1H), 6.24 (t, J = 5.9 Hz, 1H), 4.91 (d, J = 6.0 Hz, 2H), 4.64 (d, J = 9.5 Hz, 1H), 4.32 - 4.20 (m, 1H), 4.04 (s, 3H), 3.47 (dd, J = 6.9, 8.3 Hz, 1H), 3.09 - 3.02 (m, 1H), 2.96 (dd, J = 4.3, 11.0 Hz, 1H), 2.59 (s, 3H), 2.54 (br s, 1H), 1.91 - 1.83 (m, 1H), 1.74 (br s, 1H), 1.53 - 1.41 (m, 1H), 1.35 (br d, J = 2.8 Hz, 2H), 1.03 (d, J = 6.9 Hz, 3H), 0.99 (s, 3H), 0.72 (dt, J = 2.2, 8.3 Hz, 2H), 0.59 - 0.51 (m, 1H), 0.40 - 0.26 (m, 3H), 0.23 - 0.13 (m, 2H)。	2.17, A

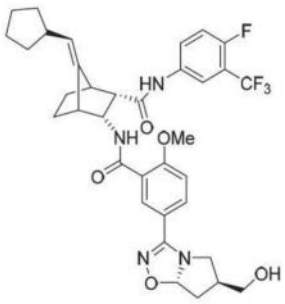
811		(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	608.1	(500 MHz, DMSO-d6) δ 9.79 (d, J=6.7 Hz, 1H), 7.82 (br d, J=8.9 Hz, 1H), 7.73 (s, 1H), 7.55 (dd, J=12.4, 2.0 Hz, 1H), 5.03 - 4.93 (m, 2H), 4.13 - 3.99 (m, 2H), 3.88 (d, J=2.1 Hz, 3H), 2.83 - 2.77 (m, 2H), 2.44 - 2.40 (m, 1H), 1.87 - 1.80 (m, 1H), 1.78 - 1.54 (m, 7H), 1.53 - 1.33 (m, 7H), 1.25 - 1.15 (m, 2H), 1.13 - 1.03 (m, 2H), 0.89 - 0.78 (m, 6H), 0.35 (br dd, J=9.0, 3.8 Hz, 1H), 0.16 (br dd, J=9.0, 3.8 Hz, 1H), 0.06 - -0.07 (m, 2H) 一些质子因水抑制而被遮挡	2.70, C

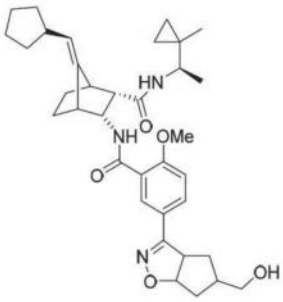
812		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	618.3	(500 MHz, DMSO-d6) δ 9.91 (d, J=6.7 Hz, 1H), 7.98 (d, J=2.1 Hz, 1H), 7.79 (br d, J=8.5 Hz, 1H), 7.62 (dd, J=8.5, 2.1 Hz, 1H), 7.05 (d, J=8.9 Hz, 1H), 5.04 (br t, J=6.9 Hz, 1H), 4.94 (dd, J=8.5, 5.2 Hz, 1H), 4.34 (br t, J=5.3 Hz, 1H), 4.12 - 3.98 (m, 2H), 3.81 (s, 3H), 2.81 - 2.73 (m, 2H), 2.39 (br s, 1H), 2.33 (br s, 3H), 2.22 - 2.07 (m, 4H), 1.81 (br dd, J=13.4, 5.5 Hz, 1H), 1.78 - 1.66 (m, 2H), 1.63 - 1.43 (m, 3H), 1.42 - 1.32 (m, 1H), 1.16 (br d, J=3.7 Hz, 2H), 0.91 - 0.83 (m, 3H), 0.81 (s, 3H), 0.36 (br dd, J=9.6, 3.5 Hz, 1H), 0.19 - 0.13 (m, 1H), 0.07 - -0.04 (m, 2H)	2.27, C

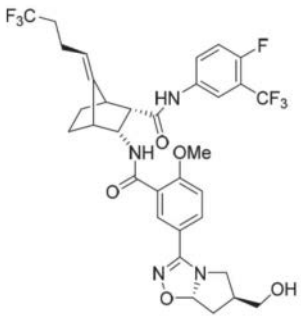
813		(1R,2S,3R,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	630.4	(500 MHz, DMSO-d6) δ 9.82 (br d, J=6.7 Hz, 1H), 7.85 (br d, J=8.9 Hz, 1H), 7.73 (s, 1H), 7.54 (br d, J=12.2 Hz, 1H), 5.18 (d, J=8.5 Hz, 1H), 5.00 (br dd, J=8.7, 5.0 Hz, 1H), 4.39 (br t, J=4.9 Hz, 1H), 4.12 - 4.00 (m, 2H), 3.88 (s, 3H), 3.19 (br s, 1H), 2.85 - 2.58 (m, 5H), 2.42 (br s, 1H), 2.31 - 2.16 (m, 2H), 1.83 (br dd, J=13.1, 5.2 Hz, 1H), 1.77 - 1.34 (m, 7H), 1.19 (br d, J=1.8 Hz, 2H), 0.89 - 0.77 (m, 7H), 0.39 - 0.31 (m, 1H), 0.22 - 0.13 (m, 1H), 0.07 - -0.05 (m, 2H)	2.45, C

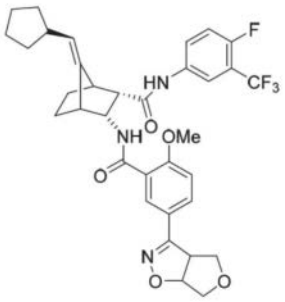
814		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(3-氟亚丙基)双环[2.2.1]庚烷-2-甲酰胺	647.9	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.88 (br d, J=7.0 Hz, 1H), 8.27 - 8.15 (m, 2H), 7.86 - 7.73 (m, 2H), 7.48 (t, J=9.6 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.28 (t, J=7.3 Hz, 1H), 5.12 (dd, J=8.7, 5.0 Hz, 1H), 4.61 - 4.47 (m, 2H), 4.44 - 4.36 (m, 2H), 4.19 (br t, J=8.7 Hz, 1H), 4.04 (s, 3H), 3.46 - 3.31 (m, 2H), 3.20 - 3.15 (m, 1H), 3.00 (br s, 1H), 2.77 (br s, 1H), 2.49 - 2.37 (m, 2H), 1.99 (br dd, J=13.3, 5.3 Hz, 1H), 1.95 - 1.84 (m, 2H), 1.83 - 1.72 (m, 2H), 1.69 - 1.60 (m, 1H), 1.60 - 1.49 (m, 1H), 1.40 (br s, 2H)	2.21, C

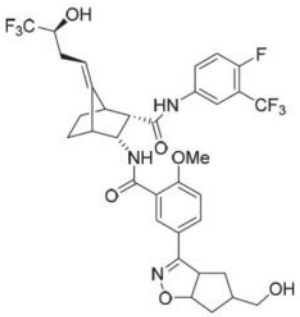
815		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	634.2	(500 MHz, DMSO-d6) δ 9.99 - 9.83 (m, 1H), 7.97 (d, J=2.1 Hz, 1H), 7.80 (br d, J=8.2 Hz, 1H), 7.62 (dd, J=8.5, 2.1 Hz, 1H), 7.05 (d, J=8.9 Hz, 1H), 6.08 (d, J=6.7 Hz, 1H), 5.08 (br t, J=7.3 Hz, 1H), 4.94 (br dd, J=8.7, 5.0 Hz, 1H), 4.11 - 3.97 (m, 2H), 3.84 - 3.76 (m, 3H), 3.36 - 3.25 (m, 1H), 3.23 - 3.10 (m, 1H), 2.81 - 2.65 (m, 3H), 2.43 - 2.39 (m, 1H), 2.26 - 2.17 (m, 1H), 2.09 (dt, J=14.6, 7.3 Hz, 1H), 1.81 (br dd, J=13.1, 5.5 Hz, 1H), 1.78 - 1.65 (m, 2H), 1.61 (br dd, J=12.7, 6.0 Hz, 1H), 1.56 - 1.43 (m, 2H), 1.40 - 1.31 (m, 1H), 1.24 - 1.10 (m, 2H), 0.99 (t, J=7.2 Hz, 2H), 0.87 - 0.66 (m, 6H), 0.41 - 0.32 (m, 1H), 0.20 - 0.11 (m, 1H), 0.04 - -0.09 (m, 2H)	2.09, C

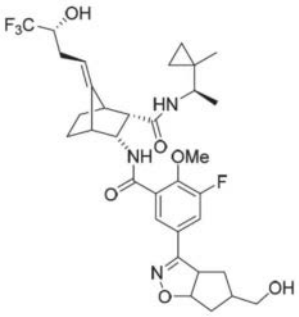
816		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aS)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	671.3	(500 MHz, DMSO-d6) δ 10.54 (br s, 1H), 10.00 - 9.86 (m, 1H), 8.34 - 8.18 (m, 2H), 7.80 (br s, 2H), 7.59 - 7.46 (m, 1H), 7.37 - 7.29 (m, 1H), 5.91 - 5.71 (m, 1H), 5.19 (br d, J=8.9 Hz, 1H), 4.67 (br d, J=4.6 Hz, 1H), 4.48 - 4.32 (m, 1H), 4.16 - 3.95 (m, 3H), 3.22 - 3.11 (m, 1H), 3.05 - 2.99 (m, 1H), 2.94 - 2.85 (m, 1H), 2.77 - 2.69 (m, 1H), 2.36 - 2.24 (m, 1H), 2.21 - 2.11 (m, 1H), 2.10 - 2.02 (m, 1H), 2.01 - 1.90 (m, 1H), 1.90 - 1.72 (m, 4H), 1.69 - 1.52 (m, 4H), 1.48 - 1.34 (m, 2H), 1.34 - 1.12 (m, 2H) 一些质子因水抑制而被遮挡	2.65, C

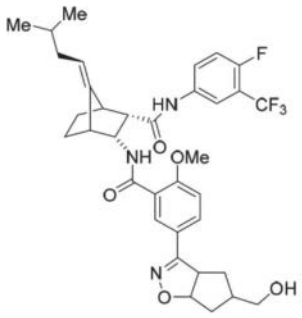
817		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环戊基亚甲基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	590.3	(500 MHz, DMSO-d6) δ 9.86 (br d, J=6.7 Hz, 1H), 7.98 (d, J=2.1 Hz, 1H), 7.74 (br d, J=8.5 Hz, 1H), 7.61 (dd, J=8.7, 2.3 Hz, 1H), 7.05 (d, J=8.9 Hz, 1H), 5.01 - 4.87 (m, 2H), 4.09 - 3.96 (m, 2H), 3.81 (s, 3H), 3.32 - 3.24 (m, 1H), 2.77 (br d, J=5.5 Hz, 2H), 2.35 (br d, J=3.7 Hz, 1H), 2.33 (br s, 4H), 1.81 (br dd, J=13.1, 5.5 Hz, 1H), 1.78 - 1.42 (m, 9H), 1.42 - 1.33 (m, 3H), 1.19 - 1.01 (m, 4H), 0.87 - 0.75 (m, 6H), 0.39 - 0.31 (m, 1H), 0.19 - 0.11 (m, 1H), 0.06 - -0.07 (m, 2H)	2.48, C

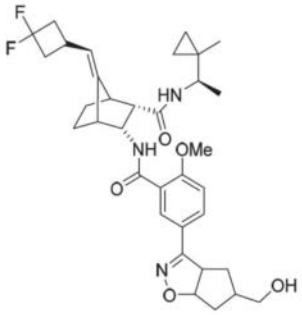
818		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aS)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	699.2	(500 MHz, DMSO-d6) δ 10.73 - 10.51 (m, 1H), 10.00 - 9.83 (m, 1H), 8.25 (br d, J=16.8 Hz, 2H), 7.81 (br s, 2H), 7.58 - 7.46 (m, 1H), 7.32 (br d, J=8.9 Hz, 1H), 5.92 - 5.70 (m, 1H), 5.29 (br d, J=6.1 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.07 (br s, 3H), 3.58 - 3.38 (m, 1H), 3.28 - 3.15 (m, 1H), 3.10 - 2.98 (m, 1H), 2.93 - 2.86 (m, 1H), 2.84 - 2.75 (m, 1H), 2.66 (br dd, J=5.2, 3.7 Hz, 1H), 2.47 - 2.25 (m, 5H), 2.22 - 2.01 (m, 2H), 2.01 - 1.70 (m, 4H), 1.41 (br s, 2H)	2.44, C

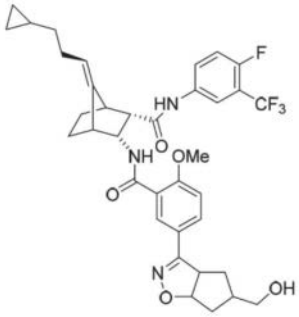
819		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	641.9	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (br d, J=7.0 Hz, 1H), 8.26 - 8.17 (m, 2H), 7.87 - 7.72 (m, 2H), 7.47 (br t, J=9.9 Hz, 1H), 7.27 (d, J=8.5 Hz, 1H), 5.34 (dd, J=9.5, 3.4 Hz, 1H), 5.19 (d, J=8.5 Hz, 1H), 4.47 (br t, J=7.5 Hz, 1H), 4.43 - 4.32 (m, 1H), 4.19 - 4.08 (m, 1H), 4.03 (s, 3H), 3.97 - 3.85 (m, 1H), 3.77 (br dd, J=9.5, 7.0 Hz, 1H), 3.15 (td, J=10.6, 4.4 Hz, 2H), 2.99 (br s, 1H), 2.71 (br s, 1H), 2.62 - 2.56 (m, 1H), 1.92 - 1.69 (m, 4H), 1.65 - 1.51 (m, 4H), 1.45 - 1.35 (m, 2H), 1.29 - 1.16 (m, 2H)	2.66, C

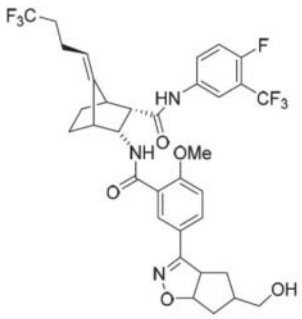
820		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	714.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.86 (br d, J=6.9 Hz, 1H), 8.22 (br s, 2H), 7.86 - 7.75 (m, 2H), 7.49 (t, J=9.6 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 6.27 (br d, J=6.6 Hz, 1H), 5.32 (t, J=7.0 Hz, 1H), 5.12 (dd, J=8.4, 5.2 Hz, 1H), 4.48 - 4.37 (m, 1H), 4.19 (br t, J=8.9 Hz, 1H), 4.04 (s, 3H), 4.02 - 3.92 (m, 1H), 2.98 (br s, 1H), 2.77 (br s, 1H), 2.51 (br s, 4H), 2.45 - 2.27 (m, 2H), 1.99 (br dd, J=13.6, 5.8 Hz, 1H), 1.95 - 1.84 (m, 2H), 1.82 - 1.71 (m, 2H), 1.68 - 1.51 (m, 2H), 1.45 - 1.35 (m, 2H)	2.27, C

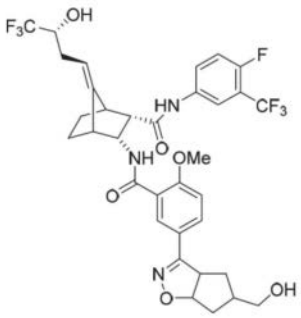
821		(1R,2S,3R,4R,7Z)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	652.2	(500 MHz, DMSO-d6) δ 9.82 (br d, J=6.6 Hz, 1H), 7.91 - 7.83 (m, 1H), 7.71 (br s, 1H), 7.53 (br d, J=12.4 Hz, 1H), 6.15 - 6.00 (m, 1H), 5.09 (br t, J=7.1 Hz, 1H), 5.02 - 4.96 (m, 1H), 4.63 (br d, J=8.4 Hz, 1H), 4.14 - 3.98 (m, 2H), 3.87 (s, 3H), 3.81 - 3.74 (m, 1H), 3.23 - 3.11 (m, 1H), 2.77 (br s, 1H), 2.34 (br s, 4H), 2.27 - 2.18 (m, 1H), 2.11 (s, 1H), 1.82 (br dd, J=13.2, 5.5 Hz, 1H), 1.77 - 1.53 (m, 4H), 1.51 - 1.32 (m, 2H), 1.28 - 1.13 (m, 2H), 0.89 - 0.70 (m, 6H), 0.38 - 0.31 (m, 1H), 0.16 (br d, J=4.3 Hz, 1H), 0.01 (br d, J=5.2 Hz, 2H)	2.16, C

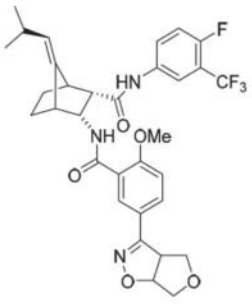
822		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	657.9	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.88 (br d, J=7.0 Hz, 1H), 8.20 (br d, J=2.1 Hz, 2H), 7.86 - 7.70 (m, 2H), 7.47 (br t, J=9.6 Hz, 1H), 7.26 (br d, J=8.8 Hz, 1H), 5.23 (br t, J=7.6 Hz, 1H), 5.12 (br dd, J=8.1, 5.0 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.18 (br t, J=8.9 Hz, 1H), 4.02 (s, 3H), 3.16 (dd, J=10.7, 2.8 Hz, 1H), 2.94 (br s, 1H), 2.73 (br s, 1H), 2.51 (br s, 3H), 2.01 - 1.81 (m, 5H), 1.80 - 1.70 (m, 2H), 1.69 - 1.49 (m, 3H), 1.46 - 1.30 (m, 2H), 0.90 (br dd, J=12.3, 6.6 Hz, 6H)	2.66, C

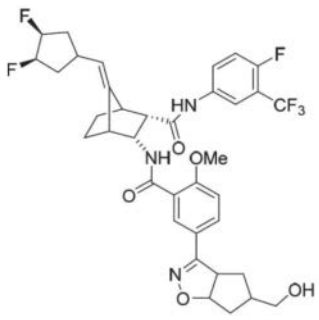
823		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(3,3-二氟环丁基)亚甲基]-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	612.6	(500 MHz, DMSO-d6) δ 9.89 (br d, J=6.7 Hz, 1H), 7.97 (d, J=2.1 Hz, 1H), 7.77 (br d, J=8.5 Hz, 1H), 7.61 (dd, J=8.5, 1.8 Hz, 1H), 7.05 (d, J=8.5 Hz, 1H), 5.15 (d, J=8.2 Hz, 1H), 4.94 (br dd, J=8.5, 5.2 Hz, 1H), 4.12 - 3.95 (m, 2H), 3.81 (s, 3H), 2.85 - 2.71 (m, 3H), 2.69 - 2.55 (m, 2H), 2.33 (br s, 3H), 2.27 - 2.11 (m, 2H), 1.87 - 1.30 (m, 7H), 1.14 (br s, 2H), 0.95 - 0.63 (m, 6H), 0.42 - 0.31 (m, 1H), 0.20 - 0.08 (m, 1H), 0.06 - -0.12 (m, 2H) 由于水抑制而未观测到一些质子	2.22, C

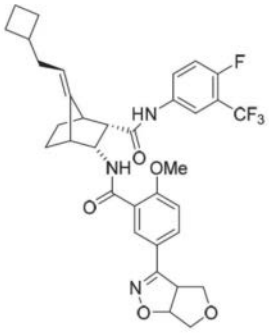
824		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(3-环丙基亚丙基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	670.0	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.85 (d, J=7.0 Hz, 1H), 8.18 (br s, 2H), 7.81 - 7.67 (m, 2H), 7.43 (t, J=9.7 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 5.24 (t, J=7.5 Hz, 1H), 5.08 (dd, J=8.6, 5.2 Hz, 1H), 4.40 - 4.34 (m, 1H), 4.15 (br t, J=8.9 Hz, 1H), 3.99 (s, 3H), 3.39 - 3.22 (m, 2H), 3.12 (br dd, J=10.7, 4.1 Hz, 1H), 2.96 (br s, 1H), 2.69 (br s, 1H), 2.48 (s, 3H), 2.18 - 2.03 (m, 2H), 1.99 - 1.91 (m, 1H), 1.88 - 1.56 (m, 5H), 1.51 (td, J=12.5, 5.1 Hz, 1H), 1.40 - 1.30 (m, 2H), 1.29 - 1.16 (m, 2H), 0.72 - 0.64 (m, 1H), 0.49 - 0.33 (m, 2H)	2.56, C

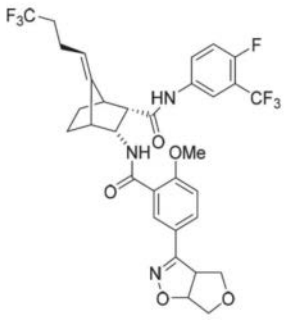
825		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	697.9	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.90 (d, J=7.0 Hz, 1H), 8.22 (br d, J=2.1 Hz, 2H), 7.85 - 7.73 (m, 2H), 7.48 (br t, J=9.7 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 5.27 (br t, J=6.7 Hz, 1H), 5.12 (dd, J=8.6, 5.1 Hz, 1H), 4.41 (br t, J=10.0 Hz, 1H), 4.19 (br t, J=9.2 Hz, 1H), 4.03 (s, 3H), 3.16 (br dd, J=11.5, 3.5 Hz, 1H), 2.99 (br s, 1H), 2.75 (br s, 1H), 2.51 (br d, J=1.6 Hz, 3H), 2.44 - 2.27 (m, 4H), 1.98 (br dd, J=13.7, 5.8 Hz, 1H), 1.93 - 1.82 (m, 2H), 1.81 - 1.72 (m, 2H), 1.70 - 1.61 (m, 1H), 1.59 - 1.50 (m, 1H), 1.39 (br d, J=6.5 Hz, 2H)	2.44, C

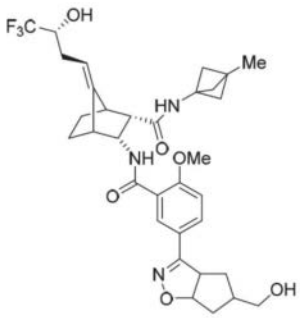
826		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	714.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.90 (br d, J=7.3 Hz, 1H), 8.23 (br d, J=2.1 Hz, 2H), 7.81 (br dd, J=8.5, 1.8 Hz, 2H), 7.49 (t, J=9.9 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.32 (br t, J=7.5 Hz, 1H), 5.12 (dd, J=8.5, 5.2 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.20 (br t, J=9.0 Hz, 1H), 4.09 - 3.93 (m, 4H), 3.18 (br dd, J=11.0, 3.7 Hz, 1H), 2.99 (br d, J=7.0 Hz, 1H), 2.77 (br s, 1H), 2.51 (br s, 4H), 2.46 - 2.37 (m, 1H), 2.34 - 2.23 (m, 1H), 1.99 (br dd, J=13.7, 5.2 Hz, 1H), 1.93 - 1.83 (m, 2H), 1.82 - 1.72 (m, 2H), 1.70 - 1.62 (m, 1H), 1.59 - 1.51 (m, 1H), 1.45 - 1.35 (m, 2H)	2.21, C

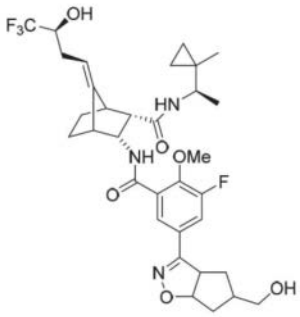
827		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-甲酰胺	616.3	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.88 (br d, J=6.7 Hz, 1H), 8.28 - 8.17 (m, 2H), 7.86 - 7.74 (m, 2H), 7.48 (br t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.34 (dd, J=9.0, 3.5 Hz, 1H), 5.11 (d, J=8.9 Hz, 1H), 4.48 (br t, J=8.1 Hz, 1H), 4.41 - 4.33 (m, 1H), 4.10 (br d, J=10.7 Hz, 1H), 4.04 (s, 3H), 3.89 (br d, J=9.2 Hz, 1H), 3.77 (dd, J=9.3, 6.9 Hz, 1H), 3.70 - 3.62 (m, 1H), 3.20 - 3.13 (m, 1H), 2.99 (br s, 1H), 2.70 (br s, 1H), 2.49 - 2.40 (m, 1H), 1.91 - 1.70 (m, 2H), 1.49 - 1.32 (m, 2H), 1.09 - 0.93 (m, 6H)	2.64, C

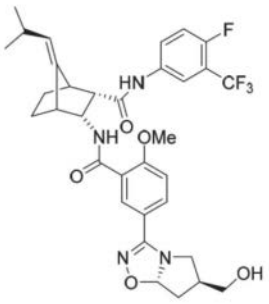
828		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-{[(3R,4S)-3,4-二氟环戊基]亚甲基}-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	706.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.90 (br d, J=6.7 Hz, 1H), 8.27 - 8.17 (m, 2H), 7.87 - 7.72 (m, 2H), 7.48 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.27 - 5.03 (m, 4H), 4.44 - 4.33 (m, 1H), 4.19 (br t, J=8.9 Hz, 1H), 4.03 (s, 3H), 3.42 - 3.30 (m, 1H), 3.23 - 3.10 (m, 2H), 2.98 (br s, 1H), 2.72 (br s, 1H), 2.52 (br s, 3H), 2.20 - 2.05 (m, 2H), 1.99 (br dd, J=13.3, 5.3 Hz, 1H), 1.93 - 1.81 (m, 2H), 1.78 - 1.62 (m, 4H), 1.60 - 1.50 (m, 1H), 1.44 - 1.33 (m, 2H)	2.36, C

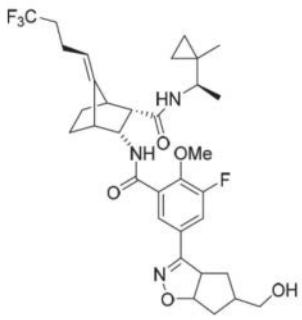
829		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2-环丁基亚乙基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	642.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.31 - 8.14 (m, 2H), 7.86 - 7.72 (m, 2H), 7.48 (t, J=9.7 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 5.34 (dd, J=9.0, 3.6 Hz, 1H), 5.17 (t, J=7.5 Hz, 1H), 4.49 (br t, J=8.3 Hz, 1H), 4.41 - 4.35 (m, 1H), 4.10 (d, J=10.6 Hz, 1H), 4.04 (s, 3H), 3.89 (br d, J=8.5 Hz, 1H), 3.77 (dd, J=9.3, 7.0 Hz, 1H), 3.66 (dd, J=10.7, 3.6 Hz, 1H), 3.15 (br dd, J=10.4, 4.1 Hz, 1H), 2.99 (br s, 1H), 2.72 (br s, 1H), 2.32 (quin, J=7.6 Hz, 1H), 2.14 (td, J=7.2, 2.6 Hz, 2H), 2.07 - 1.96 (m, 2H), 1.89 - 1.74 (m, 4H), 1.71 - 1.57 (m, 2H), 1.37 (br s, 2H)	2.74, C

