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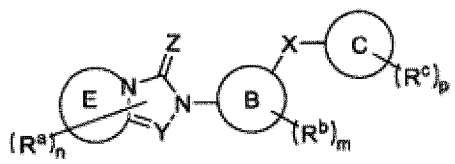
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(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS OF TREATING CANCER

(57) Abstract: The present disclose includes, among other things, compounds that treat or lessen the severity of cancer, pharmaceutical compositions and methods of making and using the same.



(A)

WO 2022/221704 A1

COMPOUNDS, COMPOSITIONS AND METHODS OF TREATING CANCER

Cross References to Related Applications

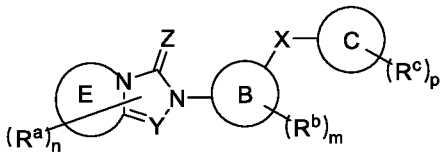
[001] This application claims priority to U.S. Provisional Application Nos. 63/175,974 filed April 16, 2021 and 63/281,493 filed November 19, 2021, the contents of each of which are incorporated herein by reference.

Background

[002] Cbl-b is a E3 ubiquitin-protein ligase that functions as a negative regulator of T-cell activation. Modulation of Cbl-b has been shown to be a therapeutic target for a diseases and disorders. There remains a need for compounds that inhibit Cbl-b.

Summary

[003] In some embodiments, the present disclosure includes a compound of formula (A):



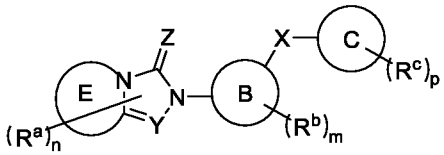
(A)

or a pharmaceutically acceptable salt thereof.

[004] Additionally, the present disclosure includes, among other things, pharmaceutical compositions, methods of using and methods of making a compound of formula (A).

Detailed Description

[005] In some embodiments, the present disclosure includes a compound of formula (A):



(A)

or pharmaceutically acceptable salts thereof,

wherein

Y is selected from the group =C(H)-, =C(R^a)- or =N-;

Z is =O or =S;

E is optionally substituted 5-6 membered heterocyclyl;

B is optionally substituted phenyl, optionally substituted 8-10 membered bicyclyl, or optionally substituted 5-6 membered heteroaryl;

C is optionally substituted 5-6 membered heterocyclyl;

X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-, optionally substituted 3-6-membered carbocyclyl, and optionally substituted 3-6-membered heterocylyl, wherein X is optionally substituted with an optionally substituted group selected from a group consisting of halogen, C_1-C_3 aliphatic, phenyl, 3-6-membered heteroaryl, 3-6-membered heterocylyl, and -(CH_2)(3-6-membered carbocyclyl);

each R^a is independently selected from the group consisting of L-Y, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -C(O)R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein R^a is optionally substituted with 1-5 instances of R^{a1};

L is an optionally substituted C_1-C_3 alkylene chain;

A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein A is optionally substituted with 1-5 instances of R^{a1};

each R^{a1} is independently selected from the group consisting of halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^b is independently selected from the group consisting of, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$S(O)(NH)R^1$, -$S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, OR^1, -NH_2, -NR^1R^2, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -$C(O)R^3$, -CO_2R^3, -$C(O)NHR^3$, and -SO_2R^3;

each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -$C(O)R^3$, -CO_2R^3, -$C(O)NHR^3$, and -SO_2R^3;

each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

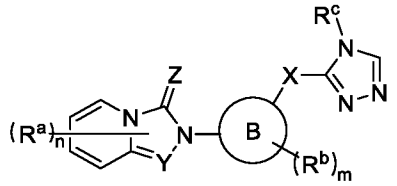
each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

n is 0, 1, 2, 3, 4, or 5;

m is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, 3, or 4.

[006] In some embodiments, the present disclosure includes a compound of Formula (B):



(B),

or pharmaceutically acceptable salts thereof,

wherein

Y is selected from the group =C(H)-, =C(R^a)- or =N-;

Z is =O or =S;

B is optionally substituted phenyl, substituted 5-6 membered heteroaryl or optionally substituted 8-10 membered bicyclyl;

X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-, optionally substituted 3-6-membered carbocyclyl, and optionally substituted 3-6-membered heterocylyl,

each R^a is independently selected from the group consisting of L-A, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -C(O)R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

L is an optionally substituted C_1-C_3 alkylene chain;

A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^b is independently selected from the group consisting of, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$S(O)(NH)R^1$, -$S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, -OR^1, -NH_2, -NR^1R^2, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -$C(O)R^3$, -CO_2R^3, -$C(O)NHR^3$, and -SO_2R^3;

each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -$C(O)R^3$, -CO_2R^3, -$C(O)NHR^3$, and -SO_2R^3;

each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

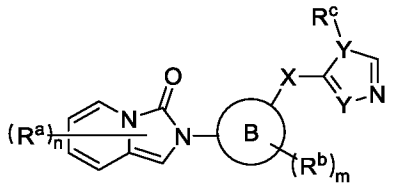
or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

n is 0, 1, 2, 3, 4, or 5; and

m is 0, 1, 2, 3, or 4.

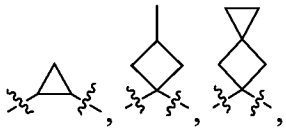
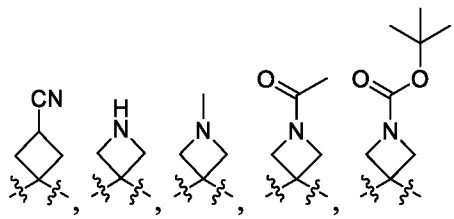
[007] In some embodiments, the present disclosure includes a compound of formula (I):



(I),

or pharmaceutically acceptable salts thereof,

wherein

X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-,  ,  , and  , and wherein each methylene unit may be substituted with 1-2 substituents independently selected from the group consisting of halogen, optionally substituted C_1-C_3 aliphatic, optionally substituted 5-membered heteroaryl, optionally substituted phenyl, optionally substituted C_3-C_4 carbocylyl, and optionally substituted C_3-C_4 heterocyclyl;

each R^a is independently selected from the group consisting of L-A, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -C(O)R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein R^a is optionally substituted with 1-5 instances of R^{a1};

each Y is independently selected from the group consisting of -C=, -O-, -N=, and -S-;

L is an optionally substituted C_1-C_3 alkylene chain;

A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein A is optionally substituted with 1-5 instances of R^{a1};

each R^{a1} is independently selected from the group consisting of halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$S(O)(NH)R^1$, -$S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

B is optionally substituted phenyl, substituted 5-6 membered heteroaryl, or optionally substituted 8-10 membered bicyclyl;

each R^b is independently selected from the group consisting of halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$S(O)(NH)R^1$, -$S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, wherein the – optionally deuterated optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -$C(O)R^3$, -CO_2R^3, -$C(O)NHR^3$, and -SO_2R^3;

each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S,

optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$;

each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

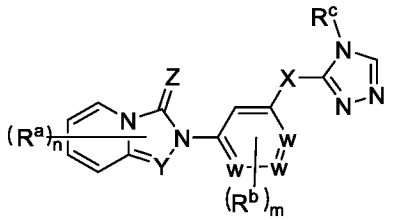
or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

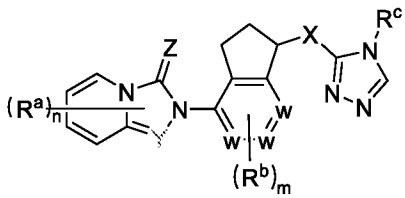
n is 0, 1, 2, 3, 4, or 5; and

m is 0, 1, 2, 3, or 4.

[008] In some embodiments, present disclosure includes a compound is of formula (Ia) or (IIa):



(Ia)



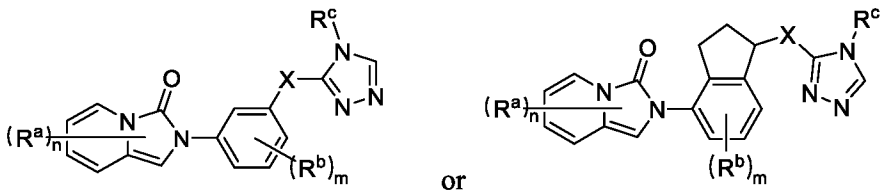
(IIa),

or pharmaceutically acceptable salts thereof,

wherein each W is independently selected from N or C; and

X, Y, Z, R^a, R^b, R^c, n, and m are defined above and described in classes and subclasses herein.

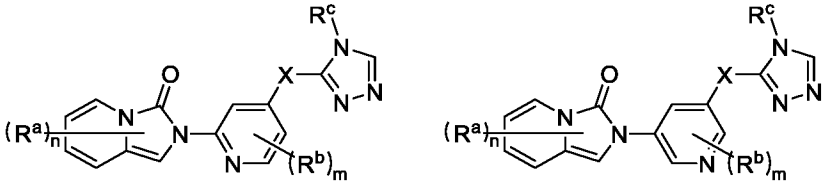
[009] In some embodiments, present disclosure includes a compound is of formula (Ia1) or (IIa1):



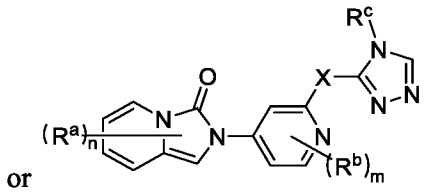
(Ia1) or (IIa1),

or a pharmaceutically acceptable salt thereof, wherein X, Y, Z, R^a, R^b, R^c, n, and m are defined above and described in classes and subclasses herein.

[010] In some embodiments, present disclosure includes a compound is of formula (Ia2), (Ia3), or (Ia4):



(Ia2) (Ia3)

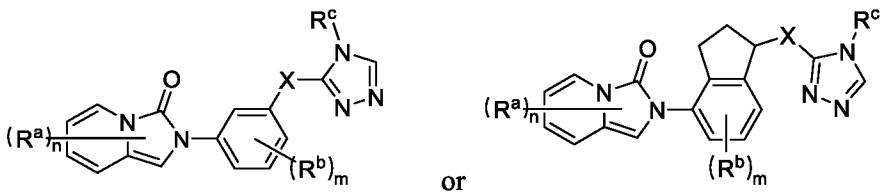


or

(Ia3)

or pharmaceutically acceptable salts thereof, wherein X, Y, Z, R^a, R^b, R^c, n, and m are defined above and described in classes and subclasses herein.

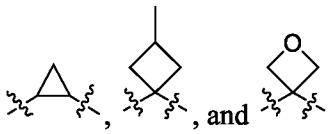
[011] In some embodiments, present disclosure includes a compound is of formula (Ia1) or (IIa1):



(Ia1) or (IIa1),

or pharmaceutically acceptable salts thereof,

wherein

X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-,  , and ;

each R^a is independently selected from the group consisting of L-A, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -C(O)R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

L is an optionally substituted C_1-C_3 alkylene chain;

A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^b is independently selected from the group consisting of, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4

heteroatoms each selected from the group consisting of N, O and S, -C(O)R^3, -CO_2R^3, -C(O)NHR^3, and -SO_2R^3;

each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, -C(O)R^3, -CO_2R^3, -C(O)NHR^3, and -SO_2R^3;

each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

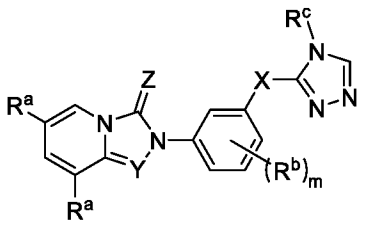
or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

n is 0, 1, 2, 3, 4, or 5; and

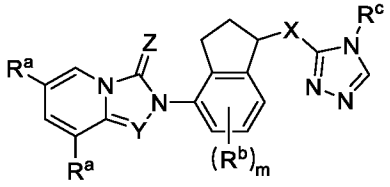
m is 0, 1, 2, 3, or 4.

[012] In some embodiments, present disclosure includes a compound is of formula (Ib) or (IIb):



(Ib)

or

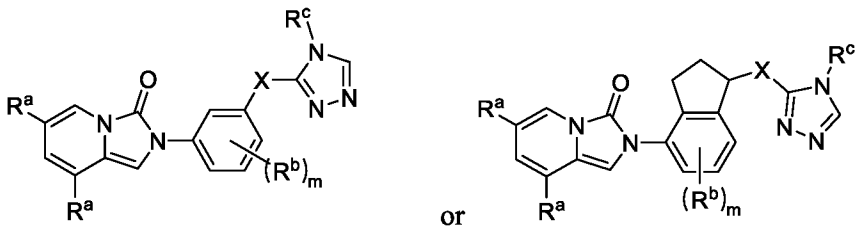


(IIb),

or pharmaceutically acceptable salts thereof, wherein X, Y, Z, R^a, R^b, R^c, and m are defined above and described in classes and subclasses herein.

[013] In some embodiments, present disclosure includes a compound of formula (Ib1) or

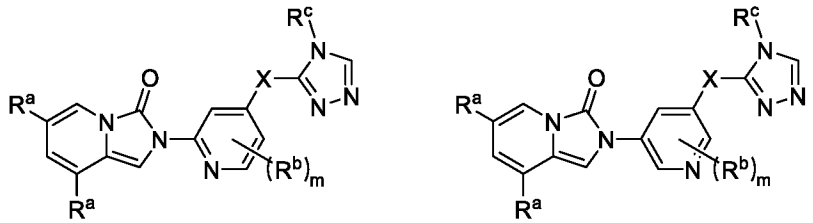
(IIb1):



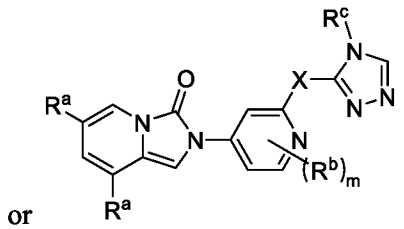
(Ib1) or (IIb1),

or a pharmaceutically acceptable salt thereof, wherein X, R^a, R^b, R^c and m are defined above and described in classes and subclasses herein.

[014] In some embodiments, present disclosure includes a compound of formula (Ib2), (Ib3), or (Ib4):



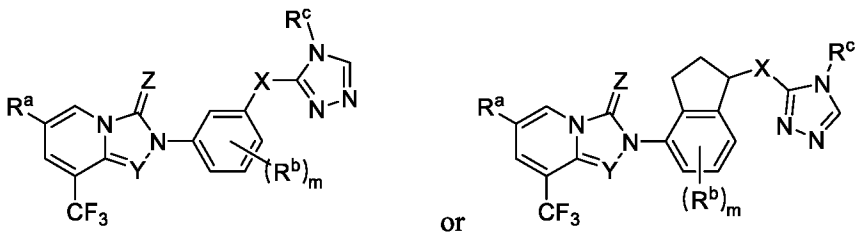
(Ib2) (Ib3)



(Ib4)

or a pharmaceutically acceptable salt thereof, wherein X, R^a, R^b, R^c and m are defined above and described in classes and subclasses herein.

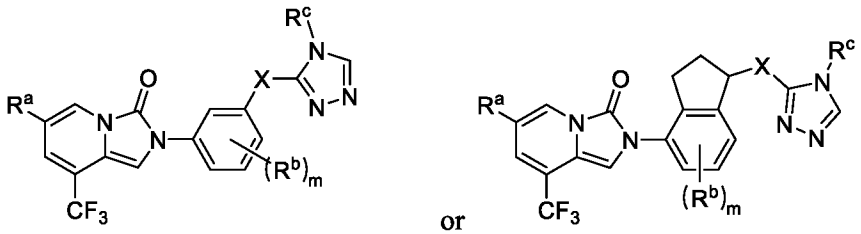
[015] In some embodiments, present disclosure includes a compound of formula (Ic) or (IIc):



(Ic) or (IIc),

or a pharmaceutically acceptable salt thereof, wherein X, Y, Z, R^a, R^b, R^c and m are defined above and described in classes and subclasses herein.

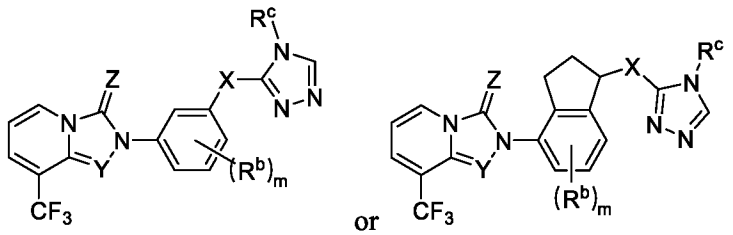
[016] In some embodiments, present disclosure includes a compound of formula (Ic1) or (IIc1):



(Ic1) or (IIc1),

or a pharmaceutically acceptable salt thereof, wherein X, R^a, R^b, R^c and m are defined above and described in classes and subclasses herein.

[017] In some embodiments, present disclosure includes a compound of formula (Id) or (IId):

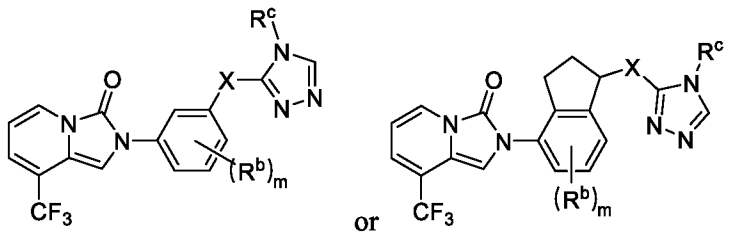


(Id) or (IId),

or a pharmaceutically acceptable salt thereof, wherein X, R^b, R^c and m are defined above and described in classes and subclasses herein.

[018] In some embodiments, present disclosure includes a compound of formula (Id1) or

(IId1):

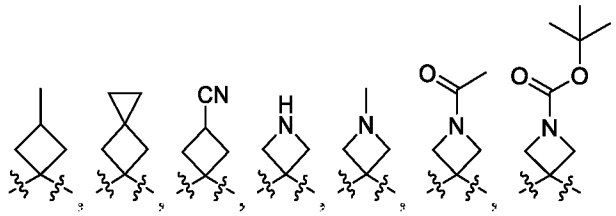


(Id1) (IId1),

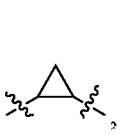
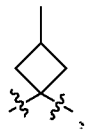
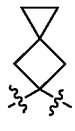
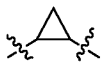
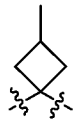
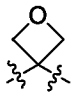
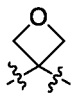
or a pharmaceutically acceptable salt thereof, wherein X, R^b, R^c and m are defined above and described in classes and subclasses herein.

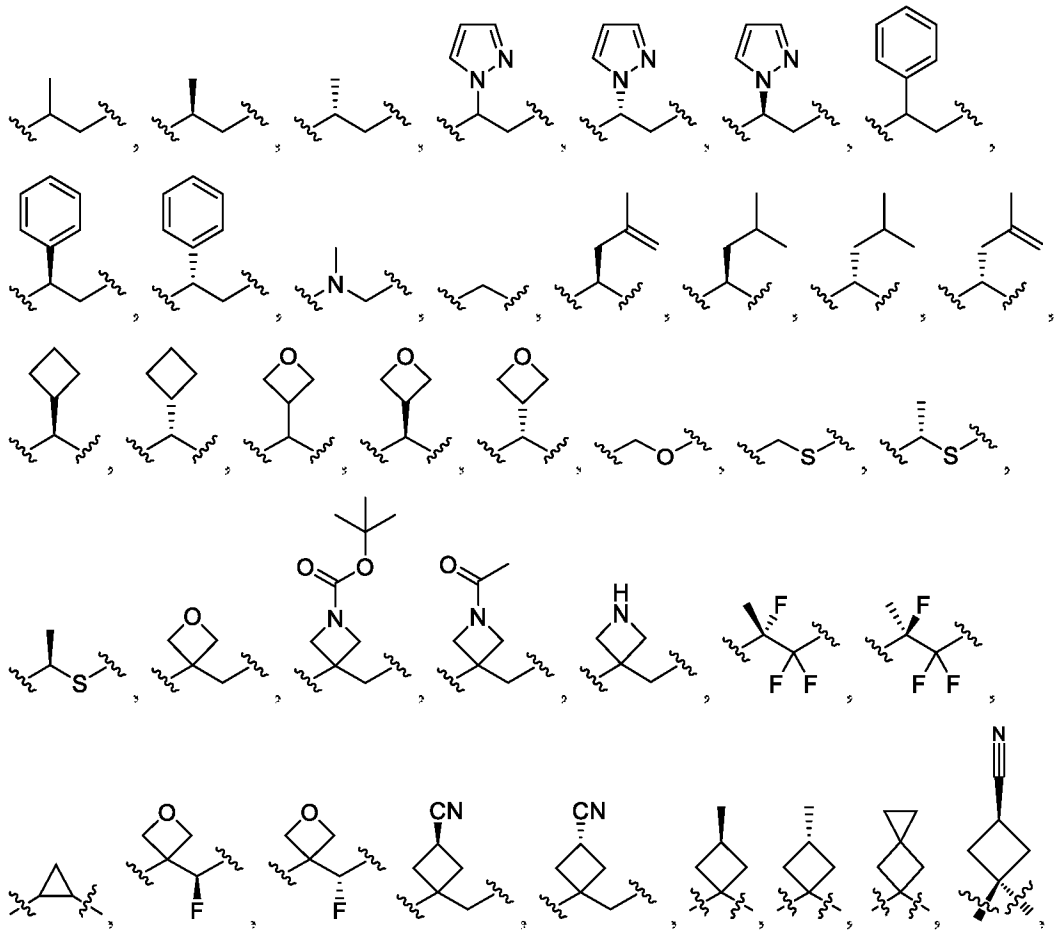
X

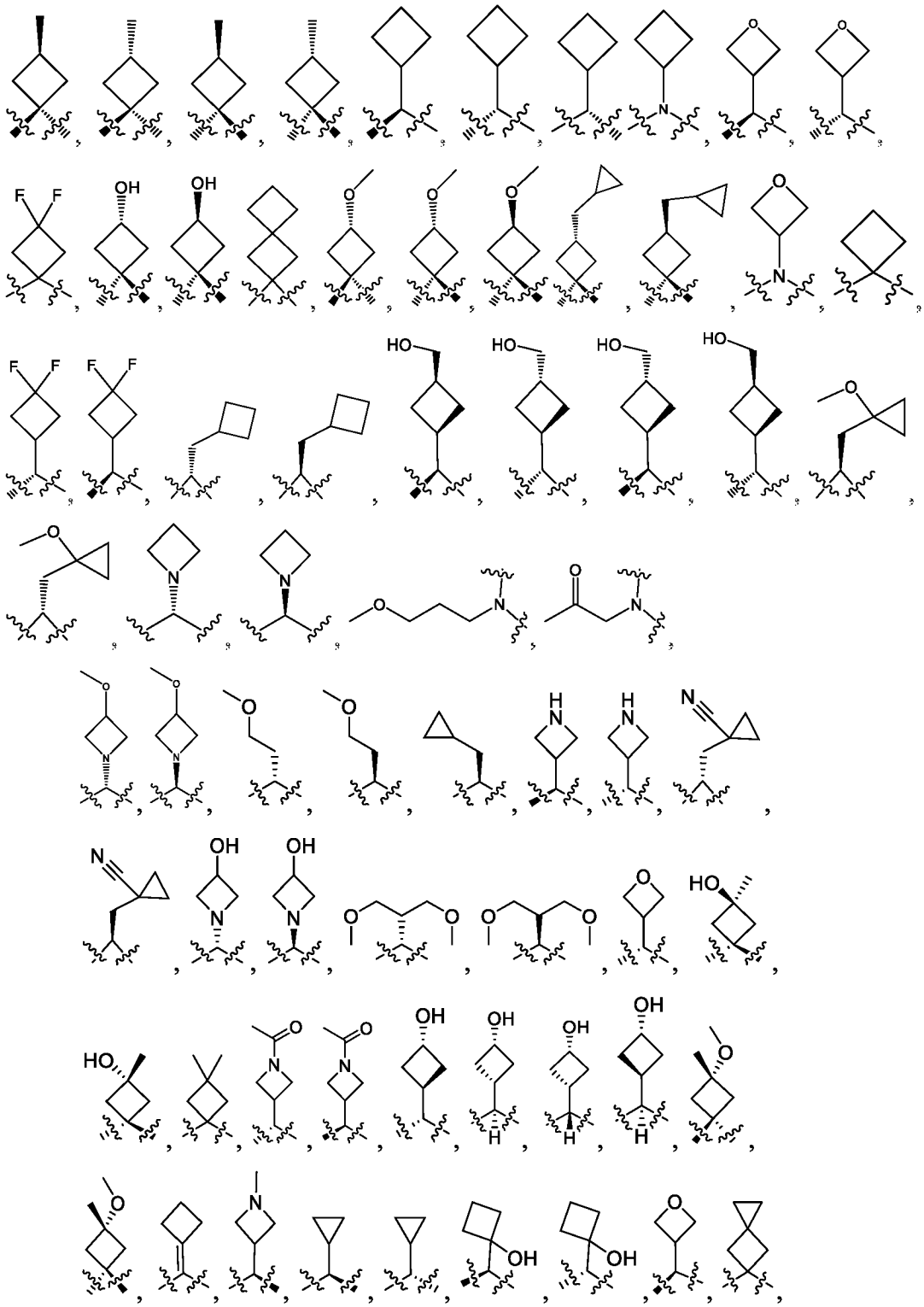
[019] In some embodiments, X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-, optionally substituted 3-6-membered carbocyclyl, and optionally substituted 3-6-membered heterocylyl, wherein X is optionally substituted with an optionally substituted group selected from the group consisting of halogen, C_1-C_3 aliphatic, phenyl, 3-6-membered heteroaryl, 3-6-membered heterocylyl, and -(CH_2)(3-6-membered carbocyclyl). In some embodiments, X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-, optionally substituted 3-6-membered carbocyclyl, and optionally substituted 3-6-membered heterocylyl. In some embodiments, X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-,  ,

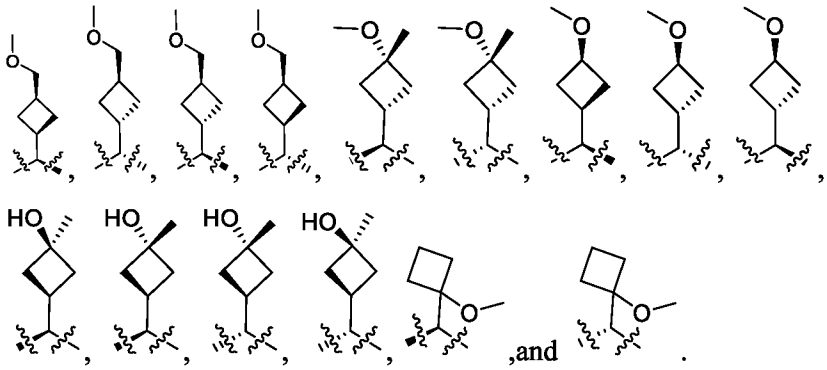


, and  , and wherein each methylene unit may be substituted with 1-2 substituents independently selected from the group consisting of halogen, optionally substituted C_1-C_3 aliphatic, optionally substituted 5-membered heteroaryl, optionally substituted phenyl, optionally substituted C_3-C_4 carbocylyl, and optionally substituted C_3-C_4 heterocylyl. In some embodiments, In some embodiments, X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is

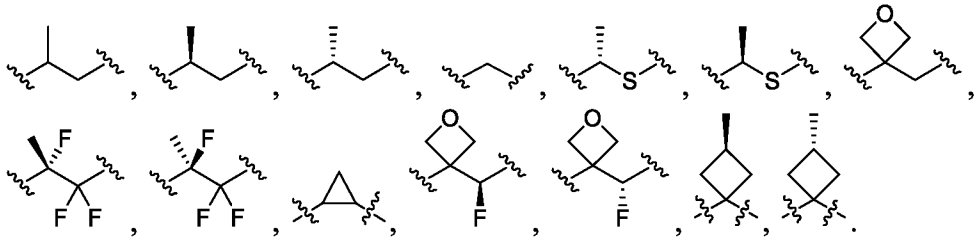
optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-,  ,  ,  , and  . In some embodiments, X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-,  ,  , and  . In some embodiments, X is optionally substituted C_1-C_2 alkylene. In some embodiments, X is  or optionally substituted C_2 alkylene, wherein one methylene unit is replaced with  . In some embodiments, X is selected from the group consisting of





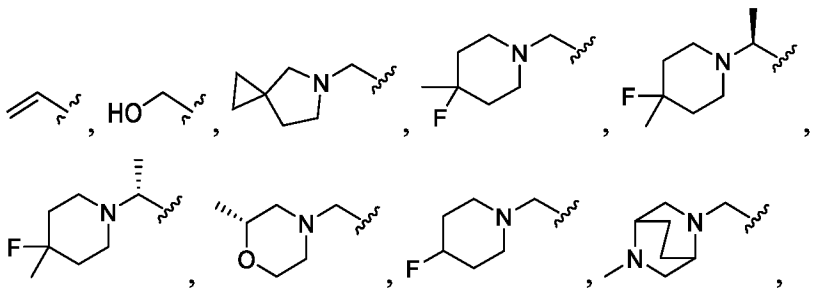


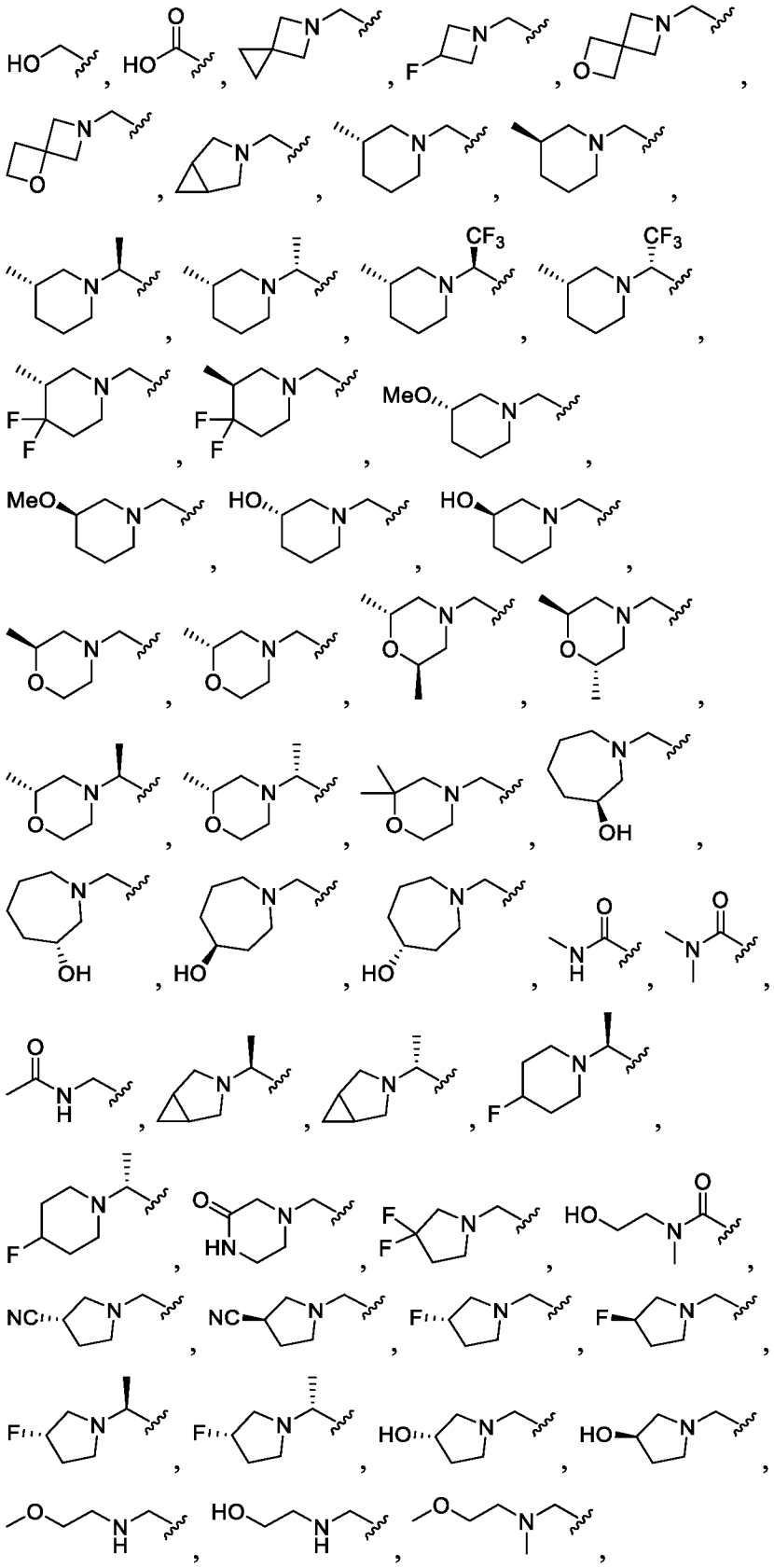
[020] In some embodiments, wherein X is selected from the group consisting of

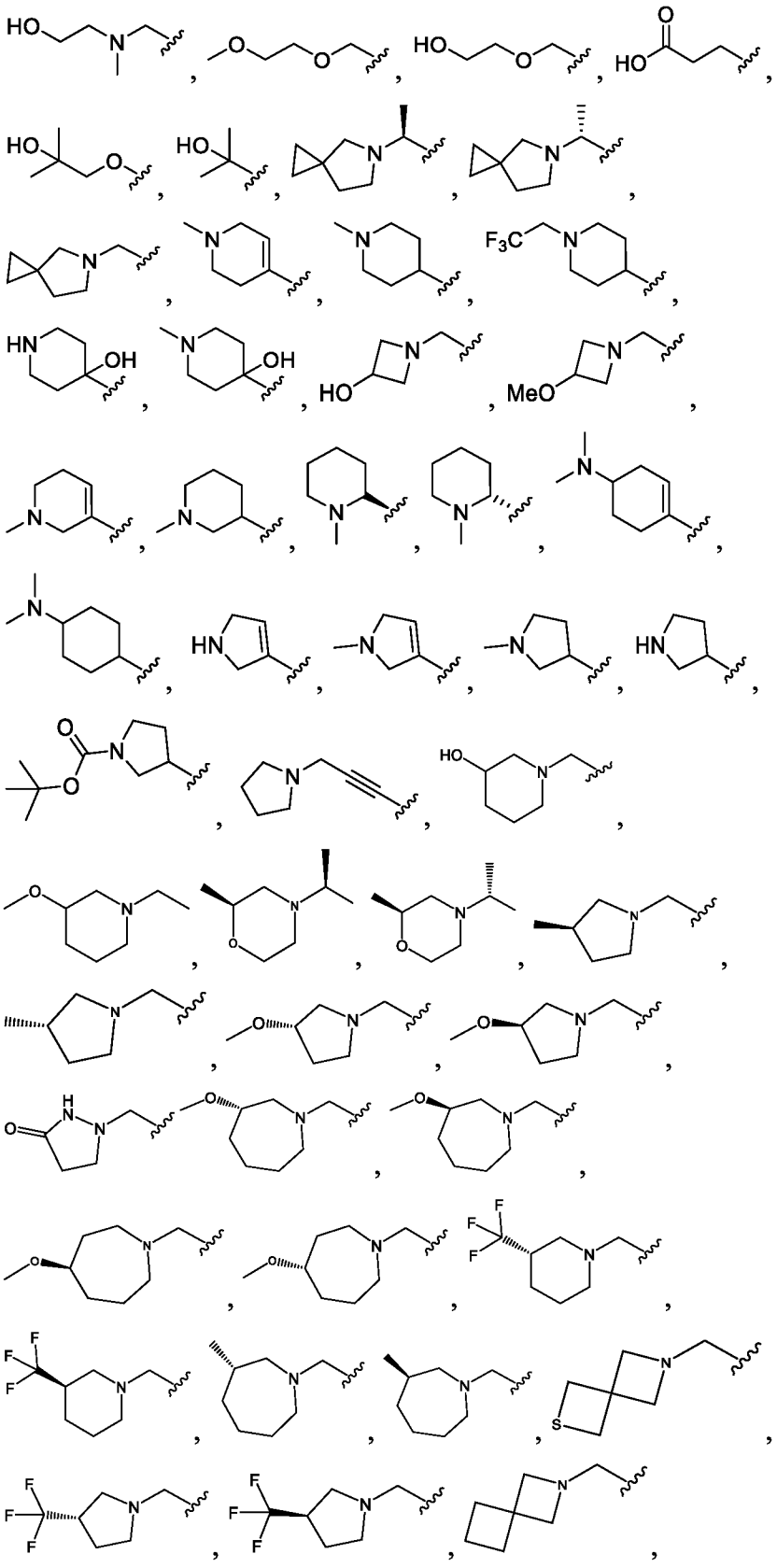


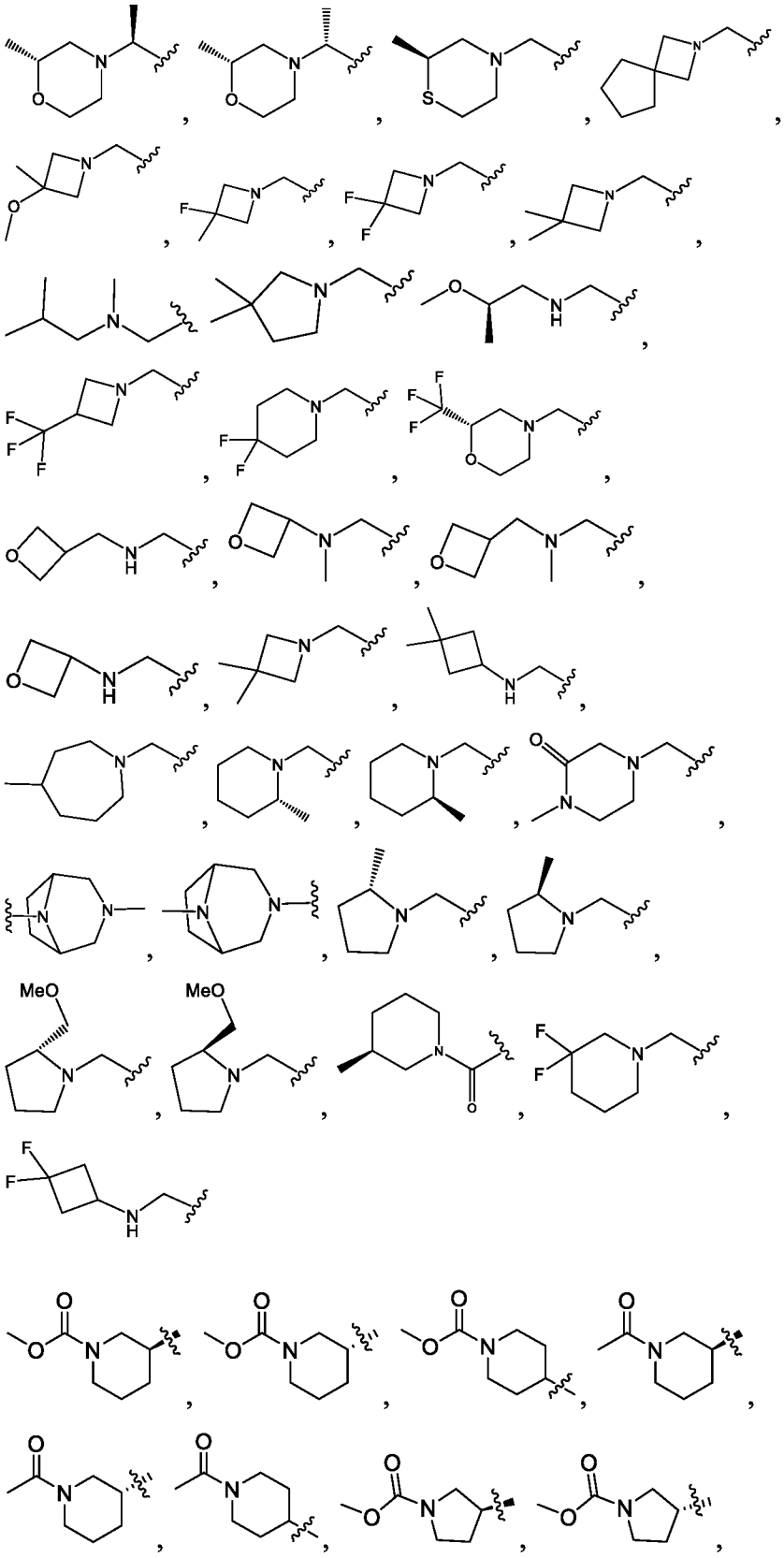
R^a

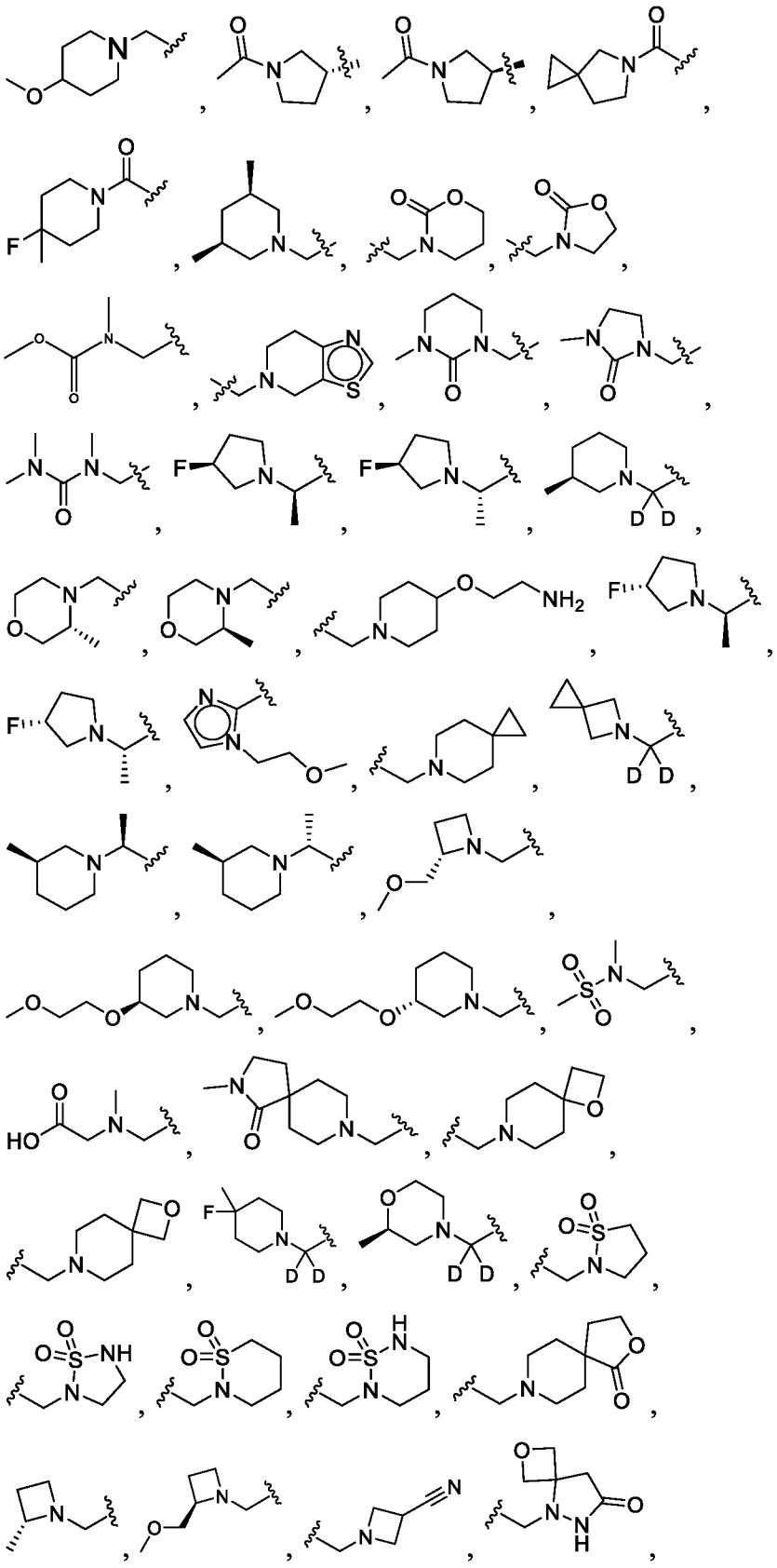
[021] In some embodiments, each R^a is independently selected from the group consisting of L-A, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -$C(O)R^1$, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -$S(O)R^1$, -$S(O)_2R^1$, -$S(O)(NH)R^1$, -$S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S. In some embodiments, L-A. In some embodiments, R^a is selected from halogen, -CN, -$C(O)R^1$, -CO_2H, -$CONR^1R^2$, optionally substituted C_1-C_6 aliphatic, and optionally substituted C_1-C_6 heteroalkyl. In some embodiments each R^a is independently selected from the group consisting of halogen, -CN, -CO_2H, -CHO, -CHF_2, -CF_3, -OMe, -$S(O)_2NHMe$,

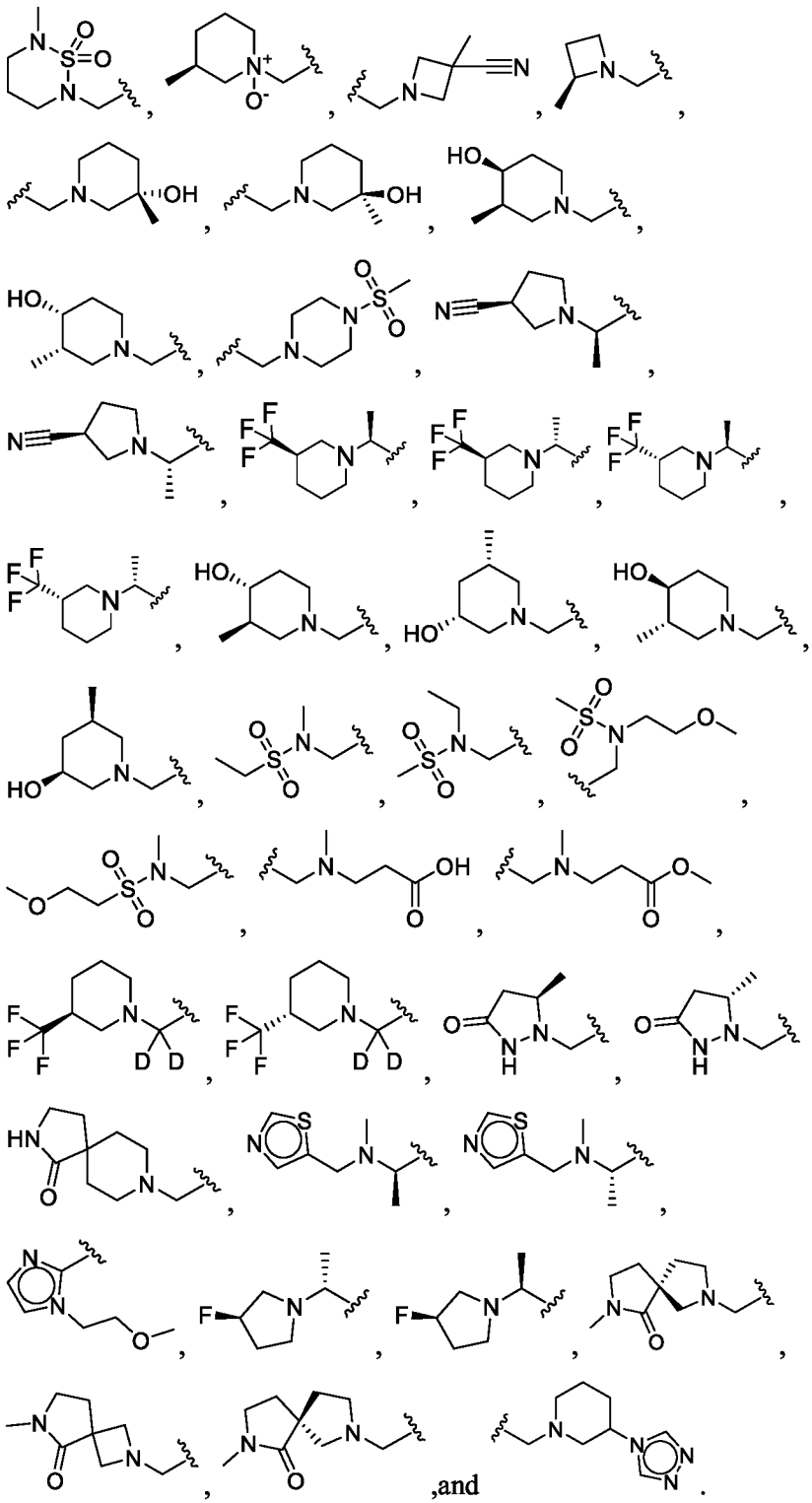




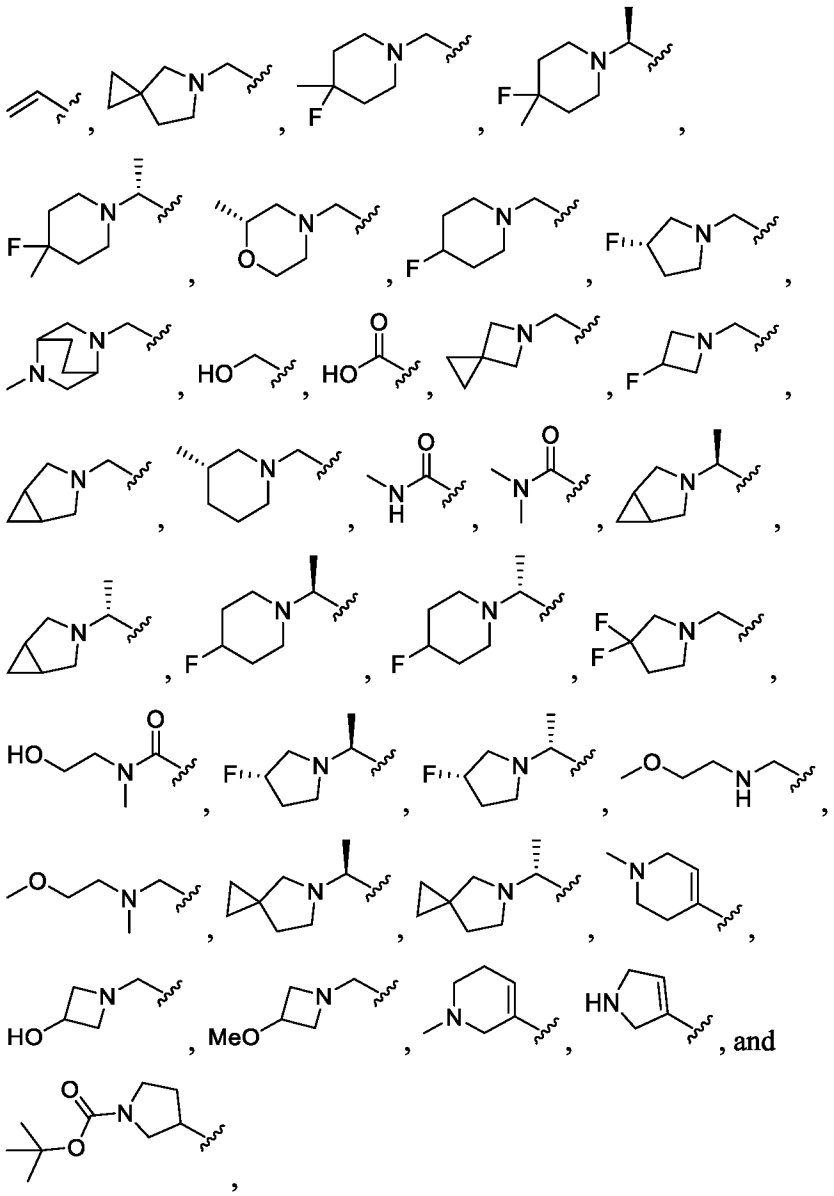








[022] In some embodiments, R^a is selected from the group consisting of halogen, -CN, -CO_2H,



L

[023] In some embodiments, L is an optionally substituted C_1-C_3 alkylene chain. In some embodiments, L is -CH_2- or -$CH(CH_3)$-.

A

[024] In some embodiments, A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-

membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S. In some embodiments, A is optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S. In some embodiments, A is selected from optionally substituted piperidine, optionally substituted tetrahydropyridine, optionally substituted pyrrolidine, optionally substituted dihydropyrrole, optionally substituted aziridine, and optionally substituted morpholine.

C

[025] In some embodiments, C is optionally substituted 5-membered heteroaryl. In some embodiments, C is optionally substituted 5-membered heteroaryl containing 3 nitrogen atoms. In some embodiments, C is optionally substituted triazolyl. In some embodiments, C is optionally substituted 1,2,4 trizaolyl. In some embodiments, C is optionally substituted 1,2,3 trizaolyl. In some embodiments, C is optionally substituted 5-membered heteroaryl containing 2 nitrogen atoms. In some embodiments, C is optionally substituted pyrazolyl. In some embodiments, C is optionally substituted isoxazolyl. In some embodiments, C is optionally substituted thiazolyl. In some embodiments, C is optionally substituted thiadizolyl. In some embodiments, C is optionally substituted 1,3,4 thiadizolyl. In some embodiments, C is optionally substituted pyridinyl. In some embodiments, C is optionally substituted pyrazinyl. In some embodiments, C is optionally substituted pyrimidinyl. In some embodiments, C is optionally substituted pyridazinyl.

R^b

[026] Im some embodiments, each R^b is independently selected from the group consisting of, halogen, -CN, -OH, $-OR^1$, $-NH_2$, $-NR^1R^2$, -SH, $-SR^1$, $-SF_5$, $-CO_2H$, $-CO_2R^1$, $-CONH_2$, $-CONR^1R^2$, $-SO_2NH_2$, $-SO_2NR^1R^2$, $-SO_2OH$, $-SO_2OR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-S(O)(NH)R^1$, $-S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S.

R^c

[027] In some embodiments, each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, $-OR^1$, $-NH_2$, $-NR^1R^2$, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each

selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$. In some embodiments, each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$. In some embodiments, R^c is optionally substituted C_1-C_3 aliphatic. In some embodiments, R^c is methyl.

R^1

[028] In some embodiments, each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$. In some embodiments, each R^1 is optionally substituted C_1-C_6 aliphatic. In some embodiments, each R^1 is methyl.

R^2

[029] In some embodiments, each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

[030] In some embodiments, each R^2 is optionally substituted C_1-C_6 aliphatic. In some embodiments, each R^2 is methyl.

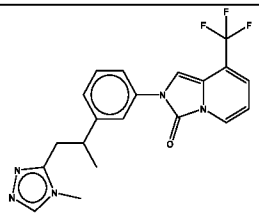
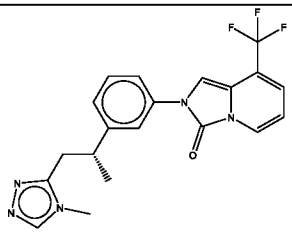
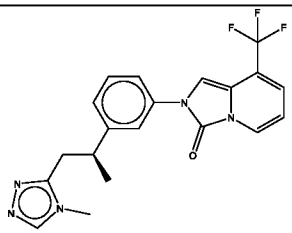
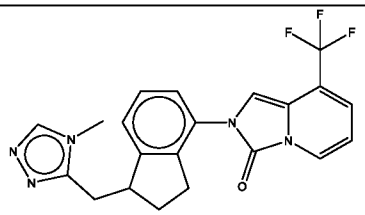
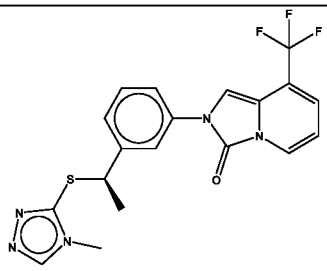
R^3

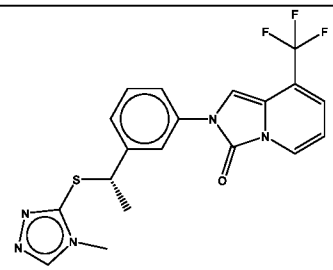
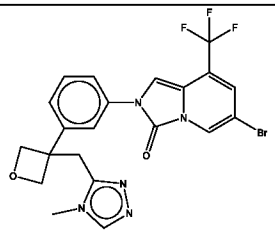
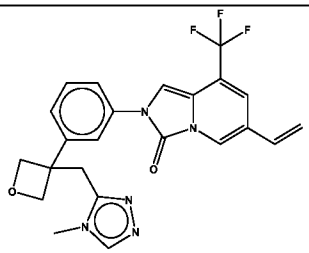
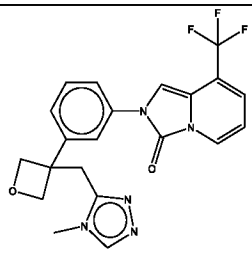
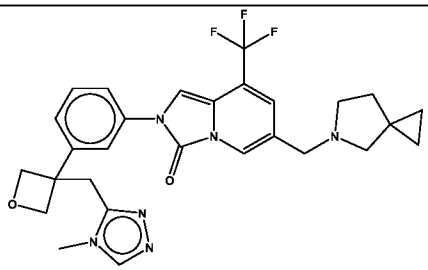
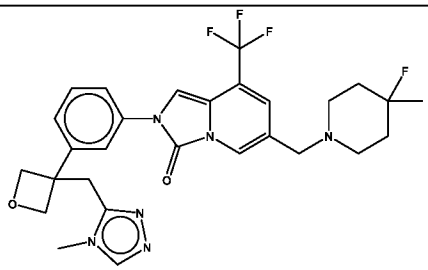
[031] In some embodiments, each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl

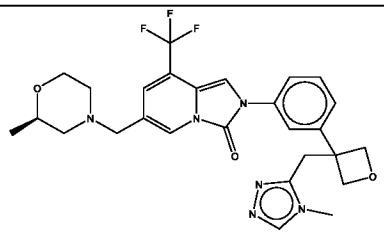
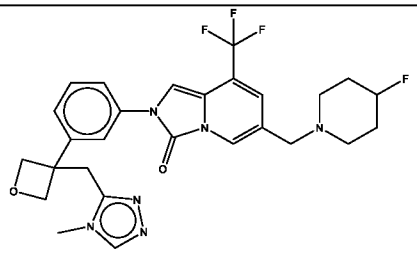
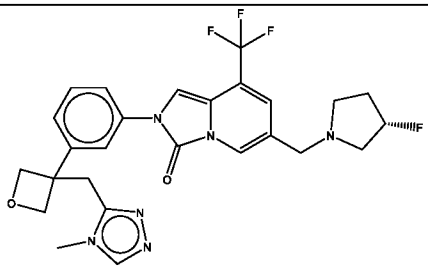
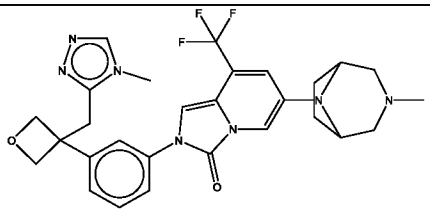
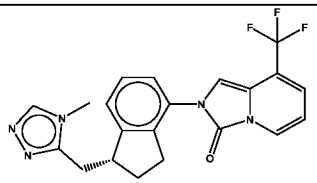
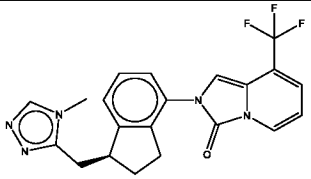
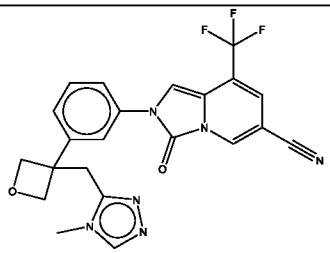
containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S.

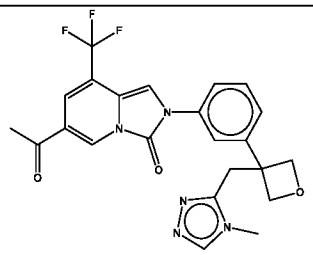
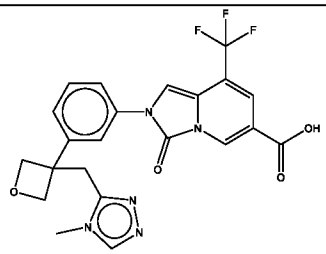
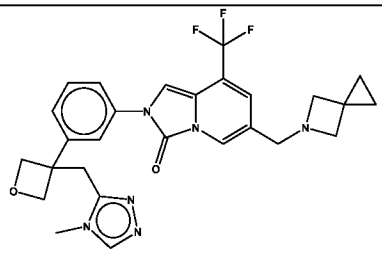
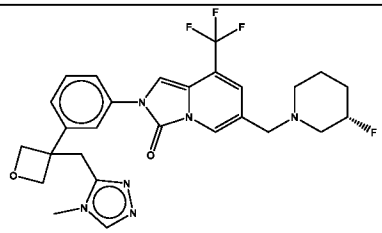
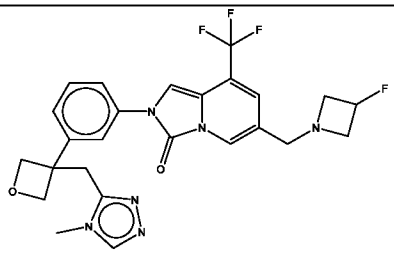
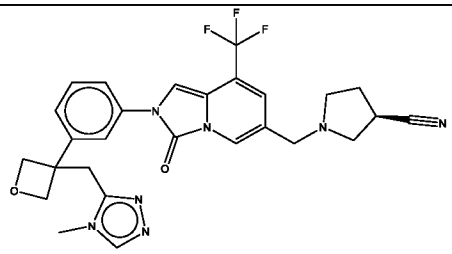
[032] In some embodiments, the present disclosure includes compounds described in **Table 1.**

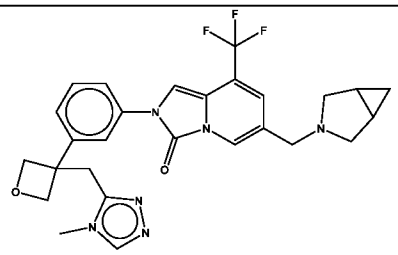
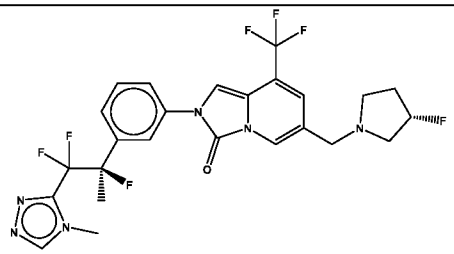
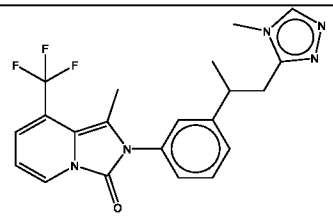
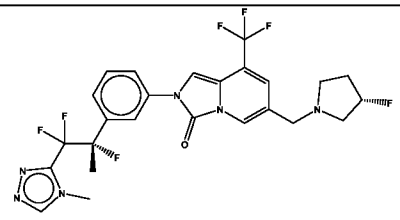
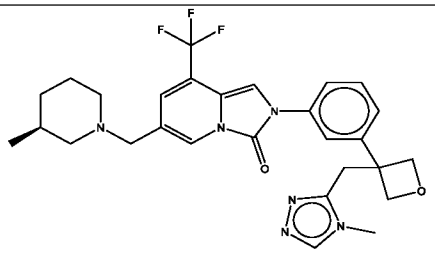
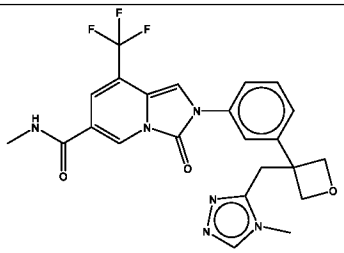
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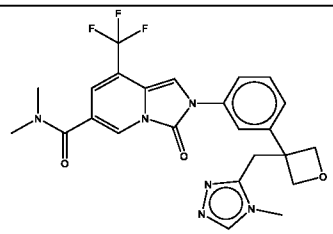
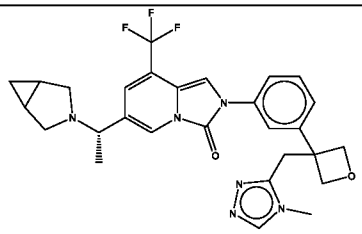
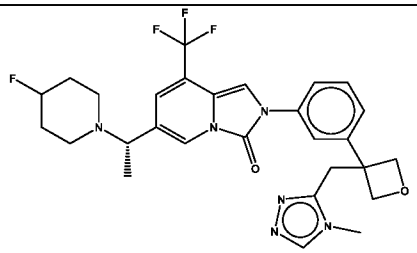
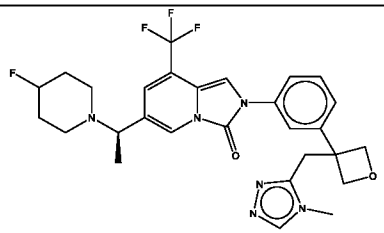
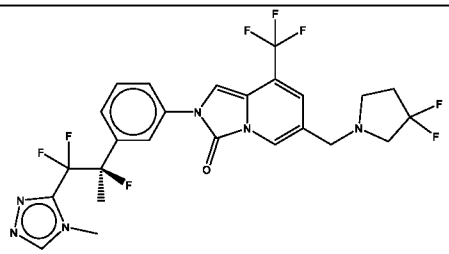
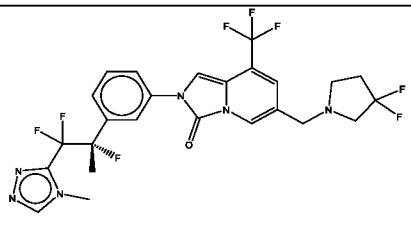
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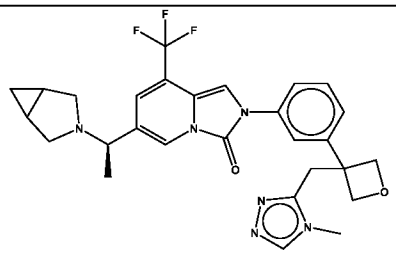
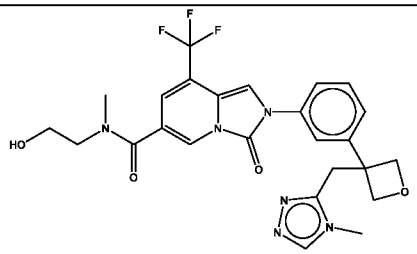
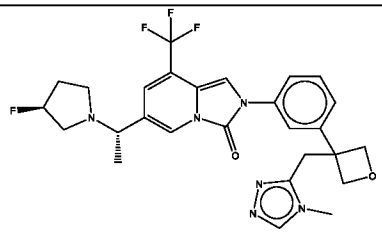
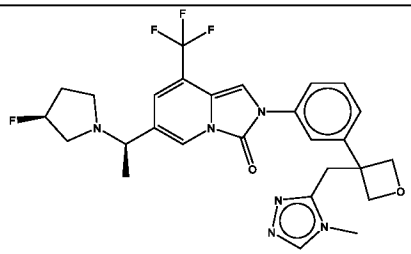
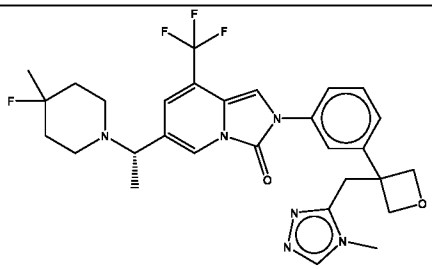
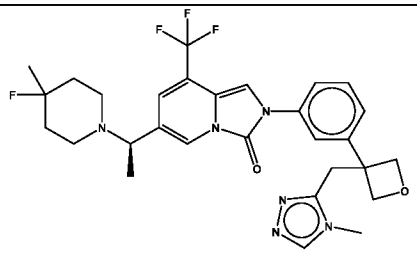
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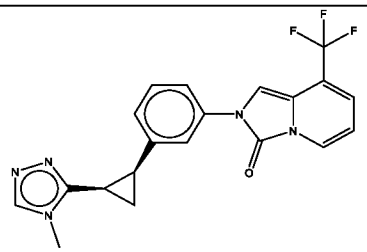
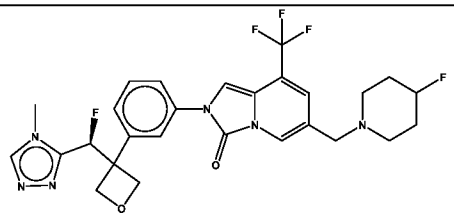
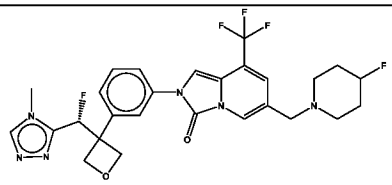
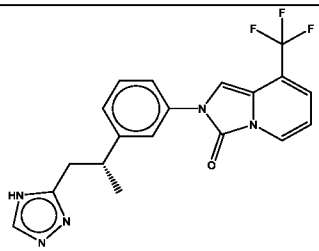
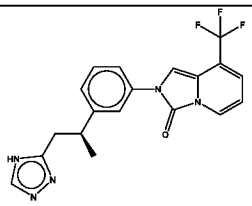
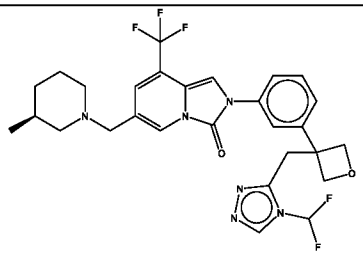
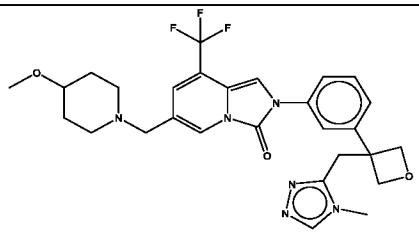
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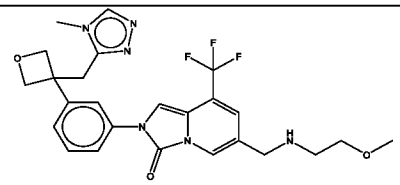
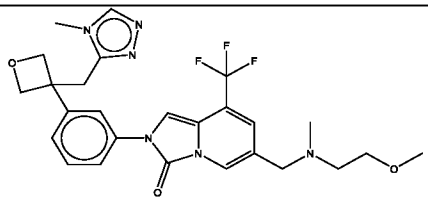
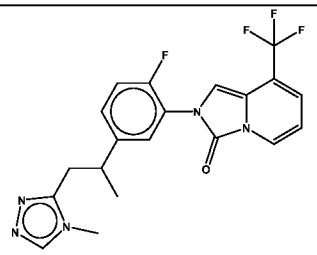
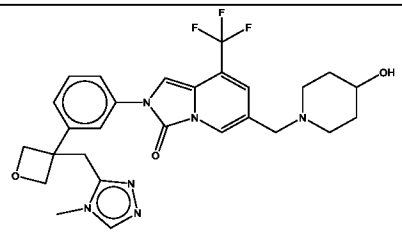
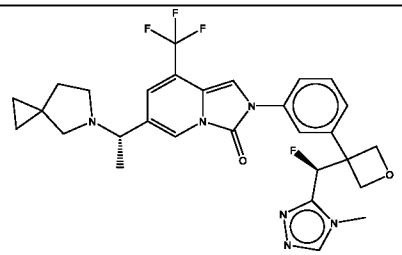
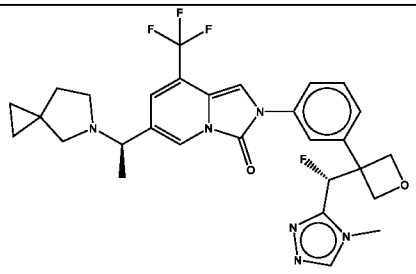
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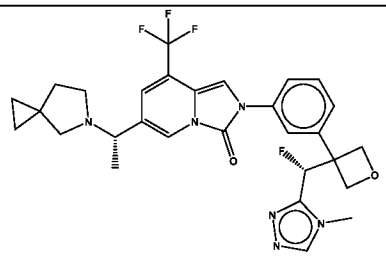
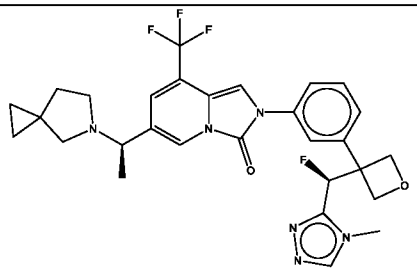
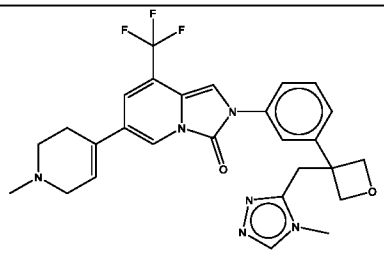
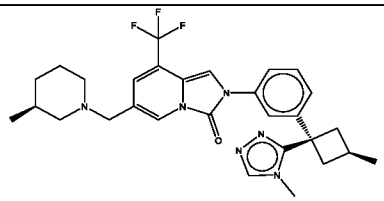
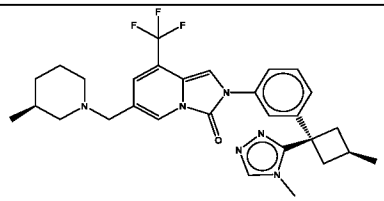
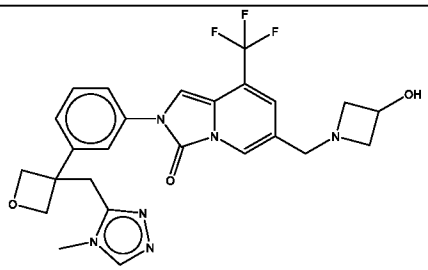
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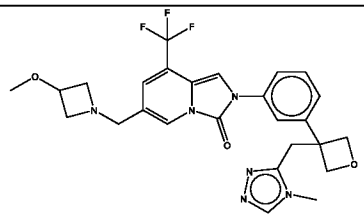
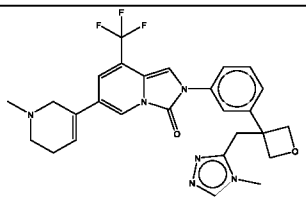
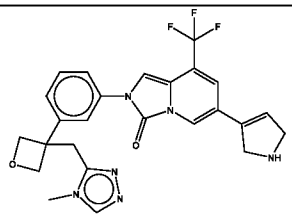
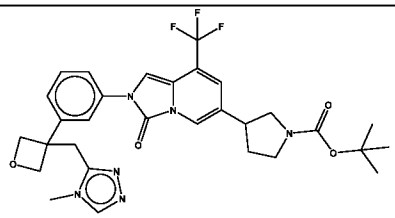
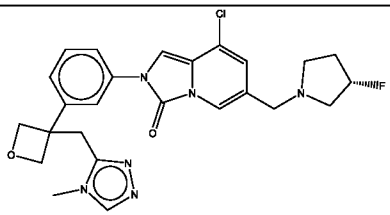
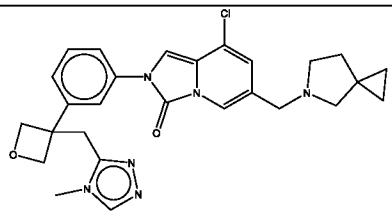
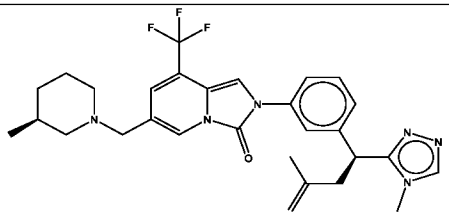
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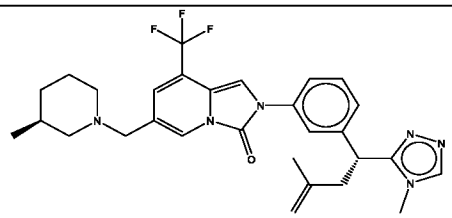
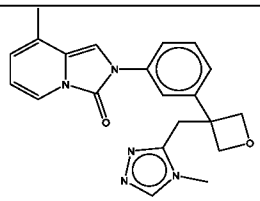
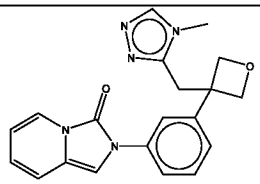
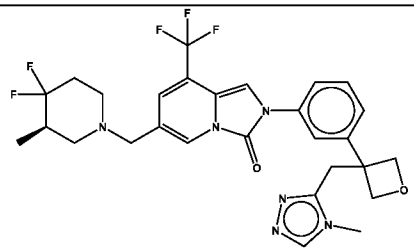
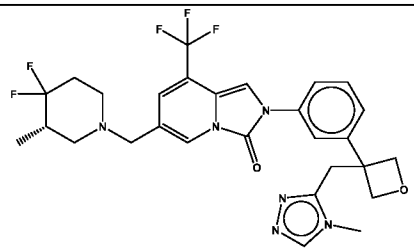
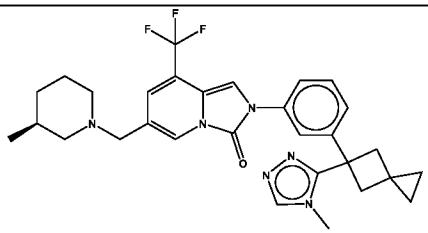
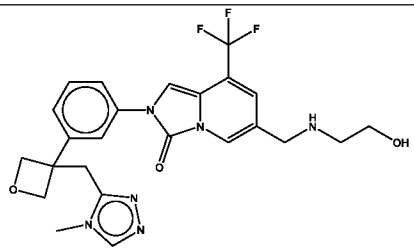
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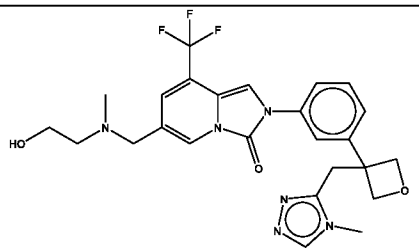
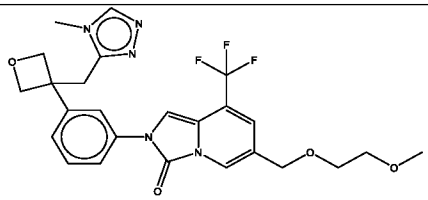
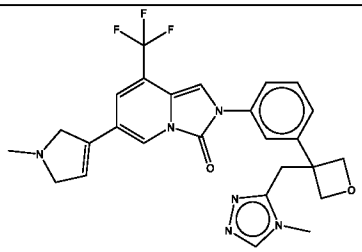
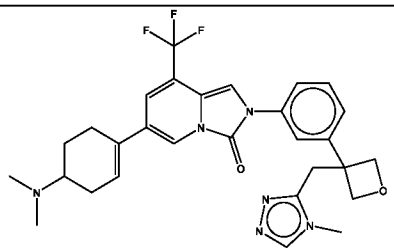
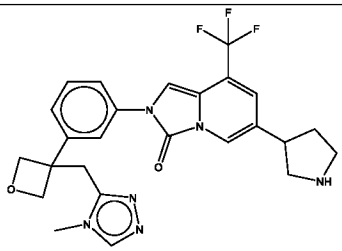
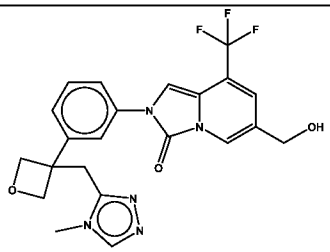
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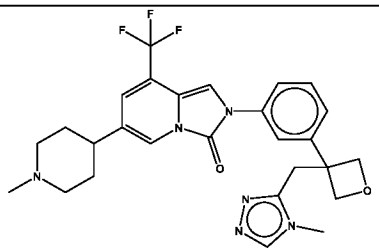
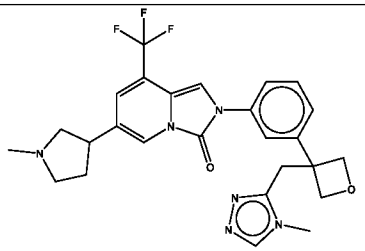
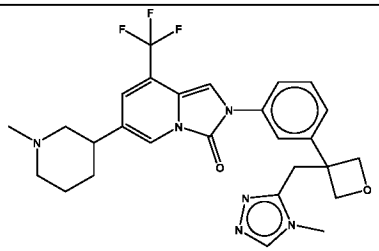
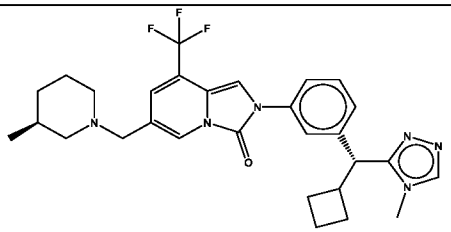
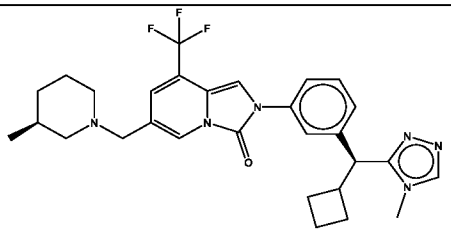
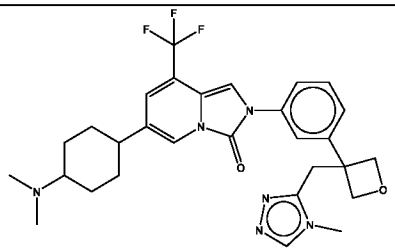
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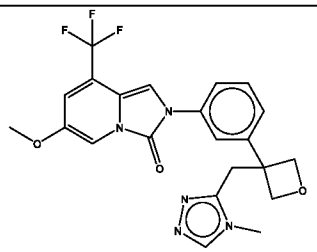
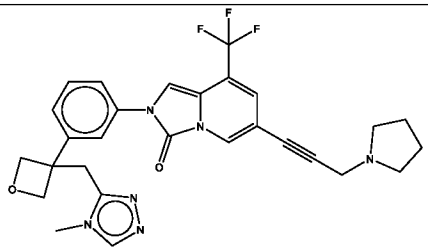
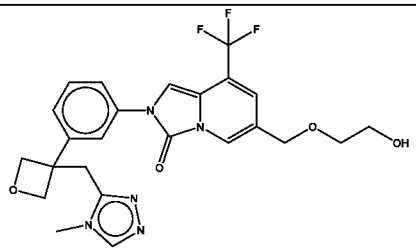
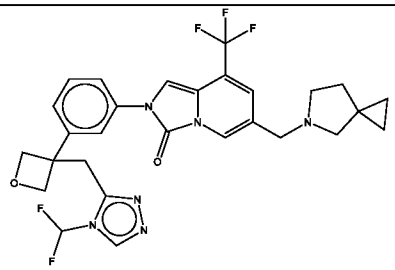
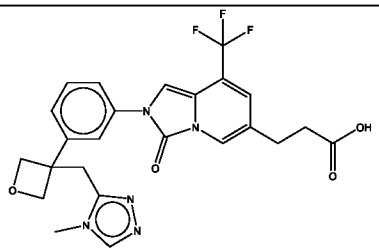
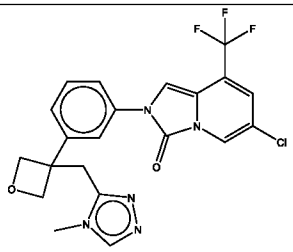
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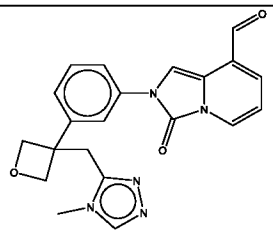
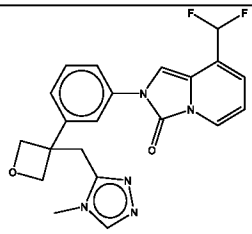
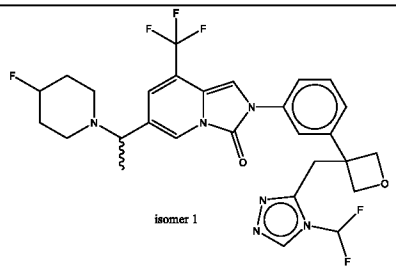
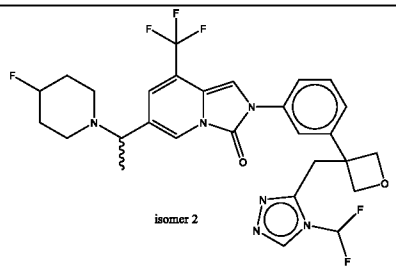
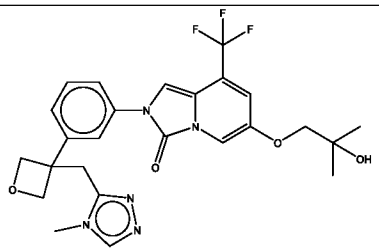
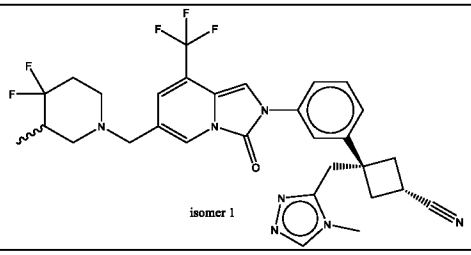
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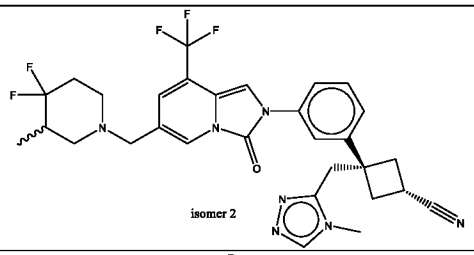
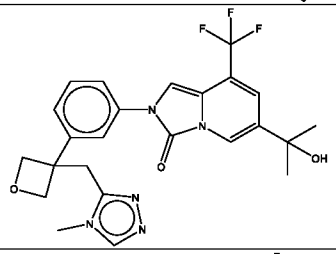
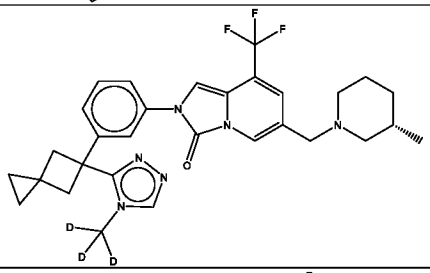
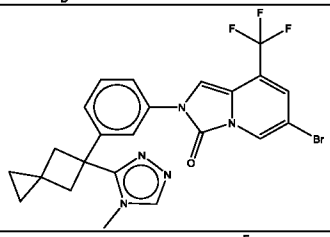
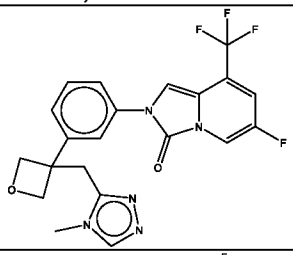
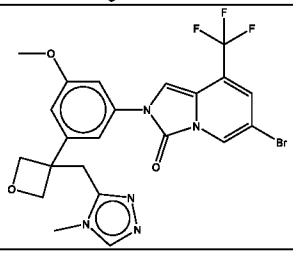
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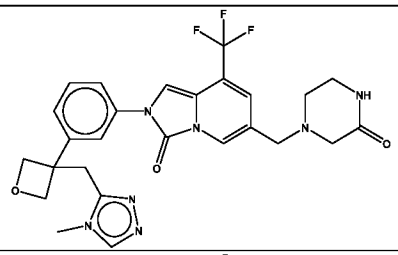
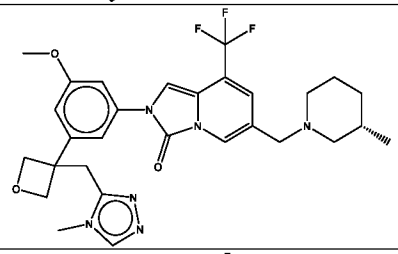
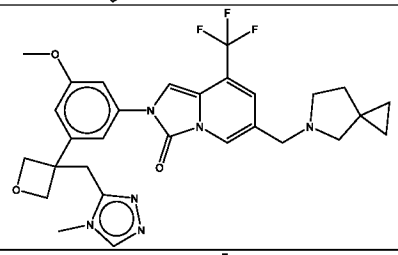
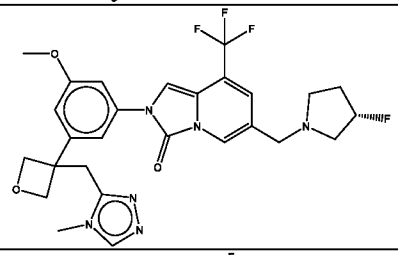
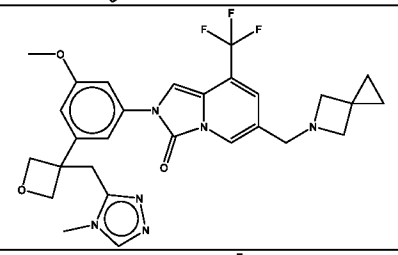
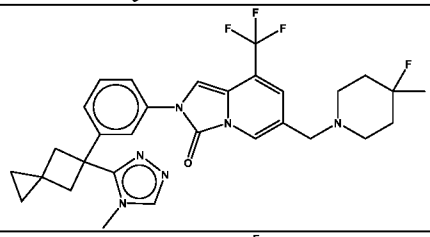
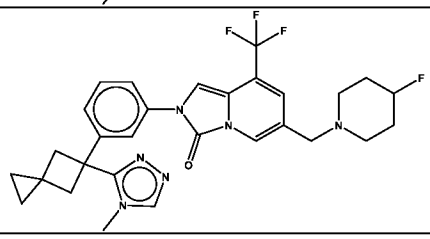
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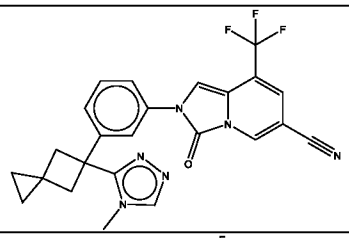
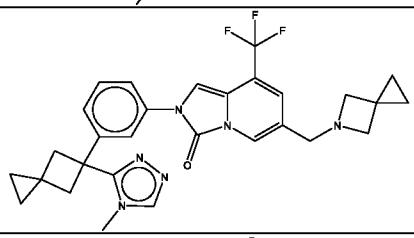
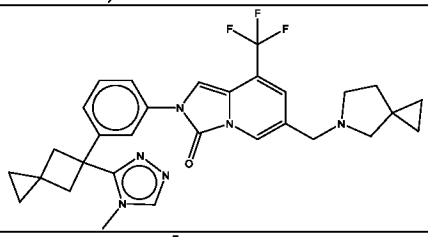
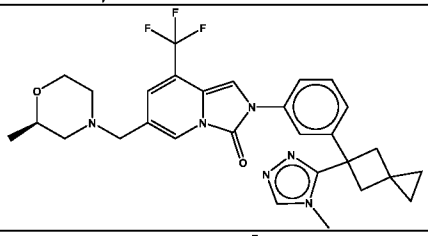
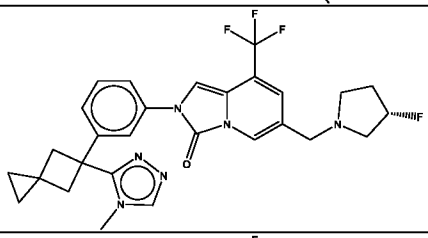
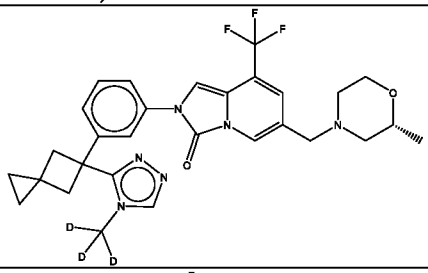
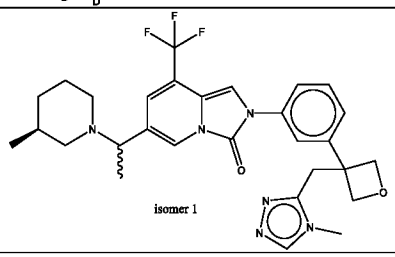
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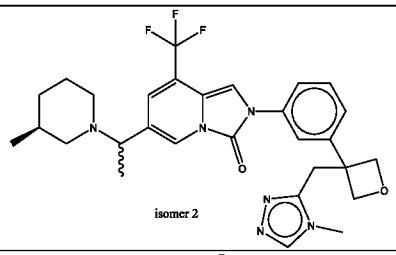
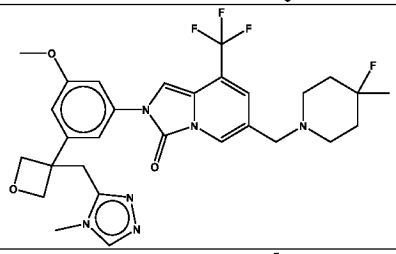
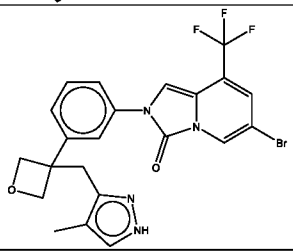
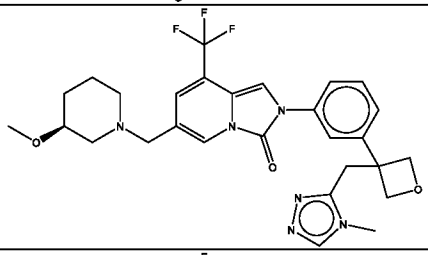
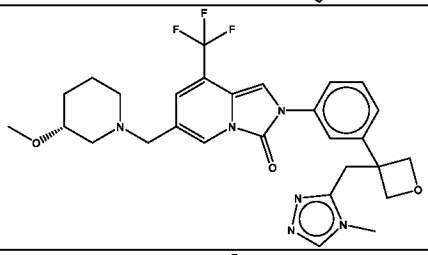
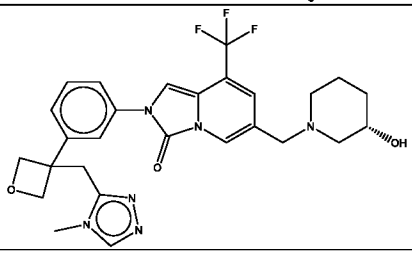
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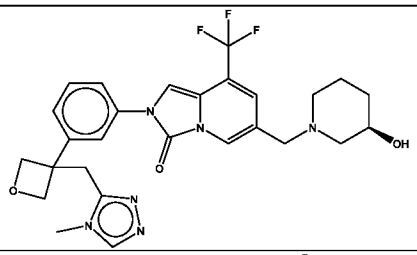
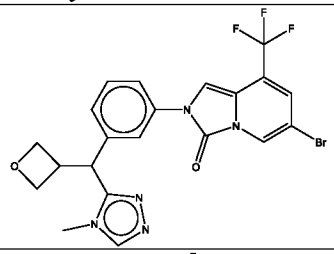
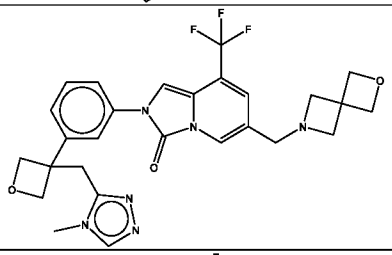
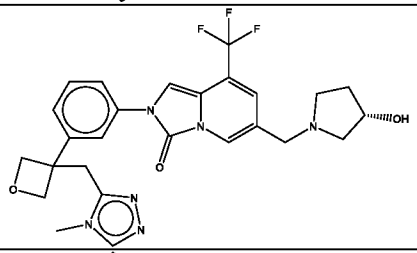
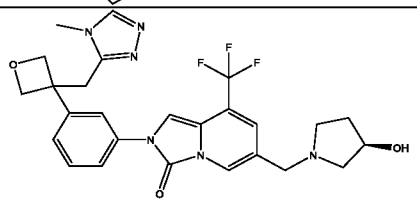
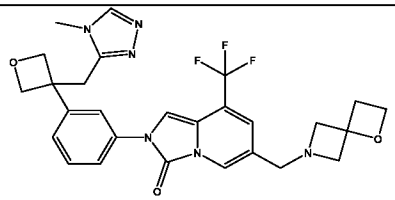
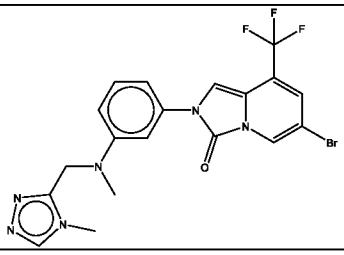
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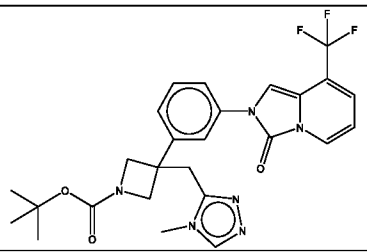
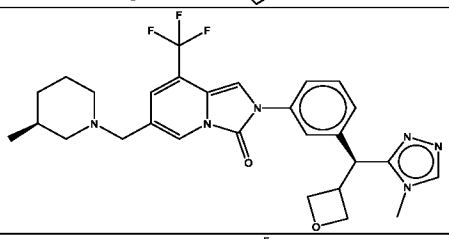
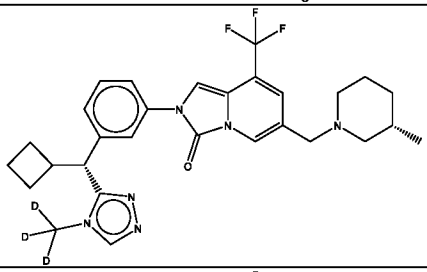
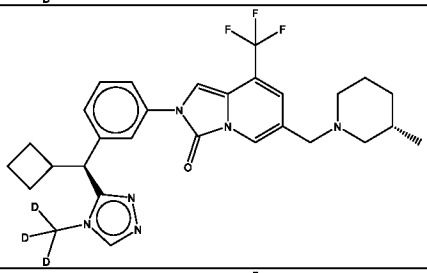
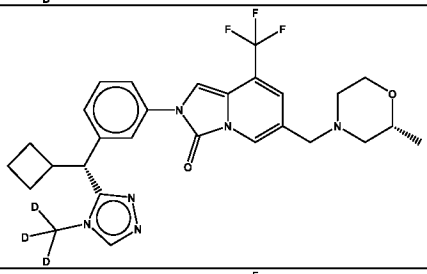
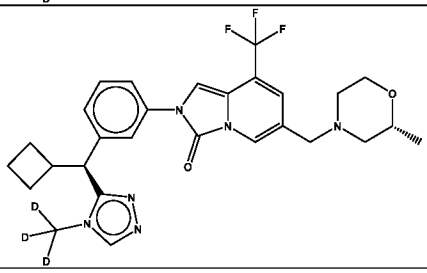
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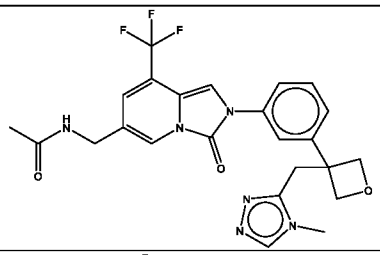
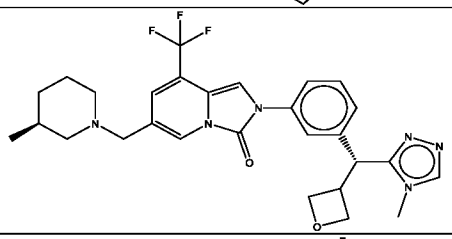
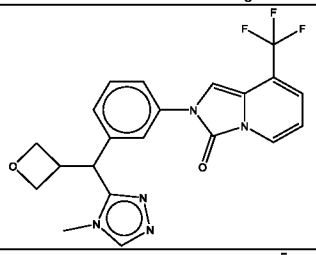
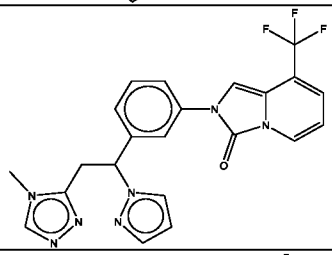
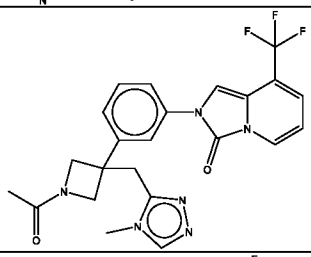
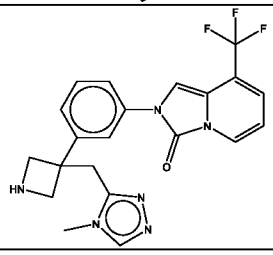
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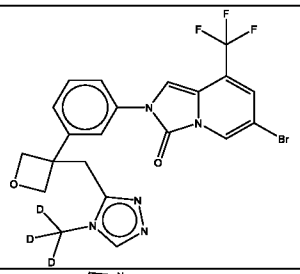
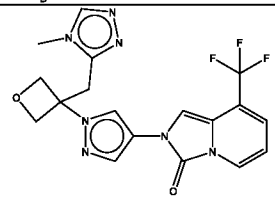
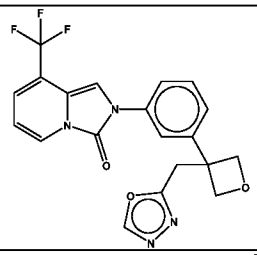
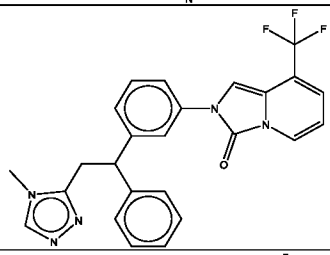
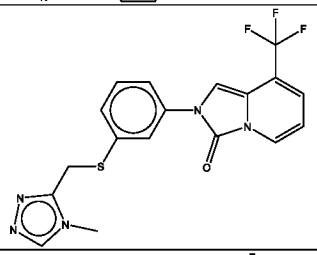
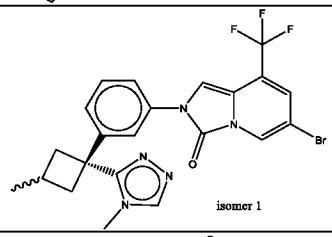
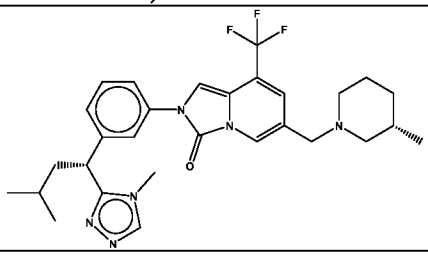
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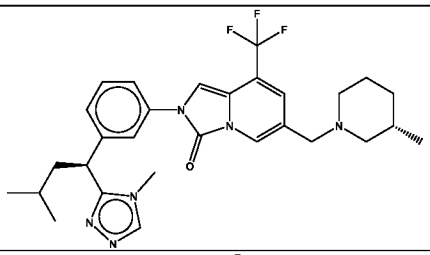
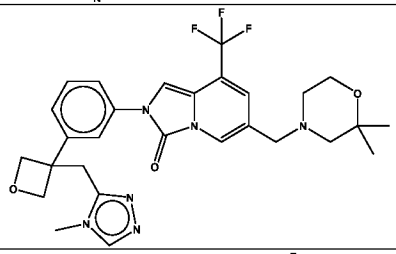
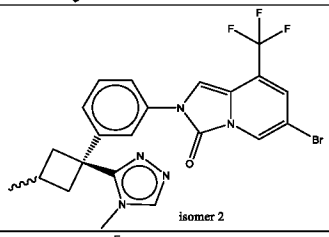
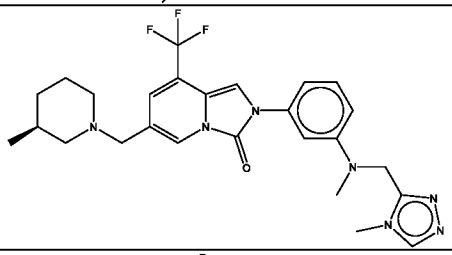
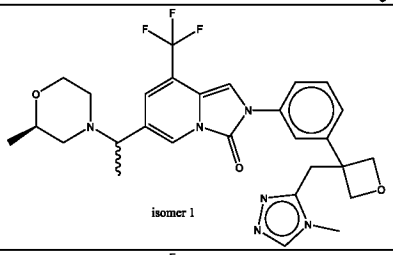
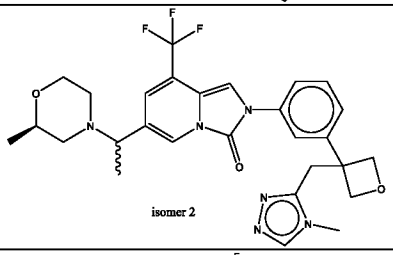
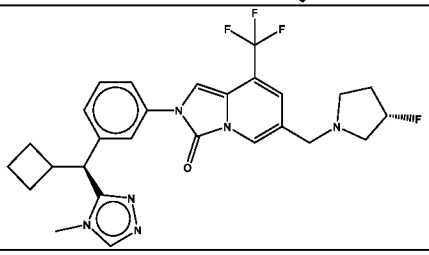
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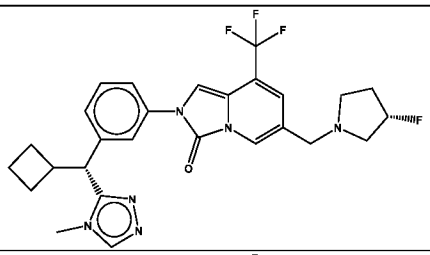
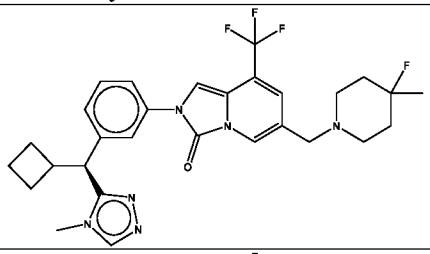
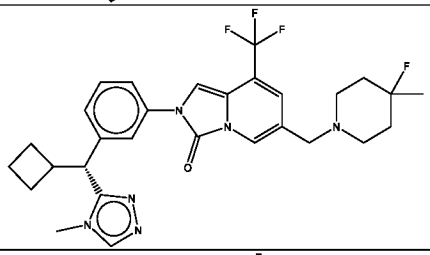
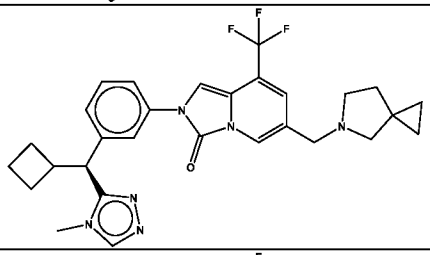
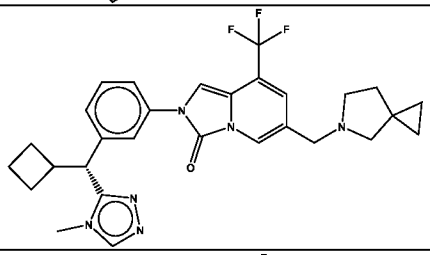
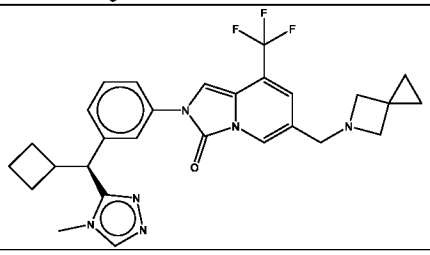
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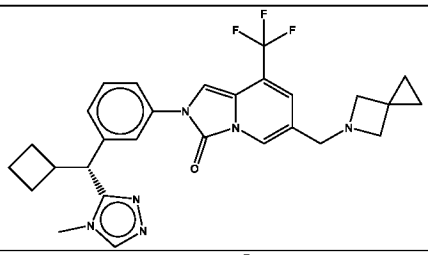
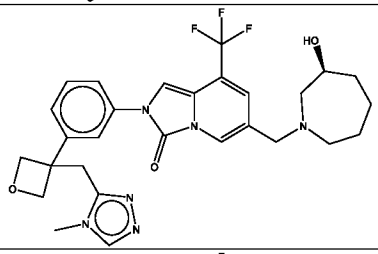
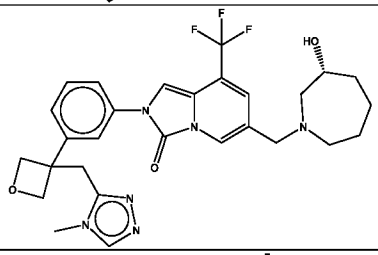
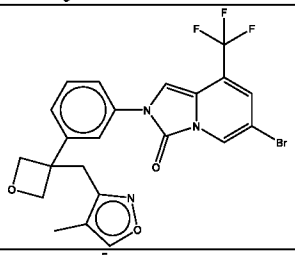
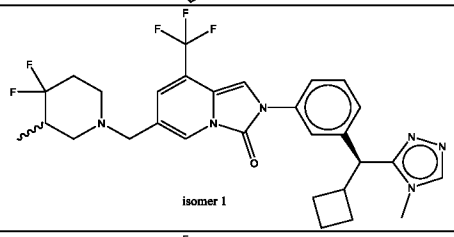
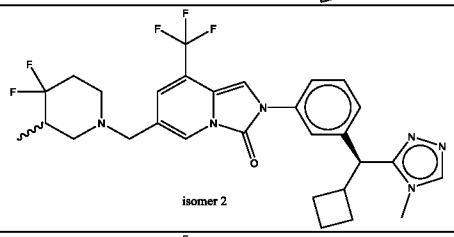
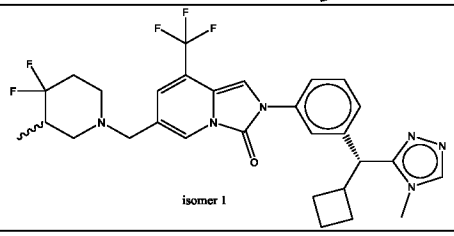
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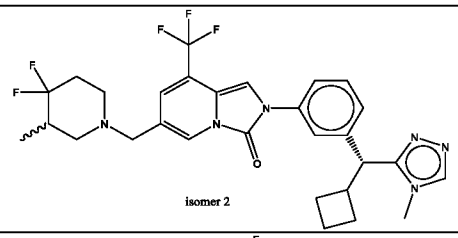
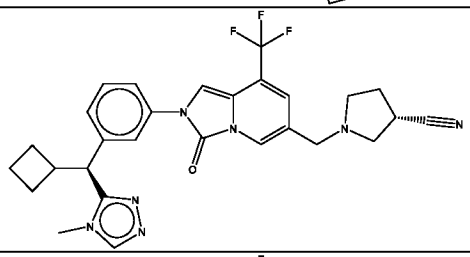
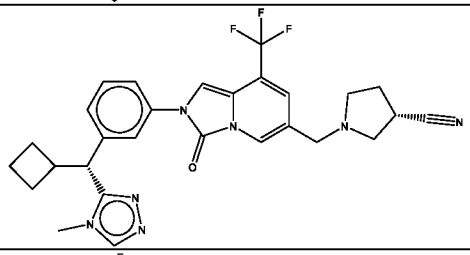
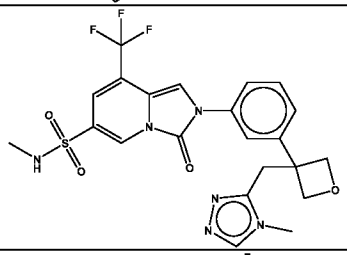
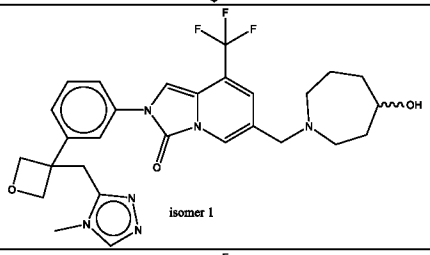
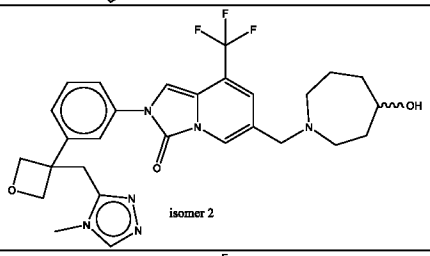
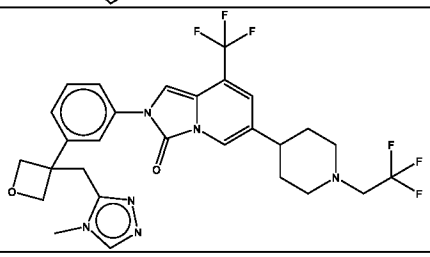
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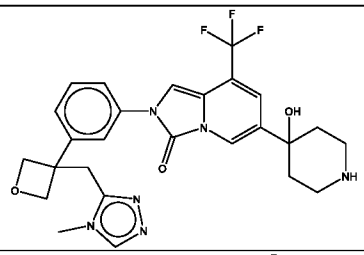
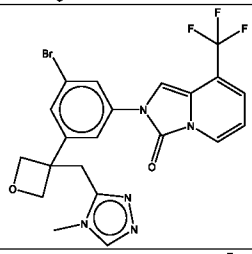
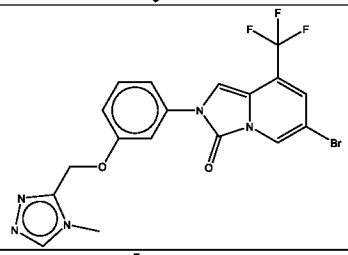
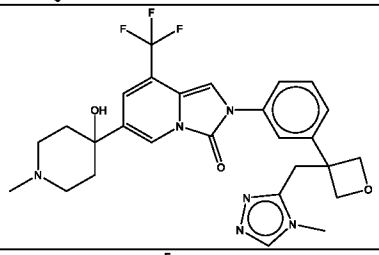
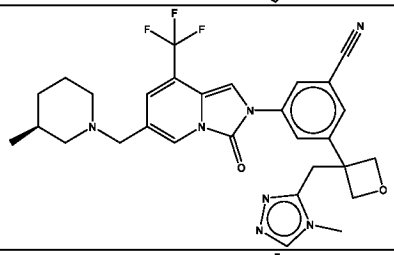
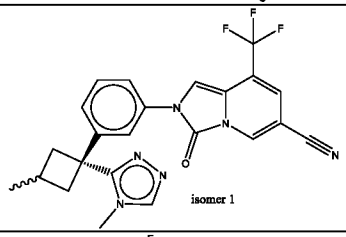
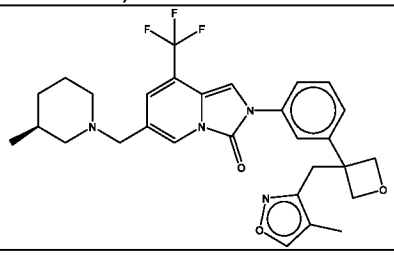
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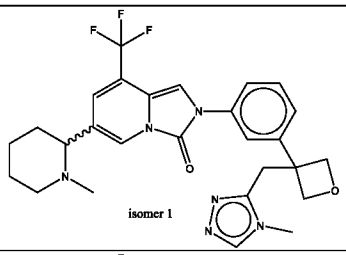
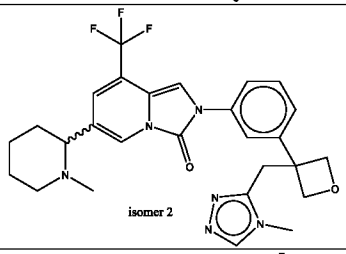
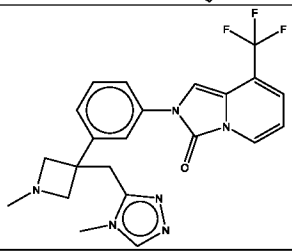
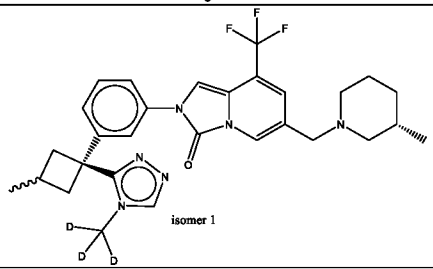
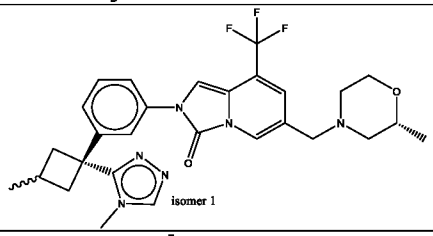
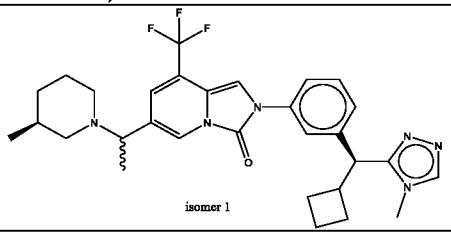
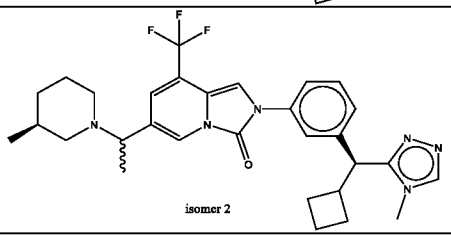
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154	 isomer 2
155	
156	 isomer 1
157	 isomer 2
158	

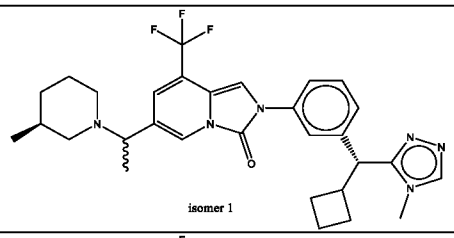
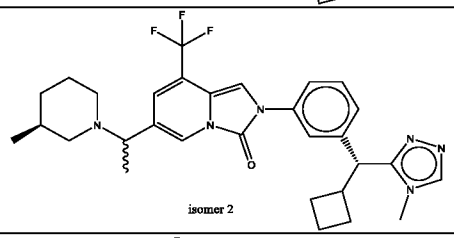
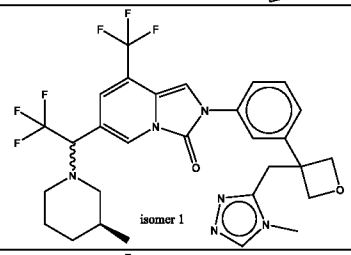
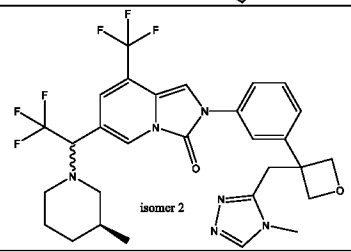
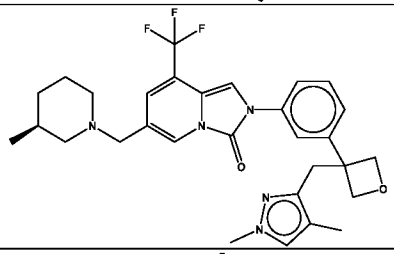
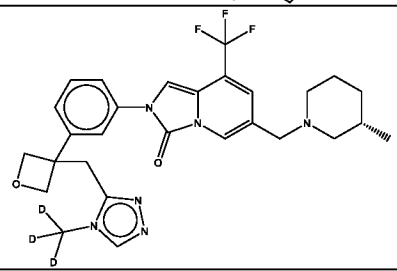
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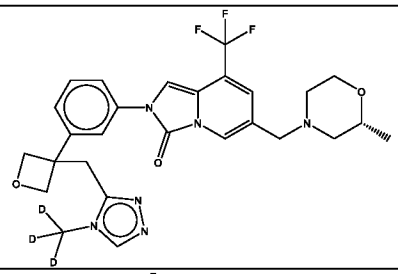
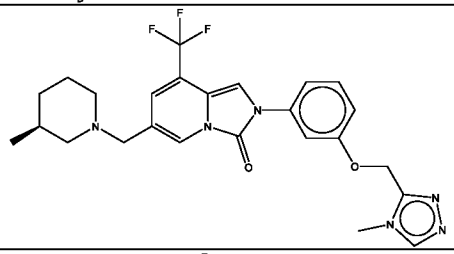
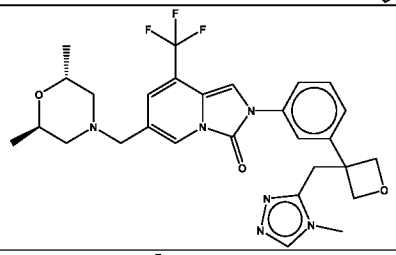
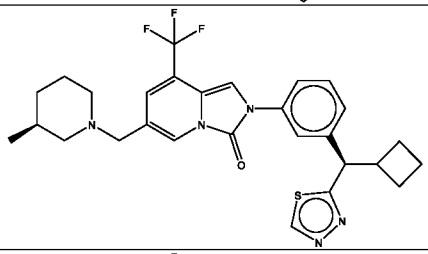
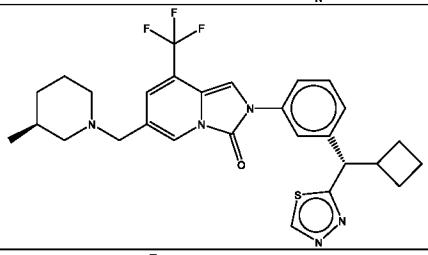
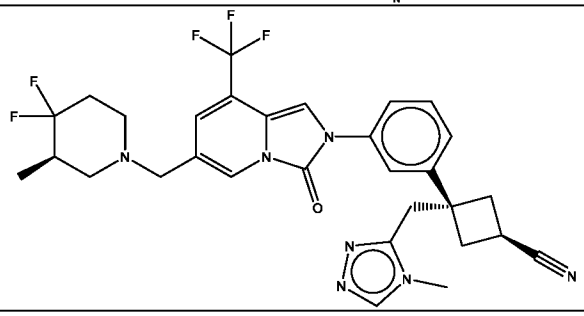
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171	 isomer 1