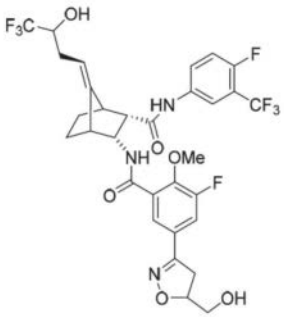
830		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	670.4	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.90 (br d, J=6.7 Hz, 1H), 8.30 - 8.14 (m, 2H), 7.87 - 7.70 (m, 2H), 7.49 (br t, J=9.6 Hz, 1H), 7.28 (d, J=8.9 Hz, 1H), 5.35 (dd, J=9.3, 3.5 Hz, 1H), 5.28 (br t, J=6.6 Hz, 1H), 4.50 (br t, J=7.9 Hz, 1H), 4.43 - 4.36 (m, 1H), 4.10 (br d, J=10.7 Hz, 1H), 4.05 (s, 3H), 3.90 (br d, J=8.9 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.66 (dd, J=11.0, 3.4 Hz, 1H), 3.17 (br dd, J=10.7, 4.0 Hz, 1H), 3.00 (br s, 1H), 2.76 (br s, 1H), 2.44 - 2.22 (m, 4H), 1.93 - 1.70 (m, 2H), 1.48 - 1.28 (m, 2H)	2.45, C

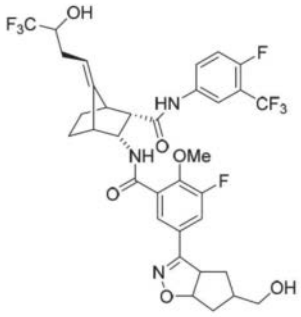
831		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,5R,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-{3-甲基双环[1.1.1]戊烷-1-基}-7-[(3R)-4,4,4-三氟-3-羟基丁亚基]双环[2.2.1]庚烷-2-甲酰胺	632.3	(500 MHz, DMSO-d6) δ 10.16 (br d, J=6.7 Hz, 1H), 8.56 (s, 1H), 8.21 (d, J=1.5 Hz, 1H), 7.86 - 7.76 (m, 1H), 7.25 (d, J=8.9 Hz, 1H), 5.23 (br t, J=7.3 Hz, 1H), 5.13 (br dd, J=8.4, 5.3 Hz, 1H), 4.62 - 4.45 (m, 1H), 4.30 - 4.18 (m, 2H), 4.10 - 3.90 (m, 4H), 2.94 (br s, 1H), 2.84 (br dd, J=10.5, 4.4 Hz, 1H), 2.58 (br s, 1H), 2.52 (br s, 4H), 2.47 - 2.34 (m, 1H), 2.26 (dt, J=14.6, 7.6 Hz, 1H), 2.00 (br dd, J=13.4, 5.2 Hz, 1H), 1.92 - 1.75 (m, 8H), 1.74 - 1.53 (m, 3H), 1.33 (br s, 2H), 1.20 (s, 3H)	2.03, C

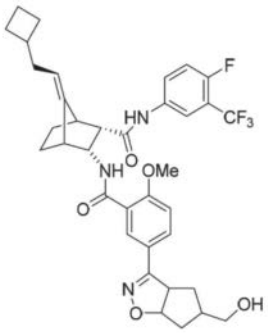
832		(1R,2S,3R,4R,7Z)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	652.3	(500 MHz, DMSO-d6) δ 9.82 (br d, J=6.6 Hz, 1H), 7.87 (br d, J=8.7 Hz, 1H), 7.72 (s, 1H), 7.53 (br d, J=12.5 Hz, 1H), 5.10 (br t, J=7.2 Hz, 1H), 5.00 (br dd, J=8.7, 5.3 Hz, 1H), 4.10 (br dd, J=10.1, 3.7 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.87 (s, 3H), 3.80 (br dd, J=5.4, 4.1 Hz, 1H), 3.34 - 3.12 (m, 2H), 2.86 - 2.74 (m, 2H), 2.43 (br s, 1H), 2.35 - 2.31 (m, 2H), 2.25 - 2.05 (m, 2H), 1.84 (br dd, J=14.0, 5.7 Hz, 1H), 1.76 - 1.71 (m, 1H), 1.72 - 1.32 (m, 6H), 1.20 (br d, J=5.2 Hz, 2H), 0.92 - 0.68 (m, 6H), 0.34 (br dd, J=5.8, 2.9 Hz, 1H), 0.20 - 0.12 (m, 1H), 0.05 - -0.08 (m, 2H)	2.26, C

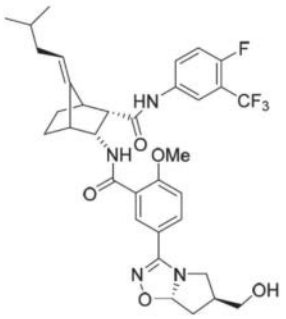
833		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aS)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-甲酰胺	645.3	(500 MHz, DMSO-d6) δ 9.99 - 9.84 (m, 1H), 8.29 - 8.18 (m, 2H), 7.82 - 7.74 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.30 (d, J=8.8 Hz, 1H), 5.83 - 5.76 (m, 1H), 5.10 (d, J=9.0 Hz, 1H), 4.43 - 4.35 (m, 1H), 4.11 - 4.00 (m, 3H), 3.38 - 3.24 (m, 2H), 3.22 - 3.10 (m, 2H), 2.98 (br s, 1H), 2.75 - 2.69 (m, 1H), 2.51 - 2.44 (m, 2H), 2.33 - 2.10 (m, 2H), 2.10 - 2.01 (m, 1H), 1.96 - 1.90 (m, 1H), 1.87 - 1.65 (m, 3H), 1.44 - 1.32 (m, 2H), 1.07 - 0.93 (m, 6H)	2.48, C

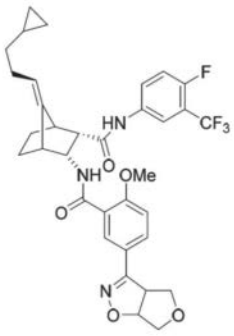
834		(1R,2S,3R,4R,7Z)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-甲酰胺	636.2	(500 MHz, DMSO-d6) δ 9.84 (br d, J=6.7 Hz, 1H), 7.87 (br d, J=8.5 Hz, 1H), 7.73 (s, 1H), 7.54 (dd, J=12.5, 1.8 Hz, 1H), 5.11 - 4.96 (m, 2H), 4.14 - 3.97 (m, 2H), 3.88 (d, J=2.1 Hz, 3H), 3.26 - 3.09 (m, 1H), 2.91 - 2.74 (m, 2H), 2.42 (br s, 1H), 2.35 (br s, 3H), 2.25 - 2.06 (m, 4H), 1.84 (br dd, J=13.4, 5.5 Hz, 1H), 1.75 - 1.53 (m, 4H), 1.52 - 1.32 (m, 2H), 1.20 (br d, J=6.7 Hz, 2H), 0.92 - 0.72 (m, 6H), 0.34 (br dd, J=9.0, 3.5 Hz, 1H), 0.22 - 0.13 (m, 1H), 0.06 - -0.06 (m, 2H)	2.48, C

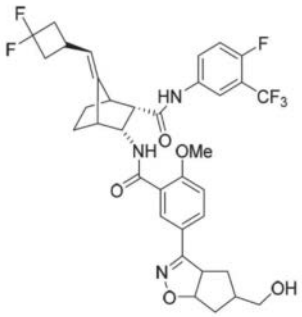
835		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	692.2	(500 MHz, DMSO-d6) δ 10.64 - 10.49 (m, 1H), 9.68 (br d, J=7.3 Hz, 1H), 8.11 (br d, J=3.7 Hz, 1H), 7.93 (s, 1H), 7.86 - 7.78 (m, 1H), 7.70 (br d, J=12.5 Hz, 1H), 7.47 (br t, J=9.8 Hz, 1H), 5.32 (br t, J=7.2 Hz, 1H), 5.07 (s, 1H), 4.74 (br dd, J=10.7, 7.3 Hz, 1H), 4.44 (br d, J=5.5 Hz, 1H), 4.08 (d, J=2.1 Hz, 3H), 4.03 - 3.93 (m, 1H), 3.23 - 3.11 (m, 2H), 3.05 - 2.97 (m, 1H), 2.78 (br s, 1H), 2.52 (br s, 4H), 2.48 - 2.39 (m, 1H), 2.34 - 2.25 (m, 1H), 1.91 - 1.74 (m, 2H), 1.53 - 1.34 (m, 2H)	2.19, C

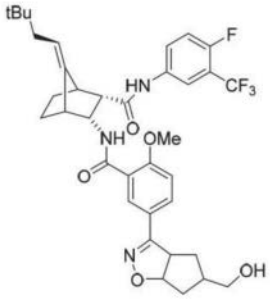
836		(1R,2S,3R,4R,7Z)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(4,4,4-三氟-3-羟基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	732.2	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.65 (br d, J=7.3 Hz, 1H), 8.11 (br d, J=5.9 Hz, 1H), 7.95 (s, 1H), 7.84 (br d, J=8.2 Hz, 1H), 7.72 (br d, J=12.4 Hz, 1H), 7.48 (br t, J=9.7 Hz, 1H), 6.27 (d, J=6.6 Hz, 1H), 5.32 (br t, J=7.2 Hz, 1H), 5.16 (br dd, J=8.2, 5.4 Hz, 1H), 4.57 - 4.38 (m, 2H), 4.19 (s, 1H), 4.08 (s, 3H), 4.03 - 3.92 (m, 1H), 3.18 (br dd, J=10.3, 3.5 Hz, 1H), 2.98 (br s, 1H), 2.78 (br s, 1H), 2.51 - 2.47 (m, 2H), 2.43 - 2.28 (m, 2H), 1.99 (br dd, J=14.0, 5.2 Hz, 1H), 1.94 - 1.84 (m, 2H), 1.84 - 1.73 (m, 2H), 1.71 - 1.51 (m, 2H), 1.47 - 1.33 (m, 2H)	2.31, C

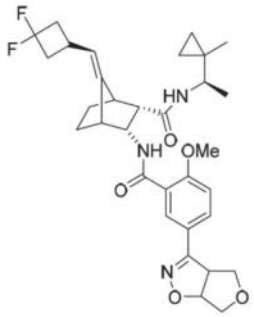
837		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(2-环丁基亚乙基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	670.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.2 Hz, 1H), 8.21 (br d, J=2.5 Hz, 2H), 7.92 - 7.73 (m, 2H), 7.47 (br t, J=9.5 Hz, 1H), 7.26 (d, J=8.9 Hz, 1H), 5.24 - 5.08 (m, 2H), 4.42 - 4.34 (m, 1H), 4.18 (br t, J=8.9 Hz, 1H), 4.03 (s, 3H), 3.38 - 3.29 (m, 1H), 3.18 - 3.10 (m, 1H), 2.98 (br d, J=3.6 Hz, 1H), 2.71 (br s, 1H), 2.31 (dt, J=15.1, 7.5 Hz, 1H), 2.21 - 2.10 (m, 3H), 2.04 - 1.91 (m, 3H), 1.85 - 1.72 (m, 5H), 1.67 - 1.61 (m, 2H), 1.60 - 1.50 (m, 1H), 1.43 - 1.28 (m, 5H)	2.61, C

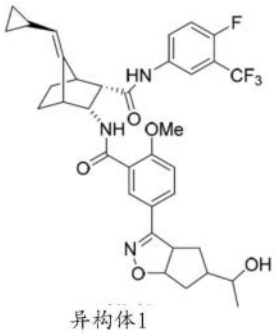
838		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aS)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-N-[4-氟-3-(三氟甲基)苯基]-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-甲酰胺	659.2	(500 MHz, DMSO-d6) δ 10.63 (br s, 1H), 10.03 - 9.79 (m, 1H), 8.26 (br s, 2H), 7.96 - 7.77 (m, 2H), 7.56 - 7.45 (m, 1H), 7.36 - 7.24 (m, 1H), 5.94 - 5.75 (m, 1H), 5.39 - 5.21 (m, 1H), 4.40 (br d, J=4.3 Hz, 1H), 4.18 - 3.99 (m, 3H), 3.56 - 3.39 (m, 1H), 3.37 - 3.09 (m, 2H), 3.04 - 2.93 (m, 1H), 2.81 - 2.73 (m, 1H), 2.60 (br s, 1H), 2.38 - 2.15 (m, 2H), 2.10 - 1.71 (m, 7H), 1.69 - 1.56 (m, 1H), 1.48 - 1.29 (m, 2H), 1.07 - 0.83 (m, 6H)	2.62, C

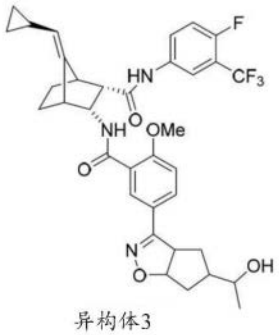
839		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(3-环丙基亚丙基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	642.4	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.85 (br d, J=7.3 Hz, 1H), 8.16 (br d, J=2.1 Hz, 2H), 7.85 - 7.70 (m, 2H), 7.52 - 7.39 (m, 1H), 7.24 (d, J=8.5 Hz, 1H), 5.30 (br dd, J=9.3, 3.2 Hz, 1H), 5.24 (br t, J=7.5 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.37 - 4.30 (m, 1H), 4.06 (br d, J=11.0 Hz, 1H), 4.00 (s, 2H), 3.89 - 3.80 (m, 1H), 3.76 - 3.67 (m, 1H), 3.18 - 3.08 (m, 1H), 2.96 (br s, 1H), 2.69 (br s, 1H), 2.51 (s, 2H), 2.10 (br dd, J=7.2, 4.1 Hz, 2H), 1.85 - 1.65 (m, 2H), 1.42 - 1.32 (m, 2H), 1.27 - 1.15 (m, 2H), 0.73 - 0.63 (m, 1H), 0.50 - 0.33 (m, 2H), 0.01 (br d, J=4.0 Hz, 2H)	2.69, C

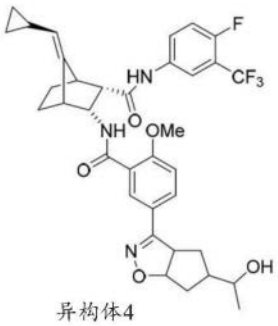
840		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(3,3-二氟环丁基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	692.3	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.89 (br d, J=7.2 Hz, 1H), 8.22 (br s, 2H), 7.86 - 7.73 (m, 2H), 7.54 - 7.43 (m, 1H), 7.27 (d, J=8.8 Hz, 1H), 5.39 (br d, J=8.4 Hz, 1H), 5.12 (br dd, J=8.4, 5.3 Hz, 1H), 4.64 - 4.50 (m, 1H), 4.43 - 4.31 (m, 1H), 4.18 (br t, J=8.6 Hz, 1H), 4.03 (s, 3H), 3.43 - 3.27 (m, 1H), 3.16 (br dd, J=10.1, 3.4 Hz, 1H), 3.02 - 2.91 (m, 2H), 2.89 - 2.72 (m, 3H), 2.51 (br s, 2H), 2.47 - 2.33 (m, 2H), 1.99 (br s, 1H), 1.94 - 1.82 (m, 2H), 1.80 - 1.69 (m, 2H), 1.61 - 1.49 (m, 1H), 1.39 (br d, J=1.3 Hz, 2H)	2.42, C

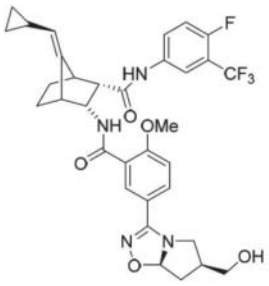
841		(1R,2S,3R,4R,7Z)-3-{5-[(3aS,6aS)-5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-(3,3-二甲基丁亚基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	672.2	(500 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.73 (br d, J=7.0 Hz, 1H), 8.15 - 8.02 (m, 2H), 7.72 - 7.59 (m, 2H), 7.33 (br t, J=9.6 Hz, 1H), 7.11 (d, J=8.5 Hz, 1H), 5.13 (t, J=7.9 Hz, 1H), 4.96 (dd, J=8.4, 5.0 Hz, 1H), 4.33 (t, J=5.3 Hz, 1H), 4.25 (br s, 1H), 4.03 (br t, J=8.7 Hz, 1H), 3.88 (s, 3H), 3.06 - 2.98 (m, 1H), 2.82 (br d, J=17.7 Hz, 1H), 2.60 (br s, 1H), 2.35 (br s, 2H), 1.90 - 1.66 (m, 5H), 1.63 - 1.54 (m, 2H), 1.50 (br d, J=9.2 Hz, 1H), 1.40 (br d, J=3.4 Hz, 1H), 1.30 - 1.14 (m, 2H), 0.76 (s, 9H)	2.30, C

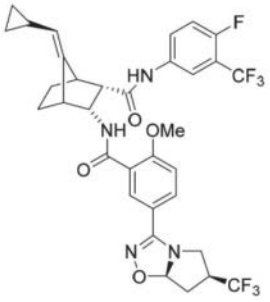
842		(1R,2S,3R,4R,7Z)-3-{5-[(3aR,6aR)-3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-7-[(3,3-二氟环丁基)亚甲基]-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	584.3	(500 MHz, DMSO-d6) δ 9.89 (br d, J=6.7 Hz, 1H), 7.96 (d, J=2.1 Hz, 1H), 7.77 (br d, J=8.5 Hz, 1H), 7.61 (dd, J=8.7, 2.3 Hz, 1H), 7.05 (d, J=8.9 Hz, 1H), 5.21 - 5.11 (m, 2H), 4.31 (br t, J=7.6 Hz, 1H), 4.10 - 4.00 (m, 1H), 3.92 (br d, J=10.7 Hz, 1H), 3.81 (s, 3H), 3.74 - 3.66 (m, 1H), 3.60 (br dd, J=9.2, 7.3 Hz, 1H), 3.48 (br dd, J=10.5, 3.5 Hz, 1H), 2.73 - 2.51 (m, 3H), 2.39 (br s, 1H), 2.32 (br s, 4H), 2.28 - 2.15 (m, 2H), 1.75 - 1.66 (m, 1H), 1.58 - 1.48 (m, 1H), 1.23 - 1.05 (m, 2H), 0.89 - 0.78 (m, 5H), 0.43 - 0.32 (m, 1H), 0.24 - 0.10 (m, 1H), 0.00 (br t, J=7.3 Hz, 2H)	2.34, C

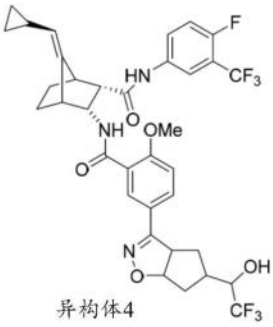
843	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.91 (br d, J=7.3 Hz, 1H), 8.24 - 8.19 (m, 2H), 7.81 - 7.76 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 5.09 (br dd, J=8.5, 4.9 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.47 - 4.42 (m, 1H), 4.17 (br t, J=8.2 Hz, 1H), 4.03 (s, 3H), 3.18 - 3.13 (m, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 2.54 (s, 2H), 1.90 - 1.81 (m, 3H), 1.79 - 1.74 (m, 1H), 1.72 - 1.64 (m, 2H), 1.60 - 1.46 (m, 2H), 1.45 - 1.34 (m, 2H), 1.01 (br d, J=6.1 Hz, 3H), 0.78 - 0.68 (m, 2H), 0.34 (br s, 2H)	2.44, B

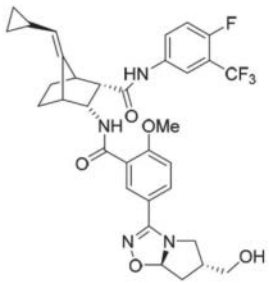
844	 异构体3	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.22 - 8.16 (m, 2H), 7.80 - 7.73 (m, 2H), 7.45 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 5.09 (dt, J=10.1, 6.7 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.41 (br t, J=10.4 Hz, 1H), 4.10 - 4.04 (m, 1H), 4.02 (s, 3H), 3.43 - 3.38 (m, 1H), 3.18 - 3.12 (m, 1H), 3.08 (br s, 1H), 2.70 (br s, 1H), 2.26 (dt, J=12.8, 6.7 Hz, 1H), 2.17 - 2.10 (m, 1H), 1.91 - 1.72 (m, 3H), 1.56 - 1.45 (m, 2H), 1.43 - 1.33 (m, 2H), 1.32 - 1.24 (m, 1H), 0.96 (d, J=6.1 Hz, 3H), 0.77 - 0.67 (m, 2H), 0.33 (br d, J=3.4 Hz, 2H)	2.45, B

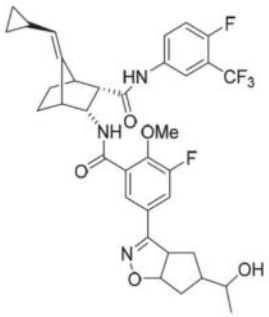
845	 异构体4	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (br d, J=7.0 Hz, 1H), 8.22 - 8.16 (m, 2H), 7.80 - 7.73 (m, 2H), 7.45 (t, J=9.8 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 5.09 (dt, J=10.1, 6.7 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.41 (br t, J=10.4 Hz, 1H), 4.10 - 4.04 (m, 1H), 4.02 (s, 3H), 3.43 - 3.38 (m, 1H), 3.18 - 3.12 (m, 1H), 3.08 (br s, 1H), 2.70 (br s, 1H), 2.26 (dt, J=12.8, 6.7 Hz, 1H), 2.17 - 2.10 (m, 1H), 1.91 - 1.72 (m, 3H), 1.56 - 1.45 (m, 2H), 1.43 - 1.33 (m, 2H), 1.32 - 1.24 (m, 1H), 0.96 (d, J=6.1 Hz, 3H), 0.77 - 0.67 (m, 2H), 0.33 (br d, J=3.4 Hz, 2H)	2.45, B

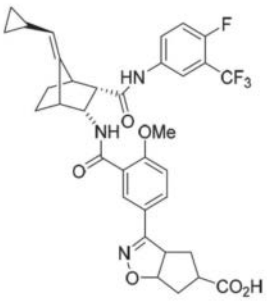
846		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aR)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	643.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (br dd, J=17.4, 7.3 Hz, 1H), 8.27 - 8.21 (m, 1H), 8.19 (br s, 1H), 7.78 (br t, J=9.3 Hz, 2H), 7.46 (br t, J=9.6 Hz, 1H), 7.30 (d, J=8.5 Hz, 1H), 5.82 - 5.74 (m, 1H), 4.67 (br d, J=9.8 Hz, 1H), 4.42 (br s, 1H), 4.04 (s, 3H), 3.36 - 3.21 (m, 2H), 3.17 - 3.07 (m, 2H), 2.70 (br s, 1H), 2.32 - 2.19 (m, 1H), 2.18 - 2.07 (m, 1H), 2.06 - 2.00 (m, 1H), 1.97 - 1.89 (m, 1H), 1.85 - 1.74 (m, 2H), 1.52 - 1.36 (m, 3H), 0.80 - 0.67 (m, 2H), 0.38 - 0.30 (m, 2H)	2.39, B

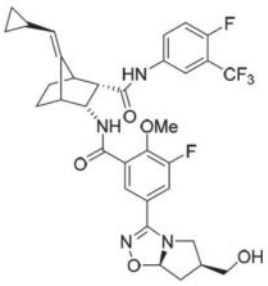
847		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aR)-6-(三氟甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	681.1	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.93 (br d, J=7.0 Hz, 1H), 8.23 - 8.19 (m, 2H), 7.81 - 7.74 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.32 (d, J=8.5 Hz, 1H), 5.93 (br t, J=4.6 Hz, 1H), 4.69 (d, J=9.8 Hz, 1H), 4.47 - 4.41 (m, 1H), 4.06 (s, 3H), 3.61 - 3.48 (m, 1H), 3.18 - 3.12 (m, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.59 (ddd, J=14.5, 9.2, 6.0 Hz, 1H), 2.00 - 1.94 (m, 1H), 1.86 - 1.76 (m, 2H), 1.53 - 1.37 (m, 3H), 0.78 - 0.69 (m, 2H), 0.34 (br d, J=1.8 Hz, 2H)	2.68, B

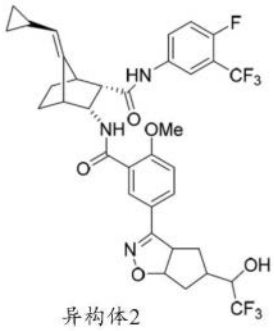
848	 异构体4	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(2,2,2-三氟-1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	710.2	(400 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.26 - 8.20 (m, 2H), 7.83 - 7.75 (m, 2H), 7.53 - 7.41 (m, 1H), 7.27 (d, J=8.8 Hz, 1H), 6.50 (s, 1H), 6.21 (d, J=6.7 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.69 (d, J=9.4 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.16 - 4.07 (m, 1H), 4.04 (s, 3H), 3.97 - 3.86 (m, 1H), 3.19 - 3.06 (m, 2H), 2.72 (br s, 1H), 2.29 - 2.20 (m, 2H), 2.03 - 1.92 (m, 1H), 1.86 - 1.74 (m, 2H), 1.68 - 1.38 (m, 4H), 0.79 - 0.67 (m, 2H), 0.29 (s, 2H)	2.65, B

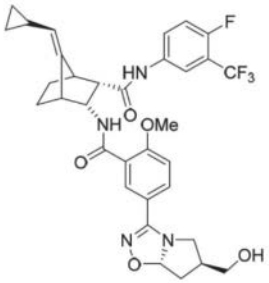
849		(1R,2S,3R,4R,7Z)-3-{5-[(6R,7aR)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	643.2	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.98 - 9.89 (m, 1H), 8.28 - 8.18 (m, 2H), 7.84 - 7.74 (m, 2H), 7.52 - 7.46 (m, 1H), 7.31 (d, J=8.7 Hz, 1H), 5.83 - 5.75 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.10 - 4.00 (m, 4H), 3.48 - 3.34 (m, 1H), 3.32 - 3.06 (m, 5H), 2.29 - 2.22 (m, 1H), 2.20 - 2.12 (m, 1H), 2.07 - 2.02 (m, 1H), 1.98 - 1.91 (m, 1H), 1.85 - 1.77 (m, 2H), 1.54 - 1.47 (m, 1H), 1.44 - 1.37 (m, 2H), 0.79 - 0.69 (m, 2H), 0.38 - 0.30 (m, 2H)	2.33, B

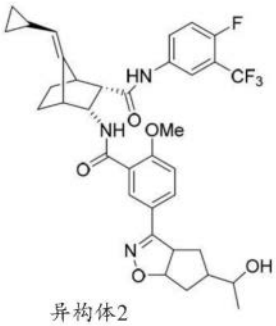
850		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	674.3	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.70 (br d, J=7.3 Hz, 1H), 8.11 - 8.06 (m, 1H), 7.97 - 7.91 (m, 1H), 7.83 - 7.76 (m, 1H), 7.68 (br d, J=12.2 Hz, 1H), 7.45 (br t, J=9.8 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.68 (br d, J=9.8 Hz, 1H), 4.47 - 4.39 (m, 1H), 4.10 - 4.00 (m, 4H), 3.62 - 3.49 (m, 1H), 3.45 - 3.34 (m, 1H), 3.17 - 3.06 (m, 2H), 2.75 - 2.68 (m, 1H), 2.28 (dt, J=13.4, 6.6 Hz, 1H), 2.18 - 2.10 (m, 1H), 1.91 - 1.74 (m, 3H), 1.56 - 1.36 (m, 4H), 1.31 - 1.22 (m, 1H), 0.97 (br d, J=6.1 Hz, 3H), 0.78 - 0.67 (m, 2H), 0.34 (br d, J=2.1 Hz, 2H)	2.49, B