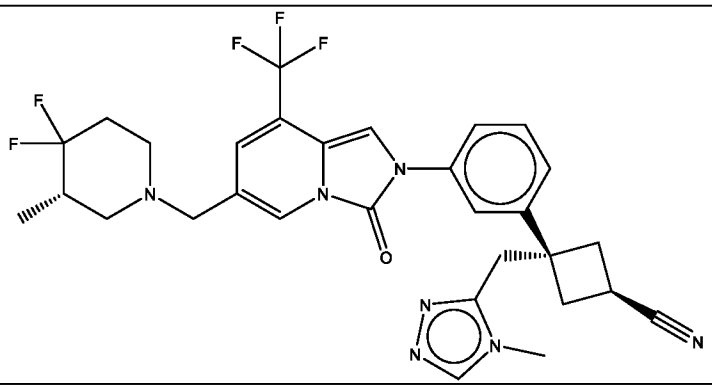
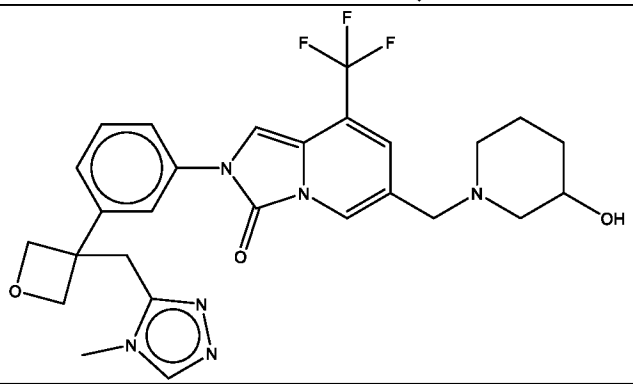
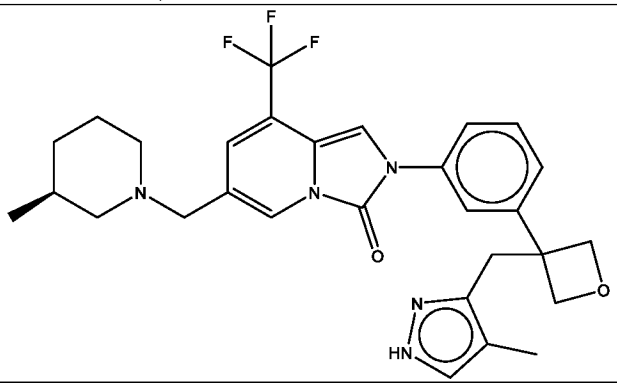
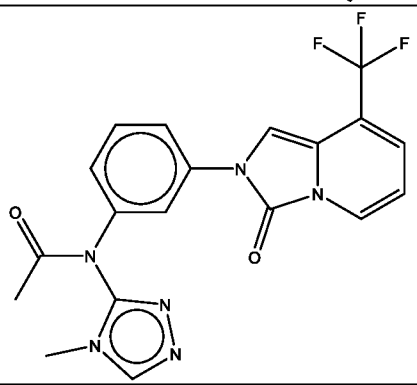
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177	 isomer 2
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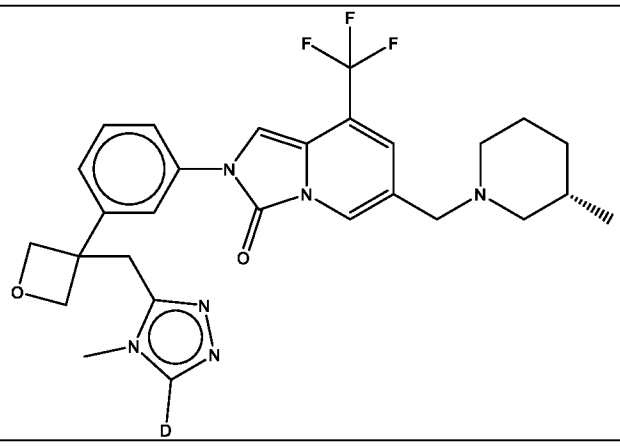
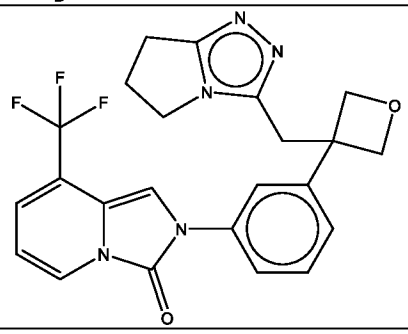
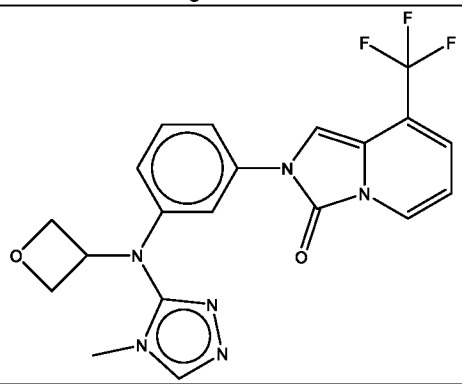
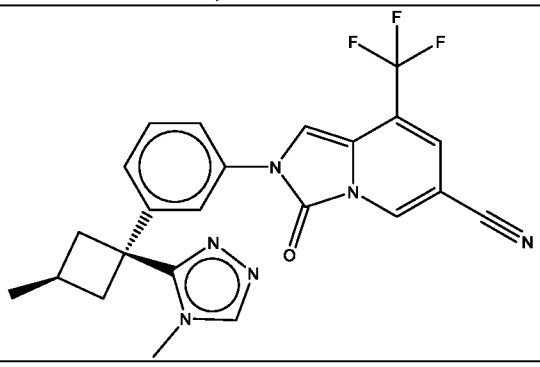
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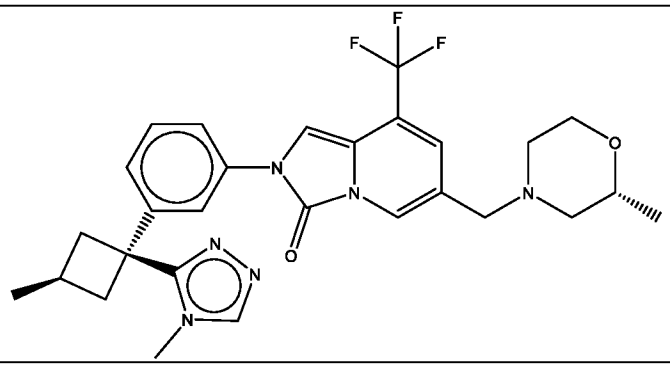
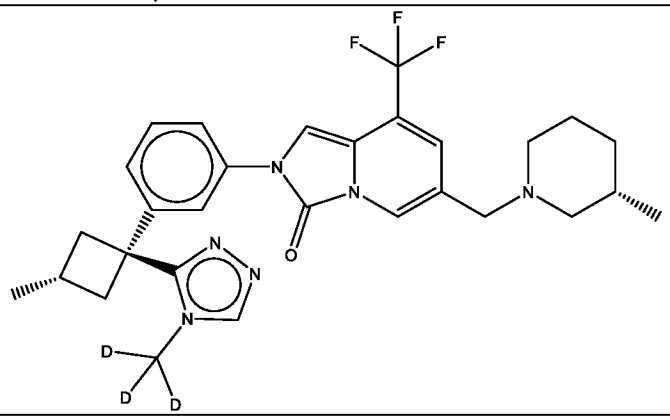
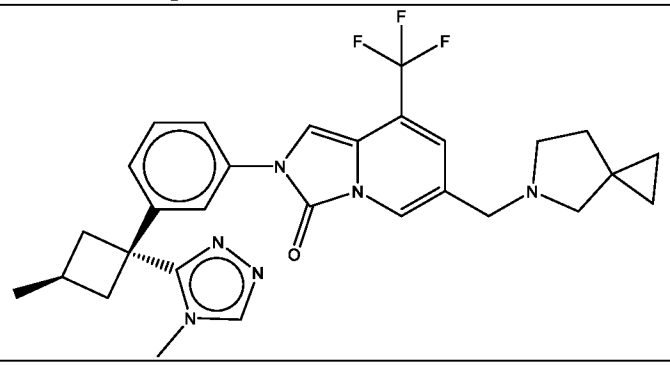
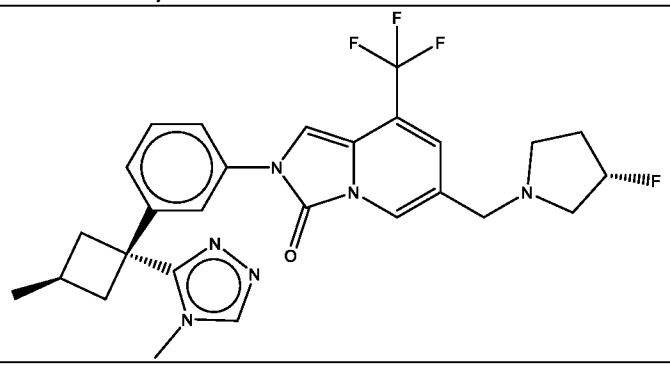
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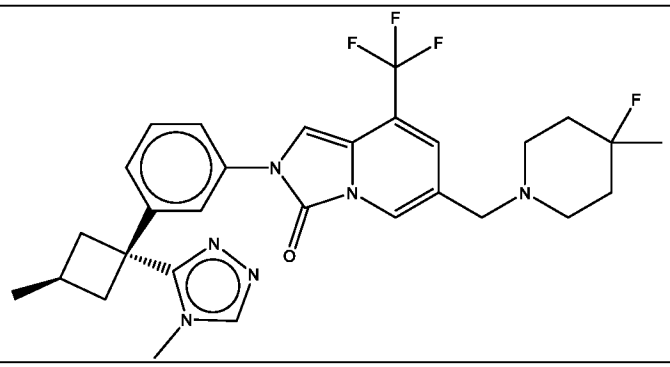
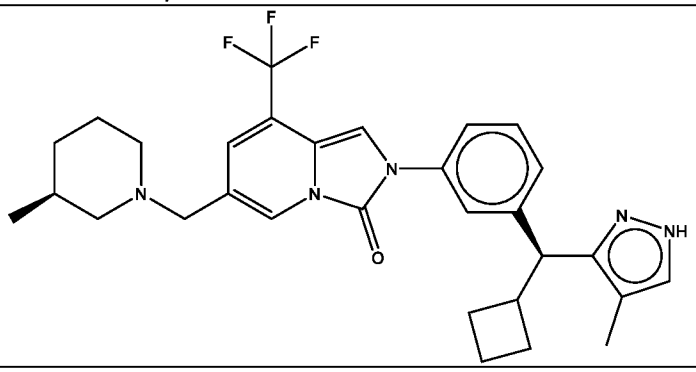
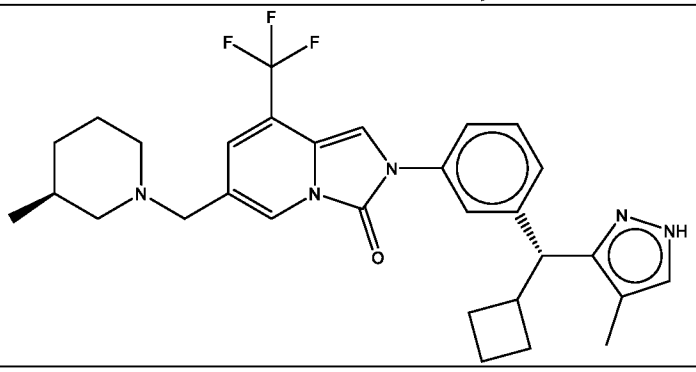
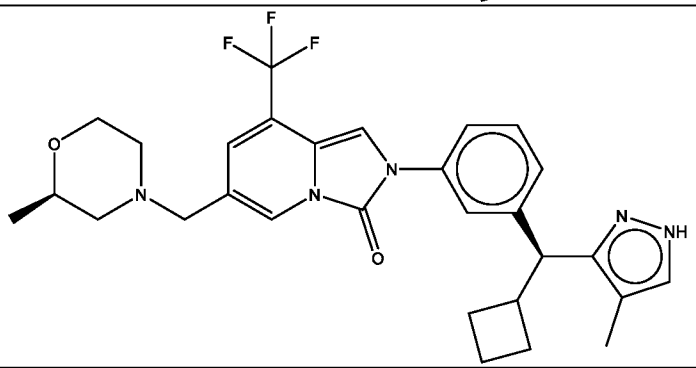
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194	 isomer 2
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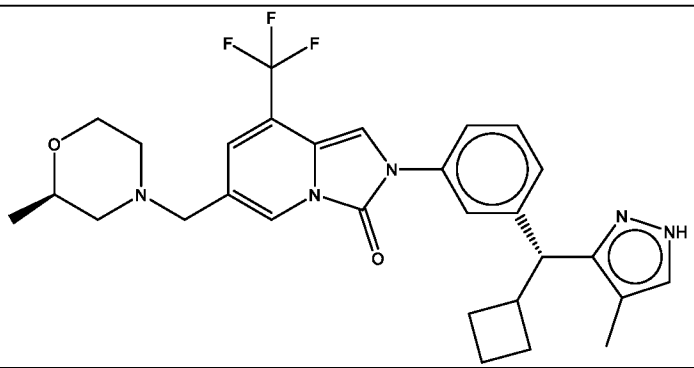
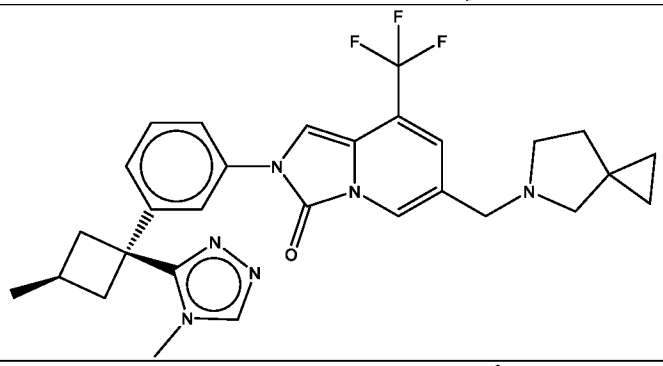
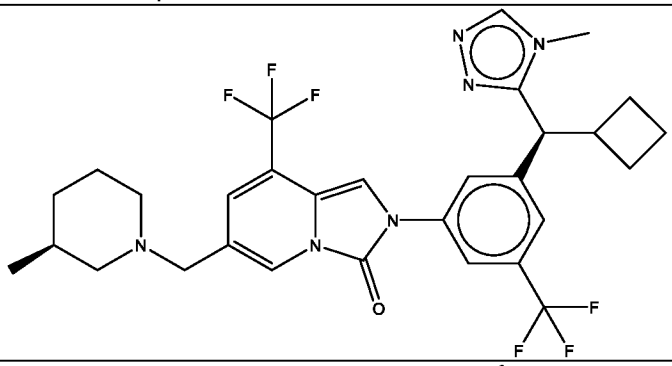
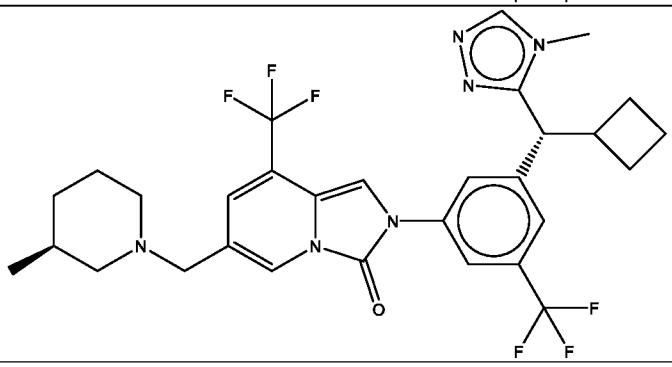
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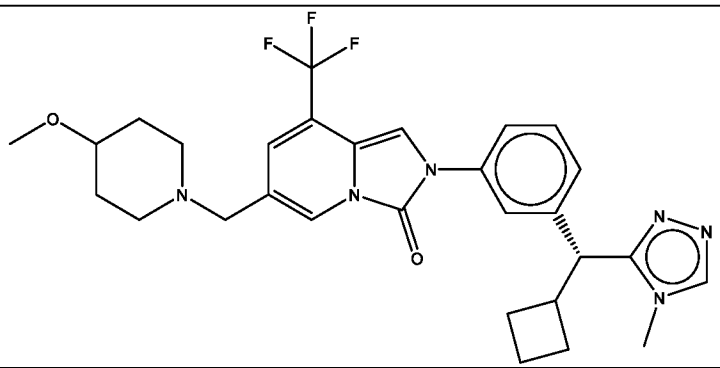
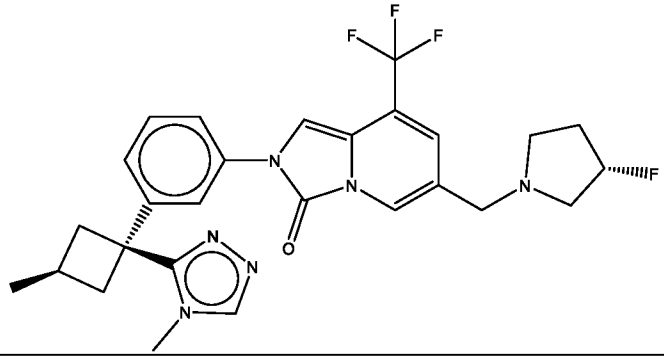
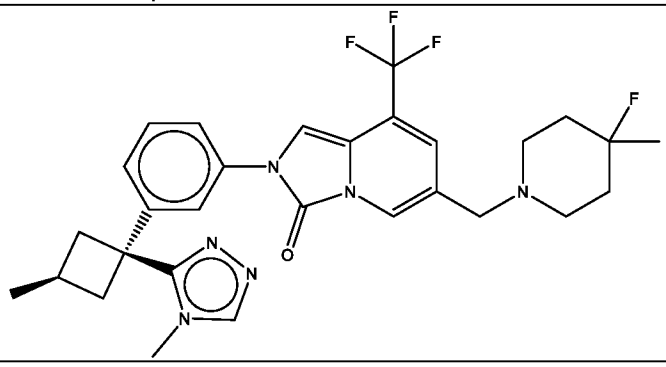
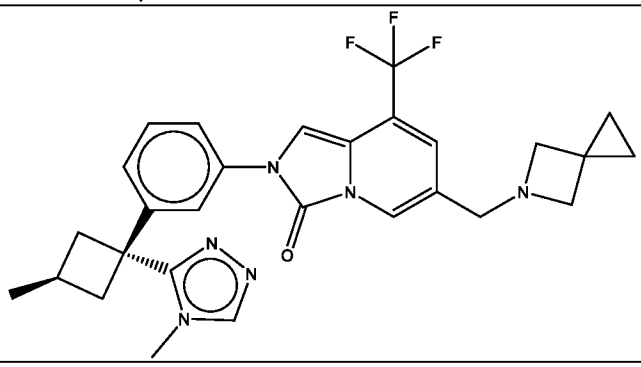
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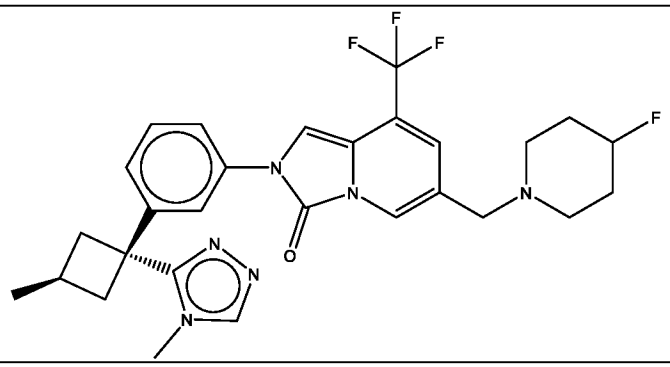
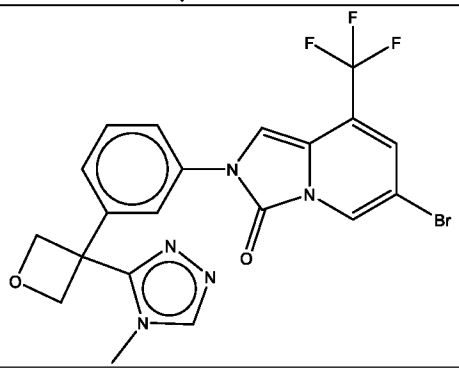
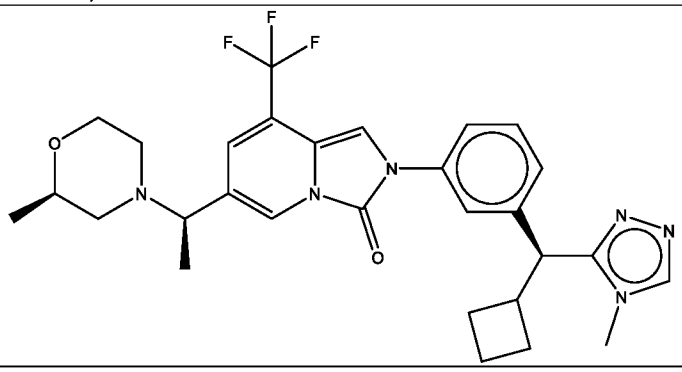
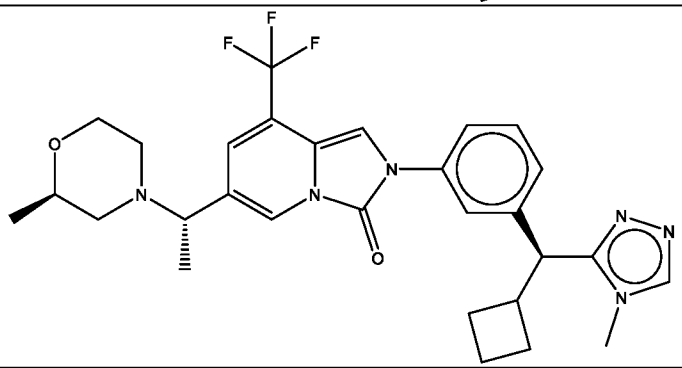
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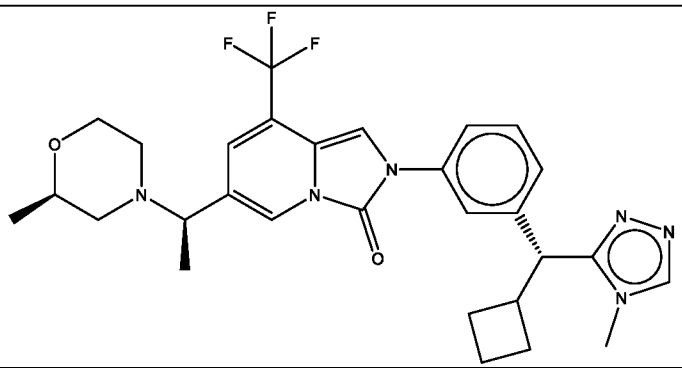
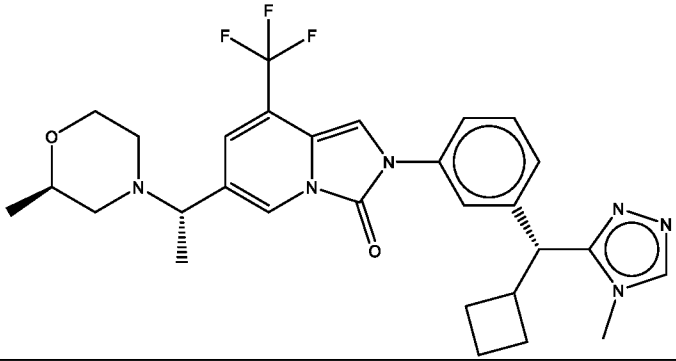
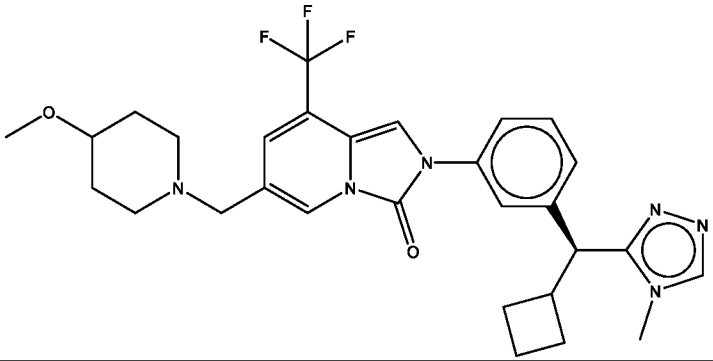
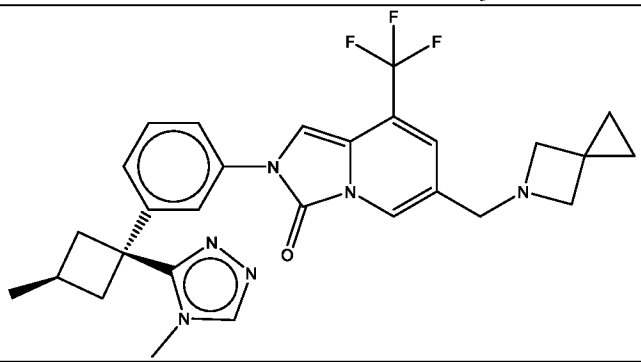
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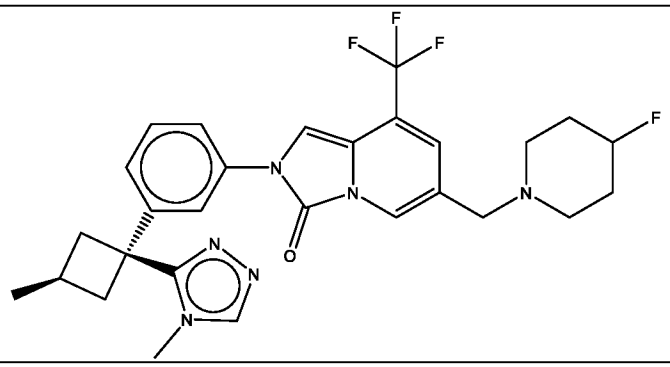
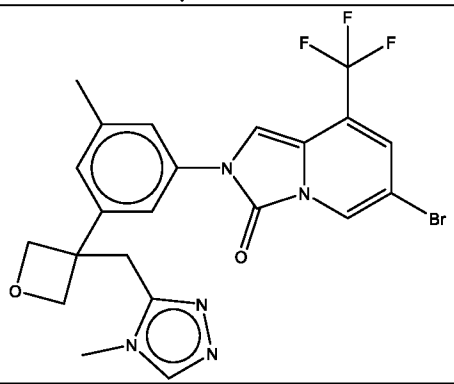
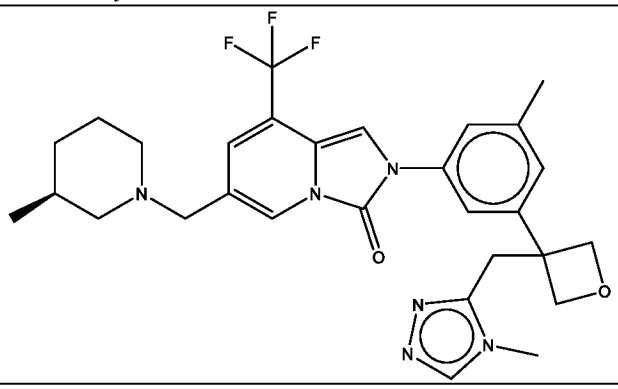
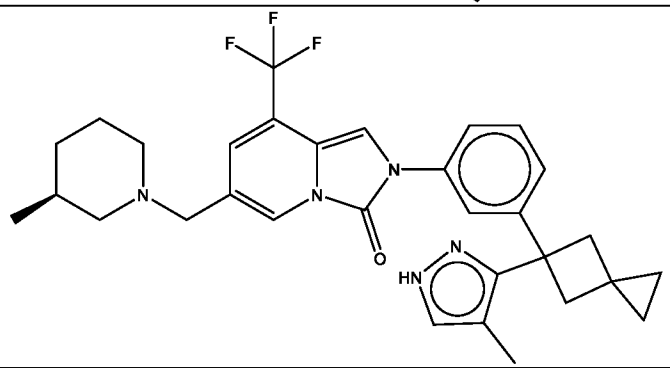
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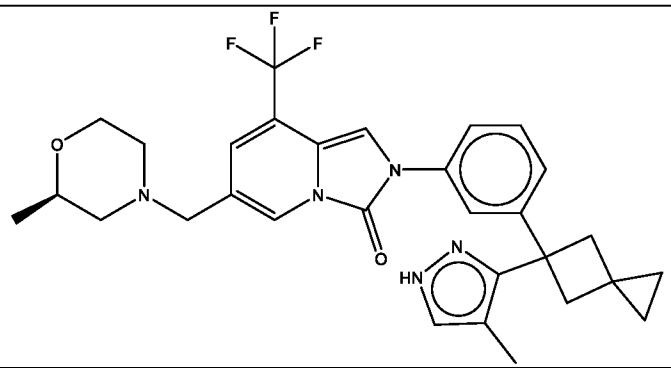
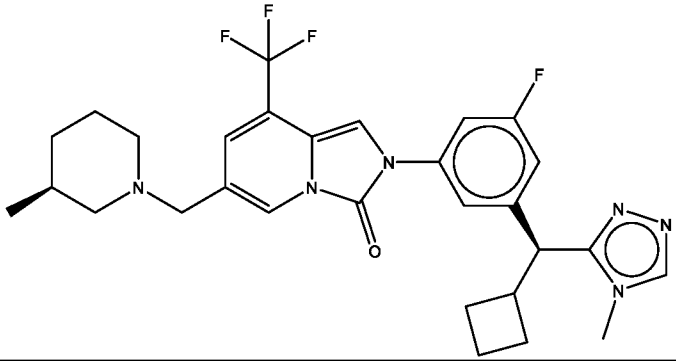
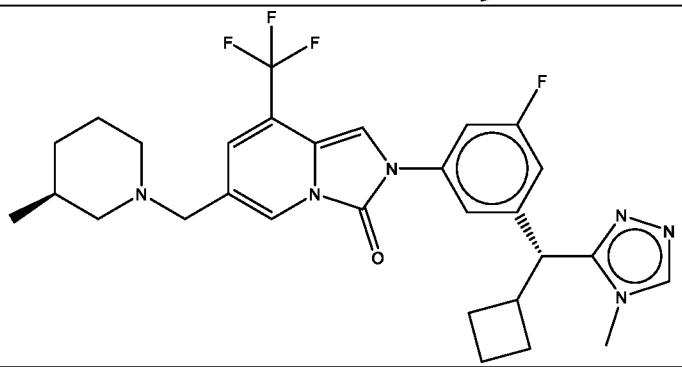
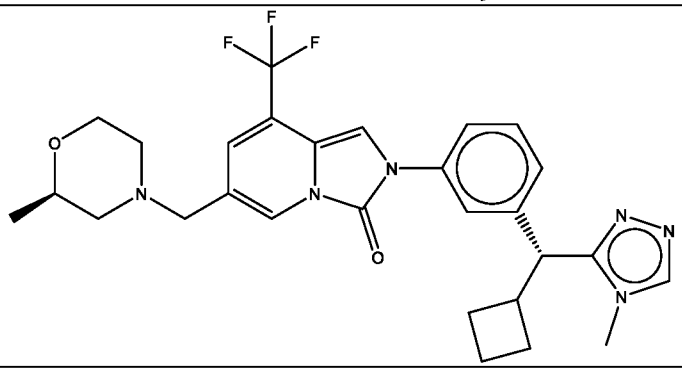
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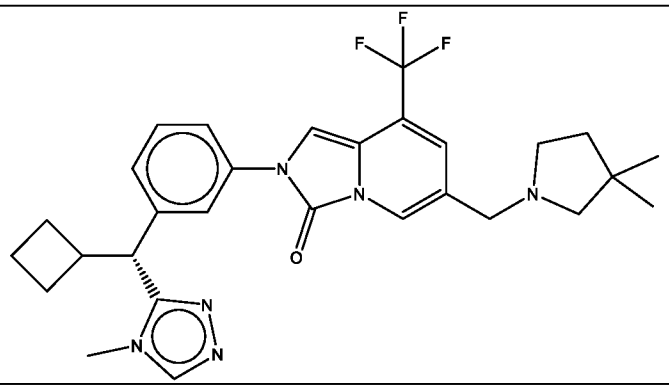
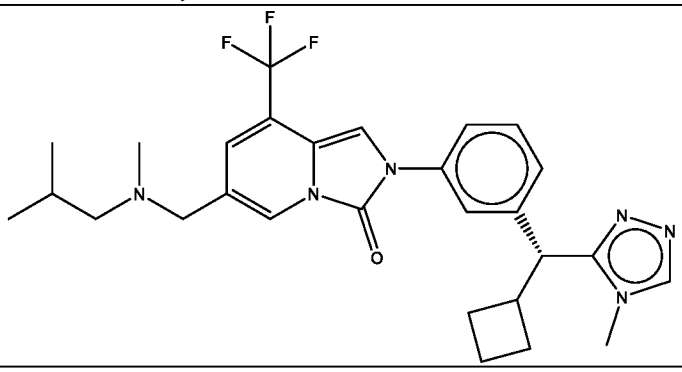
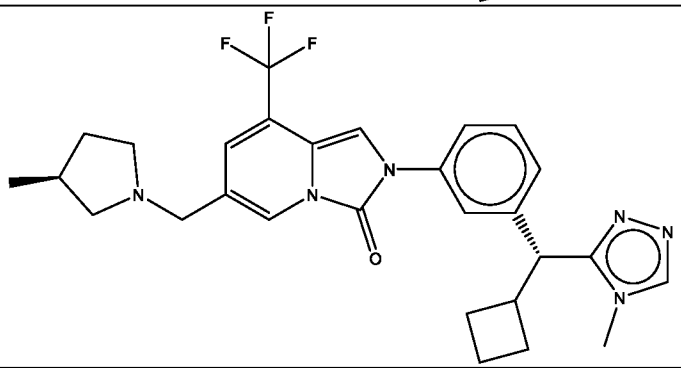
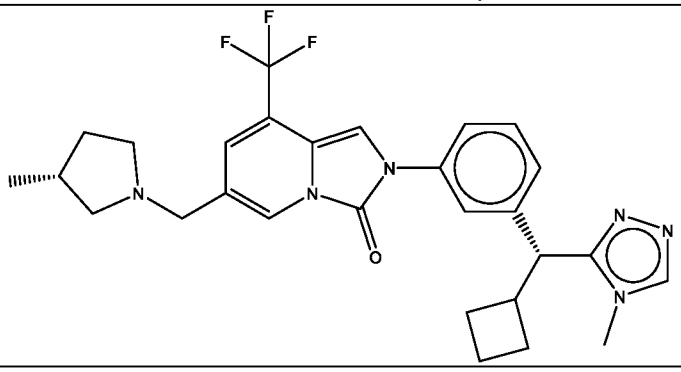
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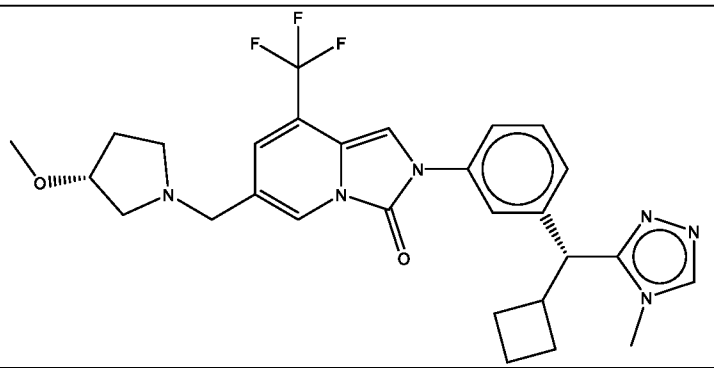
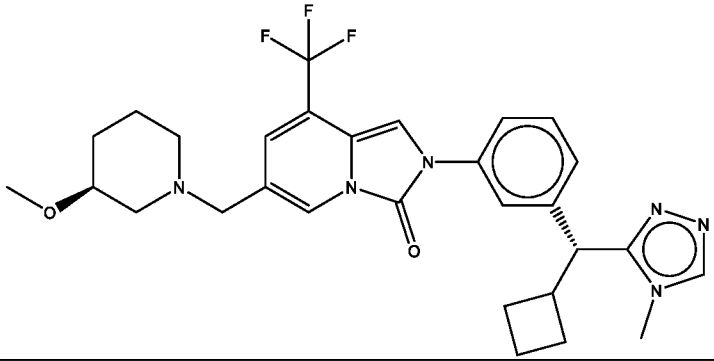
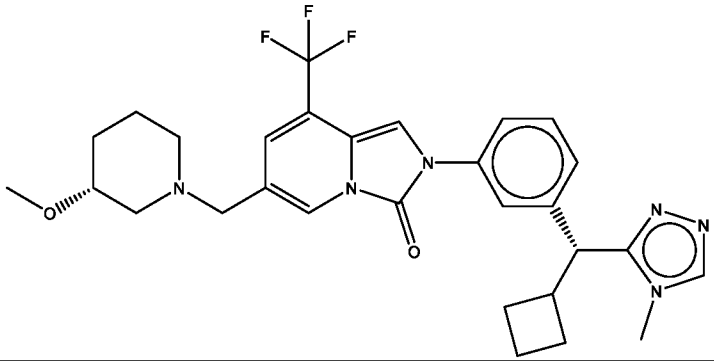
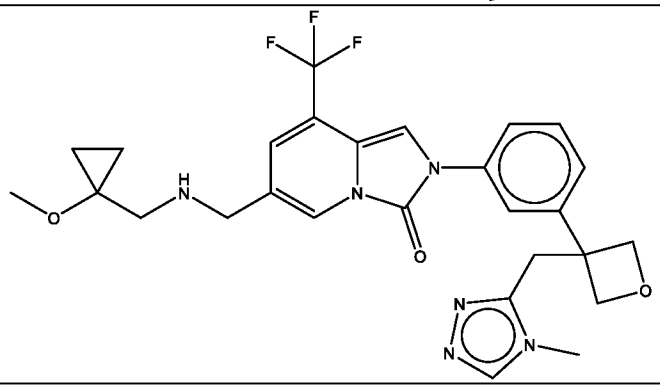
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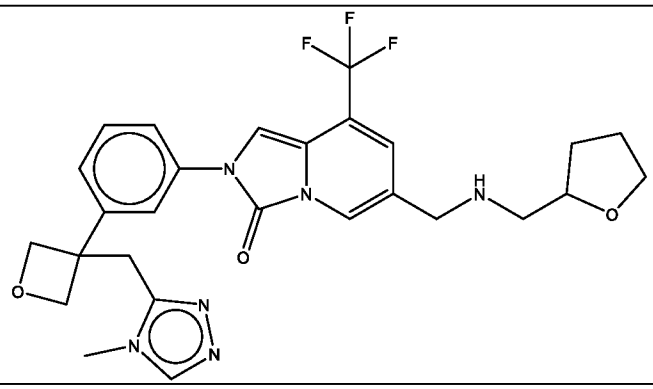
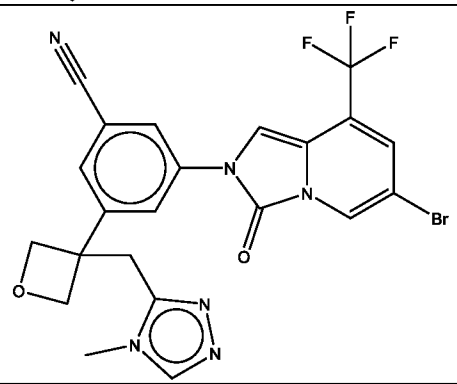
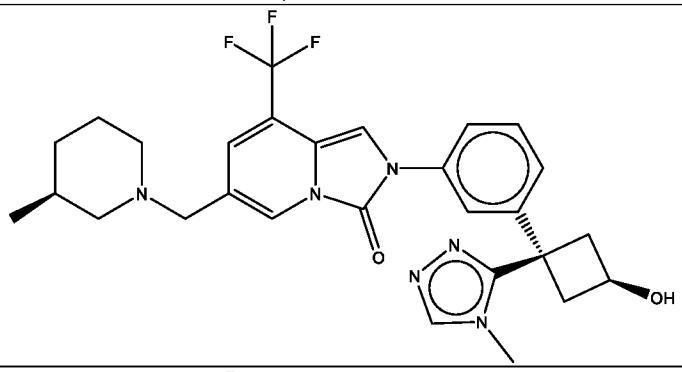
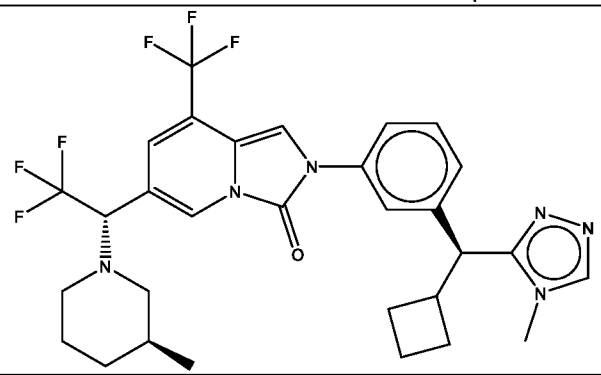
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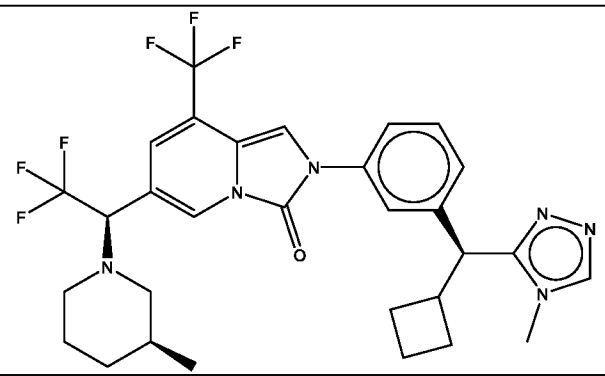
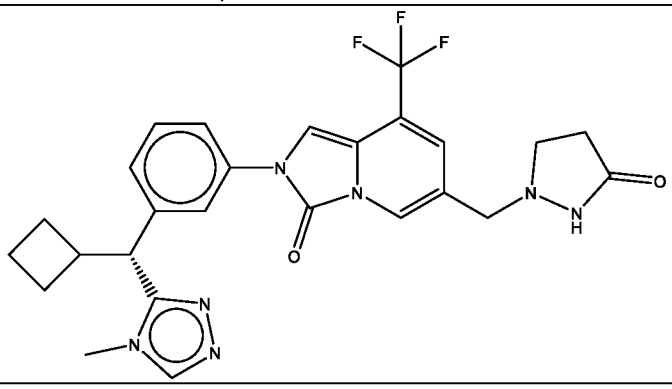
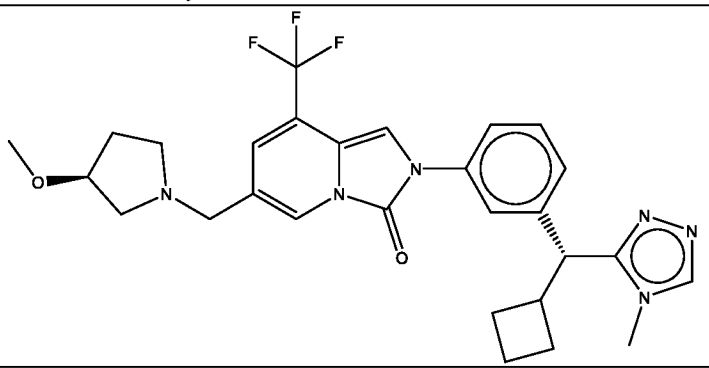
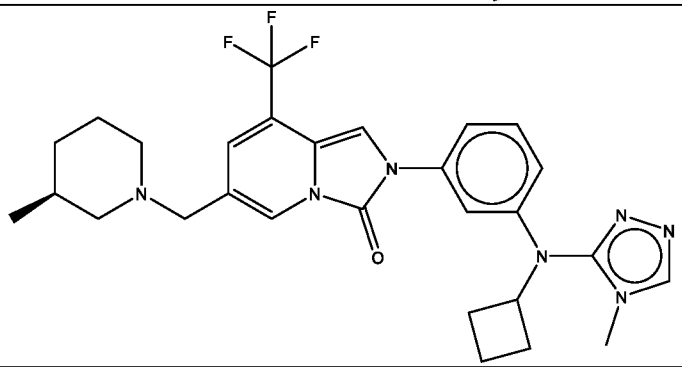
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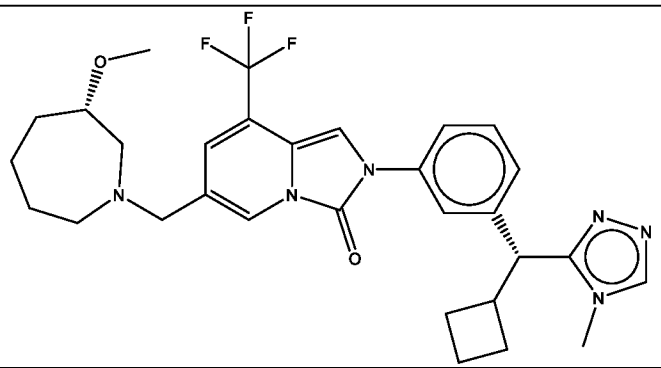
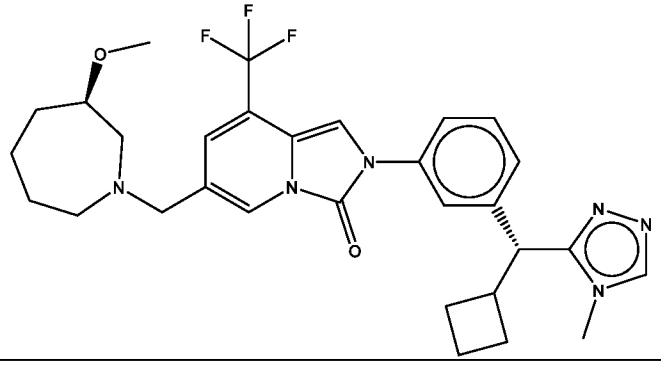
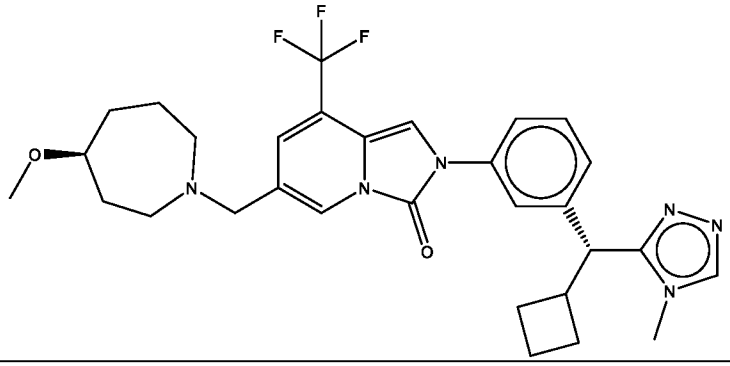
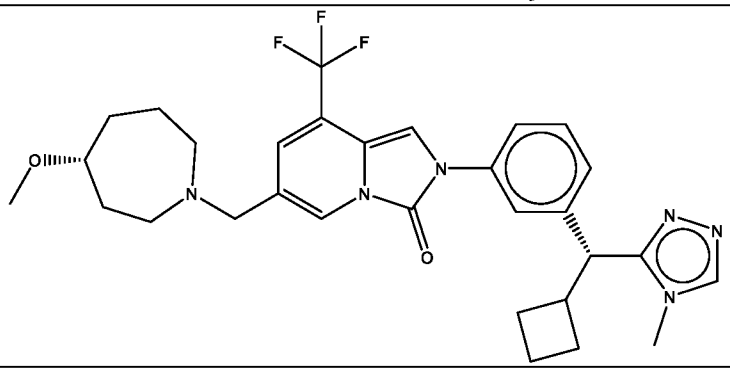
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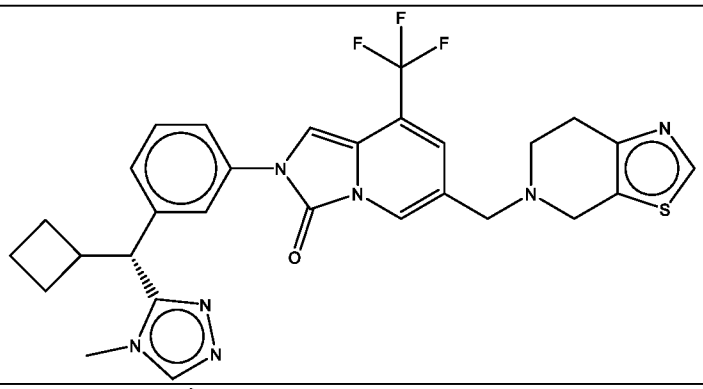
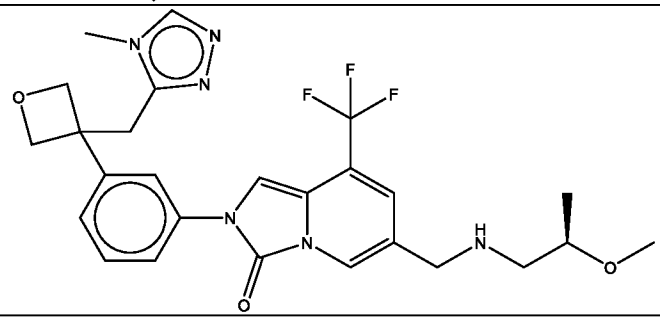
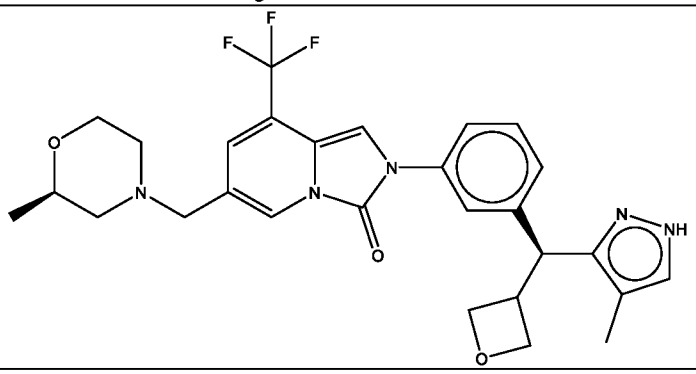
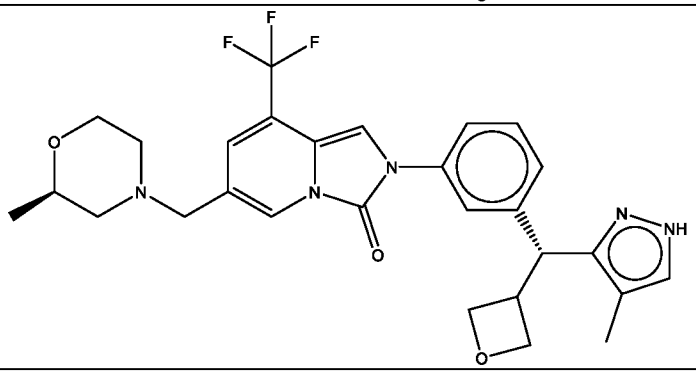
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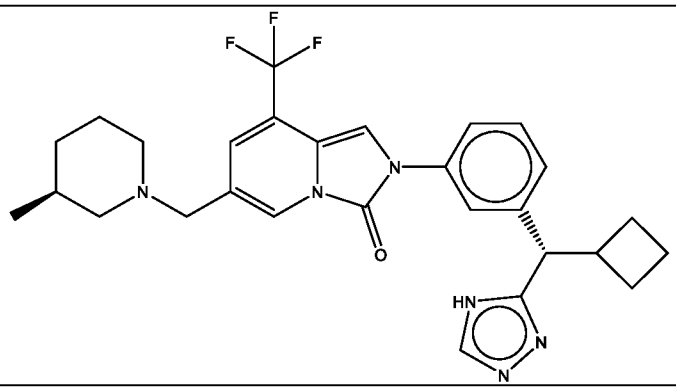
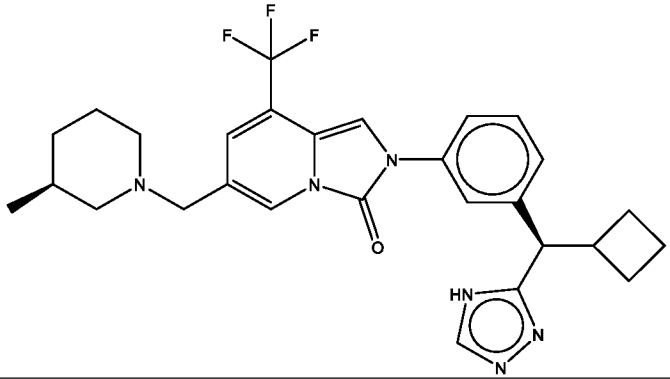
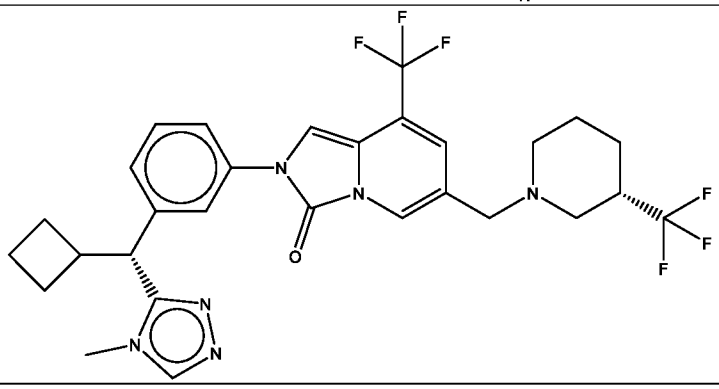
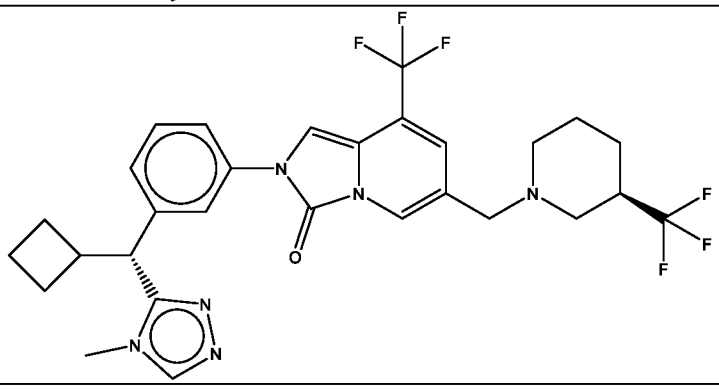
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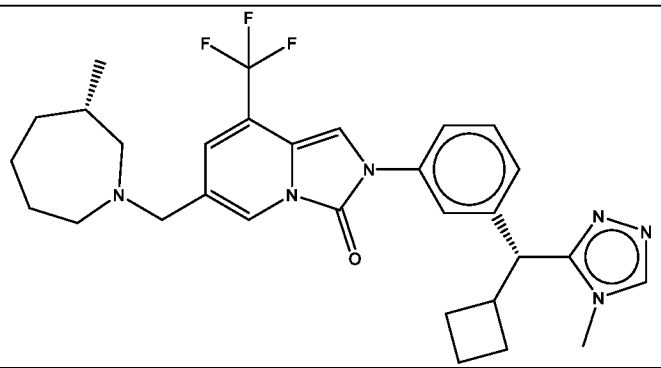
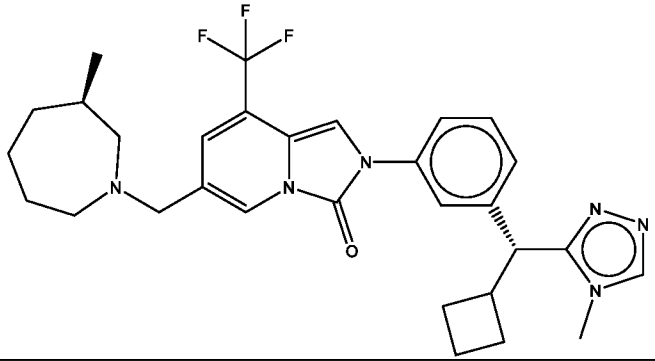
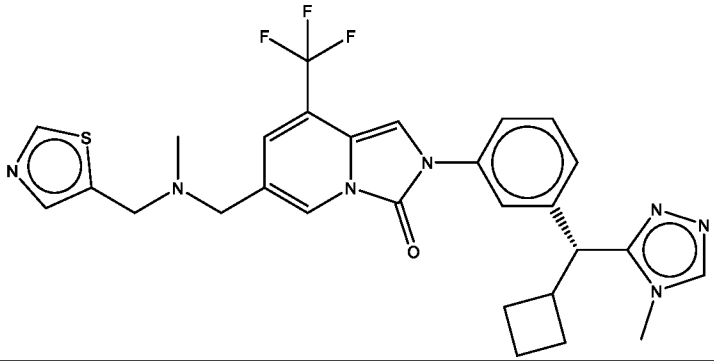
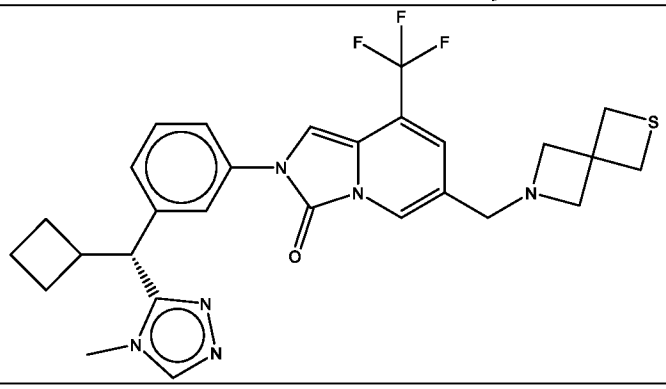
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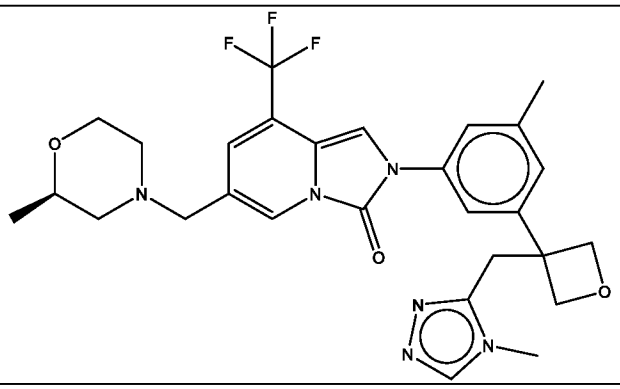
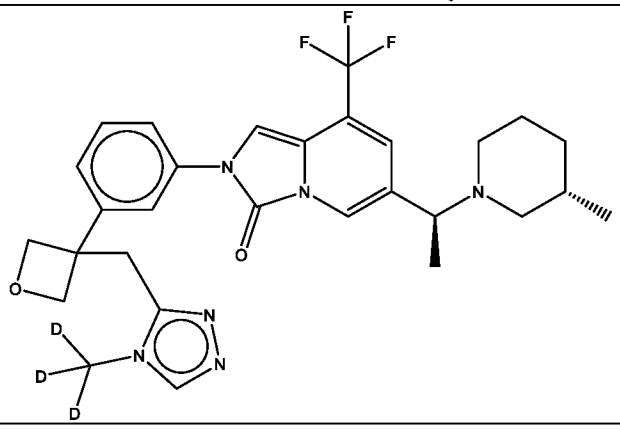
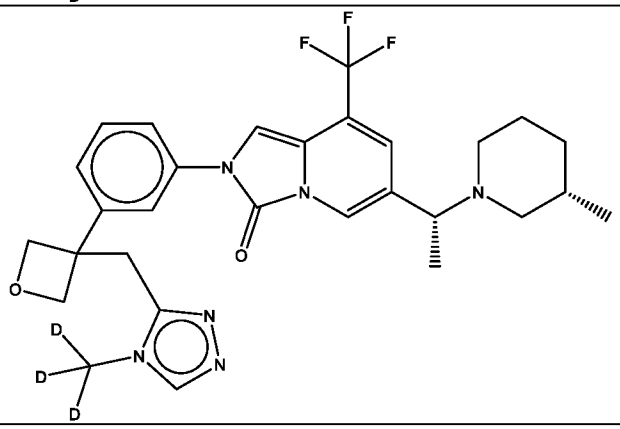
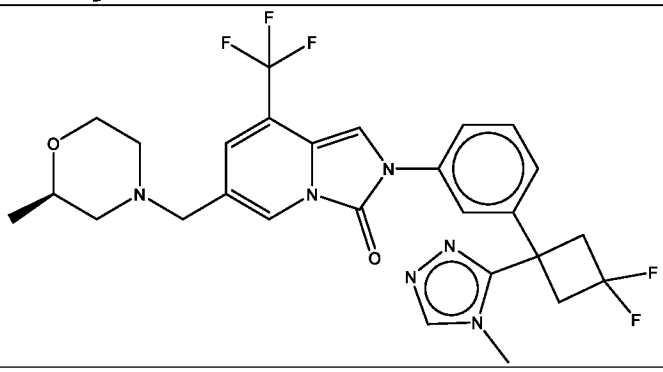
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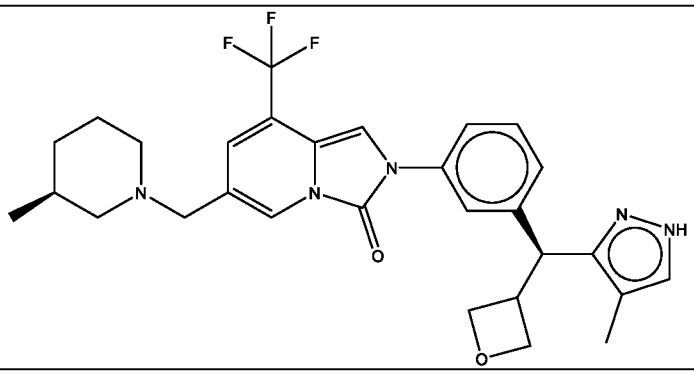
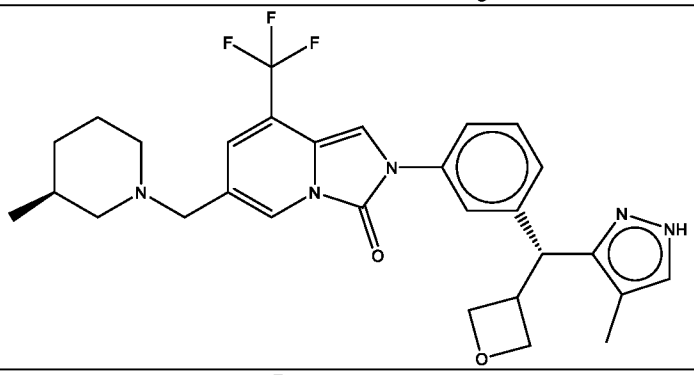
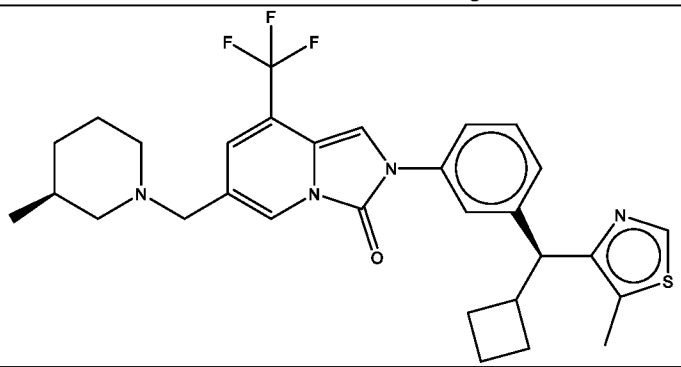
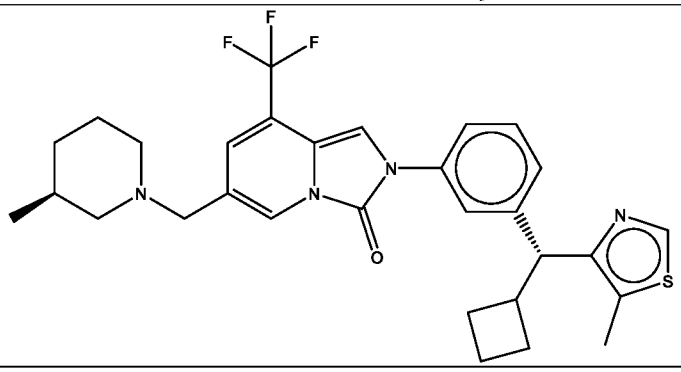
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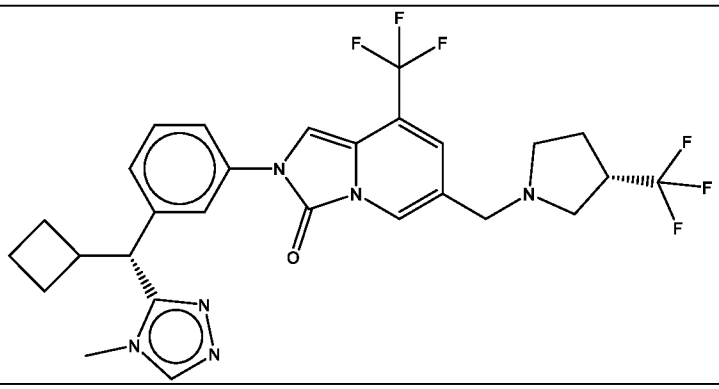
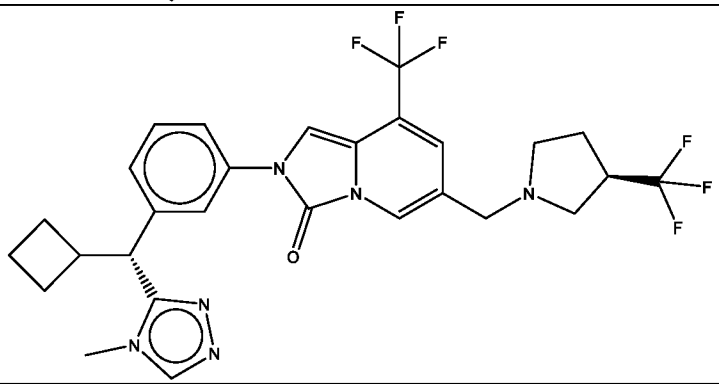
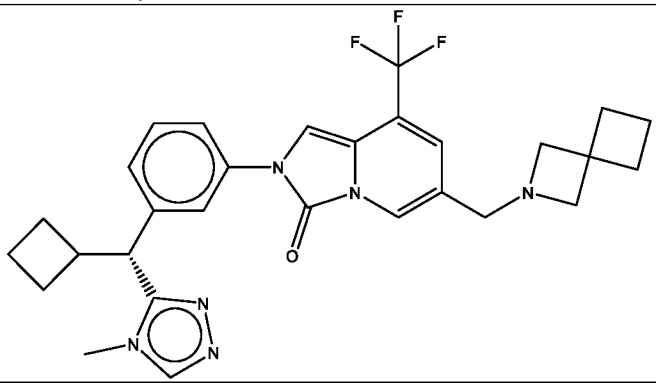
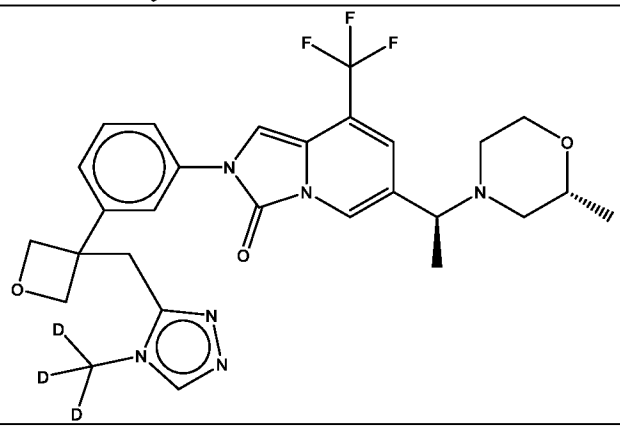
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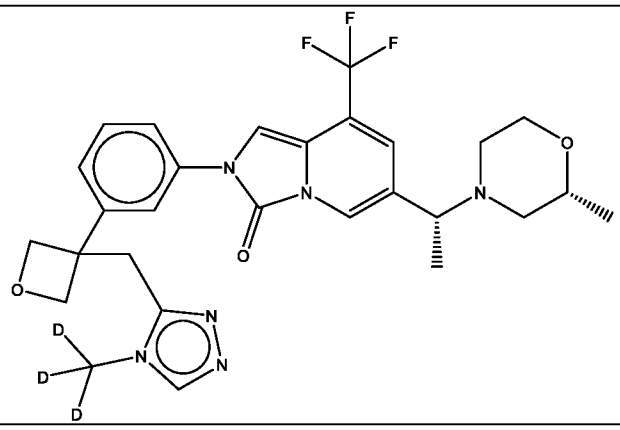
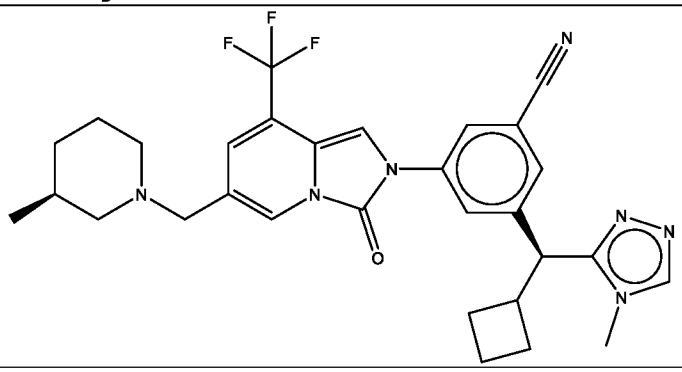
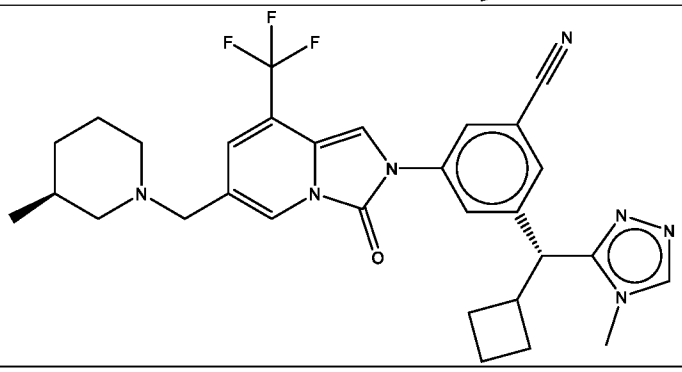
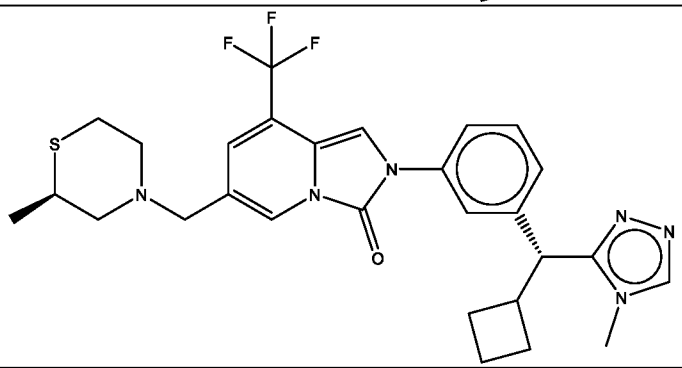
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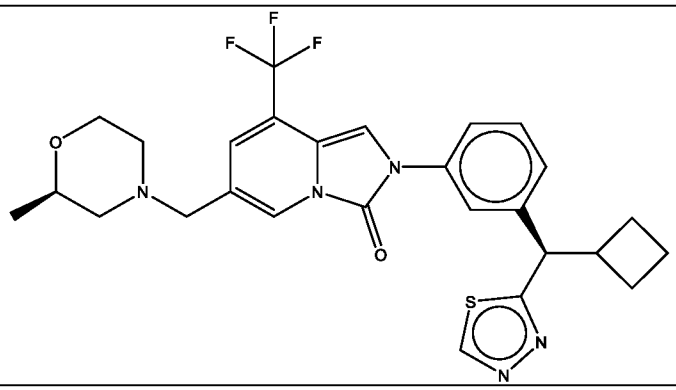
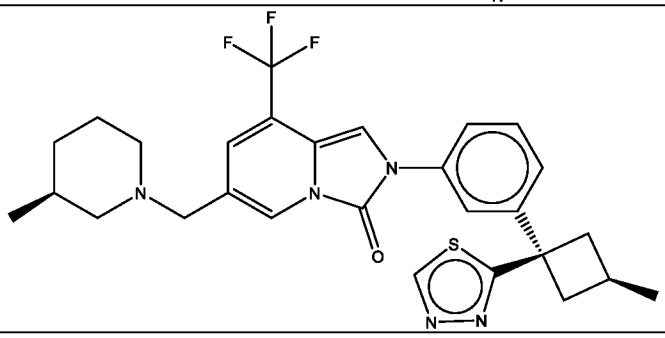
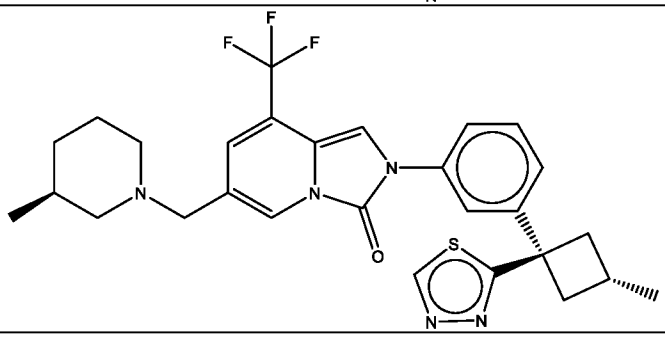
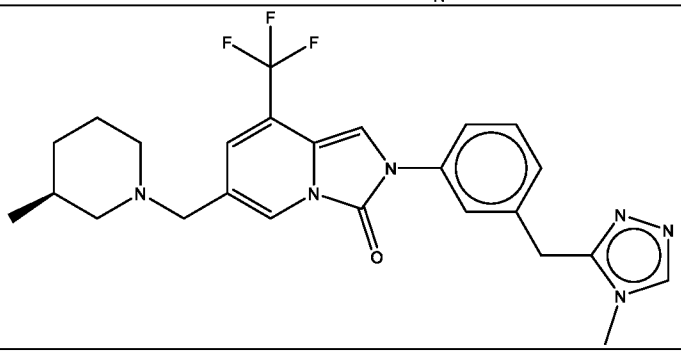
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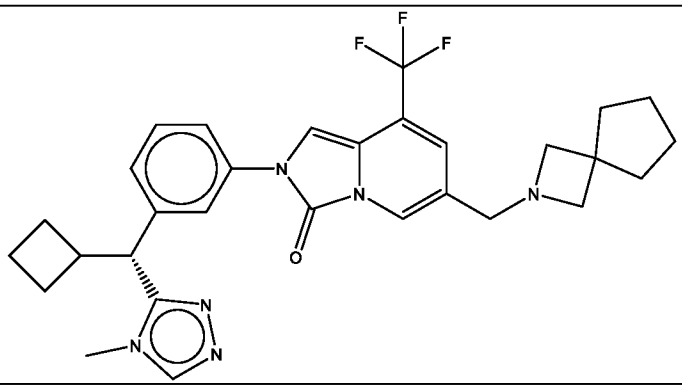
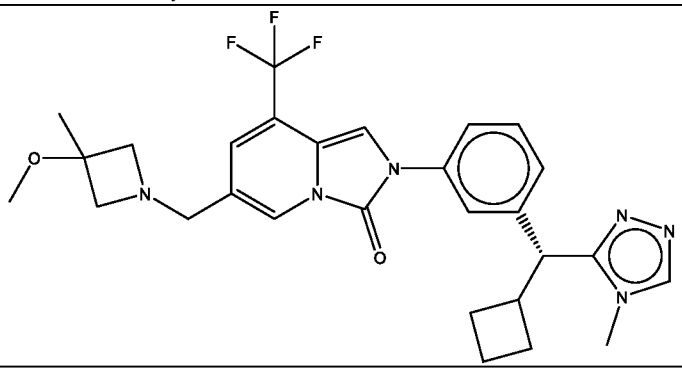
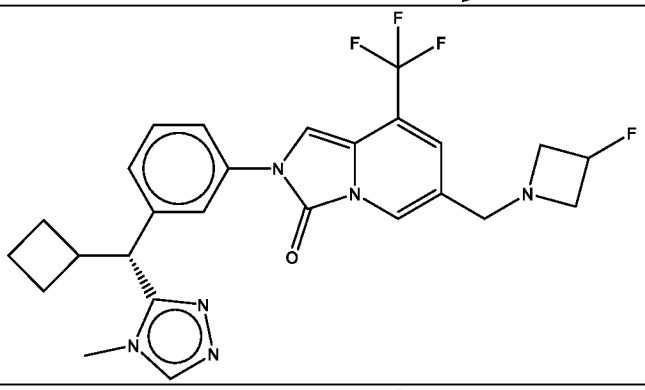
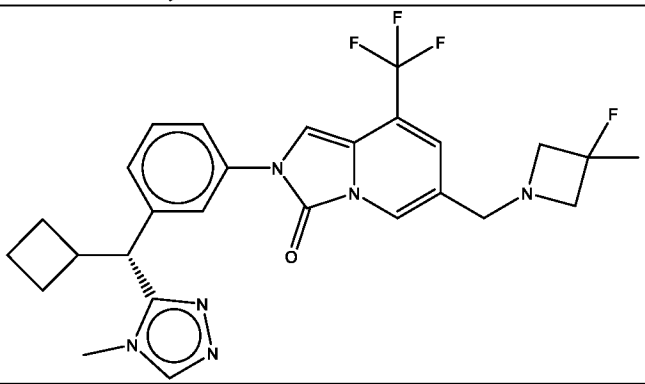
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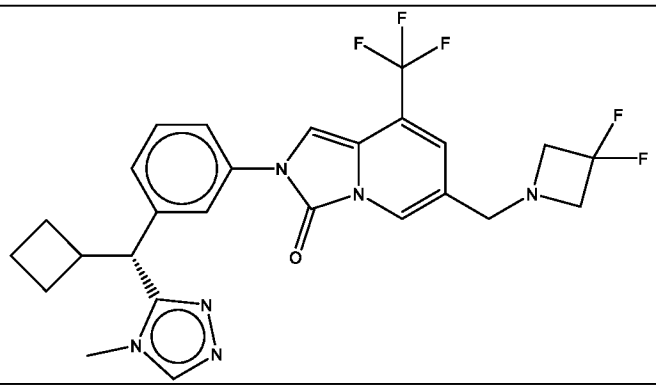
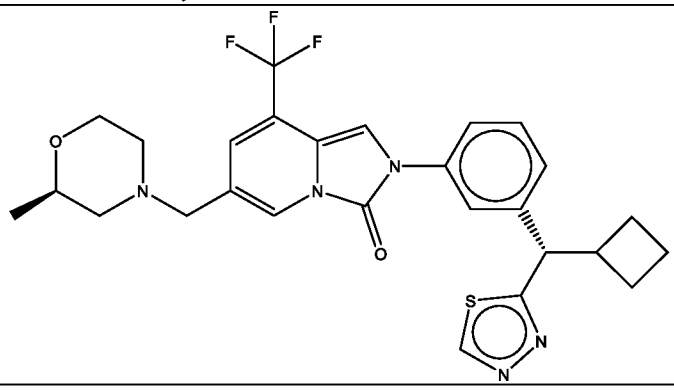
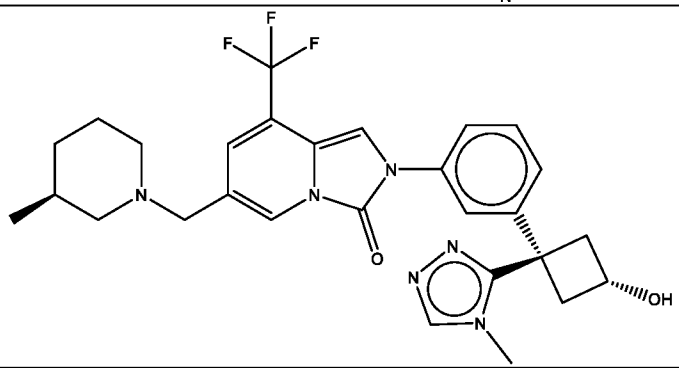
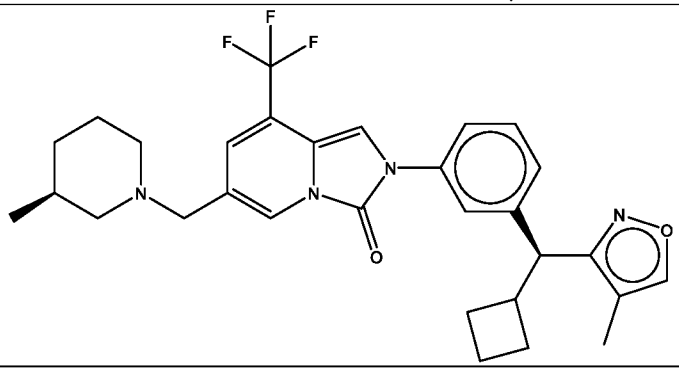
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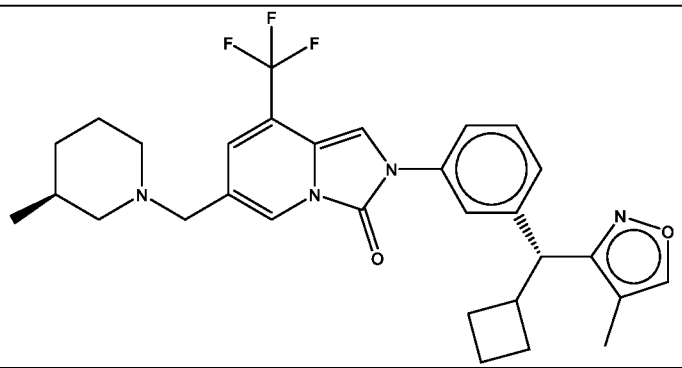
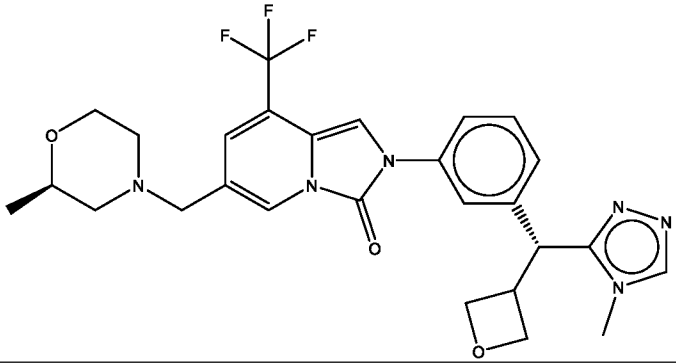
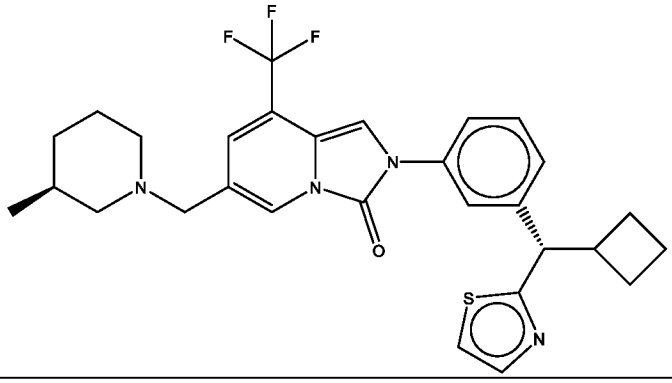
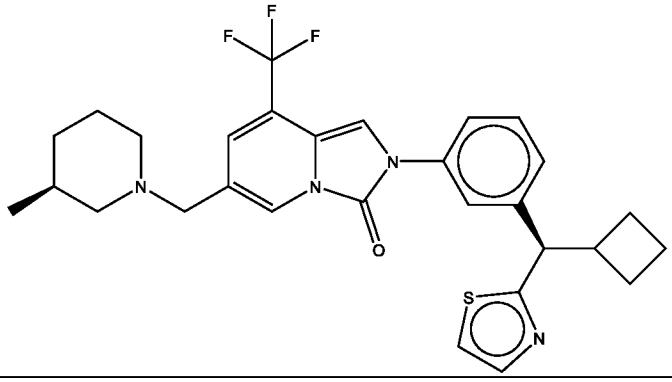
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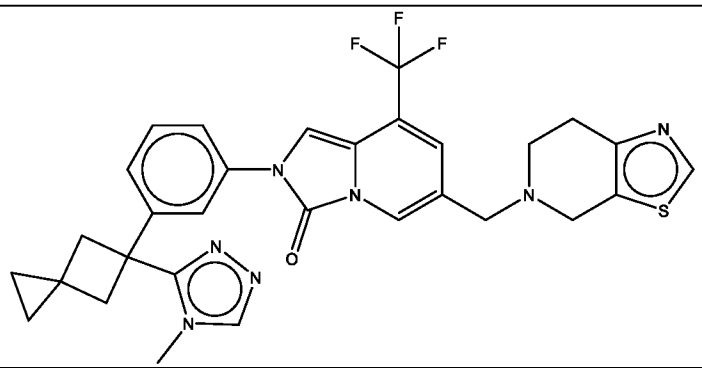
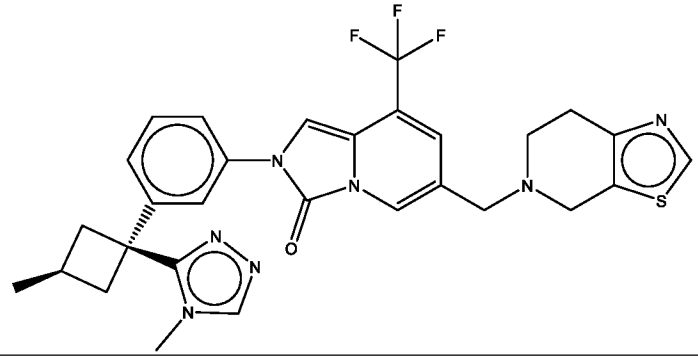
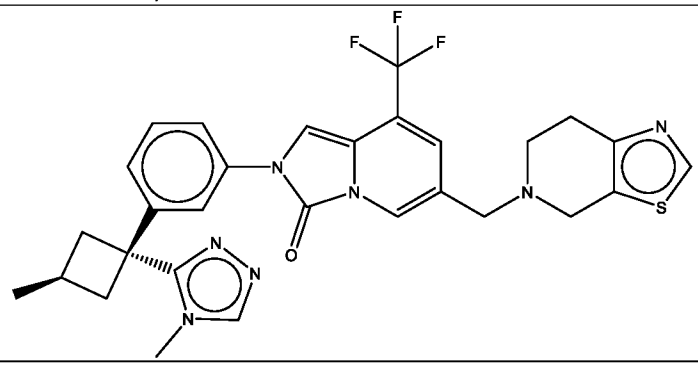
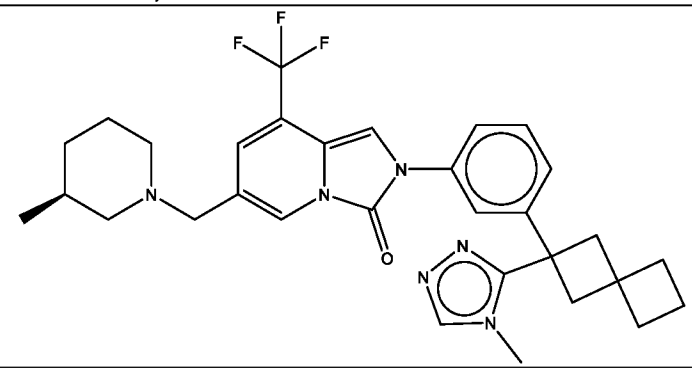
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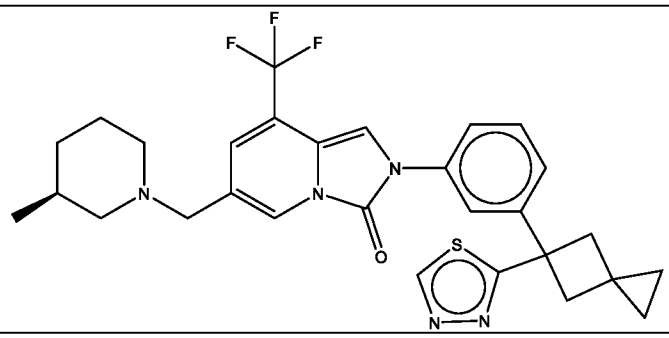
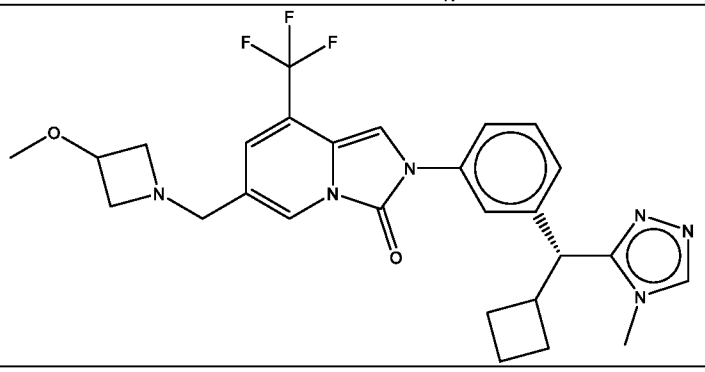
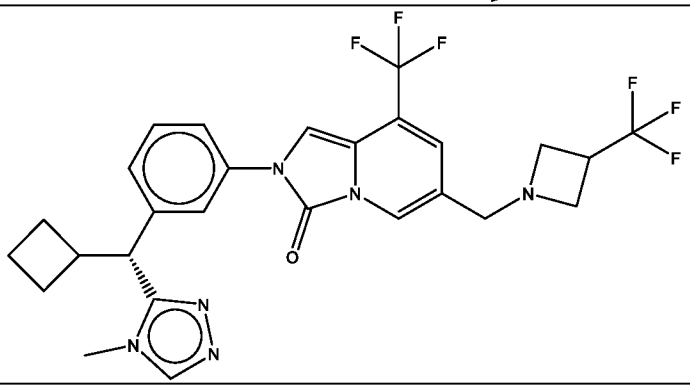
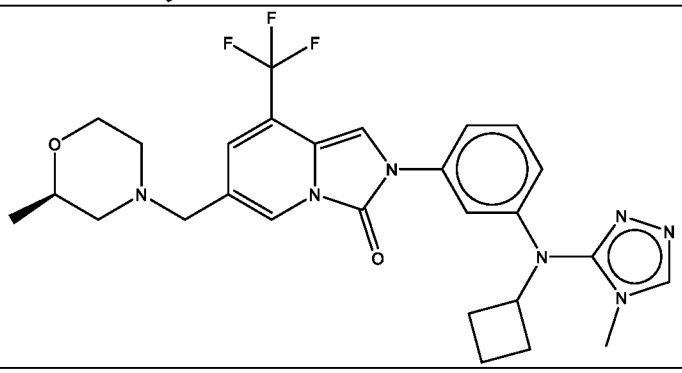
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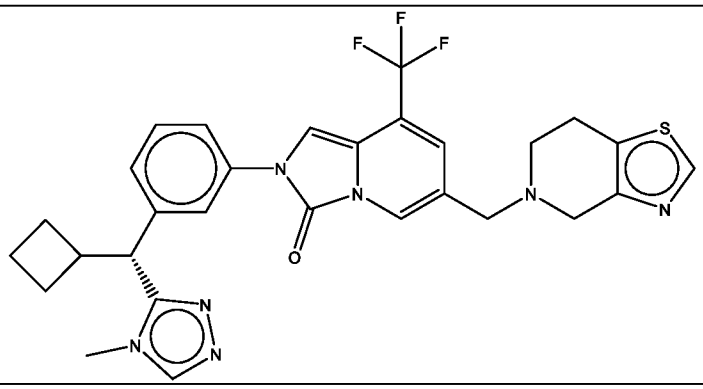
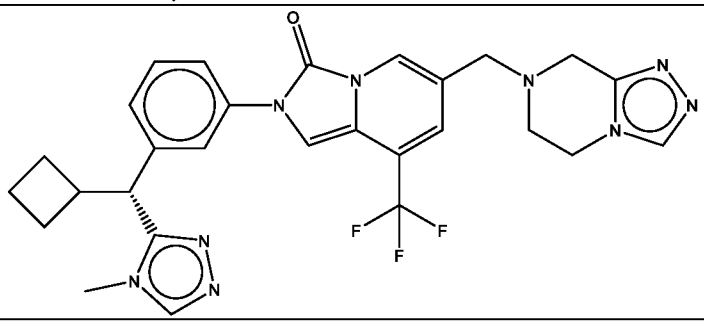
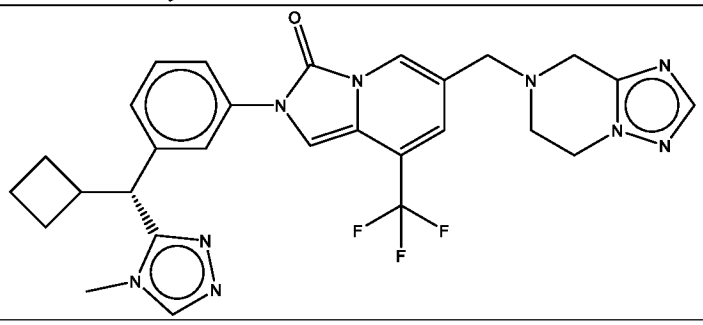
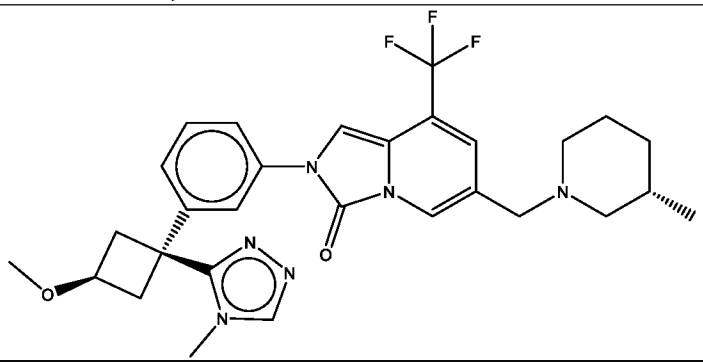
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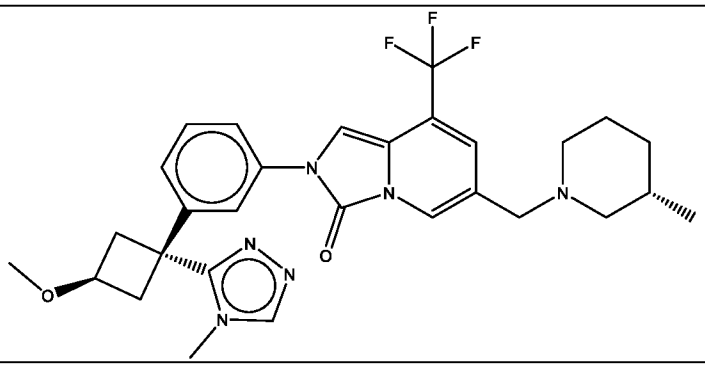
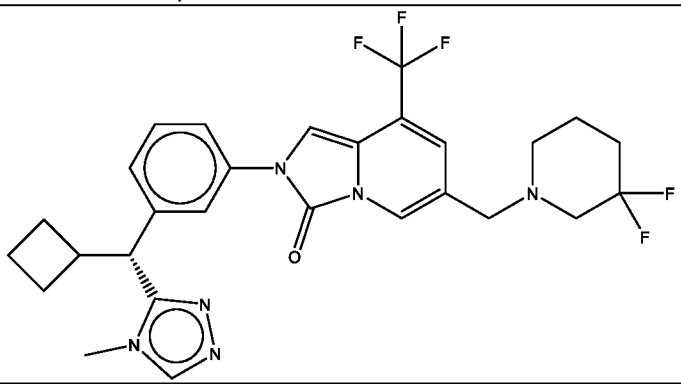
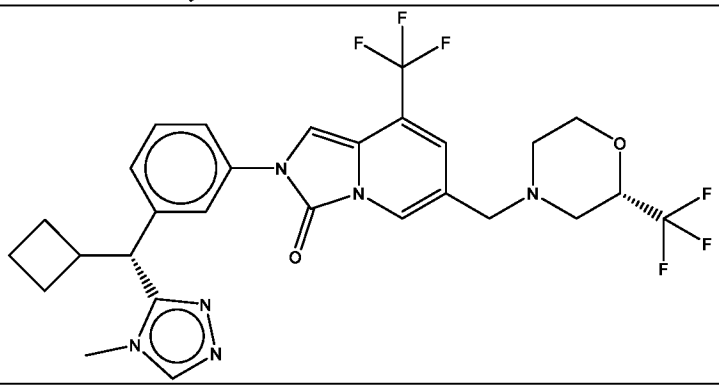
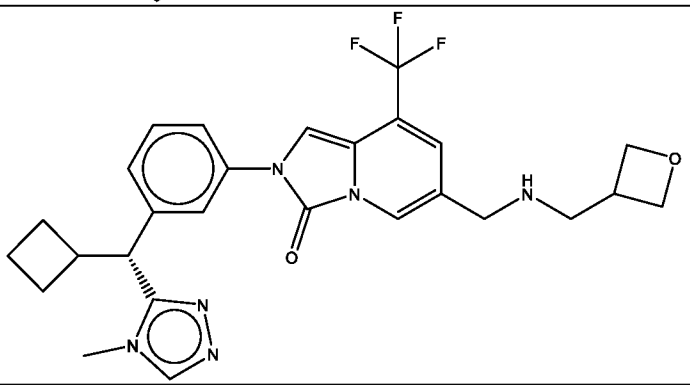
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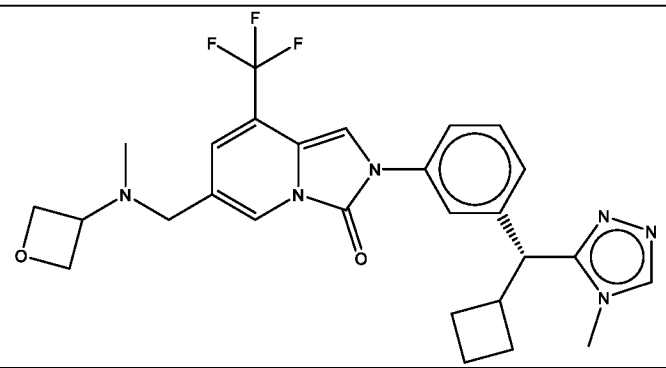
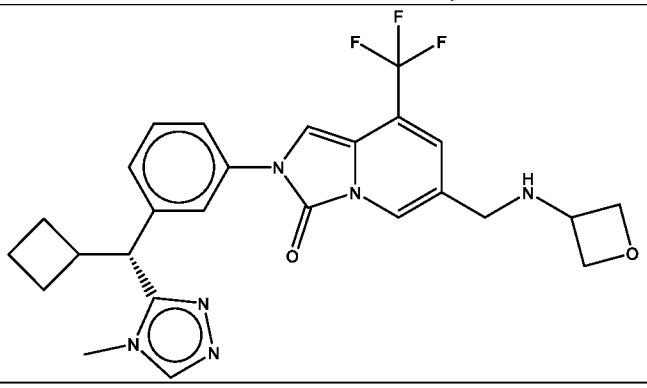
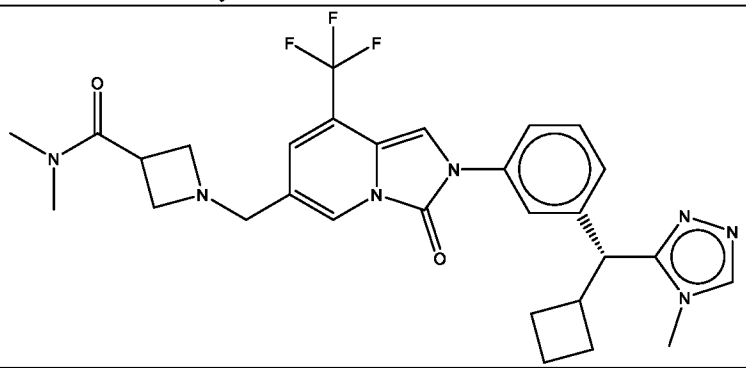
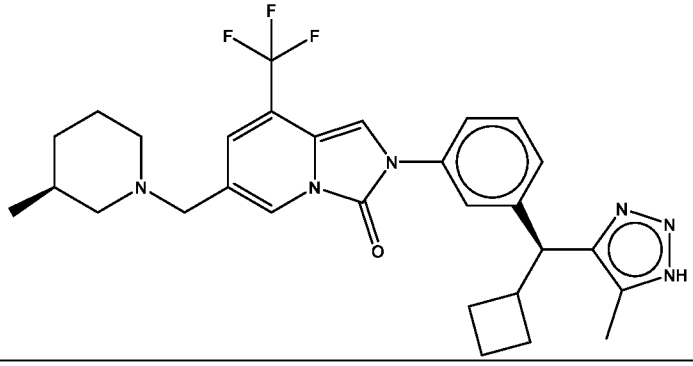
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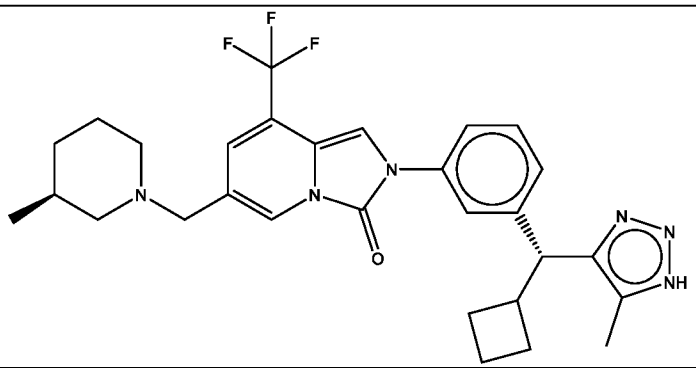
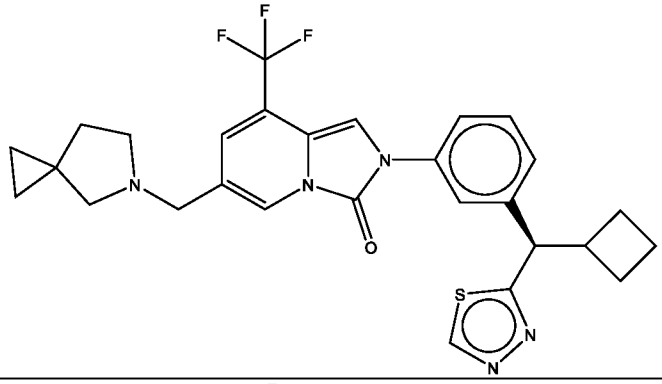
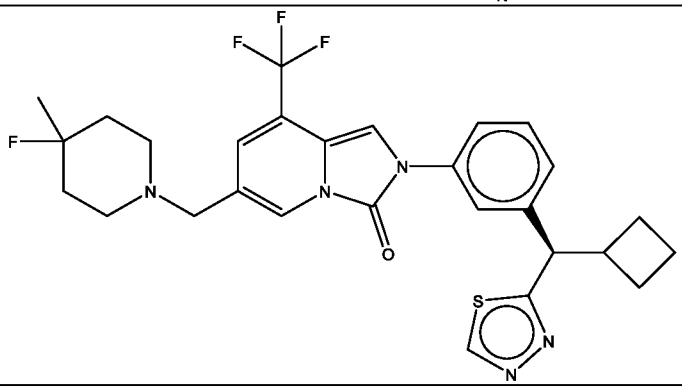
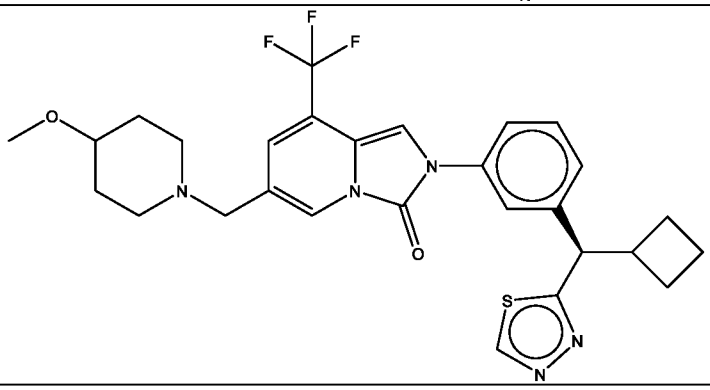
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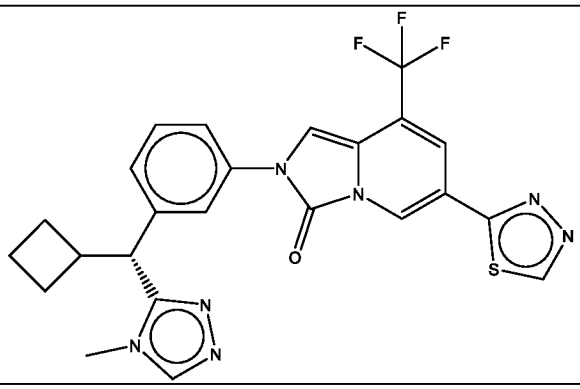
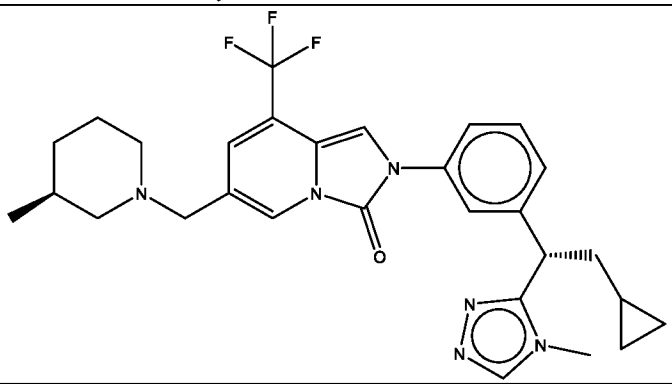
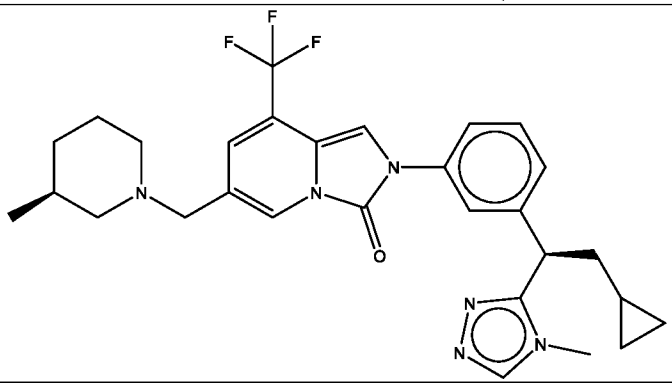
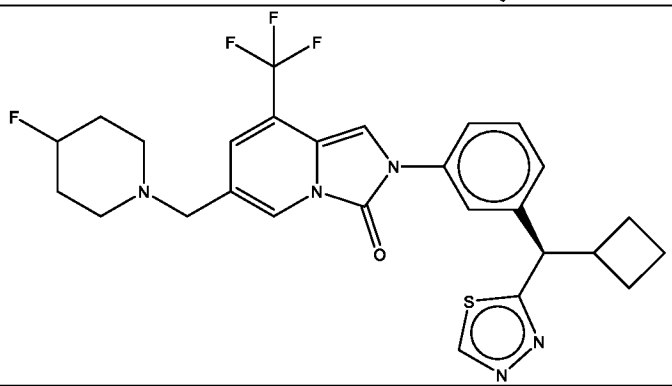
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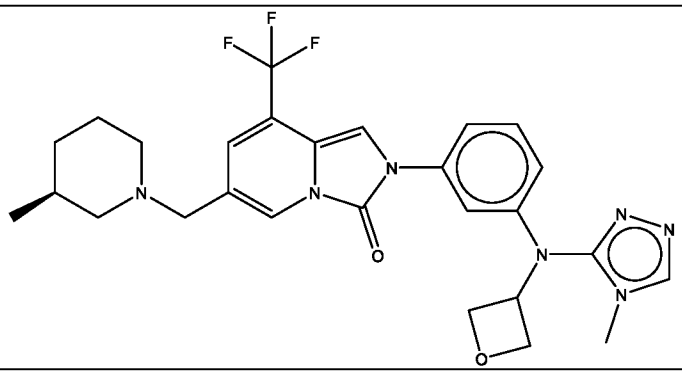
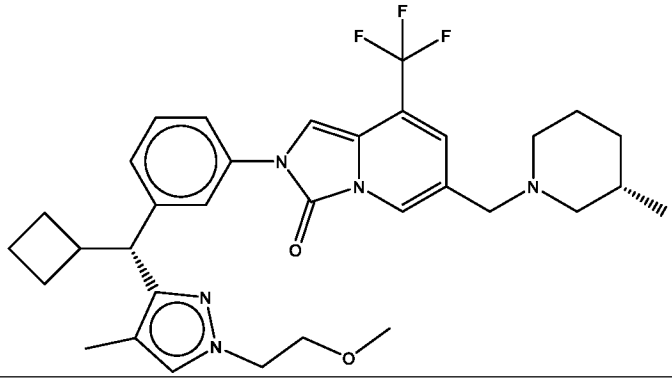
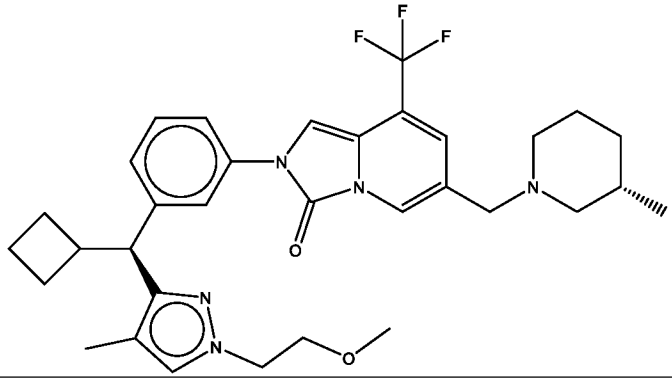
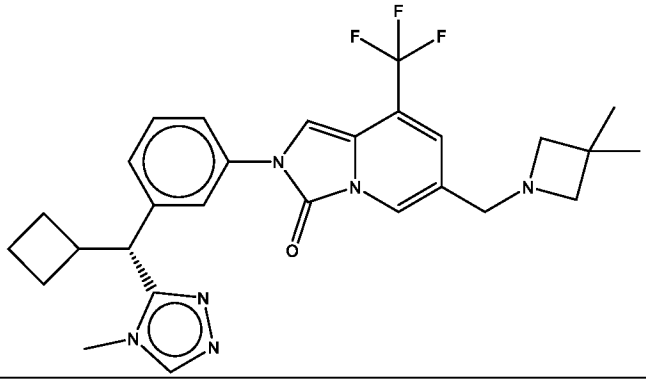
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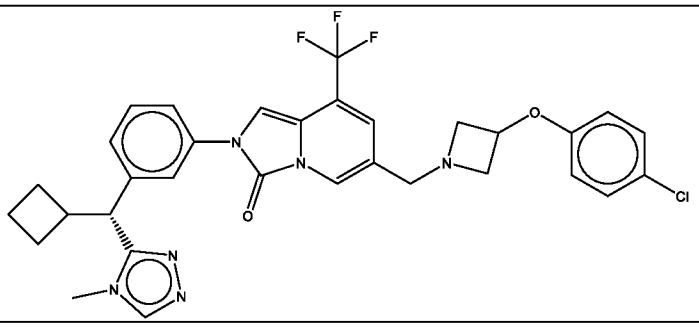
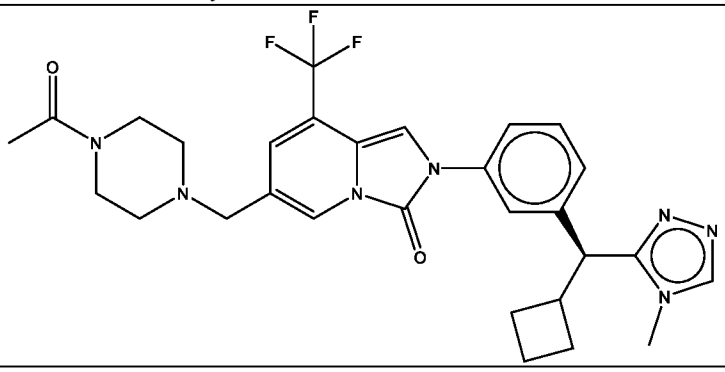
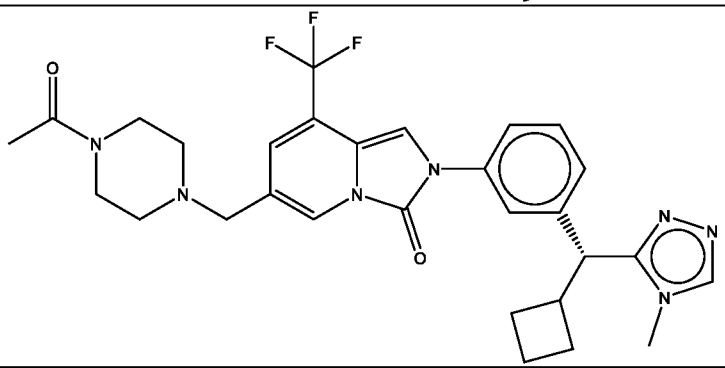
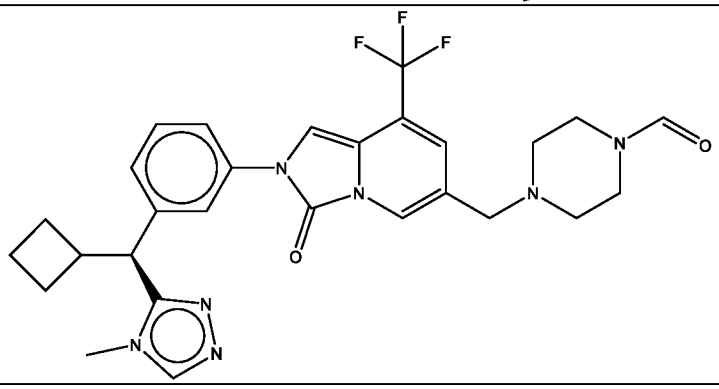
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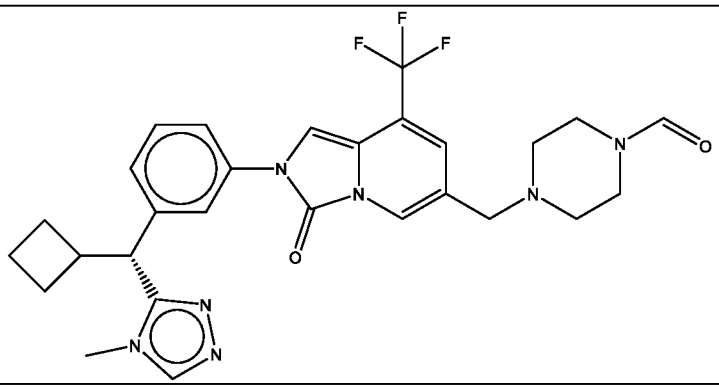
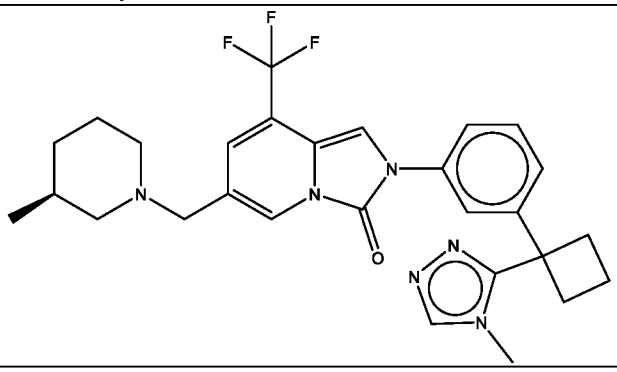
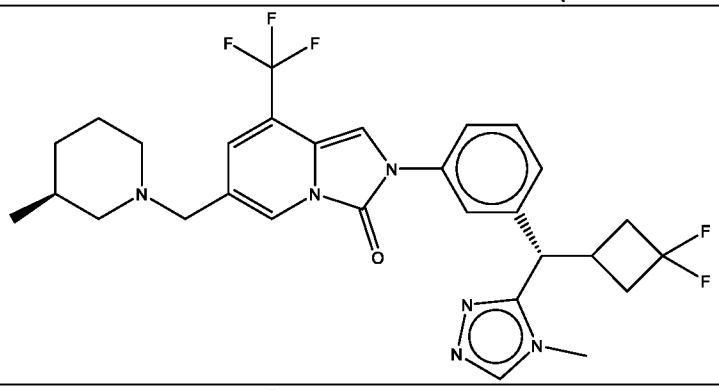
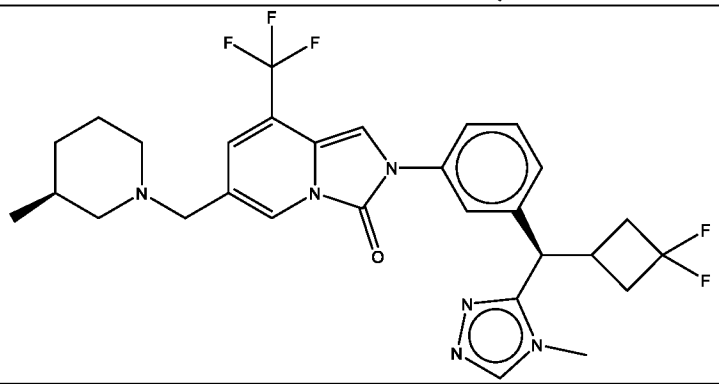
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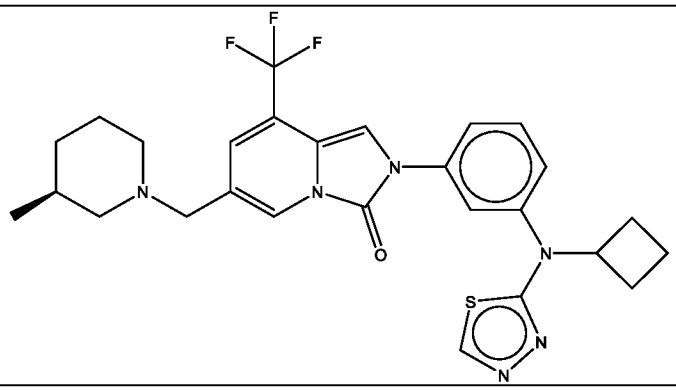
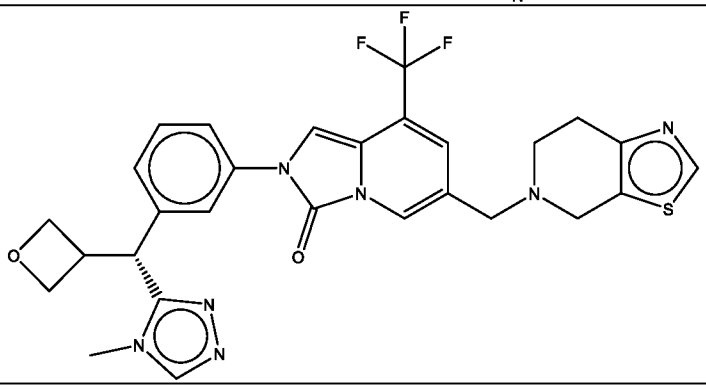
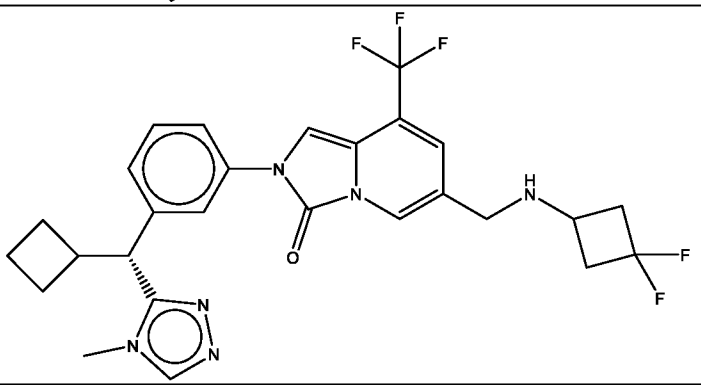
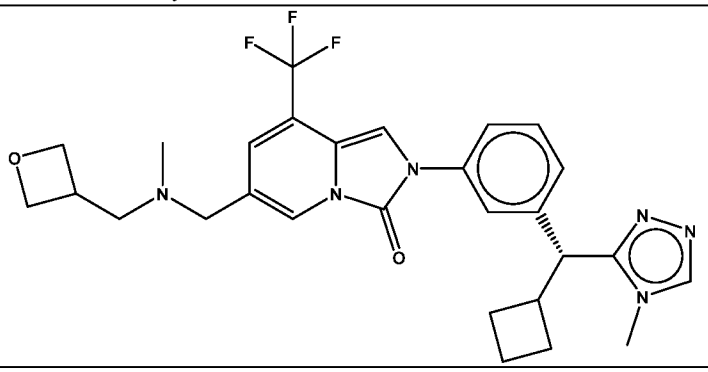
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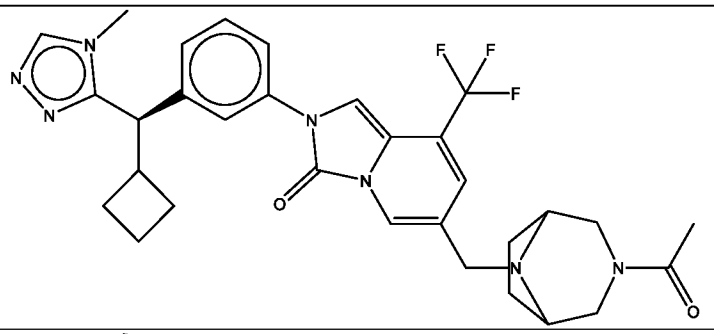
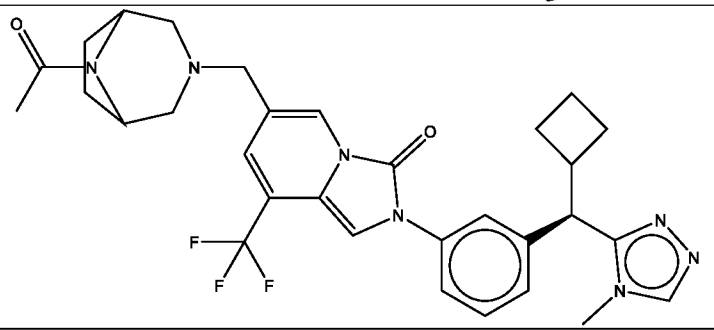
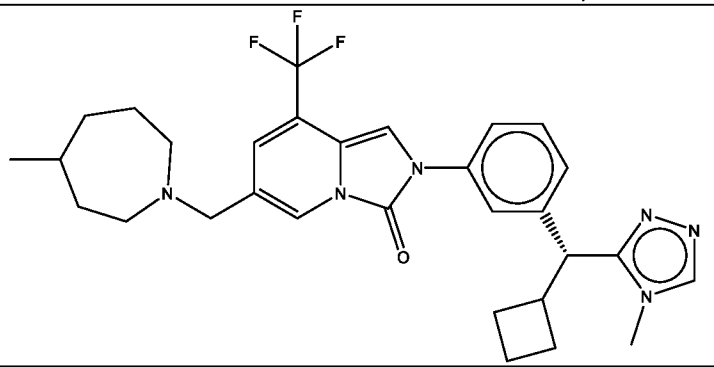
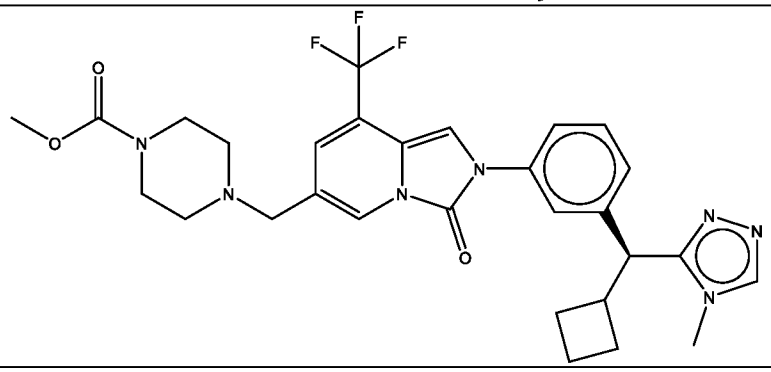
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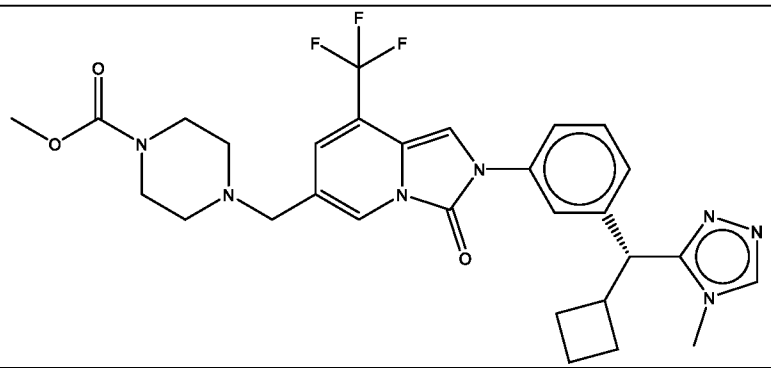
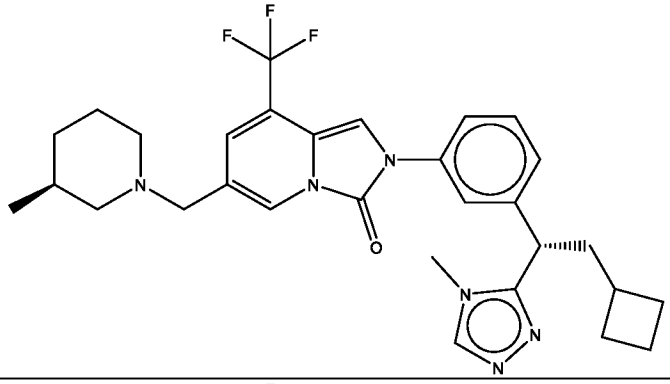
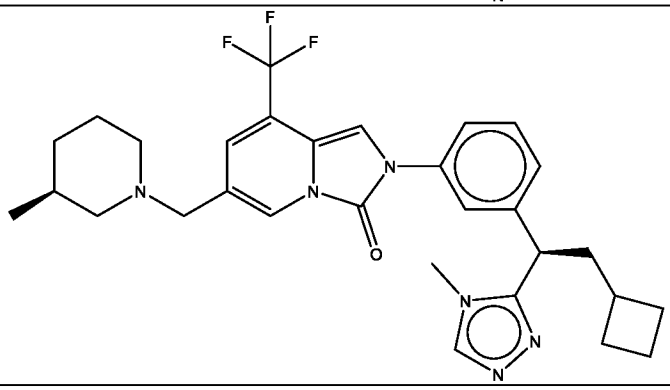
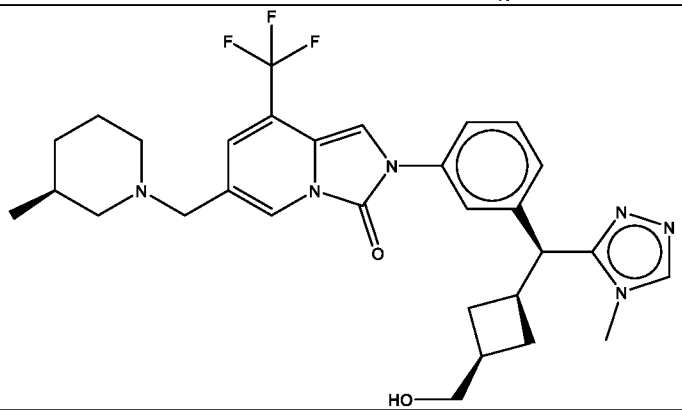
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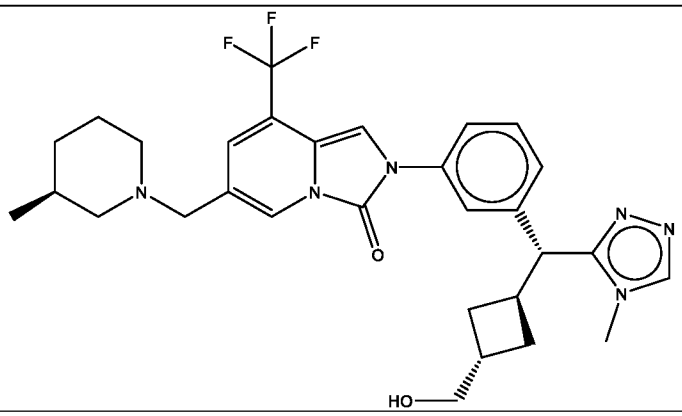
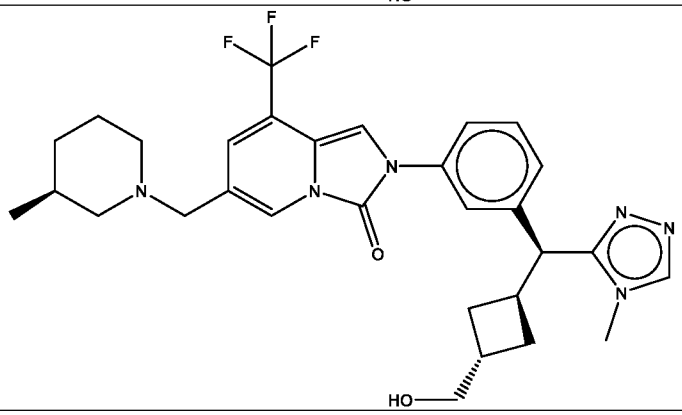
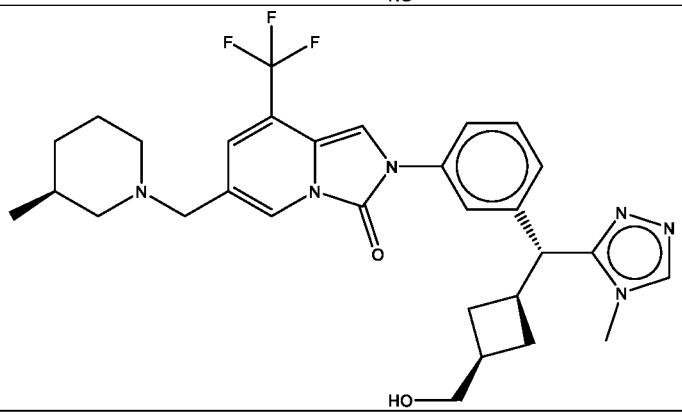
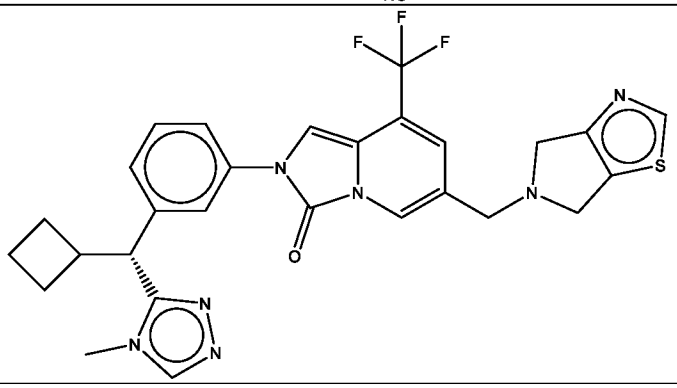
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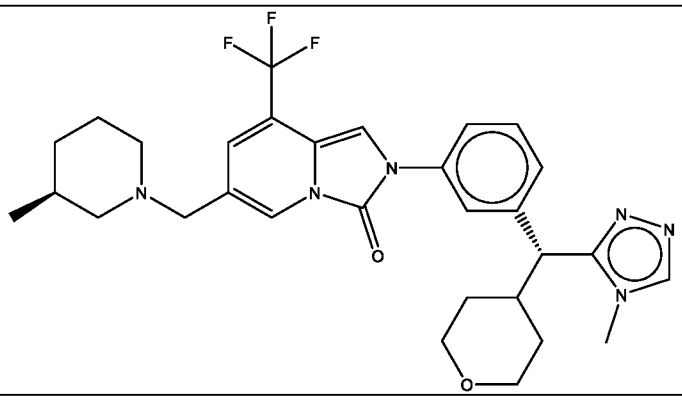
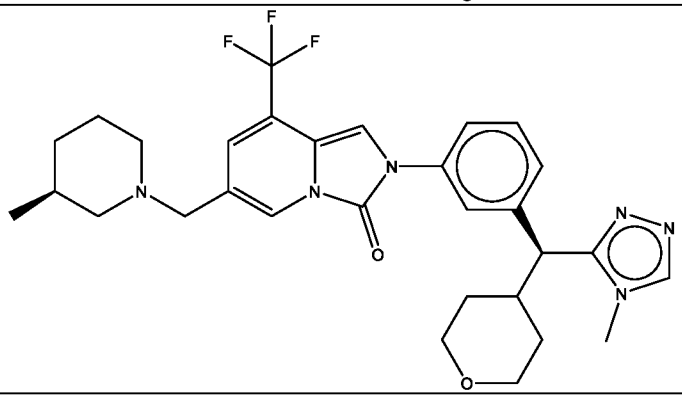
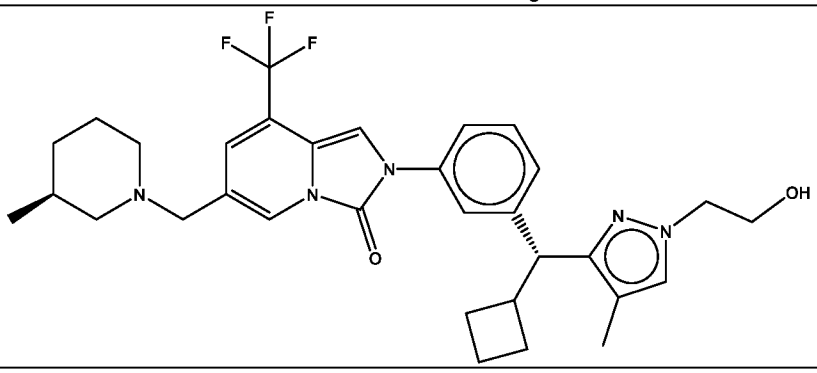
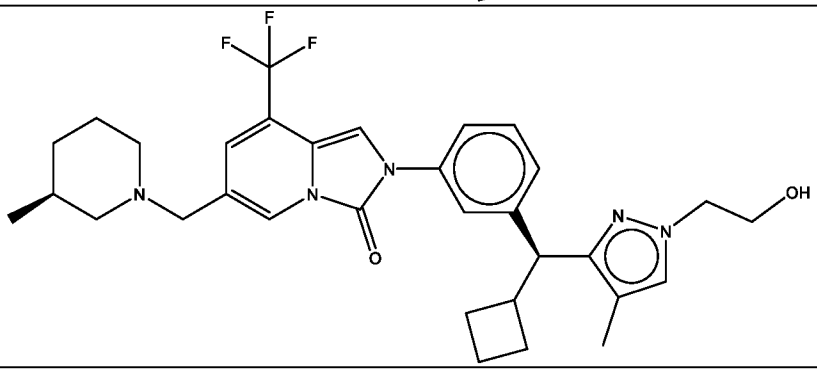
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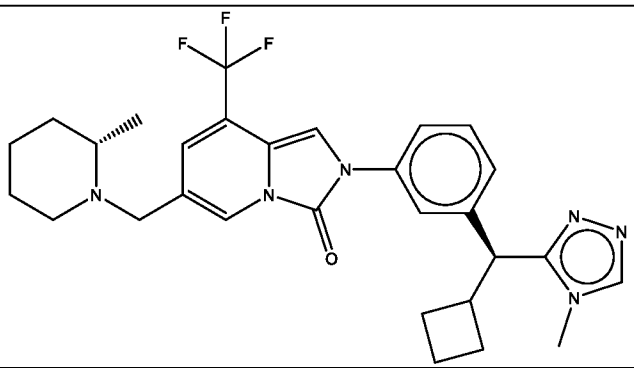
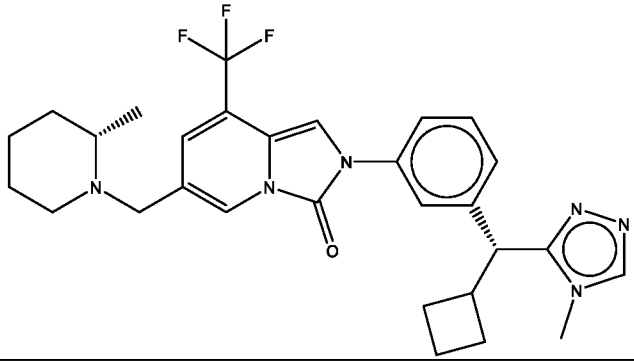
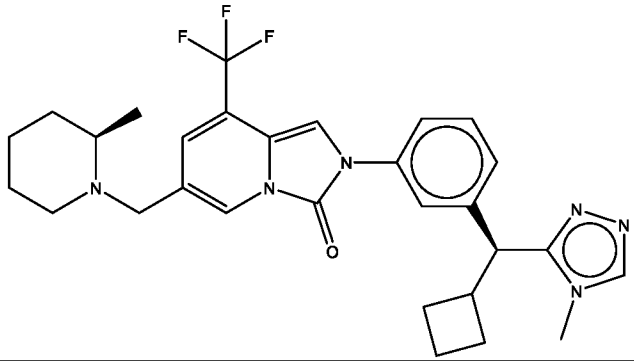
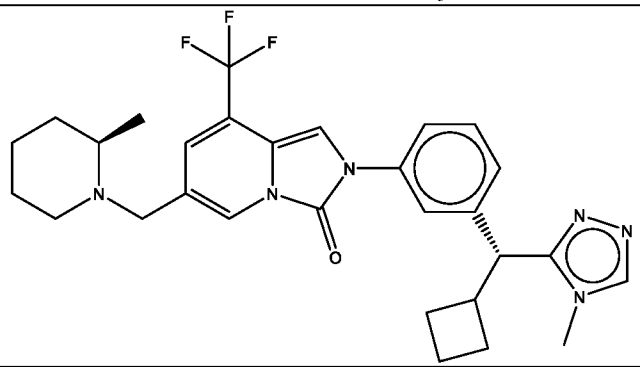
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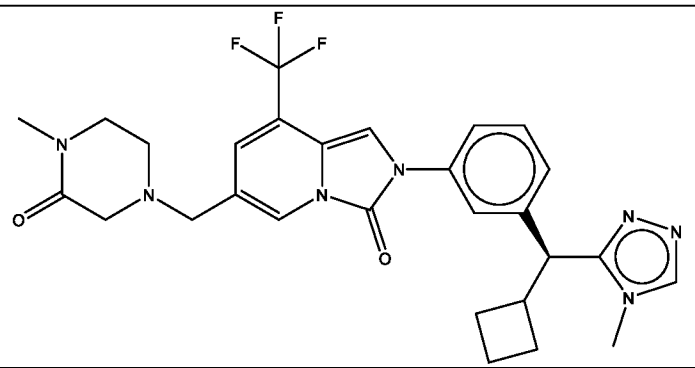
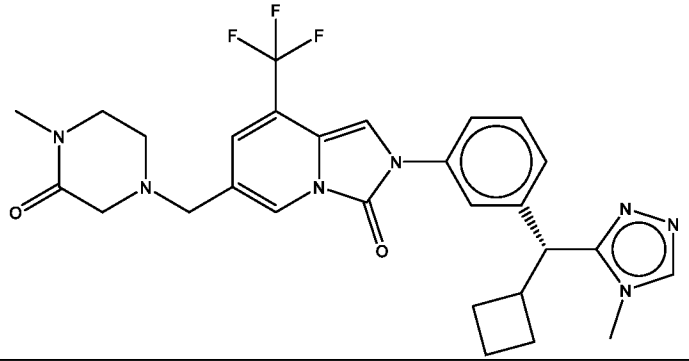
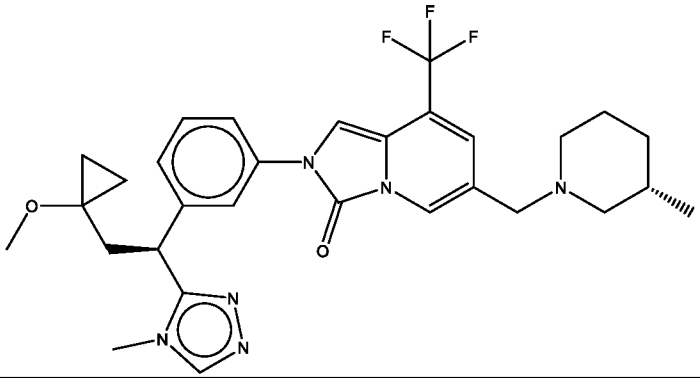
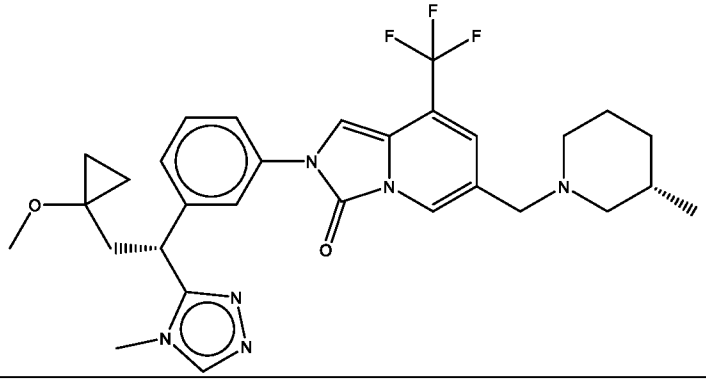
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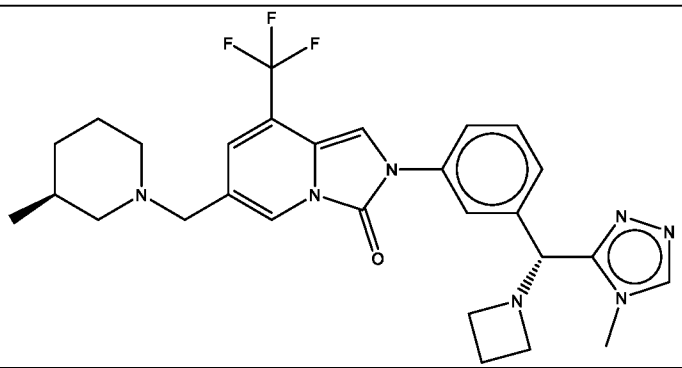
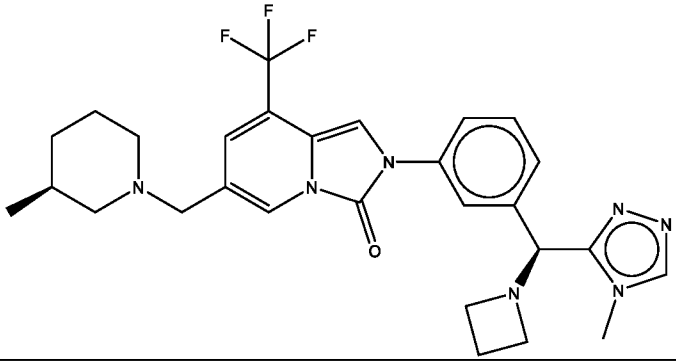
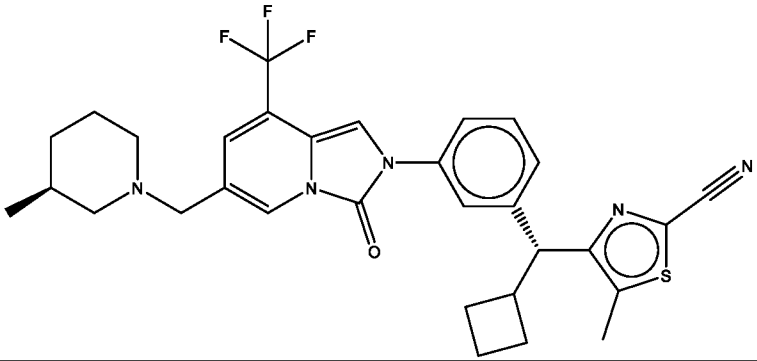
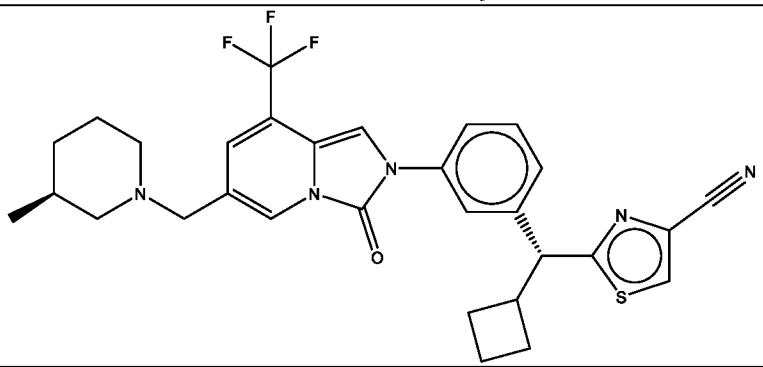
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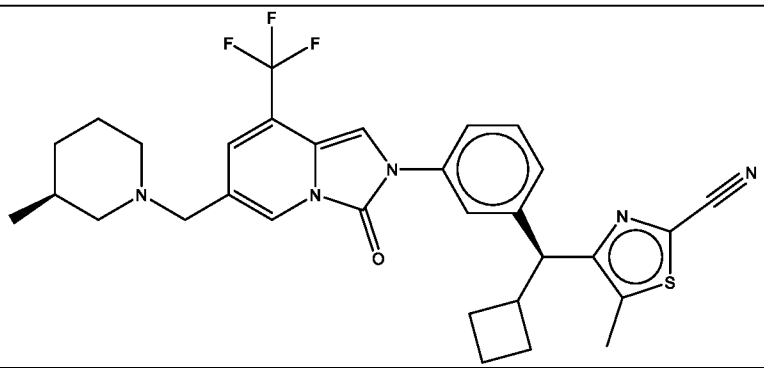
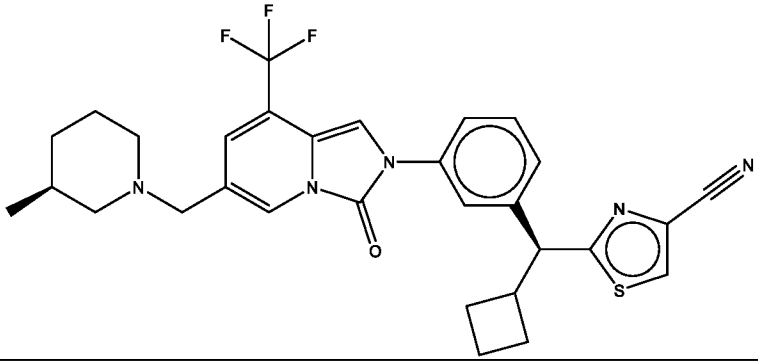
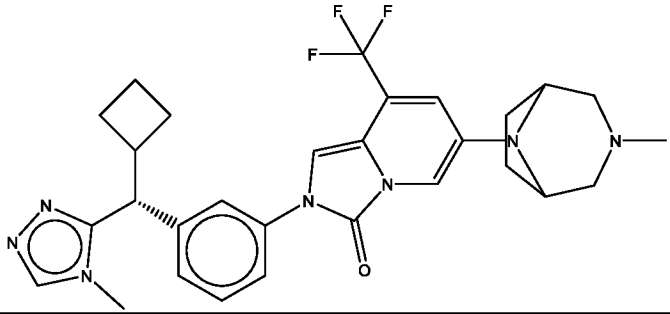
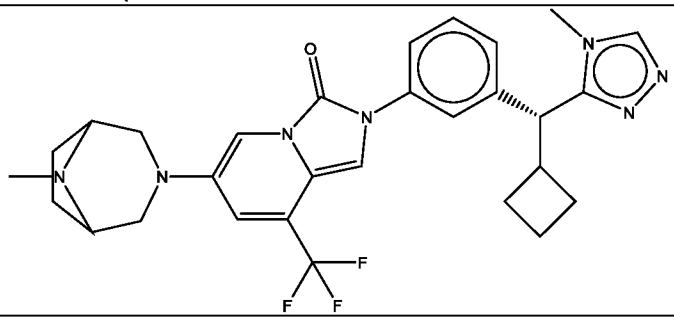
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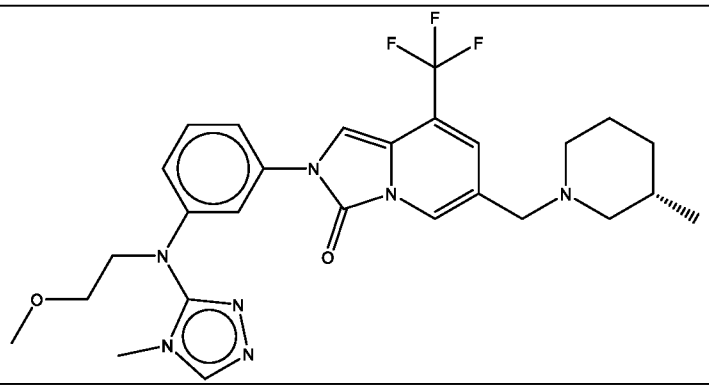
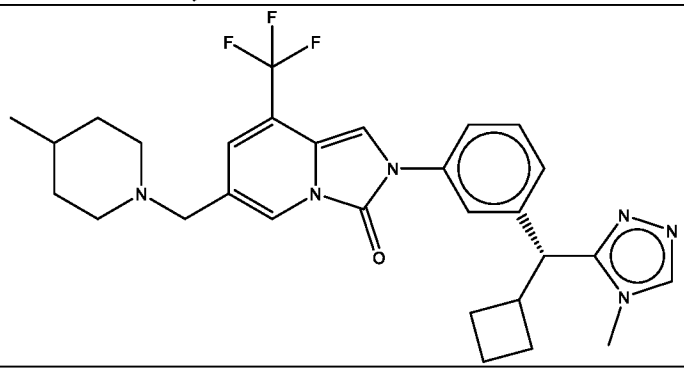
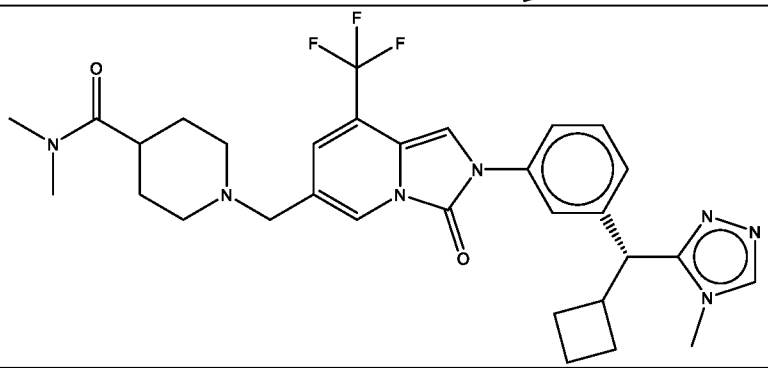
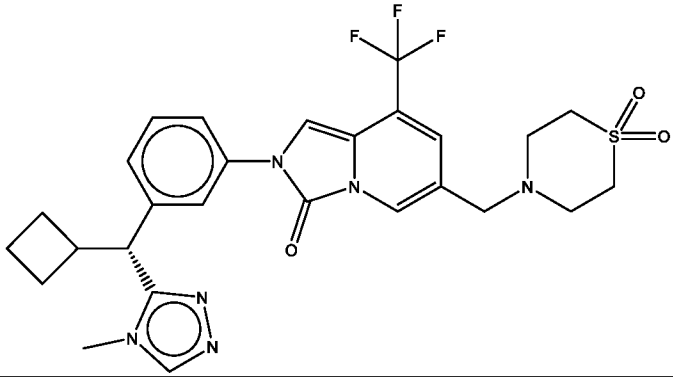
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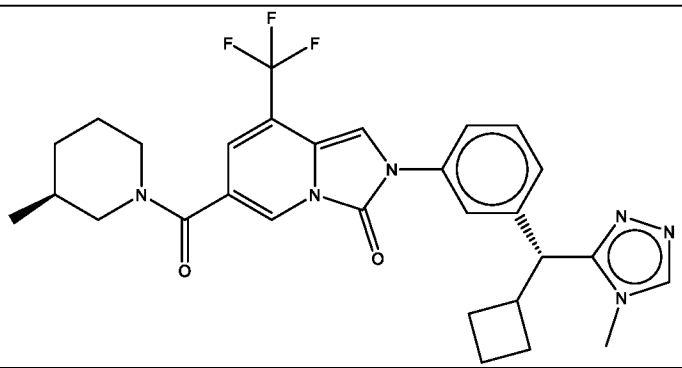
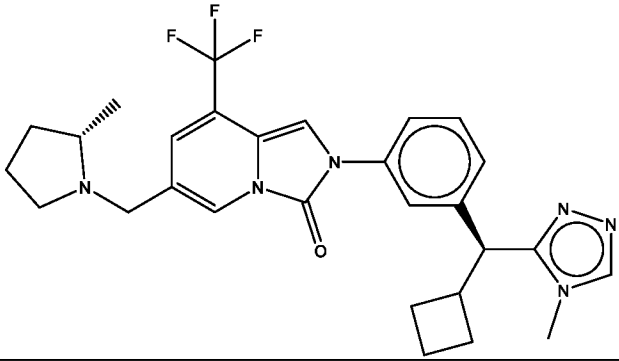
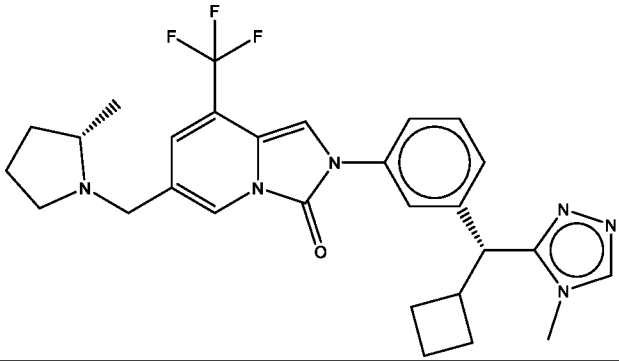
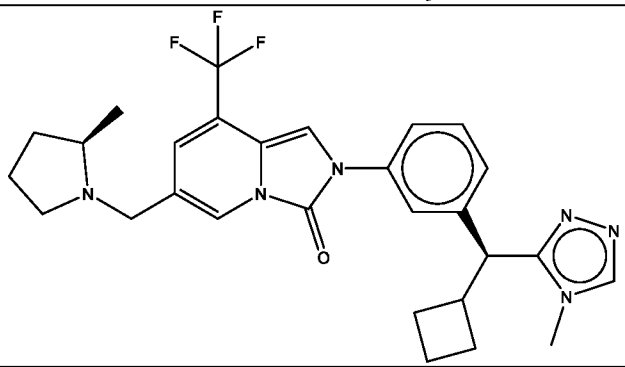
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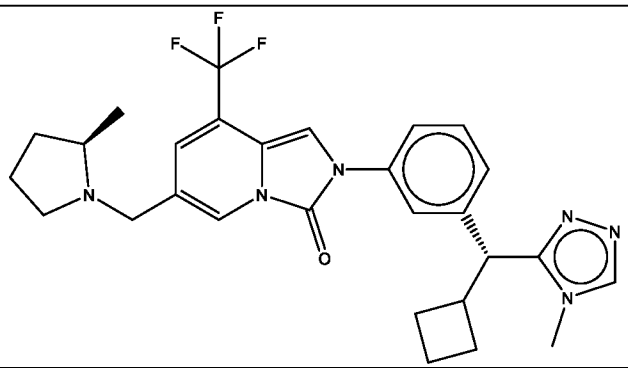
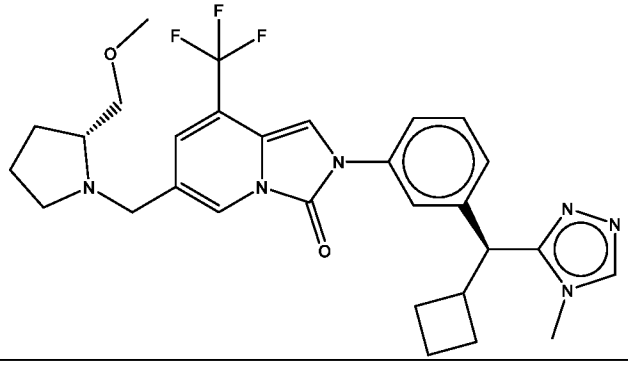
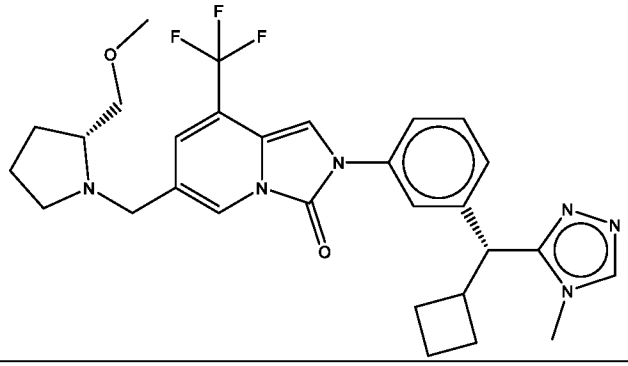
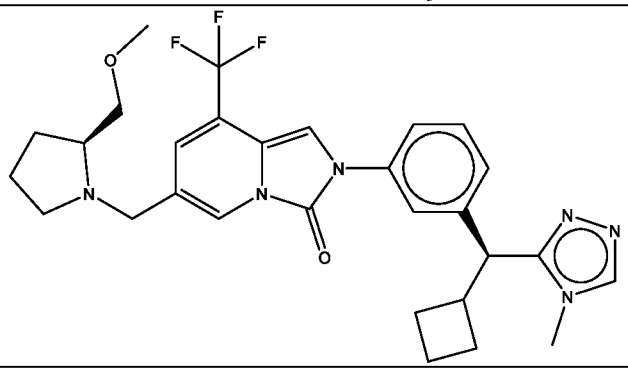
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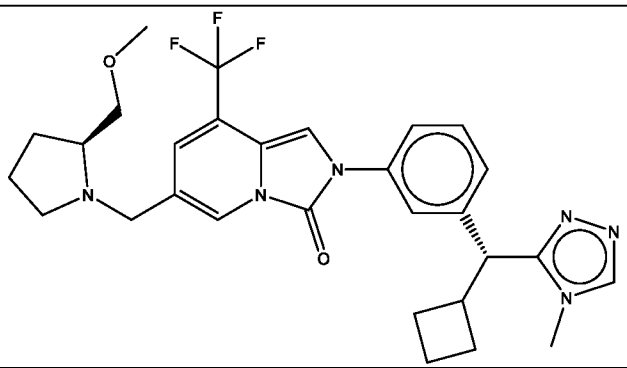
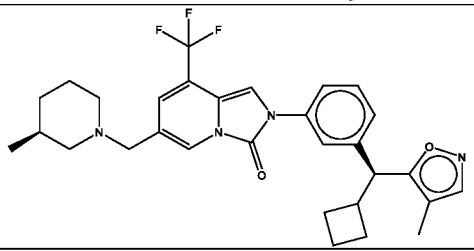
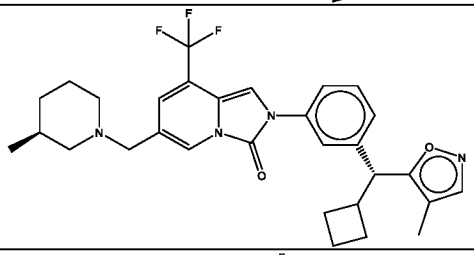
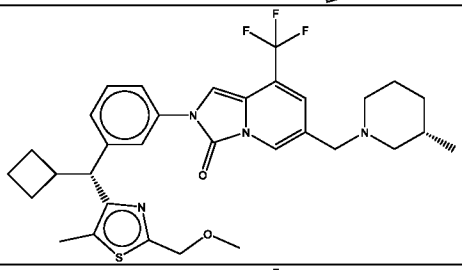
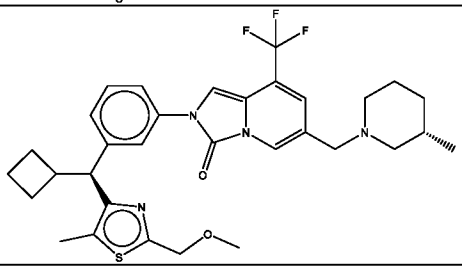
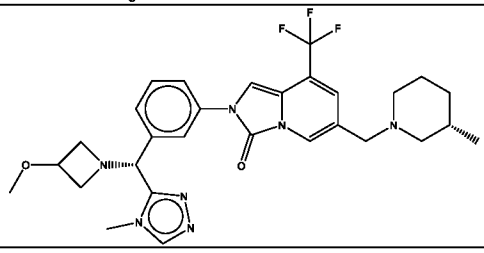
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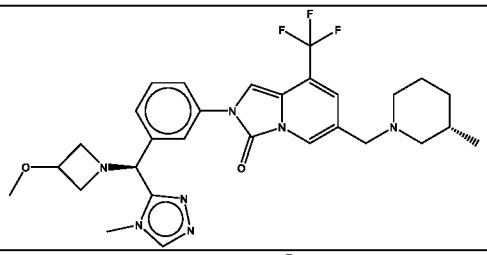
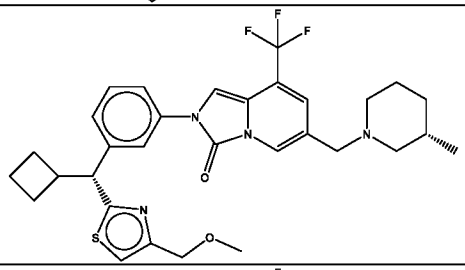
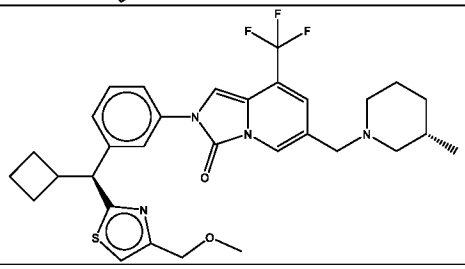
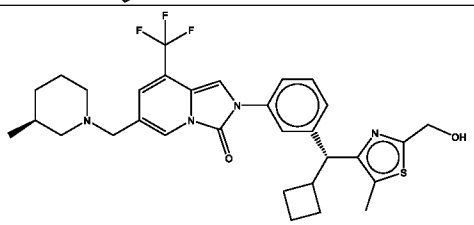
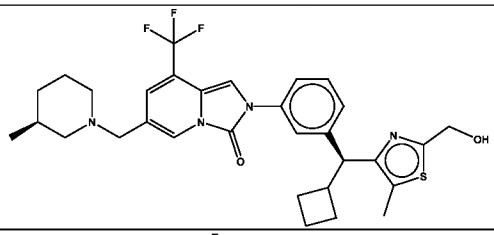
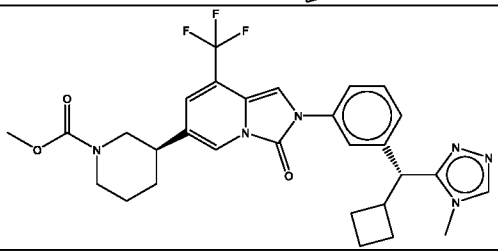
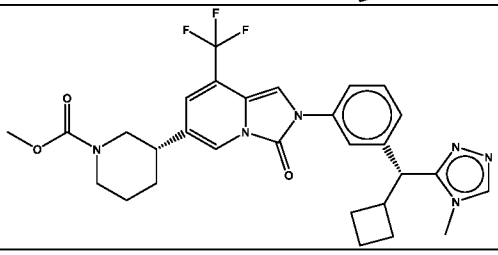
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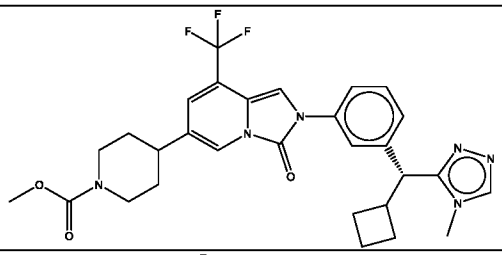
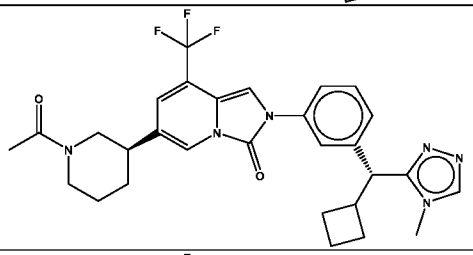
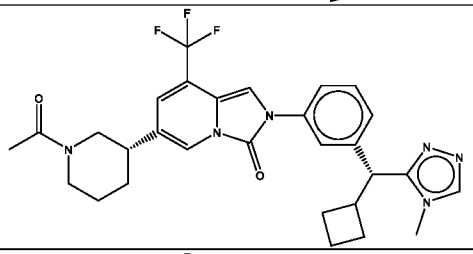
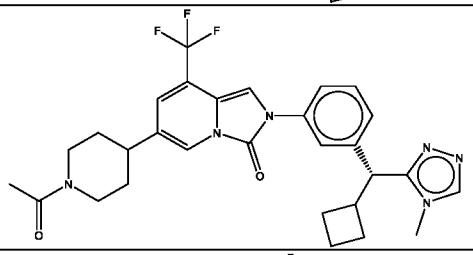
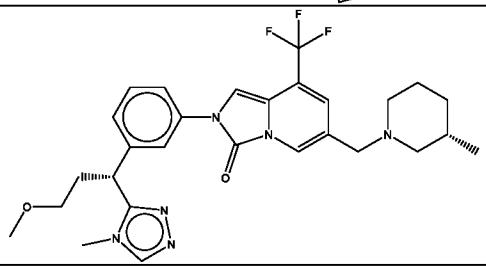
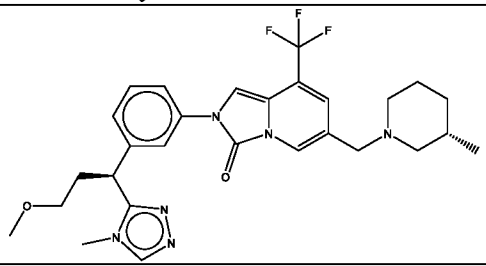
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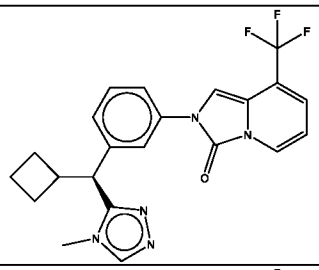
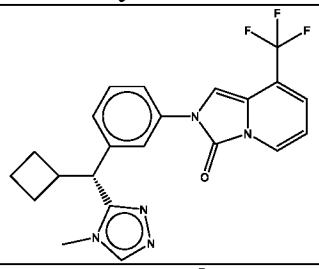
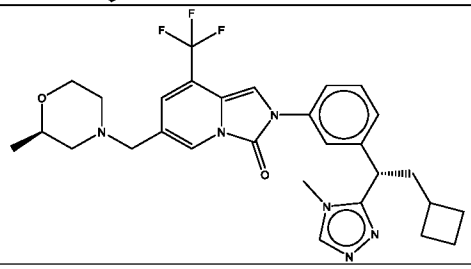
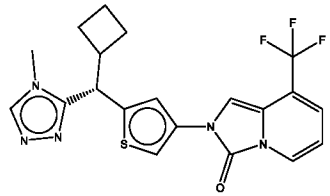
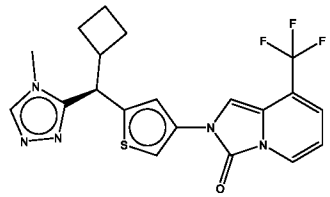
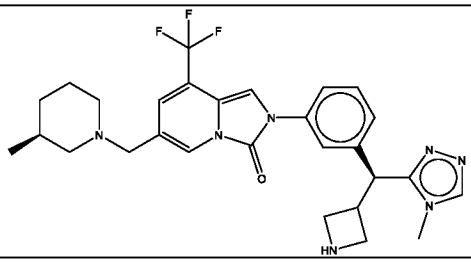
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381_P1	

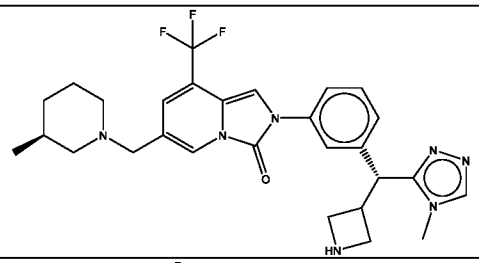
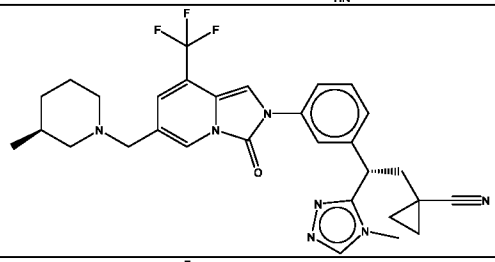
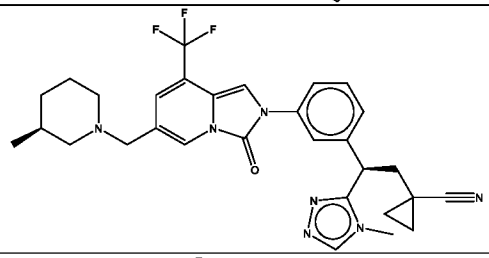
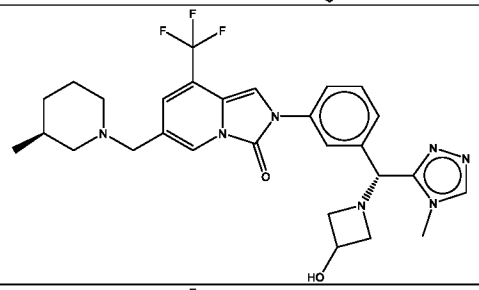
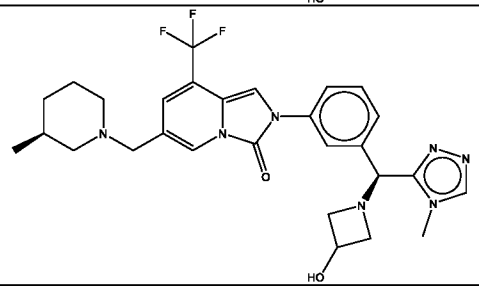
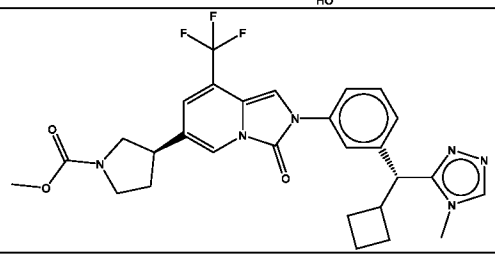
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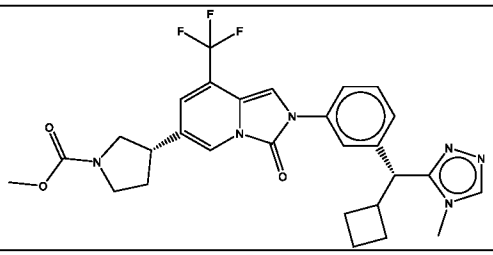
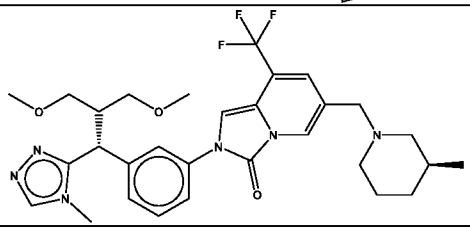
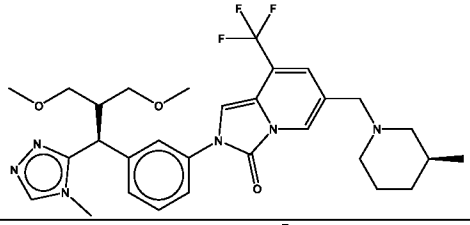
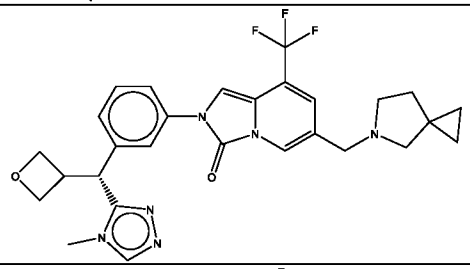
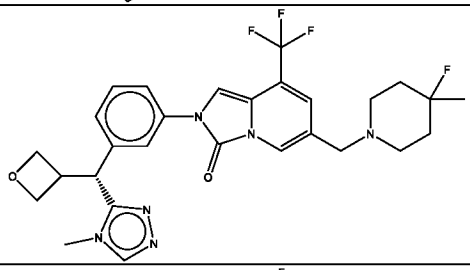
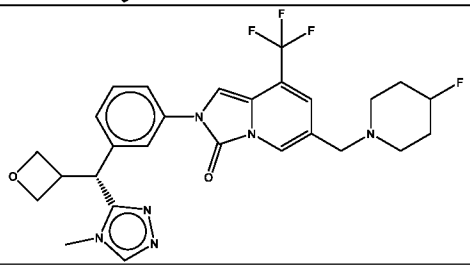
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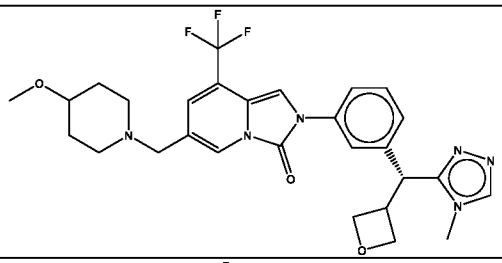
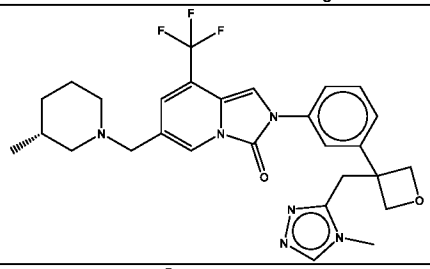
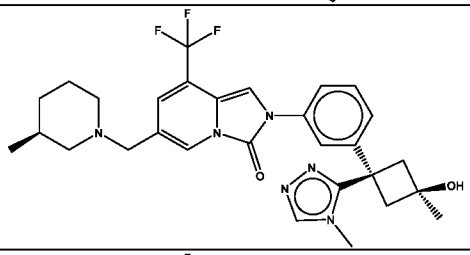
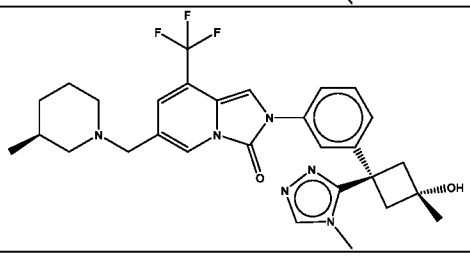
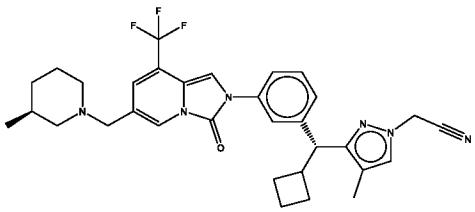
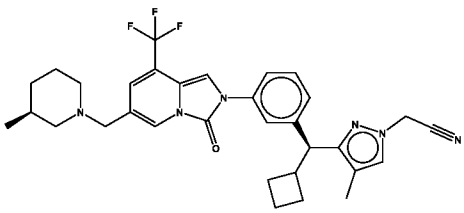
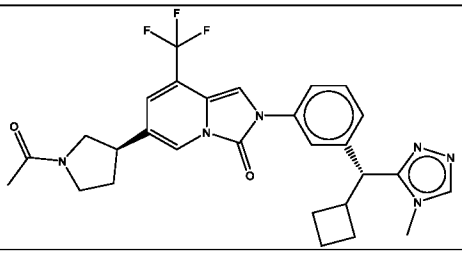
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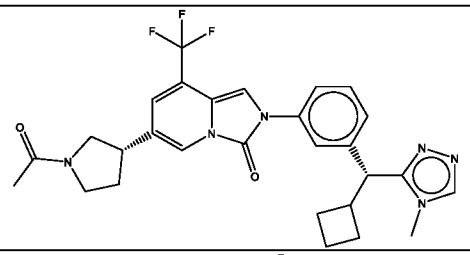
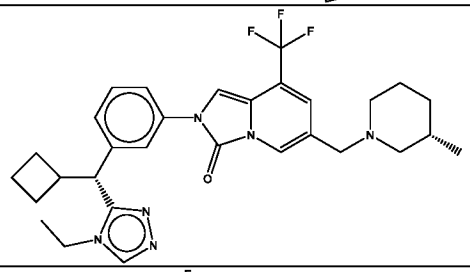
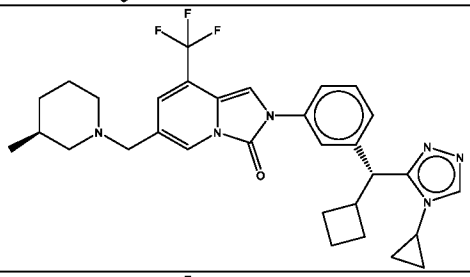
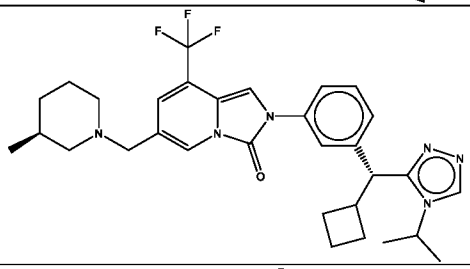
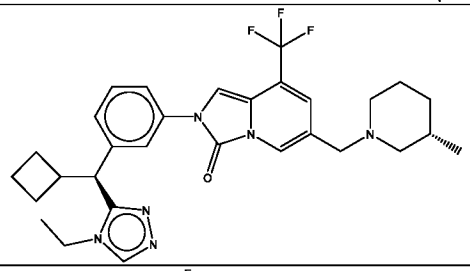
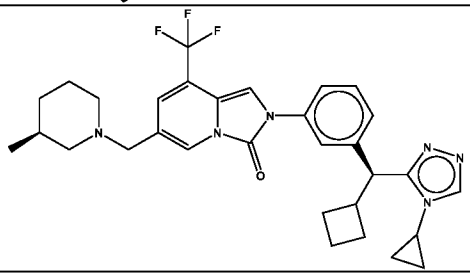
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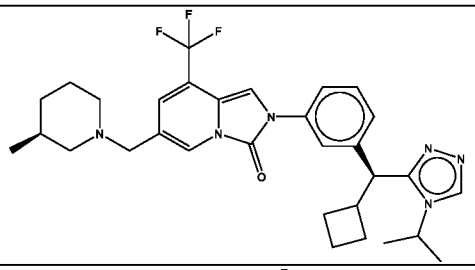
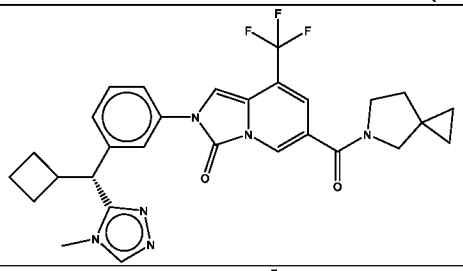
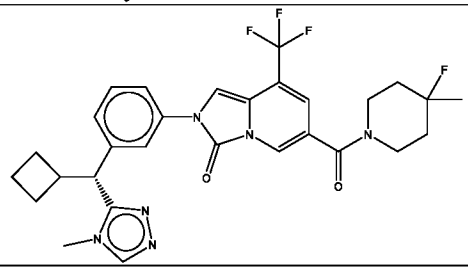
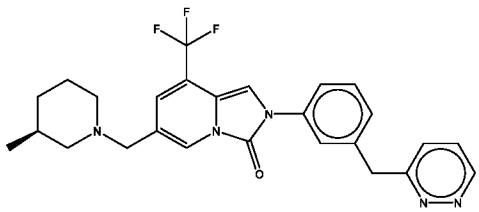
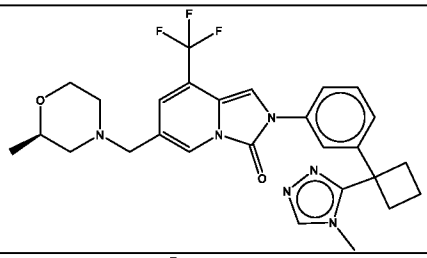
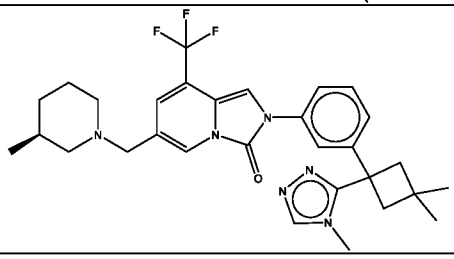
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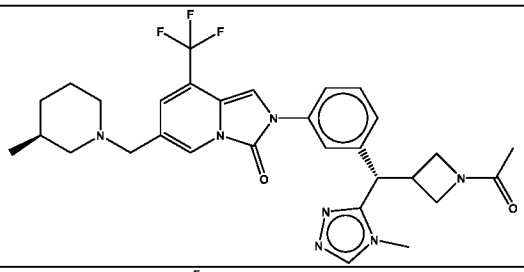
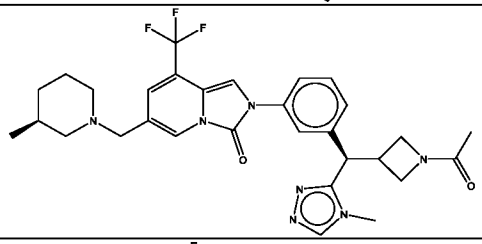
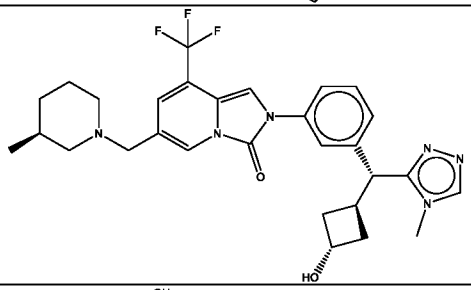
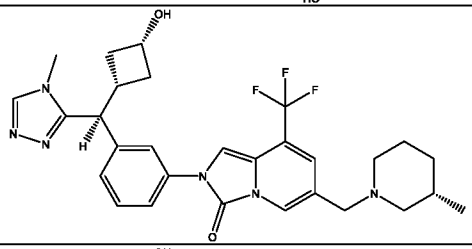
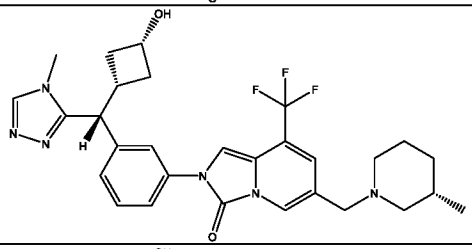
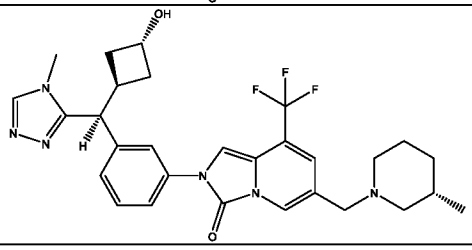
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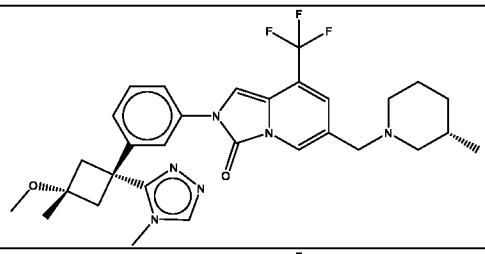
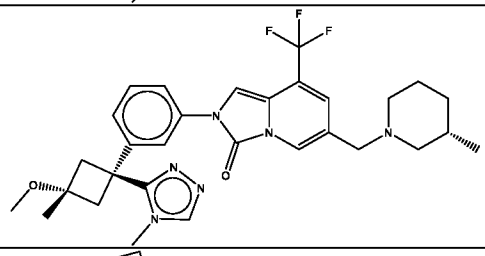
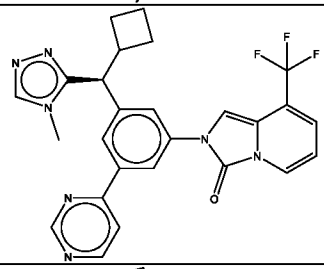
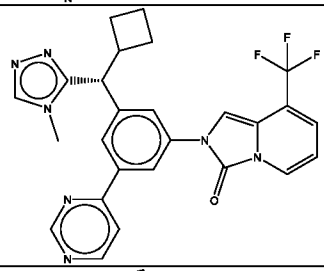
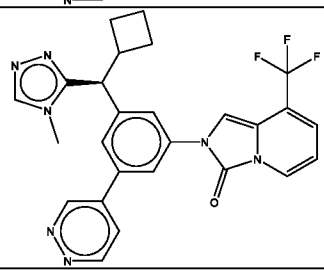
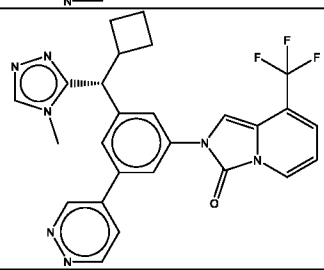
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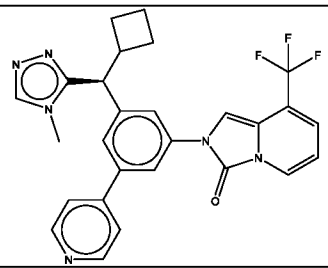
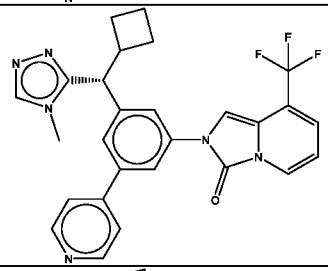
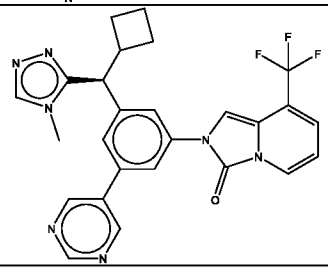
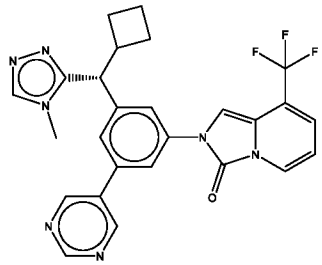
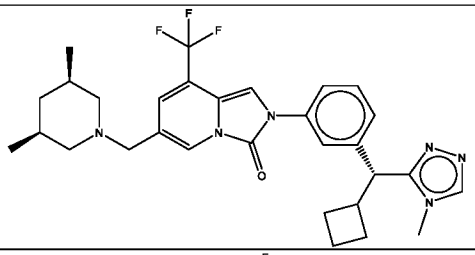
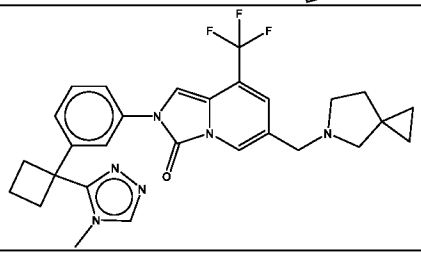
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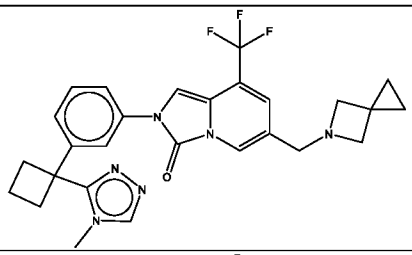
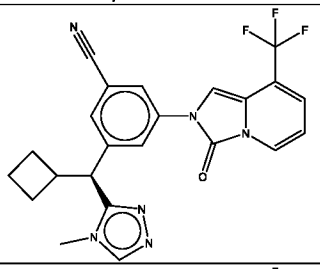
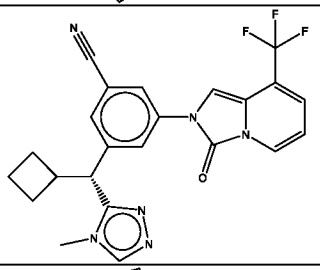
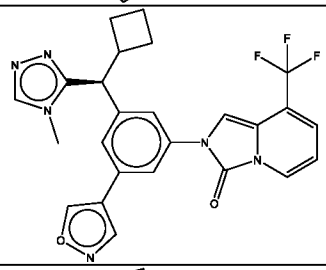
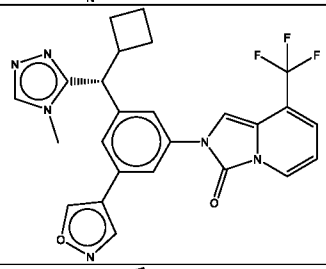
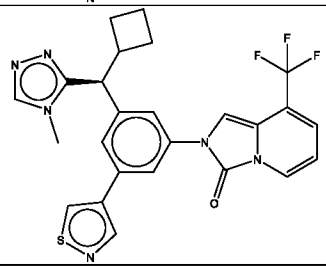
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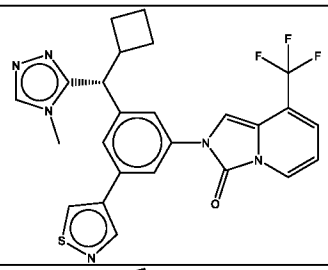
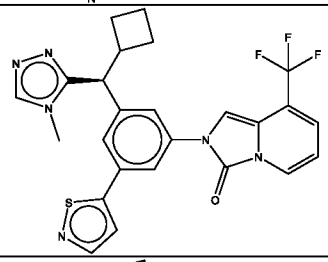
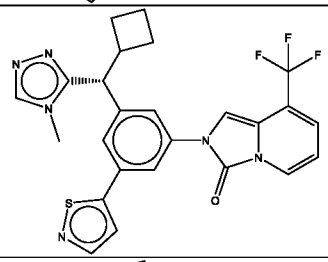
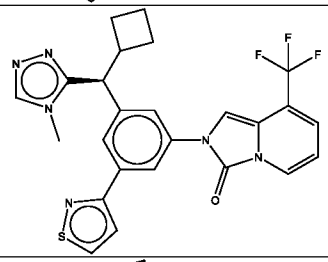
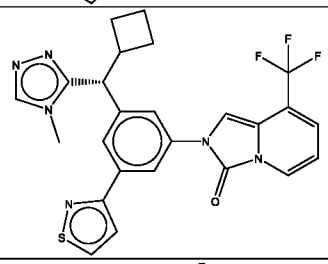
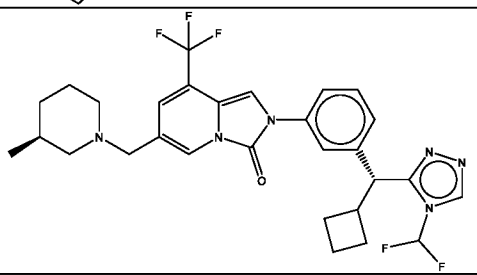
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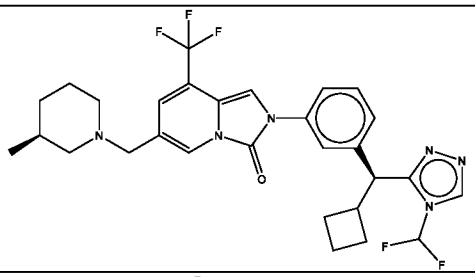
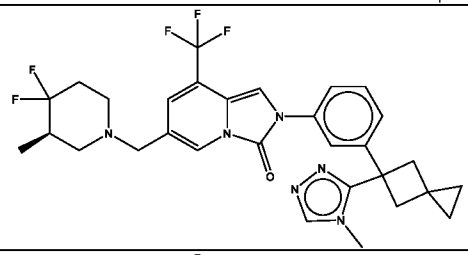
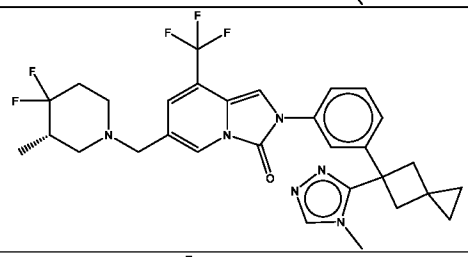
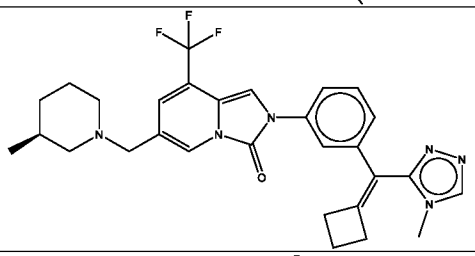
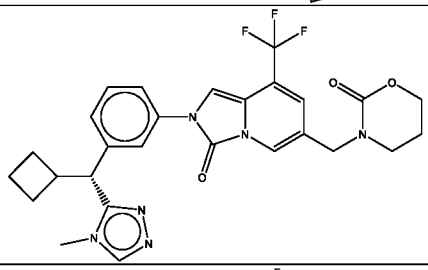
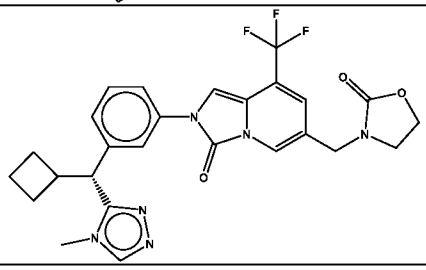
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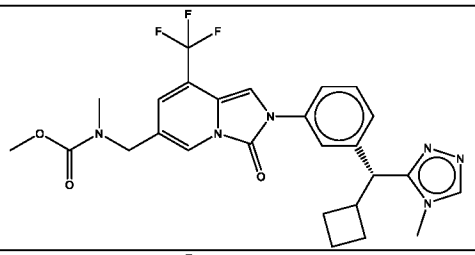
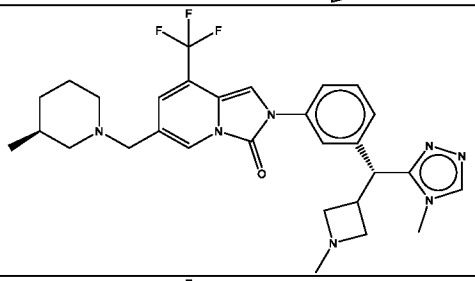
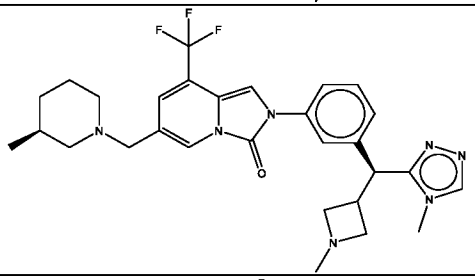
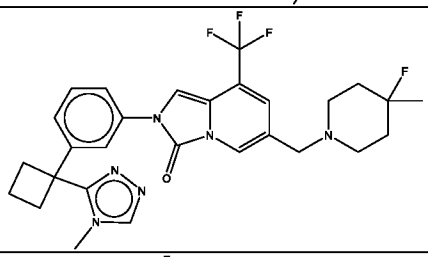
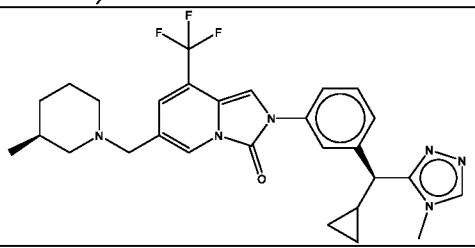
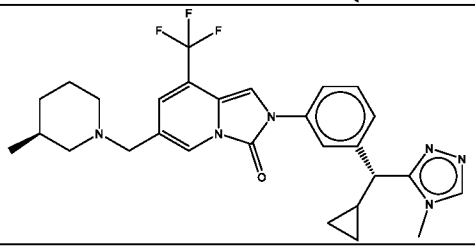
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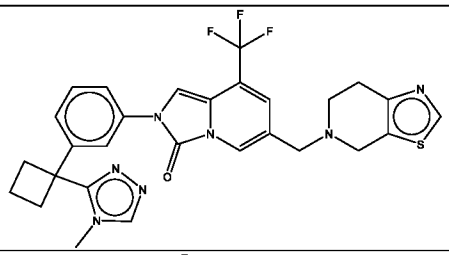
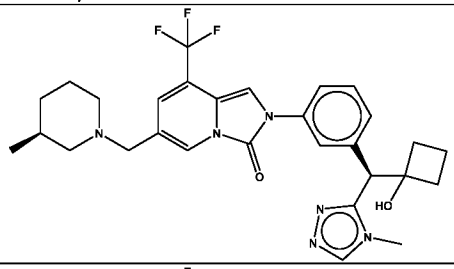
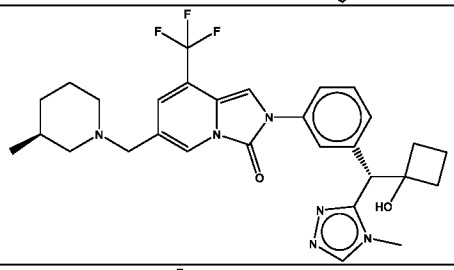
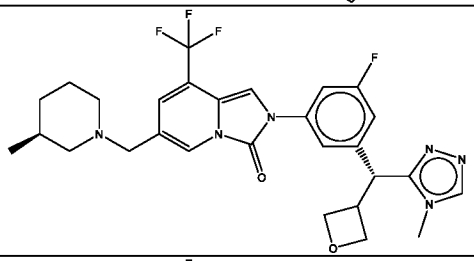
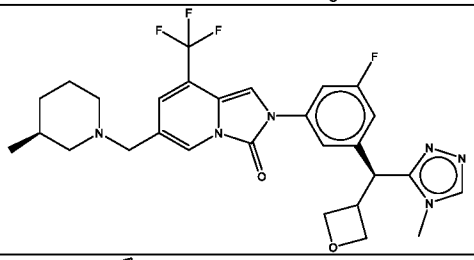
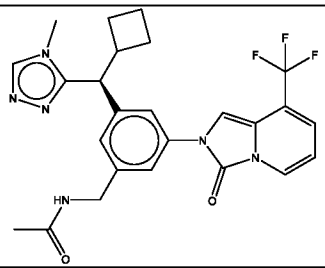
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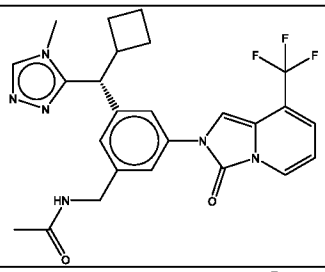
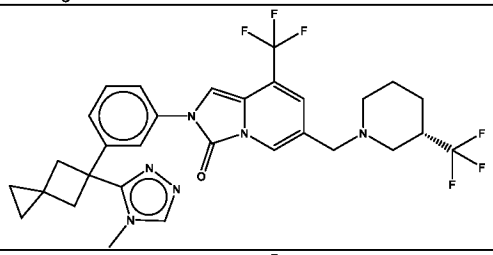
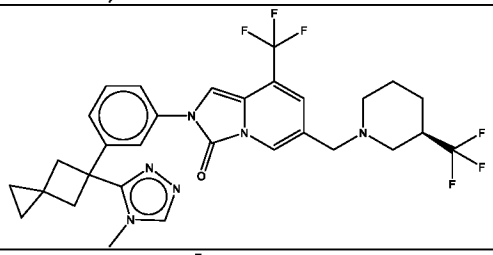
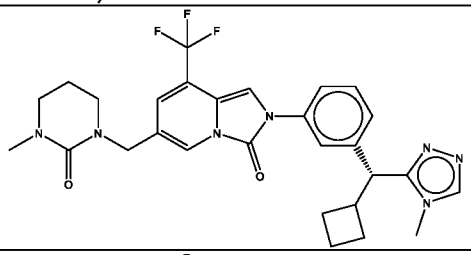
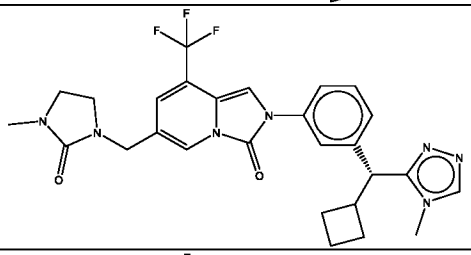
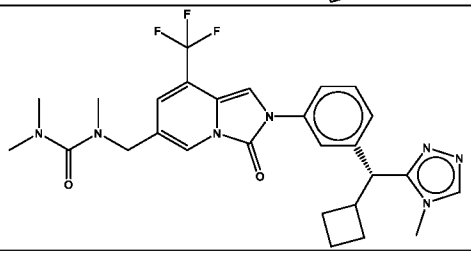
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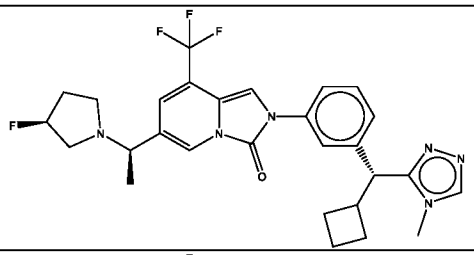
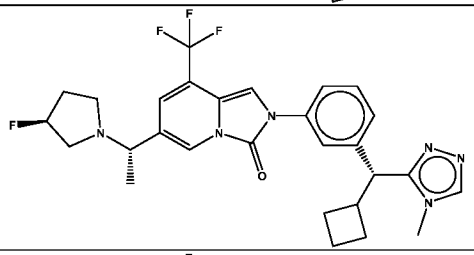
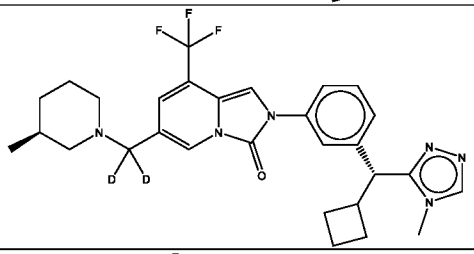
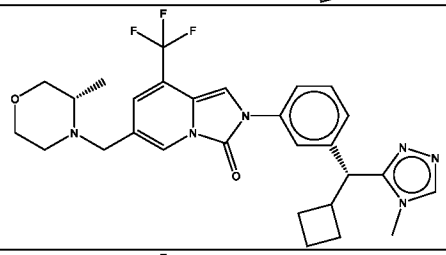
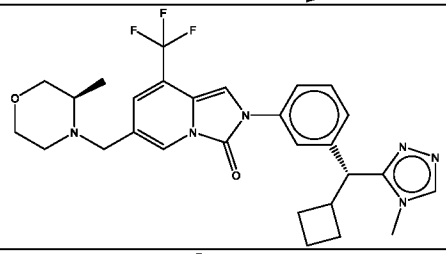
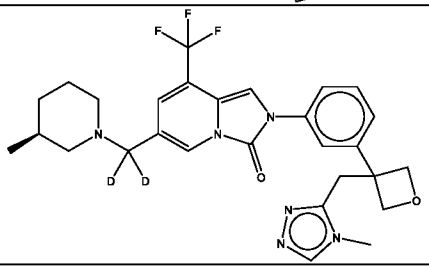
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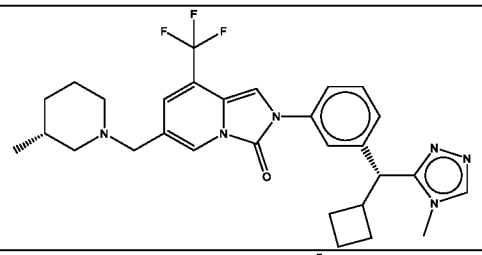
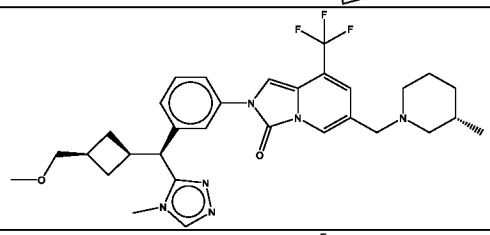
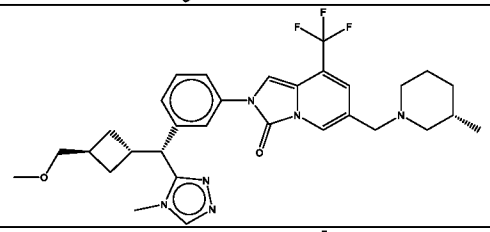
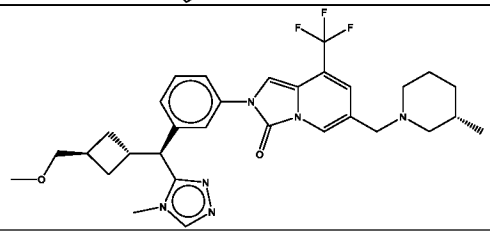
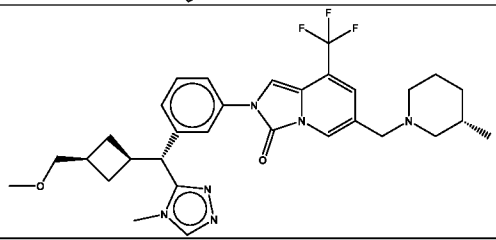
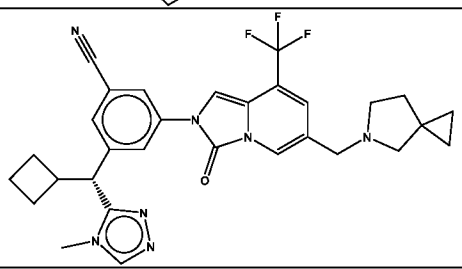
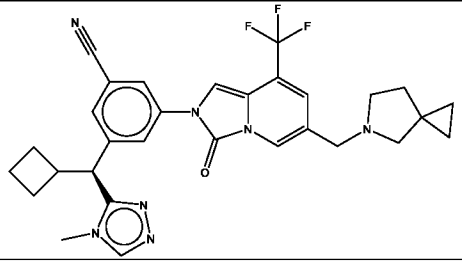
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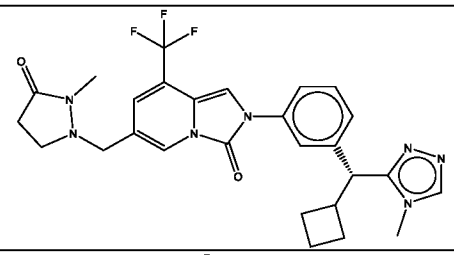
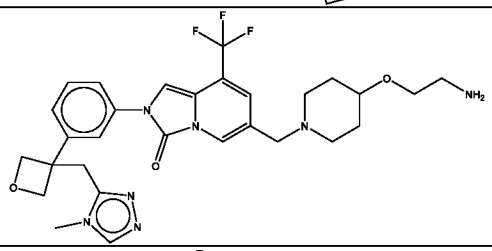
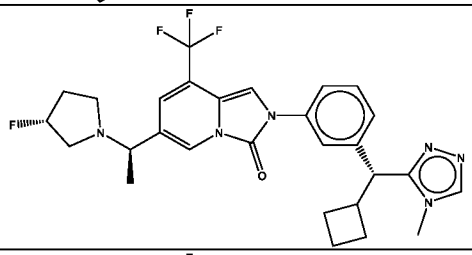
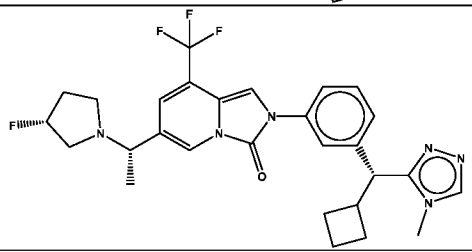
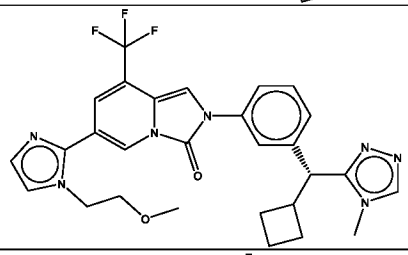
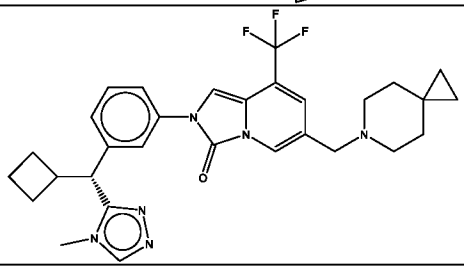
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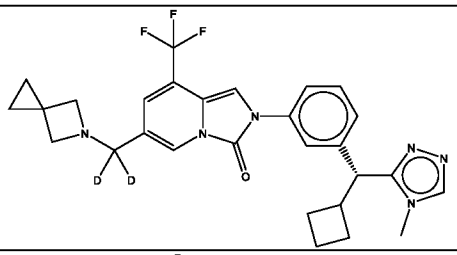
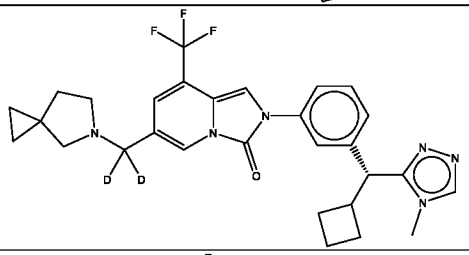
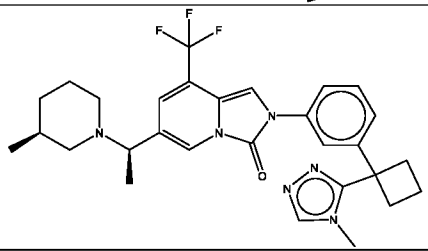
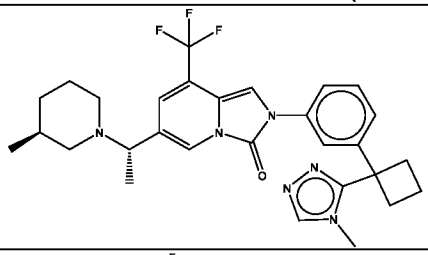
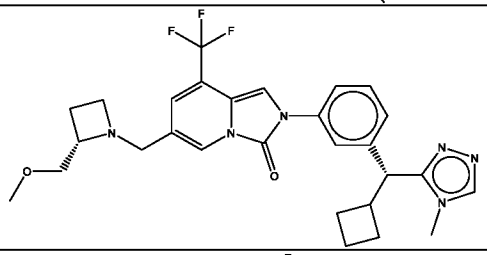
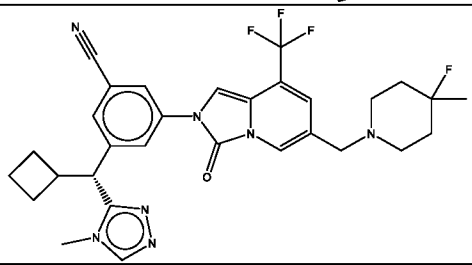
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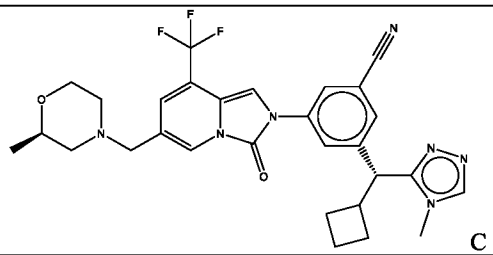
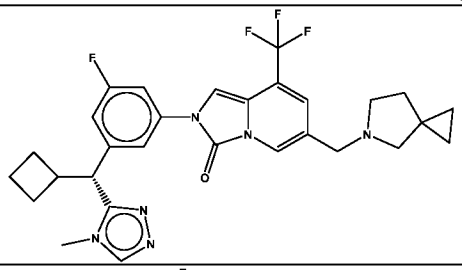
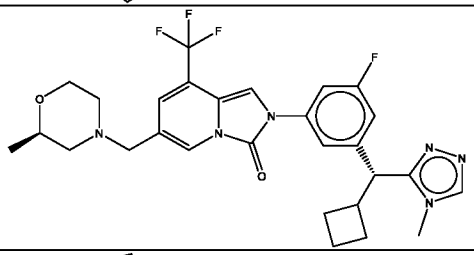
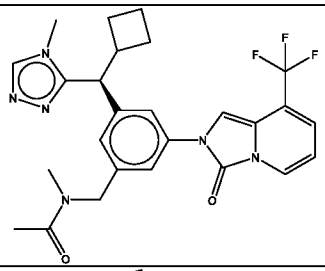
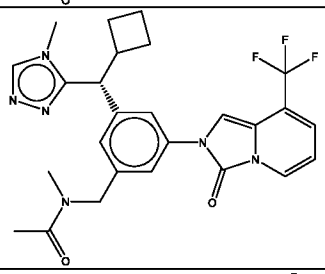
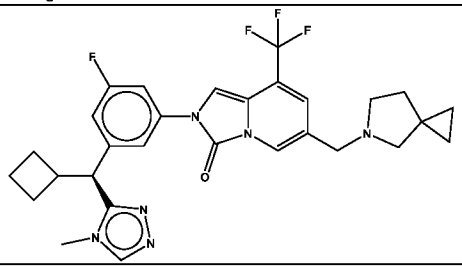
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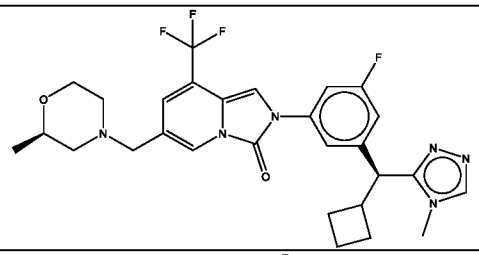
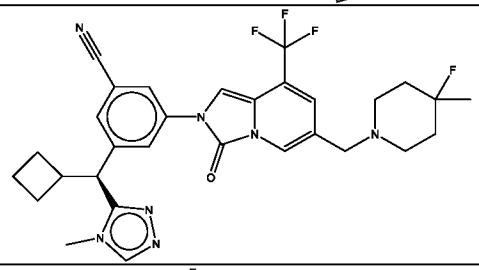
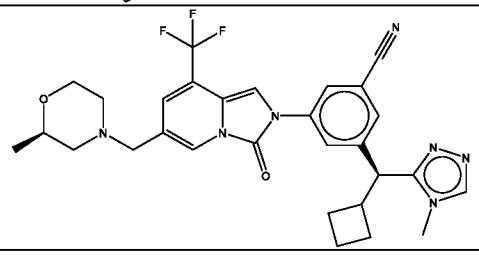
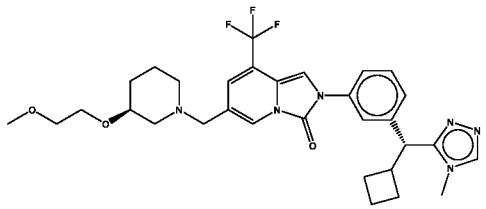
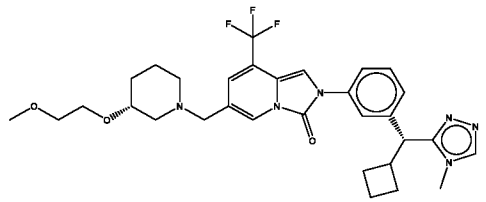
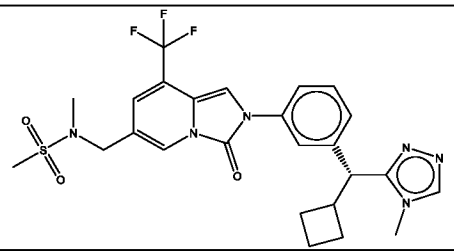
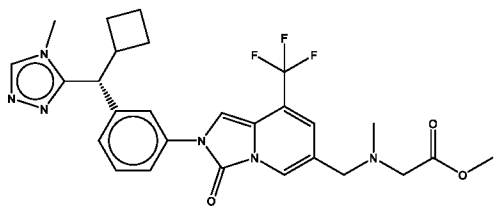
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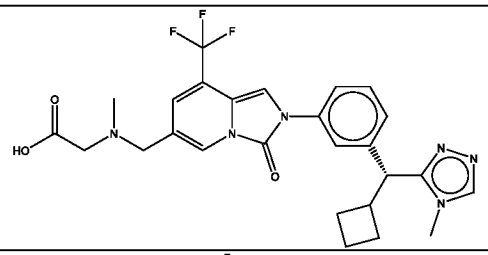
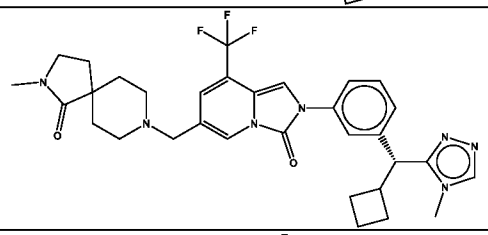
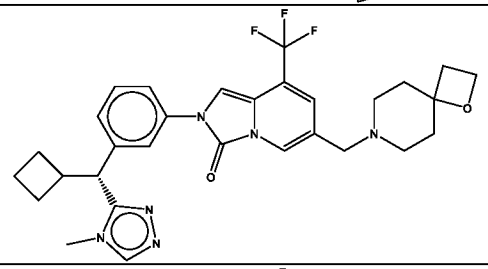
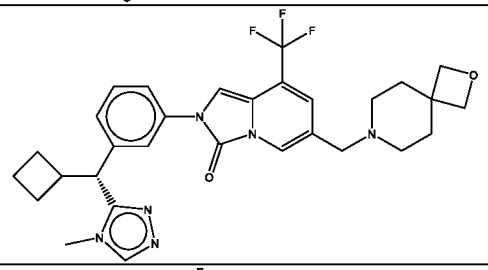
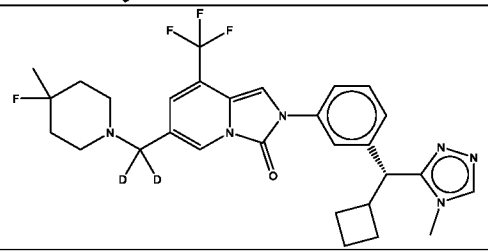
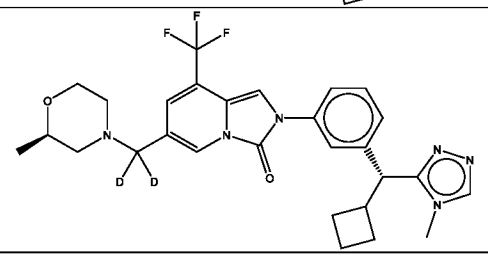
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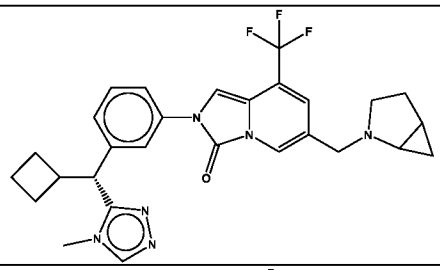
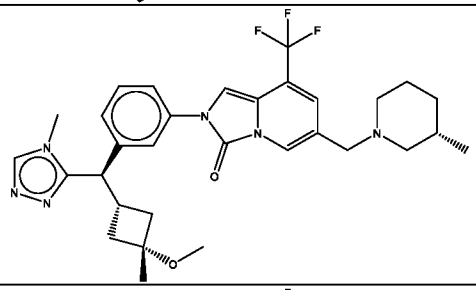
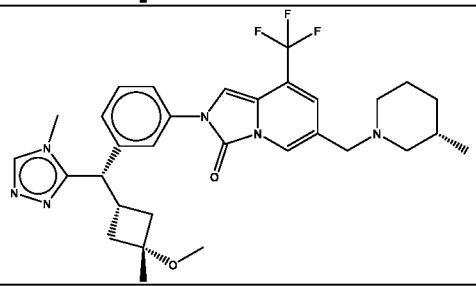
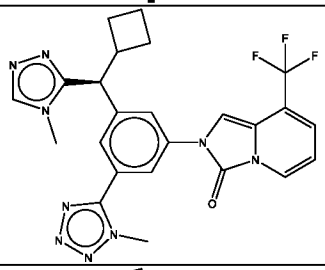
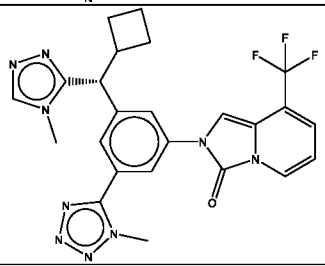
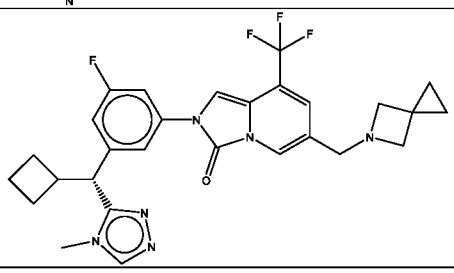
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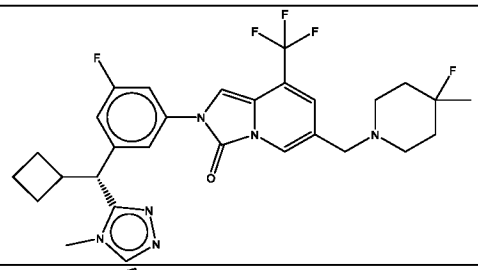
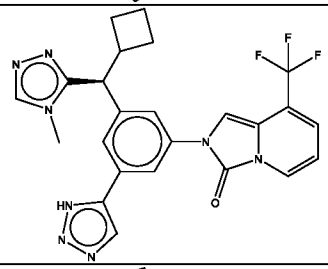
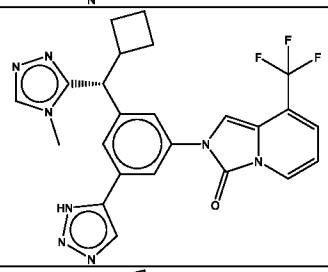
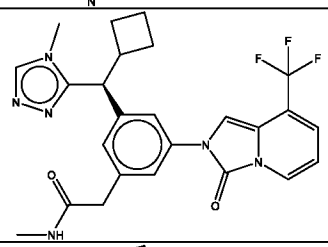
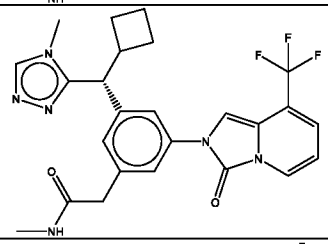
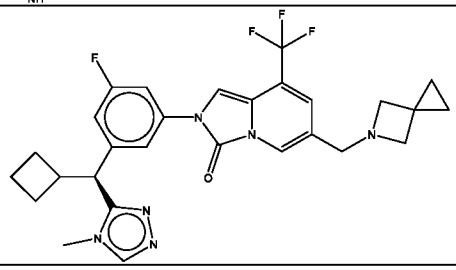
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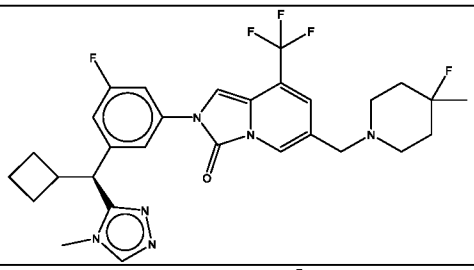
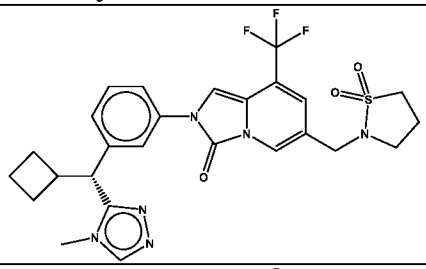
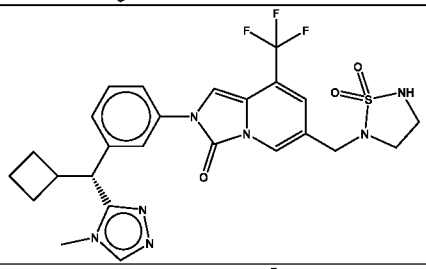
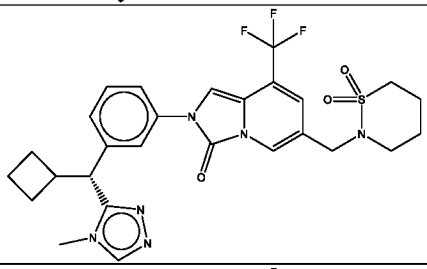
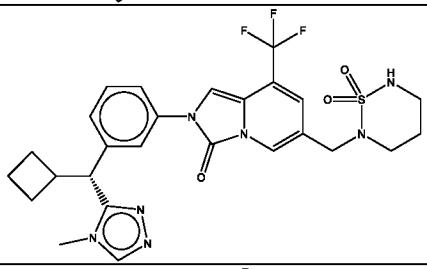
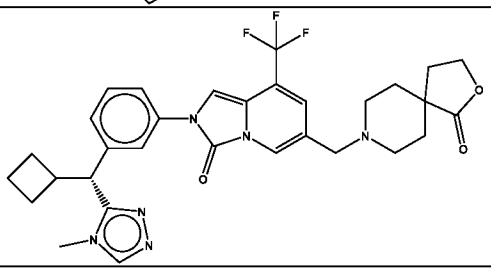
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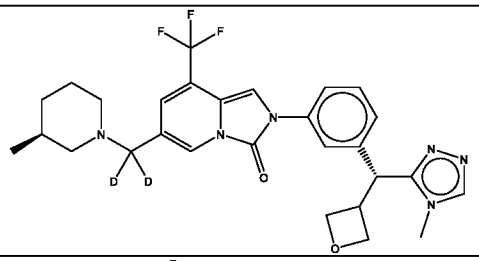
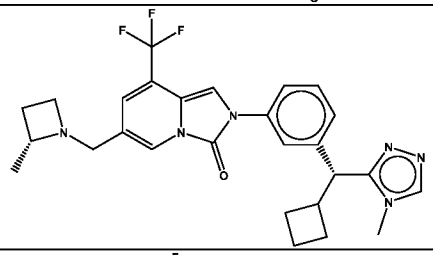
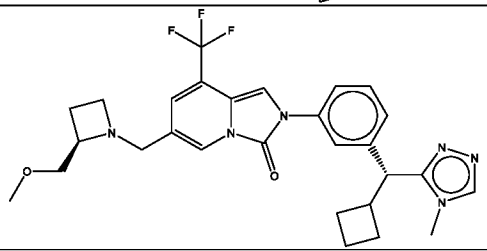
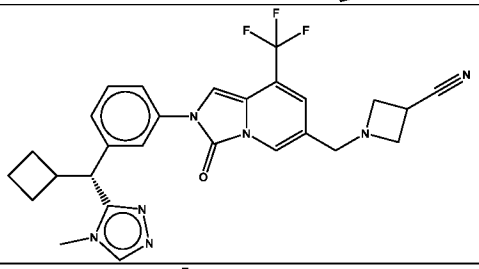
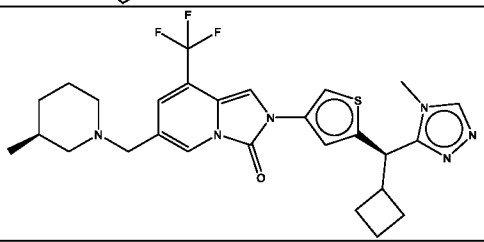
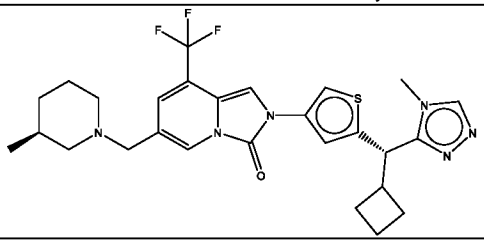
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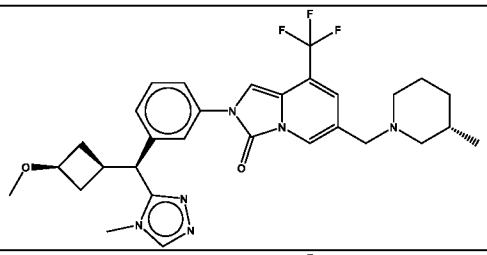
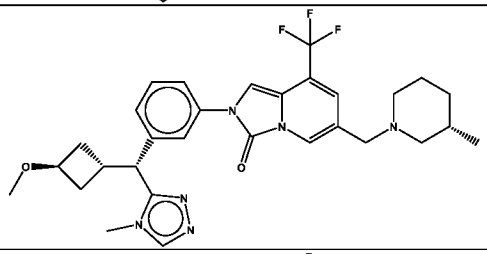
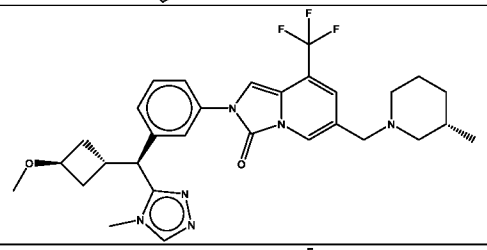
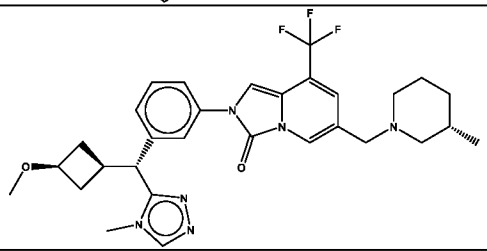
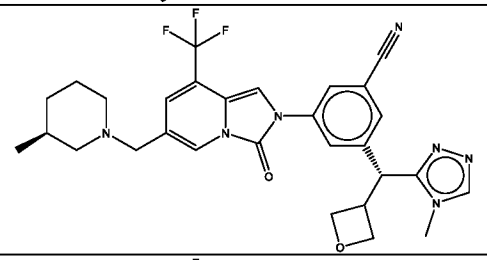
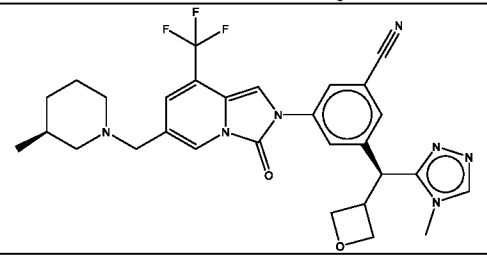
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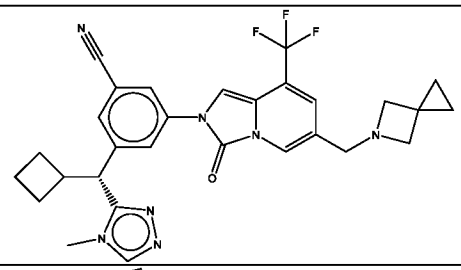
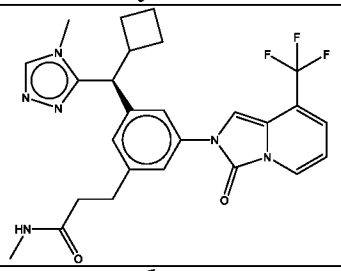
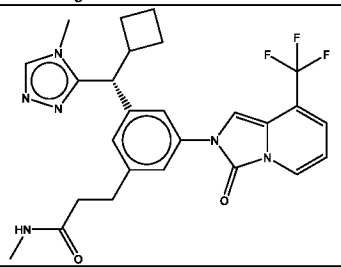
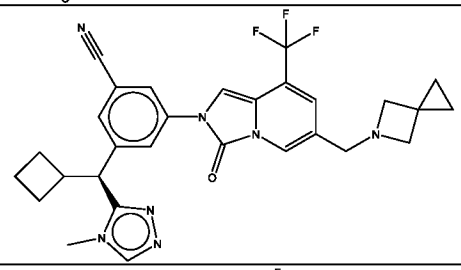
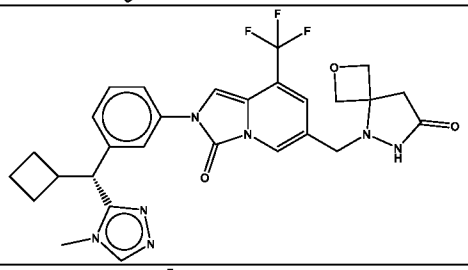
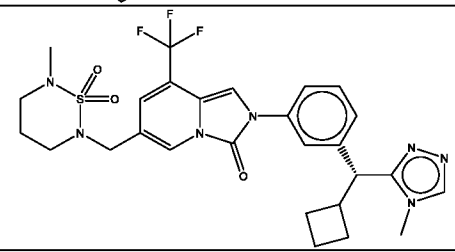
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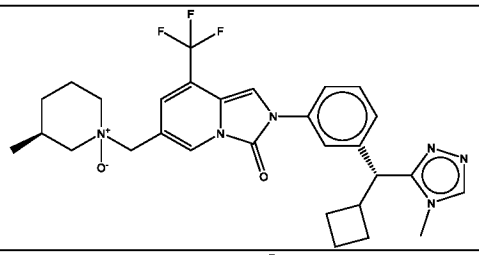
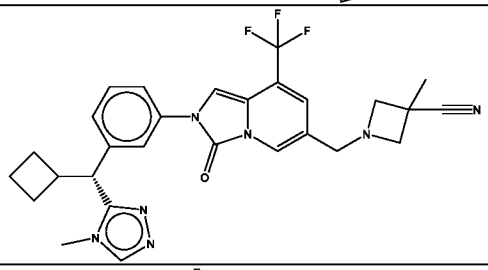
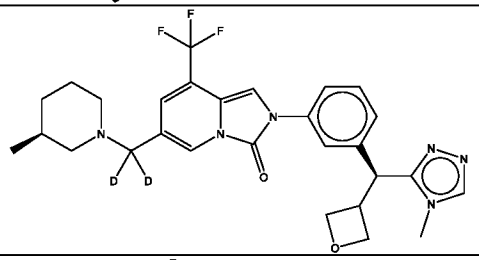
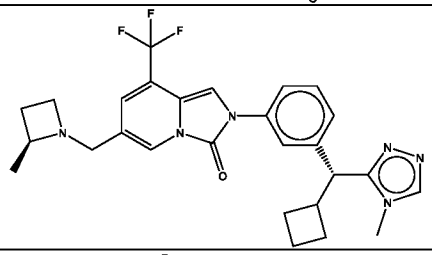
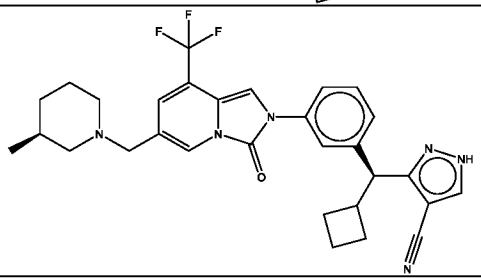
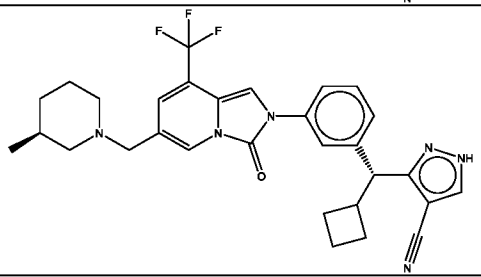
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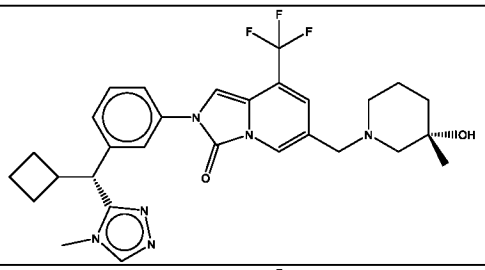
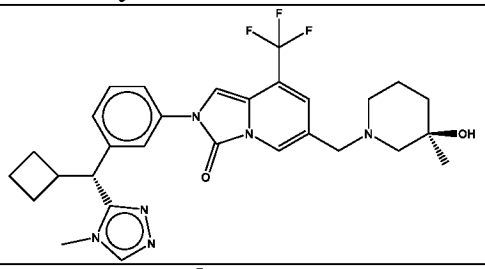
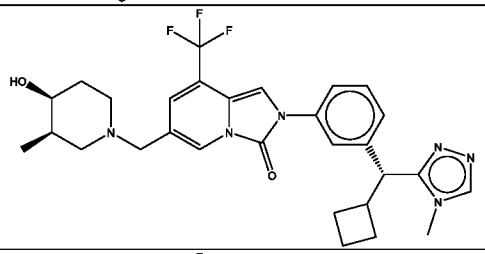
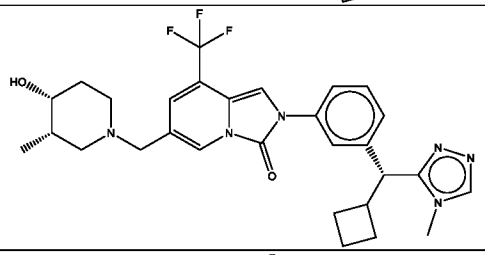
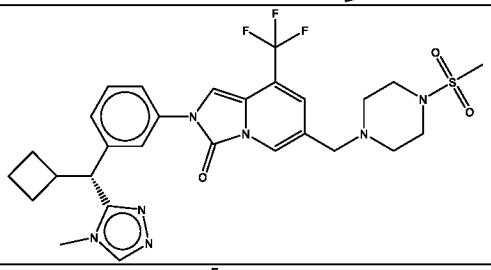
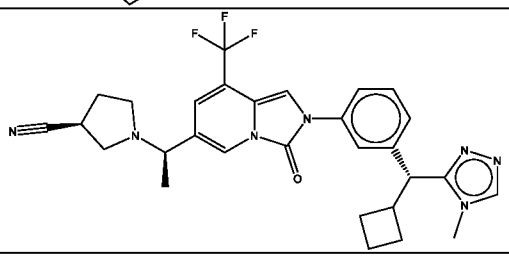
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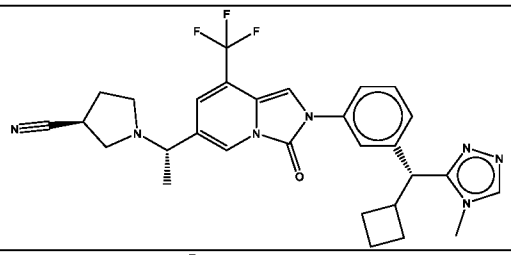
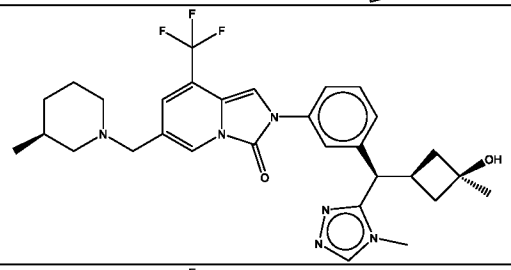
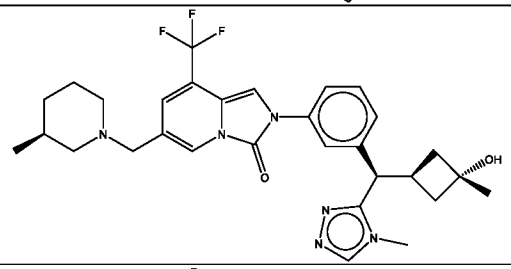
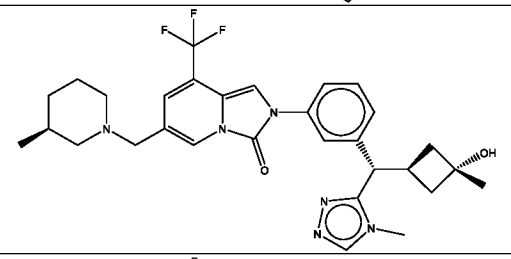
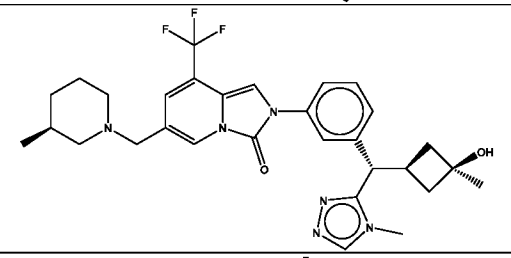
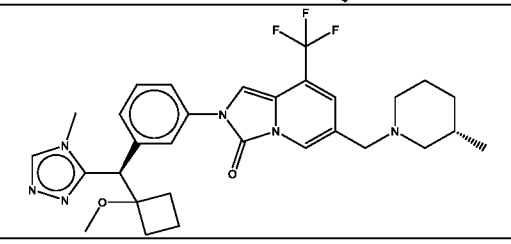
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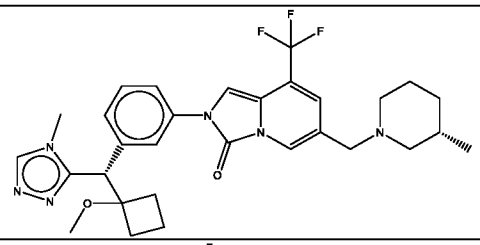
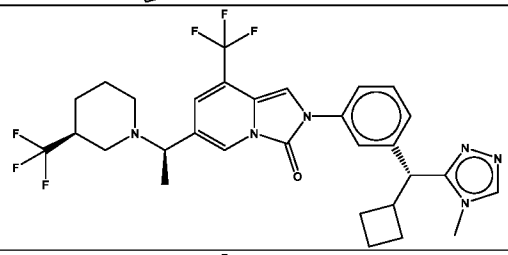
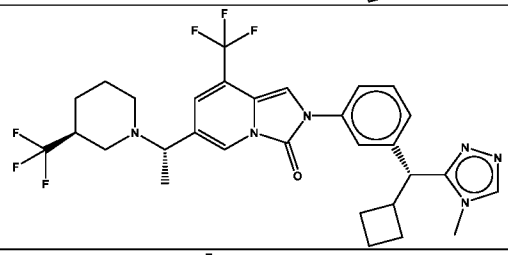
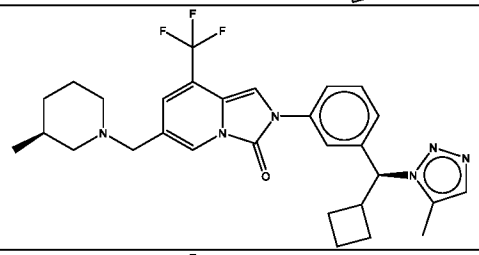
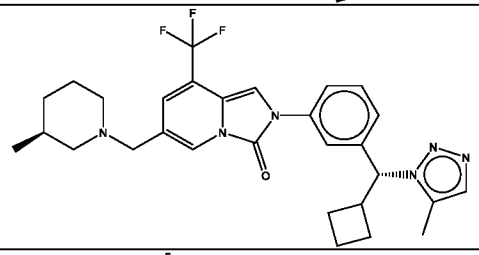
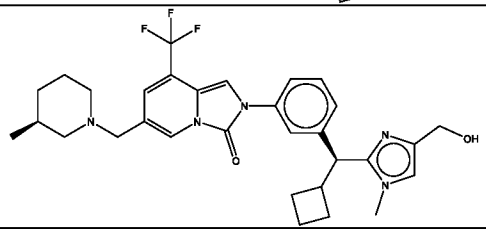
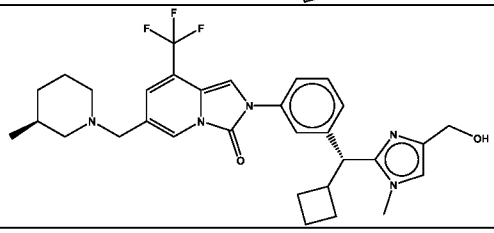
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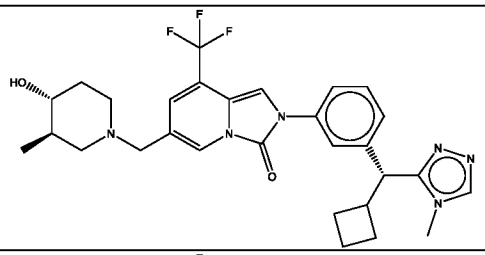
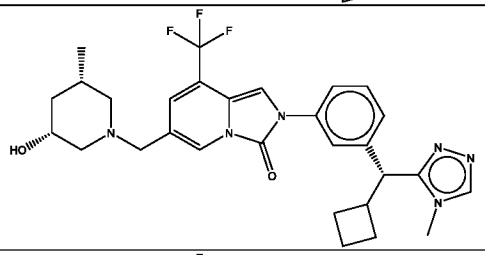
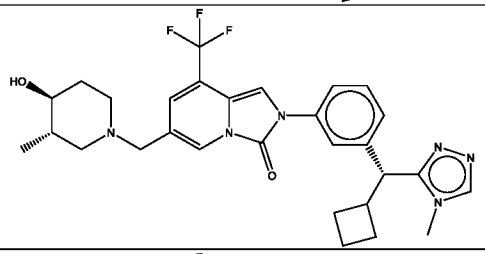
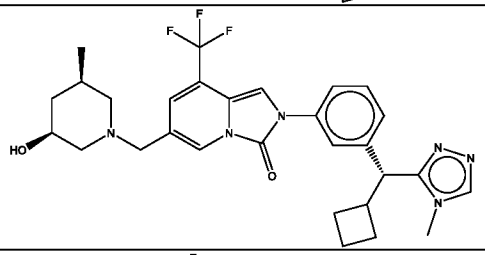
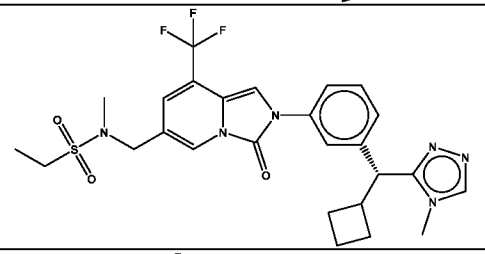
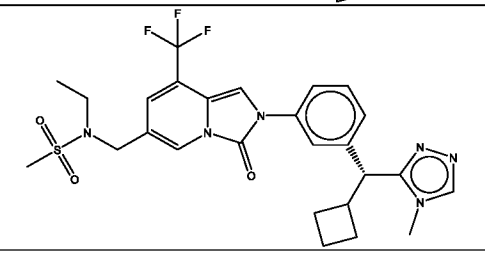
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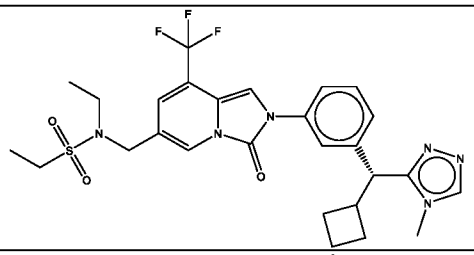
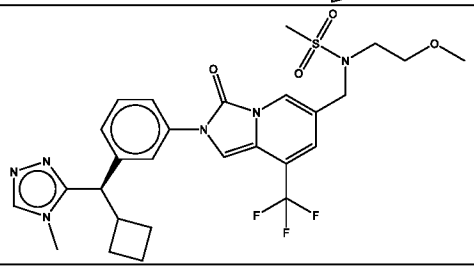
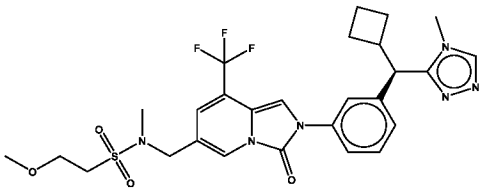
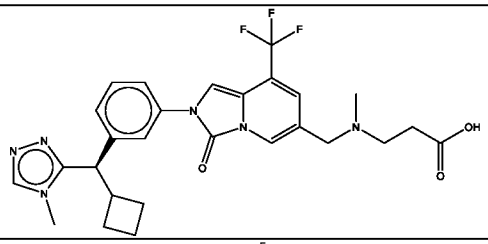
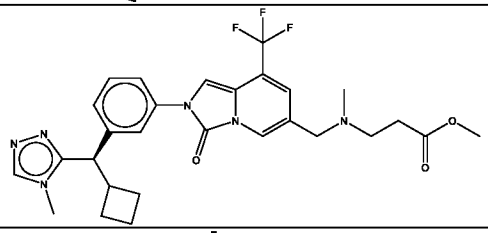
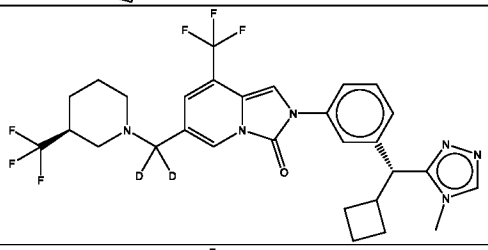
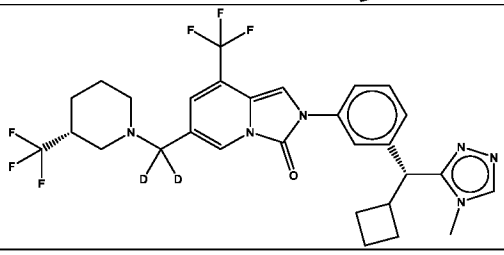
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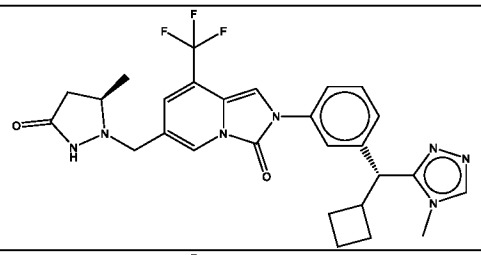
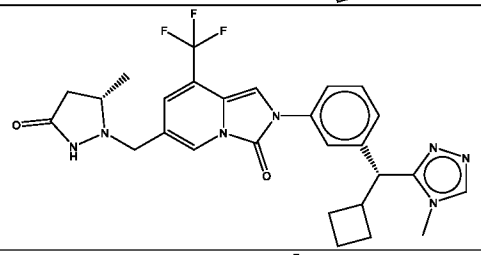
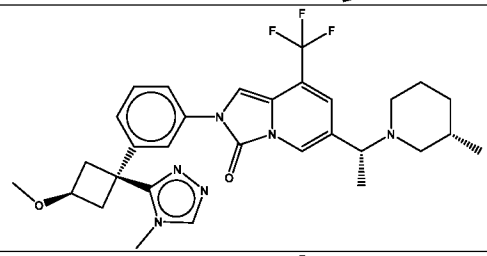
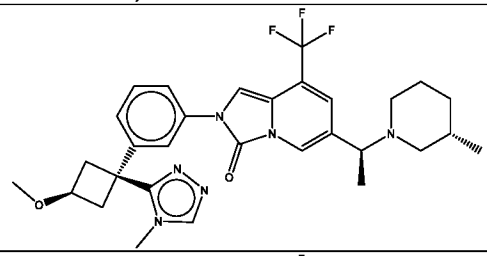
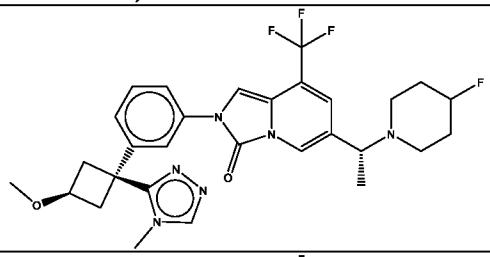
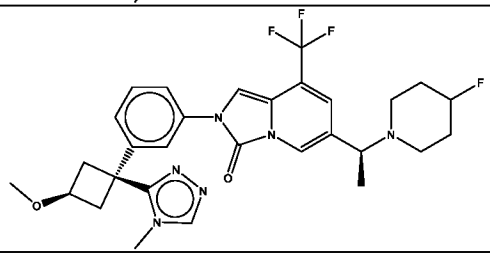
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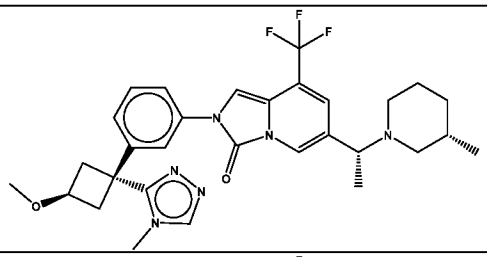
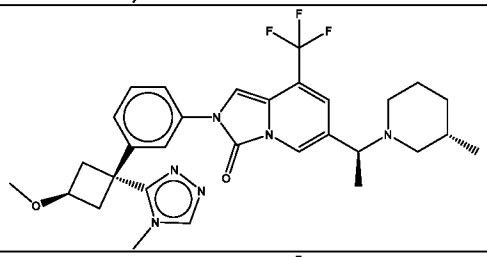
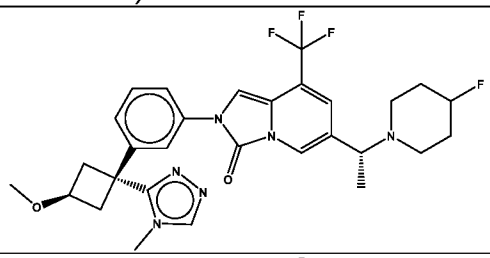
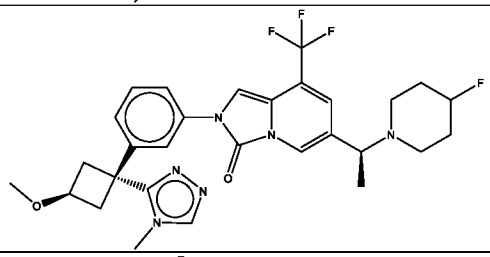
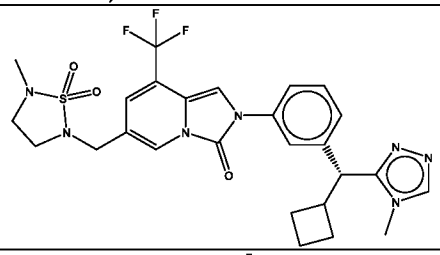
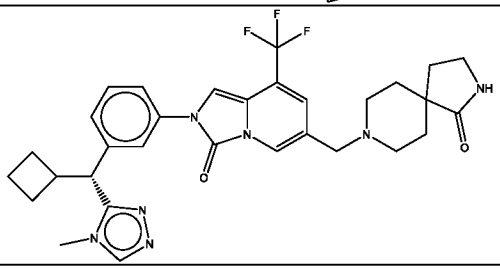
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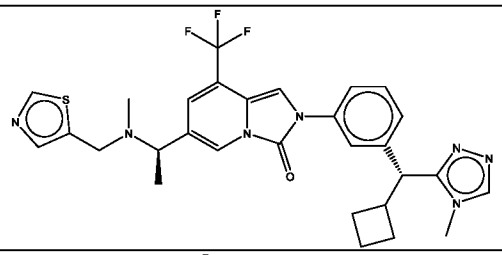
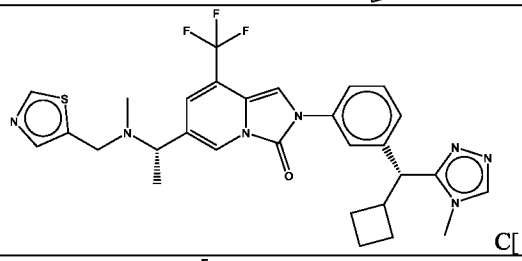
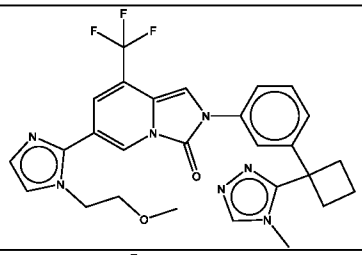
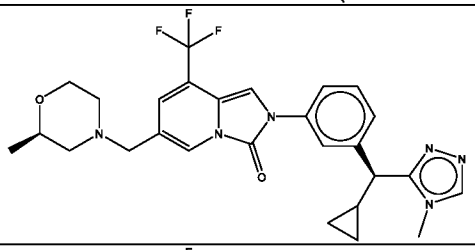
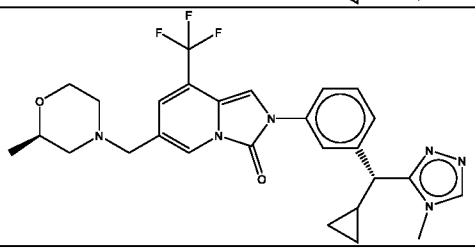
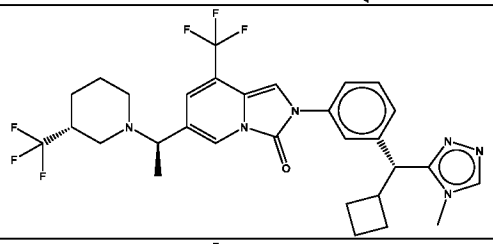
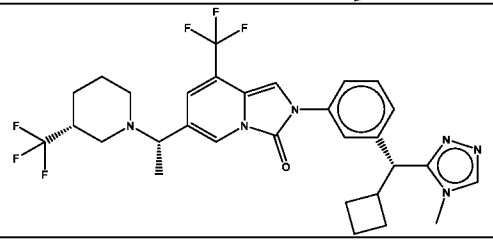
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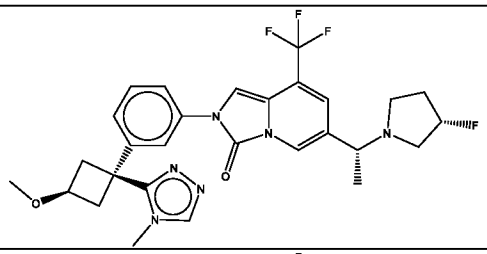
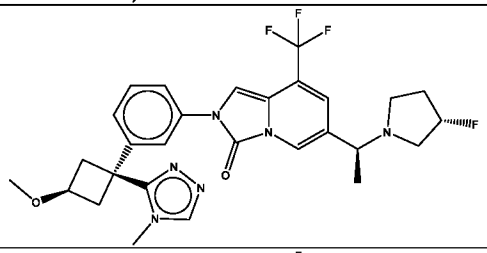
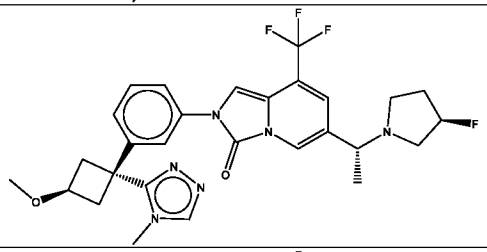
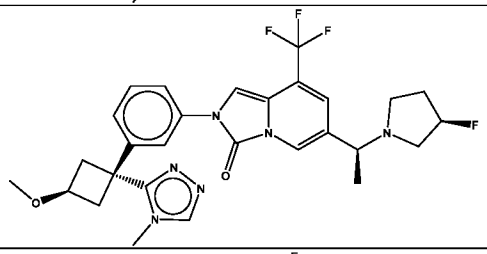
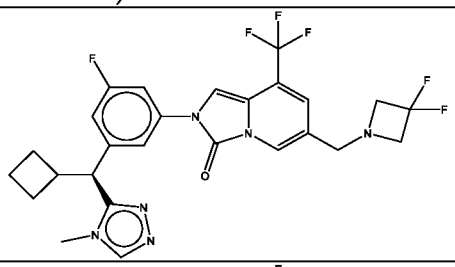
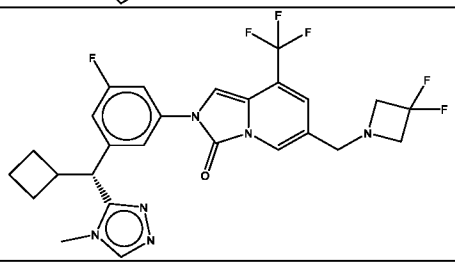
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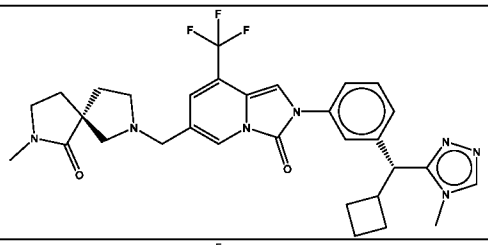
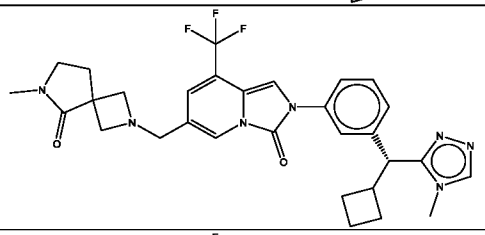
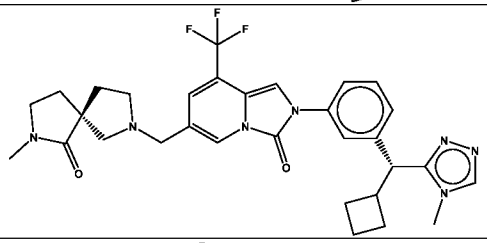
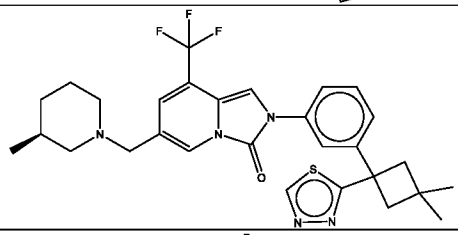
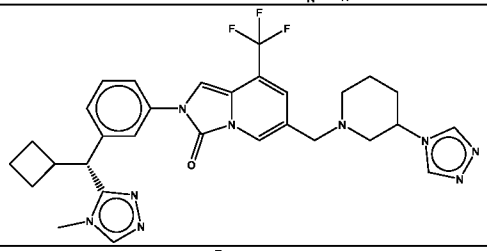
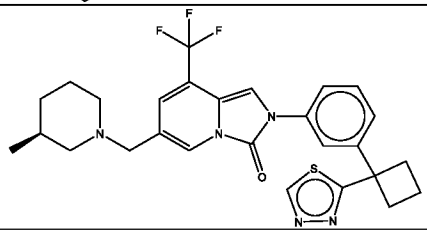
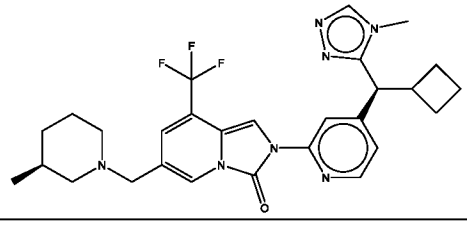
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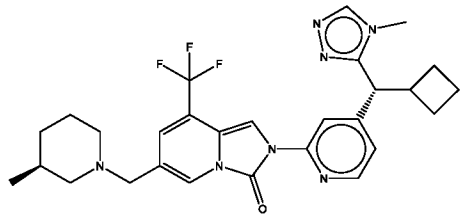
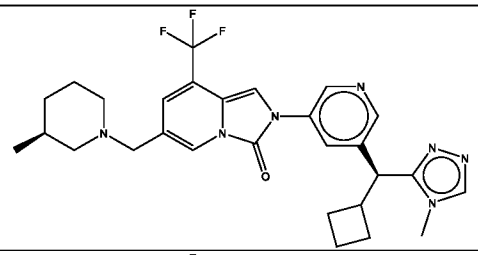
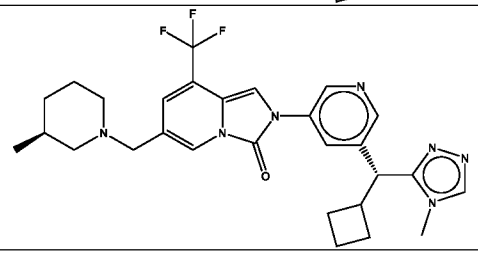
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or a pharmaceutically acceptable salt thereof

[033] A person of skill in the art will understand the present disclosure includes compounds with the stereochemistry which are the opposite of how they have been drawn. Additionally, the present disclosure contemplates tautomers of the compounds as drawn herein.