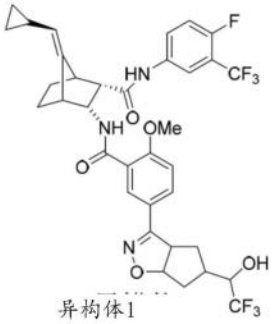
851		3-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-5-甲酸	656.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.24 - 8.20 (m, 2H), 7.81 - 7.76 (m, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 5.16 (dd, J=8.4, 4.9 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.46 - 4.41 (m, 1H), 4.29 (br t, J=8.5 Hz, 1H), 4.04 (s, 3H), 3.15 (br dd, J=10.6, 4.3 Hz, 1H), 3.10 (br s, 1H), 2.71 (br s, 1H), 2.18 (br dd, J=13.6, 6.3 Hz, 1H), 2.13 - 2.05 (m, 1H), 2.02 - 1.92 (m, 2H), 1.86 - 1.74 (m, 2H), 1.53 - 1.46 (m, 1H), 1.44 - 1.36 (m, 2H), 0.78 - 0.68 (m, 2H), 0.39 - 0.31 (m, 2H)	2.13, B

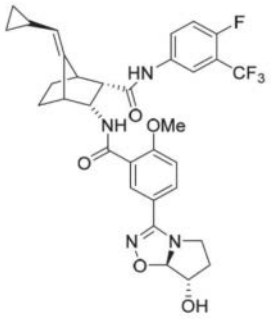
852		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aR)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-3-氟-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	661.3	(500 MHz, DMSO-d6) δ 10.56 - 10.49 (m, 1H), 9.79 - 9.69 (m, 1H), 8.15 - 8.08 (m, 1H), 8.04 - 7.97 (m, 1H), 7.87 - 7.78 (m, 1H), 7.69 (br d, J=12.2 Hz, 1H), 7.47 (t, J=9.7 Hz, 1H), 5.87 - 5.79 (m, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.50 - 4.42 (m, 1H), 4.11 (d, J=2.1 Hz, 3H), 3.35 - 3.21 (m, 1H), 3.21 - 3.07 (m, 2H), 2.94 - 2.85 (m, 1H), 2.77 - 2.71 (m, 1H), 2.34 - 2.23 (m, 1H), 2.20 - 2.10 (m, 1H), 2.09 - 2.01 (m, 1H), 1.99 - 1.92 (m, 1H), 1.89 - 1.75 (m, 2H), 1.54 - 1.37 (m, 3H), 0.79 - 0.69 (m, 2H), 0.40 - 0.30 (m, 2H)	2.42, B

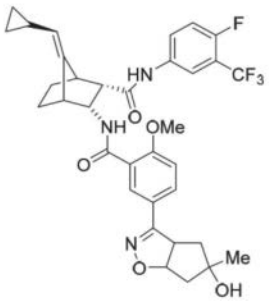
853	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(2,2,2-三氟-1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	710.3	(400 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.92 (d, J=7.0 Hz, 1H), 8.26 - 8.21 (m, 2H), 7.84 - 7.76 (m, 2H), 7.49 (t, J=9.7 Hz, 1H), 7.28 (d, J=8.8 Hz, 1H), 6.21 (br d, J=7.0 Hz, 1H), 5.14 (dd, J=8.6, 4.9 Hz, 1H), 4.70 (d, J=9.4 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.25 (t, J=8.2 Hz, 1H), 4.05 (s, 3H), 3.98 - 3.91 (m, 1H), 3.16 (dd, J=10.7, 4.0 Hz, 1H), 3.13 - 3.09 (m, 1H), 2.72 (br s, 1H), 2.04 - 1.89 (m, 3H), 1.87 - 1.75 (m, 4H), 1.55 - 1.45 (m, 1H), 1.44 - 1.37 (m, 2H), 0.80 - 0.68 (m, 2H), 0.40 - 0.32 (m, 2H)	2.64, B

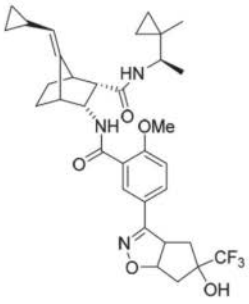
854		(1R,2S,3R,4R,7Z)-3-{5-[(6S,7aS)-6-(羟基甲基)-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	643.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.96 - 9.89 (m, 1H), 8.29 - 8.18 (m, 2H), 7.82 - 7.76 (m, 2H), 7.47 (br t, J=9.8 Hz, 1H), 7.30 (d, J=8.9 Hz, 1H), 5.83 - 5.75 (m, 1H), 4.68 (br d, J=9.5 Hz, 1H), 4.43 (br s, 1H), 4.05 (s, 3H), 3.52 - 3.42 (m, 1H), 3.35 - 3.25 (m, 1H), 3.19 - 3.07 (m, 2H), 2.93 - 2.84 (m, 1H), 2.71 (br s, 1H), 2.32 - 2.21 (m, 1H), 2.18 - 2.09 (m, 1H), 2.07 - 2.00 (m, 1H), 1.98 - 1.90 (m, 1H), 1.86 - 1.74 (m, 2H), 1.53 - 1.36 (m, 3H), 0.79 - 0.68 (m, 2H), 0.38 - 0.27 (m, 2H)	2.39, B

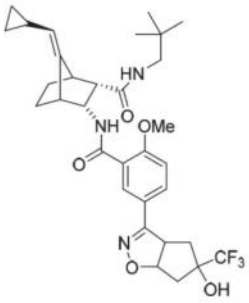
855	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	656.2	(500 MHz, DMSO-d6) δ 10.55 - 10.51 (m, 1H), 9.91 (br d, J=7.0 Hz, 1H), 8.26 - 8.20 (m, 2H), 7.82 - 7.76 (m, 2H), 7.48 (t, J=9.6 Hz, 1H), 7.26 (d, J=8.9 Hz, 1H), 5.11 (dt, J=10.3, 6.4 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.43 (br t, J=10.5 Hz, 1H), 4.10 - 4.05 (m, 1H), 4.04 (s, 3H), 3.93 - 3.86 (m, 1H), 3.15 (br dd, J=10.5, 4.1 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 2.31 - 2.24 (m, 1H), 2.13 (dt, J=13.0, 6.4 Hz, 1H), 1.93 - 1.74 (m, 3H), 1.53 - 1.36 (m, 5H), 1.05 - 0.98 (m, 3H), 0.79 - 0.68 (m, 2H), 0.35 (br d, J=1.2 Hz, 2H)	2.44, B

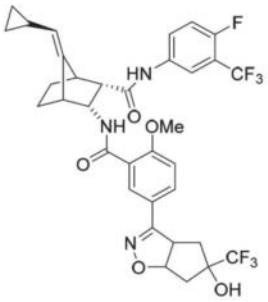
856	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{2-甲氧基-5-[5-(2,2,2-三氟-1-羟基乙基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	710.3	(400 MHz, DMSO-d6) δ 10.54 - 10.47 (m, 1H), 9.95 - 9.87 (m, 1H), 8.27 - 8.17 (m, 2H), 7.85 - 7.74 (m, 2H), 7.54 - 7.42 (m, 1H), 7.35 - 7.23 (m, 1H), 6.51 (br s, 1H), 6.28 - 6.21 (m, 1H), 5.16 - 5.09 (m, 1H), 4.70 (d, J=9.4 Hz, 1H), 4.48 - 4.41 (m, 1H), 4.26 (t, J=8.7 Hz, 1H), 4.05 (s, 3H), 4.00 - 3.92 (m, 1H), 3.16 (dd, J=10.7, 4.4 Hz, 1H), 3.13 - 3.07 (m, 1H), 2.75 - 2.69 (m, 1H), 2.07 - 1.96 (m, 2H), 1.92 - 1.72 (m, 5H), 1.54 - 1.46 (m, 1H), 0.80 - 0.68 (m, 2H), 0.39 - 0.30 (m, 2H)	2.59, B

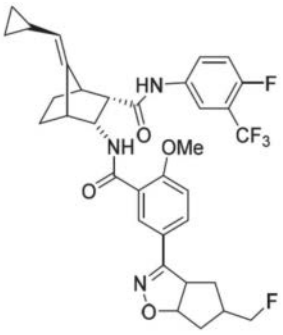
857		(1R,2S,3R,4R,7Z)-3-{5-[(7S,7aR)-7-羟基-5H,6H,7H,7aH-吡咯并[1,2-d][1,2,4]噁二唑-3-基]-2-甲氧基苯甲酰胺基}-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	629.2	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (br d, J=7.3 Hz, 1H), 8.27 - 8.18 (m, 2H), 7.78 (br dd, J=8.5, 2.4 Hz, 2H), 7.47 (t, J=9.8 Hz, 1H), 7.31 (d, J=8.9 Hz, 1H), 5.42 (s, 1H), 4.72 - 4.66 (m, 1H), 4.47 - 4.40 (m, 1H), 4.19 - 4.12 (m, 1H), 4.05 (s, 3H), 3.23 - 3.07 (m, 2H), 2.74 - 2.68 (m, 1H), 1.87 - 1.75 (m, 2H), 1.72 - 1.62 (m, 2H), 1.54 - 1.34 (m, 3H), 0.79 - 0.68 (m, 2H), 0.34 (br s, 2H)	2.40, B

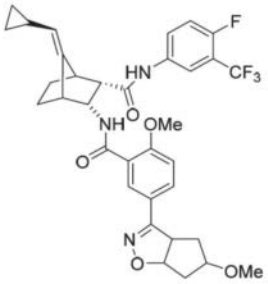
858		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(5-{5-羟基-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	642.3	(400 MHz, DMSO-d6) δ = 10.55 (s, 1H), 9.90 (d, J = 7.0 Hz, 1H), 8.30 - 8.15 (m, 2H), 7.85 - 7.70 (m, 2H), 7.49 (t, J = 9.8 Hz, 1H), 7.26(d, J = 8.8 Hz, 1H), 5.20 - 5.02 (m, 1H), 4.70 (d, J = 9.6 Hz, 1H), 4.45 (ddd, J = 4.1, 6.7, 10.3 Hz, 1H), 4.26 (s, 1H), 4.16 (dt, J = 3.5, 9.6 Hz, 1H),4.04 (s, 3H), 3.17 (dd, J = 4.1, 10.8 Hz, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 2.04 - 1.90 (m, 3H), 1.87 - 1.71 (m, 3H), 1.55 - 1.34 (m, 3H), 1.20 (s,3H), 0.81 - 0.65 (m, 2H), 0.36 (dd, J = 1.9, 4.3 Hz, 2H)	2.35, A

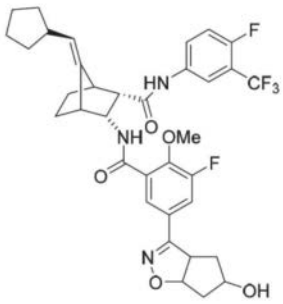
859		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	616.3	(400 MHz, DMSO-d6) δ = 10.05 (d, J = 6.8 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 2.4, 8.6 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.27 (br dd, J = 6.6, 9.0 Hz, 1H), 4.64 (d, J = 9.5 Hz, 1H), 4.40 (br t, J = 9.3 Hz, 1H), 4.32 - 4.23 (m, 1H), 3.99 (s, 3H), 3.47 (dd, J = 6.9, 8.4 Hz, 1H), 3.08 - 3.03 (m, 1H), 2.95 (dd, J = 4.3, 10.8 Hz, 1H), 2.32 - 2.18 (m, 3H), 2.00 (br d, J = 14.0 Hz, 1H), 1.85 (br d, J = 10.1 Hz, 1H), 1.78 - 1.71 (m, 1H), 1.47 (td, J = 4.3, 9.0 Hz, 1H), 1.35 (br s, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H), 0.72 (qd, J = 8.5, 10.4 Hz, 2H), 0.53 (br dd, J = 3.7, 8.7 Hz, 1H), 0.39 - 0.26 (m, 3H), 0.23 - 0.12 (m, 2H)	2.31, A

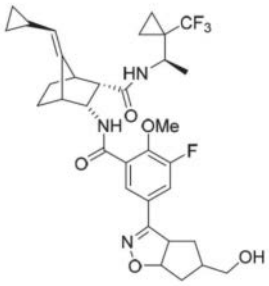
862		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-(2,2-二甲基丙基)-3-{5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	604.2	(400 MHz, DMSO-d6) δ = 9.95 (d, J = 6.3 Hz, 1H), 8.16 (d, J = 2.5 Hz, 1H), 7.98 - 7.93 (m, 1H), 7.76 (dd, J = 2.4, 8.9 Hz, 1H), 7.23 (d, J= 8.8 Hz, 1H), 5.92 (s, 1H), 5.29 - 5.22 (m, 1H), 4.63 (d, J = 9.8 Hz, 1H), 4.44 - 4.37 (m, 1H), 4.29 (s, 1H), 4.00 (s, 3H), 3.06 - 2.98 (m, 3H), 2.78(br d, J = 5.0 Hz, 1H), 2.30 - 2.21 (m, 3H), 2.02 - 1.95 (m, 1H), 1.90 - 1.82 (m, 1H), 1.77 - 1.70 (m, 1H), 1.51 - 1.45 (m, 1H), 1.34 (br d, J = 1.3 Hz,2H), 0.88 - 0.77 (m, 10H), 0.75 - 0.68 (m, 2H), 0.32 (br d, J = 2.8 Hz, 2H)	2.21, A

864		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	696.3	(400 MHz, DMSO-d6) δ = 10.0 (d, J = 4.4 Hz, 1H), 9.90 (d, 1H), 8.26 - 8.17 (m, 2H), 7.77 (dd, J = 2.5, 8.5 Hz, 2H), 7.45 (t, J = 9.8 Hz, 1H), 7.26 (d, J = 9.0 Hz, 1H), 5.99 (s, 1H), 5.28 - 5.23 (m, 1H), 4.68 (d, J = 9.5 Hz, 1H), 4.46 - 4.28 (m, 3H), 4.02 (s, 5H), 3.91 - 3.77 (m, 3H), 3.16 - 3.07 (m, 2H), 2.72 - 2.68 (m, 1H), 2.32 - 2.16 (m, 4H), 1.95 (br d, J = 14.1 Hz, 1H), 1.86 - 1.69 (m, 2H), 1.63 (s, 6H), 1.53 - 1.43 (m, 2H), 1.40 (br s, 2H), 1.33 (s, 3H), 0.72 (br t, J = 8.0 Hz, 2H), 0.33 (br d, J = 4.5 Hz, 2H)	2.87, C

866		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	644.3	(400 MHz, DMSO-d6) δ = 10.52 (s, 1H), 9.90 (d, J = 7.0 Hz, 1H), 8.27 - 8.20 (m, 2H), 7.85 - 7.75 (m, 2H), 7.55 - 7.44 (m, 2H), 7.28 (d, J= 8.8 Hz, 1H), 7.10 (s, 1H), 5.19 - 5.12 (m, 1H), 4.70 (d, J = 9.8 Hz, 1H), 4.48 (br d, J = 5.8 Hz, 2H), 4.36 (d, J = 5.0 Hz, 1H), 4.31 - 4.23 (m, 1H),4.05 (s, 4H), 3.18 - 3.14 (m, 1H), 3.12 - 3.09 (m, 1H), 2.72 (br d, J = 3.0 Hz, 1H), 2.17 - 2.03 (m, 3H), 1.87 - 1.61 (m, 10H), 1.54 - 1.48 (m, 2H),1.42 (br dd, J = 3.1, 5.1 Hz, 2H), 1.36 (s, 3H), 1.31 - 1.14 (m, 13H), 0.95 - 0.83 (m, 3H), 0.75 (br t, J = 8.9 Hz, 2H), 0.40 - 0.31 (m, 2H)	2.64, A

867		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(2-甲氧基-5-{5-甲氧基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	642.2	(400 MHz, DMSO-d6) δ = 10.51 (s, 1H), 9.89 (d, J = 7.0 Hz, 1H), 8.28 - 8.12 (m, 2H), 7.83 - 7.67 (m, 2H), 7.48 (t, J = 9.9 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 5.13 (ddd, J = 2.8, 6.1, 9.4 Hz, 1H), 4.69 (d, J = 9.8 Hz, 1H), 4.49 - 4.37 (m, 1H), 4.22 (dt, J = 4.3, 9.6 Hz, 1H), 4.04 (s, 3H), 3.83 - 3.73 (m, 1H), 3.22 - 3.12 (m, 4H), 3.10 (t, J = 3.8 Hz, 1H), 2.75 - 2.69 (m, 1H), 2.13 - 1.94 (m, 3H), 1.92 - 1.71 (m, 3H), 1.54 - 1.31 (m, 3H), 0.81 - 0.64 (m, 2H), 0.35 (dd, J = 2.1, 4.6 Hz, 2H)	2.50, A

868		(1R,2S,3R,4R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-(3-氟-5-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)双环[2.2.1]庚烷-2-甲酰胺	674.2	(400 MHz, DMSO-d6) δ ppm 10.52 (s, 1H), 9.68 (d, J = 7.0 Hz, 1H), 8.12 (dd, J = 2.8, 6.5 Hz, 1H), 7.94 (dd, J = 1.0, 2.0 Hz, 1H), 7.88 - 7.77 (m, 1H), 7.71 (dd, J = 2.3, 12.5 Hz, 1H), 7.48 (t, J = 9.9 Hz, 1H), 5.24 - 5.15 (m, 2H), 4.85 (d, J = 4.3 Hz, 1H), 4.47 - 4.37 (m, 1H), 4.20 (dt, J = 4.0, 9.3 Hz, 1H), 4.09 (d, J = 2.8 Hz, 4H), 3.22 - 3.13 (m, 1H), 3.00 (br s, 1H), 2.73 (br s, 1H), 2.64 - 2.56 (m, 1H), 2.04 - 1.73 (m, 8H), 1.72 - 1.53 (m, 4H), 1.47 - 1.37 (m, 2H), 1.35 - 1.21 (m, 2H)	2.61, A

869		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-[1-(三氟甲基)环丙基]乙基]双环[2.2.1]庚烷-2-甲酰胺	634.2	(500 MHz, DMSO-d6) δ 9.63 (br d, J=7.0 Hz, 1H), 7.92 (br d, J=8.5 Hz, 1H), 7.68 (s, 1H), 7.52 - 7.40 (m, 1H), 4.92 (br dd, J=8.5, 4.9 Hz, 1H), 4.41 (d, J=9.5 Hz, 1H), 4.27 (t, J=5.2 Hz, 1H), 4.16 - 4.03 (m, 1H), 3.97 (br t, J=9.2 Hz, 1H), 3.93 - 3.84 (m, 1H), 3.82 (d, J=2.1 Hz, 3H), 2.86 - 2.67 (m, 3H), 1.76 (br dd, J=13.6, 5.6 Hz, 1H), 1.65 (td, J=11.4, 5.8 Hz, 1H), 1.59 - 1.47 (m, 3H), 1.46 - 1.37 (m, 1H), 1.37 - 1.28 (m, 1H), 1.27 - 1.18 (m, 1H), 1.18 - 1.05 (m, 2H), 0.87 (br d, J=7.0 Hz, 3H), 0.73 (br d, J=9.8 Hz, 1H), 0.68 - 0.57 (m, 2H), 0.55 - 0.40 (m, 3H), 0.09 (br d, J=3.4 Hz, 2H)	2.39, C

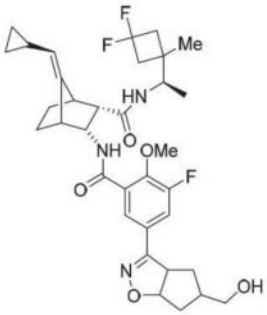
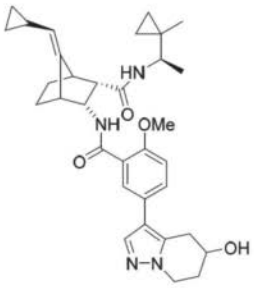
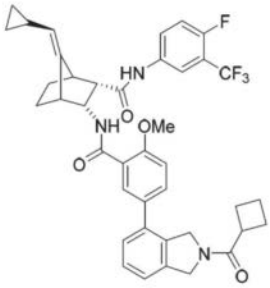
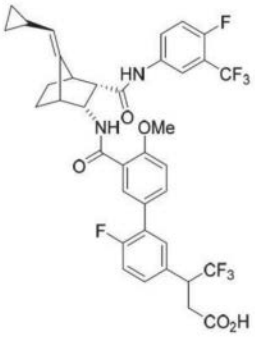
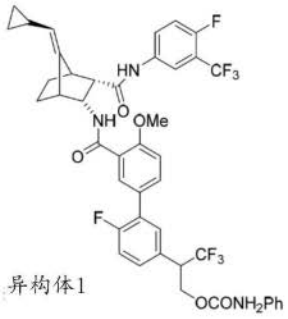
870		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[(1R)-1-(3,3-二氟-1-甲基环丁基)乙基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	630.2	(500 MHz, DMSO-d6) δ 9.66 (br d, J=7.0 Hz, 1H), 7.88 (br d, J=9.2 Hz, 1H), 7.68 (s, 1H), 7.48 (br dd, J=12.5, 1.8 Hz, 1H), 4.93 (br dd, J=8.5, 5.2 Hz, 1H), 4.41 (d, J=9.5 Hz, 1H), 4.17 - 4.03 (m, 1H), 3.97 (br t, J=8.7 Hz, 1H), 3.86 - 3.71 (m, 3H), 3.66 (s, 1H), 2.84 (br s, 1H), 2.75 (br dd, J=10.8, 4.1 Hz, 1H), 2.44 - 2.33 (m, 1H), 2.24 - 2.11 (m, 2H), 2.03 - 1.80 (m, 3H), 1.76 (br dd, J=13.6, 5.3 Hz, 1H), 1.65 (td, J=11.7, 5.5 Hz, 1H), 1.59 - 1.47 (m, 3H), 1.45 - 1.28 (m, 2H), 1.27 - 1.04 (m, 4H), 0.90 (s, 3H), 0.69 (d, J=7.0 Hz, 3H), 0.55 - 0.41 (m, 2H), 0.09 (br d, J=4.0 Hz, 2H)	2.36, C

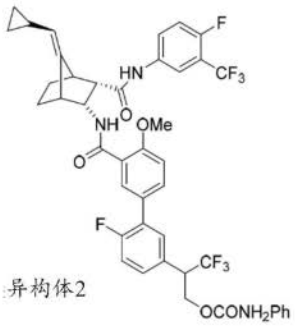
表5

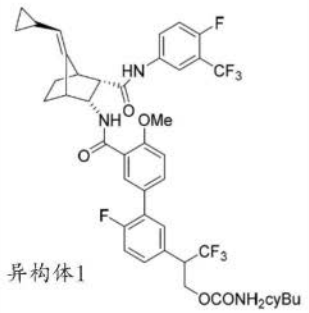
实施例编号	结构	名称	MS (ESI) (M+H)	1H NMR	LC RT Meth. (min)
871		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-(5-{5-羟基-4H,5H,6H,7H-吡唑并[1,5-a]吡啶-3-基}-2-甲氧基苯甲酰胺基)-N-[(1S)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	559.3	(400 MHz, DMSO-d6) δ = 10.03 (d, J = 6.6 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.54 (dd, J = 2.4, 8.6 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 5.10 (dd, J = 3.4, 5.9 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 4.35 - 4.25 (m, 1H), 4.23 - 4.05 (m, 3H), 3.96 (s, 3H),3.52 - 3.44 (m, 1H), 3.13 - 3.01 (m, 2H), 2.95 (dd, J = 4.4, 10.9 Hz, 1H), 2.80 (dd, J = 5.6, 16.3 Hz, 1H), 2.14 - 1.97 (m, 2H), 1.88 (br d, J = 10.4 Hz, 1H), 1.81 - 1.72 (m, 1H), 1.53 - 1.43 (m, 1H), 1.35 (br s, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H), 0.79 - 0.63 (m, 2H), 0.53 (br dd, J = 3.8,8.7 Hz, 1H), 0.40 - 0.25 (m, 3H), 0.23 - 0.09 (m, 2H)	2.05, A

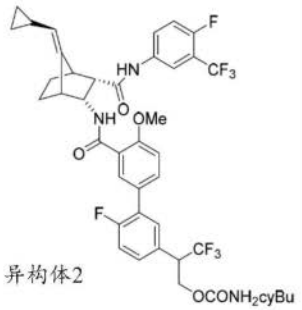
872		(2S,3R,7Z)-3-[5-(2-环丁烷羰基-2,3-二氢-1H-异吲哚-4-基)-2-甲氧基苯甲酰胺基]-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	702.5	(500 MHz, DMSO-d6) δ 10.60 - 10.43 (m, 1H), 10.00 - 9.84 (m, 1H), 8.21 (br d, J=4.4 Hz, 1H), 8.00 (dd, J=13.8, 2.3 Hz, 1H), 7.77 (br dd, J=7.9, 3.7 Hz, 1H), 7.74 - 7.62 (m, 1H), 7.47 (br t, J=9.8 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.36 - 7.30 (m, 1H), 7.30 - 7.23 (m, 2H), 4.77 (br s, 2H), 4.71 - 4.60 (m, 3H), 4.55 - 4.33 (m, 1H), 4.05 (s, 3H), 3.47 - 3.24 (m, 1H), 3.24 - 3.12 (m, 1H), 3.14 - 3.03 (m, 1H), 2.79 - 2.62 (m, 1H), 2.24 - 2.15 (m, 2H), 2.11 - 2.03 (m, 1H), 1.99 - 1.85 (m, 2H), 1.84 - 1.69 (m, 2H), 1.62 - 1.48 (m, 1H), 1.45 - 1.32 (m, 2H), 0.78 - 0.64 (m, 2H), 0.47 - 0.12 (m, 2H), 一个H隐藏于水/溶剂峰下	2.83, C

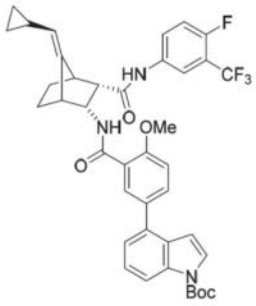
873		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,4,4-三氟丁酸	737.1	(500 MHz, DMSO-d6) δ 10.63 - 10.50 (m, 1H), 9.92 (d, J=7.0 Hz, 1H), 8.22 (dd, J=6.2, 2.2 Hz, 1H), 8.11 (s, 1H), 7.88 - 7.77 (m, 1H), 7.69 (br d, J=8.6 Hz, 1H), 7.56 (br s, 1H), 7.50 - 7.40 (m, 2H), 7.35 - 7.23 (m, 2H), 4.69 (d, J=9.5 Hz, 1H), 4.50 - 4.38 (m, 1H), 4.23 - 4.09 (m, 1H), 4.05 (s, 3H), 3.25 - 3.15 (m, 1H), 3.11 (br s, 1H), 3.01 - 2.89 (m, 2H), 2.76 - 2.66 (m, 1H), 1.88 - 1.73 (m, 2H), 1.57 - 1.48 (m, 1H), 1.45 - 1.34 (m, 2H), 0.86 - 0.64 (m, 2H), 0.41 - 0.25 (m, 2H), 一个H隐藏于水/溶剂峰下	2.32, A

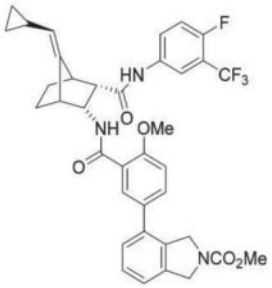
875	 异构体1	N-苯基氨基甲酸2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙酯	828.0	(500 MHz, DMSO-d6) δ 10.57 - 10.49 (m, 1H), 9.92 (d, J=7.1 Hz, 1H), 9.69 (br s, 1H), 8.23 (dd, J=6.4, 2.4 Hz, 1H), 8.14 (s, 1H), 7.89 - 7.77 (m, 1H), 7.70 (br d, J=8.9 Hz, 1H), 7.65 (br d, J=7.0 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.45 (m, 2H), 7.42 (br s, 2H), 7.39 - 7.33 (m, 1H), 7.30 (d, J=8.8 Hz, 1H), 7.25 (br t, J=7.8 Hz, 2H), 6.99 (t, J=7.3 Hz, 1H), 4.76 - 4.68 (m, 2H), 4.62 - 4.55 (m, 1H), 4.49 - 4.44 (m, 1H), 4.34 - 4.26 (m, 1H), 4.05 (s, 3H), 3.17 (br dd, J=10.3, 3.9 Hz, 1H), 3.12 - 3.08 (m, 1H), 1.91 - 1.84 (m, 1H), 1.83 - 1.77 (m, 1H), 1.54 - 1.49 (m, 1H), 1.46 - 1.38 (m, 2H), 0.78 - 0.70 (m, 2H), 0.41 - 0.33 (m, 2H)	2.96, A