[034] The present disclosure includes the racemate of any compound disclosed herein.

Definitions

[035] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments,

"cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[036] The term "haloaliphatic" refers to an aliphatic group that is substituted with one or more halogen atoms.

[037] The term "alkyl" refers to a straight or branched alkyl group. Exemplary alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl.

[038] The term "haloalkyl" refers to a straight or branched alkyl group that is substituted with one or more halogen atoms.

[039] The term "halogen" means F, Cl, Br, or I.

[040] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[041] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the

heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-l,4-oxazin- 3(4H)-one. A heteroaryl group may be mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[042] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4- dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in TV-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3H-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[043] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass

rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[044] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[045] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; —$(CH_2)_{0-4}R^\circ$; —$(CH_2)_{0-4}OR^\circ$; —$O(CH_2)_{0-4}R^\circ$, —O—$(CH_2)_{0-4}C(O)OR^\circ$; —$(CH_2)_{0-4}CH(OR^\circ)_2$; —$(CH_2)_{0-4}SR^\circ$; —$(CH_2)_{0-4}Ph$, which may be substituted with R°; —$(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; —CH=CHPh, which may be substituted with R°; —$(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; —NO_2; —CN; —N_3; —$(CH_2)_{0-4}N(R^\circ)_2$; —$(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; —$N(R^\circ)C(S)R^\circ$; —$(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ{}_2$; —$N(R^\circ)C(S)NR^\circ{}_2$; —$(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; —$N(R^\circ)N(R^\circ)C(O)R^\circ$; —$N(R^\circ)N(R^\circ)C(O)NR^\circ{}_2$; —$N(R^\circ)N(R^\circ)C(O)OR^\circ$; —$(CH_2)_{0-4}C(O)R^\circ$; —$C(S)R^\circ$; —$(CH_2)_{0-4}C(O)OR^\circ$; —$(CH_2)_{0-4}C(O)SR^\circ$; —$(CH_2)_{0-4}C(O)OSiR^\circ{}_3$; —$(CH_2)_{0-4}OC(O)R^\circ$; —$OC(O)(CH_2)_{0-4}SR^\circ$, SC(S)SR°; —$(CH_2)_{0-4}SC(O)R^\circ$; —$(CH_2)_{0-4}C(O)NR^\circ{}_2$; —$C(S)NR^\circ{}_2$; —C(S)SR°; —SC(S)SR°, —$(CH_2)_{0-4}OC(O)NR^\circ{}_2$; —$C(O)N(OR^\circ)R^\circ$; —$C(O)C(O)R^\circ$; —$C(O)CH_2C(O)R^\circ$; —$C(NOR^\circ)R^\circ$; —$(CH_2)_{0-4}SSR^\circ$; —$(CH_2)_{0-4}S(O)_2R^\circ$; —$(CH_2)_{0-4}S(O)_2OR^\circ$; —$(CH_2)_{0-4}OS(O)_2R^\circ$; —$S(O)_2NR^\circ{}_2$; —$(CH_2)_{0-4}S(O)R^\circ$; —$N(R^\circ)S(O)_2NR^\circ{}_2$; —$N(R^\circ)S(O)_2R^\circ$; —$N(OR^\circ)R^\circ$; —$C(NH)NR^\circ{}_2$; —$P(O)_2R^\circ$; —$P(O)R^\circ{}_2$; —$OP(O)R^\circ{}_2$; —$OP(O)(OR^\circ)_2$; $SiR^\circ{}_3$; —(C_{1-4} straight or branched alkylene)O—$N(R^\circ)_2$; or —(C_{1-4} straight or branched alkylene)C(O)O—$N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, —CH_2Ph, —$O(CH_2)_{0-1}Ph$, —CH_2-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or,

notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[046] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, —$(CH_2)_{0-2}R^\bullet$, -(halo$R^\bullet$), —$(CH_2)_{0-2}OH$, —$(CH_2)_{0-2}OR^\bullet$, —$(CH_2)_{0-2}CH(OR^\bullet)_2$; —O(halo$R^\bullet$), —CN, —$N_3$, —$(CH_2)_{0-2}C(O)R^\bullet$, —$(CH_2)_{0-2}C(O)OH$, —$(CH_2)_{0-2}C(O)OR^\bullet$, —$(CH_2)_{0-2}SR^\bullet$, —$(CH_2)_{0-2}SH$, —$(CH_2)_{0-2}NH_2$, —$(CH_2)_{0-2}NHR^\bullet$, —$(CH_2)_{0-2}NR^\bullet{}_2$, —$NO_2$, —$SiR^\bullet{}_3$, —$OSiR^\bullet{}_3$, —$C(O)SR^\bullet$, —($C_{1-4}$ straight or branched alkylene)$C(O)OR^\bullet$, or —$SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, —CH_2Ph, —$O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[047] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, =NNR^*_2, =NNHC(O)R^*, =NNHC(O)OR^*, =$NNHS(O)_2R^*$, =NR^*, =NOR^*, —$O(C(R^*_2))_{2-3}O$—, or —$S(C(R^*_2))_{2-3}S$—, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: —$O(CR^*_2)_{2-3}O$—, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[048] Suitable substituents on the aliphatic group of R^* include halogen, —$R^\bullet$, -(halo$R^\bullet$), —OH, —$OR^\bullet$, —O(halo$R^\bullet$), —CN, —C(O)OH, —$C(O)OR^\bullet$, —NH_2, —$NHR^\bullet$, —$NR^\bullet{}_2$, or —NO_2, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, —CH_2Ph, —$O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[049] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include —$R^{\dagger}$, —$NR^{\dagger}_2$, —$C(O)R^{\dagger}$, —$C(O)OR^{\dagger}$, —$C(O)C(O)R^{\dagger}$, —$C(O)CH_2C(O)R^{\dagger}$, —$S(O)_2R^{\dagger}$, —$S(O)_2NR^{\dagger}_2$, —$C(S)NR^{\dagger}_2$, —$C(NH)NR^{\dagger}_2$, or —$N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted —OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[050] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, —$R^{\bullet}$, -(halo$R^{\bullet}$), —OH, —$OR^{\bullet}$, —O(halo$R^{\bullet}$), —CN, —C(O)OH, —$C(O)OR^{\bullet}$, —NH_2, —$NHR^{\bullet}$, —$NR^{\bullet}_2$, or —NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, —CH_2Ph, —$O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[051] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-

naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[052] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[053] Combinations of substituents and variables envisioned by this disclosure are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

[054] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[055] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Examples of such purposes include, but are not limited to, blood transfusion, organ transplantation, biological specimen storage, and biological assays.

[056] As used herein, a "therapeutically effective amount" means an amount of a substance (e.g., a therapeutic agent, composition, and/or formulation) that elicits a desired biological response. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered as part of a dosing regimen to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of a provided compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or

more symptoms or features of the disease, disorder, and/or condition. I

[057] As used herein, the terms "treatment," "treat," and "treating" refer to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disorder or condition, or one or more symptoms of the disorder or condition, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In some embodiments, the term "treating" includes preventing or halting the progression of a disease or disorder. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence. Thus, in some embodiments, the term "treating" includes preventing relapse or recurrence of a disease or disorder.

[058] The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[059] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound(s) with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of the compounds disclosed herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[060] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitorily active metabolite or residue thereof.

[061] The expression “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that total daily usage of compounds and compositions of the present disclosure will be decided by the

attending physician within the scope of sound medical judgment. Specific effective dose level for any particular patient or organism will depend upon a variety of factors including disorder being treated and severity of the disorder; activity of specific compound employed; specific composition employed; age, body weight, general health, sex and diet of the patient; time of administration, route of administration, and rate of excretion of a specific compound employed; duration of treatment; drugs used in combination or coincidental with a specific compound employed, and like factors well known in the medical arts.

Alternative Embodiments

[062] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be ^{2}H (D or deuterium) or ^{3}H (T or tritium); carbon may be, for example, ^{13}C or ^{14}C; oxygen may be, for example, ^{18}O; nitrogen may be, for example, ^{15}N, and the like. In other embodiments, a particular isotope (*e.g.*, ^{3}H, ^{13}C, ^{14}C, ^{18}O, or ^{15}N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

Pharmaceutical Compositions

[063] In some embodiments, the present disclosure provides a composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In some embodiments, the amount of compound in compositions contemplated herein is such that is effective to measurably treat a disease or disorder in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this disclosure is such that is effective to measurably treat a disease or disorder in a biological sample or in a patient. In certain embodiments, a composition contemplated by this disclosure is formulated for administration to a patient in need of such composition. In some embodiments, a composition contemplated by this disclosure is formulated for oral administration to a patient.

[064] In some embodiments, compositions of the present disclosure may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some preferred embodiments, compositions are administered

orally, intraperitoneally or intravenously. In some embodiments, sterile injectable forms of the compositions comprising one or more compounds of Formula (I) may be aqueous or oleaginous suspension. In some embodiments, suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. In some embodiments, sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. In some embodiments, among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In some embodiments, additional examples include, but are not limited to, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[065] The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

[066] Pharmaceutically acceptable compositions comprising one or more compounds of Formula (I) may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In some embodiments, carriers used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. In some embodiments, useful diluents include lactose and dried cornstarch. In some embodiments, when aqueous suspensions are required for oral use, an active ingredient is combined with emulsifying and suspending agents. In some embodiments, certain sweetening, flavoring or coloring agents may also be added.

[067] Alternatively, pharmaceutically acceptable compositions comprising a compound of Formula (I) may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[068] Pharmaceutically acceptable compositions comprising a compound of Formula (I) may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs. In some embodiments, pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene

glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[069] Pharmaceutically acceptable compositions comprising a compound of Formula (I) may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[070] In some embodiments, an amount of a compound of the present disclosure that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

Methods of Using Compounds of the Present Disclosure

[071] In some embodiments, the present disclosure provides a method for treating or lessening the severity of a disease or condition associated with cell proliferation in a patient comprising the step of administering to said patient a composition according to the present disclosure.

[072] The term "disease or condition associated with cell proliferation", as used herein means any disease or other deleterious condition in which cell proliferation is known to play a role. Accordingly, another embodiment of the present disclosure relates to treating or lessening the severity of one or more diseases in which cell proliferation is known to play a role. In some embodiments, a disease or condition associated with cell proliferation is hyperplasia or cancer. In some embodiments, a disease or condition associated with cell proliferation is cancer.

[073] In some embodiments, administration of a compound of the present disclosure results in arrest of mitosis.

[074] In some embodiments, administration of a compound of the present disclosure results

in arrest of mitosis. In some embodiments, mitotic arrest is defined as a 10-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 20-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 30-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 40-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 50-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 60-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 70-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 80-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 90-100% reduction in mitosis. In some embodiments, mitotic arrest is defined as a 100% reduction in mitosis.

[075] In some embodiments, compounds and compositions, according to a method of the present disclosure, may be administered using any amount and any route of administration effective for treating or lessening the severity of cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, severity of the infection, particular agent, its mode of administration, and the like. Compounds of the present disclosure are preferably formulated in dosage unit form for ease of administration and uniformity of dosage.

[076] In some embodiments, cancer is a hematologic cancer. In some embodiments, a hematologic cancer is selected from a group consisting of lymphoma, leukemia, and myeloma. In some embodiments, a hematologic cancer is lymphoma. In some embodiments, a hematologic cancer is leukemia. In some embodiments, a hematologic cancer is myeloma.

[077] In some embodiments, cancer is a non-hematologic cancer. In some embodiments, a non-hematologic cancer is a sarcoma or a carcinoma. In some embodiments, a non-hematologic cancer is a sarcoma. In some embodiments, a non-hematologic cancer is carcinoma.

[078] In some embodiments, a subject has one or more of increased T-cell activation, increased T-cell proliferation, decreased T-cell exhaustion, decreased T-cell anergy and decreased T-cell tolerance after administration of compound of the present disclosure. In some embodiments, administration of a compound of the present disclosure to a subject in need there of results in one or more of increased T-cell activation, increased T-cell proliferation, decreased T-cell exhaustion, decreased T-cell anergy and decreased T-cell tolerance.

[079] In some embodiments, a subject has increased NK-cell activation. In some embodiments, increased NK-cell activation comprises increased production of cytokines.

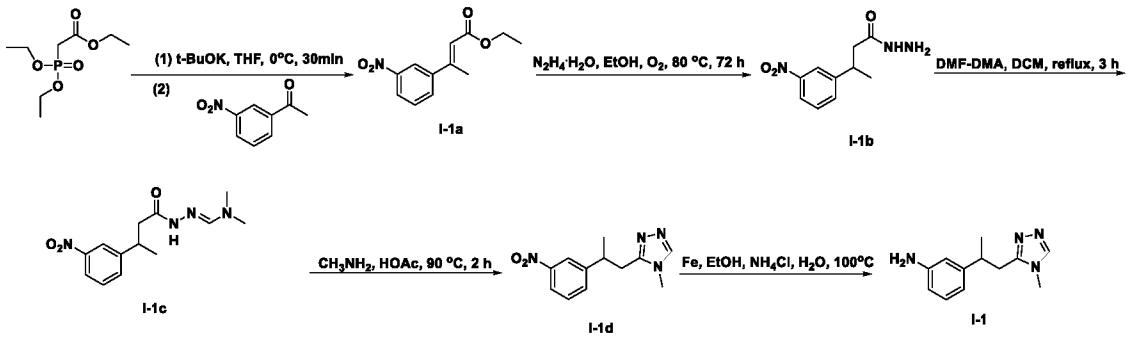
[080] In some embodiments, pharmaceutically acceptable compositions of comprising compounds of the present disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of infection being treated. In certain embodiments, compounds of the present disclose may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain desired therapeutic effect.

[081] In some embodiments, one or more additional therapeutic agents, may also be administered in combination with compounds of the present disclosure. In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be administered as part of a multiple dosage regime. In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be administered may be administered simultaneously, sequentially or within a period of time. In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be administered within five hours of one another. In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be administered within 24 hours of one another. In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be administered within one week of one another.

[082] In some embodiments, a compound of the present disclosure and one or more additional therapeutic agents may be formulated into a single dosage form.

Exemplification

Intermediate I-1: Synthesis of Intermediate 1



Synthesis of I-1a

[083] To a stirred mixture of triethyl phosphonoacetate (4.00 g, 17.842 mmol, 1.00 equiv) in THF (50.00 mL) was added t-BuOK (2.00 g, 17.842 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C under argon atmosphere. Then 3-nitroacetophenone (0.97 g, 5.888 mmol, 0.33 equiv) was added, the resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (150 mL), extracted with EA (2x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (10:1) to afford I-1a (1.2 g, 28.63%) as an orange oil.

Synthesis of I-1b

[084] To a stirred mixture of I-1a (1.20 g, 5.101 mmol, 1.00 equiv) in EtOH (20.00 mL) was added $N_2H_4.H_2O$ (2.57 g, 51.012 mmol, 10.00 equiv) in 1 portion at room temperature. The resulting mixture was stirred for 72 h at 80 °C under oxygen. The resulting mixture was concentrated under reduced pressure. The residue was dissolved with EA (30 mL), washed with water (2x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford I-1b (1.00 g, 82.5%) as an orange oil.

Synthesis of I-1c

[085] To a stirred mixture of I-1b (500.00 mg, 2.240 mmol, 1.00 equiv) in DCM (10.00 mL) was added DMF-DMA (1.07 g, 8.959 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 3 h at 40 °C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was dissolved with EA (50 mL), washed with water (10 mL), dried over anhydrous Na_2SO_4. After filtration, the combined organic layers were concentrated under reduced pressure. The residue was purified by trituration with CH_2Cl_2 / MeOH =10/1 (200 mL). The resulting mixture was concentrated under reduced pressure to afford I-1c (500 mg, 80.25%) as an orange oil.

Synthesis of I-1d

[086] To a stirred mixture of I-1c (500.00 mg, 1.796 mmol, 1.00 equiv) in HOAc (5.00 ml) was added CH_3NH_2 (5.00ml, 2M in THF) at room temperature. The resulting mixture was stirred for 2 h at 40 °C under argon atmosphere. The resulting mixture was diluted with EA (60 mL), washed with water (10 mL), dried over anhydrous Na_2SO_4. After filtration, the combined organic layers were concentrated under reduced pressure. The residue was purified by trituration with CH_2Cl_2 / MeOH =10/1 (200 mL). The resulting mixture was concentrated

under reduced pressure to afford I-1d (380 mg, 85.97%) as an orange oil.

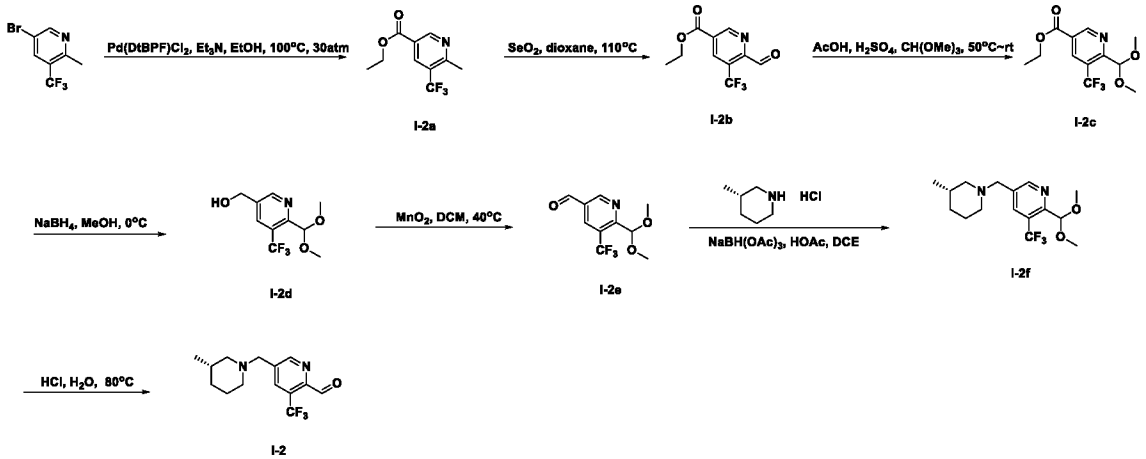
Synthesis of I-1

[087] To a stirred mixture of I-1d (380 mg, 2.030 mmol, 1.00 equiv) in EtOH (5.00 mL) were added NH_4Cl (100.00 mg, 1.869 mmol, 0.92 equiv), H_2O (5.00 mL) and Fe (566.91 mg, 10.151 mmol, 5.00 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The reaction was quenched with $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EA (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (150 mg) was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, A: water (0.05% $NH_3 \cdot H_2O$), B: CH_3CN, 3% B to 23% B gradient in 20 min; detector, UV 254 nm. This resulted in product. These product and Si-thiol (20 mg) in THF (3 mL) was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dried by lyophilization to afford I-1 (86.6 mg, 26.01%) as an orange oil.

LC-MS: (ES, *m/z*): $[M+H]^+$:216

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.19-1.21 (d, 3H), 2.86-2.88 (d, 2H), 2.99-3.04 (m, 1H), 3.31-3.38 (m, 3H), 4.95 (s, 1H), 6.36-6.42 (m, 3H), 6.88-6.93 (m, 1H), 8.27 (s, 1H).

Intermediate I-2: Synthesis of Intermediate 2



Synthesis of I-2a

[088] To a solution of 5-bromo-2-methyl-3-(trifluoromethyl) pyridine (10.00 g, 41.663 mmol, 1.00 equiv), $Pd(DtBPF)Cl_2$ (1.00 g, 4.1663 mmol, 0.10 equiv) in 500 mL EtOH was added TEA (5.00 g, 83.326 mmol, 2.00 equiv) in a pressure tank. The mixture was purged with nitrogen for 10 min and then was pressurized to 30 atm with carbon monoxide at 100 °C

and stirred overnight. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The resulting mixture was diluted with water (1 L). The resulting mixture was extracted with EtOAc (5 x 200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1) to afford I-2a (7.1 g, 73.08%) as a brown liquid.

Synthesis of I-2b

[089] To a stirred solution of I-2a (3.50 g, 15.009 mmol, 1.00 equiv) and SeO_2 (3.33 g, 30.018 mmol, 2.00 equiv) was added dioxane (400.00 mL) at room temperature under air atmosphere. The resulting mixture was stirred overnight at 110 °C. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford I-2b (3 g, 73.59%) as an off-white solid.

Synthesis of I-2c

[090] Into a 250 mL 3-necked round-bottom flask were added I-2b (3.00 g, 0.012 mmol, 1.00 equiv), AcOH (6.40 mL), H_2SO_4 (0.50 mL) and $CH(OMe)_3$ (40.00 mL) at room temperature. The resulting mixture was stirred for an additional 30 min at 50 °C. The resulting mixture was stirred for overnight at room temperature under air atmosphere. The reaction was quenched with water/$NaHCO_3$ at room temperature. The aqueous layer was extracted with EtOAc (2x40 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford I-2c 2.8 g (75.52%) as an off-white solid.

Synthesis of I-2d

[091] Into a 100 mL 3-necked round-bottom flask were added I-2c (2.80 g, 9.548 mmol, 1.00 equiv), MeOH (30.00 mL) at room temperature. To the above mixture was added $NaBH_4$ (5.01 g, 18.096 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 2h at 0 °C under air atmosphere. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3 x 20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (6:1) to afford I-2d (1.2 g, 40.02%) as an off-white solid.

Synthesis of I-2e

[092] Into a 50 mL 2-necked round-bottom flask were added I-2d (1.10 g, 4.379 mmol, 1.00 equiv), MnO_2 (5.71 g, 65.685 mmol, 15.00 equiv) and DCM (15.00 mL) at room temperature. The resulting mixture was stirred overnight at 40 °C under air atmosphere. The reaction was

quenched with water (15 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford I-2e (500 mg, 41.24%) as an off-white solid.

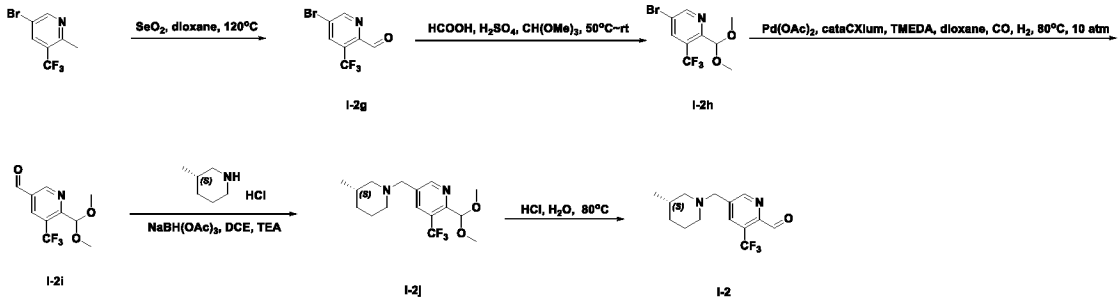
Synthesis of I-2f

[093] Into a 20 mL vial were added I-2e (500.00 mg, 2.007 mmol, 1.00 equiv), (3S)-3-methylpiperidine (398.00 mg, 4.013 mmol, 2 equiv), TEA (406.08 mg, 4.014 mmol, 2.00 equiv) and DCE (6 ml), $NaBH(OAc)_3$ (1275.78 mg, 6.021 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by prep-TLC (PE/EtOAc 5:1) to afford I-2f (500 mg, 71.23%) as an off-white solid.

Synthesis of I-2

[094] Into a 20 mL vial were added I-2f (500.00 mg, 1.504 mmol, 1.00 equiv), H_2O (5.50 mL) and HCl (0.50 mL) at room temperature. The resulting mixture was stirred overnight at 80 °C under air atmosphere. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with EtOAc (2x5 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford I-2 (300 mg, 55.72%) as a yellow oil.

[095] Alternatively, I-2 Can also be made as follows:



Synthesis of I-2g

[096] A solution of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (60 g, 249.976 mmol, 1 equiv) in dioxane (350 mL) was added SeO2 (69.35 g, 624.940 mmol, 2.5 equiv). The resulting mixture was stirred overnight at 120 degrees C. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x50 mL). The filtrate was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford I-2g (49 g, 69.45%) as a yellow oil.

Synthesis of I-2h

[097] Into a 250 mL round-bottom flask were added I-2g (10 g 40.48 mmol, 1.00 equiv) and CH(OMe)3 (100 mL) at room temperature. To the above mixture was added HCOOH (3 mL) and H2SO4 (1 mL) at room temperature. The resulting mixture was stirred overnight at 50 degrees C. The reaction was quenched by the addition of NaHCO3 (aq.) (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford I-2h (8 g 67.45%) as yellow oil.

Synthesis of I-2i

[098] To a solution of I-2h (8 g, 26.660 mmol, 1 equiv) in 100 mL dioxane was added Pd(OAc)2 (0.60 g, 2.666 mmol, 0.1 equiv) in a pressure tank. The mixture was purged with nitrogen and then was pressurized to 10 atm with carbon monoxide/hydrogen (1:1) at 80 °C overnight. The reaction mixture was cooled to room temperature and diluted with water (600 mL). The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford I-2i (5 g, 60.21%) as a brown oil.

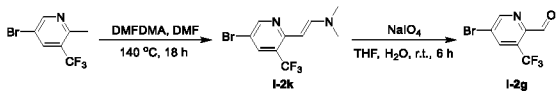
Synthesis of I-2j

[099] Into a 100 mL round-bottom flask were added I-2i (1.9 g, 7.625 mmol, 1.00 equiv), (3S)-3-methylpiperidine hydrochloride (1.24 g, 9.150 mmol, 1.2 equiv), DCE (30 mL) and Et3N (0.93 g, 9.150 mmol, 1.2 equiv) at room temperature. The mixture was stirred for 10 min at room temperature. To the above mixture was added NaBH(OAc)3 (4.85 g, 22.875 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford I-2j (1.7 g, 61.04%) as brown oil.

Synthesis of I-2

[100] Into a 50 mL round-bottom flask were added I-2j (1.7 g, 5.115 mmol, 1.00 equiv) and 1 M HCl (20 mL) at room temperature. The resulting mixture was stirred for 3 h at 80 °C. The residue was basified to pH 7 with NH4HCO3 (aq.). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford Compound I-2 (1.5 g, 94.24%) as colorless oil.

Alternatively, I-2g can also be made as follows:



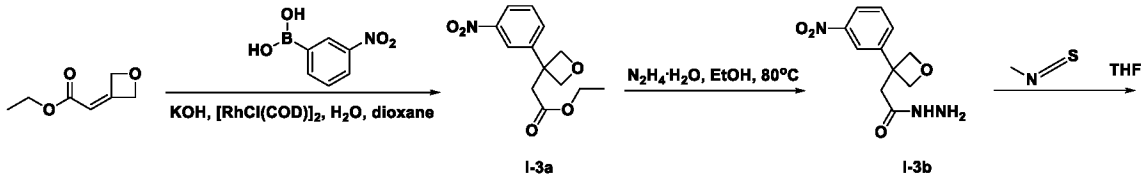
Synthesis of I-2k

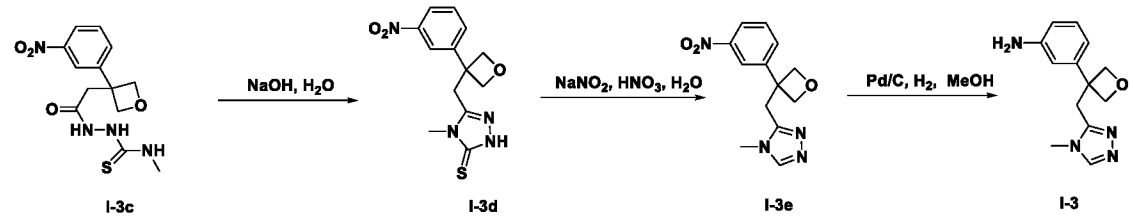
[101] A mixture of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (25 g, 104.16 mmol, 1 eq) in DMF (300 mL) and DMF-DMA (269.10 g, 2.26 mol, 300 mL) was stirred at 140 °C for 18 hr. The reaction mixture was concentrated in vacuum to afford I-2k (30 g, crude) as a brown oil, which was used directly without further purification.

Synthesis of I-2g

[102] To a solution of I-2k (30 g, 101 mmol) in THF (150 mL) and water (150 mL) was added NaIO4 (65.2 g, 304 mmol). The mixture was stirred at 20 °C for 6 hr. The reaction mixture was filtered and the filter cake was washed with ethyl acetate (200 mL). The filtrate was washed with saturated aqueous sodium bicarbonate solution (200 mL) and saturated aqueous brine solution (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-20% EtOAc/petroleum ether) to afford I-2g (8 g, 30.9% yield) as a brown oil.

Intermediate I-3: Synthesis of Intermediate 3





Synthesis of I-3a

[103] To a stirred solution of KOH (23.68 g, 422.077 mmol, 1.2 equiv) in H_2O (285.00 mL) and dioxane (1000.00 mL) were added $[Rh(COD)Cl]_2$ (4.00 g, 8.112 mmol, 0.02 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. To the above mixture were added

ethyl 2-(oxetan-3-ylidene)acetate (50.00 g, 351.731 mmol, 1.00 equiv) and 3-nitrophenylboronic acid (117.43 g, 703.462 mmol, 2 equiv) in portions at room temperature. The resulting mixture was stirred for an additional 16 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of NH_4Cl (aq.) (3 L) at room temperature. The aqueous layer was extracted with EtOAc (3x5 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford I-3a (41 g, 73.24%) as a yellow solid.

Synthesis of I-3b

A mixture of I-3a (30.00 g, 113.094 mmol, 1.00 equiv) in EtOH (150 mL) and hydrazine hydrate (98%) (45.29 g, 904.756 mmol, 8 equiv) was stirred for 24 h at 80 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (750 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (5x1 L). The resulting oil was dried with anhydrous sodium sulfate. The resulting mixture was filtered, and the filter cake was washed with MeOH (3x100 mL). The filtrate was concentrated under reduced pressure to afford I-3b (26.0 g, crude) as a yellow oil.

Synthesis of I-3c

[104] To a stirred solution of I-3b (26.00 g, 103.486 mmol, 1.00 equiv) in tetrahydrofuran (260.00 mL) was added methyl isothiocyanate (15.13 g, 206.972 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was diluted with water (600 mL). The precipitated solids were collected by filtration and washed with water (3x50 mL) to afford I-3c (35.0 g) as a yellow solid.

Synthesis of I-3d

[105] To a stirred solution of I-3c (35 g, 107.905 mmol, 1.00 equiv) was added NaOH (864 mL, 863.240 mmol, 8.00 equiv, 1 M) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (1 L). The mixture was acidified to pH 5 with HCl (1 M). The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (3x2 L). The resulting mixture was concentrated under reduced pressure to afford I-3d (24 g) as a yellow solid.

Synthesis of I-3e

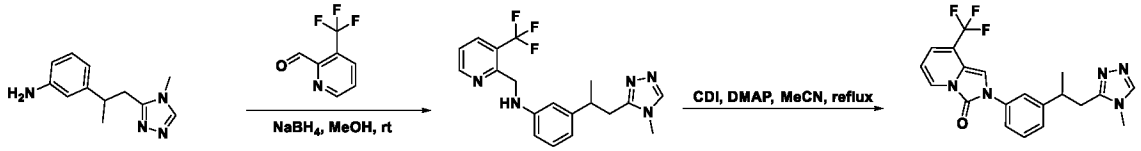
[106] To a stirred solution of I-3d (24.00 g, 78.344 mmol, 1.00 equiv) and $NaNO_2$ (54.05 g, 783.443 mmol, 10.00 equiv) in H_2O (150.00 mL) and ethyl acetate (50.0 mL) was added HNO_3 (500 mL, 783.443 mmol, 10.00 equiv, 1 M) dropwise at 0 °C. The resulting mixture was stirred overnight at 0 °C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (1

L) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (3x2 L). The resulting mixture was concentrated under reduced pressure to afford I-3e (19 g) as a yellow solid.

Synthesis of I-3

[107] To a solution of I-3e (19.00 g) in 190 mL MeOH was added Pd/C (30%, 5.7 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for 4 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in I-3 (16 g) as a yellow solid.

Example 1. Synthesis of Compound 1



I-1 1a 1

Synthesis of 1a

[108] To a stirred solution of I-1 (300.00 mg, 1.387 mmol, 1.00 equiv) in MeOH (4.00 mL) was added 3-(trifluoromethyl)pyridine-2-carbaldehyde (242.88 mg, 1.387 mmol, 1.00 equiv) at room temperature under air atmosphere. The resulting mixture was stirred overnight at room temperature. To the above mixture was added $NaBH_4$ (104.95 mg, 2.774 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred for an additional 1 h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 1a (200 mg, 38.41%) as a yellow solid.

Synthesis of 1

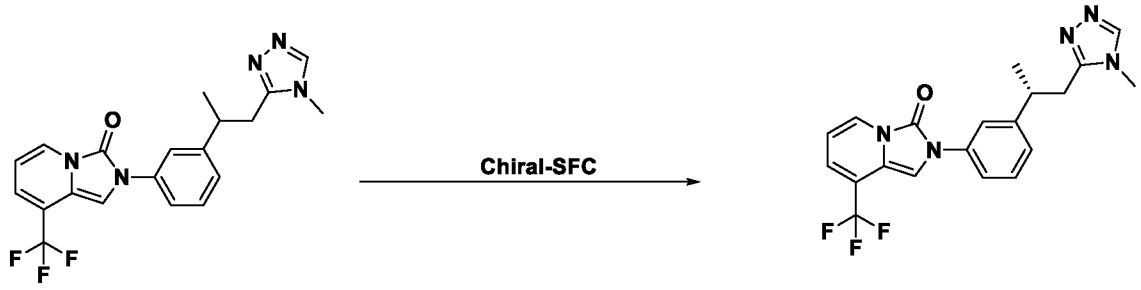
[109] To a stirred mixture of 1a (180.00 mg, 0.479 mmol, 1.00 equiv) and CDI (116.62 mg, 0.718 mmol, 1.50 equiv) in CH_3CN (3.00 mL) was added DMAP (117.16 mg, 0.958 mmol, 2.00 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 90 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2/MeOH=20:1) to afford Compound 1 (80 mg) as a yellow solid. The crude product (80 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile

Phase A: water (10 mmol/L NH_4HCO_3 + 0.1% $NH_3.H_2O$), Mobile Phase B: MeOH; Flow rate: 60 mL/min; Gradient: 41% B to 71% B in 8 min; Wave Length: 254; 220 nm; RT1 (min): 7.17) to afford Compound 1 (30.2 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 401.

^{1}H NMR: (300 MHz, DMSO-d6, ppm): δ 1.30-1.33 (d, 3H), 3.01-3.04 (m, 2H), 3.32-3.35 (m, 1H), 3.46 (s, 3H), 6.26-6.31 (m, 1H), 7.08-7.10 (m, 1H), 7.23-7.25 (m, 1H), 7.33 (s, 1H), 7.42-7.44 (m, 1H), 7.70-7.73 (m, 2H), 7.78-7.81 (d, 1H), 8.28 (s, 1H).

Example 2. Synthesis of Compound 2



1 2

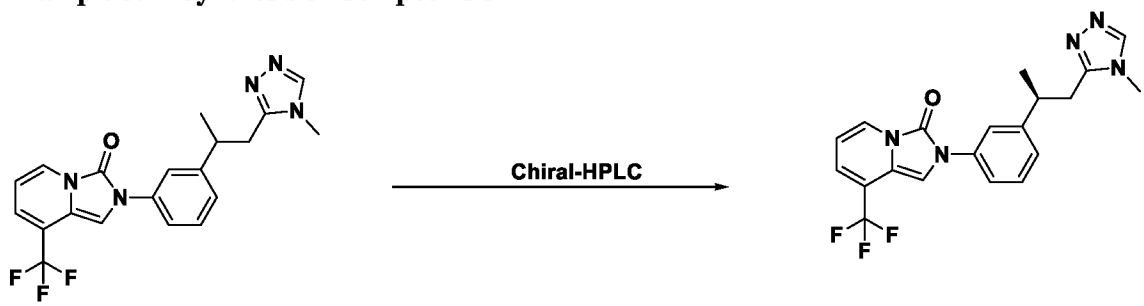
Synthesis of 2

[110] The Compound 1 (340 mg) was separated by prep-chiral HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 21.5 min; Wave Length: 254/220 nm; RT1 (min): 14.79; Sample Solvent: EtOH; Injection Volume: 0.4 mL; Number Of Runs: 18) to afford Compound 2 (92.4 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 402.

^{1}H NMR: (400 MHz, DMSO-d6, ppm): δ 1.36-1.38 (d, 3H), 3.02-3.19 (m, 2H), 3.35-3.40 (m, 1H), 3.43 (s, 3H), 6.31-6.35 (m, 1H), 7.01-7.03 (m, 1H), 7.10 (s, 1H), 7.22-7.24 (m, 1H), 7.40-7.45 (m, 1H), 7.53-7.58 (m, 2H), 7.73-7.76 (m, 1H), 8.24 (s, 1H).

Example 3. Synthesis of Compound 3



1 3

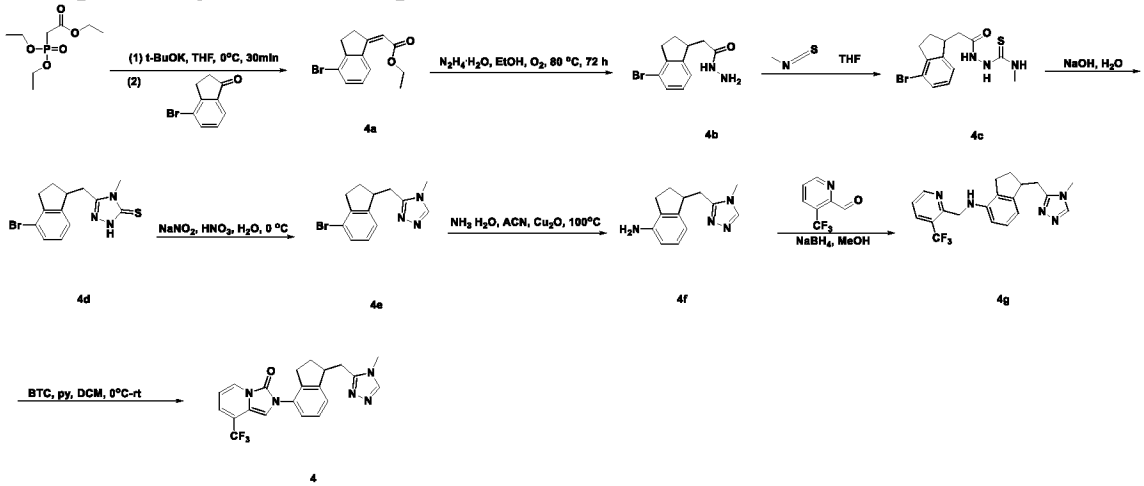
Synthesis of 3

[111] Compound 1 (340 mg) was purified by prep-chiral HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 21.5 min; Wave Length: 254/220 nm; RT2 (min): 18.83; Sample Solvent: EtOH; Injection Volume: 0.4 mL; Number Of Runs: 18) to afford Compound 3 (92.0 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 402.

^1H NMR: (400 MHz, DMSO-d6, ppm): δ 1.36-1.38 (d, 3H), 3.02-3.19 (m, 2H), 3.35-3.40 (m, 1H), 3.43 (s, 3H), 6.31-6.35 (m, 1H), 7.01-7.03 (m, 1H), 7.10 (s, 1H), 7.22-7.24 (m, 1H), 7.40-7.45 (m, 1H), 7.53-7.58 (m, 2H), 7.73-7.76 (m, 1H), 8.24 (s, 1H).

Example 4. Synthesis of Compound 4



Synthesis of 4a

[112] A solution of triethyl phosphonoacetate (10.00 g, 44.604 mmol, 1.00 equiv) and t-BuOK (10.01 g, 0.089 mmol, 2 equiv) in THF (100 mL) was stirred for 30 min at 0 °C under nitrogen atmosphere. To the above mixture was added 4-bromo-2,3-dihydroinden-1-one (9.41 g, 0.045 mmol, 1 equiv) in THF (20 mL) dropwise over 20 min at 0 °C. The resulting mixture was stirred for an additional 3 h at 0 °C. The reaction was quenched by the addition of NH_4Cl (aq.) (150 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 4a (4.4 g, 34.03%) as a light yellow oil.

Synthesis of 4b

[113] Into a 250 mL 3-necked round-bottom flask were added 4a (4.40 g, 15.650 mmol, 1.00 equiv), EtOH (70.00 mL) and hydrazine hydrate (7.83 g, 156.500 mmol, 10.00 equiv) at room temperature. The resulting mixture was stirred for 72 h at 80 °C under oxygen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with EtOAc (100 mL), washed with water (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 4b (4.0 g, 83.57%) as a light yellow oil.

Synthesis of 4c

[114] Into a 250 mL 3-necked round-bottom flask were added 4b (4.00 g, 14.862 mmol, 1.00 equiv), tetrahydrofuran (50.00 mL) and methyl isothiocyanate (2.17 g, 29.681 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 5 h at room temperature under nitrogen atmosphere. The reaction was quenched with water (100 mL) at room temperature. The resulting mixture was filtered; the filter cake was washed with water (3x5 mL). This resulted in 4c (4.5 g, 88.47%) as an off-white solid.

Synthesis of 4d

[115] Into a 250 mL 3-necked round-bottom flask were added 4c (4.50 g, 13.148 mmol, 1.00 equiv), H_2O (50.00 mL) and NaOH (0.53 g, 0.000 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The resulting mixture was filtered; the filter cake was washed with water (3x5 mL). This resulted in 4d (3 g, 63.33%) as an off-white solid.

Synthesis of 4e

[116] Into a 500 mL 3-necked round-bottom flask were added 4d (2.50 g, 7.710 mmol, 1.00 equiv), ethyl acetate (50.00 mL) and $NaNO_2$ (5.32 g, 77.100 mmol, 10.00 equiv) at 0 °C. To the above mixture was added HNO_3 (4.86 g, 77.127 mmol, 10.00 equiv) in H_2O (150.00 mL) dropwise over 0.5 h at 0 °C. The resulting mixture was stirred for 5 h at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of ice/salt (100 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 4e (1.6 g, 63.92%) as a light yellow oil.

Synthesis of 4f

[117] Into a 250 mL sealed tube were added 4e (500.00 mg, 1.711 mmol, 1.00 equiv), $NH_3.H_2O$ (70.00 mL), CH_3CN (70.00 mL) and Cu_2O (48.97 mg, 0.342 mmol, 0.20 equiv) at room temperature. The resulting mixture was stirred for 12 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 10:1) to afford 4f (270 mg, 67.04%) as light yellow solid.

Synthesis of 4g

[118] Into a 100 mL 3-necked round-bottom flask were added 4f (230.00 mg, 1.007 mmol, 1.00 equiv), MeOH (5.00 mL and 3-(trifluoromethyl)pyridine-2-carbaldehyde (264.62 mg, 1.511 mmol, 1.50 equiv) at room temperature. The resulting mixture was stirred for 12 h at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH_4$ (76.23 mg, 2.014 mmol, 2.00 equiv) in portions over 10 min at 0 °C. The resulting mixture was stirred for additional 2 h at 0 °C. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 4g (130 mg, 30.98%) as a light yellow solid.

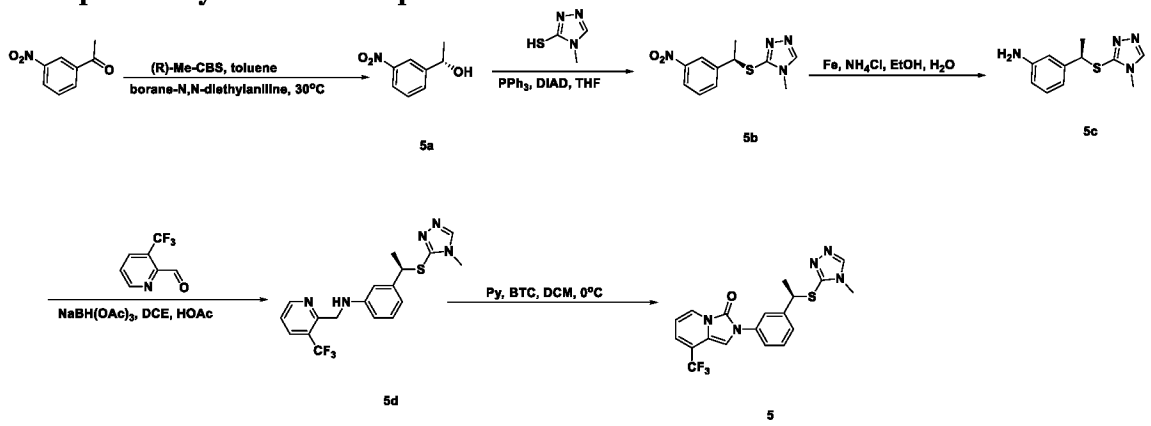
Synthesis of 4

[119] Into a 8 mL sealed tube were added 4g (130.00 mg, 0.336 mmol, 1.00 equiv), DCM (2.00 mL), pyridine (159.26 mg, 2.016 mmol, 6.00 equiv) and triphosgene (39.83 mg, 0.134 mmol, 0.40 equiv) at 0 °C. The resulting mixture was stirred for 3 h at 0 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude product (120 mg). The crude product (120 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1 (min): 7.32;) to afford Compound 4 (53.2 mg, 37.97%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 414

^1H NMR: (400 MHz, DMSO-d6, ppm): δ 1.76-1.83 (m, 1H), 2.24-2.32 (m, 1H), 2.78-2.92 (m, 3H), 3.20-3.34 (m, 1H), 3.69 (s, 3H), 3.71-3.73 (m, 1H), 6.27-6.31 (m, 1H), 7.08-7.14 (m, 2H), δ7.30-7.35 (m, 3H), δ7.79-7.81 (d, 1H), δ8.34 (m, 1H).

Example 5. Synthesis of Compound 5



Synthesis of 5a

[120] A solution of borane-N,N-diethylaniline (1.99 g, 13.321 mmol, 1.10 equiv) and (R)-Me-CBS (12.00 mL, 12.0 mmol, 1.00 equiv, 1M in toluene) in toluene (50.00 mL) was stirred for 20 min at 30 °C under nitrogen atmosphere. Then 3-nitroacetophenone (2.00 g, 12.110 mmol, 1.00 equiv) was added at room temperature. The reaction was washed with water (20 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE/EtOAc 2:1) to afford 5a (1.7 g, 80.62%) as a white solid.

Synthesis of 5b

[121] To a stirred mixture of 5a (1.50 g, 8.973 mmol, 1.00 equiv), 4-methyl-1,2,4-triazole-3-thiol (1.24 g, 10.769 mmol, 1.20 equiv) and PPh_3 (4.71 g, 17.946 mmol, 2 equiv) in THF (25.00 mL) was added DIAD (2.72 g, 13.460 mmol, 1.5 equiv) dropwise at 0 °C under nitrogen atmosphere. The reaction was quenched with water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (CH_2Cl_2 / MeOH 25:1) to afford 5b (1.8 g, 70%) as a yellow solid.

Synthesis of 5c

[122] A mixture of 5b (1.80 g, 6.810 mmol, 1.00 equiv), Fe (1.14 g, 20.431 mmol, 3 equiv) and NH_4Cl (2.19 g, 40.863 mmol, 6 equiv) in EtOH (20.00 mL) and H_2O (5.00 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered with filter paper, the filter cake was

washed with EtOAc (3x5 mL). The resulting mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This resulted in 5c (1.5 g, 87.42%) as a yellow solid.

Synthesis of 5d

[123] A mixture of 5c (800.00 mg, 3.414 mmol, 1.00 equiv), 3-(trifluoromethyl)pyridine-2-carbaldehyde (896.77 mg, 5.121 mmol, 1.50 equiv), $NaBH(OAc)_3$ (2170.79 mg, 10.242 mmol, 3 equiv) and HOAc (1025.13 mg, 17.071 mmol, 5 equiv) in DCE (7.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was washed with water (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc 1:1) to afford 5d (540 mg, 37.79%) as a yellow solid.

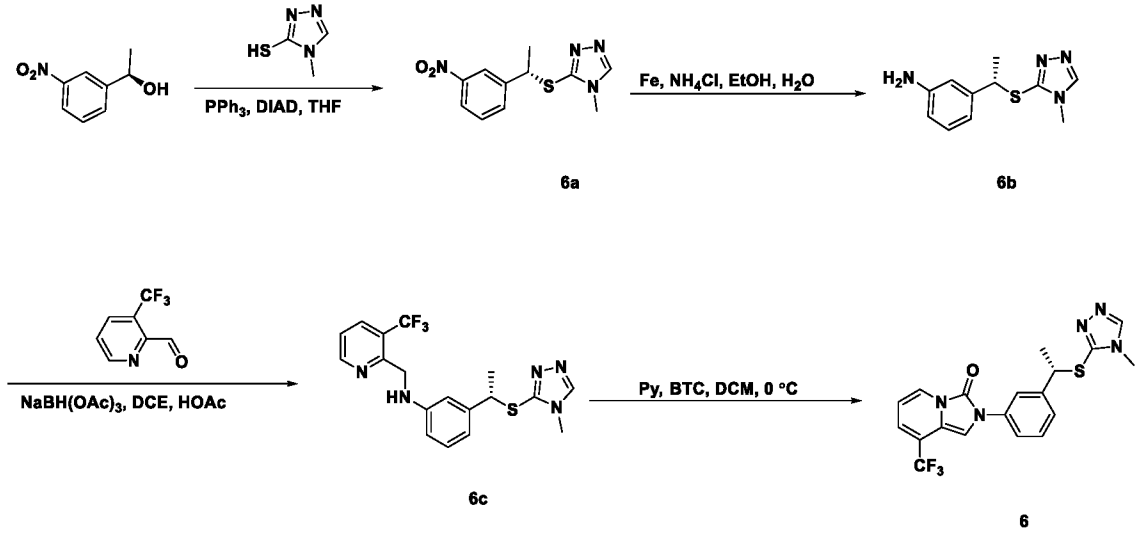
Synthesis of 5

[124] To a stirred mixture of 5d (350.00 mg, 0.890 mmol, 1.00 equiv) and pyridine (422.21 mg, 5.338 mmol, 6.00 equiv) in DCM (4.00 mL) was added triphosgene (92.40 mg, 0.311 mmol, 0.35 equiv) dropwise at 0 °C under nitrogen atmosphere. The reaction was washed with water (10 mL) at room temperature. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 5 (53.1 mg, 13.79%) as an orange solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 420

^1H NMR: (400 MHz, DMSO-d6, δ ppm): δ 1.72-1.76 (d, 3H), 3.48 (s, 3H), 6.09-6.13 (d, 1H), 6.27-6.30 (m, 1H), 7.09-7.10 (d, 1H), 7.27-7.29 (d, 1H), 7.33 (s, 1H), 7.48-7.50 (m, 1H), 7.73-7.75 (d, 1H), 7.78-7.80 (d, 1H), 7.87 (s, 1H), 8.55 (s, 1H).

Example 6. Synthesis of Compound 6



Synthesis of 6a

[125] To a stirred mixture of (1R)-1-(3-nitrophenyl)ethanol (2.00 g, 11.964 mmol, 1.00 equiv), 4-methyl-1,2,4-triazole-3-thiol (1.65 g, 14.329 mmol, 1.20 equiv) and PPh_3 (6.28 g, 23.929 mmol, 2 equiv) in THF (25.00 mL) were added DIAD (3.63 g, 17.946 mmol, 1.5 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with brine (100 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 6a (1.6 g, 49.59%) as a yellow solid.

Synthesis of 6b

[126] A mixture of 6a (1.60 g, 6.054 mmol, 1.00 equiv), Fe (1.01 g, 18.161 mmol, 3 equiv) and NH_4Cl (1.94 g, 36.322 mmol, 6 equiv) in EtOH (20.00 mL) and H_2O (4.00 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (20 mL). The resulting mixture was filtered, the filter cake was washed with EtOAc (3x10 mL). The combined organic layers were washed with brine (3x4 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 6b (610 mg, 41.71%) as a yellow solid.

Synthesis of 6c

[127] A mixture of 6b (610.00 mg, 2.603 mmol, 1.00 equiv), 3-(trifluoromethyl) pyridine-2-carbaldehyde (683.79 mg, 3.905 mmol, 1.5 equiv), $NaBH(OAc)_3$ (1655.22 mg, 7.810 mmol, 3 equiv) and HOAc (781.66 mg, 13.016 mmol, 5 equiv) in DCE (6.50 mL) was stirred for 2 h

at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with DCM (10 mL). The resulting mixture was washed with water (10 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 6c (375 mg, 35.52%) as a yellow solid.

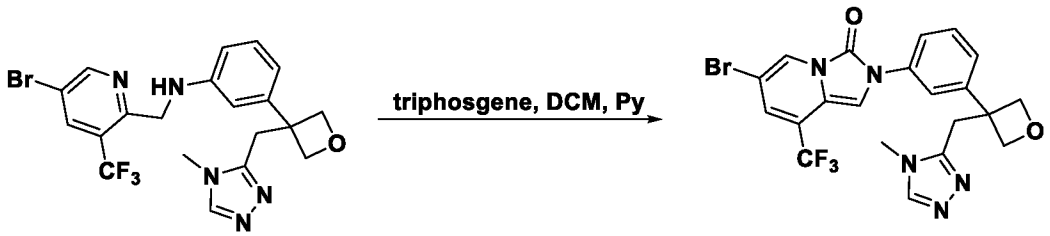
Synthesis of 6

[128] To a stirred mixture of 6c (280.00 mg, 0.712 mmol, 1.00 equiv) and pyridine (337.77 mg, 4.270 mmol, 6 equiv) in DCM (3.00 mL) was added triphosgene (73.92 mg, 0.249 mmol, 0.35 equiv) dropwise at 0 °C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with DCM (3 x 5 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 6 (151.8 mg, 50.24%) as an orange solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 420

^1H NMR: (400 MHz, DMSO-d6, δ ppm): δ 1.74-1.76 (d, 3H), 3.48 (s, 3H), 6.09-6.12 (m, 1H), 6.27-6.30 (m, 1H), 7.09-7.10 (d, 1H), 7.27-7.29 (d, 1H), 7.35 (s, 1H), 7.46-7.50 (m, 1H) , 7.73-7.75 (d, 1H) , 7.78-7.80 (d, 1H) , 7.87 (s, 1H) , 8.56 (s, 1H).

Example 7. Synthesis of Compound 7



10c 7

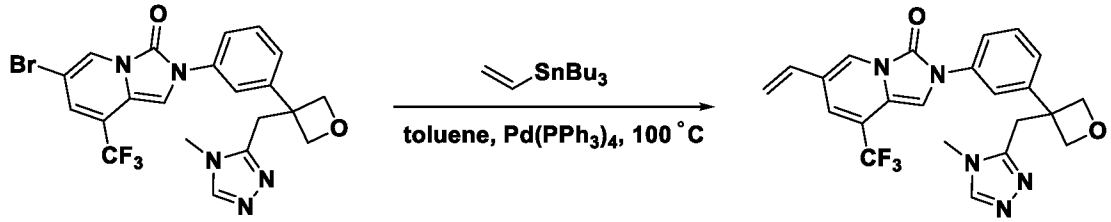
Synthesis of 7

[129] To a stirred solution of 10c (4.40 g, 9.123 mmol, 1.00 equiv) and pyridine (4.33 g, 54.741 mmol, 6.00 equiv) in DCM (250.00 mL) was added triphosgene (0.95 g, 3.193 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred 1 h at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (100 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with methyl tert-butyl ether (50 mL). This resulted in Compound 7 (4.2 g, 90.57%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 508

^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.97 (s, 3H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.18 (s, 1H), 7.39-7.45 (m, 3H), 7.73-7.75 (m, 1H), 8.04 (s, 1H), 8.20 (s, 1H).

Example 8. Synthesis of Compound 8



7 8

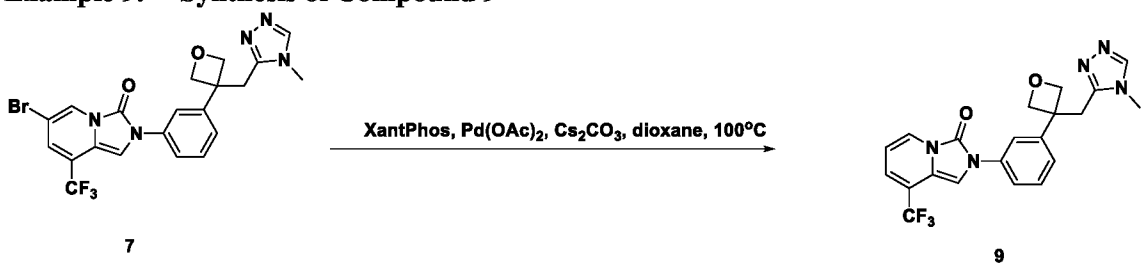
Synthesis of 8

[130] To a stirred solution of Compound 7 (680.00 mg, 1.338 mmol, 1.00 equiv) and tributyl(ethenyl)stannane (636.33 mg, 2.007 mmol, 1.50 equiv) in dioxane (10.00 mL) was added $Pd(PPh_3)_4$ (155.00 mg, 0.1338 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford Compound 8 (400 mg, crude). The crude product (20 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 8 min, 45% B; Wave Length: 220 nm; RT1 (min): 7.92) to Compound 8 (7.4 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 456

^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.98 (s, 3H), 3.54 (s, 2H), 4.92-4.97 (m, 4H), 5.25-5.27 (d, 1H), 5.80-5.85 (d, 1H), 6.66-6.73 (m, 1H), 6.88-6.90 (d, 1H), 7.39-7.43 (m, 4H), 7.75-7.77 (m, 1H), 7.91 (s, 1H), 8.21 (s, 1H).

Example 9. Synthesis of Compound 9



7 9

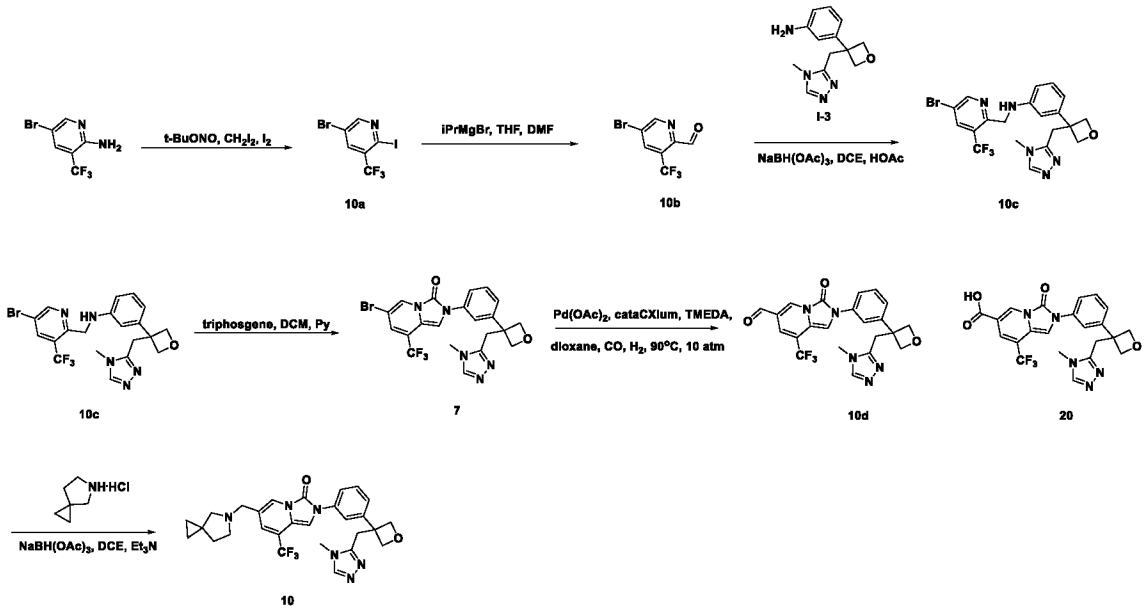
Synthesis of 9

[131] Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed dioxane (2.00 mL), Compound 7 (50.00 mg, 0.098 mmol, 1.00 equiv), XantPhos (22.77 mg, 0.039 mmol, 0.40 equiv), $Pd(OAc)_2$ (4.42 mg, 0.020 mmol, 0.20 equiv), Cs_2CO_3 (96.15 mg, 0.295 mmol, 3.00 equiv). The resulting solution was stirred overnight at 100 °C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x20 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford crude product. The crude product (20 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 45% B in 8 min, Wave Length: 220 nm; RT1 (min): 7.35) to afford Compound 9 (2.5 mg, 5.91%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 430

^1H NMR: (400 MHz, DMSO-d_6, *ppm*): δ 2.97 (s, 3H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.27-6.30 (m, 1H), 6.88-6.90 (d, 1H), 7.09-7.11 (d, 1H), 7.38 (s, 1H), 7.40-7.42 (m, 2H), 7.74-7.79 (m, 2H), 8.20 (s, 1H).

Example 10. Synthesis of Compound 10



Synthesis of 10a

[132] To a stirred mixture of 5-bromo-3-(trifluoromethyl)pyridin-2-amine (25.00 g, 103.730 mmol, 1.00 equiv) in CH_2I_2 (75.00 mL) was added t-$BuNO_2$ (12.84 g, 124.515 mmol, 1.20 equiv) dropwise. The resulting mixture was stirred for 1 h at room temperature. To the above

mixture was added I_2 (28.96 g, 114.102 mmol, 1.10 equiv) in portions. The resulting mixture was stirred for additional 6 h at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (300 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1) to afford 10a (17 g, 46.57%) as a light yellow oil.

Synthesis of 10b

[133] To a stirred solution of 10a (17.00 g, 48.310 mmol, 1.00 equiv) in THF (300.00 mL) was added i-PrMgBr (18.32 mL, 53.141 mmol, 1.10 equiv) dropwise at -78 °C under argon atmosphere. The resulting mixture was stirred for 30 min at -78 °C under argon atmosphere. To the above mixture was added DMF (7.06 g, 96.588 mmol, 2.00 equiv) dropwise at -78 °C. The resulting mixture was stirred for additional 2 hours at -78 °C. The reaction was quenched by the addition of NH_4Cl (aq.) (800 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x400 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20:1) to afford 10b (4.5 g, 36.67%) as a white solid.

Synthesis of 10c

[134] To a stirred solution of 10b (3.50 g, 13.779 mmol, 1.00 equiv) and I-3 (3.37 g, 13.795 mmol, 1.00 equiv) in DCE (50.00 mL) were added HOAc (1.65 g, 27.558 mmol, 2.00 equiv) and $NaBH(OAc)_3$ (5.84 g, 27.558 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 10c (4.5 g, 67.71%) as a light yellow solid.

Synthesis of Compound 7

[135] To a stirred solution of 10c (4.40 g, 9.123 mmol, 1.00 equiv) and pyridine (4.33 g, 54.741 mmol, 6.00 equiv) in DCM (250.00 mL) was added triphosgene (0.95 g, 3.193 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred 1 h at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (100 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with methyl tert-butyl ether (50 mL). This resulted in Compound 7 (4.2 g, 90.57%) as a yellow solid.

Synthesis of 10d

[136] To a solution of Compound 7 (2.20 g, 4.328 mmol, 1.00 equiv), TMEDA (0.50 g,

4.328 mmol, 1.00 equiv) in dioxane (180.00 mL) was added butyldi-1-adamantylphosphine (0.31 g, 0.866 mmol, 0.20 equiv) and $Pd(OAc)_2$ (0.10 g, 0.433 mmol, 0.10 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 90 °C and stirred overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 10d (1.1g, 55.56%) as a yellow solid, eluted with CH_2Cl_2 / MeOH (5:1) to afford Compound 20 (600 mg) as a yellow solid.

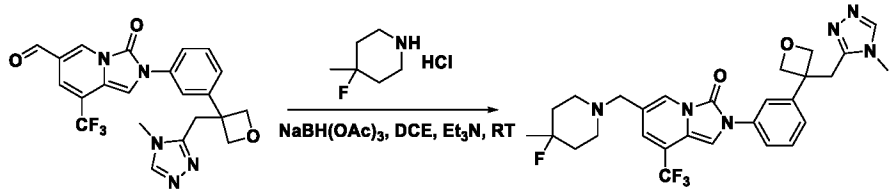
Synthesis of 10

[137] To a stirred mixture of 10d (300.00 mg, 0.656 mmol, 1.00 equiv) and 5-azaspiro[2.4]heptane hydrochloride (175.27 mg, 1.312 mmol, 2.00 equiv) in DCE (10.00 mL) were added Et_3N (132.73 mg, 1.312 mmol, 2.00 equiv) and $NaBH(OAc)_3$ (278.01 mg, 1.312 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x30 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 7 min, 50% B; Wave Length: 220 nm; RT1 (min): 6.57;) to afford Compound 10 (120.5 mg, 34.11%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$: 539

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.50-0.52 (m, 4H), 1.73-7.76 (t, 2H), 2.46 (s, 2H), 2.68-2.70 (t, 3H), 3.40 (s, 2H), 3.43 (2, 2H), 4.91-4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.05 (s, 1H), 7.30 (s, 1H), 7.38-7.45 (m, 2H), 7.68 (s, 1H), 7.77-7.81 (d, 1H), 8.20 (s, 1H).

Example 11. Synthesis of Compound 11



10d 11

Synthesis of 11

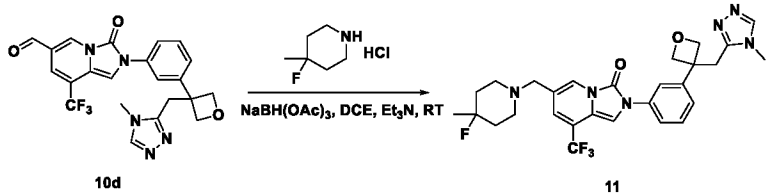
[138] To a stirred solution/mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), 4-fluoro-4-methylpiperidine hydrochloride (67.17 mg, 0.438 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction

was quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1 (min): 7.83;) to afford Compound 11 (40.9 mg, 33.49%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 559

^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.29-1.35 (d, 3H), 1.61-1.69 (m, 1H), 1.70-1.78 (m, 3H), 2.22-2.31 (m, 2H), 2.60-2.69 (m, 2H), 2.98 (s, 3H), 4.93-4.95 (m, 4H), 6.86-6.91 (d, 1H), 7.03 (s, 1H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.68 (s, 1H), 7.77-7.81 (d, 1H), 8.20 (s, 1H).

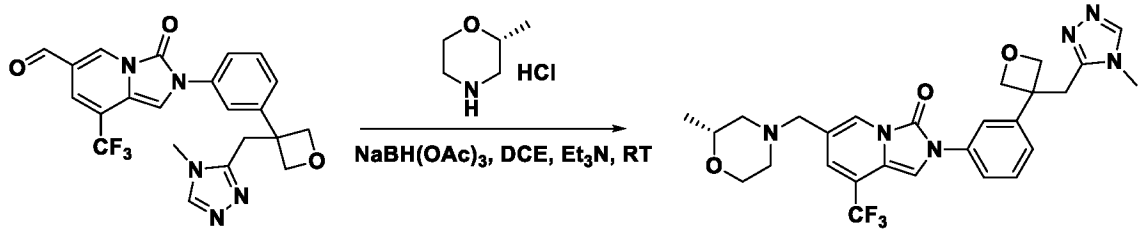
Alternatively, Compound 11 may be also prepared in the manner outlined below:



[139] To a stirred mixture of 10d (3 g, 6.559 mmol, 1 equiv) and 4-fluoro-4-methylpiperidine hydrochloride (3.02 g, 19.677 mmol, 3 equiv) in DCE (50 mL) was added TEA (2.65 g, 26.236 mmol, 4 equiv).The resulting mixture was stirred for 2 h at room temperature.To the above mixture was added NaBH(OAc)3 (2.78 g, 13.118 mmol, 2 equiv) . The resulting mixture was stirred for additional overnight at room temperature.The resulting mixture was diluted with water (20 mL).The resulting mixture was extracted with CH2Cl2 (3 x 25 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol NH4HCO3), 5% to 85% gradient in 40 min; detector, UV 254 nm. This resulted in Compound 11 (929.3 mg, 25.37%) as a yellow solid.

LC-MS- 11: (ES, m/z): [M+H] + 559. H-NMR- 11: (400 MHz, DMSO-d6, ppm): δ 1.29-1.35 (d, 3H), δ 1.61-3 (m, 4H), δ 2.23-2.33 (m, 2H), δ 2.60-2.63 (m, 2H), δ 2.97 (s, 3H), δ 3.31 (s, 2H), δ 3.53 (s, 2H), δ 4.91-4.96 (m, 4H), δ 6.88-6.90 (d, 1H), δ 7.02 (s, 1H), δ 7.33 (s, 1H), δ 7.38-7.42 (m, 2H), δ 7.69 (s, 1H), δ 7.75-7.77 (m, 1H), δ 8.21 (s, 1H).

Example 12. Synthesis of Compound 12



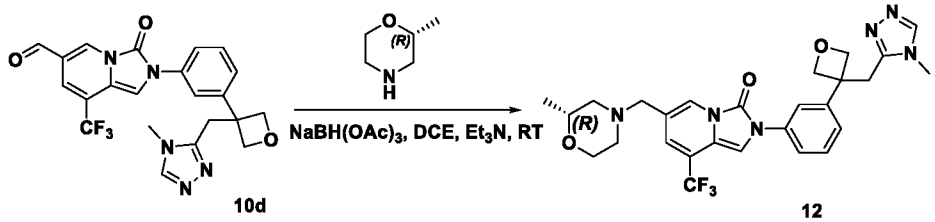
10d 12

Synthesis of 12

[140] To a stirred mixture of 10d (100.00 mg, 1.00 equiv), (2R)-2-methylmorpholine hydrochloride (60.17 mg, 0.437 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.437 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$(92.67 mg, 0.437 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*50 mm, 5 μm 13 nm; Mobile Phase A: Water(20 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 44% B in 8 min, 44% B; Wave Length: 220 nm; RT1 (min): 7.83;) to afford Compound 12 (30.8 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 543. ^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.04-1.06 (d, 3H), 1.71-1.78(m, 1H), 2.02-2.10 (m, 1H), 2.67-2.71 (m, 1H), 2.72-2.76 (m, 1H), 2.98 (s, 3H), 3.28 (s, 3H), 3.35-3.54 (m, 4H), 3.73-3.78 (d, 1H), 4.92-4.97 (m, 4H), 6.86-6.91 (d, 1H), 7.03 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 2H), 7.70 (s, 1H), 7.77-7.81 (d, 1H), 8.21 (s, 1H).

Alternatively, Compound 12 may also be prepared in the manner below:



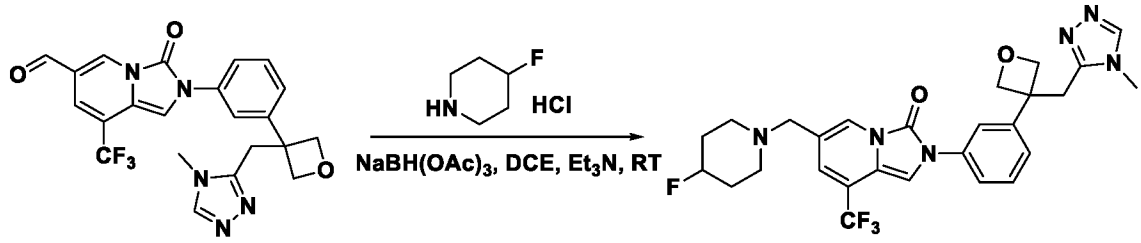
10d 12

1. Synthesis of 12

To a stirred solution of 10d (2 g, 4.372 mmol, 1.00 equiv) and (2R)-2-methylmorpholine (1.33 g, 13.116 mmol, 3 equiv) in DCE (60 mL) was added NaBH(OAc)3 (1.85 g, 8.744

mmol, 2 equiv). The resulting mixture was stirred for 6 h at room temperature. The resulting mixture was diluted with water (50 mL).The resulting mixture was extracted with CH2Cl2/MeOH (2 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 65% gradient in 30 min; detector, UV 254 nm. This resulted in 12 (1.1056 g, 46.60%) as a yellow solid.
LC-MS- 12: (ES, m/z): [M+H] + 543. H-NMR- 12: (400 MHz, DMSO-d6, ppm): δ 1.04-1.06 (d, 3H), δ 1.71-1.78 (m, 1H), δ 2.05-2.08 (m, 1H), δ 2.67-2.72 (m, 1H), δ 2.72-2.75 (m, 1H), δ 2.97 (s, 3H), δ 3.28 (s, 2H), δ 3.45-3.54 (m, 4H), δ 3.73-3.76 (d, 1H), δ 4.91-4.96 (m, 4H), δ 6.88-6.91 (d, 1H), δ 7.02 (s, 1H), δ 7.33 (s, 1H), δ 7.40-7.42 (m, 2H), δ 7.68 (s, 1H), δ 7.77-7.81 (d, 1H), δ 8.21 (s, 1H).

Example 13. Synthesis of Compound 13



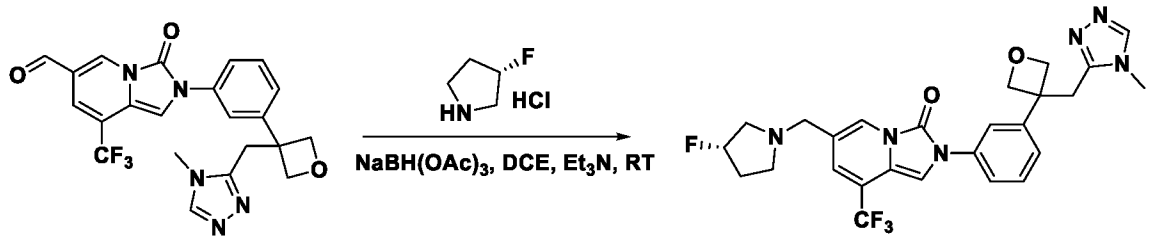
10d 13

Synthesis of 13

[141] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), 4-fluoropiperidine hydrochloride (61.04 mg, 0.437 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature . The reaction was quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(20 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1 (min): 7.75;) to afford Compound 13 (44.2 mg, 37.13%) as a yellow solid.
LCMS: (ES, *m/z*): $[M+H]^+$ 545
^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.62-1.81 (m, 2H), 1.83-1.90 (m, 2H), 2.33-2.37 (m, 2H), 2.55-2.67 (m, 2H), 2.98 (s, 3H), 3.54 (s, 2H), 4.62-4.77 (m, 1H), 4.91-4.96 (m, 4H),

6.89-6.91 (d, 1H), 7.02 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.68 (s, 1H), 7.74-7.76 (d, 1H), 8.20 (s, 1H).

Example 14. Synthesis of Compound 14



10d 14

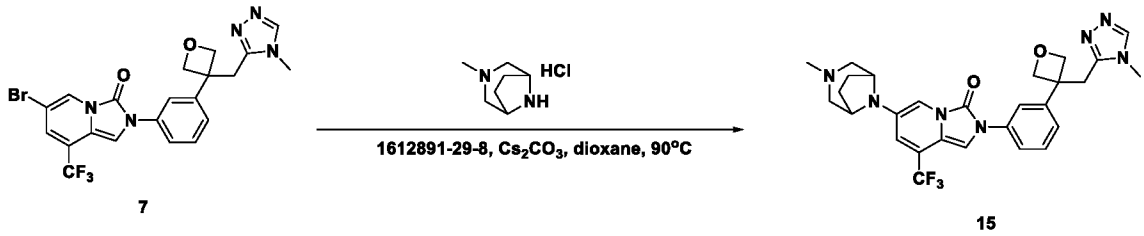
Synthesis of 14

[142] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), (3S)-3-fluoropyrrolidine hydrochloride (54.90 mg, 0.438 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (15 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 7 min, 45% B; Wave Length: 220 nm; RT1 (min): 6.32;) to afford Compound 14 (50.8 mg, 43.80%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 531

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.84-1.95 (m, 1H), 2.10-2.20 (m, 1H), 2.33-2.37 (m, 1H), 2.60-2.72 (m, 1H), 2.77-2.87 (m, 2H), 2.97 (s, 3H), 3.43 (s, 2H), 3.54 (s, 2H), 4.91-4.96 (m, 4H), 5.13-5.30 (m, 1H), 6.88-6.90 (d, 1H), 7.03 (s, 1H), 7.32 (s, 1H), 7.38-7.42 (m, 2H), 7.71 (s, 1H), 7.74-7.77 (m, 1H), 8.20 (s, 1H).

Example 15. Synthesis of Compound 15



7 15

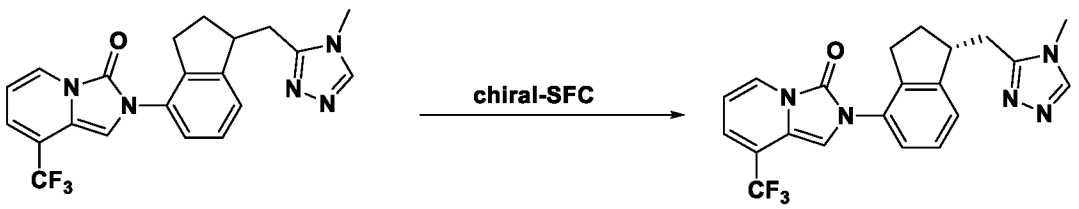
Synthesis of 15

[143] Into a 20 mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed dioxane (10 mL), Compound 7 (200.00 mg, 0.393 mmol, 1.00 equiv), 3-methyl-3,8-diazabicyclo[3.2.1]octane hydrochloride (320.01 mg, 1.967 mmol, 5.00 equiv), Cs_2CO_3 (641.00 mg, 1.967 mmol, 5 equiv), Pd PEPPSI IPentCl (169.30 mg, 0.197 mmol, 0.50 equiv). The resulting solution was stirred overnight at 90 °C. The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (1x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: Water B: MeCN, 45% B to 60% B gradient in 15 min; detector, UV 254 nm. This resulted in Compound 15 (33.7 mg, 15.19%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 554

^1H NMR: (400 MHz, DMSO-d_6, δ *ppm*): δ 1.84-1.86 (m, 4H), 2.12 (s, 3H), 2.77-2.34 (m, 2H), 2.48-2.50 (m, 2H), 2.98 (s, 3H),3.53 (s, 2H), 4.09 (s, 2H), 4.90-4.96 (m, 4H), 6.86-6.88 (d, 1H), 6.93 (s, 1H), 7.14-7.16 (m, 1H), 7.28 (s, 1H), 7.37-7.41 (m, 2H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 16. Synthesis of Compound 16



4 16

Synthesis of 16

[144] The Compound 4 (59.00 mg) was separated by prep-CHIRAL-SFC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% TEA), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 15 min; Wave Length: 220/254 nm; RT1 (min): 10.54; RT2 (min): 12.60; the first peak was the product). This resulted in Compound 16 (15.9 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 414

^{1}H NMR: (400 MHz, DMSO-d6 δ ppm) δ 1.76-1.81 (m, 1H), 2.25-2.30 (m, 1H), 2.78-2.92 (m, 3H), 3.20-3.34 (m, 1H), 3.69 (s, 3H), 3.71-3.73 (m, 1H), 6.27-6.31 (m, 1H), 7.07-7.08 (d, 1H), 7.09 (s, 1H), 7.30-7.32 (m, 3H), 7.79-7.81 (d, 1H), 8.38 (s, 1H).

Example 17. Synthesis of Compound 17



4 17

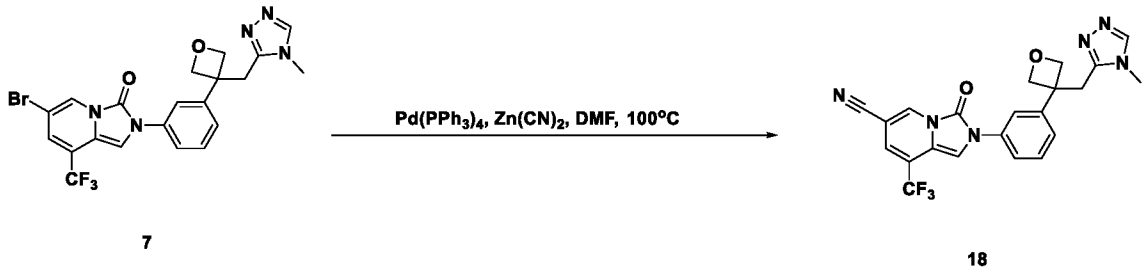
Synthesis of 17

[145] Compound 4 (59.00 mg) was separated by prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.2% TEA), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 15 min; Wave Length: 220/254 nm; RT2 (min): 12.60;). This resulted in Compound 17 (17.7 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 414

^{1}H NMR: (400 MHz, DMSO-d6, ppm): δ 1.78-1.82 (m, 1H), 2.26-2.34 (m, 1H), 2.80-2.89 (m, 3H), 3.20-3.25 (m, 1H), 3.69 (s, 3H), 3.71-3.73 (m, 1H), 6.28-6.31(m, 1H), 7.08-7.10 (d, 1H), 7.14 (s, 1H), 7.29-7.35 (m, 3H), 7.79-7.81 (d, 1H), 8.39 (s, 1H).

Example 18. Synthesis of Compound 18



7 18

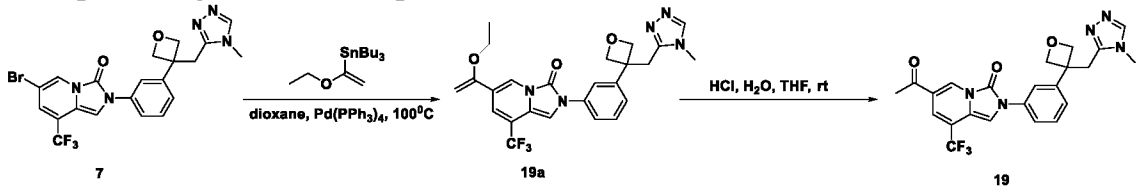
Synthesis of 18

[146] Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed DMF (2.00 mL), Compound 7 (50.00 mg, 0.098 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (11.37 mg, 0.010 mmol, 0.10 equiv), $Zn(CN)_2$ (23.11 mg, 0.197 mmol, 2 equiv). The resulting solution was stirred for 3 hr at 100 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 17.9 mg (39.24%) of Compound 18 as a dark yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 455

^1H NMR: (400 MHz, DMSO-d_6, ppm): δ 2.98 (s, 3H), 3.53 (s, 2H), 4.89-4.96 (m, 4H), 6.91-6.93 (d, 1H), 7.30 (s, 1H), 7.42-7.43 (m, 2H), 7.52 (s, 1H), 7.71-7.74 (d, 1H), 8.20 (s, 1H), 8.71 (s, 1H).

Example 19. Synthesis of Compound 19



7 19a 19

Synthesis of 19a

[147] To a stirred mixture of Compound 7 (2000.00 mg, 3.935 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (2131.56 mg, 5.902 mmol, 1.5 equiv) in dioxane (20.00 mL) was added $Pd(PPh_3)_4$ (454.68 mg, 0.393 mmol, 0.1 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 4 h at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of NH_4Cl (aq.) (60 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography,

eluted with CH_2Cl_2 / MeOH (20:1) to afford 19a (1550 mg, 70.98%) as a yellow solid.

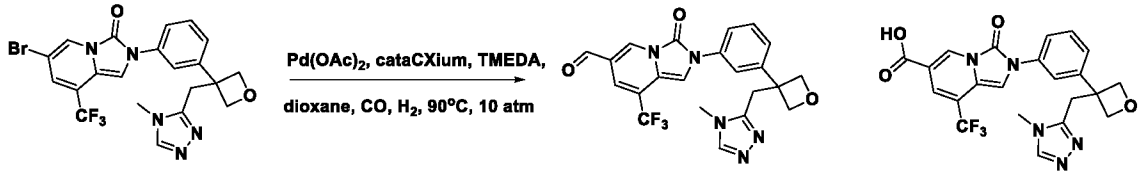
Synthesis of 19

[148] To a stirred mixture of 6-(1-ethoxyethenyl)-2-(3-[3-[(4-methyl-1,2,4-triazol-3-yl)methyl]oxetan-3-yl]phenyl)-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (19a) (1550.00 mg, 3.103 mmol, 1.00 equiv) in THF (10.00 mL) was added HCl (1.00 mL, 1M) and H_2O (10.00 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure to afford crude product (1.44 g) as a yellow solid. The crude product (20 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(20 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 45% B in 8 min, 45% B; Wave Length: 220 nm; RT1 (min): 7.48;) to afford Compound 19 (16.8 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 472

^1H NMR: (400 MHz, DMSO, *ppm*): δ 2.57 (s, 3H), 3.00 (s, 3H), 3.55 (s, 2H), 4.93-4.98 (m, 4H), 6.93-6.95 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 2H), 7.51 (s, 1H), 7.76-7.77 (m, 1H), 8.22 (s, 1H), 8.58 (s, 1H).

Example 20. Synthesis of Compound 20



Synthesis of 20

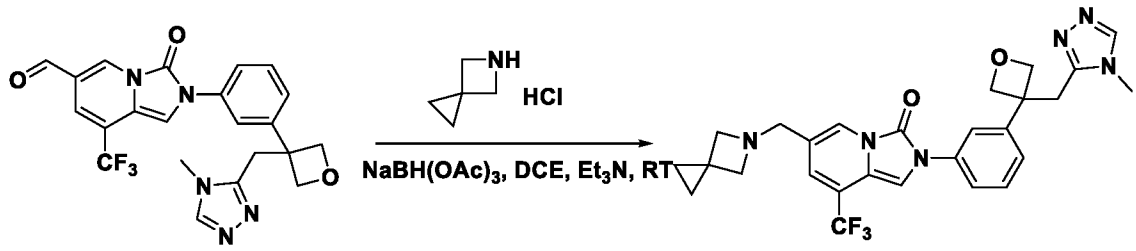
[149] To a solution of Compound 7 (2.20 g, 4.328 mmol, 1.00 equiv), TMEDA(502.95 mg, 4.328 mmol, 1.00 equiv) in dioxane (100.00 mL) was added butyldi-1-adamantylphosphine (0.31 g, 0.866 mmol, 0.20 equiv) and $Pd(OAc)_2$ (97.17 mg, 0.433 mmol, 0.10 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 100 °C and stirred overnight. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 10d (1.1 g, 55.56%) as a yellow solid, eluted with CH_2Cl_2 / MeOH (5:1) to afford Compound 20 (600 mg) as a yellow solid. The crude product (50 mg) was purified by prep-HPLC with

the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 9% B to 35% B in 8 min, 35% B; Wave Length: 220 nm; RT1 (min): 6.08;) to afford Compound 20 (11.6 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 474

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.97 (s, 3H), 3.54 (s, 2H), 4.91-4.97 (m, 4H), 6.87-6.89 (d, 1H), 7.31 (s, 1H), 7.38-7.44 (m, 3H), 7.75-7.77 (d, 1H), 8.16 (s, 1H), 8.20 (s, 1H).

Example 21. Synthesis of Compound 21



10d 21

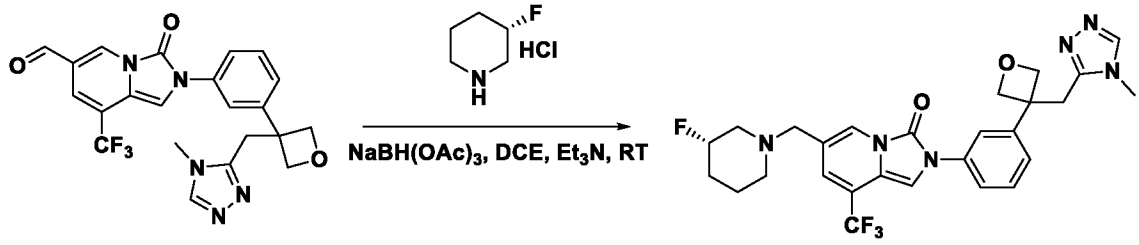
Synthesis of 21

[150] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), 5-azaspiro[2.3]hexane hydrochloride (52.29 mg, 0.438 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 7 min, 45% B; Wave Length: 220 nm; RT1 (min): 6.77;) to afford Compound 21 (38.6 mg, 33.66%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 525

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.51 (s, 4H), 2.97 (s, 3H), 3.29 (s, 4H), 3.46 (s, 2H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.00 (s, 1H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 22. Synthesis of Compound 22



10d 22

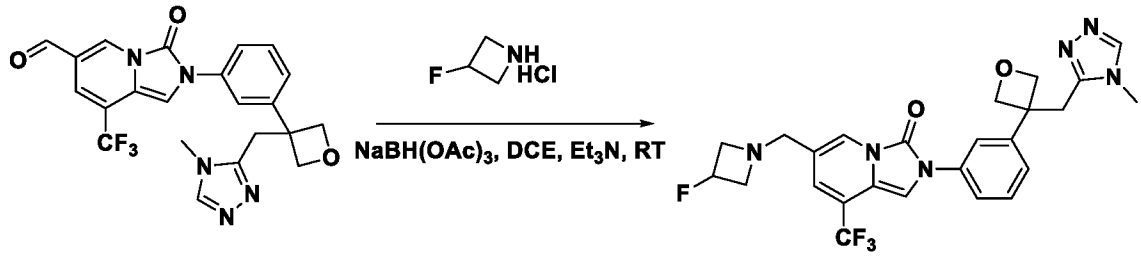
Synthesis of 22

[151] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), (3S)-3-fluoropiperidine hydrochloride (61.04 mg, 0.438 mmol, 2.00 equiv) and Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1 (min): 7.65;) to afford Compound 22 (42.9 mg, 36.03%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 545

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.44-1.67 (m, 2H), 1.72-1.82 (m, 2H), 2.28-2.39 (m, 1H), 2.42-2.50 (m, 2H), 2.71-2.75 (m, 1H), 2.98 (s, 3H), 3.54 (s, 2H), 4.58-4.72 (m, 1H), 4.91-4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.69 (s, 1H), 7.74-7.75 (d, 1H), 8.20 (s, 1H).

Example 23. Synthesis of Compound 23



10d 23

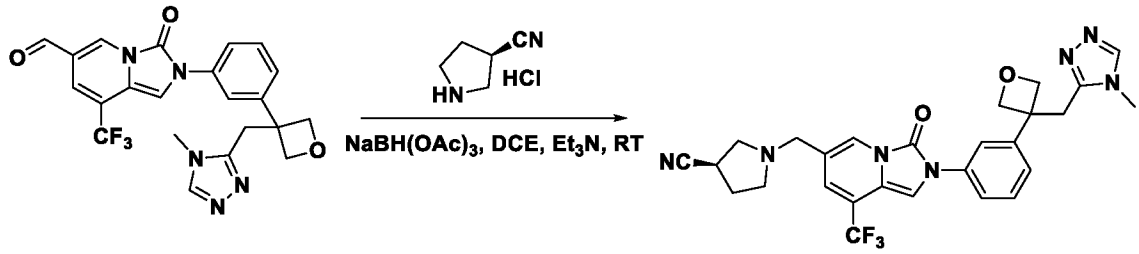
Synthesis of 23

[152] To a stirred mixture of 10d (1.00 equiv), 3-fluoroazetidine hydrochloride (2.00 equiv) and Et_3N (2 equiv) in DCE (2 mL) was added $NaBH(OAc)_3$ (2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 35% B in 7 min, 35% B; Wave Length: 254/220 nm; RT1 (min): 7.13;) to afford Compound 23 (26.5 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 517

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.97 (s, 3H), 3.13-3.17 (m, 1H), 3.19-3.23 (m, 1H), 3.44 (s, 2H), 3.50-3.60 (m, 4H), 4.91-4.97 (m, 4H), 5.11-5.30 (m, 1H), 6.88-6.91 (d, 1H), 6.98 (s, 1H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.70-7.76 (m, 2H), 8.20 (s, 1H).

Example 24. Synthesis of Compound 24



10d 24

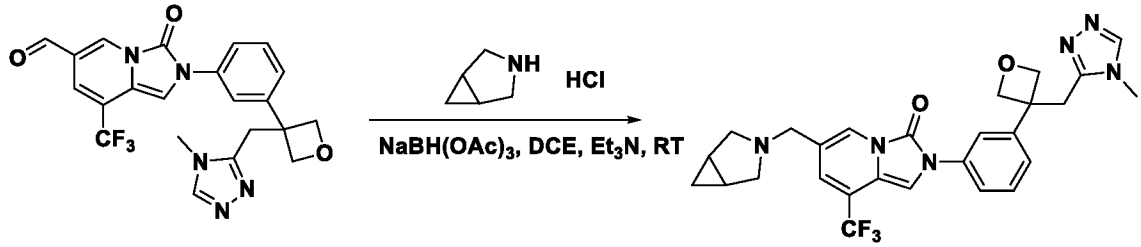
Synthesis of 24

[153] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv), (3R)-pyrrolidine-3-carbonitrile hydrochloride (57.97 mg, 0.437 mmol, 2 equiv) and Et_3N (44.24 mg, 0.437 mmol, 2 equiv) in DCE (2.00 mL) was added $NaBH(OAc)_3$ (92.67 mg, 0.437 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 35% B in 7 min, 35% B; Wave Length: 254/220 nm; RT1 (min): 7.0;) to afford Compound 24 (39.5 mg, 33.61%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 538

^1H NMR: (400 MHz, DMSO-d6, ppm): δ 1.92-2.00 (m, 1H), 2.16-2.25(m, 1H), 2.50-2.51 (m, 1H), 2.67-2.75 (m, 2H), 2.78-2.82 (m, 1H), 2.98 (s, 3H), 3.25-3.30 (m, 2H), 3.45 (s, 2H), 3.54 (s, 2H), 4.91-4.97 (m, 4H), 6.89-6.91 (d, 1H), 7.03 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.72-7.77 (m, 2H), 8.20 (s, 1H).

Example 25. Synthesis of Compound 25



10d 25

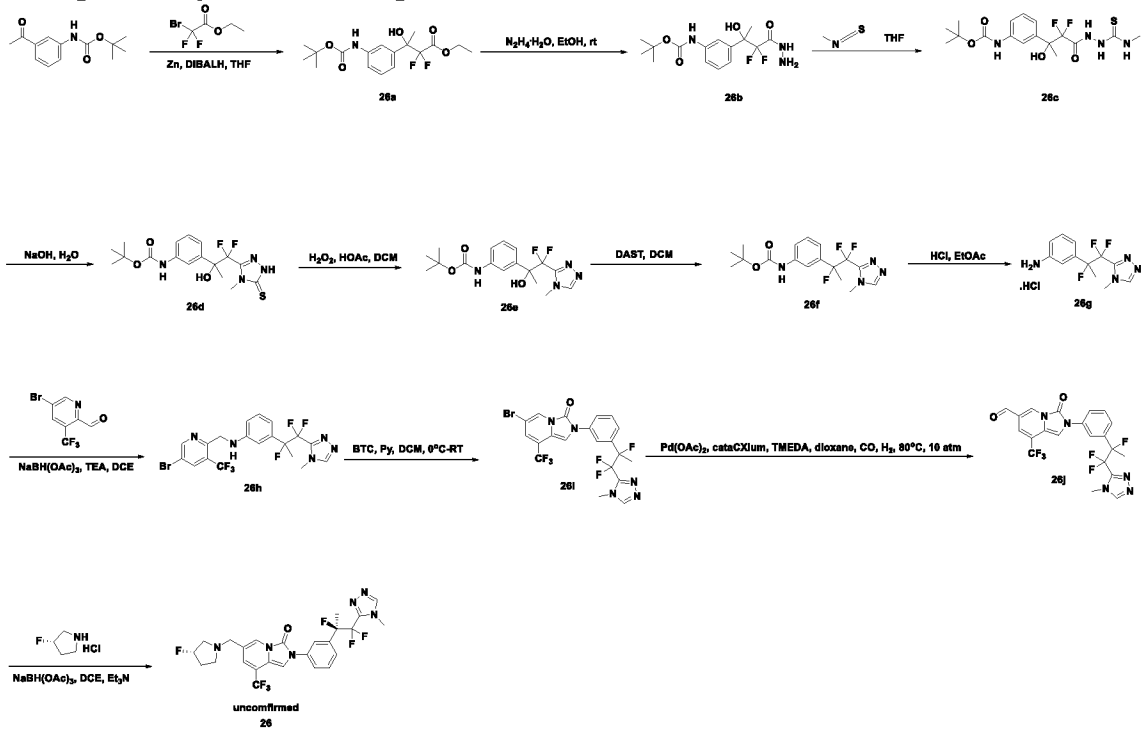
Synthesis of 25

[154] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv) and 3-azabicyclo[3.1.0]hexane hydrochloride(52.29 mg, 2.00 equiv) in DCE (2.00 mL) were added Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) and $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred overnight at room temperature . The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: Kinetex EVO C18 Column, 30*150, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 7 min, 50% B; Wave Length: 220 nm; RT1 (min): 6.63;) to afford Compound 25 (39.2 mg, 34.18%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 525

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.36-0.37 (m, 1H), 0.61-0.64 (m, 1H), 1.38-1.39 (m, 2H), 2.34-2.36 (m, 2H), 2.87-2.89 (m, 2H), 2.97 (s, 3H), 3.39 (s, 2H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 6.95 (s, 1H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.64 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 26. Synthesis of Compound 26



Synthesis of 26a

[155] To a mixture of Zn (23.77 g, 0.363 mmol, 4.5 equiv) and ethyl 2-bromo-2,2-difluoro-acetate (0.2 g, 9.85 mmol) in THF (200 mL) was added DIBAL-H (0.46 g, 0.003 mmol, 0.04 equiv) at 30 °C. Then the mixture was stirred for 1 h at 30 °C. Then tert-butyl N-(3-acetylphenyl)carbamate (19.00 g, 80.754 mmol, 1.00 equiv) and ethyl 2-bromo-2,2-difluoroacetate (24.59 g, 0.121 mmol, 1.5 equiv) in THF (200 mL) was added dropwise at 40 °C and stirred for 3 h at 40 °C. The mixture was filtered and the filtrate was poured into saturated NH_4Cl (200 mL). Then the mixture extracted with EtOAc (3x200 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1) to afford 26a (11.1 g, 36.34%) as light yellow oil.

Synthesis of 26b

[156] To a solution of 26a (11.00 g, 30.609 mmol, 1.00 equiv) in EtOH (150 mL) was added hydrazine hydrate (98%) (7.66 g, 153.046 mmol, 5 equiv). Then the mixture was stirred at 25 °C for 16 h. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (4x100 mL). The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 26b (10.1 g, 92.49%) as a light yellow solid.

Synthesis of 26c

[157] To a solution of 26b (10.00 g, 28.956 mmol, 1.00 equiv) in THF (100 mL) was added methyl isothiocyanate (4.23 g, 0.058 mmol, 2 equiv). Then the mixture was stirred at 70 °C for 2 h. The mixture was concentrated to give the crude product 26c (12 g, 84.18%) as a yellow oil, which was used without purification.

Synthesis of 26d

[158] A solution of 26c (12 g, 28.677 mmol, 1.00 equiv) in NaOH (1.00 M, 100 mL) was stirred at 50 °C for 2 h. The mixture was acidified to pH 7 with HCl (1 M) and filtered. This resulted in 26d (10 g, 79.25%) as an off-white solid.

Synthesis of 26e

[159] To a stirred solution of 26d (10.00 g, 24.973 mmol, 1.00 equiv) in DCM (100.00 mL) was added H_2O_2 (8.49 g, 74.879 mmol, 3.00 equiv, 30%) in HOAc (3.00 g, 49.957 mmol, 2.00 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 3h at room temperature under air atmosphere. The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.) and quenched with Na_2SO_3 (aq.). The aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 26e (4.5 g, 46.96%) as an off-white solid.

Synthesis of 26f

[160] To a stirred solution of 26e (4.50 g, 12.215 mmol, 1.00 equiv) in DCM (100.00 mL) was added DAST (5.91 g, 0.037 mmol, 3.00 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc (1:1) to afford 26f (3.5 g, 72.72%) as an off-white solid.

Synthesis of 26g

[161] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed HCl (g) in EtOAc (50.00 mL, 875.874 mmol, 92.69 equiv). This was followed by the addition of 26g (3.50 g, 9.450 mmol, 1.00 equiv) at room temperature. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 3 g (93.15%) of 26g as an off-white solid.

Synthesis of 26h

[162] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed DCE (20.00 mL), 26g (1.50 g, 4.890 mmol, 1.00 equiv), TEA (0.49 g,

0.005 mmol, 1 equiv), 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (1.24 g, 0.005 mmol, 1.00 equiv), $NaBH(OAc)_3$ (3.11 g, 0.015 mmol, 3 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was diluted with DCM (100 mL), washed with 50 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 26h (1.2 g, 45.86%) as a light yellow solid.

Synthesis of 26i

[163] To a stirred solution of 26h (1.20 g, 2.361 mmol, 1.00 equiv) and pyridine (1.12 g, 0.014 mmol, 6 equiv) in DCM (60.00 mL) was added triphosgene (0.25 g, 0.001 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The resulting mixture was washed with 30 mL of $NaHCO_3$ (aq.). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 26i (1.1 g, 82.39%) as a yellow solid.

Synthesis of 26j

[164] To a solution of 26i (1.00 g, 1.872 mmol, 1.00 equiv) in dioxane (30.00 mL) was added cataCXium (0.13 g, 0.363 mmol, 0.19 equiv), $Pd(OAc)_2$ (0.04 g, 0.178 mmol, 0.10 equiv), TMEDA (0.44 g, 3.744 mmol, 2.00 equiv) in a pressure tank. The mixture was purged with nitrogen for 3 min and then was pressurized to 10 atm with CO/H_2 (1:1) at 80 °C and stirred overnight. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 26j (500 mg, 50.29%) as a yellow solid.

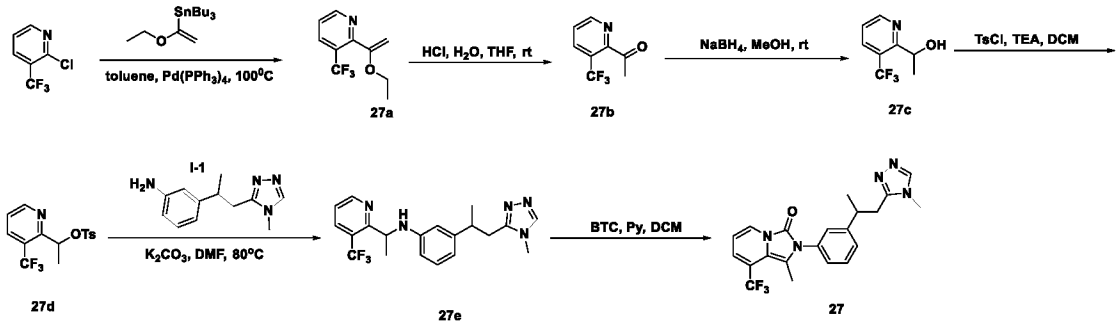
Synthesis of 26

[165] To a stirred solution of 26j (250.00 mg, 0.517 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (194.83 mg, 1.552 mmol, 3.00 equiv) in DCE (10.00 mL) was added Et_3N (157.01 mg, 1.552 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (328.85 mg, 1.552 mmol, 3 equiv), and then the mixture was stirred overnight at room temperature. The resulting mixture was washed with 10 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford the crude product (up). The crude product (120 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 57% B in 8 min, 57% B; Wave Length: 220 nm; RT1 (min): 7.23) to afford Compound 26 (59.3 mg, 20.42%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.83-1.95 (m, 1H), 1.99-2.17 (m, 3H), 2.19-2.24 (m, 1H), 2.41-2.49 (m, 1H), 2.67-2.71 (m, 1H), 2.75-2.84 (m, 2H), 3.31-3.52 (m, 5H), 5.16-5.29 (m, 1H), 7.05 (s, 1H), 7.36-7.38 (m, 2H), 7.56-7.60 (m, 1H), 7.73-7.75 (d, 1H), 7.89-7.92 (m, 2H), 8.64 (s, 1H).

Example 27. Synthesis of Compound 27



Synthesis of 27a

[166] To a stirred solution of 2-chloro-3-(trifluoromethyl) pyridine (1.00 g, 5.508 mmol, 1.00 equiv) in toluene (10.00 mL) was added tributyl(1-ethoxyethenyl) stannane (2.98 g, 8.263 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (0.64 g, 0.551 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The residue was washed with water (15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (40:1) to afford 27a (1.1 g, 86.35%) as a white oil.

Synthesis of 27b

[167] To a stirred solution of 27a (1.08 g, 4.973 mmol, 1.00 equiv) in THF (2.00 mL) was added HCl (2.00 mL, 1M) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The mixture was quenched with saturated Na_2CO_3 (aq.)(20 mL). The resulting mixture was extracted with EtOAc (3x25 mL), dried over anhydrous Na_2SO_4. The resulting mixture was concentrated under vacuum to afford 27b (850 mg, 90.42%) as a yellow oil.

Synthesis of 27c

[168] To a stirred solution of 27b (800.00 mg, 4.230 mmol, 1.00 equiv) in MeOH (10.00 mL) was added $NaBH_4$ (80.01 mg, 2.115 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under

nitrogen atmosphere. The resulting mixture was diluted with 40 mL of water. The resulting mixture was extracted with 3x40 mL of EtOAc. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 27c (400 mg, 44.53%) as a yellow oil.

Synthesis of 27d

[169] To a stirred solution of 27c (500.00 mg, 2.616 mmol, 1.00 equiv) in DCM (6 mL) was added TsCl (997.35 mg, 5.232 mmol, 2.00 equiv) and TEA (794.05 mg, 7.848 mmol, 3.00 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0 °C under nitrogen atmosphere. The resulting mixture was washed with 2x5 mL of water. The organic layer was concentrated under vacuum. The residue was purified by prep-TLC (PE/EtOAc 2:1) to afford 27d (500 mg, 52.03%) as a yellow oil.

Synthesis of 27e

[170] To a stirred solution of 27d (500.00 mg, 1.448 mmol, 1.00 equiv) in DMF (6.00 mL) was added 3-[1-(4-methyl-1,2,4-triazol-3-yl) propan-2-yl] aniline (375.78 mg, 1.738 mmol, 1.20 equiv) and K_2CO_3 (600.30 mg, 4.344 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with 20 mL of water. The resulting mixture was extracted with 3x20 mL of EtOAc. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 27e (80 mg, 13.20%) as a yellow oil.

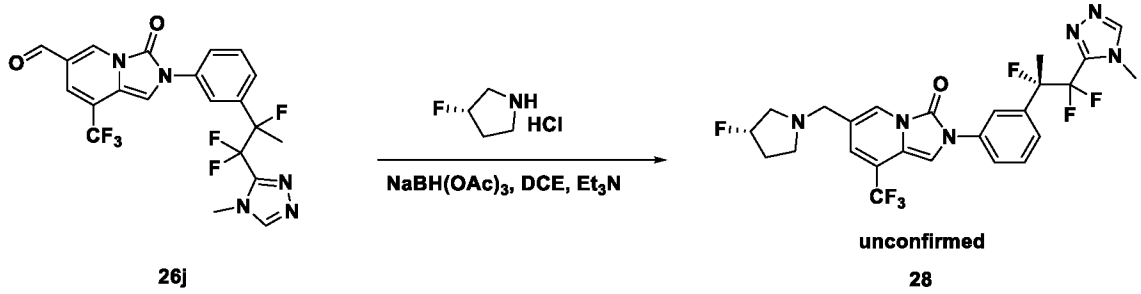
Synthesis of 27

[171] To a stirred solution of 27e (80.00 mg, 0.205 mmol, 1.00 equiv) in DCM (2 mL) was added pyridine (98.72 mg, 1.230 mmol, 6.00 equiv) and BTC (16.38 mg, 0.072 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0 °C under nitrogen atmosphere. The resulting mixture was diluted with 15 mL of water, extracted with DCM (3x20 mL). The crude product was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, A: water (0.1%NH_4HCO_3), B: CH_3CN, 45% B to 55% B gradient in 10 min; detector, UV 254 nm. The resulting mixture was concentrated under reduced pressure to afford Compound 27 (15.6 mg, 17.95%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 416

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.31-1.33 (d, 3H), 1.99 (s, 3H), 2.99-3.03 (m, 2H), 3.30-3.33 (m, 1H), 3.42 (s, 3H), 6.15-6.19 (m, 1H), 7.01-7.02 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.42 (d, 1H), 7.46-7.49 (m, 1H), 7.70-7.72 (d, 1H), 8.27 (s, 1H).

Example 28. Synthesis of Compound 28



26j 28

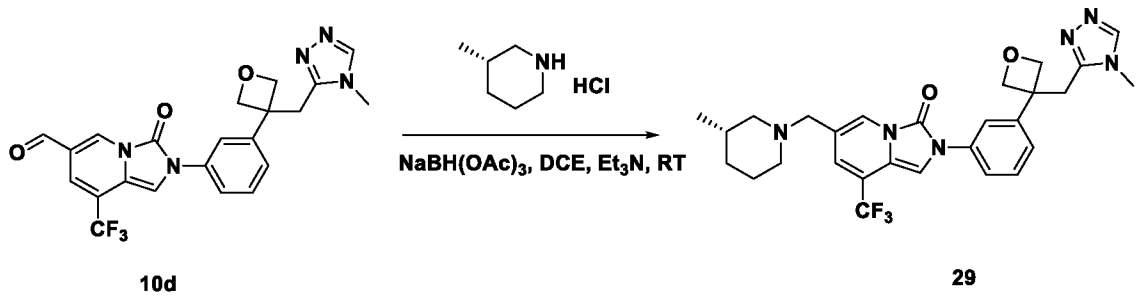
Synthesis of 28

[172] To a stirred solution of 26j (250.00 mg, 0.517 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (194.83 mg, 1.552 mmol, 3.00 equiv) in DCE (10.00 mL) was added Et_3N (157.01 mg, 1.552 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (328.85 mg, 1.552 mmol, 3 equiv), and then the mixture was stirred overnight at room temperature. The resulting mixture was washed with 10 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford the crude product (down). The crude product (100 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min, 60% B; Wave Length: 220 nm; RT1 (min): 7.55;) to afford Compound 28 (27.2 mg, 9.33%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.83-1.95 (m, 1H), 1.99-2.17 (m, 3H), 2.19-2.24 (m, 1H), 2.41-2.49 (m, 1H), 2.67-2.91 (m, 3H), 3.31-3.36 (m, 1H), 3.36-3.42 (m, 1H), 3.52 (s, 3H), 5.17-5.31 (m, 1H), 7.06 (s, 1H), 7.37-7.39 (m, 2H), 7.56-7.60 (m, 1H), 7.73-7.75 (d, 1H), 7.89-7.92 (m, 2H), 8.64 (s, 1H).

Example 29. Synthesis of Compound 29



10d 29

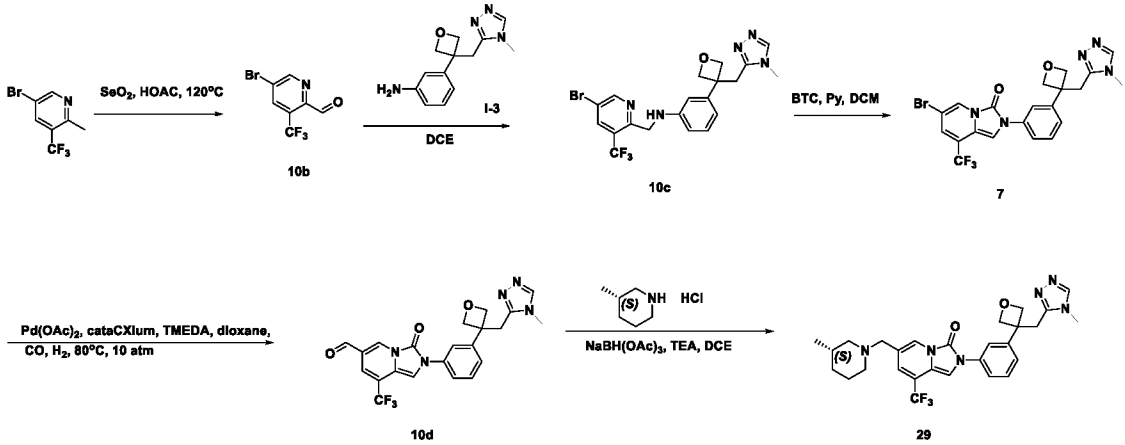
Synthesis of 29

[173] To a stirred mixture of 10d (100.00 mg, 0.219 mmol, 1.00 equiv) and (3S)-3-methylpiperidine hydrochloride (59.31 mg, 0.438 mmol, 2.00 equiv) in DCE (2.00 mL) were added Et_3N (44.24 mg, 0.438 mmol, 2.00 equiv) and $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x15 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min, 60% B; Wave Length: 220 nm; RT1 (min): 7.43) to afford Compound 29 (46.2 mg, 39.09%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 541

^1H NMR: (400 MHz, DMSO-d6, ppm): δ 0.82-0.83 (d, 4H), 1.30-1.51 (m, 1H), 1.52-1.72 (m, 4H), 1.82-1.91 (m, 1H), 2.65-2.83 (m, 2H), 2.97 (s, 3H), 3.24 (s, 2H), 3.53 (s, 2H), 4.90-4.92 (d, 2H), 4.94-4.96 (d, 2H), 6.88-6.90 (d, 1H), 7.00 (s, 1H), 7.38 (s, 1H), 7.40-7.42 (m, 2H), 7.65 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Alternatively, Compound 20 may be also prepared in the manner outlined below:



1. Synthesis of 10b

A mixture of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (100 g, 416.627 mmol, 1 equiv) and SeO_2 (92.47 g, 833.254 mmol, 2 equiv) in AcOH (500 mL) was stirred for overnight at 120°C. The resulting mixture was diluted with water (1000 mL). The aqueous layer was extracted with methyl tert- butyl ether (2x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with hexane

(100 mL). This resulted in 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (62 g, 58.81%) as a off-white solid.

2. Synthesis of 10c

To a stirred solution of 10b (100 g, 395.26 mmol, 1.20 equiv) and I-3 (80 g, 329.38 mmol, 1.00 equiv) in DCE (1000.00 mL) were added $NaBH(OAc)_3$ (139.65 g, 658.761 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (2500.00 mL). The aqueous layer was extracted with EtOAc (3x1000.00 mL). The organic layers were concentrated under reduced pressure. The residue was purified by trituration with MTBE (2x300.00 mL). This resulted in 10c (116 g, 61.01 %) as a white solid.

3. Synthesis of 7

To a stirred solution of 10c (130 g, 269.539 mmol, 1 equiv) and Pyridine (127.92 g, 1617.234 mmol, 6 equiv) in DCM (2600 mL) was added Triphosgene (26.39 g, 94.594 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (1500 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 300 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with methyl tert-butyl ether (600 mL). This resulted in 7 (110 g, 80.29%) as a yellow solid.

(ES, *m/z*): $[M+H]^+$: 508

4. Synthesis of 10d

To a solution of 7 (110 g, 216.408 mmol, 1 equiv), TMEDA (50.30 g, 432.816 mmol, 2 equiv) in dioxane (4400 mL) was added bis(adamantan-1-yl)(butyl)phosphane (15.52 g, 43.282 mmol, 0.2 equiv) and $Pd(OAc)_2$ (4.86 g, 21.641 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 80 degrees overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 10d (58 g, 58.59%) as a yellow solid.

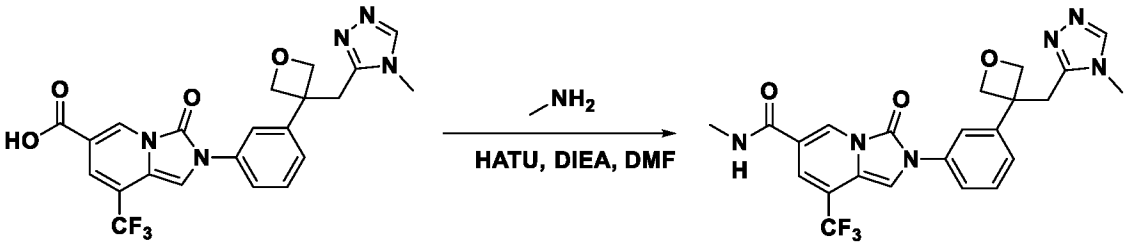
(ES, *m/z*): $[M+H]^+$: 458

5. Synthesis of 29

To a stirred mixture of 10d (58 g, 126.800 mmol, 1.00 equiv) and (s)-3-methylpiperidine hydrochloride (34.40 g, 253.600 mmol, 2 equiv) in DCE (1600 mL) was added TEA (38.49 g, 380.400 mmol, 3 equiv). The resulting mixture was stirred for 2 h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (53.75 g, 253.600 mmol, 2 equiv). The resulting

mixture was stirred overnight at room temperature. The reaction was quenched by the addition of Water (1000 mL). The resulting mixture was extracted with CH_2Cl_2/MEOH=10/1 (2 x 1000 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmoL/L NH_4HCO_3), 15% to 80% gradient in 40 min; detector, UV 254 nm. This resulted in 29 (30.9 g, 45.08%) as a yellow solid.
LC-MS-29: (ES, *m/z*): $[M+H]^+$ 541. H-NMR-29: (400 MHz, CD_3OD, δ *ppm*): 0.75-0.95 (m, 4H), 1.43-1.49 (m, 1H), 1.49-1.66 (m, 4H), 1.86-1.91 (m, 1H), 2.67-2.76 (m, 2H), 2.96 (s, 3H), 3.31 (s, 2H), 3.53 (s, 2H), 4.90-4.95 (m, 1H), 6.88-9.90 (d, 1H), 7.00 (s, 1H), 7.29 (s, 1H), 7.37-7.40 (d, 1H), 7.64 (s, 1H), 7.74-7.76 (d, 1H), 8.19 (s, 1H).

Example 30. Synthesis of Compound 30

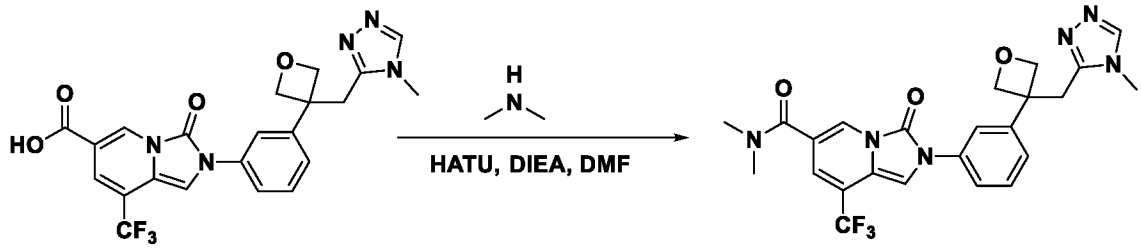


20 30

Synthesis of 30

[174] To a stirred solution of Compound 20 (180.00 mg, 0.380 mmol, 1.00 equiv), methylamine (0.57 mL, 1.140 mmol, 3.00 equiv, 2M in THF) and DIEA (147.42 mg, 1.141 mmol, 3.00 equiv) in DMF (2.00 mL) was added HATU (289.14 mg, 0.760 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature . The crude product was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 40% B in 8 min, Wave Length: 220 nm; RT1 (min): 6.82;) to afford Compound 30 (34.5 mg, 18.65%) as a yellow solid.
LCMS: (ES, *m/z*): $[M+H]^+$ 487
^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.88 (s, 3H), 2.97 (s, 3H), 3.68 (s, 2H), 5.05-5.10 (m, 4H), 6.91-6.93 (d, 1H), 7.18 (s, 1H), 7.33 (s, 1H), 7.42 (s, 1H), 7.46-7.50 (m, 1H), 7.63-7.65 (d, 1H), 8.20 (s, 1H), 8.38 (s, 1H).

Example 31. Synthesis of Compound 31



20 31

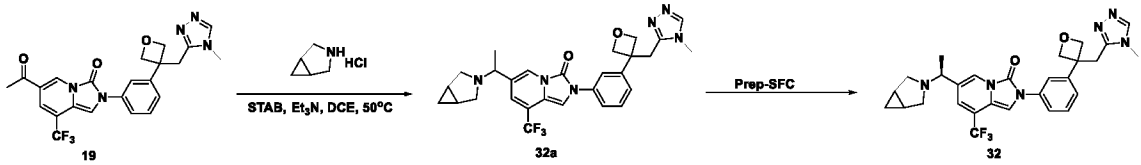
Synthesis of 31

[175] To a stirred solution of Compound 20 (180.00 mg, 0.380 mmol, 1.00 equiv), dimethylamine (0.57 mL, 1.140 mmol, 3.00 equiv, 2M in THF) and DIEA (147.42 mg, 1.140 mmol, 3.00 equiv) in DMF (2.00 mL) was added HATU (289.14 mg, 0.760 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction solution was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 35% B in 8 min; Wave Length: 220 nm; RT1 (min): 7.77;) to afford Compound 31 (45 mg, 23.65%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 501

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.99 (s, 6H), 3.03 (s, 3H), 3.54 (s, 2H), 4.91-4.97 (m, 4H), 6.90-6.92 (d, 1H), 7.08 (s, 1H), 7.40-7.45 (m, 3H), 7.74-7.76 (m, 1H), 7.90 (s, 1H), 8.20 (s, 1H).

Example 32. Synthesis of Compound 32



Synthesis of 32a

[176] To a stirred mixture of 32a (400.00 mg, 0.848 mmol, 1.00 equiv) and 3-azabicyclo[3.1.0]hexane hydrochloride (152.20 mg, 1.273 mmol, 1.5 equiv) in DCE (5.00 mL) were added STAB (539.47 mg, 2.545 mmol, 3 equiv) and Et_3N (257.57 mg, 2.545 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 50 °C. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated

under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 32a (45 mg, 9.65%) as a yellow solid.

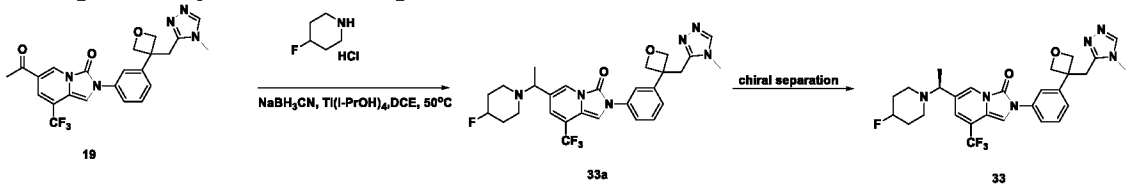
Synthesis of 32

[177] The 32a (45 mg) was separated by prep-SFC with the following conditions (Column: Lux 5μm Cellulose-4, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3-MEOH); Flow rate: 80 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 254 nm; RT2 (min): 13.78;) to afford Compound 32 (4.3 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 539

^{1}H NMR (400 MHz, DMSO, δ *ppm*): δ 0.31-0.37 (d, 1H), 0.59-0.66 (d, 1H), 1.20-1.27 (m, 3H), 1.31-1.37 (d, 1H), 1.38-1.42 (m, 1H), 2.20-2.31 (m, 1H), 2.32-2.43 (m, 1H), 2.61-2.71 (d, 1H), 2.97 (s, 3H), 3.00-3.04 (d, 1H), 3.25-3.30 (d, 1H), 3.50-3.55 (d, 2H), 4.87-5.05 (m, 4H), 6.80-6.95 (d, 1H), 6.97 (s, 1H), 7.31 (s, 1H), 7.38-7.51 (m, 2H), 7.63 (s, 1H), 7.70-7.80 (m, 1H), 8.20 (s, 1H).

Example 33. Synthesis of Compound 33



Synthesis of 33a

[178] To a stirred solution of 19a (200.00 mg, 0.424 mmol, 1.00 equiv) and 4-fluoropiperidine hydrochloride (59.22 mg, 0.424 mmol, 1.00 equiv) in DCE (2.00 mL) were added Ti(Oi-Pr)$_4$ (241.15 mg, 0.848 mmol, 2.00 equiv) and $NaBH_3CN$ (31.99 mg, 0.509 mmol, 1.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 50 °C. The resulting mixture was diluted with water (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x10 mL). The residue was purified by prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 33a (40 mg, 16.88%) as a yellow solid.

Synthesis of 33

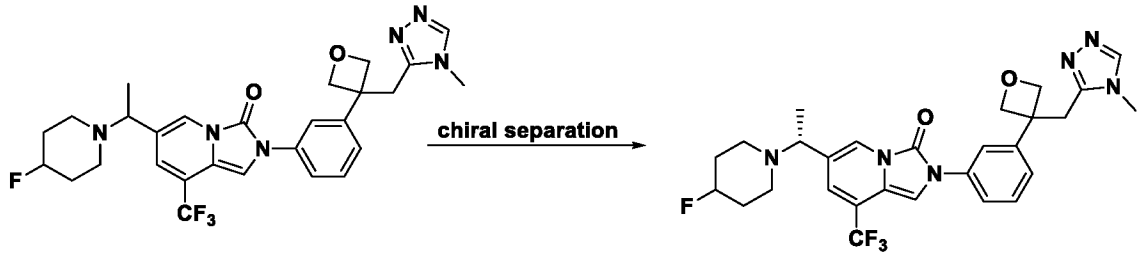
[179] The compound of 33a (40 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 18 min; Wave Length: 220 nm; RT2 (min): 16.44) to afford

Compound 33 (4.4 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 559.

^{1}H NMR: (400 MHz, DMSO, δ ppm): δ 1.24-1.28 (m, 3H), 1.69-1.80 (m, 2H), 1.80-1.91 (m, 2H), 2.33-2.37 (m, 2H), 2.58-2.68 (m, 2H), 2.97 (s, 3H), 3.49-3.53 (m, 3H), 4.59-4.73 (m, 1H), 4.83-4.96 (m, 4H), 6.89-6.91 (m, 1H), 7.08 (s, 1H), 7.31-7.38 (m, 1H), 7.40-7.42 (m, 1H), 7.60-7.61 (m, 1H), 7.73-7.76 (m, 1H), 8.20 (s, 1H).

Example 34. Synthesis of Compound 34



33a 34

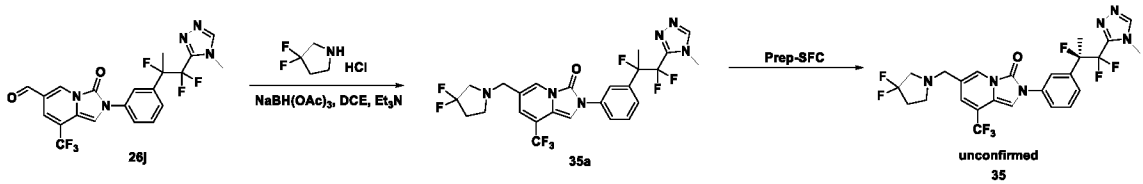
Synthesis of 34

[180] The compound of 33a (40 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 18 min; Wave Length: 220 nm; RT1 (min): 14.61) to afford Compound 34 (5.2 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 559

^{1}H NMR (400 MHz, DMSO, δ ppm): δ 1.22-1.28 (m, 3H), 1.69-1.80 (m, 2H), 1.81-1.87 (m, 2H), 2.34-2.36 (m, 2H), 2.57-2.68 (m, 2H), 2.87-2.88 (m, 1H), 2.97 (s, 2H), 3.48-3.53 (m, 3H), 4.60-4.72 (m, 1H), 4.82-4.96 (m, 4H), 6.89-6.91 (m, 1H),7.08-7.09 (m, 1H), 7.31-7.38 (m, 1H), 7.40-7.42 (m, 2H), 7.60-7.61 (m, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 35. Synthesis of Compound 35



26j 35a unconfirmed 35

Synthesis of 35a

[181] To a stirred solution of 26j (250.00 mg, 0.517 mmol, 1.00 equiv) and 3,3-difluoropyrrolidine hydrochloride (222.75 mg, 1.552 mmol, 3.00 equiv) in DCE (10.00 mL)

was added Et_3N (157.01 mg, 1.552 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (328.85 mg, 1.552 mmol, 3 equiv), and then the mixture was stirred overnight at room temperature. The resulting mixture was washed with 10 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 35a (220 mg, 69.60%) as a yellow solid.

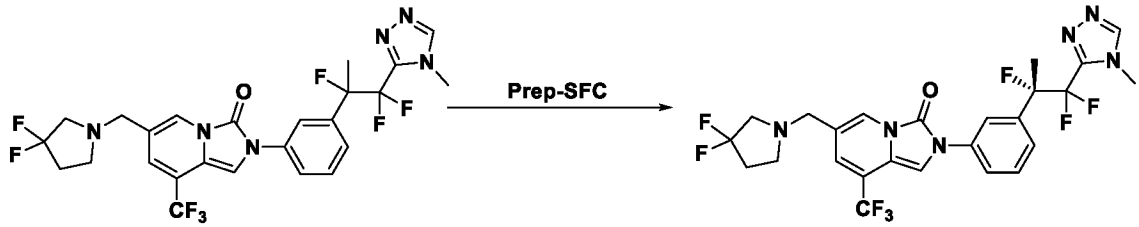
Synthesis of 35

[182] The crude product (35a, 220 mg) was purified by prep-SFC with the following conditions (Column: CHIRALPAK IF, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.5% 2M NH_3-MeOH)--HPLC; Flow rate: 100 mL/min; Gradient: isocratic 25% B; Back Pressure(bar): 100; Wave Length: 220 nm; RT1 (min): 5.6; Sample Solvent: MeOH; Injection Volume: 1.8 mL; Number Of Runs: 11) to afford Compound 35 (31.9 mg, 14.38%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 575

^1H NMR: (400 MHz, CD_3OD-d4, *ppm*): δ 2.05-2.08 (m, 3H), 2.26-2.37 (m, 2H), 2.82-2.84 (m, 2H), 2.93-3.00 (m, 2H), 3.47 (s, 2H), 3.65 (s, 3H), 7.10 (s, 1H), 7.15 (s, 1H), 7.43-7.45 (d, 1H), 7.60-7.62 (m, 1H), 7.72 (s, 1H), 7.76-7.80 (m, 2H), 8.54 (s, 1H).

Example 36. Synthesis of Compound 36



35a 36

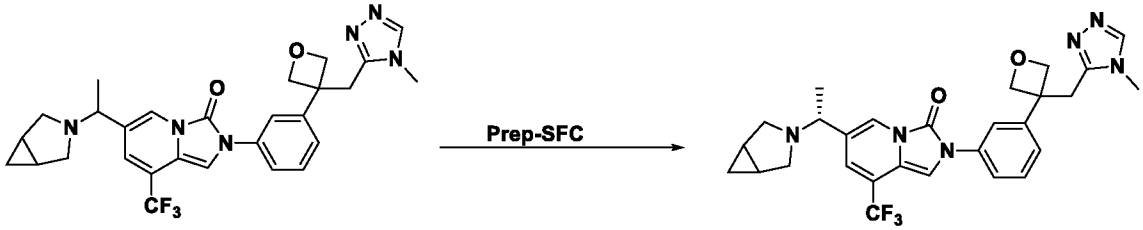
Synthesis of 36

[183] The crude product (35a, 220 mg) was purified by prep-SFC with the following conditions (Column: CHIRALPAK IF, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.5% 2M NH_3)--HPLC; Flow rate: 100 mL/min; Gradient: isocratic 25% B; Column Temperature °C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT2 (min): 6.82;) to afford Compound 36 (78.3 mg, 34.17%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 575

^{1}H NMR: (400 MHz, CD_3OD-d4, *ppm*): δ 1.99-2.08 (m, 3H), 2.26-2.37 (m, 2H), 2.81-2.84 (m, 2H), 2.93-3.00 (m, 2H), 3.48 (s, 2H), 3.65 (s, 3H), 7.10 (s, 1H), 7.14 (s, 1H), 7.42-7.47 (d, 1H), 7.57-7.61 (m, 1H), 7.72 (s, 1H), 7.76-7.82 (m, 2H), 8.53 (s, 1H).

Example 37. Synthesis of Compound 37



32a 37

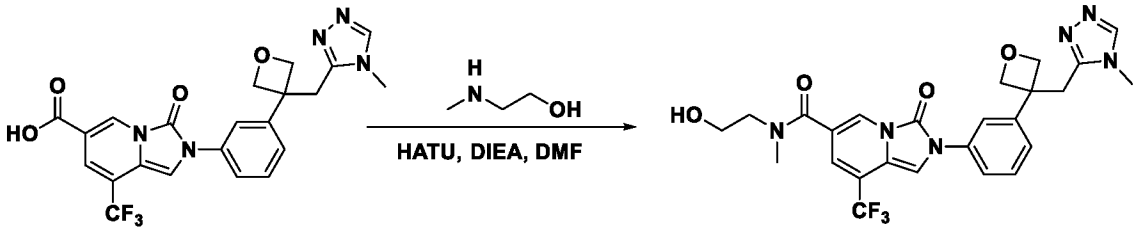
Synthesis of 37

[184] The compound of 32a (45 mg) was separated by prep-SFC with the following conditions (Column: Lux 5μm Cellulose-4, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH (0.1% 2M NH_3-MEOH); Flow rate: 80 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 254 nm; RT1 (min): 11.52;) to afford Compound 37 (3.3 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 539

^{1}H NMR: (400 MHz, DMSO, δ *ppm*): δ 0.26-0.40 (d, 1H), 0.57-0.66 (d, 1H), 1.22-1.27 (t, 3H), 1.31-1.37 (d, 1H), 1.38-1.45 (m, 1H), 2.19-2.31 (m, 1H), 2.35-2.44 (m, 1H), 2.61-2.71 (d, 1H), 2.95-2.98 (d, 2H), 3.00-3.07 (m, 1H), 3.25-3.30 (d, 1H), 3.41-3.50 (d, 1H), 3.51-3.61 (d, 2H), 4.87-5.05 (m, 4H), 6.88-6.90 (d, 1H), 6.97 (s, 1H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.62 (s, 1H), 7.73-7.76 (m, 1H), 8.20 (s, 1H).

Example 38. Synthesis of Compound 38



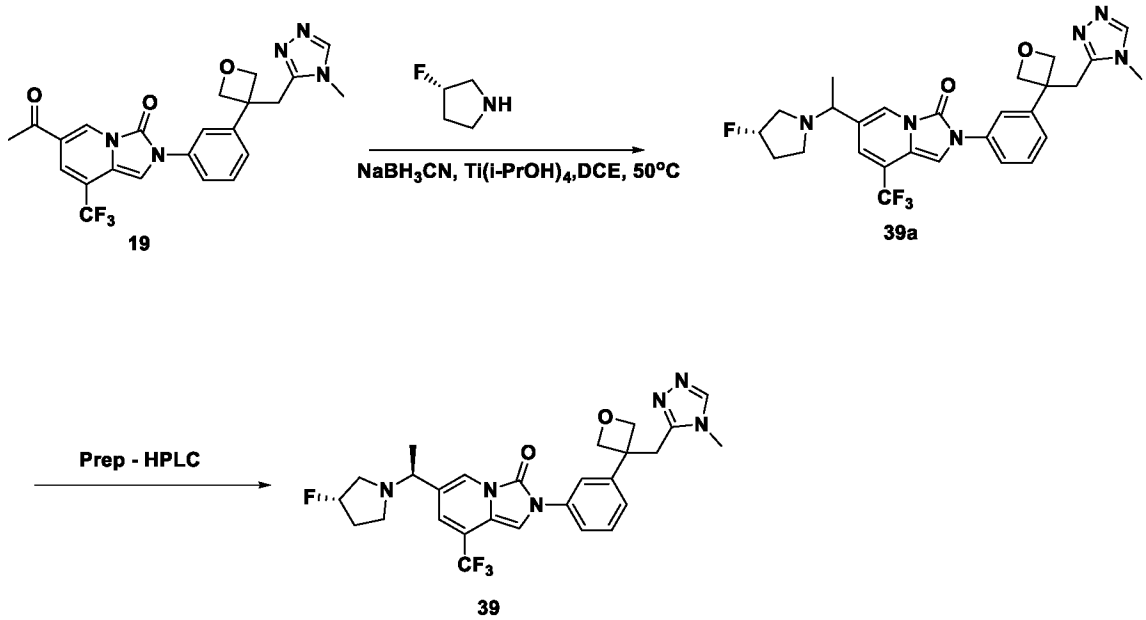
20 38

Synthesis of 38

[185] To a stirred solution of Compound 20 (180.00 mg, 0.380 mmol, 1.00 equiv) and methylethanolamine (57.12 mg, 0.760 mmol, 2.00 equiv) in DMF (2.00 mL) were added DIEA (98.28 mg, 0.760 mmol, 2.00 equiv) and DIEA (98.28 mg, 0.760 mmol, 2.00 equiv).

The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 35% B in 8 min, 35% B; Wave Length: 220 nm; RT1 (min): 7.50;) to afford Compound 38 (34.3 mg, 17.00%) as a yellow solid.
LCMS: (ES, *m/z*): $[M+H]^+$ 531
^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.86-3.01 (m, 6H), 3.44-3.49 (m, 2H), 3.54 (s, 2H), 3.58-3.62 (m, 2H), 4.89-4.97 (m, 4H), 6.89-6.91 (d, 1H), 7.09 (s, 1H), 7.39-7.45 (m, 3H), 7.74-7.76 (m, 1H), 8.09 (s, 1H), 8.21 (s, 1H).

Example 39. Synthesis of Compound 39



19 39a 39

Synthesis of 39a

[186] To a stirred mixture of Compound 19 (150.00 mg, 0.318 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine (42.53 mg, 0.477 mmol, 1.5 equiv) in DCE (2.00 mL) were added $NaBH_3CN$ (59.98 mg, 0.955 mmol, 3 equiv) and titanium(IV) isopropoxide (90.43 mg, 0.318 mmol, 1 equiv) dropwise at room temperature. The resulting mixture was stirred for 4 h at 50 °C under nitrogen atmosphere. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 39a (48 mg, 26.32%) as a yellow solid.

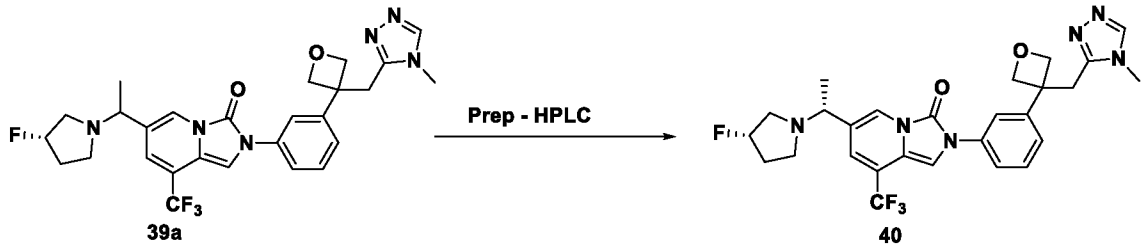
Synthesis of 39

[187] The 39a (48 mg) was separated by prep- HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 40% B in 7 min, 40% B; Wave Length: 254 nm; RT1 (min): 7.48;) to afford Compound 39 (4.4 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 545

^{1}H NMR: (400 MHz, DMSO, *ppm*): δ 1.23-1.36 (d, 3H), 1.76-2.00 (m, 1H), 2.00-2.21 (m, 1H), 2.37-2.47 (d, 1H), 2.58-2.71 (m, 2H), 2.77-2.96 (m, 1H), 2.96-3.01 (s, 3H), 3.27-3.31 (t, 1H), 3.45-3.57 (s, 2H), 4.85-5.06 (m, 4H), 5.10-5.39 (d, 1H), 6.89-6.94 (d, 1H), 7.05 (s, 1H), 7.27-7.36 (d, 1H), 7.36-7.48 (m, 2H), 7.70 (s, 1H), 7.74-7.76 (d, 1H), 8.20(s, 1H).

Example 40. Synthesis of Compound 40



39a 40

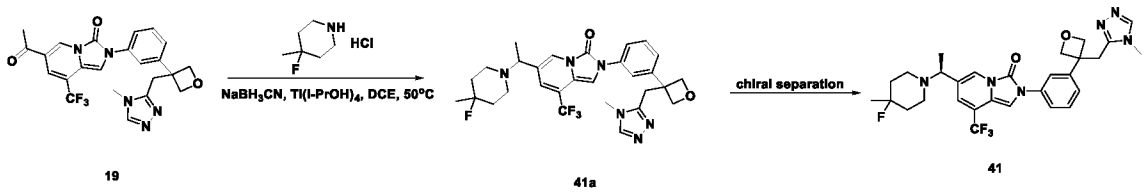
Synthesis of 40

[188] Compound 39a (48 mg) was separated by prep- HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 40% B in 7 min, 40% B; Wave Length: 254 nm; RT1 (min): 7.48) to afford Compound 40 (3.0 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 545

^{1}H NMR: (400 MHz, DMSO, *ppm*): δ 1.27-1.36 (d, 3H), 1.78-2.01 (m, 1H), 2.00-2.22 (m, 1H), 2.22-2.34 (d, 1H), 2.58-2.80 (m, 2H), 2.80-2.95 (m, 1H), 2.95-3.01 (s, 3H), 3.23-3.31 (t, 1H), 3.53-3.57 (s, 2H), 4.85-5.00 (m, 4H), 5.05-5.32 (d, 1H), 6.82-6.92 (d, 1H), 7.06 (s, 1H), 7.32-7.36 (s, 1H), 7.40-7.42 (m, 2H), 7.70 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 41. Synthesis of Compound 41



19 41a 41

Synthesis of 41a

[189] To a stirred solution of Compound 19 (60.00 mg, 0.552 mmol, 1.00 equiv) and 4-fluoro-4-methylpiperidine hydrochloride (84.73 mg, 0.552 mmol, 1.00 equiv) in DCE (3.00 mL) were added $Ti(Oi\text{-}Pr)_4$ (156.75 mg, 0.552 mmol, 1.00 equiv) and $NaBH_3CN$ (41.59 mg, 0.662 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for overnight at 50 °C. The resulting mixture was diluted with water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL).The residue was purified by prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 41a (50 mg) as a yellow solid. The crude product (50 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 8 min, 55% B; Wave Length: 220 nm; RT1 (min): 7.55; Number Of Runs: 0) to afford 41a (20 mg, 6.33%) as a yellow solid.

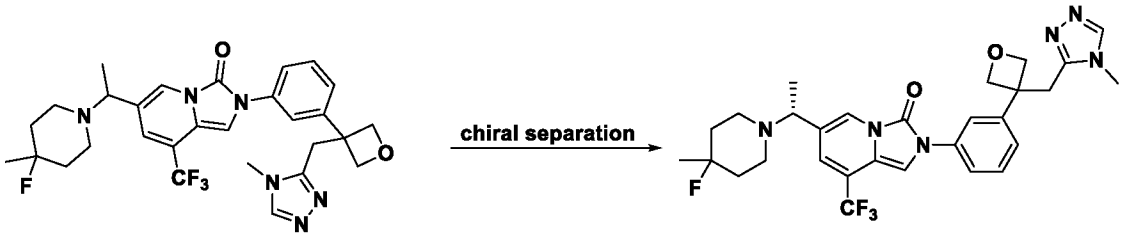
Synthesis of 41

[190] The compound of 41a (20 mg) was separated by prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 15 min; Wave Length: 220 nm; RT2 (min): 13.73) to afford Compound 41 (6.9 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 573

^1H NMR (400 MHz, DMSO, δ ppm): δ 1.22-1.38 (m, 6H), 1.55-1.63 (m, 1H), 1.63-1.74 (m, 3H), 2.25-2.36 (m, 2H), 2.60-2.67 (m, 2H), 2.97 (s, 3H), 3.47-3.53 (m, 3H), 4.91-4.96 (m, 4H), 6.89-6.91 (m, 1H), 7.07-7.08 (m, 1H), 7.31-7.32 (m, 1H), 7.38-7.42 (m, 2H), 7.60-7.61 (m, 1H), 7.73-7.76 (m, 1H), 8.20 (s, 1H).

Example 42. Synthesis of Compound 42



41a 42

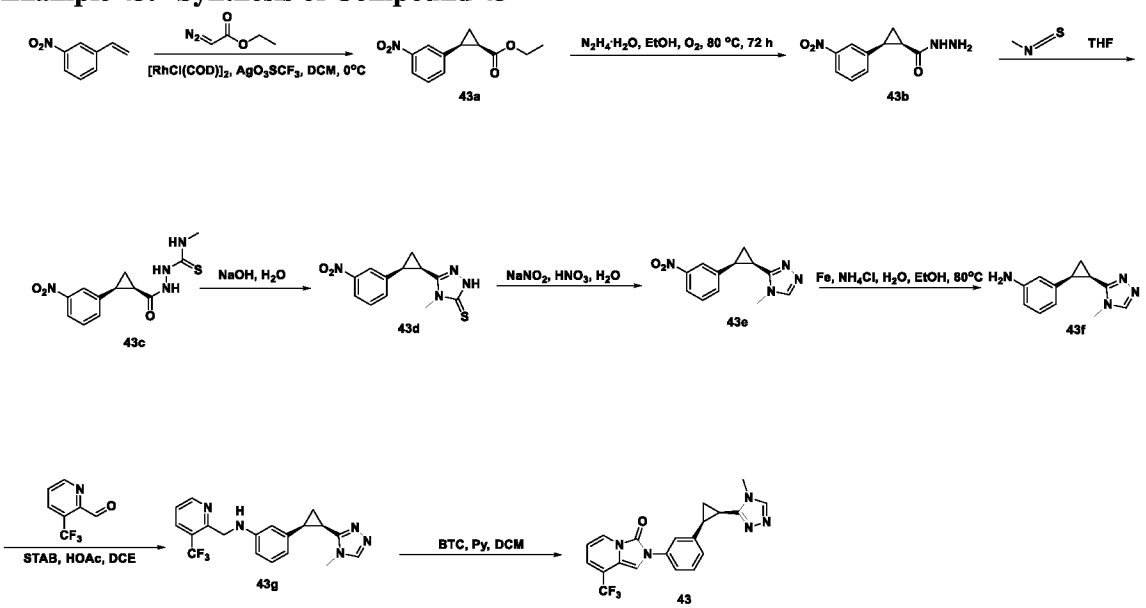
Synthesis of 42

[191] The compound of 41a (20 mg) was separated by prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH; DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 15 min; Wave Length: 220 nm; RT1 (min): 12.42) to afford Compound 42 (6.6 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 573

^{1}H NMR (400 MHz, DMSO, δ ppm): δ 1.24-1.33 (m, 6H), 1.59-1.62 (m, 1H), 1.71-1.74 (m, 3H), 2.29-2.33 (m, 2H), 2.61-2.67 (m, 2H), 2.97 (s, 3H), 3.47-3.53 (m, 3H), 4.91-4.96 (m, 4H), 6.89-6.91 (m, 1H), 7.08-7.08 (m, 1H), 7.31-7.32 (m, 1H), 7.38-7.42 (m, 2H), 7.61-7.62 (m, 1H), 7.73-7.76 (m, 1H), 8.20 (s, 1H).

Example 43. Synthesis of Compound 43



Synthesis of 43a

[192] To a stirred solution of cyclooctadiene rhodium chloride dimer (3.31 g, 6.713 mmol, 0.10 equiv) in DCM (150.00 mL) were added silver triflate (1.72 g, 6.694 mmol, 0.10 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C. To the above mixture was added ethyl diazoacetate (38.25 g, 0.335 mmol, 5 equiv) and (3-nitrophenyl)ethene (10.00 g, 67.047 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature. The resulting mixture was washed with 1x100 mL of water. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford the crude product. The residue was purified by prep-TLC (PE/EtOAc 8:1) to afford 43a (1.1 g, 6.63%) as a light yellow oil.

Synthesis of 43b

[193] To a stirred solution of 43a (1.10 g, 4.676 mmol, 1.00 equiv) in EtOH (20.00 mL) was added hydrazine hydrate (98%) (3.51 g, 70.140 mmol, 15.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10:1 (3x100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 43b (600 mg, 52.20%) as a light yellow oil.

Synthesis of 43c

[194] To a stirred solution of 43b (600.00 mg, 2.712 mmol, 1.00 equiv) in tetrahydrofuran (10.00 mL) was added methyl isothiocyanate (297.44 mg, 4.068 mmol, 1.50 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (50 mL). The precipitated solids were collected by filtration. This resulted in 43c (700 mg, 78.92%) as an off-white solid.

Synthesis of 43d

[195] To a stirred solution of NaOH (92.41 mg, 2.310 mmol, 1.00 equiv) in H_2O (23.00 mL) was added 43c (680.00 mg, 2.310 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The precipitated solids were collected by filtration and washed with water (10 mL). This resulted in 43d (600 mg, 84.59%) as an off-white solid.

Synthesis of 43e

[196] To a stirred solution of 43d (600.00 mg, 2.171 mmol, 1.00 equiv) in H_2O (10.00 mL) was added $NaNO_2$ (1498.22 mg, 21.715 mmol, 10.00 equiv) and HNO_3 (10.00 mL, 1 M) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0 °C. The mixture was basified to pH 7 with saturated $NaHCO_3$. The precipitated solids were collected by

filtration and washed with water (10 mL). This resulted in 43e (400 mg, 68.63%) as an off-white solid.

Synthesis of 43f

[197] To a stirred solution of Fe (411.54 mg, 7.369 mmol, 5.00 equiv) and 43e (360.00 mg, 1.474 mmol, 1.00 equiv) in EtOH (10.00 mL) was added NH_4Cl (788.39 mg, 14.739 mmol, 10 equiv) in H_2O (10.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 43f (300 mg, 89.29%) as a light yellow solid.

Synthesis of 43g

[198] To a stirred solution of 43f (280.00 mg, 1.307 mmol, 1.00 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (228.83 mg, 1.307 mmol, 1.00 equiv) in DCE (10.00 mL) were added HOAc (156.95 mg, 2.614 mmol, 2 equiv) and STAB (830.86 mg, 3.920 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was washed with 20 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 43g (400 mg, 75.42%) as a light yellow solid.

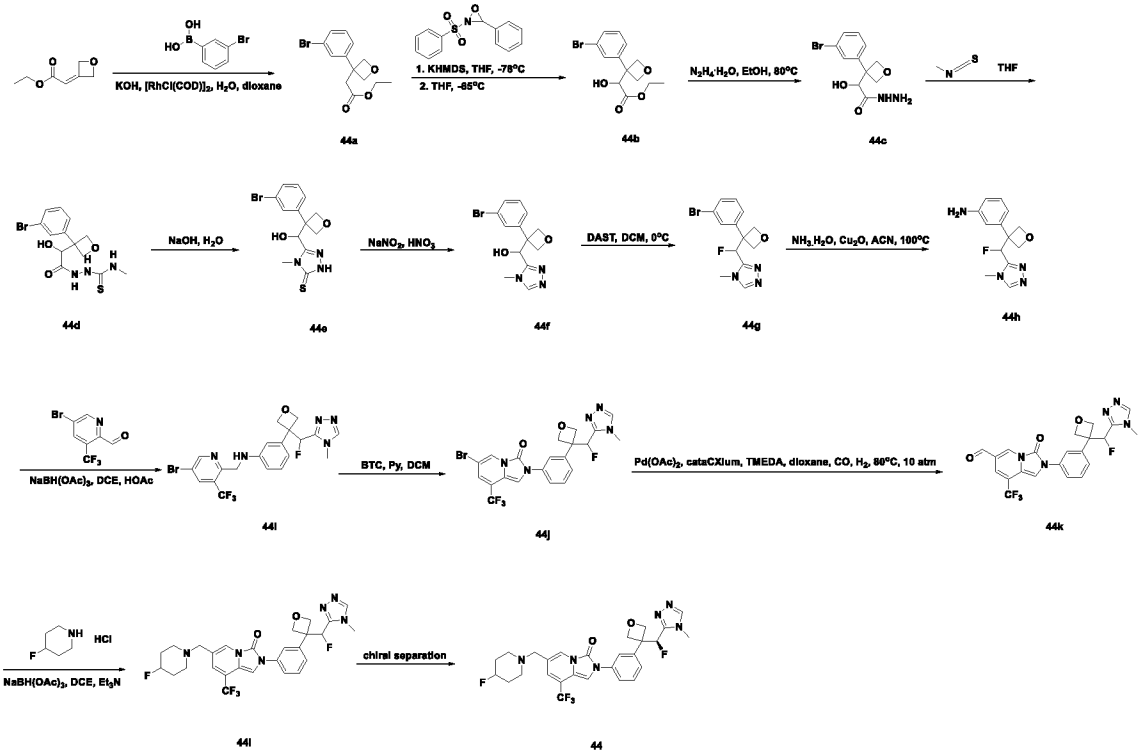
Synthesis of 43

[199] To a stirred solution of 43g (200.00 mg, 0.536 mmol, 1.00 equiv) and pyridine (254.22 mg, 3.214 mmol, 6 equiv) in DCM (10.00 mL) was added triphosgene (55.63 mg, 0.187 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: water, B: MeCN, 35% to 45% gradient in 15 min; detector, UV 254 nm. This resulted in Compound 43 (112.3 mg, 51.08%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 400

^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.52-1.65 (m, 1H), 1.90-1.95 (m, 1H), 2.51-2.57 (m, 1H), 2.66-2.72 (m, 1H), 3.40 (s, 3H), 6.26-6.29 (m, 1H), 6.90-6.92 (d, 1H), 7.08-7.12 (m, 2H), 7.20-7.24 (m, 1H), 7.42-7.43 (m, 1H), 7.54-7.57 (d, 1H), 7.76-7.78 (d, 1H), 8.15 (s, 1H).

Example 44. Synthesis of Compound 44



Synthesis of 44a

[200] To a stirred solution of $[Rh(COD)Cl]_2$ (700 mg, 0.011 mmol, 0.015 equiv) in dioxane (120 mL) was added KOH (79 mL, 118.182 mmol, 1.2 equiv, 1.5 M) at room temperature. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. To the above mixture was added ethyl 2-(oxetan-3-ylidene)acetate (14.00 g, 98.485 mmol, 1.00 equiv) and 3-bromophenylboronic acid (33.62 g, 167.424 mmol, 1.7 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 44a (16 g) as yellow oil.

Synthesis of 44b

[201] Into a 100 mL 3-necked round-bottom flask were added 44a (2.00 g, 6.685 mmol, 1.00 equiv), KHMDS (1mol/L in THF) (10 mL, 10.028 mmol, 1.5 equiv) and THF (20.00 mL) at -78 °C. The resulting mixture was stirred for 1h at -78 °C under nitrogen atmosphere. To the above mixture was added 2-(benzenesulfonyl)-3-phenyloxaziridine (2.27 g, 8.691 mmol, 1.3 equiv). The resulting mixture was stirred for additional 3h at -65 °C. The resulting

mixture was quenched with 60 mL of NH_4Cl (aq.). The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 44b (520 mg, 22.46%) as a yellow oil.

Synthesis of 44c

[202] Into a 250 mL 3-necked round-bottom flask were added 44b (4.00 g, 12.692 mmol, 1.00 equiv), $NH_2NH_2.H_2O$ (6.35 g, 126.918 mmol, 10 equiv) and EtOH (40.00 mL, 688.541 mmol, 54.25 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The precipitated solids were collected by filtration and washed with water (3x10 mL) to afford 44c (2.5 g, 58.87%) as an off-white solid.

Synthesis of 44d

[203] Into a 250 mL 3-necked round-bottom flask were added 44c (2.50 g, 8.302 mmol, 1.00 equiv), methyl isothiocyanate (1.21 g, 16.604 mmol, 2.00 equiv) and tetrahydrofuran (25.00 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with EtOAc (3x10 mL) to afford 44d (2.4 g, 69.52%) as an off-white solid.

Synthesis of 44e

[204] Into a 100 mL 3-necked round-bottom flask were added 44d (2.00 g, 5.344 mmol, 1.00 equiv), NaOH (0.43 g, 10.688 mmol, 2 equiv) and H_2O (20.00 mL) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The residue was neutralized to pH 7 with HCl (1 M). The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum to afford 44e (1.9 g, 91.82%) as an off-white solid.

Synthesis of 44f

[205] Into a 100 mL 3-necked round-bottom flask were added 44e (1.90 g, 5.333 mmol, 1.00 equiv), $NaNO_2$ (3.68 g, 53.335 mmol, 10 equiv), EtOAc (4.00 mL), H_2O (20.00 mL,) at room temperature. To the above HNO_3 (53.3 mL, 53.335 mmol, 10 equiv, 1M) was added dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum to afford 44f (1.3 g, 69.17%) as an off-white solid.

Synthesis of 44g

[206] Into a 100 mL 3-necked round-bottom flask were added 44f (1.90 g, 5.861 mmol, 1.00 equiv) and DCM (20.00 mL) at room temperature. To the above mixture was added DAST (1889.45 mg, 11.722 mmol, 2 equiv) dropwise at 0 °C. The resulting mixture was stirred for

additional 1 h at 0 °C. The reaction was quenched with $NaHCO_3$(20 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 44g (1 g, 52.31%) as a yellow solid.

Synthesis of 44h

[207] Into a 50 mL round-bottom flask were added 44g (1.00 g, 3.066 mmol, 1.00 equiv) and CH_3CN (20.00 mL), $NH_3.H_2O$ (20 mL), Cu_2O (43.87 mg, 0.307 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C. The reaction was diluted with water (60 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 20:1) to afford 44h (680 mg, 84.56%) as a yellow solid.

Synthesis of 44i

[208] Into a 25 mL 3-necked round-bottom flask were added 44h (650.00 mg, 2.478 mmol, 1.00 equiv) and DCE (10.00 mL), 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (1258.95 mg, 4.956 mmol, 2 equiv), $NaBH(OAc)_3$ (1050.46 mg, 4.956 mmol, 2 equiv), HOAc (446.46 mg, 7.435 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (20 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 20:1) to afford 44i (980 mg, 79.04%) as a yellow solid.

Synthesis of 44j

[209] Into a 25 mL 3-necked round-bottom flask were added 44i (980.00 mg, 1.959 mmol, 1.00 equiv) and DCM (10.00 mL), pyridine (309.89 mg, 3.918 mmol, 2.00 equiv) at room temperature. To the above mixture was added triphosgene (232.50 mg, 0.784 mmol, 0.40 equiv) at 0 °C. The resulting mixture was stirred for additional 1 h at 0 °C. The reaction was quenched with NaHCO3 (aq. 20 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 20:1) to afford 44j (900 mg, 87.30%) as a yellow solid.

Synthesis of 44k

[210] Into a 50 mL pressure tank reactor were added 44j (300.00 mg, 0.570 mmol, 1.00 equiv) and dioxane (20.00 mL), $Pd(OAc)_2$ (12.80 mg, 0.057 mmol, 0.1 equiv), TMEDA (132.48 mg, 1.140 mmol, 2 equiv), cataCXium (81.86 mg, 0.228 mmol, 0.4 equiv) at room

temperature. The resulting mixture was stirred overnight at 80 °C under H_2:CO=1:1 atmosphere, 20 atm. The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 20:1) to afford 44k (150 mg, 55.35%) as a yellow solid.

Synthesis of 44l

[211] Into a 8 mL vial were added 44k (140.00 mg, 0.294 mmol, 1.00 equiv) and DCE (2.00 mL), 4-fluoropiperidine (60.75 mg, 0.589 mmol, 2 equiv), $NaBH(OAc)_3$ (124.83 mg, 0.589 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by prep-TLC (CH_2Cl_2/MeOH 15:1) to afford 44l (90 mg, 54.33%) as a yellow solid.

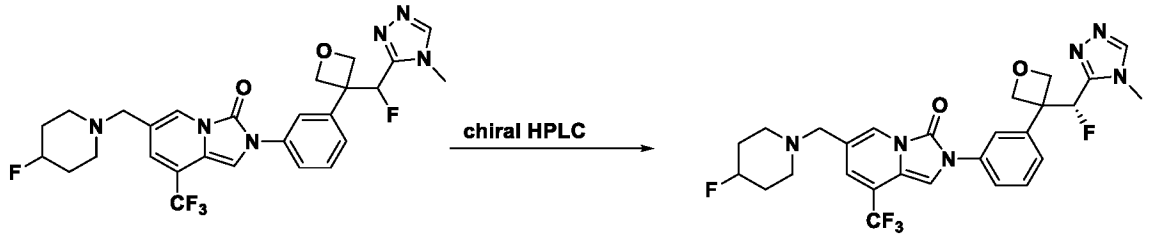
Synthesis of 44

[212] The 44l (90 mg) was purified by prep-chiral HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 40% B to 50% B in 17 min; Wave Length: 220/254 nm; RT1 (min): 11.29) to afford Compound 44 (15.5 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 563

^{1}H NMR: (300 MHz, DMSO-d_6, *ppm*): δ 1.72 (s, 2H), 1.96 (s, 2H), 2.33-2.36 (m, 2H), 2.55 (s, 2H), 3.28 (s, 5H), 4.60-4.85 (m, 1H), 4.86-4.87 (d, 1H), 5.18-5.22 (m, 2H), 5.34-5.36 (d, 1H), 6.22-6.34 (s, 1H), 7.03 (s, 1H), 7.13-7.15 (d, 1H), 7.34 (s, 1H), 7.42-7.46 (m, 1H), 7.56 (s, 1H), 7.69 (s, 1H), 7.78-7.80 (m, 1H), 8.38 (s, 1H).