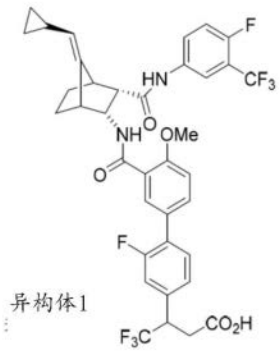
876	 异构体2	N-苯基氨基甲酸2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙酯	828.0	(500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.67 (d, J=7.2 Hz, 1H), 9.45 (br s, 1H), 7.99 (dd, J=6.4, 2.4 Hz, 1H), 7.90 (s, 1H), 7.55 (br dd, J=8.4, 3.6 Hz, 1H), 7.45 (br d, J=8.9 Hz, 1H), 7.42 - 7.39 (m, 1H), 7.32 - 7.28 (m, 1H), 7.26 - 7.22 (m, 1H), 7.17 (br d, J=1.2 Hz, 1H), 7.14 - 7.11 (m, 1H), 7.06 (d, J=8.7 Hz, 1H), 7.01 (br t, J=7.7 Hz, 2H), 6.74 (t, J=7.4 Hz, 1H), 4.51 - 4.47 (m, 1H), 4.45 (d, J=9.2 Hz, 1H), 4.34 (dd, J=11.7, 7.2 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.10 - 4.01 (m, 1H), 3.88 - 3.75 (m, 3H), 3.17 - 3.13 (m, 1H), 2.96 - 2.90 (m, 1H), 2.86 (br s, 1H), 2.48 (br d, J=3.9 Hz, 1H), 1.66 - 1.60 (m, 1H), 1.58 - 1.53 (m, 1H), 1.30 - 1.23 (m, 1H), 1.20 - 1.12 (m, 2H), 0.54 - 0.45 (m, 2H), 0.14 - 0.05 (m, 2H)	2.96, A

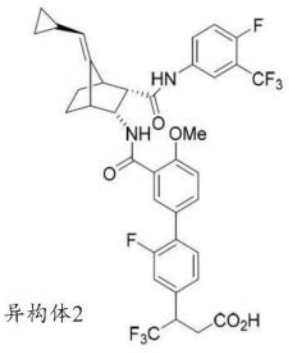
878	 异构体1	N-环丁基氨基甲酸 2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙酯	806.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.93 (br d, J=6.9 Hz, 1H), 8.29 - 8.21 (m, 1H), 8.14 (s, 1H), 7.80 (br dd, J=4.5, 3.4 Hz, 1H), 7.70 (br d, J=8.4 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.55 - 7.50 (m, 1H), 7.49 - 7.45 (m, 2H), 7.38 - 7.35 (m, 1H), 7.32 (d, J=8.8 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.60 - 4.52 (m, 1H), 4.50 - 4.46 (m, 1H), 4.43 - 4.39 (m, 1H), 4.22 - 4.16 (m, 1H), 4.06 (s, 3H), 3.94 - 3.88 (m, 1H), 3.17 (br dd, J=11.2, 4.2 Hz, 1H), 3.12 (br s, 1H), 2.73 (br s, 1H), 2.11 - 2.03 (m, 2H), 1.86 (br d, J=8.5 Hz, 2H), 1.83 - 1.78 (m, 1H), 1.57 - 1.49 (m, 2H), 1.46 - 1.38 (m, 2H), 0.80 - 0.71 (m, 2H), 0.39 - 0.31 (m, 2H)	2.84, A

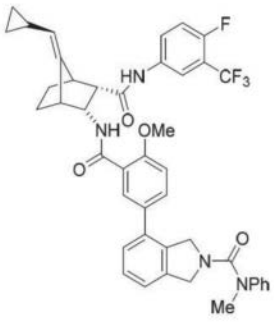
879	 异构体2	N-环丁基氨基甲酸 2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙酯	806.0	(500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.68 (d, J=7.2 Hz, 1H), 7.99 (dd, J=6.4, 2.3 Hz, 1H), 7.89 (s, 1H), 7.60 - 7.51 (m, 1H), 7.46 (br d, J=9.3 Hz, 1H), 7.35 (br d, J=7.1 Hz, 1H), 7.29 (br d, J=8.0 Hz, 1H), 7.23 (br d, J=9.5 Hz, 2H), 7.16 - 7.09 (m, 1H), 7.08 (d, J=8.7 Hz, 1H), 4.46 (d, J=9.5 Hz, 1H), 4.35 - 4.27 (m, 1H), 4.26 - 4.21 (m, 1H), 4.20 - 4.13 (m, 1H), 4.00 - 3.92 (m, 1H), 3.82 (s, 3H), 2.93 (br dd, J=10.6, 4.0 Hz, 1H), 2.87 (br s, 1H), 2.49 (br s, 1H), 1.83 (br dd, J=6.0, 2.2 Hz, 2H), 1.62 (br d, J=8.5 Hz, 2H), 1.60 - 1.52 (m, 2H), 1.35 - 1.25 (m, 3H), 1.20 - 1.13 (m, 2H), 0.50 (quin, J=9.3 Hz, 2H), 0.11 (br d, J=2.0 Hz, 2H),	2.84, A

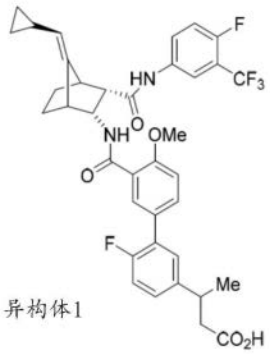
880		4-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-1H-吲哚-1-甲酸叔丁酯	718.5	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (d, J=7.3 Hz, 1H), 8.22 (dd, J=6.4, 2.1 Hz, 1H), 8.17 (d, J=2.4 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H), 7.81 - 7.77 (m, 1H), 7.74 - 7.70 (m, 2H), 7.47 (t, J=9.7 Hz, 1H), 7.40 (d, J=8.1 Hz, 1H), 7.34 (d, J=8.7 Hz, 1H), 7.28 (d, J=7.4 Hz, 1H), 6.68 (d, J=3.8 Hz, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.53 - 4.44 (m, 1H), 4.06 (s, 3H), 3.16 (dd, J=10.7, 4.6 Hz, 1H), 3.13 - 3.09 (m, 1H), 2.76 - 2.69 (m, 1H), 1.93 - 1.86 (m, 1H), 1.85 - 1.79 (m, 1H), 1.64 (s, 9H), 1.58 - 1.48 (m, 1H), 1.42 (br s, 2H), 0.81 - 0.66 (m, 2H), 0.38 - 0.32 (m, 2H	3.18, A

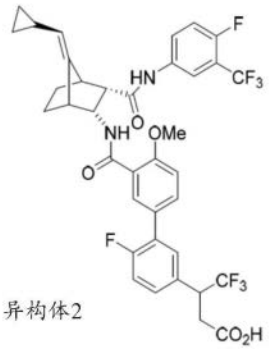
881		4-(3-{[(2R,3S,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-2,3-二氢-1H-异吲哚-2-甲酸甲酯	678.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (br d, J=6.3 Hz, 1H), 8.23 (dd, J=6.6, 2.4 Hz, 1H), 8.02 (dd, J=12.6, 2.1 Hz, 1H), 7.90 - 7.76 (m, 1H), 7.72 - 7.63 (m, 1H), 7.48 (t, J=9.7 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.37 - 7.33 (m, 1H), 7.32 - 7.27 (m, 2H), 7.26 - 7.02 (m, 2H), 4.81 - 4.62 (m, 5H), 4.53 - 4.40 (m, 1H), 4.06 (s, 3H), 3.65 (d, J=14.3 Hz, 2H), 3.24 - 3.13 (m, 1H), 3.11 (br d, J=3.0 Hz, 1H), 1.96 - 1.86 (m, 1H), 1.82 (br t, J=8.2 Hz, 1H), 1.61 - 1.50 (m, 1H), 1.43 (br t, J=11.7 Hz, 2H), 0.74 (br dd, J=10.4, 9.2 Hz, 2H), 0.41 - 0.27 (m, 2H)	2.75, C

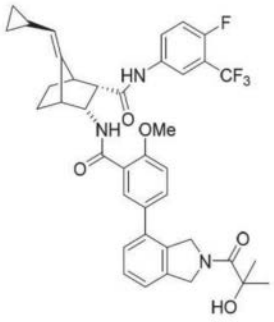
883	 异构体1	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-2-氟-4'-甲氧基-[1,1'-联苯]-4-基)-4,4,4-三氟丁酸	737.1	(500 MHz, DMSO-d6) δ 10.61 - 10.52 (m, 1H), 9.91 (d, J=7.1 Hz, 1H), 8.23 (dd, J=6.6, 2.4 Hz, 1H), 8.14 (s, 1H), 7.89 - 7.79 (m, 1H), 7.70 (br d, J=8.6 Hz, 1H), 7.54 - 7.45 (m, 2H), 7.39 (s, 1H), 7.33 - 7.24 (m, 2H), 4.69 (d, J=9.7 Hz, 1H), 4.55 - 4.42 (m, 1H), 4.21 - 4.10 (m, 1H), 4.05 (s, 3H), 3.90 (s, 1H), 3.24 - 3.14 (m, 2H), 3.11 (br s, 1H), 2.76 - 2.66 (m, 1H), 1.84 - 1.77 (m, 1H), 1.51 (qd, J=8.6, 4.9 Hz, 1H), 1.46 - 1.38 (m, 2H), 0.86 - 0.70 (m, 2H), 0.35 (br s, 2H),	2.31, A

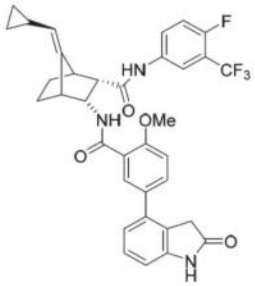
884	 异构体2	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-2-氟-4'-甲氧基-[1,1'-联苯]-4-基)-4,4,4-三氟丁酸	737.1	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.91 (d, J=7.2 Hz, 1H), 8.24 (dd, J=6.4, 2.2 Hz, 1H), 8.14 (s, 1H), 7.88 - 7.79 (m, 1H), 7.70 (br d, J=8.9 Hz, 1H), 7.55 - 7.45 (m, 2H), 7.38 (br d, J=11.5 Hz, 1H), 7.33 - 7.25 (m, 2H), 4.69 (d, J=9.6 Hz, 1H), 4.52 - 4.40 (m, 1H), 4.18 - 4.09 (m, 1H), 4.05 (s, 3H), 3.90 (s, 1H), 3.13 - 3.09 (m, 1H), 2.73 (br d, J=6.7 Hz, 1H), 1.89 - 1.79 (m, 2H), 1.56 - 1.48 (m, 1H), 1.46 - 1.38 (m, 2H), 0.83 - 0.68 (m, 2H), 0.35 (br d, J=2.4 Hz, 2H	2.31, A

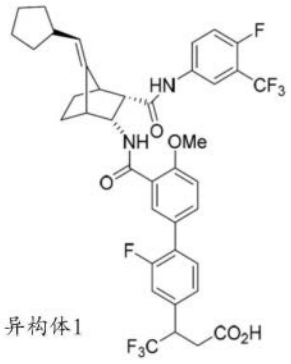
886		4-(3-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-4-甲氧基苯基)-N-甲基-N-苯基-2,3-二氢-1H-异吲哚-2-甲酰胺	753.0	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.24 (dd, J=6.2, 2.6 Hz, 1H), 7.94 (d, J=2.4 Hz, 1H), 7.80 (dt, J=7.9, 3.9 Hz, 1H), 7.54 - 7.46 (m, 2H), 7.38 - 7.33 (m, 2H), 7.32 - 7.29 (m, 1H), 7.26 - 7.23 (m, 2H), 7.21 (s, 1H), 7.18 - 7.13 (m, 2H), 4.71 (d, J=9.5 Hz, 1H), 4.50 (br d, J=5.7 Hz, 2H), 4.33 (s, 2H), 4.05 (s, 3H), 3.51 - 3.40 (m, 1H), 3.14 (s, 3H), 2.73 (br s, 1H), 1.93 - 1.88 (m, 1H), 1.88 - 1.82 (m, 1H), 1.56 - 1.50 (m, 1H), 1.44 - 1.37 (m, 2H), 1.26 - 1.20 (m, 2H), 0.76 - 0.65 (m, 2H), 0.44 - 0.32 (m, 2H), 一个H隐藏于水/溶剂峰下	2.77, A

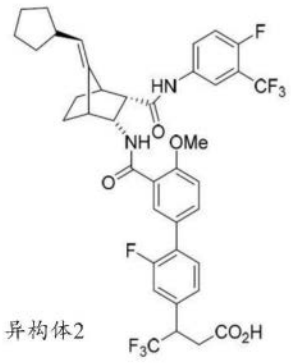
887	 异构体1	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)丁酸	683.4	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.92 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.4, 2.3 Hz, 1H), 8.12 (s, 1H), 7.83 - 7.75 (m, 1H), 7.69 (br d, J=9.2 Hz, 1H), 7.48 (t, J=9.7 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.30 (d, J=8.8 Hz, 1H), 7.28 - 7.26 (m, 1H), 7.24 - 7.18 (m, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.51 - 4.44 (m, 1H), 4.05 (s, 3H), 3.21 (br d, J=7.0 Hz, 1H), 3.12 (br s, 1H), 2.73 (br d, J=4.4 Hz, 1H), 1.89 - 1.73 (m, 2H), 1.57 - 1.48 (m, 1H), 1.45 - 1.35 (m, 2H), 1.25 (d, J=6.9 Hz, 3H), 0.84 - 0.68 (m, 2H), 0.35 (br d, J=2.0 Hz, 2H), 四个H隐藏于水/溶剂峰下	2.42, A

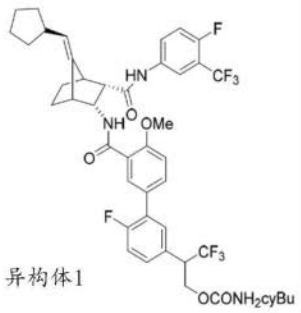
888	 异构体2	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)丁酸	683.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (d, J=7.2 Hz, 1H), 8.23 (dd, J=6.6, 2.4 Hz, 1H), 8.12 (s, 1H), 7.90 - 7.77 (m, 1H), 7.69 (br d, J=8.8 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 7.36 (dd, J=7.7, 2.0 Hz, 1H), 7.32 - 7.28 (m, 1H), 7.27 (br dd, J=4.8, 2.2 Hz, 1H), 7.23 - 7.17 (m, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.55 - 4.41 (m, 1H), 4.05 (s, 3H), 3.24 - 3.19 (m, 1H), 3.19 - 3.14 (m, 1H), 3.11 (br s, 1H), 2.73 (br s, 1H), 1.90 - 1.85 (m, 1H), 1.83 - 1.77 (m, 1H), 1.56 - 1.48 (m, 1H), 1.45 - 1.37 (m, 2H), 1.30 - 1.21 (m, 3H), 0.81 - 0.70 (m, 2H), 0.44 - 0.31 (m, 2H), 三个H隐藏于水/溶剂峰下	2.40, A

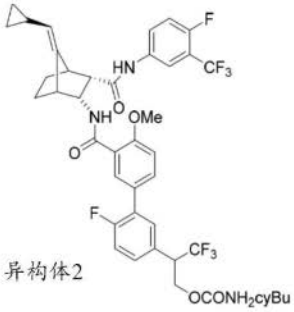
889		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[2-(2-羟基-2-甲基丙酰基)-2,3-二氢-1H-异吲哚-4-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	706.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 10.01 - 9.87 (m, 1H), 8.24 (dd, J=6.3, 2.3 Hz, 1H), 8.04 (dd, J=14.9, 2.3 Hz, 1H), 7.86 - 7.75 (m, 1H), 7.70 - 7.61 (m, 1H), 7.57 - 7.47 (m, 1H), 7.43 - 7.33 (m, 2H), 7.32 - 7.24 (m, 2H), 5.36 (s, 1H), 5.19 (br d, J=9.5 Hz, 2H), 4.79 - 4.66 (m, 3H), 4.53 - 4.35 (m, 1H), 4.07 (s, 3H), 3.17 (br dd, J=10.9, 3.7 Hz, 1H), 3.14 - 3.04 (m, 1H), 2.73 (s ,1H), 1.95 - 1.76 (m, 2H), 1.56 - 1.48 (m, 1H), 1.47 - 1.40 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 0.89 - 0.58 (m, 2H), 0.35 (br dd, J=3.9, 2.6 Hz, 2H)	2.63, A

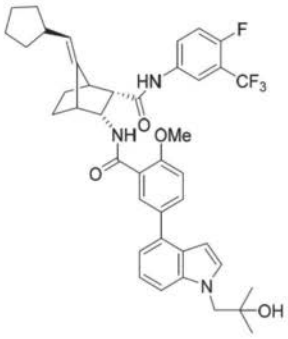
890		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-[2-甲氧基-5-(2-氧代-2,3-二氢-1H-indol-4-基)苯甲酰胺基]双环[2.2.1]庚烷-2-甲酰胺	634.0	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 10.00 - 9.80 (m, 1H), 8.24 (dd, J=6.4, 2.4 Hz, 1H), 8.09 (d, J=2.4 Hz, 1H), 7.87 - 7.78 (m, 1H), 7.76 - 7.70 (m, 1H), 7.49 (t, J=9.6 Hz, 1H), 7.36 - 7.20 (m, 2H), 7.00 (d, J=7.6 Hz, 1H), 6.82 (d, J=7.7 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.55 - 4.43 (m, 1H), 4.05 (s, 3H), 3.56 (s, 1H), 3.17 (br dd, J=10.9, 3.9 Hz, 1H), 3.11 (br s, 1H), 2.73 (br d, J=3.7 Hz, 1H), 1.97 - 1.86 (m, 1H), 1.84 - 1.74 (m, 1H), 1.58 - 1.48 (m, 1H), 1.45 - 1.34 (m, 2H), 0.74 (quin, J=10.0 Hz, 2H), 0.45 - 0.29 (m, 2H)，两个H隐藏于水/溶剂峰下	2.50, A

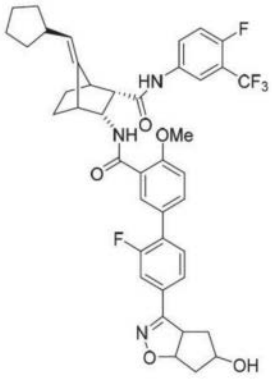
891	 异构体1	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-2-氟-4'-甲氧基-[1,1'-联苯]-4-基)-4,4,4-三氟丁酸	765.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.88 (d, J=7.2 Hz, 1H), 8.24 (dd, J=6.4, 2.3 Hz, 1H), 8.15 (s, 1H), 7.88 - 7.76 (m, 1H), 7.72 (br d, J=8.5 Hz, 1H), 7.64 - 7.52 (m, 1H), 7.50 - 7.43 (m, 2H), 7.37 (br d, J=8.3 Hz, 1H), 7.30 (s, 1H), 5.19 (d, J=8.8 Hz, 1H), 4.51 - 4.35 (m, 1H), 4.29 - 4.10 (m, 1H), 4.06 (s, 3H), 3.10 - 2.96 (m, 3H), 2.66 - 2.57 (m, 2H), 1.93 - 1.86 (m, 2H), 1.85 - 1.82 (m, 2H), 1.81 - 1.73 (m, 3H), 1.65 (br dd, J=7.0, 3.6 Hz, 2H), 1.58 (br d, J=5.3 Hz, 2H), 1.43 - 1.38 (m, 2H), 1.29 - 1.25 (m, 1H)	2.25, A

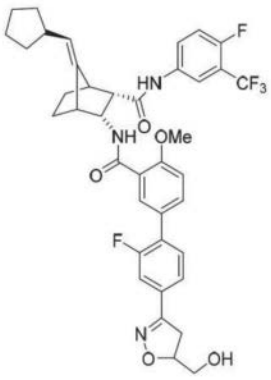
892	 异构体2	3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-2-氟-4'-甲氧基-[1,1'-联苯]-4-基)-4,4,4-三氟丁酸	765.5	(500 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.88 (d, J=7.2 Hz, 1H), 8.25 (dd, J=6.5, 2.3 Hz, 1H), 8.14 (s, 1H), 7.89 - 7.79 (m, 1H), 7.71 (br d, J=8.2 Hz, 1H), 7.60 - 7.48 (m, 1H), 7.49 - 7.45 (m, 1H), 7.42 (br d, J=11.7 Hz, 1H), 7.35 (br d, J=7.6 Hz, 1H), 7.30 (d, J=8.8 Hz, 1H), 5.19 (d, J=8.9 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.24 - 4.06 (m，3H？水抑制？), 2.85 (q, J=7.3 Hz, 2H), 2.77 - 2.68 (m, 1H), 2.66 - 2.59 (m, 1H), 1.96 - 1.85 (m, 1H), 1.85 - 1.74 (m, 3H), 1.72 - 1.64 (m, 2H), 1.61 - 1.52 (m, 2H), 1.48 - 1.36 (m, 2H), 1.36 - 1.21 (m, 3H), 1.12 (t, J=7.2 Hz, 3H)	2.53, A

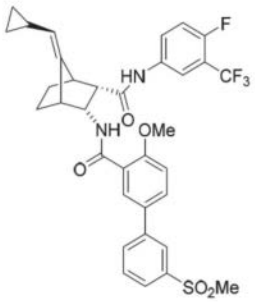
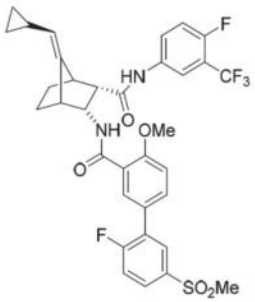
893	 异构体1	N-环丁基氨基甲酸 2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙基酯	834.1	(500 MHz, DMSO-d6) δ 10.58 - 10.49 (m, 1H), 9.90 (d, J=7.0 Hz, 1H), 8.25 (dd, J=6.3, 2.1 Hz, 1H), 8.14 (s, 1H), 7.87 - 7.78 (m, 1H), 7.70 (br d, J=8.2 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.53 (br d, J=7.9 Hz, 1H), 7.48 (br d, J=9.5 Hz, 2H), 7.36 (br d, J=10.2 Hz, 1H), 7.34 - 7.29 (m, 1H), 5.20 (d, J=8.9 Hz, 1H), 4.59 - 4.51 (m, 1H), 4.42 (br dd, J=11.0, 7.3 Hz, 2H), 4.23 - 4.16 (m, 1H), 4.06 (s, 3H), 3.97 - 3.91 (m, 1H), 3.17 (dd, J=10.4, 3.8 Hz, 1H), 3.01 (br s, 1H), 2.72 (br s, 1H), 2.64 - 2.57 (m, 1H), 2.13 - 2.04 (m, 2H), 1.91 - 1.82 (m, 3H), 1.81 - 1.73 (m, 2H), 1.70 - 1.62 (m, 2H), 1.60 - 1.47 (m, 3H), 1.43 - 1.37 (m, 2H), 1.32 - 1.20 (m, 2H), 一个H隐藏于水/溶剂峰下	3.20, A

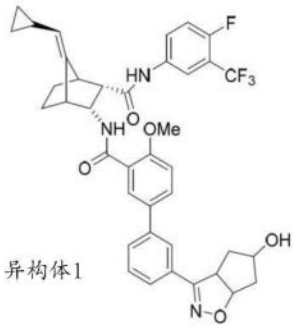
894	 异构体2	N-环丁基氨基甲酸 2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙基酯	834.1	(500 MHz, DMSO-d6) δ 10.65 - 10.48 (m, 1H), 9.90 (d, J=7.2 Hz, 1H), 8.25 (dd, J=6.4, 2.5 Hz, 1H), 8.14 (s, 1H), 7.84 - 7.75 (m, 1H), 7.70 (br d, J=9.0 Hz, 1H), 7.60 (br s, 1H), 7.54 (br d, J=7.9 Hz, 1H), 7.50 - 7.46 (m, 2H), 7.36 (br d, J=10.3 Hz, 1H), 7.32 (d, J=8.9 Hz, 1H), 5.20 (d, J=8.9 Hz, 1H), 4.60 - 4.49 (m, 1H), 4.47 - 4.38 (m, 2H), 4.26 - 4.15 (m, 1H), 4.06 (s, 3H), 3.97 - 3.89 (m, 1H), 3.17 (dd, J=10.5, 4.3 Hz, 1H), 3.01 (br s, 1H), 2.72 (br s, 1H), 2.63 - 2.57 (m, 1H), 2.15 - 2.05 (m, 2H), 1.94 - 1.82 (m, 4H), 1.81 - 1.72 (m, 2H), 1.71 - 1.63 (m, 2H), 1.60 - 1.48 (m, 4H), 1.46 - 1.37 (m, 2H), 1.33 - 1.21 (m, 2H)	3.21, A

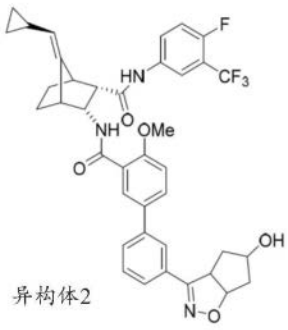
895		(2S,3R,7Z)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[1-(2-羟基-2-甲基丙基)-1H-indol-4-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	718.0	(500 MHz, DMSO-d6) δ 10.63 - 10.45 (m, 1H), 9.91 (d, J=7.0 Hz, 1H), 8.30 (d, J=2.4 Hz, 1H), 8.25 (dd, J=6.6, 2.4 Hz, 1H), 7.84 - 7.76 (m, 2H), 7.54 (d, J=8.2 Hz, 1H), 7.49 (t, J=9.7 Hz, 1H), 7.41 (d, J=3.1 Hz, 1H), 7.32 (d, J=8.8 Hz, 1H), 7.19 (t, J=7.8 Hz, 1H), 7.05 (d, J=7.1 Hz, 1H), 6.50 (d, J=3.1 Hz, 1H), 5.20 (d, J=8.9 Hz, 1H), 4.50 - 4.39 (m, 1H), 4.11 (s, 2H), 4.07 (s, 3H), 3.17 (dd, J=10.8, 4.1 Hz, 1H), 3.02 (br s, 1H), 2.72 (br s, 1H), 2.66 - 2.58 (m, 1H), 1.92 (br t, J=8.7 Hz, 1H), 1.87 - 1.81 (m, 2H), 1.79 - 1.75 (m, 1H), 1.70 - 1.63 (m, 2H), 1.61 - 1.54 (m, 2H), 1.45 - 1.38 (m, 2H), 1.34 - 1.22 (m, 2H), 1.12 (s, 6H), 一个H隐藏于水/溶剂峰下	3.07, C

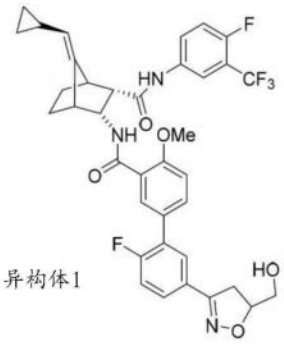
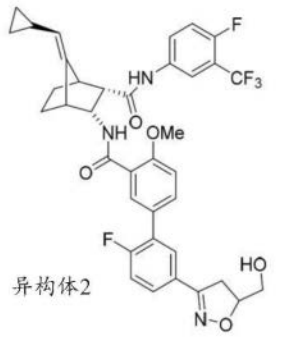
896		N-[(2R,3S,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4'-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-4-甲氧基-[1,1'-联苯]-3-甲酰胺	857.1	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.96 - 9.84 (m, 1H), 8.24 (br d, J=5.8 Hz, 1H), 8.18 (br s, 1H), 7.87 - 7.77 (m, 1H), 7.74 (br d, J=8.9 Hz, 1H), 7.66 - 7.53 (m, 3H), 7.50 - 7.42 (m, 1H), 7.32 (d, J=8.9 Hz, 1H), 5.33 - 5.14 (m, 2H), 4.49 - 4.39 (m, 1H), 4.26 (td, J=9.4, 3.7 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.06 (s, 3H), 3.44 - 3.32 (m, 1H), 3.16 (br dd, J=10.9, 3.7 Hz, 1H), 3.00 (br d, J=4.5 Hz, 1H), 2.72 (br s, 1H), 2.64 - 2.57 (m, 1H), 2.18 - 2.07 (m, 1H), 2.04 - 1.94 (m, 1H), 1.89 - 1.71 (m, 5H), 1.70 - 1.61 (m, 2H), 1.58 - 1.52 (m, 2H), 1.44 - 1.37 (m, 2H), 1.31 - 1.20 (m, 2H)	3.26, A

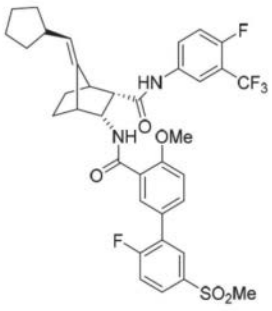
897		N-[(2R,3S,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4'-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	724.6	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.25 (dd, J=6.6, 2.4 Hz, 1H), 8.18 - 8.12 (m, 1H), 7.80 (br dd, J=9.0, 3.0 Hz, 1H), 7.74 (br d, J=8.7 Hz, 1H), 7.64 - 7.54 (m, 3H), 7.49 (t, J=9.7 Hz, 1H), 7.32 (d, J=8.9 Hz, 1H), 5.19 (d, J=8.6 Hz, 1H), 5.02 (t, J=5.8 Hz, 1H), 4.77 (qd, J=7.7, 4.3 Hz, 1H), 4.50 - 4.32 (m, 1H), 4.06 (s, 3H), 3.61 - 3.52 (m, 2H), 3.50 - 3.37 (m, 1H), 3.29 - 3.13 (m, 1H), 3.06 - 2.94 (m, 1H), 2.72 (br s, 1H), 2.61 (s, 2H), 1.89 - 1.74 (m, 4H), 1.70 - 1.62 (m, 2H), 1.59 - 1.48 (m, 2H), 1.45 - 1.35 (m, 2H), 1.32 - 1.17 (m, 2H)	2.81, A

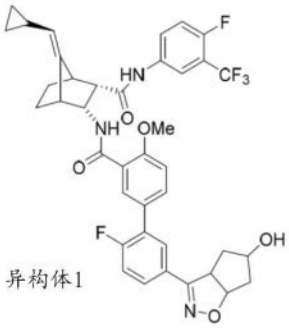
898		N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-3'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3-甲酰胺	657.2	(500 MHz, DMSO-d6) δ 10.65 - 10.47 (m, 1H), 10.04 - 9.89 (m, 1H), 8.32 - 8.28 (m, 1H), 8.25 - 8.21 (m, 1H), 8.14 - 8.10 (m, 1H), 8.04 - 7.99 (m, 1H), 7.96 - 7.87 (m, 1H), 7.77 - 7.71 (m, 1H), 7.52 - 7.46 (m, 1H), 7.38 - 7.31 (m, 1H), 4.75 - 4.67 (m, 1H), 4.53 - 4.44 (m, 1H), 4.09 - 4.01 (m, 1H), 3.33 - 3.26 (m, 1H), 3.20 - 3.09 (m, 1H), 2.57 - 2.53 (m, 32H), 1.92 - 1.75 (m, 1H), 1.56 - 1.36 (m, 1H), 0.81 - 0.68 (m, 1H), 0.40 - 0.30 (m, 1H)	2.56, C
899		N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3-甲酰胺	675.1	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.93 (br d, J=7.3 Hz, 1H), 8.26 - 8.12 (m, 2H), 8.02 (br d, J=5.1 Hz, 1H), 7.99 - 7.89 (m, 1H), 7.79 (br d, J=6.3 Hz, 2H), 7.60 (br t, J=9.5 Hz, 1H), 7.47 (br t, J=9.6 Hz, 1H), 7.35 (br d, J=8.6 Hz, 1H), 4.69 (br d, J=9.6 Hz, 1H), 4.45 (br s, 1H), 4.06 (s, 3H), 3.15 (br d, J=7.6 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.89 - 1.68 (m, 2H), 1.49 (br s, 1H), 1.41 (br s, 2H), 0.84 - 0.66 (m, 2H), 0.34 (br s, 2H)	2.61, C

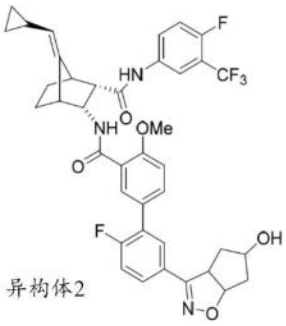
901	 异构体1	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-3'-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-4-甲氧基-[1,1'-联苯]-3-甲酰胺	704.2	(500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.68 (d, J=7.2 Hz, 1H), 8.06 - 7.92 (m, 1H), 7.65 - 7.52 (m, 2H), 7.54 (m, 1H), 7.45 (br d, J=7.6 Hz, 1H), 7.38 (d, J=7.6 Hz, 1H), 7.32 - 7.20 (m, 1H), 7.06 (d, J=8.8 Hz, 1H), 4.94 (td, J=6.2, 3.2 Hz, 1H), 4.45 (d, J=9.7 Hz, 1H), 4.23 (br s, 1H), 4.07 (td, J=9.5, 4.2 Hz, 1H), 3.95 - 3.84 (m, 1H), 3.81 (s, 3H), 2.93 (br dd, J=10.5, 4.3 Hz, 1H), 2.87 (br s, 1H), 2.48 (br s, 1H), 1.78 - 1.55 (m, 4H), 1.51 (s, 1H), 1.26 (br dd, J=8.8, 4.2 Hz, 1H), 1.21 - 0.98 (m, 2H), 0.49 (br dd, J=12.6, 8.9 Hz, 2H), 0.10 (br s, 2H)	2.67, A

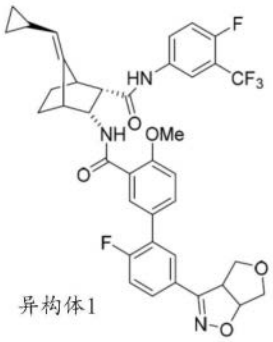
902	 异构体2	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-3'-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-4-甲氧基-[1,1'-联苯]-3-甲酰胺	704.3	(500 MHz, DMSO-d6) δ 9.94 (d, J=7.0 Hz, 1H), 8.25 (br d, J=2.4 Hz, 2H), 7.87 - 7.79 (m, 3H), 7.68 (br d, J=8.0 Hz, 1H), 7.64 (d, J=7.9 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.49 (t, J=9.9 Hz, 1H), 7.32 (d, J=8.7 Hz, 1H), 5.18 - 5.13 (m, 1H), 4.70 (d, J=9.6 Hz, 1H), 4.48 (br s, 1H), 4.24 - 4.15 (m, 2H), 4.06 (s, 3H), 3.91 (s, 1H), 3.20 - 3.17 (m, 1H), 3.13 (br s, 1H), 2.74 (br s, 1H), 2.17 - 2.09 (m, 2H), 1.95 - 1.79 (m, 4H), 1.51 (br dd, J=8.9, 4.5 Hz, 1H), 1.47 - 1.38 (m, 2H), 0.75 (br dd, J=12.7, 8.9 Hz, 2H), 0.36 (br s, 2H)	2.57, A

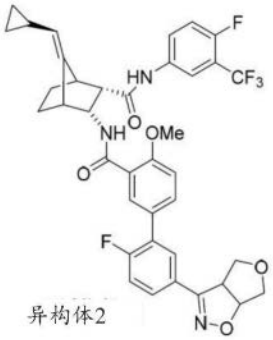
905	 异构体1	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	696.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.93 (d, J=7.2 Hz, 1H), 8.24 (dd, J=6.4, 2.5 Hz, 1H), 8.16 (s, 1H), 7.82 - 7.68 (m, 4H), 7.49 (t, J=9.8 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.33 (d, J=8.7 Hz, 1H), 4.76 - 4.68 (m, 2H), 4.47 (br t, J=10.6 Hz, 1H), 4.07 (s, 3H), 3.55 - 3.49 (m, 1H), 3.17 (dd, J=10.4, 4.3 Hz, 1H), 3.12 (br s, 1H), 2.73 (br s, 1H), 1.90 - 1.78 (m, 2H), 1.54 - 1.37 (m, 3H), 0.74 (quin, J=10.1 Hz, 2H), 0.38 - 0.33 (m, 2H)	2.61, A
906	 异构体2	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-4,5-二氢-1,2-噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	696.1	(500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.69 (d, J=7.4 Hz, 1H), 8.00 (d, J=6.7 Hz, 1H), 7.92 (s, 1H), 7.58 - 7.45 (m, 3H), 7.25 (t, J=9.7 Hz, 1H), 7.17 (dd, J=10.5, 8.7 Hz, 1H), 7.09 (d, J=8.8 Hz, 1H), 4.77 (t, J=5.7 Hz, 1H), 4.52 - 4.44 (m, 1H), 4.23 (br s, 1H), 3.83 (s, 3H), 3.29 (q, J=5.0 Hz, 1H), 2.95 - 2.87 (m, 1H), 2.49 (br s, 1H), 1.66 - 1.55 (m, 1H), 1.30 - 1.21 (m, 1H), 1.21 - 1.14 (m, 1H), 0.55 - 0.46 (m, 1H), 0.12 (br s, 1H)	2.57, C

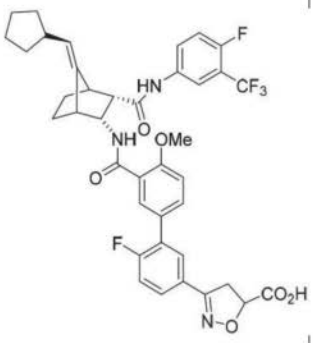
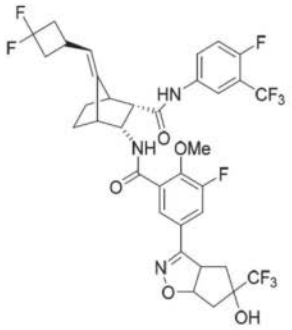
907		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-甲磺酰基-4-甲氧基-[1,1'-联苯]-3-甲酰胺	703.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (d, J=7.2 Hz, 1H), 8.24 (dd, J=6.4, 2.3 Hz, 1H), 8.19 (s, 1H), 8.04 (dd, J=7.2, 2.3 Hz, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.82 - 7.77 (m, 2H), 7.61 (t, J=9.0 Hz, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.36 (d, J=8.8 Hz, 1H), 5.20 (d, J=8.9 Hz, 1H), 4.42 (br t, J=10.5 Hz, 1H), 4.07 (s, 3H), 3.30 (s, 1H), 3.17 (dd, J=10.7, 4.0 Hz, 1H), 3.02 (br s, 1H), 2.72 (br s, 1H), 2.63 - 2.57 (m, 1H), 2.55 (s, 3H), 1.90 - 1.74 (m, 5H), 1.68 - 1.54 (m, 2H), 1.40 (br s, 2H), 1.31 - 1.23 (m, 2H)	2.83, C

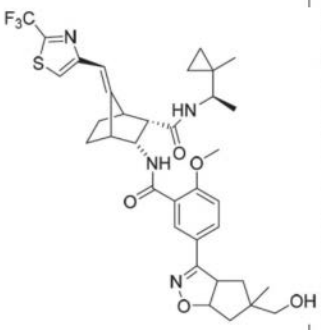
908	 异构体1	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-4-甲氧基-[1,1'-联苯]-3-甲酰胺	722.5	(500 MHz, DMSO-d6) δ 9.69 (d, J=7.2 Hz, 1H), 7.99 (d, J=6.7 Hz, 1H), 7.91 (s, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.51 - 7.43 (m, 2H), 7.24 (t, J=9.7 Hz, 1H), 7.16 (t, J=9.5 Hz, 1H), 7.09 (d, J=8.7 Hz, 1H), 4.96 - 4.91 (m, 1H), 4.45 (d, J=9.5 Hz, 1H), 4.25 - 4.20 (m, 1H), 4.06 (td, J=9.4, 4.0 Hz, 1H), 3.89 - 3.85 (m, 1H), 3.82 (s, 3H), 2.93 (br dd, J=10.6, 4.1 Hz, 1H), 2.87 (br s, 1H), 2.49 (br s, 1H), 1.78 - 1.55 (m, 5H), 1.29 - 1.15 (m, 2H), 0.54 - 0.45 (m, 2H), 0.13 - 0.09 (m, 2H)	2.61, C

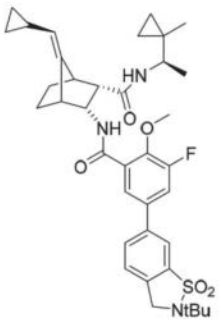
909	 异构体2	N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-{5-羟基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基}-4-甲氧基-[1,1'-联苯]-3-甲酰胺	722.6	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.94 (d, J=7.2 Hz, 1H), 8.24 (dd, J=6.5, 2.4 Hz, 1H), 8.15 (s, 1H), 7.82 - 7.78 (m, 1H), 7.75 - 7.67 (m, 3H), 7.49 (t, J=9.7 Hz, 1H), 7.41 (t, J=9.0 Hz, 1H), 7.34 (d, J=8.7 Hz, 1H), 5.17 - 5.13 (m, 1H), 4.70 (d, J=9.7 Hz, 1H), 4.47 (br s, 1H), 4.22 - 4.15 (m, 2H), 4.07 (s, 3H), 3.17 (dd, J=10.5, 4.4 Hz, 1H), 3.12 (br s, 1H), 2.73 (br s, 1H), 2.14 - 2.07 (m, 2H), 1.94 - 1.78 (m, 4H), 1.51 (br dd, J=8.7, 4.2 Hz, 1H), 1.46 - 1.39 (m, 2H), 0.79 - 0.70 (m, 2H), 0.35 (br d, J=2.5 Hz, 2H)	2.59, A

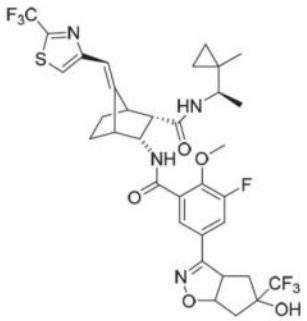
910	 异构体1	5'-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	708.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (d, J=7.3 Hz, 1H), 8.24 (dd, J=6.3, 2.4 Hz, 1H), 8.15 (s, 1H), 7.81 - 7.70 (m, 4H), 7.49 (t, J=9.8 Hz, 1H), 7.42 (t, J=8.8 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 5.39 (dd, J=9.2, 3.7 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.58 (br t, J=7.7 Hz, 1H), 4.50 - 4.45 (m, 1H), 4.13 - 4.11 (m, 1H), 4.07 (s, 3H), 3.98 (br d, J=9.5 Hz, 1H), 3.77 (dd, J=9.4, 7.0 Hz, 1H), 3.67 (dd, J=10.7, 3.5 Hz, 1H), 3.19 - 3.10 (m, 2H), 2.73 (br s, 1H), 1.90 - 1.79 (m, 2H), 1.54 - 1.45 (m, 1H), 1.45 - 1.38 (m, 2H), 0.74 (quin, J=10.1 Hz, 2H), 0.38 - 0.33 (m, 2H)	2.75, C

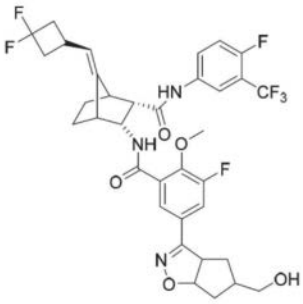
911	 异构体2	5'-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	708.4	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 (d, J=7.3 Hz, 1H), 8.24 (dd, J=6.3, 2.4 Hz, 1H), 8.15 (s, 1H), 7.81 - 7.70 (m, 4H), 7.49 (t, J=9.8 Hz, 1H), 7.42 (t, J=8.8 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 5.39 (dd, J=9.2, 3.7 Hz, 1H), 4.70 (d, J=9.5 Hz, 1H), 4.58 (br t, J=7.7 Hz, 1H), 4.50 - 4.45 (m, 1H), 4.13 - 4.11 (m, 1H), 4.07 (s, 3H), 3.98 (br d, J=9.5 Hz, 1H), 3.77 (dd, J=9.4, 7.0 Hz, 1H), 3.67 (dd, J=10.7, 3.5 Hz, 1H), 3.19 - 3.10 (m, 2H), 2.73 (br s, 1H), 1.90 - 1.79 (m, 2H), 1.54 - 1.45 (m, 1H), 1.45 - 1.38 (m, 2H), 0.74 (quin, J=10.1 Hz, 2H), 0.38 - 0.33 (m, 2H)	2.69, A

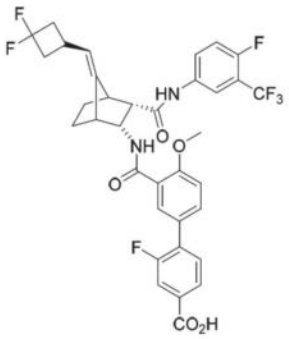
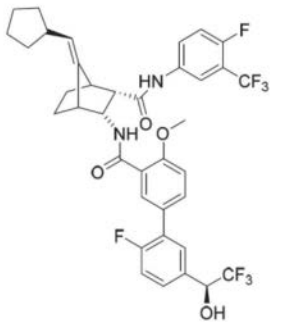
913		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,5-二氢-1,2-噁唑-5-甲酸	738.4	(500 MHz, DMSO-d6) δ 10.58 (s, 1H), 9.89 (br d, J=6.9 Hz, 1H), 8.26 - 8.20 (m, 1H), 8.16 (s, 1H), 7.82 - 7.70 (m, 3H), 7.48 (t, J=9.8 Hz, 1H), 7.40 (t, J=9.0 Hz, 1H), 7.32 (d, J=8.7 Hz, 1H), 5.19 (d, J=8.9 Hz, 1H), 5.08 - 5.03 (m, 1H), 4.41 (br s, 1H), 4.06 (s, 3H), 3.19 - 3.15 (m, 1H), 3.01 (br s, 1H), 2.72 (br s, 1H), 1.92 - 1.86 (m, 1H), 1.86 - 1.71 (m, 3H), 1.70 - 1.50 (m, 4H), 1.39 (br s, 2H), 1.32 - 1.19 (m, 2H)	2.38, A
914		(1R,2S,3R,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	764.2	(DMSO-d6, 400 MHz) δ 10.5-10.6 (m, 1H), 9.7-9.7 (m, 1H), 8.1-8.2 (m, 1H), 7.9-8.0 (m, 1H), 7.8-7.9 (m, 1H), 7.7-7.8 (m, 1H), 7.4-7.5 (m, 1H), 5.9-6.0 (m, 1H), 5.4-5.4 (m, 1H), 5.3-5.4 (m, 1H), 4.3-4.4 (m, 2H), 4.0-4.1 (m, 3 H), 3.1-3.2 (m, 1H), 2.6-3.0 (m, 8H), 2.4-2.5 (m, 1H), 2.2-2.3 (m, 2H), 1.9-2.1 (m, 1H), 1.8-1.9 (m, 2H), 1.3-1.5 (m, 2H)	2.50, B

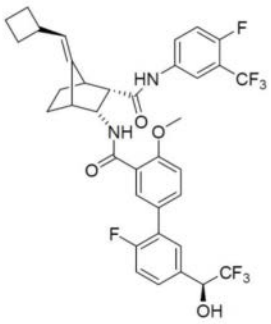
915		(1R,2S,3R,4R,7Z)-3-{5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-{[2-(三氟甲基)-1,3-噻唑-4-基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	687.3	(400 MHz, DMSO-d6) δ = 10.11 (d, J = 6.8 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.97 (s, 1H), 7.79 (dd, J = 2.4, 8.6 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H), 6.43 (s, 1H), 5.30 - 5.09 (m, 1H), 4.59 (t, J = 5.3 Hz, 1H), 4.37 (ddd, J = 4.4, 6.5, 10.4 Hz, 1H), 4.25 (dt, J = 6.6, 9.8 Hz, 1H), 4.01 (s, 3H), 3.70 (br s, 1H), 3.53 - 3.48 (m, 1H), 3.21 - 3.12 (m, 2H), 3.09 (dd, J = 4.4, 10.9 Hz, 1H), 2.78 (br s, 1H), 2.06 - 1.96 (m, 1H), 1.92 - 1.76 (m, 4H), 1.66 (dd, J = 6.5, 12.9 Hz, 1H), 1.47 (br d, J = 6.0 Hz, 2H), 1.04 (d, J = 6.9 Hz, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.63 - 0.50 (m, 1H), 0.40 - 0.29 (m, 1H), 0.25 - 0.10 (m, 2H)	2.36, B

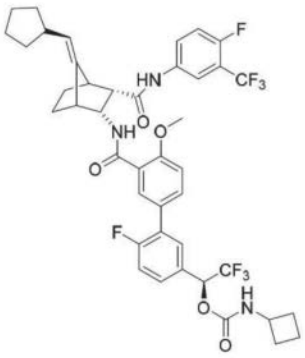
916		(1R,2S,3R,4R,7Z)-3-[5-(2-叔丁基-1,1-二氧代-2,3-二氢-1λ⁶,2-苯并噻唑-6-基)-3-氟-2-甲氧基苯甲酰胺基]-7-(环丙基亚甲基)-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	664.3	(400 MHz, DMSO-d6) δ 9.98 (d, J = 6.9 Hz, 1H), 8.06 (d, J = 1.1 Hz, 1H), 8.04 - 7.87 (m, 4H), 7.66 (d, J = 8.3 Hz, 1H), 4.66 (d, J = 9.5 Hz, 1H), 4.59 (s, 2H), 4.38 - 4.29 (m, 1H), 4.05 (d, J = 2.3 Hz, 3H), 3.50 - 3.45 (m, 1H), 3.11 - 3.04 (m, 1H), 2.98 (dd, J = 4.4, 10.9 Hz, 1H), 2.59 - 2.54 (m, 1H), 1.93 - 1.72 (m, 2H), 1.54 - 1.30 (m, 12H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H), 0.80 - 0.66 (m, 2H), 0.58 - 0.47 (m, 1H), 0.41 - 0.27 (m, 3H), 0.24 - 0.08 (m, 2H)。	2.69, A

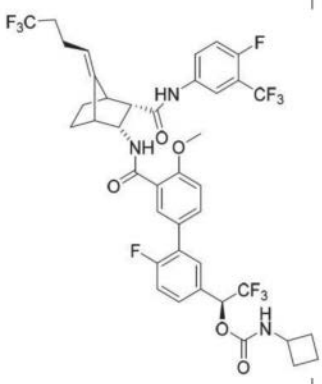
917		(1R,2S,3R,4R,7Z)-3-{3-氟-5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]-7-{[2-(三氟甲基)-1,3-噻唑-5-基]亚甲基}双环[2.2.1]庚烷-2-甲酰胺	745.2	(400 MHz, DMSO-d6) δ 10.15 (d, J = 6.5 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.09 (s, 1H), 7.94 - 7.87 (m, 1H), 7.71 (dd, J = 2.3, 12.5 Hz, 1H), 6.67 (s, 1H), 5.92 (s, 1H), 5.31 (dd, J = 6.3, 9.5 Hz, 1H), 4.54 - 4.27 (m, 2H), 4.06 (d, J = 2.5 Hz, 3H), 3.48 (dd, J = 7.0, 8.8 Hz, 1H), 3.12 (dd, J = 4.4, 11.1 Hz, 1H), 2.85 (br d, J = 2.5 Hz, 1H), 2.32 - 2.18 (m, 3H), 2.00 (br d, J = 14.0 Hz, 1H), 1.96 - 1.84 (m, 2H), 1.58 - 1.44 (m, 2H), 1.04 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 0.58 - 0.49 (m, 1H), 0.40 - 0.31 (m, 1H), 0.28 - 0.11 (m, 2H)。	2.56, A

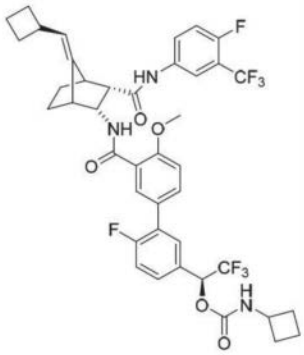
918		(1R,2S,3R,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	710.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.69 (d, J=7.2 Hz, 1H), 8.11 (dd, J=6.3, 2.1 Hz, 1H), 7.96 (s, 1H), 7.86 - 7.81 (m, 1H), 7.72 (dd, J=12.6, 1.9 Hz, 1H), 7.48 (t, J=9.8 Hz, 1H), 5.40 (d, J=8.5 Hz, 1H), 5.16 (dd, J=8.7, 5.1 Hz, 1H), 4.51 (t, J=5.1 Hz, 1H), 4.45 - 4.36 (m, 1H), 4.19 (br t, J=8.6 Hz, 1H), 4.08 (s, 1H), 4.09 (s, 2H), 3.17 (dd, J=10.4, 4.3 Hz, 1H), 3.05 - 2.99 (m, 1H), 2.97 - 2.79 (m, 3H), 2.78 - 2.73 (m, 1H), 2.47 - 2.36 (m, 2H), 1.99 (br dd, J=13.3, 5.8 Hz, 1H), 1.93 - 1.73 (m, 4H), 1.68 - 1.51 (m, 2H), 1.41 (br d, J=4.6 Hz, 2H), 由于水抑制未观测到两个质子	2.54, C

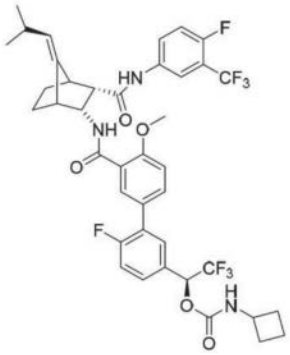
919		3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-2-氟-4'-甲氧基-[1,1'-联苯]-4-甲酸	691.2	(500 MHz, DMSO-d6) δ 10.60 - 10.52 (m, 1H), 9.90 (br d, J=7.2 Hz, 1H), 8.24 - 8.11 (m, 2H), 7.84 (br d, J=8.1 Hz, 1H), 7.79 - 7.68 (m, 3H), 7.62 (br t, J=8.0 Hz, 1H), 7.51 - 7.42 (m, 1H), 7.32 (br d, J=8.8 Hz, 1H), 5.38 (br d, J=8.5 Hz, 1H), 4.43 - 4.35 (m, 1H), 4.04 (s, 3H), 3.62 (br s, 3H), 3.19 - 3.11 (m, 1H), 2.99 (br s, 1H), 2.96 - 2.90 (m, 1H), 2.75 (br s, 1H), 2.46 - 2.33 (m, 2H), 1.94 - 1.74 (m, 2H), 1.45 - 1.32 (m, 2H)	2.18, C
920		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-[(1S)-2,2,2-三氟-1-羟基乙基]-[1,1'-联苯]-3-甲酰胺	723.2	(500 MHz, DMSO-d6) δ 10.57 - 10.49 (m, 1H), 9.91 (d, J=7.2 Hz, 1H), 8.22 (dd, J=6.2, 2.2 Hz, 1H), 8.12 (s, 1H), 7.82 - 7.75 (m, 1H), 7.70 (br d, J=8.6 Hz, 1H), 7.61 (br d, J=7.6 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.38 - 7.28 (m, 2H), 7.03 (d, J=5.6 Hz, 1H), 5.30 - 5.22 (m, 1H), 5.18 (s, 1H), 4.46 - 4.37 (m, 1H), 4.05 (s, 3H), 3.15 (dd, J=10.5, 4.3 Hz, 1H), 3.00 (br s, 1H), 2.71 (br s, 1H), 2.64 - 2.57 (m, 1H), 1.92 - 1.70 (m, 4H), 1.67 - 1.49 (m, 4H), 1.46 - 1.34 (m, 2H), 1.29 - 1.19 (m, 2H)	3.00, C