Example 45. Synthesis of Compound 45



44l 45

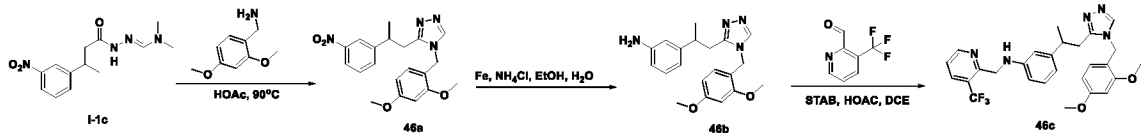
Synthesis of 45

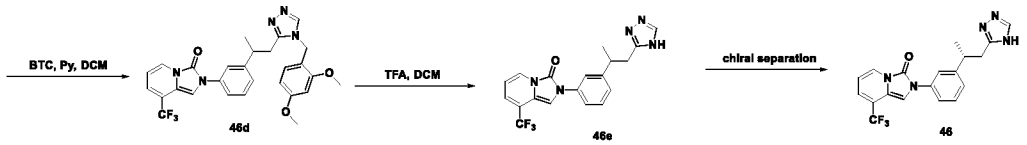
[213] The 44l (90 mg) was purified by prep-chiral HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 40% B to 50% B in 17 min; Wave Length: 220/254 nm; RT1 (min): 11.29) to afford Compound 45 (14.5 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 563

^1H NMR: (400 MHz, DMSO-d_6, *ppm*): δ 1.72 (s, 2H), 1.96 (s, 2H), 2.33-2.36 (m, 2H), 2.55 (s, 2H), 3.28 (s, 5H), 4.60-4.85 (m, 1H), 4.86-4.87 (d, 1H), 5.18-5.22 (m, 2H), 5.34-5.36 (d, 1H), 6.22-6.34 (s, 1H), 7.03 (s, 1H), 7.13-7.15 (d, 1H), 7.34 (s, 1H), 7.42-7.46 (m, 1H), 7.56 (s, 1H), 7.69 (s, 1H), 7.78-7.80 (m, 1H), 8.38 (s, 1H).

Example 46. Synthesis of Compound 46





Synthesis of 46a

[214] To a stirred solution of I-1c (3.60 g, 12.935 mmol, 1.00 equiv) in HOAc (50.00 mL) were added 1-(2,4-dimethoxyphenyl)methanamine (21.63 g, 129.360 mmol, 10.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 90 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (2x100 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 46a (1.2 g, 21.35%) as a yellow oil.

Synthesis of 46b

[215] To a stirred solution of 46a (1.20 g, 3.138 mmol, 1.00 equiv) in EtOH (50.00 mL) was added NH_4Cl (1.68 g, 31.379 mmol, 10 equiv) in H_2O (50.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was

extracted with CH_2Cl_2/MeOH=10:1 (3x100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 46b (1.1 g, 90.51%) as a light yellow oil.

Synthesis of 46c

[216] To a stirred solution of 46b (1.10 g, 3.121 mmol, 1.00 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (0.55 g, 0.003 mmol, 1 equiv) in DCE (50.00 mL) were added HOAc (0.37 g, 0.006 mmol, 2 equiv) and STAB (1.98 g, 0.009 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6h at room temperature. The resulting mixture was washed with water (50 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 46c (1.4 g, 78.92%) as a yellow oil.

Synthesis of 46d

[217] To a stirred solution of 46c (1.50 g, 2.932 mmol, 1.00 equiv) and pyridine (1.39 g, 17.594 mmol, 6 equiv) in DCM (60.00 mL) was added triphosgene (0.30 g, 1.026 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The resulting mixture was washed $NaHCO_3$ (aq.) (100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 46d (1.2 g, 75.86%) as a yellow solid.

Synthesis of 46e

[218] To a stirred solution of 46d (1.20 g, 2.232 mmol, 1.00 equiv) in DCM (10.00 mL) was added TFA (10.00 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 46e (300 mg, 32.96%) as a yellow solid.

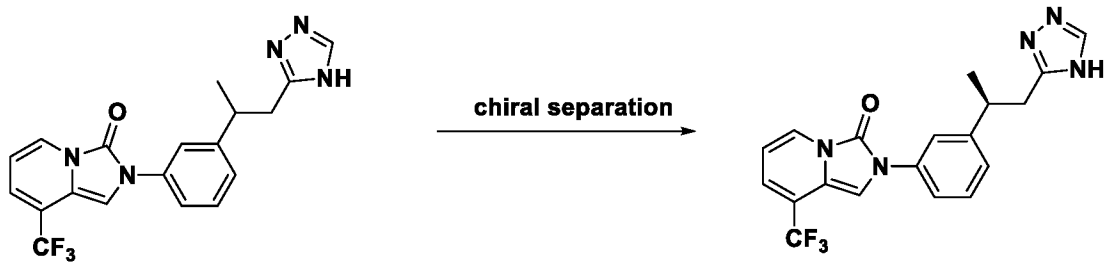
Synthesis of 46

[219] The crude product (46e, 300 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 12.5 min; Wave Length: 254 nm; RT1 (min): 9.43) to afford Compound 46 (90.6 mg, 29.90%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 388

^1H NMR: (400 MHz, CD_3OD-d4, *ppm*): δ 1.27-1.39 (d, 3H), 3.03-3.15 (m, 2H), 3.37-3.42 (m, 1H), 6.34-6.38 (m, 1H), 7.04-7.05 (d, 1H), 7.11 (s, 1H), 7.18-7.29 (m, 1H), 7.41-7.45 (m, 1H), 7.54-7.56 (m, 1H), 7.56-7.60 (m, 1H), 7.77-7.79 (m, 1H), 7.79-8.40 (m, 1H).

Example 47. Synthesis of Compound 47



46e 47

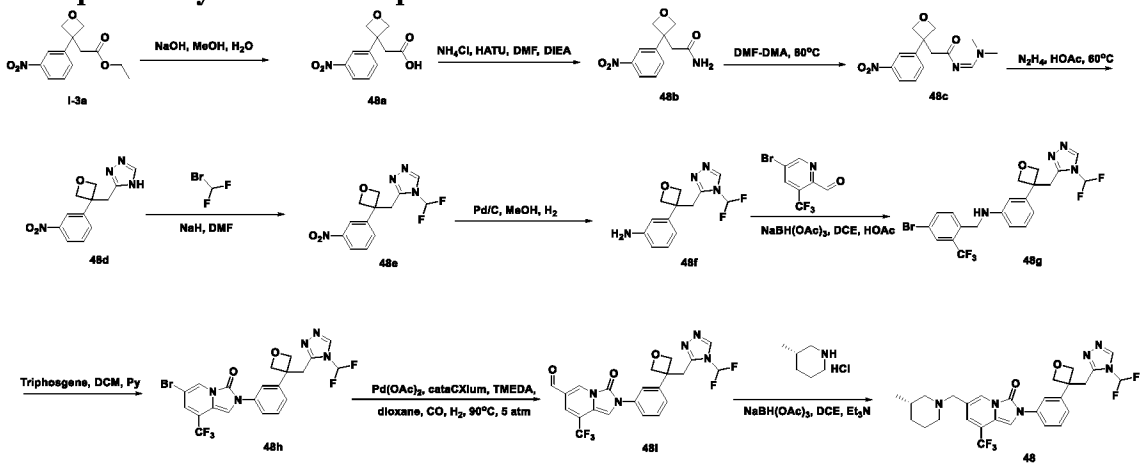
Synthesis of 47

[220] Compound 46e (300 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 12.5 min; Wave Length: 220/254 nm; RT2 (min): 10.8) to afford Compound 47 (95.0 mg, 31.35%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 388

^1H NMR: (400 MHz, CD_3OD-d4, *ppm*): δ 1.30-1.43 (d, 3H), 3.03-3.15 (m, 2H), 3.37-3.42 (m, 1H), 6.34-6.38 (m, 1H), 7.03-7.05 (d, 1H), 7.11 (s, 1H), 7.18-7.25 (m, 1H), 7.41-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.55-7.59 (m, 1H), 7.76-7.78 (m, 1H), 7.88-8.40 (m, 1H).

Example 48. Synthesis of Compound 48



Synthesis of 48a

[221] To a stirred solution of I-3a (5.00 g, 18.867 mmol, 1.00 equiv) in MeOH (100.00 mL)

was added NaOH (29.85 mL, 29.850 mmol, 1.50 equiv, 1M). The resulting mixture was stirred overnight at room temperature. The MeOH was removed under vacuum. The mixture was acidified to pH 4 with HCl (1 M). The precipitated solids were collected by filtration and washed with water (10 mL). The resulting solid was dried in an oven under reduced pressure. This resulted in 48a (4 g, 89.45%) as a white solid.

Synthesis of 48b

[222] To a stirred mixture of 48a (4.00 g, 16.863 mmol, 1.00 equiv) and NH_4Cl (2.71 g, 50.589 mmol, 3.00 equiv) in DMF (100.00 mL) were added DIEA (8.72 g, 67.470 mmol, 4.00 equiv) and HATU (9.62 g, 25.295 mmol, 1.50 equiv). The resulting mixture was stirred overnight at room temperature under argon atmosphere. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with water (15 mL). The resulting solid was dried in an oven under reduced pressure. This resulted in 48b (3.2 g, 80.33%) as a light brown solid.

Synthesis of 48c

[223] A solution of 48b (3.50 g, 1 equiv) in DMF-DMA (16.00 mL) was stirred overnight at 80 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 48c (3.4 g, 78.78%) as a grey solid.

Synthesis of 48d

[224] To a stirred solution of 48c (3.20 g, 10.985 mmol, 1.00 equiv) in HOAc (16.00 mL) was added hydrazine hydrate (14.00 mL, 98%) dropwise at room temperature. The resulting mixture was stirred overnight at 60 °C. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 48d (2.9 g, 101.44%) as a grey solid.

Synthesis of 48e

[225] To a stirred solution of 48d (2.90 g, 11.143 mmol, 1.00 equiv) in DMF (30.00 mL) was added NaH (2.23 g, 55.715 mmol, 5.00 equiv, 60%) in portions at 0 °C under argon atmosphere. The resulting mixture was stirred for 30 min at 0 °C under argon atmosphere. To the above mixture was added bromodifluoromethane (87.53 g, 66.858 mmol, 6.00 equiv, 10% in DMF). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (400 mL). The aqueous layer was extracted with EtOAc

(3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol NH_3H_2O), 0% to 80% gradient in 35 min; detector, UV 254 nm. This resulted in 48e (0.8 g, 23.14%) as a white solid.

Synthesis of 48f

[226] To a solution of 48e (780.00 mg, 2.514 mmol, 1.00 equiv) in MeOH (30.00 mL) was added Pd/C (70.00 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 48f (710 mg, 92.70%) as a light brown solid.

Synthesis of 48g

[227] To a stirred solution of 48f (300.00 mg, 1.070 mmol, 1.00 equiv) and 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (271.88 mg, 1.070 mmol, 1.00 equiv) in DCE (10.00 mL) was added HOAc (64.28 mg, 1.070 mmol, 1 equiv) and $NaBH(OAc)_3$ (680.56 mg, 3.211 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was washed with 10 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 48g (370 mg, 63.48%) as a light yellow solid.

Synthesis of 48h

[228] To a stirred solution of 48g (350.00 mg, 0.677 mmol, 1.00 equiv) and pyridine (321.11 mg, 4.060 mmol, 6 equiv) in DCM (10.00 mL) was added triphosgene (70.27 mg, 0.237 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was washed with 10 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 48h (300 mg, 79.02%) as a yellow solid.

Synthesis of 48i

[229] To a solution of 48h (280.00 mg, 0.514 mmol, 1.00 equiv) in dioxane (8.00 mL) was added cataCXium (36.89 mg, 0.103 mmol, 0.20 equiv), $Pd(OAc)_2$ (11.55 mg, 0.051 mmol, 0.1 equiv), TMEDA (119.56 mg, 1.029 mmol, 2 equiv) in a pressure tank. The mixture was purged with nitrogen for 3 min and then was pressurized to 10 atm with $CO:H_2$=1:1 at 90 °C for overnight. The reaction mixture was cooled to room temperature and diluted with water. The aqueous layer was extracted with EtOAc (2x50 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 48i (160 mg, 57.36%) as a yellow solid.

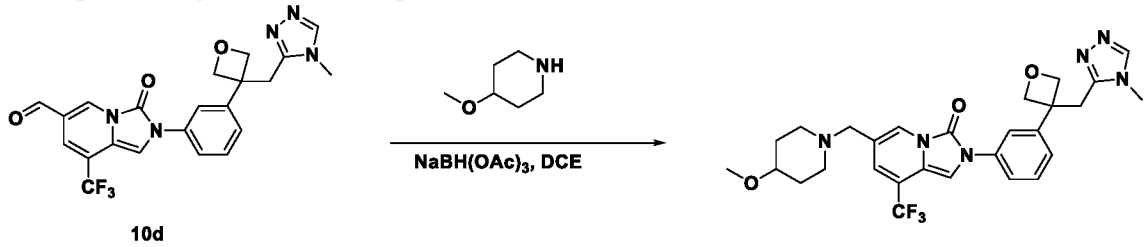
Synthesis of 48

[230] To a stirred solution of 48i (150.00 mg, 0.304 mmol, 1.00 equiv) and (3S)-3-methylpiperidine hydrochloride (123.71 mg, 0.912 mmol, 3.00 equiv) in DCE (6.00 mL) was added Et_3N (92.29 mg, 0.912 mmol, 3 equiv) and $NaBH(OAc)_3$ (193.30 mg, 0.912 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with CH_2Cl_2 (20 mL). The resulting mixture was washed with 20 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford Compound 48 (60.0 mg, 33.89%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 577

^1H NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.82-0.86 (d, 3H), 1.41-1.50 (m, 1H), 1.50-1.66 (m, 4H), 1.91-1.94 (m, 2H), 2.74-2.84 (m, 2H), 3.27 (s, 2H), 3.75 (s, 2H), 4.95 (s, 4H), 7.01-7.02 (m, 1H), 7.06-7.08 (m, 1H), 7.31 (s, 1H), 7.38-7.55 (m, 3H), 7.70-7.72 (m, 1H), 7.73-7.75 (d, 1H), 8.82 (s, 1H).

Example 49. Synthesis of Compound 49



10d

49

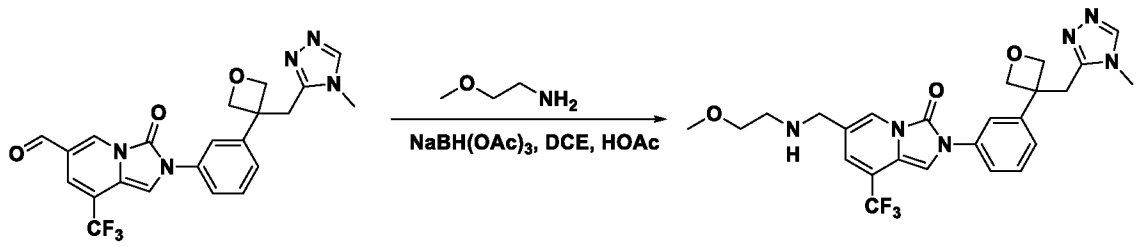
Synthesis of 49

[231] To a stirred solution/mixture of 10d (100 mg, 0.21 mmol, 1.0 equiv) and 4-methoxypiperidine (25 mg, 0.21 mmol, 1.0 equiv) in DCE (1 mL) was added $NaBH(OAc)_3$ (923 mg, 0.43 mmol, 2.0 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with NH_4Cl (aq.) (20 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product (100 mg) was purified by prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 42% B in 8 min, 42% B; Wave Length: 254/220 nm; RT1 (min): 7.38) to afford Compound 49 (18.8 mg, 15%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557

^{1}H NMR: (400 MHz, DMSO-*d6*, δ ppm): δ 1.42-1.44 (m, 2H), 1.81-1.83 (m, 2H), 2.11-2.16 (m, 2H), 2.61-2.67 (m, 2H), 2.97 (s, 3H), 3.18-3.22 (m, 4H), 3.28-3.30 (m, 2H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.66 (s, 1H), 7.74-7.76 (d, 1H), 8.20 (s, 1H).

Example 50. Synthesis of Compound 50



10d 50

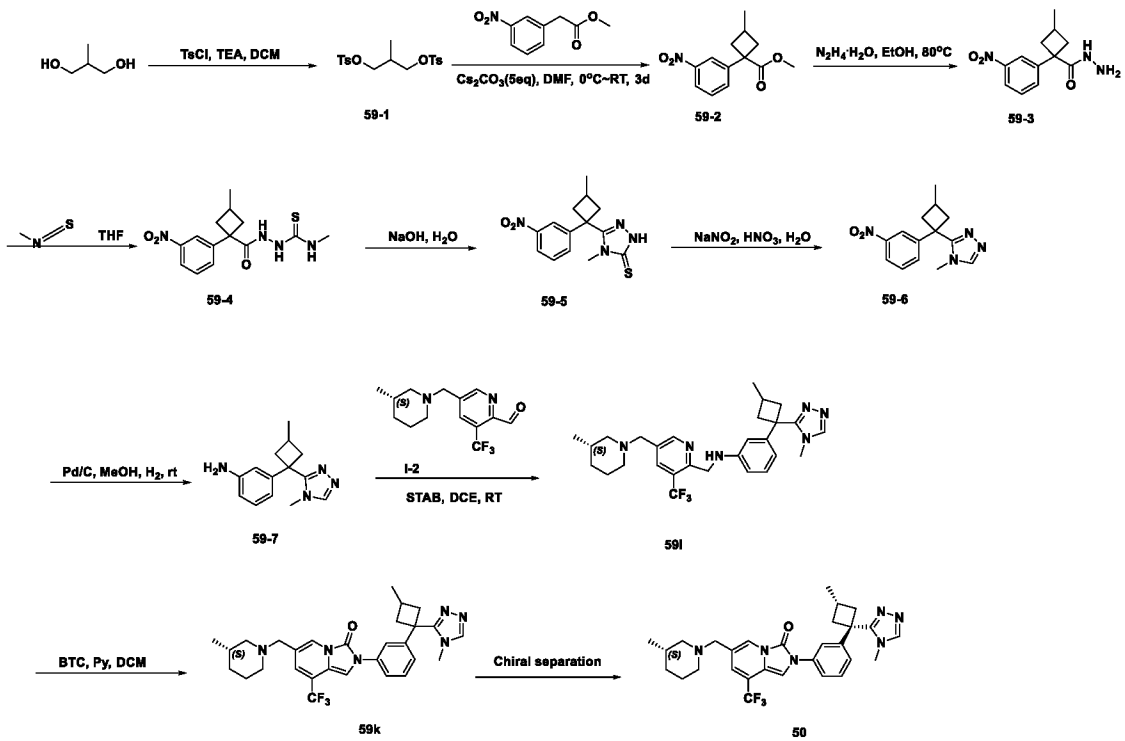
Synthesis of 50

[232] Into a 8 mL sealed tube were added 10d (100.00 mg, 0.219 mmol, 1.00 equiv) and DCE (1.00 mL) and 2-methoxy-ethanamine (16.42 mg, 0.219 mmol, 1 equiv), $NaBH(OAc)_3$ (92.67 mg, 0.437 mmol, 2 equiv) and HOAc (26.26 mg, 0.437 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 8 min, 45% B; Wave Length: 254 nm; RT1 (min): 7.23 to afford Compound 50 (30.9 mg, 27.04%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 517

^{1}H NMR: (400 MHz, DMSO-d_6, *ppm*): δ 2.62-2.64 (d, 2H), 3.22 (s, 3H), 3.33-3.38 (m, 3H), 3.40-3.43 (m, 2H), 3.52-3.53 (d, 4H), 4.91-4.96 (m, 4H), 6.87-6.89 (d, 1H), 7.12 (s, 1H), 7.30 (s, 1H), 7.38-7.41 (m, 2H), 7.42 (s, 1H), 7.68-7.77 (d, 1H), 8.20 (s, 1H).

Alternatively, Compound 50 may be also prepared in the manner outlined below:



59-1 59-2 59-3 59-4 59-5 59-6 59-7 59l 59k 50

1. Synthesis of 59-1

To a solution of methylpropanediol (59 g, 554.803 mmol, 1 equiv) and TsCl (264.42 g, 1387.007 mmol, 2.5 equiv) in DCM (590 mL) was added TEA (168.43 g, 1664.409 mmol, 3 equiv) dropwise at room temperature. The mixture was stirred for 12h at room temperature under nitrogen atmosphere. The reaction was quenched with water (800 mL) at room temperature. The aqueous layer was extracted with DCM (2x800 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (80:1) to afford 59-1 (190 g, 79.38%) as a yellow oil.

2. Synthesis of 59-2

To a stirred solution of methyl 2-(3-nitrophenyl)acetate (59 g, 256.182 mmol, 1.00 equiv) and Cs_2CO_3 (392.30 g, 1204.055 mmol, 5 equiv) in DMF (590 mL) was added 59-1 (190 g, 476.800 mmol, 1.86 equiv) at room temperature. The resulting mixture was stirred for 3days at room temperature under nitrogen atmosphere. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x600 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (80:1) to afford 59-2 (18 g, 26.99%) as a yellow oil.

3. Synthesis of 59-3

A solution of 59-2 (51 g, 204.601 mmol, 1 equiv) and hydrazine hydrate (65.56 g, 2046.010 mmol, 10 equiv) in EtOH (510 mL) was stirred overnight at 80°C. The reaction was quenched by the addition of NH_4Cl (aq.) (800mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3x100 mL). This resulted in 59-3 (46 g, 81.18%) as an off-white solid.

4. Synthesis of 59-4

A solution of 59-3 (46 g, 184.539 mmol, 1 equiv) and methyl isothiocyanate (26.98 g, 369.078 mmol, 2 equiv) in THF (460 mL) was stirred for 5h at room temperature. The reaction was quenched with water (400 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water (3x100 mL). This resulted in 59-4 (45 g, 68.08%) as a yellow solid.

5. Synthesis of 59-5

To a stirred solution of 59-4 (45 g, 139.587 mmol, 1 equiv) in H_2O (459 mL) was added NaOH (55.83 g, 1395.870 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 5h at room temperature. The mixture was acidified to pH 5 with HCl (aq.). The precipitated solids were collected by filtration and washed with water (3x200 mL). This resulted in 59-5 (42 g, 88.97%) as a yellow solid.

6. Synthesis of 59-6

To a stirred solution of 59-5 (42 g, 137.990 mmol, 1 equiv) and $NaNO_2$ (95.21 g, 1379.900 mmol, 10 equiv) in H_2O (420 mL) was added HNO_3 (1380 mL, 1379.90 mmol, 10 equiv, 1M) dropwise at room temperature. The resulting mixture was stirred for 5h at room temperature. The mixture was neutralized with saturated $NaHCO_3$ (aq.) (590 mL). The aqueous layer was extracted with EtOAc (3x400 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/ MeOH (80:1) to 59-6 (30 g, 71.85%) as a yellow solid.

7. Synthesis of 59-7

To a solution of 59-6 (30 g, 110.169 mmol, 1 equiv) in MeOH (590 mL) was added Pd/C (10%, 3.0g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 59-7 (22 g, 74.17%) as a yellow solid.

8. Synthesis of 59l

To a stirred solution of 59-7(10 g, 41.267 mmol, 1 equiv) and I-2(14.18 g, 49.520 mmol, 1.2 equiv) in DCE (100 mL) was added STAB (17.49 g, 82.534 mmol, 2 equiv) at room temperature .The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated Na_2CO_3 (aq.) (159 mL) at room temperature. The aqueous layer was extracted with DCM (3x159 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (70:1) to 59l (16.7 g, 71.05%) as a yellow solid.

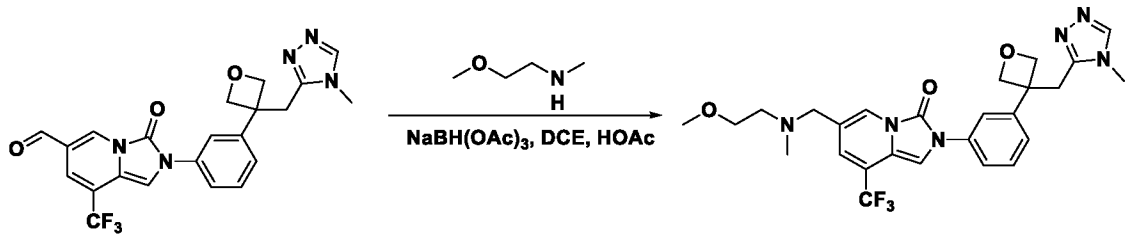
9. Synthesis of 59k

To a stirred solution of 59l (16.5 g, 32.187 mmol, 1 equiv) and Pyridine (15.28 g, 193.122 mmol, 6 equiv) in DCM (200 mL) was added triphosgene (3.53 g, 11.909 mmol, 0.37 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (159 mL) at room temperature. The aqueous layer was extracted with DCM (3x159 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 30% to 59% gradient in 30 min; detector, UV 254 nm. This resulted in 59k (12 g, 65.76%) as a yellow solid.

10. Synthesis of 50

The 59k (11.5 g) was purified by Prep-SFC with the following conditions (Column: CHIRALPAK AD-H, 5*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B:ETOH (0.1% 2M NH_3-MEOH); Flow rate: 200 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.55; RT2(min): 4.71; the second peak is product) to 50 (2.0630 g, 19.11%) as a yellow solid. LC-MS-50 (ES, m/z): $[M+H]^+$ 539. H-NMR-59: (400 MHz, DMSO-d6, δ *ppm*): 0.79-0.84 (d, 3H), 0.86-0.92 (m, 1H), 1.01-1.18 (d, 3H), 1.41-1.52 (m, 1H), 1.53-1.65 (m, 4H), 1.91-2.03 (m, 1H), 2.25-2.40 (m, 3H), 2.69-2.77 (m, 2H), 3.07-3.10 (m, 2H), 3.25 (s, 3H), 3.34-3.42 (m, 2H), 7.02 (s, 1H), 7.08-7.10 (d, 1H), 7.35 (s, 1H), 7.44-7.48 (m, 1H), 7.61-7.63 (d, 1H), 7.67-7.71 (m, 2H), 8.37 (s,1H).

Example 51. Synthesis of Compound 51



10d 51

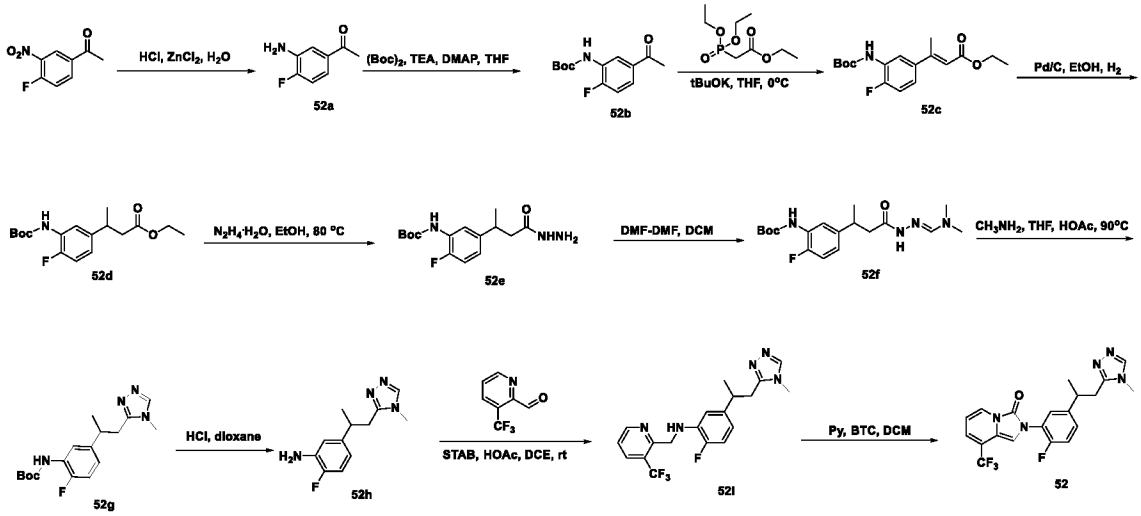
Synthesis of 51

[233] Into a 8 mL sealed tube were added 10d (100.00 mg, 0.219 mmol, 1.00 equiv) and (2-methoxyethyl)(methyl)amine (19.49 mg, 0.000 mmol, 1.00 equiv), $NaBH(OAc)_3$ (92.67 mg, 0.438 mmol, 2.00 equiv), HOAc (26.26 mg, 0.438 mmol, 2.00 equiv) and DCE (1.50 mL). The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under vacuum. The crude product (80 mg) was purified by prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 50% B in 8 min, 50% B; Wave Length: 220/254 nm; RT1 (min): 7.23 to afford Compound 51 (34.9 mg, 29.85%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 531

^1H NMR: (400 MHz, DMSO-d_6, *ppm*): δ 2.30 (s, 2H), 2.50-2.57 (m, 2H), 2.93-2.97 (m, 3H), 3.32 (s, 3H), 3.40-3.46 (m, 2H), 3.53 (s, 2H), 3.60 (s, 2H), 4.88-4.96 (m, 4H), 6.87-6.89 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.68-7.77 (m, 1H), 8.20 (s, 1H).

Example 52. Synthesis of Compound 52



Synthesis of 52a

[234] To a stirred solution of 1-(4-fluoro-3-nitrophenyl)ethanone (30.00 g, 163.811 mmol, 1.00 equiv) in HCl (78.00 mL, 1M) was added $SnCl_2$ (93.19 g, 491.457 mmol, 3.00 equiv), H_2O (300.00 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 15 min at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 25 min at 100 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with ice at room temperature. The mixture was acidified to pH 12 with NaOH. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 52a (20 g, 73.34%) as a yellow solid.

Synthesis of 52b

[235] To a stirred solution of 52a (5.00 g, 32.646 mmol, 1.00 equiv) and TEA (9.91 g, 97.939 mmol, 3 equiv) in THF (100.00 mL) was added DMAP (0.40 g, 3.265 mmol, 0.1 equiv) and Boc_2O (14.25 g, 65.293 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with 200 mL of brine. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (30:1) to afford 52b (6 g, 65.31%) as a white solid.

Synthesis of 52c

[236] To a stirred solution of triethyl phosphonoacetate (7.97 g, 0.036 mmol, 3 equiv) in THF (50.00 mL) was added tert-butoxypotassium (3.99 g, 0.036 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room

temperature. To the above mixture was added 52b (3.00 g, 11.845 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (15:1) to afford 52c (3 g, 70.49%) as an off-white solid.

Synthesis of 52d

[237] To a solution of 52c (3.00 g, 9.277 mmol, 1.00 equiv) in EtOH (100.00 mL) was added Pd/C (0.3 g) in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 52d (2.8 g, 83.48%) as a light yellow oil.

Synthesis of 52e

[238] To a stirred solution of 52d (2.80 g, 8.605 mmol, 1.00 equiv) in EtOH (80.00 mL) was added hydrazine hydrate (98%) (4.31 g, 86.050 mmol, 10.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 days at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with DCM/MeOH=10:1 (3x100 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 52e (1.5 g, 51.51%) as an off-white solid.

Synthesis of 52f

[239] To a stirred solution of 52e (1.00 g, 3.212 mmol, 1.00 equiv) in DCM (10.00 mL) was added DMF-DMA (1.91 g, 16.059 mmol, 5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 52f (800 mg, 61.18%) as an off-white solid.

Synthesis of 52g

[240] To a stirred solution of 52f (750.00 mg, 2.047 mmol, 1.00 equiv) in HOAc (3.00 mL) was added CH_3NH_2 in THF (5.00 mL, 1M) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 90 °C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 52g (350 mg, 30.68%) as an off-white solid.

Synthesis of 52h

[241] A solution of 52g (350.00 mg, 0.628 mmol, 1.00 equiv, 60%) in HCl in 1,4-dioxane (5.00 mL) was stirred overnight. The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM (5 mL). The residue was basified to pH 8 with NH_3 in MeOH. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 52h (200 mg, 108.75%) as an off-white solid.

Synthesis of 52i

[242] To a stirred solution of 52h (180.00 mg, 0.768 mmol, 1.00 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (134.54 mg, 0.768 mmol, 1.00 equiv) in DCE (10.00 mL) were added HOAc (46.14 mg, 0.768 mmol, 1 equiv) and STAB (488.51 mg, 2.305 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with DCM (50 mL). The resulting mixture was washed with 50 mL of water. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 52i (200 mg, 60.22%) as a light yellow oil.

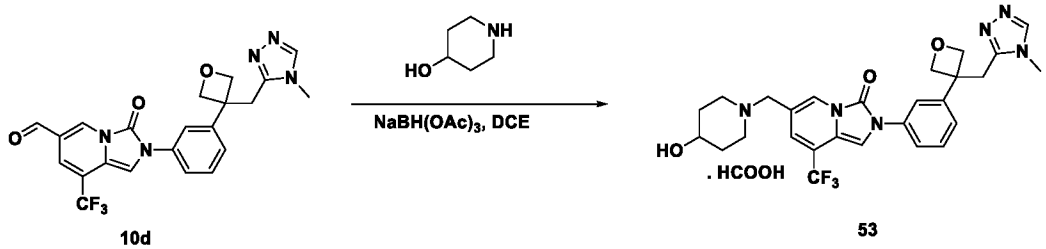
Synthesis of 52

[243] To a stirred solution of 52i (180.00 mg, 0.458 mmol, 1.00 equiv) and pyridine (217.16 mg, 2.745 mmol, 6 equiv) in DCM (20.00 mL) were added triphosgene (47.52 mg, 0.160 mmol, 0.35 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford the crude product. The crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: water, B:MeCN, 30% B to 40% B gradient in 15 min; detector, UV 254 nm. This resulted in Compound 52 (18.9 mg, 9.63%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 420

^{1}H NMR: (400 MHz, CD_3OD-d4, *ppm*): δ 1.42-1.43 (d, 3H), 3.06-3.18 (m, 2H), 3.35-3.47 (m, 1H), 3.53 (s, 3H), 6.35-6.38 (m, 1H), 7.00 (s, 1H), 7.04-7.06 (d, 1H), 7.25-7.30 (m, 1H), 7.34-7.38 (m, 1H), 7.48-7.51 (d, 1H), 7.75-7.77 (d, 1H), 8.30 (s, 1H).

Example 53. Synthesis of Compound 53



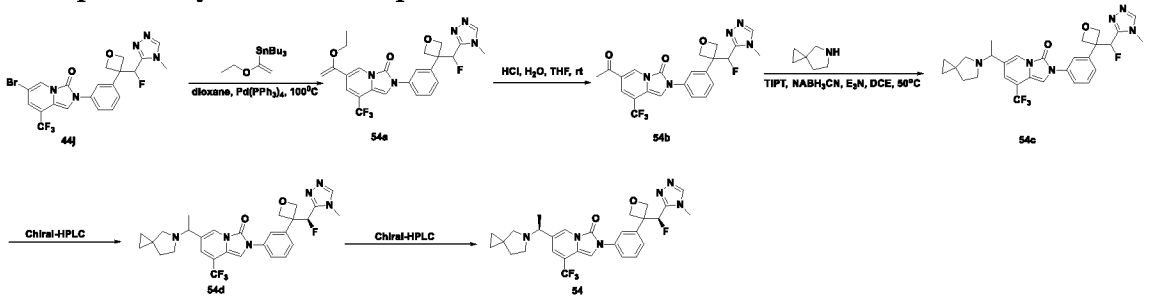
Synthesis of 53

[244] To a stirred solution of 10d (40 mg, 0.08 mmol, 1.0 equiv) and piperidin-4-ol (9 mg, 0.08 mmol, 1.0 equiv) in DCE (0.8 mL) was added $NaBH(OAc)_3$ (37 mg, 0.17 mmol, 2.0 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with MeOH (3 mL). The resulting mixture was concentrated under reduced pressure. The crude product (50 mg) was purified by prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150 mm 5 μm, n; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 8% B to 15% B in 7 min, 15% B; Wave Length: 220 nm; RT1 (min): 7.62) to afford Compound 53 (14.5 mg, 28%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 543

^1H NMR: (400 MHz, CD_3OD, δ ppm): δ 1.65-7.74 (m, 2H), 1.87-1.98 (m, 2H), 2.75-2.83 (m, 2H), 2.97 (s, 3H), 3.10-3.15 (m, 2H), 3.68 (s, 2H), 3.77-3.83 (m, 3H), 5.09 (s, 4H), 6.92-6.94 (d, 1H), 7.14-7.17 (d, 2H), 7.31 (s, 1H), 7.46-7.50 (m, 1H), 7.63-7.65 (m, 1H), 7.85 (s, 1H), 8.21-8.28 (m, 1H), 8.40 (s, 1H).

Example 54. Synthesis of Compound 54



Synthesis of 54a

[245] To a stirred mixture of 44j (700.00 mg, 1.330 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (720.54 mg, 1.995 mmol, 1.5 equiv) in dioxane (7.00 mL) was added $Pd(PPh_3)_4$ (153.70 mg, 0.133 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 54a (510 mg, 67.43%) as a yellow solid.

Synthesis of 54b

[246] To a stirred mixture of 54a (500.00 mg, 0.966 mmol, 1.00 equiv) in THF (5.00 mL)

was added HCl (5.00 mL, 1M) dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 54b (440 mg, 84.67%) as a yellow solid.

Synthesis of 54c

[247] To a stirred mixture of 54b (400.00 mg, 0.817 mmol, 1.00 equiv) and 5-azaspiro[2.4]heptane (119.11 mg, 1.226 mmol, 1.5 equiv) in DCE (4.00 mL) were added $NaBH_3CN$ (154.08 mg, 2.452 mmol, 3 equiv), TEA (248.10 mg, 2.452 mmol, 3 equiv) and titanium(IV) isopropoxide (232.28 mg, 0.817 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at 50 °C. The resulting mixture was diluted with water (15 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL) The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 54c (180 mg, 37.83%) as a yellow solid.

Synthesis of 54d

[248] The 54c (180 mg) was separated by prep-Chiral HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 9 min; Wave Length: 220/254 nm; RT1(min): 5.66;) to afford 54d (65 mg) as a yellow solid.

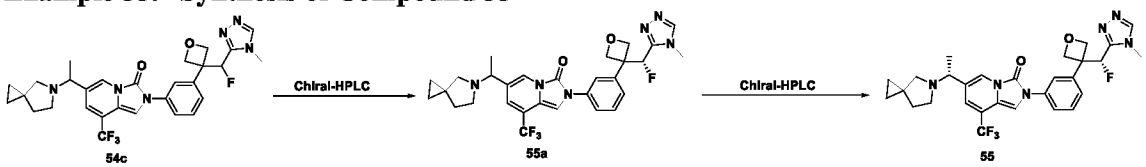
Synthesis of 54

[249] The 54d (65 mg) was separated by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 16 min; Wave Length: 220/254 nm; RT1 (min): 10.09;) to afford Compound 54 (22.8 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 571

^1H NMR (400 MHz, DMSO, δ *ppm*): δ 0.40-0.58 (d, 4H), 1.02-1.32 (d, 3H), 1.74 (s, 2H), 2.35-2.41 (d, 1H), 2.52-2.63 (d, 2H), 2.67-2.80 (d, 1H), 3.14-3.33 (m, 4H), 4.80-4.94 (d, 1H), 5.16-5.25 (t, 2H), 5.25-5.40 (d, 1H), 6.16-6.40 (d, 1H), 7.09 (s, 1H), 7.13-7.15 (d, 1H), 7.34 (s, 1H), 7.42-7.44 (m, 1H), 7.55 (s, 1H), 7.68 (s, 1H), 7.79-7.83 (d, 1H), 8.38 (s, 1H).

Example 55. Synthesis of Compound 55



Synthesis of 55a

[250] Compound 54c (180 mg) was separated by prep-Chiral HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 9 min; Wave Length: 220 nm; RT2 (min): 7.34;) to afford 55a (65 mg) as a yellow solid.

Synthesis of 55

[251] The crude product (55a, 65 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220 nm; RT1 (min): 12.01) to afford Compound 55 (19.3 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 571

^{1}H NMR: (400 MHz, DMSO, δ *ppm*): δ 0.45-0.58 (d, 4H), 1.20-1.30 (d, 3H), 1.74 (s, 2H), 2.35-2.41 (d, 1H), 2.52-2.63 (d, 2H), 2.68-2.80 (d, 1H), 3.12-3.25 (d, 1H), 3.28 (s, 3H), 4.76-4.94 (d, 1H), 5.13-5.28 (t, 2H), 5.28-5.40 (d, 1H), 6.22-6.33 (d, 1H), 7.09 (s, 1H), 7.13-7.15 (d, 1H), 7.34 (s, 1H), 7.41-7.45 (m, 1H), 7.55 (s, 1H), 7.68 (s, 1H), 7.77-7.79 (d, 1H), 8.38 (s, 1H).

Example 56. Synthesis of Compound 56



Synthesis of 56

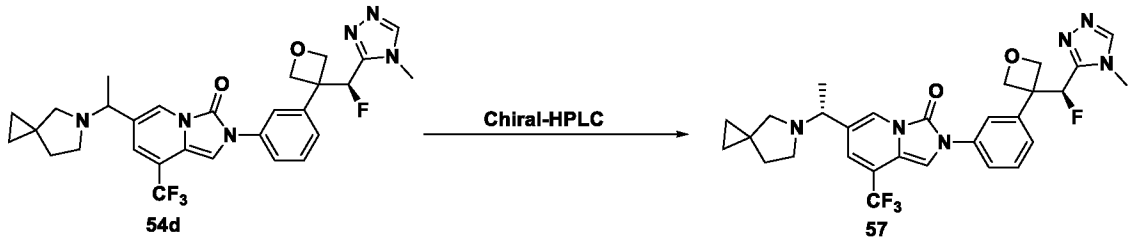
[252] Compound 55a was separated by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm; RT2 (min): 15.44; the first peak is the product) to afford

Compound 56 (20.6 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 571.3

^{1}H NMR (400 MHz, DMSO, δ *ppm*): δ 0.40-0.58 (d, 4H), 1.20-1.31 (d, 3H), 1.74 (s, 2H), 2.31-2.40 (d, 1H), 2.52-2.60 (d, 2H), 2.68-2.81 (d, 1H), 3.15-3.25 (d, 1H), 3.25-3.30 (d, 3H), 4.86 (s, 1H), 5.10-5.29 (t, 2H), 5.29-5.42 (d, 1H), 6.22-6.34 (d, 1H), 7.08(s, 1H), 7.13-7.15 (d, 1H), 7.33 (s, 1H), 7.41-7.46 (t, 1H), 7.55 (s, 1H), 7.68 (s, 1H), 7.77-7.79 (d, 1H), 8.37 (s, 1H).

Example 57. Synthesis of Compound 57



54d 57

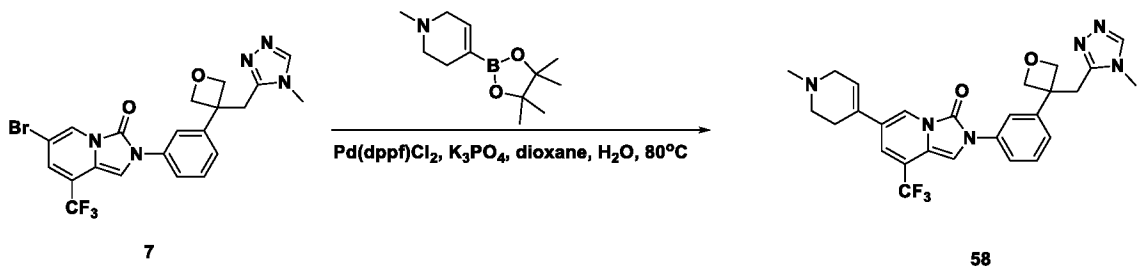
Synthesis of 57

[253] Compound 54d (65 mg) was purified by prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 16 min; Wave Length: 220/254 nm; RT2 (min): 12.95;) to afford Compound 57 (20.0 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 571.3

^{1}H NMR (400 MHz, DMSO, δ *ppm*): δ 0.40-0.58 (d, 4H), 1.02-1.32 (d, 3H), 1.74 (s, 2H), 2.35-2.41 (d, 1H), 2.52-2.63 (d, 2H), 2.67-2.80 (d, 1H), 3.14-3.30 (d, 4H), 4.86 (s, 1H), 5.16-5.25 (t, 2H), 5.25-5.40 (d, 1H), 6.16-6.40 (d, 1H), 7.00-7.11 (d, 1H), 7.11-7.19 (d, 1H), 7.33 (s, 1H), 7.39-7.48 (t, 1H), 7.56 (s, 1H), 7.68 (s, 1H), 7.72-7.83 (d, 1H), 8.38 (s, 1H).

Example 58. Synthesis of Compound 58



7 58

Synthesis of 58

[254] To a stirred mixture of Compound 7 (100.00 mg, 0.197 mmol, 1.00 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (65.84 mg, 0.296 mmol, 1.50 equiv), K_3PO_4 (83.52 mg, 0.394 mmol, 2.00 equiv) in dioxane (2.00 mL) and H_2O (0.50 mL) was added $Pd(dppf)Cl_2$ (14.40 mg, 0.020 mmol, 0.10 equiv) under argon atmosphere. The resulting mixture was stirred for 2 h at 80 °C under argon atmosphere. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC, eluted with CH_2Cl_2 / MeOH (50:1). The crude was dissolved in CH_2Cl_2 (10 mL). To the above mixture was added SiliaMetS thiol (200 mg). The resulting mixture was stirred overnight. The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (5 mL). The filtrate was concentrated under reduced pressure. The crude product was re-crystallized from MeOH to afford 2-(3-[3-[(4-methyl-1,2,4-triazol-3-yl)methyl]oxetan-3-yl]phenyl)-6-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (Compound 58, 57 mg, 55.23%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 525

^{1}H NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.24-3.01 (s, 3H), 2.39-2.44 (m, 2H), 2.54-2.56 (m, 2H), 2.92 (s, 3H), 2.97-3.02 (m, 2H), 3.54 (s, 2H), 4.89-4.96 (m, 4H), 6.32 (s, 1H), 6.88-6.90 (d, 1H), 7.36-7.43 (m, 4H), 7.55 (s, 1H), 7.75-7.77 (d, 1H), 8.21 (s, 1H).

Example 59. Synthesis of Compound 59



Synthesis of 59a

[255] To a stirred solution of methylpropanediol (5 g, 55.480 mmol, 1 equiv) and Et_3N (5.61 g, 55.480 mmol, 1 equiv) in DCM (50 mL) were added TsCl (21.15 g, 110.960 mmol, 2 equiv) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (500 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x150 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=50:1 to afford 59a (15 g, 63.10%) as a brown solid.

Synthesis of 59b

[256] To a stirred mixture of methyl 2-(3-nitrophenyl)acetate (5 g, 25.618 mmol, 1 equiv) in DMF (50 mL) was added Cs_2CO_3 (41.74 g, 128.090 mmol, 5.0 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added 59a (15.31 g, 38.427 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 2 days at room temperature. The reaction was quenched by the addition of 200 mL NH_4Cl (aq.) at 0 °C. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=100:1 to afford 59b (1

g, 14.09%) as a white solid.

Synthesis of 59c

[257] To a stirred solution of 59b (1 g, 4.012 mmol, 1 equiv) in EtOH (10 mL) were added $NH_2NH_2H_2O$ (2.01 g, 40.120 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C. The reaction was quenched by the addition of H_2O (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2:MeOH=10:1 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 59c (900 mg, 87.30%) as a white solid.

Synthesis of 59d

[258] To a stirred mixture of 59c (880 mg, 3.530 mmol, 1 equiv) in tetrahydrofuran (9 mL) was added methyl isothiocyanate (516.20 mg, 7.060 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water (10 mL). The resulting solid was dried under vacuum to afford 59d (900 mg, 73.54%) as a yellow solid.

Synthesis of 59e

[259] To a stirred solution of 59d (900 mg, 2.792 mmol, 1 equiv) was added NaOH (558.31 mg, 13.960 mmol, 5 equiv) in 7 mL of H_2O at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 5 with HCl (aq.) (1 M). The aqueous layer was extracted with CH_2Cl_2:MeOH=10:1 (3x5 mL). The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 59e (700 mg, 79.08%) as a white solid.

Synthesis of 59f

[260] To a stirred solution of 59e (700 mg, 2.300 mmol, 1 equiv) and $NaNO_2$ (1586.78 mg, 23.000 mmol, 10 equiv) in H_2O (7 mL) were added HNO_3 (23 mL, 1 M, 23.000 mmol, 10 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (20 mL) at 0°C. The aqueous layer was extracted with CH_2Cl_2:MeOH=10:1 (2x10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=15:1 to afford 59f (600 mg, 91.97%) as a white solid.

Synthesis of 59g

[261] To a solution of 59f (600 mg, 2.203 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (10%, 60 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was

hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 59g (500 mg, 88.03%) as a yellow solid.

Synthesis of 59h

[262] To a stirred solution of 59g (480 mg, 1.981 mmol, 1.00 equiv) and I-2g (754.70 mg, 2.972 mmol, 1.5 equiv) in DCE (5 mL) was added HOAc (118.95 mg, 1.981 mmol, 1 equiv) and $NaBH(OAc)_3$ (1259.44 mg, 5.943 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of 10 mL of H_2O at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 59h (500 mg, 50.45%) as a yellow solid.

Synthesis of 59i

[263] To a stirred solution of 59h (480 mg, 1.763 mmol, 1 equiv) and pyridine (836.58 mg, 10.578 mmol, 6 equiv) in DCM (5 mL) was added triphosgene (261.54 mg, 0.881 mmol, 0.5 equiv) in one portion at 0 °C. The reaction was quenched by the addition of 30 mL $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 59i (400 mg, 84.28%) as a yellow solid.

Synthesis of 59j

[264] To a stirred solution of 59i (14 g, 27.650 mmol, 1 equiv) and TMEDA (6.43 g, 55.300 mmol, 2 equiv) in dioxane (500 mL) were added Butyldi-1-adamantylphosphine (1.985 g, 5.530 mmol, 0.2 equiv) and $Pd(OAc)_2$ (0.62 g, 2.765 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The mixture was purged with nitrogen and then was pressurized to 10 atm with CO and H_2 (1:1) at 80 °C overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=20:1 to afford 59j (8 g, 60.35%) as an orange solid.

Synthesis of 59k

[265] To a stirred mixture of 59j (800 mg, 1.757 mmol, 1.00 equiv) and (3S)-3-methylpiperidine hydrochloride (476.51 mg, 3.514 mmol, 2 equiv) in DCE (8 mL) was added Et_3N (533.25 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1116.84 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x30 mL). The resulting

mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford the crude product. The crude product (500 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 73% B in 8 min, Wave Length: 220 nm; RT1 (min): 7.68) to afford 59k (400 mg, 41.43%) as a yellow solid.

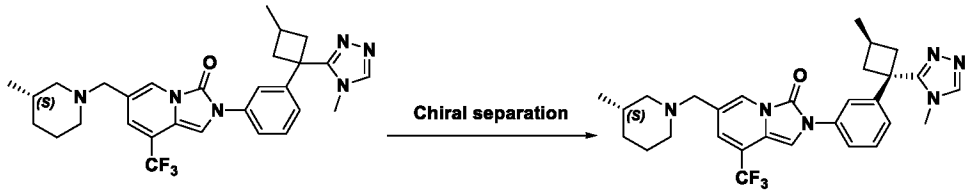
Synthesis of 59

[266] 59k (400 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 20 min; Wave Length: 220/254 nm; RT1 (min): 9.69; RT2 (min): 13.84; the first peak is product) to afford Compound 59 (216.6 mg, 42.40%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 539.

H-NMR: (400 MHz, DMSO-d_6, ppm, δ): 0.78-0.95 (d, 4H), 1.05-1.16 (d, 3H), 1.37-1.53 (m, 1H), 1.53-1.70 (m, 4H), 1.89 (s, 1H), 2.54-2.56 (s, 3H), 2.72-2.80 (m, 2H), 2.90 (s, 2H), 3.21 (s, 3H), 3.24 (s, 2H), 7.00 (s, 1H), 7.24-7.26 (d, 1H),7.37 (s, 1H), 7.47-7.52 (m, 1H), 7.63-7.65 (m, 2H), 7.84 (s, 1H), 8.29 (s, 1H).

Alternatively, Compound 59 may be also prepared in the manner outlined below:

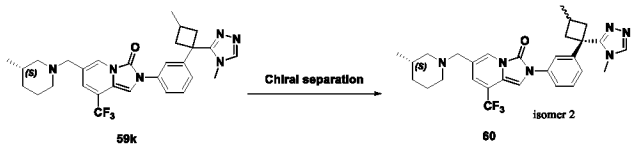


50-9 59

1. Synthesis of 59

50-9(11.5 g) was purified by Prep-SFC with the following conditions (Column: CHIRALPAK AD-H, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: ETOH(0.1% 2M NH_3-MEOH); Flow rate: 200 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.55; RT2(min): 4.71; the first peak is product) to afford 59 (5.7744 g, 53.79%) as a yellow solid. LC-MS-: (ES, m/z): $[M+H]^+$ 539 H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 0.79-0.92 (m, 4H), 0.98-1.15 (d, 3H), 1.35-1.52 (m, 1H), 1.55-1.71 (m, 4H), 1.81-1.93 (m, 1H), 2.50-2.61 (m, 3H), 2.69-2.77 (m, 2H), 2.81-2.93 (m, 2H), 3.15-3.22 (m, 4H), 6.99 (s, 1H), 7.23-7.25 (d, 1H), 7.35 (s, 1H), 7.47-7.51 (m, 1H), 7.64-7.66 (m, 2H), 7.85 (s, 1H), 8.29 (s, 1H).

Example 60. Synthesis of Compound 60



59k 60

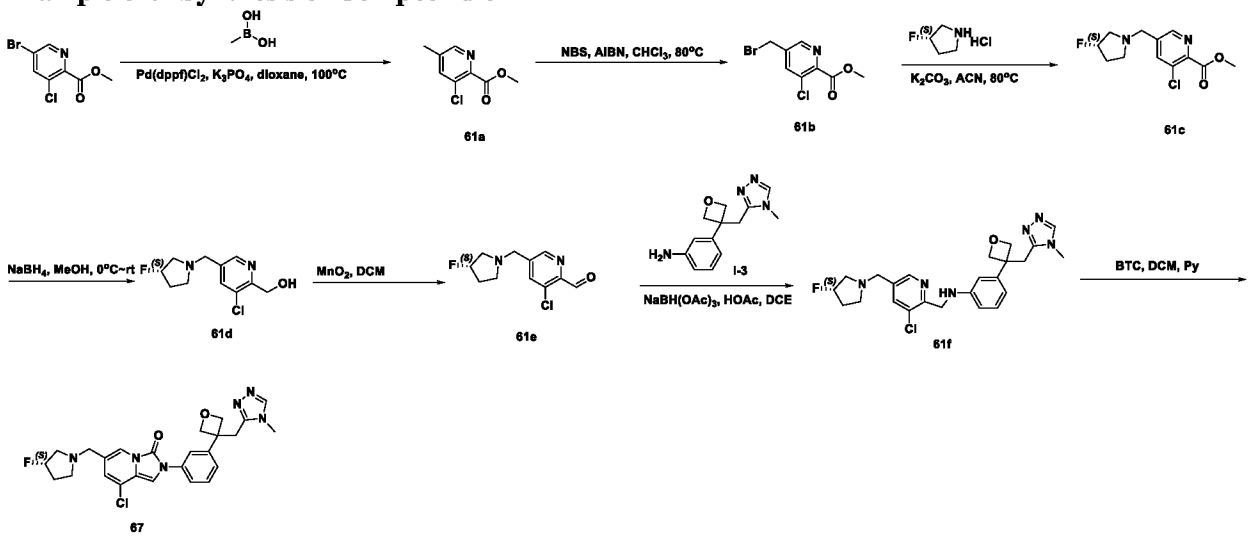
Synthesis of 60

[267] 59k (400 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 20 min; Wave Length: 220/254 nm; RT1 (min): 9.69; RT2 (min): 13.84; the second peak is product) to afford Compound 60 (97.3 mg, 19.05%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 539.

H-NMR: (400 MHz, DMSO-d_6, ppm, δ): 0.75-0.98 (d, 4H), 1.05-1.28 (d, 3H), 1.35-1.45 (m, 1H), 1.45-1.66 (m, 4H), 1.89 (s, 1H), 2.25-2.34 (m, 2H), 2.34-2.41 (m, 1H), 2.75 (s, 2H), 3.10-3.14 (m, 2H), 3.25 (s, 5H), 6.98-7.02 (m, 1H), 7.08-7.10 (m, 1H),7.36 (s, 1H), 7.45-7.49 (m, 1H), 7.60-7.67 (m, 2H), 7.70 (s, 1H), 8.36 (s, 1H).

Example 61. Synthesis of Compound 61



61a 61b 61c 61d 61e 61f 67

Synthesis of 61a

[268] To a stirred solution of methyl 5-bromo-3-chloropyridine-2-carboxylate (30.00 g, 119.770 mmol, 1.00 equiv) and methylboronic acid (21.51 g, 359.310 mmol, 3 equiv) in dioxane (350.00 mL) were added K_3PO_4(50.85 g, 239.540 mmol, 2 equiv) and $Pd(dppf)Cl_2$(8.76 g, 11.977 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The aqueous layer

was extracted with EtOAc (3x600 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (20:1) to afford 61a (14 g, 56.68%) as an off-white oil.

Synthesis of 61b

[269] To a stirred solution of 61a (3.00 g, 16.163 mmol, 1.00 equiv) and NBS (4.32 g, 24.272 mmol, 1.50 equiv) in $CHCl_3$ (30.00 mL) were added AIBN (7.96 g, 48.489 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (3x80 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (30:1) to afford 61b (1.5 g, 21.05%) as an off-white oil.

Synthesis of 61c

[270] To a stirred solution of 61b (1.50 g, 5.671 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (1.42 g, 11.342 mmol, 2 equiv) in ACN (15.00 mL) was added K_2CO_3 (1.57 g, 11.342 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 61c (800 mg, 50.18%) as an off-white solid.

Synthesis of 61d

[271] To a stirred solution of 61c (800.00 mg, 2.934 mmol, 1.00 equiv) in MeOH (10.00 mL) was added $NaBH_4$ (221.98 mg, 5.867 mmol, 2 equiv) at 0 degrees C. The resulting mixture was stirred for 5 h at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 61d (500 mg, 65.48%) as a white oil.

Synthesis of 61e

[272] To a stirred solution of 61d (500.00 mg, 2.043 mmol, 1.00 equiv) in DCM (7.00 mL) was added MnO_2 (1776.47 mg, 20.434 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 40 degrees C. The resulting mixture was filtered and the filter cake was washed with DCM (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 61e (400 mg,

75.82%) as a white oil.

Synthesis of 61f

[273] To a stirred solution of 61e (400.00 mg, 1.648 mmol, 1.00 equiv) in DCE (6.00 mL) was added I-3 (402.67 mg, 1.648 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1048.00 mg, 4.945 mmol, 3 equiv) and HOAc (9.9 mg, 0.165 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 61f (500 mg, 62.48%) as a white solid.

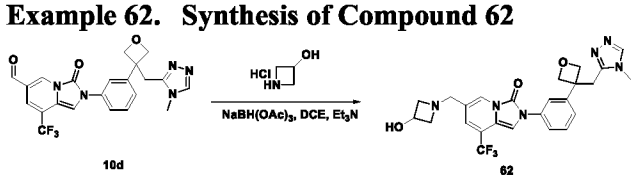
Synthesis of 61

[274] To a stirred solution of 61f (35.00 mg, 0.074 mmol, 1.00 equiv) and Pyridine (35.27 mg, 0.446 mmol, 6 equiv) in DCM (1.00 mL) was added Triphosgene (7.72 mg, 0.026 mmol, 0.35 equiv) at 0 degrees C. The resulting mixture was stirred for 30 min at 0 degrees C. The reaction was quenched with $NaHCO_3$ (aq.) (10.00 mL) at room temperature. The aqueous layer was extracted with DCM (3x8 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: water (0.5% NH_4HCO_3), B: CH_3CN, 30% B to 50% B gradient in 30 min; detector, UV 254 nm. This resulted in 61 (2.3 mg, 6.10%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 497

H-NMR: (400 MHz, $CDCl_3$, *ppm,* δ): 2.40-2.48 (m, 2H), 2.95 (s, 3H), 3.26-3.39 (m, 2H), 3.62 (s, 2H), 3.72-3.78 (m, 2H), 4.06 (s, 2H), 5.07-5.09 (d, 2H), 5.13-5.14 (d, 2H), 5.36-5.49 (d, 1H), 6.79 (s, 1H), 6.88-6.91 (d, 2H), 7.16 (s, 1H), 7.42-7.48 (m, 2H), 7.65 (s, 1H), 8.12 (s, 1H).

Example 62. Synthesis of Compound 62



10d 62

Synthesis of 62

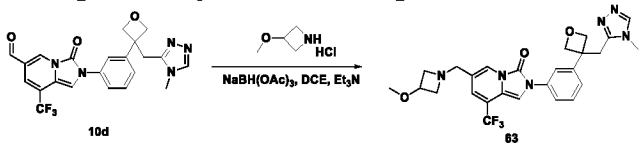
[275] To a stirred mixture of 10d (200 mg, 0.437 mmol, 1 equiv) and azetidin-3-ol hydrochloride (143.70 mg, 1.311 mmol, 3 equiv) in DCE (2 mL) were added Et_3N (44.24 mg,

0.437 mmol, 1 equiv) and $NaBH(OAc)_3$ (185.34 mg, 0.874 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 9:1) to afford 62 (150 mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5m; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm; RT1(min): 7.23) to afford Compound 62 (23.1 mg, 10.27%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 515

H-NMR: (400 MHz, DMSO, δ ppm): 2.67-2.96 (m, 2H), 2.96-3.00 (d, 3H), 3.33-3.35 (d, 2H), 3.46-3.53 (m, 4H), 4.18-4.23 (m, 1H), 4.88-4.96 (m, 4H), 5.32-5.34 (d, 1H), 6.87-6.89 (d, 1H), 6.96 (s, 1H), 7.31 (s, 1H), 7.38-7.41 (m, 2H), 7.64 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 63. Synthesis of Compound 63



Synthesis of 63

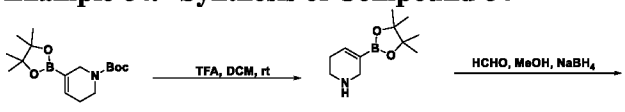
[276] To a stirred mixture of 10d (200 mg, 0.437 mmol, 1 equiv) and 3-methoxyazetidine hydrochloride (162.10 mg, 1.311 mmol, 3 equiv) in DCE (2 mL) were added Et_3N (176.96 mg, 1.748 mmol, 4 equiv) and $NaBH(OAc)_3$ (185.34 mg, 0.874 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with water (20 ml) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude product (150 mg). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A:Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm; RT1(min): 7.23.This resulted in Compound 63 (63.6 mg, 27.52%) as a

yellow solid.

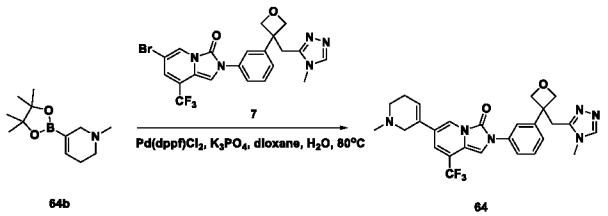
LC-MS: (ES, m/z): $[M+H]^+$ 529

H-NMR: (400 MHz, DMSO, ppm): δ2.86-2.89 (m, 2H), 2.96 (s, 3H), 3.00 (s, 3H), 3.15 (m, 2H), 3.33-3.38 (d, 2H), 3.45-3.53 (m, 2H), 3.95-3.99 (m,1H), 4.90-4.96 (m, 4H), 6.87-6.89 (d, 1H), 6.97 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 64. Synthesis of Compound 64



64a



64b 64

Synthesis of 64a

[277] Into a 100 mL round-bottom flask were added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate (2 g) and TFA (5 mL) in DCM (15 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 64a (1g, 73.94%) as colorless oil.

Synthesis of 64b

[278] A solution of 64a (1.00 g, 4.782 mmol, 1.00 equiv) and formaldehyde solution (1.16 g, 14.346 mmol, 3.00 equiv, 37%) in MeOH (10.00 mL) was stirred overnight at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH_4$ (0.36 g, 9.516 mmol, 1.99 equiv). The resulting mixture was stirred for 5h at room temperature under nitrogen atmosphere. The reaction was quenched with NH_4Cl (aq) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 64b (500 mg, 46.86%) as colorless oil.

Synthesis of 64

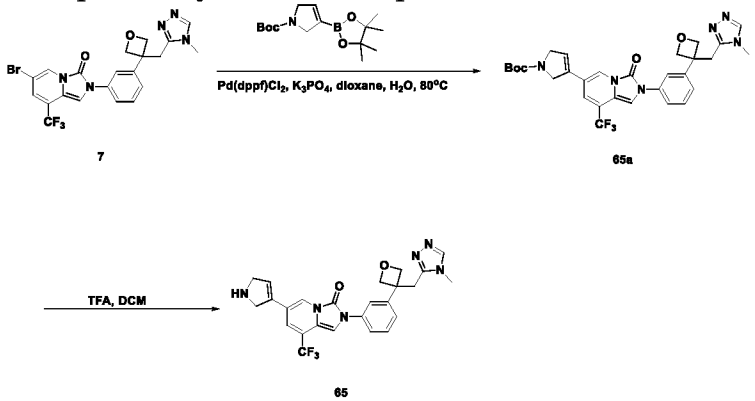
[279] To a stirred mixture of 64b (200.00 mg, 0.393 mmol, 1.00 equiv) and 7 (131.69 mg,

0.590 mmol, 1.50 equiv) in dioxane (1.60 mL) and H_2O (0.4 mL) were added $Pd(dppf)Cl_2$ (57.58 mg, 0.079 mmol, 0.20 equiv) and K_3PO_4 (167.04 mg, 0.787 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The product was dissolved in DCM (10 mL) and isolute Si-thiol (100 mg) was added. The mixture was stirred for 30 min. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 43% B in 8 min; Wave Length: 254/220 nm; RT1(min): 8.22;) to afford Compound 64 (36.7 mg, 17.78%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 525

H-NMR: (400 MHz, DMSO, δ ppm): δ2.29 (s, 2H), 2.34 (s, 3H), 2.44-2.49 (m, 2H), 2.97 (s, 3H), 3.15 (s, 2H), 3.57 (s, 2H), 4.91-4.96 (m, 4H), 6.35 (s, 1H), 6.88-6.90 (d, 1H), 7.33-7.36 (d, 1H), 7.39-7.41 (d, 1H), 7.42-7.43 (m, 2H), 7.51 (s, 1H), 7.75-7.77 (d, 1H), 8.21 (s, 1H).

Example 65. Synthesis of Compound 65



7 65a 65

Synthesis of 65a

[280] To a stirred mixture of 7 (200.00 mg, 0.393 mmol, 1.00 equiv), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate (174.22 mg, 0.590 mmol, 1.50 equiv) and K_3PO_4 (167.04 mg, 0.786 mmol, 2.00 equiv) in dioxane (4.00 mL) and H_2O (1.00 mL) was added $Pd(dppf)Cl_2$ (28.79 mg, 0.039 mmol, 0.10 equiv) under argon atmosphere. The resulting mixture was stirred overnight at 80 degrees C under argon atmosphere. The resulting mixture was diluted with water (15 mL). The aqueous layer was

extracted with DCM (2x15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (40:1). The product was dissolved in CH_2Cl_2 (20 mL). To the above mixture was added SiliaMetS thiol (250 mg). The resulting mixture was stirred overnight at room temperature. The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (5 mL). The filtrate was concentrated under reduced pressure. This resulted in 65a (220 mg, 93.72%) as a yellow solid.

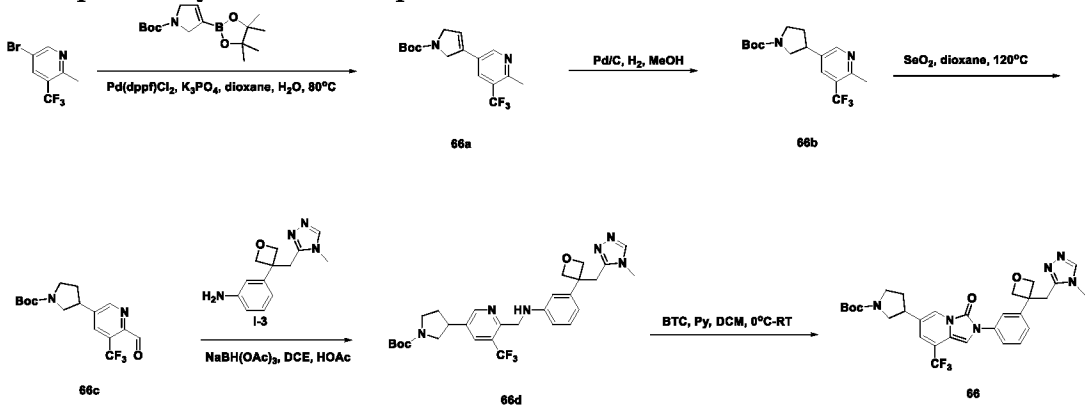
Synthesis of 65

[281] To a stirred solution of 65a (200.00 mg, 0.335 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford 65 (150 mg, 90.12%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 497

H-NMR: (400 MHz, CD_3OD, ppm): δ 2.95 (s, 3H), δ3.68 (s, 2H), δ3.94-3.95 (d, 2H), δ4.05-4.06 (d, 2H), δ5.08 (s, 4H), δ6.40(s, 1H), δ6.91-6.93 (d, 1H), δ7.17(s, 1H), δ7.31(s, 1H), δ7.35(s, 1H), δ7.46-7.49 (m, 1H), δ7.54 (s, 1H), δ7.63-7.65 (m, 1H), δ8.21 (s, 1H).

Example 66. Synthesis of Compound 66



Synthesis of 66a

[282] Into a 20mL round-bottom flask were added 5-bromo-2-methyl-3-(trifluoromethyl)pyridine(1.00 g, 4.166 mmol, 1.00 equiv), dioxane (8.00 mL),H_2O(2.00 mL), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate(1.23 g, 4.167 mmol, 1.00 equiv), $Pd(dppf)Cl_2$(0.30 g, 0.417 mmol, 0.1 equiv) and K_3PO_4(1.77 g, 8.333 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 5h at 80 degrees C under nitrogen atmosphere. The

resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EtOAc 5:1) to afford 66a (1.1 g, 77.20%) as a white solid.

Synthesis of 66b

[283] To a stirred solution of 66a (1.00 g, 3.046 mmol, 1.00 equiv) in MeOH (30.00 mL) was added Pd/C (200.00 mg, 10%) at room temperature under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 4 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 66b (1 g, 99.39%) as a white oil.

Synthesis of 66c

[284] To a stirred solution of 66b (1 g, 3.027 mmol, 1 equiv) in dioxane (10 mL) was added SeO_2 (1.01 g, 9.081 mmol, 3 equiv). The resulting mixture was stirred overnight at 110 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 66c (860 mg, 82.51%) as a yellow solid.

Synthesis of 66d

[285] To a stirred solution of 66c (350 mg, 1.016 mmol, 1 equiv) and I-3 (248.32 mg, 1.016 mmol, 1 equiv) in DCE (10 mL) was added HOAc (122.08 mg, 2.032 mmol, 2 equiv) and $NaBH(OAc)_3$ (430.86 mg, 2.032 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 66d (300 mg, 51.54%) as a light yellow solid.

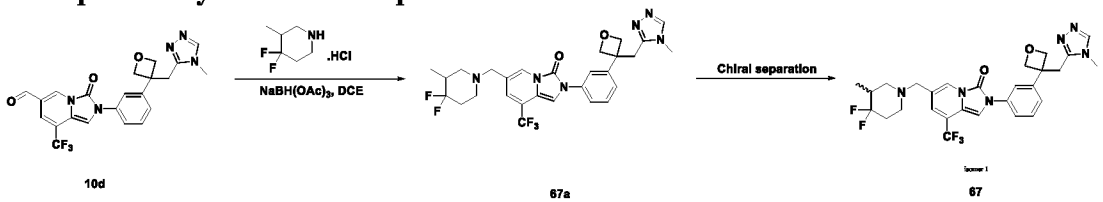
Synthesis of 66

[286] To a stirred solution of 66d (300.00 mg, 0.524 mmol, 1.00 equiv) and Pyridine (248.64 mg, 3.144 mmol, 6.00 equiv) in DCM (5.00 mL) was added Triphosgene (54.41 mg, 0.183 mmol, 0.35 equiv) at 0 degrees C. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (10 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (3x20 mL). The resulting mixture was concentrated under vacuum. The crude product was re-crystallized from CH_2Cl_2/methyl tert-butyl ether (1:5) to afford Compound 66 (200 mg, 63.77%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 599

H-NMR: (400 MHz, DMSO-d6, ppm): δ1.42 (s, 9H), δ 1.89-2.01 (m, 1H), δ2.02-2.08 (m, 1H), δ2.97 (s, 3H), δ3.14-3.16 (m, 1H), δ3.20-3.29 (m, 2H), δ3.42-3.46 (m, 1H), δ3.53(s, 2H), δ3.60-3.65 (m, 1H), δ4.91-4.96 (m, 4H), δ6.89-6.91 (d, 1H), δ7.18-7.19 (d, 1H), δ7.32 (s, 1H), δ7.38-7.42 (m, 2H), δ7.61 (s, 1H), δ7.74-7.77 (m, 1H), δ8.20 (s, 1H).

Example 67. Synthesis of Compound 67



Synthesis of 67a

[287] Into a 100 mL round-bottom flask were added 10d (400 mg, 0.874 mmol, 1.00 equiv), DCE (5.00 mL), 4,4-difluoro-3-methylpiperidine hydrochloride (149.45 mg, 0.874 mmol, 1 equiv) and $NaBH(OAc)_3$ (556.02 mg, 2.622 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 67a (100 mg, 19.83%) as a yellow solid.

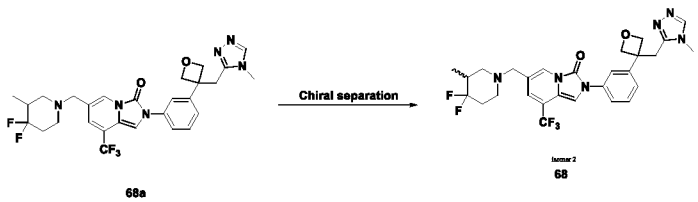
Synthesis of 67

[288] The 67a (100 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 18 min; Wave Length: 220/254 nm; RT1(min): 14.18, RT2(min): 16.17, the first peak is product) to afford Compound 67 (34.3 mg, 34.30%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 577

H-NMR: 1H NMR (300 MHz, DMSO-d6, *ppm*, δ) 0.92-0.94 (d, 3H), 1.99-2.15 (m, 4H), 2.21 -2.32(m, 1H), 2.62-2.81(m, 2H), 2.97 (s, 3H), 3.32-3.35 (d, 2H), 3.53 (s, 2H), 4.91 – 4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.03 (s, 1H), 7.32 (s, 1H), 7.38-7.42 (m, 2H), 7.71 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 68. Synthesis of Compound 68



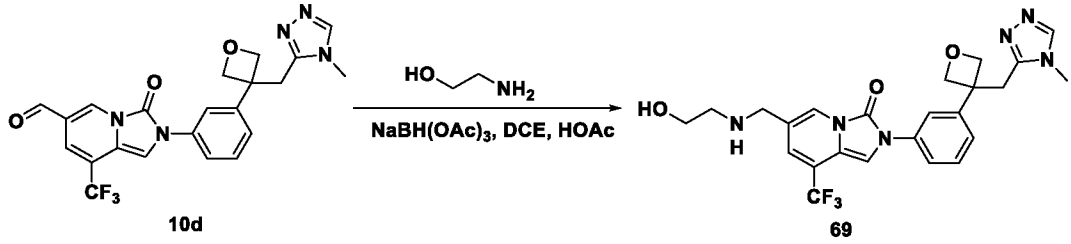
Synthesis of 68

[289] The 68a (100 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 18 min; Wave Length: 220/254 nm; RT1(min): 14.18, RT2(min): 16.17, the second peak is product) to afford Compound 68 (34.2 mg, 34.20%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 577

H-NMR: 1H NMR (300 MHz, DMSO-d6) δ 0.92-0.94 (d, 3H), 1.99-2.15 (m, 4H), 2.21 - 2.32(m, 1H), 2.62-2.81(m, 2H), 2.97 (s, 3H), 3.32-3.35 (d, 2H), 3.53 (s, 2H), 4.91 – 4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.03 (s, 1H), 7.32 (s, 1H), 7.38-7.42 (m, 2H), 7.71 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 69. Synthesis of Compound 69



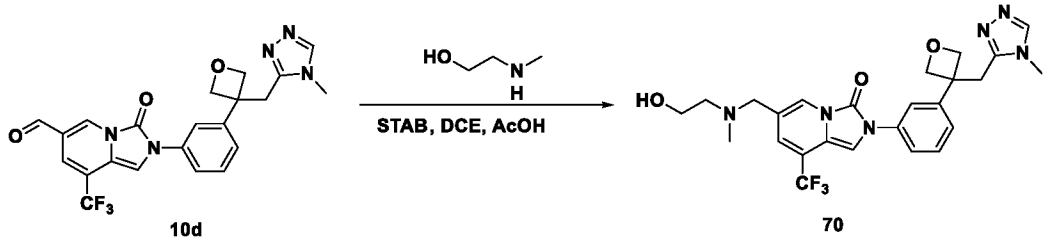
Synthesis of 69

[290] To a stirred solution of 10d (200.00 mg, 0.437 mmol, 1.00 equiv) and ethanolamine (40.06 mg, 0.656 mmol, 1.50 equiv) in DCE (3 mL) were added STAB (278.01 mg, 1.311 mmol, 3.00 equiv) and AcOH (26.26 mg, 0.437 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (101mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 47% B in 7 min; Wave Length: 220 nm; RT1(min): 5.81) to afford Compound 69 (43.6 mg, 18.73%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:503

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.61-2.64 (m, 2H), δ 2.90-2.91 (m, 3H), δ 3.30-3.32 (d, 2H), δ 3.47-3.57 (m, 4H), δ 4.91-4.96 (m, 4H), δ 6.88-6.90 (d, 1H), δ 7.14 (s, 1H), δ 7.38-7.40 (d, 1H), δ 7.41-7.42 (d, 2H), δ 7.42 (s, 1H), δ 7.43-7.44 (d, 1H), δ 8.20-8.21 (d, 2H).

Example 70. Synthesis of Compound 70



10d 70

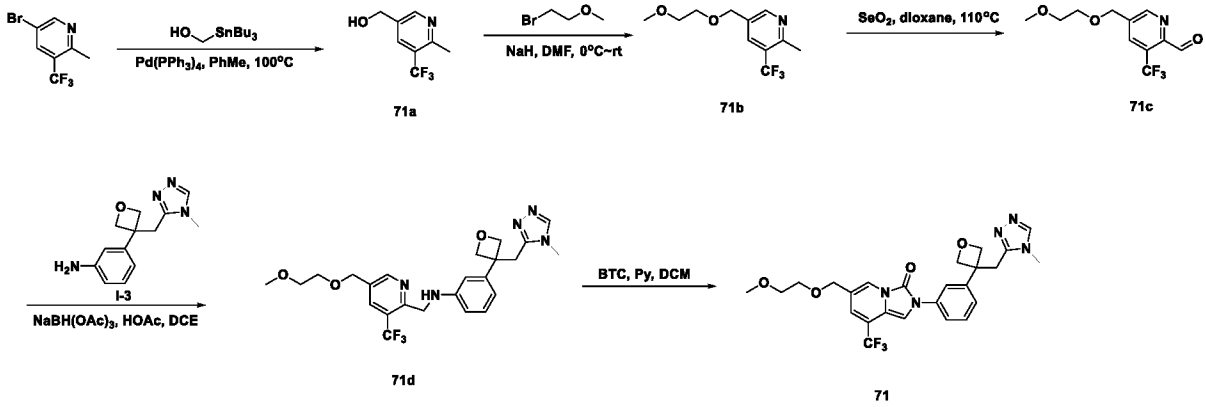
Synthesis of 70

[291] To a stirred solution of 10d (200.00 mg, 0.437 mmol, 1.00 equiv) and methylethanolamine (49.26 mg, 0.656 mmol, 1.50 equiv) in DCE (3mL) were added STAB (278.01 mg, 1.311 mmol, 3.00 equiv) and AcOH (26.26 mg, 0.437 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (5 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (2 x 10 mL), The resulting mixture was concentrated under reduced pressure. The crude product (110mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3·H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 28% B in 10 min; Wave Length: 220 nm; RT1(min): 10.25) to afford 70 (42.3 mg, 18.62%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:517

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.19 (m, 3H), δ 2.45-2.51 (m, 2H), δ 2.97 (s, 3H), δ 3.33 (s, 2H), δ 3.49-3.53 (m, 4H), δ 4.43-4.46 (m, 1H), δ 4.91-4.96 (m, 4H), δ 6.88-6.90 (d, 1H), δ 7.05 (s, 1H), δ 7.30 (s, 1H), δ 7.38-7.42 (m, 2H), δ 7.74 (s, 1H), δ 7.76-7.77 (d, 1H), δ 8.20 (s, 1H).

Example 71. Synthesis of Compound 71



Synthesis of 71a

[292] To a stirred solution of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (3 g, 12.499 mmol, 1 equiv) and (tributylstannyl)methanol (6.02 g, 18.748 mmol, 1.5 equiv) in toluene (30 mL, 281.967 mmol, 22.56 equiv) was added $Pd(PPh_3)_4$ (0.29 g, 0.250 mmol, 0.02 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=30:1 to afford 71a (1.3 g, 48.97%) as colorless oil.

Synthesis of 71b

[293] To a stirred mixture of 71a (380 mg, 1.988 mmol, 1 equiv) in DMF (5 mL) was added NaH (159.01 mg, 3.976 mmol, 2 equiv, 60%) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added 2-bromoethyl methyl ether (414.46 mg, 2.982 mmol, 1.5 equiv) at 0 °C. The above mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The reaction was quenched by NH_4Cl(aq.) (30 mL). The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=100:1) to afford 71b (300 mg, 54.49%) as a colorless oil.

Synthesis of 71b

[294] To a stirred mixture of 71b (290 mg, 1.164 mmol, 1 equiv) in dioxane (4 mL) was added SeO_2 (516.44 mg, 4.656 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for 4 h at 110 °C. The resulting mixture was diluted with water (30 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=100:1) to

afford 71c (180 mg, 52.31%) as a colorless oil.

Synthesis of 71c

To a stirred mixture of 71c (170 mg, 0.646 mmol, 1 equiv) and I-3 (173.56 mg, 0.711 mmol, 1.1 equiv) in DCE (2 mL) were added HOAc (38.79 mg, 0.646 mmol, 1 equiv) and $NaBH(OAc)_3$ (410.65 mg, 1.938 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by water (30 mL). The aqueous layer was extracted with DCM (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 71d (200 mg, 59.22%) as a yellow solid.

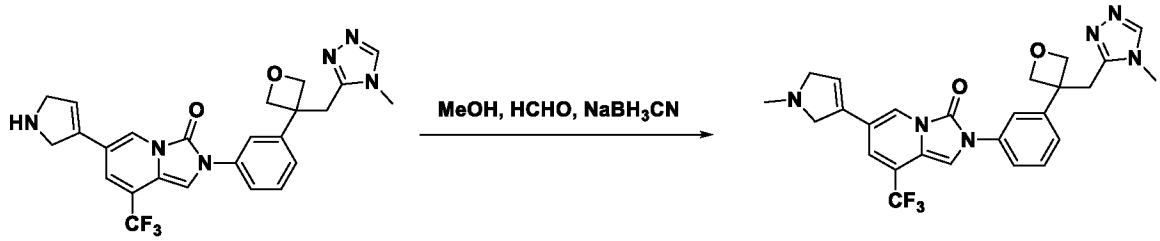
Synthesis of 71

[295] To a stirred solution of 71d (190 mg, 0.387 mmol, 1.00 equiv) and pyridine (607.52 mg, 2.322 mmol, 6 equiv) in DCM (2 mL) was added triphosgene (45.88 mg, 0.155 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 71 (200 mg) as a yellow solid. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 8 min, Wave Length: 220 nm; RT1 (min): 7.23) to afford Compound 71 (30.7 mg, 15.35%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 518.

H-NMR: (400 MHz, DMSO-d_6, ppm) δ 2.97 (s, 3H), 3.26 (s, 3H), 3.32-3.47 (m, 2H), 3.47-3.49 (m, 2H), 3.53-3.58 (m, 2H), 4.32 (s, 2H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 2H), 7.03 (s, 1H), 7.33-7.42 (m, 3H), 7.75-7.80 (m, 2H), 8.20 (s, 1H).

Example 72. Synthesis of Compound 72



65 72

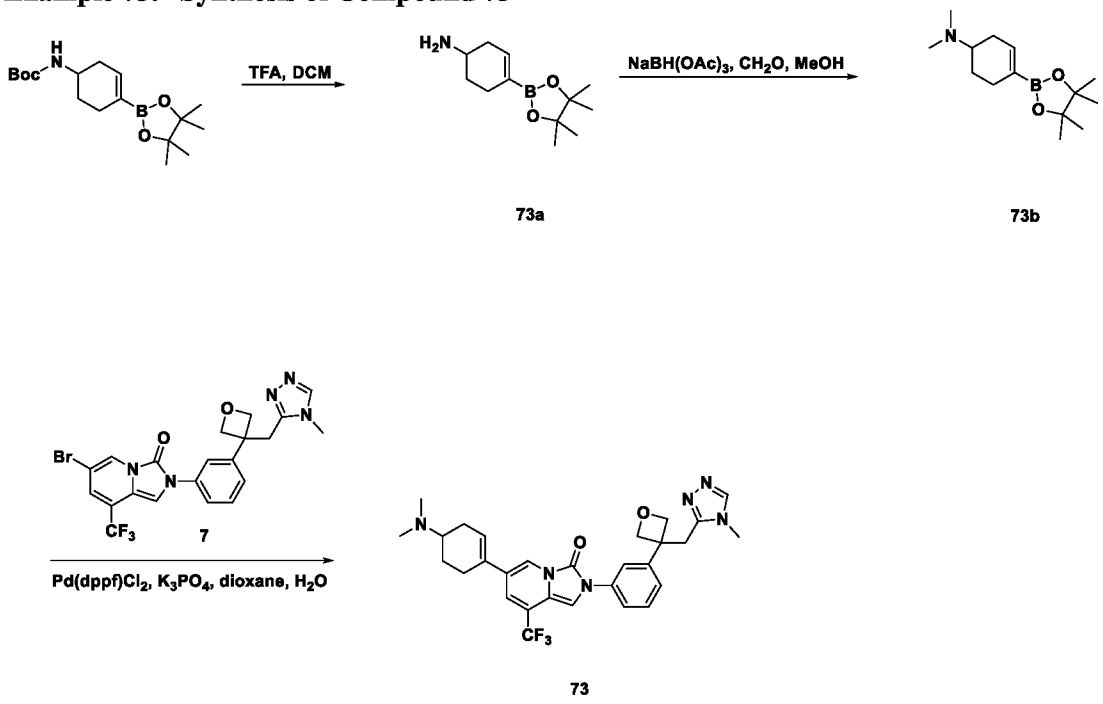
Synthesis of 72

[296] To a stirred solution of 65 (130.00 mg, 0.262 mmol, 1.00 equiv) and HCHO (63.75 mg, 0.786 mmol, 3 equiv, 37%) in MeOH (4.00 mL) were added HOAc (15.72 mg, 0.262 mmol, 1 equiv) and $NaBH_3CN$ (110.99 mg, 0.524 mmol, 2 equiv). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 22% B in 7 min, Wave Length: 220 nm; RT1(min): 6.62) to afford Compound 72 (49.7 mg, 37.18%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 511

H-NMR: (400 MHz, DMSO-d6, ppm): δ 2.33 (s, 3H), δ2.97 (s, 3H), δ3.51-3.56 (m, 4H), δ3.71 (s, 2H), δ4.88-4.96 (m, 4H), δ6.45(s, 1H), δ6.88-6.90 (d, 1H), δ7.39-7.43 (m, 5H), δ7.74-7.76 (m, 1H), δ8.21 (s, 1H).

Example 73. Synthesis of Compound 73



Synthesis of 73a

[297] To a stirred solution of tert-butyl N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]carbamate (1 g, 3.094 mmol, 1 equiv) in DCM (10 mL) was added TFA (2 mL). The resulting mixture was stirred for 3 h at room temperature. The resulting

mixture was concentrated under reduced pressure. The residue was basified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. This resulted in 73a (600 mg, crude) as a light yellow solid.

Synthesis of 73b

[298] To a stirred solution of 73a (600 mg, 2.689 mmol, 1 equiv) and formaldehyde solution (872.91 mg, 10.756 mmol, 4 equiv, 37%) in MeOH (10 mL) were added $NaBH_3CN$ (506.97 mg, 8.067 mmol, 3 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (50 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (4 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 73b (310 mg, 45.89%) as a light yellow solid.

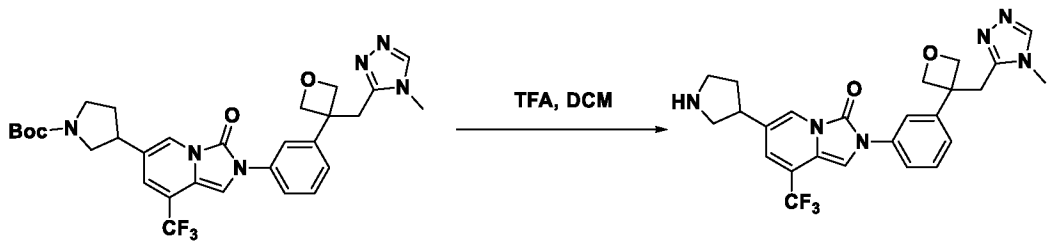
Synthesis of 73

[299] To a stirred mixture of Compound 7 (100 mg, 0.197 mmol, 1 equiv) and 73b (98.83 mg, 0.394 mmol, 2 equiv) in dioxane (4 mL) and H_2O (1 mL) were added K_3PO_4 (83.52 mg, 0.394 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (14.40 mg, 0.020 mmol, 0.1 equiv). The resulting mixture was stirred overnight at 80 °C under argon atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: MeOH; Flow rate: 60 mL/min; Gradient: 40% B to 62% B in 8 min, Wave Length: 220 nm; RT1(min): 7.23) to afford Compound 73 (20.2 mg, 18.58%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 497

H-NMR: (400 MHz, DMSO, ppm): δ 1.45-1.46 (m, 1H), δ1.99-2.02 (m, 1H), δ2.10-2.15 (m, 1H), δ2.22 (s, 6H), δ2.31-2.36 (m, 3H), δ2.45-2.49 (m, 1H), δ2.97 (s, 3H), δ3.54 (s, 2H), δ4.88-4.96 (m, 4H), δ6.28(s, 1H), δ6.89-6.90 (d, 1H), δ7.33-7.42(m, 4H), δ7.54 (s, 1H), δ7.75-7.77 (m, 1H), δ8.22 (s, 1H).

Example 74. Synthesis of Compound 74



66 74

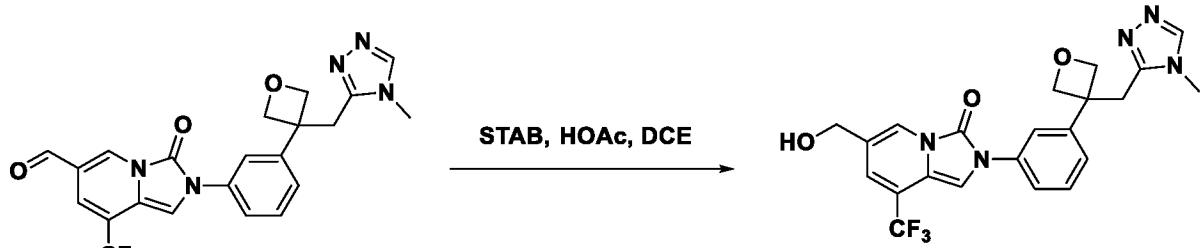
Synthesis of 74

[300] To a stirred solution of 66 (200 mg, 0.334 mmol, 1 equiv) in DCM (2 mL) was added TFA (0.4 mL). The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford Compound 74 (140 mg, 84.06%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 599

H-NMR: (400 MHz, DMSO-d6, ppm): δ1.66-1.71 (m, 1H), δ 2.18-2.12 (m, 1H), δ2.73-2.77 (m, 1H), δ2.89-2.93 (m, 1H), δ2.98 (s, 3H), δ3.14-3.20 (m, 3H), δ3.53(s, 2H), δ4.93-4.97 (m, 4H), δ6.90-6.91 (d, 1H), δ7.13 (s, 1H), δ7.32 (s, 1H), δ7.39-7.43 (m, 2H), δ7.61 (s, 1H), δ7.75-7.77 (m, 1H), δ8.21 (s, 1H).

Example 75. Synthesis of Compound 75



10d 75

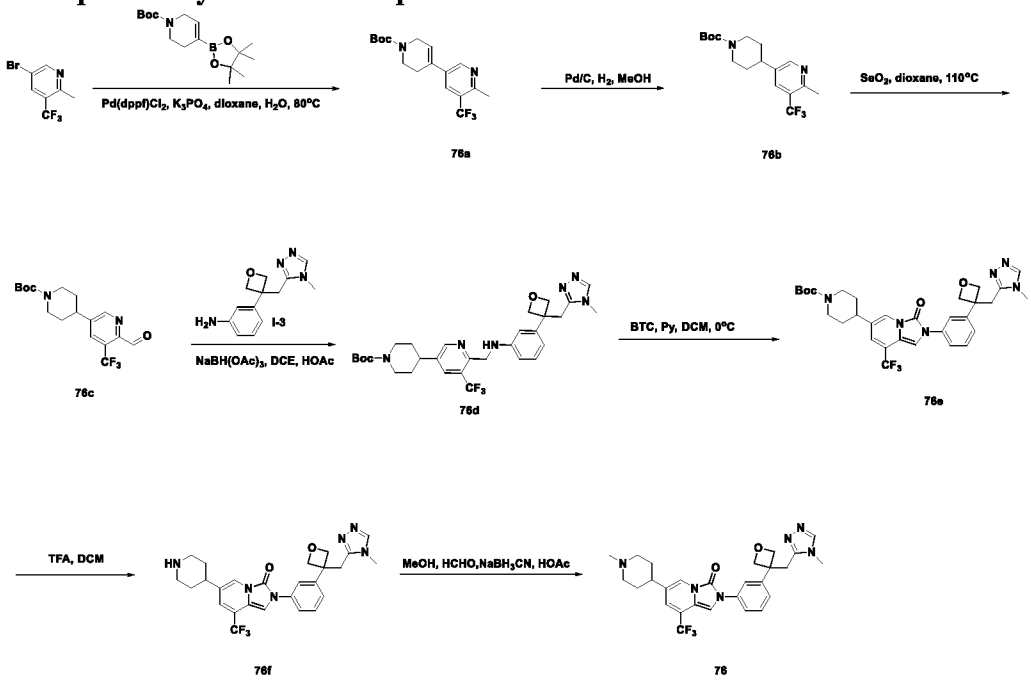
Synthesis of 75

[301] To a stirred solution of 10d (20.00 mg, 0.044 mmol, 1.00 equiv) and $NaBH(OAc)_3$ (27.80 mg, 0.131 mmol, 3.00 equiv) in DCE (1.00 mL) were added AcOH (2.63 mg, 0.044 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford Compound 75 (2.6 mg, 12.81%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 460

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 2.96 (s, 3H), 3.66 (s, 2H), 4.44 (s, 2H), 5.06 (s, 4H), 6.88-6.90 (m, 1H), 7.07-7.12 (m, 2H), 7.32-7.33 (m, 1H), 7.47-7.49 (m, 1H), 7.62-7.65 (d, 1H), 7.72 (s, 1H), 8.21 (s, 1H).

Example 76. Synthesis of Compound 76



Synthesis of 76a

[302] Into a 20mL sealed tube were added 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (1.00 g, 4.166 mmol, 1.00 equiv), dioxane (8.00 mL), H_2O (2.00 mL), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.29 g, 4.172 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ (0.30 g, 0.417 mmol, 0.10 equiv), and K_3PO_4 (1.77 g, 8.333 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 6h at 80 degrees C under nitrogen atmosphere. The reaction was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 3:1) to afford 76a (1 g, 70.11%) as a white solid.

Synthesis of 76b

[303] To a solution of 76a (810 mg, 2.366 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (10%, 20 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 4 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 76b (820 mg) as a colorless oil.

Synthesis of 76c

[304] To a stirred solution of 76b (820 mg, 2.381 mmol, 1 equiv) in dioxane (20 mL) was added SeO_2 (792.62 mg, 7.143 mmol, 3 equiv). The resulting mixture was stirred overnight at

110 °C. The resulting mixture was diluted with water (80 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 76c (760 mg, 89.07%) as a yellow oil.

Synthesis of 76d

[305] To a stirred mixture of 76c (350 mg, 0.977 mmol, 1 equiv) and I-3 (238.60 mg, 0.977 mmol, 1 equiv) in DCE (10 mL) was added HOAc (58.65 mg, 0.977 mmol, 1 equiv) and $NaBH(OAc)_3$ (413.99 mg, 1.954 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH (2 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 76d (360 mg, 62.83%) as a off-white solid.

Synthesis of 76e

[306] To a stirred solution of 76d (360 mg, 0.614 mmol, 1 equiv) and Pyridine (291.23 mg, 3.684 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (72.84 mg, 0.246 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 1h at 0°C.The reaction was quenched by the addition of $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 76e (220 mg, 58.52%) as a yellow solid.

Synthesis of 76f

[307] To a stirred solution of 76e (320 mg, 0.522 mmol, 1 equiv) in DCM (2 mL) was added TFA (0.5 mL). The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 76f (170 mg, 63.50%) as a yellow solid.

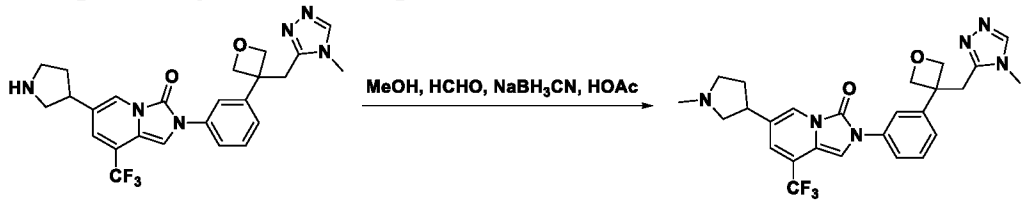
Synthesis of 76

[308] To a stirred solution of 76f (150 mg, 0.293 mmol, 1 equiv) and formaldehyde solution (71.25 mg, 0.879 mmol, 3 equiv, 37%) in MeOH (5 mL) were added HOAc (17.57 mg, 0.293 mmol, 1 equiv) and $NaBH_3CN$ (36.78 mg, 0.586 mmol, 2 equiv). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford Compound 76 (107 mg, 69.43%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 527

H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.62-1.66 (m, 2H), δ1.68-1.79 (m, 2H), δ1.92-1.98 (m, 2H), δ2.21 (s, 3H), δ2.34-2.40 (m, 1H), δ2.83-2.89 (m, 2H), δ3.02 (s, 3H), δ3.59 (s, 2H), δ4.91-4.96(m, 4H), δ6.89-6.91(d, 1H), δ7.10 (s, 1H), δ7.29 (s, 1H), δ7.38-7.42 (m, 2H), δ7.47(s, 1H), δ7.74-7.76(d, 1H), δ8.20 (s, 1H).

Example 77. Synthesis of Compound 77



74 77

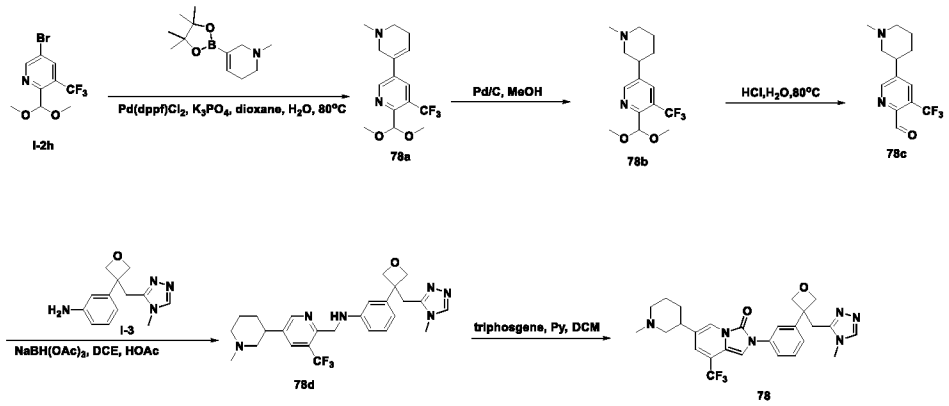
Synthesis of 77

[309] To a stirred solution of 74 (130 mg, 0.261 mmol, 1 equiv) and HCHO (63.49 mg, 0.783 mmol, 3 equiv, 37%) in MeOH (2 mL) were added HOAc (15.66 mg, 0.261 mmol, 1 equiv) and $NaBH_3CN$ (32.78 mg, 0.522 mmol, 2 equiv). The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of water (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 77 (48.2 mg, 36.06%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 513

H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.65-1.72 (m, 1H), δ2.14-2.19 (m, 1H), δ2.20 (s, 3H), δ2.31-2.45 (m, 2H), δ2.63-2.67 (m, 1H), δ2.72-2.76 (m, 1H), δ2.97(s, 3H), δ3.23-3.29 (m, 1H), δ3.54 (s, 3H), δ4.91-4.96 (m, 4H), δ6.88-6.91 (d, 1H), δ7.12 (s, 1H), δ7.31 (s, 1H), δ7.38-7.42 (m, 2H), δ7.74-7.77 (d, 1H), δ8.20 (s, 1H).

Example 78. Synthesis of Compound 78



Synthesis of 78a

[310] To a stirred mixture of 1-2h (500.00 mg, 1.666 mmol, 1.00 equiv) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine (446.13 mg, 2.000 mmol, 1.20 equiv) in dioxane (4.00 mL) and H_2O (1.00 mL) were added K_3PO_4 (707.38 mg, 3.333 mmol, 2.00 equiv) and $Pd(dppf)Cl_2$ (243.84 mg, 0.333 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 78a (400 mg, 75.89%) as a brown yellow oil.

Synthesis of 78b

[311] To a solution of 78a (400.00 mg, 1.265 mmol, 1.00 equiv) in MeOH (5.00 mL) was added Pd/C (79.40 mg, 0.746 mmol, 0.59 equiv) in a pressure tank. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 78b (300 mg, 74.53%) as colorless oil.

Synthesis of 78c

[312] Into a 50 mL 3-necked round-bottom flask were added 78b (300.00 mg, 0.942 mmol, 1.00 equiv) and H_2O (6.00 mL) and HCl (0.50 mL) at room temperature. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 78c (200

mg, 77.95%) as colorless oil.

Synthesis of 78d

[313] To a stirred mixture of 78c (180.00 mg, 0.661 mmol, 1.00 equiv) and I-3 (193.81 mg, 0.793 mmol, 1.20 equiv) in DCE (2.00 mL) were added HOAc (39.70 mg, 0.661 mmol, 1.00 equiv) and $NaBH(OAc)_3$ (280.23 mg, 1.322 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 5:1) to afford 78d (150 mg, 45.33%) as colorless oil.

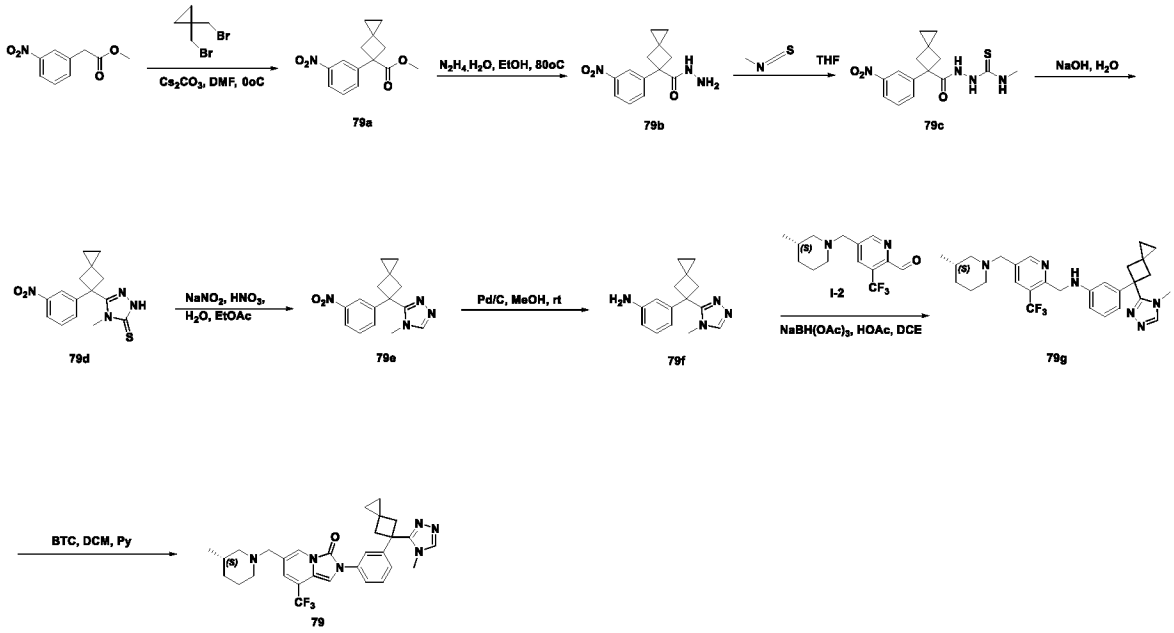
Synthesis of 78

[314] To a stirred mixture of 78d (200.00 mg, 0.400 mmol, 1.00 equiv) and Pyridine (191.99 mg, 2.397 mmol, 6.00 equiv) in DCM (8.00 mL) was added triphosgene (15.26 mg, 0.140 mmol, 0.35 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with $NaHCO_3$ (aq.) (100 mL) at room temperature. The precipitated solids were collected by filtration and washed with DCM (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 5:1) to afford Compound 78 (52.3 mg, 24.86%) as a yellow solid

LC-MS: (ES, m/z): $[M+H]^+$ 527

H-NMR: (400 MHz, DMSO, δ ppm): 1.32-1.40 (m, 1H), 1.50-1.59 (m, 1H), 1.66-1.70 (m, 1H), 1.76-1.79 (m, 1H), 1.97-2.00 (d, 2H), 2.20 (s, 3H), 2.63-2.68 (m, 2H), 2.77-2.80 (d, 1H), 2.97-3.01 (d, 3H), 3.53 (s, 2H), 4.87-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.11 (s, 1H), 7.28-7.38 (d, 1H), 7.40-7.42 (t, 2H), 7.58 (s, 1H), 7.73-7.76 (m, 1H), 8.19-8.22 (d, 1H).

Example 79. Synthesis of Compound 79



Synthesis of 79a

[315] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (3.5 g, 17.933 mmol, 1 equiv) in DMF (70 mL) was added Cs_2CO_3 (11.69 g, 35.866 mmol, 2 equiv) at 0°C under air atmosphere. The resulting mixture was stirred for 2h at 0 degrees C under air atmosphere. To the above mixture was added 1,1-bis(bromomethyl)cyclopropane (12.26 g, 53.799 mmol, 3 equiv) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1) to afford 79a (560 mg, 11.00%) as a colorless oil.

Synthesis of 79b

[316] To a stirred solution of 79a (560 mg, 2.143 mmol, 1 equiv) in EtOH (6 mL, 103.281 mmol, 48.19 equiv) was added hydrazine hydrate (98%) (1071.5 mg, 21.43 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The reaction was quenched with water (40.00 mL) at room temperature. The aqueous layer was extracted with (CH_2Cl_2 / MeOH 10:1) (2x80 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 79b (480 mg, 81.43%) as a colorless oil.

Synthesis of 79c

[317] To a stirred solution of 79b (480 mg, 1.837 mmol, 1 equiv) in tetrahydrofuran (6 mL) was added methyl isothiocyanate (265.93 mg, 3.637 mmol, 1.98 equiv) at room temperature.

The resulting mixture was stirred for 2h at room temperature. The resulting mixture was diluted with water (30mL). The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x2 mL). This resulted in 79c (510 mg, 80.53%) as a white solid.

Synthesis of 79d

[318] To a stirred mixture of NaOH (122.00 mg, 3.050 mmol, 2 equiv) in H_2O (6 mL) was added 79c (510 mg, 1.525 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 4 with HCl (aq.). The resulting mixture was filtered and the filter cake was washed with water (3x1 mL). The filtrate was concentrated under reduced pressure. This resulted in 79d (480 mg, 94.50%) as a white solid.

Synthesis of 79e

[319] To a stirred solution of 79d (250 mg, 0.790 mmol, 1.00 equiv) and $NaNO_2$ (545.19 mg, 7.900 mmol, 10 equiv) in ethyl acetate (13 mL) and H_2O (3 mL) were added HNO_3 (497.92 mg, 7.900 mmol, 10 equiv) at 0°C. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x7 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 79e (180 mg, 74.51%) as a white solid.

Synthesis of 79f

[320] To a stirred solution of 79e (150 mg, 0.528 mmol, 1 equiv) in MeOH (4mL) was added Pd/C (45 mg, 10%) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 5h at room temperature under hydrogen atmosphere. The resulting mixture was filtered through a celite pad and the filter cake was washed with MeOH (3x5 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 79f (110 mg, 73.78%) as a white solid.

Synthesis of 79g

To a stirred solution of 79f (80 mg, 0.315 mmol, 1 equiv) and I-2 (90.05 mg, 0.315 mmol, 1 equiv) in DCE (2 mL) were added $NaBH(OAc)_3$ (199.99 mg, 0.945 mmol, 3 equiv) and HOAc (37.78 mg, 0.630 mmol, 2 equiv) at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The resulting mixture was stirred for 2h at 0°C. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated

under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 79g (69 mg, 36.80%) as a white solid.

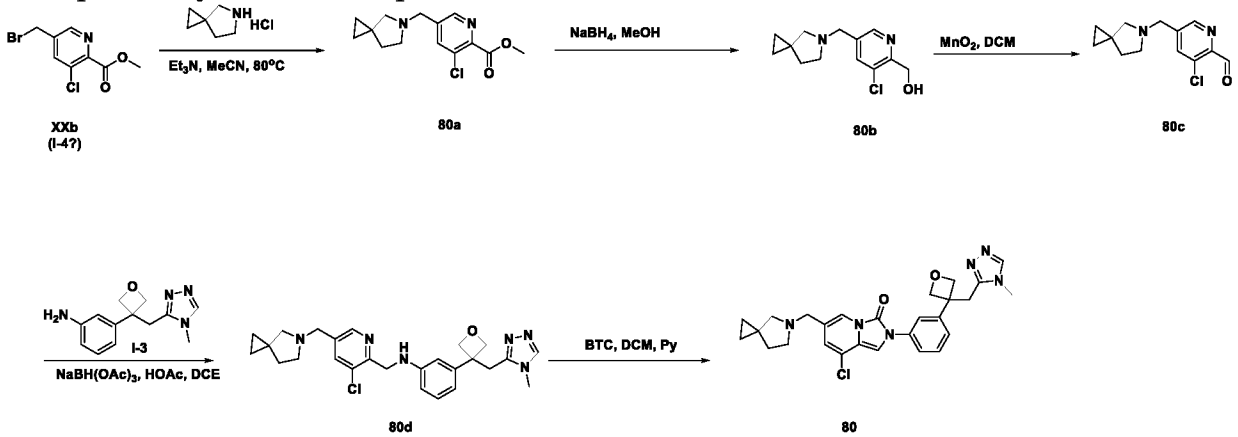
Synthesis of 79

[321] To a stirred solution of 79g (60.00 mg, 0.114 mmol, 1.00 equiv) and Pyridine (54.28 mg, 0.686 mmol, 6 equiv) in DCM (1.50 mL) was added Triphosgene (30.54 mg, 0.103 mmol, 0.90 equiv) at 0°C. The resulting mixture was stirred for 30min at 0°C. The reaction was quenched with $NaHCO_3$ (aq.) (3.00 mL) at room temperature. The aqueous layer was extracted with DCM (3x8 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: water (0.5% NH_4HCO_3), B: CH_3CN, 30% B to 50% B gradient in 30 min; detector, UV 254 nm. This resulted in Compound 79 (14.8 mg, 23.22%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 551

H-NMR: (400 MHz, DMSO-d_6, *ppm,* δ): 0.42-0.47 (m, 2H), 0.53-0.62(m, 2H), 1.44-1.50 (m, 1H), 1.58-1.67 (m, 4H), 1.86-1.92 (m, 1H), 2.68-2.79 (d, 4H), 3.18-3.33 (t, 7H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.36 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.67 (d, 2H), 7.84 (s, 1H), 8.40 (s, 1H).

Example 80. Synthesis of Compound 80



Synthesis of 80a

[322] To a stirred solution of 61b (950.00 mg, 3.592 mmol, 1.00 equiv) and 5-azaspiro[2.4]heptane hydrochloride (955.34 mg, 7.183 mmol, 2 equiv) in acetonitrile (10.00 mL) were added Et_3N (725.48 mg, 7.183 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc

(3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 80a (700 mg, 65.95%) as an off-white solid.

Synthesis of 80b

[323] To a stirred solution of 80a (700.00 mg, 2.493 mmol, 1.00 equiv) in MeOH (8.00 mL) was added $NaBH_4$ (188.66 mg, 4.987 mmol, 2 equiv) at 0 degrees C. The resulting mixture was stirred for 5 h at room temperature under air atmosphere. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 80b (310 mg, 47.72%) as a white oil.

Synthesis of 80c

[324] To a stirred solution of 80b (290.00 mg, 1.147 mmol, 1.00 equiv) in DCM (3.00 mL) was added MnO_2 (997.53 mg, 11.474 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 40 degrees C. The resulting mixture was filtered and the filter cake was washed with DCM (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 80c (310 mg, 96.98%) as a white oil.

Synthesis of 80d

[325] To a stirred solution of 80c (300.00 mg, 1.197 mmol, 1.00 equiv) in DCE (3.00 mL) were added I-3 (292.30 mg, 1.197 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (760.77 mg, 3.590 mmol, 3.00 equiv) and HOAc (7.19 mg, 0.120 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for an additional 2h at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 80d (140 mg, 14.66%) as an off-white oil.

Synthesis of 80

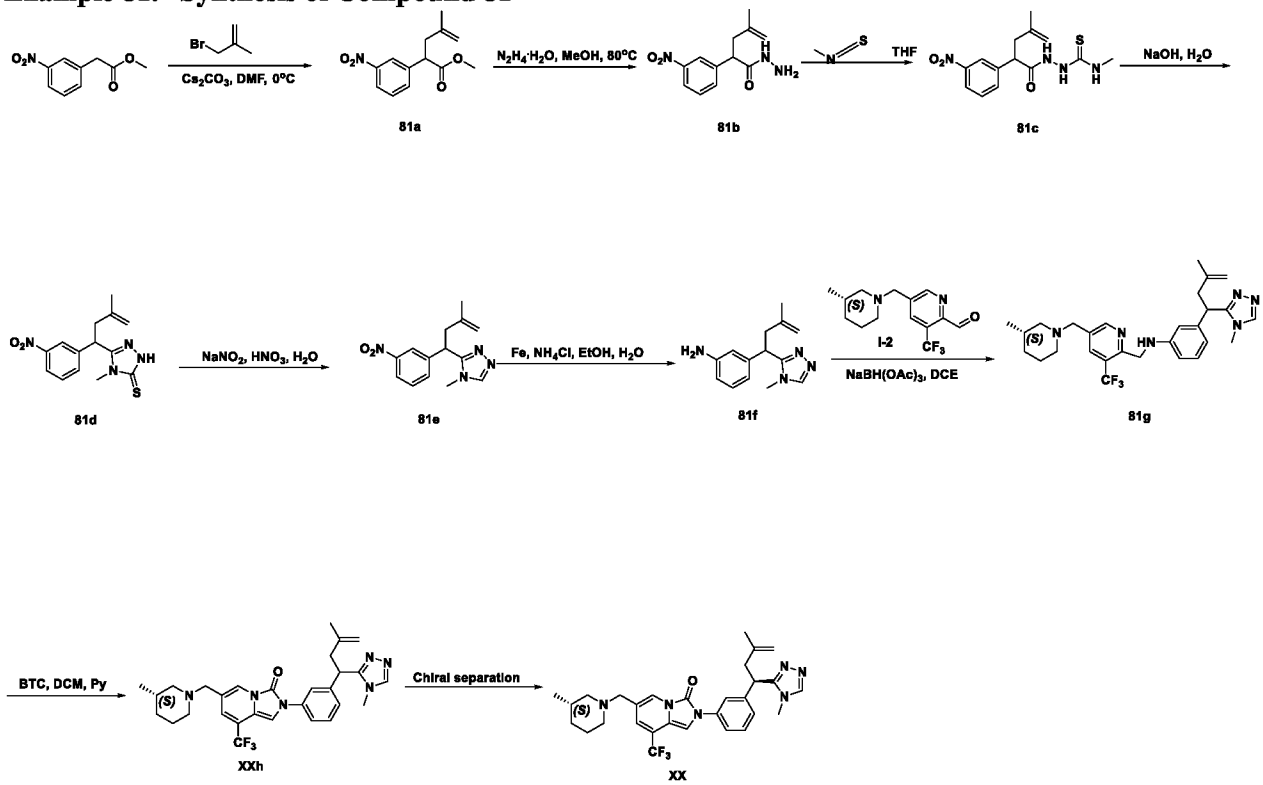
[326] To a stirred solution of 80d (140.00 mg, 0.292 mmol, 1.00 equiv) and Pyridine (138.71 mg, 1.754 mmol, 6 equiv) in DCM (2.00 mL) was added Triphosgene (30.35 mg, 0.102 mmol, 0.35 equiv) at 0 degrees C. The resulting mixture was stirred for 30 min at 0 degrees C. The reaction was quenched with $NaHCO_3$ (aq.) (3.00 mL) at room temperature. The aqueous layer was extracted with DCM (3x8 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with

the following conditions: column, C18 silica gel; mobile phase, A: water (0.5% NH_4HCO_3), B: CH_3CN, 30% B to 50% B gradient in 30 min; detector, UV 254 nm. This resulted in Compound 80 (4.8 mg, 3.20%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 505

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.60 (s, 1H), δ1.84-1.91 (m, 1H), δ2.05-2.06 (m, 1H), δ3.06 (s, 3H), δ3.23 (s, 2H), δ3.32-3.33 (m, 1H), δ0.68-0.74 (m, 3H), δ3.60 (s, 3H), δ4.16-4.26 (m, 2H), δ4.93 (s, 4H), δ6.88 (s, 1H), δ6.97-6.99 (d, 1H), δ7.41-7.78 (m, 4H), δ7.93 (s, 1H), δ8.47 (s, 1H),.

Example 81. Synthesis of Compound 81



Synthesis of 81a

[327] Into a 250 mL 3-necked round-bottom flask were added methyl 2-(3-nitrophenyl)acetate (5 g, 25.618 mmol, 1 equiv) and DMF (50 mL) at room temperature. To the above mixture was added Cs_2CO_3 (25.04 g, 76.854 mmol, 3 equiv) at 0 °C. The mixture was stirred for 3h at 0 °C. To the above mixture was added 3-bromo-2-methylprop-1-ene (6.92 g, 51.236 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture

was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 81a (3.4 g, 53.24%) as a white solid.

Synthesis of 81b

[328] A solution of 81a (3.4 g, 13.640 mmol, 1 equiv) and hydrazine hydrate (10.93 g, 218.240 mmol, 16 equiv) in MeOH (17 mL) was stirred for 2h at 80 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with MeCN (2x30 mL). This resulted in 81b (3 g, 88.23%) as a white solid.

Synthesis of 81c

[329] To a stirred solution of 81b (3 g, 12.035 mmol, 1 equiv) in tetrahydrofuran (30 mL) was added methyl isothiocyanate (1.76 g, 24.070 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with MeCN (2x20 mL). This resulted in 81c (2.98 g, 76.81%) as a white solid.

Synthesis of 81d

[330] Into a 100 mL round-bottom flask were added H_2O (40 mL) and NaOH (1 g, 25.002 mmol, 2.69 equiv) at room temperature. To the above mixture was added 81c (3 g, 9.306 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The residue was acidified to pH 5 with 1 mol/L HCl (aq.). The resulting mixture was filtered, the filter cake was washed with water (3x20 mL). The resulting solid was dried under vacuum. This resulted in 81d (2.5 g, 80.32%) as a yellow solid.

Synthesis of 81e

[331] Into a 100 mL round-bottom flask were added H_2O (25 mL), $NaNO_2$ (2.83 g, 41.070 mmol, 5 equiv) and 81d (2.5 g, 8.214 mmol, 1 equiv) at room temperature. To the above mixture was added HNO_3 (25 mL, 1 mol/L) dropwise at 0 °C. The resulting mixture was stirred for 5 h at 0 °C. The reaction was quenched with $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (100:1) to afford 81e (2 g, 80.48%) as a yellow oil.

Synthesis of 81f

[332] Into a 100 mL 3-necked round-bottom flask were added 81e (2 g, 7.345 mmol, 1

equiv), Fe (2.05 g, 36.725 mmol, 5 equiv), NH_4Cl (1.96 g, 36.725 mmol, 5 equiv), EtOH (30 mL) and H_2O (10 mL) at room temperature. The resulting mixture was stirred overnight at 95°C. The resulting mixture was filtered, the filter cake was washed with DCM/MeOH (20:1) (3x20 mL). The filtrate was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 81f (800 mg, 42.70%) as a white solid.

Synthesis of 81g

[333] Into a 50 mL round-bottom flask were added 81f (400 mg, 1.651 mmol, 1 equiv), I-2 (519.84 mg, 1.816 mmol, 1.1 equiv) and DCE (10 mL) at room temperature. To the above mixture was added STAB (699.69 mg, 3.302 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 81g (300 mg, 33.33%) as a Brown yellow solid.

Synthesis of 81h

[334] Into a 50 mL round-bottom flask were added 81g (280 mg, 0.546 mmol, 1 equiv), DCM (10 mL) and pyridine (345.64 mg, 4.368 mmol, 8 equiv) at room temperature. To the above mixture was added Triphosgene (113.46 mg, 0.382 mmol, 0.7 equiv) at room temperature. The resulting mixture was stirred for 5min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (40 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 81h (150 mg, 47.42%) as a yellow solid.

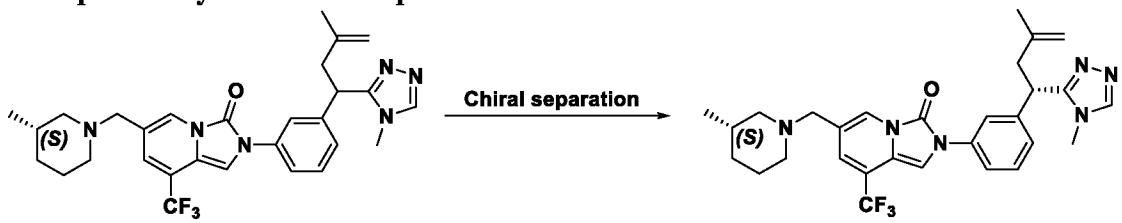
Synthesis of 81

[335] The 81h (150 mg, 0.278 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 11 min; Wave Length: 220/254 nm; RT1(min): 6.93; RT2(min): 9.14; the first peak is product) to afford Compound 81 (26.2 mg, 17.34%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 539

H-NMR: 1H NMR (400 MHz, DMSO-d_6, *ppm*, δ): 0.78-0.95 (m, 4H), 1.44-1.49 (m, 1H), 1.58-1.67 (m, 4H), 1.71 (s, 3H), 1.87-1.89 (m, 1H), 2.76-2.81 (m, 3H), 2.95-3.00 (m, 1H), 3.25 (s, 1H), 3.49 (s, 3H), 4.53-4.69 (t, 1H), 4.61-4.69 (d, 2H), 7.01 (s, 1H), 7.25-7.27 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (t, 1H), 7.66-7.71 (m, 2H), 7.78 (s, 1H), 8.34 (s, 1H).

Example 82. Synthesis of Compound 82



82h 82

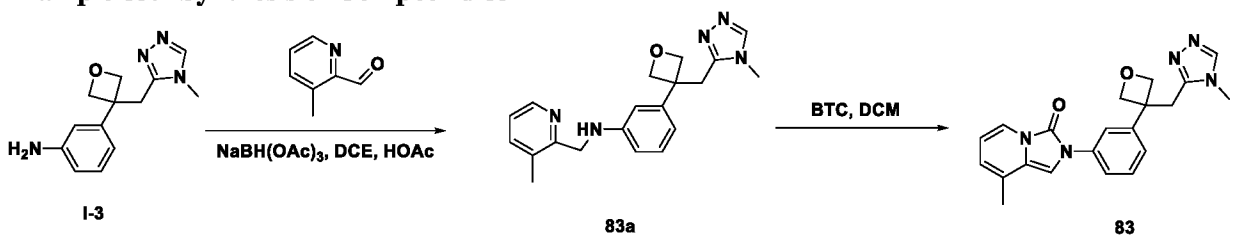
Synthesis of 82

[336] The Compound 82h (150 mg, 0.278 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 11 min; Wave Length: 220/254 nm; RT1(min): 6.93; RT2(min): 9.14; the second peak is product) to afford Compound 82 (36.1 mg, 23.99%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 539

H-NMR: 1H NMR (400 MHz, DMSO-d_6, *ppm*, δ): 0.78-0.95 (m, 4H), 1.44-1.49 (m, 1H), 1.58-1.67 (m, 4H), 1.71 (s, 3H), 1.87-1.89 (m, 1H), 2.76-2.81 (m, 3H), 2.95-3.00 (m, 1H), 3.25 (s, 1H), 3.49 (s, 3H), 4.53-4.69 (t, 1H), 4.61-4.69 (d, 2H), 7.01 (s, 1H), 7.25-7.27 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (t, 1H), 7.66-7.71 (m, 2H), 7.78 (s, 1H), 8.34 (s, 1H).

Example 83. Synthesis of Compound 83



I-3 83a 83

Synthesis of 83a

[337] To a stirred solution of I-3 (300 mg, 1.228 mmol, 1 equiv) and 3-methylpyridine-2-carbaldehyde (178.51 mg, 1.474 mmol, 1.2 equiv) in DCE was added HOAc (73.74 mg, 1.228 mmol, 1 equiv) and $NaBH(OAc)_3$ (520.53 mg, 2.456 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was

purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 83a (160 mg, 37.29%) as a white solid.

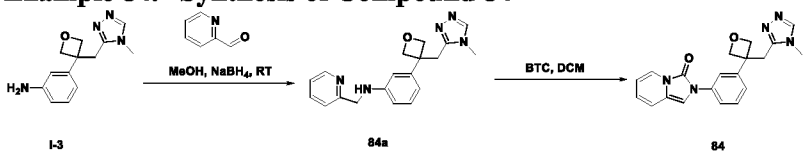
Synthesis of 83

[338] To a stirred solution of 83a (150.00 mg, 0.429 mmol, 1.00 equiv) in DCM (10.00 mL) was added Triphosgene (44.58 mg, 0.150 mmol, 0.35 equiv) at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was washed with 10 mL of $NaHCO_3$(aq.). The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 40% B to 50% B in 7 min, Wave Length: 220 nm; RT1(min): 6.28) to afford Compound 83 (42.5mg,25.58%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 376

H-NMR: (400 MHz, CD_3OD, ppm): δ 2.22 (s, 3H), δ2.95 (s, 3H), δ3.73 (s, 2H), δ5.11 (s, 4H), δ6.24-6.27 (m, 1H), δ6.39-6.41 (d, 1H), δ6.87-6.88(d, 1H), δ7.01 (s, 1H), δ7.31-7.48 (m, 2H), δ7.67-7.69 (m, 1H), δ8.22 (s, 1H).

Example 84. Synthesis of Compound 84



Synthesis of 84a

[339] To a stirred solution of I-3 (200 mg, 0.819 mmol, 1 equiv) in MeOH (10 mL) was added 2-formylpyridine (87.69 mg, 0.819 mmol, 1 equiv). The resulting mixture was stirred overnight at room temperature. To the above mixture was added $NaBH_4$ (30.97 mg, 0.819 mmol, 1 equiv). The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (40 mL). The resulting mixture was extracted with EtOAc (2 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 84a (200 mg, 72.84%) as a white solid.

Synthesis of 84

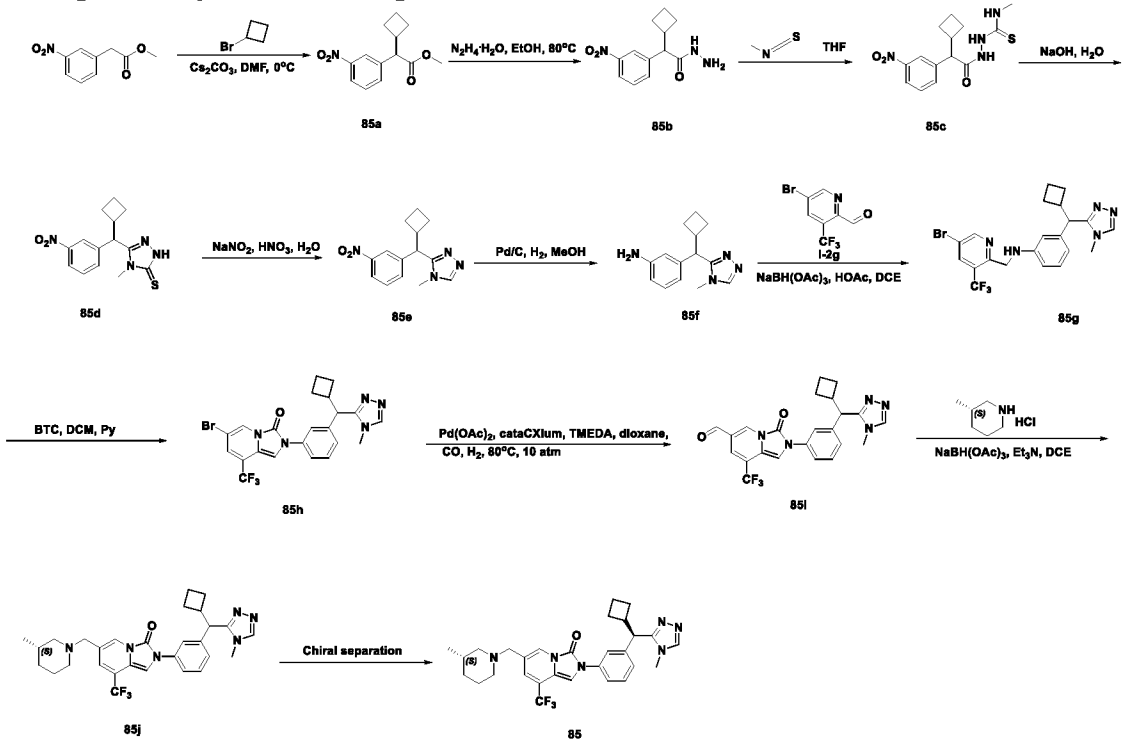
[340] To a stirred solution of 84a (220.00 mg, 0.656 mmol, 1.00 equiv) in DCM (10.00 mL) was added Triphosgene (64.23 mg, 0.216 mmol, 0.33 equiv) at 0°C. The resulting mixture was stirred for 30 min at 0°C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (15 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH=10/1 (2x30 mL). The

resulting mixture was concentrated under vacuum. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 20% B in 16 min, Wave Length: 220 nm; RT1(min): 15.20) to afford Compound 84 (45.3 mg, 19.11%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 376

H-NMR: (400 MHz, CD_3OD, ppm): δ2.95 (s, 3H), δ3.67 (s, 2H), δ5.11 (s, 4H), δ6.25-6.27 (m, 1H), δ6.56-6.58 (d, 1H), δ6.87-6.89(d, 1H), δ7.01 (s, 1H), δ7.03-7.05 (d, 1H), δ7.29 (s, 1H), δ7.41-7.44 (m, 1H), δ7.54-7.56 (d, 1H), δ7.63-7.65 (d, 1H), δ8.22 (s, 1H).

Example 85. Synthesis of Compound 85



Synthesis of 85a

[341] A mixture of methyl 2-(3-nitrophenyl)acetate (48.1 g, 246.447 mmol, 1 equiv) and Cs_2CO_3 (401.49 g, 1232.235 mmol, 5 equiv) in DMF (500 mL) was stirred for 3h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (99.81 g, 739.341 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was diluted with NH_4Cl (aq.) (3L) at 0°C.The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with

PE / EA (150:1) to afford 85a (49 g, 73.38%) as a off-white solid

Synthesis of 85b

[342] To a stirred solution of 85a (49 g, 196.577 mmol, 1 equiv) in EtOH (500 mL) was added hydrazine hydrate (98%) (251.04 g, 4914.425 mmol, 25 equiv, 98%) at room temperature. The resulting mixture was stirred overnight at 80°C.The reaction was diluted by the addition of water (500mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 / MEOH (10:1) (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 85b (43 g, 79.86%) as a yellow oil.

Synthesis of 85c

[343] To a stirred solution of 85b (45 g, 180.527 mmol, 1 equiv) in THF (450 mL) was added methyl isothiocyanate (33.00 g, 451.317 mmol, 2.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (280 mL). The resulting mixture was filtered, the filter cake was washed with water (3x50 mL). The resulting solid was dried under vacuum. This resulted in 85c (55 g, 86.00%) as a white solid.

Synthesis of 85d

[344] To a stirred solution of NaOH (66 g, 1650.120 mmol, 9.67 equiv) in H_2O (1.65 L) was added 85c (55 g, 170.606 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 5 with HCl (1 M). The resulting mixture was filtered, the filter cake was washed with water (3x50 mL). The resulting solid was dried under vacuum. This resulted in 85d (50 g, 86.66%) as a off-white solid.

Synthesis of 85e

[345] To a stirred mixture of 85d (50 g, 164.274 mmol, 1 equiv) in EtOAc (190 mL) and H_2O (760 mL) was added $NaNO_2$ (113.3 g 1642.74 mmol, 10 equiv) at room temperature. To the above mixture was added HNO_3 (1642 mL, 1642.74 mmol, 10.00 equiv, 1 M) dropwise at 0 degrees C. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2/MeOH(10:1) (3x500 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 85e (40 g, 85.84%) as a yellow solid.

Synthesis of 85f

[346] To a solution of 85e (40 g, 146.892 mmol, 1 equiv) in 1.2L MeOH was added Pd/C

(20%, 8g) in a 2L round-bottom flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 85f (35 g, 94.39%) as a off-white solid.

Synthesis of 85g

[347] To a stirred solution of 85f (31.45 g, 123.800 mmol, 1.2 equiv) and I-2g (31.45 g, 123.800 mmol, 1.2 equiv) in DCE (300 mL) were added $NaBH(OAc)_3$ (43.73 g, 206.334 mmol, 2 equiv) and HOAc (6.20 g, 103.167 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with MTBE (2x 50 mL). This resulted in 85g (34 g, 65.18%) as a white solid.

Synthesis of 85h

[348] To a stirred solution of 85g (34 g, 70.784 mmol, 1 equiv) and pyridine (33.59 g, 424.704 mmol, 6 equiv) in DCM (400 mL) were added Triphosgene (7.35 g, 24.774 mmol, 0.35 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (500 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 500 mL) and dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with MTBE (2x 100 mL). This 85h (33 g, 87.47%) as a yellow solid.

Synthesis of 85i

[349] To a solution of 85h (33 g, 65.175 mmol, 1 equiv) and TMEDA (15.15 g, 130.350 mmol, 2 equiv) in dioxane (1000 mL) was added bis(adamantan-1-yl)(butyl)phosphane (4.67 g, 13.035 mmol, 0.2 equiv) and $Pd(OAc)_2$ (1.46 g, 6.518 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) and run overnight at 80 degrees C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to CH_2Cl_2 / MeOH (5:1) to afford 85i (20 g, 67.38%) as a yellow solid.

Synthesis of 85j

[350] To a stirred mixture of 85i (10 g, 21.957 mmol, 1 equiv) and (3S)-3-methylpiperidine

hydrochloride (8.93 g, 65.871 mmol, 3 equiv) in DCE (150 mL) was added Et_3N (8.89 g, 87.828 mmol, 4 equiv). The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH(OAc)_3$ (6.98 g, 32.936 mmol, 1.5 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (200 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 200 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(10 mol/L NH_4HCO_3), 15% to 60% gradient in 40 min; detector, UV 254 nm. This resulted in 85j (6.5 g, 54.96%) as a yellow solid.

Synthesis of 85

[351] The 85j (6.5 g) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 5*25 cm, 10 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3-MeOH); Flow rate: 200 mL/min; Gradient: isocratic 30% B; Column Temperature(℃): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT2(min): 6.26; Sample Solvent: MEOH(0.1% 2M NH_3-MEOH); Injection Volume: 1 mL; Number Of Runs: 30). This resulted in Compound 85 (3.0062g) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 540

H-NMR: (400 MHz, DMSO-d6, ppm): δ0.84-0.91 (m, 4H), δ1.38-1.95 (m, 12H), δ2.08-2.10 (m, 1H), δ2.68-2.77 (m, 2H), δ3.19-3.25 (m, 3H), δ3.43 (s, 3H), δ4.25-4.28 (d, 1H), δ7.01 (s, 1H), δ7.19-7.21 (d 1H), δ7.32 (s, 1H), δ7.43-7.46 (t, 1H), δ7.66-7.75 (m, 3H), δ8.34 (s, 1H).

Example 86. Synthesis of Compound 86



85j 86

Synthesis of 86

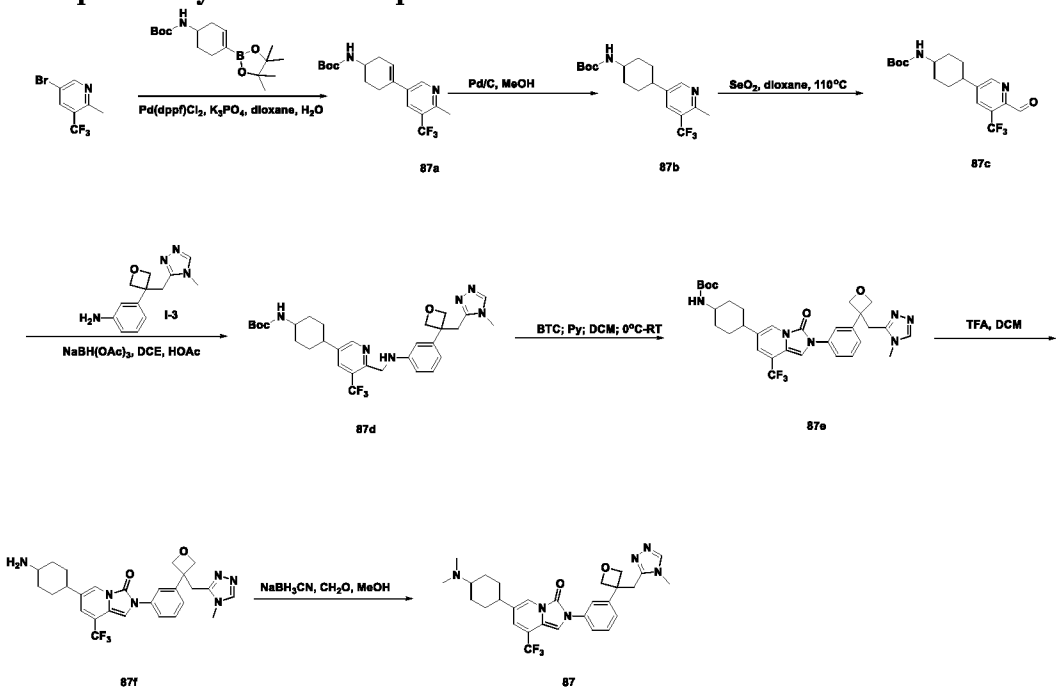
[352] 85j (85.00 mg, 0.158 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 5.19) to afford

Compound 86 (24.1 mg, 27.90%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 539

H-NMR: (400 MHz, $CDCl_3$, *ppm*): δ0.81-0.83 (d, 4H), δ1.66-1.78(m, 11H), δ2.04-2.11 (m, 1H), δ2.65-3.69 (m, 1H), δ2.72-3.73 (m, 1H), δ3.22-3.35 (m, 3H), δ3.42 (s, 3H), δ4.24-4.28 (d, 1H), δ7.00 (s, 1H), δ7.19-7.22 (d, 1H), δ7.33 (s, 1H), δ7.44-7.47 (m, 1H), δ7.70-7.72 (m, 3H), δ8.32 (s, 1H).

Example 87. Synthesis of Compound 87



Synthesis of 87a

[353] Into a 20mL sealed tube were added 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (1.00 g, 4.166 mmol, 1.00 equiv), dioxane (8.00 mL), H_2O (2.00 mL), tert-butyl N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]carbamate (1.35 g, 4.176 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ (0.30 g, 0.417 mmol, 0.1 equiv), and K_3PO_4 (1.77 g, 8.333 mmol, 2 equiv) under nitrogen atmosphere. The resulting mixture was stirred for 6h at 80 degrees C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EtOAc 3:1) to afford 87a (1.1 g, 71.12%) as a colorless oil.

Synthesis of 87b

[354] Into a 50mL round-bottom flask were added 87a (1.10 g, 3.087 mmol, 1 equiv),

MeOH (30.00 mL), Pd/C (200.00 mg) under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 87b (920mg,79.84%) as a colorless oil.

Synthesis of 87c

[355] To a stirred solution of 87b (910 mg, 2.539 mmol, 1 equiv) in dioxane (20 mL) was added SeO_2 (845.19 mg, 7.617 mmol, 3 equiv). The resulting mixture was stirred overnight at 110 °C. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 87c (710 mg, 75.09%) as a yellow oil.

Synthesis of 87d

[356] To a stirred mixture of 87c (370 mg, 0.994 mmol, 1 equiv) and I-3 (242.73 mg, 0.994 mmol, 1 equiv) in DCE (15 mL) was added HOAc (59.67 mg, 0.994 mmol, 1 equiv) and $NaBH(OAc)_3$ (421.16 mg, 1.988 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 87d (320 mg, 53.62%) as a light yellow solid.

Synthesis of 87e

[357] To a stirred solution of 87d (320 mg, 0.533 mmol, 1 equiv) and Pyridine (252.83 mg, 3.198 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (63.23 mg, 0.213 mmol, 0.4 equiv). The resulting mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH (10/1) (4 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 87e (240 mg, 71.89%) as a yellow solid.

Synthesis of 87f

[358] To a stirred solution of 87e (240 mg, 0.383 mmol, 1 equiv) in DCM (3 mL) was added TFA (0.6 mL). The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford 87f (180 mg, 89.26%) as a yellow solid.

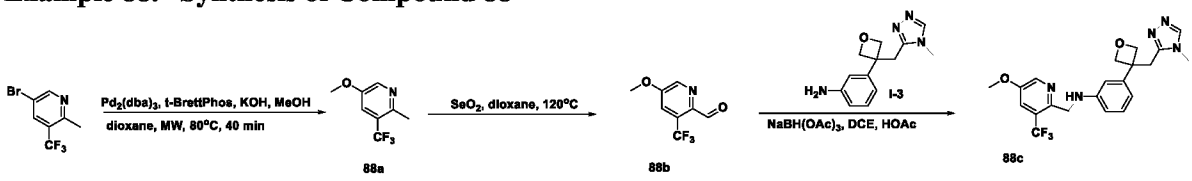
Synthesis of 87

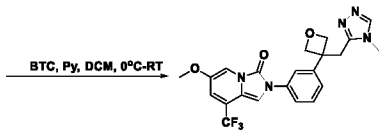
[359] To a stirred solution of 87f (180 mg, 0.342 mmol, 1 equiv) and formaldehyde solution (83.22 mg, 1.026 mmol, 3 equiv, 37%) in MeOH (3 mL) was added HOAc (20.5 mg, 0.342 mmol, 1 equiv) and $NaBH_3CN$ (42.96 mg, 0.684 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0°C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (15mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (4 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford Compound 87 (49.1 mg, 25.90%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 556

H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.48-1.58 (m, 4H), δ 1.66-1.75 (m, 2H), δ1.93-1.96 (m, 4H), δ2.19-2.33 (m, 6H), δ2.97 (s, 1H), δ3.54 (s, 2H), δ4.91-4.96 (m, 4H), δ6.89-6.91(d, 1H), δ7.04 (s, 1H), δ7.39-7.45 (m, 3H), δ7.75-7.77 (d, 1H), δ8.21 (s, 1H).

Example 88. Synthesis of Compound 88





88

Synthesis of 88a

[360] To a stirred mixture of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (1 g, 4.166 mmol, 1 equiv) and $Pd_2(dba)_3$ (0.38 g, 0.417 mmol, 0.1 equiv) in MeOH (5 mL) were added dioxane (10 mL) and KOH (0.70 g, 12.498 mmol, 3 equiv) at room temperature under nitrogen atmosphere. To the above mixture was added t-Brettphos (0.40 g, 0.833 mmol, 0.2 equiv) in one portion at room temperature. The final reaction mixture was irradiated with microwave radiation for 40 min at 80°C. The reaction was quenched with NH_4Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x50 mL). The combined organic layers were washed with water (3x50 mL), dried over anhydrous Na_2SO_4.

After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=40:1 to afford 88a (300 mg, 37.67%) as a colorless oil.

Synthesis of 88b

[361] A mixture of 88a (280 mg, 1.465 mmol, 1 equiv) and SeO_2 (487.60 mg, 4.395 mmol, 3 equiv) in 1,4-dioxane was stirred overnight at 110 °C under nitrogen atmosphere. The resulting mixture was washed with 3x20 mL of water. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with water (3x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=40:1) to afford 88b (60 mg, 19.97%) as a yellow oil.

Synthesis of 88c

[362] To a stirred mixture of 88b (580 mg, 2.827 mmol, 1 equiv) and I-3 (1036.09 mg, 4.240 mmol, 1.5 equiv) in DCE were added HOAc (169.79 mg, 2.827 mmol, 1 equiv) and $NaBH(OAc)_3$ (1797.72 mg, 8.481 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 88c (700 mg, 51.41%) as a yellow solid.

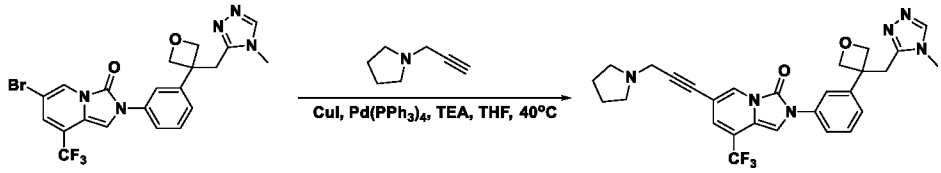
Synthesis of 88

[363] To a stirred solution of 88c (90 mg, 0.208 mmol, 1 equiv) and pyridine (98.55 mg, 1.248 mmol, 6 equiv) in DCM (4 mL) was added triphosgene (21.56 mg, 0.073 mmol, 0.35 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 5 min at 0 °C. The resulting mixture was washed with 3x10 mL of water. The resulting mixture was extracted with CH_2Cl_2 (3 x10 mL). The combined organic layers were washed with water (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford Compound 88 (42.1 mg, 42.01%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 460.

H-NMR: (400 MHz, DMSO-d_6, ppm, δ): 2.82-3.01 (s, 3H), 3.53 (s, 2H), 3.77 (s, 3H), 4.91-5.02 (m, 4H), 6.88 (s, 1H), 6.94 (s, 1H), 7.24 (s, 1H), 7.33-7.40 (m, 2H), 7.69-7.77 (m, 1H), 8.20 (s, 1H).

Example 89. Synthesis of Compound 89



7 89

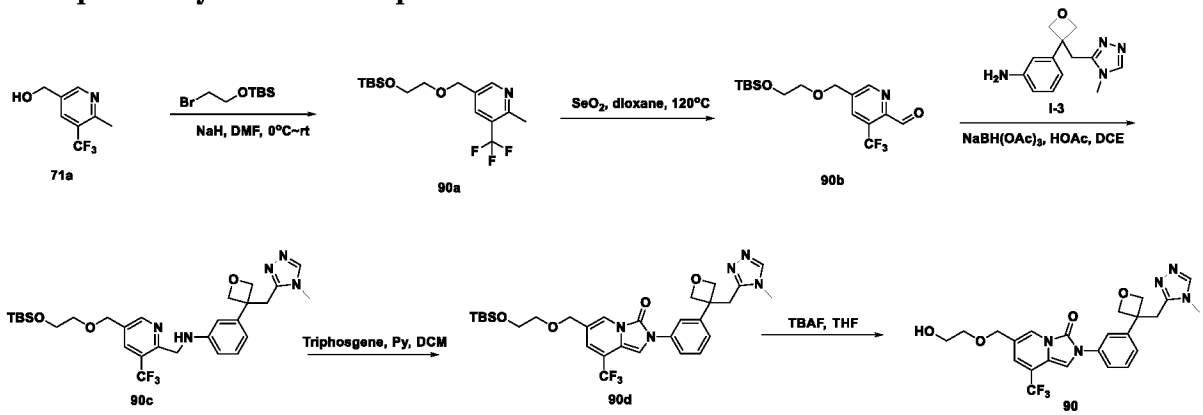
Synthesis of 89

[364] Into a 8 mL sealed tube were added 7 (150 mg, 0.295 mmol, 1.00 equiv), THF (2 mL), TEA (89.58 mg, 0.885 mmol, 3 equiv), 1-(prop-2-yn-1-yl)pyrrolidine (48.33 mg, 0.443 mmol, 1.5 equiv), CuI (11.24 mg, 0.059 mmol, 0.2 equiv), and $Pd(PPh_3)_4$ (34.10 mg, 0.029 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for 12 h at 40°C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford the crude product (55 mg). The crude product was purified by reverse phase flash with the following conditions (Column: Xselect CSH C18 OBD Column; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 44% B to 54% B in 7 min, Wave Length: 254) to afford Compound 89 (57.6 mg, 35.43%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 537

H-NMR: 1H NMR (400 MHz, DMSO-d6) δ 1.72-1.76 (m, 4H), δ2.58 (s, 4H), δ2.97 (s, 3H), δ3.37 (s, 2H), δ3.47-3.67 (m, 2H), δ4.84-4.96 (m, 4H), δ6.88-6.90 (d, 1H), δ6.84 (s, 1H), δ7.38-7.43 (m, 3H), δ7.73-7.75 (t, 1H), δ7.89 (s, 1H), δ8.14 (s, 1H), δ8.17-8.22 (t, 1H).

Example 90. Synthesis of Compound 90



71a 90a 90b 90c 90d 90

Synthesis of 90a

[365] To a stirred solution of 71a (1 g, 5.231 mmol, 1 equiv) in DMF (10 mL) were added NaH (0.25 g, 10.462 mmol, 2 equiv) in two portions at 0 °C. The resulting mixture was stirred for 30 min at 0°C under nitrogen atmosphere. To the above mixture was added (2-bromoethoxy)(tert-butyl)dimethylsilane (1.88 g, 7.846 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=3:1) to afford 90a (220 mg, 12.03%) as colorless oil.

Synthesis of 90b

[366] To a stirred solution of 90a (300 mg, 0.858 mmol, 1 equiv) in dioxane (3 mL) were added SeO_2 (190.51 mg, 1.716 mmol, 2 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 120°C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 90b (140 mg, 40.38%) as colorless oil.

Synthesis of 90c

[367] To a stirred solution of 90b (260 mg, 0.715 mmol, 1 equiv) and I-3 (192.24 mg, 0.786 mmol, 1.1 equiv) in DCE (3 mL) were added $NaBH(OAc)_3$ (454.84 mg, 2.145 mmol, 3 equiv) and HOAc (42.96 mg, 0.715 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 6 h at room temperature. The resulting mixture was diluted with sat NH_4Cl (aq.) (60 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=40:1) to afford 90c (240 mg, 54.99%) as a yellow solid.

Synthesis of 90d

[368] To a stirred solution of 90c (220 mg, 0.372 mmol, 1 equiv) and Pyridine (176.45 mg, 2.232 mmol, 6 equiv) in DCM (8 mL) were added Triphosgene (38.61 mg, 0.130 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 5 min at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of sat $NaHCO_3$(aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 90d (170 mg, 74.02%) as a yellow solid.

Synthesis of 90

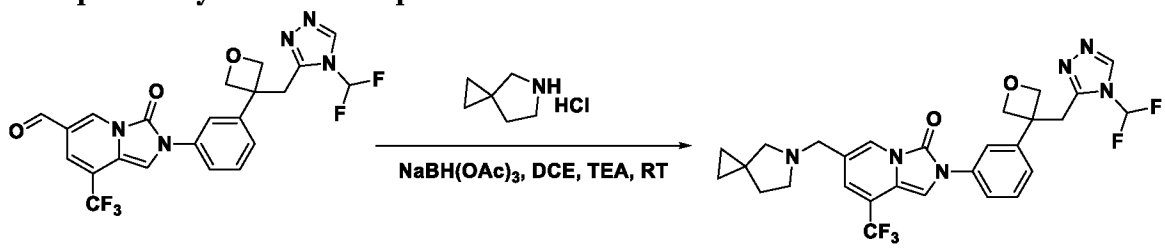
[369] A solution of 90d (160 mg, 0.259 mmol, 1.00 equiv) and TBAF (0.48 mL) in THF (2

mL) was stirred for 2h at room temperature under nitrogen atmosphere. The mixture was acidified to pH 6 with saturated NH_4Cl (aq.) (5mL). The reaction was quenched with water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 34% B in 9 min; Wave Length: 220 nm; RT1(min): 8.82) to afford Compound 90 (47.7 mg, 36.58%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 504

H-NMR: (400 MHz, DMSO, δ ppm): 2.97 (s, 3H), 3.45-3.56 (m, 6H), 4.32 (s, 2H), 4.67-4.69 (t, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.06 (s, 1H), 7.73-7.74 (m, 3H), 7.75-7.78 (m, 2H), 8.21 (s, 1H).

Example 91. Synthesis of Compound 91



48i 91

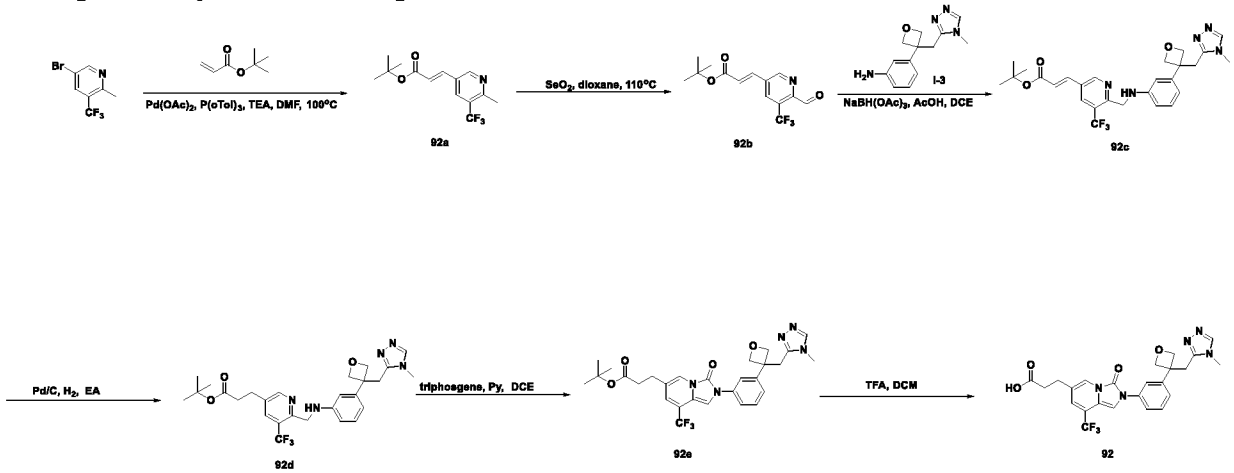
Synthesis of 91

[370] To a stirred mixture of 48i (200 mg, 0.405 mmol, 1 equiv) and 5-azaspiro[2.4]heptane hydrochloride (162.49 mg, 1.215 mmol, 3 equiv) in DCE (4 mL) was added TEA (164.07 mg, 1.620 mmol, 4 equiv) and $NaBH(OAc)_3$ (171.82 mg, 0.810 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 10mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 8 min, Wave Length: 220 nm; RT1(min): 7.62) to afford Compound 91 (52.1 mg, 22.37%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 575

H-NMR: (400 MHz, DMSO-d6, ppm): δ0.50-0.53 (d, 4H), δ1.74-1.78 (m, 1H), δ2.47-2.49 (m, 2H), δ2.67-2.69 (m, 2H), δ3.41 (s, 2H), δ3.75 (s, 2H), δ4.96 (s, 4H), δ7.06-7.08 (m, 1H), δ7.32 (s, 1H), δ7.38-7.42(m, 1H), δ7.54-7.55(m, 2H), δ7.70-7.75 (m, 2H), δ8.83 (s, 1H).

Example 92. Synthesis of Compound 92



Synthesis of 92a

[371] To a stirred solution of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (1 g, 4.166 mmol, 1 equiv) and tert-butyl prop-2-enoate (0.53 g, 4.166 mmol, 1 equiv) in DMF (10 mL) were added $Pd(OAc)_2$ (0.09 g, 0.417 mmol, 0.1 equiv), TEA (1.26 g, 12.498 mmol, 3 equiv) and $P(o\text{-}Tol)_3$ (0.51 g, 1.666 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was quenched with Water/Ice (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 6:1) to afford 92a (450 mg, 37.60%) as colorless oil.

Synthesis of 92b

[372] A solution of 92a (420 mg, 1.462 mmol, 1 equiv) and SeO_2 (420.15 mg, 3.787 mmol, 2.59 equiv) in dioxane (4 mL) was stirred overnight at 110°C under nitrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with CH_2Cl_2 (3x6 mL). The filtrate was concentrated under reduced pressure. This resulted in 92b (300 mg, 54.49%) as brown oil.

Synthesis of 92c

[373] Into a 100 mL round-bottom flask were added 92b (280 mg, 0.929 mmol, 1 equiv), DCE (4 mL) and I-3 (272.46 mg, 1.115 mmol, 1.2 equiv) at room temperature. The resulting

mixture was stirred for 30 min at room temperature. To the above mixture was added AcOH (55.81 mg, 0.929 mmol, 1 equiv) and $NaBH(OAc)_3$ (393.96 mg, 1.858 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 92c (300 mg, 60.95%) as colorless oil.

Synthesis of 92d

[374] To a solution of 92c (300 mg, 0.567 mmol, 1 equiv) in EA (8 ml) was added Pd/C (74.76 mg) in a pressure tank. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 92d (280 mg, 92.98%) as colorless oil.

Synthesis of 92e

[375] To a stirred mixture 92d (280 mg, 0.527 mmol, 1.00 equiv) and Pyridine (249.99 mg, 3.162 mmol, 6 equiv) in DCE (5.00 mL) was added triphosgene (54.70 mg, 0.184 mmol, 0.35 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with sat $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x7 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 5:1) to afford 92e (200 mg, 68.10%) as a yellow solid

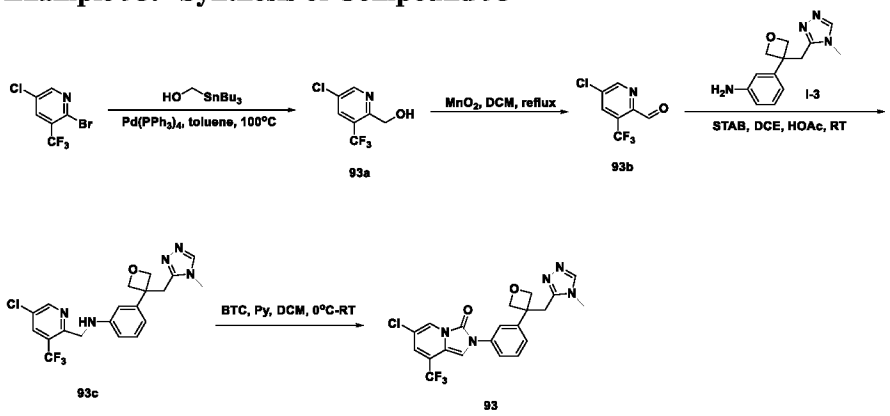
Synthesis of 92

[376] A solution of 92e (200 mg, 0.359 mmol, 1.00 equiv) in DCM (1.6 mL) and TFA (0.4 mL) was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude product (150 mg). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 25% B in 12 min; Wave Length: 220 nm; RT1(min): 11.33 to afford Compound 92 (30.2 mg, 16.79%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 502

H-NMR: (400 MHz, DMSO, δ ppm): 2.45-2.51 (m, 2H), 2.61-2.67 (m, 2H), 2.96 (s, 3H), 3.53 (s, 2H), 4.90-4.95 (m, 4H), 6.87-6.89 (d, 1H), 7.12 (s, 1H), 7.28 (s, 1H), 7.37-7.41 (t, 2H), 7.58 (s, 1H), 7.74 (s, 1H), 7.76 (s, 1H), 8.20 (s, 1H).

Example 93. Synthesis of Compound 93



Synthesis of 93a

[377] To a stirred solution of 2-bromo-5-chloro-3-(trifluoromethyl) pyridine (1.6 g, 6.143 mmol, 1 equiv) and (tributylstannyl)methanol (2.96 g, 9.214 mmol, 1.5 equiv) in Toluene (20 mL) were added $Pd(PPh_3)_4$ (0.71 g, 0.614 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (2:1) to afford 93a (600 mg, 41.55%) as a colorless oil.

Synthesis of 93b

[378] To a stirred solution of 93a (600 mg, 2.836 mmol, 1 equiv) in DCM (8 mL) were added MnO_2 (2465.48 mg, 28.360 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 50°C under nitrogen atmosphere. The resulting mixture was filtered by filter paper; the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford 93b (260 mg, 40.25%) as a colorless oil.

Synthesis of 93c

[379] To a stirred solution of 93b (260 mg, 1.241 mmol, 1 equiv) and I-3 (303.11 mg, 1.241 mmol, 1 equiv) in DCE (4 mL) were added STAB (525.93 mg, 2.482 mmol, 2 equiv) and AcOH (74.51 mg, 1.241 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL) then dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated

under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 /MeOH 20:1) to afford 93c (230 mg, 39.37%) as a yellow oil.

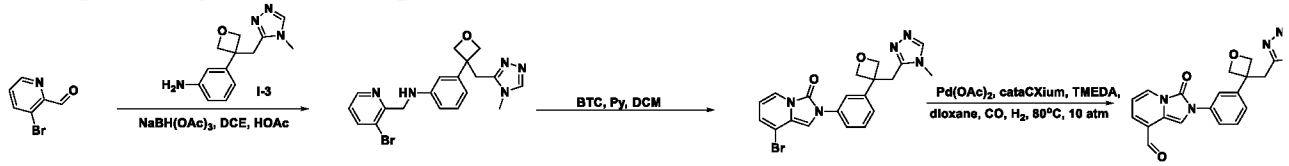
Synthesis of 93

[380] To a stirred solution of 93c (220 mg, 0.502 mmol, 1 equiv) and Pyridine (238.46 mg, 3.012 mmol, 6 equiv) in DCE (3 mL) were added Triphosgene (52.19 mg, 0.176 mmol, 0.35 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat $NaHCO_3$ (aq.) (5 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (2 x 10mL), dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 93 (145.7 mg, 61.64%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:464

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.50-2.51 (m, 3H), δ 2.48-2.54 (m, 2H), δ 4.91-4.96 (m, 4H), δ 6.89-6.91 (d, 1H), δ 7.14 (s, 1H), δ 7.38-7.46 (m, 3H), δ 7.73-7.75 (m, 1H), δ 7.98 (m, 1H), δ 8.22 (s, 1H).

Example 94. Synthesis of Compound 94



Synthesis of 94a

[381] To a stirred solution of 3-bromopyridine-2-carbaldehyde (800 mg, 4.30 mmol, 1.0 equiv) and I-3 (1.0 g, 4.30 mmol, 1.0 equiv) in DCE (10 mL) were added $NaBH(OAc)_3$ (1.8 g, 8.60 mmol, 2.0 equiv) and HOAc (258 mg, 4.30 mmol, 1.0 equiv) at 0°C. The resulting mixture was stirred for 6h at 0°C. The reaction was quenched with sat. NH_4Cl (aq.) (60 ml) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE/EA=5:1) to afford 94a (800 mg, 42%) as a white solid.

Synthesis of 94b

[382] To a stirred solution of 94a (600 mg, 1.44 mmol, 1.0 equiv) and Pyridine (687 mg, 8.68 mmol, 6.0 equiv) in DCE (10 mL) were added triphosgene (150 mg, 0.50 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 0.5h at 0°C. The reaction was quenched

with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 94b (360 mg, 56%) as a white solid.

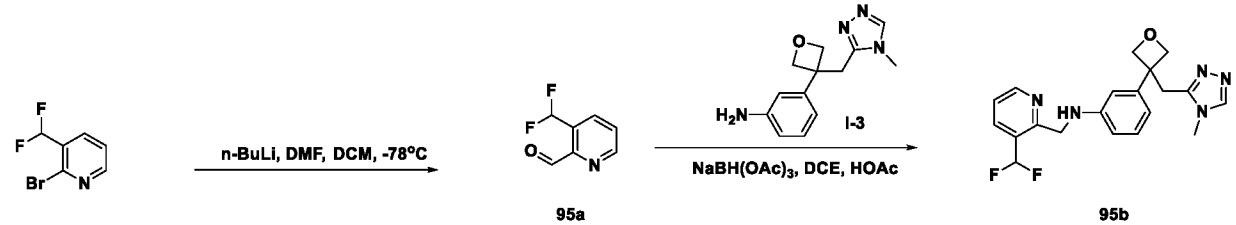
Synthesis of 94

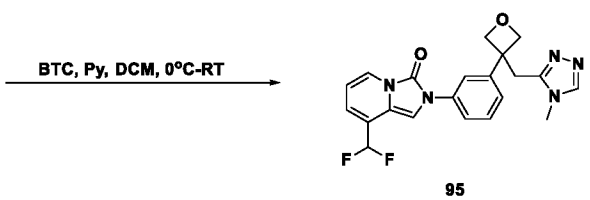
[383] To a stirred solution of 94b (410 mg, 0.931 mmol, 1 equiv) and CataCxium (333.36 mg, 0.931 mmol, 1 equiv) in dioxane (10 mL) were added TMEDA (324.62 mg, 2.793 mmol, 3 equiv) and $Pd(OAc)_2$ (2090.59 mg, 9.310 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The mixture was purged with nitrogen and then was pressurized to 10 atm with carbon monoxide/hydrogen (1:1) at 80 °C overnight. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (2x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=12:1) to afford crude product (100 mg). The crude product (100 mg) was purified by reverse flash chromatography with the following conditions (column, C18 silica gel; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 40 mL/min; Gradient: 50% B to 60% B in 10 min; Wave Length: 254 nm to afford Compound 94 (50 mg, 15%) as a purple solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 390

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 2.96 (s, 3H), 3.54 (s, 2H), 4.79-5.00 (m, 4H), 6.42-6.46 (m, 1H), 6.85-6.87 (d, 1H), 7.31-7.48 (m, 2H), 7.51 (s, 1H), 7.54-7.56 (d, 2H), 7.72-7.77 (d, 1H), 7.93-7.95 (d, 1H), 8.21-8.23 (d, 1H), 9.82 (s, 1H).

Example 95. Synthesis of Compound 95





Synthesis of 95a

[384] In a 50-mL round bottom flask, to a solution of 2-bromo-3-(difluoromethyl) pyridine (1.0 g, 4.80 mmol, 1.0 equiv) in THF (10 mL) was added dropwise n-butyllithium solution (1.5 M in hexane, 2.5 mL, 1.5 mmol, 0.3 equiv) at -78 degrees C under nitrogen atmosphere. The reaction mixture was stirred at -78 degrees C for 30 min. Then a solution of DMF (40 mg, 0.48 mmol, 0.1 equiv) in 0.5 mL THF was added dropwise and the mixture was stirred for another 120 min. The reaction was quenched with sat. NH_4Cl (aq.) (30 mL), and then the mixture was extracted with EtOAc (3x20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=50:1) to afford 95a (250 mg, 33%) as a yellow oil.

Synthesis of 95b

[385] To a stirred solution of I-3 (100 mg, 0.63 mmol, 1.0 equiv) and 95a (233 mg, 0.95 mmol, 1.5 equiv) in DCE (3 ml) were added HOAc (38 mg, 0.63 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (404 mg, 1.90 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (10 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 95b (80 mg, 29%) as a yellow solid.

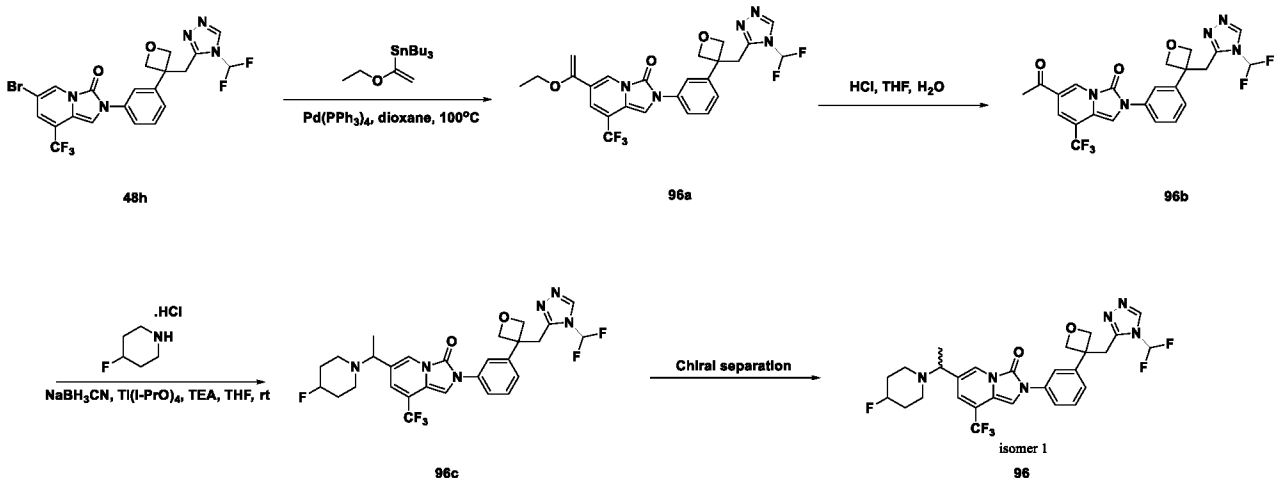
Synthesis of 95

[386] To a stirred solution of 95b (80 mg, 0.20 mmol, 1.0 equiv) and Pyridine (98 mg, 1.24 mmol, 6.0 equiv) in DCE (2 ml) was added triphosgene (21 mg, 0.07 mmol, 0.35 equiv) at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 20 min at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) (10 ml) and extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford Compound 95 (31 mg, 36%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 412

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 2.96 (s, 3H), 3.53 (s, 2H), 4.90-4.96 (t, 4H), 6.24-6.28 (m, 1H), 6.86-6.88 (m, 2H), 6.96-7.10 (m, 1H), 7.26 (s, 1H), 7.38-7.42 (m, 2H), 7.67-7.69 (d, 1H), 7.73-7.76 (m, 1H), 8.20 (s, 1H).

Example 96. Synthesis of Compound 96



Synthesis of 96a

[387] To a stirred solution of 48h (2 g, 3.675 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (1.73 g, 4.777 mmol, 1.3 equiv) in dioxane (20 mL) was added $Pd(PPh_3)_4$ (0.42 g, 0.363 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 degrees C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x50 mL). The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to 96a (1.5 g, 75.47%) as a yellow solid.

Synthesis of 96b

[388] To a stirred solution of 96a (1.5 g, 2.801 mmol, 1.00 equiv) in THF (10 mL) was added HCl (10 mL, 1M) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 96b (1.2 g, 82.73%) as a yellow solid.

Synthesis of 96c

[389] To a stirred solution of 96b (500 mg, 0.985 mmol, 1.00 equiv) and 4-fluoropiperidine hydrochloride (304.89 mg, 2.956 mmol, 3.00 equiv) in THF (10 mL) was added TEA (997.10 mg, 9.854 mmol, 10.00 equiv) and tetrakis(propan-2-yloxy)titanium (840.18 mg, 2.955 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 50 degrees C under nitrogen atmosphere. To the above mixture was added $NaBH_3CN$ (185.77 mg, 2.955 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous

NH_4Cl at room temperature. The aqueous layer was extracted with CH_2Cl2 (2x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 96c (300 mg, 49.16%) as a yellow solid.

Synthesis of 96

[390] 96c (300 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 10.56, RT2(min): 13.76, the first peak is product) to afford Compound 96 (106.1 mg, 34.31%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$595

H-NMR: (400 MHz, DMSO-d6, ppm): (400 MHz, DMSO-d6, ppm): δ 1.26-1.27 (d, 1H), δ1.68-1.80 (m, 2H), δ2.33-2.36 (m, 2H), δ2.51-2.57 (m, 2H), δ3.50-3.51 (m, 1H), δ3.75 (s, 2H), δ4.55-4.66 (m, 1H), δ4.96 (s, 4H), δ7.06-7.08(d, 2H), δ7.33 (s, 1H), δ7.39-7.43 (m, 1H), δ7.54-7.61 (m, 2H), δ7.69 (s, 1H), δ7.72-7.75 (m, 1H), δ8.84 (s, 1H).

Example 97. Synthesis of Compound 97



96c

isomer 2
97

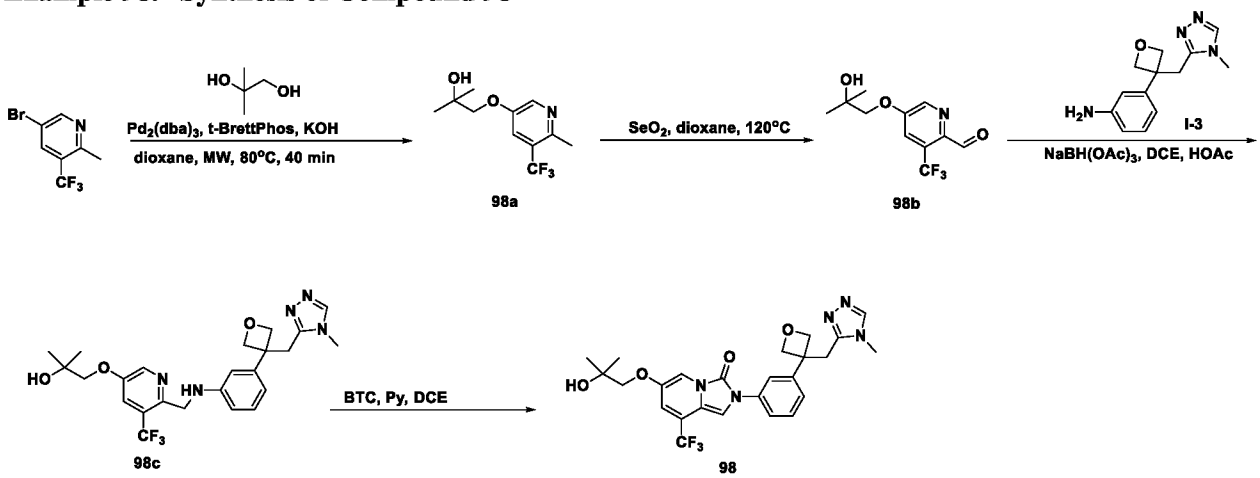
Synthesis of 97

[391] 96c (300 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 10.56, RT2(min): 13.76, the first peak is product) to afford Compound 97 (102.5 mg, 33.82%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 595

H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.26-1.27 (d, 1H), δ1.68-1.81 (m, 2H), δ1.82-1.86 (m, 2H), δ2.33-2.36 (m, 2H), δ2.51-2.54 (m, 2H), δ3.50-3.51 (m, 1H), δ3.75 (s, 2H), δ4.60-4.72 (m, 1H), δ4.96 (s, 4H), δ7.06-7.08(d, 2H), δ7.33 (s, 1H), δ7.39-7.43 (m, 1H), δ7.54-7.61 (m, 2H), δ7.69 (s, 1H), δ7.72-7.75 (m, 1H), δ8.84 (s, 1H).

Example 98. Synthesis of Compound 98



Synthesis of 98a

[392] To a stirred solution of 5-bromo-2-methyl-3-(trifluoromethyl) pyridine (2 g, 8.33 mmol, 1.0 equiv) and 2-methyl-propane-1,2-diol (4 mL) in 1,4-dioxane (20 ml) were added $Pd_2(dba)_3$ (763 mg, 0.83 mmol, 0.1 equiv) and t-BuBrettPhos (807 mg, 1.66 mmol, 0.2 equiv) at room temperature. To the above mixture was added KOH (1.4 g, 24.99 mmol, 3.0 equiv) in three portions over 2 min at room temperature. The final reaction mixture was irradiated with microwave radiation for 40 min at 80 °C. The reaction was quenched with sat. NH_4Cl (aq.) (30 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with water (3x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 98a (260 mg, 13%) as a yellow oil.

Synthesis of 98b

A solution of 98a (240 mg, 0.96 mmol, 1.0 equiv) and SeO_2 (641 mg, 5.77 mmol, 6 equiv) in 1,4-dioxane (5 ml) was stirred overnight at 120 °C. The reaction was quenched with water (30 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with water (3x20 mL) and dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=50:1) to afford 98b (200 mg, 79%) as a yellow oil.

Synthesis of 98c

[393] To a stirred solution of 98b (190 mg, 0.72 mmol, 1.0 equiv) and I-3 (264 mg, 1.08 mmol, 1.5 equiv) in DCE (3 ml) were added HOAc (43 mg, 0.72 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (458 mg, 2.16 mmol, 3.0 equiv) at room temperature. The resulting mixture

was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (20 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with water (3x10 mL) then dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 98c (170 mg, 44%) as a yellow solid.

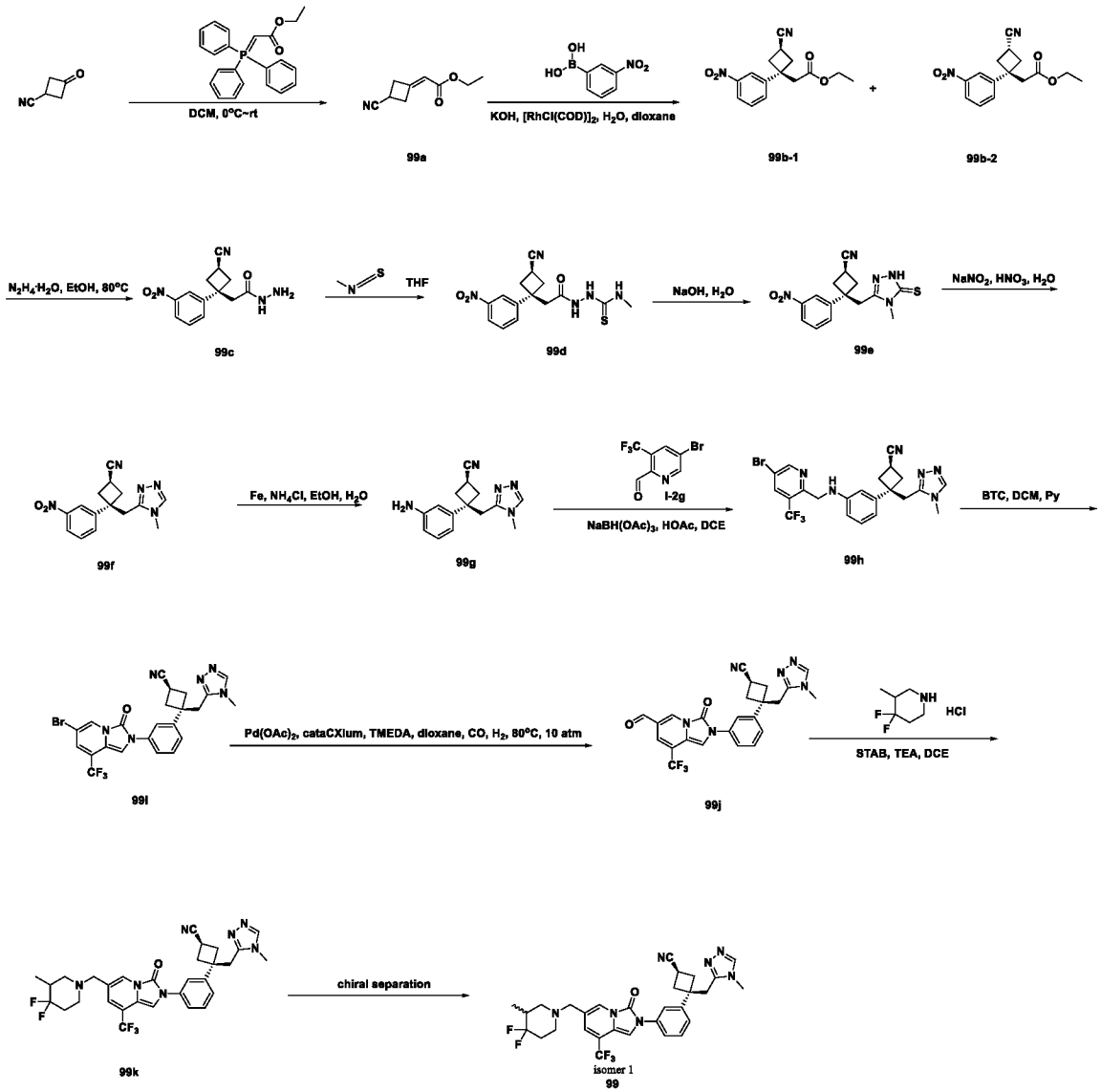
Synthesis of 98

[394] To a stirred solution of 98c (160 mg, 0.32 mmol, 1.0 equiv) and Pyridine (154 mg, 1.95 mmol, 6.0 equiv) in DCE (3 ml) was added triphosgene (34 mg, 0.11 mmol, 0.35 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The resulting mixture was washed with 3x10 mL of sat. $NaHCO_3$ (aq.) (10 ml). The resulting mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with water (3x10 mL) and dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford Compound 98 (61 mg, 35%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 518

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 1.19 (s, 6H), 2.97 (s, 3H), 3.53 (s, 2H), 3.71 (s, 2H), 4.66 (s, 1H), 4.91-4.96 (m, 4H), 6.87-6.89 (d, 1H), 6.98 (s, 1H), 7.23 (s, 1H), 7.37-7.42 (m, 3H), 7.75-7.77 (m, 1H), 8.20 (s, 1H).