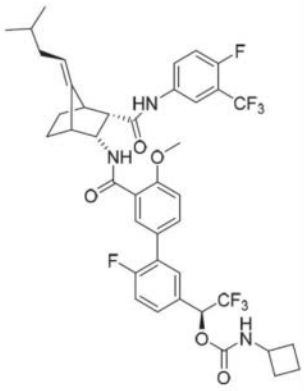
921		N-[(1R,2R,3S,4R,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-5'-[(1S)-2,2,2-三氟-1-羟基乙基]-[1,1'-联苯]-3-甲酰胺	709.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.21 (br d, J=4.2 Hz, 1H), 8.12 (s, 1H), 7.82 - 7.75 (m, 1H), 7.69 (br d, J=8.5 Hz, 1H), 7.62 (br d, J=7.2 Hz, 1H), 7.53 - 7.43 (m, 2H), 7.38 - 7.28 (m, 2H), 5.37 (d, J=8.5 Hz, 1H), 5.29 - 5.21 (m, 1H), 4.43 - 4.32 (m, 1H), 4.04 (s, 3H), 3.22 - 3.04 (m, 2H), 2.96 (br s, 1H), 2.70 (br s, 1H), 2.20 - 2.07 (m, 2H), 1.95 - 1.67 (m, 7H), 1.48 - 1.29 (m, 2H) 质子由于溶胶而缺失	2.92, C

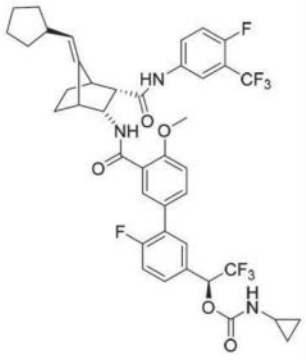
922		N-环丁基氨基甲酸 (1S)-1-(3'-{[(2R,3S,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	820.1	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.91 (br d, J=7.1 Hz, 1H), 8.28 - 8.19 (m, 1H), 8.17 - 8.05 (m, 2H), 7.81 - 7.75 (m, 1H), 7.67 (br dd, J=18.3, 7.9 Hz, 2H), 7.54 (br dd, J=3.5, 2.3 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.32 (d, J=8.6 Hz, 1H), 6.42 - 6.26 (m, 1H), 5.19 (d, J=8.9 Hz, 1H), 4.48 - 4.37 (m, 1H), 4.04 (s, 3H), 3.96 - 3.85 (m, 1H), 3.15 (br dd, J=10.8, 3.7 Hz, 1H), 2.99 (br s, 1H), 2.71 (br s, 1H), 2.64 - 2.57 (m, 1H), 2.27 - 2.03 (m, 2H), 1.98 - 1.74 (m, 6H), 1.67 - 1.47 (m, 6H), 1.46 - 1.35 (m, 2H), 1.29 - 1.17 (m, 2H)	3.26, C

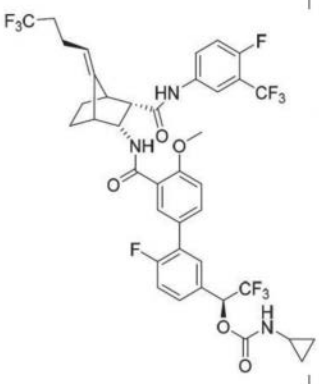
923		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(2R,3S,7Z)-3-{[4- 氟 -3-(三氟甲基)苯基]胺甲酰基 }-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'- 甲氧基 -[1,1'-联苯]-3-基)乙酯	848.0	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.93 (br d, J=7.2 Hz, 1H), 8.28 - 8.19 (m, 1H), 8.16 - 8.08 (m, 2H), 7.83 - 7.77 (m, 1H), 7.70 - 7.62 (m, 2H), 7.54 (br s, 1H), 7.48 - 7.37 (m, 2H), 7.33 (d, J=8.7 Hz, 1H), 6.41 - 6.31 (m, 1H), 5.27 (br t, J=7.1 Hz, 1H), 4.51 - 4.39 (m, 1H), 4.05 (s, 3H), 3.98 - 3.86 (m, 1H), 3.16 (br dd, J=10.3, 3.6 Hz, 1H), 3.00 (br s, 1H), 2.75 (br s, 1H), 2.44 - 2.27 (m, 4H), 2.24 - 2.04 (m, 2H), 1.98 - 1.84 (m, 3H), 1.81 - 1.71 (m, 1H), 1.70 - 1.50 (m, 2H), 1.45 - 1.35 (m, 2H)	3.08, C

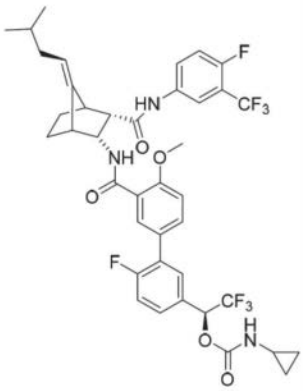
924		N-环丁基氨基甲酸 (1S)-1-(3'-{[(2R,3S,7Z)-7-(环丁基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	806.0	(500 MHz, DMSO-d6) δ 11.95 - 11.95 (m, 1H), 10.53 (s, 1H), 9.91 (br d, J=6.9 Hz, 1H), 8.29 - 8.22 (m, 1H), 8.16 - 8.10 (m, 2H), 7.85 - 7.77 (m, 1H), 7.69 (br t, J=9.1 Hz, 2H), 7.54 (br dd, J=2.9, 2.0 Hz, 1H), 7.52 - 7.39 (m, 2H), 7.35 - 7.26 (m, 1H), 6.39 - 6.28 (m, 1H), 5.38 (d, J=8.3 Hz, 1H), 4.42 - 4.34 (m, 1H), 4.06 (s, 3H), 3.98 - 3.91 (m, 1H), 3.14 - 3.06 (m, 1H), 2.97 (br s, 1H), 2.72 (br d, J=2.7 Hz, 1H), 2.23 - 2.08 (m, 4H), 1.97 - 1.75 (m, 8H), 1.70 - 1.51 (m, 2H), 1.45 - 1.31 (m, 2H)	3.19, C

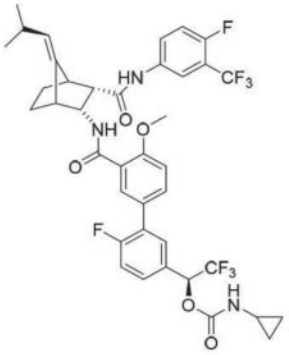
925		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(2R,3S,7Z)-3-{[4- 氟 -3-(三氟甲基) 苯基] 胺甲酰基 }-7-(2- 甲基亚丙基) 双环 [2.2.1] 庚烷 -2-基] 胺甲酰基 }-4'- 甲氧基 -[1,1'- 联苯]-3- 基) 乙酯	794.1	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.91 (br d, J=6.9 Hz, 1H), 8.23 (br d, J=4.1 Hz, 1H), 8.16 - 8.08 (m, 2H), 7.80 - 7.76 (m, 1H), 7.68 (br dd, J=13.7, 8.3 Hz, 2H), 7.55 (br dd, J=6.1, 2.7 Hz, 1H), 7.50 - 7.39 (m, 2H), 7.33 (d, J=8.8 Hz, 1H), 6.35 (br d, J=6.9 Hz, 1H), 5.11 (d, J=8.9 Hz, 1H), 4.46 - 4.38 (m, 1H), 4.05 (s, 3H), 3.95 - 3.85 (m, 1H), 3.16 (dd, J=10.9, 3.9 Hz, 1H), 2.99 (s, 1H), 2.70 (br s, 1H), 2.48 - 2.41 (m, 1H), 2.21 - 2.04 (m, 2H), 1.98 - 1.84 (m, 3H), 1.81 - 1.74 (m, 1H), 1.64 - 1.52 (m, 2H), 1.45 - 1.35 (m, 2H), 1.07 - 0.93 (m, 6H)	3.15. C

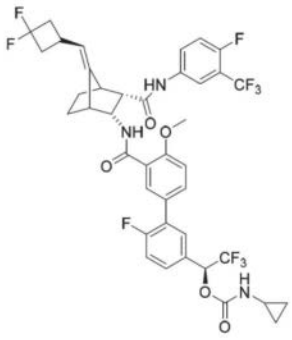
926		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(2R,3S,7Z)-3-{[4- 氟 -3-(三氟甲基) 苯基] 胺甲酰基 }-7-(3- 甲基丁亚基) 双环 [2.2.1] 庚烷 -2-基] 胺甲酰基 }-4'- 甲氧基 -[1,1'- 联苯]-3- 基) 乙酯	808.0	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.92 (br d, J=7.0 Hz, 1H), 8.28 - 8.22 (m, 1H), 8.16 - 8.09 (m, 2H), 7.85 - 7.76 (m, 1H), 7.69 (br dd, J=13.9, 8.1 Hz, 2H), 7.54 (br s, 1H), 7.50 - 7.38 (m, 2H), 7.33 (d, J=8.8 Hz, 1H), 6.41 - 6.26 (m, 1H), 5.24 (t, J=7.6 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.05 (s, 3H), 3.96 - 3.89 (m, 1H), 3.18 (br dd, J=10.7, 3.7 Hz, 1H), 2.96 (br s, 1H), 2.74 (br s, 1H), 2.20 - 2.04 (m, 2H), 1.99 - 1.84 (m, 5H), 1.80 - 1.72 (m, 1H), 1.67 - 1.53 (m, 3H), 1.46 - 1.33 (m, 2H), 0.91 (dd, J=12.3, 6.6 Hz, 6H)	3.23, C

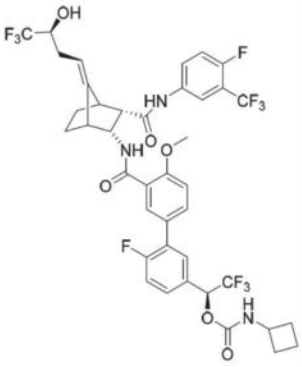
927		N-环丙基氨基甲酸 (1S)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	806.4	(500 MHz, DMSO-d6) δ 10.30 (s, 1H), 9.68 (br d, J=6.9 Hz, 1H), 8.04 - 7.95 (m, 1H), 7.89 (s, 1H), 7.77 (br s, 1H), 7.58 - 7.52 (m, 1H), 7.45 (br d, J=1.1 Hz, 2H), 7.30 (br s, 1H), 7.27 - 7.14 (m, 2H), 7.09 (d, J=8.8 Hz, 1H), 6.14 (br d, J=7.5 Hz, 1H), 4.95 (d, J=8.9 Hz, 1H), 4.24 - 4.10 (m, 1H), 3.82 (s, 3H), 2.92 (br dd, J=10.4, 4.2 Hz, 1H), 2.78 - 2.76 (m, 1H), 2.75 - 2.72 (m, 1H), 2.48 (br s, 1H), 2.35 (br d, J=8.6 Hz, 1H), 1.66 - 1.50 (m, 4H), 1.46 - 1.25 (m, 4H), 1.15 (br d, J=3.0 Hz, 2H), 1.03 (td, J=8.0, 3.9 Hz, 2H), 0.41 - 0.30 (m, 2H), 0.25 - 0.12 (m, 2H)	3.06, C

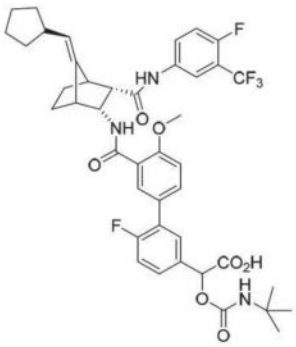
928		N-环丙基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(1R,2R,3S,4R,7Z)-3-{[4- 氟 -3-(三氟甲基)苯基]胺甲酰基 }-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基 }-4'- 甲氧基 -[1,1'-联苯]-3-基)乙酯	834.2	(500 MHz, DMSO-d6) δ 10.38 - 10.30 (m, 1H), 9.70 (br d, J=7.0 Hz, 1H), 8.04 - 7.99 (m, 1H), 7.90 (s, 1H), 7.78 (br d, J=2.2 Hz, 1H), 7.57 (br dd, J=8.6, 3.3 Hz, 1H), 7.46 (br t, J=9.6 Hz, 2H), 7.35 - 7.30 (m, 1H), 7.28 - 7.17 (m, 2H), 7.10 (d, J=8.8 Hz, 1H), 6.22 - 6.12 (m, 1H), 5.05 (br t, J=6.7 Hz, 1H), 4.20 (ddd, J=10.3, 6.8, 3.9 Hz, 1H), 3.83 (s, 3H), 3.01 - 2.91 (m, 1H), 2.78 (br s, 1H), 2.53 (br s, 1H), 2.20 - 2.02 (m, 4H), 1.72 - 1.50 (m, 2H), 1.22 - 1.11 (m, 2H), 0.81 (d, J=6.0 Hz, 1H), 0.40 - 0.30 (m, 2H), 0.25 - 0.14 (m, 2H)	2.84, C

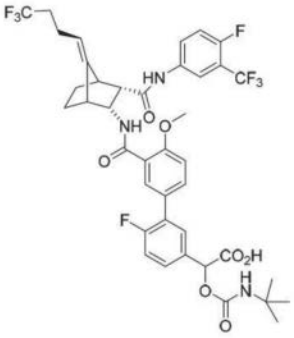
929		N-环丙基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(1R,2R,3S,4R,7Z)-3-{[4- 氟 -3-(三氟甲基)苯基]胺甲酰基}-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'- 甲氧基 -[1,1'-联苯]-3-基)乙酯	794.2	(500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.70 (br d, J=7.1 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.91 (s, 1H), 7.79 (br d, J=2.4 Hz, 1H), 7.57 (dt, J=7.8, 3.9 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.31 (br d, J=3.4 Hz, 1H), 7.29 - 7.18 (m, 2H), 7.10 (d, J=8.8 Hz, 1H), 6.17 (br d, J=6.3 Hz, 1H), 5.02 (t, J=7.7 Hz, 1H), 4.26 - 4.16 (m, 1H), 3.83 (s, 3H), 2.97 (dd, J=10.8, 4.1 Hz, 1H), 2.74 (br s, 1H), 2.52 (t, J=3.4 Hz, 1H), 1.80 - 1.71 (m, 2H), 1.70 - 1.54 (m, 2H), 1.47 - 1.35 (m, 1H), 1.25 - 1.12 (m, 2H), 0.69 (dd, J=12.3, 6.6 Hz, 6H), 0.36 (br d, J=3.2 Hz, 2H), 0.23 - 0.12 (m, 2H) 质子由于水抑制而缺失	3.00, C

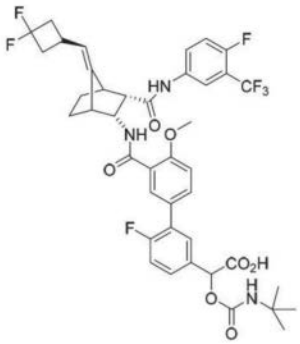
930		N-环丙基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(1R,2R,3S,4R,7Z)-3-{[4- 氟 -3-(三氟甲基)苯基]胺甲酰基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'- 甲氧基 -[1,1'-联苯]-3-基)乙酯	780.1	(500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.73 (br d, J=6.9 Hz, 1H), 8.10 - 8.02 (m, 1H), 7.95 (s, 1H), 7.83 (br d, J=2.7 Hz, 1H), 7.64 - 7.57 (m, 1H), 7.55 - 7.48 (m, 2H), 7.36 (br s, 1H), 7.32 - 7.20 (m, 2H), 7.15 (d, J=8.8 Hz, 1H), 6.21 (br d, J=6.6 Hz, 1H), 4.93 (d, J=9.0 Hz, 1H), 4.24 (ddd, J=10.7, 7.2, 3.8 Hz, 1H), 3.88 (s, 3H), 2.99 (dd, J=10.8, 4.1 Hz, 1H), 2.83 - 2.80 (m, 1H), 2.52 (br s, 1H), 2.28 (br s, 1H), 1.76 - 1.58 (m, 2H), 1.21 (br d, J=7.6 Hz, 2H), 0.86 - 0.77 (m, 6H), 0.44 - 0.35 (m, 2H), 0.28 - 0.17 (m, 2H) 质子由于水抑制而缺失	2.93, C

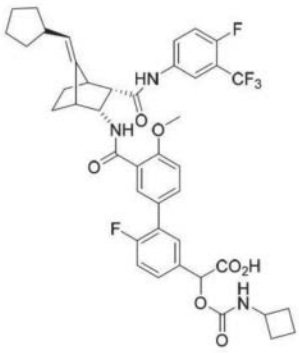
931		N-环丙基氨基甲酸 (1S)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	828.2	(500 MHz, DMSO-d6) δ 10.32 (s, 1H), 9.70 (br d, J=6.9 Hz, 1H), 8.04 - 7.98 (m, 1H), 7.90 (s, 1H), 7.79 (br d, J=2.1 Hz, 1H), 7.56 (br dd, J=8.1, 3.3 Hz, 1H), 7.46 (br t, J=9.0 Hz, 2H), 7.35 - 7.17 (m, 3H), 7.11 (d, J=8.6 Hz, 1H), 6.23 - 6.10 (m, 1H), 5.17 (d, J=8.5 Hz, 1H), 4.24 - 4.14 (m, 1H), 3.83 (s, 3H), 2.99 - 2.93 (m, 1H), 2.78 (br s, 1H), 2.74 - 2.58 (m, 3H), 2.54 (br s, 1H), 2.25 - 2.13 (m, 2H), 1.72 - 1.51 (m, 2H), 1.24 - 1.11 (m, 2H), 0.45 - 0.31 (m, 2H), 0.24 - 0.12 (m, 2H) 质子由于水抑制而缺失	2.82, C

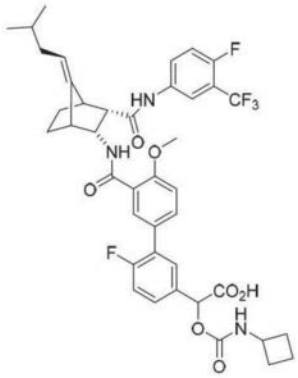
932		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟 -1-(6- 氟 -3'-{[(1R,2R,3S,4R,7Z)-3-{[4- 氟 -3-(三氟甲基)苯基]胺甲酰基 }-7-[(3R)-4,4,4- 三氟 -3- 羟基丁亚基]双环[2.2.1]庚烷-2-基]胺甲酰基}-4'- 甲氧基 -[1,1'-联苯]-3-基)乙酯	864.0	(500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.93 (br d, J=7.1 Hz, 1H), 8.29 - 8.22 (m, 1H), 8.17 - 8.09 (m, 2H), 7.83 - 7.78 (m, 1H), 7.69 (br t, J=9.0 Hz, 2H), 7.59 - 7.30 (m, 4H), 6.43 - 6.31 (m, 1H), 5.32 (t, J=7.3 Hz, 1H), 4.50 - 4.38 (m, 1H), 4.07 (s, 3H), 4.01 - 3.93 (m, 2H), 3.44 - 3.32 (m, 1H), 3.19 (dd, J=10.8, 4.2 Hz, 1H), 3.00 (br s, 1H), 2.78 (br s, 1H), 2.46 - 2.40 (m, 1H), 2.30 (dt, J=14.7, 7.4 Hz, 1H), 2.19 - 2.05 (m, 2H), 1.96 - 1.82 (m, 3H), 1.78 (br d, J=7.6 Hz, 1H), 1.65 - 1.52 (m, 2H), 1.42 (br d, J=5.8 Hz, 2H)	2.77, C

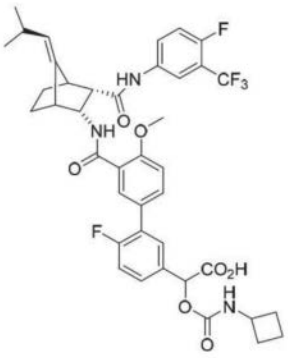
933		2-[(叔丁基胺甲酰基)氧基]-2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	798.2	(500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.68 (d, J=7.2 Hz, 1H), 8.01 (dd, J=6.4, 2.4 Hz, 1H), 7.88 (s, 1H), 7.56 (br dd, J=8.4, 3.6 Hz, 1H), 7.43 (br d, J=8.7 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.28 - 7.19 (m, 2H), 7.09 - 7.01 (m, 2H), 6.88 (br d, J=2.7 Hz, 1H), 5.43 (s, 1H), 4.95 (d, J=8.9 Hz, 1H), 4.23 - 4.10 (m, 1H), 3.81 (s, 3H), 3.66 (s, 1H), 2.93 (dd, J=10.5, 4.3 Hz, 1H), 2.82 - 2.74 (m, 1H), 2.48 (br s, 1H), 2.42 - 2.33 (m, 1H), 1.65 - 1.50 (m, 4H), 1.45 - 1.38 (m, 2H), 1.32 (br dd, J=7.3, 5.1 Hz, 2H), 1.14 (br d, J=2.6 Hz, 2H), 1.07 - 1.01 (m, 2H), 0.99 - 0.93 (m, 9H)	2.91, C

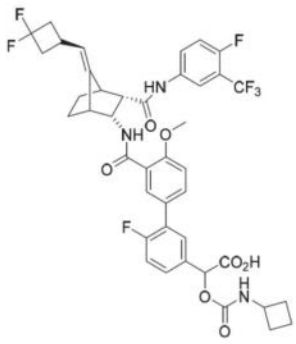
934		2-[(叔丁基胺甲酰基)氧基]-2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	826.2	(500 MHz, DMSO-d6) δ 10.67 - 10.53 (m, 1H), 9.94 (br d, J=7.2 Hz, 1H), 8.26 (dd, J=6.6, 2.4 Hz, 1H), 8.13 (s, 1H), 7.82 (br dd, J=8.2, 3.5 Hz, 1H), 7.69 (br d, J=8.2 Hz, 1H), 7.60 (br d, J=7.7 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.37 - 7.29 (m, 2H), 7.20 (br d, J=1.6 Hz, 1H), 5.72 (s, 1H), 5.28 (t, J=6.7 Hz, 1H), 4.50 - 4.31 (m, 1H), 4.06 (s, 3H), 3.19 (dd, J=10.3, 4.1 Hz, 1H), 3.05 - 2.96 (m, 1H), 2.77 (br s, 1H), 2.43 - 2.23 (m, 5H), 1.96 - 1.71 (m, 2H), 1.47 - 1.35 (m, 2H), 1.23 (s, 9H)	2.73, C

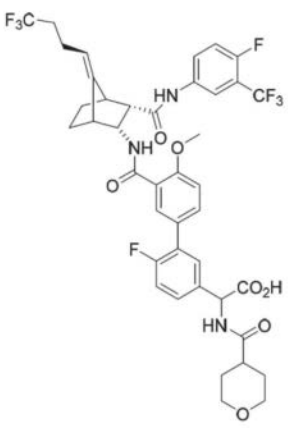
935		2-[(叔丁基胺甲酰基)氧基]-2-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	820.1	(500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.94 (br d, J=7.2 Hz, 1H), 8.25 (dd, J=6.4, 2.1 Hz, 1H), 8.13 (s, 1H), 7.88 - 7.79 (m, 1H), 7.69 (br d, J=8.5 Hz, 1H), 7.61 (br d, J=7.2 Hz, 1H), 7.53 - 7.45 (m, 2H), 7.38 - 7.31 (m, 2H), 7.20 (br s, 1H), 5.72 (s, 1H), 5.40 (d, J=8.5 Hz, 1H), 4.48 - 4.33 (m, 1H), 4.06 (s, 3H), 3.19 (dd, J=10.9, 3.3 Hz, 1H), 3.02 (br s, 1H), 2.98 - 2.81 (m, 3H), 2.77 (br s, 1H), 2.48 - 2.38 (m, 2H), 1.92 - 1.76 (m, 2H), 1.51 - 1.36 (m, 2H), 1.23 (s, 10H)	2.71, C

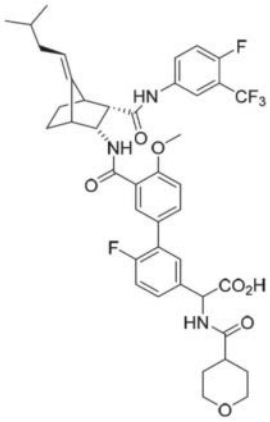
936		2-[(环丁基胺甲酰基)氧基]-2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	796.3	(500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.93 (br d, J=6.9 Hz, 1H), 8.25 (dd, J=6.4, 2.1 Hz, 1H), 8.13 (s, 1H), 7.80 (br dd, J=7.9, 3.5 Hz, 1H), 7.67 (br d, J=6.9 Hz, 2H), 7.57 (br d, J=6.9 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.33 - 7.26 (m, 2H), 5.69 (s, 1H), 5.19 (d, J=8.8 Hz, 1H), 4.47 - 4.36 (m, 1H), 4.06 (s, 3H), 4.01 - 3.93 (m, 1H), 3.25 - 3.17 (m, 1H), 3.11 - 3.03 (m, 1H), 2.72 (br s, 1H), 2.60 (br d, J=8.4 Hz, 1H), 2.18 - 2.07 (m, 2H), 1.96 - 1.76 (m, 6H), 1.66 - 1.51 (m, 6H), 1.44 - 1.35 (m, 2H), 1.34 - 1.25 (m, 2H)	2.87, C

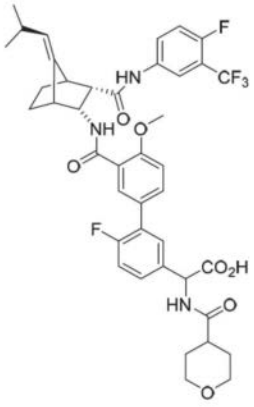
937		(2S)-2-[(环丁基胺甲酰基)氧基]-2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	784.1	(500 MHz, DMSO-d6) δ 10.35 (s, 1H), 9.70 (br d, J=7.2 Hz, 1H), 8.03 (dd, J=6.3, 2.5 Hz, 1H), 7.89 (s, 1H), 7.58 (br dd, J=8.7, 3.8 Hz, 1H), 7.47 (br dd, J=15.1, 8.1 Hz, 2H), 7.34 (br d, J=7.0 Hz, 1H), 7.29 - 7.19 (m, 2H), 7.13 - 7.00 (m, 2H), 5.48 (s, 1H), 5.01 (t, J=7.6 Hz, 1H), 4.25 - 4.11 (m, 1H), 3.83 (s, 3H), 3.76 - 3.70 (m, 1H), 2.96 (dd, J=11.0, 4.4 Hz, 1H), 2.78 - 2.69 (m, 1H), 2.52 (t, J=3.4 Hz, 1H), 1.99 - 1.85 (m, 2H), 1.77 - 1.57 (m, 6H), 1.41 - 1.27 (m, 3H), 1.23 - 1.10 (m, 2H), 0.69 (dd, J=12.3, 6.6 Hz, 6H)	2.84, C