Example 99. Synthesis of Compound 99



Synthesis of 99a

[395] To a stirred solution of 3-oxocyclobutane-1-carbonitrile (25 g, 262.878 mmol, 1 equiv) in DCM (500 mL) was added ethyl 2-(triphenyl-lambda5-phosphanylidene)acetate (137.37 g, 394.317 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (2x50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 99a (25 g, 57.57%) as a colorless oil.

Synthesis of 99b

[396] A mixture of Chloro(1,5-cyclooctadiene)rhodium(I) Dimer (1 g, 2.028 mmol, 0.01 equiv) in dioxane (450 mL) and KOH (151.34 mL, 227.008 mmol, 1.5 equiv, 1M) was

stirred for 1 h at room temperature under argon atmosphere. To the above mixture was added 3-nitrophenylboronic acid (50.53 g, 302.678 mmol, 2 equiv) and 99a (25 g, 151.339 mmol, 1 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1500 mL). The resulting mixture was extracted with EtOAc (2 x 2 L). The combined organic layers concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford 99b (2.1 g, 4.81%) as a light yellow solid; eluted with PE / EA (6:1) to afford 99b-2 (1.2 g, 2.75%) as a light yellow solid.

Synthesis of 99c

[397] To a stirred solution of 99b (2.1 g, 7.284 mmol, 1 equiv) in EtOH (10 mL) was added hydrazine hydrate (98%) (1.82 g, 36.420 mmol, 5 equiv). The resulting mixture was stirred overnight at 80 °C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 50mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 99c (1.3 g, 65.07%) as a light yellow solid.

Synthesis of 99d

[398] To a stirred solution of 99c (1.3 g, 4.740 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added methyl isothiocyanate (0.69 g, 9.480 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (60 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were concentrated under reduced pressure. This resulted in 99d (1.5 g, 91.10%) as a light yellow solid.

Synthesis of 99e

[399] To a stirred mixture of 99d (1.5 g, 4.318 mmol, 1 equiv) in H_2O (15 mL) was added NaOH (0.43 g, 10.751 mmol, 2.49 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The mixture was acidified to pH 4 with HCl (aq.) (1M). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. This resulted in 99e (1 g, 70.31%) as a yellow solid.

Synthesis of 99f

[400] To a stirred mixture of 99e (1 g, 3.036 mmol, 1 equiv) and $NaNO_2$ (2.09 g, 30.299 mmol, 9.98 equiv) in H_2O (10 mL) was added HNO_3 (30.36 mL, 30.360 mmol, 10 equiv, 1M) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (20 mL) at room temperature. The

resulting mixture was extracted with EtOAc (3 x40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 99f (850 mg, 94.17%) as a light yellow solid.

Synthesis of 99g

[401] To a stirred mixture of 99f (850 mg, 2.859 mmol, 1 equiv) and NH_4Cl (764.62 mg, 14.295 mmol, 5 equiv) in EtOH (20 mL) and H_2O (5 mL) was added Fe (478.96 mg, 8.577 mmol, 3 equiv). The resulting mixture was stirred for 3 h at 80 °C. The resulting mixture was diluted with water (80 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 99g (800 mg) as a yellow solid.

Synthesis of 99h

[402] To a stirred solution of 99g (800 mg, 2.992 mmol, 1 equiv), HOAc (179.70 mg, 2.992 mmol, 1 equiv) and I-2g (1140.17 mg, 4.488 mmol, 1.5 equiv) in DCE (20 mL) was added $NaBH(OAc)_3$ (1268.46 mg, 5.984 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by trituration with methyl tert-butyl ether (10 mL). This resulted in 99h (1.3 g, 85.97%) as a light yellow solid.

Synthesis of 99i

[403] To a stirred solution of 99h (1.3 g, 2.573 mmol, 1 equiv) and Pyridine (1.22 g, 15.424 mmol, 6.00 equiv) in DCM (30 mL) was added Triphosgene (0.31 g, 1.029 mmol, 0.4 equiv) at 0 °C. The resulting mixture was stirred for 30 min at 0°C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with methyl tert-butyl ether (10 mL). This resulted in 99i (1 g, 73.16%) as a yellow solid.

Synthesis of 99j

[404] To a solution of 99i (1 g, 1.882 mmol, 1 equiv) in dioxane (30 mL) and TMEDA (0.44 g, 3.764 mmol, 2 equiv) was added bis(adamantan-1-yl)(butyl)phosphane (0.13 g, 0.376 mmol, 0.2 equiv) and Pd(OAc)2 (0.04 g, 0.188 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 80 degrees C overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2

/ MeOH (20:1) to CH_2Cl_2 / MeOH (5:1) to afford 99j (550 mg, 60.83%) as a yellow solid.

Synthesis of 99k

[405] To a stirred mixture of 99j (300 mg, 0.624 mmol, 1 equiv) and 4,4-difluoro-3-methylpiperidine hydrochloride (321.49 mg, 1.872 mmol, 3 equiv) in DCE (10 mL) was added TEA (252.74 mg, 2.496 mmol, 4 equiv). The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (264.68 mg, 1.248 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of Water (10 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmoL NH_4HCO_3), 15% to 75% gradient in 30 min; detector, UV 254 nm. This resulted in 99k (100 mg, 26.71%) as a yellow solid.

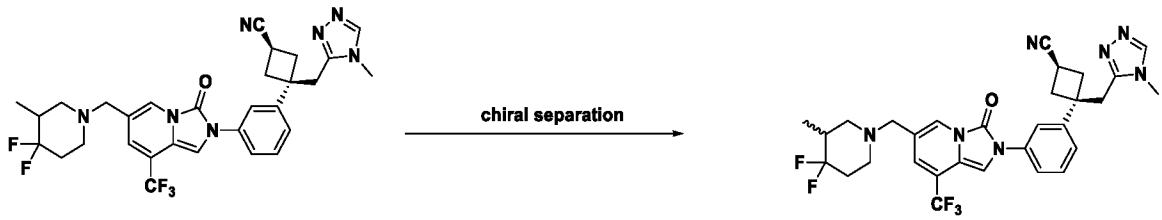
Synthesis of 99

[406] 99k (100mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH3-MEOH); Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14.5 min; Wave Length: 220/254 nm; RT1(min): 12.07, RT2(min): 13.38, the first peak is product) to afford Compound 99 (37.2 mg, 37.20%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 600

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.93-0.94 (d, 3H), δ1.90-2.21 (m, 4H), δ2.25-2.36 (m, 1H), δ2.72-2.95 (m, 9H), δ3.22-3.24 (m, 1H), δ3.35-3.36 (m, 4H), δ6.94-6.96 (d, 1H), δ7.04 (s, 1H), δ7.32-7.33 (d, 1H), δ7.40-7.45 (m, 2H), δ7.71-7.74 (m, 2H), δ8.18 (s, 1H).

Example 100. Synthesis of Compound 100



99k

isomer 2

100

Synthesis of 100

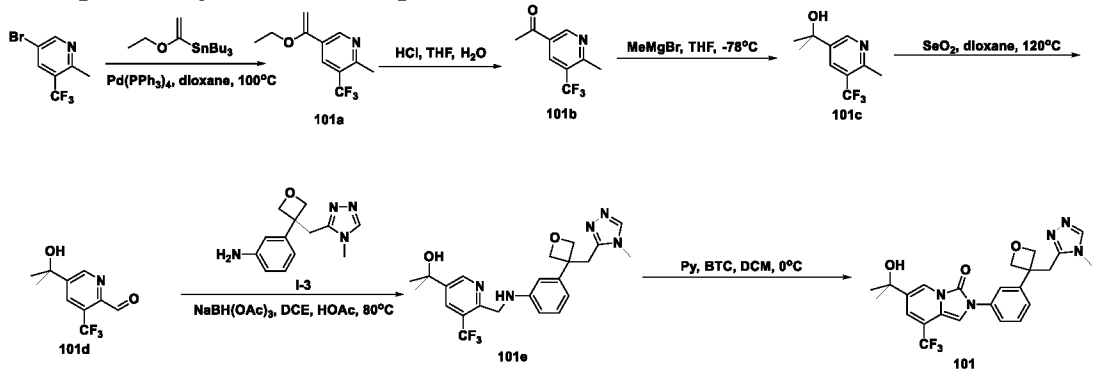
[407] 99k (100mg) was purified by chiral separation with the following conditions

(Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MEOH); Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14.5 min; Wave Length: 220/254 nm; RT1(min): 12.07, RT2(min): 13.38, the second peak is product) to afford Compound 100 (38.6 mg, 38.00%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 600

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.93-0.94 (d, 3H), δ1.90-2.20 (m, 4H), δ2.25-2.31 (m, 1H), δ2.74-2.93 (m, 9H), δ3.22-3.24 (m, 1H), δ3.32 (s, 2H), δ3.35 (s, 2H), δ6.93-6.95 (d, 1H), δ7.03 (s, 1H), δ7.33 (s, 1H), δ7.37-7.44 (m, 2H), δ7.72-7.75 (m, 2H), δ8.19 (s, 1H).

Example 101. Synthesis of Compound 101



Synthesis of 101a

[408] Into a 8 mL vial were added 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (500 mg, 2.083 mmol, 1 equiv), 1,4-dioxane (5 mL), tributyl(1-ethoxyethenyl)stannane (1504.68 mg, 4.166 mmol, 2 equiv), and $Pd(PPh_3)_4$ (240.72 mg, 0.208 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 101a (400 mg, 83.05%) as a white solid.

Synthesis of 101b

[409] Into a 8 mL vial were added 101a (400 mg, 1.730 mmol, 1 equiv), THF (2 mL), HCl (2 mL, 2M), and H_2O (2 mL) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 101b (350 mg, 99.58%) as a white solid.

Synthesis of 101c

[410] Into a 25 mL 3-necked round-bottom flask were added 101b (500 mg, 2.461 mmol, 1

equiv) and THF (5 mL) at room temperature. To the above mixture was added MeMgBr (2.7 mL, 2.707 mmol, 1.1 equiv, 1M in THF) at -78°C. The resulting mixture was stirred for additional 1 h at -78°C. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at -78°C.The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 101c (300 mg, 55.61%) as a white solid.

Synthesis of 101d

[411] Into a 8 mL vial were added 101c (300 mg, 1.369 mmol, 1 equiv), dioxane (5 mL), and SeO_2 (759.28 mg, 6.845 mmol, 5 equiv) at room temperature. The resulting mixture was stirred overnight at 110 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The residue was purified by Prep-TLC (PE / EA 1:1) to afford 101d (260 mg, 81.47%) as a white solid.

Synthesis of 101e

[412] Into a 8 mL vial were added 101d (260 mg, 1.115 mmol, 1 equiv), DCE (4 mL), I-3 (299.62 mg, 1.227 mmol, 1.1 equiv), $NaBH(OAc)_3$ (708.92 mg, 3.345 mmol, 3 equiv), and HOAc (133.91 mg, 2.230 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of water (5 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 30:1) to afford 101e (200 mg, 38.87%) as a white solid.

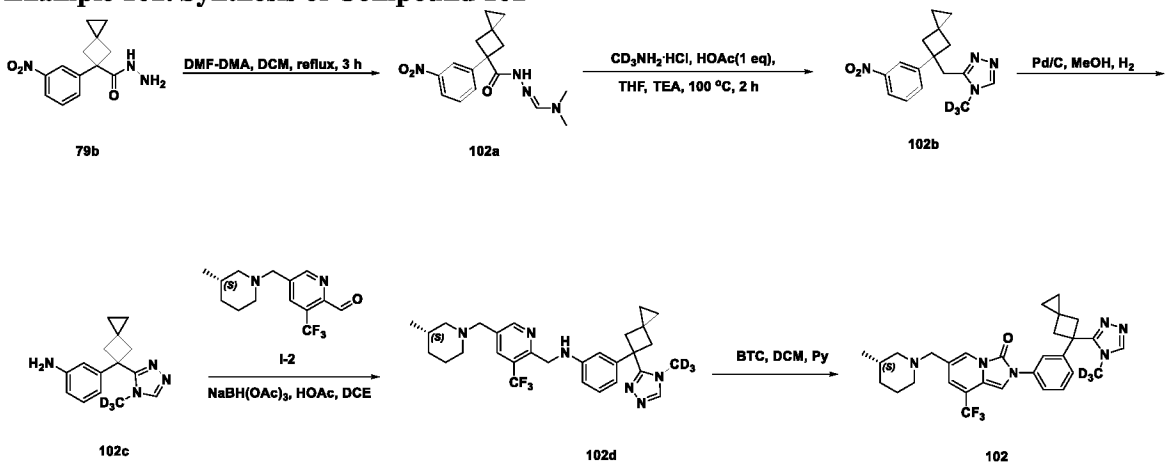
Synthesis of 101

[413] Into a 20 mL vial were added 101e (100 mg, 0.217 mmol, 1.00 equiv), DCM (2 mL) and Pyridine (85.70 mg, 1.085 mmol, 5 equiv) at 0 degrees C. To the above mixture was added BTC (22.51 mg, 0.076 mmol, 0.35 equiv) at 0 degrees C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of water (5 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: water, mobile phase B: CH_3CN, 10% B to 100% B gradient in 30 min; detector, UV 254 nm to afford Compound 101 (50.7 mg 70.02%) as a white solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 488

H-NMR: (400 MHz, DMSO-d_6, *ppm,* δ): 1.41 (s, 6H), 2.97 (s, 3H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 5.29 (s, 1H), 6.89-6.91 (d, 1H), 7.20 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.65 (s, 1H), 7.75-7.77 (m, 1H), 8.20 (s, 1H).

Example 102. Synthesis of Compound 102



Synthesis of 102a

[414] Into a 100 mL round-bottom flask were added 79b (3 g, 11.482 mmol, 1 equiv) and DMF-DMA (2.74 g, 22.964 mmol, 2 equiv) in DCM (50 mL) at room temperature. The resulting mixture was stirred for 8 h at 50°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to afford 102a (3 g, 75.98%) as a white solid.

Synthesis of 102b

[415] Into a 100 mL 3-necked round-bottom flask were added Methyl-d3-amine hydrochloride (2.23 g, 31.610 mmol, 5 equiv) and TEA (1.92 g, 18.966 mmol, 3 equiv) in THF (50 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture were added 102a (2 g, 6.322 mmol, 1 equiv) and HOAc (0.38 g, 6.322 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 days at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was diluted with water (150 mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to 102b (500 mg, 24.67%) as a white solid.

Synthesis of 102c

[416] To a solution of 102b (500 mg, 1.659 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (50 mg) under nitrogen atmosphere in a 50 round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 102c (200 mg) as a yellow solid.

Synthesis of 102d

[417] To a stirred solution of 102c (180 mg, 0.699 mmol, 1 equiv) and I-2 (200.24 mg, 0.699 mmol, 1 equiv) in DCE (5 mL) were added HOAc (42.00 mg, 0.699 mmol, 1 equiv) and $NaBH(OAc)_3$ (222.35 mg, 1.048 mmol, 1.5 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 102d (276 mg, 74.79%) as a white solid.

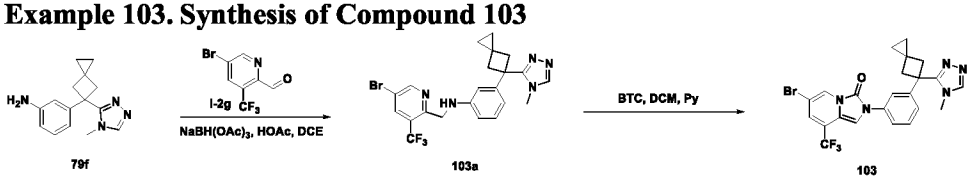
Synthesis of 102

[418] To a stirred solution of 102d (256 mg, 0.485 mmol, 1 equiv) and Pyridine (230.26 mg, 2.910 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (57.59 mg, 0.194 mmol, 0.4 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 102 (147.2 mg, 54.80%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 554

H-NMR: (400 MHz, DMSO-d6, ppm): δ 0.44-0.59 (m, 4H), δ0.75-0.93 (m, 4H), δ1.43-1.66 (m, 5H), δ1.87-1.91 (m, 1H), δ2.67-2.78 (m, 4H), δ3.17-3.25 (m, 4H), δ7.00(s, 1H), δ7.17-7.19 (d, 1H), δ7.30-7.53 (m, 2H), δ7.63-7.67 (m, 2H), δ7.83-7.84 (d, 1H), δ8.40 (s, 1H).

Example 103. Synthesis of Compound 103



Synthesis of 103a

[419] To a stirred mixture of 79f (200 mg, 0.786 mmol, 1 equiv) and I-2g (239.69 mg, 0.943 mmol, 1.2 equiv) in DCE (2 mL) were added HOAc (47.22 mg, 0.786 mmol, 1 equiv) and $NaBH(OAc)_3$ (499.98 mg, 2.358 mmol, 3 equiv) at room temperature. The resulting mixture

was stirred overnight at room temperature. The reaction was quenched by the addition of H_2O (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 103a (230 mg, 55.25%) as a yellow solid.

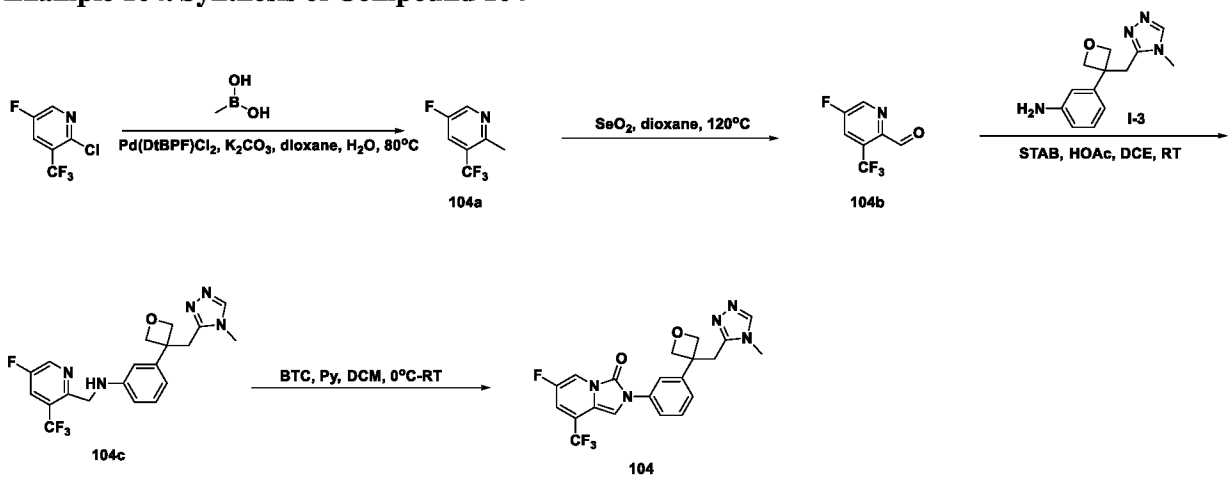
Synthesis of 103

To a stirred solution of 103a (210 mg, 0.427 mmol, 1.00 equiv) and pyridine (202.43 mg, 2.562 mmol, 6 equiv) in DCM (5 mL) was added triphosgene (44.30 mg, 0.149 mmol, 0.35 equiv) at 0 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford Compound 103 (107.4 mg, 48.29%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 518.

H-NMR: (400 MHz, DMSO-d_6, ppm) δ0.44-0.58 (m, 4H), 2.74-2.78 (d, 2H), 3.16-3.23 (m, 5H), 7.16-7.21 (m, 2H), 7.21-7.53 (m, 2H), 7.62-7.64 (d, 1H), 7.82 (s, 1H), 8.04 (s, 1H), 8.39 (s, 1H).

Example 104. Synthesis of Compound 104



Synthesis of 104a

[420] To a stirred solution of 2-chloro-5-fluoro-3-(trifluoromethyl)pyridine (1 g, 5.012 mmol, 1.00 equiv) and methylboronic acid (0.90 g, 15.036 mmol, 3 equiv) in dioxane (20 mL) was added K_2CO_3 (1.39 g, 10.024 mmol, 2 equiv), H_2O (4 mL), and Pd(DtBPF)Cl_2 (0.33 g, 0.501 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C under nitrogen atmosphere. The

residue was purified by silica gel column chromatography, eluted with PE to afford 104a (10 mL, product in dioxane) as a light yellow liquid.

Synthesis of 104b

To a stirred solution of 104a (product in dioxane) (10 mL) was added SeO_2 (3.10 g, 27.910 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 120 degrees C. The residue was purified by silica gel column chromatography, eluted with PE to afford 104b (80 mg, 12.62%) as a light yellow oil.

Synthesis of 104c

To a stirred solution of 104b (70 mg, 0.363 mmol, 1.00 equiv) and I-3 (88.56 mg, 0.363 mmol, 1 equiv) in DCE (5 mL) was added STAB (230.49 mg, 1.089 mmol, 3 equiv) and HOAc (21.77 mg, 0.363 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 104c (60 mg, 35.74%) as a light yellow oil.

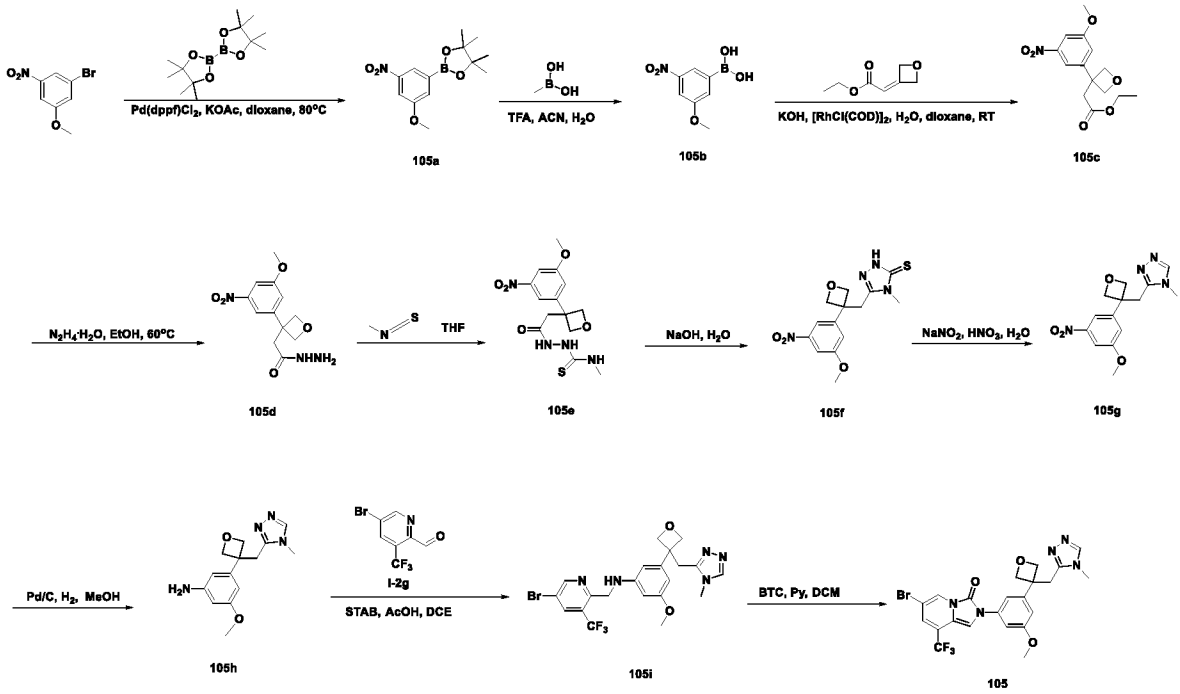
Synthesis of 104

[421] To a stirred solution of 104c (50 mg, 0.119 mmol, 1.00 equiv) and Pyridine (187.71 mg, 2.380 mmol, 20 equiv) in DCM (10 mL) was added Triphosgene (35.21 mg, 0.119 mmol, 1 equiv) at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford Compound 104 (17.7 mg, 32.68%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 448

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 2.96 (s, 3H), 3.66 (s, 3H), 5.10(s, 4H), 6.90-9.92 (d, 1H), 7.14-7.16 (m, 1H), 7.25 (s, 1H), 7.31-7.32 (d, 1H), 7.45-7.49 (m, 1H), 7.61-7.74 (m, 1H), 7.77-7.78 (d, 1H), 8.20 (s, 1H).

Example 105. Synthesis of Compound 105



Synthesis of 105a

[422] Into a 500 mL 3-necked round-bottom flask were added 1-bromo-3-methoxy-5-nitrobenzene (20 g, 86.195 mmol, 1 equiv), dioxane (200 mL), KOAc (16.92 g, 172.390 mmol, 2 equiv), bis(pinacolato)diboron (43.78 g, 172.390 mmol, 2 equiv), and $Pd(dppf)Cl_2$ (1.26 g, 1.722 mmol, 0.02 equiv) at room temperature. The resulting mixture was stirred for 12 h at 80°C under nitrogen atmosphere. The reaction was diluted with water (600 mL). The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with water (3x10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 105a (25 g, 98.72%) as a light yellow solid.

Synthesis of 105b

[423] Into a 500 mL 3-necked round-bottom flask were added 105a (17 g, 60.910 mmol, 1 equiv), MeCN (200 mL), H_2O (20 mL), HCl (20 mL, 12 M) and methylboronic acid (18.23 g, 304.550 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 12 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 105b (10 g, 80.03%) as a white solid.

Synthesis of 105c

[424] To a solution of Chloro(1,5-cyclooctadiene)rhodium(I) Dimer (1.25 g, 2.539 mmol,

0.05 equiv) in dioxane (150 mL) was added KOH (61 mL, 60.929 mmol, 1.2 equiv, 1 M) at room temperature under nitrogen atmosphere. The mixture was stirred for 30 min. 105b (10 g, 50.774 mmol, 1 equiv) and ethyl 2-(oxetan-3-ylidene)acetate (7.22 g, 50.774 mmol, 1 equiv) were added and the mixture was stirred at room temperature for 12 h under nitrogen atmosphere. The reaction mixture was quenched with NH_4Cl (aq.) (300 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 105c (5.9 g, 37.78%) as a light yellow solid.

Synthesis of 105d

[425] Into a 250 mL 3-necked round-bottom flask were added 105c (4.8 g, 16.255 mmol, 1 equiv), EtOH (50 mL), and hydrazine (8.12 g, 162.550 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 12 h at 80°C. The resulting mixture was diluted with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 105d (4.8 g, 100.79%) as a light yellow oil.

Synthesis of 105e

[426] Into a 250 mL 3-necked round-bottom flask were added 105d (4.8 g, 17.066 mmol, 1 equiv), tetrahydrofuran (50 mL), and methyl isothiocyanate (3.12 g, 42.665 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred for 12 h at room temperature under nitrogen atmosphere. The reaction was quenched with water (150 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3x10 mL). The resulting solid was dried under vacuum. This resulted in 105e (5.3 g, 81.50%) as a white solid.

Synthesis of 105f

[427] To a stirred mixture of 105e (5.3 g, 14.956 mmol, 1 equiv) in H_2O (110 mL) was added NaOH (4.79 g, 119.648 mmol, 8 equiv). The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 4 with HCl (aq, 1M). The precipitated solids were collected by filtration and washed with water (3x15 mL) to afford 105f (7 g, crude) as a yellow solid.

Synthesis of 105g

[428] To a stirred mixture of 105f (6.9 g, 20.513 mmol, 1 equiv) and $NaNO_2$ (14.15 g, 205.130 mmol, 10 equiv) in H_2O (70 mL) was added HNO_3 (205 mL, 205.130 mmol, 10 equiv) dropwise at 0°C. The resulting mixture was stirred for 1h at 0°C. The reaction was

quenched with $NaHCO_3$(aq) (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x200 mL). The resulting mixture was concentrated under reduced pressure to afford 105g (3.3 g, 49.16%) as a yellow solid.

Synthesis of 105h

[429] To a solution of 105g (3.2 g, 10.516 mmol, 1 equiv) in 100mL MeOH was added Pd/C (10%, 300 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 105h (2.5 g, 78.00%) as a yellow solid.

Synthesis of 105i

[430] To a stirred solution of 105h (600 mg, 2.187 mmol, 1 equiv) and I-2g (833.34 mg, 3.280 mmol, 1.5 equiv) in DCE (6 mL) were added STAB (927.11 mg, 4.374 mmol, 2 equiv) and AcOH (131.35 mg, 2.187 mmol, 1 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 105i (626 mg, 51.95%) as a yellow solid.

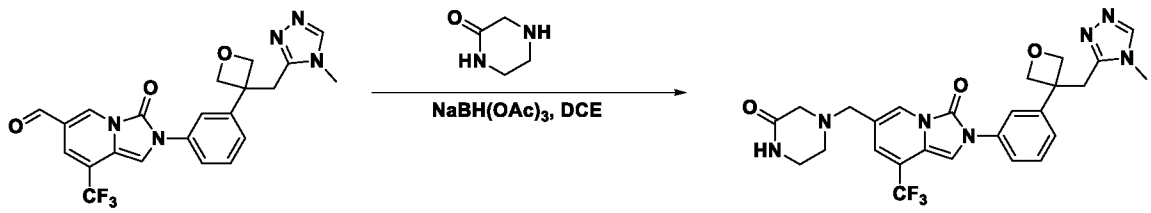
Synthesis of 105

[431] To a stirred solution of 105i (620 mg, 1.210 mmol, 1 equiv) and Pyridine (574.34 mg, 7.260 mmol, 6 equiv) in DCM (20 mL) was added Triphosgene (143.64 mg, 0.484 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 105 (460 mg, 70.61%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 538

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ2.97 (s, 3H), δ3.52 (s, 2H), δ3.71 (s, 2H), δ4.88-4.93 (m, 4H), δ6.40-6.41 (d, 1H), δ7.02 (s, 1H), δ7.17 (s, 1H), δ7.32-7.34(d, 1H), δ7.45 (s, 1H), δ8.02 (s, 1H), δ8.21 (s, 1H).

Example 106. Synthesis of Compound 106



10d 106

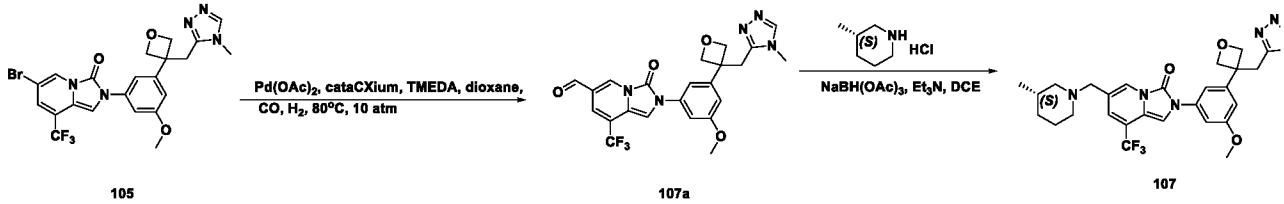
Synthesis of 106

[432] To a stirred solution of 10d (150 mg, 0.328 mmol, 1.00 equiv) and piperazin-2-one (98.50 mg, 0.984 mmol, 3 equiv) in DCE (2 mL) were added HOAc (19.69 mg, 0.328 mmol, 1 equiv) and $NaBH(OAc)_3$ (139.00 mg, 0.656 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 36% B in 8 min, Wave Length: 220 nm; RT1(min): 7.90) to afford Compound 106 as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542

H-NMR: (400 MHz, DMSO-d6, ppm): δ 2.67-2.68 (m, 2H), δ2.86-3.02 (m, 5H), δ3.10-3.16 (m, 2H), δ3.43 (s, 2H), δ3.53 (s, 2H), δ4.87-4.96 (m, 4H), δ6.88-6.90(m, 1H), δ7.04 (s, 1H), δ7.33 (s, 1H), δ7.38-7.42 (m, 2H), δ7.74-7.77 (m, 3H), δ8.20 (s, 1H).

Example 107. Synthesis of Compound 107



105 107a 107

Synthesis of 107a

[433] To a solution of 105 (3 g, 5.573 mmol, 1 equiv) and TMEDA (1.30 g, 11.146 mmol, 2 equiv) in dioxane (90 mL) was added bis(adamantan-1-yl)(butyl)phosphane (0.40 g, 1.115 mmol, 0.2 equiv) and $Pd(OAc)_2$ (0.13 g, 0.557 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 80 degrees C overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to CH_2Cl_2 / MeOH (5:1) to afford 107a (1.5 g, 55.22%) as a yellow solid.

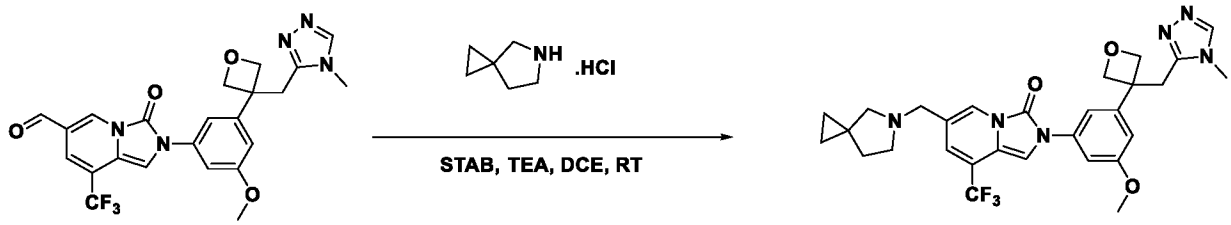
Synthesis of 107

[434] To a stirred mixture of 107a (200 mg, 0.410 mmol, 1 equiv) and (3S)-3-methylpiperidine hydrochloride (166.96 mg, 1.230 mmol, 3 equiv) in DCE (10 mL) was added Et_3N (166.08 mg, 1.640 mmol, 4 equiv) and $NaBH(OAc)_3$ (173.92 mg, 0.820 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 107 (64.1 mg, 27.38%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 414

H-NMR: (400 MHz, DMSO-d6, ppm): δ0.82-0.86 (m, 4H), δ1.46-1.58 (m, 1H), δ1.62-1.66 (m, 4H), δ1.87-1.92 (m, 1H), δ2.72-2.77 (m, 2H), δ2.99 (s, 3H), δ3.25 (s, 2H), δ3.52 (s, 2H), δ3.71 (s, 3H), δ4.89-4.94 (m, 4H), δ6.40 (s, 1H), δ7.01 (s, 2H), δ7.33 (s, 1H), δ7.37-7.37 (d, 1H), δ7.64 (s, 1H), δ8.22 (s, 1H).

Example 108. Synthesis of Compound 108



107a 108

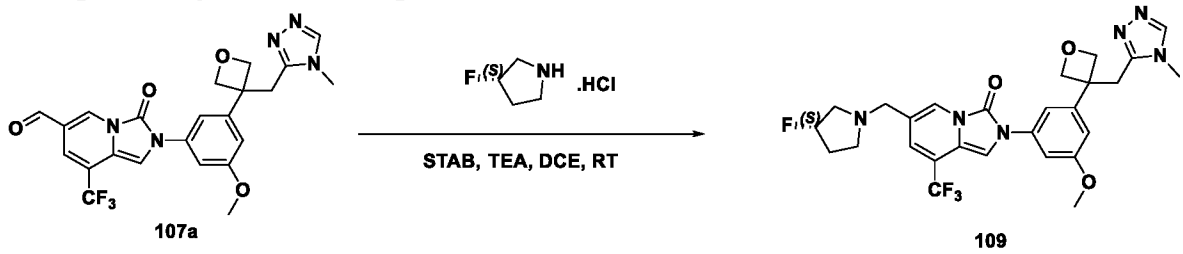
Synthesis of 108

[435] To a stirred solution of 107a (150 mg, 0.308 mmol, 1.00 equiv) and 5-azaspiro[2.4]heptane hydrochloride (123.36 mg, 0.924 mmol, 3 equiv) in DCE (5 mL) was added TEA (93.42 mg, 0.924 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (130.44 mg, 0.616 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: water (10 mmol/L $NaHCO_3$), mobile phase B: MeCN, 0%B to 50%B gradient in 15 min; detector, UV 254 nm. This resulted in Compound 108 (31.3 mg, 17.33%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 569

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 0.57-0.64 (m, 4H), 1.88-1.91 (m, 2H), 2.58 (s, 2H), 2.81-2.84 (m, 2H), 3.01 (s, 3H), 3.50 (s, 2H), 3.69 (s, 2H), 3.78 (s, 3H), 5.06 (s, 4H), 6.38 (m, 1H), 6.85-6.86 (m, 1H), 7.11 (s, 1H), 7.12-7.16 (m, 1H), 7.25-7.26 (m, 1H), 7.71(s, 1H), 8.23 (s, 1H).

Example 109. Synthesis of Compound 109



107a 109

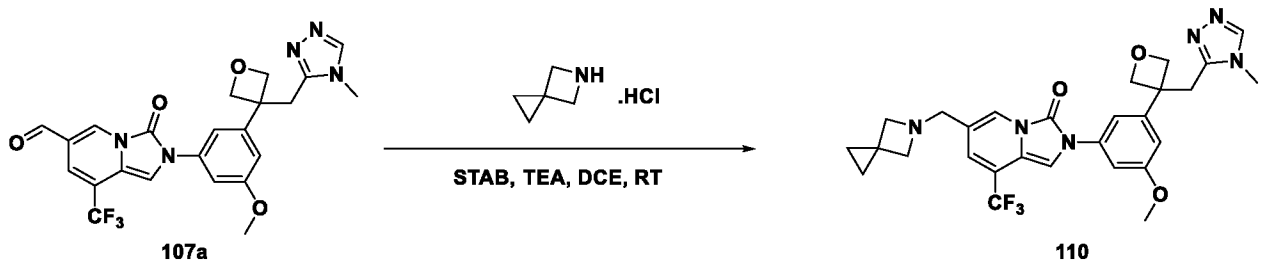
Synthesis of 109

[436] To a stirred solution of 107a (150 mg, 0.308 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (115.93 mg, 0.924 mmol, 3 equiv) in DCE (5 mL) were added TEA (93.42 mg, 0.924 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (130.44 mg, 0.616 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 7 min, Wave Length: 220 nm; RT1(min): 6.70) to afford 109 (33.7 mg, 19.24%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 561

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 1.99-2.11 (m, 1H), 2.18-2.25 (m, 1H), 2.47-2.51 (m, 1H), 2.69-2.81 (m, 1H), 2.89-2.98 (m, 2H), 3.01 (s, 3H), 3.51 (s, 2H), 3.66 (s, 2H), 3.78 (s, 3H), 5.06 (s, 4H), 5.12-5.26 (m, 1H), 6.38 (s, 1H), 6.85-6.86 (m, 1H), 7.11-7.13 (m, 2H), 7.25-7.26 (m, 1H), 7.70(s, 1H), 8.23 (s, 1H).

Example 110. Synthesis of Compound 110



107a 110

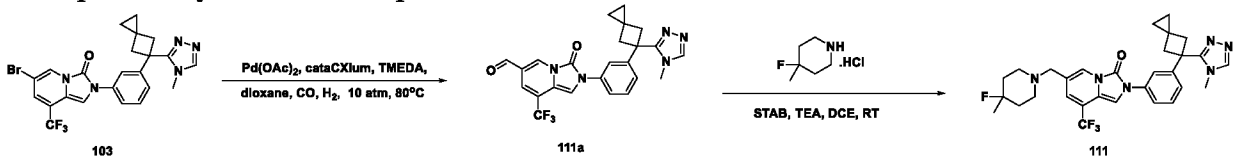
Synthesis of 110

[437] To a stirred solution of 107a (200 mg, 0.410 mmol, 1.00 equiv) and 5-azaspiro[2.3]hexane hydrochloride (147.21 mg, 1.230 mmol, 3 equiv) in DCE (5 mL) were added TEA (124.56 mg, 1.230 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (173.92 mg, 0.820 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Gradient: 0% B to 50% B in 15 min; detector, UV 254 nm. This resulted in Compound 110 (95.0 mg, 40.87%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 555

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 0.61 (s, 4H), 3.01 (s, 3H), 3.46 (s, 4H), 3.50 (s, 2H), 3.66 (s, 2H), 3.78 (s, 3H), 5.06 (s, 4H), 6.38-6.39 (m, 1H), 6.85-6.86 (m, 1H), 7.07 (s, 1H), 7.13 (s, 1H), 7.25-7.26 (m, 1H), 7.71 (s, 1H), 8.23 (s, 1H).

Example 111. Synthesis of Compound 111



103 111a 111

Synthesis of 111a

[438] To a mixture of 103 (4 g, 7.717 mmol, 1 equiv) in 400 mL dioxane was added bis(adamantan-1-yl)(butyl)phosphane (0.55 g, 1.543 mmol, 0.2 equiv), $Pd(AcO)_2$ (0.17 g, 0.772 mmol, 0.1 equiv), TMEDA (1.79 g, 15.434 mmol, 2 equiv) in a pressure tank. The mixture was purged with nitrogen and then was pressurized to 10 atm with CO : H_2 =1:1 and heated to 80 °C overnight. The reaction mixture was cooled to room temperature. The

reaction was diluted with H_2O (1500 mL) at room temperature. The aqueous layer was extracted with EA (3x500 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=50:1 to afford 111a (2.0 g, 55.44%) as a yellow solid.

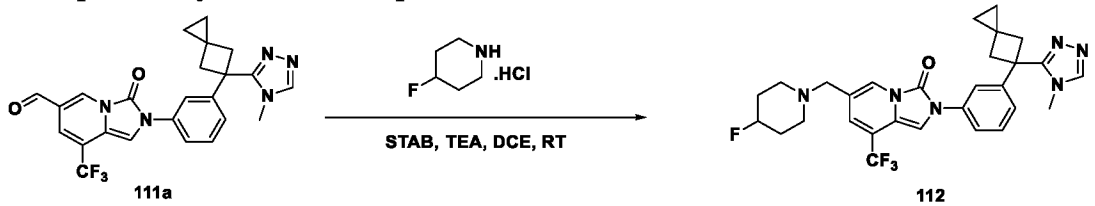
Synthesis of 111

[439] To a stirred mixture of 111a (250 mg, 0.535 mmol, 1 equiv) and 4-fluoro-4-methylpiperidine hydrochloride (246.49 mg, 1.605 mmol, 3 equiv) in DCE (3.00 mL) were added TEA (162.35 mg, 1.605 mmol, 3 equiv) and $NaBH(OAc)_3$ (226.70 mg, 1.070 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 111 (250 mg, crude). The crude product (250 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 58% B in 8 min; Wave Length: 220 nm; RT1(min): 7.72) to afford Compound 111 (79 mg, 25.98%) as yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 569

H-NMR: (400 MHz, DMSO, δ ppm): 0.44-0.55 (m, 2H), 0.56-0.59 (t, 2H), 1.29-1.34 (d, 3H), 1.61-1.74 (m, 4H), 2.24-2.33 (m, 2H), 2.60-2.67 (m, 2H), 2.75-2.78 (d, 2H), 3.17 (s, 2H), 3.20-3.24 (d, 3H), 3.32-3.35 (m, 2H), 6.99(s, 1H), 7.10 (s, 1H), 7.18-7.20 (d, 1H), 7.35 (s, 1H), 7.49-7.53 (t, 1H), 7.63-7.69 (t, 1H), 7.83 (s, 1H), 8.39(s, 1H).

Example 112. Synthesis of Compound 112



Synthesis of 112

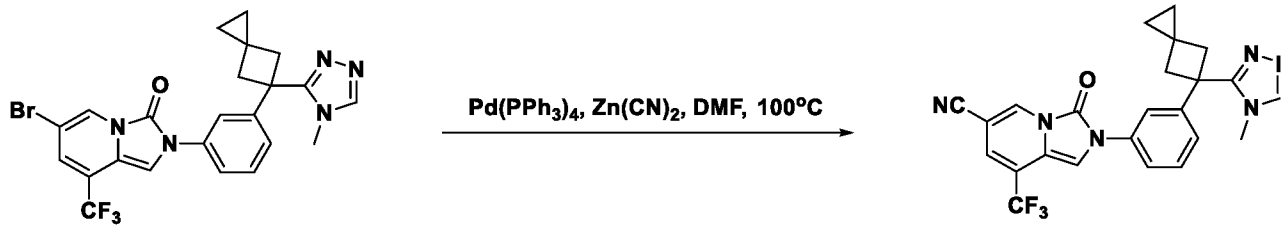
[440] To a stirred solution of 111a (250 mg, 0.535 mmol, 1.00 equiv) and 4-fluoropiperidine hydrochloride (223.98 mg, 1.605 mmol, 3 equiv) in DCE (5 mL) was added TEA (162.35 mg, 1.605 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (226.70 mg, 1.070

mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford the crude product. The crude product (260 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 57% B in 8 min, Wave Length: 220 nm; RT1(min): 7.62) to afford Compound 112 (130.7 mg, 43.89%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 555

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 0.53-0.57 (m, 2H), 0.63-0.67 (m, 2H), 1.84-2.05 (m, 4H), 2.47-2.53 (m, 2H), 2.65-2.73 (m, 2H), 2.81-2.90 (m, 2H), 3.22-3.29 (m, 2H), 3.32 (s, 3H), 3.33 (s, 2H), 4.59-4.80 (m, 1H), 7.11-7.15 (m, 2H), 7.30-7.33 (m, 1H), 7.54-7.62 (m, 2H), 7.68 (s, 1H), 7.84 (s, 1H), 8.41 (s, 1H).

Example 113. Synthesis of Compound 113



103 113

Synthesis of 113

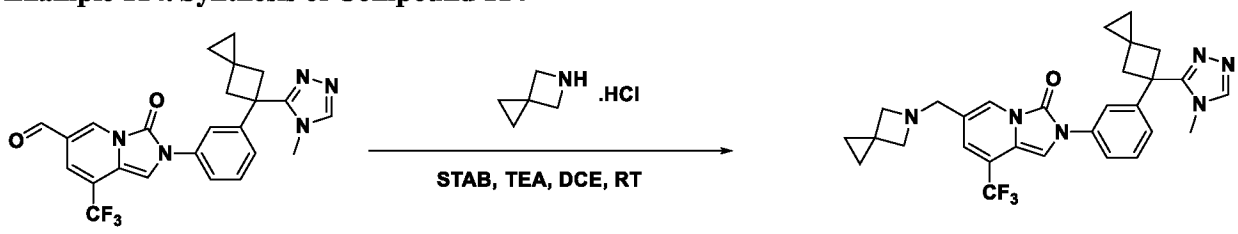
[441] To a stirred mixture of 103 (600 mg, 1.158 mmol, 1.00 equiv) and $Zn(CN)_2$ (271.89 mg, 2.316 mmol, 2 equiv) in dioxane (6 mL) was added $Pd(PPh_3)_4$ (133.76 mg, 0.116 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 100 degrees C under nitrogen atmosphere. The reaction was quenched by the addition of saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (4x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 113 (400 mg) as a yellow solid. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: SunFire C18 OBD Prep Column, 19*250 mm, 5μm; Mobile Phase A: water (0.1 % FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 42% B to 52% B in 8 min, Wave Length: 254; 220 nm; RT1 (min): 7.53) to afford Compound 113 (143.0 mg, 26.6%) as a

yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 465.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ0.47-0.49 (m, 2H), 0.55-0.59 (m, 2H), 2.75-2.78 (d, 2H), 3.17-3.23 (m, 5H), 7.22-7.27 (m, 2H), 7.51-7.55 (m, 2H), 7.61-7.64 (d, 1H), 7.79 (s, 1H), 8.39 (s, 1H), 8.70 (s, 1H).

Example 114. Synthesis of Compound 114



111a 114

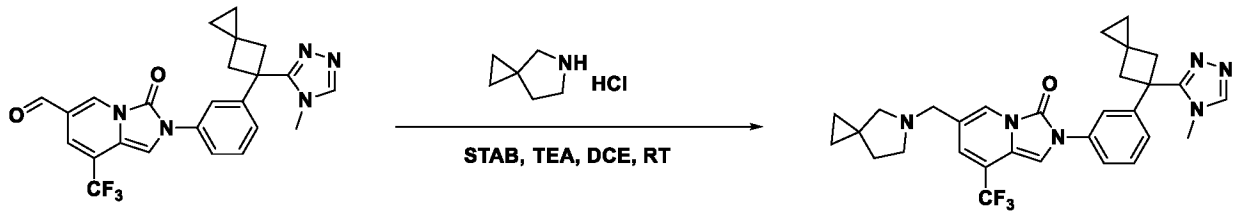
Synthesis of 114

[442] To a stirred mixture of 111a (400 mg, 0.856 mmol, 1.00 equiv) and 5-azaspiro[2.3]hexane hydrochloride (307.00 mg, 2.568 mmol, 3 equiv) in DCE (5 mL) were added Et_3N (259.77 mg, 2.568 mmol, 3 equiv) and STAB (362.72 mg, 1.712 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 114 (150 mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 56% B in 8 min; Wave Length: 254/220 nm; RT1(min): 7.75) to afford Compound 114 (57.1 mg, 12.48%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 535

H-NMR: (400 MHz, DMSO, δ ppm): 0.45-0.50 (m, 6H), 0.55-0.59 (m, 2H), 2.75-2.78 (d, 2H), 3.17-3.24 (t, 2H), 3.28-3.32 (m, 3H), 3.33-3.44 (m, 4H), 3.45 (s, 2H), 7.00 (s, 1H), 7.17-7.19 (d, 1H), 7.34 (s, 1H), 7.48-7.52 (m, 1H), 7.53-7.56 (m, 1H), 7.63-7.68 (t, 1H), 7.84 (s, 1H), 8.39 (s, 1H).

Example 115. Synthesis of Compound 115



111a 115

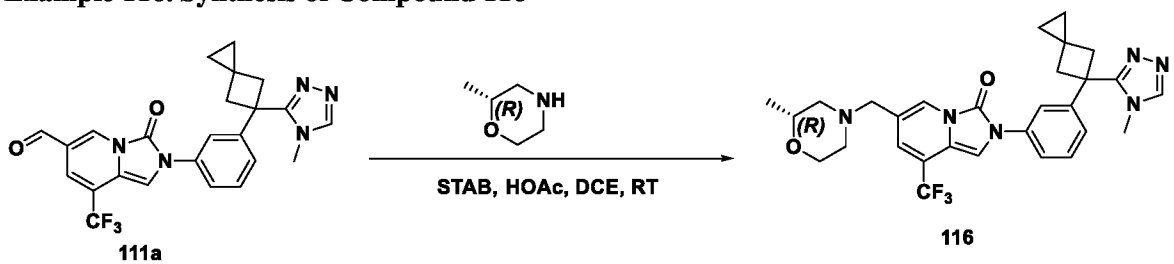
Synthesis of 115

[443] To a stirred mixture of 111a (600 mg, 1.284 mmol, 1.00 equiv) and 5-azaspiro[2.4]heptane hydrochloride (187.07 mg, 1.926 mmol, 1.5 equiv) in DCE (6 mL) was added TEA (259.77 mg, 2.568 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (816.11 mg, 3.852 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 115 as a yellow solid. The crude product (120 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 58% B in 8 min, Wave Length: 220 nm; RT1(min): 7.7;) to afford Compound 115 (95.2 mg, 13.52%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 549.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ0.55-0.59 (m, 8H), 1.73-1.77 (m, 2H), 2.46 (s, 2H), 2.67-2.68 (m, 2H), 2.70-2.76 (m, 2H), 3.17-3.20 (m, 2H), 3.24 (s, 3H), 3.40 (s, 2H), 7.04 (s, 1H), 7.18-7.20 (m, 1H), 7.35 (s, 1H), 7.48-7.52 (m, 1H), 7.63-7.65 (m, 1H), 7.69 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 116. Synthesis of Compound 116



111a 116

Synthesis of 116

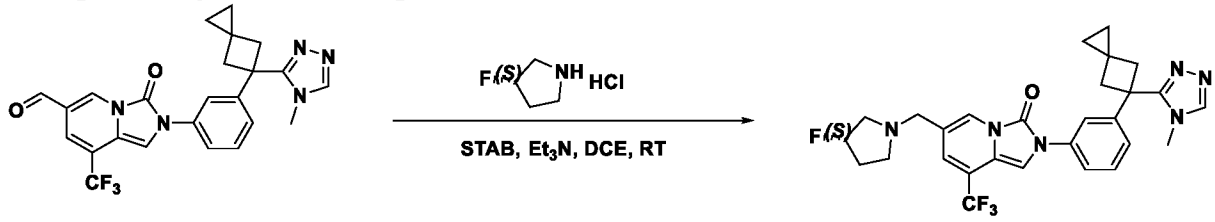
[444] To a stirred solution of 111a (10 mg, 0.021 mmol, 1.00 equiv) and (2R)-2-methylmorpholine (3.25 mg, 0.032 mmol, 1.5 equiv) in DCE (9 mL) were added TEA (4.33

mg, 0.042 mmol, 2 equiv) and STAB (13.60 mg, 0.063 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 116 as a yellow solid. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 8 min, Wave Length: 220 nm; RT1 (min): 7.42) to afford Compound 116 (129.5 mg, 12.17%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 553.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ0.45-0.49 (m, 2H), 0.55-0.57 (m, 2H), 1.03-1.05 (d, 3H),1.74-1.74 (m, 1H), 2.04-2.08 (m, 1H), 2.53-2.68 (m, 1H), 2.72-2.78 (m, 3H), 3.17-3.24 (m, 2H), 3.27 (s, 3H), 3.28-3.32 (m, 2H), 3.48-3.51 (m, 2H), 3.72-3.75 (m, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.35 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.65 (m, 1H), 7.65 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 117. Synthesis of Compound 117



111a 117

Synthesis of 117

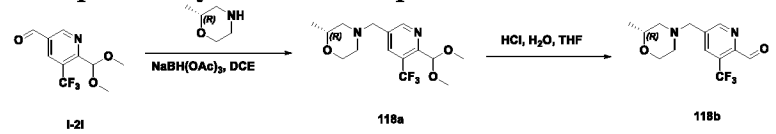
[445] To a stirred mixture of 111a (450 mg, 0.963 mmol, 1.00 equiv) and (S)-3-fluoropyrrolidine hydrochloride (128.68 mg, 1.444 mmol, 1.5 equiv) in DCE (5 mL) was added Et_3N (291.78 mg, 2.889 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (612.08 mg, 2.889 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford 117 (150 mg) as a yellow solid. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column,

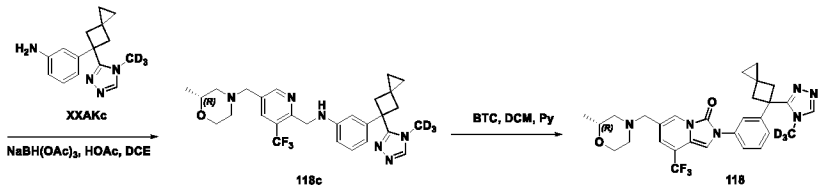
30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 50% B in 11 min, Wave Length: 220 nm; RT1 (min): 10.83) to afford Compound 117 (81.8 mg, 15.72%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 541.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ0.45-0.49 (m, 2H), 0.55-0.59 (m, 2H), 1.78-2.00 (m, 1H), 2.01-2.25 (m, 1H), 2.34-2.36 (m, 1H), 2.59-2.71 (m, 1H), 2.75-2.83 (m, 4H), 3.17-3.20 (m, 2H), 3.28 (s, 3H), 3.43 (s, 2H), 5.14-5.28 (m, 1H), 7.03 (s, 1H), 7.18-7.20 (d, 1H), 7.36 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.66 (m, 1H), 7.72 (s, 1H), 7.84 (s, 1H), 8.39 (s, 1H).

Example 118. Synthesis of Compound 118





Synthesis of 118a

[446] Into a 25 mL vial were added I-2i (350 mg, 1.405 mmol, 1 equiv), DCE (5 mL), and (2R)-2-methylmorpholine (170.48 mg, 1.686 mmol, 1.2 equiv) at room temperature. To the above mixture was added STAB (595.37 mg, 2.810 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 118a (300 mg, 58.77%) as a brown oil.

Synthesis of 118b

[447] Into a 25 mL vial were added 118a (300 mg, 0.897 mmol, 1 equiv) and THF (2 mL) at room temperature. To the above mixture was added HCl (5 mL, 1mol/L) dropwise at room temperature. The resulting mixture was stirred for 2 h at 80°C. The residue was neutralized to pH 7 with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 5:1) to afford 118b (220 mg, 79.10%) as a brown oil.

Synthesis of 118c

[448] To a stirred solution of 102c (200 mg, 0.777 mmol, 1 equiv) and 118b (224.03 mg, 0.777 mmol, 1 equiv) in DCE (5 mL) were added HOAc (46.67 mg, 0.777 mmol, 1 equiv) and $NaBH(OAc)_3$ (329.41 mg, 1.554 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 118c (270 mg, 65.60%) as a white solid.

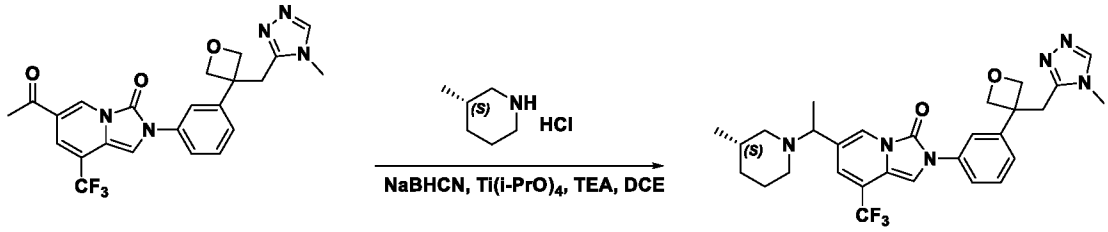
Synthesis of 118

[449] To a stirred solution of 118c (260 mg, 0.491 mmol, 1 equiv) and Pyridine, 6 equiv) in DCM (10 mL) were added Triphosgene (58.27 mg, 0.196 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 1 h at 0°C.The reaction was quenched by the addition of sat. NH_4Cl (aq.) (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford Compound 118 (162.9 mg, 59.72%) as a yellow solid.

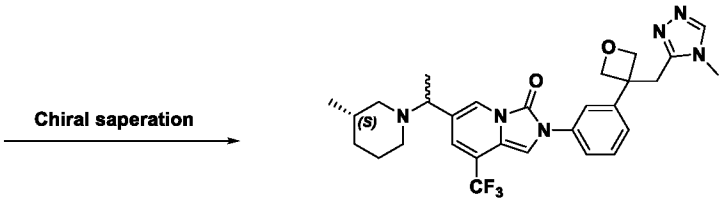
LC-MS: (ES, *m/z*): $[M+H]^+$ 577

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.49-0.59 (m, 4H), δ1.03-1.05 (d, 3H), δ1.72-1.77 (m, 1H), δ2.06-2.12 (m, 1H), δ2.65-2.78 (m, 4H), δ3.17-3.20 (m, 2H), 3.20-3.28 (m, 2H), 3.46-3.56 (m, 2H), 3.73-3.76 (m, 1H), δ7.02(s, 1H), δ7.19-7.20 (d, 1H), δ7.36 (s, 1H), δ7.49-7.53 (m, 1H), δ7.63-7.65 (d, 1H), δ7.70 (s, 1H), δ7.83 (s, 1H), δ8.40 (s, 1H).

Example 119. Synthesis of Compound 119



19 119a



isomer 1

119

Synthesis of 119a

[450] To a stirred mixture of 19 (1 g, 2.121 mmol, 1 equiv) and (S)-3-METHYLPIPERIDINE HYDROCHLORIDE (1.44 g, 10.605 mmol, 5 equiv) TEA (2.15 g, 21.210 mmol, 10 equiv) in THF (30 mL) was added Ti(Oi-Pr)4 (3.01 g, 10.605 mmol, 5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 60 °C. To the above mixture was added $NaBH_3CN$ (0.27 g, 4.296 mmol, 2.03 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water (10 mmoL/L NH_4HCO_3), 10% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in 119a (350 mg, 29.75%) as a yellow solid.

Synthesis of 119

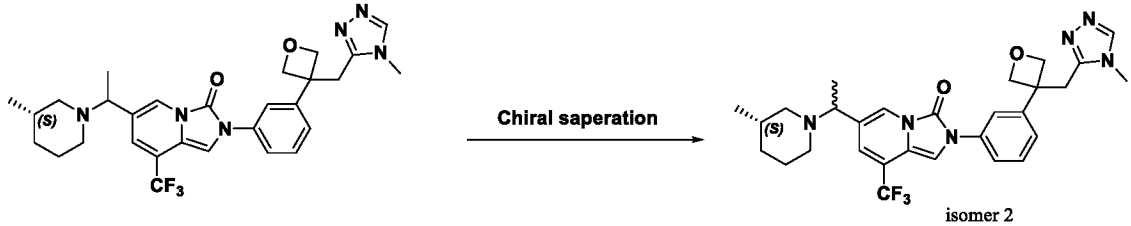
[451] 119a (350 mg) was purified by chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 15.5 min; Wave Length: 220/254 nm; RT1(min): 10.51, RT2(min): 12.60, the first

peak is product) to afford Compound 119 (106.6 mg, 30.46%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 555

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.82-0.86 (m, 4H), δ1.21-1.26 (d, 3H), δ1.40-1.66 (m, 5H), δ1.98-2.03 (m, 1H), δ2.68-2.75 (m, 2H), δ2.97 (s, 3H), δ3.40-3.45 (m, 1H), δ3.53 (s, 2H), δ4.91-4.96 (m, 4H), δ6.88-6.90 (d, 1H), δ7.07 (s, 1H), δ7.31 (s, 1H), δ7.38-7.42(m, 2H), δ7.57 (s, 1H), δ7.74-7.76 (m, 1H), δ8.20 (s, 1H).

Example 120. Synthesis of Compound 120



119a 120

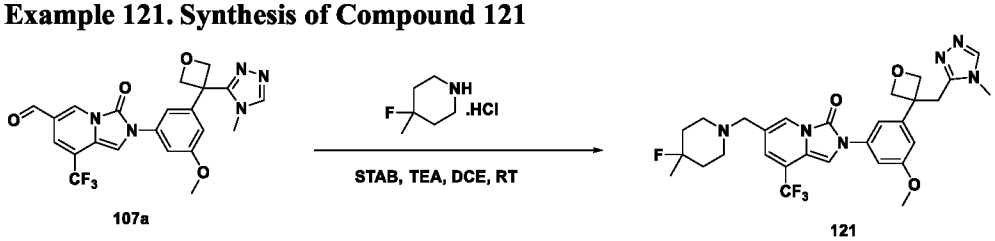
Synthesis of 120

[452] 119a (300 mg, 0.541 mmol, 1.00 equiv) was purified by chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 15.5 min; Wave Length: 220/254 nm; RT1(min): 10.51, RT2(min): 12.60, the second peak is product) to afford Compound 120 (89.5 mg, 29.83%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 555

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.82-0.86 (m, 4H), δ1.24 (s, 2H), δ1.32-1.98 (m, 6H), δ2.67-2.74 (m, 2H), δ2.98 (s, 3H), δ3.32-3.53 (m, 3H), δ4.91-4.96 (m, 4H), δ6.88-6.90 (d, 1H), δ7.07 (s, 1H), δ7.31-7.43 (m, 5H), δ7.74-7.76 (m, 1H), δ8.20 (s, 1H).

Example 121. Synthesis of Compound 121



107a 121

Synthesis of 121

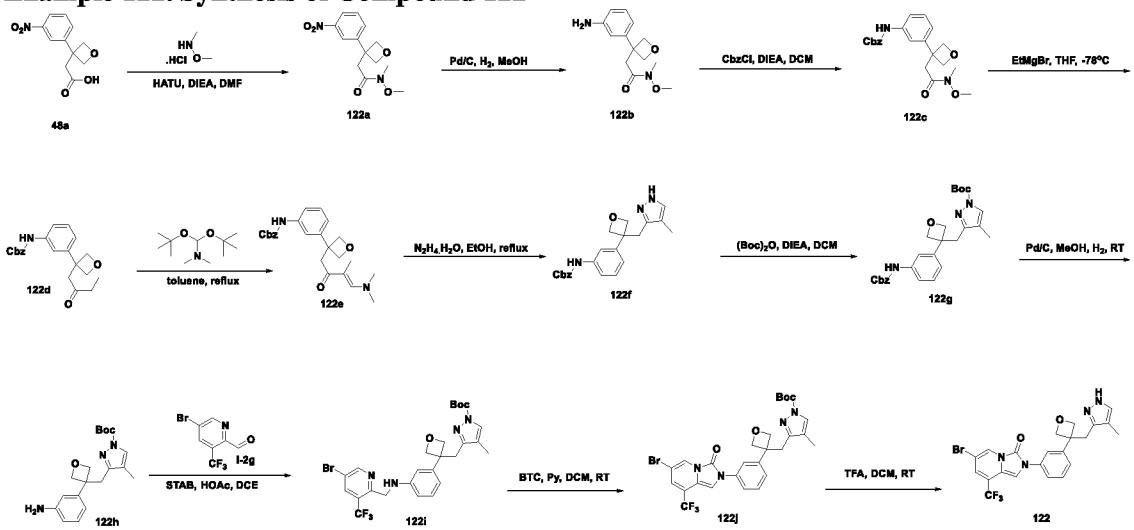
[453] To a stirred mixture of 107a (190 mg, 0.401 mmol, 1 equiv) and 4-fluoro-4-methylpiperidine hydrochloride (184.97 mg, 1.203 mmol, 3 equiv) in DCE (2.00 mL) were added TEA (121.84 mg, 1.203 mmol, 3 equiv) and STAB (170.12 mg, 0.802 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The

reaction was quenched with sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 121 (150 mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 51% B in 8 min; Wave Length: 220 nm; RT1(min): 7.77 min) to afford Compound 121 (43.7 mg, 18.50%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 589

H-NMR: (400 MHz, DMSO, δ ppm): 1.71-1.74 (d, 3H), 1.75-1.79 (m, 4H), 2.24-2.33 (m, 2H), 2.58-2.76 (m, 2H), 3.00 (s, 3H), 3.32 (s, 2H), 3.52 (s, 2H), 3.71 (s, 3H), 4.89-4.94 (m, 4H), 6.40-6.41 (d, 1H), 7.00-7.01 (m, 2H), 7.33-7.37 (m, 2H), 7.76 (s, 1H), 8.22 (s, 1H).

Example 122. Synthesis of Compound 122



Synthesis of 122a

[454] To a stirred solution of 48a (10 g, 42.157 mmol, 1.00 equiv) and N,O-dimethylhydroxylamine (5.15 g, 84.314 mmol, 2 equiv) in DMF (150 mL) was added HATU (17.63 g, 46.373 mmol, 1.1 equiv) and DIEA (16.35 g, 126.471 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (300 mL). The precipitated solids were collected by filtration and washed with water (1x20 mL). The resulting mixture was concentrated under vacuum. This resulted in 122a (11 g, 83.79%) as an off-white solid.

Synthesis of 122b

[455] A solution of 122a (10 g, 35.679 mmol, 1.00 equiv) and Pd/C (0.99 g, 9.277 mmol,

0.26 equiv) in MeOH (300 mL, 0.046 mmol) was stirred for 6 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered through a celite pad and the filter cake was washed with MeOH (2x50 mL). The filtrate was concentrated under reduced pressure. This resulted in 122b (9 g, 90.70%) as a light yellow oil.

Synthesis of 122c

[456] To a stirred solution of 122b (10 g, 39.952 mmol, 1.00 equiv) and DIEA (15.49 g, 119.856 mmol, 3 equiv) in DCM (200 mL) was added CbzCl (13.63 g, 79.904 mmol, 2 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was washed with 100 mL of water. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 122c as an off-white solid.

Synthesis of 122d

[457] To a stirred solution of 122c (8 g, 20.810 mmol, 1.00 equiv) in THF (100 mL) was added EtMgBr (62.4 mL, 62.430 mmol, 3 equiv, 1M) dropwise at -78 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 4h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (15:1) to afford 122d as an off-white solid.

Synthesis of 122e

[458] To a stirred solution of 122d (4 g, 11.318 mmol, 1.00 equiv) in methylbenzene (50 mL) was added [bis(tert-butoxy)methyl]dimethylamine (6.90 g, 33.954 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 100 degrees C. The resulting mixture was concentrated under vacuum. This resulted in 122e (5 g, 91.92%) as a yellow oil. The crude product was used in the next step directly without further purification.

Synthesis of 122f

[459] To a stirred solution of 122e (5 g, 12.240 mmol, 1.00 equiv) in EtOH (2 mL) was added hydrazine hydrate (98%) (61.27 mg, 1.220 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 degrees C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (30:1) to afford 122f (3 g, 55.20%) as a light yellow oil.

Synthesis of 122g

[460] To a stirred solution of 122f (3 g, 7.948 mmol, 1.00 equiv) and (Boc)2O (5.20 g, 23.844 mmol, 3 equiv) in DCM (150 mL) was added DIEA (4.11 g, 31.792 mmol, 4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was washed with 100 mL of water. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 122g (1.3 g, 30.82%) as an off-white solid.

Synthesis of 122h

[461] To a solution of 122g (1.3 g, 2.780 mmol, 1.00 equiv) in MeOH (30 mL) was added Pd/C (100 mg, 0.940 mmol, 0.34 equiv) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 122h (850 mg, 80.12%) as an off-white solid.

Synthesis of 122i

[462] To a stirred solution of 122h (350 mg, 1.019 mmol, 1.00 equiv) and I-2g (258.87 mg, 1.019 mmol, 1 equiv) in DCE (10 mL) was added HOAc (61.20 mg, 1.019 mmol, 1 equiv) and STAB (431.99 mg, 2.038 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 122i (400 mg, 62.78%) as an off-white solid.

Synthesis of 122j

[463] To a stirred solution of 122i (380 mg, 0.654 mmol, 1.00 equiv) and Pyridine (516.96 mg, 6.540 mmol, 10 equiv) in DCM (15 mL) was added BTC (77.43 mg, 6.540 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ at room temperature. The aqueous layer was extracted with DCM (2x10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 30:1) to afford 122j (310 mg, 72.62%) as a yellow solid.

Synthesis of 122

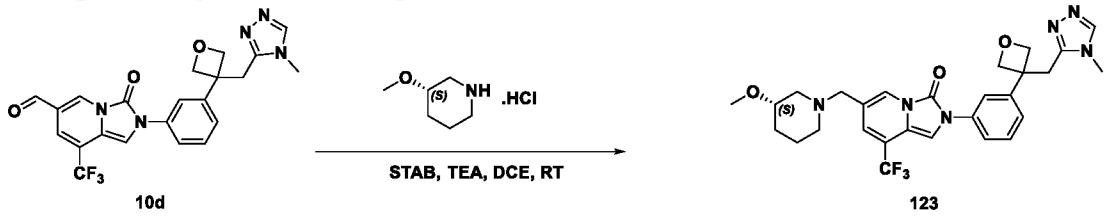
[464] To a stirred solution of 122j (280 mg, 0.461 mmol, 1.00 equiv) in DCM (5 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel;

mobile phase, MeCN in water, 0% to 55% gradient in 15 min; detector, UV 254 nm. This resulted in Compound 122 (133.0 mg, 54.14%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 507

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 0.98 (s, 3H), 3.37 (s, 2H), 5.02 (s, 4H), 6.90-6.92 (m, 1H), 7.05-7.10 (m, 3H), 7.20 (s, 1H), 7.42-7.46 (m, 1H), 7.58-7.61 (d, 1H), 7.99 (s, 1H).

Example 123. Synthesis of Compound 123



10d 123

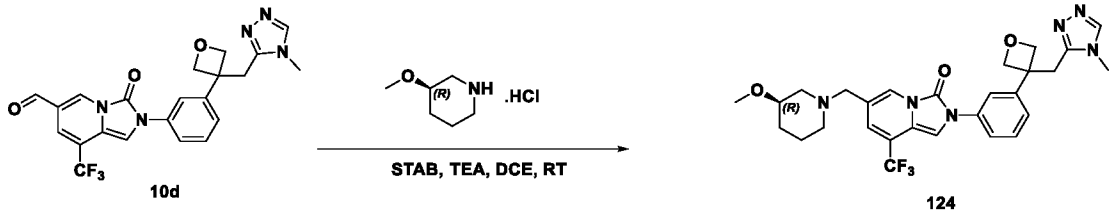
Synthesis of 123

[465] To a stirred solution of 10d (150 mg, 0.328 mmol, 1.00 equiv) and (S)-3-methoxypiperidine hydrochloride (149.17 mg, 0.984 mmol, 3 equiv) in DCE (5 mL) was added TEA (99.55 mg, 0.984 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (139.00 mg, 0.656 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for an additional 5h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phaseA: water(10 mmol/L), mobile phaseB:MeCN, 0%B to 40%B gradient in 15 min; detector, UV 254 nm. This resulted in Compound 123 (45.0 mg, 24.65%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 557

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 1.25-1.37 (m, 1H), 1.37-1.57 (m, 1H), 1.74-1.85 (m, 1H), 1.93-1.99 (m, 1H), 2.17-2.23 (m, 2H), 2.64-2.66 (m, 1H), 2.86-2.88 (m, 1H), 2.96 (s, 3H), 3.33-3.41 (m, 6H), 3.68 (s, 2H), 5.10 (s, 4H), 6.88-6.91 (m, 1H), 7.11-7.14 (m, 2H), 7.31-7.32 (d, 1H), 7.44-7.48 (m, 1H), 7.62-7.65 (m, 1H), 7.68 (s, 1H), 8.20 (s, 1H).

Example 124. Synthesis of Compound 124



10d 124

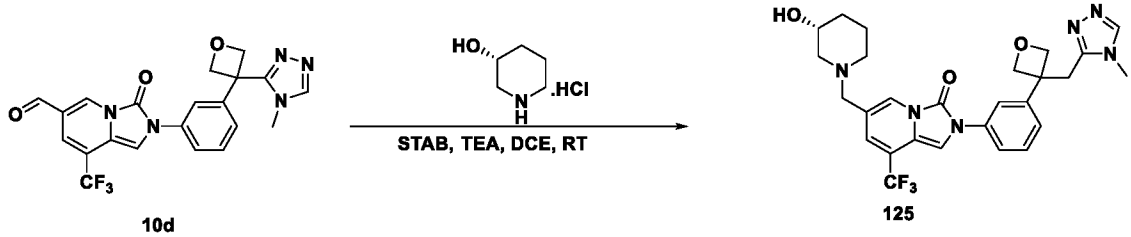
Synthesis of 124

[466] To a stirred solution of 10d (150 mg, 0.328 mmol, 1.00 equiv) and (R)-3-methoxypiperidine hydrochloride (149.17 mg, 0.984 mmol, 3 equiv) in DCE (5 mL) were added TEA (99.55 mg, 0.984 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (139.00 mg, 0.656 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 5h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phaseA: water(10 mmol/L), mobile phaseB:MeCN, 0%B to 40%B gradient in 15 min; detector, UV 254 nm. This resulted in 124 (39.8 mg, 21.81%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 557

H-NMR: (400 MHz, CD_3OD, δ *ppm*): 1.25-1.37 (m, 1H), 1.37-1.57 (m, 1H), 1.74-1.85 (m, 1H), 1.93-1.99 (m, 1H), 2.17-2.23 (m, 2H), 2.64-2.66 (m, 1H), 2.86-2.88 (m, 1H), 2.96 (s, 3H), 3.33-3.41 (m, 6H), 3.68 (s, 2H), 5.10 (s, 4H), 6.89-6.91 (m, 1H), 7.11-7.14 (m, 2H), 7.31-7.32 (d, 1H), 7.44-7.48 (m, 1H), 7.62-7.65 (m, 1H), 7.68 (s, 1H), 8.20 (s, 1H).

Example 125. Synthesis of Compound 125



10d 125

Synthesis of 125

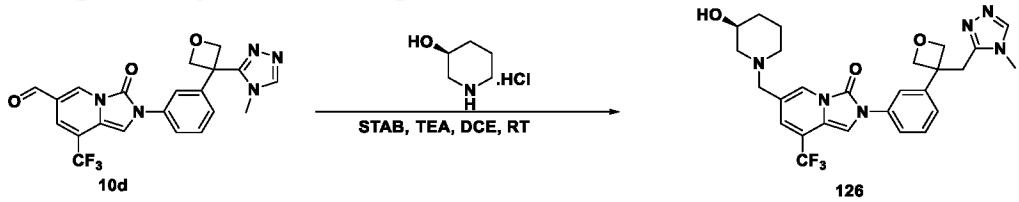
[467] To a stirred mixture of 10d (200 mg, 0.422 mmol, 1 equiv) and (3R)-piperidin-3-ol hydrochloride (174.41 mg, 1.266 mmol, 3 equiv) in DCE (3.00 mL) were added TEA (128.25

mg, 1.266 mmol, 3 equiv) and STAB (179.08 mg, 0.844 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH 20:1) to afford 125 (150mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 38% B in 8 min; Wave Length: 220 nm; RT1(min): 7.95) to afford Compound 125 (79.9 mg, 34.86%) as yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 543

H-NMR: (400 MHz, DMSO, δ ppm): 0.98-1.19 (m, 1H), 1.35-1.49 (m, 1H), 1.66-1.71 (m, 1H), 1.72-1.82 (m, 2H), 1.87-1.94 (m, 1H), 2.65-2.68 (m, 1H), 2.80-2.82 (d, 1H), 2.97 (s, 3H), 3.23-3.26 (d, 2H), 3.45-3.46 (d, 1H), 3.53 (s, 2H), 4.60-4.61 (d, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.74-7.76 (d, 1H), 8.20 (s, 1H).

Example 126. Synthesis of Compound 126



Synthesis of 126

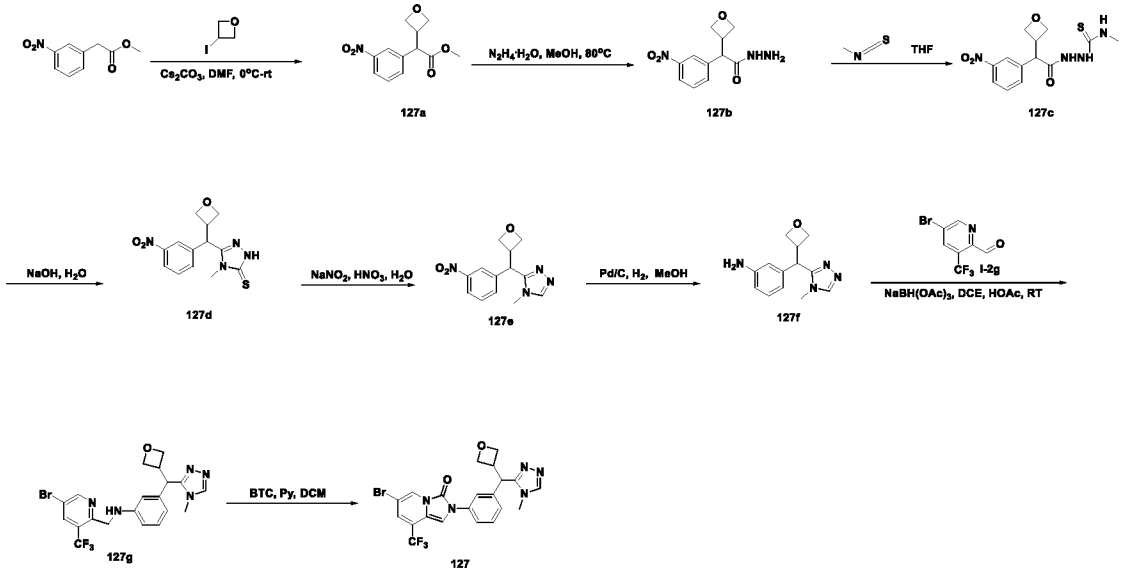
[468] To a stirred mixture of 10d (200 mg, 0.422 mmol, 1 equiv) and (3S)-piperidin-3-ol hydrochloride (174.41 mg, 1.266 mmol, 3 equiv) in DCE (3.00 mL) were added TEA (128.25 mg, 1.266 mmol, 3 equiv) and $NaBH(OAC)_3$ (179.08 mg, 0.844 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 126 (150 mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 37% B in 8 min; Wave Length: 220 nm; RT1(min): 8.03) to afford Compound 126 (80.6

mg, 35.16%) as yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 543

H-NMR: (400 MHz, DMSO, δ ppm): 0.98-1.19 (m, 1H), 1.35-1.49 (m, 1H), 1.66-1.71 (m, 1H), 1.72-1.82 (m, 2H), 1.87-1.94 (m, 1H), 2.65-2.67 (m, 1H), 2.80-2.82 (d, 1H), 2.97 (s, 3H), 3.23-3.26 (d, 2H), 3.42-3.46 (d, 1H), 3.53 (s, 2H), 4.60-4.61 (d, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.74-7.76 (d, 1H), 8.20 (s, 1H).

Example 127. Synthesis of Compound 127



Synthesis of 127a

[469] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (10 g, 51.236 mmol, 1 equiv) and 3-iodooxetane (18.85 g, 102.472 mmol, 2 equiv) in DMF (200 mL) was added Cs_2CO_3 (33.39 g, 102.472 mmol, 2 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The resulting mixture was extracted with EtOAc (3 x300 mL). The combined organic layers were washed with water (3x100 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 127a (5 g, 35.35%) as a colorless oil.

Synthesis of 127b

[470] A solution of 127a (5 g, 19.901 mmol, 1 equiv) and $NH_2NH_2.H_2O$ (7.97 g, 159.208 mmol, 8 equiv) in MeOH (50 mL) was stirred overnight at 90 °C under nitrogen atmosphere.

The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 127b (1.8 g, 35.28%) as a colorless oil.

Synthesis of 127c

[471] A solution of 127b (1.8 g, 7.164 mmol, 1 equiv) and methyl isothiocyanate (1.05 g, 14.328 mmol, 2 equiv) in THF (20 mL) was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water (3x10 mL) to afford 127c (2.2 g, 85.20%) as a white solid.

Synthesis of 127d

[472] A solution of 127c (2.15 g, 6.628 mmol, 1 equiv) and NaOH (2.12 g, 53.024 mmol, 8 equiv) in water (20 mL) was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The mixture was acidified to pH 5 with conc. HCl. The precipitated solids were collected by filtration and washed with water (3x10 mL) to afford 127d (2 g, 91.60%) as a white solid.

Synthesis of 127e

[473] To a stirred solution of 127d (2 g, 6.529 mmol, 1 equiv) and $NaNO_2$ (4.50 g, 65.290 mmol, 10 equiv) in water (20 mL) was added HNO_3 (4.11 g, 65.290 mmol, 10 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated aqueous $NaHCO_3$ at room temperature. The resulting mixture was extracted with EtOAc (3 x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 127e (1.4 g, 71.93%) as a colorless oil.

Synthesis of 127f

[474] To a solution of 127e (1.4 g, 5.104 mmol, 1 equiv) in 30 mL MeOH was added Pd/C (0.42 g, 10%) under nitrogen atmosphere. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 127f (1.3 g, 96.96%) as a yellow solid.

Synthesis of 127g

[475] To a stirred mixture of 127f (1 g, 4.093 mmol, 1 equiv) and I-2g (1.56 g, 6.139 mmol, 1.5 equiv) in DCE (10 mL) were added $NaBH(OAc)_3$ (2.60 g, 12.279 mmol, 3 equiv) and HOAc (0.25 g, 4.093 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) at room temperature. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 127g (1.1 g, 50.70%) as a yellow solid.

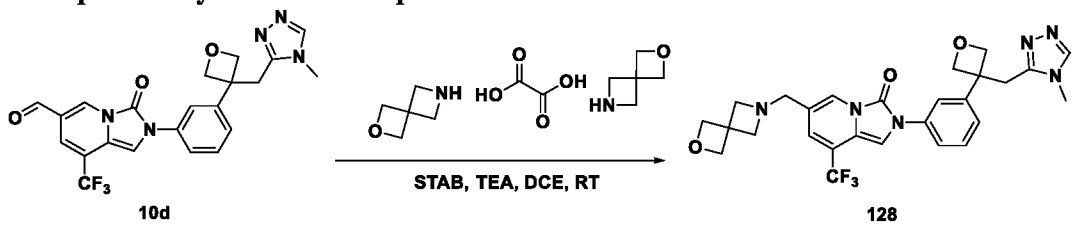
Synthesis of 127

[476] Into a 50 mL 3-necked round-bottom flask were added 127g (1.1 g, 2.281 mmol, 1 equiv), DCM (15 mL), and Pyridine (1.08 g, 13.686 mmol, 6 equiv) at room temperature. To the above mixture was added bis(trichloromethyl) carbonate (0.24 g, 0.798 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for additional 1 h at 0 °C. The reaction was quenched with water (30 mL) at room temperature. The aqueous layer was extracted with DCM (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (80:1) to afford Compound 127 (900 mg, 75.31%) as a yellow solid, 9.1 mg submitted.

LC-MS: (ES, *m/z*): $[M+H]^+$ 508

H-NMR: (400 MHz, DMSO-d_6, *ppm,* δ): 3.37 (s, 3H), 3.87-3.97 (m, 1H), 4.26-4.33 (m, 1H), 4.47-4.49 (d, 2H), 4.78-4.81 (m, 2H), 7.17-7.21 (m, 2H), 7.48-7.50 (m, 2H), 7.74-7.75 (m, 2H), 8.03 (s, 1H), 8.37 (s, 1H).

Example 128. Synthesis of Compound 128



10d 128

Synthesis of 128

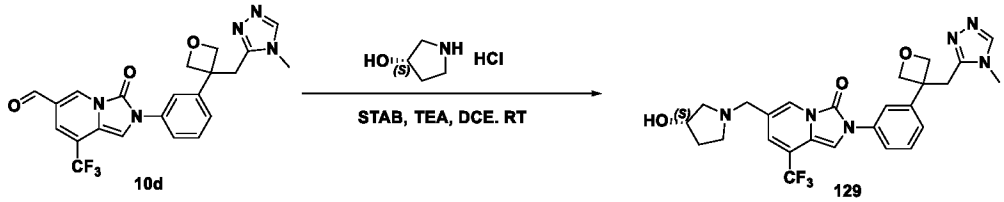
[477] To a stirred solution of 10d (80 mg, 0.175 mmol, 1 equiv) and 2-oxa-6-azaspiro [3.3] heptane hemioxalate (60.49 mg, 0.210 mmol, 1.2 equiv) in DCE (2 mL) were added TEA (35.40 mg, 0.350 mmol, 2 equiv) and STAB (74.14 mg, 0.350 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (5mL) at room temperature. The resulting

mixture was extracted with EtOAc (3 x 8mL) and the organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: C18 silicagel column 40 g; Mobile Phase A: Water(0.1%NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B to 60% B in 15 min; 220 nm) to afford Compound 128 (47.7 mg, 50.45%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:541

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.49-2.51 (m, 2H), δ 2.97 (s, 3H), δ3.32 -3.38 (m, 4H), δ 3.53 (s, 2H), δ 4.61 (s, 4H), δ 4.90-4.96 (m, 4H), δ 6.88-6.94 (m, 1H), δ 6.95-7.00 (m, 1H), δ 7.30 (s, 1H), δ 7.38-7.42 (m, 2H), δ 7.63 (s, 1H), δ 7.73-7.76 (m, 1H), δ 8.20 (s, 1H).

Example 129. Synthesis of Compound 129



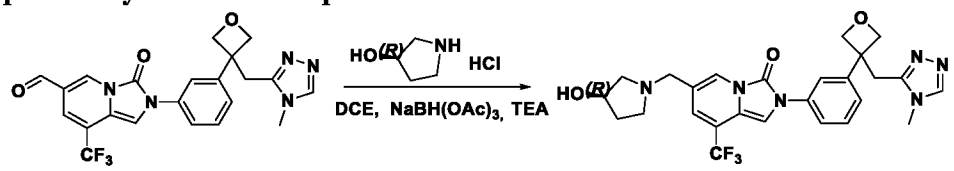
Synthesis of 129

[478] To a stirred solution of 10d (150 mg, 0.328 mmol, 1 equiv) and (3S)-pyrrolidin-3-ol hydrochloride (121.58 mg, 0.984 mmol, 3 equiv) in DCE (2 mL, 25.263 mmol) was added TEA (132 mg, 4 equiv) and STAB (139.00 mg, 0.656 mmol, 2 equiv) at room temperature. The reaction was quenched by the addition of water (20 ml). The resulting mixture was extracted with DCM (3x25ml). The organic layers were concentrated under reduced pressure. The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 8 min, Wave Length: 220 nm; RT1(min): 7.57) to afford Compound 129 (47.3 mg 26.42%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 529

H-NMR: H NMR (400 MHz, DMSO, *ppm,* δ): 1.43-1.65 (m, 1H), 1.91-2.09 (m, 1H), 2.31-2.38 (m, 1H), 2.38-2.47 (m, 1H), 2.58-2.65 (m, 1H), 2.68-2.72 (m, 1H), 2.97 (s, 3H), 3.39-3.45 (m,2H), 3.54 (s, 2H), 4.20-4.21 (m, 1H),4.71 (s, 1H), 4.90-5.02 (m, 4H), 6.76-6.95 (d, 1H), 7.02 (s, 1H), 7.31 (s, 1H), 7.38-7.42(m, 2H), 7.68 (s, 1H), 7.74-7.77 (d, 1H), 8.20 (s, 1H).

Example 130. Synthesis of Compound 130



10d 130

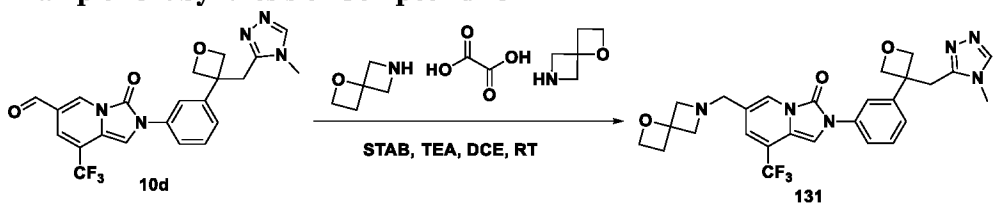
Synthesis of 130

[479] To a stirred solution of 10d (150 mg, 0.328 mmol, 1 equiv) and (3R)-pyrrolidin-3-ol hydrochloride (121.58 mg, 0.984 mmol, 3 equiv) in DCE (2 mL, 25.263 mmol) and TEA (132 mg, 4 equiv) was added STAB (139.00 mg, 0.656 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 ml). The resulting mixture was extracted with DCM/MeOH (5:1, 3x25ml). The organic layers were concentrated under reduced pressure. The crude product (130 mg) was purified by Prep-HPLC with the following condition: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 11% B to 30% B in 11 min, 30% B; Wave Length: 220 nm; RT1(min): 11.25 to afford 130 (48 mg 26.81%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 529

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ1.49-1.54(d, 1H), δ1.93-2.13(m, 1H), δ2.23-2.40(t, 1H), δ2.40-2.48(m, 1H), δ2.57-2.66(d, 1H), δ2.66-2.72(m, 1H), δ2.91-3.03(d, 3H), δ3.37-3.49(t, 2H), δ3.49-3.61(m, 2H), δ4.08-4.29(m, 1H), δ4.62-4.81(d, 1H), δ4.85-5.05(m, 4H), δ6.88-6.90(d, 1H), δ7.03 (s, 1H), δ7.31(s, 1H), δ7.38-7.42(m, 2H), δ7.68(s, 1H), δ7.75-7.77(m, 1H), δ8.20(s, 1H).

Example 131. Synthesis of Compound 131



10d 131

Synthesis of 131

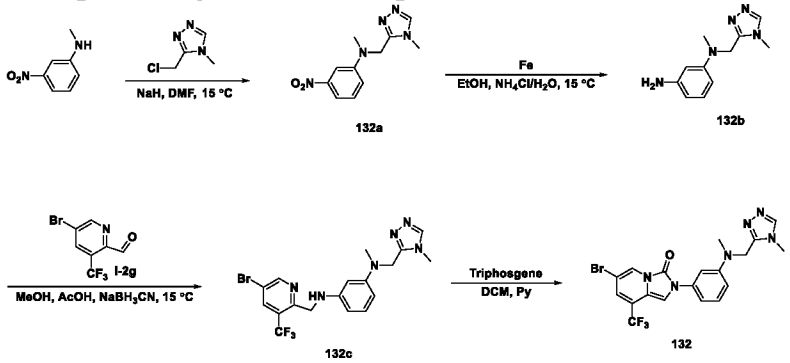
[480] To a stirred solution of 10d (80 mg, 0.175 mmol, 1 equiv) and 1-Oxa-6-azaspiro[3.3]heptane oxalate(2:1) (50.4 mg, 0.350 mmol, 1 equiv) in DCE (1.5 mL) were added TEA (35.40 mg, 0.350 mmol, 2 equiv) and STAB (74.14 mg, 0.350 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at

room temperature. The reaction was quenched by water (5mL) at room temperature. The resulting mixture was extracted with DCM (3 x 8mL). The organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: CAN, 55%B to 60%B gradient in 10 min; detector, UV 254 nm. This resulted in Compound 131 (54.4 mg, 56.62%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:541

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 2.74-2.78 (m, 2H), δ 2.97 (s, 3H), δ 3.11-3.13 (d, 2H), δ 3.32-3.34 (m, 2H), δ 3.49-3.53 (m, 4H), δ 4.35-4.39 (m, 2H), δ 4.91-4.96 (m, 4H), δ 6.88-6.90 (d, 1H), δ 6.96 (s, 1H), δ 7.30 (s, 1H), δ 7.38-7.42 (m, 2H), δ 7.66 (s, 1H), δ 7.73-7.76 (m, 1H), δ 8.20 (s, 1H).

Example 132. Synthesis of Compound 132



Synthesis of 132a

[481] To a solution of N-methyl-3-nitro-aniline (500 mg, 3.29 mmol) in DMF (10 mL) was added NaH (394.31 mg, 9.86 mmol, 60% purity) slowly at 15 °C under N_2. The mixture was stirred at 15 °C for 0.5 h. Then to the mixture was added 3-(chloromethyl)-4-methyl-1,2,4-triazole (1.10 g, 6.57 mmol, as a hydrochloride salt) slowly at 15 °C under N_2. The mixture was stirred at 50 °C for 3.5 h. The reaction mixture was quenched by slow addition of saturated aqueous ammonium chloride solution (30 ml) under N_2 and stirred for another 10 min after addition. The mixture was poured into water (20 ml) and extracted with EtOAc (2*30 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by normal phase SiO_2 chromatography (0-30% ethyl acetate/petroleum ether) to afford compound 132a (300 mg, 36.92% yield) as a yellow solid.

Synthesis of 132b

[482] A mixture of 132a (1.1 g, 4.45 mmol) and Fe (1.49 g, 26.69 mmol) in EtOH (20 mL)

and NH_4Cl (sat. aq.)/H_2O (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15 °C for 2 hr under N_2 atmosphere. The reaction mixture was filtered and the filtrate was poured into water (100 ml) and extracted with EtOAc (2*100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by normal phase SiO_2 chromatography (0-50% ethyl acetate/petroleum ether) to afford compound 132b (500 mg, 55.30% yield) as a yellow solid

Synthesis of 132c

[483] To a mixture of 132b (500 mg, 2.30 mmol) and I-2g (701.44 mg, 2.76 mmol) in MeOH (10 mL) and CH_3COOH (0.01 mL) was added $NaBH_3CN$ (433.85 mg, 6.90 mmol). The mixture was purged with N_2 3 times, and then the mixture was stirred at 15 °C for 12 hr under N_2 atmosphere. The reaction mixture was diluted with saturated aqueous sodium carbonate solution 50 mL and extracted with EtOAc (2 * 30 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was purified by normal phase SiO_2 chromatography (0-60% CH2Cl2/ methyl alcohol) to afford Compound 132c (250 mg, 24.62% yield) as a yellow solid.

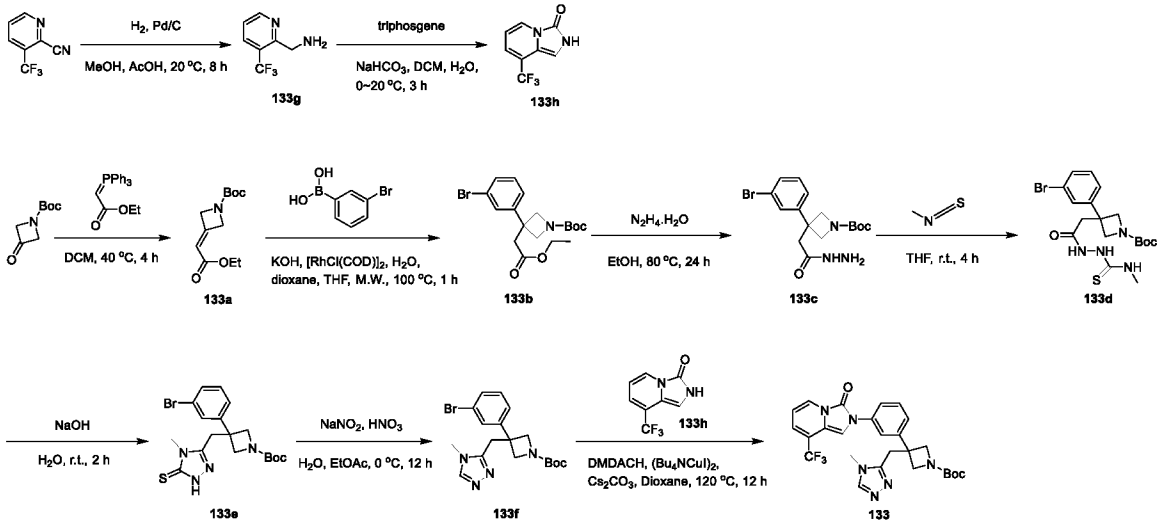
Synthesis of 132

[484] To a mixture of 132c (200 mg, 439.30 umol) and pyridine (208.49 mg, 2.64 mmol, 212.74 uL) in DCM (10 mL) was added TRIPHOSGENE (130.36 mg, 439.30 umol) at 0 °C, and then the mixture was stirred at 15°C for 4 hr under N_2 atmosphere. The reaction mixture was diluted with saturated aqueous sodium carbonate solution (10 mL) and extracted with DCM (2 * 30 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was purified by normal phase SiO_2 chromatography (0-60% CH2Cl2/ methyl alcohol) to afford Compound 132 (38.9 mg, 16%) was obtained as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$: 481

H-NMR (400 MHz, DMSO): δ 8.39 (s, 1H), 8.02 (s, 1H), 7.40 (s, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.89-6.88 (m, 1H), 4.74 (s, 2H), 3.61 (s, 3H), 2.98 (s, 3H).

Example 133. Synthesis of Compound 133



Synthesis of 133a

[485] To a solution of tert-butyl 3-oxoazetidine-1-carboxylate (10.0 g, 58.0 mmol) in DCM (4 mL) was added ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (22.4 g, 64.3 mmol). The mixture was stirred at 40 °C for 4 hr. The mixture was concentrated in vacuum. The residue was diluted with water (20 mL) and the mixture was filtered. The filtrate was extracted with DCM (50 mL x3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-20% EtOAc/petroleum ether) to afford 133a as a yellow oil. (14 g, 95% yield).

Synthesis of 133b

[486] To a solution of chlororhodium;(1Z,5Z)-cycloocta-1,5-diene (49.0 mg, 1.00 mmol) in dioxane (1 mL) was added 1.5 *N* aqueous KOH solution (4.42 mL) in water (2 mL). After stirring for 5 min, 133a (800 mg, 3.30 mmol) and (3-bromophenyl)boronic acid (1.30 g, 6.60 mmol) in THF (8 mL) was added to the mixture and stirred at 100 °C for 1 hr under microwave. The mixture was concentrated to give the residue. To the residue was added water (30 ml) and saturated aqueous brine solution (20 ml). The mixture was extraced with EtOAc (2x20 ml). The combined organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated to give the residue. The residue was purified by normal phase SiO2 chromatography (0-15% EtOAc/petroleum ether) to afford 133b as yellow oil (5.4 g, 45% yield).

Synthesis of 133c

[487] To a solution of 133b (4.20 g, 10.6 mmol) in ethanol (40 mL) was added hydrazine hydrate (8 mL, 161 mmol, 98% purity). It was stirred at 80 °C for 24 hr. The resulting mixture was diluted with water (30 mL). The aqueous layer was extracted with DCM/MeOH (10/1) (5x 50 ml). The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated to afford 133c as a white solid. (2.8 g, 52% yield).

Synthesis of 133d

[488] To a solution of 133c (3.30 g, 8.50 mmol) in THF (40 mL) was added methylimino(thioxo)methane (1.20 g, 17.0 mmol). The mixture was stirred at r.t. for 4 hr. To the mixture was added water (20 mL) and filtered. The filter cake was concentrated by vacuum to afford 133d as a yellow solid. (5 g, crude).

Synthesis of 133e

[489] To a solution of NaOH (3.50 g, 87.4 mmol) in water (90 mL) was added 133d (5 g, 11 mmol). The mixture was stirred at r.t. for 2 hr. The resulting mixture was diluted with water (10 mL). The mixture was acidified to pH=5 with 1 N HCl solution in H_2O. The aqueous layer was extracted with EtOAc (50 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated to afford 133e as a yellow solid (3.5 g, 59% yield).

Synthesis of 133f

[490] To a solution of 133e (3.5 g, 8.0 mmol) and sodium nitrite (5.0 g, 80 mmol) in water (30 mL) and EtOAc (5 mL) was added 1 M aqueous HNO3 (80 mL) dropwise at 0 °C. The mixture was stirred at r.t. for 12 hr. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (100 mL) at r.t. The aqueous layer was extracted with EtOAc (100 mL). The resulting mixture was concentrated under reduced pressure to afford 133f as a yellow solid. (2.5 g, 63% yield)

Synthesis of 133g

[491] To a solution of 3-(trifluoromethyl)pyridine-2-carbonitrile (1 g, 5.81 mmol) in the mixture of MeOH (6 mL) and HOAc (2 mL) was added palladium on carbon (10 wt. 10%, 0.5 g). The suspension was degassed under vacuum and purged with H2 several times. The mixture was stirred under H2 (15 psi) at 20 °C for 8 h. The reaction mixture was filtered through celite, the filtrate was concentrated in vacuum to afford 133g (1.8 g, crude, acetate) as a green solid.

Synthesis of 133h

[492] To a solution of sodium bicarbonate (1.66 g, 19.8 mmol) in water (10.8 mL) was added a solution of TRIPHOSGENE (1.5 g, 5.05 mmol) in DCM (9 mL). Then a solution of 133g (1.8 g, 7.62 mmol, acetate) in DCM (18 mL) was added at 0°C. Then the resulting

mixture was slowly warmed to 20 °C and stirred for 3 h. The reaction mixture was poured into water (30 mL) and stirred for 10 min. The aqueous phase was extracted with DCM (30 mL x2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by normal phase SiO_2 chromatography (0-50% EtOAc/petroleum ether) to afford 133h (800 mg, 52% yield) as a yellow solid.

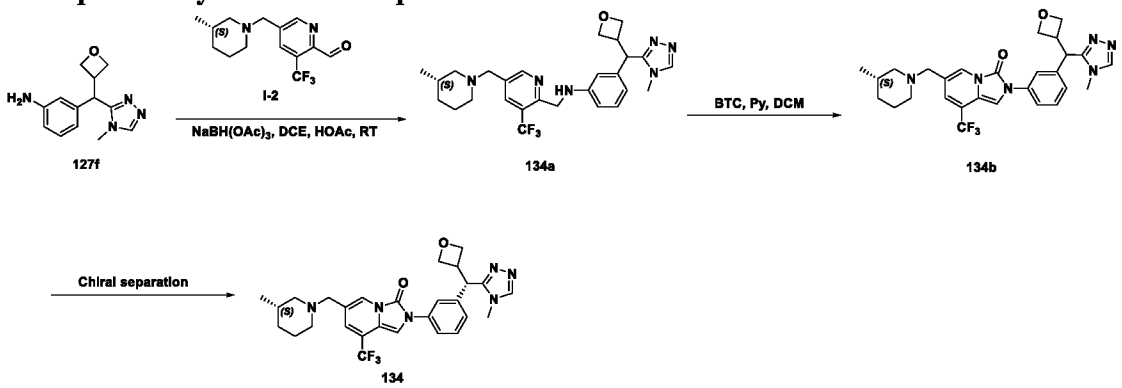
Synthesis of 133

[493] To a solution of 133f (100 mg, 0.25 mmol) and 133h (59.6 mg, 0.30 mmol) in dioxane (8 mL) was added cesium carbonate (160 mg, 0.50 mmol) and iodocopper;tetrabutylammonium;diiodide (55.0 mg, 0.49 mmol,) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (14 mg, 0.98 mmol). The mixture was stirred at 120 °C for 12 hr under N2 in a glove box. To the mixture was added water (5 mL). The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic phase was washed with saturated aqueous brine solution (2x5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated to give the residue. The residue was purified by reverse phase HPLC to afford Compound 133 as a yellow solid. (11.9 mg, 8 %).

LCMS: (ES, *m/z*): $[M+H]^+$ 529

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ 8.22 (s, 1H), 7.79 (t, *J* = 7.6 Hz, 2H), 7.52-7.29 (m, 3H), 7.12 (d, *J* = 6.8 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.30 (t, *J* = 7.2 Hz, 1H), 4.45-4.11 (m, 4H), 3.40 (s, 2H), 3.33 (s, 3H), 2.89 (s, 3H), 1.41 (s, 9H)

Example 134. Synthesis of Compound 134



Synthesis of 134a

[494] Into a 8 mL vial were added 127f (300 mg, 1.228 mmol, 1 equiv), DCE (3 mL), I-2 (703.15 mg, 2.456 mmol, 2 equiv), $NaBH(OAc)_3$ (780.80 mg, 3.684 mmol, 3 equiv), and HOAc (147.49 mg, 2.456 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 1:1) to afford

134a (500 mg, 79.12%) as a white solid.

Synthesis of 134b

[495] To a stirred mixture of 134a (490 mg, 0.952 mmol, 1 equiv) and pyridine (451.91 mg, 5.712 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (98.90 mg, 0.333 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 1h at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 134b (260 mg, 49.50%) as a yellow solid.

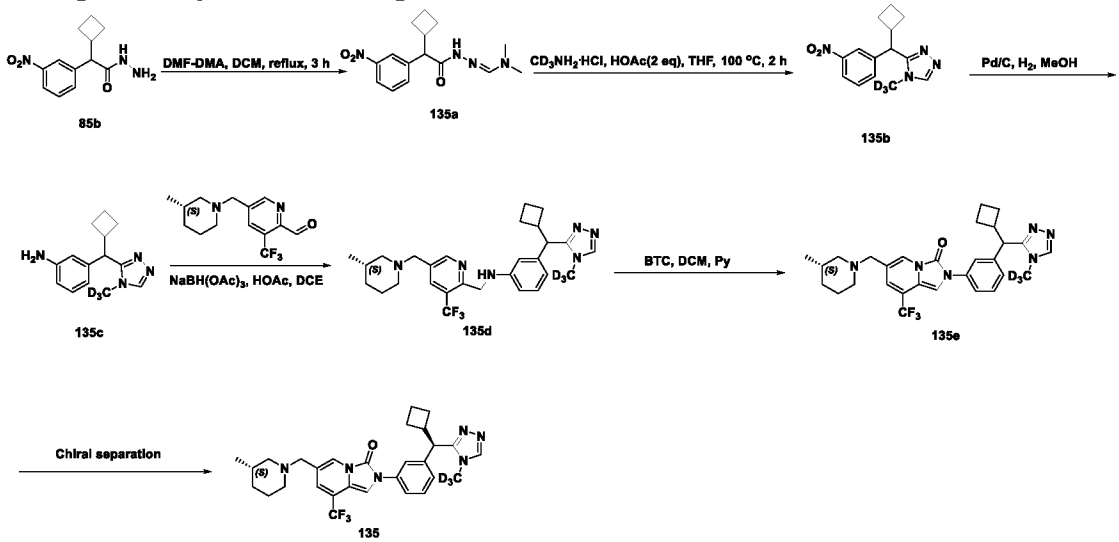
Synthesis of 134

[496] The 134b (260 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 17 min; Wave Length: 220/254 nm; RT2(min): 13.93) to afford Compound 134 (101.9 mg, 38.80%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 541

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.82-0.84 (m, 4H), δ1.58-1.63 (m, 5H), δ1.81-1.98 (m, 1H), δ2.68-2.80 (m, 2H), δ3.28 (s, 2H), δ3.38 (s, 3H), δ3.88-4.02 (m, 1H), δ4.27-4.29 (m, 1H), δ4.48-4.51 (m, 2H), δ4.72-4.82 (m, 2H), δ7.01 (s, 1H), δ7.17-7.20 (d, 1H), δ7.38 (s, 1H), δ7.46-7.49 (m, 1H), δ7.65 (s, 1H), δ7.75-7.78 (t, 2H), δ8.38 (s, 1H).

Example 135. Synthesis of Compound 135



Synthesis of 135a

[497] To a stirred solution of 85b (8 g, 32.094 mmol, 1 equiv) in DCM (100 mL) was added

DMF-DMA (19.12 g, 160.454 mmol, 5.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 50°C under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 135a (6 g, 59.58%) as a light yellow solid.

Synthesis of 135b

[498] To a stirred solution of 135a (6 g, 19.714 mmol, 1 equiv) and $CD_3NH_2.HCl$ (4.17 g, 59.142 mmol, 3 equiv) in THF (60 mL) was added HOAc (2.37 g, 39.428 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 100°C under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (40:1) to afford crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 135b (1.2 g, 21.00%) as a white solid.

Synthesis of 135c

[499] To a solution of 135b (1.2 g, 4.358 mmol, 1 equiv) in MeOH (200 mL) was added Pd/C (0.1 g, 10%) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 135c (780 mg, 68.57%) as a white solid.

Synthesis of 135d

[500] To a stirred solution of 135c (380 mg, 1.549 mmol, 1 equiv) and I-2 (443.43 mg, 1.549 mmol, 1 equiv) in DCE (8 mL) was added HOAc (93.01 mg, 1.549 mmol, 1 equiv) and $NaBH(OAc)_3$ (656.53 mg, 3.098 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 5h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 135d (400 mg, 47.58%) as a light yellow solid.

Synthesis of 135e

[501] To a stirred solution of 135d (380 mg, 0.737 mmol, 1 equiv) and Pyridine (582.92 mg, 7.370 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (87.47 mg, 0.295 mmol, 0.4

equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 135e (250 mg, 59.50%) as a yellow solid.

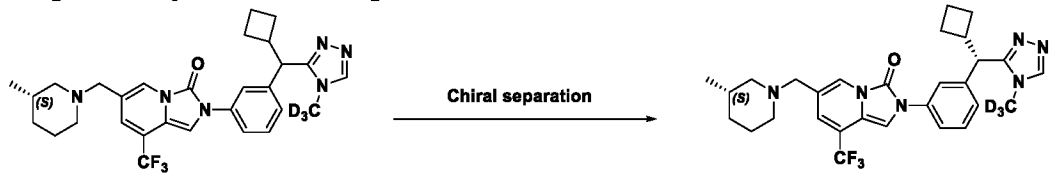
Synthesis of 135

[502] The 135e (250 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 15.5 min; Wave Length: 220/254 nm; RT1(min): 9.60; RT2(min): 12.83, the second peak is product) to afford Compound 135 (86.3 mg, 33.48%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.82-0.83 (m, 4H), 1.41-1.51 (m, 1H), 1.55-1.66 (m, 5H), 1.77-1.93 (m, 5H), 2.05-2.15 (m, 1H), 2.73-2.75 (m, 2H), 3.25-3.32 (m, 3H), 4.24-4.27 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (m, 1H), 7.30 (s, 1H), 7.44-7.46 (m, 1H), 7.65-7.68 (m, 1H), 7.68-7.70 (d, 1H), 7.70-7.74 (d, 1H), 8.32 (s, 1H).

Example 136. Synthesis of Compound 136



135g

unconfirmed
136

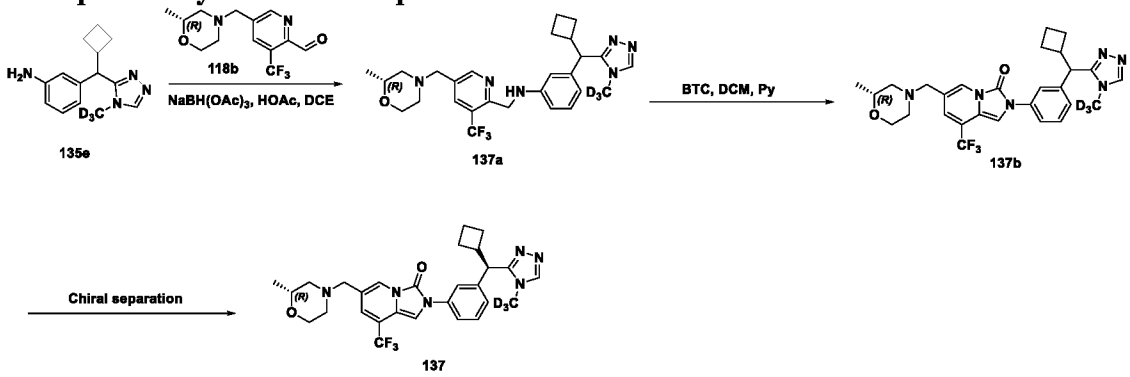
Synthesis of 136

[503] The 135g (250 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 15.5 min; Wave Length: 220/254 nm; RT1(min): 9.60; RT2(min): 12.83, the first peak is product) to afford Compound 136 (82.3 mg, 31.93%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.82-0.84 (m, 4H), 1.45-1.55 (m, 1H), 1.59-1.70 (m, 5H), 1.72-1.93 (m, 5H), 2.05-2.15 (m, 1H), 2.73-2.75 (m, 2H), 3.25-3.32 (m, 3H), 4.24-4.27 (d, 1H), 7.01 (s, 1H), 7.19-7.20 (m, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.68 (m, 1H), 7.68-7.70 (d, 1H), 7.70-7.73 (d, 1H), 8.32 (s, 1H).

Example 137. Synthesis of Compound 137



Synthesis of 137a

[504] To a stirred solution of 135e (380 mg, 1.549 mmol, 1 equiv) and 118b (446.49 mg, 1.549 mmol, 1 equiv) in DCE (8 mL) was added STAB (656.53 mg, 3.098 mmol, 2 equiv) and HOAc (93.01 mg, 1.549 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 137a (280 mg, 34.23%) as a yellow solid.

Synthesis of 137b

[505] To a stirred solution of 137a (380 mg, 0.734 mmol, 1 equiv) and Pyridine (580.70 mg, 7.340 mmol, 10 equiv) in DCM (10 mL) were added Triphosgene (87.14 mg, 0.294 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 137b (280 mg, 68.76%) as a yellow solid.

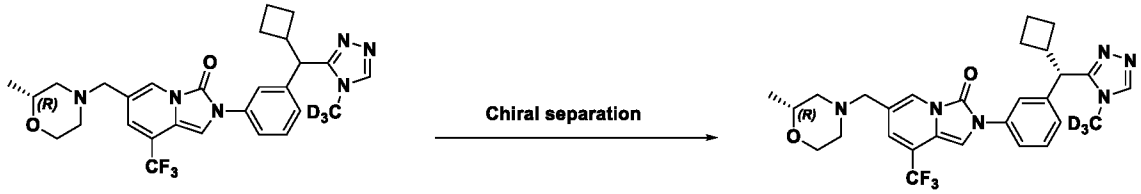
Synthesis of 137

[506] The 137b (280 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 17.5 min; Wave Length: 220/254 nm; RT1(min): 7.02; RT2(min): 12.54, the second peak is product) to afford Compound 137 (82.5 mg, 29.46%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 544

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.03-1.05 (d, 3H), 1.65-1.79 (m, 6H), 1.99-2.13 (m, 2H), 2.58-2.81 (m, 2H), 3.21-3.32 (m, 3H), 3.41-3.52 (m, 2H), 3.71-3.82 (m, 1H), 4.24-4.27 (d, 1H), 7.02 (s, 1H), 7.19-7.20 (m, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.73 (m, 3H), 8.32 (s, 1H).

Example 138. Synthesis of Compound 138



137b 138

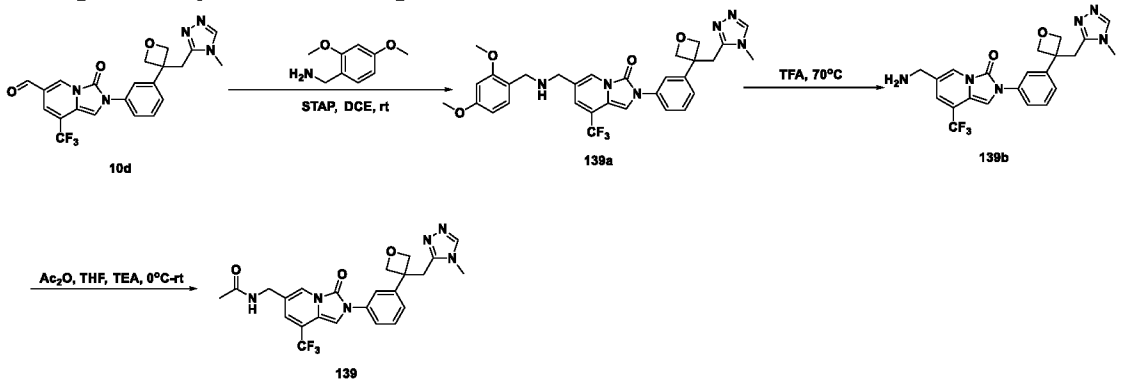
Synthesis of 138

[507] The 137b (280 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 17.5 min; Wave Length: 220/254 nm; RT1(min): 7.02; RT2(min): 12.54, the first peak is product) to afford Compound 138 (75.1 mg, 26.02%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 544

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.03-1.05 (d, 3H), 1.65-1.79 (m, 6H), 1.99-2.13 (m, 2H), 2.58-2.81 (m, 2H), 3.21-3.32 (m, 3H), 3.41-3.52 (m, 2H), 3.71-3.82 (m, 1H), 4.24-4.27 (d, 1H), 7.02 (s, 1H), 7.19-7.20 (m, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.73 (m, 3H), 8.32 (s, 1H).

Example 139. Synthesis of Compound 139



10d 139a 139b 139

Synthesis of 139a

[508] To a stirred solution of 10d (300 mg, 0.65 mmol, 1.0 equiv) and 1-(2,4-dimethoxyphenyl) methanamine (109 mg, 0.65 mmol, 1.0 equiv) in DCE (4 ml) was added STAB (278 mg, 1.31 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (10

ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 and MeOH (10:1) (3x10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 139a (150 mg, 38%) as a yellow solid.

Synthesis of 139b

Into an 8 mL sealed tube were added 139a (130 mg, 0.21 mmol, 1.0 equiv) and TFA (1.3 mL) at room temperature. The resulting mixture was stirred for 1 h at 70°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. This resulted in 139b (80 mg, 33%) as a brown oil.

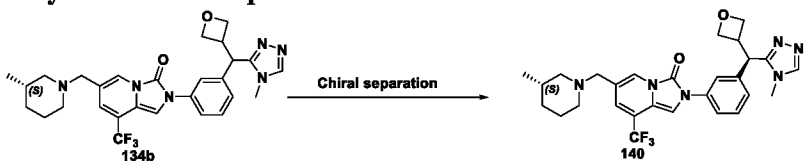
Synthesis of 139

[509] To a stirred solution of 139b (200 mg, 0.43 mmol, 1.0 equiv) and acetic anhydride (9 mg, 0.09 mmol, 0.2 equiv) in THF (3 ml) was added TEA (88 mg, 0.87 mmol, 2.0 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) (10 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=8:1). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 36% B in 8 min; Wave Length: 220 nm; RT1(min): 7.35) to afford Compound 139 (11 mg, 5%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 501

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 1.88 (s, 3H), 2.91-2.97 (m, 3H), 3.53 (s, 2H), 4.06-4.08 (m, 2H), 4.91-4.96 (m, 4H), 6.89-6.90 (d, 1H), 7.02 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 2H), 7.65 (s, 1H), 7.74-7.77 (m, 1H), 8.20 (s, 1H), 8.30-8.33 (m, 1H).

Example 140. Synthesis of Compound 140



Synthesis of 140

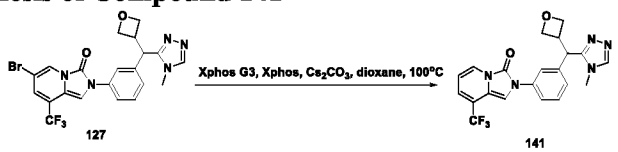
[510] 134b (260 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 17

min; Wave Length: 220/254 nm; RT1(min): 11.36) to afford Compound 140 (95.2 mg) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 541

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.82-0.84 (m, 4H), δ1.58-1.79 (m, 5H), δ1.81-1.98 (m, 1H), δ2.63-2.80 (m, 2H), δ3.25 (s, 2H), δ3.39 (s, 3H), δ3.85-4.00 (m, 1H), δ4.27-4.31 (m, 1H), δ4.48-4.51 (d, 2H), δ4.72-4.82 (m, 2H), δ7.01 (s, 1H), δ7.17-7.20 (d, 1H), δ7.38 (s, 1H), δ7.44-7.49 (m, 1H), δ7.65 (s, 1H), δ7.75-7.78 (m, 2H), δ8.38 (s, 1H).

Example 141. Synthesis of Compound 141



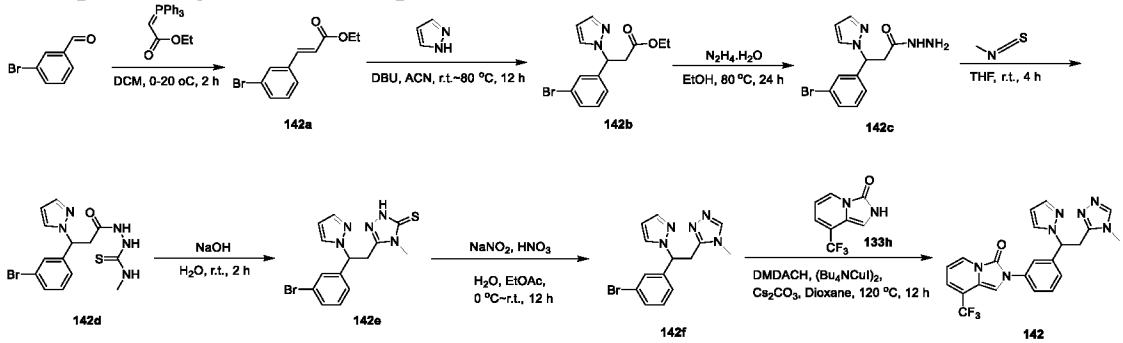
Synthesis of 141

[511] To a stirred solution of 127 (40 mg, 0.079 mmol, 1 equiv) and Cs_2CO_3 (76.92 mg, 0.237 mmol, 3 equiv) in dioxane (2 mL) were added XPhos Pd G3 (6.66 mg, 0.008 mmol, 0.1 equiv) and Xphos (7.50 mg, 0.016 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 6 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: C18 silicagel column 40 g; Mobile Phase A: Water(0.1%NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 40% B to 60% B in 14 min; Wave Length: 220 nm) to afford Compound 141 (5.3 mg, 15.51%) as a white solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:430

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 3.42 (s, 3H), δ 3.89-3.95 (m, 1H), δ 4.27-4.30 (m, 1H), δ 4.48-4.50 (d, 2H), δ 4.72-4.81 (m, 2H), δ 6.26-6.30 (m, 1H), δ 7.09-7.10 (d, 1H), δ 7.17-7.19 (d, 1H), δ 7.37 (s, 1H), δ 7.45-7.47 (m, 1H), δ 7.75-7.79 (m, 3H), δ 8.37 (s, 1H).

Example 142. Synthesis of Compound 142



Synthesis of 142a

[512] To a solution of 3-bromobenzaldehyde (5 g, 27.0 mmol) in DCM (60 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (9.41 g, 27.0 mmol) at 0°C, then the mixture was stirred at r.t. for 2 h under N_2. The mixture was diluted with water (20 mL), then extracted with EtOAc (2 x30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to afford 142a (6.8 g, 98% yield) as a white solid.

Synthesis of 142b

[513] To a solution of 142a (1 g, 3.92 mmol) and 1H-pyrazole (0.80 g, 11.8 mmol) in MeCN (6 mL) was added a solution of DBU (2.95 mL, 19.6 mmol) in CH3CN (9 mL). Then the mixture was stirred at 50 °C for 5 h under N_2. The mixture was concentrated in vacuum to give a residue, which was further purified by reverse phase HPLC to afford 142b (0.97 g, 76% yield) as a yellow oil.

Synthesis of 142c

[514] To a solution of 142b (0.8 g, 2.5 mmol) in EtOH (8 mL) was added hydrazine hydrate (1.84 mL, 37.0 mmol, 98% purity). The mixture was stirred at 80 °C for 24 hr. The resulting mixture was diluted with water (30 mL). The aqueous layer was extracted with DCM/MeOH (10/1) (5x50 ml). The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated to afford 142c (650 mg, 85% yield) as a yellow solid.

Synthesis of 142d

A solution of 142c (0.40 mg, 1.3 mmol) and methylimino(thioxo)methane (189 mg, 2.6 mmol) in THF (9 mL) was stirred at r.t. for 4 hr. To the mixture was added water (8 ml) and filtered. The filter cake was concentrated by vacuum to afford 142d as a yellow solid (450 mg, 91% yield)

Synthesis of 142e

[515] To a solution of 142d (450 mg, 1.2 mmol,) in H_2O (10 mL) was added sodium hydroxide (470 mg, 11.8 mmol). The mixture was stirred at r.t. for 2 hr. The resulting mixture was diluted with water (5 mL). The mixture was acidified to pH 5 with HCl (1 M). The aqueous layer was extracted with CH2Cl2/MeOH (10/1) (3x5 mL). The resulting mixture was concentrated under reduced pressure to afford 142e as a yellow solid. (420 mg, 98% yield).

Synthesis of 142f

[516] To a solution of 142e (420 mg, 1.2 mmol,) and $NaNO_2$ (800 mg, 11.5 mmol,) in H_2O (4 mL) and ethyl acetate (1 mL) was added HNO_3 (730 mg, 11.5 mmol,) at 0 °C. The mixture was stirred at r.t. for 12 hr. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL) at r.t.. The aqueous layer was extracted with ethyl acetate (3 x10 mL). The resulting mixture was concentrated under reduced pressure to afford 142f as a yellow solid (220 mg, 57% yield).

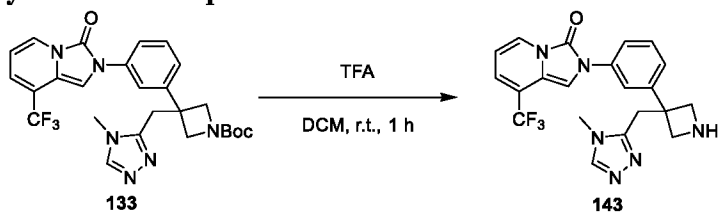
Synthesis of 142

[517] To a solution of 142f (200 mg, 0.6 mmol) and 133h (146 mg, 0.72 mmol,) in dioxane (6 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (34.3 mg, 0.24 mmol) and iodocopper;tetrabutylammonium;diiodide (135 mg, 0.12 mmol) and cesium carbonate (392 mg, 1.2 mmol). The mixture was stirred at 120 °C for 12 hr. Water (5 mL) was added to the mixture. The mixture was extracted with ethyl acetate (2x5 mL). The combined organic phase was washed with saturated aqueous brine solution (2 x 5 mL), dried with anhydrous sodium sulfate, filtered and concentrated to give the residue. The residue was purified by reverse phase HPLC to afford 142 as a yellow solid. (30.2 mg, 10% yield)

LCMS: (ES, *m/z*): $[M+H]^+$ 454.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.33 (br s, 1H), 7.92 (s, 2H), 7.87-7.78 (m, 2H), 7.54-7.43 (m, 2H), 7.40-7.30 (m, 2H), 7.12 (br d, J = 6.8 Hz, 1H), 6.30 (t, J = 6.8 Hz, 1H), 6.23 (s, 1H), 6.16-6.13 (m, 1H), 4.00-3.85 (m, 1H), 3.74-3.61 (m, 1H), 3.55 (s, 3H)

Example 143. Synthesis of Compound 143



133 143

Synthesis of 143

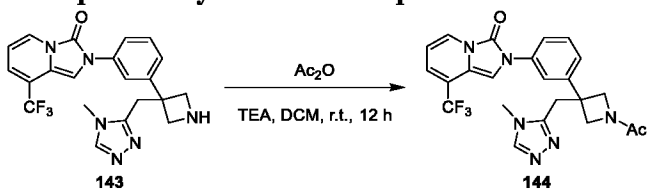
[518] To a solution of 133 (450 mg, 0.85 mmol) in DCM (8 mL) was added trifluoroacetic

acid (2.25 mL, 30.4 mmol). The mixture was stirred at r.t. for 1 hr. The mixture was concentrated in vacuum. The residue was purified by reverse phase HPLC to afford Compound 143 (8.4 mg, 1.9%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 429.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.18 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.75-7.72 (m, 1H), 7.43-7.32 (m, 2H), 7.27 (s, 1H), 7.09 (d, *J* = 6.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.28 (t, *J* = 7.2 Hz, 1H), 4.15-4.01 (m, 4H), 3.46 (s, 3H), 2.84 (s, 3H).

Example 144. Synthesis of Compound 144



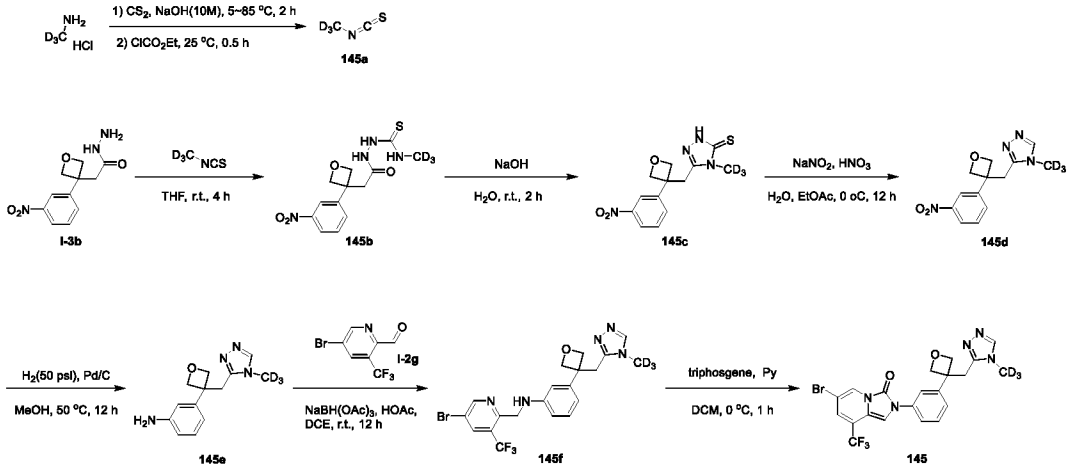
Synthesis of 144

[519] To a solution of 143 (500 mg, 1.17 mmol) in DCM (5 mL) was added acetic anhydride (0.16 mL, 1.8 mmol) and triethylamine (6.0 mL, 43.1 mmol). The mixture was stirred at r.t. for 12 hr. To the mixture was added water (10 mL). The mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated to give the residue. The residue was purified by reverse phase HPLC to afford 144 as a yellow solid. (20.1 mg, 3% yield)

LCMS: (ES, *m/z*): $[M+H]^+$ 471.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.22 (s, 1H), 7.84-7.75 (m, 2H), 7.47 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.12 (d, *J* = 6.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.30 (t, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 8.4 Hz, 1H), 4.50 (d, *J* = 8.4 Hz, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 4.19 (d, *J* = 9.6 Hz, 1H), 3.43 (s, 2H), 2.93 (s, 3H), 1.83 (s, 3H)

Example 145. Synthesis of Compound 145



Synthesis of 145a

[520] To a solution of carbon disulfide (4.28 mL, 70.8 mmol) and NaOH (5.67 g, 141 mmol) in water (15 mL) was added trideuteriomethanamine (5.0 g, 70.8 mmol, as a hydrochloride salt) at 5 °C, then the mixture was stirred at 85 °C for 2 h. Then the mixture was cooled to 30 °C, ethyl carbonochloridate (7.69 g, 70.89 mmol, 6.75 mL) was added to the mixture, and the resulting mixture was stirred at 25 °C for 0.5 hr. The reaction mixture was standing for 12 h, then diluted with water 40 mL and extracted with DCM (40 mLx3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 145a (3.5 g, crude) as a yellow oil.

Synthesis of 145b

[521] To the mixture of I-3b (749 mg, 2.99 mmol) in THF (12 mL) was added 145a (0.5 g, 6.57 mmol) then the mixture was stirred at r.t. for 4 h. The resulting mixture was diluted with water (600 mL). The precipitated solids were collected by filtration and washed with water (3x50 mL) to afford 145b (0.5 g, 51.16% yield) as a yellow solid.

Synthesis of 145c

[522] To the mixture of NaOH (0.4 g, 10.00 mmol) in water (10 mL) was added 145b (0.4 g, 1.22 mmol), and the mixture was stirred at r.t. for 2 h. The resulting mixture was diluted with water (50 mL) and acidified to pH = 5 by 1 N aqueous HCl solution. The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (20 mlx3). The resulting organic phase was concentrated under reduced pressure to afford 145c (0.5 g, crude) as a yellow solid.

Synthesis of 145d

[523] HNO_3 (1.07 mL, 16.16 mmol, 68% purity) was added to water (15 mL) to afford 1 N aqueous HNO_3 solution (16 mL). To a stirred solution of 145c (0.5 g, 1.62 mmol) and sodium nitrite (1.12 g, 16.1 mmol) in water (5 mL) and EtOAc (1 mL) was added 1 N aqueous HNO_3

solution (16 mL) dropwise at 0 °C. The resulting mixture was stirred at r.t. for 12 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was extracted with DCM (50 mLx3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 145d (200 mg, crude) as a white solid.

Synthesis of 145e

[524] To a solution of 145d (70 mg, 252 umol) in MeOH (5 mL) was added palladium on carbon (10 wt. 10%, 50 mg). The mixture was stirred at 50 °C for 12 h under H_2 (50 psi). The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 145e (60 mg, crude) as a yellow oil.

Synthesis of 145f

[525] To a solution of 145e (60 mg, 242 umol) and I-2g (123 mg, 485 umol) in DCE (2 mL) was added sodium triacetoxyborohydride (102 mg, 485 umol) and acetic acid (41.6 uL, 727 umol). The mixture was stirred at r.t. for 12 h. The mixture was neutralized with saturated aqueous sodium bicarbonate solution (20 ml) and extracted with DCM (3x10 ml). The combined organic layers were washed with water (2x20 ml) and dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum to afford 145f (450 mg, crude) as a brown oil.

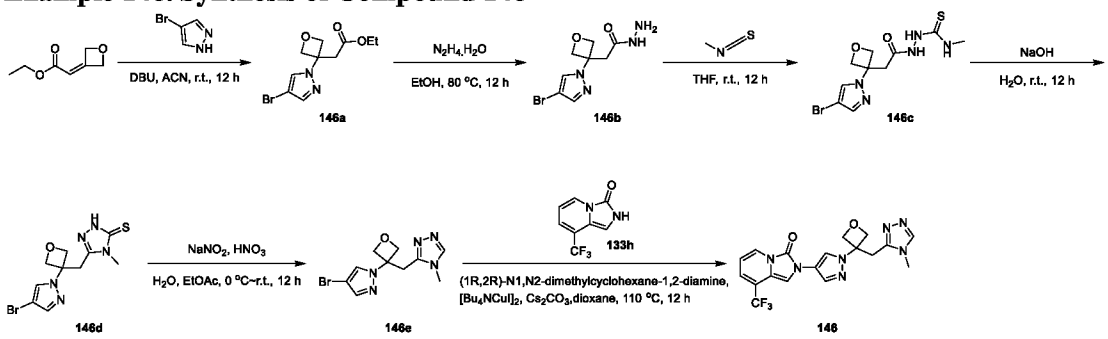
Synthesis of 145

[526] To a solution of 145f (400 mg, 824 umol) in DCM (10 mL) was added pyridine (266 uL, 3.30 mmol) and TRIPHOSGENE (97.8 mg, 329 umol) at 0 °C. The mixture was stirred at 0 °C for 1 h under N_2. The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase HPLC to afford 145 (5 mg, 1.12% yield) as a brown solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 511.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.20 (s, 1H), 8.04 (s, 1H), 7.77-7.71 (m, 1H), 7.46-7.38 (m, 3H), 7.18 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.96-4.90 (m, 4H), 3.53 (s, 2H)

Example 146. Synthesis of Compound 146



Synthesis of 146a

[527] To a solution of ethyl 2-(oxetan-3-ylidene)acetate (5 g, 35.17 mmol) in ACN (50 mL) was added DBU (7.95 mL, 52.7 mmol) and 4-bromo-1H-pyrazole (5.69 g, 38.6 mmol). The mixture was stirred at r.t. for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by normal phase SiO_2 chromatography (0-20% EtOAc/petroleum ether) to afford 146a (8.6 g, 80% yield) as yellow oil.

Synthesis of 146b

[528] To a solution of 146a (8.6 g, 29.7 mmol) in EtOH (80 mL) was added $N_2H_4.H_2O$ (14.7 mL, 297 mmol, 98% purity). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The mixture was diluted with water (100 mL) and extracted with DCM (100 mLx3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 146b (8.7 g, crude) as white solid.

Synthesis of 146c

[529] To a solution of 146b (8.9 g, 32.3 mmol) in THF (180 mL) was added methylimino(thioxo)methane (4.42 mL, 64.7 mmol). The mixture was stirred at r.t. for 12 h. The reaction mixture was concentrated under reduced pressure to afford 146c (13 g, crude) as a white solid.

Synthesis of 146d

[530] A solution of 146c (11 g, 31.5 mmol) in 1 N aqueous NaOH solution (252.71 mL) was stirred at r.t. for 12 h. The reaction mixture was diluted with H_2O (200 mL) and adjusted to pH=3 with HCl (1M). The mixture was extracted with DCM (200 mLx3). The combined organic layers were washed by saturated aqueous brine solution (100 mLx2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 146d (6

g, crude) as a white solid.

Synthesis of 146e

[531] HNO_3 (8.86 mL, 196 mmol) was added dropwise to water (188 mL) to afford 1 N aqueous HNO_3 solution (196 mL). To a stirred solution of 146d (6.5 g, 19.6 mmol) and sodium nitrite (13.5 g, 196 mmol) in water (60 mL) and EtOAc (10 mL) was added 1 N aqueous HNO_3 solution (196 mL) dropwise at 0°C. The resulting mixture was stirred at r.t. for 12 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (200 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (100 mLx3). The resulting mixture was concentrated under reduced pressure to afford 146e (2.2 g, crude) as a white solid.

Synthesis of 146

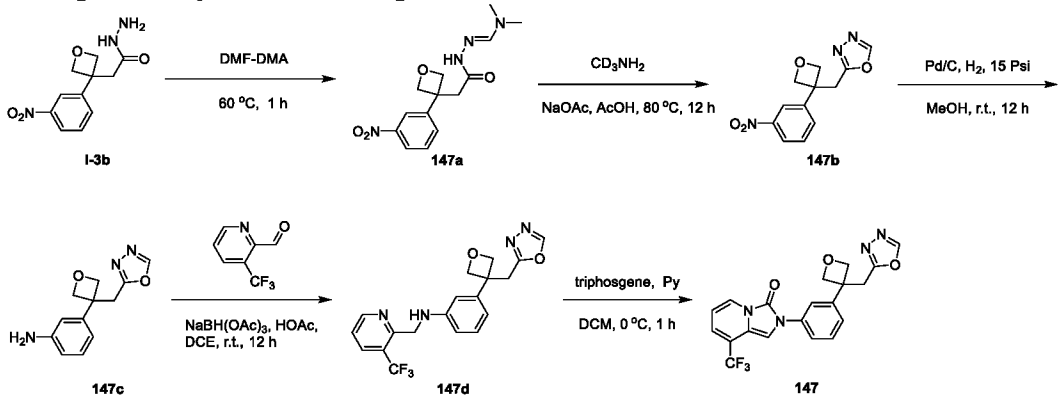
[532] The reaction was run in 50 mg scale with 10 batches in parallel.

[533] A mixture of 146e (50 mg, 167 umol), 133h (37.2 mg, 184 umol), iodocopper;tetrabutylammonium;diiodide (18.7 mg, 16.7 umol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (4.77 mg, 33.5 umol) and cesium carbonate (109 mg, 335 umol) in dioxane (1 mL) was stirred at 110 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase HPLC to afford a crude product. NMR showed it contained TPPO, so it was further purified by PCX (polymer strong cation exchange) (MeOH : H_2O = 1:1) to afford Compound 146 (35 mg, 4% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 420.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.50 (s, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 6.8 Hz, 1H), 7.37 (s, 1H), 7.10 (d, *J* = 6.4 Hz, 1H), 6.29 (t, *J* = 6.8 Hz, 1H), 5.10-4.94 (m, 4H), 3.75 (s, 2H), 3.29 (s, 3H)

Example 147. Synthesis of Compound 147



Synthesis of 147a

[534] A solution of I-3b (1.8 g, 7.16 mmol, 1 eq) in DMF-DMA (16.15 g, 135.50 mmol,18.00 mL, 18.91 eq) was stirred at 60 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a crude product 147a (3 g, crude) as brown oil, which was used in the next step without further purification.

Synthesis of 147b

[535] To a solution of 147a (1.9 g, 6.20 mmol) in AcOH (20 mL) was added sodium acetate (1.02 g, 12.4 mmol) and trideuteriomethanamine (656 mg, 9.30 mmol, as a hydrochloride salt). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by normal phase SiO2 chromatography (0-50% EtOAc/petroleum ether) to afford 147b (210 mg, 13% yield) as a white solid.

Synthesis of 147c

[536] A mixture of 147b (150 mg, 574 umol) and palladium on carbon (10 wt. 10%, 100 mg) in MeOH (5 mL) was stirred at 20 °C for 12 hr under H_2 (15 psi) atmosphere. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to afford 147c (90 mg, crude).

Synthesis of 147d

[537] To a solution of 147c (0.08 g, 345 umol) in DCE (2 mL) was added 3-(trifluoromethyl)pyridine-2-carbaldehyde (60.5 mg, 345 umol), NaOAc (113 mg, 1.38 mmol), and $NaBH(OAc)_3$ (146 mg, 691 umol). The mixture was stirred at 20 °C for 12 h. The mixture was adjusted to pH=8 with saturated aqueous sodium bicarbonate solution and extracted with DCM (5 ml *3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to afford 147d (90 mg, crude) as a yellow oil.

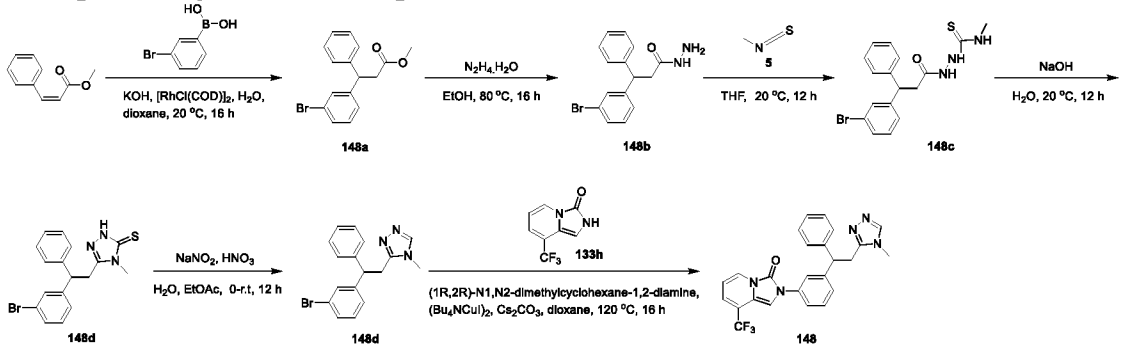
Synthesis of 147

[538] To a solution of 147d (40.0 mg, 102 umol) in DCM (1 mL) was added pyridine (33.1 uL, 409 umol) and TRIPHOSGENE (12.1 mg, 40.9 umol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 ml). The aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuum. The residue was purified by reverse phase HPLC to afford Compound 147 (13 mg, 28% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 417.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ = 9.09 (s, 1H), 7.81 (br d, *J* = 6.8 Hz, 2H), 7.57 (s, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14-7.06 (m, 2H), 6.30 (t, *J* = 6.4 Hz, 1H), 4.96 (d, *J* = 6.4 Hz, 2H), 4.89 (d, *J* = 6.4 Hz, 2H), 3.75 (s, 2H)

Example 148. Synthesis of Compound 148



Synthesis of 148a

[539] To a solution of potassium hydroxide (1.38 g, 24.6 mmol) in water (10 mL) and dioxane (30 mL) was added chlororhodium;(1Z,5Z)-cycloocta-1,5-diene (304 mg, 616 umol) at 20 °C. After addition, the mixture was stirred at this temperature for 0.5 h, then methyl (Z)-3-phenylprop-2-enoate (2 g, 12.3 mmol) and (3-bromophenyl)boronic acid (4.95 g, 24.6 mmol) was added. The resulting mixture was stirred at r.t. for 15.5 h. The reaction mixture was concentrated in vacuum to remove the dioxane. Then the residue was diluted with water (20 mL) and extracted with EtOAc (20 mL x2). The combined organic phase was washed with saturated aqueous brine solution (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by normal phase SiO_2 chromatography (0-18% EtOAc/petroleum ether) to afford 148a (3.4 g, 86% yield).

Synthesis of 148b

[540] To a solution of 148a (3.2 g, 10.0 mmol) in EtOH (50 mL) was added $NH_2NH_2.H_2O$ (7.31 mL, 150 mmol). The mixture was stirred at 80 °C for 16 hr. The reaction was concentrated under reduced pressure to give a residue that was then diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (2x100 mL). The combined organic phase was washed with saturated aqueous brine solution (30 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum to afford 148b (3.2 g, 100% yield) as a colorless oil.

Synthesis of 148c

[541] A mixture of 148b (3.2 g, 10.0 mmol), methylimino(thioxo)methane (1.37 mL, 20.0 mmol) in THF (30 mL) was stirred at 20 °C for 12 h under N_2 atmosphere. The reaction was poured into water (50 mL) and solid formed. The solid was collected and dried to afford 148c

(3.9 g, 99% yield) as a white solid.

Synthesis of 148d

[542] A suspension of 148c (3.9 g, 9.94 mmol) in 1 N aqueous NaOH solution (79.5 mL) was stirred at 20 °C for 12 hr under N_2 atmosphere. The resulting mixture was diluted with water (40 mL). The mixture was acidified to pH 5 with HCl (1 M). The aqueous layer was extracted with ethyl acetate (2x80 mL). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum to afford 148d (3.4 g, 91% yield) as a white solid.

Synthesis of 148e

[543] HNO_3 (6.01 mL, 90.8 mmol, 68% purity) was added drop wised to water (80 mL) afford a 1 M aqueous HNO_3 solution (86 mL). To a stirred solution of 148d (3.4 g, 9.08 mmol) and sodium nitrite (6.27 g, 90.8 mmol) in water (60 mL) and EtOAc (20 mL) was added 1 M aqueous HNO_3 solution (86 mL) dropwise at 0°C. The resulting mixture was stirred at r.t. for 12 h. The reaction was poured into saturated aqueous sodium bicarbonate solution (100 mL) and the resulting mixture was extracted with EtOAc (2 x 100 mL). The organic phase was washed with saturated aqueous brine solution (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuum to give a residue. The residue was purified by normal phase SiO2 chromatography (0-10% MeOH/DCM) to afford 148e as a white solid. (2.9 g, 82% yield)

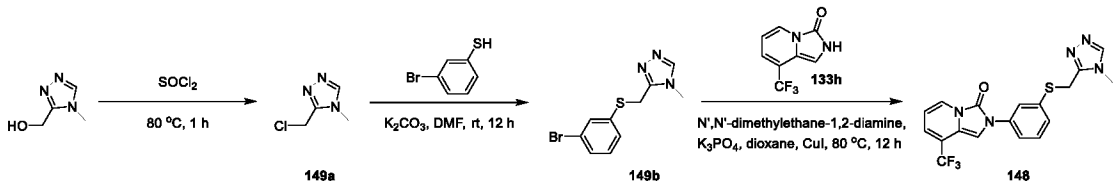
Synthesis of 148

[544] A mixture of 148e (150 mg, 438 umol), 133h (106 mg, 525 umol), iodocopper;tetrabutylammonium;diiodide (98.1 mg, 87.6 umol), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (24.9 mg, 175 umol), and cesium carbonate (285.61 mg, 876.60 umol) in dioxane (10 mL) was stirred at 110 °C for 12 h under N_2 atmosphere. The mixture was poured into water (60 mL). The aqueous phase was extracted with ethyl acetate (2x50 mL). The combined organic phase was washed with saturated aqueous brine solution (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by reverse phase HPLC to afford Compound 148 as a yellow solid. (28.7 mg, 6% yield)

LCMS: (ES, *m/z*): $[M+H]^+$ 464.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.33 (s, 1H), 7.92 (s, 2H), 7.87-7.78 (m, 2H), 7.54-7.43 (m, 2H), 7.40-7.30 (m, 2H), 7.12 (d, J = 6.8 Hz, 1H), 6.30 (t, J = 6.8 Hz, 1H), 6.23 (s, 1H), 6.16-6.13 (m, 1H), 4.00-3.85 (m, 1H), 3.74-3.61 (m, 1H), 3.55 (s, 3H)

Example 149. Synthesis of Compound 149



Synthesis of 149a

[545] A solution of (4-methyl-1,2,4-triazol-3-yl)methanol (1.00 g, 8.84 mmol) in thionyl chloride (10 mL, 137 mmol) was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give 149a (1.5 g, crude, hydrochloride salt) as yellow oil.

Synthesis of 149b

[546] To a solution of 149a (1.50 g, 8.93 mmol, as a hydrochloride salt) in DMF (10 mL) was added potassium carbonate (2.71 g, 19.6 mmol) and 3-bromobenzenethiol (968 uL, 9.37 mmol,). The mixture was stirred at room temperature for 12 hr. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were washed with brine (50 mLx2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by normal phase SiO_2 chromatography (0-25% EtOAc/petroleum ether) to afford 149b (1.6 g, 57% yield) as a white solid.

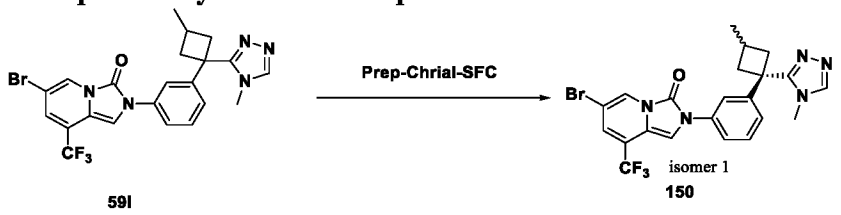
Synthesis of 149

[547] A mixture of 149b (500 mg, 1.75 mmol), 133h (355 mg, 1.75 mmol), CuI (67.0 mg, 351 umol), N',N'-dimethylethane-1,2-diamine (38.4 uL, 351 umol) and potassium phosphate (747 mg, 3.51 mmol) in dioxane (20 mL) was stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction mixture was poured into water (50 mL), while yellow solid formed. The solid was filtered and washed by water (2x10 mL). The cake was collected and dried under reduced pressure to give residue. The residue was triturated with MeOH (10 mL) for 30 min, then the mixture was filtered and the filtrate was concentrated in vacuum to give crude product. The crude product was purified by reverse phase HPLC to afford Compound 149 (4 mg, 1% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 406

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.42 (s, 1H), 7.90-7.73 (m, 3H), 7.51-7.37 (m, 3H), 7.12 (d, J = 6.4 Hz, 1H), 6.30 (t, J = 6.8 Hz, 1H), 4.55 (s, 2H), 3.69 (s, 3H)

Example 150. Synthesis of Compound 150



59l 150

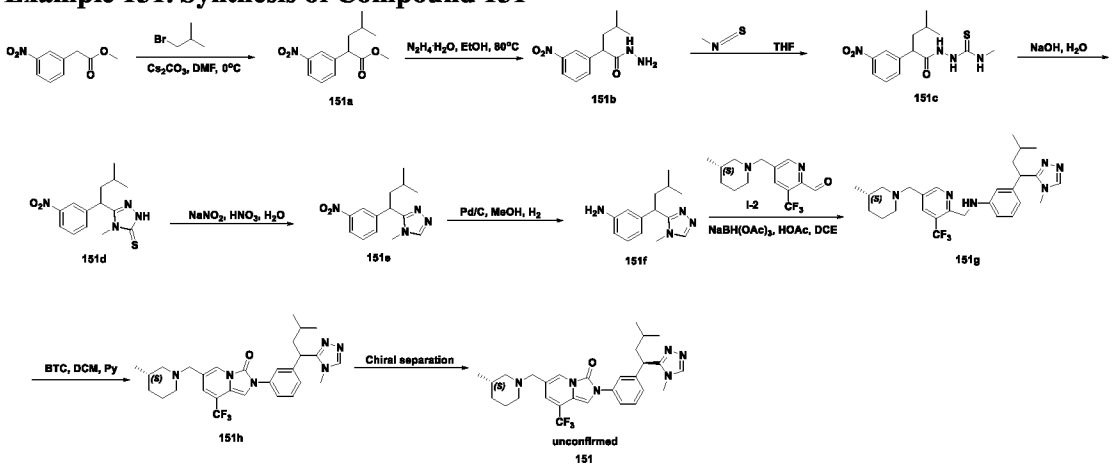
Synthesis of 150

[548] 59l (150 mg) was purified by Prep-SFC with the following conditions (Column: CHIRALPAK IG, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.1% 2M NH_3-MeOH); Flow rate: 70 mL/min; Gradient: isocratic 50% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm; RT1(min): 9.31, RT2 (min): 13.5, the second peak is product) to Compound 150 (62.4 mg, 15.52%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 506.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ1.09-1.11 (d, 3H), 2.22-2.29 (m, 2H), 2.31-2.36 (m, 1H), 3.10-3.14 (m, 2H), 3.24 (s, 3H), 7.09-7.11 (d, 1H), 7.16 (s, 1H), 7.45-7.49 (m, 2H), 7.60-7.62 (m, 1H), 7.69 (s, 1H), 8.03 (s, 1H), 8.36 (s, 1H).

Example 151. Synthesis of Compound 151



Synthesis of 151a

[549] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (20 g, 102.473 mmol, 1 equiv) in DMF (500 mL) was added Cs_2CO_3 (100.16 g, 307.419 mmol, 3 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 3h at 0°C. To the above mixture was added isobutyl bromide (42.12 g, 307.419 mmol, 3 equiv) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (1.5 L). The aqueous layer was extracted with EtOAc (2x800 mL). The residue was

purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 151a (12.5 g, 45.15%) as an off-white solid.

Synthesis of 151b

[550] To a stirred solution of 151a (12 g, 47.755 mmol, 1 equiv) in EtOH (100 mL) was added hydrazine hydrate (98%) (23.91 g, 477.550 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with DCM/MeOH (10/1) (5x300 mL). The resulting mixture was dried with N_2SO_4, filtered, and the filter cake was washed with MeOH (3x100 mL). The filtrate was concentrated under reduced pressure to afford 151b (9 g, 69.00%) as a yellow solid.

Synthesis of 151c

[551] To a stirred solution of 151b (9 g, 35.816 mmol, 1 equiv) in tetrahydrofuran (100 mL) was added methyl isothiocyanate (5.24 g, 71.63 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was diluted with water (300 mL). The precipitated solids were collected by filtration and washed with water (2x50 mL) to afford 151c (10 g, 79.18%) as a yellow solid.

Synthesis of 151d

[552] To a stirred solution of NaOH (9.86 g, 246.608 mmol, 8 equiv) in H_2O (250 mL) was added 151c (10 g, 30.826 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (500 mL). The mixture was acidified to pH 5 with HCl (1 M). The aqueous layer was extracted with DCM/MeOH (10/1) (3x500 mL). The resulting mixture was concentrated under reduced pressure to afford 151d (9 g, 85.76%) as a yellow solid.

Synthesis of 151e

[553] To a stirred solution of 151d (9 g, 29.375 mmol, 1 equiv) and $NaNO_2$ (20.27 g, 293.750 mmol, 10 equiv) in H_2O (100 mL) and EA (200 mL) was added HNO_3 (293.75 mL, 293.750 mmol, 10 equiv) dropwise at 0 degrees C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (aq.)(1 L) at room temperature. The aqueous layer was extracted with DCM/MeOH (10/1)(3x1 L). The resulting mixture was concentrated under reduced pressure to afford 151e (6.8 g, 78.48%) as a yellow solid.

Synthesis of 151f

[554] To a solution of 151e (6.8 g, 24.788 mmol, 1 equiv) in MeOH (200 mL) was added Pd/C (1 g, 9.397 mmol, 0.38 equiv) under nitrogen atmosphere in a 1000 mL round-bottom

flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 151f (4 g, 59.44%) as a yellow solid.

Synthesis of 151g

[555] To a stirred solution of 151f (500 mg, 2.046 mmol, 1.00 equiv) and I-2 (585.86 mg, 2.046 mmol, 1.00 equiv) in DCE (8 mL) was added HOAc (122.89 mg, 2.046 mmol, 1 equiv) and $NaBH(OAc)_3$ (867.39 mg, 4.092 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 151g (500 mg, 43.21%) as a light yellow oil.

Synthesis of 151h

[556] To a stirred solution of 151g (500 mg, 0.972 mmol, 1 equiv) and Pyridine (768.50 mg, 9.720 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (100.91 mg, 0.340 mmol, 0.35 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 151h (280 mg, 52.24%) as a yellow solid.

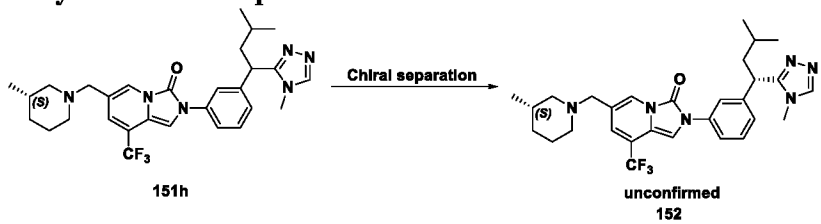
Synthesis of 151

[557] The 151h (280 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 9.65; RT2(min): 11.67, the first peak is product) to afford Compound 151 (98.9 mg, 35.00%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 541

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.79-0.83 (m, 4H), 0.83-0.90 (d, 3H), 0.90-0.96 (d, 3H), 1.44-1.51 (m, 2H), 1.55-1.66 (m, 4H), 1.85-1.94 (m, 2H), 2.10-2.17 (m, 1H), 2.72-2.77 (m, 2H), 3.24 (s, 2H), 3.46 (s, 3H), 4.29-4.33 (m, 1H), 7.00 (s, 1H), 7.22-7.24 (d, 1H), 7.30 (s, 1H), 7.43-7.47 (m, 1H), 7.68-7.70 (m, 2H), 7.77 (d, 1H), 8.33 (s, 1H).

Example 152. Synthesis of Compound 152



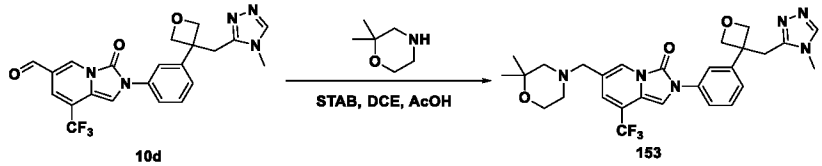
Synthesis of 152

[558] The 151h (280 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 9.65; RT2(min): 11.67, the second peak is product) to afford Compound 152 (95.9 mg, 32.85%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 541

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.81-0.83 (m, 4H), 0.83-0.89 (d, 3H), 0.89-0.94 (d, 3H), 1.43-1.49 (m, 2H), 1.55-1.66 (m, 4H), 1.87-1.94 (m, 2H), 2.10-2.15 (m, 1H), 2.72-2.76 (m, 2H), 3.24 (s, 2H), 3.46 (s, 3H), 4.29-4.33 (m, 1H), 7.00 (s, 1H), 7.22-7.24 (d, 1H), 7.30 (s, 1H), 7.43-7.47 (m, 1H), 7.68-7.70 (m, 2H), 7.77 (d, 1H), 8.33 (s, 1H).

Example 153. Synthesis of Compound 153



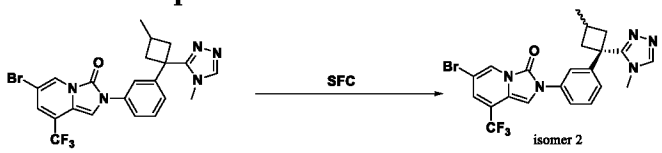
Synthesis of 153

[559] To a stirred solution of 10d (300 mg, 0.656 mmol, 1 equiv) and 2,2-dimethylmorpholine (151.08 mg, 1.312 mmol, 2 equiv) in DCE (5 mL) were added STAB (278.01 mg, 1.312 mmol, 2 equiv) and AcOH (39.39 mg, 0.656 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (8mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 7.17) to afford Compound 153 (119.5 mg, 32.74%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:557

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.14 (s, 6H), δ 2.16 (s, 2H), δ 2.33 (s, 2H), δ 2.97 (s, 3H), δ 3.26 (s, 2H), δ 3.53 (s, 2H), δ 3.60-3.63 (m, 2H), δ 4.91-4.92 (d, 2H), δ 4.94-4.96 (d, 2H), δ 6.88-6.90 (d, 1H), δ 7.04 (s, 1H), δ 7.31 (s, 1H), δ 7.38-7.42 (m, 2H), δ 7.68 (s, 1H), δ 7.74-7.76 (m, 1H), δ 8.20 (s, 1H).

Example 154. Synthesis of Compound 154



591 154

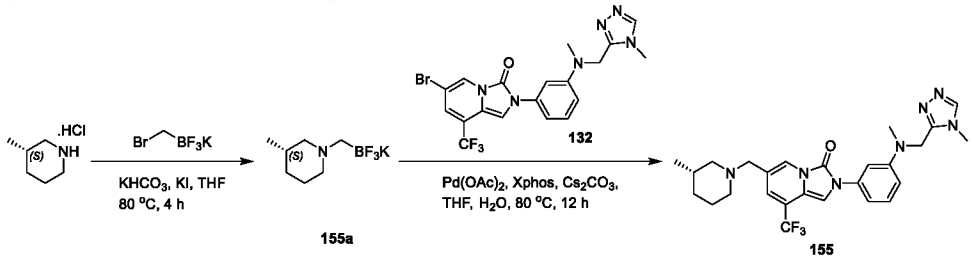
Synthesis of 154

[560] 59l (150 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRALPAK IG, 3*25 cm, 5 um; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.1% 2M NH_3-MeOH); Flow rate: 70 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 9.31, RT2 (min): 13.5, the first peak is product) to Compound 154 (247.8 mg, 61.63%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 506.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ1.08-1.09 (d, 3H), 2.54-2.57 (m, 3H), 2.86-2.90 (m, 2H), 3.20 (s, 3H), 7.16 (s, 1H), 7.25-7.27 (d, 1H), 7.48-7.52 (m, 2H), 7.63-7.65 (d, 1H), 7.83 (s, 1H), 8.03 (s, 1H), 8.29 (s, 1H).

Example 155. Synthesis of Compound 155



155a 155

Synthesis of 155a

[561] A mixture of (3S)-3-methylpiperidine (1 g, 7.37 mmol,), bromomethyl(trifluoro)boron;potassium (1.48 g, 7.37 mmol), $KHCO_3$ (1.48 g, 14.75 mmol), KI (122.39 mg, 737.28 umol) in THF (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 4 hr under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue dissolved in acetone (10 ml), filtered, and the filtrate was concentrated under reduced pressure to give a residue. The

crude product 155a (800 mg, 80% purity) was used into the next step without further purification.

[562] Alternatively, 155a can be prepared as outlined below:

[563] To a solution of (3S)-3-methylpiperidine (1.0 g, 7.37 mmol, as a hydrochloride salt), potassium;bromomethyl(trifluoro)boranuide (1.48 g, 7.37 mmol), potassium bicarbonate (1.48 g, 14.7 mmol), KI (122 mg, 737 umol) in THF (20 mL) was stirred at 90 °C for 12 h under N_2. The mixture was concentrated under reduced pressure. The crude product was triturated with acetone (30 ml) at 25 °C for 30 min then filtered. The filtrate was concentrated under reduced pressure to afford 155a (1.2 g, 74% yield) as a light yellow oil.

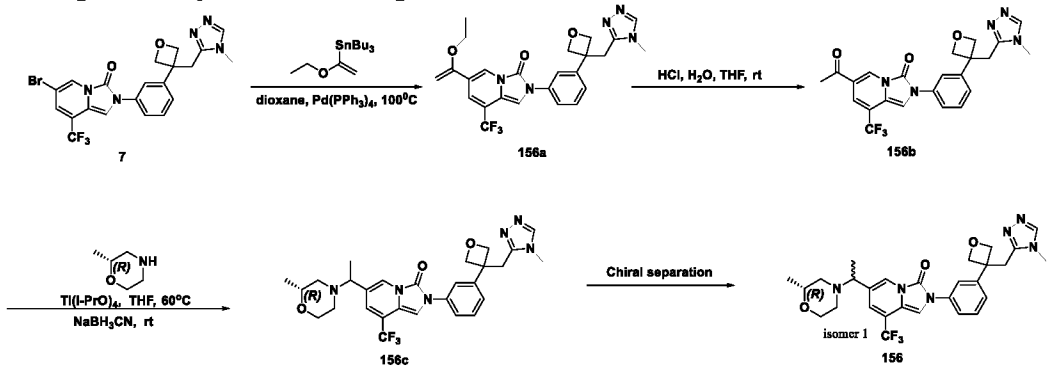
Synthesis of 155

[564] A mixture of 132 (100 mg, 207.78 umol), 155a (136.57 mg, 623.34 umol), $Pd(OAc)_2$ (4.66 mg, 20.78 umol), XPhos (19.81 mg, 41.56 umol) and Cs_2CO_3 (203.10 mg, 623.34 umol) in THF (4 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction mixture was quenched by addition of saturated aqueous sodium carbonate solution (10 mL) and extracted with DCM (10 mL * 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase HPLC (column: Phenomenex C18 75*30mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 45%-75%,8min) to afford Compound 155 (9 mg, 8.43% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 514.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.40 (s, 1H), 7.657 (s, 1H), 7.28 (d, J = 6 Hz, 2H), 7.22 (s, 1H), 7.13(d, J = 7.6 Hz, 1H), 6.99 (s, 1H), 6.89-6.87 (m, 1H), 4.754 (s, 2H), 3.62 (s, 3H), 3.24 (s, 2H), 2.99 (s, 3H),2.77-2.72(m, 2H) ,1.92-1.89(m, 1H), 1.66-1.58(m, 4H), 146-1.43(m, 1H), 0.83-0.82(m, 3H)

Example 156. Synthesis of Compound 156



Synthesis of 156a

[565] To a stirred mixture of 7 (4 g, 7.869 mmol, 1 equiv) and tributyl (1-ethoxyethenyl) stannane (4.26 g, 11.803 mmol, 1.5 equiv) in dioxane (40 mL) was added $Pd(PPh_3)_4$ (0.91 g, 0.787 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was diluted with water (50mL). The aqueous layer was extracted with CH_2Cl_2 / MeOH (10:1) (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with tert-Butyl methyl ether (50mL). The precipitated solids were collected by filtration and washed with tert-Butyl methyl ether (3x20 mL). The resulting mixture was concentrated under reduced pressure to afford 156a (3.2 g, 74.90%) as a yellow solid.

Synthesis of 156b

[566] To a stirred mixture of 156a (3.2 g, 6.406 mmol, 1 equiv) in THF (30 mL) was added HCl (33 mL, 1 M) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (50mL). The aqueous layer was extracted with CH_2Cl_2 / MeOH (10:1) (3x100 mL). The resulting mixture was concentrated under reduced pressure to afford 156b (2.4 g, 71.52%) as a yellow solid.

Synthesis of 156c

[567] To a stirred mixture of 156b (2.4 g, 5.091 mmol, 1 equiv) and (2R)-2-methylmorpholine (1.54 g, 15.273 mmol, 3 equiv) in THF (25 mL) was added $Ti(Oi\text{-}Pr)_4$ (5.79 g, 20.364 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for 3h at 60°C. To the above mixture was added $NaBH_3CN$ (0.96 g, 15.273 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (60 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (60:1) to afford 156c (800 mg). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 156c (600 mg). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN, 10% to 90% gradient in 40 min; detector, UV 254 nm to afford 156c (400 mg, 13.83%) as a yellow solid.

Synthesis of 156

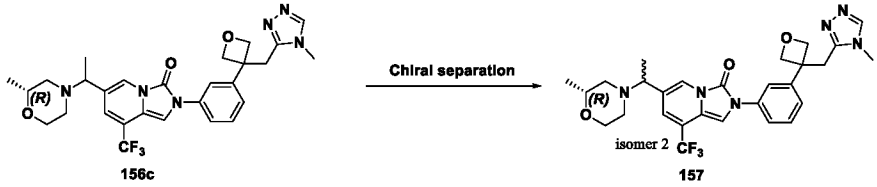
[568] 156c (400 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH),

Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 14 min; Wave Length: 220/254 nm; RT1(min): 10.91; RT2(min): 12.43; the first peak is product) to afford 156 (130 mg). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 156 (70 mg). The crude product (70 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 50% B in 8 min, Wave Length: 220 nm; RT1(min): 7.82) to afford Compound 156 (54 mg, 13.12%) as a yellow solid.

LCMS: (ES, m/z): $[M+H]^+$ 557

H-NMR: H NMR (400 MHz, DMSO, ppm): δ0.92-1.10 (d, 3H), δ1.24-1.26 (d, 3H), δ1.74-1.79 (m, 1H), δ2.03-2.08 (m, 1H), δ2.67-2.74 (m, 2H), δ2.97 (s, 3H), δ3.44-3.54 (m, 5H), δ3.76-3.79 (d, 1H), δ4.90-4.97 (m, 4H), δ6.98-6.92 (d, 1H), δ7.05 (s, 1H), δ7.32 (s, 1H), δ7.38-7.43 (m, 2H), δ7.62 (s, 1H), δ7.73-7.77 (m, 1H), δ8.20 (s, 1H).

Example 157. Synthesis of Compound 157



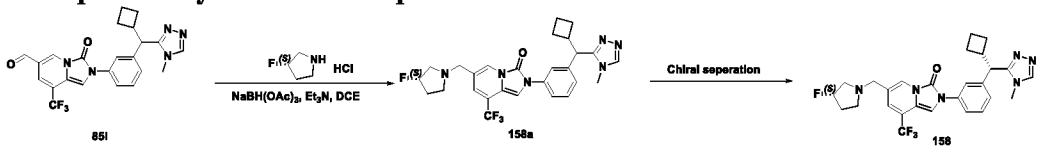
Synthesis of 157

[569] 156c (400 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 14 min; Wave Length: 220/254 nm; RT1(min): 10.91; RT2(min): 12.43; the second peak is product) to afford Compound 157 (120.9 mg, 29.08%) as a yellow solid.

LCMS: (ES, m/z): $[M+H]^+$ 557

H-NMR: H NMR (400 MHz, DMSO, ppm): δ1.10 (s, 3H), δ1.24-1.26 (s, 3H), δ1.79 (s, 1H), δ2.10 (s, 1H), δ2.61-2.68 (m, 1H), δ2.79-2.89 (m, 1H), δ2.97 (s, 3H), δ3.33-3.54 (m, 5H), δ3.64-3.75 (m, 1H), δ4.81-5.00 (m, 4H), δ6.98-6.92 (d, 1H), δ7.06 (s, 1H), δ7.33 (s, 1H), δ7.39-7.43 (m, 2H), δ7.64 (s, 1H), δ7.74-7.77 (m, 1H), δ8.20 (s, 1H).

Example 158. Synthesis of Compound 158



Synthesis of 158a

[570] To a stirred solution of 85i (800 mg, 1.757 mmol, 1 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (441.14 mg, 3.514 mmol, 2 equiv) in DCE (10 mL) were added Et_3N (355.49 mg, 3.514 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (744.57 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford 158a (380 mg, 39.70%) as a yellow solid.

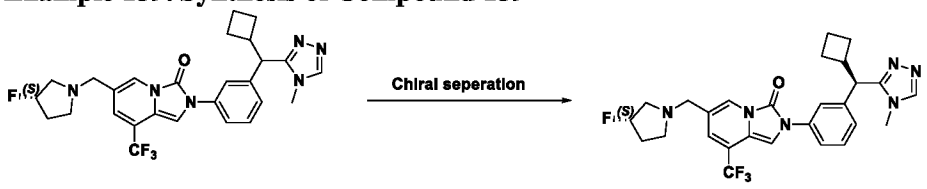
Synthesis of 158

[571] The 158a (380 mg, 0.719 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MeOH); Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.30; RT2(min): 11.45; the first peak is product) to afford Compound 158 (129.8 mg, 33.30%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 529

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.68-1.95 (m, 6H), 2.01-2.21 (m, 2H), 2.31-2.43 (m, 1H), 2.61-2.71 (m, 1H), 2.81-2.91 (m, 2H), 3.15-3.29 (m, 1H), 3.34-3.47 (m, 5H), 4.25-4.27 (d, 2H), 5.14-5.28 (m, 1H), 6.94-6.96 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (m, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H),.

Example 159. Synthesis of Compound 159



158a 159

Synthesis of 159

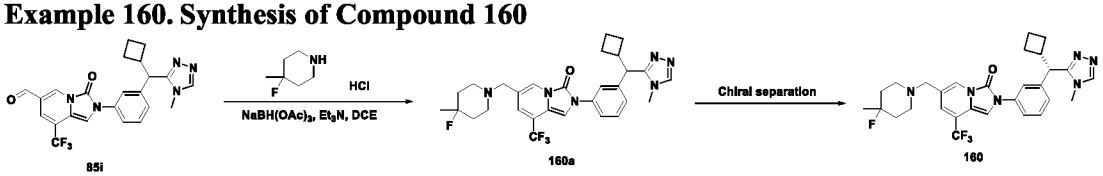
[572] The 158a (380 mg, 0.719 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MeOH); Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.30; RT2(min): 11.45; the second peak is product) to afford Compound 159

(134.1 mg, 35.29%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 529

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.68-1.95 (m, 6H), 2.01-2.21 (m, 2H), 2.31-2.43 (m, 1H), 2.61-2.71 (m, 1H), 2.81-2.91 (m, 2H), 3.15-3.29 (m, 1H), 3.34-3.47 (m, 5H), 4.25-4.27 (d, 2H), 5.14-5.28 (m, 1H), 6.94-6.96 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (m, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H),.

Example 160. Synthesis of Compound 160



Synthesis of 160a

[573] To a stirred mixture of 4-fluoro-4-methylpiperidine hydrochloride (269.86 mg, 1.757 mmol, 1 equiv) and 85i (800 mg, 1.757 mmol, 1.00 equiv) in DCE (8 mL) was added Et_3N (533.23 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1116.85 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of H_2O (30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 160a (400 mg) as a yellow solid. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 65% B in 8 min, Wave Length: 220 nm; RT1 (min): 6.90) to afford 160a (200 mg, 19.84%) as a yellow solid.

Synthesis of 160

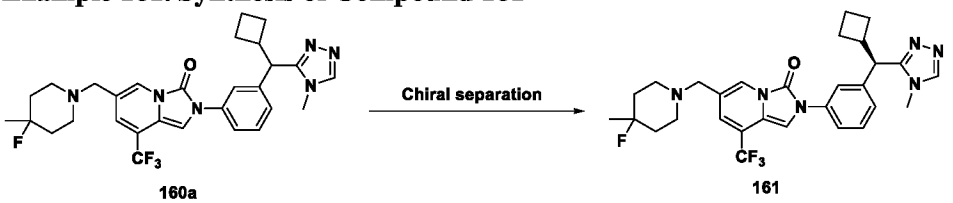
[574] 160a (200 mg) was purified by chiral separation separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.47, RT2 (min): 14.52, the first peak is product) to afford Compound 160 (73.6 mg, 36.73%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ1.30-1.42 (d, 3H), 1.58-1.85 (m, 9H), 2.02-2.09 (m, 1H), 2.24-2.29 (m, 2H), 2.60-2.63 (m, 2H), 3.19-3.23 (m, 1H), 3.25 (s, 2H), 3.43 (s, 3H),

4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.73 (m, 3H), 8.33 (s, 1H).

Example 161. Synthesis of Compound 161



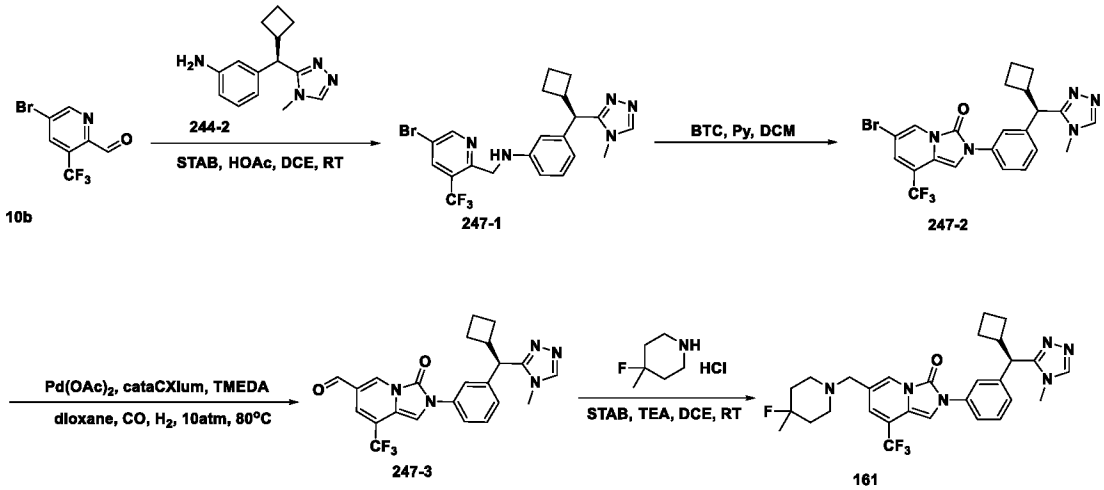
Synthesis of 161

[575] 160a (200 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.47, RT2 (min): 14.52, the second peak is product) to afford Compound 161 (54.9 mg, 27.34%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ1.30-1.42 (d, 3H), 1.61-1.81 (m, 9H), 2.02-2.09 (m, 1H), 2.27-2.34 (m, 2H), 2.60-2.63 (m, 2H), 3.18-3.23 (m, 1H), 3.25 (s, 2H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.73 (m, 3H), 8.33 (s, 1H).

Alternatively, Compound 161 may be also prepared in the manner outlined below:



1. Synthesis of 247-1

[576] To a stirred solution of 10b (72.95 g, 287.216 mmol, 1.2 equiv) and 244-2 (58 g, 239.347 mmol, 1.00 equiv) in DCE (800 mL) were added STAB (101.45 g, 478.694 mmol, 2 equiv) and HOAc (7.19 g, 119.674 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated

NaHCO3 (aq.) (800 mL) at room temperature. The resulting mixture was extracted with DCM (3x400 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (50:1) to afford 247-1 (90 g, 74.37%) as a light yellow solid.

2. Synthesis of 247-2

[577] To a stirred solution of 247-1 (90 g, 187.370 mmol, 1 equiv) and Pyridine (88.93 g, 1124.274 mmol, 6.00 equiv) in DCM (1000 mL) were added triphosgene (19.46 g, 65.582 mmol, 0.35 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 20min at room temperature under nitrogen atmosphere. The reaction was quenched with saturated NaHCO3 (aq.) (800 mL) at room temperature. The resulting mixture was extracted with DCM (3x300 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MTBE (300 mL). This resulted in 247-1 (80 g, 80.11%) as a yellow solid.

3. Synthesis of 247-3

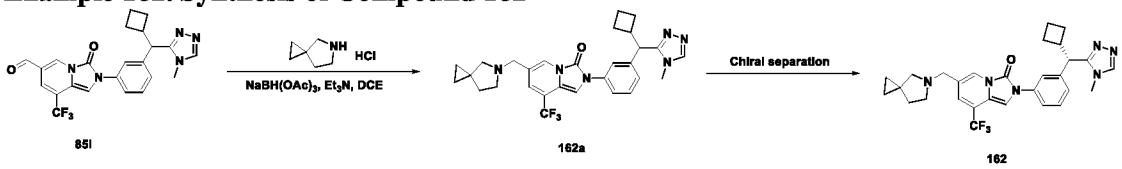
[578] To a stirred solution of 247-2 (40 g, 79.000 mmol, 1 equiv) and TMEDA (18.36 g, 158.000 mmol, 2 equiv) in 1,4-dioxane (1.2 L) were added Pd(OAc)2 (1.77 g, 7.884 mmol, 0.10 equiv) and bis(adamantan-1-yl)(butyl)phosphane (5.66 g, 15.786 mmol, 0.20 equiv) at room temperature. The mixture was purged with nitrogen for 3min and then was pressurized to 10atm with CO:H2=1:1 at 80°C for overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (30:1) to afford 247-3 (24 g, 63.37%) as a yellow solid.

4. Synthesis of 161

[579] To a stirred solution of 247-3 (76 g, 166.871 mmol, 1.00 equiv) and 4-fluoro-4-methylpiperidine hydrochloride (38.45 g, 250.307 mmol, 1.5 equiv) in DCE (1000 mL) were added TEA (33.77 g, 333.742 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (70.73 g, 333.742 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with NH4Cl (aq.) (1500 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x1500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH4HCO3), 30% to 55% gradient in 20 min; detector, UV 254 nm. This resulted in 161 (28.0756 g, 29.77%) as a yellow solid.

LCMS-161: (ES, m/z): [M+H]+ 557. H-NMR-161: (400 MHz, DMSO-d6, δ ppm): 1.30-1.42 (d, 3H), 1.61-1.81 (m, 9H), 2.02-2.18 (m, 1H), 2.23-2.34 (m, 2H), 2.59-2.65 (m, 2H), 3.18-3.23 (m, 1H), 3.25 (s, 2H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.74 (m, 3H), 8.33 (s, 1H).

Example 162. Synthesis of Compound 162



Synthesis of 162a

[580] To a stirred solution of 5-azaspiro[2.4]heptane hydrochloride (352.06 mg, 2.635 mmol, 1.5 equiv) and 85i (800 mg, 1.757 mmol, 1.00 equiv) in DCE (8 mL) was added Et_3N (533.23 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at 0 °C. To the above mixture was added $NaBH(OAc)_3$ (1116.85 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of 30 mL H_2O at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 162a (400 mg) as a yellow solid. 162a (400 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 65% B in 8 min, Wave Length: 220 nm; RT1(min): 7.15) to afford 162a (240 mg, 24.95%) as a yellow solid.

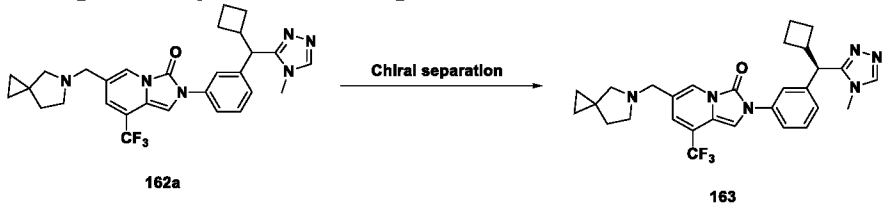
Synthesis of 162

[581] 162a (240 mg) was purified by chiral separation separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT1 (min): 7.75, RT2 (min): 10.35, the first peak is product) to afford Compound 162 (109.2 mg, 45.27%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 537.

H-NMR: (400 MHz, $DMSO-d_6$, ppm): δ0.51-0.53 (d, 4H), 1.70-1.80 (m, 7H), 2.07-2.09 (m, 1H), 2.45-2.50 (m, 2H), 2.66-2.69 (m, 2H), 3.13-3.25 (m, 1H), 3.39 (s, 2H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.73 (m, 3H), 8.32 (s, 1H).

Example 163. Synthesis of Compound 163



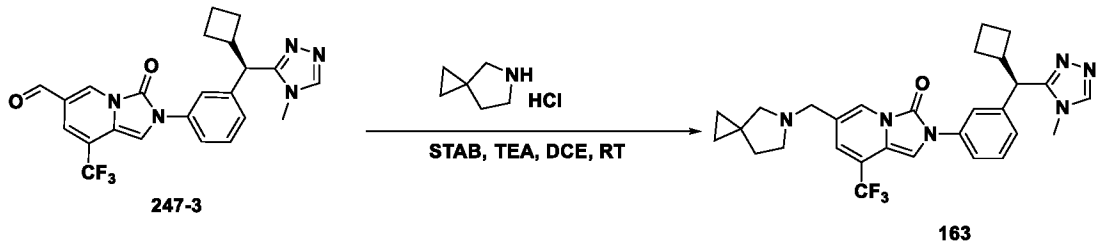
Synthesis of 163

[582] 162a (240 mg) was purified by Prep-Chiral-HPLC separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT1 (min): 7.75, RT2 (min): 10.35, the second peak is product) to afford Compound 163 (104.6 mg, 45.50%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 537.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ0.51-0.53 (d, 4H), 1.73-1.80 (m, 7H), 2.05-2.14 (m, 1H), 2.46-2.49 (m, 2H), 2.66-2.68 (m, 2H), 3.19-3.25 (m, 1H), 3.40-3.43 (m, 5H), 4.25-4.27 (d, 1H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.73 (m, 3H), 8.33 (s, 1H).

Alternatively, compound 163 may be also prepared in the manner outlined below:

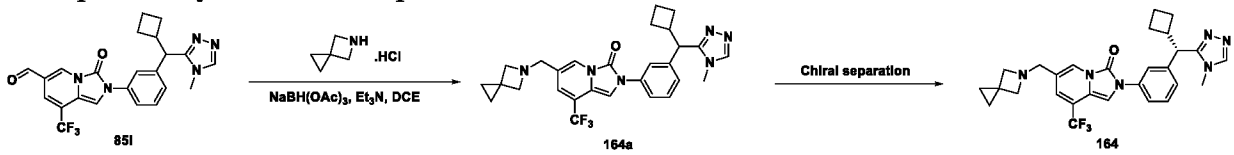


1. Synthesis of 163

To a stirred mixture of 247-3 (50 g, 109.784 mmol, 1 equiv) and 5-azaspiro[2.4]heptane (16.00 g, 164.676 mmol, 1.5 equiv) in DCE (500 mL) was added TEA (22.22 g, 219.568 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (46.54 g, 219.568 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The residue was dissolved in water (1000 mL). The aqueous layer was extracted with CH_2Cl_2 (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 15% to 50% gradient in 45 min; detector, UV 254 nm. This resulted in 163 (25.6175 g, 43.49%) as a yellow solid.

LC-MS-163: (ES, *m/z*): $[M+H]^+$ 537. H-NMR-163: (400 MHz, DMSO-d_6, δ *ppm*): 0.50-0.52 (m, 4H), 1.68-1.81 (m, 7H) 2.08-2.09 (m, 1H), 2.46-2.51 (m, 2H), 2.67-2.70 (m, 2H) 3.19-3.25 (m, 1H) 3.31-3.43(m, 5H) 4.25-4.27 (m, 3H), 7.04 (d, 1H), 7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.42-7.46 (m,1H), 7.67 (m, 1H), 7.70-7.73 (m, 1H), 8.32 (s, 1H).

Example 164. Synthesis of Compound 164



Synthesis of 164a

[583] To a stirred solution of 85i (800 mg, 1.757 mmol, 1 equiv) and 5-azaspiro [2.3] hexane hydrochloride (421.7 mg, 3.514 mmol, 2 equiv) in DCE (10 mL) were added TEA (355.49 mg, 3.514 mmol, 2 equiv) and $NaBH(OAc)_3$ (744.57 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (15mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 20mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (550mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 7.65) to afford 164a (400 mg, 42.71%) as a yellow solid.

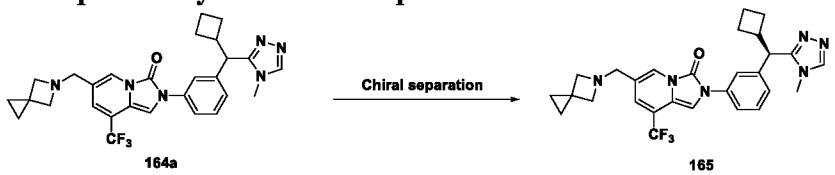
Synthesis of 164

[584] The 164a (400 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)- -HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 50% B in 16 min; Wave Length: 220/254 nm; RT1(min): 9.69; RT2(min): 12.92; The first peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 6) to afford Compound 164 (152.5 mg, 37.71%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:523

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.52-0.56 (m, 4H), δ 1.73-1.86 (m, 5H), δ 2.02-2.16 (m, 1H), δ 3.18-3.21 (m, 1H), δ 3.31-3.35 (m, 4H), δ 3.45 (s, 3H), δ 3.51-3.62 (m, 2H), δ 4.62-4.64 (d, 1H), δ 7.02 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 3H), δ 7.67-7.73 (m, 3H), δ 8.33 (s, 1H).

Example 165. Synthesis of Compound 165



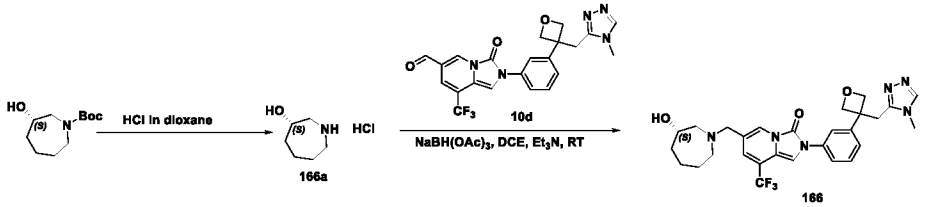
Synthesis of 165

[585] The 164a (400 mg, 0.765 mmol, 1 equiv) (400 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)- -HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 45% B to 50% B in 16 min; Wave Length: 220/254 nm; RT1(min): 9.69; RT2(min): 12.92; The second peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 6) to afford Compound 165 (132.5 mg, 33.03%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:523

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 0.52-0.56 (m, 4H), δ 1.73-1.86 (m, 5H), δ 2.02-2.16 (m, 1H), δ 3.18-3.21 (m, 1H), δ 3.31-3.35 (m, 4H), δ 3.45 (s, 3H), δ 3.51-3.62 (m, 2H), δ 4.62-4.64 (d, 1H), δ 7.02 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 3H), δ 7.67-7.73 (m, 3H), δ 8.33 (s, 1H).

Example 166. Synthesis of Compound 166



Synthesis of 166a

[586] Into a 20 mL sealed tube were added tert-butyl (3S)-3-hydroxyazepane-1-carboxylate (500 mg, 2.32 mmol, 1.0 equiv) and HCl (gas) in 1,4-dioxane (5 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 166a (250 mg, 71%) as an off-white solid.

Synthesis of 166

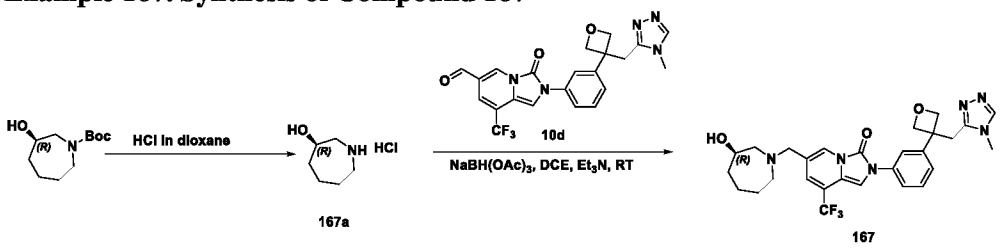
[587] To a stirred solution of 10d (150 mg, 0.32 mmol, 1.0 equiv) and 166a (149 mg, 0.98 mmol, 3.0 equiv) in DCE (3 ml) were added Et_3N (99 mg, 0.98 mmol, 3.0 equiv) and $NaBH(OAc)_3$ (139 mg, 0.66 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat

NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford crude product (100 mg). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 49% B in 8 min; Wave Length: 220 nm; RT1(min): 7.43) to afford Compound 166 (33 mg, 18%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 557

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 1.35-1.45 (m, 2H), 1.55-1.70 (m, 3H), 1.72-1.82 (m, 1H), 2.36-2.40 (m, 1H), 2.52-2.57 (m, 1H), 2.61-2.78 (m, 2H), 2.96 (s, 3H), 3.43 (s, 2H), 3.53 (s, 2H), 3.60-3.64 (m, 1H), 4.39-4.41 (d, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.07 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.69 (s, 1H), 7.74-7.75 (d, 1H), 8.20 (s, 1H).

Example 167. Synthesis of Compound 167



Synthesis of 167a

[588] Into a 20 mL sealed tube were added tert-butyl (3R)-3-hydroxyazepane-1-carboxylate (500 mg, 2.32 mmol, 1.0 equiv) and HCl (gas) in 1,4-dioxane (5 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford 167a (250 mg, 71%) as an off-white solid.

Synthesis of 167

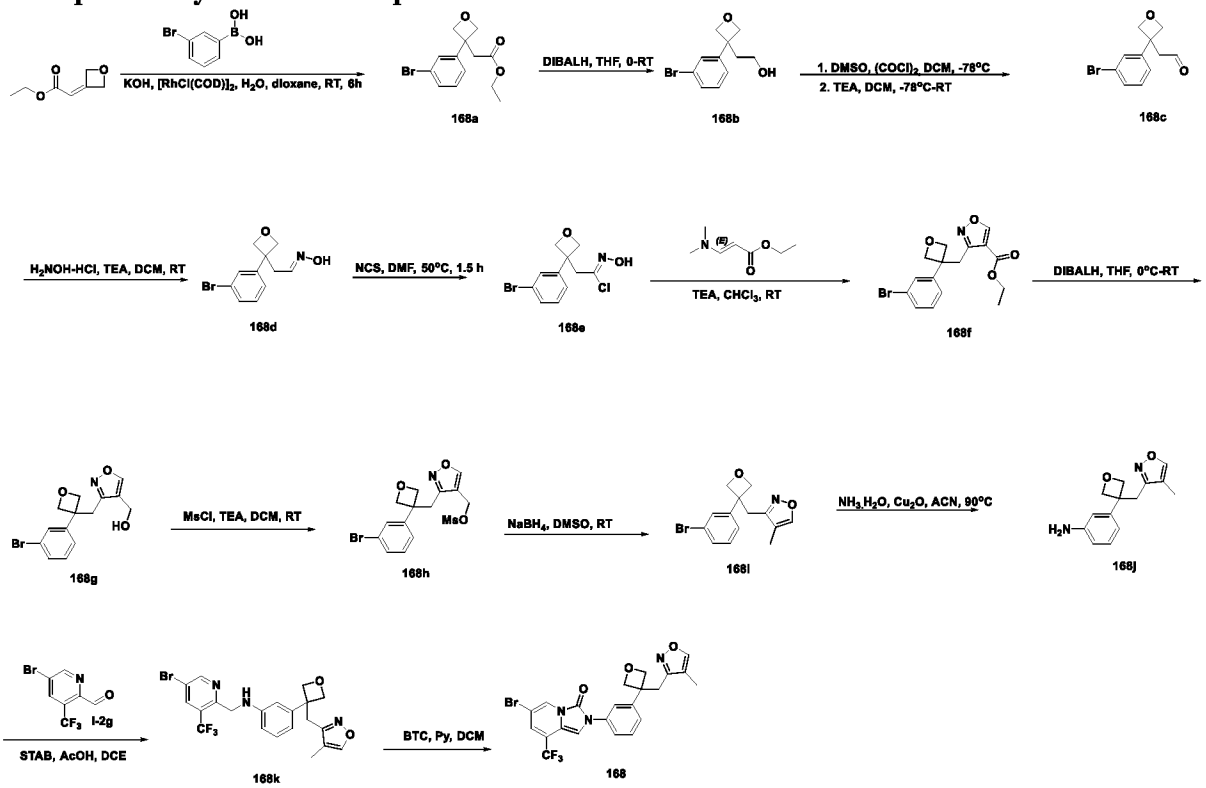
[589] To a stirred solution of 10d (150 mg, 0.32 mmol, 1.0 equiv) and 167a (149 mg, 0.98 mmol, 3.0 equiv) in DCE (3 ml) were added Et_3N (99 mg, 0.98 mmol, 3.0 equiv) and $NaBH(OAc)_3$ (139 mg, 0.66 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford crude product (100 mg). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column:

XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 49% B in 8 min; Wave Length: 220 nm; RT1(min): 7.43) to afford Compound 167 (28 mg, 15%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 557

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 1.35-1.45 (m, 2H), 1.55-1.70 (m, 3H), 1.72-1.82 (m, 1H), 2.36-2.40 (m, 1H), 2.52-2.57 (m, 1H), 2.61-2.78 (m, 2H), 2.96 (s, 3H), 3.43 (s, 2H), 3.53 (s, 2H), 3.60-3.64 (m, 1H), 4.39-4.41 (d, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.07 (s, 1H), 7.31 (s, 1H), 7.38-7.42 (m, 2H), 7.69 (s, 1H), 7.74-7.75 (d, 1H), 8.20 (s, 1H).

Example 168. Synthesis of Compound 168



Synthesis of 168a

[590] Into a 2 L 3-necked round-bottom flask were added bis((1Z,5Z)-cycloocta-1,5-diene); bis(chlororhodium) (2.08 g, 4.221 mmol, 0.02 equiv), dioxane (750 mL), H_2O (150 mL), and KOH (17.76 g, 316.558 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. To the above mixture was added 3-bromophenylboronic acid (50.86 g, 253.247 mmol, 1.2 equiv) and ethyl 2-(oxetan-3-ylidene)acetate (30 g, 211.039 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of

saturated aqueous NH_4Cl (1000 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (12:1) to afford 168a (40 g, 63.36%) as a light yellow oil.

Synthesis of 168b

[591] Into a 500 mL 3-necked round-bottom flask were added 168a (20 g, 66.853 mmol, 1 equiv), THF (200 mL) and DIBALH (33.91 mL, 167.132 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: SNP C18 330 g; Mobile Phase A: Water(0.1%NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B to 32% B in 15 min; 220 nm; to afford 168b (15 g, 87.26%) as a light brown oil.

Synthesis of 168c

[592] To a stirred solution of DCM (30 mL) and $(COCl)_2$ (5.92 g, 46.669 mmol, 1.20 equiv) was added DMSO (0.8 mL) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 20 min at -78°C under nitrogen atmosphere. To the above mixture was added 168b (10 g, 38.891 mmol, 1 equiv) at -78°C. The resulting mixture was stirred for additional 1 h at -78°C. To the above mixture was added TEA (20.42 g, 201.844 mmol, 5.19 equiv) dropwise at -78°C. The resulting mixture was stirred for additional 10 min at -78°C. The final reaction mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: SNAP C18 330 g; Mobile Phase A: Water(0.1%NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B to 32% B in 15 min; 220 nm;) to afford 168c (5.5 g, 55.43%) as a light brown oil.

Synthesis of 168d

[593] Into a 250 mL 3-necked round-bottom flask was added 168c (5.5 g, 21.559 mmol, 1 equiv), DCM (60 mL), TEA (6.54 g, 64.677 mmol, 3 equiv) and $NH_2OH.HCl$ (2.95 g, 43.118 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture

was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 168d (5.5 g, 94.44%) as a light yellow oil.

Synthesis of 168e

[594] Into a 250 mL round-bottom flask were added 168d (5.2 g, 19.250 mmol, 1 equiv), DMF (60 mL), and NCS (3.86 g, 28.875 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2 h at 50°C under nitrogen atmosphere. The reaction was quenched by the addition of water (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure to afford 168e (6 g, 102.34%) as a light brown oil. The crude product was used in the next step directly without further purification.

Synthesis of 168f

[595] Into a 250 mL 3-necked round-bottom flask were added 168e (6 g, 19.700 mmol, 1 equiv), $CHCl_3$ (100 mL), ethyl (2E)-3-(dimethylamino)prop-2-enoate (4.23 g, 29.550 mmol, 1.5 equiv), and TEA (2.99 g, 29.550 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 168f (2.2 g, 30.49%) as a light brown oil.

Synthesis of 168g

[596] Into a 100 mL 3-necked round-bottom flask were added 168f (2 g, 5.461 mmol, 1 equiv), THF (20 mL) and DIBAL-H (1.94 g, 13.652 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: C18 Column, 330 g; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 70% B in 8 min, 70% B; Wave Length: 220 nm; RT1(min): 7.65 to afford 168g (1 g, 52.53%) as a white oil.

Synthesis of 168h

[597] Into a 100 mL round-bottom flask were added 168g (1 g, 3.085 mmol, 1 equiv), DCM (15 mL), TEA (0.62 g, 6.170 mmol, 2 equiv) and MsCl (0.53 g, 4.627 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The

reaction was quenched by the addition of water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure to afford 168h (1 g, 80.59%) as a brown oil.

Synthesis of 168i

[598] Into a 100 mL round-bottom flask were added 168h (1 g, 2.486 mmol, 1 equiv), DMSO (15 mL), and $NaBH_4$ (0.19 g, 4.972 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x25 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (Column: C18 Column,120 g; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 40% B in 10 min; Wave Length: 220 nm; RT1(min): 10) to afford 168i (400 mg, 52.21%) as a brown solid.

Synthesis of 168j

[599] Into a 50 mL sealed tube were added 168i (400 mg, 1.298 mmol, 1 equiv), ACN (8 mL), $NH_3.H_2O$ (8 mL) and Cu_2O (371.45 mg, 2.596 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 90°C under nitrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with MeCN (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 168j (110 mg, 34.69%) as a light yellow solid.

Synthesis of 168k

[600] Into a 8 mL sealed tube were added 168j (20 mg, 0.082 mmol, 1 equiv), DCE (1 mL), I-2g (22.87 mg, 0.090 mmol, 1.1 equiv), AcOH (4.92 mg, 0.082 mmol, 1 equiv), and STAB (34.70 mg, 0.164 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 168k (21 mg, 53.18%) as a light yellow solid.

Synthesis of 168

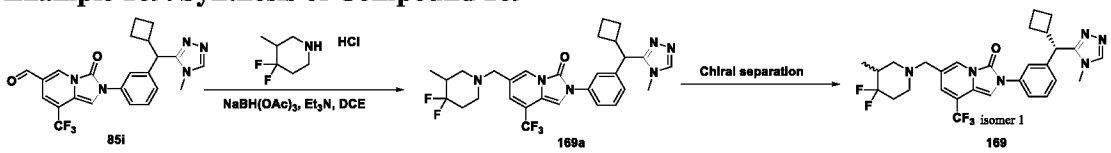
[601] Into a 8 mL sealed tube were added 168k (21 mg, 0.044 mmol, 1 equiv), DCM (1 mL), Pyridine (17.22 mg, 0.220 mmol, 5 equiv) and Triphosgene (9.04 mg, 0.031 mmol, 0.7 equiv) at room temperature. The resulting mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The

resulting mixture was concentrated under reduced pressure. The crude product (20 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 70% B in 8 min, 70% B; Wave Length: 254 nm; RT1(min): 7.65) to afford Compound 168 (12.0 mg, 54.22%) as a Brown yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 508

H-NMR: 1H NMR (300 MHz, CD_3OD-d4, *ppm*, δ) 1.35 (s, 3H), 3.48 (s, 2H), 4.99-5.01 (d, 2H), 5.05-5.06 (d, 2H), 6.99-7.00 (d, 1H), 7.08 (s, 1H), 7.16 (s, 1H), 7.36 (s, 1H), 7.44-7.48 (m, 1H), 7.62-7.64 (d, 1H), 7.97 (s, 1H), 8.18 (s, 1H).

Example 169. Synthesis of Compound 169



Synthesis of 169a

[602] To a stirred solution of 85i (1.5 g, 3.296 mmol, 1 equiv), 4,4-difluoro-3-methylpiperidine hydrochloride (680 mg,3.955 mmol, 1.2 equiv) in DCE (15 mL) were added Et_3N (0.67 g, 6.588 mmol, 2 equiv) and $NaBH(OAc)_3$ (1.40 g, 6.588 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (30mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 40mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (800mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 62% B in 7 min; Wave Length: 220 nm; RT1(min): 7.97) to afford 169a (500 mg, 25.89%) as a yellow solid.

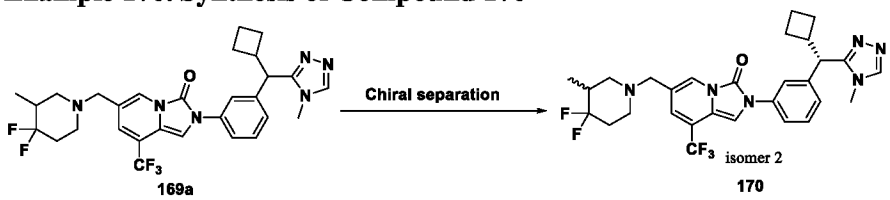
Synthesis of 169

[603] The 169a (500 mg, 0.870 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 42% B to 50% B in 20 min; Wave Length: 220/254 nm; RT(min): 7.21; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 8) to afford Compound 169 (72.5 mg, 14.40%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:575

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.01-1.03 (d, 3H), δ 1.73-1.74 (d, 1H), δ 1.81-1.98 (m, 5H), δ 2.01-2.21 (m, 4H), δ 2.23-2.24 (d, 1H), δ 2.31-2.34 (m, 1H), δ 2.81-2.95 (m, 2H), δ 3.42-3.42 (d, 2H), δ 3.68 (s, 3H), δ 4.30-4.31 (d, 1H), δ 7.11-7.13 (d, 1H), δ 7.26 (s, 1H), δ 7.46-7.47 (d, 1H), δ 7.62-7.75 (m, 3H), δ 8.41 (s, 1H).

Example 170. Synthesis of Compound 170



169a 170

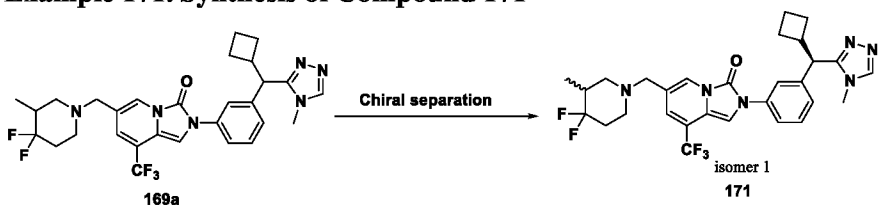
Synthesis of 170

[604] The 169a (500 mg, 0.870 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)- -HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 50% B in 20 min; Wave Length: 220/254 nm; RT(min): 8.78; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 8) to afford Compound 170 (82.9 mg, 16.45%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:575

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.01-1.03 (d, 3H), δ 1.73-1.74 (d, 1H), δ 1.81-1.98 (m, 5H), δ 2.01-2.21 (m, 4H), δ 2.23-2.24 (d, 1H), δ 2.31-2.34 (m, 1H), δ 2.81-2.95 (m, 2H), δ 3.42-3.42 (d, 2H), δ 3.68 (s, 3H), δ 4.30-4.31 (d, 1H), δ 7.11-7.13 (d, 1H), δ 7.26 (s, 1H), δ 7.46-7.47 (d, 1H), δ 7.62-7.75 (m, 3H), δ 8.41 (s, 1H).

Example 171. Synthesis of Compound 171



169a 171

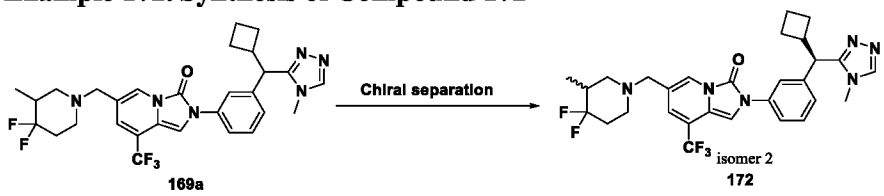
Synthesis of 171

[605] The 169a (500 mg, 0.870 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)- -HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 45% B to 50% B in 20 min; Wave Length: 220/254 nm; RT(min): 9.88; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 8) to afford Compound 171 (83.9 mg, 16.73%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:575

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.01-1.03 (d, 3H), δ 1.73-1.74 (d, 1H), δ 1.81-1.98 (m, 5H), δ 2.01-2.21 (m, 4H), δ 2.23-2.24 (d, 1H), δ 2.31-2.34 (m, 1H), δ 2.81-2.95 (m, 2H), δ 3.42-3.42 (d, 2H), δ 3.68 (s, 3H), δ 4.30-4.31 (d, 1H), δ 7.11-7.13 (d, 1H), δ 7.26 (s, 1H), δ 7.46-7.47 (d, 1H), δ 7.62-7.75 (m, 3H), δ 8.41 (s, 1H).

Example 172. Synthesis of Compound 172



169a 172

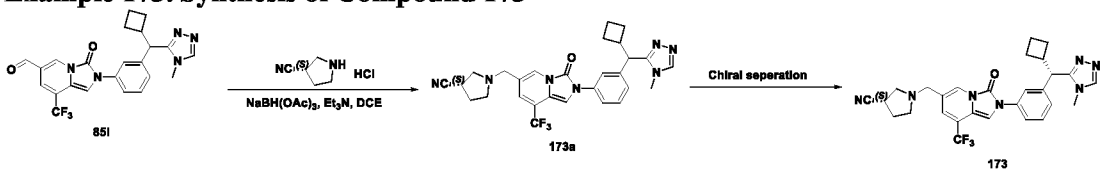
Synthesis of 172

[606] The 169a (500 mg, 0.870 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)- -HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 47% B to 50% B in 20 min; Wave Length: 220/254 nm; RT(min): 14.73; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 8) to afford Compound 172 (88.6 mg, 17.72%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:575

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.01-1.03 (d, 3H), δ 1.73-1.74 (d, 1H), δ 1.81-1.98 (m, 5H), δ 2.01-2.21 (m, 4H), δ 2.23-2.24 (d, 1H), δ 2.31-2.34 (m, 1H), δ 2.81-2.95 (m, 2H), δ 3.42-3.42 (d, 2H), δ 3.68 (s, 3H), δ 4.30-4.31 (d, 1H), δ 7.11-7.13 (d, 1H), δ 7.26 (s, 1H), δ 7.46-7.47 (d, 1H), δ 7.62-7.75 (m, 3H), δ 8.41 (s, 1H).

Example 173. Synthesis of Compound 173



85l 173a 173

Synthesis of 173a

[607] To a stirred solution of 85l (800 mg, 1.757 mmol, 1 equiv) and (s)-pyrrolidine-3-carbonitrile hydrochloride (463.73 mg, 3.514 mmol, 2 equiv) in DCE (10 mL) were added Et_3N (355.49 mg, 3.514 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (744.57 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for an additional 3h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. The aqueous layer was extracted with DCM

(2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford the crude product. The crude product (700 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 49% B in 9 min, 49% B; Wave Length: 220 nm; RT1(min): 8.87) to afford 173a (350 mg, 35.34%) as a yellow solid.

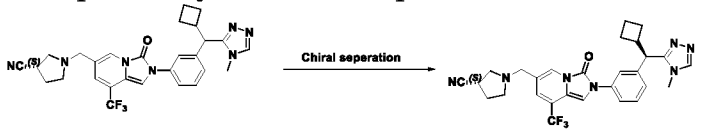
Synthesis of 173

[608] The 173a (350 mg, 0.654 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 14 min; Wave Length: 220/254 nm; RT1(min): 7.06; RT2(min): 10.54, the first peak is product) to afford Compound 173 (147.4 mg, 41.90%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 536

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.70-1.83 (m, 5H), 1.95-2.01 (m, 1H), 2.08-2.13 (m, 1H), 2.13-2.25 (m, 1H), 2.50-2.51 (m, 1H), 2.68-2.82 (m, 3H), 3.24-3.30 (m, 2H), 3.43-3.44 (m, 5H), 4.25-4.27 (d, 2H), 7.03 (s, 1H), 7.18-7.20 (m, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H),.

Example 174. Synthesis of Compound 174



173a 174

Synthesis of 174

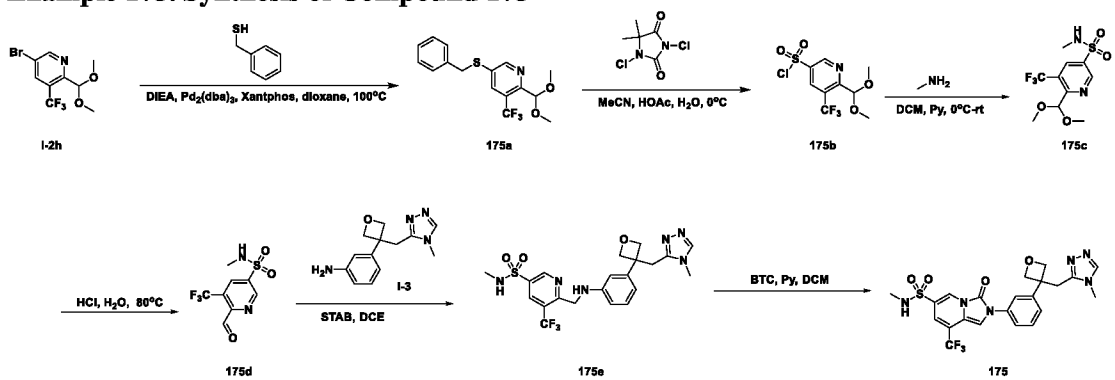
[609] The 173a (350 mg, 0.654 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 14 min; Wave Length: 220/254 nm; RT1(min): 7.06; RT2(min): 10.54, the second peak is product) to afford Compound 174 (140.8 mg, 39.87%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 536

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.70-1.83 (m, 5H), 1.95-2.01 (m, 1H), 2.08-2.13 (m, 1H), 2.13-2.25 (m, 1H), 2.50-2.51 (m, 1H), 2.68-2.82 (m, 3H), 3.24-3.30 (m, 2H), 3.43-3.44

(m, 5H), 4.25-4.27 (d, 2H), 7.03 (s, 1H), 7.18-7.20 (m, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H),.

Example 175. Synthesis of Compound 175



Synthesis of 175a

[610] Into a 40 mL vial were added I-2h (1 g, 3.333 mmol, 1 equiv), benzyl mercaptan (0.62 g, 5.000 mmol, 1.5 equiv), DIEA (0.86 g, 6.666 mmol, 2 equiv), XantPhos (0.39 g, 0.667 mmol, 0.2 equiv), $Pd_2(dba)_3$ (0.31 g, 0.333 mmol, 0.1 equiv), and dioxane (15 mL) at room temperature. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (150 mL). The aqueous layer was extracted with EtOAc (3x60 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 175a (750 mg, 60.30%) as an orange oil.

Synthesis of 175b

[611] Into a 50 mL round-bottom flask were added 175a (750 mg, 2.184 mmol, 1 equiv), ACN (8 mL), HOAc (0.3 mL) and H_2O (0.1 mL) at room temperature. To the above mixture was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (645.53 mg, 3.276 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for 5 h at 0 °C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The crude product 175b (800 mg) obtained as a colorless oil was used in the next step directly without further purification.

Synthesis of 175c

[612] Into a 50 mL round-bottom flask were added 175b (800 mg, 2.503 mmol, 1 equiv), DCM (10 mL) and pyridine (593.84 mg, 7.509 mmol, 3 equiv) at room temperature. To the above mixture was added methylamine (5 mL, 2.5 mol/L in THF, 12.515 mmol, 5 equiv) dropwise at room temperature. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-

TLC (DCM / MeOH 40:1) to afford 175c (500 mg, 60.40%) as a colorless oil.

Synthesis of 175d

[613] Into a 40 mL vial were added 175c (500 mg, 1.591 mmol, 1 equiv) and HCl (10 mL, 1mol/L in H_2O) at room temperature. The resulting mixture was stirred for 3 h at 80 °C. The residue was neutralized to pH 8 with sat. $NaHCO_3$ (aq.) (30 ml). The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 175d (300 mg, 66.79%) as a colorless oil.

Synthesis of 175e

[614] Into a 25 mL vial were added 175d (240 mg, 0.895 mmol, 1 equiv), I-3 (262.32 mg, 1.074 mmol, 1.2 equiv) and DCE (5 mL) at room temperature. To the above mixture was added STAB (379.30 mg, 1.790 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 175e (120 mg, 25.66%) as an off-white solid.

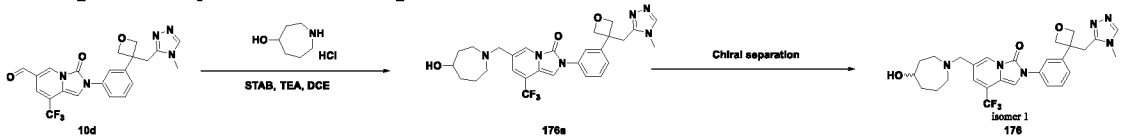
Synthesis of 175

[615] Into a 50 mL round-bottom flask were added 175e (120 mg, 0.242 mmol, 1 equiv), pyridine (152.94 mg, 1.936 mmol, 8 equiv) and DCM (10 mL) at room temperature. To the above mixture was added triphosgene (50.20 mg, 0.169 mmol, 0.7 equiv) at room temperature. The resulting mixture was stirred for 5 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x25 mL). The resulting mixture was concentrated under vacuum. The crude product (120 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 40% B in 8 min; Wave Length: 220 nm; RT1(min): 7.85) to afford Compound 175 (30.9 mg, 23.88%) as an orange solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 523

H-NMR: 1H NMR (400 MHz, DMSO-d6) δ2.99 (s, 3H), δ3.33 (s, 3H), δ3.54 (s, 2H), δ4.91-4.96 (m, 4H), δ6.93-6.95 (d, 1H), δ7.11 (s, 1H), δ7.41-7.45 (m, 2H), δ7.56 (s, 1H), δ7.68-7.75 (m, 2H), δ8.02 (s, 1H), δ8.21 (s, 1H).

Example 176. Synthesis of Compound 176



10d 176a 176

Synthesis of 176a

[616] To a stirred mixture of azepan-4-ol hydrochloride (596.69 mg, 3.936 mmol, 3 equiv) and 10d (600 mg, 1.312 mmol, 1.00 equiv) in DCE (6 mL) were added Et_3N (398.20 mg, 3.936 mmol, 3 equiv) and $NaBH(OAc)_3$ (556.02 mg, 2.624 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 176a (280 mg, 38.35%) as yellow solid.

Synthesis of 176

[617] 176a (200 mg) was purified by Chiral separation with the following conditions (Column: DZ-CHIRALPAK IE-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: MtBE(0.2% DEA) : (EtOH: DCM=1: 1) = 45: 55; Flow rate: 1 mL/min; Gradient: 40% B to 50% B; Injection Volume: 5ul mL in 15 min; 220/254 nm; RT1 14.36 min; RT2: 23.94 min. The first peak was the product). The resulting mixture was concentrated under reduced pressure. This resulted in Compound 176 (74.1 mg, 37.05%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 557

H-NMR: (400 MHz, DMSO, δ ppm): 1.71-1.80 (m, 4H), 1.95-1.99 (m, 2H), 2.71-2.76 (m, 4H), 2.96 (s, 3H), 3.49 (s, 2H), 3.68 (s, 2H), 3.91-3.93 (t, 1H), 5.07-5.08 (d, 4H), 6.88-6.89 (m, 1H), 6.90-7.13 (m, 2H), 7.31-7.32 (t, 1H), 7.45-7.49 (m, 1H), 7.62-7.63 (m, 1H), 7.64-7.68 (m, 1H), 8.20 (s, 1H).

Example 177. Synthesis of Compound 177



176a 177

Synthesis of 177

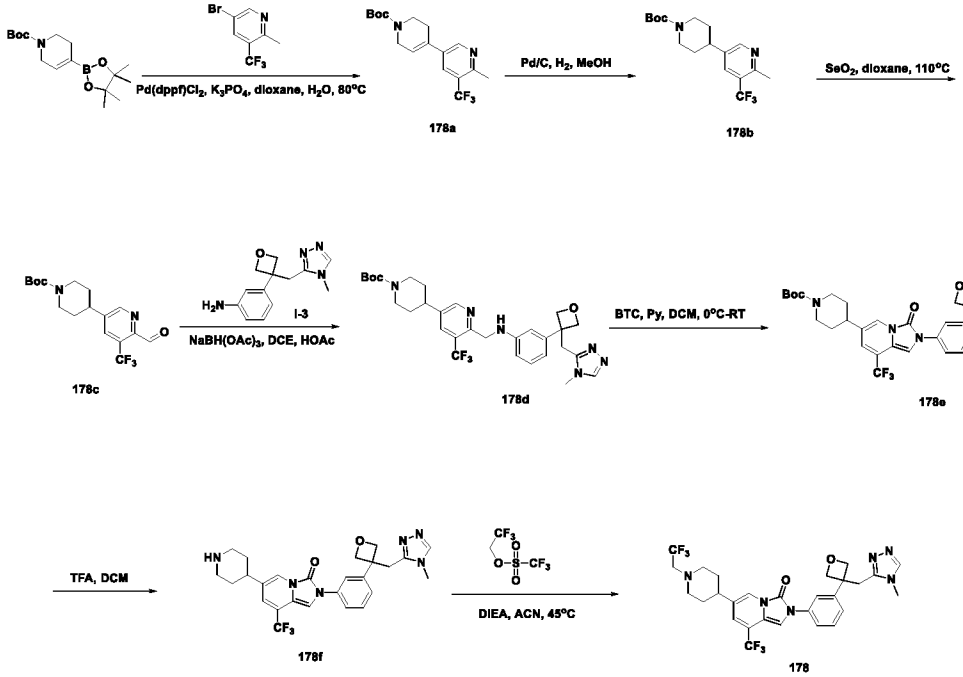
[618] 176a (200 mg) was purified by Chiral separation with the following conditions (Column: DZ-CHIRALPAK IE-3, 4.6*50 mm, 3.0 μm; Mobile Phase A: MtBE(0.2% DEA) :

(EtOH: DCM=1: 1) = 45: 55; Flow rate: 1 mL/min; Gradient: 50% B to 50% B; Injection Volume: 5ul mL in 23 min; 220/254 nm; RT1 14.36 min; RT2: 23.94 min. The second peak was the product). The resulting mixture was concentrated under reduced pressure. This resulted in 177 (76.5 mg, 38.25%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 557

H-NMR: (400 MHz, DMSO, δ ppm): 1.71-1.76 (d, 2H), 1.84-1.86 (d, 2H), 1.94-2.04 (m, 2H), 2.78-2.96 (m, 7H), 3.67-3.68 (d, 4H), 3.95-3.97 (t, 1H), 5.07-5.10 (t, 4H), 6.90-6.93 (m, 1H), 7.14 (s, 2H), 7.30-7.31 (m, 1H), 7.45-7.49 (m, 1H), 7.62-7.65 (m, 1H), 7.76 (s, 1H), 8.20 (s, 1H).

Example 178. Synthesis of Compound 178



Synthesis of 178a

[619] Into a 250 mL 3-necked round-bottom flask were added tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyridine-1-carboxylate (3.86 g, 12.499 mmol, 1 equiv), 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (3 g, 12.499 mmol, 1 equiv), K_3PO_4 (7.96 g, 37.497 mmol, 3 equiv), $Pd(dppf)Cl_2$ (1.37 g, 1.875 mmol, 0.15 equiv), dioxane (40 mL), and H_2O (10 mL) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched with water (60 ml) at room temperature. The aqueous layer was extracted with EtOEt (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 178a (4.1 g, 95.81%) as a

yellow oil.

Synthesis of 178b

[620] Into a 250mL round-bottom flask were added 178a (4.1 g, 11.976 mmol, 1 equiv), MeOH (60 ml), and Pd/C (10%, 0.4 g) at room temperature. The resulting mixture was stirred overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered through filter paper then the filter cake was washed with MeOH (3x10 mL). The filtrate as concentrated under reduced pressure. This resulted in 178b (3.6 g, 80.31%) as an orange oil.

Synthesis of 178c

[621] Into a 250 mL 3-necked round-bottom flask were added 178b (3.6 g, 10.454 mmol, 1 equiv), SeO_2 (4.64 g, 41.816 mmol, 4 equiv) and dioxane (40 mL) at room temperature. The resulting mixture was stirred overnight at 110°C. The precipitated solids were collected by filtration and washed with dioxane (3x10 mL). The filtrate as concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 178c (1.2 g, 30.11%) as a brown yellow oil.

Synthesis of 178d

[622] A solution of 178c (280 mg, 0.781 mmol, 1 equiv) in DCE (5 mL) was treated with I-3 (190.88 mg, 0.781 mmol, 1 equiv) for 1h at room temperature followed by the addition of HOAc (93.84 mg, 1.562 mmol, 2 equiv) and $NaBH(OAc)_3$ (331.19 mg, 1.562 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (5 ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 178d (240 mg, 52.36%) as a yellow solid.

Synthesis of 178e

[623] To a stirred solution of 178d (220 mg, 0.375 mmol, 1 equiv) and Pyridine (59.33 mg, 0.750. mmol, 2 equiv) in DCM (4 mL) were added Triphosgene (44.51 mg, 0.150 mmol, 0.4 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) (4 ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 178e (160 mg, 69.64%) as a yellow solid.

Synthesis of 178f

[624] Into an 8 mL vial were added 178e (150 mg, 0.245 mmol, 1 equiv), DCM (3 mL) and TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 178f (120 mg, 95.63%) as a yellow solid.

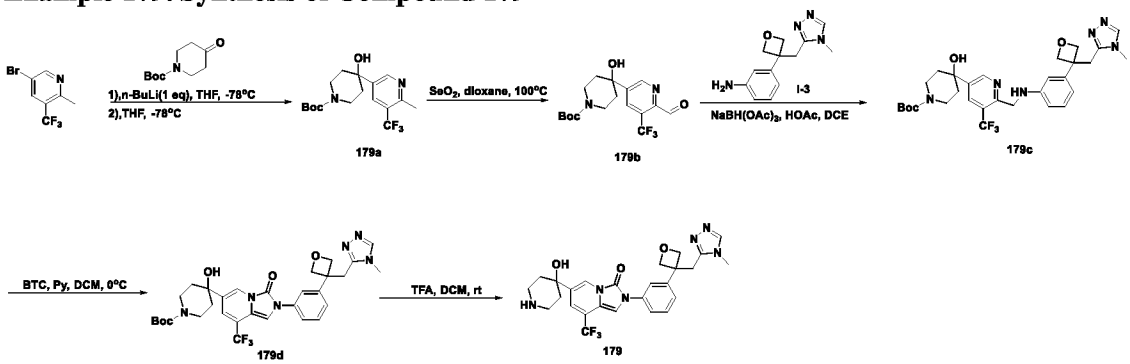
Synthesis of 178

[625] Into an 8 mL vial were added 178f (110 mg, 0.215 mmol, 1 equiv), 2,2,2-trifluoroethyl trifluoromethanesulfonate (99.63 mg, 0.430 mmol, 2 equiv), ACN (2 mL), and DIEA (83.21 mg, 0.645 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 45°C under nitrogen atmosphere. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (10:1) (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude product (100 mg). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 50% B to 72% B in 11 min; Wave Length: 220 nm; RT1(min): 10.85) to afford Compound 178 (47.3 mg, 37.07%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 595

H-NMR: (400 MHz, DMSO-d6, ppm): δ1.59-1.62 (m, 2H), δ1.74-1.77 (m, 2H), δ2.42-2.50 (m, 3H), δ2.97 (s, 3H), δ3.00-3.03 (m, 2H), δ3.19-3.25 (m, 2H), δ3.53 (s, 2H), δ4.96-4.98 (dd, 4H), δ6.88-6.90 (d, 1H), δ7.14 (s, 1H), δ7.30 (s, 1H), δ7.38-7.42 (t, 2H), δ7.50 (s, 1H), δ7.74-7.76 (dd, 1H), δ8.20 (s, 1H).

Example 179. Synthesis of Compound 179



Synthesis of 179a

[626] To a stirred solution of 5-bromo-2-methyl-3-(trifluoromethyl) pyridine (5 g, 20.831 mmol, 1 equiv) in THF (60 mL) were added n-BuLi (1.60 g, 24.997 mmol, 1.2 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at -

78°C under nitrogen atmosphere. To the above mixture was added tert-butyl 4-oxopiperidine-1-carboxylate (4.98 g, 24.997 mmol, 1.2 equiv). The resulting mixture was stirred for additional 1h at -78°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (70mL) at -78°C. The resulting mixture was extracted with EtOAc (2 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (1:1) to afford 179a (3 g, 36.77%) as a colorless oil.

Synthesis of 179b

[627] To a stirred solution of 179a (1.5 g, 4.162 mmol, 1 equiv) in dioxane (20 mL) were added SeO2 (1.85 g, 16.648 mmol, 4 equiv) at room temperature under air atmosphere. The resulting mixture was stirred overnight at 120°C under air atmosphere. The resulting mixture was filtered through filter paper and the filter cake was washed with 1,4-dioxane (2x20 mL). The filtrate was concentrated under reduced pressure. The reaction was quenched by the addition of Water (40mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 60mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (5:1) to afford 179b (500 mg, 29.52%) as a colorless oil.

Synthesis of 179c

[628] To a stirred solution of 179b (500 mg, 1.336 mmol, 1 equiv) and I-3 (391.55 mg, 1.603 mmol, 1.2 equiv) in DCE (10 mL) were added $NaBH(OAc)_3$ (566.14 mg, 2.672 mmol, 2 equiv) and HOAc (80.21 mg, 1.336 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 179c (650 mg, 74.29%) as a light yellow oil.

Synthesis of 179d

[629] To a stirred solution of 179c (600 mg, 0.996 mmol, 1 equiv) in DCM (8 mL) were added pyridine (472.51 mg, 5.976 mmol, 6 equiv) and triphosgene (103.40 mg, 0.349 mmol, 0.35 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat $NaHCO_3$ (aq) (13 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (2 x 20mL) and dried over anhydrous $CaCl_2$. After filtration, the filtrate was

concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 5:1) to afford 179d (450 mg, 66.87%) as a yellow solid.

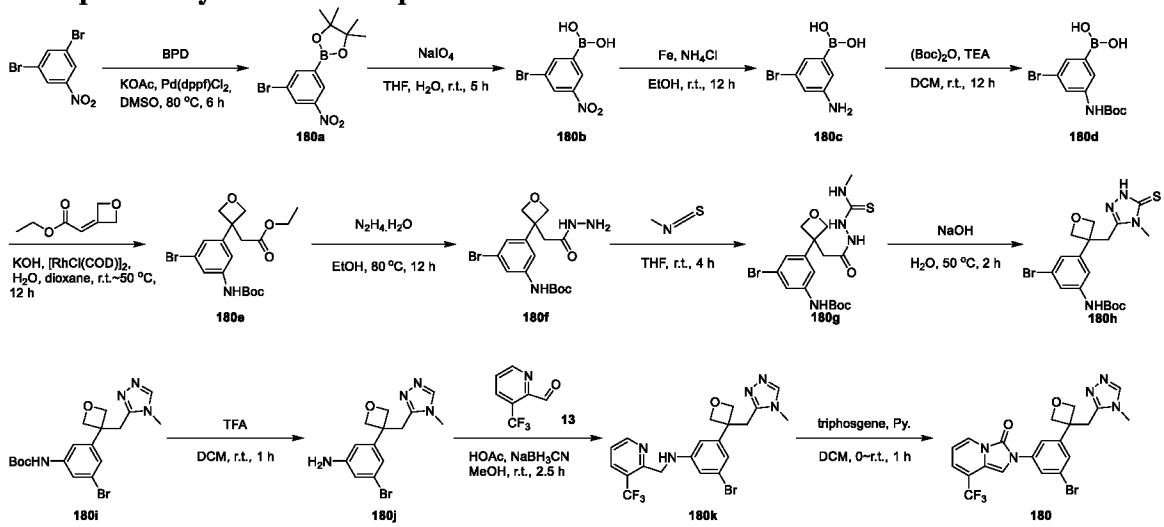
Synthesis of 179

[630] To a stirred solution of 179d (400 mg, 0.636 mmol, 1 equiv) in DCM (3 mL) were added TFA (1 mL) at room temperature. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was concentrated under vacuum. The crude product (40 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 65% B in 12 min; Wave Length: 220 nm; RT1(min): 9.87) to afford Compound 179 (250 mg, 74%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:529

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.55-1.58 (m, 2H), δ 1.71-1.82 (m, 2H), δ 2.71-2.76 (m, 2H), δ 2.83-2.86 (m, 2H), δ 2.96 (s, 3H), δ 3.52 (s, 2H), δ 4.91-4.93 (m, 2H), δ 4.94-4.96 (d, 2H), δ 5.11 (s, 1H), δ 6.91-6.92 (d, 1H), δ 7.16 (s, 1H), δ 7.28 (s, 1H), δ 7.35-7.39 (m, 2H), δ 7.62-7.63 (d, 1H), δ 7.76-7.78 (d, 1H), δ 8.20 (s, 1H).

Example 180. Synthesis of Compound 180



Synthesis of 180a

[631] To a solution of 1,3-dibromo-5-nitro-benzene (20 g, 71.20 mmol) in dioxane (200 mL) was added bis(pinacolato)diboron (18.08 g, 71.20 mmol), $Pd(dppf)Cl_2$ (2.60 g, 3.56 mmol) and KOAc (13.98 g, 142.40 mmol). The mixture was stirred at 80 °C for 6 hr under N_2. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (3 * 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified

by column chromatography (SiO_2, petroleum ether/Ethyl acetate=50/1 to 0/1). Compound 180a (13 g, 55.67% yield) was obtained as a white solid.

Synthesis of 180b

[632] To a solution of 180a (13 g, 39.64 mmol) in THF (90 mL) and H_2O (30 mL) was added $NaIO_4$ (25.43 g, 118.91 mmol, 6.59 mL) under N_2. The mixture was stirred at r.t. for 5 hr. The reaction mixture was quenched by addition a.q. Na_2SO_3 (200 mL), and then extracted with Ethyl acetate (3 * 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound 180b (7 g, 71.84% yield) was obtained as a white solid.

Synthesis of 180c

[633] To a solution of 180b (7 g, 28.48 mmol) in H_2O (20 mL) and EtOH (60 mL) was added Fe (7.95 g, 142.38 mmol) and NH_4Cl (1.52 g, 28.48 mmol) under N_2. The mixture was stirred at r.t. for 12 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 0/1). Compound 180c (4 g, 65.08% yield) was obtained as a white solid.

Synthesis of 180d

[634] To a solution of 180c (4 g, 18.53 mmol) in THF (30 mL) and H_2O (15 mL) was added TEA (5.63 g, 55.60 mmol, 7.74 mL) and $(Boc)_2O$ (12.13 g, 55.60 mmol, 12.77 mL). The mixture was stirred at r.t. for 12 hr. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 * 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound 180d (4 g, 43.04% yield) was obtained as a white solid.

Synthesis of 180e

[635] To a solution of 180d (3 g, 9.50 mmol) in dioxane (30 mL) was added KOH (1.39 g, 24.69 mmol) in H_2O (6 mL), ethyl 2-(oxetan-3-ylidene)acetate (2.70 g, 18.99 mmol) and chlororhodium;(1Z,5Z)-cycloocta- 1,5-diene (936.36 mg, 1.90 mmol). The mixture was stirred at 50 °C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent to give a residue. The residue was diluted with H_2O (30 mL) and extracted with DCM (3 * 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl

acetate=50/1 to 0/1). Compound 180e (2 g, 4.83 mmol, 50.84% yield) was obtained as a white solid.

Synthesis of 180f

[636] To a solution of 180e (2 g, 4.83 mmol) in EtOH (4 mL) was added $NH_2NH_2.H_2O$ (4.12 g, 69.96 mmol, 4 mL, 85% purity) slowly under N_2. The mixture was stirred at 80 °C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent at 30 °C. Compound 180f (1.8 g, 4.50 mmol, 93.15% yield) was obtained as a white solid.

Synthesis of 180g

[637] To a solution of 180f (1.8 g, 4.50 mmol) in THF (20 mL) was added methylimino(thioxo)methane (657.61 mg, 8.99 mmol, 614.59 uL) under N_2. The mixture was stirred at r.t. for 4 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound 180g (1.55 g, 72.81% yield) was obtained as a white solid.

Synthesis of 180h

[638] To a solution of 180g (1.55 g, 3.27 mmol) in H_2O (12 mL) was added NaOH (468.85 mg, 11.72 mmol) under N_2 atmosphere. The mixture was stirred at 50 °C for 2 hr. To the reaction mixture was added 1M HCl to pH<7, and then filtered. The filter cake was dried under reduced pressure to give a residue. Compound 180h (1.3 g, crude) was obtained as a white solid.

Synthesis of 180i

[639] To a solution of 180h (1.25 g, 2.75 mmol) in EtOH (20 mL) was added Raney-Ni (0.25 g, 2.92 mmol). The mixture was stirred at r.t. for 1 hr under N_2. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 0/1). Compound 180i (0.92 g, 79.18% yield) was obtained as a white solid.

Synthesis of 180j

[640] 180i (870 mg, 2.06 mmol) was added to a mixture of DCM (6 mL) and TFA (4.57 g, 40.06 mmol, 2.97 mL). The mixture was stirred at 15 °C for 1 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with DCM (50 mL) and added AMBERLYST(R) A-21 to pH>7. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. Compound 180j (820 mg, crude) was obtained as a white solid.

Synthesis of 180k

[641] To a solution of 180j (0.65 g, 2.01 mmol) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (387.40 mg, 2.21 mmol) in MeOH (6.5 mL) was added HOAc (12.08 mg, 201.12 umol, 11.50 uL). The mixture was stirred at r.t. for 0.5 hr under N_2. Then to the mixture was added $NaBH_3CN$ (379.15 mg, 6.03 mmol). The mixture was stirred at r.t. for 2 hr under N_2. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) under N_2, and then extracted with DCM (3 * 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 0/1). Compound 180k (0.5 g, 51.55% yield) was obtained as a white solid.

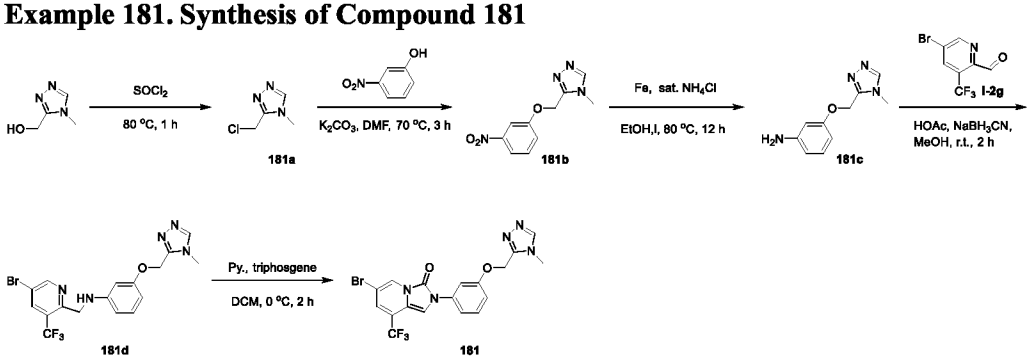
Synthesis of 180

[642] To a solution of 180k (0.28 g, 580.56 umol) and Py. (137.77 mg, 1.74 mmol, 140.58 uL) in DCM (3 mL) was added bis(trichloromethyl) carbonate (0.17 g, 572.88 umol) in DCM (0.5 mL) slowly at 0 °C under N_2. The mixture was stirred at r.t. for 1 hr under N_2. To the reaction mixture was added saturated aqueous $NaHCO_3$ (3 mL) slowly at 0 °C under N_2. Then the mixture was stirred at r.t. for 0.5 hr under N_2. The mixture was extracted with EtOAc (3 * 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 0/1). The residue (20 mg) was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 20%-50%,8min). Compound 180 (5.8 mg) was obtained as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 508.

H-NMR: (400 MHz, CD_3OD-d_4, ppm): δ 8.25 (s, 1H), 8.06 (t, *J*=2Hz, 2H), 7.77 (d, *J*=7.6Hz, 1H), 7.43 (s, 1H), 7.20 (s, 1H), 7.10 (d, *J*=6.8Hz, 1H), 6.29 (t, *J*=6.8Hz, 1H), 4.91 (s, 4H), 3.55 (s, 2H), 3.15 (s, 3H).

Example 181. Synthesis of Compound 181



Synthesis of 181a

[643] A mixture of (4-methyl-1,2,4-triazol-3-yl)methanol (2.90 g, 25.6 mmol) in thionyl chloride (29.0 mL, 399 mmol) was stirred at 80 °C for 1 hr under N_2 atmosphere. The mixture was concentrated to afford the residue 181a (4.12 g, 95% yield, as a hydrochloride salt) obtained as a white solid.

Synthesis of 181b

[644] To a solution of 3-nitrophenol (3.35 mL, 16.86 mmol) and 181a (3.40 g, 20.2 mmol, as a hydrochloride salt) in DMF (20 mL) was added potassium carbonate (11.6 g, 84.3 mmol), the mixture was stirred at 70 °C for 3 hr. Water (50 mL) was added to the reaction mixture and extracted with ethyl acetate (200 mLx2). The combined organic phase was dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated in vacuum to afford 181b (3.49 g, 88% yield) as a brown solid.

Synthesis of 181c

[645] A mixture of 181b (3.10 g, 13.2 mmol), ammonium chloride (708 mg, 13.24 mmol), and Fe (3.70 g, 66.1 mmol) in EtOH (30 mL) and water (10 mL) was stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction mixture was filtered, the filtrate was concentrated to give the residue. The residue was purified by normal phase SiO_2 chromatography (0-50% MeOH/EtOAc) to afford 181c (2.0 g, 74% yield) as yellow solid.

Synthesis of 181d

[646] To a solution of 181c (1.50 g, 7.34 mmol) and I-2g (1.68 g, 6.61 mmol) in MeOH (20 mL) was added acetic acid (7.5 mL g, 131 mmol). The mixture was stirred at 25 °C for 1 hr then sodium cyanoborohydride (1.38 g, 22.0 mmol) was added to the mixture and was stirred at 25 °C for 1 hr. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with EtOAc (30 mLx3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-10% MeOH/EtOAc) to afford 181d (0.56 g, 17% yield) as orange solid.

Synthesis of 181

[647] To a solution of 181d (0.56 g, 1.27 mmol) in DCM (20 mL) was added pyridine (408 uL, 5.07 mmol) and bis(trichloromethyl) carbonate (150 mg, 506 umol) at 0 °C, the mixture was stirred at 0 °C for 2 hr under N_2. The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 mL). The aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was

purified by normal phase SiO_2 chromatography (0-75% EtOAc/petroleum ether) to afford crude product. The crude product was purified by reverse phase HPLC to afford Compound 181 (35 mg, 5.71% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 468.

H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.53 (s, 1H), 8.06 (s, 1H), 7.59-7.51 (m, 3H), 7.50-7.43 (m, 1H), 7.18 (s, 1H), 7.13-7.07 (m, 1H), 5.40 (s, 2H), 3.73 (s, 3H)

Example 182. Synthesis of Compound 182



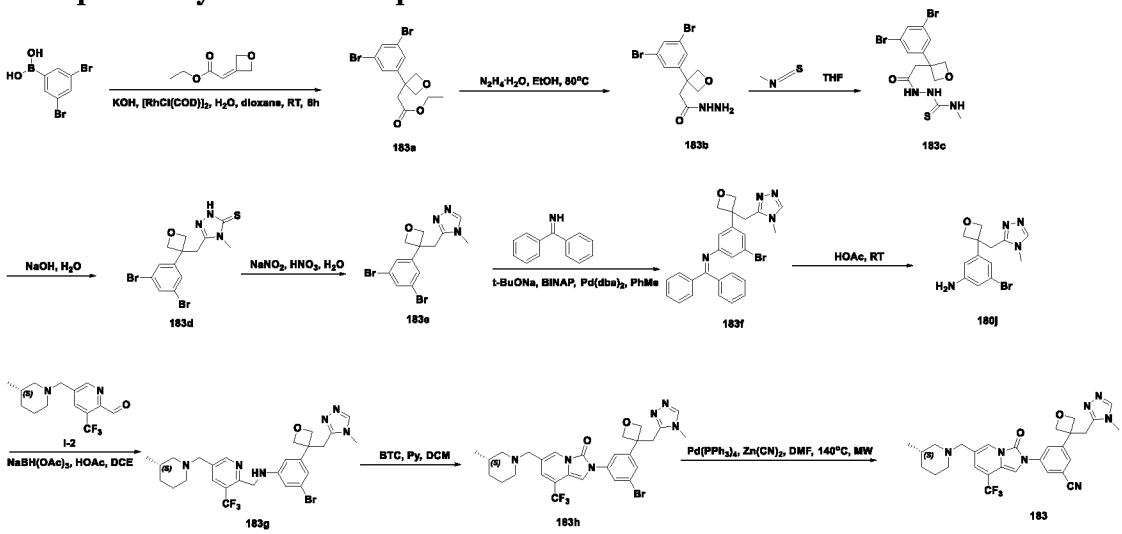
Synthesis of 182

[648] To a stirred solution of 179 (50 mg, 0.095 mmol, 1 equiv) and Formaldehyde Solution (8.52 mg, 0.285 mmol, 3 equiv) in MeOH (1 mL) were added STAB (40.10 mg, 0.190 mmol, 2 equiv) and HOAc (5.68 mg, 0.095 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (4 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (2 x 4mL) and dried over anhydrous $CaCl_2$. After filtration, the filtrate was concentrated under reduced pressure. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 4% B to 15% B in 10 min; Wave Length: 254/220 nm; RT1(min): 9.5) to afford Compound 182 (5.2 mg, 9.62%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$:544

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.99-2.05 (m, 2H), δ 2.17-2.23 (m, 2H), δ 2.80-2.81 (d, 3H), δ 2.87-2.90 (m, 3H), δ 3.32-3.33 (d, 2H), δ 3.68 (s, 2H), δ 4.65 (s, 2H), δ 5.03-5.07 (m, 4H), δ 6.96-6.97 (s, 1H), δ 7.15-7.18 (m, 2H), δ 7.29 (s, 1H), δ 7.46-7.52 (m, 1H), δ 7.66-7.67 (d, 1H), δ 7.79 (s, 1H), δ 8.21-8.22 (d, 1H), δ 8.21 (s, 1H).

Example 183. Synthesis of Compound 183



Synthesis of 183a

[649] Into a 1L vial were added KOH (6 g, 107.25 mmol, 1.5 equiv) in H_2O (47 mL), dioxane (200 mL), and $[Rh(COD)Cl]_2$ (5.3 g, 10.72 mmol, 0.15 equiv) at room temperature. The mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 3,5-dibromophenylboronic acid (20 g, 71.50 mmol, 1.0 equiv) and ethyl 2-(oxetan-3-ylidene) acetate (20.3 g, 143.00 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (1.5L) at room temperature. The aqueous layer was extracted with EtOAc (3x2 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 183a (9 g, 33%) as an off-white oil.

Synthesis of 183b

[650] A solution of 183a (5.9 g, 15.60 mmol, 1.0 equiv) and hydrazine hydrate (6.3 g, 124.84 mmol, 8.0 equiv) in EtOH (30 mL) was stirred overnight at 80 °C. The mixture was allowed to cool down to room temperature. The residue was dissolved in water (60 mL). The resulting mixture was filtered by filter paper; the filter cake was washed with water (3x50 mL). The filter cake was concentrated under reduced pressure to afford 183b (5.1 g, 70%) as a white solid.

Synthesis of 183c

[651] A solution of 183b (5.1 g, 14.01 mmol, 1.0 equiv) and methyl isothiocyanate (2 g, 28.02 mmol, 2.0 equiv) in THF (50 mL) was stirred for 2 h at room temperature. The residue

was dissolved in water (100 mL). The resulting mixture was concentrated under reduced pressure. The resulting mixture was filtered through filter paper; the filter cake was washed with water (2x20 mL). The filter cake was dried under reduced pressure to afford 183c (4.8 g, 73%) as a white solid.

Synthesis of 183d

[652] A solution of 183c (4.8 g, 10.98 mmol, 1.0 equiv) and NaOH (3.5 g, 87.84 mmol, 8.0 equiv) in water (100 mL) was stirred overnight at room temperature. The mixture was acidified to pH 5 with 1M HCl (aq.). The resulting mixture was concentrated under reduced pressure. The resulting mixture was filtered through filter paper; the filter cake was washed with water (3x10 mL). The filter cake was dried under reduced pressure to afford 183d (4.0 g, 85%) as a white solid.

Synthesis of 183e

[653] A solution of 183d (4 g, 9.54 mmol, 1.0 equiv) in EtOAc (7 mL) was treated with $NaNO_2$ (6.6 g, 95.43 mmol, 10.0 equiv) followed by the addition of HNO_3 (6 g, 95.43 mmol, 10.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1h at 0°C. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with water (3x50 mL) and dried over anhydrous Na_2SO_4. The combined organic layers were filtered by filter paper; the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 183e (2 g, 54%) as a white solid.

Synthesis of 183f

[654] To a stirred solution of 183e (2.0 g, 5.17 mmol, 1.0 equiv) and t-BuONa (0.6 g, 6.20 mmol, 1.2 equiv) in toluene (20 mL) were added BINAP (0.24 g, 0.388 mmol, 0.075 equiv), Pd(dba)2 (0.15 g, 0.258 mmol, 0.05 equiv), and diphenylmethanimine (0.94 g, 5.167 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x20 mL). The combined organic layers were washed with water (3x20 mL) and dried over anhydrous Na_2SO_4. The combined organic layers were filtered through filter paper and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 183f (1 g, 40%) as an off-white solid.

Synthesis of 180j

[655] Into a 250 mL round-bottom flask were added 183f (880 mg, 1.805 mmol, 1 equiv) and HOAc (10 mL) at room temperature. The resulting mixture was stirred overnight at room

temperature under nitrogen atmosphere. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq) (250 mL). The aqueous layer was extracted with EtOAc (2x150 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 180j (240 mg, 41.13%) as colorless oil.

Synthesis of 183g

[656] A solution of 180j (240 mg, 0.743 mmol, 1 equiv) in DCE (3 mL) was treated with I-2 (255.12 mg, 0.892 mmol, 1.2 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of $NaBH(OAc)_3$ (314.77 mg, 1.486 mmol, 2 equiv) and HOAc (44.59 mg, 0.743 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x7 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 183g (300 mg, 68.07%) as a yellow oil.

Synthesis of 183h

[657] To a stirred solution of 183g (280 mg, 0.472 mmol, 1 equiv) and Pyridine (223.91 mg, 2.832 mmol, 6 equiv) in DCE (5 mL) was added Triphosgene (49.00 mg, 0.165 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with saturated $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with DCM (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 183h (200 mg, 68.43%) as a yellow solid.

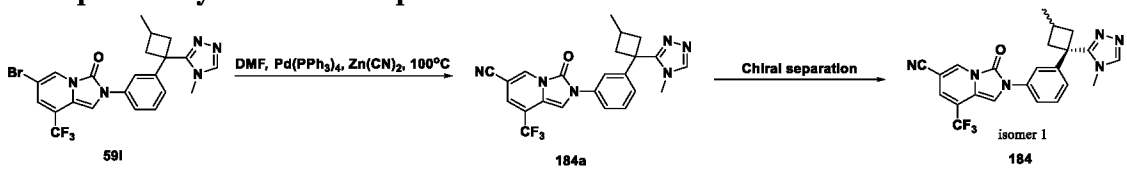
Synthesis of 183

[658] To a stirred solution of 183h (160 mg, 0.258 mmol, 1 equiv) and $Pd(PPh_3)_4$ (59.69 mg, 0.052 mmol, 0.2 equiv) in DMF (2 mL) was added $Zn(CN)_2$ (60.67 mg, 0.516 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The final reaction mixture was irradiated with microwave radiation for 2h at 140 degrees C. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (4x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 7:1) to afford 183 (150 mg, crude). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 64% B in 8 min; Wave Length: 220 nm; RT1(min): 7.27) to afford Compound 183 (82.1

mg, 56.20%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 566. H-NMR: (400 MHz, DMSO, δ ppm): 0.82-0.87 (t, 4H), 1.46 (s, 1H), 1.58-1.66 (m, 4H), 1.89 (s, 1H), 2.72-2.77 (t, 2H), 3.22 (s, 3H), 3.25 (s, 2H), 3.58 (s, 2H), 4.91-4.92 (d, 2H), 4.95-4.97 (d, 2H), 7.03 (s, 1H), 7.51 (s, 1H), 7.58-7.59 (t, 1H), 7.66 (s, 1H), 7.97-7.98 (d, 1H), 8.25-8.27 (m, 2H).

Example 184. Synthesis of Compound 184



Synthesis of 184a

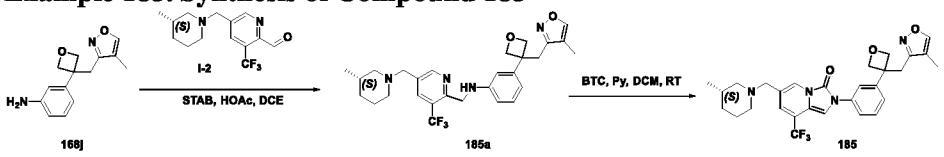
[659] To a stirred solution of 59i (500 mg, 0.988 mmol, 1 equiv) and $Zn(CN)_2$ (231.95 mg, 1.976 mmol, 2 equiv) in DMF (5 mL) was added $Pd(PPh_3)_4$ (114.11 mg, 0.099 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 100°C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (2 x 100 mL). The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: water(10 mmol/L NH_4HCO_3), B: MeCN, 10%B to 50%B gradient in 20 min; detector, UV 254 nm. This resulted in 184a (240 mg, 53.63%) as a yellow solid.

Synthesis of 184

[660] The 184a (240 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 17 min; Wave Length: 220/254 nm; RT2(min): 11.69; RT2(min): 14.54, the second peak is product) to afford Compound 184 (129.8 mg, 33.30%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 453. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.08-1.09 (m, 3H), 2.55-2.58 (m, 3H), 2.87-2.89 (m, 2H), 3.23-3.25(s, 3H), 7.27-7.31 (m, 2H), 7.50-7.52 (m, 1H), 7.54-7.58 (m, 1H), 7.63-7.65 (m, 1H), 7.80(s, 1H), 8.41 (s, 1H) 8.70 (s, 1H).

Example 185. Synthesis of Compound 185



Synthesis of 185a

[661] To a stirred solution of 168j and I-2 (105.47 mg, 0.368 mmol, 1 equiv) in DCE (5

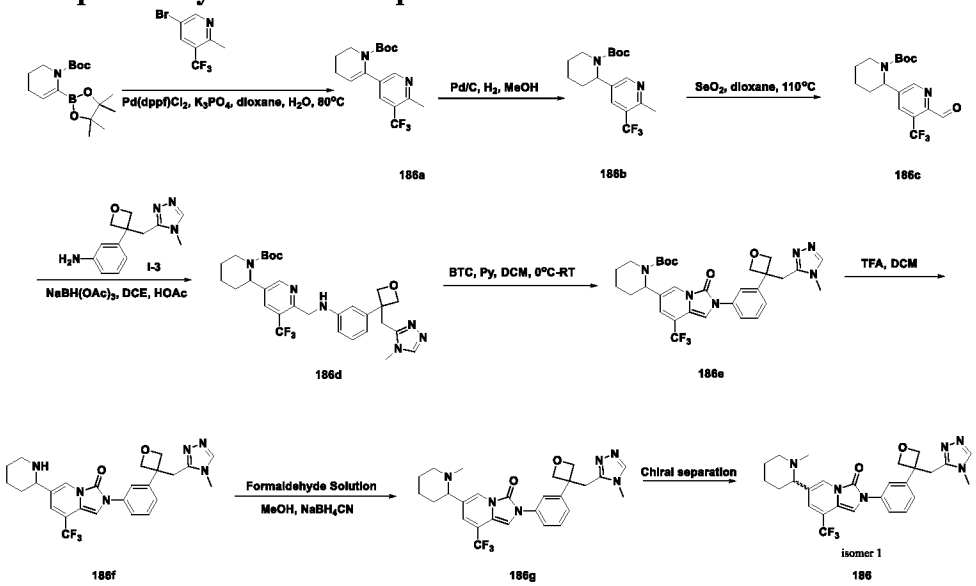
mL) was added AcOH (22.12 mg, 0.368 mmol, 1 equiv) and STAB (156.16 mg, 0.737 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (20mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 185a (120 mg, 60.13%) as a light yellow oil.

Synthesis of 185

[662] A solution of 185a (110 mg, 0.214 mmol, 1 equiv) and Pyridine (169.08 mg, 2.140 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (31.72 mg, 0.107 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x10 mL). The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 51% B to 81% B in 8 min, 81% B; Wave Length: 220 nm; RT1(min): 7.50) to afford Compound 185 (49.3 mg, 42.36%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 540. H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.82-0.92 (m, 4H), 1.32 (s, 3H), 1.39-1.47 (m, 1H), 1.47-1.66 (m, 4H), 1.89-1.95 (m, 1H), 2.75-2.77 (m, 2H), 3.30 (s, 2H), 3.41 (s, 2H), 4.84-4.90 (m, 4H), 6.94-6.96 (d, 1H), 7.01 (s, 1H), 7.31 (s, 1H), 7.39-7.43 (m, 1H), 7.46 (s, 1H), 7.75 (s, 1H), 7.76-7.77 (d, 1H), 8.42 (s, 1H),.

Example 186. Synthesis of Compound 186



Synthesis of 186a

[663] Into a 100 mL 3-necked round-bottom flask were added tert-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyridine-1-carboxylate (2 g, 6.468 mmol, 1 equiv), dioxane (20 mL), H_2O (5 mL), 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (2.33 g, 9.702 mmol, 1.5 equiv), K_3PO_4 (4.12 g, 19.404 mmol, 3 equiv), and $Pd(dppf)Cl_2$ (0.71 g, 0.970 mmol, 0.15 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 186a (1.8 g, 81.29%) as a light brown solid.

Synthesis of 186b

[664] To a solution of 186a (1.8 g, 5.258 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (0.56 g) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 186b (1.4 g, 77.32%) as a light brown solid.

Synthesis of 186c

[665] Into a 100 mL round-bottom flask were added 186b (1.4 g, 4.065 mmol, 1 equiv), dioxane (20 mL, 236.082 mmol, 58.07 equiv), and SeO_2 (1.80 g, 16.260 mmol, 4 equiv) at room temperature. The resulting mixture was stirred overnight at 110°C under nitrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with 1,4-dioxane (3x7 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (6:1) to afford 186c (620 mg, 42.56%) as a light brown solid.

Synthesis of 186d

[666] Into a 100 mL round-bottom flask were added 186c (600 mg, 1.674 mmol, 1 equiv), DCE (10 mL) and I-3 (409.03 mg, 1.674 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature. To the above mixture was added HOAc (100.54 mg, 1.674 mmol, 1 equiv) and $NaBH(OAc)_3$ (709.70 mg, 3.348 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted

with PE / EA (1:1) to afford 186d (800 mg, 81.45%) as a light brown solid.

Synthesis of 186e

[667] Into a 100 mL round-bottom flask were added 186d (780 mg, 1.330 mmol, 1 equiv), DCM (10 mL), Pyridine (525.84 mg, 6.650 mmol, 5 equiv) and Triphosgene (276.18 mg, 0.931 mmol, 0.7 equiv) at 0°C. The resulting mixture was stirred for 0.5 h at room temperature. The reaction was quenched by the addition of sat. Na_3HCO_3 (aq.) (5 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x6 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 186e (450 mg, 55.24%) as a yellow solid.

Synthesis of 186f

[668] Into a 100 mL sealed tube were added 186e (430 mg, 0.702 mmol, 1 equiv), DCM (6 mL) and TFA (2 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 186f (200 mg, 55.60%) as a yellow solid.

Synthesis of 186g

[669] Into a 100 mL round-bottom flask were added 186f (190 mg, 0.371 mmol, 1 equiv), MeOH (5 mL), formaldehyde Solution (16.70 mg, 0.556 mmol, 1.5 equiv) and $NaBH_3CN$ (46.59 mg, 0.742 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 186g (150 mg, 76.84%) as a yellow solid.

Synthesis of 186

[670] The 186g (150 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 35% B in 22 min; Wave Length: 220/254 nm; RT1(min): 18.11; RT2(min): 20.28; The first peak was the product; Sample Solvent: MeOH: DCM=1: 1--HPLC; Injection Volume: 0.3 mL; Number of Runs: 15) to afford Compound 186 (31.0 mg, 20.07%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 527

H-NMR: 1H NMR (300 MHz, CD_3OD-d4) δ 1.15-1.38 (m, 1H), 1.39-1.92 (m, 5H), 2.02 (s, 4H), 2.79 (s, 1H), 2.93-2.97 (m, 4H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.02 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 2H), 7.70 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 187. Synthesis of Compound 187



186g 187

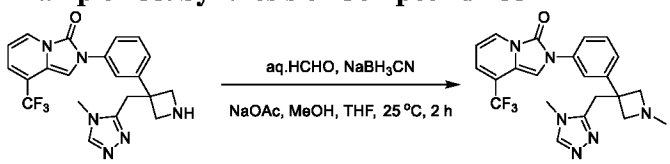
Synthesis of 187

[671] The 186g (150 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH) --HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 32% B to 35% B in 22 min; Wave Length: 220/254 nm; RT1(min): 18.11; RT2(min): 20.28; The second peak was the product Sample Solvent: MeOH: DCM=1: 1--HPLC; Injection Volume: 0.3 mL; Number of Runs: 15) to afford Compound 187 (40.1 mg, 26.33%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 527

H-NMR: 1H NMR (300 MHz, CD_3OD-d4) δ 1.15-1.38 (m, 1H), 1.39-1.92 (m, 5H), 2.02 (s, 4H), 2.79 (s, 1H), 2.93-2.97 (m, 4H), 3.53 (s, 2H), 4.91-4.96 (m, 4H), 6.89-6.91 (d, 1H), 7.02 (s, 1H), 7.33 (s, 1H), 7.38-7.42 (m, 2H), 7.70 (s, 1H), 7.74-7.76 (m, 1H), 8.20 (s, 1H).

Example 188. Synthesis of Compound 188



143 188

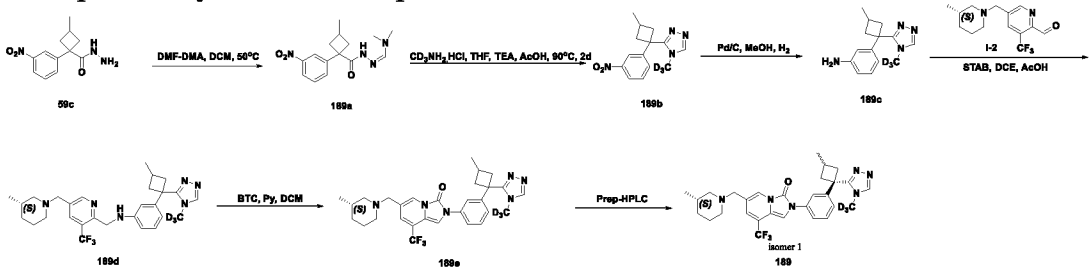
Synthesis of 188

[672] To a solution of 143 (0.47 g, 1.10 mmol) in THF (10 mL) and MeOH (10 mL) was added HCHO (238 uL, 3.29 mmol, 38% purity), sodium acetate (179 mg, 2.19 mmol) and sodium cyanoborohydride (68.9 mg, 1.10 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was adjusted to pH = 8 with saturated aqueous sodium bicarbonate solution (20 ml) and extracted with DCM (5x10 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC to afford Compound 188 (15 mg, 2% yield) as a white solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 443. H-NMR: (400 MHz, CD_3OD-d_4, ppm): δ 8.27 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56-7.45 (m, 2H), 7.14 (s, 1H), 7.07-7.03 (m,

2H), 6.37 (t, *J* = 7.2 Hz, 1H), 4.61 (d, *J* = 9.6 Hz, 2H), 4.36 (d, *J* = 9.6 Hz, 2H), 3.57 (s, 2H), 3.02 (s, 3H), 2.87 (s, 3H)

Example 189. Synthesis of Compound 189



Synthesis of 189a

[673] To a stirred solution of 59c (5 g, 20.059 mmol, 1 equiv) in DCM (100 mL) were added DMF-DMA (11.95 g, 100.295 mmol, 5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 50°C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 189a (5 g, 76.17%) as a yellow solid.

Synthesis of 189b

[674] Into a 250mL 3-necked round-bottom flask were added $CD_3NH_2.HCl$ (2.90 g, 41.070 mmol, 5 equiv), THF (50 mL), TEA (4.24 g, 41.891 mmol, 5.1 equiv), 189a (2.5 g, 8.214 mmol, 1 equiv) and AcOH (0.49 g, 8.214 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 2 days at 90°C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 189b (680 mg, 27.36%) as a Brown yellow solid.

Synthesis of 189c

[675] To a solution of 189b (630 mg, 2.288 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (80 mg, 12%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 189c (500 mg, 81.94%) as an off-white solid. The crude product was used in the next step directly without further purification.

Synthesis of 189d

[676] To a stirred solution of 189c (480 mg, 1.956 mmol, 1 equiv) and I-2 (560.12 mg, 1.956 mmol, 1 equiv) in DCE (5 mL) were added STAB (829.30 mg, 3.912 mmol, 2 equiv) and AcOH (117.49 mg, 1.956 mmol, 1 equiv) at room temperature under nitrogen

atmosphere. The reaction was quenched with saturated NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 189d (530 mg, 49.91%) as a white solid.

Synthesis of 189e

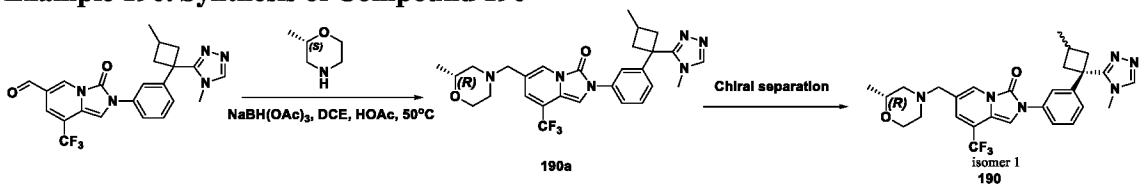
[677] To a stirred solution of 189d (510 mg, 0.989 mmol, 1 equiv) and pyridine (782.34 mg, 9.890 mmol, 10 equiv) in DCM (10 mL) were added triphosgene (117.40 mg, 0.396 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 189e (400 mg, 67.20%) as a yellow solid.

Synthesis of 189

[678] The 189e (400 mg, 0.739 mmol, 1 equiv) was purified by Prep-HPLC with the following conditions (Column: Kinetex EVO C18 Column, 30*150, 5um; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 60% B in 8 min, 60% B; Wave Length: 220 nm; RT1(min): 7.37) to afford Compound 189 (143.3 mg, 35.47%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542. H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.81-0.93 (m, 4H), 1.02-1.13 (d, 3H), 1.43-1.46 (m, 1H), 1.57-1.66 (m, 4H), 1.86-1.91 (m, 5H), 2.51-2.56 (m, 3H), 2.72-2.77 (m, 2H), 2.81-2.93 (m, 2H), 3.24 (s, 2H), 7.00 (s, 1H), 7.24-7.26 (d, 1H), 7.37 (s, 1H), 7.47-7.51 (m, 1H), 7.63-7.65 (m, 2H), 7.84 (s, 1H), 8.29 (s, 1H).

Example 190. Synthesis of Compound 190



59j 190a 190

Synthesis of 190a

[679] Into a 50 mL 3-necked round-bottom flask were added 59j (700 mg, 1.537 mmol, 1 equiv), (2S)-2-methylmorpholine (310.93 mg, 3.074 mmol, 2 equiv), DCE (15 mL) and HOAc (184.60 mg, 3.074 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added $NaBH(OAc)_3$ (651.49 mg, 3.074 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat.

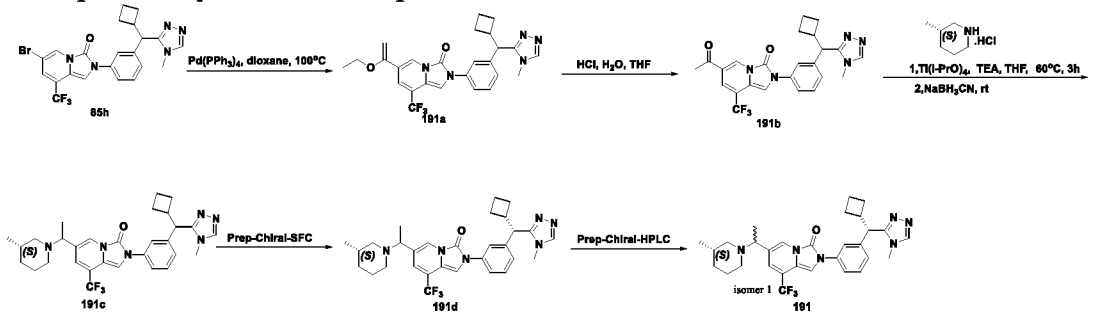
NH_4Cl (aq.) (10 ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2 and MeOH (10:1) (5x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 27% B in 8 min; Wave Length: 254; 220 nm; RT1(min): 7.85) to afford 190a (350 mg, 42.12%) as a yellow solid.

Synthesis of 190

[680] The crude 190a (350mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 65% B in 20 min; Wave Length: 220/254 nm; RT1(min): 8.96; RT2(min): 13.78; The second peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 2 mL; Number Of Runs: 6) to afford crude product (150 mg). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 7.73) to afford product. The product was dissolved in THF (5 mL) and isolute Si-thiol (3 mg) was added. The mixture was stirred for 30 min. Then the solution was filtered. After concentrated the filtrate, this resulted in Compound 190 (42.8 mg, 12.23%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 541. H-NMR: (400 MHz, CD_3OD, *ppm*): δ1.14-1.18 (m, 6H), δ1.86-1.91 (t, 1H), δ2.19-2.20 (m, 1H), δ2.41-2.55 (m, 2H), δ2.74-2.83 (m, 2H), δ3.14-3.19 (m, 2H), δ3.32-3.37 (m, 5H), δ3.66-3.70 (m, 2H), δ3.84-3.85 (m, 1H), δ7.11-7.15 (dd, 2H), δ7.21-7.23(m, 1H), δ7.51-7.59 (m, 2H), δ7.69 (s, 2H), δ8.39 (s, 1H).

Example 191. Synthesis of Compound 191



Synthesis of 191a

[681] To a stirred mixture of 85h (15 g, 29.625 mmol, 1 equiv) and tributyl (1-ethoxyethenyl) stannane (16.05 g, 44.438 mmol, 1.5 equiv) in dioxane (150 mL) was added $Pd(PPh_3)_4$ (3.42 g, 2.963 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (3 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 / MeOH (10:1) (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (80:1) to afford 191a (11.5 g, 70.22%) as a yellow solid.

Synthesis of 191b

[682] To a stirred mixture of 191a (11.5 g, 23.115 mmol, 1 equiv) in THF (115 mL) was added HCl (115 mL, 1M) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (230 mL). The aqueous layer was extracted with CH_2Cl_2 / MeOH (10:1) (3x200 mL). The resulting mixture was concentrated under reduced pressure to afford 191b (10.2 g, 89.30%) as a yellow solid.

Synthesis of 191c

[683] To a stirred mixture of 191b (2.5 g, 5.325 mmol, 1 equiv) and (3S)-3-methylpiperidine hydrochloride (2.17 g, 15.975 mmol, 3 equiv) in THF (25 mL) were added TEA (5.39 g, 53.250 mmol, 10 equiv) and $Ti(Oi\text{-}Pr)_4$ (6.05 g, 21.300 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for 3h at 60°C under air atmosphere. To the above mixture was added $NaBH_3CN$ (1.00 g, 15.975 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 / MeOH (10:1) (3x80 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (60:1) to afford 191c (1.2g). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 191c (950 mg). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN, 2% to 100% gradient in 40 min; detector, UV 254 nm to afford 191c (740 mg, 24.39%) as a yellow solid.

Synthesis of 191d

[684] The 191c (740 mg) was purified by SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 um; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.1% DEA); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C):

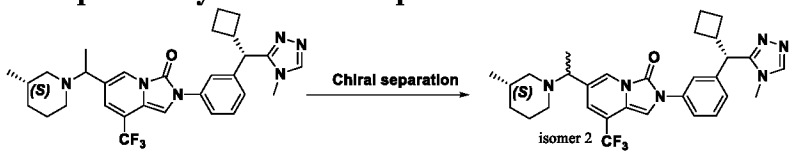
35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.48, RT1(min): 8.72, the first peak is product) to afford 191d (340 mg) as a yellow solid.

Synthesis of 191

[685] The 191d (340 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 10.50; RT2(min): 12.00; the first peak is product) to afford Compound 191 (100.2 mg, 29.78%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 553. H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.70-0.90 (m, 4H), δ1.25 (s, 3H), δ1.30-1.50 (m, 2H), δ1.61-1.89 (m, 8H), δ1.91-1.95 (m, 1H), δ2.08-2.10 (m, 1H), δ2.67-2.75 (m, 2H), δ3.18-3.26 (m, 1H), δ3.34-3.44 (m, 4H), δ4.24-4.28 (d, 1H), δ7.08 (s, 1H), δ7.18-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.47 (m, 1H), δ7.56 (s, 1H), δ7.68-7.74 (m, 2H), δ8.33 (s, 1H).

Example 192. Synthesis of Compound 192



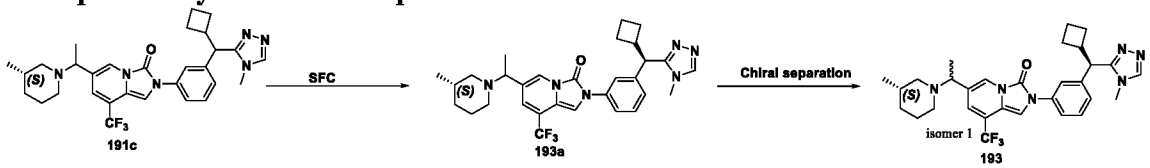
191d 192

Synthesis of 192

[686] The 191d (340 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 10.50; RT2(min): 12.00; the second peak is product) to afford Compound 192 (95.8 mg, 27.39%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 553. H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.75-0.90 (m, 4H), δ1.25 (s, 3H), δ1.41-1.81 (m, 10H), δ2.01-2.11 (m, 2H), δ2.67-2.73 (m, 2H), δ3.18-3.30 (m, 1H), δ3.34-3.44 (m, 4H), δ4.25-4.28 (d, 1H), δ7.08 (s, 1H), δ7.18-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.47 (m, 1H), δ7.58 (s, 1H), δ7.67-7.70 (m, 1H), δ7.73 (s, 1H), δ8.33 (s, 1H).

Example 193. Synthesis of Compound 193



191c 193a 193

Synthesis of 193a

[687] The 191c (740 mg) was purified by Prep-SFC with the following conditions (Column:

CHIRAL ART Cellulose-SB, 3*25 cm, 5 um; Mobile Phase A: CO_2, Mobile Phase B: MeOH(0.1% DEA); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.48, RT1(min): 8.72, the second peak is product) to afford 193a (320 mg) as a yellow solid.

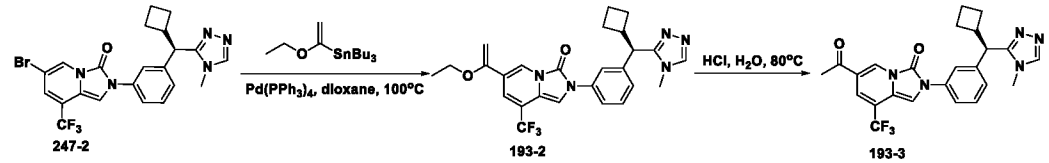
Synthesis of 193

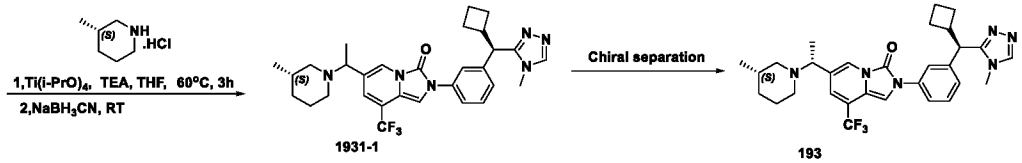
[688] The 193a (320mg) was purified by chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 11 min; Wave Length: 220/254 nm; RT1(min): 7.03; RT2(min): 8.52; the first product is product) to afford Compound 193 (92.9 mg, 28.74%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 553

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.80-0.98 (m, 4H), δ1.23 (s, 3H), δ1.40-1.50 (m, 1H), δ1.55-1.81 (m, 9H), δ2.01-2.10 (m, 2H), δ2.67-2.75 (n, 2H), δ3.16-3.26 (m, 1H), δ3.39-3.47 (m, 4H), δ4.19-4.30 (d, 1H), δ7.08 (s, 1H), δ7.18-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.47 (m, 1H), δ7.59 (s, 1H), δ7.67-7.70 (m, 1H), δ7.73 (s, 1H); δ8.33 (s, 1H).

Alternatively, Compound 193may be also prepared in the manner outlined below:





1. Synthesis of 193-2

[689] To a stirred solution of 247-2 (30 g, 59.250 mmol, 1 equiv) and tributyl(1-ethoxyethenyl)stannane (32.10 g, 88.875 mmol, 1.5 equiv) in dioxane (400 mL) were added Pd(PPh3)4 (6.85 g, 5.925 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was quenched with water (800 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 193-2 (22 g, 70.90%) as a yellow solid.

2. Synthesis of 193-3

[690] A solution of 193-2 (55 g, 110.548 mmol, 1 equiv) in HCl (1 M, 600 mL) was stirred overnight at 80°C. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was extracted with CH2Cl2 (3x1000 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 193-3 (20 g, 37.00%) as a yellow solid.

3. Synthesis of 193-1

[691] To a stirred solution of 193-3 (17 g, 36.211 mmol, 1.00 equiv) and (3S)-3-methylpiperidine hydrochloride (14.74 g, 108.633 mmol, 3 equiv) in THF (300 mL) were added Ti(Oi-Pr)4 (41.17 g, 144.844 mmol, 4 equiv) and TEA (36.64 g, 362.110 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 3h at 60°C. To the above mixture was added NaBH3CN (6.83 g, 108.633 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH4Cl (aq.) (500 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 800 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH4HCO3), 30% to 55% gradient in 20 min; detector, UV 254 nm. This resulted in 193-1 (6.5 g, 32.16%) as a yellow solid.

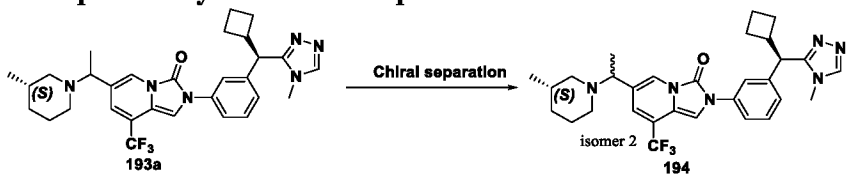
4. Synthesis of 193-0

[692] The 193-1 (6.5 g) was purified by Prep-SFC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: IPA(0.5% 2M NH3-MeOH); Flow rate: 200 mL/min; Gradient: isocratic 60% B; Column Temperature(°C):35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 9.2; RT2(min): 12.83; the first product is product.) to afford 193 (2.1913g, 33.54%) as a yellow solid.

LCMS-193: (ES, m/z): [M+H]+ 553

H-NMR-193: H NMR (400 MHz, DMSO, ppm): δ0.80-0.98 (m, 4H), δ1.23-1.32 (m, 3H), δ1.40-1.50 (m, 1H), δ1.45-1.69 (m, 4H), δ1.70-1.85 (m, 5H), δ2.01-2.10 (m, 2H), δ2.67-2.75 (n, 2H), δ3.16-3.26 (m, 1H), δ3.39-3.47 (m, 4H), δ4.19-4.30 (d, 1H), δ7.08 (s, 1H), δ7.18-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.47 (m, 1H), δ7.59 (s, 1H), δ7.67-7.70 (m, 1H), δ7.73 (s, 1H); δ8.33 (s, 1H).

Example 194. Synthesis of Compound 194



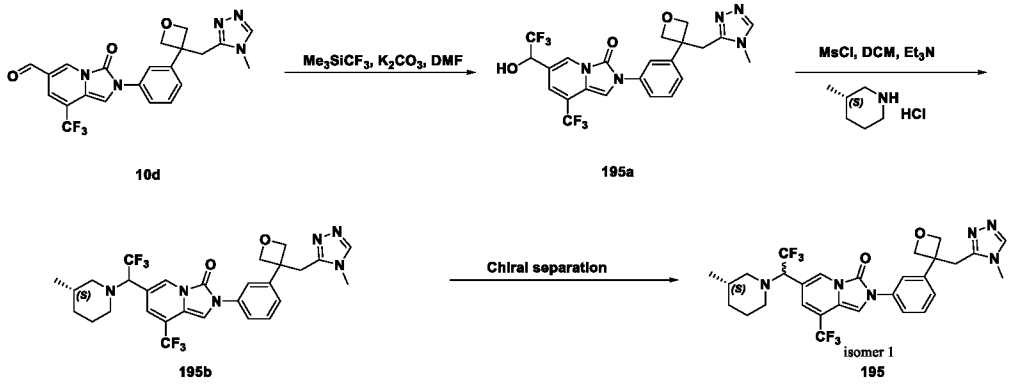
Synthesis of 194

[693] 193a (320mg) was purified by chiral ceparation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 11 min; Wave Length: 220/254 nm; RT1(min): 7.03; RT2(min): 8.52; the second product is product) to afford Compound 194 (92.1 mg, 28.46%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 553

H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ0.80-0.93 (m, 4H), δ1.21-1.31 (d, 3H), δ1.34-1.44 (m, 1H), δ1.45-1.56 (m, 3H), δ1.57-1.82 (m, 6H), δ1.85-2.10 (m, 2H), δ2.67-2.75 (m, 2H), δ3.20-3.26 (m, 1H), δ3.34-3.44 (m, 4H), δ4.25-4.28 (d, 1H), δ7.08 (s, 1H), δ7.18-7.21 (m, 1H), δ7.31 (s, 1H), δ7.42-7.47 (m, 1H), δ7.58 (s, 1H), δ7.67-7.70 (m, 1H), δ7.73 (s, 1H); δ8.33 (s, 1H).

Example 195. Synthesis of Compound 195



Synthesis of 195a

[694] To a stirred solution of 10d (1 g, 2.186 mmol, 1 equiv) and $TMSCF_3$ (0.62 g, 4.372 mmol, 2 equiv) in DMF (10 mL) was added K_2CO_3 (0.03 g, 0.219 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction solution was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmoL/L NH_4HCO_3), 10% to 65% gradient in 40 min; detector, UV 254 nm. This resulted in 195a (600 mg, 52.04%) as a yellow solid.

Synthesis of 195b

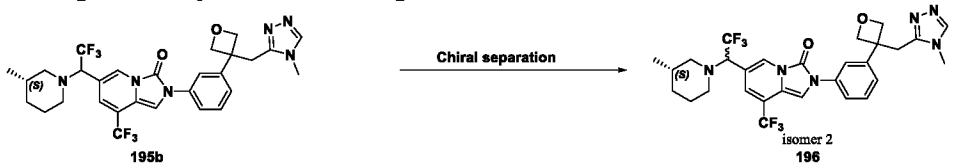
[695] To a stirred solution of 195a (600 mg, 1.138 mmol, 1 equiv) and Et_3N (575.57 mg, 5.690 mmol, 5 equiv) in DCM (15 mL) was added MsCl (195.47 mg, 1.707 mmol, 1.5 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 h at 0°C. To the above mixture was added (3S)-3-methylpiperidine hydrochloride (462.91 mg, 3.414 mmol, 3 equiv). The resulting mixture was stirred for additional 4 h at room temperature. The reaction was quenched by the addition of water (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 25 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 195b (200 mg, 28.89%) as a yellow solid.

Synthesis of 195

[696] 195b (200 mg, 0.329 mmol, 1 equiv) (200 mg) was purified by Prep-Chrial-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 35 min; Wave Length: 220/254 nm; RT1(min): 29.32;) to afford crude product (44.2 mg). The crude product (44.2 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 8 min, Wave Length: 220 nm; RT1(min): 7.42) to afford Compound 195 (22.3 mg, 11.15%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 609. H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.81-0.90 (m, 4H), δ1.38-1.64 (m, 4H), δ1.94-2.27 (m, 2H), δ2.72-2.94 (m, 5H), δ3.53 (s, 2H), δ4.56-4.65 (m, 1H), δ4.90-4.96 (m, 4H), δ6.89-6.96 (m, 2H), δ7.38-7.44 (m, 3H), δ7.72-7.80 (m, 2H), δ8.20 (s, 1H).

Example 196. Synthesis of Compound 196



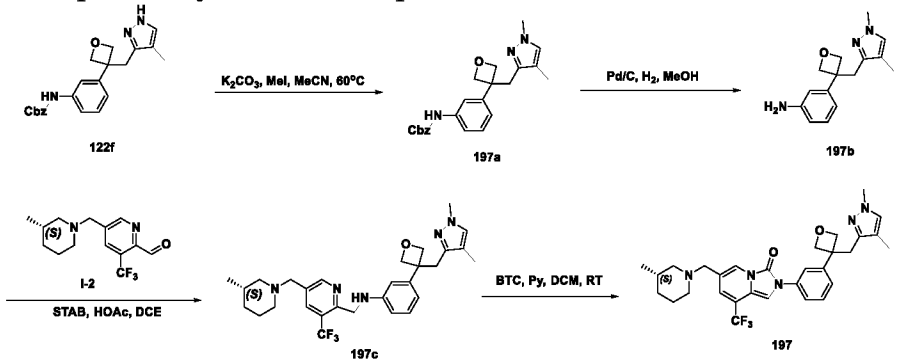
Synthesis of 196

[697] 195b (200 mg, 0.329 mmol, 1 equiv) (200 mg) was purified by Prep-Chrial-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 35 min; Wave Length: 220/254 nm; RT2(min): 33.20) to

Compound 196 (44.2 mg, 22.10%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 609. H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.82-088 (m, 4H), δ1.32-1.40 (m, 1H), δ1.42-1.65 (m, 3H), δ1.93-1.98 (m, 1H), δ2.26-2.34 (m, 1H), δ2.83-2.92 (m, 2H), δ2.97(s, 3H), δ3.53 (s, 2H), δ4.62-4.64 (m, 1H), δ4.91-4.97 (m, 4H), δ6.90-6.92 (m, 2H), δ6.98 (s, 1H), δ7.39-7.43 (m, 3H), δ7.74-7.77 (m, 2H), δ8.20 (s, 1H).

Example 197. Synthesis of Compound 197



Synthesis of 197a

[698] To a stirred mixture of 122f (650 mg, 1.722 mmol, 1 equiv) and K_2CO_3 (714.02 mg, 5.166 mmol, 3.00 equiv) in MeCN (10 mL) were added MeI (488.87 mg, 3.444 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 60°C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 197a (300 mg, 42.28%) as a white solid.

Synthesis of 197b

[699] To a solution of 197a (360 mg, 0.920 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (40 mg, 10%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad, and concentrated under reduced pressure. This resulted in 197b (240 mg, 91.27%) as a light yellow oil. The crude product was used in the next step directly without further purification.

Synthesis of 197c

[700] To a stirred solution of 197b (120 mg, 0.466 mmol, 1 equiv) and I-2 (133.50 mg, 0.466 mmol, 1 equiv) in DCE (5 mL) were added STAB (197.66 mg, 0.932 mmol, 2 equiv) and HOAc (28.00 mg, 0.466 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched

with saturated NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 197c (180 mg, 68.04%) as an off-white solid.

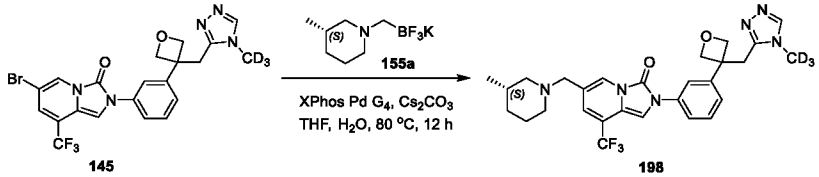
Synthesis of 197

[701] To a stirred solution of 197c (180 mg, 0.341 mmol, 1 equiv) and pyridine (269.84 mg, 3.410 mmol, 10 equiv) in DCM (10 mL) was added triphosgene (40.49 mg, 0.136 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; 10%B to 60%B gradient in 15 min; detector, UV 254 nm. This resulted in Compound 197 (99.3 mg, 52.31%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 554

H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.82-0.89 (m, 4H), 1.23 (s, 3H), 1.35-1.72 (m, 5H), 1.84-1.93 (m, 1H), 2.67-2.77 (m, 2H), 3.16 (s, 2H), 3.24 (s, 2H), 3.70 (s, 3H), 4.82-4.90 (m, 4H), 6.87-6.89 (d, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.19 (s, 1H), 7.24 (s, 1H), 7.37-7.39 (m, 1H), 7.65 (s, 1H), 7.72-7.74 (d, 1H).

Example 198. Synthesis of Compound 198

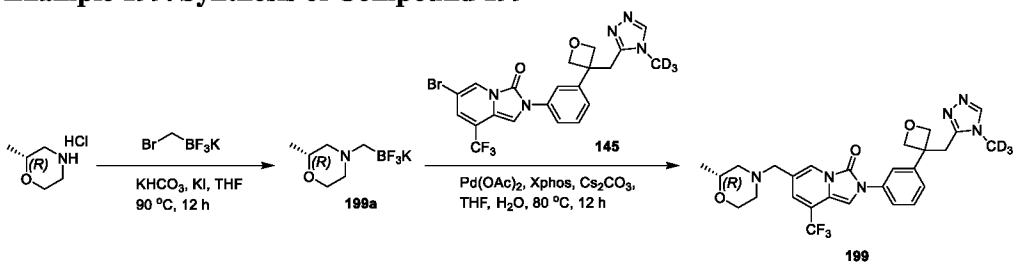


Synthesis of 198

[702] To a solution of 155a (205 mg, 938 umol) and 145 (240 mg, 469 umol) in THF (6 mL) and water (1.5 mL) was added cesium carbonate (458 mg, 1.41 mmol), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl] phenyl]palladium(1+) (40.3 mg, 46.9 umol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was washed with water (30 ml) and extracted with DCM (3x20 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC to afford Compound 198 (50 mg, 19% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 544. H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.21 (s, 1H), 8.16 (s, 1H), 7.80-7.73 (m, 1H), 7.67 (s, 1H), 7.44-7.39 (m, 2H), 7.33 (s, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.98-4.92 (m, 4H), 3.55 (s, 2H), 3.27 (s, 2H), 2.84-2.71 (m, 2H), 1.94-1.88 (m, 1H), 1.68-1.58 (m, 4H), 1.50-1.43 (m, 1H), 0.84 (d, *J* = 6.0 Hz, 4H)

Example 199. Synthesis of Compound 199



Synthesis of 199a

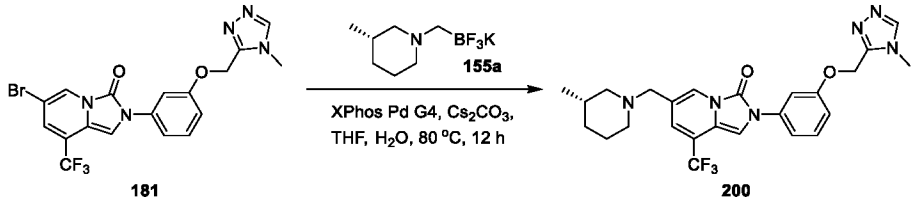
[703] To a solution of (2R)-2-methylmorpholine (0.2 g, 1.45 mmol, as a hydrochloride salt), potassium;bromomethyl(trifluoro)boranuide (291 mg, 1.45 mmol), potassium bicarbonate (291 mg, 2.91 mmol) and KI (24.1 mg, 145 umol) in THF (5 mL) was stirred at 90 °C for 12 h under N_2. The mixture was concentrated under reduced pressure. The crude product was triturated with acetone (30 ml) at 25 °C for 30 min. Then the mixture was filtered, and the filtrate was concentrated under reduced pressure to afford 199a (250 mg, 77.81% yield) was obtained as a light yellow oil.

Synthesis of 199

[704] To a solution of 145 (220 mg, 430 umol) and 199a (190 mg, 860 umol) in THF (15 mL) and water (4 mL) was added XPhos (41 mg, 86 umol), cesium carbonate (420 mg, 1.29 mmol) and $Pd(OAc)_2$ (48.3 mg, 215 umol). The mixture was stirred at 80 °C for 12 h. The mixture was washed with water (50 ml) and extracted with EtOAc (3x30 ml), the combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC to afford Compound 199 (17 mg, 6.91% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 546. H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.20 (s, 1H), 7.80-7.72 (m, 1H), 7.69 (s, 1H), 7.45-7.37 (m, 2H), 7.32 (s, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.9-4.87 (m, 4H), 3.75 (d, *J* = 10.0 Hz, 1H), 3.57-3.44 (m, 4H), 3.28 (d, *J* = 4.4 Hz, 2H), 2.74 (d, *J* = 11.2 Hz, 1H), 2.68 (d, *J* = 1.2 Hz, 1H), 2.10-2.00 (m, 1H), 1.74 (t, *J* = 10.8 Hz, 1H), 1.04 (d, *J* = 6.4 Hz, 3H).

Example 200. Synthesis of Compound 200

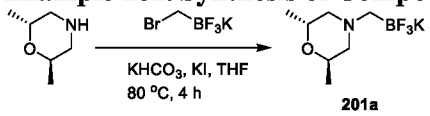


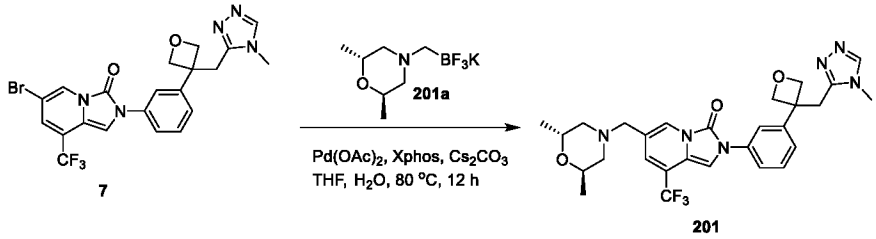
Synthesis of 200

[705] To a solution of 181 (300 mg, 640 umol) and 155a (280 mg, 1.28 mmol) in THF (4 mL) and water (1 mL) was added cesium carbonate (626 mg, 1.92 mmol), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl] palladium(1+) (55.1 mg, 64.1 umol), the mixture was stirred at 80 °C for 12 hr under N_2. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mLx3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by reverse phase HPLC to afford Compound 200 (50 mg, 13% yield) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 501. H-NMR: (400 MHz, CD_3OD-d_4, ppm): δ 8.53 (s, 1H), 7.69 (s, 1H), 7.54 (t, *J* = 2.0 Hz, 1H), 7.52-7.46 (m, 1H), 7.40 (br d, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 7.16-7.12 (m, 2H), 5.43 (s, 2H), 4.62 (br d, *J* = 0.8 Hz, 2H), 3.86 (s, 3H), 2.94-2.82 (m, 2H), 2.04-1.94 (m, 1H), 1.80-1.67 (m, 4H), 1.65-1.58 (m, 1H), 0.91-0.90 (m, 4H)

Example 201. Synthesis of Compound 201





Synthesis of 201a

[706] To a solution of (2R,6R)-2,6-dimethylmorpholine (0.2 g, 1.74 mmol) and potassium bromomethyl (trifluoro)boronate (348.75 mg, 1.74 mmol) in THF (2 mL) was added $KHCO_3$ (347.70 mg, 3.47 mmol) and KI (28.83 mg, 173.65 umol). The mixture was stirred at 80 °C for 4 hr. The reaction mixture was evaporated under reduced pressure to give a residue. Then it was poured into acetone (5 ml) and stirred for 20 min at room temperature. The mixture

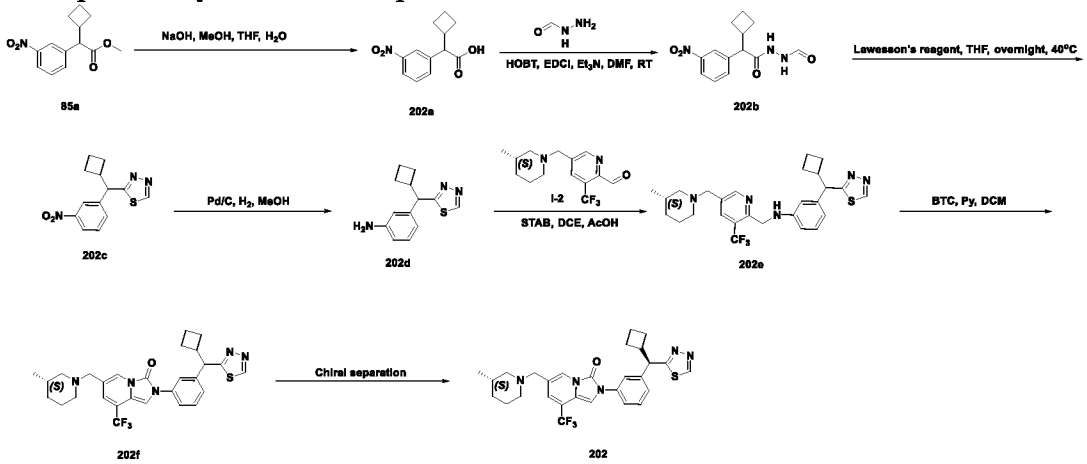
was filtered and the filtrate was evaporated under reduced pressure to get crude product 201a (0.19 g, crude) as colorless oil, which was used into the next step without further purification.

Synthesis of 201

[707] To a solution of Compound 7 (0.1 g, 196.74 umol) and 201a (138.76 mg, 590.21 umol) in THF (0.5 mL) and H_2O (0.1 mL) was added diacetoxypalladium (4.42 mg, 19.67 umol), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (14.07 mg, 29.51 umol), and cesium carbonate (128.20 mg, 393.48 umol). The mixture was stirred at 100 °C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Phenomenex C18 80*40mm*3um;mobile phase: [water(NH4HCO3)-ACN];B%: 25%-60%,8min). Compound 201 (0.022 g, 19.09% yield) was obtained as a white solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557. H-NMR: (400 MHz, DMSO-d_6, ppm): δ 8.20 (s, 1H),7.74 (dd, *J*=6.8Hz, *J*=8.4Hz, 1H), 7.67 (s, 1H), 7.42-7.38 (m, 2H), 7.31 (s, 1H), 7.03 (s, 1H), 6.89 (d, *J*=8 Hz, 1H), 4.94 (d, J=6.4Hz, 2H), 4.91(d, J=6.0Hz, 2H), 3.91-3.89 (m, 2H), 3.53 (s, 2H), 3.36-3.21 (m, 2H), 2.96 (s, 3H), 2.50-5.41(m, 2H), 2.13-2.10 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 6H).

Example 202. Synthesis of Compound 202



Synthesis of 202a

[708] Into a 500 mL 3-necked round-bottom flask were added 85a (20 g, 80.236 mmol, 1 equiv), MeOH (200 mL), THF (50 mL), H_2O (50 mL) and NaOH (6.42 g, 160.472 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 3 with HCl (aq, 1M). The precipitated solids were collected by filtration and washed with Et_2O (3x30 mL) to afford 202a (17 g, 90.07%) as a white solid.

Synthesis of 202b

[709] Into a 250 mL 3-necked round-bottom flask were added 202a (8 g, 34.008 mmol, 1 equiv), DMF (80 mL), N-formylhydrazine (3.06 g, 51.012 mmol, 1.5 equiv), HOBT (6.89 g, 51.012 mmol, 1.5 equiv), EDCI (9.78 g, 51.012 mmol, 1.5 equiv) and Et_3N (10.32 g, 102.024 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (1:1) to afford 202b (7.5 g, 79.54%) as a white solid.

Synthesis of 202c

[710] Into a 100 mL 3-necked round-bottom flask were added 202b (1 g, 3.606 mmol, 1 equiv) and Lawesson Reagent (2.92 g, 7.212 mmol, 2 equiv) in THF (10 mL) at room temperature. The resulting mixture was stirred overnight at 40°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (5:1) to afford 202c (900 mg, 90.64%) as a colorless oil.

Synthesis of 202d

[711] Into a 50 mL 3-necked round-bottom flask were added 202c (1 g, 3.632 mmol, 1 equiv) and Pd/C (0.2 g, 1.879 mmol, 0.52 equiv) in MeOH (10 mL) at room temperature. The resulting mixture was stirred overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered through filter paper and the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure to afford 202d (800 mg, 89.78%) as white solid.

Synthesis of 202e

[712] Into a 100 mL 3-necked round-bottom flask were added 202d (800 mg, 3.261 mmol, 1 equiv), DCE (8 mL), I-2 (933.56 mg, 3.261 mmol, 1 equiv), STAB (1382.18 mg, 6.522 mmol, 2 equiv) and AcOH (195.82 mg, 3.261 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (1:1) to afford 202e (800 mg, 47.58%) as a white solid.

Synthesis of 202f

[713] Into a 8 mL sealed tube were added 202e (500 mg, 0.970 mmol, 1 equiv), pyridine

(459.78 mg, 5.820 mmol, 6 equiv), and DCM (5 mL) at room temperature. To the above mixture was added triphosgene (115.09 mg, 0.388 mmol, 0.4 equiv). The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated $NaHCO_3$ (aq) (15 mL) at room temperature. The aqueous layer was extracted with DCM (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 202f (250 mg, 47.60%) as a yellow solid.

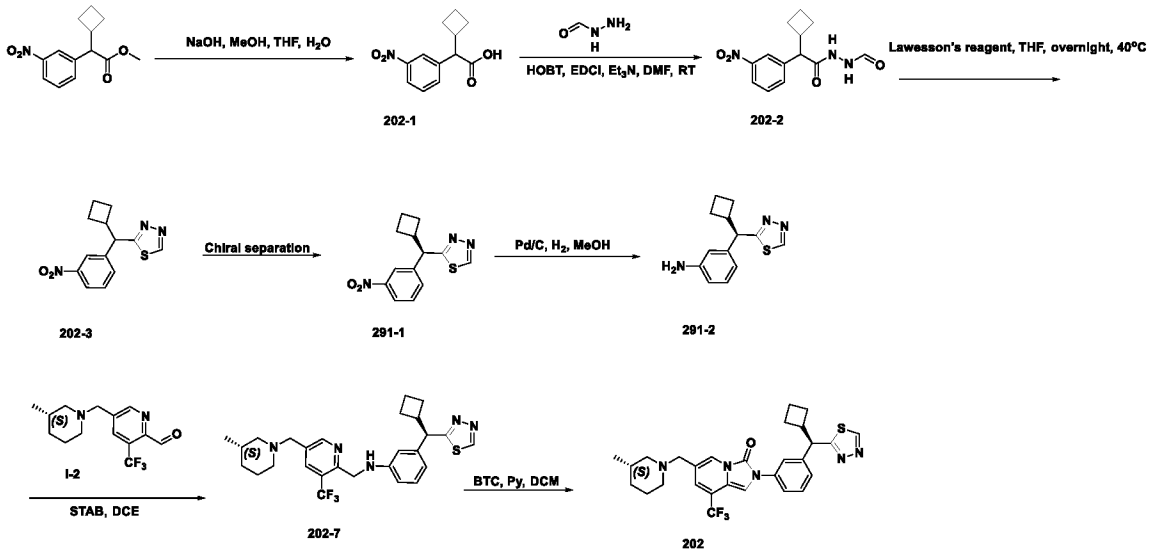
Synthesis of 202

[714] The 202f (250 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 18.5 min; Wave Length: 220/254 nm; RT1(min): 11.29; RT2(min): 14.80; The first peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1.15 ml). This result in Compound 202 (96.8 mg, 38.72%) as a white solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 0.80-0.88 (m, 4H), 1.45-1.48 (m, 1H), 1.60-1.63 (m, 4H), 1.67-1.89 (m, 6H), 2.04-2.09 (m, 1H), 2.78 (s, 2H), 3.22-3.33 (m, 3H), 4.71-4.74 (d, 1H), 7.02 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.68 (s, 1H), 7.75-7.78 (d, 1H), 7.86-7.87 (d, 1H), 9.51 (s, 1H).

Alternatively, Compound 202 may be also prepared in the manner outlined below:



1. Synthesis of 202-1

[715] To a stirred solution of methyl 2-cyclobutyl-2-(3-nitrophenyl)acetate (110 g, 441.296 mmol, 1 equiv) in MeOH (220 mL),THF (660 mL) and H_2O (220 mL) was added NaOH (52.95 g, 1323.888 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was diluted with water (500 mL). The MeOH and THF was removed in vacuum. The resulting mixture was acidified to pH 2 with HCl (1M). The precipitated solids were collected by filtration and washed with water (3x200 mL). Thesolid was dried under vacuum. This resulted in 202-1 (102 g, 98.26%) as a white solid.

2. Synthesis of 202-2

To a stirred mixture of 202-1 (102 g, 433.602 mmol, 1 equiv), HOBT (117.18 g, 867.204 mmol, 2 equiv), EDCI (166.24 g, 867.204 mmol, 2 equiv) and Et_3N (131.63 g, 1300.806 mmol, 3 equiv) in DMF (1020 mL) were added N-formylhydrazine (78.12 g, 1300.806 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.)(3L) at room temperature. The resulting mixture was extracted with EtOAc (2 x 1L). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford crude product. The crude product (55 g) was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 220 nm. This resulted in 202-2 (46 g, 38.26%) as a white solid.

3. Synthesis of 202-3

[716] To a stirred solution of 202-2 (25.8 g, 93.047 mmol, 1 equiv) in THF (260 mL) was added Lawesson Reagent (75.27 g, 186.094 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (260 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford crude product. The crude product (18 g) was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 20% to 65% gradient in 30 min; detector, UV 254 nm. This resulted in 202-3 (13.4 g, 52.31%) as a yellow oil.

4. Synthesis of 291-1

[717] 202-10 (10 g,) was purified by Prep-Chiral- SFC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 5*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile

Phase B: MeOH; Flow rate: 200 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.08; RT2(min): 6.08; the second peak was product) to afford 291-1 (4.09 g, 40.90%) as a yellow oil.

5. Synthesis of 291-2

To a solution of 291-1 (4.09 g, 14.855 mmol, 1 equiv) in MeOH (120 mL) was added Pd/C (10%, 1.2g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere by using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 291-2 (3.65 g, 96.14%) as a brown solid.

6. Synthesis of 202-7

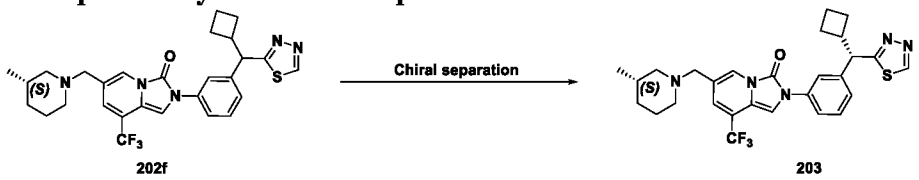
[718] To a stirred solution of 291-2 (2.4 g, 9.782 mmol, 1 equiv) and I-2(3.08 g, 10.760 mmol, 1.1 equiv) in DCE (70 mL) was added STAB (4.15 g, 19.564 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (100 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(10 mmoL/L NH_4HCO_3), 40% to 90% gradient in 35 min; detector, UV 254 nm. This resulted in 202-7 (4.3 g, 85.25%) as a white solid.

7. Synthesis of 202-0

[719] To a stirred solution of 202-7 (4.3 g, 8.339 mmol, 1 equiv) and Pyridine (3.96 g, 50.034 mmol, 6 equiv) in DCM (120 mL) was added Triphosgene (0.99 g, 3.336 mmol, 0.4 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (100 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10mmoL/L NH_4HCO_3), 40% to 90% gradient in 40 min; detector, UV 254 nm. This resulted in 202 (2.2 g, 48.71%) as a yellow solid.

LC-MS-202: (ES, *m/z*): $[M+H]^+$ 542. H-NMR-202: (400 MHz, dmso-*d6*, δ ppm): 0.80-0.88 (m, 4H), 1.45-1.47 (m, 1H), 1.50-1.63 (m, 4H), 1.66-1.91 (m, 6H), 2.06-2.08 (m, 1H), 2.72-2.77 (m, 2H), 3.22-3.30 (m, 3H), 4.71-4.74 (d, 1H), 7.00 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.65 (s, 1H), 7.75-7.77 (d, 1H), 7.87 (s, 1H), 9.51 (s, 1H).

Example 203. Synthesis of Compound 203



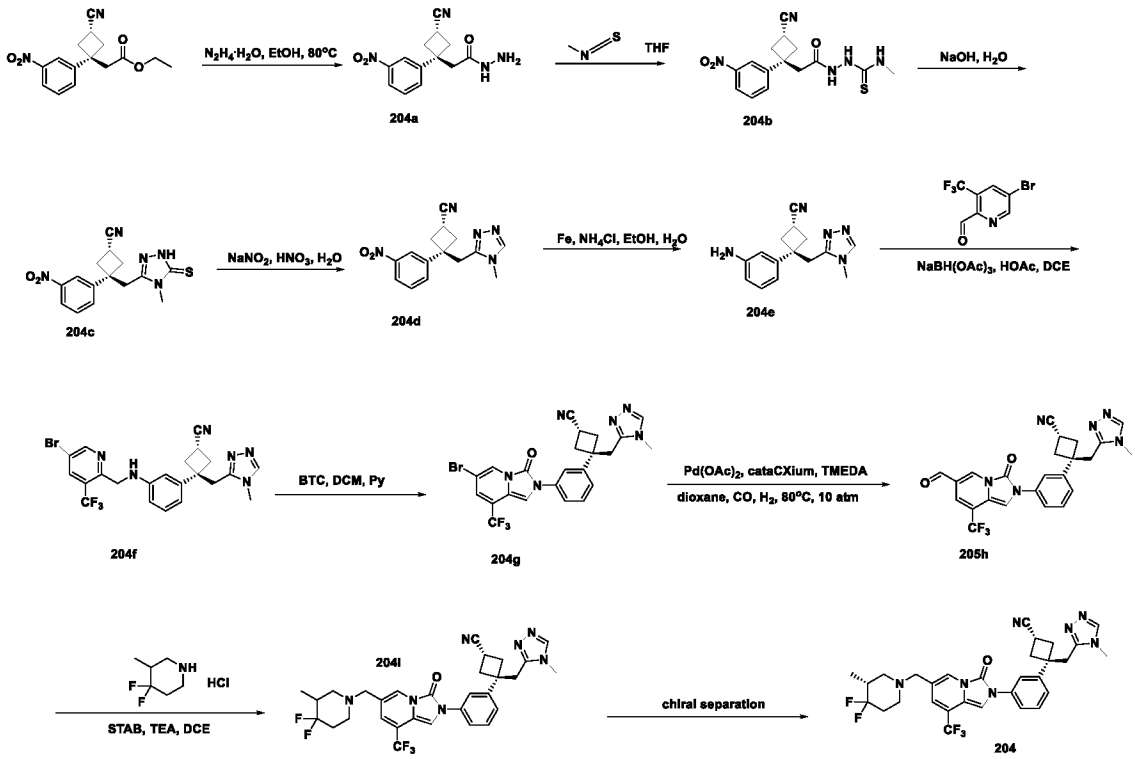
Synthesis of 203

[720] The 202f (250 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 18.5 min; Wave Length: 220/254 nm; RT1(min): 11.29; RT2(min): 14.80; The second peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1.15 mL; Number Of Runs: 4) to afford Compound 203 (97 mg, 38.80%) as a white solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542

H-NMR: (400 MHz, dmso-*d6*, δ ppm): 0.80-0.88 (m, 4H), 1.45-1.48 (m, 1H), 1.60-1.63 (m, 4H), 1.67-1.89 (m, 6H), 2.04-2.09 (m, 1H), 2.78 (s, 2H), 3.22-3.33 (m, 3H), 4.71-4.74 (d, 1H), 7.02 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.68 (s, 1H), 7.75-7.78 (d, 1H), 7.86-7.87 (d, 1H), 9.51 (s, 1H).

Example 204. Synthesis of Compound 204



1. Synthesis of 204a

[721] To a stirred solution of 204-1 (1.2 g, 4.162 mmol, 1 equiv) in EtOH (10 mL) was added hydrazine hydrate (98%) (1.04 g, 20.810 mmol, 5 equiv). The resulting mixture was stirred for overnight at 80 °C .The resulting mixture was diluted with water (40 mL).The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The combined organic layers were concentrated under reduced pressure. This resulted in 204a (1 g, 87.59%) as a white solid.

2. Synthesis of 204b

[722] To a stirred solution of 204a (1 equiv) in tetrahydrofuran (20 mL) was added methyl isothiocyanate (2 equiv).The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (20 mL).The THF was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x5 mL).The resulting solid was dried under vacuum. This resulted in 204b (1.2 g, NaN) as a yellow solid.

3. Synthesis of 204c

[723] Into a 100 mL round-bottom flask were added 204b (1.2 g, 3.454 mmol, 1 equiv) and NaOH (17.27 mL, 17.270 mmol, 5 equiv, 1M) at room temperature. The resulting mixture

was stirred for overnight at room temperature. The mixture was acidified to pH 4 with HCl (1M).The precipitated solids were collected by filtration and washed with water (2 mL).The resulting solid was dried under vacuum. This resulted in 204c (860 mg, 75.59%) as a yellow solid.

4. Synthesis of 204d

[724] To a stirred mixture of 204c (860 mg, 2.611 mmol, 1 equiv) and $NaNO_2$ (1801.44 mg, 26.110 mmol, 10 equiv) in H_2O (10 mL) and EtOAc (10 mL) was added HNO_3 (26.11 mL, 26.110 mmol, 10 equiv, 1M) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The mixture basified to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 204d (710 mg, 91.46%) as a yellow solid.

5. Synthesis of 204e

[725] To a stirred mixture of 204d (710 mg, 2.388 mmol, 1 equiv) in EtOH (20 mL) and H_2O (5 mL) were added NH_4Cl (510.95 mg, 9.552 mmol, 4 equiv) and Fe (400.08 mg, 7.164 mmol, 3 equiv). The resulting mixture was stirred for 3 h at 80 °C. The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (2x10 mL). The resulting mixture was diluted with water (80 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 204e (700 mg, 109.65%) as a yellow solid.

6. Synthesis of 204f

[726] To a stirred solution of 204e (700 mg, 2.618 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (798.12 mg, 3.142 mmol, 1.2 equiv) in DCE (15 mL) were added HOAc (157.24 mg, 2.618 mmol, 1 equiv) and NaBH(OAc)3 (832.43 mg, 3.927 mmol, 1.5 equiv).The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with methyl tert-butyl ether (5 mL). This resulted in 204f (900 mg, 68.02%) as a light yellow solid.

7. Synthesis of 204g

[727] To a stirred solution of 204f (900 mg, 1.781 mmol, 1 equiv) and Pyridine (845.25 mg, 10.686 mmol, 6 equiv) in DCM (25 mL) was added Triphosgene (211.40 mg, 0.712 mmol,

0.4 equiv) at 0°C.The resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by trituration with methyl tert-butyl ether (5 mL).This resulted in 204g (700 mg, 73.97%) as a yellow solid.

8. Synthesis of 204h

[728] To a solution of 204g (700 mg, 1.317 mmol, 1 equiv) , TMEDA (306.18 mg, 2.634 mmol, 2 equiv) in 1,4-dioxane (20 mL) was added and $Pd(OAc)_2$ (29.58 mg, 0.132 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 80 degrees C for overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to CH_2Cl_2 / MeOH (5:1) to afford 204h (489 mg, 77.26%) as a yellow solid.

9. Synthesis of 204i

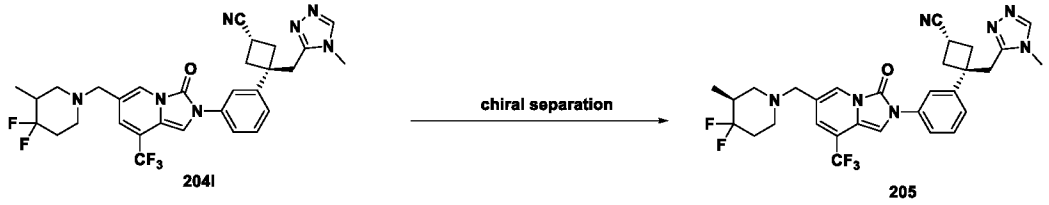
[729] To a stirred mixture of 204h (300 mg, 0.624 mmol, 1 equiv) and 4,4-difluoro-3-methylpiperidine hydrochloride (321.49 mg, 1.872 mmol, 3 equiv) in DCE (10 mL) were added TEA (252.74 mg, 2.496 mmol, 4 equiv) and STAB (264.68 mg, 1.248 mmol, 2 equiv).The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (10 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 204i (150 mg, 40.06%) as a yellow solid.

10. Synthesis of 204

[730] 204 (150 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MeOH); Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT1(min): 7.48; the first peak is product) to afford 204 (49.9 mg, 33.27%) as a yellow solid.

LC-MS-204: (ES, *m/z*): $[M+H]^+$ 600. H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.82-0.86 (d, 3H), δ1.85-2.19 (m, 4H), δ2.26-2.33 (m, 1H), δ2.64-2.67 (m, 3H), δ2.69-2.79 (m, 4H), δ3.00-3.06(m, 2H), δ3.26 (s, 2H), δ3.35 (s, 2H), δ3.74-3.78 (t, 1H), δ6.73-6.75 (d, 1H), δ7.03 (s, 1H), δ7.25 (s, 1H), δ7.32-7.39 (m, 2H), δ7.70-7.73 (m, 1H), δ8.16 (s, 1H).

Example 205. Synthesis of Compound 205



204I 205

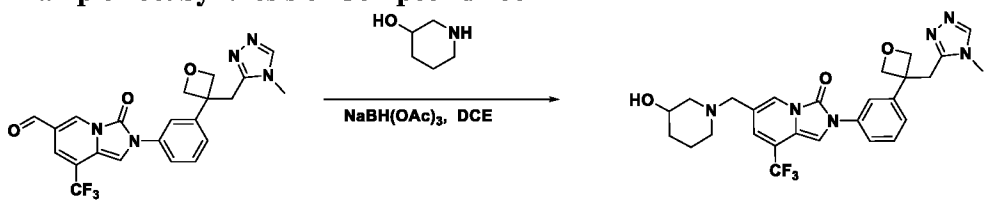
1. Synthesis of 205

[731] 205 (150 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH3-MEOH); Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT2(min): 9.73; the second peak is product) to afford 205 (52.7 mg, 35.13%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 600

H-NMR: (400 MHz, DMSO-d6, *ppm*): δ0.86-0.89 (d, 3H), δ1.89-2.11 (m, 4H), δ2.26-2.33 (m, 1H), δ2.64-2.67 (m, 2H), δ2.69-2.79 (m, 5H), δ3.00-3.06(m, 2H), δ3.26 (s, 2H), δ3.35 (s, 2H), δ3.74-3.78 (t, 1H), δ6.73-6.75 (d, 1H), δ7.03 (s, 1H), δ7.25 (s, 1H), δ7.32-7.39 (m, 2H), δ7.70-7.73 (m, 1H), δ8.16 (s, 1H).

Example 206. Synthesis of Compound 206



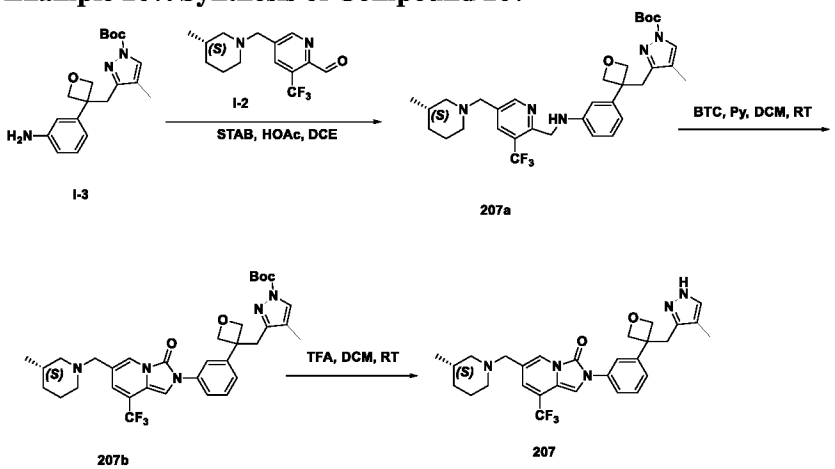
252-1 206

[732] To a stirred solution of 252-1 (90 mg, 0.19 mmol, 1.0 equiv) and piperidin-3-ol (39.8 mg, 0.39 mmol, 2.0 equiv) in DCE was added NaBH(OAc)3 (83.4 mg, 0.39 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with water(20 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=10:1) to afford 206(51 mg, 44%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 543. H-NMR: (400 MHz, DMSO, δ ppm): 1.06-1.11 (m, 1H), 139-1.45 (m, 1H), 1.61-1.64 (m, 1H), 1.73-1.80 (m, 2H), 1.88-1.93 (m, 1H), 2.65-2.67 (m, 1H), 2.80-2.86 (m, 1H), 2.91 (s, 3H), 3.23-3.27 (m, 1H), 3.31-3.33 (m, 1H), 3.46-3.53 (m,

1H), 3.61 (s, 2H), 4.62 (s, 1H), 4.91-4.96 (m, 4H), 6.88-6.90 (d, 1H), 7.01 (s, 1H), 7.32 (s, 1H), 7.38-7.42 (m, 2H), 7.67 (s, 1H), 7.74-7.76 (m, 1H), 8.18-8.22 (m, 2H).

Example 207. Synthesis of Compound 207



1. Synthesis of 207a

[733] To a stirred solution of I-3 (200 mg, 0.582 mmol, 1.00 equiv) and I-2(166.73 mg, 0.582 mmol, 1 equiv) in DCE (5 mL) was added HOAc (34.97 mg, 0.582 mmol, 1 equiv) and STAB (246.85 mg, 1.164 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$ (aq.) (50mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 207a (200 mg, 52.04%) as a light yellow oil.

2. Synthesis of 207b

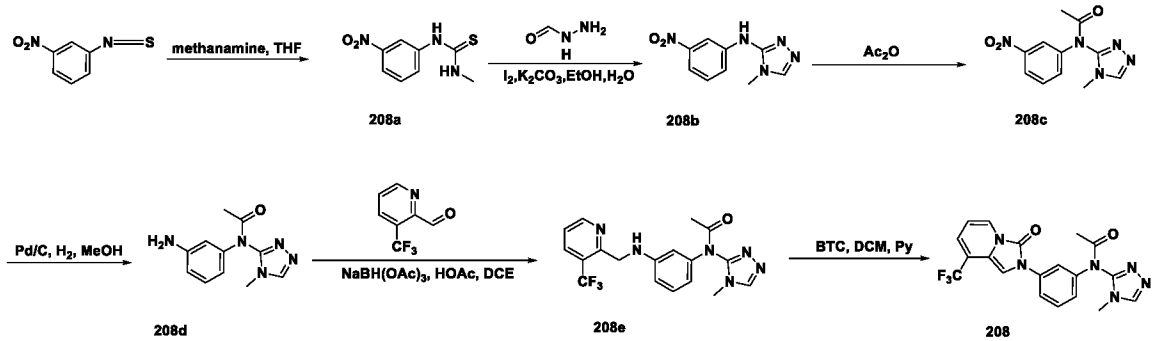
[734] To a stirred solution of 207a (180 mg, 0.293 mmol, 1.00 equiv) and Pyridine (463.98 mg, 5.860 mmol, 20 equiv) in DCM (10 mL) was added Triphosgene (43.52 mg, 0.146 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 207b (150 mg, 74.35%) as a yellow solid.

3. Synthesis of 207

[735] To a stirred solution of 207b (150 mg, 0.234 mmol, 1.00 equiv) in DCM (5 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The resulting mixture was concentrated under vacuum. The crude product was

purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 54% B to 73% B in 8 min, Wave Length: 220 nm; RT1(min): 7.85) to afford 207 (35.6 mg, 27.29%) as a yellow solid. LC-MS: (ES, *m/z*): $[M+H]^+$ 540. H-NMR: (400 MHz, CD_3OD, δ *ppm*): 0.90-0.98 (m, 4H), 1.29-1.42 (m, 3H), 1.56-1.77 (m, 5H), 1.96-2.01 (m, 1H), 2.83-2.91 (m, 2H), 3.34-3.50 (m, 4H), 5.02 (s, 4H), 6.90-6.92 (m, 2H), 7.10-7.12 (m, 2H), 7.21 (s, 1H), 7.42-7.46 (m, 1H), 7.62-7.64 (d, 1H), 7.67 (s, 1H).

Example 208. Synthesis of Compound 208



Synthesis of 208a

[736] To a stirred solution of 1-isothiocyanato-3-nitrobenzene (5 g, 27.750 mmol, 1 equiv) and THF (50 mL) was added methanamine (13.87 mL, 27.750 mmol, 1 equiv, 2M in THF) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was quenched with Water (100 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (2x20 mL) to afford 208a (4 g, 68.24%) as a white solid.

Synthesis of 208b

[737] To a stirred solution of 208a (4 g, 18.936 mmol, 1 equiv) and N-formylhydrazine (2.84 g, 47.340 mmol, 2.5 equiv) in EtOH (62 mL) and H_2O (15 mL) were added K_2CO_3 (6.54 g, 47.340 mmol, 2.5 equiv) and I_2 (5.77 g, 22.723 mmol, 1.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. The reaction was quenched with Water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (5x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 208b (860 mg, 20.72%) as a yellow solid.

Synthesis of 208c

[738] A solution of 208b (800 mg, 3.650 mmol, 1 equiv) in acetic anhydride (5 mL) was

stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with $NaHCO_3$ (aq.) (100 mL) at 0°C. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 208c (300 mg, 31.47%) as yellow oil.

Synthesis of 208d

[739] To a solution of 208c (200 mg, 0.766 mmol, 1 equiv) in MeOH (4 mL) was added Pd/C (10%, 40 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 208d (140 mg, 79.08%) as white solid.

Synthesis of 208e

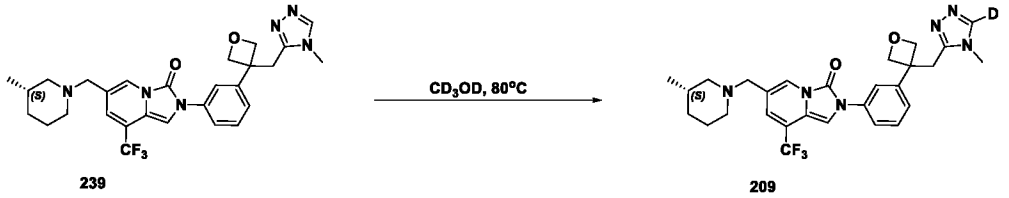
[740] A solution of 208d (130 mg, 0.562 mmol, 1 equiv) in DCE (2 mL) was treated with 3-(trifluoromethyl)pyridine-2-carbaldehyde (147.65 mg, 0.843 mmol, 1.5 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of $NaBH(OAc)_3$ (238.28 mg, 1.124 mmol, 2 equiv) and HOAc (33.76 mg, 0.562 mmol, 1 equiv) at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x7 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 208e (140 mg, 63.80%) as yellow solid.

Synthesis of 208

[741] To a stirred solution of 208e (140 mg, 0.359 mmol, 1 equiv) and Pyridine (170.21 mg, 2.154 mmol, 6 equiv) in DCM (6 mL) was added triphosgene (37.25 mg, 0.126 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 208 (80 mg, crude). The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 40% B in 8 min, Wave Length: 220 nm; RT1(min): 7.40;) to afford 208 (41.4 mg, 27.73%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 417. H-NMR: (400 MHz, DMSO, δ ppm): 2.07 (s, 3H), 3.56 (s, 3H), 6.27-6.31 (t, 1H), 7.10-7.12 (d, 1H), 7.42 (s, 2H), 7.57-7.61 (m, 1H), 7.79-7.81 (d, 1H), 7.83-88.12 (m, 2H), 8.56 (s, 1H).

Example 209. Synthesis of Compound 209

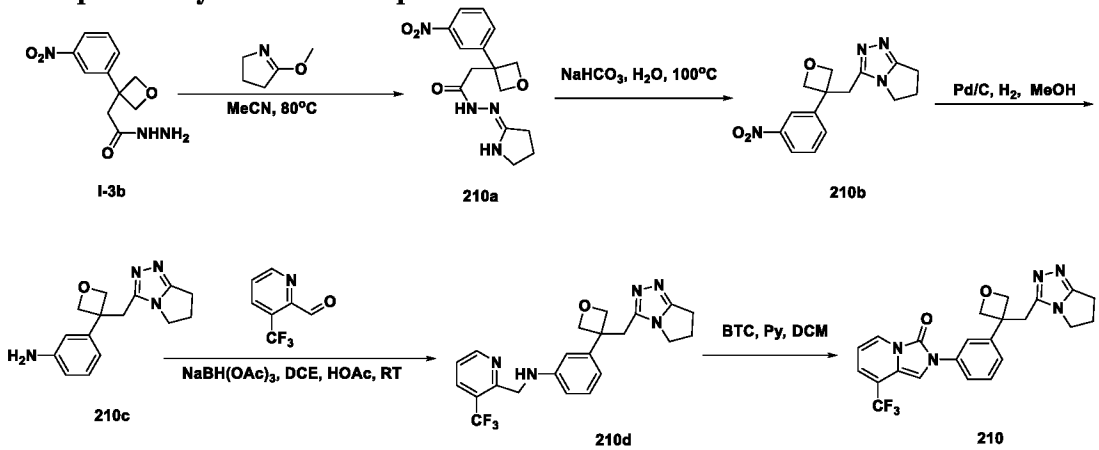


Synthesis of 209

[742] A solution of 239 (180 mg, 0.333 mmol, 1 equiv) in CD_3OD (3 mL) was stirred for 2 h at 80°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 209 (97.9 mg, 53.74%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 542. H-NMR: (400 MHz, DMSO-d_6, ppm, δ): 0.84-0.97 (m, 4H), 1.36-1.59 (m, 1H), 1.59-1.83 (m, 4H), 1.80-1.90 (m, 1H), 2.75-2.86 (m, 2H), 3.01 (s, 3H), 3.25-3.33 (m, 2H), 3.53 (s, 2H), 4.87-4.96 (m, 4H), 6.88-6.90 (m, 1H), 7.02 (s, 1H), 7.32 (s, 1H), 7.38-7.41 (m, 2H), 7.66 (s, 1H), 7.74-7.76 (m, 2H).

Example 210. Synthesis of Compound 210



1. Synthesis of 210

[743] A solution of I-3b (1.8 g, 7.164 mmol, 1 equiv) in MeCN (30 mL) was stirred 2-methoxy-4,5-dihydro-3H-pyrrole (1.07 g, 10.746 mmol, 1.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. This resulted in 210a (1.8 g, 63.14%) as a yellow solid. The crude product was used in the next step directly without further purification.

2. Synthesis of 210b

[744] To a stirred solution of 210a (1.8 g, 5.654 mmol, 1 equiv) in H2O (30 mL) was added $NaHCO_3$ (4.75 g, 56.540 mmol, 10 equiv) at room temperature. The resulting mixture was

stirred overnight at 100°C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (5x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 210b (200 mg, 9.42%) as a yellow solid.

3. Synthesis of 210c

[745] To a solution of 210b (180 mg, 0.599 mmol, 1 equiv) in 10mL MeOH was added Pd/C (20 mg, 10%) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 210c (100 mg, 49.37%) as an off-white solid. The crude product was used in the next step directly without further purification.

4. Synthesis of 210d

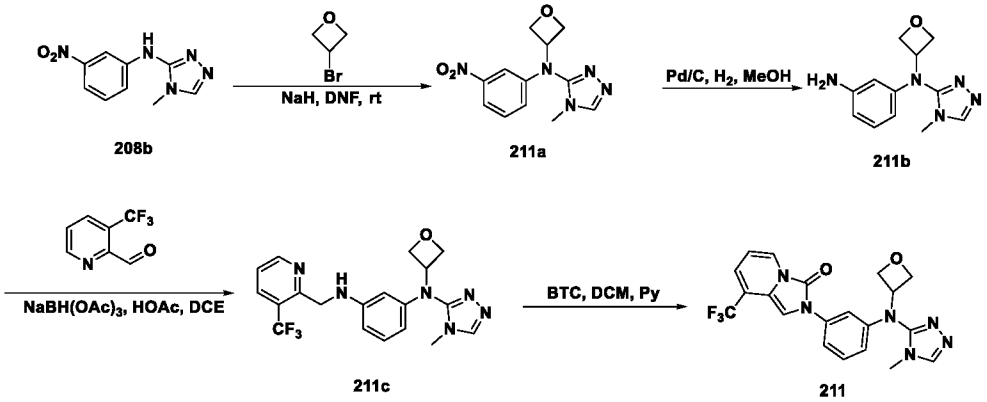
[746] To a stirred solution of 210c (80 mg, 0.296 mmol, 1 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (51.82 mg, 0.296 mmol, 1 equiv) in DCE (3 mL) was added $NaBH(OAc)_3$ (125.44 mg, 0.592 mmol, 2 equiv) and HOAc (17.77 mg, 0.296 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 210d (50 mg, 35.80%) as an off-white solid.

5. Synthesis of 210

[747] To a stirred solution of 210d (40 mg, 0.093 mmol, 1 equiv) and Pyridine (73.68 mg, 0.931 mmol, 10.00 equiv) in DCM (5 mL) were added Triphosgene (9.67 mg, 0.033 mmol, 0.35 equiv) at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x10 mL). The organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 210 (19.2 mg, 43.00%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 456. H-NMR: (400 MHz, CD_3OD, δ *ppm*): 2.37-2.45 (m, 2H), 2.75-2.78 (m, 2H), 2.94-2.97 (m, 2H), 3.59 (s, 2H), 5.00-5.03 (m, 2H), 5.03-5.07 (m, 2H), 6.33-6.37 (m, 1H), 6.93-6.96 (d, 1H), 7.04-7.05 (d, 1H), 7.11 (s, 1H), 7.24 (s, 1H), 7.50-7.54 (m, 1H), 7.64-7.66 (d, 1H), 7.75-7.77 (d, 1H).

Example 211. Synthesis of Compound 211



208b 211a 211b

211c 211

1. Synthesis of 211a

[748] To a solution of 208b (800 mg, 3.650 mmol, 1 equiv) in DMF (10 mL) was added NaH (218.95 mg, 5.475 mmol, 1.5 equiv, 60% in oil) at 0 degrees C. The resulting mixture was stirred for 1h at 0 degrees C. To the above 3-bromooxetane (999.81 mg, 7.300 mmol, 2 equiv) was added. The resulting mixture was allowed to warm to RT and stirred for overnight. The reaction mixture was quenched by water (30 mL) and extracted with DCM (3*25 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 9:1) to afford 211a (134 mg, 13.34%) as yellow oil.

2. Synthesis of 211b

[749] To a solution of 211a (120 mg, 0.436 mmol, 1 equiv) in MeOH (2 mL) was added Pd/C (10%, 30 mg) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 211b (103 mg, 96.32%) as yellow solid.

3. Synthesis of 211c

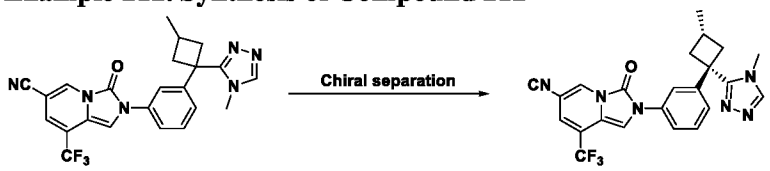
[750] A solution of 211b (103 mg, 0.420 mmol, 1 equiv) in DCE (2 mL) was treated with 3-(trifluoromethyl)pyridine-2-carbaldehyde (88.24 mg, 0.504 mmol, 1.2 equiv) for 30 min at room temperature followed by the addition of $NaBH(OAc)_3$ (178.00 mg, 0.840 mmol, 2 equiv) and HOAc (25.22 mg, 0.420 mmol, 1 equiv). The resulting mixture was stirred for overnight. The reaction was quenched by the addition of NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x7 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 211c (89.9 mg, 52.94%) as yellow solid.

4. Synthesis of 211

[751] To a stirred solution of 211c (80 mg, 0.198 mmol, 1 equiv) and Pyridine (93.89 mg, 1.188 mmol, 6 equiv) in DCM (2 mL) was added Triphosgene (20.55 mg, 0.069 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. NaHCO3 (aq.)(10 mL) at room temperature. The resulting mixture was extracted with DCE/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1). The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 46% B in 8 min, 46% B; Wave Length: 220 nm; RT1(min): 7.65;) to afford 211 (35.7 mg, 41.93%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 431. H-NMR: (400 MHz, DMSO, δ ppm): 3.42 (s, 3H), 4.42-4.45 (t, 2H), 4.77-4.80 (t, 2H), 5.18-5.20 (t, 1H), 6.26-6.29 (m, 1H), 6.49-6.52 (m, 1H), 7.08-7.10 (d, 1H), 7.17 (s, 1H), 7.33-7.42 (m, 3H), 7.78-7.79 (d, 1H), 8.57 (s, 1H).

Example 212. Synthesis of Compound 212



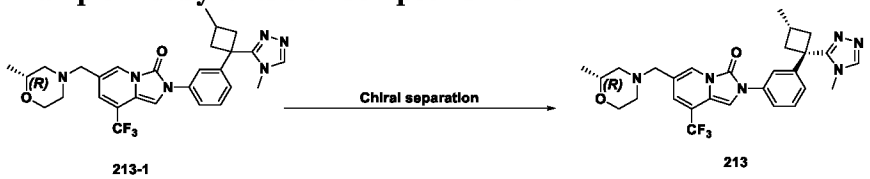
212-1 212

Synthesis of 212

[752] The 212-1 (240 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 17 min; Wave Length: 220/254 nm; RT2(min): 11.69; RT2(min): 14.54, the first peak is product) to afford 212 (129.8 mg, 33.30%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 453. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.08-1.09 (m, 3H), 2.55-2.58 (m, 3H), 2.87-2.89 (m, 2H), 3.23-3.25(s, 3H), 7.27-7.31 (m, 2H), 7.50-7.52 (m, 1H), 7.54-7.58 (m, 1H), 7.63-7.65 (m, 1H), 7.80(s, 1H), 8.41 (s, 1H) 8.70 (s, 1H).

Example 213. Synthesis of Compound 213

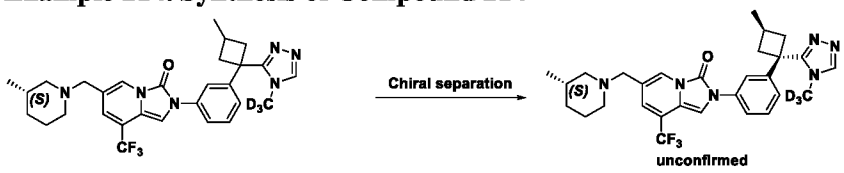


213-1 213

Synthesis of 213

[753] The 213-1 (350 mg) was purified by Chiral separation with the following conditions Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 20 min; Wave Length: 220/254 nm; RT1(min): 8.96; RT2(min): 13.78; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 2 mL; Number of Runs: 6 to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 55% B in 8 min, 55% B; Wave Length: 220 nm; RT1(min): 7.73) to afford 213 (71.9 mg, 21.50%) as a yellow solid.

Example 214. Synthesis of Compound 214



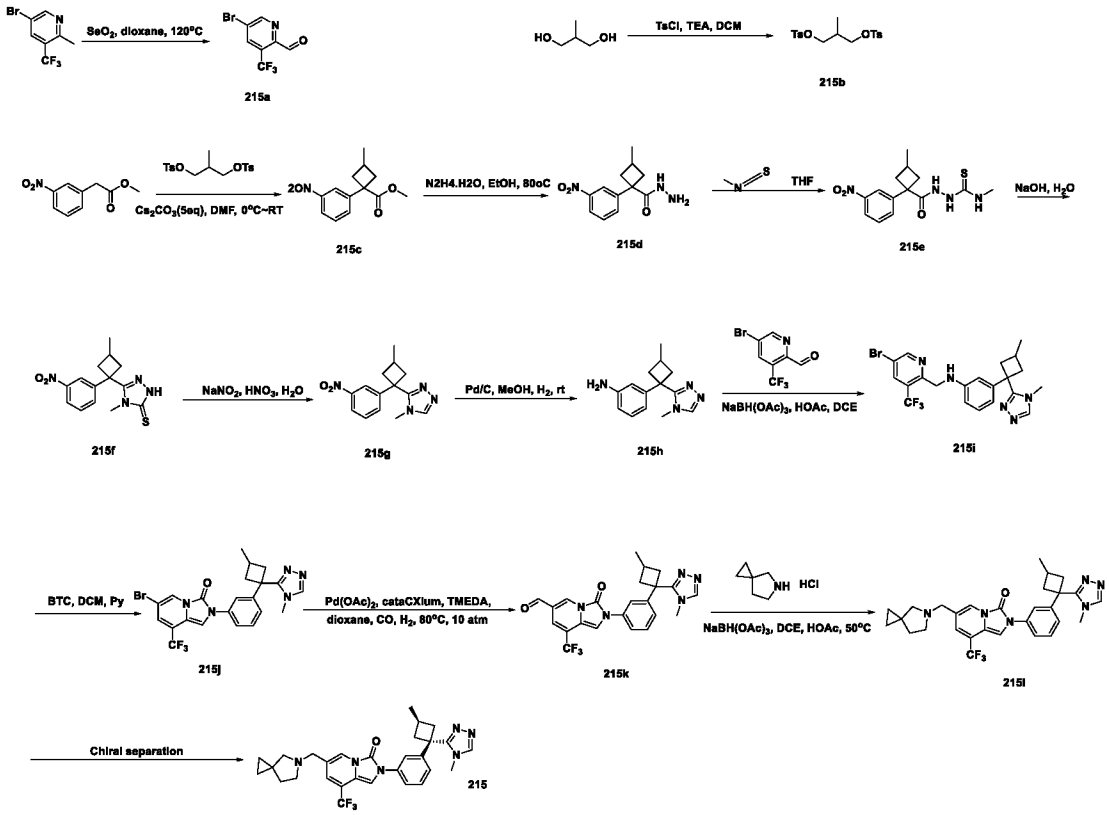
214-1 214

Synthesis of 214

The 214-1 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 28 min; Wave Length: 220/254 nm; RT2(min): 11.87, RT2(min): 16.98, the second peak is product) to afford 214 (25.7 mg, 31.87%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 542. H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 0.81-0.93 (m, 4H), 1.09-1.11 (d, 3H), 1.43-1.46 (m, 1H), 1.57-1.66 (m, 4H), 1.86-1.91 (m, 1H), 2.29-2.46 (m, 3H), 2.72-2.77 (m, 2H), 3.09-3.14 (m, 2H), 3.24 (s, 2H), 7.00 (s, 1H), 7.07-7.09 (d, 1H), 7.36 (s, 1H), 7.44-7.48 (m, 1H), 7.60-7.65 (m, 2H), 7.71 (s, 1H), 8.36 (s, 1H).

Example 215. Synthesis of Compound 215



1. Synthesis of 215a

[754] To a stirred solution of 5-bromo-2-methyl-3-(trifluoromethyl) pyridine (30 g, 124.988 mmol, 1 equiv) in 1,4-dioxane was added SeO_2 (55.47 g, 499.952 mmol, 4 equiv) at room temperature under nitrogen atmosphere. The final reaction mixture was irradiated with microwave radiation for overnight at 120°C. The resulting mixture was filtered; the filter cake was washed with DCM (3x100 mL). The filtrate was concentrated under reduced pressure. The reaction was quenched by the addition of Water (500mL) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (20:1) to afford 215a (25 g, 78.75%) as a yellow oil.

2. Synthesis of 215b

[755] A solution of methylpropanediol (50 g, 554.803 mmol, 1 equiv) in DCM (1.5 L) was treated with TEA (168.43 g, 1664.409 mmol, 3 equiv) for 1 h at room temperature under nitrogen atmosphere followed by the addition of TsCl (317.30 g, 1664.409 mmol, 3 equiv) in three portions at room temperature. The resulting mixture was stirred for 6 h at room temperature under nitrogen atmosphere. The mixture was acidified to pH 7 with saturated NH_4Cl (aq.). The aqueous layer was extracted with EtOAc (4x 300 mL). The resulting

mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (200:1) to afford 215b (170 g, 70.74%) as a yellow solid.

3. Synthesis of 215c

[756] A solution of methyl 2-(3-nitrophenyl)acetate (50 g, 256.182 mmol, 1 equiv) in DMF (2 L) was treated with Cs_2CO_3 (417.34 g, 1280.910 mmol, 5 equiv) for 3 h at 0°C under nitrogen atmosphere followed by the addition of 2-methylpropane-1,3-diyl bis(4-methylbenzenesulfonate) (204.17 g, 512.364 mmol, 2 equiv) in two portions at 0 °C. The resulting mixture was stirred for 2 days at room temperature under nitrogen atmosphere. The mixture was acidified to pH 7 with saturated NH_4Cl (aq.). The aqueous layer was extracted with EtOAc (4x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (200:1) to afford 215c (13 g, 18.73%) as a yellow oil.

4. Synthesis of 215d

[757] A solution of 215c (13 g, 52.153 mmol, 1 equiv) and hydrazine (16.71 g, 521.530 mmol, 10 equiv) in EtOH (300 mL) was stirred for 8 h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (4x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2 / MeOH (10:1) to afford 215d (12 g, 85.84%) as a yellow solid.

5. Synthesis of 215e

[758] A solution of 215d (18 g, 72.211 mmol, 1 equiv) and methyl isothiocyanate (15.84 g, 216.633 mmol, 3 equiv) in tetrahydrofuran (300 mL) was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL). The precipitated solids were collected by filtration and washed with water (3x10 mL). The resulting solid was dried under vacuum. This resulted in 215e(19 g, 78.35%) as a white solid.

6. Synthesis of 215f

[759] A solution of 215e (19 g, 58.937 mmol, 1 equiv) and NaOH (11.79 g, 294.685 mmol, 5 equiv) in H_2O (400 mL) was stirred for 8 h at room temperature under nitrogen atmosphere. The mixture was acidified to pH 6 with HCl (1 M). The precipitated solids were collected by filtration and washed with water (3x60 mL). The resulting solid was dried under vacuum. This resulted in 215f (16 g, 83.84%) as a white solid.

7. Synthesis of 215g

[760] A solution of 215f (16 g, 52.568 mmol, 1 equiv) in EtOAc (200 mL) and H_2O (200 mL) was treated with $NaNO_2$ (36.27 g, 525.680 mmol, 10 equiv) at room temperature under nitrogen atmosphere followed by the addition of HNO_3 (33.12 g, 525.680 mmol, 10 equiv)/500 ml H_2O dropwise at room temperature. The resulting mixture was stirred for 6 h at room temperature under nitrogen atmosphere. The mixture to pH 7 with saturated $NaHCO_3$ (aq.). The precipitated solids were collected by filtration and washed with water (3x100 mL). The resulting solid was dried under vacuum. This resulted in 215g (14 g, 94.87%) as a yellow solid.

8. Synthesis of 215h

[761] To a solution of 215g(14 g, 51.412 mmol, 1 equiv) in 500 mL MeOH was added Pd/C (10%, 1.6 g) under nitrogen atmosphere in a 1 L round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The resulting mixture was filtered; the filter cake was washed with MeOH (3x60 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. This resulted in 215h (10 g, 72.24%) as a yellow solid.

9. Synthesis of 215i

[762] To a stirred solution of 215h (3 g, 12.380 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (4.72 g, 18.570 mmol, 1.5 equiv) in DCE (60 mL) were added $NaBH(OAc)_3$ (5.25 g, 24.760 mmol, 2 equiv) and HOAc (0.74 g, 12.380 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Sat. NH_4Cl(aq) (60 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford PH-215i (3 g, 48.94%) as a yellow solid.

10. Synthesis of 215j

[763] To a stirred solution of 215i (3 g, 6.220 mmol, 1 equiv) and Pyridine (2.95 g, 37.320 mmol, 6 equiv) in DCM (30 mL) were added Triphosgene (0.65 g, 2.177 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 20 min at room temperature under air atmosphere. The reaction was quenched by the addition of Sat. $NaHCO_3$ (aq) (50mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 80mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2 / MeOH (40:1) to afford 215j (2.8 g, 84.47%) as

a yellow solid.

11. Synthesis of 215k

[764] To a solution of 215j (2.2 g, 4.345 mmol, 1 equiv), TMEDA (1.01 g, 8.690 mmol, 2 equiv) in dioxane (70.00 mL) was added bis(adamantan-1-yl)(butyl)phosphane (0.31 g, 0.869 mmol, 0.2 equiv) and $Pd(OAc)_2$ (0.10 g, 0.434 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H_2 (1:1), the mixture was pressurized to 10 atm with CO/H_2 (1:1) at 80 °C for overnight. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2 / MeOH (20:1) to afford 215k (1.4 g, 70.75%) as a yellow solid.

12. Synthesis of 215l

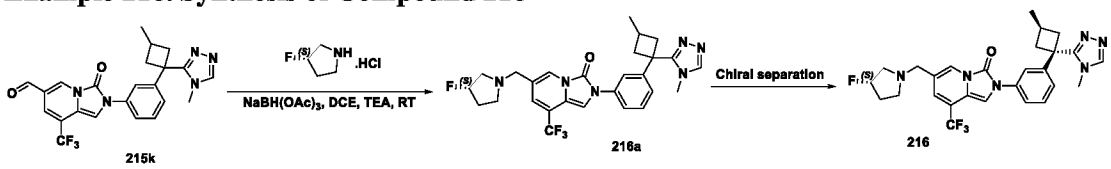
[765] Into a 50 mL 3-necked round-bottom flask were added 215k (700 mg, 1.537 mmol, 1 equiv) and 5-azaspiro [2.4] heptane hydrochloride (224.00 mg, 2.305 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added HOAc (184.60 mg, 3.074 mmol, 2 equiv) and $NaBH(OAc)_3$ (651.49 mg, 3.074 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) at room temperature. The resulting mixture was extracted with CH_2Cl_2 and MeOH (10:1) (5x10 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 67% B in 8 min; Wave Length: 220 nm; RT(min): 7.17;) to afford 215l (340 mg, 41.22%) as a yellow solid.

13. Synthesis of 215

[766] The 215l (340mg) was purified by Chiral separation with the following conditions Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 7.70; RT2(min): 10.08; The first peak was the product. Sample Solvent: EtOH--HPLC; Injection Volume: 0.1 mL; Number Of Runs: 34 to afford 215 (71.7 mg, 21.08%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 537. H-NMR: (400 MHz, CD_3OD, ppm): δ 0.58-0.64 (m, 4H), δ1.17-1.19 (m, 3H), δ1.89-1.92 (t, 2H), δ2.38-2.41 (m, 2H), δ2.43-2.53 (m, 1H), δ2.61 (s, 2H), δ2.83-2.87 (m, 2H), δ3.14-3.19 (m, 2H), δ3.32-3.36 (m, 3H), δ3.53 (s, 2H), δ7.16-7.17 (d, 2H), δ7.21-7.24 (m, 1H), δ7.51-7.59 (m, 2H), δ7.68-7.69 (m, 2H), δ8.39 (s, 1H).

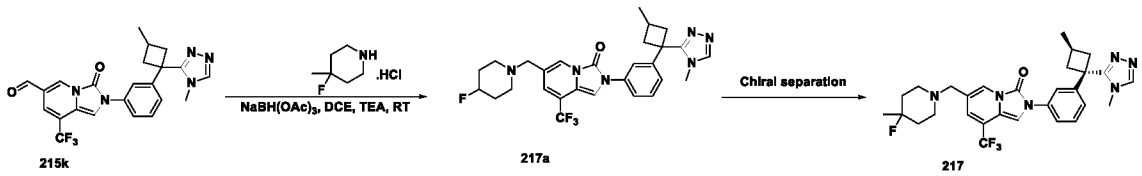
Example 216. Synthesis of Compound 216



Synthesis of 216

[767] To a stirred solution of 215k (800 mg, 1.757 mmol, 1.00 equiv) and (3S)-3-fluoropyrrolidine hydrochloride (441.14 mg, 3.514 mmol, 2 equiv) in DCE (10 mL) were added TEA (355.50 mg, 3.514 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (744.56 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30mL). The resulting mixture was concentrated under reduced pressure. The crude product (500 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Flow rate: 60 mL/min; Gradient: 32% B to 54% B in 8 min, 54% B; Wave Length: 220 nm; RT1(min): 7.52) to afford 216 (300 mg, 31.67%) as a yellow solid

Example 217. Synthesis of Compound 217



Synthesis of 217a

[768] To a stirred mixture of 4-fluoro-4-methylpiperidine hydrochloride (539.71 mg, 3.514 mmol, 2 equiv) and 215k (800 mg, 1.757 mmol, 1.00 equiv) in DCE (8 mL) was added TEA (533.25 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1116.84 mg, 5.271 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 3 h at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford the crude product (500 mg). The crude product (500 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 65% B in 8

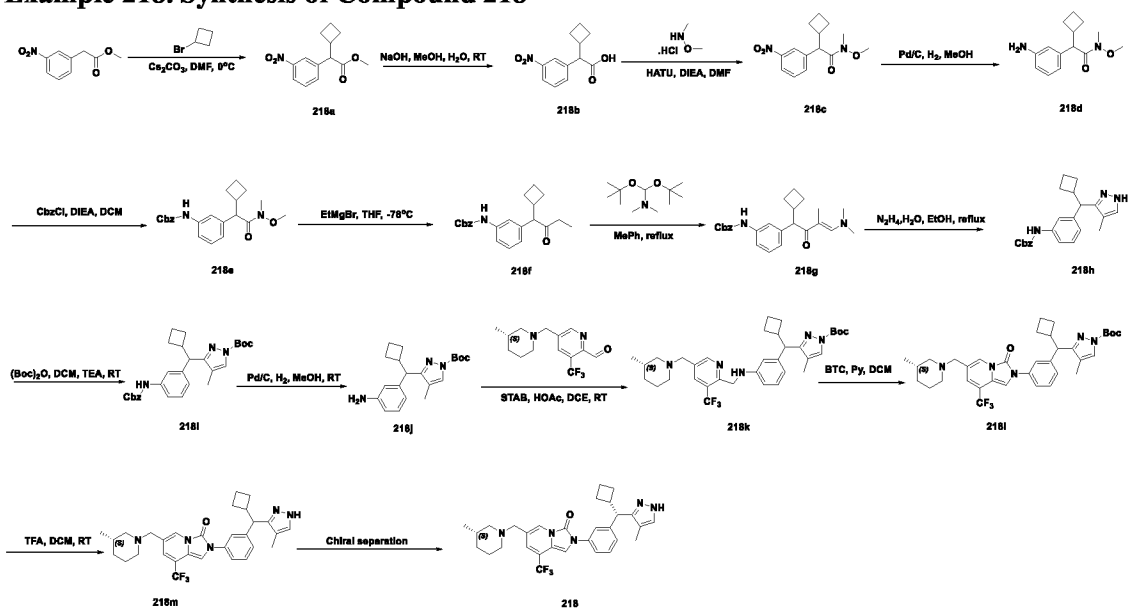
min, 65% B; Wave Length: 220 nm; RT1(min): 7.68) to afford 217a (400 mg, 41.97%) as a yellow solid.

Synthesis of 217

[769] 217a (400 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 18.5 min; Wave Length: 220/254 nm; RT1 (min): 9.93; RT2 (min): 13.92; the second peak is product) to afford 217 (103.5 mg, 20.20%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 557. H-NMR: (400 MHz, DMSO-d_6, ppm, δ): 1.09-1.11 (d, 3H), 1.29-1.34 (d, 3H), 1.50-1.71 (m, 1H), 1.71-1.75 (m, 3H), 2.27-2.49 (m, 5H), 2.60-2.62 (m, 2H), 3.10-3.14 (m, 2H), 3.25 (s, 3H), 7.01 (s, 1H), 7.08-7.10 (d, 1H), 7.40-7.49 (m, 1H), 7.60-7.63 (m, 1H), 7.68-7.69 (m, 1H), 7.69-7.70 (m, 1H), 8.36 (s, 1H).

Example 218. Synthesis of Compound 218



1. Synthesis of 218a

[770] To a stirred mixture of methyl 2-(3-nitrophenyl)acetate (48 g, 245.934 mmol, 1 equiv) in DMF (1000 mL) was added Cs_2CO_3 (400.65 g, 1229.670 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (99.61 g, 737.802 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 2days at room temperature. The resulting mixture was diluted with NH_4Cl (aq.) (3000 mL). The aqueous layer was extracted with EtOAc (2x1000 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA

(100:1) to afford 218a (45 g, 68.27%) as a white solid.

2. Synthesis of 218b

[771] To a stirred solution of 218a (45 g, 180.530 mmol, 1 equiv) in MeOH (800 mL) were added NaOH (21.66 g, 541.590 mmol, 3 equiv) in H_2O (200 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 5 with HCl (aq.). The aqueous layer was extracted with EtOAc (3x1000 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 218b (32.1 g, 68.78%) as an off-white solid.

3. Synthesis of 218c

[772] A solution of 218b (32 g, 136.032 mmol, 1 equiv) and methoxy(methyl)aminehydrochloride (17.25 g, 176.842 mmol, 1.3 equiv) in DMF (500 mL) was added HATU (56.90 g, 149.635 mmol, 1.1 equiv) and DIEA (52.74 g, 408.096 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (2000 mL). The aqueous layer was extracted with EtOAc (2x1000 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 218c (35 g, 85.98%) as a white solid.

4. Synthesis of 218d

[773] To a solution of 218c (34 g, 122.167 mmol, 1 equiv) in MeOH (800 mL) was added Pd/C (3.4 g, 10%) under nitrogen atmosphere in a 2L round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 218d (26 g, 77.13%) as an off-white solid.

5. Synthesis of 218e

[774] To a stirred solution of 218d (26 g, 104.701 mmol, 1 equiv) and DIEA (40.60 g, 314.103 mmol, 3 equiv) in DCM (500 mL) were added CbzCl (35.72 g, 209.402 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The residue was washed with water (500 mL). The aqueous layer was extracted with DCM (200 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 218e (28 g, 66.43%) as a white solid.

6. Synthesis of 218f

[775] To a stirred solution of 218e (28 g, 73.210 mmol, 1 equiv) in THF (300 mL) was added EtMgBr (366.05 mL, 366.050 mmol, 5 equiv, 1M) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated NH_4Cl (aq.) (1000 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 218f (17 g, 62.11%) as a white solid.

7. Synthesis of 218g

[776] To a stirred solution of 218f (13 g, 36.990 mmol, 1 equiv) in Toluene (150 mL) was added [bis(tert-butoxy)methyl]dimethylamine (22.56 g, 110.970 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 110°C. The resulting mixture was concentrated under vacuum. This resulted in 218g (16.5 g, 87.78%) as a light yellow oil.

8. Synthesis of 218h

[777] To a stirred solution of 218g (16.5 g, 40.588 mmol, 1 equiv) in EtOH (200 mL) was added hydrazine hydrate (98%)(20.32 g, 405.880 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6h at 80°C. The reaction was quenched with water (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 218h (5.28 g, 30.49%) as a light yellow solid.

9. Synthesis of 218i

[778] To a stirred solution of 218h (4.7 g, 12.518 mmol, 1 equiv) and $(Boc)_2O$ (3.55 g, 16.273 mmol, 1.3 equiv) in DCM (50 mL) was added TEA (2.53 g, 25.036 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 40°C. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 218i (2.5 g, 37.79%) as an off-white solid.

10. Synthesis of 218j

[779] To a solution of 218i (2.5 g, 5.257 mmol, 1 equiv) in MeOH (150 mL) was added Pd/C (0.25 g, 10%) under nitrogen atmosphere in a 500mL round-bottom flask. The mixture was hydrogenated at room temperature for 4h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted

in 218j (1.7 g, 80.51%) as an off-white solid. The crude product was used in the next step directly without further purification.

11. Synthesis of 218k

[780] To a stirred solution of 218j (500 mg, 1.464 mmol, 1 equiv) and I-2(419.23 mg, 1.464 mmol, 1 equiv) in DCE (8 mL) were added STAB (620.70 mg, 2.928 mmol, 2 equiv) and HOAc (87.94 mg, 1.464 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford tert-butyl 218k (510 mg, 52.95%) as an off-white solid.

12. Synthesis of 218l

[781] To a stirred solution of 218k (500 mg, 0.817 mmol, 1 equiv) and Pyridine (646.50 mg, 8.170 mmol, 10 equiv) in DCM (10 mL) were added Triphosgene (97.02 mg, 0.327 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 218l (410 mg, 70.79%) as a yellow solid.

13. Synthesis of 218m

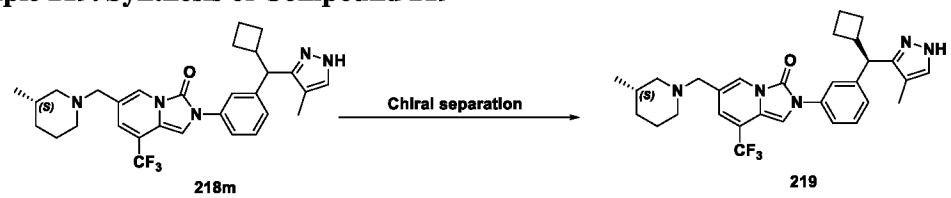
[782] To a stirred solution of 218l (400 mg, 0.627 mmol, 1 equiv) in DCM (5 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 59% B to 88% B in 8 min; Wave Length: 220 nm; RT1(min): 7.85) to afford 218m (280 mg, 81.37%) as a yellow solid.

14. Synthesis of 218

[783] 218 (280 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 15 min; Wave Length: 220/254 nm; RT1(min): 10.96; RT2(min): 12.91; the first peak is product) to afford 218 (89.5 mg, 31.80%) as a yellow solid.

LC-MS:(ES, *m/z*):[M+H]$^+$ 538. H-NMR:(400 MHz, CD_3OD, δ *ppm*):0.89-0.99 (m, 4H), 1.57-1.71 (m, 6H), 1.73-2.12 (m, 9H), 2.85-2.91 (m, 2H), 3.32-3.32 (m, 1H), 4.09-4.22 (m, 1H), 7.08-7.12 (m, 2H), 7.21-7.35 (m, 2H), 7.41-7.43 (m, 1H), 7.53-7.55 (m, 1H), 7.62 (s, 1H), 7.69 (s, 1H).

Example 219. Synthesis of Compound 219

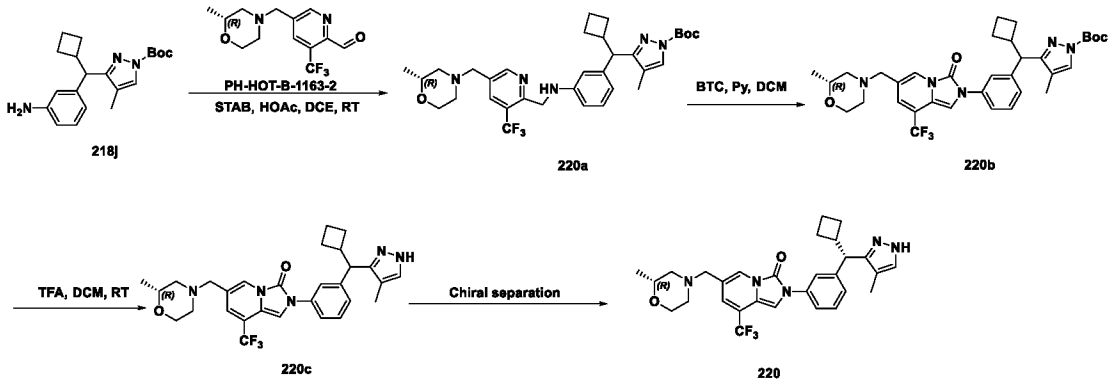


1. Synthesis of 219

[784] 218m (280 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 15 min; Wave Length: 220/254 nm; RT1(min): 10.96; RT2(min): 12.91; the second peak is product) to afford 219 (89.5 mg, 31.80%) as a yellow solid.