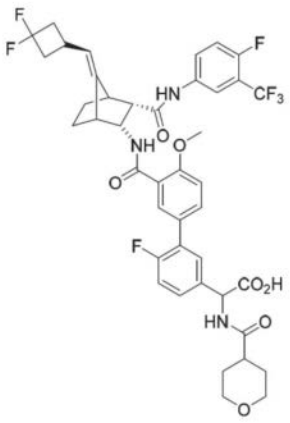
938		2-[(环丁基胺甲酰基)氧基]-2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	770.4	(500 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.88 (br d, J=7.2 Hz, 1H), 8.20 (dd, J=6.9, 2.0 Hz, 1H), 8.08 (s, 1H), 7.82 - 7.73 (m, 2H), 7.64 (br d, J=8.9 Hz, 1H), 7.54 (br s, 1H), 7.50 - 7.39 (m, 2H), 7.38 - 7.25 (m, 2H), 7.20 - 7.00 (m, 1H), 5.73 (s, 1H), 5.07 (d, J=9.0 Hz, 1H), 4.44 - 4.28 (m, 1H), 4.01 (s, 3H), 3.94 - 3.87 (m, 1H), 3.12 (br dd, J=7.1, 3.9 Hz, 1H), 2.99 - 2.94 (m, 1H), 2.66 (br s, 1H), 2.15 - 2.04 (m, 2H), 1.97 - 1.80 (m, 3H), 1.79 - 1.71 (m, 1H), 1.58 - 1.49 (m, 2H), 1.35 (br d, J=7.2 Hz, 2H), 1.02 - 0.93 (m, 6H)	2.76, C

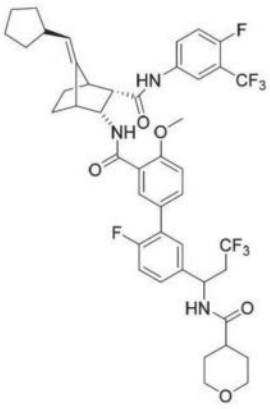
939		2-[(环丁基胺甲酰基)氧基]-2-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	818.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.94 (br d, J=6.9 Hz, 1H), 8.32 - 8.19 (m, 1H), 8.12 (s, 1H), 7.85 - 7.77 (m, 2H), 7.69 (br d, J=8.7 Hz, 1H), 7.59 (br d, J=7.3 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.37 - 7.28 (m, 2H), 5.76 (s, 1H), 5.40 (d, J=8.5 Hz, 1H), 4.50 - 4.37 (m, 1H), 4.06 (s, 3H), 4.00 - 3.93 (m, 1H), 3.18 (dd, J=10.4, 4.4 Hz, 1H), 3.02 (br s, 1H), 2.97 - 2.71 (m, 4H), 2.48 - 2.31 (m, 2H), 2.20 - 2.10 (m, 2H), 2.01 - 1.74 (m, 4H), 1.67 - 1.54 (m, 2H), 1.40 (br d, J=1.8 Hz, 2H)	2.67, C

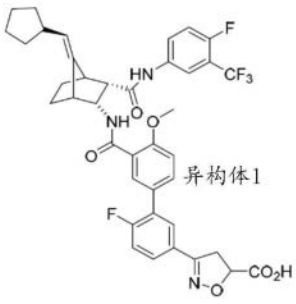
940		2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(4,4,4-三氟丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	838.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.94 (br d, J=7.1 Hz, 1H), 8.33 - 8.20 (m, 2H), 8.13 (br s, 1H), 7.80 (br dd, J=5.0, 3.4 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.54 - 7.46 (m, 2H), 7.41 - 7.27 (m, 2H), 7.22 - 7.14 (m, 1H), 5.27 (br t, J=5.8 Hz, 2H), 4.48 - 4.37 (m, 1H), 4.04 (s, 3H), 3.83 (br dd, J=10.6, 3.1 Hz, 2H), 3.32 - 3.25 (m, 1H), 3.17 (br dd, J=10.7, 3.7 Hz, 1H), 3.02 - 2.95 (m, 1H), 2.75 (br s, 1H), 2.59 - 2.56 (m, 1H), 2.40 - 2.26 (m, 4H), 1.93 - 1.76 (m, 3H), 1.64 - 1.49 (m, 4H), 1.47 - 1.36 (m, 2H)	2.49, C

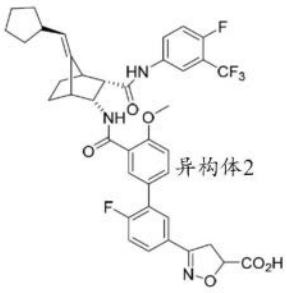
941		2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(3-甲基丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	798.2	(500 MHz, DMSO-d6) δ 10.57 (s, 1H), 9.92 (d, J=6.9 Hz, 1H), 8.46 - 8.34 (m, 1H), 8.26 (dd, J=6.5, 2.3 Hz, 1H), 8.15 (s, 1H), 7.81 (br dd, J=8.4, 3.5 Hz, 1H), 7.68 (br d, J=8.8 Hz, 1H), 7.55 - 7.45 (m, 2H), 7.37 (br d, J=2.8 Hz, 1H), 7.31 (d, J=8.7 Hz, 1H), 7.27 - 7.21 (m, 1H), 5.33 - 5.11 (m, 2H), 4.51 - 4.34 (m, 1H), 4.06 (s, 3H), 3.88 - 3.79 (m, 2H), 3.34 - 3.26 (m, 1H), 3.19 (dd, J=10.8, 4.7 Hz, 1H), 3.01 - 2.93 (m, 1H), 2.81 - 2.73 (m, 1H), 2.61 - 2.57 (m, 1H), 2.02 - 1.93 (m, 2H), 1.91 - 1.84 (m, 1H), 1.81 - 1.73 (m, 1H), 1.70 - 1.49 (m, 6H), 1.44 - 1.29 (m, 2H), 0.92 (dd, J=12.3, 6.6 Hz, 6H)	2.64, C

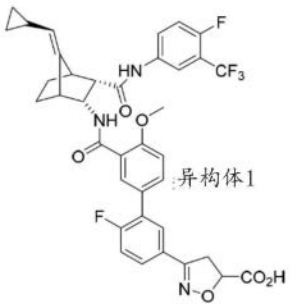
942		2-(6-氟-3'-{[(1R,2R,3S,4R,7Z)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}-7-(2-甲基亚丙基)双环[2.2.1]庚烷-2-基]胺甲酰基}-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	784.2	(500 MHz, DMSO-d6) δ 10.36 - 10.27 (m, 1H), 9.69 (d, J=7.1 Hz, 1H), 8.36 (br d, J=7.6 Hz, 1H), 8.02 (dd, J=6.4, 2.3 Hz, 1H), 7.92 (s, 1H), 7.65 - 7.54 (m, 1H), 7.47 (br d, J=8.4 Hz, 1H), 7.34 - 7.16 (m, 3H), 7.13 - 7.02 (m, 2H), 5.16 (br d, J=7.4 Hz, 1H), 4.89 (d, J=8.9 Hz, 1H), 4.27 - 4.12 (m, 1H), 3.83 (s, 3H), 3.66 - 3.57 (m, 2H), 3.12 - 3.02 (m, 1H), 2.95 (dd, J=10.8, 3.9 Hz, 1H), 2.78 (br s, 1H), 2.48 (br s, 1H), 2.36 - 2.33 (m, 1H), 2.26 - 2.20 (m, 1H), 1.73 - 1.51 (m, 2H), 1.44 - 1.28 (m, 4H), 1.22 - 1.10 (m, 2H), 0.84 - 0.74 (m, 6H) 质子由于水抑制而缺失	2.55, C

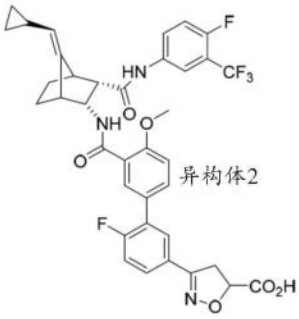
943		2-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	832.0	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.93 (br d, J=6.9 Hz, 1H), 8.44 (br s, 1H), 8.30 - 8.20 (m, 1H), 8.14 (br s, 1H), 7.87 - 7.76 (m, 1H), 7.68 (br d, J=8.0 Hz, 1H), 7.54 - 7.46 (m, 2H), 7.38 (br d, J=2.7 Hz, 1H), 7.36 - 7.23 (m, 2H), 5.39 (d, J=8.5 Hz, 1H), 5.30 (br d, J=5.8 Hz, 1H), 4.48 - 4.34 (m, 1H), 4.05 (s, 3H), 3.88 - 3.80 (m, 2H), 3.33 - 3.25 (m, 1H), 3.21 (s, 1H), 2.96 - 2.73 (m, 4H), 2.46 - 2.36 (m, 2H), 1.92 - 1.67 (m, 3H), 1.67 - 1.51 (m, 4H), 1.44 - 1.31 (m, 2H) 质子由于水抑制而缺失	2.47, C

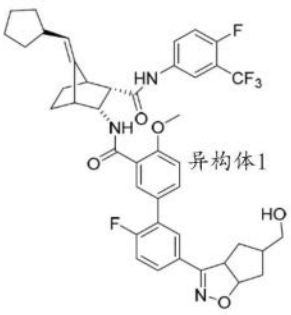
944		N-[1-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-3,3,3-三氟丙基]噁烷-4-甲酰胺	848.2	(500 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.90 (br d, J=7.0 Hz, 1H), 8.50 (d, J=8.5 Hz, 1H), 8.27 - 8.23 (m, 1H), 8.15 (s, 1H), 7.82 - 7.77 (m, 1H), 7.71 (br d, J=8.9 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.49 (t, J=9.8 Hz, 1H), 7.39 - 7.35 (m, 1H), 7.32 - 7.25 (m, 2H), 5.28 - 5.22 (m, 1H), 5.19 (d, J=8.8 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.05 (s, 3H), 3.84 (br t, J=9.6 Hz, 2H), 3.19 - 3.15 (m, 1H), 3.01 (br s, 1H), 2.81 - 2.75 (m, 2H), 2.73 (br d, J=4.6 Hz, 1H), 2.64 - 2.57 (m, 1H), 1.87 - 1.75 (m, 4H), 1.67 - 1.54 (m, 9H), 1.39 (br d, J=2.5 Hz, 2H), 1.31 - 1.20 (m, 4H)	2.84, C

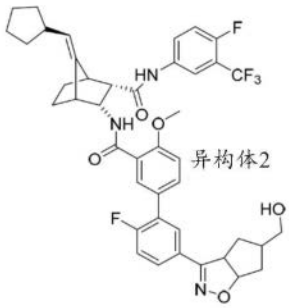
945		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,5-二氢-1,2-噁唑-5-甲酸	738.1	(500 MHz, DMSO-d6) δ 10.59 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.24 (dd, J=6.3, 2.4 Hz, 1H), 8.15 (s, 1H), 7.82 - 7.77 (m, 1H), 7.76 - 7.69 (m, 3H), 7.47 (t, J=9.8 Hz, 1H), 7.39 (dd, J=10.3, 8.7 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 5.19 - 5.15 (m, 1H), 5.03 - 4.99 (m, 1H), 4.43 - 4.38 (m, 1H), 4.05 (s, 3H), 3.18 - 3.13 (m, 1H), 3.02 - 2.98 (m, 1H), 2.71 (br s, 1H), 2.62 - 2.55 (m, 1H), 1.91 - 1.85 (m, 1H), 1.84 - 1.73 (m, 3H), 1.67 - 1.59 (m, 2H), 1.59 - 1.51 (m, 2H), 1.43 - 1.35 (m, 2H), 1.30 - 1.19 (m, 2H)	2.42, C

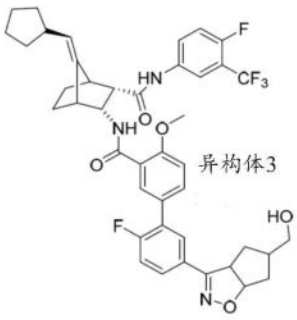
946		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,5-二氢-1,2-噁唑-5-甲酸	738.2	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.89 (br d, J=7.2 Hz, 1H), 8.26 - 8.23 (m, 1H), 8.17 - 8.14 (m, 1H), 7.82 - 7.71 (m, 4H), 7.48 (t, J=9.7 Hz, 1H), 7.41 (t, J=9.5 Hz, 1H), 7.33 - 7.29 (m, 1H), 5.21 - 5.14 (m, 2H), 4.44 - 4.38 (m, 1H), 4.05 (s, 3H), 3.81 - 3.72 (m, 1H), 3.70 - 3.61 (m, 1H), 3.18 - 3.13 (m, 1H), 3.02 - 2.98 (m, 1H), 2.71 (br s, 1H), 2.63 - 2.56 (m, 1H), 1.91 - 1.73 (m, 4H), 1.69 - 1.60 (m, 2H), 1.60 - 1.51 (m, 2H), 1.43 - 1.35 (m, 2H), 1.32 - 1.20 (m, 2H)	2.42, C

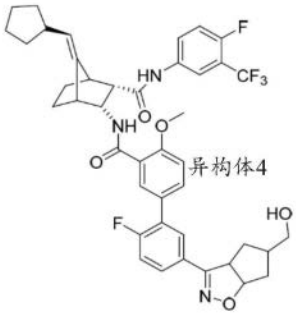
947		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,5-二氢-1,2-噁唑-5-甲酸	710.1	(500 MHz, DMSO-d6) δ 10.57 - 10.53 (m, 1H), 9.92 (d, J=7.1 Hz, 1H), 8.25 - 8.19 (m, 1H), 8.15 (s, 1H), 7.80 - 7.70 (m, 4H), 7.47 (t, J=9.7 Hz, 1H), 7.40 (dd, J=10.4, 8.7 Hz, 1H), 7.31 (d, J=8.7 Hz, 1H), 5.15 - 5.08 (m, 1H), 4.68 (d, J=9.6 Hz, 1H), 4.50 - 4.41 (m, 1H), 4.08 - 4.03 (m, 3H), 3.77 - 3.69 (m, 1H), 3.19 - 3.08 (m, 2H), 2.74 - 2.69 (m, 1H), 1.89 - 1.75 (m, 2H), 1.54 - 1.34 (m, 3H), 0.78 - 0.65 (m, 2H), 0.38 - 0.29 (m, 2H)	2.19, C

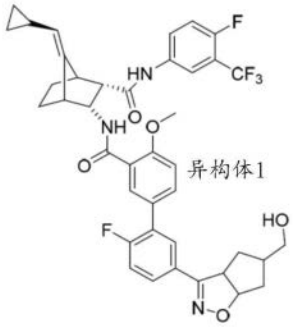
948		3-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-4,5-二氢-1,2-噁唑-5-甲酸	710.2	(500 MHz, DMSO-d6) δ 10.59 - 10.54 (m, 1H), 9.91 (d, J=7.2 Hz, 1H), 8.25 - 8.20 (m, 1H), 8.14 (s, 1H), 7.82 - 7.67 (m, 4H), 7.50 - 7.43 (m, 1H), 7.39 (dd, J=10.4, 8.7 Hz, 1H), 7.32 - 7.29 (m, 1H), 5.07 - 5.00 (m, 1H), 4.69 - 4.65 (m, 1H), 4.48 - 4.42 (m, 1H), 4.08 - 4.02 (m, 3H), 3.72 - 3.52 (m, 1H), 3.19 - 3.14 (m, 1H), 3.13 - 3.07 (m, 1H), 2.73 - 2.69 (m, 1H), 1.92 - 1.75 (m, 2H), 1.53 - 1.35 (m, 3H), 0.78 - 0.67 (m, 2H), 0.38 - 0.29 (m, 2H)	2.19, C

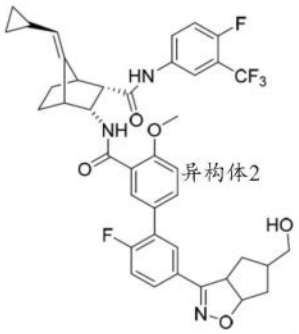
949		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	764.5	(500 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.89 (d, J=7.0 Hz, 1H), 8.24 (dd, J=6.6, 2.4 Hz, 1H), 8.14 (s, 1H), 7.80 - 7.68 (m, 4H), 7.48 (t, J=9.8 Hz, 1H), 7.40 (dd, J=10.4, 8.7 Hz, 1H), 5.20 - 5.13 (m, 2H), 4.43 - 4.38 (m, 1H), 4.28 (t, J=8.9 Hz, 1H), 4.06 (s, 3H), 3.16 (dd, J=10.7, 4.2 Hz, 1H), 3.00 (br d, J=5.5 Hz, 1H), 2.71 (br s, 1H), 2.63 - 2.56 (m, 1H), 2.02 - 1.74 (m, 8H), 1.70 - 1.62 (m, 3H), 1.57 (td, J=12.5, 5.1 Hz, 3H), 1.42 - 1.36 (m, 2H), 1.31 - 1.21 (m, 3H)	2.51, C

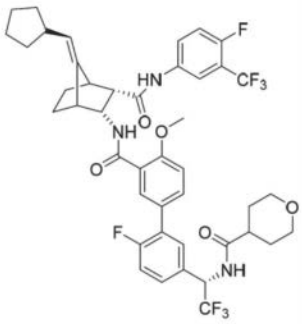
950		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	764.2	(500 MHz, DMSO-d6) δ 10.53 - 10.51 (m, 1H), 9.89 (d, J=7.1 Hz, 1H), 8.25 - 8.21 (m, 1H), 8.14 (s, 1H), 7.80 - 7.68 (m, 4H), 7.47 (t, J=9.7 Hz, 1H), 7.40 (dd, J=10.5, 8.7 Hz, 1H), 7.34 - 7.30 (m, 1H), 5.21 - 5.15 (m, 2H), 4.40 (ddd, J=10.4, 6.7, 4.2 Hz, 1H), 4.21 - 4.14 (m, 1H), 4.05 (s, 3H), 3.30 - 3.21 (m, 1H), 3.16 (dd, J=10.6, 4.4 Hz, 1H), 3.02 - 2.98 (m, 1H), 2.71 (br s, 1H), 2.63 - 2.56 (m, 1H), 2.25 - 2.10 (m, 3H), 1.91 - 1.86 (m, 1H), 1.84 - 1.73 (m, 3H), 1.68 - 1.60 (m, 3H), 1.59 - 1.53 (m, 2H), 1.52 - 1.46 (m, 1H), 1.43 - 1.35 (m, 2H), 1.31 - 1.21 (m, 2H)	2.50, C

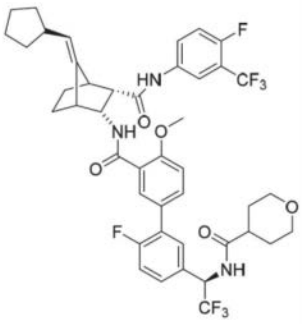
951		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	764.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.92 - 9.87 (m, 1H), 8.26 - 8.22 (m, 1H), 8.16 - 8.13 (m, 1H), 7.81 - 7.77 (m, 1H), 7.76 - 7.69 (m, 3H), 7.48 (t, J=9.8 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.34 - 7.30 (m, 1H), 5.20 - 5.15 (m, 2H), 4.54 - 4.50 (m, 1H), 4.44 - 4.38 (m, 1H), 4.21 - 4.15 (m, 1H), 4.06 (s, 3H), 3.32 - 3.21 (m, 1H), 3.16 (dd, J=10.7, 4.1 Hz, 1H), 3.02 - 2.98 (m, 1H), 2.71 (br s, 1H), 2.63 - 2.56 (m, 1H), 2.26 - 2.09 (m, 3H), 1.91 - 1.73 (m, 4H), 1.68 - 1.61 (m, 3H), 1.60 - 1.52 (m, 2H), 1.49 (dt, J=12.8, 6.4 Hz, 1H), 1.43 - 1.34 (m, 2H), 1.32 - 1.20 (m, 2H)	2.49, C

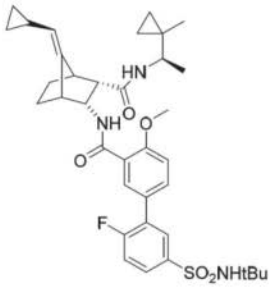
952		N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	764.5	(500 MHz, DMSO-d6) δ 10.54 - 10.51 (m, 1H), 9.89 (d, J=7.2 Hz, 1H), 8.26 - 8.21 (m, 1H), 8.15 - 8.12 (m, 1H), 7.81 - 7.76 (m, 1H), 7.75 - 7.68 (m, 3H), 7.48 (t, J=9.8 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.34 - 7.29 (m, 1H), 5.20 - 5.13 (m, 2H), 4.49 (t, J=5.3 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.28 (t, J=8.8 Hz, 1H), 4.06 (s, 3H), 3.16 (dd, J=10.5, 4.1 Hz, 1H), 3.02 - 2.98 (m, 1H), 2.71 (br s, 1H), 2.63 - 2.56 (m, 1H), 2.03 - 1.75 (m, 7H), 1.70 - 1.61 (m, 3H), 1.60 - 1.52 (m, 3H), 1.41 - 1.36 (m, 2H), 1.32 - 1.20 (m, 2H)	2.86, C

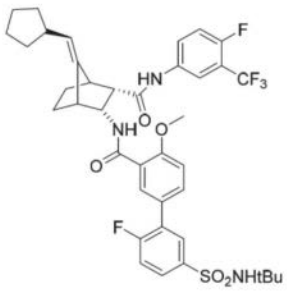
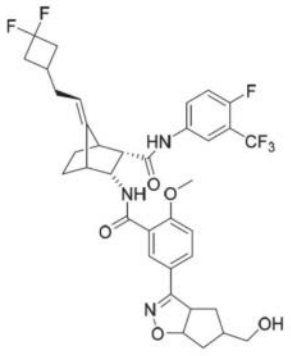
953		N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	736.2	(500 MHz, DMSO-d6) δ 10.53 (s, 1H), 9.93 (d, J=7.1 Hz, 1H), 8.23 (dd, J=6.4, 2.6 Hz, 1H), 8.15 (s, 1H), 7.81 - 7.68 (m, 4H), 7.48 (t, J=9.7 Hz, 1H), 7.40 (dd, J=10.4, 8.7 Hz, 1H), 7.33 (d, J=8.7 Hz, 1H), 5.21 - 5.14 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.52 (t, J=5.3 Hz, 1H), 4.46 (br t, J=10.8 Hz, 1H), 4.18 (td, J=9.5, 6.1 Hz, 1H), 4.06 (s, 3H), 3.32 - 3.21 (m, 1H), 3.17 (dd, J=10.8, 4.1 Hz, 1H), 3.13 - 3.09 (m, 1H), 2.74 - 2.70 (m, 1H), 2.27 - 2.09 (m, 3H), 1.91 - 1.78 (m, 2H), 1.68 - 1.62 (m, 1H), 1.54 - 1.37 (m, 4H), 0.78 - 0.69 (m, 2H), 0.38 - 0.32 (m, 2H)	2.26, C

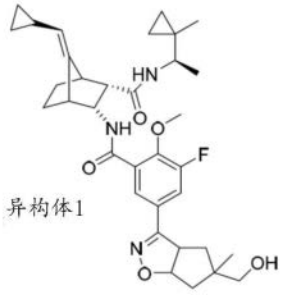
954		N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-5'-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-4-甲氧基-[1,1'-联苯]-3-甲酰胺	736.2	(500 MHz, DMSO-d6) δ 10.54 - 10.50 (m, 1H), 9.95 - 9.90 (m, 1H), 8.23 (dd, J=6.4, 2.6 Hz, 1H), 8.14 (s, 1H), 7.81 - 7.77 (m, 1H), 7.76 - 7.68 (m, 3H), 7.48 (t, J=9.7 Hz, 1H), 7.40 (dd, J=10.5, 8.6 Hz, 1H), 7.32 (d, J=8.8 Hz, 1H), 5.20 - 5.14 (m, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.51 (t, J=5.2 Hz, 1H), 4.49 - 4.44 (m, 1H), 4.18 (td, J=9.7, 6.3 Hz, 1H), 4.06 (s, 3H), 3.32 - 3.21 (m, 1H), 3.16 (dd, J=10.9, 4.1 Hz, 1H), 3.13 - 3.08 (m, 1H), 2.74 - 2.70 (m, 1H), 2.26 - 2.09 (m, 3H), 1.89 - 1.77 (m, 2H), 1.68 - 1.61 (m, 1H), 1.53 - 1.37 (m, 4H), 0.78 - 0.67 (m, 2H), 0.38 - 0.30 (m, 2H)	2.26, C

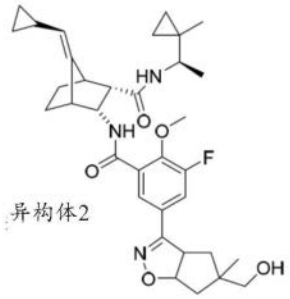
955		N-[(1S)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙基]噁烷-4-甲酰胺	834.6	(500 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.90 (d, J=7.0 Hz, 1H), 9.11 (d, J=9.8 Hz, 1H), 8.25 (dd, J=6.4, 2.3 Hz, 1H), 8.15 (s, 1H), 7.79 (br d, J=7.7 Hz, 2H), 7.70 (br d, J=8.6 Hz, 1H), 7.62 - 7.56 (m, 1H), 7.48 (t, J=9.7 Hz, 1H), 7.39 - 7.30 (m, 2H), 5.93 - 5.83 (m, 1H), 5.19 (d, J=8.9 Hz, 1H), 4.43 - 4.37 (m, 1H), 4.05 (s, 3H), 3.90 - 3.82 (m, 2H), 3.21 - 3.12 (m, 1H), 3.02 - 2.97 (m, 1H), 2.75 - 2.68 (m, 1H), 2.64 - 2.55 (m, 2H), 1.90 - 1.73 (m, 4H), 1.68 - 1.51 (m, 9H), 1.43 - 1.34 (m, 2H), 1.31 - 1.17 (m, 3H)	2.94, C

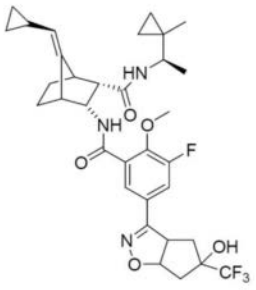
956		N-[(1R)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙基]噁烷-4-甲酰胺	834.3	(500 MHz, DMSO-d6) δ 10.60 - 10.55 (m, 1H), 9.90 (d, J=6.9 Hz, 1H), 9.12 (d, J=9.6 Hz, 1H), 8.25 (dd, J=6.6, 2.4 Hz, 1H), 8.15 (s, 1H), 7.82 - 7.76 (m, 2H), 7.71 (br d, J=8.6 Hz, 1H), 7.61 - 7.56 (m, 1H), 7.48 (t, J=9.7 Hz, 1H), 7.40 - 7.30 (m, 2H), 5.92 - 5.83 (m, 1H), 5.22 - 5.15 (m, 1H), 4.43 - 4.37 (m, 1H), 4.05 (s, 3H), 3.90 - 3.84 (m, 2H), 3.20 - 3.13 (m, 1H), 3.03 - 2.96 (m, 1H), 2.75 - 2.69 (m, 1H), 2.65 - 2.56 (m, 2H), 1.87 - 1.72 (m, 4H), 1.68 - 1.51 (m, 9H), 1.42 - 1.34 (m, 2H), 1.31 - 1.21 (m, 3H)	2.95, C