LC-MS:(ES, *m/z*):[M+H]$^+$ 538. H-NMR:(400 MHz, CD_3OD, δ *ppm*):0.89-0.99 (m, 4H), 1.57-1.71 (m, 6H), 1.73-2.12 (m, 9H), 2.85-2.91 (m, 2H), 3.32-3.32 (m, 1H), 4.09-4.22 (m, 1H), 7.08-7.12 (m, 2H), 7.21-7.35 (m, 2H),7.41-7.43 (m, 1H), 7.53-7.55 (m, 1H), 7.62 (s, 1H), 7.69 (s, 1H).

Example 220. Synthesis of Compound 220



1. Synthesis of 220a

[785] To a stirred solution of 218j (500 mg, 1.464 mmol, 1 equiv) and 218j (422.12 mg, 1.464 mmol, 1 equiv) in DCE (5 mL) was added HOAc (87.94 mg, 1.464 mmol, 1 equiv) and STAB (620.70 mg, 2.928 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched

with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 220a (560 mg, 56.70%) as a white solid.

2. Synthesis of 220b

[786] To a stirred solution of 220a (550 mg, 0.896 mmol, 1 equiv) and Pyridine (708.87 mg, 8.960 mmol, 10 equiv) in DCM (10 mL) were added Triphosgene (106.37 mg, 0.358 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL)at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 220b (430 mg, 67.50%) as a yellow solid.

3. Synthesis of 220c

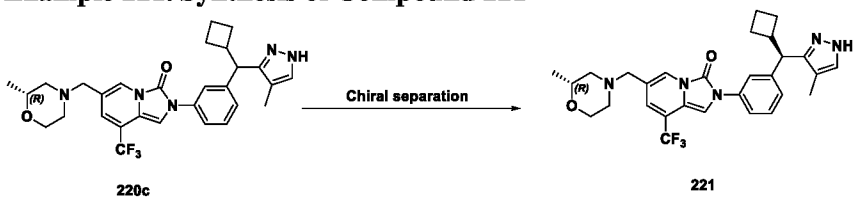
[787] To a stirred solution of 220b (420 mg, 0.657 mmol, 1 equiv) in DCM (5 mL) was added TFA (1 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 74% B in 8 min, Wave Length: 220 nm; RT1(min): 7.43) to afford 220c (300 mg, 82.99%) as a yellow solid.

4. Synthesis of 220

[788] 220c (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.13; RT2(min): 12.97; the first peak is product) to afford 220 (132.7 mg, 43.88%) as a yellow solid.

LC-MS-220 (ES, *m/z*): $[M+H]^+$ 540. H-NMR-220 (400 MHz, CD_3OD, δ *ppm*): 1.13-1.15 (d, 3H), 1.61-1.77 (m, 1H), 1.77-1.90 (m, 4H), 1.90-2.05 (m, 4H), 2.05-2.10 (m, 1H), 2.10-2.22 (m, 1H), 2.74-2.83 (m, 2H), 3.24-3.32 (m, 1H), 3.34 (s, 2H), 3.63-3.71 (m, 2H), 3.84-3.88 (m, 1H), 4.03-4.18 (m, 1H), 7.08-7.10 (m, 2H), 7.27-7.29 (m, 2H), 7.43-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.61 (s, 1H), 7.70 (s, 1H).

Example 221. Synthesis of Compound 221



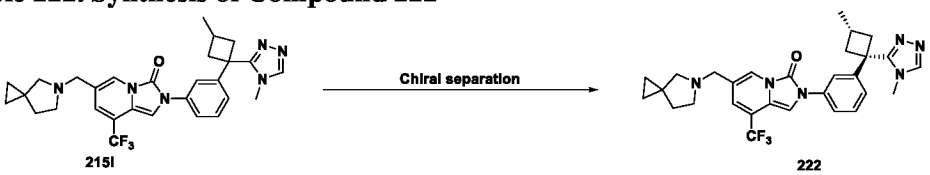
220c 221

Synthesis of 221

[789] The 220c (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.13; RT2(min): 12.97; the second peak is product) to afford 221 (139.2 mg, 45.94%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 540. H-NMR 0: (400 MHz, CD_3OD, δ *ppm*): 1.13-1.15 (d, 3H), 1.61-1.77 (m, 1H), 1.77-1.91 (m, 4H), 1.91-2.10 (m, 5H), 2.10-2.22 (m, 1H), 2.74-2.83 (m, 2H), 3.21-3.32 (m, 1H), 3.35 (s, 2H), 3.64-3.71 (m, 2H), 3.84-3.87 (m, 1H), 4.08-4.18 (m, 1H), 7.08-7.10 (m, 2H), 7.27-7.30 (m, 2H), 7.41-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.61 (s, 1H), 7.70 (s,1H).

Example 222. Synthesis of Compound 222



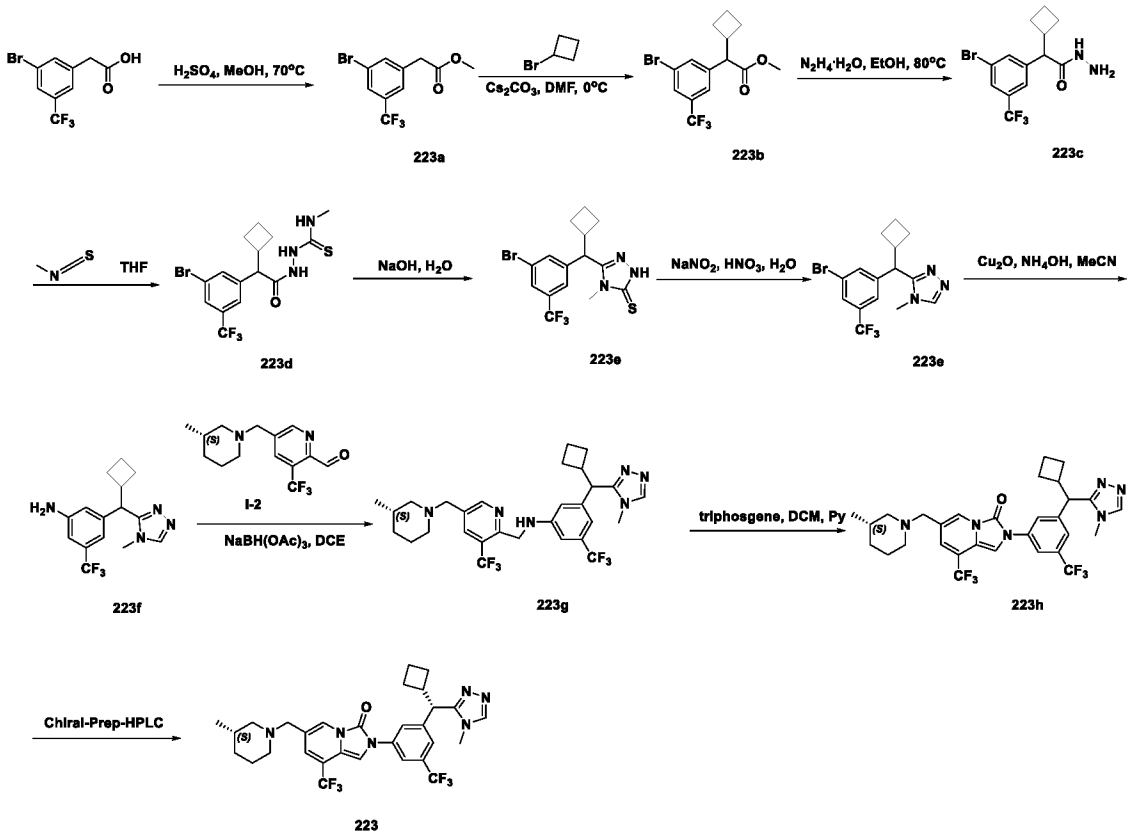
215l 222

1. Synthesis of 222

[790] The 215l (340mg) was purified by Chiral separation with the following conditions Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 7.70; RT2(min): 10.08; The second peak was the product. Sample Solvent: EtOH--HPLC; Injection Volume: 0.1 mL; Number of Runs: 34 to afford 222 (131.0 mg, 38.52%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 537. H-NMR: (400 MHz, CD3OD, ppm): δ 0.58-0.65 (m, 4H) δ1.17-1.18 (d, 3H), δ1.89-1.92 (t, 2H), δ2.38-2.41 (m, 3H), δ2.43-2.53 (m, 1H), δ2.61 (m, 1H), δ2.83-2.87 (m, 2H), δ2.97-3.01 (m, 2H), δ3.32-3.36 (m, 3H), δ3.53 (s, 2H), δ7.16-7.17 (dd, 2H), δ7.21-7.24 (m, 1H), δ7.51-7.59 (m, 2H), δ7.68-7.69 (m, 2H), δ8.39 (s, 1H).

Example 223. Synthesis of Compound 223



1. Synthesis of 223a

[791] A solution of [3-bromo-5-(trifluoromethyl)phenyl]acetic acid (8 g, 28.264 mmol, 1 equiv) in MeOH (80 mL) was added H_2SO_4 (0.28 g, 2.826 mmol, 0.1 equiv). The resulting solution was stirred for 3h at 70 °C under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$(aq) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 223a(8 g, 95.28%) as colorless oil.

2. Synthesis of 223b

[792] To a stirred mixture of 223a (8 g, 26.930 mmol, 1 equiv) and Cs_2CO_3 (4.74 g, 14.542 mmol, 0.54 equiv) in DMF (90 mL) was added bromocyclobutane (2.84 g, 21.005 mmol, 0.78 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) (500 ml) at room temperature. The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (50:1) to afford 223b (9 g, 95.17%) as colorless oil.

3. Synthesis of 223c

[793] A solution of 223b (8 g, 22.781 mmol, 1 equiv) and hydrazine hydrate (98%) (9.11 g,

182.248 mmol, 8 equiv) in EtOH (40 mL) was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was diluted with water (50 mL) at room temperature. The EtOH was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x10 mL). This resulted in 223c (7.9 g, 98.75%) as a white solid.

4. Synthesis of 223d

[794] To a stirred solution of 223c (7.9 g, 22.496 mmol, 1 equiv) in tetrahydrofuran (80 mL) was added methyl isothiocyanate (3.29 g, 45.001 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL) at room temperature. The THF was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x10 mL). This resulted in 223d (8.5 g, 89.05%) as a white solid.

5. Synthesis of 223e

[795] A solution of 223d (8.45 g, 6.639 mmol, 1 equiv) in NaOH (53.112 mL, 53.112 mmol, 8 equiv, 1M) was stirred overnight at room temperature. The reaction solution was acidified to pH 6 with HCl(1 M). The precipitated solids were collected by filtration and washed with water (2x10 mL). This resulted in 223e (6 g, 74.15%) as a white solid.

6. Synthesis of 223f

[796] To a stirred mixture of 223e (6 g, 14.769 mmol, 1 equiv) and $NaNO_2$ (10.19 g, 147.690 mmol, 10 equiv) in EA (8 mL) and H_2O (24 mL) were added HNO_3 (147.748 mL, 147.748 mmol, 10.00 equiv, 1M) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (4x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 223f (1.8 g, 32.57%) as a white solid.

7. Synthesis of 223g

[797] To a stirred solution of 223f (3 g, 8.017 mmol, 1 equiv) in NH_4OH (15 mL) and MeCN (15 mL) were added Cu_2O (0.23 g, 1.603 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for 7h at 100°C. The reaction was diluted with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (5x40 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 223g (1.6 g, 64.31%) as a white solid.

8. Synthesis of 223h

[798] To a stirred mixture of 223g(600 mg, 1.933 mmol, 1 equiv) and 5-{[(3S)-3-

methylpiperidin-1-yl]methyl}-3-(trifluoromethyl)pyridine-2-carbaldehyde (1107.09 mg, 3.866 mmol, 2 equiv) in DCE (7 mL) were added HOAC (116.11 mg, 1.933 mmol, 1 equiv) and $NaBH(OAc)_3$ (819.56 mg, 3.866 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH 20:1) to afford 223h (820 mg, 73.04%) as yellow solid.

9. Synthesis of 223i

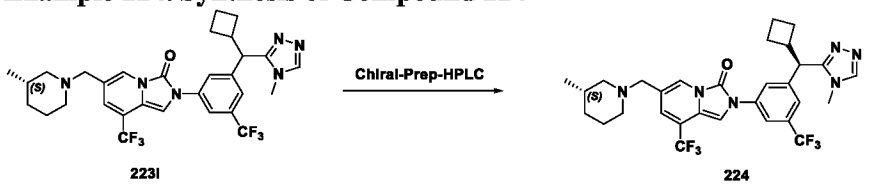
[799] To a stirred solution of 223h (820 mg, 1.412 mmol, 1 equiv) and Pyridine (670.27 mg, 8.472 mmol, 6 equiv) in DCM (24 mL) was added triphosgene (146.68 mg, 0.494 mmol, 0.35 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched with $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 223i (480 mg, 56.03%) as a yellow solid

10. Synthesis of 223

[800] 223i (480 mg) was separated by Chiral-Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 4.52; RT2(min): 5.64; Sample Solvent: EtOH: DCM=1: 1; The first peak was the product). This resulted in 223 (195.1 mg, 40.65%) as a yellow solid.

LC-MS-223 (ES, m/z): $[M+H]^+$ 607. H-NMR-223 (400 MHz, DMSO, δ ppm): 0.82-0.90 (m, 4H), 1.31-1.42 (m, 1H), 1.59-1.76 (m, 2H), 1.78-1.84 (m, 2H), 1.85-1.99 (m, 6H), 2.01-2.12 (m, 1H), 2.52-2.74 (m, 2H), 3.21-3.25 (m, 3H), 3.49 (s, 3H), 4.44-4.46 (d, 1H), 7.03 (s, 1H), 7.55-7.59 (d, 2H), 7.65 (s, 1H), 8.14-8.18 (d, 2H), 8.36 (s, 1H).

Example 224. Synthesis of Compound 224



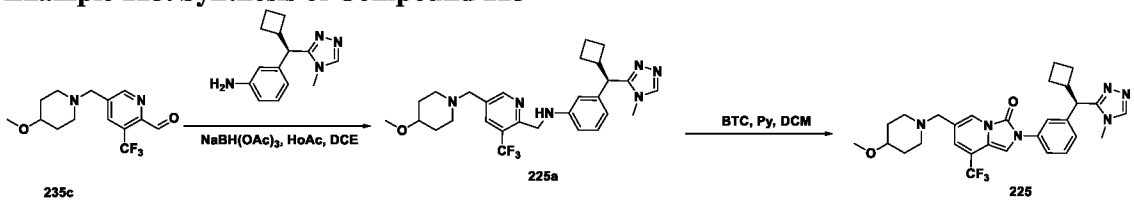
223I 224

Synthesis of Compound 224

[801] 223i (480 mg) was separated by Chiral-Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 4.52; RT2(min): 5.64; Sample Solvent: EtOH: DCM=1: 1; The second peak was the product). This resulted in 2224 (185.3 mg, 38.60%) as a yellow solid.

LC-MS-224 (ES, m/z): $[M+H]^+$ 607. H-NMR-224 (400 MHz, DMSO, δ ppm): 0.82-0.90 (m, 4H), 1.31-1.42 (m, 1H), 1.67-1.78 (m, 4H), 1.80-1.99 (m, 6H), 2.05-2.08 (m, 1H), 2.60-2.74 (m, 2H), 3.21-3.25 (m, 3H), 3.49 (s, 3H), 4.44-4.46 (d, 1H), 7.04 (s, 1H), 7.55-7.59 (d, 2H), 7.65 (s, 1H), 8.14-8.18 (d, 2H), 8.36 (s, 1H).

Example 225. Synthesis of Compound 225



235c 225a 225

Synthesis of 225a

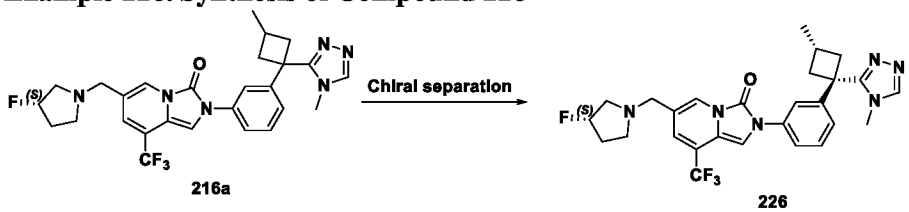
[802] To a stirred solution of 235c (299.40 mg, 0.990 mmol, 1.2 equiv) and (R)-3-(cyclobutyl(4-methyl-4H-1,2,4-triazol-3-yl)methyl)aniline (200 mg, 0.825 mmol, 1 equiv) in DCE (3 mL) were added STAB (349.84 mg, 1.650 mmol, 2 equiv) and HOAc (49.56 mg, 0.825 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Sat. NH_4Cl(aq) (10 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 225a (300 mg, 65.32%) as a yellow solid.

[803] **Synthesis of 225**

[804] To a stirred solution of 225a (200 mg, 0.378 mmol, 1 equiv) and pyridine (39.30 mg, 0.132 mmol, 0.35 equiv) in DCM (3 mL) were added Triphosgene (39.30 mg, 0.132 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 20min at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 silica gel 120 g; mobile phase, MeCN in 0.1% NH_4HCO_3 water, 20% to 40% gradient in 10 min; detector, UV 254 nm. This resulted in 225 (96.6 mg, 45.71%) as a yellow solid.

LC-MS-PH-225 (ES, *m/z*): $[M+H]^+$:555. H-NMR-PH-225 (400 MHz, DMSO-d6, *ppm*): δ 1.32-1.50 (m, 2H), δ 1.62-1.85 (m, 7H), δ 2.03-2.21 (m, 3H), δ 2.63-2.73 (m, 2H), δ 3.18-3.25 (m, 7H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.01 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.44-7.48 (m, 1H), δ 7.60-7.62 (d, 2H), δ 7.70 (s, 1H), δ 8.33 (s, 1H).

Example 226. Synthesis of Compound 226

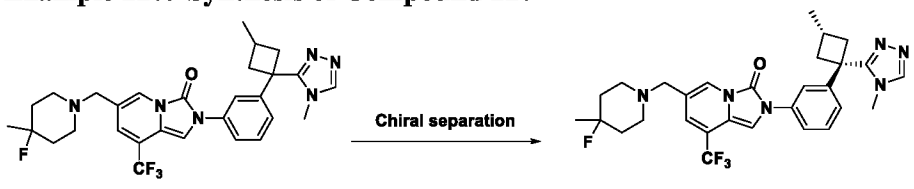


216a 226

Synthesis of 226

[805] The 216a (300mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 20 min; Wave Length: 220/254 nm; RT1(min): 13.77; RT2(min): 16.98; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.2 mL; Number of Runs: 15). This resulted in 226 (156.8 mg, 51.64%) as a yellow solid. LC-MS: (ES, *m/z*): $[M+H]^+$:529. H-NMR: (400 MHz, DMSO-d6, *ppm*): δ 1.12-1.13 (m, 3H), δ 1.80-1.97 (m, 1H), δ 2.04-2.25 (m, 1H), δ 2.28-2.33 (m, 1H), δ 2.51 (s, 3H), δ 2.63-2.65 (d, 1H), δ 2.81-2.95 (m, 2H), δ 3.21 (s, 3H), δ 3.33 (s, 1H), δ 3.45 (s, 1H), δ 5.12-5.31 (d, 1H), δ 7.02 (s, 1H), δ 7.23-7.25 (d, 1H), δ 7.41 (s, 1H), δ 7.43-7.46 (m, 1H), δ 7.62-7.63(d, 1H), δ 7.68 (s, 1H), δ 7.82 (s, 1H), δ 8.31 (s, 1H).

Example 227. Synthesis of Compound 227



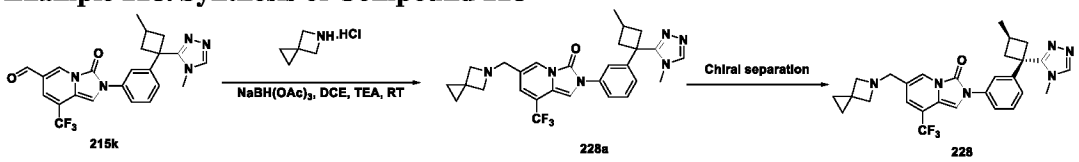
217a 227

[806] 217a (400 mg) was separated by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 18.5 min; Wave Length: 220/254 nm; RT1 (min): 9.93; RT2 (min): 13.92; the first peak is product) to afford 227 (210.3 mg, 40.63%) as a yellow solid.

LCMS-227 (ES, *m/z*): $[M+H]^+$ 557. H-NMR-227 (400 MHz, DMSO-d_6, ppm, δ): 1.09 (s, 3H), 1.29-1.34 (d, 3H), 1.61-1.65 (m, 1H), 1.65-1.73 (m, 3H), 2.24-2.29 (m, 2H), 2.51-2.54

(m, 2H), 2.54-2.62 (m, 2H), 2.88 (s, 2H), 3.21 (s, 3H), 7.01 (s, 1H), 7.22-7.26 (d, 1H), 7.37 (s, 1H), 7.48-7.52 (t, 1H), 7.63-7.68 (m, 1H),7.84 (s, 1H), 8.29 (s, 1H)

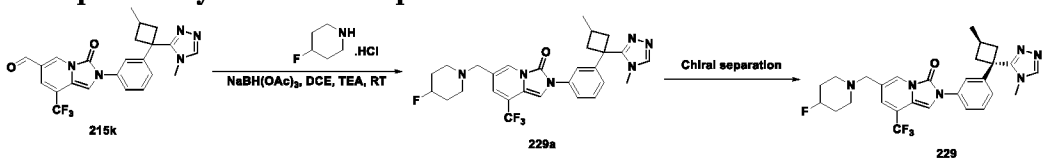
Example 228. Synthesis of Compound 228



Synthesis of 228a

[807] To a stirred solution of 215k (800 mg, 1.757 mmol, 1.00 equiv) and 5-azaspiro[2.3]hexane hydrochloride (420.13 mg, 3.514 mmol, 2 equiv) in DCE (10 mL) were added TEA (355.50 mg, 3.514 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (744.56 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (20mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 30mL). The resulting mixture was concentrated under reduced pressure. The crude product (400mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min, 60% B; Wave Length: 220 nm; RT1(min): 7.36/7.63) to afford 228a (320 mg, 34.16%) as a yellow solid.

Example 229. Synthesis of Compound 229

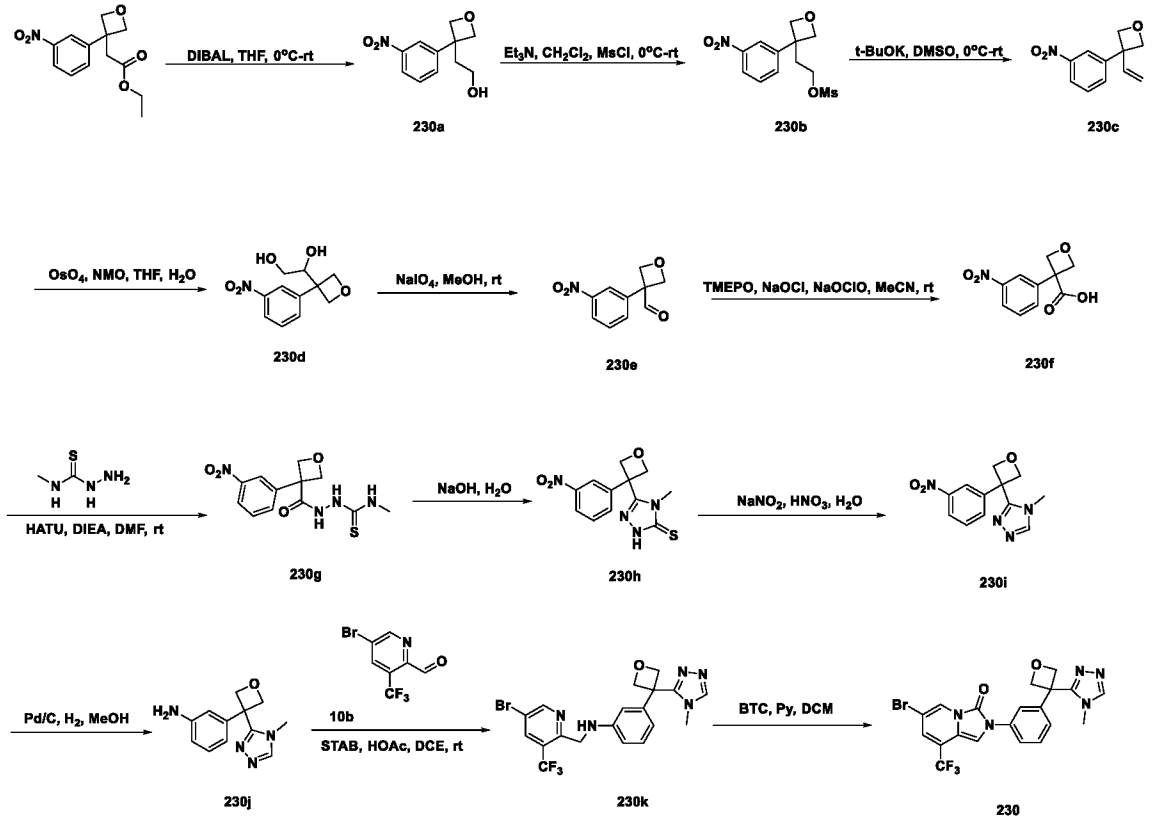


Synthesis of 229a

[808] To a stirred solution of 215k (800 mg, 1.757 mmol, 1 equiv) and 4-fluoropiperidine hydrochloride (490.42 mg, 3.514 mmol, 2 equiv) in DCE (8 mL) was added TEA (355.49 mg, 3.514 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (744.57 mg, 3.514 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product (500 mg) was

purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 30% B in 7 min; Wave Length: 254; 220 nm; RT1(min): 5.27) to afford 229a (400 mg, 41.13%) as a yellow solid.

Example 230. Synthesis of Compound 230



1. Synthesis of 230a

[809] To a stirred solution of ethyl 2-(3-(3-nitrophenyl)oxetan-3-yl)acetate (10 g, 37.698 mmol, 1 equiv) in THF (100 mL) was added DIBAl-H (37.70 mL, 75.396 mmol, 2 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 230a (4 g, 43.25%) as a light yellow oil.

2. Synthesis of 230b

[810] To a stirred solution of 230a (4 g, 17.919 mmol, 1 equiv) and MsCl (3.08 g, 26.879 mmol, 1.5 equiv) in DCM (100 mL) was added TEA (5.44 g, 53.757 mmol, 3 equiv) at room

temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (200 mL) at room temperature. The resulting mixture was extracted with DCM (2 x 100mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 230b (4 g, 66.68%) as a yellow oil.

3. Synthesis of 230c

[811] To a stirred solution of 230b (4 g, 13.275 mmol, 1 equiv) in DMSO (100 mL) was added t-BuOK (4.47 g, 39.825 mmol, 3 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 230c (2 g, 71.21%) as an off-white solid..

4. Synthesis of 230d

[812] To a stirred solution of 230c (1.5 g, 7.309 mmol, 1 equiv) and OsO4 (0.19 g, 0.731 mmol, 0.1 equiv) in THF (20 mL) was added NMO (2.57 g, 21.927 mmol, 3 equiv) in H2O (10 mL) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The organic layers were concentrated under reduced pressure. This resulted in 230d (1.5 g, 78.92%) as a brown oil.

5. Synthesis of 230e

[813] To a stirred solution of 230d (1.5 g, 6.270 mmol, 1 equiv) in MeOH (30 mL) was added NaIO4 (2.68 g, 12.540 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 230e (750 mg, 51.96%) as an off-white solid.

6. Synthesis of 230f

[814] To a stirred solution of 230e (400 mg, 1.931 mmol, 1 equiv) and TEMPO (30.17 mg, 0.193 mmol, 0.1 equiv) in MeCN (5 mL)/H2O (2 mL) was added NaOCl (114.97 mg, 1.545 mmol, 0.8 equiv) and NaOClO (698.44 mg, 7.724 mmol, 4 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.5% FA), 30% to 50% gradient in 10 min; detector, UV 254 nm.

This resulted in 230f (200 mg, 45.02%) as an off-white solid.

7. Synthesis of 230g

[815] To a stirred solution of 230f (200 mg, 0.896 mmol, 1 equiv) and 1-amino-3-methylthiourea (141.35 mg, 1.344 mmol, 1.5 equiv) in DMF (3 mL) was added HATU (442.96 mg, 1.165 mmol, 1.3 equiv) and DIEA (231.64 mg, 1.792 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (10 mL). The precipitated solids were collected by filtration. This resulted in 230g (180 mg, 58.25%) as an off-white solid.

8. Synthesis of 230h

[816] To a stirred solution of NaOH (92.80 mg, 2.320 mmol, 4 equiv) in H2O (3 mL) was added 230g (180 mg, 0.580 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 6 with HCl (aq.). The aqueous layer was extracted with DCM (3x10 mL). The resulting mixture was concentrated under vacuum. This resulted in 230h (120 mg, 65.11%) as an off-white solid.

9. Synthesis of 230i

[817] To a stirred solution of 230h (120 mg, 0.411 mmol, 1 equiv) and NaNO2 (283.24 mg, 4.110 mmol, 10 equiv) in H2O (3 mL) was added HNO3 (4.11 mL, 4.110 mmol, 10 equiv, 1M) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (3x10 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 230i (80 mg, 68.89%) as an off-white solid.

10. Synthesis of 230j

[818] To a solution of 230i (75 mg, 0.288 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (7.5 mg, 10%) under nitrogen atmosphere in a 50mL round-bottom flask. The mixture was hydrogenated at room temperature for 2h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 230j (50 mg, 67.81%) as an off-white solid. The crude product was used in the next step directly without further purification.

11. Synthesis of 230k

[819] To a stirred solution of 230i (50 mg, 0.217 mmol, 1 equiv) and 10b (60.67 mg, 0.239 mmol, 1.1 equiv) in DCE (2 mL) were added HOAc (13.04 mg, 0.217 mmol, 1 equiv) and STAB (92.04 mg, 0.434 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was

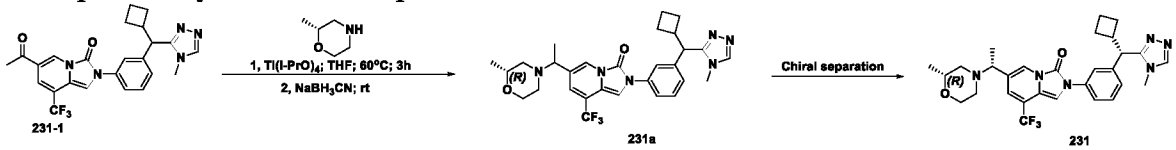
concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 230k (50 mg, 45.73%) as an off-white solid.

12. Synthesis of 230

[820] To a stirred solution of 230k (50 mg, 0.107 mmol, 1 equiv) and Pyridine (126.69 mg, 1.605 mmol, 15 equiv) in DCM (3 mL) were added Triphosgene (19.01 mg, 0.064 mmol, 0.6 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x10 mL). The organic layers were concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phaseA: water (10mmol/L NH4HCO3), B:MeCN, 50% B to 60% B gradient in 10 min; detector, UV 254 nm. This resulted in 230 (31.3 mg, 58.71%) as a yellow solid.

LC-MS-230 (ES, m/z): [M+H]+ 494. H-NMR-230(400 MHz, DMSO-d6, δ ppm): 3.25 (s, 3H), 5.12-5.14 (d, 2H), 5.38-5.40 (d, 2H), 7.17-7.20 (m, 2H), 7.54-7.58 (m, 2H), 7.76-7.80 (m, 2H), 8.04 (s, 1H), 8.49 (s, 1H).

Example 231. Synthesis of Compound 231



1. **Synthesis of 231a**

[821] To a stirred mixture of 231-1 (4 g, 8.520 mmol, 1 equiv) and (2R)-2-methylmorpholine (2.59 g, 25.560 mmol, 3 equiv) in THF (40 mL) was added $Ti(Oi\text{-}Pr)_4$ (9.69 g, 34.080 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for 3h at 60°C. To the above mixture was added $NaBH_3CN$ (1.61 g, 25.560 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of NH_4Cl (aq.) (40 mL) at room temperature. The resulting mixture was diluted with water (120 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (60:1) to afford 231a (1.2 g, crude) as a yellow solid. The crude product was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 231a (1 g, crude) as a yellow solid. The crude product was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water(10 mmol/L NH_4HCO_3), 2% to 100% gradient in 40

min; detector, UV 254 nm to afford 231a (850 mg, 16.55%) as a yellow solid.

2. Synthesis of 231

[822] 231a (830 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH(0.1% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.72; RT2(min): 6.96; RT3(min): 7.75; RT4(min): 9.80; first peak is product) to afford 231 (174.1 mg, 19.93%) as a yellow solid.

LCMS: (ES, *m/z*): $[M+H]^+$ 555. H-NMR: H NMR (400 MHz, DMSO, *ppm*): δ1.00-1.00-1.02 (d, 3H), δ1.24-1.27 (d, 3H), δ1.76-1.81 (m, 6H), δ2.01-2.12 (m, 2H), δ2.69-2.80 (m, 2H), δ3.17-3.28 (m, 1H), δ3.39-3.48 (m, 6H), δ3.71-4.28 (m, 2H), δ7.05 (s, 1H), δ7.11-7.24 (d, 1H), δ7.32 (s, 1H), δ7.40-7.55 (t, 1H), δ7.62 (s, 1H), δ7.65-7.80 (m, 2H), δ8.33 (s, 1H).

Example 232. Synthesis of Compound 232



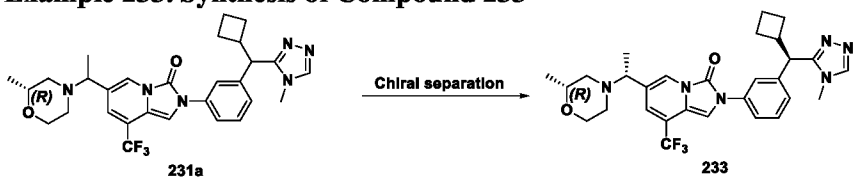
231a 232

1. Synthesis of 232

[823] 231a (830 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH(0.1% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.72; RT2(min): 6.96; RT3(min): 7.75; RT4(min): 9.80; second peak is product) to afford 232 (122.5 mg, 14.61%) as a yellow solid.

LCMS-232 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-232 H NMR (400 MHz, DMSO, *ppm*): δ1.00-1.06 (d, 3H), δ1.25-1.27 (d, 3H), δ1.72-1.81 (m, 6H), δ2.01-2.12 (m, 2H), δ2.59-2.63 (m, 1H), δ2.77-2.80 (d, 1H), δ3.17-3.28 (m, 1H), δ3.36-3.50 (m, 6H), δ3.71-3.74 (d, 1H), δ4.24-4.28 (d, 1H), δ7.05 (s, 1H), δ7.18-7.24 (d, 1H), δ7.32 (s, 1H), δ7.41-7.48 (t, 1H), δ7.62 (s, 1H), δ7.66-7.70 (d, 1H), δ7.73 (s, 1H), δ8.33 (s, 1H).

Example 233. Synthesis of Compound 233



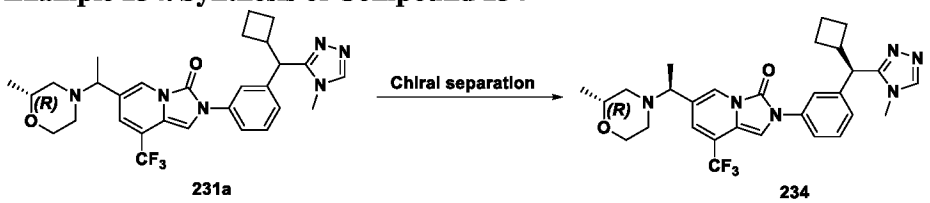
231a 233

Synthesis of 233

[824] 231a (830 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH(0.1% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.72; RT2(min): 6.96; RT3(min): 7.75; RT4(min): 9.80; third peak is product) to afford 233 (101.8 mg, 12.14%) as a yellow solid.

LCMS-233 (ES, m/z): [M+H]+ 555. H-NMR-233 H NMR (400 MHz, DMSO, ppm): δ0.96-1.05 (d, 3H), δ1.24-1.27 (d, 3H), δ1.72-1.81 (m, 6H), δ2.03-2.12 (m, 2H), δ2.65-2.74 (m, 2H), δ3.17-3.25 (m, 1H), δ3.39-3.50 (m, 6H), δ3.75-3.80 (d, 1H), δ4.24-4.28 (d, 1H), δ7.05 (s, 1H), δ7.18-7.24 (d, 1H), δ7.31 (s, 1H), δ7.41-7.48 (t, 1H), δ7.62 (s, 1H), δ7.66-7.70 (d, 1H), δ7.73 (s, 1H), δ8.33 (s, 1H).

Example 234. Synthesis of Compound 234

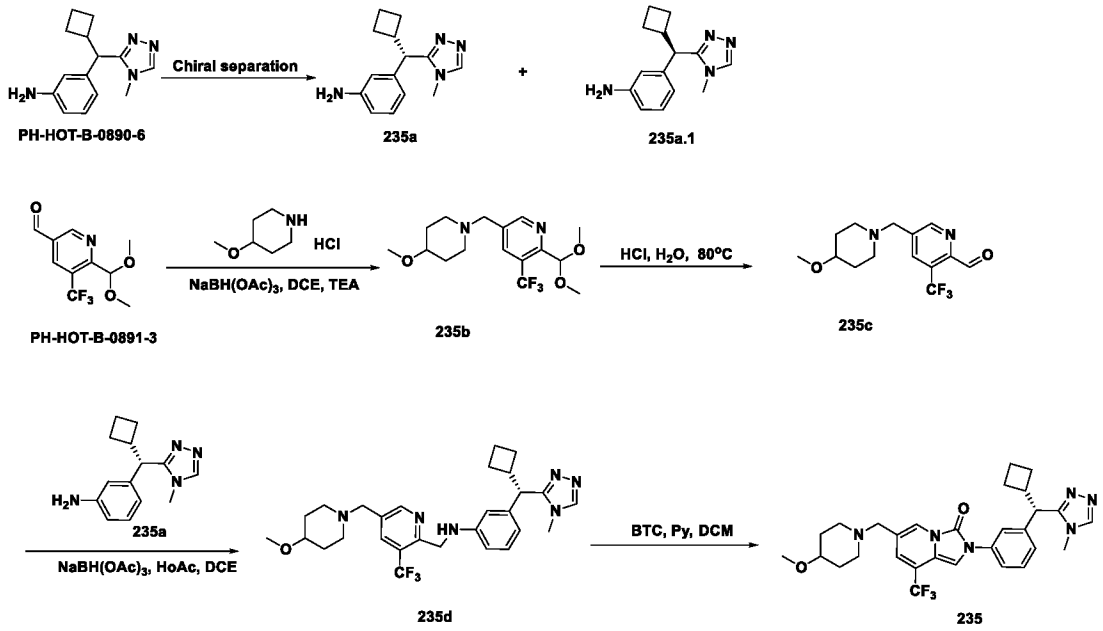


Synthesis of 234

[825] 231a (830 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH(0.1% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.72; RT2(min): 6.96; RT3(min): 7.75; RT4(min): 9.80; fourth peak is product) to afford 234(117.6 mg, 13.89%) as a yellow solid.

LCMS-234 (ES, m/z): [M+H]+ 555. H-NMR-234 H NMR (400 MHz, DMSO, ppm): δ1.02-1.08 (d, 3H), δ1.21-1.31 (d, 3H), δ1.72-1.81 (m, 6H), δ2.03-2.12 (d, 2H), δ2.31-2.49 (m, 1H), δ2.58-2.63 (d, 1H), δ274-2.83 (d, 1H), δ3.17-3.25 (m, 1H), δ3.39-3.43 (d, 4H), δ3.43-3.51 (m, 1H), 3.68-3.82 (d, 1H), δ4.24-4.28 (d, 1H), δ7.05 (s, 1H), δ7.18-7.24 (d, 1H), δ7.31 (s, 1H), δ7.41-7.48 (t, 1H), δ7.62 (s, 1H), δ7.66-7.70 (d, 1H), δ7.73 (s, 1H), δ8.33 (s, 1H).

Example 235. Synthesis of Compound 235



1. Synthesis of 235a

[826] 235a (900mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: EtOH--HPLC; Flow rate: 200 mL/min; Gradient: isocratic 30% B; Column Temperature (35°C); Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.11; RT2(min): 6.28; The first peak was 235a, The second peak was 235a.1. Sample Solvent: MeOH--HPLC; Injection Volume: 1 mL; Number of Runs: 30). This resulted in 235a (299.40 mg, 33.26%) as a yellow solid

2. Synthesis of 235b

[827] To a stirred solution of I-2 (2.5 g, 10.033 mmol, 1.00 equiv) and 4-methoxypiperidine hydrochloride (3.04 g, 20.066 mmol, 2 equiv) in DCE (30 mL) were added TEA (2.03 g, 20.066 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (4.25 g, 20.066 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 80mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 235b (2.5 g, 67.95%) as a light yellow oil.

3. Synthesis of 235c

[828] To a stirred solution of 235b (2 g, 5.741 mmol, 1 equiv) in HCl (1 M, 30 mL) at room

temperature. The resulting mixture was stirred for overnight at 80°C. The residue was basified to pH 7 with sat. NH4HCO3 (aq.) (30 ml). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 235c (1.4 g, 76.63%) as a light yellow oil.

4. Synthesis of 235d

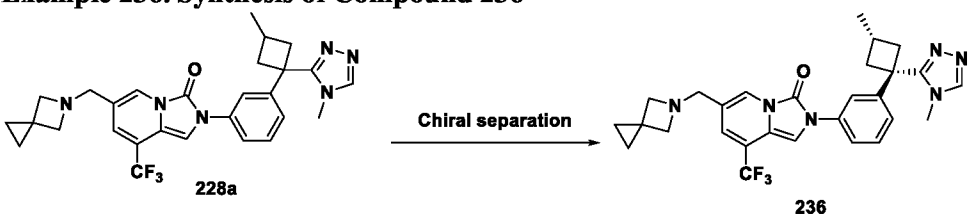
[829] To a stirred solution of 235a (299.40 mg, 0.990 mmol, 1.2 equiv) and 235c (200 mg, 0.825 mmol, 1 equiv) in DCE (3 mL) were added STAB (349.84 mg, 1.650 mmol, 2 equiv) and HOAc (49.56 mg, 0.825 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Sat. NH4Cl(aq) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 10mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 235d (300 mg, 65.32%) as a yellow solid.

5. Synthesis of 235

[830] To a stirred solution of 235d (200 mg, 0.378 mmol, 1 equiv) and pyridine (39.30 mg, 0.132 mmol, 0.35 equiv) in DCM (3 mL) were added Triphosgene (39.30 mg, 0.132 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 20 min at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (5mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 10mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 silica gel 120 g; mobile phase, MeCN in 0.1% NH4HCO3 water, 20% to 40% gradient in 10 min; detector, UV 254 nm. This resulted in 235 (85.9 mg, 28.18%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :555. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.32-1.50 (m, 2H), δ 1.62-1.85 (m, 7H), δ 2.03-2.21 (m, 3H), δ 2.63-2.73 (m, 2H), δ 3.18-3.25 (m, 5H), δ 3.31 (s, 2H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.01 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.44-7.48 (m, 1H), δ 7.60-7.62 (d, 2H), δ 7.70 (s, 1H), δ 8.33 (s, 1H).

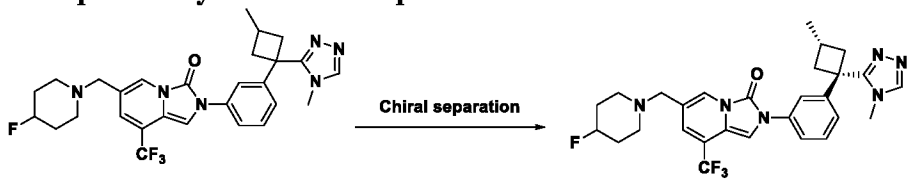
Example 236. Synthesis of Compound 236



Synthesis of 236

[831] 228a (320 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 20 min; Wave Length: 220/254 nm; RT1(min): 13.77; RT2(min): 16.98; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.2 mL; Number of Runs: 15). This resulted in 236 (190.2 mg, 59.14%) as a yellow solid. LC-MS: (ES, m/z): [M+H] + :523. H-NMR: (400 MHz, DMSO-d6, ppm): δ 0.50 (s, 4H), δ 1.07-1.09 (s, 3H), δ 2.51-2.55 (m, 3H), δ 2.87-2.89 (d, 2H), δ 3.15 (s, 3H), δ 3.30-3.33 (m, 4H), δ 4.47 (s,2H), δ 7.00 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.44-7.48 (m, 1H), δ 7.60-7.62 (d, 1H), δ 7.70 (s, 1H), δ 7.83 (s, 1H), δ 8.29 (s, 1H).

Example 237. Synthesis of Compound 237



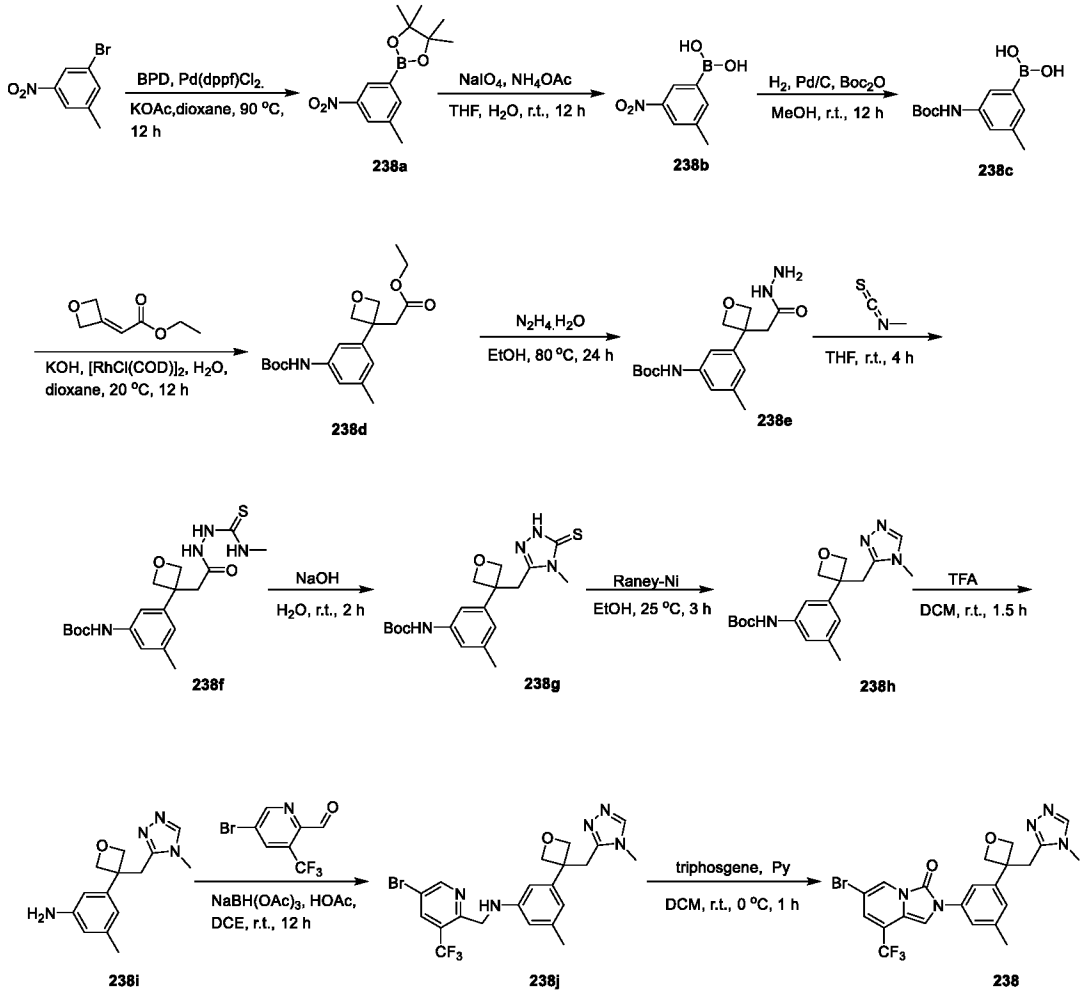
229a 237

Synthesis of 237

[832] 229a (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 16 min; Wave Length: 220/254 nm; RT1(min): 10.58; RT2(min): 14.29, the first peak is product) to afford 237 (176.0 mg, 43.56%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 543. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.03-1.13 (d, 3H), 1.61-1.88 (m, 2H), 1.88-1.96 (m, 2H), 2.36-2.46 (m, 2H), 2.51-2.67 (m, 3H), 2.83-2.95 (m, 2H), 3.21 (s, 3H), 3.32 (s, 2H), 4.64-4.77 (m, 1H), 7.01 (s, 1H), 7.24-7.26 (d, 1H), 7.38 (s, 1H), 7.44-7.52 (m, 1H), 7.63-7.66 (m, 1H), 7.69 (s, 1H), 7.83 (s, 1H), 8.29 (s, 1H).

Example 238. Synthesis of Compound 238



1. Synthesis of 238a

[833] A mixture of 1-bromo-3-methyl-5-nitro-benzene (12 g, 55.55 mmol, 1 equiv), BPD (21.1 g, 83.3 mmol, 1.5 equiv), KOAc (16.35 g, 166.64 mmol, 3 equiv) and Pd(dppf)Cl2 (3.25 g, 4.44 mmol, 0.08 equiv) in dioxane (150 mL) was degassed and purged with nitrogen atmosphere for 3 times, and then the mixture was stirred at 90 °C for 12 hr under nitrogen atmosphere. The reaction was poured to water (50 mL) and the resulting mixture was extracted with EtOAc (2 x 100 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA=5:1 to afford 238a (8 g, 55% yield) as a yellow oil.

2. Synthesis of 238b

[834] To a solution of 238a (8 g, 30.4 mmol, 1 equiv) in THF (90 mL) and water (30 mL) was added NaIO4 (5.05 mL, 91.2 mmol, 3 equiv) and NH4OAc (11.7 g, 152. mmol, 5 equiv). The mixture was stirred at 25 °C for 12 hr. The reaction was added NaHSO4 and poured to

water (100 mL) and the resulting mixture was extracted with EtOAc (2 x 100 mL). The organic phase was washed with brine (50 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA=1:1 to afford 238b (7.2 g, 65.43% yield) as a white solid.
H-NMR: (400 MHz, DMSO-d6) δ 8.42 (d, J=8.0 Hz, 2H) 8.09 (s, 2H) 8.00-8.04 (m, 1H) 2.44 (s, 3H)

3. Synthesis of 238c

[835] To a solution of 238b (2.3 g, 12.71 mmol, 1 equiv) in MeOH (40 mL) was added Pb/C (1.2 g, 10% purity) and Boc2O (14.6 mL, 63.5 mmol, 5 equiv). The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 Psi) at 25 °C for 12 h. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 40ml). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH=10:1 to afford 238c (7.9 g, 82.5%) as a white solid. H-NMR: (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.45 (s, 1H), 7.86 (s, 2H), 7.54 (s, 1H), 7.28 (s, 1H), 2.22 (s, 3H), 1.44 (s, 9H).

4. Synthesis of 238d

[836] To a stirred solution of chlororhodium;(1Z,5Z)-cycloocta-1,5-diene (102 mg, 208 umol, 0.023 equiv) in dioxane (45 mL) was added KOH (558 mg, 9.96 mmol, 1.1 equiv) in water (35 mL) dropwise at 20°C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 25°C under nitrogen atmosphere. To the above mixture were added 238c (3.5 g, 13.9 mmol, 1.54 equiv) and ethyl 2-(oxetan-3-ylidene)acetate (1.29 g, 9.05 mmol, 1 equiv) at 25°C for 17.5 hr under nitrogen atmosphere. The reaction mixture was diluted with water (80 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE=1:1 to afford 238d (3.66 g, 57.8%) as a brown solid.
H-NMR: (400 MHz, CHLOROFORM-d) δ 7.09 (s, 1H), 6.92 (s, 1H), 6.61 (s, 1H), 6.42 (s, 1H), 4.98 (d, J = 6.0 Hz, 2H), 4.82 (d, J = 6.0 Hz, 2H), 4.05 - 3.98 (m, 2H), 3.07 (s, 2H), 2.29 (s, 3H), 2.04 (s, 1H), 1.50 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H).

5. Synthesis of 238e

[837] To a solution of 238d (3.66 g, 10.4 mmol, 1 equiv) in EtOH (30 mL) was added N2H4.H2O (8.31 mL, 167 mmol, 98% purity, 16 equiv). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was concentrate in vacuum to remove EtOH (20 mL), then the

mixture was diluted with water (30 mL), and extracted with CH2Cl2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 238e (3.05g, crude) as a yellow solid.

6. Synthesis of 238f

[838] To a solution of 238e (3.05 g, 9.09 mmol, 1 equiv) in THF (40 mL) was added methylimino(thioxo)methane (1.33 g, 18.19 mmol, 1.24 mL, 2 equiv). The mixture was stirred at 25 °C for 4 hr. The reaction mixture was diluted with water 40 mL and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 238f (4.71 g, crude) as a white solid.

7. Synthesis of 238g

[839] To a solution of NaOH (3.69 g, 92.24 mmol, 8 equiv) in water (40 mL) was added 238f (71 g, 11.53 mmol, 1 equiv).The mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with water (40 mL), adjusted pH to 5 by 1N HCl, filtered and the filter cake was concentrated in vacuum to afford 238g (4.07 g, 90.4%) as a white solid.

[840] H-NMR-238g: (400 MHz, DMSO-d6): δ 13.49 (s, 1H), 9.39-9.04 (m, 1H), 7.16 (s, 1H), 6.99 (s, 1H), 6.44 (s, 1H), 4.80-4.77 (m, 2H), 4.77-4.74 (m, 2H), 3.43 (s, 2H), 2.84 (s, 3H), 2.19 (s, 3H), 1.46 (s, 9H)

8. Synthesis of 238h

[841] To a solution of 238g (4.07 g, 10.4 mmol, 1 equiv) in EtOH (50 mL) was added Raney-Ni (8 g, 93.38 mmol, 8.96 equiv).The mixture was stirred at 25 °C for 3 hr under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford 238h (1.68 g, crude) as a white solid.

9. Synthesis of 238i

[842] To a solution of 238h (1.68 g, 4.69 mmol, 1 equiv) in DCM (16 mL) was added TFA (8 mL). The mixture was stirred at 25 °C for 1.5 hr. The reaction mixture was concentrated under reduced pressure to afford 238i (1.2 g, crude) was obtained as a purple oil.

10. Synthesis of 238j

[843] To a solution of 238i (580 mg, 2.25 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (456 mg, 1.80 mmol, 0.8 equiv) in MeOH (30 mL) was added HOAc (385 uL, 6.74 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. Then NaBH3CN (282 mg, 4.49 mmol, 2 equiv) was added, the result mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure and diluted with NaHCO3 (100 ml), extracted with

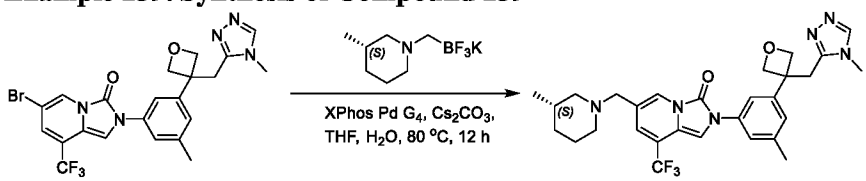
DCM (30 ml x 3), dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH=10:1 to afford 238j (440 mg, 39.4%) as a yellow solid.

11. Synthesis of 238

[844] To a solution of 238j (220 mg, 443.26 umol, 1 equiv) in DCM (10 mL) was added pyridine (214 uL, 2.66 mmol, 6 equiv) and bis(trichloromethyl) carbonate (52.6 mg, 177 umol, 0.4 equiv) at 0 °C. The mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. Then pyridine (214 uL, 2.66 mmol, 6 equiv) and bis(trichloromethyl) carbonate (52.61 mg, 177.30 umol, 0.4 equiv) was added. The mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. The reaction was quenched with Sat.NaHCO3 (20 mL). The aqueous layer was extracted with CH2Cl2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH=10:1 to give crude product. The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 150*30mm*5um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 15% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 9.0) to afford 238 (52.5 mg, 10.53%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 522.0/524.0. H-NMR: (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 8.02 (s, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.30-7.11 (m, 2H), 6.72 (s, 1H), 4.98-4.87 (m, 4H), 3.52 (s, 2H), 2.99 (s, 3H), 2.30 (s, 3H).

Example 239. Synthesis of Compound 239

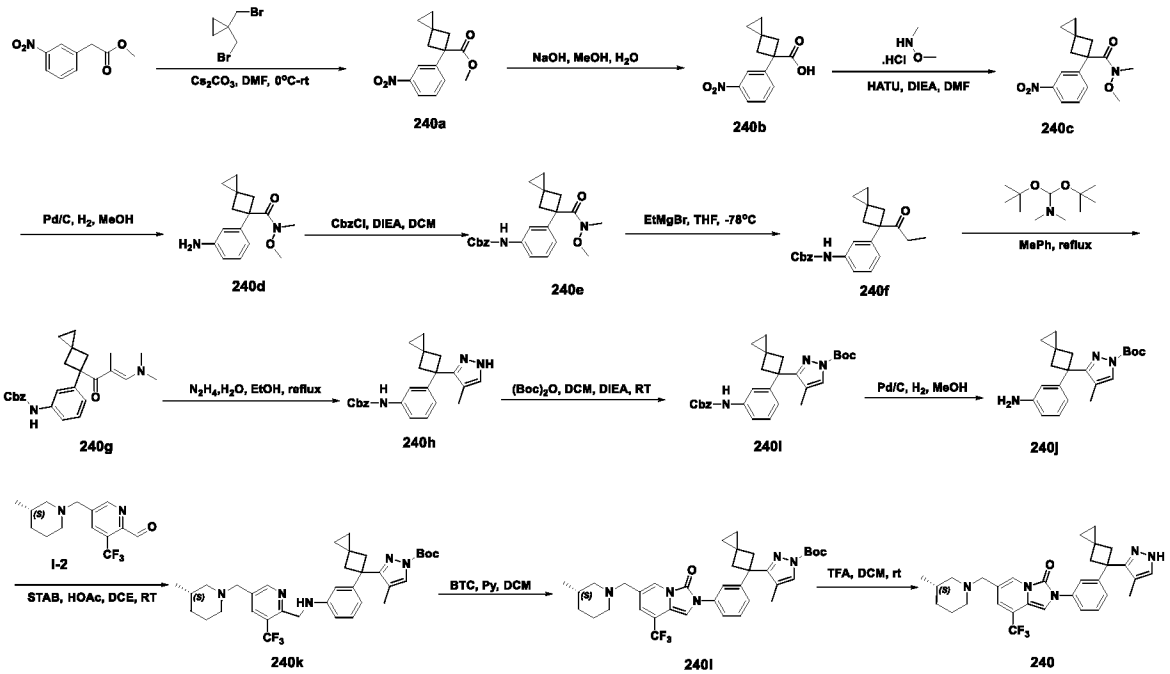


Synthesis of 239

[845] To a solution of 238 (80 mg, 153 umol, 1 equiv) and BF_3 salt (67.1 mg, 306 umol, 2 equiv) in THF (4 mL) and water (1 mL) was added Cs2CO3 (149.71 mg, 459.49 umol, 3 eq) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate;[2-[2-(methylamino) phenyl]phenyl]palladium(1+) (13.1 mg, 15.3 umol, 0.1 eq). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was diluted with water (50

ml) and extracted with DCM (20 ml x3). The combined organic was dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 150*30mm*5um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 35 mL/min; Gradient: 15% B to 55% B in 8 min; Wave Length: 220 nm; RT (min): 10.0) to afford 239(10.8 mg, 12.7%) as a yellow solid.
LCMS: (ES, m/z): [M+H]+ 555.3. H-NMR: (400 MHz, METHANOL-d4) δ 8.38 (s, 1H), 8.22 (s, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.06 (s, 1H), 6.75 (s, 1H), 5.07 (s, 4H), 3.79 (s, 2H), 3.66 (s, 2H), 3.22-3.16 (m, 1H), 2.98 (s, 3H), 2.54-2.44 (m, 1H), 2.38 (s, 3H), 2.25-2.17 (m, 1H), 1.93-1.65 (m, 5H), 1.16-1.05 (m, 1H), 0.98 (d, J = 6.4 Hz, 3H)

Example 240. Synthesis of Compound 240



1. Synthesis of 240a

[846] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (50 g, 256.182 mmol, 1 equiv) in DMF (800 mL) was added Cs2CO3 (417.35 g, 1280.910 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. To the above mixture was added 1,1-bis(bromomethyl)cyclopropane (175.17 g, 768.546 mmol, 3 equiv) at 0degrees C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated NH4Cl(aq.) (3 L)

at room temperature. The aqueous layer was extracted with EtOAc (2x800 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (50:1) to afford 240a (37 g, 50.86%) as a colorless oil.

2. Synthesis of 240b

[847] Into a 1000mL 3-necked round-bottom flask was added 240a (37 g, 141.612 mmol, 1 equiv) and NaOH (5.66 g, 141.612 mmol, 1 equiv), MeOH (370 mL), H2O (20 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 5 with HCl (4M). The resulting mixture was extracted with EtOAc (3 x 500mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 240b (34 g, 97.11%) as a yellow oil.

3. Synthesis of 240c

[848] Into a 500mL 3-necked round-bottom flask were added 240b (17 g, 68.8 mmol, 1 equiv) and DMF (170 mL), HATU (39.21 g, 103.2 mmol, 1.5 equiv), DIEA (26.42 g, 206.4 mmol, 3 equiv), N,O-dimethylhydroxylamine hydrochloride (10.11 g, 103.2 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (800 mL). The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 240c (17 g, 40.32%) as a yellow oil.

4. Synthesis of 240d

[849] To a solution of 240c (18.7 g, 64.412 mmol, 1 equiv) in MeOH (400 mL) was added Pd/C (1.87 g, 10%) under nitrogen atmosphere in a 1L round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 240d (16 g, 95.42%) as a yellow oil.

5. Synthesis of 240e

[850] To a stirred solution of 240d (16 g, 61.459 mmol, 1 equiv) and DIEA (27.80 g, 215.107 mmol, 3.5 equiv) in DCM (500 mL) were added CbzCl (20.97 g, 122.918 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The residue was washed with water (500 mL). The aqueous layer was extracted with DCM (200 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 240e (22 g, 90.75%) as a yellow oil.

6. Synthesis of 240f

[851] To a stirred solution of 240e (17.2 g, 43.603 mmol, 1 equiv) in THF (200 mL) was added EtMgBr (109 mL, 109.00 mmol, 2.5 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 240f (7.13 g, 44.99%) as a yellow oil.

7. Synthesis of 240g

[852] To a stirred solution of 240f (11.83 g, 32.549 mmol, 1 equiv) in Toluene (150 mL) was added [bis(tert-butoxy)methyl]dimethylamine (33.09 g, 162.745 mmol, 5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 110°C. The resulting mixture was concentrated under vacuum. This resulted in 240g (13 g, crude) as a yellow oil.

8. Synthesis of 240h

[853] To a stirred solution of 240g (13 g, 31.10 mmol, 1 equiv) in EtOH (200 mL) was added hydrazine hydrate (98%)(15.55 g, 311.00 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 6h at 80°C. The reaction was quenched with water (600 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 240h (6 g, 49.87%) as a light yellow solid.

9. Synthesis of 240i

[854] To a stirred solution of 240h (3 g, 7.742 mmol, 1 equiv) and (Boc)2O (3.38 g, 15.484 mmol, 2 equiv) in DCM (50 mL) were added DIEA (3.00 g, 23.226 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 240i (2.7 g, 67.94%) as a white solid.

10. Synthesis of 240j

[855] To a solution of 240i (2.7 g, 5.537 mmol, 1 equiv) in MeOH (50 mL) was added Pd/C

(270 mg, 10%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 240j (1.7 g, 78.17%) as an off-white solid. The crude product was used in the next step directly without further purification.

11. Synthesis of 240k

[856] To a stirred solution of 240j (300 mg, 0.849 mmol, 1 equiv) and I-2(267.29 mg, 0.934 mmol, 1.1 equiv) in DCE (5 mL) were added HOAc (5.10 mg, 0.085 mmol, 0.1 equiv) and STAB (359.76 mg, 1.698 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 240k (400 mg, 68.76%) as an off-white solid.

12. Synthesis of 240l

[857] To a stirred solution of 240k (400 mg, 0.641 mmol, 1 equiv) and Pyridine (507.24 mg, 6.410 mmol, 10 equiv) in DCM (10 mL) were added Triphosgene (76.11 mg, 0.256 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. This resulted in 240l (200 mg, 43.20%) as a yellow solid. The crude product was used in the next step directly without further purification.

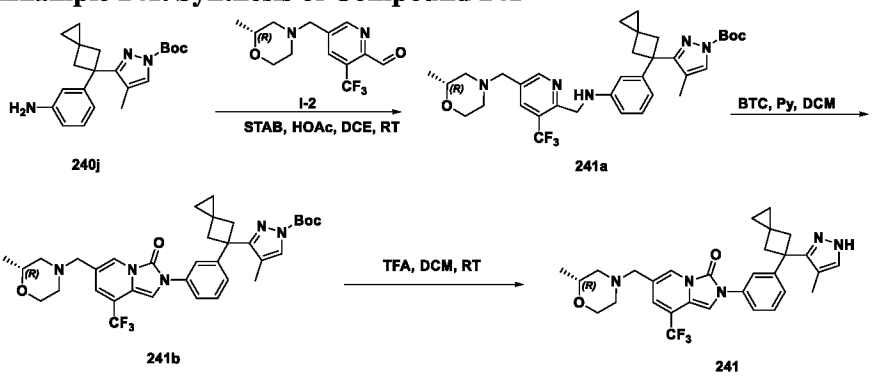
13. Synthesis of 240

[858] To a stirred solution of 240l (200 mg) in DCM (5 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred for 1h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 60% B to 90% B in 8 min, Wave Length: 220 nm; RT1(min): 7.53) to afford 240 (106.2 mg, 61.08%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 550. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.40-0.50 (m, 2H), 0.50-0.60 (m, 2H), 0.79-0.95 (m, 4H), 1.43-1.53 (m, 1H), 1.53-1.73 (m, 4H), 1.74 (s, 3H), 1.86-1.92 (m, 1H), 2.67-2.81 (m, 4H), 3.02-3.12 (m, 2H), 3.24 (s, 2H), 7.00 (s, 1H),

7.23-7.39 (m, 3H), 7.39-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.66 (s, 1H), 7.84 (s, 1H), 12.26 (s, 1H).

Example 241. Synthesis of Compound 241



1. Synthesis of 241a

[859] To a stirred solution of 240j (300 mg, 0.849 mmol, 1 equiv) and I-2 (269.13 mg, 0.934 mmol, 1.1 equiv) in DCE (5 mL) was added HOAc (5.10 mg, 0.085 mmol, 0.10 equiv) and STAB (359.76 mg, 1.698 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 241a (400 mg, 71.55%) as a white solid.

2. Synthesis of 241b

[860] To a stirred solution of 241a (400 mg, 0.639 mmol, 1 equiv) and Pyridine (505.64 mg, 6.390 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (75.87 mg, 0.256 mmol, 0.4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. This resulted in 241b (300 mg, 64.81%) as a yellow solid. The crude product was used in the next step directly without further purification.

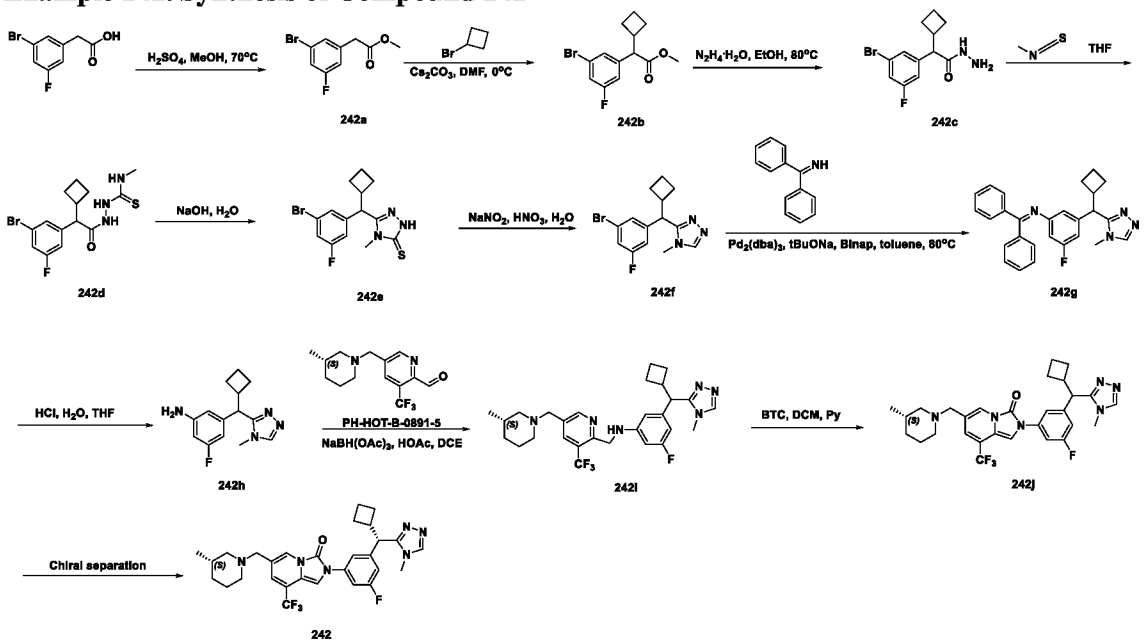
3. Synthesis of 241

[861] To a stirred solution of 241b (300 mg) in DCM (8 mL) was added TFA (2 mL) at room temperature . The resulting mixture was stirred for 1h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150

mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 8 min, Wave Length: 220 nm; RT1(min): 7.52) to afford 241 (151.3 mg, 58.93%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 552. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.41-0.48 (m, 2H), 0.48-0.52 (m, 2H), 1.03-1.05 (d, 3H), 1.71-1.76 (m, 4H), 2.02-2.08 (m, 1H), 2.65-2.75 (m, 4H), 3.02-3.05 (m, 2H), 3.23-3.28 (m, 2H), 3.35 (s, 2H), 3.46-3.51 (m, 2H), 3.73-3.75 (m, 2H), 7.01 (s, 1H), 7.23-7.27 (m, 2H), 7.27-7.45 (m, 2m, 2H), 7.52-7.54 (m, 1H), 7.70 (s, 1H), 7.83 (s, 1H), 12.21 (s, 1H).

Example 242. Synthesis of Compound 242



1. Synthesis of 242a

[862] A solution of (3-bromo-5-fluorophenyl)acetic acid (10 g, 42.912 mmol, 1 equiv) and H2SO4 (0.42 g, 4.291 mmol, 0.1 equiv) in MeOH (100 mL) was stirred for 3h at 70 °C under nitrogen atmosphere. The reaction was quenched with water/ice (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL).The resulting mixture was concentrated under reduced pressure. This resulted in 242a (10 g, 94.32%) as a colorless oil.

2. Synthesis of 242b

[863] Into a 500mL 3-necked round-bottom flask were added 242a (10 g, 40.476 mmol, 1 equiv), Cs2CO3 (39.56 g, 121.428 mmol, 3 equiv) and DMF (100 mL) at 0°C. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. To the above mixture was added bromocyclobutane (10.93 g, 80.952 mmol, 2 equiv) at room temperature.

The resulting mixture was stirred overnight at room temperature. The reaction was quenched by saturated NH4Cl (aq.) (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (1x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 242b (10 g, 74.66%) as a yellow oil.

3. Synthesis of 242c

[864] Into a 500mL 3-necked round-bottom flask were added 242b (10 g, 33.205 mmol, 1 equiv), N2H4.H2O (16.62 g, 332.05 mmol, 10 equiv) and EtOH (100 mL, 2754.023 mmol) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was allowed to cool down to room temperature. The reaction was quenched by water (100mL) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 242c (10 g, 91.00%) as a yellow oil.

4. Synthesis of 242d

[865] Into a 500mL 3-necked round-bottom flask were added 242c (10 g, 33.205 mmol, 1 equiv), methyl isothiocyanate (5.34 g, 73.051 mmol, 2.2 equiv) and tetrahydrofuran (150 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (100 mL) and moved the THF under vacuum. The precipitated solids were collected by filtration and washed with water (20 mL). This resulted in 242d (10 g, 74.83%) as a white solid.

5. Synthesis of 242e

[866] To a stirred mixture of NaOH (4.27 g, 106.876 mmol, 4 equiv) in H2O (100 mL) was added 242d (10 g, 26.719 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The mixture was acidified to pH 5 with HCl (aq.). The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 242e (9 g, 86.04%) as a yellow oil.

6. Synthesis of 242f

[867] To a stirred mixture of 242e (10 g, 28.069 mmol, 1 equiv) and NaNO2 (19.37 g, 280.690 mmol, 10 equiv) in H2O (90 mL) was added HNO3 (280 mL, 280.690 mmol, 10 equiv, 1M) at 0°C. The resulting mixture was stirred for 2h at room temperature. The mixture was neutralized to pH 8 with NaHCO3 (aq.). The aqueous layer was extracted with DCM (1x90 mL).The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (500:1) to afford 242f (3 g, 30.33%) as an off-white solid.

7. Synthesis of 242g

[868] Into a 100mL 3-necked round-bottom flask were added 242f (3 g, 9.254 mmol, 1 equiv), benzenemethanimine (1.68 g, 9.254 mmol, 1 equiv), Pd2(dba)3.CHCl3 (0.48 g, 0.463 mmol, 0.05 equiv) , Binap (0.43 g, 0.694 mmol, 0.075 equiv) , t-BuONa (1.07 g, 11.105 mmol, 1.2 equiv) and toluene (30 mL) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by saturated NH4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 242g (4 g, 61.10%) as a yellow oil. The crude product was used in the next step directly without further purification.

8. Synthesis of 242h

[869] Into a 100mL 3-necked round-bottom flask was added 242g (2.5 g, 5.889 mmol, 1 equiv), HCl(1M)(20 mL) and THF (5 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was concentrated under vacuum. The crude product was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, A: water (10mmol/L 0.1%NH4HCO3), B: MeCN, 15% B to 30% B gradient in 20 min; detector, UV 254 nm. The residue was dried by lyophilization to afford 242h (300 mg, 18.00%) as a white soild.

9. Synthesis of 242i

[870] To a stirred solution of 242h (280 mg, 1.076 mmol, 1 equiv) and I-2(677.48 mg, 2.368 mmol, 2.2 equiv) in DCE (5 mL) were added HOAc (64.59 mg, 1.076 mmol, 1.00 equiv) and NaBH(OAc)3 (455.93 mg, 2.152 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 6h at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 242i (320 mg, 52.14%) as a light yellow oil.

10. Synthesis of 242j

[871] To a stirred solution of 242i (300 mg, 0.565 mmol, 1 equiv) and Pyridine (447.22 mg, 5.654 mmol, 10.00 equiv) in DCM (10 mL) were added Triphosgene (83.89 mg, 0.283 mmol, 0.50 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were

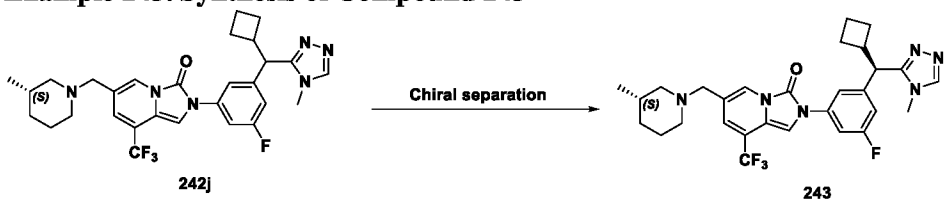
concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 242j (200 mg, 60.38%) as a yellow solid.

11. Synthesis of 240

[872] 242j (200 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.72; RT2(min): 11.1, the first peak is product) to afford 242 (65.7 mg, 32.52%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 557. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.41-1.55 (m, 1H), 1.58-1.78 (m, 5H), 1.78-1.93 (m, 5H), 2.06-2.08 (m, 1H), 2.65-2.81 (m, 2H), 3.22-3.31 (m, 3H), 3.47 (s, 3H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.42 (s, 1H), 7.65 (s, 1H), 7.69-7.71 (m, 2H), 8.36 (s, 1H).

Example 243. Synthesis of Compound 243

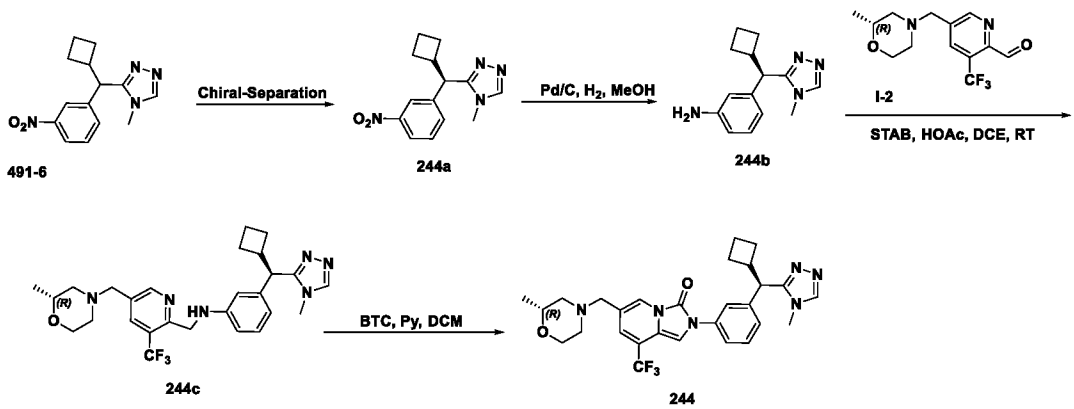


Synthesis of 243

[873] 242j (200 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.72; RT2(min): 11.1, the second peak is product) to afford 243 (74.3 mg, 36.78%) as a yellow solid.

LC-MS-243 (ES, *m/z*): $[M+H]^+$ 557. H-NMR-243 (400 MHz, DMSO-d6, δ *ppm*): 0.82-0.93 (m, 4H), 1.41-1.55 (m, 1H), 1.58-1.78 (m, 5H), 1.78-1.93 (m, 5H), 2.06-2.08 (m, 1H), 2.65-2.81 (m, 2H), 3.22-3.31 (m, 3H), 3.47 (s, 3H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.42 (s, 1H), 7.65 (s, 1H), 7.69-7.71 (m, 2H), 8.36 (s, 1H).

Example 244. Synthesis of Compound 244



1. Synthesis of 244a

[874] 491-6 (40 g) was separated by Prep-SFC with the following conditions (Column: CHIRAL ART Cellulose-SC, 5*25 cm, 10 μm; Mobile Phase A: CO2, Mobile Phase B: ACN: MeOH=1: 1(1% 2M NH3-MeOH); Flow rate: 250 mL/min; Gradient: isocratic 36% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 9.7; RT2(min): 12; The first peak was product) to afford 244a (13 g, 32.50%) as a off-white solid.

2. Synthesis of 244b

[875] To a solution of 244a (22 g, 76.751 mmol, 1 equiv, 95%) in 250 mL MeOH was added Pd/C (20%,5 g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 244b (18 g, 92.91%) as a white solid.

3. Synthesis of 244c

[876] To a stirred mixture of 244b (200 mg, 0.825 mmol, 1 equiv) and I-2 (285.50 mg, 0.990 mmol, 1.2 equiv) in DCE (4 mL) was added STAB (524.76 mg, 2.475 mmol, 3 equiv) and HOAc (49.56 mg, 0.825 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with water (10 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 244c (180 mg, 39.41%) as a yellow solid.

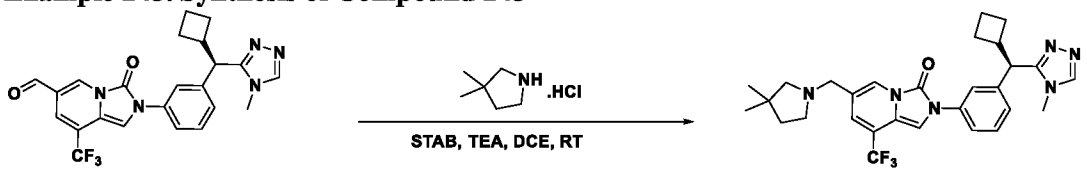
4. Synthesis of 244

[877] To a stirred solution of 244c (180 mg, 0.350 mmol, 1 equiv) and Pyridine (166.01 mg, 2.100 mmol, 6 equiv) in DCM (5 mL) was added Triphosgene (85.11 mg, 0.287 mmol, 0.82 equiv) at 0 °C. The resulting mixture was stirred for 30 min at room temperature. The

reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH=15:1 to afford the crude product (110 mg) as a yellow solid. The crude product (110 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 8 min, 58% B; Wave Length: 220 nm; RT1(min): 7.53) to afford 244 (43.3 mg, 22.07%) as a yellow solid.

LCMS-244 (ES, m/z): [M+H]+ 541. H-NMR-244 (400 MHz, DMSO-d6, ppm, δ): 1.05 (s, 3H), 1.77-1.81 (m, 6H), 2.02-2.08 (m, 2H), 2.65-2.68 (m, 1H), 2.72-2.75 (m, 1H), 3.23-3.27 (m, 3H), 3.46 (s, 3H), 3.46-3.52 (m, 2H), 3.73-3.76 (d, 1H), 4.25-4.28 (d, 1H), 7.02 (s, 1H), 7.19-7.21 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (t, 2H), 7.68-7.70 (m, 2H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 245. Synthesis of Compound 245



247c 245

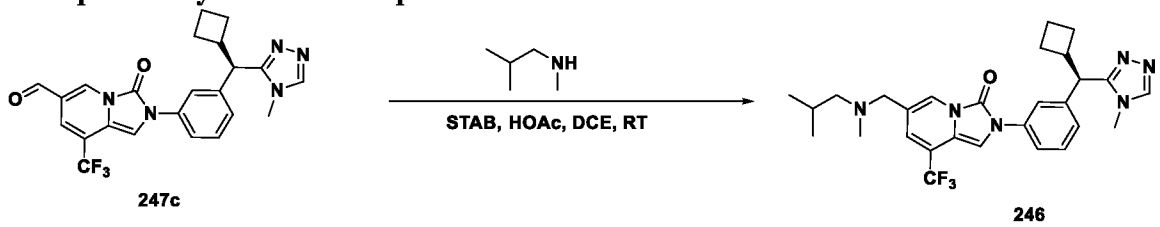
Synthesis of 245

[878] To a stirred solution of 247c (250 mg, 0.549 mmol, 1 equiv) and 3,3-dimethylpyrrolidine hydrochloride (148.91 mg, 1.098 mmol, 2 equiv) in DCE (5 mL) was added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product (250 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 74% B in 8 min, Wave Length: 220 nm; RT1(min): 7.32) to afford 245 (159.5 mg, 53.41%) as a yellow

solid.

LC-MS: (ES, m/z): [M+H]+ 539. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.05 (s, 6H), 1.52-1.56 (m, 2H), 1.68-1.88 (m, 5H), 2.03-2.13 (m, 1H), 2.28-2.33 (m, 2H), 2.51-2.59 (m, 2H), 3.19-3.25 (m, 1H), 3.38 (s, 2H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (d, 1H), 7.42 (s, 1H), 7.44-7.46 (m, 1H), 7.66-7.70 (m, 2H), 7.74 (s, 1H), 8.32 (s, 1H).

Example 246. Synthesis of Compound 246

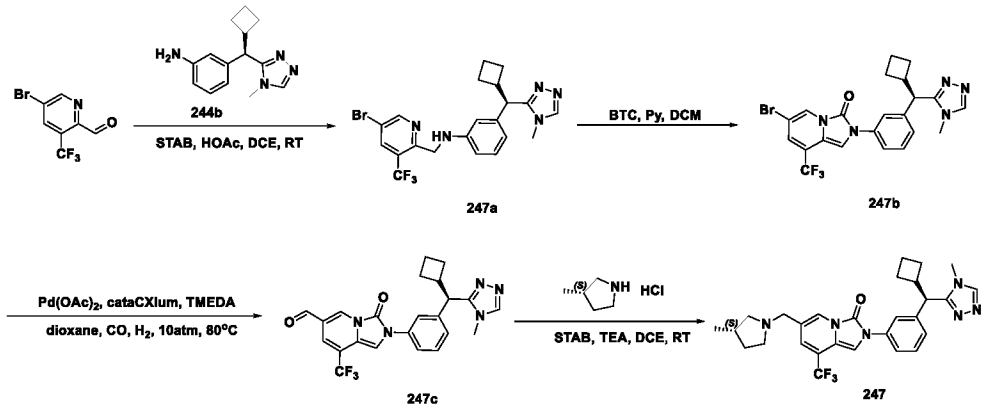


Synthesis of 246

[879] To a stirred solution of 247c (250 mg, 0.549 mmol, 1 equiv) and methyl(2-methylpropyl)amine (95.69 mg, 1.098 mmol, 2 equiv) in DCE (5 mL) was added HOAc (3.30 mg, 0.055 mmol, 0.1 equiv) and STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under. The reaction was quenched with saturated NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product (250 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 49% B to 79% B in 8 min, Wave Length: 220 nm; RT1(min): 7.70) to afford 246 (62.3 mg, 21.42%) as a yellow solid.

LC-MS-246: (ES, m/z): [M+H]+ 527. H-NMR-246 (400 MHz, DMSO-d6, δ ppm): 0.79-0.93 (d, 6H), 1.68-1.93 (m, 6H), 2.01-2.09 (m, 3H), 3.27-3.33 (m, 3H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.42 (s, 1H), 7.44-7.46 (m, 1H), 7.67-7.70 (m, 2H), 7.74 (s, 1H), 8.32 (s, 1H).

Example 247. Synthesis of Compound 247



1. Synthesis of 247a

[880] To a stirred solution of 215a (10.38 g, 40.854 mmol, 1.1 equiv) and 244b (9 g, 37.140 mmol, 1.00 equiv) in DCE (120 mL) were added STAB (15.74 g, 74.280 mmol, 2 equiv) and HOAc (2.23 g, 37.140 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Sat. NH4Cl(aq) (200mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 350mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 247a (14 g, 74.55%) as a light yellow oil.

2. Synthesis of 247b

[881] To a stirred solution of 247a (14 g, 29.146 mmol, 1 equiv) and Pyridine (13.83 g, 174.876 mmol, 6 equiv) in DCM (150 mL) were added Triphosgene (3.03 g, 10.201 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 20 min at room temperature. The reaction was quenched by the addition of Sat. NaHCO3 (aq) (200mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 300mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MTBE (20 mL) to afford 247b (12 g, 77.25%) as a yellow solid.

3. Synthesis of 247c

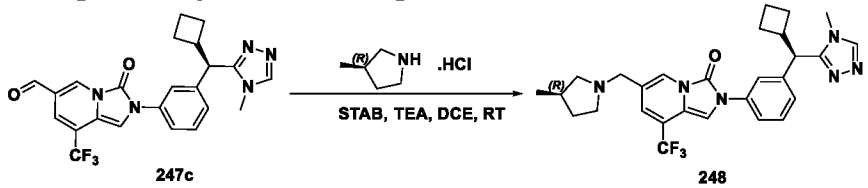
[882] To a solution of 247b (14 g, 27.650 mmol, 1 equiv), TMEDA (6.43 g, 55.300 mmol, 2 equiv) in dioxane (400.00 mL) was added bis(adamantan-1-yl)(butyl)phosphane (1.98 g, 5.530 mmol, 0.2 equiv) and Pd(OAc)2 (0.62 g, 2.765 mmol, 0.1 equiv) in an autoclave. After flushing the autoclave three times with CO/H2 (1:1), the mixture was pressurized to 10 atm with CO/H2 (1:1) at 80 oC for overnight. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography eluted with CH2Cl2 / MeOH (20:1) to afford 247c (12 g, 90.53%) as a yellow solid.

4. Synthesis of 247

[883] To a stirred solution of 247c (250 mg, 0.549 mmol, 1.00 equiv) and (3S)-3-methylpyrrolidine hydrochloride (133.51 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) were added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (7mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 10mL). The resulting mixture was concentrated under reduced pressure. The crude product (143 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 64% B in 8 min, 64% B; Wave Length: 220 nm; RT1(min): 7.78) to afford 247 (101.3 mg, 34.97%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :525. H-NMR: (400 MHz, DMSO-d6, ppm): δ 0.97-1.03 (m, 3H), δ 1.22-1.35 (m, 1H), δ 1.61-1.85 (m, 5H), δ 1.86-2.13 (m, 3H), δ 2.15-2.22 (m, 1H), δ 2.52 (s, 1H), δ 2.53-2.56 (d, 1H), δ 2.72-2.76 (m, 1H), δ 3.15-7.23 (m, 1H), δ 3.35 (s, 2H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.00 (s, 1H), δ 7.21-7.23 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 8.32 (s, 1H).

Example 248. Synthesis of Compound 248



247c 248

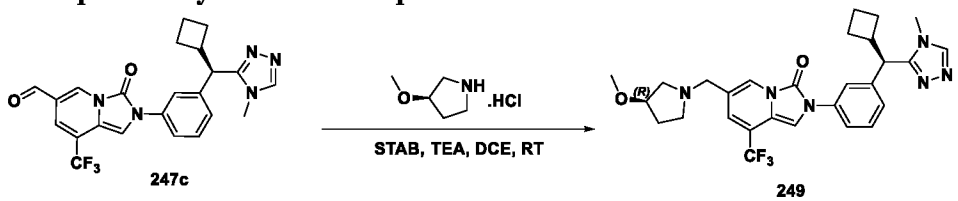
Synthesis of 248

[884] To a stirred solution of 247c (250 mg, 0.549 mmol, 1.00 equiv) and (3R)-3-methylpyrrolidine hydrochloride (133.51 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) were added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 15mL). The resulting mixture was concentrated under reduced pressure. The crude product (120 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN;

Flow rate: 60 mL/min; Gradient: 34% B to 62% B in 8 min, 62% B; Wave Length: 220 nm; RT1(min): 7.83) to afford 248 (81.7 mg, 28.09%) as a yellow solid.

LCMS: (ES, m/z): [M+H] + :525. H-NMR: (400 MHz, DMSO-d6, ppm): δ 0.97-1.03 (m, 3H), δ 1.22-1.35 (m, 1H), δ 1.61-1.85 (m, 5H), δ 1.86-2.13 (m, 3H), δ 2.15-2.22 (m, 1H), δ 2.52 (s, 1H), δ 2.53-2.56 (d, 1H), δ 2.72-2.76 (m, 1H), δ 3.15-7.23 (m, 1H), δ 3.35 (s, 2H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.00 (s, 1H), δ 7.21-7.23 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 2H), δ 7.73 (s, 1H), δ 8.32 (s, 1H)

Example 249. Synthesis of Compound 249

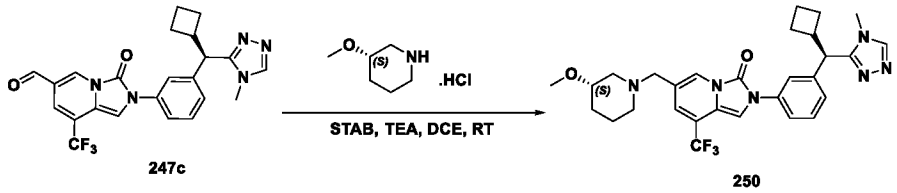


Synthesis of 249

[885] To a stirred solution of 247c (250 mg, 0.549 mmol, 1.00 equiv) and (3R)-3-methoxypyrrolidine hydrochloride (151.07 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) were added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (5mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 51% B in 11 min, 51% B; Wave Length: 220 nm; RT1(min): 10.68) to afford 249 (69.5 mg, 23.19%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :541. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.60-1.72 (m, 2H), δ 1.73-1.85 (m, 4H), δ 1.93-2.15 (m, 1H), δ 2.51-2.53 (d, 1H), δ 2.52-2.54 (m, 2H), δ 2.54-2.57 (m, 1H), δ 2.71-2.73 (d, 1H), δ 3.16 (s, 3H), δ 3.21-3.23 (d, 1H), δ 3.35-3.36 (m, 2H), δ 3.58 (s, 3H), δ 3.85-3.87 (d, 1H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 2H), δ 7.72 (s, 1H), δ 8.33 (s, 1H).

Example 250. Synthesis of Compound 250



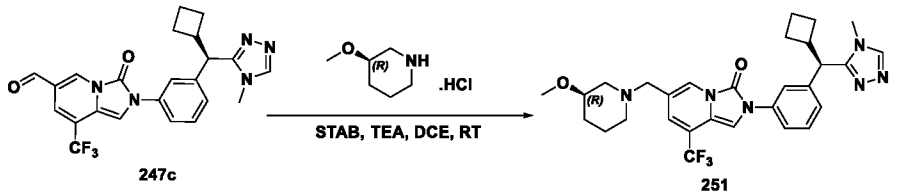
247c 250

Synthesis of 250

[886] To a stirred solution of 247c (250 mg, 0.549 mmol, 1 equiv) and (3S)-3-methoxypiperidine hydrochloride (126.44 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) was added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 63% B in 8 min, 63% B; Wave Length: 220 nm; RT1(min): 7.12) to afford 250 (111.7 mg, 36.36%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :555. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.02-1.13 (m, 1H) δ 1.28-1.32 (m, 1H), δ 1.61-1.75 (m, 2H), δ 1.76-1.89 (m, 4H), δ 1.90-1.98 (m, 2H), δ 2.01 (s, 1H), δ 2.14-2.46 (d, 1H), δ 2.62 (s, 1H), δ 2.90 (s, 1H), δ 3.56 (s, 5H), δ 3.32-3.36 (m, 2H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 2H), δ 7.75 (s, 1H), δ 8.35 (s, 1H).

Example 251. Synthesis of Compound 251



247c 251

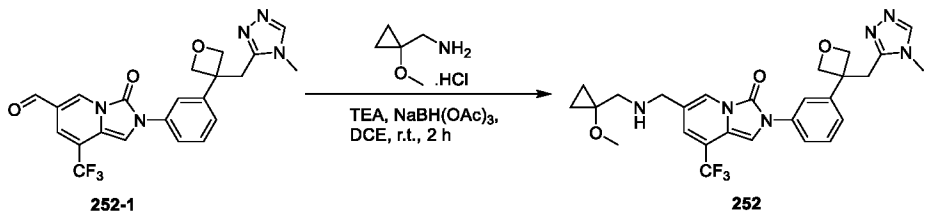
Synthesis of 251

[887] To a stirred solution of 247c (250 mg, 0.549 mmol, 1 equiv) and (3R)-3-methoxypiperidine hydrochloride (126.44 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) was added TEA (111.09 mg, 1.098 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room

temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (89 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 63% B in 8 min, 63% B; Wave Length: 220 nm; RT1(min): 7.12) to afford 251 (71.0 mg, 23.20%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :555. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.02-1.13 (m, 1H) δ 1.28-1.32 (m, 1H), δ 1.61-1.75 (m, 2H), δ 1.76-1.89 (m, 4H), δ 1.90-1.98 (m, 3H), δ 2.01 (s, 1H), δ 2.14-2.46 (d, 1H), δ 2.62 (s, 1H), δ 3.56 (s, 5H), δ 3.32-3.36 (m, 2H), δ 3.45 (s, 3H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 2H), δ 7.75 (s, 1H), δ 8.35 (s, 1H).

Example 252. Synthesis of Compound 252



252-1 252

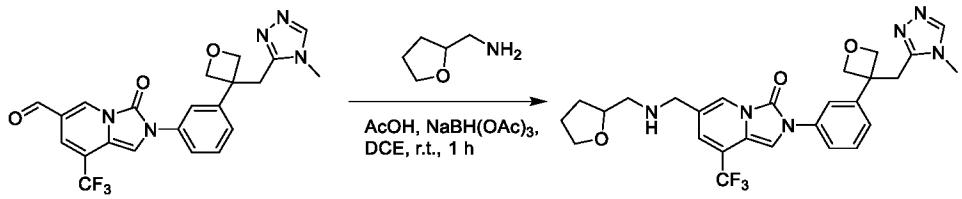
Synthesis of 252

To a solution of 252-1 (0.1 g, 218 umol, 1 equiv) and (1-methoxycyclopropyl)methanamine (90.2 mg, 655 umol, HCl salt, 3 equiv) in DCE (1.5 mL) was added TEA (121 uL, 874 umol, 4 equiv). The mixture was stirred at 20 °C for 1 hr. Then it was added NaBH(OAc)3 (231.68 mg, 1.09 mmol, 5 equiv). The mixture was stirred at 20 °C for 1 hr. The reaction was quenched by the addition of water (10 mL) and extracted with CH2Cl2 (2x 30 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 50% B in 8 min; Wave Length: 220 nm; RT (min): 8.0) to afford 252 (17 mg, 14% yield) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 543.3. H-NMR: (400 MHz, DMSO-d6) δ 8.18 (d, J =12 Hz, 2 H), 7.75 (d, J =6.8 Hz, 1 H), 7.70 (s, 1 H), 7.41-7.37 (m, 2 H), 7.29 (s, 1 H), 7.15 (s, 1 H), 6.88

(d, J =7.6 Hz, 1 H), 4.96-4.89 (m, 4 H), 3.59 (s, 2 H), 3.53 (s, 2 H), 3.18 (s, 3 H), 2.96 (s, 3 H), 2.68 (s, 2 H), 0.62-0.68 (m, 2 H), 0.47 (d, J =2.0 Hz, 2 H)

Example 253. Synthesis of Compound 253



252-11 253

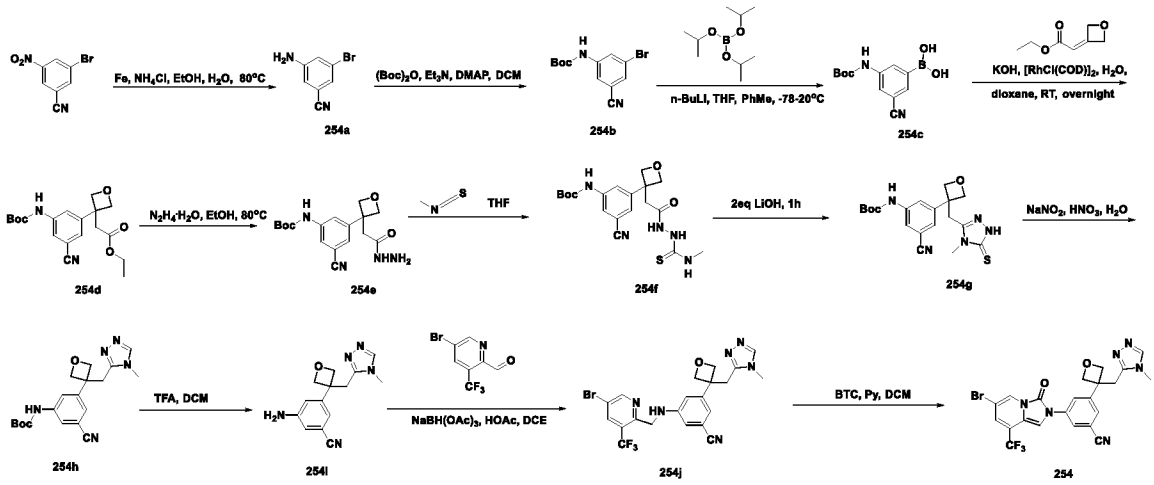
Synthesis of 253

To a solution of 252-11 (100 mg, 218 umol, 1 equiv) and tetrahydrofuran-2-ylmethanamine (135 uL, 1.31 mmol, 6 equiv) in DCE (0.5 mL) was added AcOH (13.1 mg, 218 umol, 1 equiv). The mixture was stirred at 20 °C for 0.5 hr. Then it was added NaBH(OAc)3 (92.6 mg, 437 umol, 2 equiv). The mixture was stirred at 20 °C for 0.5 h. The reaction was quenched by the addition of water (10 mL) and extracted with CH2Cl2 (2x 30 ml). The combined organic layers were dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 20% B to 60% B in 8 min; Wave Length: 220 nm; RT (min): 9.0) to afford 253 (15 mg, 13% yield) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 543.3.

H-NMR: (400 MHz, DMSO-d6) δ 8.18 (d, J =10.8 Hz, 2 H), 7.73-7.78 (m, 1 H), 7.69 (s, 1 H), 7.40 (d, J =3.6 Hz, 2 H), 7.29 (s, 1 H), 7.13 (s, 1 H), 6.88 (d, J =8.0 Hz, 1 H), 4.96-4.89 (m, 4 H), 3.92-3.84 (m, 2 H), 3.76-3.70 (m, 2 H) 3.63-3.58 (m, 3 H), 3.55 (s, 2 H), 3.53 (s, 2 H), 2.97 (s, 3 H), 2.91-2.86 (m, 1 H), 1.91-1.77 (m, 4 H), 1.54-1.51 (m, 1 H).

Example 254. Synthesis of Compound 254



1. Synthesis 254a

[888] Into a 2L 3-necked round-bottom flask were added 3-bromo-5-nitrobenzonitrile (100 g, 440.496 mmol, 1 equiv), Fe (73.80 g, 1321.488 mmol, 3 equiv), NH4Cl (117.81 g, 2202.480 mmol, 5 equiv), EtOH (800 mL) and H2O (200 mL) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by trituration with water (500 mL). This resulted in 254a (88 g, 96.32%) as a light yellow solid.

2. Synthesis of 254b

[889] Into a 2L 3-necked round-bottom flask were added 254a (88 g, 446.621 mmol, 1 equiv), (Boc)2O (99.42 g, 455.553 mmol, 1.02 equiv), Et3N (90.39 g, 893.242 mmol, 2 equiv), DMAP (5.46 g, 44.662 mmol, 0.1 equiv) and DCM (880 mL) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with water (1000 mL) at room temperature. The resulting mixture was extracted with DCM (3 x 200mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 254b (21 g, 15.03%) as a light yellow solid.

3. Synthesis of 254c

[890] To a stirred solution of 254b (15 g, 50.479 mmol, 1 equiv) and triisopropyl borate (408.07 mg, 2.020 mmol, 1.2 equiv) in THF (30 mL)/Toluene (120 mL) was added n-BuLi (60.58 mL, 151.437 mmol, 3 equiv, 2.5M) at -78°C under nitrogen atmosphere. The reaction mixture was stirred at -20°C for 30 mins under nitrogen atmosphere. The reaction was quenched with saturated NH4Cl (aq.) (300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the

following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 40% gradient in 10 min; detector, UV 254 nm. This resulted in 254c (4 g, 28.72%) as a yellow solid.

4. Synthesis of 254d

[891] To a stirred solution of KOH (16.79 mL, 25.184 mmol, 1.2 equiv) in H2O (15 mL)/dioxane (55 mL) was added [Rh(COD)Cl]2 (0.52 g, 1.049 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. To the above mixture was added 254c (5.5 g, 20.987 mmol, 1 equiv) and ethyl 2-(oxetan-3-ylidene)acetate (5.97 g, 41.974 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The mixture was neutralized to pH 7 with saturated NH4Cl (aq.) (300 mL). The resulting mixture was extracted with EtOAc (3 x 200mL). The combined organic layers were washed with water (2x50 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (12:1) to afford 254d (2.4 g, 30.14%) as a light yellow solid.

5. Synthesis of 254e

[892] Into a 100mL 3-necked round-bottom flask were added 254d (2.4 g, 6.659 mmol, 1 equiv) and EtOH (24 mL) and hydrazine hydrate (98%)(173.62 mg, 3.475 mmol, 25 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of water (100mL) at room temperature. The resulting mixture was extracted with DCM (3 x150 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 254e (1.4 g, 57.66%) as a pink solid.

6. Synthesis of 254f

[893] To a stirred solution of 254e (1.35 g, 3.897 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added methyl isothiocyanate (712.34 mg, 9.742 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 254f (1.05 g, 61.65%) as a light yellow solid.

7. Synthesis of 254g

[894] To a stirred mixture of 254f (1 g, 2.384 mmol, 1 equiv) in H2O (5 mL) was added LiOH (228.37 mg, 9.535 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The mixture was acidified to pH 4 with HCl(aq.). The aqueous layer was extracted with DCM/MeOH (10:1) (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 254g (540 mg, 54.17%) as a white solid.

8. Synthesis of 254h

[895] To a stirred mixture of 254g (520 mg, 1.295 mmol, 1 equiv) and NaNO2 (893.61 mg, 12.950 mmol, 10 equiv) in H2O (8 mL) were added HNO3 (13 mL, 12.950 mmol, 10 equiv, 1M) dropwise at 0°C. The resulting mixture was stirred for 1h at 0°C. The mixture was acidified to pH 7 with saturated NaHCO3(aq.). The aqueous layer was extracted with DCM/ MeOH (10:1) (3x20 mL). The resulting mixture was concentrated under reduced pressure to afford 254h (400 mg, 75.24%) as a yellow solid.

9. Synthesis of 254i

[896] To a stirred mixture of 254h (410 mg, 1.110 mmol, 1 equiv) in DCM (10 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM/MeOH (10:1) (4x20 mL). The resulting mixture was concentrated under reduced pressure to afford 254i (300 mg, 89.33%) as a yellow oil.

10. Synthesis of 254j

[897] To a stirred solution of 254i (280 mg, 1.040 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (396.14 mg, 1.560 mmol, 1.5 equiv) in DCE (5 mL) was added NaBH(OAc)3 (440.71 mg, 2.080 mmol, 2 equiv) and HOAc (6.24 mg, 0.104 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 254j (120 mg, 20.70%) as a light yellow solid.

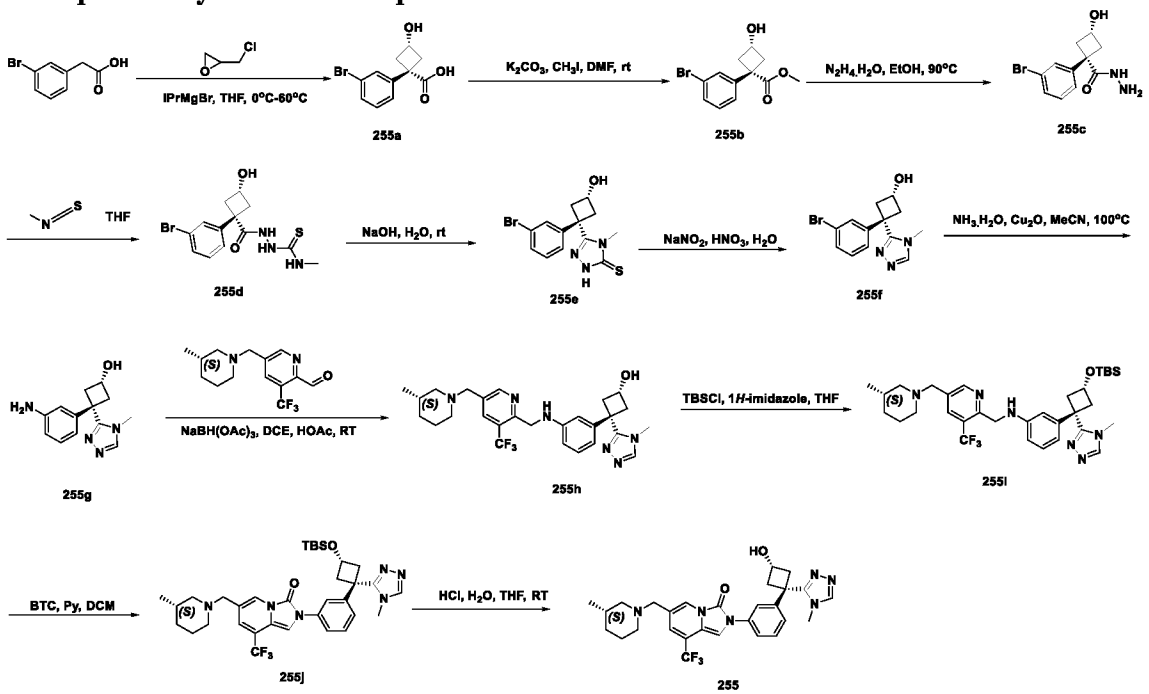
11. Synthesis of 254

[898] To a stirred solution of 254j (110 mg, 0.217 mmol, 1 equiv) and Pyridine (171.51 mg, 2.170 mmol, 10 equiv) in DCM (5 mL) was added Triphosgene (32.17 mg, 0.108 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The reaction was quenched with

saturated NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The product was precipitated by the addition of MeOH. This resulted in 254 (64.0 mg, 54.96%) as a yellow solid.

LC-MS:(ES, m/z):[M+H]+ 533, H-NMR:(400 MHz, DMSO-d6, δ ppm):3.23(s, 3H), 3.41 (s, 2H), 4.90-4.96(m, 4H),7.21(s, 1H),7.60-7.63(m, 2H),7.99(s, 1H),8.06(s, 1H),8.24-8.26(m, 2H).

Example 255. Synthesis of Compound 255



1. Synthesis of 255a

[899] To a stirred solution of M-bromophenylacetic acid (100 g, 465.017 mmol, 1 equiv) in THF (700 mL) was added i-PrMgBr (511.52 mL, 511.52 mmol, 1.1 equiv) dropwise at 0°C under nitrogen atmosphere. To the above mixture was added epichlorohydrin (64.54 g, 697.525 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for additional 45min at 0°C. To the above mixture was added i-PrMgBr (511.52 mL, 511.52 mmol, 1.1 equiv, 1M) dropwise at 0°C. The resulting mixture was slowly heated to at 60°C and stirred for 16h. The reaction was quenched with saturated NH4Cl (aq.) (3.5 L) at room temperature. The aqueous layer was extracted with EtOAc (3x1 L). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 220 nm. This resulted in 255a (34 g, 21.58%) as a colorless

oil.

2. Synthesis of 255b

[900] To a stirred solution of 255a (16 g, 59.017 mmol, 1 equiv) and CH3I (25.13 g, 177.051 mmol, 3 equiv) in DMF (200 mL) were added K2CO3 (24.47 g, 177.051 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (2x500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 20% to 70% gradient in 20 min; detector, UV 220 nm. This resulted in 255b (1.4 g, 7.90%) as an off-white solid.

3. Synthesis of 255c

[901] To a stirred solution of 255b (1.4 g, 4.910 mmol, 1 equiv) in EtOH (20 mL) was added hydrazine hydrate (98%)(2.46 g, 49.100 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for overnight at 90°C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with DCM/MeOH=10:1 (2x20 mL). The resulting mixture was concentrated under vacuum. This resulted in 255c (1.2 g, 78.86%) as a light yellow solid.

4. Synthesis of 255d

[902] To a stirred solution of 255c (1.2 g, 4.208 mmol, 1 equiv) in tetrahydrofuran (15 mL) was added methyl isothiocyanate (0.77 g, 10.520 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with DCM/MeOH=10:1 (3x20 mL). The resulting mixture was concentrated under vacuum. This resulted in 255d (1.5 g, 99.49%) as an off-white solid.

5. Synthesis of 255e

[903] To a stirred solution of NaOH (1.34 g, 33.496 mmol, 8 equiv) in H2O (35 mL) was added 255d (1.5 g, 4.187 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 6 with HCl (aq.). The aqueous layer was extracted with DCM/MeOH=10:1 (2x20 mL). The resulting mixture was concentrated under vacuum. This resulted in 255e (1.5 g, 94.76%) as an off-white solid.

6. Synthesis of 255f

[904] To a stirred solution of 255e (1.5 g, 4.409 mmol, 1 equiv) and NaNO2 (3.04 g, 44.090 mmol, 10 equiv) in H2O (20 mL) was added HNO3 (44.09 mL, 44.090 mmol, 10 equiv, 1M)

dropwise at 0°C. The resulting mixture was stirred for overnight at room temperature. The mixture was basified to pH 7 with NaHCO3 (aq.). The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under vacuum. This resulted in 255f (1.3 g, 86.11%) as a light yellow solid.

7. Synthesis of 255g

[905] Into a 20mL pressure tank reactor was added 255f (500 mg, 1.622 mmol, 1 equiv), Cu2O (46.43 mg, 0.324 mmol, 0.2 equiv), NH3.H2O (5 mL) and MeCN (5 mL) at room temperature. The resulting mixture was stirred overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 255g (350 mg, 79.47%) as a brown light solid.

8. Synthesis of 255h

[906] To a stirred solution of 255g (350 mg, 1.433 mmol, 1 equiv) and I-2(533.22 mg, 1.863 mmol, 1.3 equiv) in DCE (8 mL) was added NaBH(OAc)3 (607.28 mg, 2.866 mmol, 2 equiv) and HOAc (8.60 mg, 0.143 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 255h (550 mg, 70.87%) as a yellow solid.

9. Synthesis of 255i

[907] To a stirred solution of 255h (550 mg, 1.069 mmol, 1 equiv) and 1H-imidazole (363.80 mg, 5.345 mmol, 5 equiv) in THF (20 mL) was added TBSCl (483.27 mg, 3.207 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 70°C. The reaction was quenched with water (80 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 255i (500 mg, 70.67%) as an off-white solid.

10. Synthesis of 255j

[908] To a stirred solution of 255i (500 mg, 0.795 mmol, 1 equiv) and Pyridine (628.92 mg, 7.950 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (117.96 mg, 0.398 mmol, 0.50 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under vacuum. The crude product was used in the next

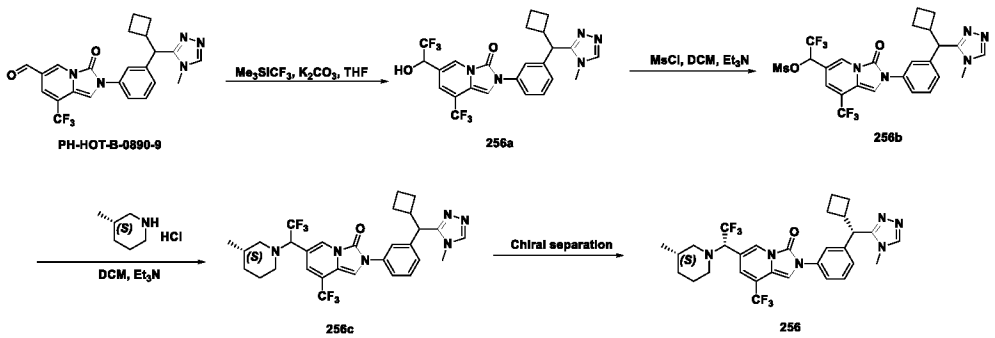
step directly without further purification. This resulted in 255j (400 mg, 69.14%) as a yellow solid.

11. Synthesis of 255

[909] To a stirred solution of 255j (380 mg, 0.580 mmol, 1 equiv) and H2O (6 mL, 2.900 mmol) in THF (2 mL) was added HCl (2 mL, 1M) at room temperature. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 9 min, Wave Length: 220 nm; RT1(min): 8.27) to afford 255 (225.8 mg, 71.26%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 541. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.39-1.41 (m, 1H), 1.41-1.65 (m, 4H), 1.85-1.91 (m, 1H), 2.73-2.78 (m, 4H), 3.05-3.10 (m, 2H), 3.22 (s, 3H), 3.24 (s, 2H), 4.27-4.32 (m, 1H), 5.30-5.32 (d, 1H), 6.99 (s, 1H), 7.23-7.25 (d, 1H), 7.38 (s, 1H), 7.46-7.50 (m, 1H), 7.64-7.66 (m, 2H), 7.80 (s, 1H), 8.29 (s, 1H).

Example 256. Synthesis of Compound 256



1. Synthesis of 256a

[910] To a stirred mixture of 247c (6 g, 13.174 mmol, 1 equiv) and K2CO3 (0.18 g, 1.317 mmol, 0.1 equiv) in THF (120 mL) was added TMSCF3 (3.75 g, 26.348 mmol, 2 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCNin water(10 mmol/L NH4HCO3), 10% to 65% gradient in 30 min; detector, UV 254 nm. This resulted in 256a (570 mg, 8.23%) as a yellow solid.

2. Synthesis of 256b

[911] To a stirred solution of 256a (570 mg, 1.085 mmol, 1 equiv) and Et3N (219.54 mg, 2.170 mmol, 2 equiv) in DCM (5 mL) was added MsCl (149.10 mg, 1.302 mmol, 1.2 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at 0 °C. The resulting mixture was concentrated under reduced pressure. This resulted in 256b (660 mg, crude) as a yellow solid.

3. Synthesis of 256c

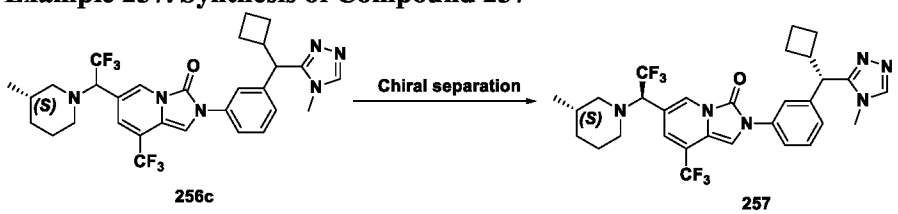
[912] To a stirred mixture of 256b (660 mg, 1.094 mmol, 1 equiv) and (3S)-3-methylpiperidine hydrochloride (296.66 mg, 2.188 mmol, 2 equiv) in DCM (5 mL) was added Et3N (331.98 mg, 3.282 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CH2Cl2 (3 x 15mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 256c (140 mg, 21.10%) as a yellow solid.

4. Synthesis of 256

[913] 256c (220 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 11.3 min; Wave Length: 220/254 nm; RT1(min): 8.02; RT2(min): 11.04; first peak is product) to afford crude product (84 mg, 38.18%) as a yellow solid. Crude product (84 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.26; RT2(min): 11.22; first peak is product) to afford 256 (17 mg, 20.24%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 607. H-NMR: (400 MHz, CD3OD, δ ppm): 0.89-0.97 (m, 5H), 1.53-1.55 (m, 1H), 1.67-1.80 (m, 5H), 1.91-1.94 (m, 5H), 2.14-2.17 (m, 1H), 2.25-2.27 (m, 1H), 2.31-2.40 (m, 1H), 2.92-2.98 (m, 2H), 3.53 (s, 3H), 4.29-4.33 (m, 2H), 7.07 (s, 1H), 7.18 (s, 1H), 7.27-7.29 (d, 1H), 7.48-7.52 (t, 1H), 7.67-7.69 (m, 2H), 7.79 (s, 1H), 8.32 (s, 1H).

Example 257. Synthesis of Compound 257



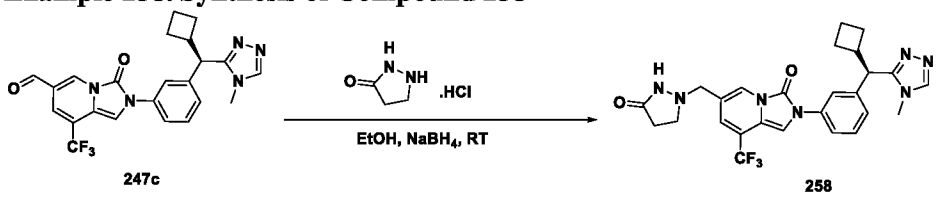
256c 257

Synthesis of 257

[914] 256c (220 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 113 min; Wave Length: 220/254 nm; RT1(min): 8.02; RT2(min): 11.04; first peak is product) to afford crude product(84 mg) as a yellow solid. Crude product(84 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.26; RT2(min): 11.22; second peak is product) to afford 257 (22 mg, 26.19%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]- 605. H-NMR: (400 MHz, CD3OD, δ ppm): 0.89-0.97 (m, 5H), 1.61-1.78 (m, 6H), 1.88-1.93 (m, 5H), 2.06-2.08 (m, 1H), 2.25-2.27 (m, 1H), 2.34-2.43 (m, 1H), 2.89-2.9t (m, 2H), 3.50 (s, 3H), 4.28-4.33 (m, 2H), 7.07 (s, 1H), 7.18 (s, 1H), 7.27-7.29 (d, 1H), 7.48-7.52 (t, 1H), 7.65-7.68 (m, 2H), 7.79 (s, 1H), 8.32 (s, 1H).

Example 258. Synthesis of Compound 258



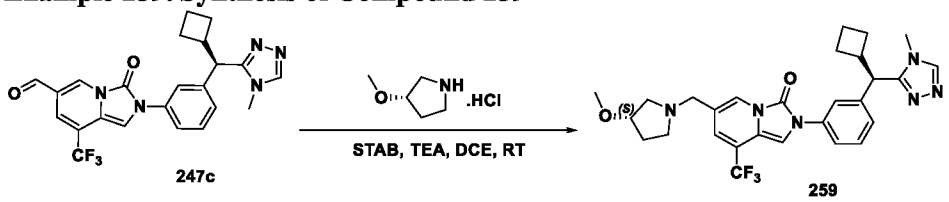
247c 258

Synthesis of 258

[915] A solution of 247c (400 mg, 0.878 mmol, 1 equiv) and pyrazolidin-3-one hydrochloride (215.26 mg, 1.756 mmol, 2 equiv) in EtOH (6 mL) was stirred overnight at room temperature under nitrogen atmosphere. To the above mixture was added NaBH4 (49.84 mg, 1.317 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for additional 1h at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford the crude product. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 46% B in 8 min, Wave Length: 220 nm; RT1(min): 7.73) to afford 258 (19.2 mg, 4.12%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 526. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.01-2.15 (m, 1H), 2.31-2.49 (m, 2H), 3.19-3.32 (m, 3H), 3.43 (s, 3H), 3.63 (s, 2H), 4.25-4.28 (d, 1H), 7.00 (s, 1H), 7.19-7.21 (d, 1H), 7.32 (s, 1H), 7.44-7.46 (m, 1H), 7.71-7.75 (m, 3H), 8.33 (s, 1H), 9.36 (s, 1H).

Example 259. Synthesis of Compound 259

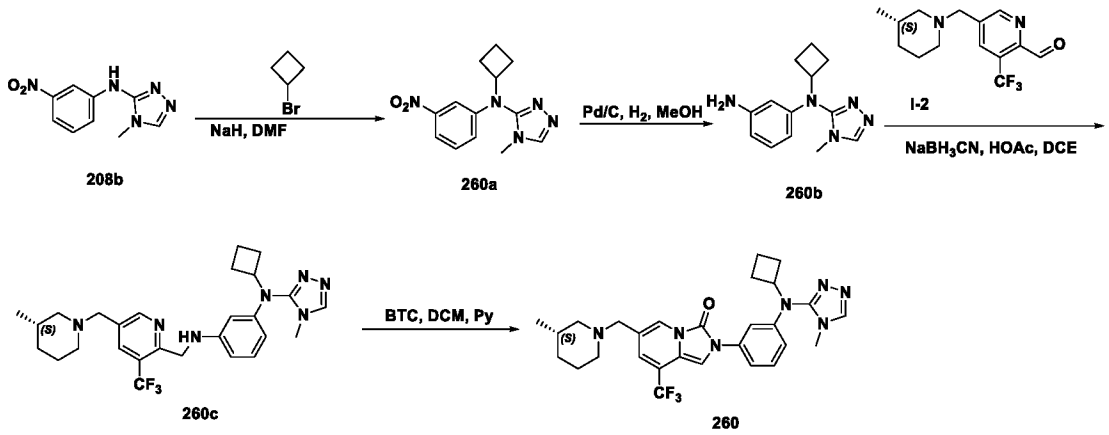


Synthesis of 259

[916] To a stirred solution of 247c (250 mg, 0.549 mmol, 1 equiv) and (3S)-3-methoxypyrrolidine hydrochloride (111.05 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) was added TEA (111.09 mg, 1.098 mmol, 2 equiv) in DCE (3 mL) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (232.68 mg, 1.098 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (89 mg) was purified by Prep-HPLC with the following conditions (Column: Kinetex EVO prep C18, 30*150, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 11 min, 40% B; Wave Length: 220 nm; RT1(min): 10.25) to afford 259 (66.6 mg, 21.26%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :541. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.60-1.72 (m, 2H), δ 1.73-1.85 (m, 4H), δ 1.93-2.15 (m, 2H), δ 2.51-2.53 (d, 2H), δ 2.52 (s, 1H), δ 2.54-2.57 (m, 1H), δ 2.71-2.73 (d, 1H), δ 3.16 (s, 3H), δ 3.21-3.23 (d, 1H), δ 3.35 (s, 1H), δ 3.52 (s, 2H), δ 3.58 (s, 3H), δ 3.85-3.87 (d, 1H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 2H), δ 7.72 (s, 1H), δ 8.33 (s, 1H).

Example 260. Synthesis of Compound 260



208b 260a 260b

260c 260

1. Synthesis of 260a

[917] Into a 100mL 3-necked round-bottom flask were added 208b (700 mg, 1.597 mmol, 1 equiv) in DMF (8 mL) and NaH (191.58 mg, 4.791 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for 1h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (646.68 mg, 4.791 mmol, 3 equiv). The resulting mixture was stirred for additional overnight at 80°C. The reaction was quenched by the addition of NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 260a (250 mg, 28.65%) as white solid.

2. Synthesis of 260b

[918] To a solution of 260a (240 mg, 0.878 mmol, 1 equiv) in MeOH (6 mL) was added Pd/C (50 mg, 10%) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere by using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 260b (210 mg, 98.28%) as white solid.

3. Synthesis of 260c

[919] Into a 8 mL sealed tube were added 260b (200 mg, 0.822 mmol, 1 equiv) and I-2 (282.40 mg, 0.986 mmol, 1.2 equiv) in DCE (3 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added NaBH(OAc)3 (261.72 mg, 1.233 mmol, 1.5 equiv) and HOAc (49.36 mg, 0.822 mmol, 1 equiv). The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (4x20 mL). The resulting mixture

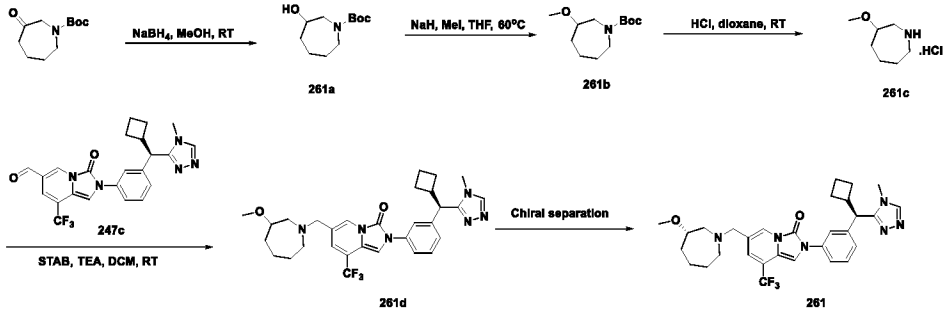
was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 260c (160 mg, 37.90%) as yellow oil.

4. Synthesis of 260

[920] To a stirred mixture 260c (150 mg, 0.292 mmol, 1 equiv) and Pyridine (138.61 mg, 1.752 mmol, 6 equiv) in DCM (6 mL) was added triphosgene (30.33 mg, 0.102 mmol, 0.35 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 260 (60.6 mg, 38.45%) as a yellow solid

LC-MS: (ES, m/z): [M+H] + 540. H-NMR: (400 MHz, DMSO, δ ppm): 0.77-0.91 (m, 4H), 1.38-1.51 (m, 1H), 1.55-1.73 (m, 6H), 1.77-1.91 (m, 3H), 2.27-2.29 (m, 2H), 2.72-7.74 (m, 2H), 3.24 (s, 2H), 3.40 (s, 3H), 4.47-4.51 (t, 1H), 6.44-6.47 (m, 1H), 6.99 (s, 1H), 7.19-7.20 (m, 2H), 7.27 (s, 1H), 7.31-7.35 (m, 1H), 7.65 (s, 1H), 8.58 (s, 1H).

Example 261. Synthesis of Compound 261



1. Synthesis of 261a

[921] Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl 3-oxoazepane-1-carboxylate (5.2 g, 24.381 mmol, 1 equiv), MeOH (60 mL), NaBH4 (1844.70 mg, 48.762 mmol, 2 equiv). The resulting solution was stirred for 2 hr at 25 degrees C. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and concentrated under vacuum. This resulted in 261a (5.2 g, 88.17%) as a brown soild.

2. Synthesis 261b

[922] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 261a (2.8 g, 13.006 mmol, 1 equiv), THF (30 mL), NaH (936.32 mg, 39.018 mmol, 3 equiv). The resulting solution was stirred for 1 hr at room temperature. To the above mixture was added CH3I (5537.98 mg, 39.018 mmol, 3 equiv).

The resulting solution was stirred for 2 hr at 60 degrees C. The reaction was then quenched by the addition of 100 mL of NH4Cl. The resulting solution was extracted with 3x100 mL of ethyl acetate and concentrated under vacuum. This resulted in 261b (2.5 g, 77.12%) as a white solid.

3. Synthesis of 261c

[923] Into a 250-mL 3-necked round-bottom flask was placed 261b (2.5 g, 10.902 mmol, 1 equiv), dioxane (30 mL), HCl in dioxane (3 mL). The resulting solution was stirred for 2 hr at 25 degrees C. The reaction solution was concentrated under vacuum. This resulted in 261c(3 g, crude) as a yellow oil.

4. Synthesis of 261d

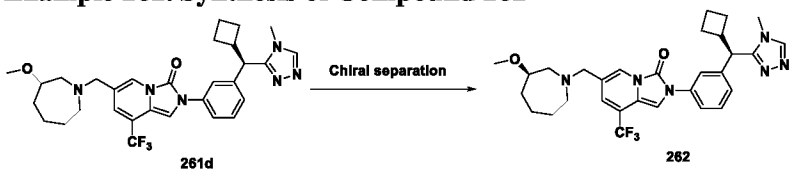
[924] To a stirred mixture of 261c (436.48 mg, 2.634 mmol, 2 equiv) and 247c (600 mg, 1.317 mmol, 1.00 equiv) in DCE (6 mL) was added Et3N (399.94 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added NaBH(OAc)3 (837.63 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4 h at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by TLC with CH2Cl2/MeOH =15:1 to afford the crude product (300 mg) as a yellow solid. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 66% B in 8 min, 66% B; Wave Length: 220 nm; RT1(min): 7.58) to afford 261d (120 mg, 15.38%) as a yellow solid.

5. Synthesis of 261

[925] 261d (120 mg, 0.211 mmol, 1 equiv) was separated by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 11 min; Wave Length: 220/254 nm; RT1(min): 6.78; RT2(min): 9.06; the first peak was product) to afford 261 (43.2 mg, 35.42%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.38-1.52 (m, 1H), 1.52-1.65 (m, 4H), 1.65-1.84 (m, 6H), 2.05-2.15 (m, 1H), 2.62-2.72 (m, 3H), 2.80-2.88 (m, 1H), 3.14 (s, 3H), 3.14-3.29 (m, 1H), 3.29-3.30 (m, 1H), 3.43 (s, 3H), 3.43-3.47 (m, 2H), 4.25-4.27 (d, 1H), 7.08 (s, 1H),7.18-7.20 (d, 1H),7.30(s, 1H),7.42-7.46(t, 1H),7.68-7.74 (m, 3H), 8.32 (s, 1H).

Example 262. Synthesis of Compound 262

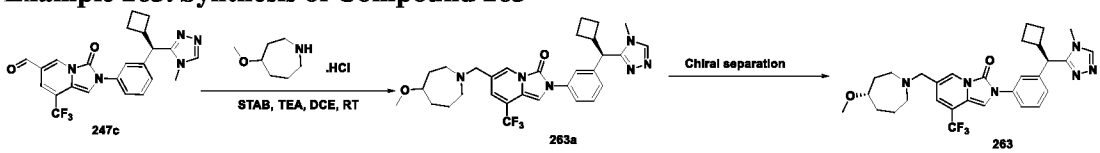


Synthesis of 262

[926] 261d (120 mg) was separated by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 11 min; Wave Length: 220/254 nm; RT1 (min): 6.78; RT2 (min): 9.06; the second peak was product) to afford 262 (43.6 mg, 36.22%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.38-1.52 (m, 1H), 1.52-1.65 (m, 4H), 1.65-1.88 (m, 6H), 2.08-2.12 (m, 1H), 2.52-2.72 (m, 3H), 2.78-2.79 (m, 1H), 3.14 (s, 3H), 3.14-3.28 (m, 2H) 3.43-3.47 (m, 5H), 4.25-4.27 (d, 1H), 7.07 (s, 1H), 7.18-7.20 (d, 1H), 7.30 (d, 1H), 7.42-7.46 (t, 1H), 7.69-7.75 (m, 3H), 8.33 (s, 1H).

Example 263. Synthesis of Compound 263



1. Synthesis of 263a

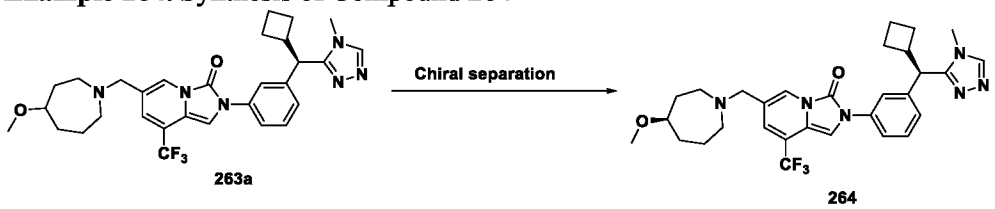
[927] To a stirred mixture of 4-methoxyazepane hydrochloride (436.48 mg, 2.634 mmol, 2 equiv) and 247c (600 mg, 1.317 mmol, 1.00 equiv) in DCE (6 mL) was added Et3N (399.94 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added NaBH(OAc)3 (837.63 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4 h at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH=15:1 to afford the crude product (400 mg) as a yellow solid. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 60% B in 7 min, 60% B; Wave Length: 220 nm; RT1 (min): 7.60) to afford 263a (170 mg, 21.79%) as a yellow solid.

2. Synthesis of 263

[928] 263a (170 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 8.20; RT2(min): 13.40; the first peak was product) to afford 263 (33.5 mg, 19.47%) as a yellow solid.

LCMS (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.38-1.52 (m, 1H), 1.52-1.90 (m, 11H), 2.04-2.15 (m, 1H), 2.55-2.72 (m, 3H), 3.19-3.27 (m, 4H), 3.39-3.43 (m, 6H), 4.25-4.27 (d, 1H), 7.03 (s, 1H), 7.20-7.20 (d, 1H), 7.30 (s, 1H), 7.44-7.46 (t, 1H), 7.67-7.74 (m, 3H), 8.32 (s, 1H).

Example 264. Synthesis of Compound 264

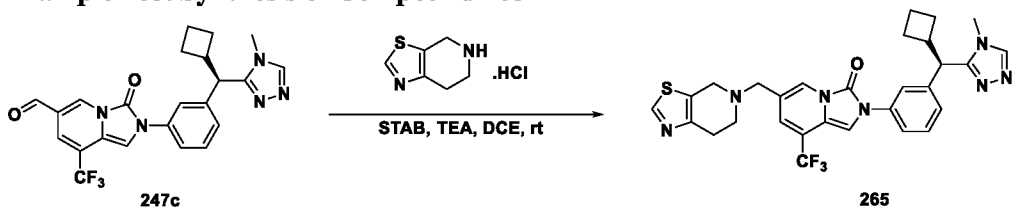


1. Synthesis of 264

[929] 263a (170 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 8.20; RT2(min): 13.40; the second peak is product) to afford 264 (33.3 mg, 19.45%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.38-1.52 (m, 1H), 1.52-1.87 (m, 11H), 2.04-2.15 (m, 1H), 2.55-2.72 (m, 3H), 3.19-3.27 (m, 4H), 3.39-3.43 (m, 6H), 4.25-4.27 (d, 1H), 7.03 (s, 1H), 7.20-7.20 (d, 1H), 7.30 (s, 1H), 7.44-7.46 (t, 1H), 7.67-7.74 (m, 3H), 8.32 (s, 1H).

Example 265. Synthesis of Compound 265



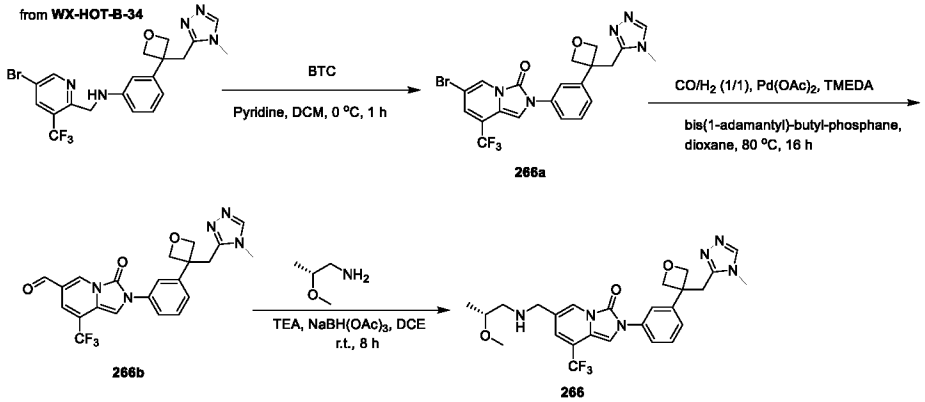
Synthesis of 265

[930] Into a 50mL 3-necked round-bottom flask were added 4H,5H,6H,7H-[1,3]thiazolo[5,4-c]pyridine hydrochloride (116.37 mg, 0.659 mmol, 1 equiv), 247c (300 mg,

0.659 mmol, 1.00 equiv), TEA (199.97 mg, 1.977 mmol, 3 equiv) and DCE (3 mL) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (418.82 mg, 1.977 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with water(10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 51% B in 8 min, 51% B; Wave Length: 220 nm; RT1(min): 7.73) to afford 265.

H-NMR: (400 MHz, DMSO-d6, ppm, δ): δ1.62-1.86 (m, 5H), δ2.11-2.12 (d, 1H), δ2.82-2.88 (m, 4H), δ3.18-3.25 (m, 1H), δ3.43 (s, 3H), δ3.53(s, 2H), δ3.77 (s, 2H), δ4.25-4.28 (d, 1H), δ7.07 (s, 1H), δ7.19-7.21 (d, 1H), δ7.32 (s, 1H), δ7.42-7.46 (t, 1H), δ7.69-7.75 (m, 3H), δ8.33 (s, 1H), δ8.91 (s, 1H).

Example 266. Synthesis of Compound 266



1. Synthesis of 266a

[931] To a solution of N-[[5-bromo-3-(trifluoromethyl)-2-pyridyl]methyl]-3-[3-[(4-methyl-1,2,4-triazol-3-yl)methyl]oxetan-3-yl]aniline (7 g, 14.51 mmol, 1 eq) in DCM(60 mL) was added Py (5.74 g, 72.57 mmol, 5.86 mL, 5 eq) at 0 oC. Then a solution of TRIPHOSGENE (4.98 g, 16.78 mmol, 1.16 eq) in DCM(10 mL) was slowly added under N2. The mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched by addition of a.q. NaHCO3 50 mL at 0 °C, then extracted with DCM 300 mL (100 mL * 3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH=50/1 to 0/1) to give 266a (2.8 g, 5.51 mmol, 37% yield) as a red solid.

2. Synthesis of 266b

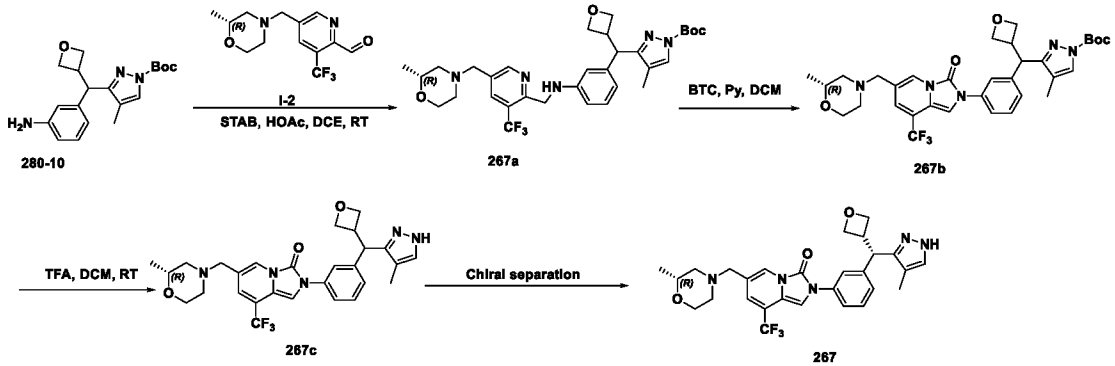
[932] To a solution of 266a (1.8 g, 3.54 mmol, 1 eq) in dioxane (72 mL) was added Pd(OAc)2 (159.01 mg, 708.26 umol, 0.2 eq), TMEDA (823.06 mg, 7.08 mmol, 1.07 mL, 2 eq) and bis(1-adamantyl)-butyl-phosphane (253.94 mg, 708.26 umol, 0.2 eq). The mixture was stirred at 80 °C for 16 hr under CO/H2(v/v=1/1). The reaction was then cooled to room temperature and poured into water (250 mL), extracted with EtOAc (3 *50 mL). The combined organic layers were combined and then concentrated. The residue was purified by column chromatography (Al2O3, DCM/MeOH=100/1 to 20/1) to give 266b (0.86 g, 1.88 mmol, 53% yield) as a yellow solid.

3. Synthesis of 266

[933] To a solution of (2R)-2-methoxypropan-1-amine (82.38 mg, 655.87 umol, HCl, 3 equiv) and 266b (0.1 g, 218.62 umol, 1 equiv) in DCE (0.5 mL) was added TEA (88.49 mg, 874.50 umol, 121.72 uL, 4 equiv). The mixture was stirred at 20 °C for 1 hr. Then it was added NaBH(OAc)3 (92.67 mg, 437.25 umol, 2 equiv) under N2. The mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched by the addition of water (10 mL) and extracted with EtOAc (2 *20 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water(FA)-ACN];B%: 20%-50%, 8 min) to afford 266 (20 mg, 37.70 umol, 17.2% yield) as a yellow solid.

MS: (ES, m/z): [M+H]+ 531.2. H-NMR: (400 MHz, DMSO-d6) δ 8.31 (s, 1 H), 8.16 (s, 1 H), 7.75 (s, 1 H), 7.62 (d, J = 8.4 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.28 (s, 1 H), 7.22 (s, 1 H), 7.14 (s, 1 H), 6.90 (d, J = 8 Hz, 1 H), 4.94 (d, J = 6 Hz ,2 H), 4.88 (d, J = 5.2 Hz ,2 H), 3.67 (s, 2 H), 3.51 (s, 2 H), 3.46-3.43 (m, 1 H), 3.22 (s, 3 H), 2.91 (s, 3 H), 2.62-2.66 (m, 2 H), 1.05 (d, J = 6. Hz, 3 H).

Example 267. Synthesis of Compound 267



1. Synthesis of 267a

[934] To a stirred solution of 280-10 (300 mg, 0.874 mmol, 1 equiv) and I-2 (327.36 mg, 1.136 mmol, 1.3 equiv) in DCE (5 mL) was added STAB (370.28 mg, 1.748 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 267a (300 mg, 51.87%) as a white solid.

2. Synthesis of 267b

[935] To a stirred solution of 267a (280 mg, 0.455 mmol, 1 equiv) and Pyridine (359.72 mg, 4.550 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (67.47 mg, 0.228 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 267b (200 mg, 61.68%) as a yellow solid.

3. Synthesis of 267c

[936] To a stirred solution of 267b (190 mg, 0.296 mmol, 1 equiv) in DCM (6 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred for 1h at room temperature. The resulting mixture was concentrated under vacuum. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 51% B in 8 min, Wave Length: 220 nm; RT1(min): 7.78) to afford 267c (110 mg, 67.23%) as a yellow solid.

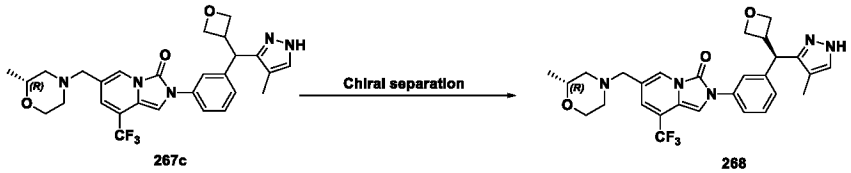
4. Synthesis of 267

[937] 267c (110 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK OD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 22 min; Wave Length: 220/254 nm; RT1(min): 13.69; RT2(min): 19.09; the first peak is product) to afford 267 (28.4 mg, 25.64%) as a yellow solid.

LC-MS-267: (ES, m/z): [M+H]+ 542. H-NMR-267 (400 MHz, CD3OD, δ ppm): 1.14-1.15 (d, 3H), 1.76 (s, 3H), 1.91-2.01 (m, 1H), 2.20-2.31 (m, 1H), 2.78-2.87 (m, 2H), 3.05-3.15 (m, 1H), 3.40 (s, 2H), 3.65-3.71 (m, 2H), 3.79-3.81 (m, 2H), 3.86-3.89 (m, 1H), 4.02-4.06 (m,

1H), 4.32-4.34 (d, 1H), 4.38-4.42 (m, 1H), 7.11 (s, 1H), 7.16 (s, 1H), 7.25-7.27 (d, 1H), 7.34 (s, 1H), 7.52-7.56 (m, 1H), 7.64-7.66 (m, 2H), 7.71 (s, 1H).

Example 268. Synthesis of Compound 268

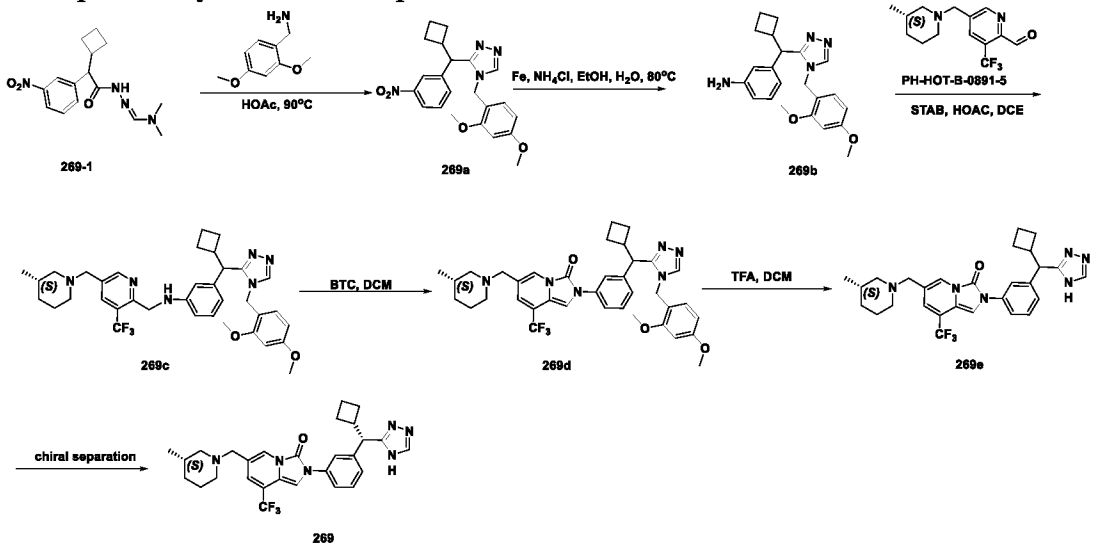


Synthesis of 268

[938] 267c (110 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK OD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 22 min; Wave Length: 220/254 nm; RT1(min): 13.69; RT2(min): 19.09; the second peak is product) to afford 268 (26.6 mg, 24.01%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 542. H-NMR: (400 MHz, CD3OD, δ ppm): 1.15-1.17 (d, 3H), 1.76 (s, 3H), 1.94-2.08 (m, 1H), 2.24-2.31 (m, 1H), 2.85-2.93 (m, 2H), 3.06-3.11 (m, 1H), 3.47 (s, 2H), 3.67-3.73 (m, 2H), 3.79-3.81 (m, 2H), 3.88-3.91 (m, 1H), 4.02-4.06 (m, 1H), 4.33-4.34 (d, 1H), 4.38-4.42 (m, 1H), 7.11 (s, 1H), 7.17 (s, 1H), 7.25-7.27 (d, 1H), 7.35 (s, 1H), 7.52-7.56 (m, 1H), 7.64-7.66 (m, 2H), 7.74 (s, 1H).

Example 269. Synthesis of Compound 269



1. Synthesis of 269a

[939] A mixture of 261-1 (3 g, 9.857 mmol, 1 equiv) and 1-(2,4-dimethoxyphenyl)methanamine (4.12 g, 24.642 mmol, 2.5 equiv) in HOAc (30 mL) was stirred for overnight at 90°C. The mixture was basified to pH 7 with saturated NaHCO3 (aq.).

The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: C18 silica gel 330 g; mobile phase, MeCN in 0.1% NH4HCO3 water, 20% to 50% gradient in 15 min; detector, UV 254 nm to afford PH-BOT-B-1302-1 (560 mg, 13.35%) as a colorless oil.

2. Synthesis of 269b

[940] To a stirred mixture of 269a (560 mg, 1.420 mmol, 1 equiv) and Fe (237.86 mg, 4.260 mmol, 3 equiv) in EtOH (6 mL) was added NH4Cl (379.72 mg, 7.100 mmol, 5 equiv) in H2O (1.5 mL) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The aqueous layer was extracted with EA (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 5:1) to afford 269b (290 mg, 51.81%) as a yellow solid.

3. Synthesis of 269c

[941] Into a 100 mL round-bottom flask were added 269b (290 mg, 0.766 mmol, 1 equiv), DCE (5 mL), I-2(219.37 mg, 0.766 mmol, 1 equiv), HOAC (46.01 mg, 0.766 mmol, 1 equiv) and STAB (324.79 mg, 1.532 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH2Cl2 / MeOH (12:1) to afford 269c (200 mg, 40.23%) as a light yellow solid.

4. Synthesis of 269d

[942] Into a 100 mL round-bottom flask were added 269c (200 mg, 0.308 mmol, 1 equiv), DCE (5 mL), Pyridine (146.31 mg, 1.848 mmol, 6 equiv) and Triphosgene (32.02 mg, 0.108 mmol, 0.35 equiv) at room temperature. The resulting mixture was stirred for 5 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Pep-TLC eluted with CH2Cl2 / MeOH (10:1) to afford 269d (90 mg, 43.27%) as a light yellow solid.

5. Synthesis of 269e

[943] Into a 8 mL sealed tube were added 269d (90 mg, 0.133 mmol, 1 equiv), DCM (1.5 mL) and TFA (0.3 mL) at room temperature. The resulting mixture was stirred for 2 h at

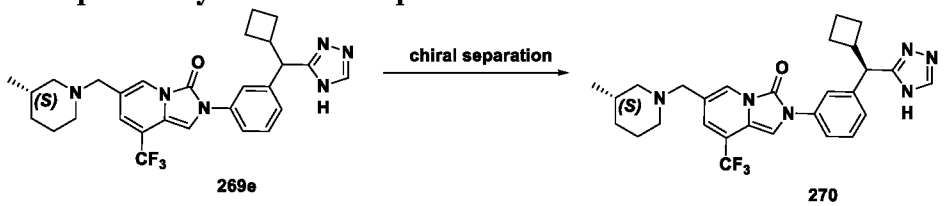
room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH2Cl2 / MeOH (10:1) to afford 269e (40 mg, 57.17%) as a light yellow solid.

6. Synthesis of 269

[944] 269e (40 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 8 min; Wave Length: 220/254 nm; RT1(min): 5.66; RT2(min): 7.25; The first peak was the product. Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.55 mL; Number of Runs: 4) to afford 269 (11.7 mg, 29.25%) as a light yellow solid.

H-NMR: 1H NMR (300 MHz, CD3OD-d4) δ 0.90-0.94 (m, 4H), 1.60-2.10 (m, 12H), 2.86-2.92 (m, 2H), 3.25-3.28 (m, 1H), 3.32-3.34 (m, 2H), 4.22-4.25 (d, 1H), 7.13-7.16 (d, 2H), 7.34-7.36 (d, 1H), 7.45-7.49 (m, 1H), 7.61-7.62 (d, 1H), 7.64-7.68 (d, 2H), 8.21 (s, 1H).

Example 270. Synthesis of Compound 270

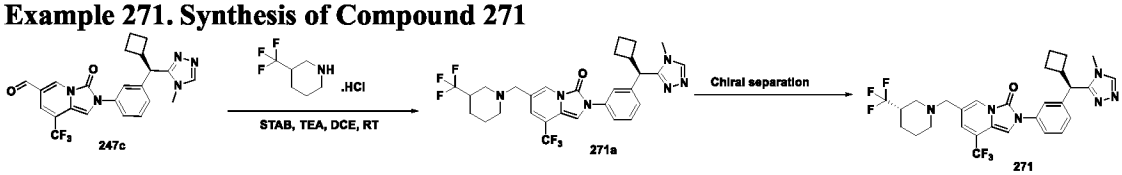


Synthesis of 270

[945] 269e (40 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 8 min; Wave Length: 220/254 nm; RT1(min): 5.66; RT2(min): 7.25; The second peak was the product. Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.55 mL; Number of Runs: 4) to afford 270 (11.9 mg, 29.75%) as a light yellow solid.

H-NMR-270 1H NMR (300 MHz, CD3OD-d4) δ 0.91-0.95 (m, 4H), 1.61-2.11 (m, 12H), 2.86-2.92 (m, 2H), 3.25-3.28 (m, 1H), 3.32-3.34 (m, 2H), 4.22-4.25 (d, 1H), 7.13-7.16 (d, 2H), 7.34-7.36 (d, 1H), 7.45-7.49 (m, 1H), 7.61-7.62 (d, 1H), 7.64-7.68 (d, 2H), 8.23 (s, 1H).

Example 271. Synthesis of Compound 271



1. Synthesis of 271a

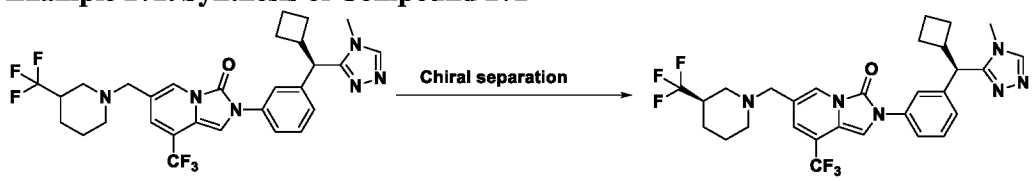
[946] To a stirred solution of 247c (500 mg, 1.098 mmol, 1.00 equiv) and 3-

(trifluoromethyl)piperidine hydrochloride (416.32 mg, 2.196 mmol, 2 equiv) in DCE (6 mL) were added TEA (222.19 mg, 2.196 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (465.35 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (15 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 25mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 70% B in 7 min, Wave Length: 220 nm; RT1(min): 6.44) to afford 271a (210 mg, 30.99%) as a yellow solid.

2. Synthesis of 271

[947] 271a (300mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 17 min; Wave Length: 220/254 nm; RT1(min): 11.23; RT2(min): 14.24; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.3 mL; Number of Runs: 11). This resulted in 271 (61.2 mg, 28.62%) as a yellow solid.
LC-MS: (ES, m/z): [M+H] + :593. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.21-1.27 (m, 2H) δ 1.45-1.52 (m, 1H), δ 1.63-1.89 (m, 8H), δ 1.92-2.14 (m, 3H), δ 2.80 (s, 1H), δ 2.97 (s, 1H), δ 3.25 (s, 1H), δ 3.46 (s, 4H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 3H), δ 8.35 (s, 1H).

Example 272. Synthesis of Compound 272



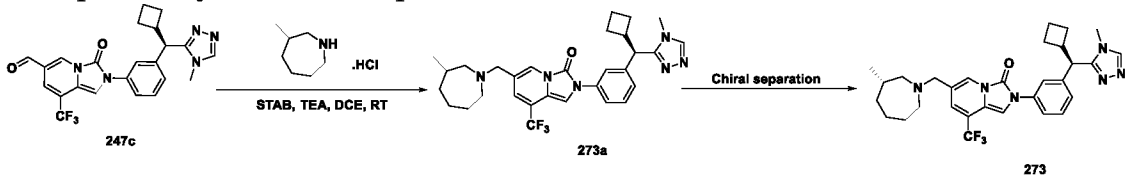
271a 272

Synthesis of 270

[948] 271a (300mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 17 min; Wave Length: 220/254 nm; RT1(min): 11.23; RT2(min): 14.24; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume:

0.3 mL; Number of Runs: 11). This resulted in 272 (65.5 mg, 30.88%) as a yellow solid. LC-MS: (ES, m/z): [M+H] + :593. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.21-1.27 (m, 2H) δ 1.45-1.52 (m, 1H), δ 1.63-1.89 (m, 8H), δ 1.92-2.14 (m, 3H), δ 2.80 (s, 1H), δ 2.97 (s, 1H), δ 3.25 (s, 1H), δ 3.46 (s, 4H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 3H), δ 8.35 (s, 1H).

Example 273. Synthesis of Compound 273



1. Synthesis of 273a

[949] To a stirred mixture of 3-methylazepane hydrochloride (394.33 mg, 2.634 mmol, 2 equiv) and 247c (600 mg, 1.317 mmol, 1.00 equiv) in DCE (6 mL) was added Et3N (399.94 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added NaBH(OAc)3 (837.63 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4 h at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC with CH2Cl2/MeOH=15:1 to afford the crude product (400 mg) as a yellow solid. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 62% B to 87% B in 8 min, 87% B; Wave Length: 220 nm; RT1(min): 7.77) to afford 273a (170 mg, 22.42%) as a yellow solid.

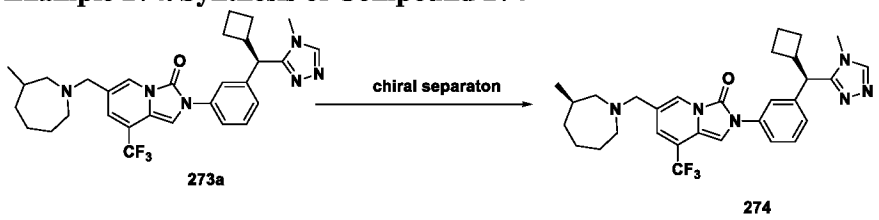
2. Synthesis of 273

[950] 273a (170 mg) was separated by Prep-SFC with the following conditions (Column: CHIRALPAK IG, 3*25 cm, 5 um; Mobile Phase A: CO2, Mobile Phase B: MeOH (0.1% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm; RT1 (min): 9.78; RT2 (min): 11.6; the first peak was product) to afford 273 (51.6 mg, 29.96%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 553. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.80 (s, 3H), 1.12-1.25 (m, 1H), 1.40-1.52 (m, 2H), 1.52-1.81 (m, 9H), 2.05-2.15 (m, 1H), 2.22-2.28 (m, 1H), 2.55-2.67 (m, 3H), 3.15-3.25 (m, 1H), 3.42-3.43 (m, 5H), 4.24-4.27 (d, 1H), 7.04 (s, 1H),

7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.70 (m, 2H), 7.74 (s, 1H), 8.32 (s, 1H).

Example 274. Synthesis of Compound 274

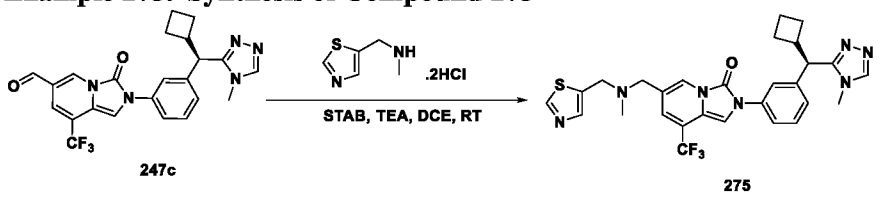


Synthesis of 274

[951] 273a (170 mg) was separated by Prep-SFC with the following conditions (Column: CHIRALPAK IG, 3*25 cm, 5 um; Mobile Phase A: CO2, Mobile Phase B: MeOH (0.1% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm; RT1 (min): 9.78; RT2 (min): 11.6; the second peak is product) to afford 274 (61.0 mg, 34.34%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 553. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.80 (s, 3H), 1.12-1.25 (m, 1H), 1.40-1.52 (m, 2H), 1.52-1.81 (m, 9H), 2.05-2.15 (m, 1H), 2.22-2.28 (m, 1H), 2.55-2.67 (m, 3H), 3.15-3.25 (m, 1H), 3.42-3.43 (m, 5H), 4.24-4.27 (d, 1H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.42-7.46 (t, 1H), 7.67-7.74 (m, 3H), 8.32 (s, 1H).

Example 275. Synthesis of Compound 275

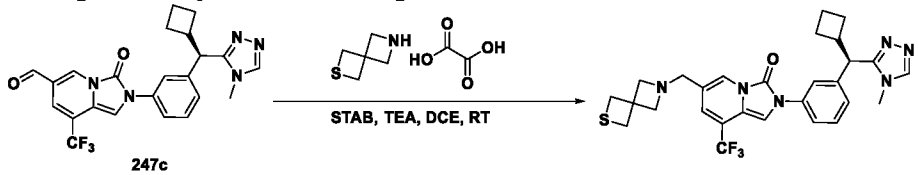


Synthesis of 275

[952] To a stirred solution of 247c (200 mg, 0.439 mmol, 1 equiv) and Methyl-thiazol-5-ylmethyl-amine dihydrochloride (175.65 mg, 0.878 mmol, 2 equiv) in DCE (5 mL) was added TEA (177.75 mg, 1.756 mmol, 4 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (186.14 mg, 0.878 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 275 (45.1 mg, 17.79%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 568. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.83 (m, 5H), 2.03-2.15 (m, 1H), 2.21 (s, 3H), 3.19-3.29 (m, 1H), 3.34 (s, 2H), 3.42 (s, 3H), 3.84 (s, 2H), 4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.79 (m, 3H), 7.80 (s, 1H), 8.32 (s, 1H), 9.04 (s, 1H).

Example 276. Synthesis of Compound 276



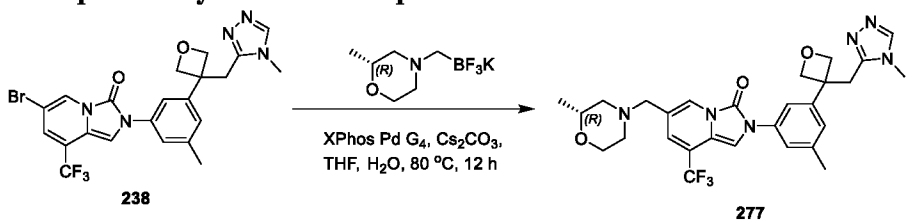
247c 276

Synthesis of 276

[953] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and 2-thia-6-azaspiro[3.3]heptane hemioxalate (405.10 mg, 1.977 mmol, 3 equiv) in DCE (5 mL) was added TEA (199.97 mg, 1.977 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: water(10 mmol/L NH4HCO3), B: MeCN, 50% B to 60% B gradient in 20 min; detector, UV 254 nm. This resulted in 276 (122.7 mg, 33.11%) as a yellow solid.

LC-MS-276 (ES, m/z): [M+H]+ 555. H-NMR-276 (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.03-2.15 (m, 1H), 3.21-3.25 (m, 5H), 3.28-3.32 (m, 6H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 6.94 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.62-7.74 (m, 3H), 8.33 (s, 1H).

Example 277. Synthesis of Compound 277



238 277

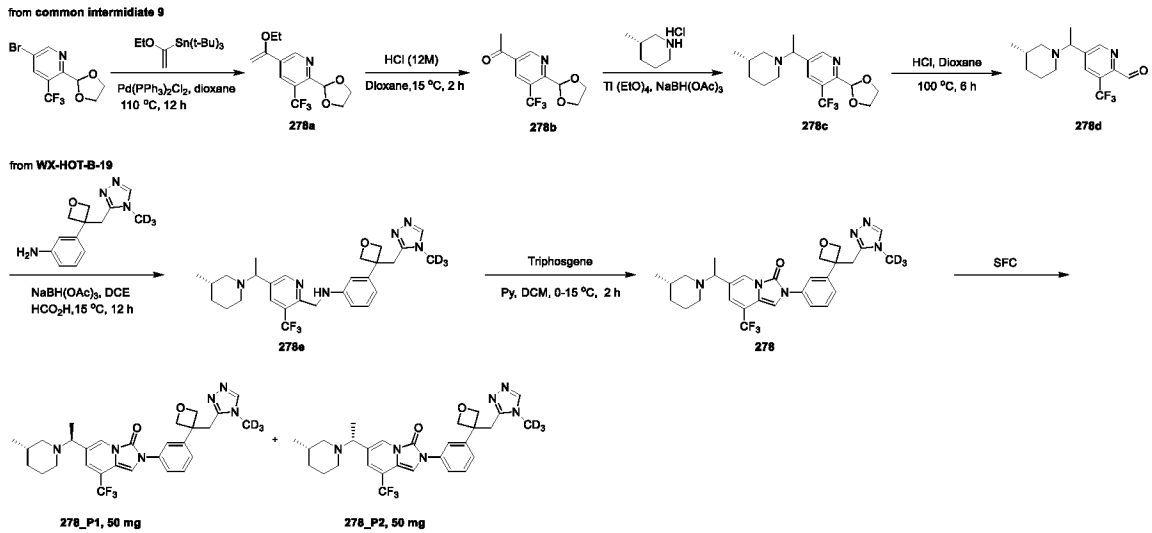
Synthesis of 277

[954] To a solution of 238 (210 mg, 402.05 umol, 1 equiv) and potassium hydride;trifluoro-

[[(2R)-2-methylmorpholin-4-yl]methyl]boron (177 mg, 804 umol, 2 equiv) in water (4 mL) and THF (16 mL) was added dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane ;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (34.6 mg, 40.2 umol, 0.1 equiv) and Cs2CO3 (393 mg, 1.21 mmol, 3 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was diluted with water (100 ml) and extracted with EtOAc (50 ml x3). The combined organic was dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 150*30mm*5um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 35 mL/min; Gradient: 1% B to 35% B in 8 min; Wave Length: 220 nm; RT (min): 8.0) to afford 277 (4.8 mg, 2%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 557.3. H-NMR: (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 7.67 (s, 1H), 7.56 (s, 1H), 7.28 (s, 1H), 7.21 (s, 1H), 7.01 (s, 1H), 6.71 (s, 1H), 4.94-4.88 (m, 4H), 3.78-3.70 (m, 1H), 3.51 (s, 2H), 3.49 (d, J = 2.0 Hz, 1H), 3.25 (d, J = 4.4 Hz, 2H), 2.98 (s, 3H), 2.74 (d, J = 10.8 Hz, 1H), 2.65 (d, J = 0.8 Hz, 1H), 2.43-2.37 (m, 1H), 2.29 (s, 3H), 2.09-2.02 (m, 1H), 1.74 (t, J = 10.4 Hz, 1H), 1.04 (d, J = 6.4 Hz, 3H)

Example 278. Synthesis of Compound 278_P1 & 278_P2



1. Synthesis of 278a

[955] A mixture of 5-bromo-2-(1,3-dioxolan-2-yl)-3-(trifluoromethyl)pyridine (10 g, 33.55 mmol, 1 equiv), tritert-butyl(1-ethoxyvinyl)stannane (13.33 g, 36.91 mmol, 1.1 equiv), Pd(PPh3)2Cl2 (1.18 g, 1.68 mmol, 0.05 equiv) in dioxane (100 mL) was degassed and

purged with N2 for 3 times, and then the mixture was stirred at 110 °C for 12 hr under N2 atmosphere. The reaction mixture was quenched by addition saturated KF 100 mL and stirred at r.t. for 1 hr under N2. Then it was diluted with H2O 500 mL and extracted with DCM (2*100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to give 278a (7 g, 24.20 mmol, 72.13% yield) as a yellow oil.

2. Synthesis of 278b

[956] A mixture of 278a (7 g, 24.20 mmol) in HCl (1 ml, 12 M) and dioxane (50 mL) was degassed and purged with N2 for 3 times, and then the mixture was stirred at r.t. for 2 hr under N2 atmosphere. The reaction mixture was quenched by addition Na2CO3 aq. 100 mL and extracted with DCM (2*250 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to give 278b (5 g, 19.14 mmol, 79.10% yield) as a yellow solid.

H-NMR-278b: (400 MHz, CDCl3): δ 9.25 (d, J=2 Hz, 1H), 8.44 (d, J=1.2 Hz, 1H), 6.25 (s, 1H), 4.27 (t, J=3.6 Hz, 2H), 3.08 (t, J=3.2 Hz, 2H), 2.62 (s, 3H).

3. Synthesis of 278c

[957] A mixture of 278b (2.5 g, 9.57 mmol, 1 equiv), (3S)-3-methylpiperidine (1.42 g, 14.36 mmol, 1.5 equiv), Ti(i-PrO)4 (10.88 g, 38.29 mmol, 4 equiv) in DCE (30 mL) was stirred at 80 °C for 6 hr under N2 atmosphere. Then it was cooled to room temperature and the reaction mixture was added NaBH(OAc)3 (6.09 g, 28.71 mmol, 3 equiv). The reaction mixture was heated to 80 °C and stirred at 80 °C for 6 hr. The reaction mixture was quenched by addition H2O 100 ml, filtered and the filtrate was extracted with DCM (2*200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to give 278c (1 g, 2.90 mmol, 30.34% yield) as a yellow solid.

H-NMR: (400 MHz, MeOD): δ 8.78 (s, 1H), 8.12 (s, 1H), 6.17 (s, 1H), 4.29-424 (m, 2H), 4.11-4.05 (m, 2H), 3.71 (d, J = 6.8 Hz, 1H), 2.94-2.92 (m, 1H), 2.73-2.60 (m, 1H), 1.93-1.69(m, 1H), 1.68-1.60(m, 6 H), 1.43 (dd, J = 6.8, 1.4 Hz, 3H), 0.88 (d, J = 6.00 Hz, 2H), 0.81 (d, J = 6.00 Hz, 1H)

4. Synthesis of 278d

[958] A mixture of 278c (1 g, 2.90 mmol, 1 equiv) in dioxane (4 mL) and HCl (4 ml, 4M) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 100 °C for 6 hr under N2 atmosphere. The reaction mixture was quenched by addition Na2CO3 aq. 20 ml and extracted with DCM (2* 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The crude product 278d (550 mg, 1.83 mmol, 63.07% yield) was obtained as yellow oil and used into the next step without further purification.

5. Synthesis of 278e

[959] To a mixture of 278d (550 mg, 1.83 mmol, 1 equiv), 3-[3-[[4-(trideuteriomethyl)-1,2,4-triazol-3-yl]methyl]oxetan-3-yl]aniline (475.57 mg, 1.92 mmol, 1.05 equiv) in HCOOH (87.98 mg, 1.83 mmol, 1 equiv) and DCE (10 mL) was added NaBH(OAc)3 (776.29 mg, 3.66 mmol, 2 equiv). The mixture was stirred at r.t. for 12 hr under N2 atmosphere. The reaction mixture was quenched by addition H2O 20 mL and extracted with DCM (2* 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM: methyl alcohol=50/1-1:1) to give 278e (300 mg, 564.30 umol, 30.81% yield) was obtained as a yellow solid.

H-NMR 5: (400 MHz, MeOD): δ 8.63 (s, 1 H), 8.08-8.01 (m, 2 H) 6.96-6.91 (m, 1 H), 6.50-6.48 (m, 1 H), 5.99-5.98(m, 1H), 5.97-5.92(m, 1H), 4.87 (t, J = 2.8 Hz, 2 H), 4.83 (t, J = 4.8 Hz, 2 H), 4.37 (s, 2 H), 3.73-3.71 (m, 1 H), 3.44 (d, J = 4.4 Hz, 2 H), 2.99-2.91 (m, 1 H), 2.70-2.67(m, 1H), 1.93-1.91(m, 1 H), 1.63-1.59(m, 6 H), 1.39(d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.0 Hz, 2 H), (d, J = 6.4 Hz, 1 H).

6. Synthesis of 278

[960] A mixture of 278e (300 mg, 564.30 umol, 1 equiv), Py. (223.18 mg, 2.82 mmol, 5 equiv) in DCM (10 mL) was added TRIPHOSGENE (184.20 mg, 620.73 umol, 1.1 equiv) under N2. The mixture was stirred at 0 °C for 2 hr under N2 atmosphere. The reaction mixture was quenched by addition a.q. NaHCO3 50 mL at 0 °C under N2 and extracted with DCM (2*200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue, The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 35%-65%,8min) to give 278 (85 mg, 143.47 umol, 25.42% yield) was obtained as a yellow solid.

H-NMR-278: (400 MHz, d6-DMSO): δ 8.25 (s, 1H), 7.82-7.79 (m, 1H), 7.62 (s, 1 H), 7.46 (t, J = 8 Hz, 2H), 7.36 (s, 1 H), 7.13(s, 1H), 6.95(d, J = 8 Hz, 1H), 5.02-4.94(m, 4H), 3.59(s,

2H), 3.51-3.46(m, 1H), 2.81-2.77(m, 2H), 2.07-1.98(m, 1H), 1.72-1.67 (m, 5H) , 1.64-1.63(m, 1H), 1.31-1.29(m, 3H), 0.89-0.87(m, 3H).

7. Synthesis of 278_P1&P2

[961] 85 mg of 278 was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um); mobile phase: [0.1%NH3H2O IPA];B%: 55%-55%,8min) to give 278_P1 (23.5 mg) as a yellow solid and 278_P2 (22 mg) as a yellow solid.

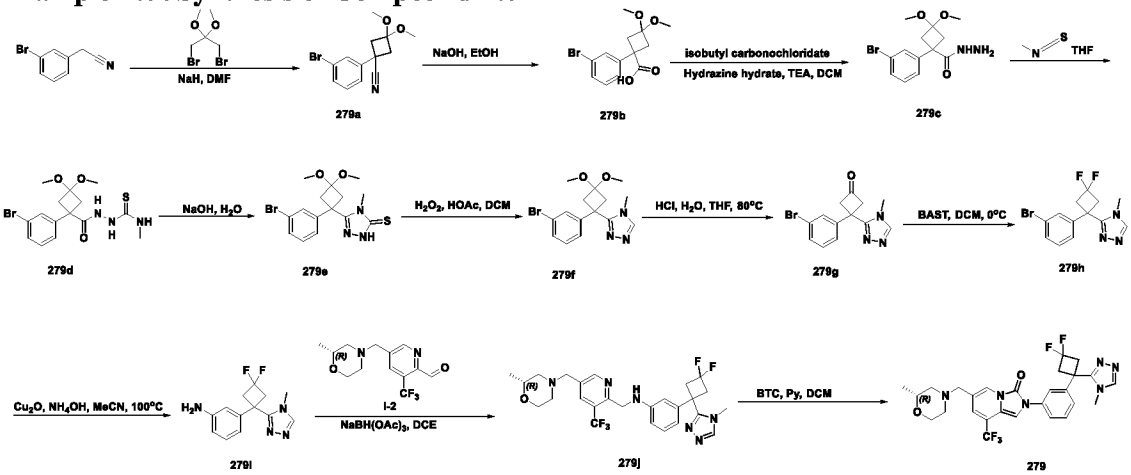
MS-278_P1: (ES, m/z): [M+H]+ 558.3.

H-NMR-278_P1: (400 MHz, DMSO-d6): δ 8.20 (s, 1H), 7.76-7.74 (m, 1H), 7.56 (s, 1 H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 (s, 1 H), 7.08(s, 1H), 6.90(d, J = 7.6 Hz, 1H), 4.96-4.91(m, 4H), 3.53(s, 2H), 3.45-3.41(m, 1H), 2.75-2.73(m, 2H), 1.97-1.90(m, 1H), 1.67-1.56 (m, 5H) , 1.45-1.36(m, 1H), 1.25-1.24(m, 3H), 0.83-0.81(m, 3H).

MS-278_P2: (ES, m/z): [M+H]+ 558.3.

H-NMR-278_P2: (400 MHz, DMSO-d6): δ 8.20 (s, 1H), 7.76-7.74 (m, 1H), 7.56 (s, 1 H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 (s, 1 H), 7.08(s, 1H), 6.90(d, J = 7.6 Hz, 1H), 4.96-4.91(m, 4H), 3.53(s, 2H), 3.45-3.41(m, 1H), 2.75-2.73(m, 2H), 1.97-1.90(m, 1H), 1.67-1.56 (m, 5H) , 1.45-1.36(m, 1H), 1.25-1.24(m, 3H), 0.85-0.83 (m, 3H).

Example 279. Synthesis of Compound 279



1. Synthesis of 279a

[962] To a stirred solution of NaH (36.54 g, 913.544 mmol, 2 equiv, 60%) in DMF (1000 mL) was added 2-(2-bromopyridin-4-yl)acetonitrile (90 g, 456.772 mmol, 1 equiv) dropwise at 0°C under nitrogen atmosphere, followed by 1,3-dibromo-2,2-dimethoxypropane (100 g, 381.765 mmol, 0.84 equiv) at 60°C under nitrogen atmosphere. The reaction was quenched with saturated NH4Cl (aq.) (3 L) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The organic layers were concentrated under reduced pressure. The

residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 279a (50 g, 34.37%) as an off-white solid.

2. Synthesis of 279b

[963] To a stirred solution of 279a (50 g, 168.825 mmol, 1 equiv) in EtOH (600 mL) was added NaOH (23.63 g, 590.887 mmol, 3.5 equiv) in H2O (600 mL) at room temperature. The resulting mixture was stirred overnight at 80°C. The EtOH was concentrated under vacuum. The mixture was acidified to pH 2 with HCl (2M). The aqueous layer was extracted with EtOAc (4x200 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 279b (44 g, 75.25%) as an off-white solid.

3. Synthesis of 279c

[964] To a stirred solution of 279b (44 g, 139.610 mmol, 1 equiv) and TEA (28.26 g, 279.220 mmol, 2 equiv) in DCM (1500 mL) was added isobutyl carbonochloridate (28.60 g, 209.415 mmol, 1.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C. To the above mixture was added Hydrazine hydrate (27.96 g, 558.440 mmol, 4 equiv) dropwise at -30°C. The resulting mixture was stirred for additional 40min at room temperature. The reaction was quenched with water (2 L) at room temperature. The aqueous layer was extracted with DCM (3x300 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 279c (45 g, 88.12%) as an off-white solid.

4. Synthesis of 279d

[965] To a stirred solution of 279c (45 g, 136.698 mmol, 1 equiv) in tetrahydrofuran (500 mL) was added methyl isothiocyanate (29.98 g, 410.094 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (400 mL). The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with water (50 mL). This resulted in 279d (65 g, 94.55%) as an off-white solid. The crude product was used in the next step directly without further purification.

5. Synthesis of 279e

[966] To a stirred solution of NaOH (51.70 g, 1292.597 mmol, 8.00 equiv) in H2O (1.2 L) was added 279d (65 g, 161.567 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The residue was acidified to pH 5 with 1 mol/L HCl (aq.). The precipitated solids were collected by filtration and washed with water (50 mL). This resulted in 279e (50 g, 76.50%) as an off-white solid.

6. Synthesis of 279f

[967] To a stirred solution of 279e (50 g, 130.110 mmol, 1 equiv) and HOAc (23.44 g, 390.330 mmol, 3 equiv) in DCM (500 mL) was added H2O2 (36.88 g, 325.275 mmol, 2.5 equiv, 30%) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH 10 with NaOH(1 M). The aqueous layer was extracted with DCM (3x200 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (100:1) to afford 279f (26 g, 53.90%) as a light yellow solid.

7. Synthesis of 279g

[968] To a stirred solution of 279f (26 g, 73.815 mmol, 1 equiv) and THF (50 mL) in H2O (200 mL) was added HCl (100 mL, 4M) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was neutralized to pH 8 with NaHCO3 (aq.). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH4HCO3), 0% to 40% gradient in 20 min; detector, UV 220 nm. This resulted in 279g (10 g, 41.15%) as a white solid.

8. Synthesis of 279h

[969] To a stirred solution of 279g (2 g, 6.532 mmol, 1 equiv) in DCM (50 mL) was added BAST (7.23 g, 32.660 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with NaHCO3 (aq.) (200 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L, NH4HCO3), 0% to 40% gradient in 20 min; detector, UV 254 nm. This resulted in 279h (300 mg, 12.60%) as a yellow solid.

9. Synthesis of 279i

[970] To a solution of 279h (300 mg, 0.914 mmol, 1 equiv) and Cu2O (26.16 mg, 0.183 mmol, 0.2 equiv) in MeCN (3 mL) was added NH4OH (3 mL) in a 10mL pressure tank reactor. The resulting mixture was stirred overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 279i (100 mg, 37.25%) as a light yellow solid.

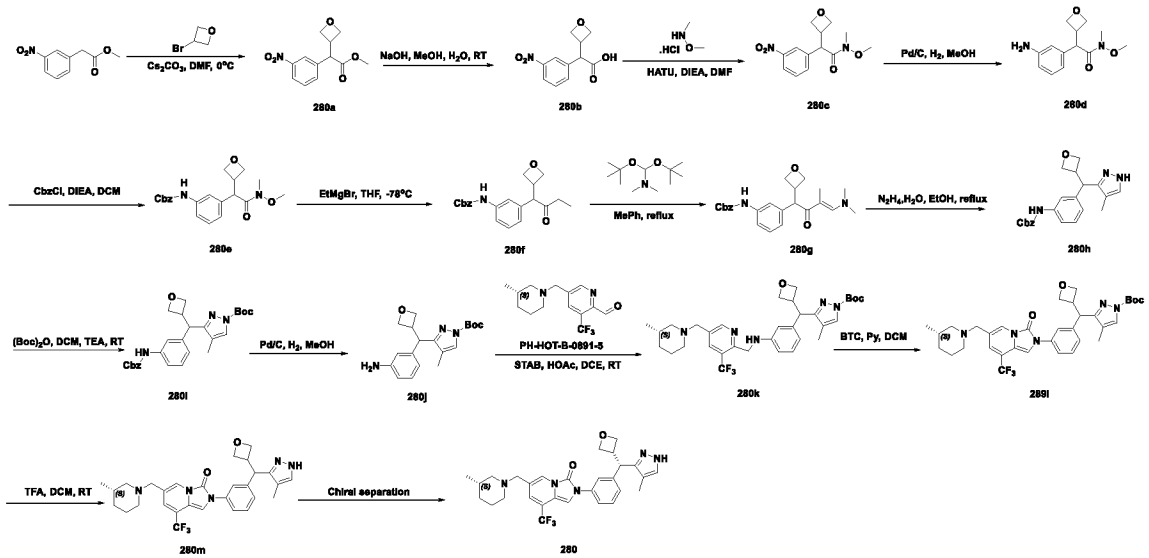
10. Synthesis of 279j

[971] To a stirred solution of 279i (90 mg, 0.341 mmol, 1 equiv) and I-2 (127.62 mg, 0.443 mmol, 1.3 equiv) in DCE (5 mL) was added NaBH(OAc)3 (216.53 mg, 1.023 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 279j (90 mg, 45.81%) as a light yellow solid.