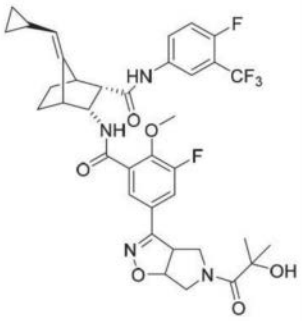
957		5'-(叔丁基胺磺酰基)-N-[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[(1R)-1-(1-甲基环丙基)乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	652.2	(400 MHz, DMSO-d6) δ 10.13 (d, J = 6.9 Hz, 1H), 8.11 (d, J = 1.5 Hz, 1H), 7.99 (dd, J = 2.4, 7.3 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.84(ddd, J = 2.4, 4.5, 8.5 Hz, 1H), 7.74 (td, J = 1.9, 8.7 Hz, 1H), 7.63 (s, 1H), 7.52 (dd, J = 8.6, 10.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.64 (d, J = 9.5Hz, 1H), 4.34 - 4.23 (m, 1H), 4.03 (s, 3H), 3.48 (dd, J = 6.9, 8.3 Hz, 1H), 3.07 (br s, 1H), 2.97 (dd, J = 4.1, 10.9 Hz, 1H), 2.54 (br s, 1H), 1.95 - 1.83 (m, 1H), 1.82 - 1.70 (m, 1H), 1.53 - 1.43 (m, 1H), 1.36 (br s, 2H), 1.12 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H), 0.99 (s, 3H), 0.72 (dt, J = 2.3, 8.2 Hz,2H), 0.61 - 0.49 (m, 1H), 0.43 - 0.26 (m, 3H), 0.25 - 0.11 (m, 2H)	2.64, A

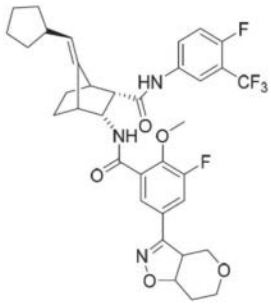
958		5'-(叔丁基胺磺酰基)-N-[(1R,2R,3S,4R,7Z)-7-(环戊基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]-2'-氟-4-甲氧基-[1,1'-联苯]-3-甲酰胺	760.3	(400 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.92 (d, J = 7.1 Hz, 1H), 8.24 (dd, J = 2.4, 6.4 Hz, 1H), 8.16 (s, 1H), 7.98 (dd, J = 2.3, 7.4 Hz, 1H), 7.89 - 7.67 (m, 3H), 7.63 (s, 1H), 7.56 - 7.42 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 5.20 (d, J = 9.0 Hz, 1H), 4.47 - 4.29 (m, 1H), 4.07 (s, 3H), 3.19- 3.06 (m, 1H), 3.01 (br s, 1H), 2.72 (br s, 1H), 2.65 - 2.57 (m, 1H), 1.92 - 1.72 (m, 4H), 1.69 - 1.49 (m, 4H), 1.46 - 1.36 (m, 2H), 1.34 - 1.18 (m,2H), 1.12 (s, 9H)	2.93, A
959		(1R,2S,3R,4R,7Z)-7-[2-(3,3-二氟环丁基)亚乙基]-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	706.5	(400 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (d, J = 7.1 Hz, 1H), 8.29 - 8.15 (m, 2H), 7.85 - 7.70 (m, 2H), 7.49 (t, J = 9.8 Hz, 1H), 7.27(d, J = 8.8 Hz, 1H), 5.22 (t, J = 7.5 Hz, 1H), 5.12 (dd, J = 5.1, 8.7 Hz, 1H), 4.56 - 4.34 (m, 2H), 4.20 (t, J = 8.8 Hz, 1H), 4.04 (s, 3H), 3.40 (br d, J =5.8 Hz, 1H), 3.18 (br dd, J = 4.2, 6.4 Hz, 1H), 3.00 (br s, 1H), 2.78 - 2.73 (m, 1H), 2.70 - 2.63 (m, 2H), 2.32 - 2.14 (m, 5H), 2.02 - 1.73 (m, 5H),1.70 - 1.54 (m, 2H), 1.39 (br s, 2H)	2.44, A

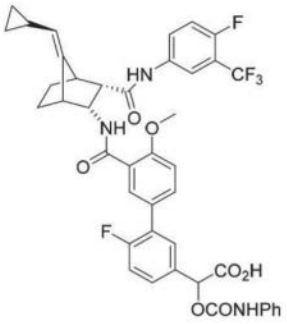
960	 异构体1	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	706.5	(400 MHz, DMSO-d6) δ 10.55 (s, 1H), 9.91 (d, J = 7.1 Hz, 1H), 8.29 - 8.15 (m, 2H), 7.85 - 7.70 (m, 2H), 7.49 (t, J = 9.8 Hz, 1H), 7.27(d, J = 8.8 Hz, 1H), 5.22 (t, J = 7.5 Hz, 1H), 5.12 (dd, J = 5.1, 8.7 Hz, 1H), 4.56 - 4.34 (m, 2H), 4.20 (t, J = 8.8 Hz, 1H), 4.04 (s, 3H), 3.40 (br d, J =5.8 Hz, 1H), 3.18 (br dd, J = 4.2, 6.4 Hz, 1H), 3.00 (br s, 1H), 2.78 - 2.73 (m, 1H), 2.70 - 2.63 (m, 2H), 2.32 - 2.14 (m, 5H), 2.02 - 1.73 (m, 5H),1.70 - 1.54 (m, 2H), 1.39 (br s, 2H)	2.44, A

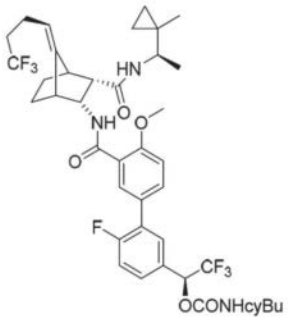
961	 异构体2	(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-(羟基甲基)-5-甲基-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	594.3	(400 MHz, DMSO-d6) δ 10.00 (d, J = 6.8 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.93 - 7.83 (m, 1H), 7.69 (dd, J = 2.3, 12.5 Hz, 1H), 5.33 - 5.19 (m, 1H), 4.73 - 4.51 (m, 2H), 4.34 - 4.15 (m, 2H), 4.05 (d, J = 2.6 Hz, 3H), 3.46 (dd, J = 7.0, 8.4 Hz, 1H), 3.18 - 3.12 (m, 2H), 3.07 (br s, 1H), 2.96 (dd, J = 4.3, 10.8 Hz, 1H), 2.55 (br d, J = 3.8 Hz, 1H), 1.93 - 1.72 (m, 5H), 1.71 - 1.62 (m, 1H), 1.53 - 1.31 (m, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 8.8 Hz, 6H), 0.81 - 0.65 (m, 2H), 0.59 - 0.47 (m, 1H), 0.42 - 0.27 (m, 3H), 0.25 - 0.08 (m, 2H)	2.38, A

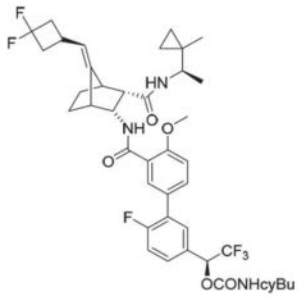
962		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-3-{3-氟-5-[5-羟基-5-(三氟甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}-N-[(1R)-1-(1-甲基环丙基)乙基]双环[2.2.1]庚烷-2-甲酰胺	717.2	(400 MHz, DMSO-d6) δ 10.52 (s, 1H), 9.75 (br d, J = 6.9 Hz, 1H), 8.12 (dd, J = 2.4, 6.3 Hz, 1H), 7.99 (br s, 1H), 7.89 - 7.80 (m, 1H),7.78 (br d, J = 12.5 Hz, 1H), 7.48 (t, J = 9.8 Hz, 1H), 5.33 (br s, 2H), 4.77 - 4.30 (m, 4H), 3.97 - 3.43 (m, 2H), 3.17 (dd, J = 4.3, 10.9 Hz, 1H), 3.13- 3.03 (m, 1H), 2.74 (br s, 1H), 1.82 (br d, J = 8.5 Hz, 2H), 1.57 - 1.32 (m, 3H), 1.24 (br s, 6H), 0.83 - 0.65 (m, 2H), 0.50 - 0.26 (m, 2H)	2.40, A

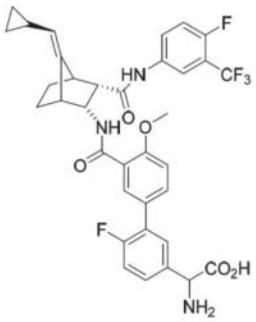
963		(1R,2S,3R,4R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{3-氟-5-[5-(2-羟基-2-甲基丙酰基)-3aH,4H,5H,6H,6aH-吡咯并[3,4-d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	634.2	(400 MHz, DMSO-d6) δ = 9.97 (d, J = 6.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.91 - 7.81 (m, 1H), 7.70 (dd, J = 2.1, 12.5 Hz, 1H), 5.93 (s,1H), 5.31 (dd, J = 6.4, 9.1 Hz, 1H), 4.65 (d, J = 9.6 Hz, 1H), 4.41 (br t, J = 9.4 Hz, 1H), 4.34 - 4.20 (m, 1H), 4.04 (d, J = 2.4 Hz, 3H), 3.50 - 3.42(m, 1H), 3.07 (t, J = 3.3 Hz, 1H), 2.96 (dd, J = 4.3, 10.9 Hz, 1H), 2.58 - 2.55 (m, 1H), 2.31 - 2.17 (m, 3H), 2.02 (br d, J = 14.0 Hz, 1H), 1.87 - 1.72(m, 2H), 1.55 - 1.28 (m, 3H), 1.07 - 0.93 (m, 6H), 0.80 - 0.63 (m, 2H), 0.51 (br dd, J = 4.0, 8.9 Hz, 1H), 0.43 - 0.26 (m, 3H), 0.24 - 0.05 (m, 2H)	2.43, A

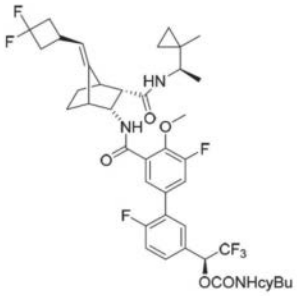
964		(1R,2S,3R,4R,7Z)-3-(5-{3aH,4H,6H,7H,7aH-吡喃o[3,4-d][1,2]噁唑-3-基}-3-氟-2-甲氧基苯甲酰胺基)-7-(环戊基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	700.2	(400 MHz, DMSO-d6) δ 10.54 (s, 1H), 10.06 (br d, J = 6.8 Hz, 1H), 8.73 - 8.49 (m, 2H), 8.24 (dd, J = 2.4, 6.6 Hz, 1H), 7.88 - 7.71 (m,1H), 7.50 (t, J = 9.8 Hz, 1H), 5.31 (br d, J = 6.3 Hz, 2H), 4.71 (d, J = 9.5 Hz, 1H), 4.60 - 4.25 (m, 2H), 4.15 (s, 3H), 3.95 - 3.38 (m, 2H), 3.18 (dd, J= 4.4, 10.5 Hz, 1H), 3.12 (br s, 1H), 2.74 (br s, 1H), 1.89 - 1.66 (m, 2H), 1.57 - 1.35 (m, 3H), 1.32 - 0.97 (m, 6H), 0.84 - 0.66 (m, 2H), 0.47 - 0.26(m, 2H)	2.30, A

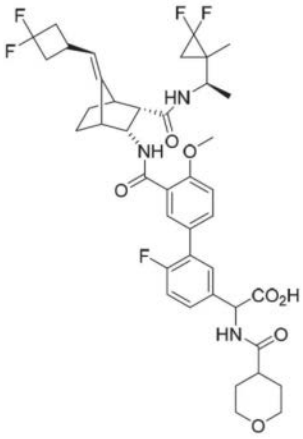
965		2-(3'-{[(1R,2R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(苯基胺甲酰基)氧基]乙酸	790.1	(400 MHz, $CDCl_3$) δ 9.73 (br d, J=8.0 Hz, 1H), 8.11 (br s, 1H), 8.07 (s, 1H), 7.96 (dd, J=6.2, 2.5 Hz, 1H), 7.93 (br s, 1H), 7.64 - 7.54 (m, 2H), 7.44 (dt, J=8.7, 3.4 Hz, 1H), 7.37 - 7.29 (m, 3H), 7.19 (t, J=7.9 Hz, 2H), 7.11 - 6.94 (m, 4H), 6.13 (s, 1H), 4.79 - 4.66 (m, 1H), 4.60 (d, J=9.5 Hz, 1H), 4.04 (s, 3H), 3.19 (t, J=3.8 Hz, 1H), 3.05 (dd, J=10.7, 3.9 Hz, 1H), 2.67 (t, J=3.8 Hz, 1H), 2.23 - 2.07 (m, 1H), 1.97 - 1.82 (m, 1H), 1.71 - 1.51 (m, 2H), 1.46 (qd, J=8.6, 4.6 Hz, 1H), 0.82 - 0.63 (m, 2H), 0.40 - 0.26 (m, 2H)	2.22, A

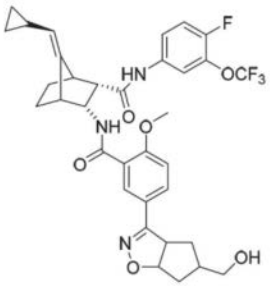
966		N-环丁基氨基甲酸 (1S)-2,2,2- 三氟-1-(6-氟-4'-甲氧基-3'-{[(1R,2R,3S,4R,7Z)-3-{[(1R)-1-(1-甲基环丙基)乙基]胺甲酰基}-7-(4,4,4- 三氟丁亚基)双环[2.2.1]庚烷-2-基]胺甲酰基}-[1,1'-联苯]-3-基)乙酯	768.4	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.6 Hz, 1H), 7.97 (br d, J=7.7 Hz, 1H), 7.90 (s, 1H), 7.84 - 7.76 (m, 1H), 7.51 (br d, J=6.5 Hz, 2H), 7.37 (br d, J=8.7 Hz, 1H), 7.30 - 7.21 (m, 1H), 7.12 (br d, J=8.8 Hz, 1H), 6.28 - 6.12 (m, 1H), 5.05 (br t, J=6.9 Hz, 1H), 4.16 - 4.04 (m, 1H), 3.84 (s, 3H), 3.80 - 3.69 (m, 1H), 3.24 (br d, J=6.6 Hz, 1H), 2.83 - 2.78 (m, 1H), 2.21 - 2.06 (m, 4H), 2.00 - 1.87 (m, 2H), 1.73 (dt, J=19.7, 9.7 Hz, 3H), 1.46 - 1.34 (m, 2H), 1.22 - 1.11 (m, 2H), 0.91 - 0.78 (m, 6H), 0.43 - 0.33 (m, 1H), 0.20 - 0.12 (m, 1H), 0.07 - -0.07 (m, 2H)	2.86, C

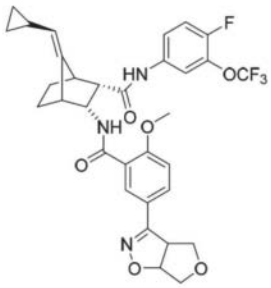
967		N-环丁基氨基甲酸 (1S)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[(1R)-1-(1-甲基环丙基)乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	762.2	(500 MHz, DMSO-d6) δ 9.95 (br d, J=6.9 Hz, 1H), 7.97 (d, J=7.9 Hz, 1H), 7.89 (s, 1H), 7.79 (d, J=8.7 Hz, 1H), 7.55 - 7.47 (m, 2H), 7.41 - 7.33 (m, 1H), 7.30 - 7.21 (m, 1H), 7.12 (d, J=8.7 Hz, 1H), 6.17 (br d, J=7.2 Hz, 1H), 5.16 (d, J=8.3 Hz, 1H), 4.13 - 3.99 (m, 1H), 3.84 (s, 3H), 2.85 - 2.57 (m, 5H), 2.41 (br s, 1H), 2.29 - 2.12 (m, 2H), 2.02 - 1.86 (m, 2H), 1.82 - 1.67 (m, 3H), 1.63 - 1.51 (m, 1H), 1.48 - 1.35 (m, 2H), 1.17 (br s, 2H), 0.85 (d, J=6.9 Hz, 3H), 0.81 (s, 3H), 0.36 (br dd, J=9.3, 4.1 Hz, 1H), 0.20 - 0.13 (m, 1H), 0.07 - -0.04 (m, 2H)	2.93, C

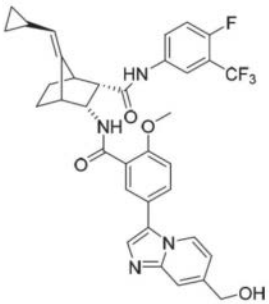
969		2-氨基-2-(3'-{[(1R,3S,4R,7Z)-7-(环丙基亚甲基)-3-{[4-氟-3-(三氟甲基)苯基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)乙酸	670.2	(500 MHz, DMSO-d6) δ 10.61 (s, 1H), 9.96 (br d, J=7.0 Hz, 1H), 8.23 (dd, J=6.4, 2.3 Hz, 1H), 8.17 (s, 1H), 7.85 - 7.75 (m, 1H), 7.73 - 7.62 (m, 2H), 7.53 - 7.43 (m, 2H), 7.42 - 7.29 (m, 2H), 5.02 (s, 1H), 4.69 (d, J=9.6 Hz, 1H), 4.52 - 4.41 (m, 1H), 4.05 (s, 3H), 3.17 (br dd, J=10.9, 3.9 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.90 - 1.75 (m, 2H), 1.54 - 1.35 (m, 3H), 0.80 - 0.67 (m, 2H), 0.34 (br d, J=3.2 Hz, 2H)	2.14, C

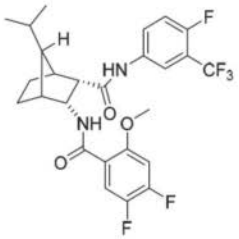
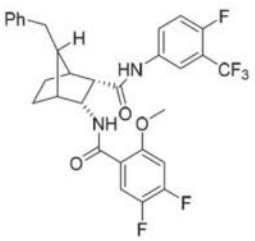
970		N-环丁基氨基甲酸 (1S)-1-(3'-{[(1R,2R,3S,4R,7Z)-7-[(3,3-二氟环丁基)亚甲基]-3-{[(1R)-1-(1-甲基环丙基)乙基]胺甲酰基}双环[2.2.1]庚烷-2-基]胺甲酰基}-5',6-二氟-4'-甲氧基-[1,1'-联苯]-3-基)-2,2,2-三氟乙酯	780.1	(500 MHz, DMSO-d6) δ 9.85 (br d, J=6.8 Hz, 1H), 7.98 (d, J=7.8 Hz, 1H), 7.85 (d, J=8.9 Hz, 1H), 7.66 (s, 1H), 7.56 (br d, J=6.6 Hz, 1H), 7.50 (br d, J=12.1 Hz, 1H), 7.43 (br s, 1H), 7.29 (dd, J=10.3, 8.7 Hz, 1H), 6.20 (q, J=7.0 Hz, 1H), 5.18 (d, J=8.5 Hz, 1H), 4.19 - 4.04 (m, 1H), 3.90 (d, J=2.1 Hz, 3H), 3.83 - 3.71 (m, 1H), 2.86 - 2.57 (m, 5H), 2.43 (br s, 1H), 2.31 - 2.16 (m, 2H), 2.05 - 1.88 (m, 2H), 1.83 - 1.66 (m, 3H), 1.65 - 1.56 (m, 1H), 1.49 - 1.34 (m, 2H), 1.20 (br d, J=6.3 Hz, 2H), 0.91 - 0.77 (m, 6H), 0.36 (br dd, J=9.3, 3.9 Hz, 1H), 0.22 - 0.12 (m, 1H), 0.08 - -0.05 (m, 2H) 由于水抑制而缺失1个质子	2.97, C

971		2-(3'-{[(1R,2R,3S,4R,7Z)-3-{[(1R)-1-(2,2-二氟-1-甲基环丙基)乙基]胺甲酰基}-7-[(3,3-二氟环丁基)亚甲基]双环[2.2.1]庚烷-2-基]胺甲酰基}-6-氟-4'-甲氧基-[1,1'-联苯]-3-基)-2-[(噁烷-4-基)甲酰胺基]乙酸	788.2	(500 MHz, DMSO-d6) δ 10.09 (d, J=6.8 Hz, 1H), 8.60 (br d, J=7.5 Hz, 1H), 8.31 (br d, J=8.4 Hz, 1H), 8.11 (s, 1H), 7.69 (br d, J=8.7 Hz, 1H), 7.58 - 7.51 (m, 1H), 7.45 - 7.38 (m, 1H), 7.35 - 7.26 (m, 2H), 5.40 (br d, J=7.3 Hz, 1H), 5.35 (d, J=8.4 Hz, 1H), 4.35 - 4.22 (m, 1H), 4.01 (s, 3H), 3.94 - 3.80 (m, 3H), 3.04 - 2.95 (m, 2H), 2.94 - 2.76 (m, 3H), 2.62 (br s, 1H), 2.47 - 2.33 (m, 2H), 1.86 - 1.71 (m, 2H), 1.68 - 1.51 (m, 5H), 1.35 (br d, J=0.6 Hz, 2H), 1.26 - 1.18 (m, 1H), 1.13 (s, 3H), 1.10 (d, J=6.9 Hz, 3H) 由于水抑制而缺失4个质子	2.36, C

972		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲氧基)苯基]-3-{5-[5-(羟基甲基)-3aH,4H,5H,6H,6aH-环戊并[d][1,2]噁唑-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	658.2	(500 MHz, DMSO-d6) δ 10.48 (s, 1H), 9.90 (br d, J=7.2 Hz, 1H), 8.23 (d, J=2.3 Hz, 1H), 8.03 (br d, J=6.8 Hz, 1H), 7.79 (dd, J=8.7, 2.3 Hz, 1H), 7.52 - 7.41 (m, 2H), 7.26 (d, J=8.8 Hz, 1H), 5.11 (dd, J=8.9, 5.0 Hz, 1H), 4.68 (d, J=9.5 Hz, 1H), 4.51 (t, J=5.3 Hz, 1H), 4.47 - 4.36 (m, 1H), 4.25 - 4.15 (m, 1H), 4.02 (s, 3H), 3.14 (br dd, J=11.0, 4.2 Hz, 1H), 3.09 (br s, 1H), 2.71 (br s, 1H), 1.98 (br dd, J=13.5, 5.3 Hz, 1H), 1.93 - 1.71 (m, 4H), 1.71 - 1.60 (m, 1H), 1.59 - 1.45 (m, 2H), 1.46 - 1.36 (m, 2H), 0.82 - 0.64 (m, 2H), 0.40 - 0.28 (m, 2H)	2.46, C

973		(2S,3R,7Z)-3-(5-{3aH,4H,6H,6aH-呋喃并[3,4-d][1,2]噁唑-3-基}-2-甲氧基苯甲酰胺基)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲氧基)苯基]双环[2.2.1]庚烷-2-甲酰胺	630.1	(500 MHz, DMSO-d6) δ 10.49 (s, 1H), 9.90 (d, J=7.1 Hz, 1H), 8.28 - 8.15 (m, 1H), 8.04 (br d, J=6.1 Hz, 1H), 7.79 (dd, J=8.6, 2.3 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.30 - 7.22 (m, 1H), 5.34 (dd, J=9.2, 3.4 Hz, 1H), 4.69 (d, J=9.7 Hz, 1H), 4.49 (br t, J=7.7 Hz, 1H), 4.46 - 4.39 (m, 1H), 4.09 (d, J=10.5 Hz, 1H), 4.03 (s, 2H), 4.06 - 4.00 (m, 1H), 3.89 (br d, J=9.2 Hz, 1H), 3.77 (dd, J=9.1, 7.1 Hz, 1H), 3.65 (dd, J=10.5, 3.5 Hz, 1H), 3.15 (dd, J=10.8, 4.2 Hz, 1H), 3.10 (br s, 1H), 2.71 (br s, 1H), 1.87 - 1.69 (m, 2H), 1.49 (td, J=8.4, 4.1 Hz, 1H), 1.44 - 1.32 (m, 2H), 0.80 - 0.66 (m, 2H), 0.34 (br d, J=2.5 Hz, 2H)	2.47, C

974		(2S,3R,7Z)-7-(环丙基亚甲基)-N-[4-氟-3-(三氟甲基)苯基]-3-{5-[7-(羟基甲基)咪唑并[1,2-a]吡啶-3-基]-2-甲氧基苯甲酰胺基}双环[2.2.1]庚烷-2-甲酰胺	649.5	(500 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.95 (d, J=7.2 Hz, 1H), 8.37 (d, J=7.0 Hz, 1H), 8.24 - 8.19 (m, 1H), 8.13 (d, J=2.3 Hz, 1H), 7.81 - 7.74 (m, 2H), 7.65 (s, 1H), 7.51 (s, 1H), 7.47 (t, J=9.7 Hz, 1H), 7.37 (d, J=8.7 Hz, 1H), 6.94 - 6.87 (m, 1H), 4.69 (d, J=9.5 Hz, 1H), 4.56 (br d, J=5.3 Hz, 2H), 4.46 (br dd, J=6.4, 2.8 Hz, 1H), 4.07 (s, 3H), 3.16 (br dd, J=10.8, 3.7 Hz, 1H), 3.10 (br s, 1H), 2.72 (br s, 1H), 1.89 - 1.77 (m, 2H), 1.56 - 1.46 (m, 1H), 1.46 - 1.37 (m, 2H), 0.78 - 0.67 (m, 2H), 0.34 (br d, J=2.1 Hz, 2H)	2.10, C

975		(1R,2R,3S,4S)-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]-7-丙烷-2-基)双环[2.2.1]庚烷-2-甲酰胺	529.2	(500 MHz, 氯仿-d) δ 9.58 (br d, J=7.7 Hz, 1H), 8.12 (s, 1H), 8.07 - 7.98 (m, 2H), 7.55 (dt, J=8.7, 3.4 Hz, 1H), 7.11 (t, J=9.4 Hz, 1H), 6.79 (dd, J=11.6, 6.3 Hz, 1H), 4.70 - 4.53 (m, 1H), 4.01 (s, 3H), 2.95 (dd, J=11.0, 3.9 Hz, 1H), 2.48 - 2.39 (m, 2H), 2.01 - 1.94 (m, 1H), 1.71 - 1.61 (m, 1H), 1.55 - 1.50 (m, 2H), 1.36 (br d, J=10.2 Hz, 1H), 1.26 (br d, J=1.9 Hz, 1H), 0.85 (d, J=6.3 Hz, 6H)	1.24, C
976		(2S,3R)-7-苯甲基-3-(4,5-二氟-2-甲氧基苯甲酰胺基)-N-[4-氟-3-(三氟甲基)苯基]双环[2.2.1]庚烷-2-甲酰胺	577.2	(400 MHz, 氯仿-d) δ 9.59 - 9.47 (m, 1H), 8.07 - 7.99 (m, 1H), 7.93 (dd, J=6.2, 2.6 Hz, 1H), 7.65 (s, 1H), 7.49 - 7.44 (m, 1H), 7.33 - 7.29 (m, 2H), 7.18 - 7.06 (m, 5H), 6.76 (dd, J=11.4, 6.2 Hz, 1H), 4.64 (ddd, J=11.1, 7.4, 4.0 Hz, 1H), 3.98 (s, 3H), 2.93 (dd, J=10.8, 3.7 Hz, 1H), 2.76 - 2.64 (m, 2H), 2.46 (br s, 1H), 2.37 (br s, 1H), 2.32 (br s, 1H), 2.15 - 2.09 (m, 2H), 2.04 (br s, 1H) 自混合物报导的主要非镜像异构体	1.24, C