11. Synthesis of 279

[972] To a stirred solution of 279j (80 mg, 0.149 mmol, 1 equiv) and Pyridine (117.94 mg, 1.490 mmol, 10 equiv) in DCM (5 mL) was added Triphosgene (22.12 mg, 0.074 mmol, 0.5 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 14% B to 25% B in 8 min; Wave Length: 254; 220 nm; RT1(min): 7.98) to afford 279 (24.9 mg, 29.60%) as a yellow solid. LC-MS: (ES, m/z): [M+H]+ 563. H-NMR: (400 MHz, CD3OD, δ ppm): 1.14-1.15 (d, 3H), 1.88-1.93 (m, 1H), 2.19-2.24 (m, 1H), 2.76-2.85 (m, 2H), 3.37 (s, 2H), 3.42 (s, 3H), 3.45-3.49 (m, 2H), 3.64-3.75 (m, 4H), 3.85-3.88 (m, 1H), 7.11 (s, 1H), 7.19 (s, 1H), 7.36-7.38 (d, 1H), 7.57-7.61 (m, 1H), 7.66-7.70 (m, 2H), 7.79 (s, 1H), 8.42 (s, 1H).

Example 280. Synthesis of Compound 280



1. Synthesis of 280a

[973] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (48 g, 245.934 mmol, 1 equiv) in DMF (1.5 L) was added Cs2CO3 (400.65 g, 1229.670 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. To the above mixture was added 3-bromooxetane (101.06 g, 737.793 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred for additional 2days at room temperature. The reaction was quenched with NH4Cl (aq.) (3 L) at room temperature. The aqueous layer was extracted with EtOAc (2x1 L). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 280a (34 g, 49.52%) as an off-white solid.

2. Synthesis of 280b

[974] To a stirred solution of 280a (34 g, 135.330 mmol, 1 equiv) in MeOH (100 mL) and H2O (300 mL) was added NaOH (16.24 g, 405.990 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (2x500 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 280b (32 g, 89.71%) as an off-white solid.

3. Synthesis of 280c

[975] To a stirred solution of 280b (19.74 g, 202.352 mmol, 1.5 equiv) in DMF (500 mL) were added HATU (66.68 g, 175.371 mmol, 1.3 equiv) and DIEA (52.31 g, 404.703 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (1L). The aqueous layer was extracted with EtOAc (2x500 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 280c (12 g, 29.52%) as an off-white solid.

4. Synthesis of 280d

[976] To a solution of 280c (12 g, 42.814 mmol, 1 equiv) in MeOH (300 mL) was added Pd/C (1.2 g, 10%) in a 1000mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. This resulted in 280d (12 g, 99.66%) as a white solid.

5. Synthesis of 280e

[977] To a stirred solution of 280d (12 g, 47.943 mmol, 1 equiv) and CbzCl (16.36 g, 95.886 mmol, 2 equiv) in DCM (200 mL) was added DIEA (18.59 g, 143.829 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with DCM (2x500 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 280e (15 g, 73.25%) as an off-white solid.

6. Synthesis of 280f

[978] To a stirred solution of 280e (14.9 g, 38.758 mmol, 1 equiv) in THF (150 mL) was added EtMgBr (193.79 mL, 387.580 mmol, 10 equiv, 2M) at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 6h at room temperature under nitrogen atmosphere. The reaction was quenched with saturated NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 280f (6 g, 39.86%) as an off-white solid.

7. Synthesis of 280g

[979] To a stirred solution of 280f (6 g, 16.977 mmol, 1 equiv) in Toluene (100 mL) was added [bis(tert-butoxy)methyl]dimethylamine (10.36 g, 50.931 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 110°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. This resulted in 280g (7 g, 90.84%) as a light yellow oil. The crude product was used in the next step directly without further purification.

8. Synthesis of 280h

[980] To a stirred solution of 280g (7 g, 17.136 mmol, 1 equiv) in EtOH (100 mL) was added hydrazine hydrate (98%)(8.58 g, 171.360 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C. The reaction was quenched with water (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 280h (1.4 g, 19.48%) as a white solid.

9. Synthesis of 280i

[981] To a stirred solution of 280h (1.4 g, 3.709 mmol, 1 equiv) and (Boc)2O (1.62 g, 7.418

mmol, 2 equiv) in DCM (20 mL) was added TEA (1.13 g, 11.127 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 3:1) to afford 280i (1 g, 50.81%) as a yellow solid.

10. Synthesis of 280j

[982] To a solution of 280i (1 g, 2.094 mmol, 1 equiv) in MeOH (30 mL) was added Pd/C (100 mg, 10%) under nitrogen atmosphere in a 250mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 280j (600 mg, 70.92%) as an off-white solid.

11. Synthesis of 280k

[983] To a stirred solution of 289j (300 mg, 0.874 mmol, 1 equiv) and I-2(325.12 mg, 1.136 mmol, 1.3 equiv) in DCE (5 mL) was added STAB (370.28 mg, 1.748 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 280k (250 mg, 42.43%) as a white solid.

12. Synthesis of 280l

[984] To a stirred solution of 280k (240 mg, 0.391 mmol, 1 equiv) and Pyridine (309.32 mg, 3.910 mmol, 10 equiv) in DCM (200 mL) was added Triphosgene (58.02 mg, 0.196 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x10 mL). The organic layers were concentrated under reduced pressure. This resulted in 280l (200 mg, 63.96%) as a yellow solid. The crude product was used in the next step directly without further purification.

13. Synthesis of 280m

[985] To a stirred solution of 289l (200 mg, 0.313 mmol, 1 equiv) in DCM (5 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred for 3h at room

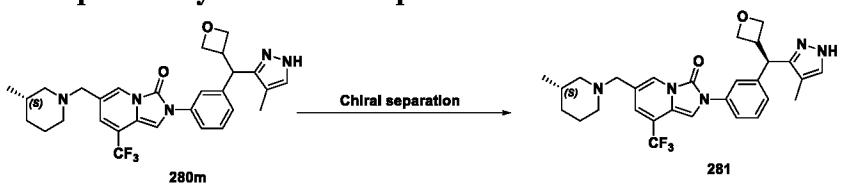
temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 72% B in 8 min, Wave Length: 220 nm; RT1(min): 7.58) to afford 280m (100 mg, 58.09%) as a yellow solid..

14. Synthesis of 280

[986] 280m (100 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK OD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 12 min; Wave Length: 220/254 nm; RT1(min): 8.33; RT2(min): 10.54; the first peak is product) to afford the crude product. The crude product (22mg) was purified by Prep-AChiral-SFC with the following conditions (Column: DAICEL DCpak P4VP, 2*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: ACN: MEOH=4: 1(0.1% 2M NH3-MEOH); Flow rate: 50 mL/min; Gradient: isocratic 20% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 254 nm; RT1(min): 3.62;) to afford 280 (8.4 mg, 8.37%) as a yellow solid.

LC-MS 0: (ES, m/z): [M+H]+ 540. H-NMR: (400 MHz, CD3OD, δ ppm): 0.85-1.02 (m, 4H), 1.61-1.84 (m, 8H), 1.99-2.09 (m, 1H), 2.88-2.94 (m, 2H), 3.06-3.11 (m, 1H), 3.38 (s, 2H), 3.76-3.82 (m, 2H), 4.02-4.06 (m, 1H), 4.33-4.34 (m, 1H), 4.38-4.40 (m, 1H), 7.13 (s, 1H), 7.14-7.16 (d, 1H), 7.25-7.26 (d, 1H), 7.35 (s, 1H), 7.52-7.56 (m, 1H), 7.65-7.66 (m, 2H), 7.69 (s, 1H).

Example 281. Synthesis of Compound 281



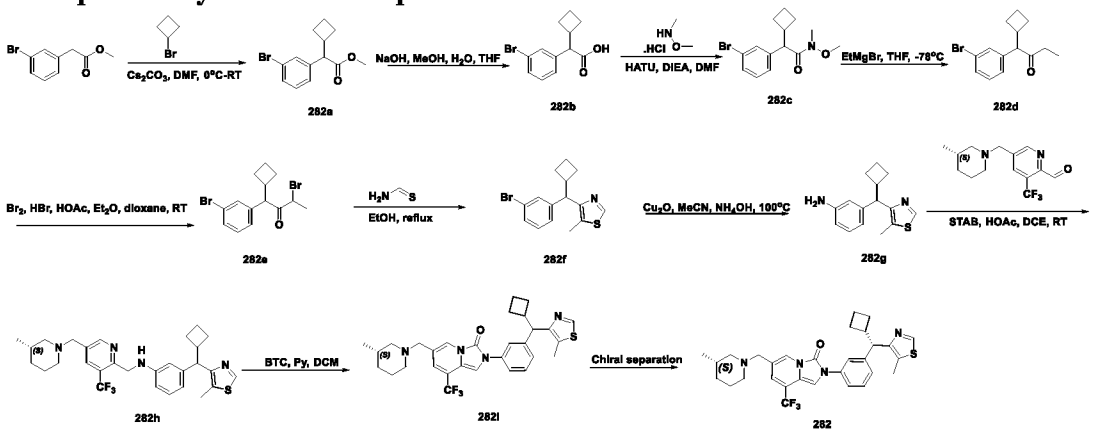
Synthesis of 281

[987] 280m (100 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK OD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 12 min; Wave Length: 220/254 nm; RT1(min): 8.33; RT2(min): 10.54; the second peak is product) to afford 281 (29.5 mg, 29.26%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 540. H-NMR: (400 MHz, CD3OD, δ ppm): 0.96-1.01 (d, 3H), 1.06-1.09 (m, 1H), 1.61-1.84 (m, 7H), 2.10-2.21 (m, 1H), 2.36-2.51 (m, 1H), 3.06-3.32 (m,

3H), 3.74-3.84 (m, 4H), 4.02-4.06 (m, 1H), 4.33-4.38 (d, 1H), 4.38-4.42 (m, 1H), 7.13 (s, 1H), 7.21-7.23 (d, 1H), 7.26-7.28 (d, 1H), 7.34 (s, 1H), 7.52-7.56 (m, 1H), 7.65-7.66 (m, 2H), 7.84 (s, 1H).

Example 282. Synthesis of Compound 282



1. Synthesis of 282a

[988] To a stirred mixture of methyl 2-(3-bromophenyl)acetate (50 g, 218.271 mmol, 1 equiv) in DMF (500 mL) was added Cs2CO3 (355.58 g, 1091.355 mmol, 5 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. To the above mixture was added bromocyclobutane (88.40 g, 654.813 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 24 h at room temperature. The resulting mixture was diluted with water (3000 mL). The aqueous layer was extracted with EtOAc (2x1000 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=50:1 to afford 282a (27 g, 43.68%) as a white solid.

2. Synthesis of 282b

[989] To a stirred mixture of 282a (48 g, 169.512 mmol, 1 equiv) in MeOH (600 mL) was added NaOH (20.34 g, 508.536 mmol, 3 equiv) in H2O (200 mL) at room temperature. The mixture was stirred for 2 h at room temperature. The mixture was neutralized to pH 6 with HCl (1 M). The aqueous layer was extracted with EtOAc (2 L). The resulting mixture was concentrated under reduced pressure. This resulted in 282b (50 g, 98.64%) as a yellow oil.

3. Synthesis of 282c

[990] To a stirred mixture of 282b (50 g, 185.778 mmol, 1 equiv) and methoxy(methyl)amine hydrochloride (36.24 g, 371.556 mmol, 2 equiv) in DMF (550 mL) was added HATU (77.70 g, 204.356 mmol, 1.1 equiv) and DIEA (72.03 g, 557.334 mmol, 3 equiv) at room temperature. The mixture was stirred for 2 h at room temperature. The

reaction was quenched with water(1500 mL) at room temperature. The aqueous layer was extracted with EtOAc (1 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=12:1 to afford 282c (50 g, 77.58%) as a yellow oil.

4. Synthesis of 282d

[991] To a stirred mixture of 282c (8 g, 25.624 mmol, 1 equiv) in THF (100 mL) was treated with EtMgBr (64.060 mL, 128.120 mmol, 5 equiv, 2 M in THF) at -78 °C under nitrogen atmosphere. The mixture was stirred for 2 h at -78 °C. The reaction was quenched by the addition of NH4Cl (aq.) (1000 mL) at room temperature. The aqueous layer was extracted with EA (500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=5/1 to afford 282d (2.8 g, 34.97%) as a yellow oil.

5. Synthesis of 282e

[992] To a stirred solution of 282d (2.4 g, 8.535 mmol, 1 equiv) in dioxane (24 mL) and Et2O (24 mL) was added HBr in AcOH (0.48 g, 5.974 mmol, 0.7 equiv, 40%) and Br2 (0.95 g, 5.974 mmol, 0.7 equiv) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=50:1 to afford 282e (1 g, 28.31%) as a colorless oil.

6. Synthesis of 282f

[993] To a stirred solution of 282e (1.08 g, 2.999 mmol, 1 equiv) in EtOH (10 mL) was added thioformamide (0.27 g, 4.498 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=40:1 to afford 282f (4.2 g, 434.54%) as a yellow oil.

7. Synthesis of 282g

[994] To a stirred mixture of 282g (400 mg, 1.241 mmol, 1 equiv) in MeCN (2 mL) and NH4OH (2 mL) were added Cu2O (35.52 mg, 0.248 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 100 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=5:1) to afford 282g (220 mg, 68.60%) as a yellow solid.

8. Synthesis of 282h

[995] To a stirred mixture 282g (200 mg, 0.774 mmol, 1.00 equiv) and I-2(221.61 mg, 0.774 mmol, 1.00 equiv) in DCE (2 mL) were added HOAc (46.48 mg, 0.774 mmol, 1 equiv) and STAB (492.16 mg, 2.322 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x10 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=40:1) to afford 282h (240 mg, 53.37%) as a yellow solid.

9. Synthesis of 282i

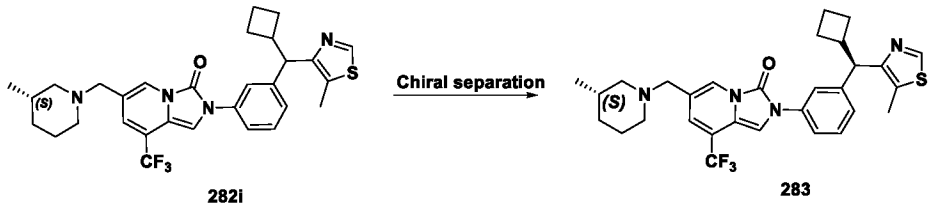
[996] To a stirred solution of 282h (220 mg, 0.416 mmol, 1 equiv) and Pyridine (197.50 mg, 2.496 mmol, 6 equiv) in DCM (5 mL) was added Triphosgene (43.22 mg, 0.146 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford the crude product (200 mg). The residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, MeCN in water (0.1% NH4HCO3), 2% to 100% gradient in 30 min; detector, UV 254 nm to afford 282i (140 mg, 60.05%) as a yellow solid.

10. Synthesis of 282

[997] 282i (140 mg) was separated by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 16 min; Wave Length: 220/254 nm; RT1 (min): 10.47; RT2 (min): 13.09; the first peak is product) to afford 282 (48.7 mg, 34.44%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 555. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.75-0.92 (m, 4H), 1.49-1.58 (m, 1H), 1.66-1.76 (m, 5H), 1.76-1.88 (m, 6H), 2.46 (s, 3H), 2.75 (s, 2H), 3.24-3.27 (m, 3H), 4.15-4.18 (d, 1H), 7.00 (s, 1H), 7.28 (s, 1H), 7.35-7.41 (m, 2H), 7.58-7.66 (m, 2H), 7.83 (s, 1H), 8.80 (s, 1H).

Example 283. Synthesis of Compound 283

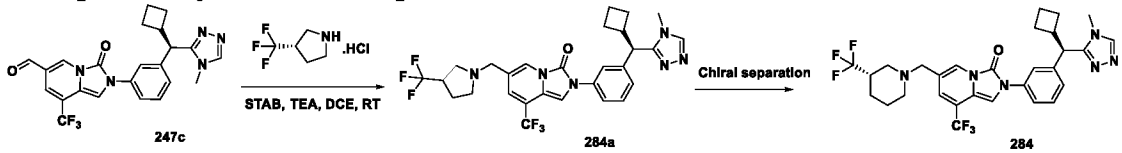


Synthesis of 283

[998] 282i (140 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 16 min; Wave Length: 220/254 nm; RT1(min): 10.47; RT2(min): 13.09; the second peak is product) to afford 283 (49.4 mg, 36.44%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 555. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.75-0.92 (m, 4H), 1.49-1.58 (m, 1H), 1.66-1.76 (m, 5H), 1.77-1.88 (m, 6H), 2.46 (s, 3H), 2.75 (s, 2H), 3.24-3.27 (m, 3H), 4.15-4.18 (d, 1H), 7.00 (s, 1H), 7.28 (s, 1H), 7.35-7.41 (m, 2H), 7.58-7.66 (m, 2H), 7.83 (s, 1H), 8.80 (s, 1H).

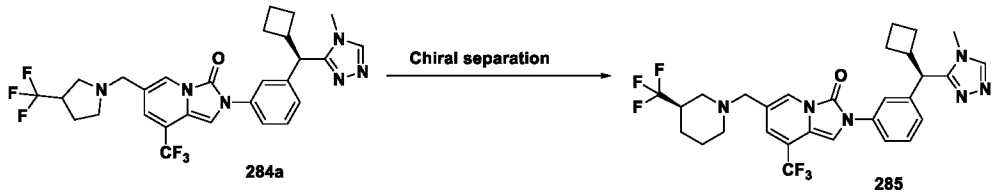
Example 284. Synthesis of Compound 284



Synthesis of 284a

[999] To a stirred solution of 247c (500 mg, 1.098 mmol, 1.00 equiv) and (3S)-3-(trifluoromethyl)pyrrolidine hydrochloride (385.52 mg, 2.196 mmol, 2 equiv) in DCE (6 mL) were added TEA (222.19 mg, 2.196 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (465.35 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperatue. The reaction was quenched by the addition of sat. NH4Cl (aq.) (15mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 30mL). The resulting mixture was concentrated under reduced pressure. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 69% B in 8 min, 69% B; Wave Length: 220 nm; RT1(min): 7.18) to afford 284a (210 mg, 32.07%) as a yellow solid.

Example 285. Synthesis of Compound 285

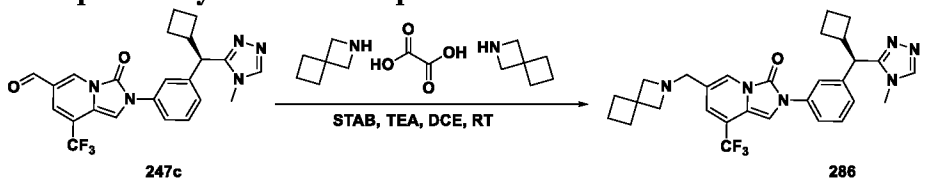


Synthesis of 285

[1000] 284a (210mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MTBE: MEOH=1: 1-HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 33 min; Wave Length: 220/254 nm; RT1(min): 24.76; RT2(min): 28.08; The second peak was the product. Sample Solvent: MTBE: MEOH=1: 1-HPLC; Injection Volume: 0.2 mL; Number of Runs: 16). This resulted in 285 (73.3 mg, 34.77%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :579. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.60-1.82 (m, 6H) δ 1.93-2.15 (m, 2H), δ 2.51-2.53 (d, 2H), δ 2.71-2.73 (m, 1H), δ 3.16-3.18 (m, 1H), δ 3.21-3.23 (m, 1H), δ 3.42-3.50 (m, 6H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 3H), δ 8.35 (s, 1H).

Example 286. Synthesis of Compound 286

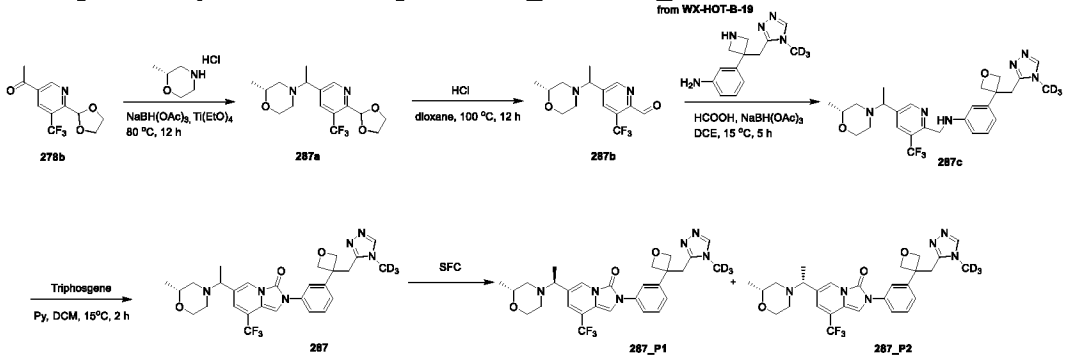


Synthesis of 286

[1001] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 2-azaspiro[3.3]heptane hemioxalate (374.14 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase A: water (10 mmol/L NH4HCO3), B: MeCN, 10 B% to 55% B gradient in 20 min; detector, UV 254 nm. This resulted in 286 (166.3 mg, 46.86%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 537. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 7H), 2.03-2.15 (m, 5H), 3.13 (s, 4H), 3.17-3.30 (m, 1H), 3.32 (s, 2H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 6.95 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.62 (s, 1H), 7.68-7.70 (m, 1H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 287. Synthesis of Compound 287_P1 & 287_P2



1. Synthesis of 287a

[1002] A mixture of 278b (1.6 g, 6.13 mmol, 1 equiv), (2R)-2-methylmorpholine (929.38 mg, 9.19 mmol, 1.5 equiv), Ti(i-PrO)4 (6.96 g, 24.50 mmol, 7.23 mL, 4 equiv) in DCE (20 mL) was degassed and purged with N2 for 3 times at 80 °C for 6 hr. Then it was added NaBH(OAc)3 (3.89 g, 18.38 mmol, 3 equiv) at r.t.. The mixture was stirred at 80°C for 6 hr under N2 atmosphere. The reaction mixture was quenched by addition Na2CO3 aq. 20 mL and diluted with H2O 50 mL. It was extracted with DCM (3 * 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to give 287a (600 mg, 1.73 mmol, 28.28% yield) as a white solid.

2. Synthesis of 287b

[1003] A mixture of 287a (1 g, 2.90 mmol, 1 equiv) in dioxane (4 mL) and HCl (4 ml, 4M) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 100 °C for 6 hr under N2 atmosphere. The reaction mixture was quenched by addition Na2CO3 aq. 20 ml and extracted with DCM (3 * 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The crude product 287b (550 mg, 1.83 mmol, 63.07% yield) was obtained as yellow oil and used into the next step without further purification.

3. Synthesis of 287c

[1004] To a mixture of 287b, 3-[3-[[4-(trideuteriomethyl)-1,2,4-triazol-3-yl]methyl]azetidin-

3-yl]aniline (285.20 mg, 1.16 mmol) in DCE (10 mL) and HCOOH (0.01 mL) was added NaBH(OAc)3 (245.39 mg, 1.16 mmol) and the mixture was stirred at r.t. for 5 hr under N2 atmosphere. The reaction mixture was quenched by addition Na2CO3 aq. 20 mL and then diluted with H2O 20 mL. The mixture was extracted with DCM (3 * 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(NH4HCO3)-ACN];B%: 30%-60%,8min). 287c (200 mg, 374.81 umol, 32.37% yield) was obtained as a white solid.

4. Synthesis of 287

[1005] A mixture of 287c (200 mg, 374.81 umol, 1 equiv), Py. (148.24 mg, 1.87 mmol, 5 equiv) in DCM (10 mL) was added TRIPHOSGENE (122.35 mg, 412.29 umol, 1.1 equiv) under N2. The mixture was stirred at 0 °C for 2 hr under N2 atmosphere. The reaction mixture was quenched by addition aq. NaHCO3 50 mL at 0 °C under N2. Then the mixture was extracted with DCM (3 * 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 35%-55%,8min). 287 (95 mg, 169.77 umol) was obtained as a yellow solid.

H-NMR: (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 7.76-7.74 (m, 1H), 7.62 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.31 (s, 1H), 7.06(s, 1H), 6.90(d, 7.6Hz, 1H), 4.96-4.91(m, 4H), 3.71-3.50(m, 1H), 3.47-3.42(m, 5H), 2.80-2.77(m, 1H), 2.76-2.72(m, 1H), 2.10-2.06(m,1H), 1.79-1.74(m, 1H), 1.27-1.25(m, 3H), 1.07-1.01(m, 1H).

5. Synthesis of 287_P1 & P2

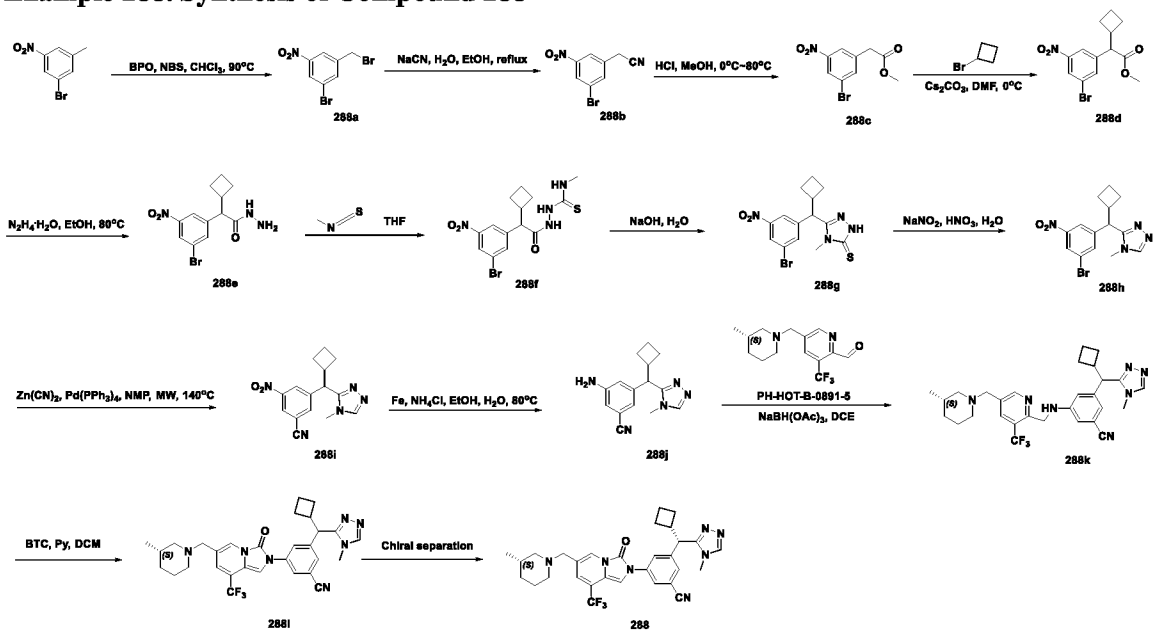
[1006] 287 (95 mg, 169.77 umol) was separated by SFC (column: Phenomenex-Cellulose-2 (250mm*30mm,10um);mobile phase: [0.1%NH3H2O MEOH];B%: 65%-65%,10min) (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [0.1%NH3.H2O IPA]; B%: 37%-37%, 10 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 4.71; RT2 (min): 6.03) to get the two targets. 287_P1 (30 mg, 53.61 umol, 31.58% yield) was obtained as a yellow solid. 287_P2 (31 mg, 55.40 umol, 32.63% yield) was obtained as a yellow solid.

LCMS-287_P1: (ES, m/z): [M+H]+ 560.3. H-NMR-287_P1: (400 MHz, DMSO-d6) δ 8.21 (s, 1H), 7.66-7.63 (m, 2H), 7.48 (t, J = 7.6Hz, 1H),7.31(s, 1H), 7.16(s,1H), 7.12(s, 1H), 6.92(d, J = 7.6Hz, 1H), 5.09(s, 4H), 3.90(d, J = 1.6 Hz, 1H), 3.70-3.60(m, 5H), 2.86(d, J =

11.2Hz, 1H), 2.74(d, J = 11.6Hz, 1H), 2.22(t, 8.4Hz, 1H), 1.92(t, J = 10.8Hz, 1H),1.37(d, J = 6.4Hz, 3H), 1.11(d, J = 6.4Hz, 3H)

LCMS-287_P2: (ES, m/z): [M+H]+ 560.3. H-NMR-287_P2: (400 MHz, DMSO-d6) δ 8.21 (s, 1H), 7.66-7.63 (m, 2H), 7.48 (t, J = 8Hz, 1H),7.31(s, 1H), 7.16(s,1H), 7.11(s, 1H), 6.91(d, J = 7.6Hz, 1H), 5.09(s, 4H), 3.82(d, J = 1.6 Hz, 1H), 3.68-3.61(m, 5H), 2.92(d, J = 11.2Hz, 1H), 2.67(d, J = 11.6Hz, 1H), 2.26(t, 8.4Hz, 1H), 1.92(t, J = 10.8Hz, 1H),.1.37 (d, J = 6.4Hz, 3H), 1.12(d, J = 6.4Hz, 3H).

Example 288. Synthesis of Compound 288



1. Synthesis of 288a

[1007] Into a 1L 3-necked round-bottom flask was added 1-bromo-3-methyl-5-nitrobenzene (50 g, 231.445 mmol, 1 equiv), BPO (11.86 g, 46.289 mmol, 0.2 equiv), NBS (82.39 g, 462.890 mmol, 2 equiv) and CHCl3 (500 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 90°C under nitrogen atmosphere. The reaction was quenched with NaHCO3 (aq.) (800 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with (PE / EA 10:1) to afford 288a (22 g, 34.08%) as an off-white solid.

2. Synthesis of 288b

[1008] To a stirred mixture of 288a (22 g, 74.594 mmol, 1 equiv) in EtOH (100 mL)/H2O (25 mL) was added at NaCN (5.48 g, 111.891 mmol, 1.5 equiv) 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. The

mixture was basified to pH 8 with saturated NaHCO3 (aq.). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 288b (3 g, 15.85%) as an off-white solid.

3. Synthesis of 288c

[1009] Into a 250mL 3-necked round-bottom flask were added 288b (3 g, 12.446 mmol, 1 equiv) and MeOH (30 mL) at 0°C. The resulting mixture was stirred for 2h at 0°C under HCl(g). Then the resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was basified to pH 7 with saturated NaHCO3 (aq.).The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 288c (2.4 g, 66.84%) as a light yellow solid.

4. Synthesis of 288d

[1010] To a stirred mixture of 288c (2.5 g, 9.122 mmol, 1 equiv) in DMF (30 mL) was added Cs2CO3 (14.86 g, 45.610 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (3.69 g, 27.366 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The mixture was acidified to pH 7 with saturated NH4Cl (aq.) (100 mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with water (2x30 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 288d (1.3 g, 41.26%) as a light yellow oil.

5. Synthesis of 288e

[1011] Into a 50mL 3-necked round-bottom flask were added 288d (1.3 g, 3.961 mmol, 1 equiv), NH2NH2.H2O (1.98 g, 39.610 mmol, 10 equiv) and EtOH (15 mL) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were concentrated under vacuum. This resulted in 288e (1.2 g, 84.00%) as a light yellow oil.

6. Synthesis of 288f

[1012] To a stirred mixture of 288e (1.2 g, 3.657 mmol, 1 equiv) in tetrahydrofuran (13 mL)

was added methyl isothiocyanate (0.59 g, 8.045 mmol, 2.2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with water (2x10 mL). This resulted in 288f (1.1 g, 67.47%) as a white solid.

7. Synthesis of 288g

[1013] To a stirred mixture of NaOH (0.44 g, 10.964 mmol, 4 equiv) in H2O (12 mL) was added 288f (1.1 g, 2.741 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature .The mixture was acidified to pH 5 with 1M HCl (aq.).The aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were concentrated under vacuum. This resulted in 288g (1 g, 86.62%) as a yellow oil. The crude product was used in the next step directly without further purification.

8. Synthesis of 288h

[1014] To a stirred mixture of 288g (1 g, 2.609 mmol, 1 equiv) and NaNO2 (1.80 g, 26.090 mmol, 10 equiv) in H2O (20 mL) was added HNO3 (26.09 mL, 26.090 mmol, 10 equiv, 1M) at 0°C. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with EtOAc (2x30 mL).The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 288h (900 mg, 90.36%) as a yellow oil.

9. Synthesis of 288i

[1015] To a solution of 288h (780 mg, 2.221 mmol, 1 equiv) and Zn(CN)2 (1043.13 mg, 8.884 mmol, 4 equiv) in NMP (10 mL) was added Pd(PPh3)4 (256.65 mg, 0.222 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The final reaction mixture was irradiated with microwave radiation for 3h at 140°C. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 40:1) to afford 288i (360 mg, 49.07%) as a light yellow solid.

10. Synthesis of 288j

[1016] To a stirred mixture of 288i (350 mg, 1.177 mmol, 1 equiv) and NH4Cl (629.68 mg, 11.770 mmol, 10 equiv) in EtOH (5 mL) was added H2O (3 mL) and Fe (197.22 mg, 3.531 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 6h at 80°C. The resulting mixture was filtered through a Celite pad, the filter cake was washed with EtOAc (2x5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 288j (210 mg, 63.39%) as a white solid.

11. Synthesis of 288k

[1017] To a stirred solution of 288j (200 mg, 0.748 mmol, 1 equiv) and I-2(642.56 mg, 2.244 mmol, 3 equiv) in DCE (5 mL) was added NaBH(OAc)3 (317.11 mg, 1.496 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 288k (200 mg, 46.24%) as an off-white solid.

12. Synthesis of 288l

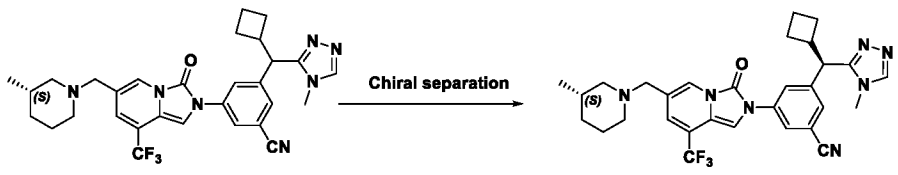
[1018] To a stirred solution of 288k (180 mg, 0.335 mmol, 1 equiv) and Pyridine (264.83 mg, 3.350 mmol, 10 equiv) in DCM (5 mL) was added Triphosgene (49.67 mg, 0.168 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford 288l (120 mg, 61.05%) as a yellow solid.

13. Synthesis of 288

[1019] The 288l (120 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14 min; Wave Length: 220/254 nm; RT1(min): 9.33; RT2(min): 12.09; the first peak is product) to afford 288 (32.6 mg, 26.95%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 564. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.79-0.93 (m, 4H), 1.43-1.53 (m, 1H), 1.58-1.69 (m, 4H), 1.71-1.93 (m, 6H), 2.03-2.08 (m, 1H), 2.64-2.83 (m, 2H), 3.19-3.30 (m, 3H), 3.48 (s, 3H), 4.38-4.40 (d, 1H), 7.03 (s, 1H), 7.52 (s, 1H), 7.65-7.70 (m, 2H), 8.23-8.24 (m, 2H), 8.37 (s, 1H).

Example 289. Synthesis of Compound 289



288l 289

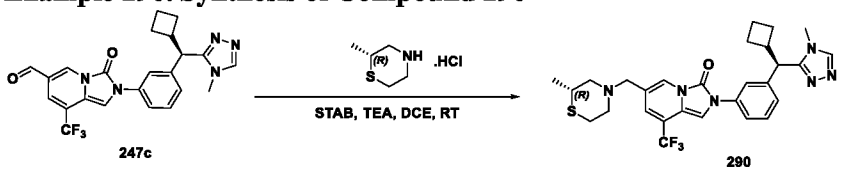
Synthesis of 289

[1020] 288l (120 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH),

Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14 min; Wave Length: 220/254 nm; RT1(min): 9.33; RT2(min): 12.09; the second peak is product) to afford 289 (37.8 mg, 31.18%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 564. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.79-0.93 (m, 4H), 1.41-1.98 (m, 11H), 2.03-2.08 (m, 1H), 2.64-2.83 (m, 2H), 3.19-3.30 (m, 3H), 3.48 (s, 3H), 4.38-4.40 (d, 1H), 7.03 (s, 1H), 7.52 (s, 1H), 7.66-7.70 (m, 2H), 8.23-8.24 (m, 2H), 8.37 (s, 1H).

Example 290. Synthesis of Compound 290



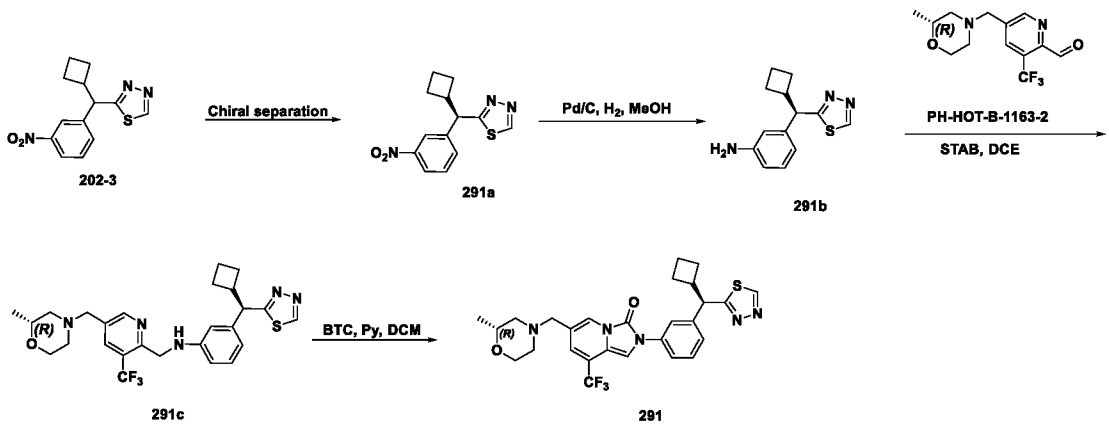
247c 290

Synthesis of 290

[1021] To a stirred solution of 247c (200 mg, 0.439 mmol, 1 equiv) and (2R)-2-methylthiomorpholine hydrochloride (134.96 mg, 0.878 mmol, 2 equiv) in DCE (5 mL) was added TEA (88.87 mg, 0.878 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (186.14 mg, 0.878 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 290 (64.0 mg, 25.29%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 557. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.18-1.24 (d, 3H), 1.69-1.93 (m, 5H), 2.01-2.15 (m, 2H), 2.24-2.33 (m, 1H), 2.51-2.59 (m, 1H), 2.71-2.77 (m, 1H), 2.87-2.91 (m, 1H), 2.98-3.01 (m, 2H), 3.21-3.25 (m, 1H), 3.32 (s, 2H), 3.43 (s, 3H), 4.25-4.28 (d, 1H), 7.01 (s, 1H), 7.19-7.21 (d, 1H), 7.33 (s, 1H), 7.43-7.47 (m, 1H), 7.69-7.71 (m, 2H), 7.74 (s, 1H), 8.34 (s, 1H).

Example 291. Synthesis of Compound 291



1. Synthesis of 291a

[1022] 202-3 (1 g, 3.559 mmol, 1 equiv) was purified by Prep-SFC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH; Flow rate: 200 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.08; RT2(min): 6.08; the first peak was product;) to afford 291a (0.397 g, 40.51%) as a yellow oil.

2. Synthesis of 292b

[1023] Into a 50 mL round-bottom flask were added 291a (397.1 mg, 1.442 mmol, 1 equiv) and Pd/C (122.79 mg 10%) in MeOH (4 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure. This resulted in 292b as light yellow solid.

3. Synthesis of 292c

[1024] A solution of 292b (200 mg, 0.815 mmol, 1 equiv) in DCE (4 mL) was treated with 330-2 (258.50 mg, 0.896 mmol, 1.1 equiv) for 2h at room temperature under nitrogen atmosphere followed by the addition of STAB (259.16 mg, 1.222 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NaHCO3 (aq.)(8ml) at room temperature. The resulting mixture was extracted with DCE/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column,C18 silica gel ; mobile phase A:Water(0.1% NH4HCO3); mobile phase B:ACN ,Gradient:20%B to 80%B in 30 min; detector, UV 254 nm. This resulted in 292c (300 mg, 71.10%) as a yellow solid.

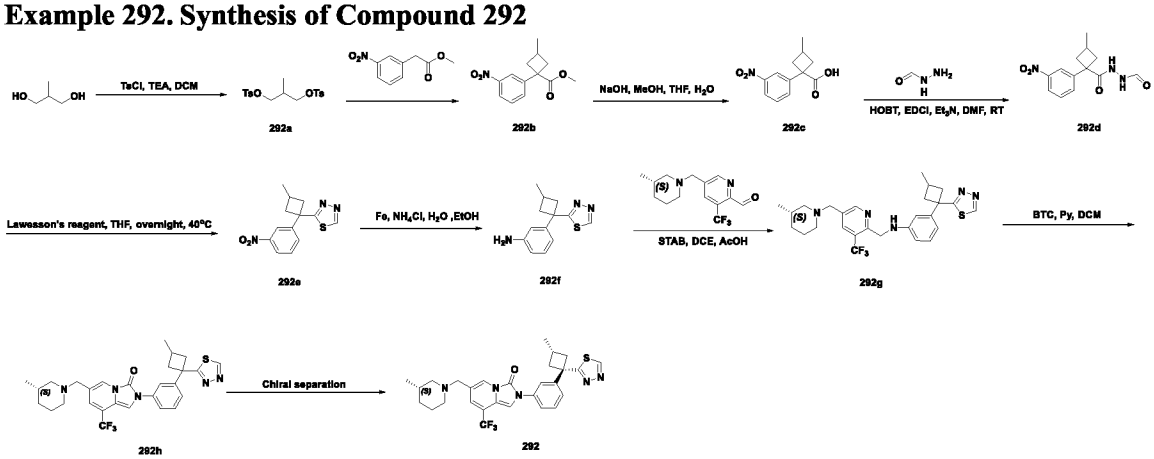
4. Synthesis of 292

[1025] A solution of 292c (310 mg, 0.599 mmol, 1 equiv) in DCM (9 mL) was treated with

Pyridine (284.24 mg, 3.594 mmol, 6 equiv) at room temperature followed by the addition of triphosgene (71.08 mg, 0.240 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched by the addition of sat. NaHCO3(8mL) at room temperature. The resulting mixture was extracted with DCM/ MeOH (10:1)(2 x 10mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, Xselect CSH C18 OBD; mobile phase, A: Water(0.1%NH4HCO3), Mobile Phase B: ACN, 20%B to 75% B in 30 min; , UV 254 nm. This resulted in 292 (246 mg, 75.56%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 544. H-NMR: (400 MHz, DMSO, ppm): δ1.03-1.05 (d, 3H), δ1.65-1.85 (m, 6H), δ2.00-2.11 (m, 2H), δ2.63-2.75 (m, 2H), δ3.20-3.29 (m, 3H), δ3.34-3.40 (m, 2H), δ3.71-3.77 (m,1H), δ4.71-4.74 (d, 1H), δ7.02 (s, 1H), δ7.35-7.38 (m, 2H), δ7.46-7.48 (m, 1H), 7.70 (s, 1H), δ7.74-7.82 (m, 1H), δ7.88 (s, 1H), δ9.50 (s, 1H).

Example 292. Synthesis of Compound 292



1. Synthesis of 292a

[1026] Into a 1L 3-necked round-bottom flask were added methylpropanediol (50 g, 554.803 mmol, 1 equiv) and TsCl (317.30 g, 1664.409 mmol, 3 equiv) in DCM (500 mL) at room temperature. To the above mixture was added TEA (280.71 g, 2774.015 mmol, 5 equiv) dropwise over 1h at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The resulting mixture was diluted with water (2L). The aqueous layer was extracted with CH2Cl2 (3x500 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (100:1) to afford 292a (110 g, 49.75%) as a white solid. 2. Synthesis of 292b

[1027] To a stirred mixture of methyl methyl 2-(3-nitrophenyl)acetate (35 g, 179.327 mmol, 1.00 equiv) in DMF(350 mL) was added Cs2CO3 (292.14 g, 896.635 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. To the above mixture was added 292a (107.19 g, 268.990 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 24h at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (2L) at room temperature. The aqueous layer was extracted with EtOAc (2 x 1 L). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl 202b (10 g, 22.37%) as a yellow oil.

3. Synthesis of 292c

[1028] To a stirred mixture of 292b (4.7g, 18.855mmol, 1 equiv) in MeOH (10ml) and THF (10ml) was added NaOH (2.26 g, 56.565 mmol, 3 equiv) in H2O (10 mL) at room temperature. The mixture was stirred for 2h at room temperature. The mixture was acidified to pH 5 with 1M HCl (aq.). The resulting mixture was extracted with EA (3 x 30ml). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 292c (4 g, 90.18%) as a white solid.

4. Synthesis of 292d

[1029] To a stirred of 292c (3.98 g, 16.919 mmol, 1 equiv) and and N-formylhydrazine (1.02 g, 16.919 mmol, 1 equiv) in DMF (40 mL) were added HOBT (3.43 g, 25.379 mmol, 1.5 equiv) and EDCI (4.87 g, 25.379 mmol, 1.5 equiv) at room temperature. To the above mixture was added TEA (2.57 g, 25.379 mmol, 1.5 equiv) dropwise over 30min at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (150mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL).The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH (100:1) to afford 292d (2.8 g, 59.69%) as a yellow oil.

5. Synthesis of 292e

[1030] Into a 100ml 3-necked round-bottom was added 292d (2.775 g, 10.008 mmol, 1 equiv), Lawesson's Reagent (8.10 g, 20.016 mmol, 2 equiv), and THF (28 mL) at room temperature. The mixture was stirred overnight at 40°C. The residue was diluted with water (90ml). The aqueous layer was extracted with EA (3x30ml). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with DCM: MeOH (100:1) to afford 292e (1.2 g, 43.55%) as a yellow oil.

6. Synthesis of 292f

[1031] Into a 25ml flasket were added 292e (1.2 g, 4.358 mmol, 1 equiv) and Fe (0.49 g, 8.716 mmol, 2 equiv), NH4Cl (0.699 g, 13.074 mmol, 3 equiv) and EtOH (6 mL) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered; the filters cake was washed with EA (2x20 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was diluted with water (20mL). The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers concentrated under reduced pressure. This resulted in 292f (1 g, 93.52%) as a yellow oil.

7. Synthesis of 292g

[1032] Into a 25mL round-bottom flask were added 292f (500 mg, 2.038 mmol, 1 equiv) and I-2(641.82 mg, 2.242 mmol, 1.1 equiv) in DCE (5 mL) at room temperature. To the above mixture was added AcOH (122.39 mg, 2.038 mmol, 1 equiv) and STAB (863.86 mg, 4.076 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 8h at room temperature. The resulting mixture was diluted with water (25mL). The aqueous layer was extracted with CH2Cl2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH 20:1) to afford 292g (800 mg, 76.13%) as a yellow oil.

8. Synthesis of 292h

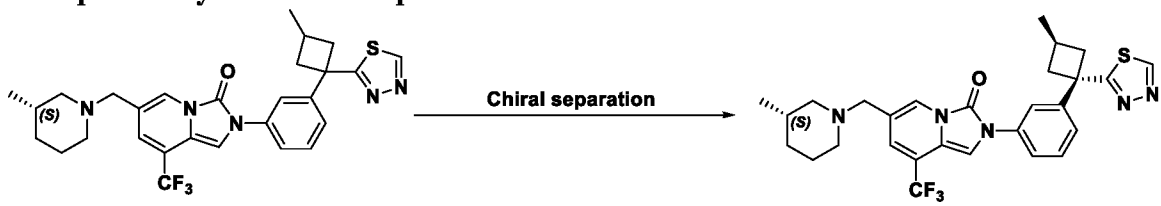
[1033] Into a 25mL round-bottom flask were added Pyridine (460.20 mg, 5.820 mmol, 6 equiv) and 292g (500 mg, 0.970 mmol, 1 equiv) in DCM (5 mL) at room temperature. To the above mixture was added BTC (115.10 mg, 0.388 mmol, 0.4 equiv) in three portions at room temperature. The resulting mixture was stirred for 2h at room temperature under N2 atmosphere. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (25mL) at room temperature. The resulting mixture was extracted with DCM (3 x 20ml). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH 25:1) to afford 292h as a yellow solid.

9. Synthesis of 292

[1034] The 292h was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.26; RT2(min): 8.10; Sample Solvent: EtOH:

DCM=1: 1; the first peak was product) to afford 292 (167.1 mg, 54.64%) as a yellow solid. H-NMR: (400 MHz, dmso-d6, δ ppm): 0.81-0.89 (m, 4H), 1.08-1.13 (d, 3H), 1.40-1.49 (m, 1H), 1.58-1.66 (m, 4H), 1.87-1.92 (m, 1H), 2.32-2.38 (m, 1H), 2.58-2.67 (m, 2H), 2.73-2.77 (m, 2H), 3.06-3.11 (m, 2H), 3.25-3.34 (m, 2H), 7.00 (s, 1H), 7.45-7.48 (m, 2H), 7.51-7.56 (m, 1H), 7.66 (s, 1H), 7.77-7.79 (m, 1H), 8.00 (s, 1H), 9.51 (s,1H).

Example 293. Synthesis of Compound 293

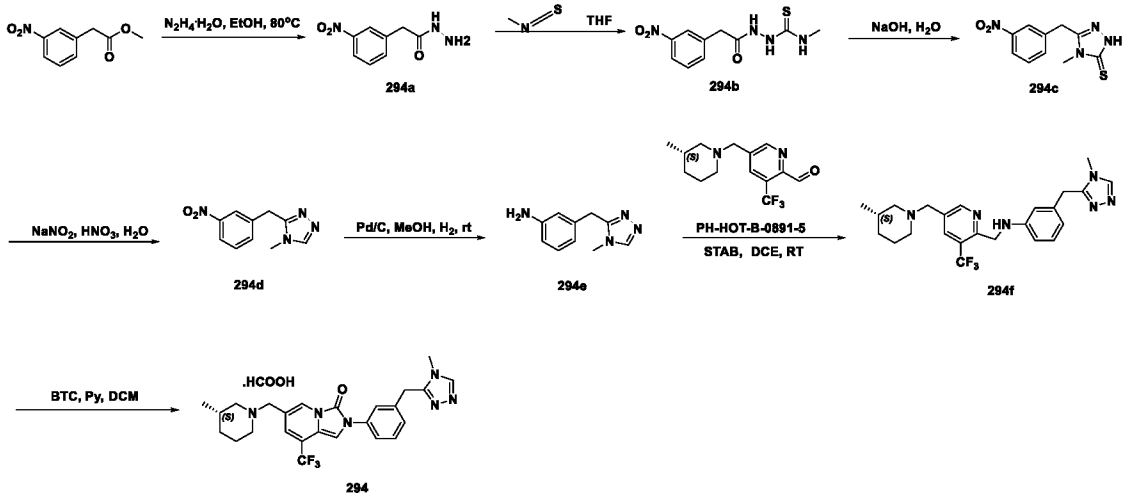


Synthesis of 293

[1035] 292h was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.26; RT2(min): 8.10; the second peak was product) to afford 293 (42.2 mg, 13.41%) as a yellow solid.

LC-MS: (ES, m/z): [M+H+ 542. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.89 (m, 4H), 1.08-1.13 (d, 3H), 1.40-1.49 (m, 1H), 1.58-1.66 (m, 4H), 1.87-1.92 (m, 1H), 2.40-2.45 (m, 2H), 2.58-2.64 (m, 1H), 2.73-2.80 (m, 2H), 3.06-3.15 (m, 2H), 3.25-3.34 (m, 2H), 7.00 (s, 1H), 7.45-7.48 (m, 2H), 7.51-7.56 (m, 1H), 7.66 (s, 1H), 7.77-7.79 (m, 1H), 8.00 (s, 1H), 9.51 (s,1H).

Example 294. Synthesis of Compound 294



1. Synthesis of 294a

[1036] A mixture of methyl 2-(3-nitrophenyl)acetate (10 g, 51.236 mmol, 1.00 equiv) and hydrazine hydrate (98%) (25.65 g, 512.360 mmol, 10 equiv) in EtOH(50 mL) was stirred for overnight at 80°C. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with CH2Cl2:MeOH=10:1 (4x300 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 294a (8.2 g, 82.00%) as a white solid.

2. Synthesis of 294b

[1037] Into a 100 mL 3-necked round-bottom flask were added methyl isothiocyanate (7.49 g, 102.470 mmol, 2.5 equiv) and 294a (8 g, 40.988 mmol, 1 equiv) in tetrahydrofuran (80 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (80 mL). The THF was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water (20 mL). This resulted in 294b (11 g, 85.03%) as a white solid.

3. Synthesis of 294c

[1038] Into a 500 mL 3-necked round-bottom flask were added NaOH (150 mL, 1M) and 294b (11 g, 41.000 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 6 with HCl (aq.) (1 M). The aqueous layer was extracted with CH2Cl2:MeOH=10:1 (3x200 mL).The resulting mixture was concentrated under reduced pressure to afford 294c (7.5 g, 73.09%) as a white solid.

4. Synthesis of 294d

[1039] Into a 1 L 3-necked round-bottom flask were added NaNO2 (21 g, 304.370 mmol) in H2O (50 mL), EtOAc(50 mL) and 294c (7.5 g, 9.989 mmol, 1 equiv) at room temperature. To the above mixture was added HNO3 (300 mL, 10 equiv, 1M in H2O) at 0 °C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE/EA =10:1 to afford 294d (5.6 g, 231.22%) as a yellow solid.

5. Synthesis of 294e

[1040] To a stirred solution of 294d (5.6 g, 25.663 mmol, 1 equiv) in MeOH (110 mL) was added Pd/C (1.2 g) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted

in 294e (4.9 g, 90.28%) as a yellow solid.

6. Synthesis of 294f

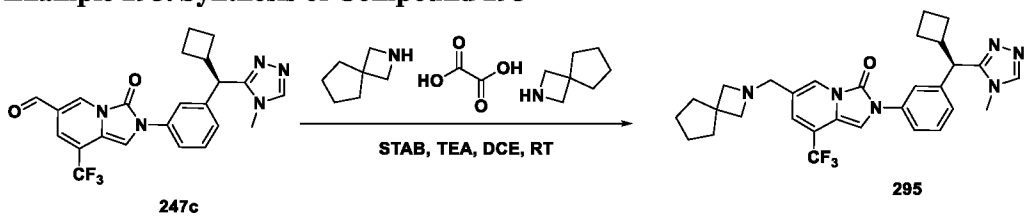
[1041] To a stirred mixture of 294e (200 mg, 1.063 mmol, 1 equiv) and I-2(304.19 mg, 1.063 mmol, 1 equiv) in DCE (3 mL) was added STAB (675.56 mg, 3.189 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 294f (220 mg, 41.09%) as a yellow solid.

7. Synthesis of 294

[1042] To a stirred solution of 294f (300 mg, 0.654 mmol, 1 equiv) and Pyridine (310.51 mg, 3.924 mmol, 6 equiv) in DCM (6 mL) was added Triphosgene (97.07 mg, 0.327 mmol, 0.5 equiv) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford the crude product (150 mg). The crude product was purified by reverse phase flash with the following conditions (Mobile Phase A: H2O (0.1% HCOOH), Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 2% B to 100% B in 30 min; Wave Length: 220/254 nm) to afford 294 (76.6 mg, 21.85%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 485. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.90-0.98 (m, 4H), 1.43-1.49 (m, 1H), 1.59-1.66 (m, 4H), 1.88-1.93 (m, 1H), 2.67-2.78 (m, 2H), 3.26 (s, 2H), 3.53 (s, 3H), 4.24 (s, 2H), 7.01 (s, 1H), 7.17-7.19 (d, 1H), 7.32 (s, 1H), 7.45-7.48 (t, 1H), 7.67-7.74 (m, 3H), 8.15 (s, 1H), 8.39 (s, 1H).

Example 295. Synthesis of Compound 295



247c 295

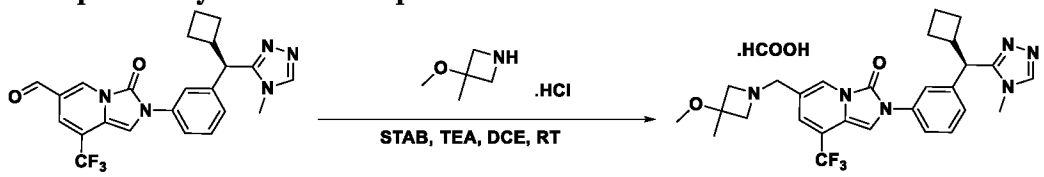
Synthesis of 295

[1043] To a stirred solution of 247c (200 mg, 0.439 mmol, 1 equiv) and 2-Aza-spiro[3.4]octane hemioxalate(2:1) (137.19 mg, 0.439 mmol, 1 equiv) in DCE (5 mL) was added TEA (88.87 mg, 0.878 mmol, 2 equiv) at room temperature. The resulting mixture was

stirred for 1h at room temperature. To the above mixture was added STAB (186.14 mg, 0.878 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 69% B in 8 min, Wave Length: 220 nm; RT1(min): 7.23) to afford 295 (45.5 mg, 18.72%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 551. H-NMR0: (400 MHz, DMSO-d6, δ ppm): 1.48-1.51 (m, 4H), 1.69-1.74 (m, 5H), 1.74-1.85 (m, 4H), 2.07-2.10 (m, 1H), 3.05 (s, 4H), 3.18-3.25 (m, 1H), 3.32 (s, 2H), 3.43 (s, 3H), 4.24-4.27 (d, 1H), 6.97 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.63 (s, 1H), 7.68-7.70 (m, 1H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 296. Synthesis of Compound 296

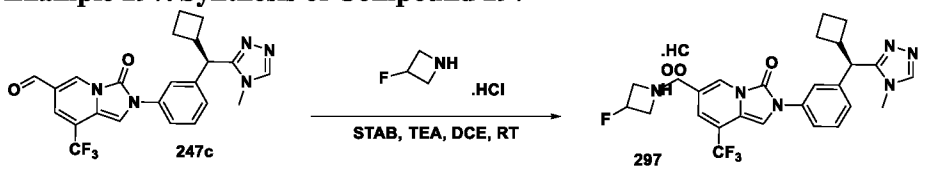


Synthesis of 296

[1044] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 3-methoxy-3-methylazetidine hydrochloride (181.29 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 30% B in 7 min, Wave Length: 254; 220 nm; RT1(min): 5.73) to afford 296 (84.4 mg, 21.54%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 541. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.41 (s, 3H), 1.63-1.93 (m, 5H), 2.07-2.12 (m, 1H), 3.04-3.06 (m, 2H), 3.10 (s, 3H), 3.14-3.18 (m, 2H), 3.24-3.28 (m, 2H), 3.43 (s, 4H), 4.25-4.27 (d, 1H), 6.99 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.70 (m, 2H), 7.74 (s, 1H), 8.15 (s, 1H), 8.33 (s, 1H).

Example 297. Synthesis of Compound 297

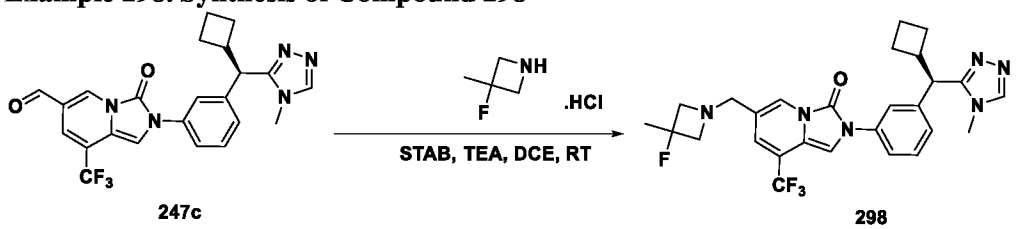


Synthesis of 297

[1045] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 3-fluoroazetidine hydrochloride (146.94 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 30% B in 7 min, Wave Length: 254; 220 nm; RT1(min): 6.40) to afford 297 (99.5 mg, 26.60%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 515. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.07-2.12 (m, 1H), 3.15-3.18 (m, 3H), 3.24-3.27 (m, 1H), 3.35-3.39 (m, 2H), 3.43 (s, 2H), 3.54-3.65 (m, 2H), 4.25-4.27 (d, 1H), 5.11-5.29 (m, 1H), 6.98 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.73 (m, 3H), 8.14 (s, 1H), 8.33 (s, 1H).

Example 298. Synthesis of Compound 298



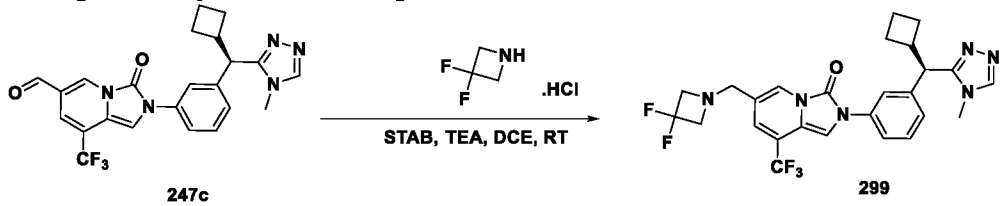
Synthesis of 298

[1046] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 3-fluoro-3-

methylazetidine hydrochloride (165.43 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min, Wave Length: 220 nm; RT1(min): 7.32) to afford 298 (95.1 mg, 27.21%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 529. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.50-1.55 (m, 3H), 1.63-1.88 (m, 5H), 2.07-2.12 (m, 1H), 3.20-3.31 (m, 5H), 3.43-3.44 (m, 5H), 3.54-3.65 (m, 2H), 4.25-4.27 (d, 1H), 6.98 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.72 (m, 2H), 7.72-7.74 (m, 1H), 8.33 (s, 1H).

Example 299. Synthesis of Compound 299



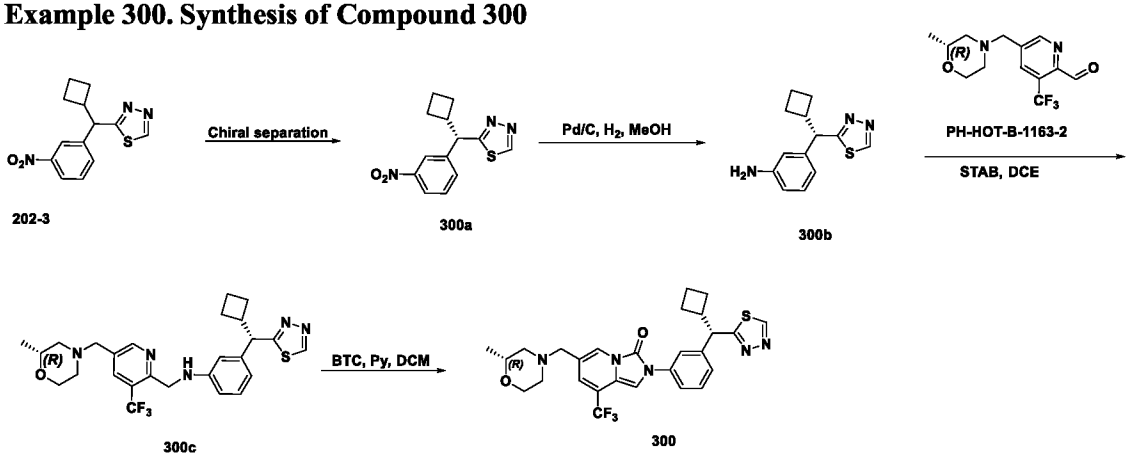
Synthesis of 299

[1047] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 3,3-difluoroazetidine hydrochloride (170.64 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60

mL/min; Gradient: 34% B to 54% B in 8 min, 54% B; Wave Length: 220 nm; RT1(min): 7.70) to afford 299 (50.7 mg, 13.82%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 533. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.88 (m, 5H), 2.07-2.12 (m, 1H), 3.20-3.23 (m, 1H), 3.41 (s, 3H), 3.53 (s, 2H), 3.66-3.66 (m, 4H), 4.25-4.27 (d, 1H), 7.00 (s, 1H), 7.19-7.21 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.76 (m, 3H), 8.33 (s, 1H).

Example 300. Synthesis of Compound 300



1. Synthesis of 300a

[1048] 202-3 (1 g, 3.559 mmol, 1 equiv) was purified by Prep-SFC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH; Flow rate: 200 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.08; RT2(min): 6.08; second peak was product);) to afford 300a (0.469 g, 46.90%) as a yellow oil.

2. Synthesis of 300b

[1049] Into a 50 mL round-bottom flask were added 300a (0.469 g, 46.90%) and Pd/C (122.79 mg 10%) in MeOH (4 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10 mL). The resulting mixture was concentrated under reduced pressure to afford 300b (397 mg, 94.85%) as light yellow solid.

3. Synthesis of 300c

[1050] A solution of 300b (397 mg, 0.814 mmol, 1 equiv) in DCE (4 mL) was treated with 330-2 (258.50 mg, 0.896 mmol, 1.1 equiv) for 2h at room temperature under nitrogen atmosphere followed by the addition of STAB (259.16 mg, 1.222 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NaHCO3 (aq.)(8ml) at room temperature. The resulting

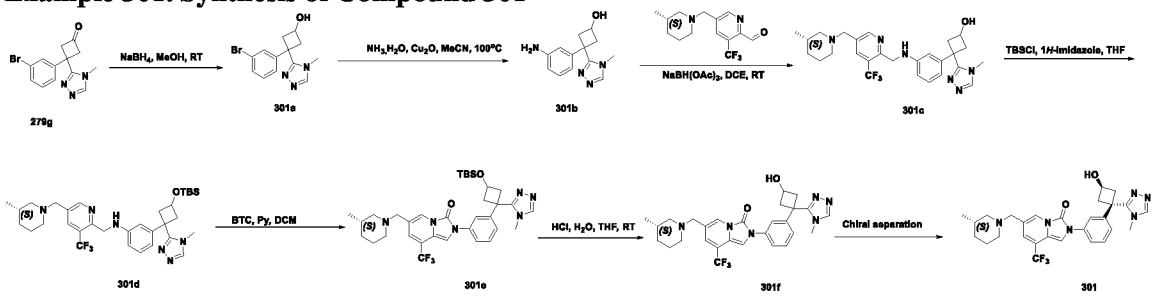
mixture was extracted with DCE/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column,C18 silica gel ; mobile phase A:Water(0.1% NH4HCO3); mobile phase B:ACN , ,Gradient:20%B to 80%B in 30 min; detector, UV 254 nm. This resulted in 300c (310 mg, 73.47%) as a yellow solid.

4. Synthesis of 300

[1051] A solution of 300c (300 mg, 0.596 mmol, 1 equiv) in DCM (9 mL) was treated with Pyridine (282.73 mg, 3.576 mmol, 6 equiv) at room temperature followed by the addition of Triphosgene (70.71 mg, 0.238 mmol, 0.4 equiv) at 0°C.The resulting mixture was stirred for 30min at room temperature. The reaction was quenched by the addition of NaHCO3(15 mL) at room temperature. The resulting mixture was extracted with DCE/ MeOH (10:1)(2 x 15 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, A: Water(0.1%NH4HCO3), Mobile Phase B: ACN, Gradient:20%B to 70% B in 30 min; UV 254 nm. This resulted in 300 (280 mg, 86.46%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 544. H-NMR: (400 MHz, DMSO, ppm): δ1.03-1.05 (d, 3H), δ1.65-1.90 (m, 6H), δ2.03-2.08 (m, 2H), δ2.65-2.75 (m, 2H), δ3.24-3.28 (m, 3H), δ3.46-3.52 (m, 2H), δ3.73-3.75 (d,1H), δ4.71-4.74 (d, 1H), δ7.02 (s, 1H), δ7.33-7.38 (m, 2H), δ7.46-7.50 (m, 1H), 7.70 (s, 1H), δ7.75-7.77 (m, 1H), δ7.86 (s, 1H), δ9.50 (s, 1H).

Example 301. Synthesis of Compound 301



1. Synthesis of 301a

[1052] To a stirred solution of 279g (1 g, 3.266 mmol, 1 equiv) in MeOH (20 mL) was added NaBH4 (0.25 g, 6.532 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x30 mL). The resulting mixture was concentrated under vacuum. This resulted in 301a (1 g, 91.40%) as an off-white solid.

2. Synthesis of 301b

[1053] A solution of 301a (1 g, 3.245 mmol, 1 equiv) and NH3.H2O (8 mL) in MeCN (8 mL) was stirred overnight at 110°C in a pressure tank. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 301b (0.6 g, 68.12%) as a yellow solid.

3. Synthesis of 301c

[1054] To a stirred solution of 301b (600 mg, 2.456 mmol, 1 equiv) and I-2(914.10 mg, 3.193 mmol, 1.3 equiv) in DCE (8 mL) was added NaBH(OAc)3 (1041.06 mg, 4.912 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (30mL). The resulting mixture was concentrated under vacuum. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 301c (600 mg, 42.73%) as a yellow solid.

4. Synthesis of 301d

[1055] To a stirred solution of 301c (600 mg, 1.166 mmol, 1 equiv) and 1H-imidazole (317.50 mg, 4.664 mmol, 4 equiv) in THF (20 mL) was added TBSCl (439.33 mg, 2.915 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at 60°C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 301d (500 mg, 64.78%) as a light yellow solid.

5. Synthesis of 301e

[1056] To a stirred solution of 301d (500 mg, 0.795 mmol, 1 equiv) and Pyridine (628.92 mg, 7.950 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (117.96 mg, 0.398 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. This resulted in 301e (400 mg, 69.91%) as a yellow solid. The crude product was used in the next step directly without further purification.

6. Synthesis of 301f

[1057] To a stirred solution of 301e (400 mg, 0.611 mmol, 1 equiv) and H2O (10 mL) in THF (5 mL) were added HCl (2 mL, 1M) at room temperature. The resulting mixture was stirred for 3h at room temperature. The mixture was neutralized to pH 7 with saturated

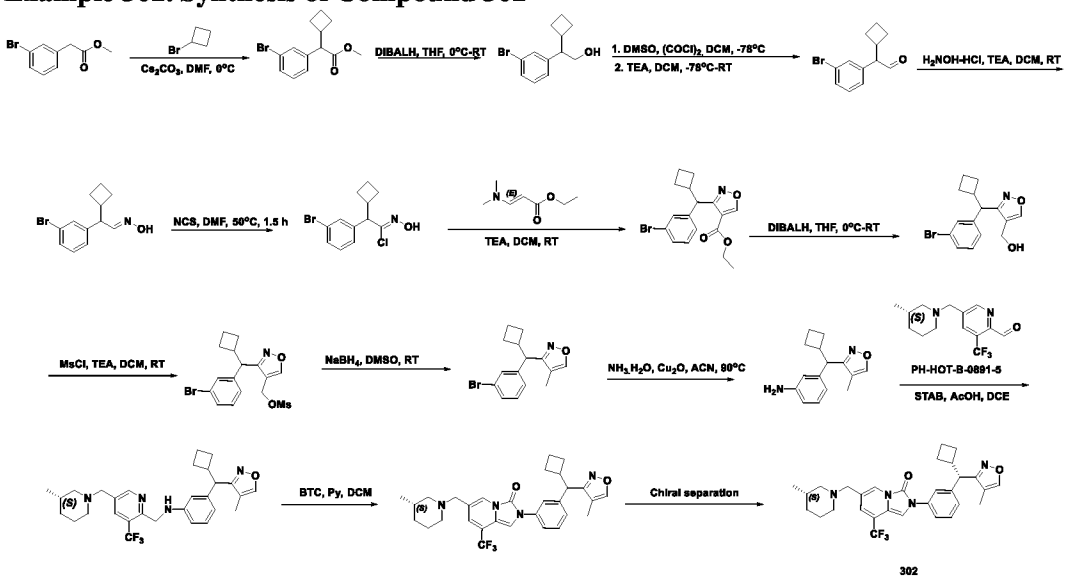
NaHCO3 (aq.). The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 8:1) to afford 301f (280 mg, 81.40%) as a yellow solid.

7. Synthesis of 301

[1058] 301f (280 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 21 min; Wave Length: 220/254 nm; RT1(min): 12.10; RT2(min): 16.72; the first peak is product) to afford 301 (105.8 mg, 36.77%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 541. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.42-1.57 (m, 1H), 1.57-1.73 (m, 4H), 1.85-1.91 (m, 1H), 2.49-2.51 (m, 1H), 2.51-2.53 (m, 1H), 3.20-3.30 (m, 7H), 4.04-4.09 (m, 1H), 5.32-5.33 (d, 1H), 7.00 (s, 1H), 7.07-7.09 (m, 1H), 7.36 (s, 1H), 7.45-7.49 (m, 1H), 7.63-7.68 (m, 3H), 8.37 (s, 1H).

Example 302. Synthesis of Compound 302



1. Synthesis of 302a

[1059] Into a 1 L 3-necked round-bottom flask were added methyl 2-(3-bromophenyl)acetate (30 g, 130.963 mmol, 1 equiv) , DMF (400 ml), Cs2CO3 (213.35 g, 654.815 mmol, 5 equiv) and bromocyclobutane (53.04 g, 392.889 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (1000 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (12:1) to afford 302a

(15 g, 40.45%) as a light yellow oil.

2. Synthesis of 302b

[1060] Into a 500 mL 3-necked round-bottom flask were added 302a (15 g, 52.973 mmol, 1 equiv), THF (200 mL) and DIBALH (18.83 g, 132.433 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 302b (10 g, 73.99%) as a light yellow oil.

3. Synthesis of 302c

[1061] Into a 250 mL 3-necked round-bottom flask were added 302b (10 g, 39.192 mmol, 1 equiv), DCM (200 mL) and DMSO (0.31 g, 3.919 mmol, 0.1 equiv) at -78°C. The resulting mixture was stirred for 0.5 h at -78°C. The resulting mixture was concentrated under reduced pressure. To a stirred solution DCM (200 mL) and TEA (7.93 g, 78.384 mmol, 2 equiv) was added at -78°C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of Water (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 302c (5 g, 50.40%) as a light brown oil.

4. Synthesis of 302d

[1062] Into a 250 mL 3-necked round-bottom flask were added 302c (5 g, 19.752 mmol, 1 equiv), DCM (60 ml), TEA (6.00 g, 59.256 mmol, 3 equiv) and NH2OH.HCl (3.43 g, 49.380 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by Water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 302d (3.3 g, 62.30%) as a light yellow oil.

5. Synthesis of 302e

[1063] Into a 250 mL 3-necked round-bottom flask were added 302d (3.3 g, 12.306 mmol, 1 equiv), DMF (50 mL) and NCS (2.46 g, 18.459 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1.5h at 50°C. The reaction was quenched by the addition of Water (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure to afford 302e (3.5 g, 93.99%) as a light yellow oil.

6. Synthesis of 302f

[1064] Into a 250 mL 3-necked round-bottom flask were added 302e (3.8 g, 12.558 mmol, 1 equiv), DCM (40 mL), TEA (3.81 g, 37.674 mmol, 3 equiv) and ethyl (2E)-3-(dimethylamino)prop-2-enoate (2.70 g, 18.837 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 302f (2.4 g, 52.47%) as a light yellow oil.

7. Synthesis of 302g

[1065] Into a 250 mL 3-necked round-bottom flask were added 302f (2.4 g, 6.589 mmol, 1 equiv), THF (30 mL) and DIBALH (2.34 g, 16.473 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (10:1) to afford 302g (2 g, 94.21%) as a light yellow oil.

8. Synthesis of 302h

[1066] Into a 100 mL 3-necked round-bottom flask were added 302g (1.9 g, 5.897 mmol, 1 equiv), DCM (20 mL), TEA (1.79 g, 17.691 mmol, 3 equiv) and MsCl (1.01 g, 8.846 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of Water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure to afford 302h (2.1 g, 88.97%) as a light yellow oil.

9. Synthesis of 302i

[1067] Into a 100 mL 3-necked round-bottom flask were added 302h (2 g, 4.996 mmol, 1 equiv), DMSO (25 mL) and NaBH4 (0.378 g, 9.992 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE / EA (5:1) to afford 302i (1 g, 65.42%) as a light yellow solid.

10. Synthesis of 302j

[1068] Into a 50 mL sealed tube were added 302i (400 mg, 1.306 mmol, 1 equiv), ACN (4

mL), NH3.H2O (4 mL) and Cu2O (37.38 mg, 0.261 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with MeCN (3x3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH2Cl2 / MeOH (10:1) to afford 302j (290 mg, 91.61%) as a light yellow solid.

11. Synthesis of 302k

[1069] Into a 100 mL sealed tube were added 302j (290 mg, 1.197 mmol, 1 equiv), DCE (5 mL), I-2(342.63 mg, 1.197 mmol, 1 equiv), AcOH (71.87 mg, 1.197 mmol, 1 equiv) and STAB (507.28 mg, 2.394 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (25 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH2Cl2 / MeOH (12:1) to afford 302k (500 mg, 81.50%) as a light yellow solid.

12. Synthesis of 302l

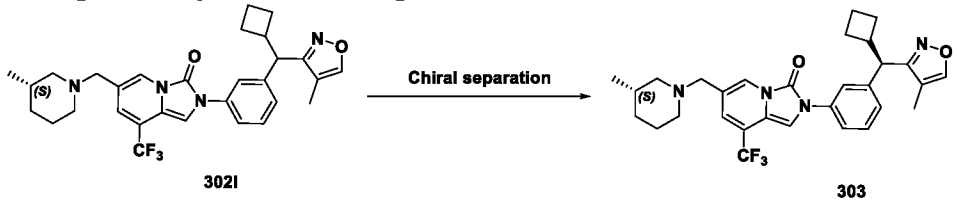
[1070] Into a 100 mL sealed tube were added 302k (480 mg, 0.936 mmol, 1 equiv), DCM (10 mL), Pyridine (444.40 mg, 5.616 mmol, 6 equiv) and Triphosgene (111.15 mg, 0.374 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH2Cl2 / MeOH (10:1) to afford 302l (200 mg, 39.66%) as a light yellow solid.

13. Synthesis of 302

[1071] The 302l (200 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 5% B to 5% B in 20 min; Wave Length: 220/254 nm; RT1(min): 13.98; RT2(min): 17.69; The first peak was the product. Injection Volume: 0.65 mL; Number of Runs:15) to afford 302 (43.6 mg, 21.08%) as a light yellow solid.

H-NMR: 1H NMR (300 MHz, DMSO-d4) δ 0.82-0.84 (m, 4H), 1.58 (s, 1H), 1.77-1.80 (m, 5H), 1.81-1.92 (m, 4H), 1.93-1.99 (m, 4H), 2.10 (s, 1H), 2.61-2.81 (m, 2H), 3.02-3.13 (m, 1H), 3.24-3.32 (m, 2H), 4.14-4.16 (d, 1H), 7.00 (s, 1H), 7.21-7.23 (d, 1H), 7.32 (s, 1H), 7.40-7.48 (m, 1H), δ 7.55-7.70 (m, 2H), 7.76 (s, 1H), 8.52 (s, 1H).

Example 303. Synthesis of Compound 303

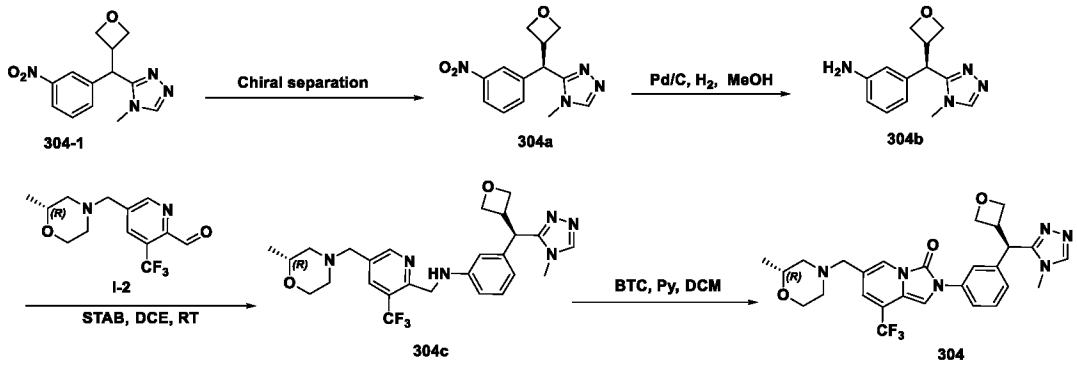


Synthesis of 303

[1072] 302I (200 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 5% B to 5% B in 20 min; Wave Length: 220/254 nm; RT1(min): 13.98; RT2(min): 17.69; The second peak was the product. Injection Volume: 0.65 mL; Number of Runs:15) to afford 303 (52.6 mg, 25.12%) as a light yellow solid.

H-NMR: 1H NMR (300 MHz, DMSO-d6) δ 0.83-0.85 (m, 4H), 1.59 (s, 1H), 1.77-1.80 (m, 5H), 1.81-1.92 (m, 4H), 1.93-1.99 (m, 4H), 2.10 (s, 1H), 2.61-2.81 (m, 2H), 3.02-3.13 (m, 1H), 3.24-3.32 (m, 2H), 4.14-4.16 (d, 1H), 7.00 (s, 1H), 7.21-7.23 (d, 1H), 7.32 (s, 1H), 7.40-7.48 (m, 1H), δ 7.55-7.70 (m, 2H), 7.76 (s, 1H), 8.53 (s, 1H).

Example 304. Synthesis of Compound 304



1. Synthesis of 304a

[1073] The 304-1 (11.5 g) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: Lux 5um Cellulose-4, 5*25 cm, 10 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH: ACN=2: 1(0.1% 2M NH3-MeOH); Flow rate: 200 mL/min; Gradient: isocratic 50% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 254 nm; RT1(min): 4.25; RT2(min): 9.57; The second peak was product) to afford 304a (5 g, 43%) as a yellow solid.

2. Synthesis of 304b

[1074] To a solution of 304a (5 g, 18.23 mmol, 1.0 equiv) in 150 mL MeOH was added Pd/C (10%, 1g) under nitrogen atmosphere in a 250 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 304b (4.2 g, 92%) as an off-white solid.

3. Synthesis of 304c

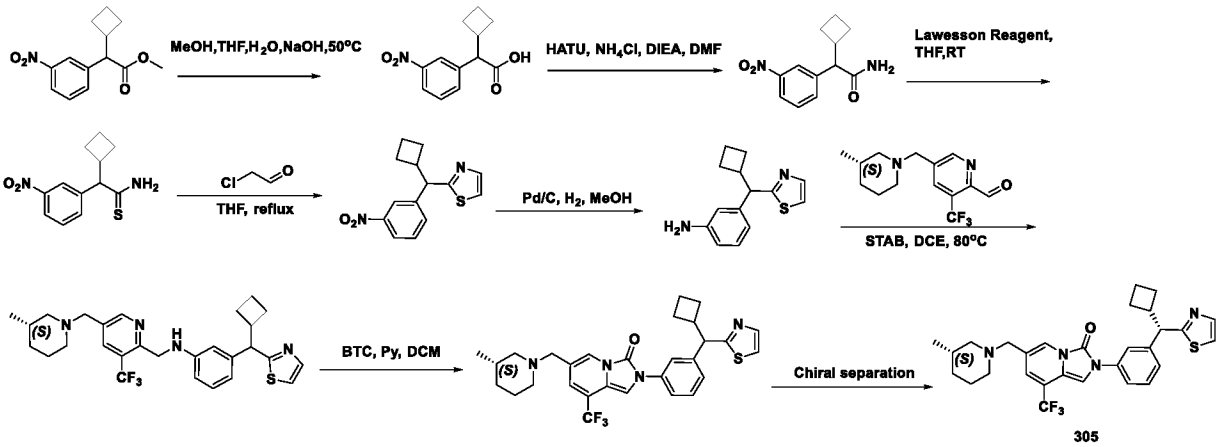
[1075] Into a 50mL 3-necked round-bottom flask were added 304b (300 mg, 1.228 mmol, 1 equiv), STAB (520.53 mg, 2.456 mmol, 2 equiv) and DCE (4 mL) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 304c (320 mg, 50.45%) as a yellow solid.

4. Synthesis of 304

[1076] Into a 50mL 3-necked round-bottom flask were added 304c (310 mg, 0.600 mmol, 1 equiv), Pyridine (284.81 mg, 3.600 mmol, 6 equiv) and DCM (4 mL) at room temperature. To the above mixture was added Triphosgene (89.04 mg, 0.300 mmol, 0.5 equiv) at 0°C. The resulting mixture was stirred for additional 30min at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford the crude product. The crude product was purified by reverse phase flash with the following conditions: (column, C18; mobile phase, A: water (10mmol/L NH4HCO3), B: CH3CN, 5% B to 75% B gradient in 30 min; detector, UV 254 nm.) to afford 304 (157.8 mg, 48.17%) as a yellow solid.

H-NMR: δ1.03 (s, 3H), δ1.71-1.76 (m, 1H), δ2.04-2.07 (m, 1H), δ2.65-2.68 (m, 1H), δ2.72-2.75 (m, 1H), δ3.23 (s, 2H), δ3.26-3.31 (m, 3H), δ3.46-3.51 (m, 2H), δ3.73-3.75 (m, 1H), δ3.91-3.94 (m, 1H), δ4.27-4.30 (t, 1H), δ4.48-4.50 (d, 2H), δ4.73-4.82 (m, 2H), δ7.02 (s, 1H), δ7.17-7.19 (d, 1H), δ7.39 (s, 1H), δ7.45-7.49 (m, 1H), δ7.68 (s, 1H), δ7.75-7.77 (d, 1H), δ8.29 (s, 1H).

Example 305. Synthesis of Compound 305



1. Synthesis of 305a

[1077] Into a 500mL 3-necked round-bottom flask were added methyl 2-cyclobutyl-2-(3-nitrophenyl)acetate (25 g, 100.294 mmol, 1 equiv), MeOH (120 mL), THF (40 mL), H2O (40 mL) and NaOH (8.02 g, 200.588 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 30 min at 50°C. The mixture was acidified to pH 4 with HCl (1M.). The precipitated solids were collected by filtration and washed with water (2x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 305a (23 g, 92.61%) as a white solid.

2. Synthesis of 305b

[1078] Into a 500mL 3-necked round-bottom flask were added 205a (23 g, 97.773 mmol, 1 equiv), DMF (230 mL), HATU (55.77 g, 146.659 mmol, 1.5 equiv), NH4Cl (10.46 g, 195.546 mmol, 2 equiv) and DIEA (25.27 g, 195.546 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was basified to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was extracted with EtOAc (3 x 300mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 205b (20 g, 82.96%) as a light yellow solid.

3. Synthesis of 305c

[1079] Into a 500mL 3-necked round-bottom flask were added 305b (20 g, 85.377 mmol, 1 equiv), THF (200 mL) and Lawesson Reagent (41.44 g, 102.452 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with Water (500 ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to

afford 305c (10 g, 44.45%) as a light yellow solid.

4. Synthesis of 305d

[1080] Into a 250mL 3-necked round-bottom flask were added 305c (10 g, 39.949 mmol, 1 equiv), THF (100mL) and chloroacetaldehyde(4.70 g, 59.923 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at 60°C under nitrogen atmosphere. The reaction was quenched by the addition of Water (200 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 300mL). The combined organic layers were washed with water (100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 305d (7 g, 63.23%) as a light yellow oil.

5. Synthesis of 305e

[1081] To a solution of 305d (7 g, 25.516 mmol, 1 equiv) in 150 mL MeOH was added Pd/C (20%, 1.4 g) under nitrogen atmosphere in a 250 mL 3-necked round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 305e (6 g, 91.42%) as a light yellow oil.

6. Synthesis of 305f

[1082] Into a 100ml 3-necked round-bottom flask were added 305e (2 g, 8.185 mmol, 1 equiv), DCE (20 mL), STAB (5.20 g, 24.555 mmol, 3 equiv) and I-2(3.05 g, 10.641 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with sat. NH4Cl (aq.) (30 ml). at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 30 mL). The resulting mixture concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2/MeOH (30:1) to afford 305f (2.9 g, 65.40%) as a light yellow oil.

7. Synthesis of 305g

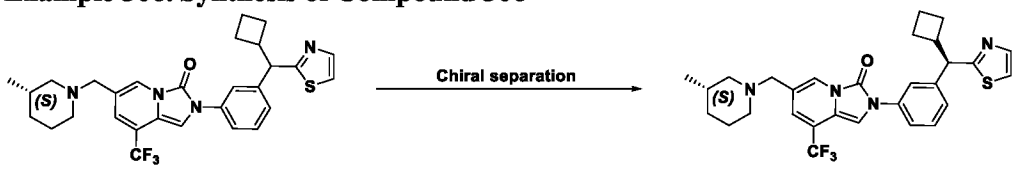
[1083] Into a 100ml round-bottom flask were added 305f (600 mg, 1.166 mmol, 1 equiv), DCM (30 mL) and Pyridine (553.3 mg, 6.996 mmol, 6 equiv) at 0°C. To the above mixture was added Triphosgene (155.7 mg, 0.524 mmol, 0.45 equiv) at 0°C. The resulting mixture was stirred for additional 8 min at 0°C. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 30:1) to afford 305g (340 mg, 51.78%) as a light yellow solid.

8. Synthesis of 305

[1084] 305g (300 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 18 min; Wave Length: 220/254 nm; RT1(min): 9.34; RT2(min): 13.32; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1.1 mL; Number of Runs: 6) to afford 305 as a light yellow solid.

LCMS: (ES, m/z): [M+H] + 541. H-NMR: (300 MHz, DMSO-d6, ppm): δ0.827-0.867 (m, 4H), δ1.47-1.66 (m, 5H), δ1.66-1.84 (m, 6H), δ2.04-2.06 (d, 1H), δ2.50 (s, 1H), δ2.51-2.75 (m, 2H), δ3.34 (s, 2H), δ4.48-4.50 (d, 1H), δ7.01 (s, 1H), δ7.32-7.34 (d, 2H), δ7.58-7.59(d, 1H), δ7.66 (s, 1H), δ7.71 (s, 1H), δ7.72-7.73(d, 2H), δ7.85 (s, 1H).

Example 306. Synthesis of Compound 306

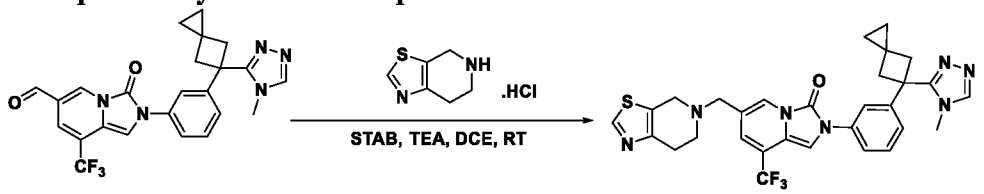


Synthesis of 306

[1085] The crude product (300 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 18 min; Wave Length: 220/254 nm; RT1(min): 9.34; RT2(min): 13.32; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1.1 mL; Number of Runs: 6) to afford 306 as a light yellow solid.

LCMS (ES, m/z): [M+H] + 541. H-NMR0: (300 MHz, DMSO-d6, ppm): δ0.82-0.83 (m, 4H), δ1.58-1.63 (m, 6H), δ1.81-1.83 (m, 6H), δ2.04-2.06 (d, 1H), δ2.75 (d, 2H), δ3.25 (s, 2H), δ4.48-4.50 (d, 1H), δ7.01 (s, 1H), δ7.32-7.34 (d, 2H), δ7.45(s, 1H), δ7.58-7.59 (s, 1H), δ7.66 (s, 1H), δ7.71-7.73(m, 2H), δ7.85 (s, 1H).

Example 307. Synthesis of Compound 307



307-1 307

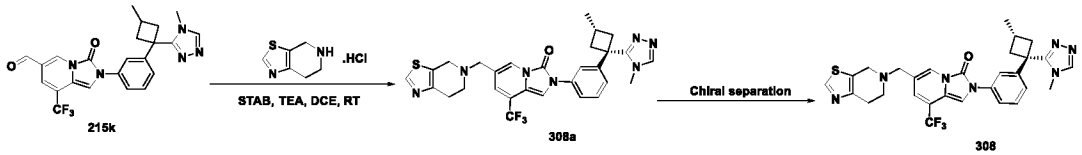
Synthesis of 307

[1086] To a stirred solution of 307-1 (400 mg, 0.856 mmol, 1 equiv) and 4H,5H,6H,7H-

[1,3]thiazolo[5,4-c]pyridine hydrochloride (226.75 mg, 1.284 mmol, 1.5 equiv) in DCE (5 mL) was added TEA (129.89 mg, 1.284 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (362.72 mg, 1.712 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford 307 (180.7 mg, 35.05%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 592. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.48-0.56 (m, 2H), 0.57-0.60 (m, 2H), 2.75-2.78 (m, 2H), 2.75-2.82 (m, 2H), 2.82-2.86 (m, 2H), 3.18-3.22 (m, 2H), 3.25 (s, 3H), 3.53 (s, 2H), 3.75 (s, 2H), 7.07 (s, 1H), 7.19-7.21 (d, 1H), 7.36 (s, 1H), 7.49-7.53 (m, 1H), 7.64-7.66 (m, 1H), 7.76 (s, 1H), 7.83 (s, 1H), 8.40 (s, 1H), 8.91 (s, 1H).

Example 308. Synthesis of Compound 308



1. Synthesis of 308a

[1087] To a stirred mixture of 4H,5H,6H,7H-[1,3]thiazolo[5,4-c]pyridine hydrochloride (465.47 mg, 2.634 mmol, 2 equiv) and 215k (600 mg, 1.317 mmol, 1.00 equiv) in DCE (6 mL) was added TEA (399.94 mg, 3.951 mmol, 3 equiv) at room temperature .The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (837.63 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 308a (380 mg, 47.27%) as a yellow solid.

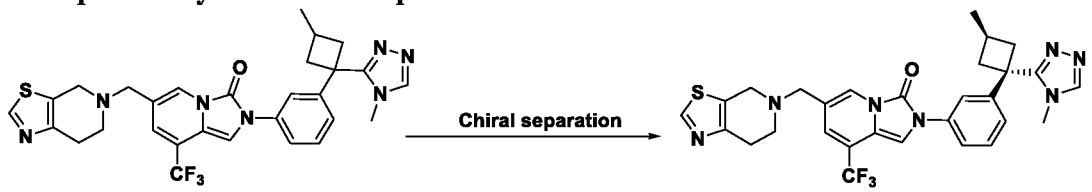
2. Synthesis of 308

[1088] 308a (380 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16.5 min; Wave Length: 220/254 nm; RT1 (min): 9.78; RT2 (min): 12.55; the first peak is product) to afford the crude product (130 mg). The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column,

30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 57% B in 8 min, 57% B; Wave Length: 220 nm; RT1 (min): 7.85) to afford 308 (72.1 mg, 18.21%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 580. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.08 (s, 3H), 2.54-2.56 (m, 2H), 2.84-2.89 (m, 6H), 3.18 (s, 3H), 3.55 (s, 2H), 3.77 (s, 2H), 7.07 (s, 1H), 7.26-7.27 (d, 1H), 7.39 (s, 1H), 7.49-7.53 (t, 1H),7.64-7.66 (m, 1H), 7.77-7.82 (m, 2H), 8.30 (s, 1H), 8.92 (s, 1H).

Example 309. Synthesis of Compound 309

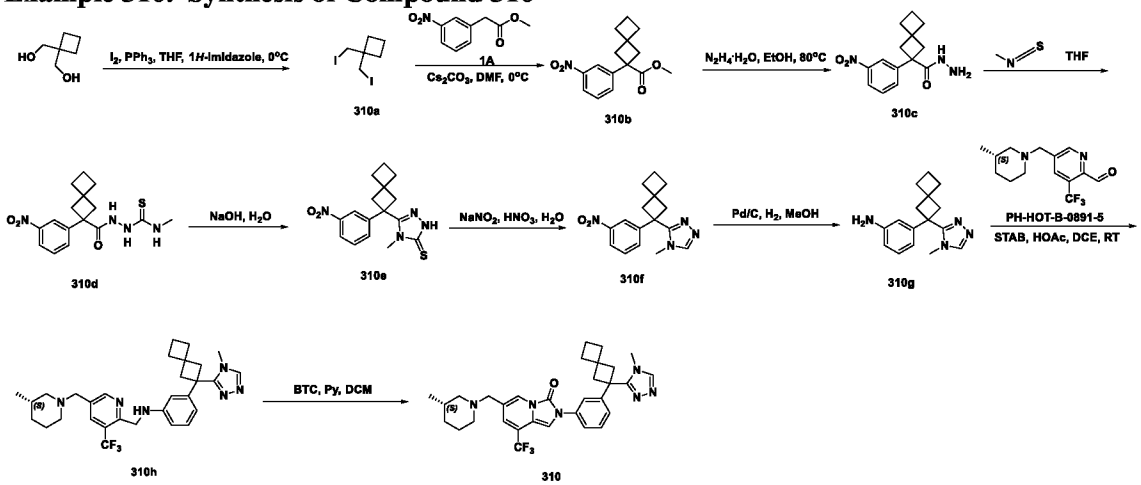


Synthesis of 309

[1089] The crude product (380 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 9.78; RT2(min): 12.55; the second peak is product) to afford 309 (47.6 mg, 12.18%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 580. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 1.08-1.11 (d, 3H), 2.27-2.36 (m, 3H), 2.75-2.96 (m, 4H), 3.10-3.13 (m, 2H), 3.25 (s, 3H), 3.56 (s, 2H), 3.77 (s, 2H), 7.09-7.11 (m, 2H), 7.38 (s, 1H), 7.46-7.50 (t, 1H),7.62-7.64 (m, 1H), 7.69-7.82 (m, 2H), 8.37 (s, 1H), 8.94 (s, 1H).

Example 310. Synthesis of Compound 310



1. Synthesis of 310a

[1090] To a stirred solution of [1-(hydroxymethyl)cyclobutyl]methanol (9 g, 77.479 mmol, 1 equiv), PPh3 (26.42 g, 100.723 mmol, 1.3 equiv) and imidazole (7.38 g, 108.471 mmol, 1.4 equiv) in THF (90 mL) were added I2 (29.50 g, 116.219 mmol, 1.5 equiv) and at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=100:1 to afford 310a (15 g, 57.63%) as a colorless oil.

2. Synthesis of 310b

[1091] To a stirred solution of methyl 2-(3-nitrophenyl)acetate (4.2 g, 21.519 mmol, 1.00 equiv) in DMF (150 mL) were added Cs2CO3 (35.06 g, 107.595 mmol, 5 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. To the above mixture was added 310a (15.00 g, 44.652 mmol, 2.075 equiv). The resulting mixture was stirred for 24h at room temperature under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (100 mL). The filtrate was diluted with water (400 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=50:1 to afford 310b (4.2 g, 70.89%) as a white solid.

3. Synthesis of 310c

[1092] To a stirred solution of 310b (4.2 g, 15.256 mmol, 1 equiv) in EtOH (42 mL) was added NH2NH2.H2O (7.64 g, 152.560 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C . The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with CH2Cl2:CH3OH=10:1 (3x100 mL). The combined organic layers were dried over Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 310c (3.9 g, 92.86%) as a yellow solid.

4. Synthesis of 310d

[1093] To a stirred solution of 310c (3.9 g, 14.166 mmol, 1 equiv) in tetrahydrofuran (40 mL) was added methyl isothiocyanate (2.59 g, 35.415 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (40 mL). The THF was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water. The resulting solid was dried under vacuum. This resulted in 310d (4.6 g, 93.20%) as a white solid.

5. Synthesis of 310e

[1094] To a stirred mixture of 310d (4.6 g, 13.202 mmol, 1 equiv) was added NaOH (1.84 g,

in 45 mL H2O) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The mixture was neutralized to pH 6 with 1 M HCl (aq.). The precipitated solids were collected by filtration and washed with water (30 mL). The resulting solid was dried under vacuum. This resulted in afford 310e (3 g, 68.77%) as a white solid.

6. Synthesis of 310f

[1095] To a stirred mixture of 310e (3 g, 9.080 mmol, 1 equiv) and NaNO2 (6.26 g, 90.800 mmol, 10 equiv) in Ethylacetate (14 mL) and H2O (52 mL) was added HNO3 (90.8 mL, 90.800 mmol, 10 equiv, 1 M) dropwise at 0 °C. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=2:1 to afford 310f (2.7 g, 99.67%) as a white solid.

7. Synthesis of 310g

[1096] To a solution of 310f (2.7 g, 9.050 mmol, 1 equiv) in 50 mL MeOH was added Pd/C (10%, 0.54 g) under nitrogen atmosphere in a 250 mL round-bottom flask. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere by using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 310g (2.35 g, 96.76%) as a white solid.

8. Synthesis of 310h

[1097] To a stirred mixture of 310g (250 mg, 0.932 mmol, 1 equiv) and I-2(266.71 mg, 0.932 mmol, 1 equiv) in DCE (3 mL) was added HOAc (55.94 mg, 0.932 mmol, 1 equiv) and STAB (592.31 mg, 2.796 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched by the addition of NaHCO3 (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH 15:1) to afford 310h (270 mg, 53.81%) as a yellow solid.

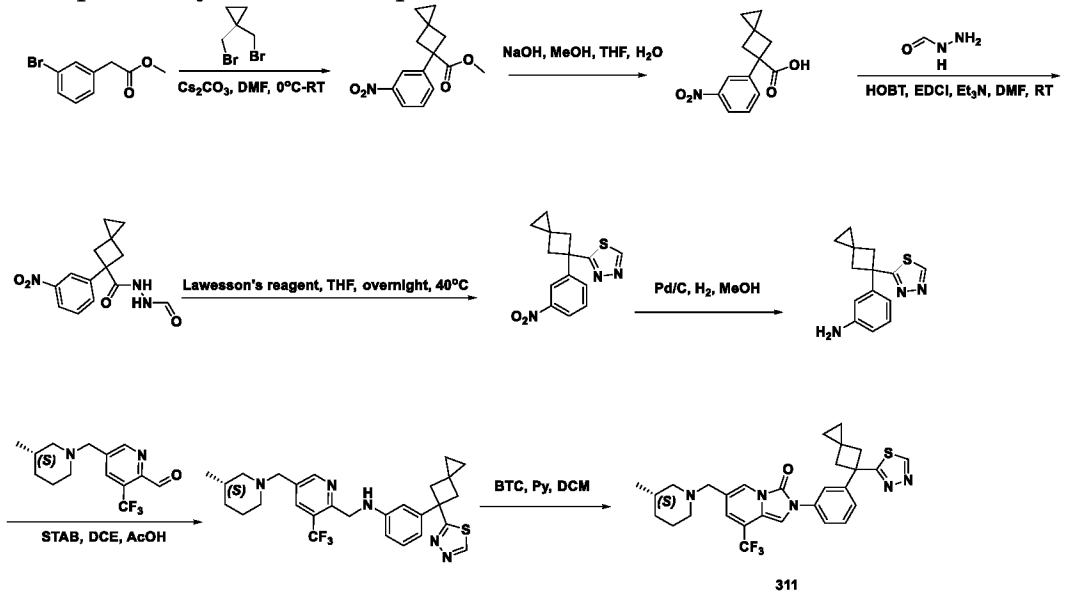
9. Synthesis of 310

[1098] To a stirred solution of 310h (250 mg, 0.464 mmol, 1 equiv) and pyridine (220.27 mg, 2.784 mmol, 6 equiv) in DCM (6 mL) was added Triphosgene (68.86 mg, 0.232 mmol, 0.5 equiv) at 0 °C. The resulting mixture was stirred for 2 min at 0 °C. The reaction was quenched by the addition of NaHCO3 (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x10 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following

conditions (Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 2% B to 100% B in 30 min) to afford the crude product (105 mg). The crude product was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 310 (75.4 mg, 27.76%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 565. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.80-0.95 (m, 4H), 1.40-1.74 (m, 5H), 1.74-1.80 (m, 2H), 1.86-1.93 (m, 3H), 1.97-2.01 (m, 2H), 2.73-2.80 (m, 4H), 3.05-3.09 (m, 2H), 3.25 (s, 5H), 7.00 (s, 1H), 7.13-7.15 (d, 1H), 7.34 (s, 1H), 7.45-7.49 (t, 1H), 7.59-7.62 (m, 1H), 7.66 (s, 1H), 7.77 (s, 1H), 8.32 (s, 1H).

Example 311. Synthesis of Compound 311



1. Synthesis of 311a

[1099] Into a 500 mL vial were added methyl 2-(3-nitrophenyl) acetate (20 g, 102.473 mmol, 1 equiv) 1,1-bis(bromomethyl)cyclopropane (70.07 g, 307.419 mmol, 3 equiv), Cs2CO3 (166.94 g, 512.365 mmol, 5 equiv) and DMF (200 mL) at 0 °C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. NH4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 311a (13 g, 44.19%) as a yellow oil.

2. Synthesis of 311b

[1100] Into a 500 mL 3-necked round-bottom were added 311a (13 g, 49.756 mmol, 1 equiv), NaOH (5.97 g, 149.268 mmol, 3 equiv), MeOH (78 mL), THF (26 mL) and H2O (26 mL) at room temperature. The resulting mixture was stirred for 30 min at 50 °C. The reaction was

quenched with HCl aq. (1 M) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 311b (10 g, 75.60%) as a yellow oil.

3. Synthesis of 311c

[1101] Into a 500 mL 3-necked round-bottom were added 311b (10 g, 40.445 mmol, 1 equiv), N-formylhydrazine (7.29 g, 121.335 mmol, 3 equiv), HOBT (10.93 g, 80.890 mmol, 2 equiv), EDCI (23.26 g, 121.335 mmol, 3 equiv), Et3N (12.28 g, 121.335 mmol, 3 equiv) and DMF (100 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL), and the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 311c (6 g, 47.69%) as a yellow oil.

4. Synthesis of 311d

[1102] Into a 250 mL 3-necked round-bottom were added 311c (6 g, 20.740 mmol, 1 equiv), Lawesson Reagent (16.78 g, 41.480 mmol, 2 equiv) and THF (60 mL) at room temperature. The resulting mixture was stirred for overnight at 40 °C. The reaction was quenched with sat. NH4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL), and the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 311d (4 g, 62.42%) as a yellow oil.

5. Synthesis of 311e

[1103] To a solution of 311d (1.3 g, 4.524 mmol, 1 equiv) in 25 mL MeOH was added Pd/C (10%, 0.13 g) under nitrogen atmosphere in a 250 mL round-bottom flask. The mixture was hydrogenated at room temperature for 5 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and the mixture was concentrated under reduced pressure. This resulted in 311e (1.1 g, 89.75%) as a yellow oil.

6. Synthesis of 311f

[1104] Into a 40 mL vial were added 311e (300 mg, 1.166 mmol, 1 equiv), I-2(400.48 mg, 1.399 mmol, 1.2 equiv), STAB (741.16 mg, 3.498 mmol, 3 equiv) and DCE (5 mL) at room temperature. The mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x20 mL) and the mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 311f (450 mg,

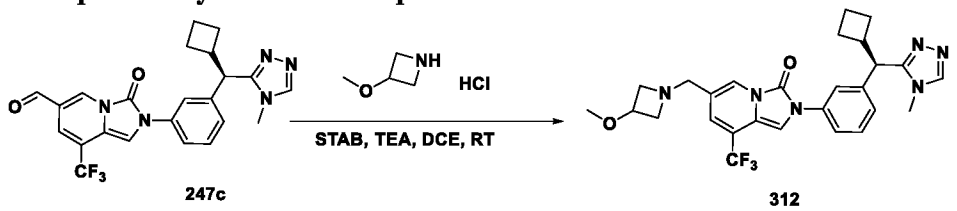
69.50%) as a yellow solid.

7. Synthesis of 311

[1105] Into a 100 mL round-bottom flask were added 311f (400 mg, 0.720 mmol, 1 equiv), DCM (12 mL) and pyridine (348.77 mg, 4.320 mmol, 6 equiv) at room temperature. To the above mixture was added triphosgene (109.03 mg, 0.360 mmol, 0.5 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, 120 g C18 silica gel; mobile phase, 0.1% NH4HCO3 in water, 50% to 60% gradient in 10 min; detector, UV 254 nm. This resulted in 311 (101.2 mg, 25.28%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 554. H-NMR: (400 MHz, CDCL3, δ ppm): 0.45-0.55 (m, 2H), 0.56-0.68 (m, 2H), 0.75-1.02 (d, 4H), 1.53-1.75 (d, 5H), 1.85-2.06 (m, 1H), 2.70-3.02 (s, 2H), 3.11-3.21 (m, 4H), 3.23-3.46 (s, 2H), 6.75-6.87 (s, 1H), 6.99-7.14 (d, 1H), 7.34-7.42 (m, 1H), 7.45-7.55 (d, 1H), 7.55-7.61(d, 1H), 7.61-7.67 (s, 1H), 7.69-7.85 (s, 1H), 9.02-9.11 (s, 1H).

Example 312. Synthesis of Compound 312



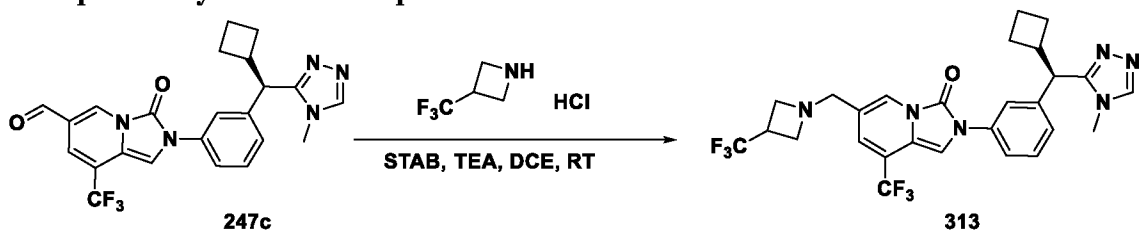
247c 312

Synthesis of 312

[1106] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and 3-methoxyazetidine hydrochloride (162.80 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20 mL). The resulting mixture was concentrated under reduced pressure. The crude product (160 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 54% B in 8 min, Wave Length: 220 nm; RT1(min): 7.02) to afford 312 (136.4 mg, 38.93%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :527. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.62-1.88 (m, 5H), δ 2.08 (s, 1H), δ 2.85-2.87 (d, 2H), δ 3.15 (s, 3H), δ 3.21-3.23 (d, 1H), δ 3.32-3.34 (d, 2H), δ 3.45 (s, 3H), δ 3.47-3.49 (d, 2H), δ 3.99-4.01 (d, 1H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 2H), δ 7.75 (s, 1H), δ 8.35 (s, 1H).

Example 313. Synthesis of Compound 313

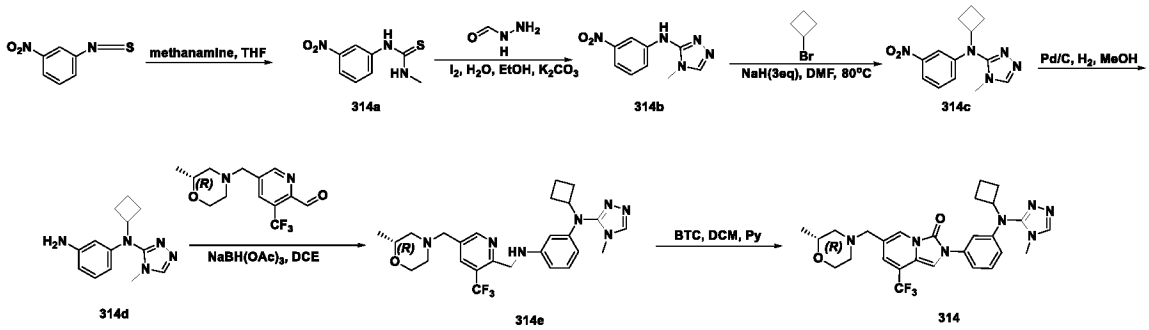


Synthesis of 313

[1107] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and 3-(trifluoromethyl)azetidine hydrochloride (212.83 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20 mL). The resulting mixture was concentrated under reduced pressure. The crude product (143mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 60% B in 8 min, 60% B; Wave Length: 220 nm; RT1(min): 7.28) to afford 313 (116.0 mg, 31.07%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :565. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.62-1.88 (m, 5H), δ 2.08 (s, 1H), δ 3.21-3.26 (m, 3H), δ 3.33-3.37 (m, 8H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 3H), δ 8.32 (s, 1H).

Example 314. Synthesis of Compound 314



1. Synthesis of 314-1

[1108] Into a 500 mL 3-necked round-bottom flask were added 1-isothiocyanato-3-nitrobenzene (25 g, 138.750 mmol, 1 equiv), Methylamine 2M in THF (138.77 mL, 277.545 mmol, 2.00 equiv) and THF (250 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (60:1) to afford 314-1 (26 g, 86.93%) as a yellow

2. Synthesis of 314-2

[1109] Into a 500 mL 3-necked round-bottom flask were added 314-1 (26 g, 123.083 mmol, 1 equiv), N-formylhydrazine (14.78 g, 246.166 mmol, 2 equiv), K2CO3 (42.53 g, 307.707 mmol, 2.5 equiv), EtOH (260 mL) and H2O (50 mL) at room temperature. To the above mixture was added I2 (37.49 g, 147.700 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with DCM (3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (80:1) to afford 314-2 (8 g, 28.17%) as a yellow solid.

3. Synthesis of 314-3

[1110] To a stirred solution of 314-2 (2 g, 9.124 mmol, 1 equiv) and DMF (30 mL) was added NaH (1.09 g, 27.372 mmol, 3 equiv, 60%) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added bromocyclobutane (3.70 g, 27.372 mmol, 3 equiv) dropwise at room temperature. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched with sat. NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=40:1) to afford 314-3 (600 mg, 23.10%) as a brown oil.

4. Synthesis of 314-4

[1111] To a solution of 314-3 (600 mg, 2.195 mmol, 1 equiv) in 10 mL MeOH was added Pd/C (20%, 120 mg) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 314-4 (500 mg, 87.05%) as a colorless oil.

5. Synthesis of 314-5

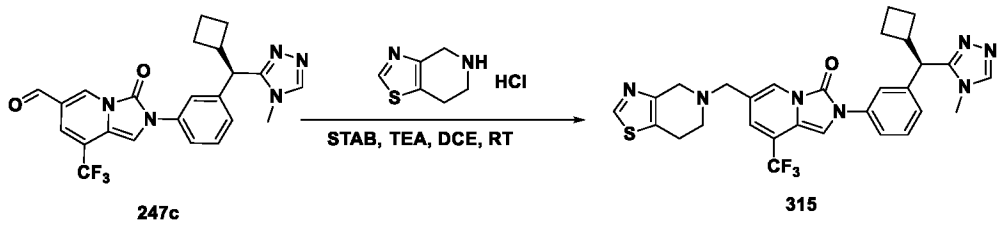
[1112] Into a 25 mL round-bottom flask were added 314-4 (300 mg, 1.233 mmol, 1 equiv), PH-I-2 (426.52 mg, 1.480 mmol, 1.2 equiv), STAB (522.63 mg, 2.466 mmol, 2 equiv) and DCE (5 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=30:1) to afford 314-5 (200 mg, 29.89%) as a brown oil.

6. Synthesis of 314-0

[1113] Into a 50 mL round-bottom flask were added 314-5 (180 mg, 0.349 mmol, 1 equiv), DCM (10 mL) and pyridine (220.92 mg, 2.792 mmol, 8 equiv) at room temperature. To the above mixture was added Triphosgene (72.52 mg, 0.244 mmol, 0.7 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, 60 g C18 silica gel; mobile phase, 0.1% NH4HCO3 in water, 40% to 60% gradient in 20 min; detector, UV 254 nm.

H-NMR-324 1H NMR (400 MHz, CDCl3) δ1.16-1.18 (m, 3H), δ1.74-1.78 (m, 2H), δ1.80-1.87 (m, 1H), δ2.02-2.07 (m, 2H), δ2.12-2.21 (m, 1H), δ2.34-2.42 (m, 2H), δ2.72-2.79 (m, 2H), δ3.26-3.33 (m, 2H), δ3.43 (s, 3H), δ3.62-3.70 (m, 2H), δ3.87-3.91 (m, 1H), δ4.48-4.52 (m, 1H), δ6.58-6.61 (d, 1H), δ6.77 (s, 1H), δ6.96-7.02 (m, 1H), δ7.09-7.11 (d, 1H), δ7.20 (s, 1H), δ7.32-7.36 (m, 1H), δ7.63 (s, 1H), δ8.21 (s, 1H).

Example 315. Synthesis of Compound 315



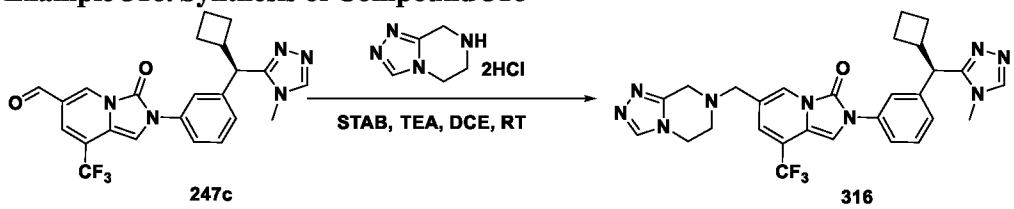
247c 315

Synthesis of 315

[1114] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 4H,5H,6H,7H-[1,3]thiazolo[4,5-c]pyridine hydrochloride (232.73 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 52% B in 8 min, Wave Length: 220 nm; RT1(min): 7.55) to afford 315 (50.6 mg, 13.21%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 580. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.83 (m, 5H), 2.07-2.12 (m, 1H), 2.81-2.91 (m, 4H), 3.19-3.25 (m, 1H), 3.43 (s, 3H), 3.54 (s, 2H), 3.66 (s, 2H), 4.25-4.28 (d, 1H), 7.07 (s, 1H), 7.18-7.20 (d, 1H), 7.33 (s, 1H), 7.69-7.77 (m, 3H), 8.33 (s, 1H), 8.90 (s, 1H).

Example 316. Synthesis of Compound 316



247c 316

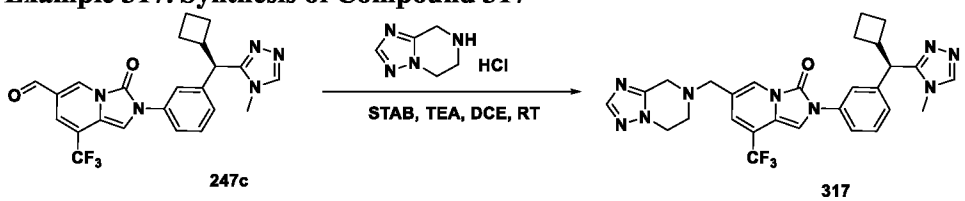
Synthesis of 316

[1115] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (317.38 mg, 1.977 mmol, 3 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred

overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 7 min, 50% B; Wave Length: 220 nm; RT1(min): 6.25) to afford 316 (34.6 mg, 9.23%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 564. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.07-2.12 (m, 1H), 2.89-2.92 (m, 2H), 3.19-3.23 (m, 1H), 3.43 (s, 3H), 3.56 (s, 2H), 3.80 (s, 2H), 4.03-4.06 (m, 2H), 4.25-4.28 (d, 1H), 7.07 (s, 1H), 7.19-7.21 (d, 1H), 7.33 (s, 1H), 7.43-7.45 (m, 1H), 7.70-7.74 (m, 2H), 7.80 (s, 1H), 8.33 (s, 1H), 8.43 (s, 1H).

Example 317. Synthesis of Compound 317



247c 317

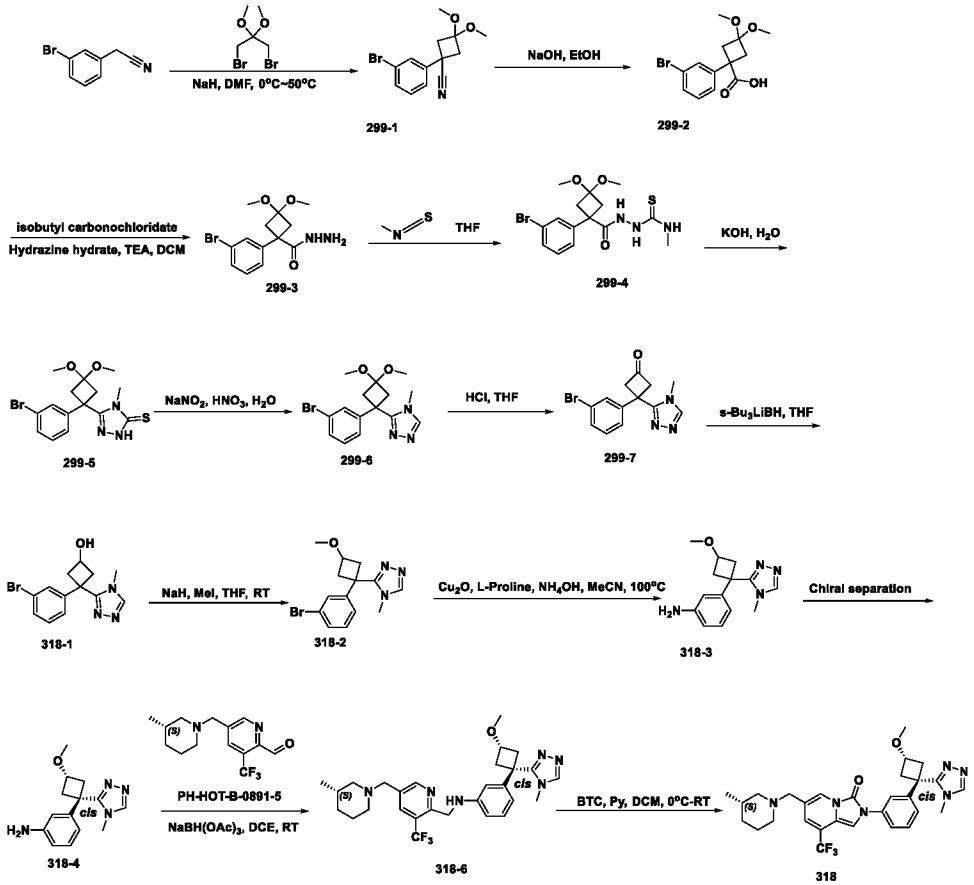
Synthesis of 317

[1116] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyrazine hydrochloride (528.97 mg, 3.295 mmol, 5 equiv) in DCE (5 mL) was added TEA (333.28 mg, 3.295 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (418.82 mg, 1.977 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: Kinetex EVO prep C18, 30*150, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 42% B in 7 min, Wave Length: 220 nm; RT1(min): 9.63) to afford 317 (20.0 mg, 5.28%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 564. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.07-2.12 (m, 1H), 3.00-3.08 (m, 2H), 3.19-3.23 (m, 1H), 3.43 (s, 3H), 3.56 (s, 2H), 3.79

(s, 2H), 4.12-4.14 (m, 2H), 4.25-4.28 (d, 1H), 7.08 (s, 1H), 7.19-7.21 (d, 1H), 7.33 (s, 1H), 7.43-7.46 (m, 1H), 7.69-7.73 (m, 2H), 7.81 (s, 1H), 7.91 (s, 1H), 8.33 (s, 1H).

Example 318. Synthesis of Compound 318



1. Synthesis of 279-1

[1117] To a stirred solution of NaH (24.48 g, 1020.164 mmol, 2 equiv) in DMF (1000 mL) was added 2-(3-bromophenyl)acetonitrile (100 g, 510.082 mmol, 1 equiv) dropwise at 0°C under nitrogen atmosphere, followed by 1,3-dibromo-2,2-dimethoxypropane (133.61 g, 510.082 mmol, 1 equiv) at 60°C under nitrogen atmosphere. The resulting mixture was stirred overnight at 60°C under nitrogen atmosphere. The reaction was quenched with NH4Cl (aq.) (2 L) at room temperature. The aqueous layer was extracted with EtOAc (2x1000 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 279-1 (60 g, 39.72%) as off-white solid.

2. Synthesis of 279-2

[1118] To a stirred solution of 279-1 (60 g, 202.590 mmol, 1 equiv) in EtOH (600 mL) was

added NaOH (28.36 g, 709.065 mmol, 3.5 equiv) in H2O (600 mL) at room temperature. The resulting mixture was stirred overnight at 80°C. The EtOH was concentrated under vacuum. The mixture was acidified to pH 2 with HCl(1M). The aqueous layer was extracted with EtOAc (4x300 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 279-2 (43 g, 67.35%) as off-white solid.

3. Synthesis of 279-3

[1119] To a stirred solution of 279-2 (43 g, 136.437 mmol, 1 equiv) and TEA (27.61 g, 272.874 mmol, 2 equiv) in DCM (1500 mL) was added isobutyl carbonochloridate (27.95 g, 204.656 mmol, 1.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C. To the above mixture was added hydrazine hydrate (27.32 g, 545.748 mmol, 4 equiv) dropwise at -30°C. The resulting mixture was stirred for additional 40min at room temperature. The reaction was quenched with water (2 L) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x800 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 279-3 (50 g, 83.49%) as off-white solid. The crude product was used in the next step directly without further purification.

4. Synthesis of 279-4

[1120] To a stirred solution of 318-3 (50 g, 113.915 mmol, 1 equiv) in tetrahydrofuran (500 mL) was added methyl isothiocyanate (24.98 g, 341.745 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (400 mL). The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with water (200 mL). This resulted in 279-4 (65 g, 99.28%) as off-white solid. The crude product was used in the next step directly without further purification.

5. Synthesis of 279-5

[1121] To a stirred solution of KOH (72.52 g, 1292.536 mmol, 8 equiv) in H2O (1.2 L) was added 318-4 (65 g, 161.567 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The residue was neutralized to pH 7 with HCl (aq.) (1M). The precipitated solids were collected by filtration and washed with water (200 mL). This resulted in 279-5 (45 g, 72.48%) as off-white solid.

6. Synthesis of 279-6

[1122] To a stirred mixture of 318-5 (45 g, 117.099 mmol, 1 equiv) and NaNO2 (80.79 g, 1170.990 mmol, 10.00 equiv) in EA (250 mL)/ H2O (250 ml) was added HNO3 (1170 mL,

1170.990 mmol, 10.00 equiv, 1M) dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 7 with saturated Na2CO3 (aq.). The aqueous layer was extracted with EtOAc (5x500 L). The resulting mixture was concentrated under vacuum. This resulted in 279-6 (35 g, 65.34%) as off-white solid.

7. Synthesis of 279-7

[1123] To a stirred solution of 279-6 (35 g, 78.747 mmol, 1 equiv, 77%) in THF (200 mL) was added HCl (150 mL, 4M) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was neutralized to pH 8 with NaHCO3 (aq.). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 40% gradient in 20 min; detector, UV 220 nm. This resulted in 279-7 (18 g, 74.66%) as a white solid.

8. Synthesis of 318-1

[1124] To a stirred solution of 279-7 (34.5 g, 112.685 mmol, 1 equiv) in THF (400 mL) was added lithium triisobutylhydroborate (42.84 g, 225.370 mmol, 2 equiv) dropwise at 0°C. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with NH4Cl (aq.) (500mL) at room temperature. The aqueous layer was extracted with EtOAc (5x400 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 60% gradient in 30 min; detector, UV 220 nm. This resulted in 318-1 (17 g, 48.95%) as a white solid.

9. Synthesis of 318-2

[1125] To a stirred mixture of 318-1 (17 g, 55.163 mmol, 1 equiv) in THF (200 mL) was added NaH (2.65 g, 110.326 mmol, 2 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 0°C under nitrogen atmosphere. To the above mixture was added MeI (9.40 g, 66.196 mmol, 1.2 equiv) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (4x300 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 60% gradient in 30 min; detector, UV 220 nm. This resulted in 318-2 as a white solid.

10. Synthesis of 318-10

[1126] To a stirred mixture of 318-2 (11 g, 34.140 mmol, 1 equiv) and Cu2O (4.89 g, 34.140 mmol, 1 equiv) in NH4OH (500 mL) and MeCN (500 mL) was added L-Proline (0.83 g, 3.414 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered; the filter cake was washed with MeOH (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in 318-3 (6.2 g, 70.30%) as off-white solid.

11. Synthesis of 318-1

[1127] The 318-3 (6.2 g) was purified by Prep-SFC with the following conditions (Column: Lux 5um Celluloes-3, 5*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH (0.1% 2M NH3-MEOH); Flow rate: 150 mL/min; Gradient: isocratic 20% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.78; RT2(min): 5.94; the first peak was product) to afford 318-1 (2.7 g) as an off-white solid.

12. Synthesis of 318-6

[1128] A solution of 318-1 (2.6 g, 10.065 mmol, 1 equiv) and I-2(3.17 g, 11.072 mmol, 1.1 equiv) in DCE (50 mL) was stirred overnight at room temperature. To the above mixture was added NaBH(OAc)3 (4.27 g, 20.130 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with NaHCO3 (aq.) (150 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (5x100 mL). The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 318-6 (2.8 g, 52.63%) as off-white solid.

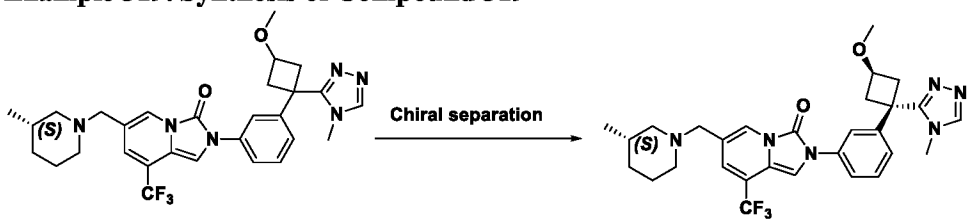
13. Synthesis of 318-0

[1129] To a stirred mixture of 318-6 (2.8 g, 5.303 mmol, 1 equiv) and Pyridine (5.39 g, 31.818 mmol, 6 equiv) in DCM (50 mL) was added triphosgene (0.596g 2.015 mmol, 0.38 equiv) at 0°C. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched with NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (4x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH4HCO3), 0% to 60% gradient in 40 min; detector, UV 254 nm. This resulted in 318 (1.577 g, 54.38%) as a yellow solid.

LC-MS-318: (ES, m/z): [M+H]+ 555

H-NMR-318: (400 MHz, DMSO-d6, δ ppm): 0.80-0.91 (m, 4H), 1.41-1.53 (m, 1H), 1.55-1.67 (m, 4H), 1.87-1.92 (m, 1H), 2.69-2.83 (m, 4H), 3.11-3.17 (m, 2H), 3.19 (s, 3H), 3.24 (s, 5H), 4.04-4.12 (m, 1H), 7.01 (s,1H), 7.25-7.27 (m, 1H), 7.41 (s, 1H), 7.49-7.53 (m, 1H), 7.67-7.69 (m, 2H), 7.79 (s, 1H), 8.32 (s, 1H).

Example 319. Synthesis of Compound 319



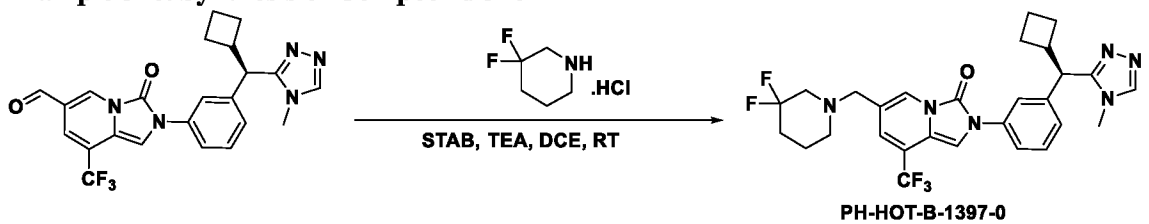
PH-HOT-B-1395-5 PH-HOT-B-1396-0

Synthesis of 319

[1130] 318-5 (280 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 35% B to 35% B in 20 min; Wave Length: 220/254 nm; RT1(min): 6.20; RT2(min): 12.59; the first peak is product) to afford 319 (155.2 mg, 68.57%) as a yellow solid.

LC-MS-319 (ES, m/z): [M+H]+ 555. H-NMR-319 (400 MHz, DMSO-d6, δ ppm): 0.80-0.91 (m, 4H), 1.40-1.48 (m, 1H),1.50-1.78 (m, 4H), 1.86-1.91 (m, 1H), 2.54-2.55 (m, 2H), 2.72-2.77 (m, 2H), 3.16 (s, 2H), 3.18 (s, 5H), 3.30-3.31 (m,1H), 3.34-3.35 (m,1H), 3.82-3.89 (m, 1H), 7.00 (s, 1H),7.07-7.09(d, 1H), 7.40 (s, 1H), 7.46-7.50 (t, 1H), 7.64-7.70 (m, 2H),7.71 (s, 1H),8.39 (s,1H).

Example 320. Synthesis of Compound 320



PH-HOT-B-1397-0

Synthesis of 320-0

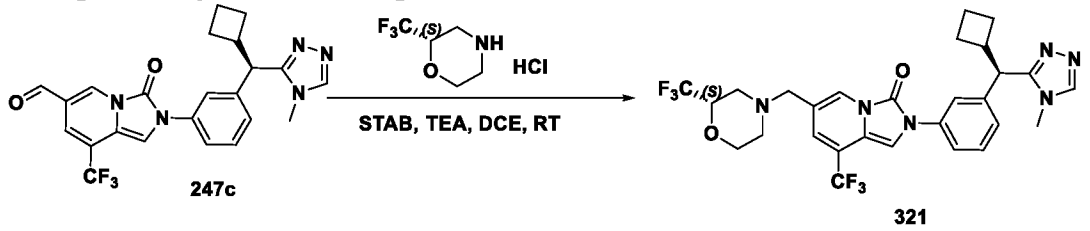
[1131] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and 3,3-difluoropiperidine hydrochloride (207.61 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) at room

temperature. The aqueous layer was extracted with CH2Cl2 (2x20 mL). The resulting mixture was concentrated under vacuum. The crude product (143 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 67% B in 8 min, 67% B; Wave Length: 220 nm; RT1(min): 7.37) to afford 320 (126.0 mg, 36.30%) as a yellow solid.

LC-MS-320 (ES, m/z): [M+H] + :561

H-NMR-320 (400 MHz, DMSO-d6, ppm): δ 1.62-1.70 (m, 3H), δ 1.71-1.83 (m, 5H), δ 1.84-1.95 (m, 2H), δ 2.11 (s, 1H), δ 2.51-2.53 (d, 2H), δ 2.65-2.67 (m, 2H), δ 3.12 (s, 1H), δ 3.46-3.49 (m, 5H), δ 4.25-4.27 (d, 1H), δ 7.30 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.64-7.68 (m, 1H), δ 7.73 (s, 1H), δ 7.65-7.68 (m, 3H), δ 8.32 (s, 1H).

Example 321. Synthesis of Compound 321



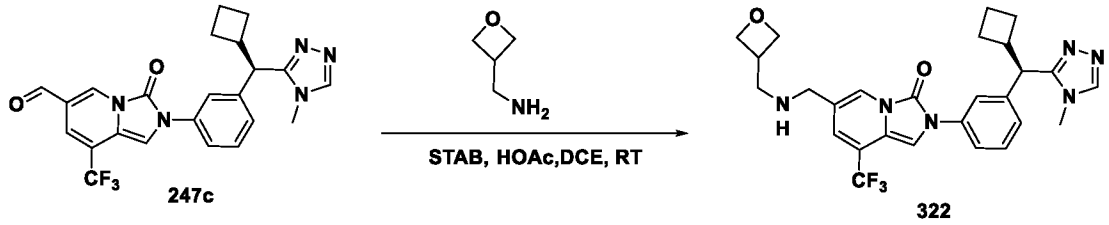
Synthesis of 321

[1132] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and (2S)-2-(trifluoromethyl)morpholine hydrochloride (252.39 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The crude product (142 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 65% B in 8 min, 65% B; Wave Length: 220 nm; RT1(min): 7.53) to afford 321 (108.9 mg, 27.44%) as a yellow solid.

LC-MS-321: (ES, m/z): [M+H] + :595. H-NMR-321: (400 MHz, DMSO-d6, ppm): δ 1.61-1.86 (m, 5H), δ 2.05-2.23 (m, 3H), δ 2.73-2.78 (m, 1H), δ 2.93-2.96 (m, 1H), δ 3.13-3.23 (m, 1H), δ 3.31-3.33 (d, 2H), δ 3.45 (s, 3H), δ 3.61-3.65 (m, 1H), δ 3.89-3.96 (m, 1H), δ 4.12-

4.22 (m, 1H), δ 4.32-4.34 (d, 1H), δ 7.02 (s, 1H), δ 7.21-7.23 (d, 1H), δ 7.33 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.71-7.73 (d, 1H), δ 7.75 (s, 2H), δ 8.33 (s, 1H).

Example 322. Synthesis of Compound 322

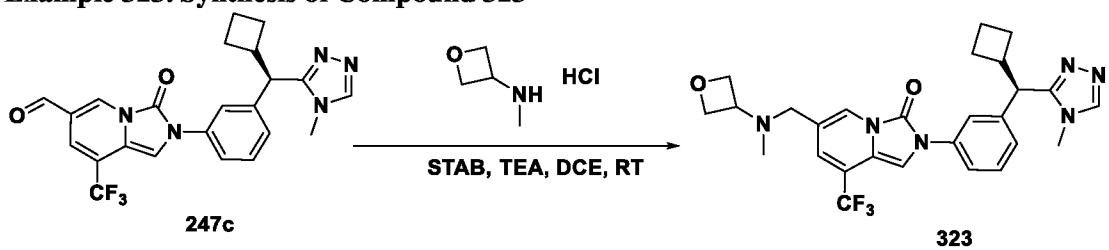


Synthesis of 322-0

[1133] To a stirred solution of 247C(300 mg, 0.659 mmol, 1 equiv) and 1-(oxetan-3-yl)methanamine (114.77 mg, 1.318 mmol, 2 equiv) in DCE (4 mL) were added STAB (279.21 mg, 1.318 mmol, 2 equiv) and HOAc (39.56 mg, 0.659 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The crude product (101 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 49% B in 8 min; Wave Length: 220 nm; RT1(min): 7.57) to afford 322 (79.9 mg, 22.94%) as a yellow solid.

LC-MS-322 (ES, m/z): [M+H] + :527. H-NMR-322 (400 MHz, DMSO-d6, ppm): δ 1.68-1.89 (m, 5H), δ 2.01-2.16 (m, 1H), δ 2.71-2.81 (m, 2H), δ 2.96-3.07 (m, 1H), δ 3.15-3.24 (m, 1H), δ 3.44 (s, 3H), δ 3.51-3.53-4.31 (d, 2H), δ 4.22-4.31 (m, 3H), δ 4.61-4.64 (m, 2H), δ 7.00 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 1H), δ 7.71-7.78 (m, 3H), δ 8.33 (s, 1H).

Example 323. Synthesis of Compound 323

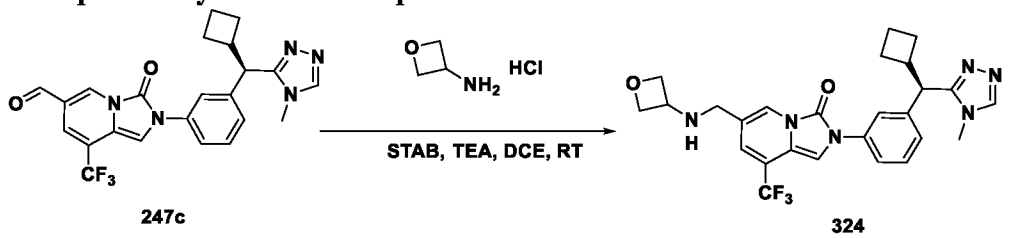


Synthesis of 323

[1134] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and N-methyloxetan-3-amine hydrochloride (162.80 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA

(133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 60% gradient in 15 min; detector, UV 254 nm. This resulted in 323 (97.3 mg, 27.94%) as a yellow solid.
LC-MS: (ES, m/z): [M+H]+ 527. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.02 (s, 3H), 2.07-2.12 (m, 1H), 3.16 (s, 2H), 3.19-3.25 (m, 1H), 3.43 (s, 3H), 3.60-3.64 (m, 1H), 4.25-4.28 (d, 1H), 4.46-4.4.49 (m, 2H), 4.53-4.4.56 (m, 2H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.33 (s, 1H), 7.42-7.46 (m, 1H), 7.69-7.74 (m, 3H), 8.33 (s, 1H).

Example 324. Synthesis of Compound 324

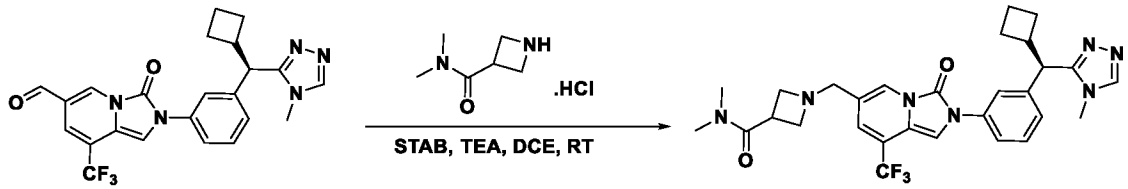


Synthesis of 324

[1135] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and oxetan-3-amine hydrochloride (144.32 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 46% B in 8 min, 46% B; Wave Length: 220 nm; RT1(min): 7.37; Number Of Runs: 0) to afford 324 (62.6 mg, 18.47%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 513. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.93 (m, 5H), 2.07-2.12 (m, 1H), 2.98-3.11 (m, 1H), 3.19-3.25 (m, 1H), 3.43 (s, 3H), 3.45 (s, 2H), 3.85-3.89 (m, 1H), 4.25-4.32 (m, 2H), 4.57-4.61 (m, 2H), 7.12 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H).

Example 325. Synthesis of Compound 325



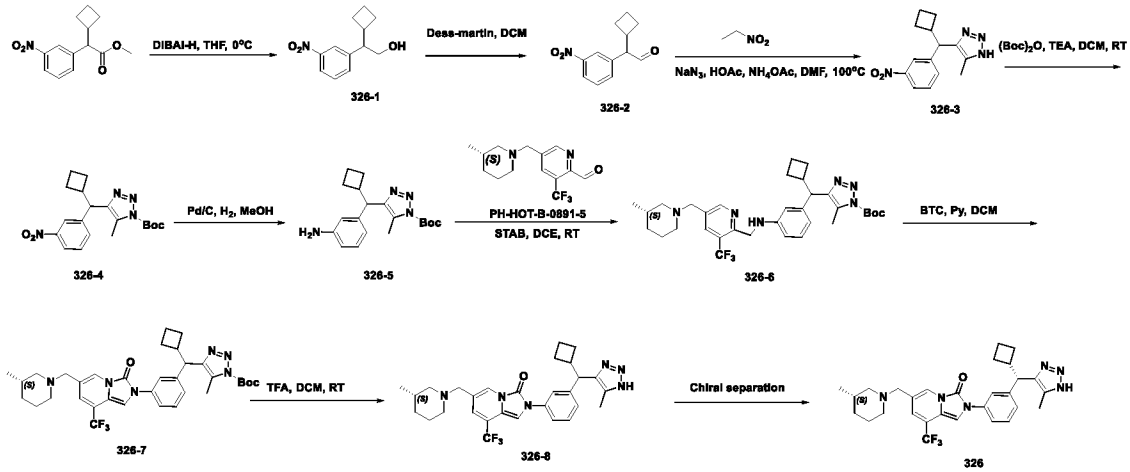
247c 325

1. Synthesis of 325

[1136] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and N,N-dimethylazetidine-3-carboxamide hydrochloride (216.88 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 49% B in 8 min, 49% B; Wave Length: 220 nm; RT1(min): 7.60) to afford 325 (94.1 mg, 24.19%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 568. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.63-1.83 (m, 5H), 2.07-2.12 (m, 1H), 2.82 (s, 6H), 3.16-3.27 (m, 3H), 3.33 (s, 2H), 3.36-3.53 (m, 6H), 4.25-4.28 (d, 1H), 6.97 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.67-7.70 (m, 2H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 326. Synthesis of Compound 326



1. Synthesis of 326-1

[1137] To a stirred solution of methyl 2-cyclobutyl-2-(3-nitrophenyl)acetate (17 g, 68.200 mmol, 1 equiv) in THF (200 mL) was added DIBAl-H (24.25 g, 170.500 mmol, 2.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 326-1 (12 g, 73.96%) as a yellow oil.

2. Synthesis of 326-2

[1138] To a stirred solution of 326-1 (11.5 g, 51.976 mmol, 1 equiv) in DCM (200 mL) was added Dess-Martin (26.45 g, 62.371 mmol, 1.2 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature. The reaction mixture was washed with water (100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 326-2 (4 g, 31.59%) as a brown oil.

3. Synthesis of 326-3

[1139] To a stirred solution of 326-2 (4 g, 18.245 mmol, 1 equiv) and nitroethane (4.11 g, 54.735 mmol, 3 equiv) in DMF (100 mL) was added NH4OAc (1.41 g, 18.245 mmol, 1 equiv), HOAc (0.55 g, 9.123 mmol, 0.5 equiv) and NaN3 (2.97 g, 45.613 mmol, 2.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C. The reaction was quenched with NaHCO3 (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 326-3 (1.3 g, 23.55%) as a yellow oil.

4. Synthesis of 326-4

[1140] To a stirred solution of 326-3 (1.2 g, 4.407 mmol, 1 equiv) and (Boc)2O (2.40 g, 11.018 mmol, 2.5 equiv) in DCM (100 mL) was added TEA (1.34 g, 13.221 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 326-4 (1.1 g, 62.33%) as a yellow oil.

5. Synthesis of 326-5

[1141] To a solution of 326-4 (1 g, 2.685 mmol, 1 equiv) in MeOH (30 mL) was added Pd/C (0.1 g, 10%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 326-5 (800 mg, 60.90%) as a yellow oil.

6. Synthesis of 326-6

[1142] To a stirred solution of 326-5 (800 mg, 1.635 mmol, 1 equiv, 70%) and I-2(702.28 mg, 2.453 mmol, 1.5 equiv) in DCE (5 mL) was added STAB (693.17 mg, 3.270 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 40:1) to afford 326-6 (520 mg, 48.26%) as a yellow solid.

7. Synthesis of 326-7

[1143] To a stirred solution of 326-6 (500 mg, 0.816 mmol, 1 equiv) and Pyridine (645.46 mg, 8.160 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (121.07 mg, 0.408 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. This resulted in 326-7 (400 mg, 61.40%) as a yellow solid.

8. Synthesis of 326-8

[1144] To a stirred solution of 326-7 (380 mg, 0.595 mmol, 1 equiv) in DCM (5 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD

Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 53% B to 78% B in 8 min, Wave Length: 220 nm; RT1(min): 7.72) to afford 326-8 (180 mg, 55.05%) as a yellow solid.

9. Synthesis of 326

[1145] The 326-8 (180 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.94; RT2(min): 12.89; the first peak is product) to afford 326 (67.1 mg, 37.20%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 539. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.89-0.99 (m, 4H), 1.46-1.72 (m, 6H), 1.72-1.96 (m, 6H), 2.13 (s, 3H), 2.74-2.85 (m, 2H), 3.05-3.25 (m, 1H), 3.24 (s, 2H), 4.07-4.09 (m, 1H), 7.00 (s, 1H), 7.21-7.30 (m, 2H), 7.36-7.42 (m, 1H), 7.61-7.65 (m, 2H), 7.75 (s, 1H), 14.27-14.77 (m, 1H).

Example 327. Synthesis of Compound 327



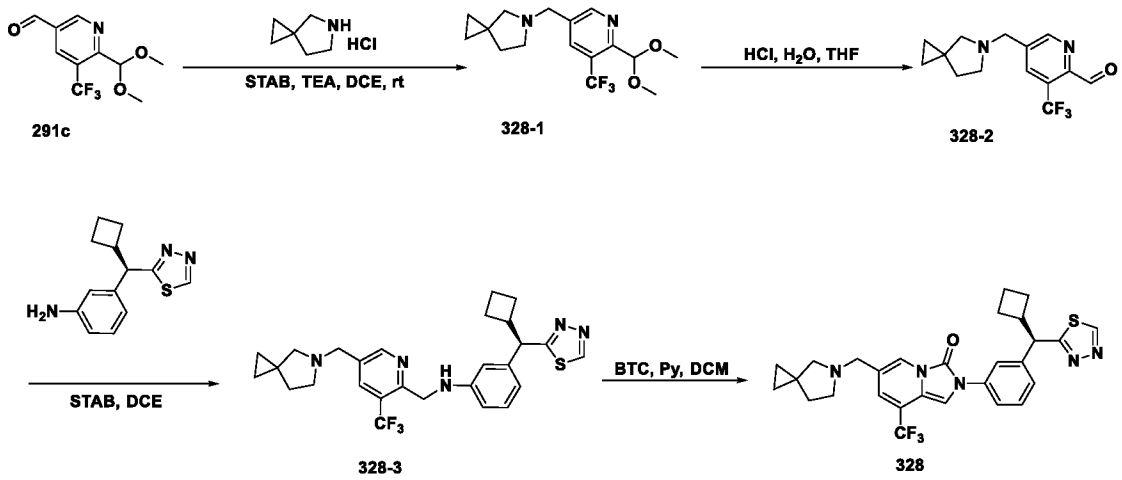
326-8 327

1. Synthesis of 327

[1146] 326-8 (180 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.94; RT2(min): 12.89; the second peak is product) to afford 327 (70.8 mg, 39.18%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 539. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.89-0.99 (m, 4H), 1.41-1.49 (m, 1H), 1.49-1.72 (m, 5H), 1.72-1.95 (m, 6H), 2.12 (s, 3H), 2.73-2.83 (m, 2H), 3.08-3.23 (m, 1H), 3.24 (s, 2H), 4.07-4.09 (m, 1H), 7.00 (s, 1H), 7.25-7.30 (m, 2H), 7.38-7.42 (m, 1H), 7.61-7.65 (m, 2H), 7.75 (s, 1H), 14.29-14.69 (m, 1H).

Example 328. Synthesis of Compound 328



291c 328-1 328-2

328-3 328

1. Synthesis of 328-1

[1147] To a stirred solution of 5-azaspiro [2.4] heptane hydrochloride (375 mg, 2.80 mmol, 1.0 equiv) and 291c (700 mg, 2.80 mmol, 1.0 equiv) in DCE (7 mL) were added TEA (284 mg, 2.80 mmol, 1.0 equiv) and STAB (1190 mg, 5.61 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NH4Cl (aq.) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 328-1 (300 mg, 31%) as a colorless oil.

2. Synthesis of 328-2

[1148] A solution of 328-1 (300 mg, 0.90 mmol, 1.0 equiv) and in THF (0.7 mL) and HCl (3 mL, 98.74 mmol, 1 M) was stirred for 2 h at room temperature. The residue was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 328-2 (190 mg, 72%) as a colorless oil.

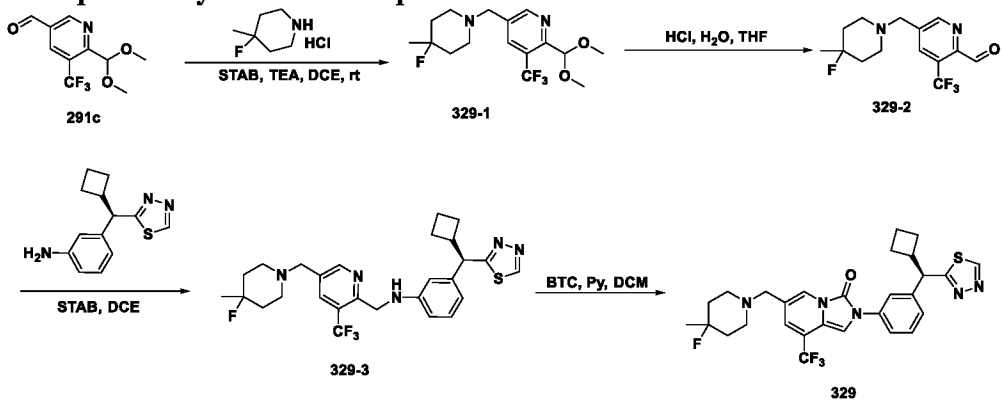
3. Synthesis of 328-3

[1149] A solution of 328-2 (256 mg, 0.90 mmol, 1.3 equiv) in DCE (1.7 mL) was treated with (R)-3-(cyclobutyl(1,3,4-thiadiazol-2-yl)methyl)aniline (170 mg, 0.69 mmol, 1.0 equiv) for 0.5 h at room temperature followed by the addition of STAB (293 mg, 1.38 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 328-3 (300 mg, 71%) as a yellow oil.

4. Synthesis of 328

[1150] To a stirred solution of 328-3 (300 mg, 0.58 mmol, 1 equiv) and pyridine (277 mg, 3.50 mmol, 6.0 equiv) in DCM (3 mL) were added triphosgene (60 mg, 0.20 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 1.5 h at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH4HCO3), 15% to 85% gradient in 40 min; UV 254 nm. This resulted in 328 (109.3 mg, 34%) as a yellow solid. LC-MS: (ES, m/z): [M+H] + 540. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.45-0.50 (m, 4H), 1.73-1.77 (m, 3H), 1.79-1.87 (m, 4H), 2.04-2.08 (m, 1H), 2.45 (s, 2H), 2.66-2.69 (t, 2H), 3.21-3.24 (m, 1H), 3.39 (s, 2H), 4.71-4.73 (d, 1H), 7.04 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.48 (t, 1H), 7.68 (s, 1H), 7.75-7.77 (m, 1H), 7.86 (s, 1H), 9.50 (s, 1H).

Example 329. Synthesis of Compound 329



291c 329-1 329-2 329-3 329

1. Synthesis of 329-1

[1151] To a stirred solution of 4-fluoro-4-methylpiperidine hydrochloride (500 mg, 3.25 mmol, 1.0 equiv) and 291c (811 mg, 3.25 mmol, 1.0 equiv) in DCE (5 mL) were added TEA (658 mg, 6.51 mmol, 2.0 equiv) and STAB (1379 mg, 6.51 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 329-1 (360 mg, 32%) as a colorless oil.

2. Synthesis of 329-2

[1152] To a stirred solution of 329-1 (350 mg, 0.99 mmol, 1.0 equiv) in THF (3.5 mL) was added HCl (3.5 mL, 1M) at room temperature. The resulting mixture was stirred for 2 h at

80°C. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 329-2 (300 mg, 97%) as a colorless oil.

3. Synthesis of 329-3

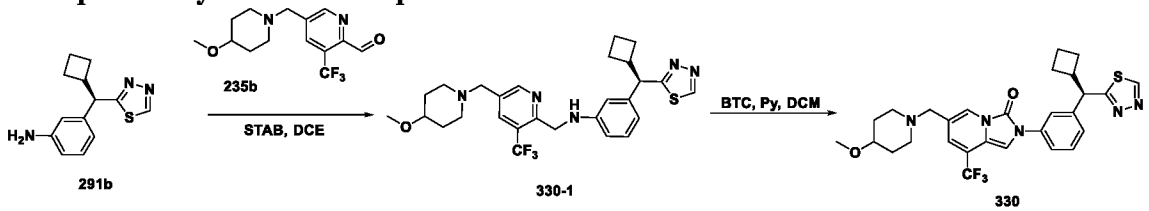
[1153] To a stirred solution of 291-2 (200 mg, 0.81 mmol, 1.0 equiv) and 329-2 (322 mg, 1.09 mmol, 1.3 equiv) in DCE (4 mL) was added STAB (345 mg, 1.63 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with water (15 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 329-3 (350 mg, 80%) as an off-white solid.

4. Synthesis of 329

[1154] To a stirred solution of 329-3 (350 mg, 0.66 mmol, 1.0 equiv) and pyridine (311 mg, 3.96 mmol, 6.0 equiv) in DCM (3.5 mL) was added triphosgene (68 mg, 0.23 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% NH4HCO3), 20% to 90% gradient in 40 min; UV 254 nm. This resulted in 329 (106 mg, 28%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 560. H-NMR: (400 MHz, dmso-d6, δ ppm): 1.29-1.34 (d, 3H), 1.58-1.67 (m, 6H), 1.71-1.88 (m, 4H), 2.05-2.06 (m, 1H), 2.24-2.29 (m, 2H), 2.60-2.63 (m, 2H), 3.20-3.23 (m, 1H), 3.26 (s, 2H), 4.71-4.73 (d, 1H), 7.01 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.69 (s, 1H), 7.75-7.77 (m, 1H), 7.86 (s, 1H) 9.51 (s, 1H).

Example 330. Synthesis of Compound 330



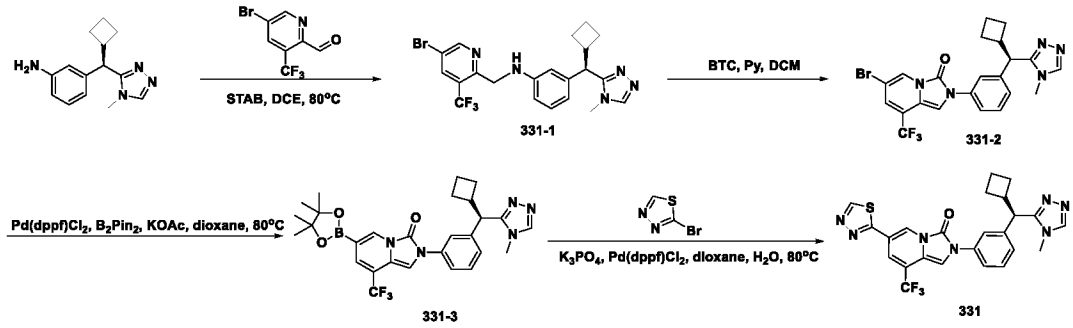
1. Synthesis of 330-1

[1155] A solution of 291b (200 mg, 0.815 mmol, 1 equiv) in DCE (2 mL) was treated with 235b (295.72 mg, 0.978 mmol, 1.2 equiv) for 2h at room temperature followed by the addition of STAB (345.54 mg, 1.630 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (8mL) at room temperature. The resulting mixture was extracted with DCM/MeOH(10:1)(30mL) The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column,C18 silica gel ; mobile phase A:Water(0.1% NH4HCO3); mobile phase B:ACN ,Gradient:25%B to 80%B in 30 min; detector, UV 254 nm . This resulted in 330-1 as a yellow solid.

2. Synthesis of 330

[1156] A solution of 330-1 (353 mg, 0.663 mmol, 1 equiv) in DCM (10 mL) was treated with Pyridine (314.54 mg, 3.978 mmol, 6 equiv) at room temperature followed by the addition of triphosgene (78.63 mg, 0.265 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 30min at room temperature . The reaction was quenched by the addition of sat. NaHCO3 (aq.) (8mL) at room temperature. The resulting mixture was extracted with DCM/MeOH(10:1)(30mL), The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column,C18 silica gel ; mobile phase A:Water(0.1% NH4HCO3); mobile phase B:ACN ,Gradient:25%B to 80%B in 30 min; detector, UV 254 nm. The crude product (190mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 72% B in 8 min, 72% B; Wave Length: 220 nm) to afford 330 (120.3 mg, 31.25%) as a yellow solid. LC-MS-330 (ES, m/z): [M+H] + 558. H-NMR: (400 MHz, DMSO, ppm): δ1.41-1.43 (m, 1H), 1.77-1.87 (m, 7H), 2.07-2.11 (m, 3H), 3.22-3.28(m, 8H), 4.71-4.74(d, 1H), 7.02 (s,1H), 7.33-7.35 (m, 2H), 7.46-7.51 (t, 1H), 7.67 (s, 1H), 7.75-7.77(s, 1H) ,7.86 (s, 1H), 9.51 (s, 1H).

Example 331. Synthesis of Compound 331



1. Synthesis of 331-1

[1157] Into a 100mL 3-necked round-bottom flask were added 244b (1 g, 4.127 mmol, 1 equiv), DCE (10 mL), I-2 (1.57 g, 6.191 mmol, 1.5 equiv) and STAB (2.62 g, 12.381 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at 80°C. The mixture was acidified to pH 7 with saturated NH_4Cl (aq.). The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 331-1 (1.1 g, 52.72%) as a light brown oil.

2. Synthesis of 331-2

[1158] Into a 100 mL round-bottom flask were added 331-1 (1 g, 2.082 mmol, 1 equiv), DCM (20 mL) and Pyridine (0.99 g, 12.492 mmol, 6 equiv) at 0°C.To the above mixture was added Triphosgene (0.28 g, 0.937 mmol, 0.45 equiv) at 0°C. The resulting mixture was stirred for additional 8 min at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 331-2 (0.8 g, 73.62%) as a light yellow solid.

3. Synthesis of 331-3

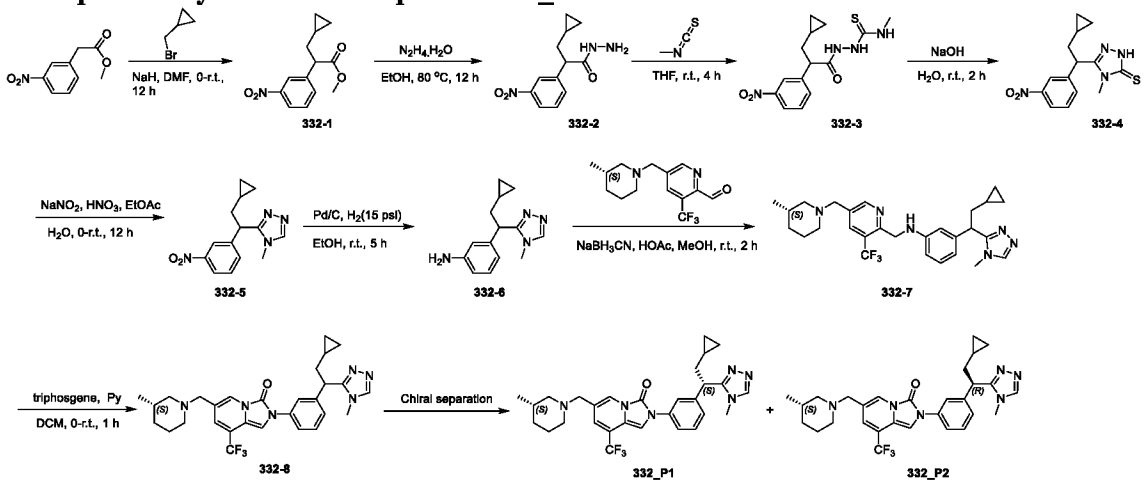
[1159] Into 100 mL round-bottom flask were added 331-3(800 mg, 1.580 mmol, 1 equiv), dioxane (10 mL), KOAc (310.13 mg, 3.160 mmol, 2 equiv), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.60 g, 6.320 mmol, 4 equiv) and $Pd(dppf)Cl_2$ (173.42 mg, 0.237 mmol, 0.15 equiv) at room temperature. The resulting mixture was stirred for 8 h at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 331-3 (300 mg, 32.60%) as a light yellow oil.

4. Synthesis of 331

[1160] Into an 8 mL sealed tube were added 331-3 (200 mg, 0.361 mmol, 1 equiv), 2-bromo-1,3,4-thiadiazole (89.45 mg, 0.541 mmol, 1.5 equiv), K_3PO_4 (230.14 mg, 1.083 mmol, 3 equiv), dioxane (1.6 mL) and H_2O (0.4 mL) at room temperature. To the above mixture was added $Pd(dppf)Cl_2$ (52.89 mg, 0.072 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for 6 h at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford crude product (70 mg) as a light yellow oil. The crude product (70 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 67% B in 8 min; Wave Length: 220 nm; RT(min): 7.17;) to afford 331 (44.4 mg, 24.02%) as a light yellow solid.

LCMS: (ES, m/z): $[M+H]^+$ 512. H-NMR: (300 MHz, DMSO-d6, *ppm*): δ1.67-1.99 (m, 5H), δ2.05-2.11 (m, 1H), δ3.22-3.26 (m, 1H), δ3.44 (s, 3H), δ4.27-4.30 (d, 1H), δ7.23-7.25 (d, 1H), δ7.46-7.48(d, 1H), δ7.50 (s, 1H), δ7.61(s, 1H), δ7.71-7.73 (d, 1H), δ7.77(s, 1H), δ8.34 (s, 1H), δ8.46 (s, 1H), δ9.63 (s, 1H).

Example 332. Synthesis of Compounds 332_P1 and P2



1. Synthesis of 332-1

[1161] To a solution of NaH (3.38 g, 84.54 mmol, 60% purity, 1.1 equiv) in DMF (150 mL) was added a solution of methyl 2-(3-nitrophenyl)acetate (15 g, 76.86 mmol, 1 equiv) in DMF (20 mL) under nitrogen atmosphere, the mixture was cooled to 0 °C. Then bromomethylcyclopropane (11 mL, 115 mmol, , 1.5 equiv) was added to the mixture at 0 °C, the result mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. The reaction

mixture was diluted with Sat.NH4Cl (150 mL), extracted with EtOAc (150 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (3:1) to afford 332-1 (13 g, 68%) as a light yellow solid.

H-NMR-332-1: (400 MHz, CHLOROFORM-d) δ 8.18 (t, J = 2.0 Hz, 1H), 8.12-8.07 (m, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 3.77 (t, J = 7.6 Hz, 1H), 3.68-3.65 (m, 3H), 1.92-1.85 (m, 1H), 1.83-1.74 (m, 1H), 0.61-0.50 (m, 1H), 0.44-0.35 (m, 2H), 0.12-0.04 (m, 1H), -0.03--0.07 (m, 1H)

2. Synthesis of 332-2

[1162] To a solution of 332-1 (12 g, 48.1 mmol, 1 equiv) in EtOH (120 mL) was added N2H4.H2O (38.2 mL, 770 mmol, 98% purity, 16 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrate in vacuum to remove EtOH (120 mL), then the mixture was diluted with water (600 mL), and extracted with EtOAc (200 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 332-2 (12 g, crude) as a yellow solid.

3. Synthesis of 332-3

[1163] To a solution of 332-2 (3.23 g, 12.96 mmol, 1 equiv) in THF (40 mL) was added methylimino(thioxo)methane (1.77 mL, 25.9 mmol, 2 equiv). The mixture was stirred at 20 °C for 4 hr. The reaction mixture was diluted water (40 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 332-3 (3.7 g, crude) as a white solid.

4. Synthesis of 332-4

[1164] To a solution of NaOH (3.67 g, 91.8 mmol, 8 equiv) in water (37 mL) was added 332-3 (3.7 g, 11.4 mmol, 1 equiv). The mixture was stirred at 25°C for 2 hr. The reaction mixture was diluted with water (40 mL), and adjusted pH to 3 by 1N HCl. Then the mixture was filtered and the filter cake was concentrated in vacuum to afford 332-4 (3.47 g, 98%) as a white solid.

H-NMR-332-4: (400 MHz, DMSO-d6) δ 13.68 (s, 1H), 8.15-8.04 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.63-7.55 (m, 1H), 4.45 (t, J = 7.6 Hz, 1H), 3.22 (s, 3H), 2.04-1.88 (m, 1H), 1.79-1.68 (m, 1H), 0.59-0.46 (m, 1H), 0.33-0.18 (m, 2H), 0.06--0.03 (m, 1H), -0.06--0.14 (m, 1H)

5. Synthesis of 332-5

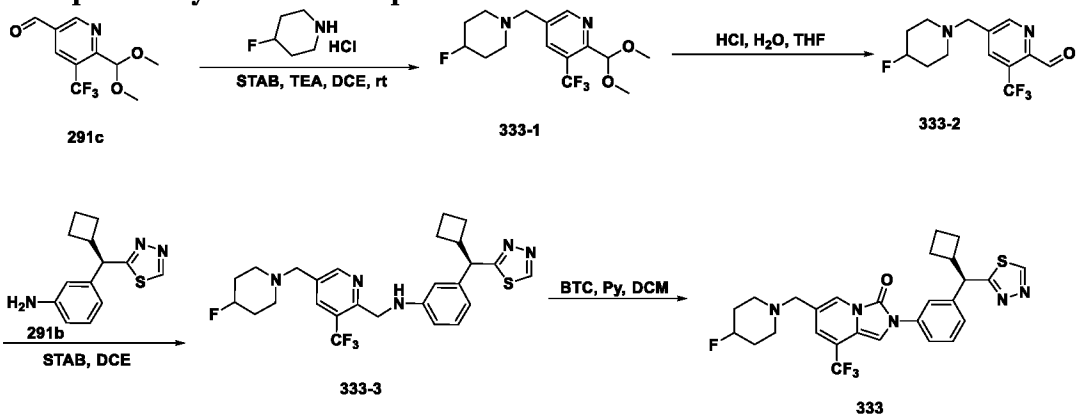
[1165] HNO3 (7.55 mL, 114 mmol, 68% purity, 10 equiv) was added to water (105.6 mL) to afford the diluted HNO3 solution (1 M, 113 mL). To a solution of 341-4 (3.47 g, 11.4 mmol,

1 equiv) and NaNO2 (7.87 g, 114 mmol, 10 equiv) in EtOAc (3.5 mL, 35.7 mmol, 3.14 equiv) and water (35 mL) was added diluted HNO3 solution (1 M, 113 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 12 hr. The reaction was quenched by the addition of Sat.NaHCO3 (100 mL) The aqueous phase was extracted with CH2Cl2 (100 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 332-5 (2.7 g, crude) as a yellow oil.

6. Synthesis of 332-6

[1166] To a 332-5(2.5 g, 9.18 mmol, 1 eq) in EtOH (30 mL) was added Pd/C (2.5 g, 10% purity). The mixture was stirred at r.t. for 5 hr under H2 (15 psi). The reaction mixture was filtered through celite, and the filtrate was concentrated in vacuum o afford 332-6 (1.9 g, 88.24%) as a gray solid. H-NMR-332-6: (400 MHz, DMSO-d6) δ 8.26 (s, 1H), 6.87 (t, J = 8.0 Hz, 1H), 6.42-6.28 (m, 3H), 4.96 (s, 2H), 3.94 (t, J = 7.6 Hz, 1H), 3.32 (s, 3H), 2.12-1.93 (m, 1H), 1.84-1.63 (m, 1H), 0.72-0.50 (m, 1H), 0.41-0.21 (m, 2H), -0.05--0.09 (m, 2H).

Example 333. Synthesis of Compound 333



1. Synthesis of 333-1

[1167] A solution of 291c (800 mg, 3.210 mmol, 1 equiv) in DCE (8 mL) was treated with 4-fluoropiperidine hydrochloride (896.34 mg, 6.420 mmol, 2 equiv) and TEA (974.61 mg, 9.630 mmol, 3 equiv) for 2h at room temperature followed by the addition of STAB (1360.83 mg, 6.420 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature . The reaction was quenched with sat. NaH4Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20mL). The combined organic was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=3:1) to afford 333-1 (550 mg, 48.90%) as a off-white oil.

2. Synthesis of 333-2

[1168] To a stirred solution of 333-1 (550 mg, 1.635 mmol, 1 equiv) in THF (5.5 mL) was

added HCl (5.5 ml, 1M) at room temperature. The resulting mixture was stirred for 2 h at 80°C. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was extracted with EtOAc (3 x20 mL). The combined organic was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=2:1) to afford 333-2 (442 mg, 90.33%) as a colorless oil.

3. Synthesis of 333-3

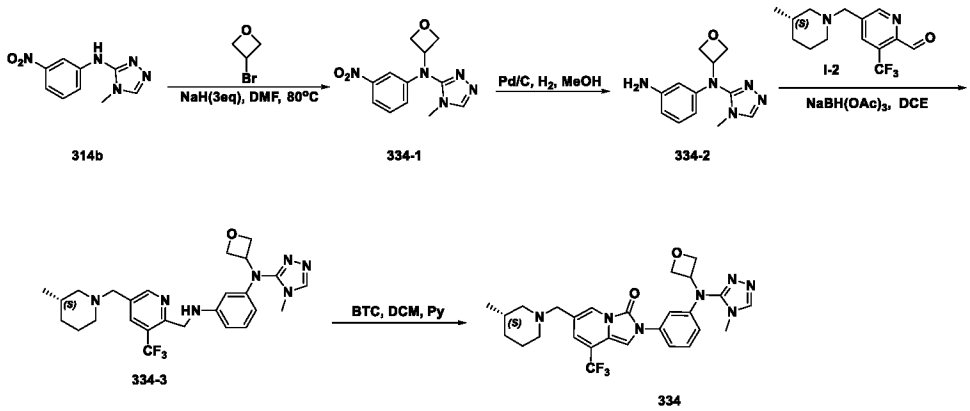
[1169] A solution of 333-2 (247.27 mg, 0.851 mmol, 1.1 equiv) in DCE (2 mL) was treated with 291b (190 mg, 0.774 mmol, 1.00 equiv) for 2h at room temperature under nitrogen atmosphere followed by the addition of STAB (328.27 mg, 1.548 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NaHCO3 (aq.)(8ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20mL). The combined organic was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column,C18 silica gel ; mobile phase A:Water(0.1% NH4HCO3); mobile phase B:ACN ,Gradient:20%B to 80%B in 30 min; detector, UV 254 nm. This resulted in 333-3 (270 mg, 63.07%) as a light yellow solid.

4. Synthesis of 333

[1170] A solution of 333-3(270 mg, 0.520 mmol, 1 equiv) in DCM (8 mL) was treated with Pyridine (246.61 mg, 3.120 mmol, 6 equiv) at room temperature then followed by the addition of triphosgene (61.72 mg, 0.208 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (8mL) at room temperature. The resulting mixture was extracted with DCM/MeOH(10:1)(30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: MeOH; Gradient: 64% B to 82% B in 8 min, 82% B; Wave Length: 220 nm) to afford 333 (100.8 mg, 35.55%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 546. H-NMR: (400 MHz, DMSO, ppm): δ1.75-2.05 (m, 9H), 2.06-2.08(m, 1H), 2.33-2.35 (m, 2H), 2.51-2.55 (m, 2H), 3.21-3.23 (m, 1H), 3.25 (s, 2H), 4.63-4.77 (m,2H), 7.02 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50(t, 1H) ,7.69(s, 1H),7.75-7.77 (m, 1H), 7.86(s, 1H), 9.50 (s, 1H).

Example 334. Synthesis of Compound 334



1. Synthesis of 334-1

[1171] To a stirred solution of 314b (2 g, 9.124 mmol, 1 equiv) and DMF (20 mL) was added NaH (1.09 g, 27.372 mmol, 3 equiv, 60%) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added 3-bromooxetane (3.75 g, 27.372 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched with sat. NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=40:1) to afford 334-1 (300 mg, 10.99%) as a brown oil.

2. Synthesis of 334-2

[1172] To a solution of 334-1 (300 mg, 1.090 mmol, 1 equiv) in 10 mL MeOH was added Pd/C (20%, 60 mg) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 334-2 (170 mg, 59.78%) as a colorless oil.

3. Synthesis of 334-3

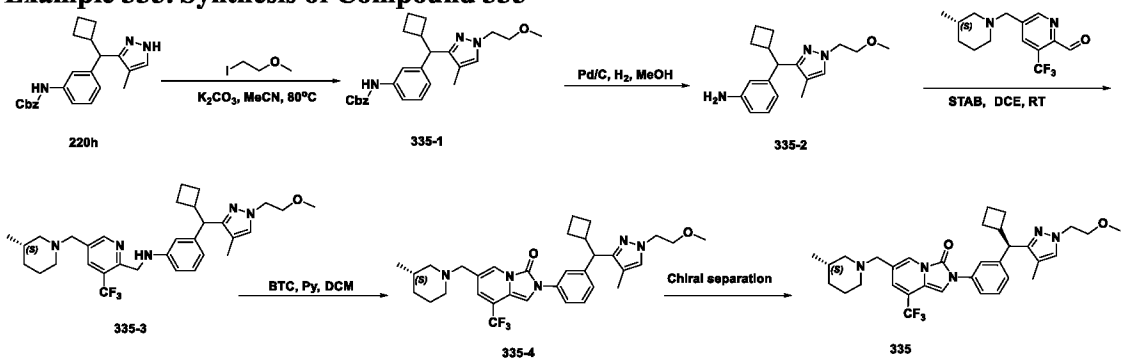
[1173] Into a 25 mL round-bottom flask were added 334-2 (170 mg, 0.693 mmol, 1 equiv), I-2(238.11 mg, 0.832 mmol, 1.2 equiv), STAB (293.78 mg, 1.386 mmol, 2 equiv) and DCE (5 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=30:1) to afford 334-3 (160 mg, 42.98%) as a brown oil.

4. Synthesis of 334

[1174] Into a 50 mL round-bottom flask were added 334-3 (170 mg, 0.330 mmol, 1 equiv), pyridine (208.65 mg, 2.640 mmol, 8 equiv) and DCM (10 mL) at room temperature. To the above mixture was added Triphosgene (68.49 mg, 0.231 mmol, 0.7 equiv) at 0 °C. The resulting mixture was stirred for additional 5 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 69% B in 8 min, 69% B; Wave Length: 220 nm;

H-NMR: 1H NMR (400 MHz, CD3OD) δ0.89-1.02 (m, 4H), δ1.60-1.78 (m, 5H), δ1.95-2.00 (m, 1H), δ2.82-2.91 (m, 2H), δ3.33 (s, 2H), δ3.52 (s, 3H), δ4.63-4.66 (m, 2H), δ4.89-4.95 (m, 2H), δ5.19-5.26 (m, 1H), δ6.68-6.71 (d, 1H), δ7.12 (s, 1H), δ7.17 (s, 1H), δ7.29 (s, 1H), δ7.34-7.36 (d, 1H), δ7.47-7.42 (m, 1H), δ7.66 (s, 1H), δ8.51 (s, 1H).

Example 335. Synthesis of Compound 335



1. Synthesis of 335-1

[1175] To a stirred solution of 220h (3.2 g, 8.523 mmol, 1 equiv) and 1-iodo-2-methoxyethane (3.17 g, 17.046 mmol, 2 equiv) in MeCN (50 mL) was added K2CO3 (3.53 g, 25.569 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The resulting mixture was diluted with water (150 mL). The aqueous layer was extracted with EtOAc (2x80 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 40:1) to afford 335-1 (750 mg, 18.88%) as a light yellow solid.

2. Synthesis of 335-2

[1176] To a solution of 335-1 (750 mg, 1.730 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (100 mg) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for 4h under hydrogen atmosphere using a hydrogen

balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 335-2 (500 mg, 86.88%) as an off-white solid.

3. Synthesis of 335-3

[1177] To a stirred solution of 335-2 (500 mg, 1.670 mmol, 1 equiv) and I-2(573.71 mg, 2.004 mmol, 1.2 equiv) in DCE (10 mL) was added STAB (707.84 mg, 3.340 mmol, 2 equiv)at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 40:1) to afford 335-3 (720 mg, 70.38%) as a light yellow oil.

4. Synthesis of 335-4

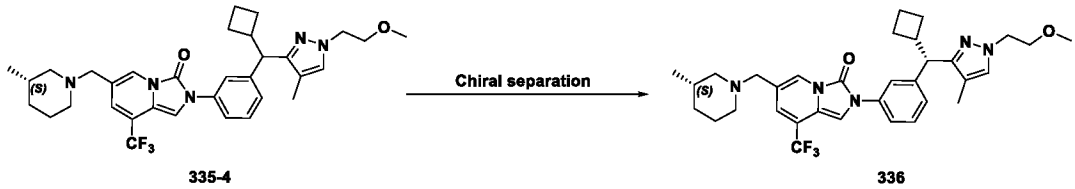
[1178] To a stirred solution of 335-3 (700 mg, 1.229 mmol, 1 equiv) and pyridine (971.91 mg, 12.290 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (182.29 mg, 0.615 mmol, 0.5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 335-4 (550 mg, 72.14%) as a yellow solid.

5. Synthesis of 335

[1179] The 335-4 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 15 min; Wave Length: 220/254 nm; RT1(min): 9.008; RT2(min): 11.926; the second peak is product) to afford 335 (125.6 mg, 30.05%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 596. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.44-1.52 (m, 1H), 1.52-1.72 (m, 5H), 1.72-1.84 (m, 4H), 1.84 (s, 3H), 1.84-2.00 (m, 2H), 2.71-2.85 (m, 2H), 3.09-3.17 (m, 1H), 3.19 (s, 3H), 3.25 (s, 2H), 3.62-3.64 (m, 2H), 3.93-3.96 (d, 1H), 4.11-4.14 (m, 2H), 7.00 (s, 1H), 7.22-7.25 (m, 2H), 7.31 (s, 1H), 7.35-7.39 (m, 1H), 7.58-7.60 (d, 1H), 7.60 (s, 1H), 7.66 (s, 1H).

Example 336. Synthesis of Compound 336



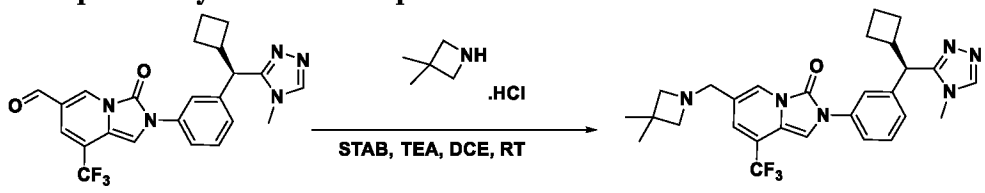
335-4 336

1. Synthesis of 336

[1180] The 335-4 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 15 min; Wave Length: 220/254 nm; RT1(min): 9.008; RT2(min): 11.926; the first peak is product) to afford 336 (117.8 mg, 28.33%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 596. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.43-1.52 (m, 1H), 1.52-1.71 (m, 5H), 1.71-1.84 (m, 4H), 1.84 (s, 3H), 1.84-2.00 (m, 2H), 2.71-2.85 (m, 2H), 3.09-3.18 (m, 1H), 3.19 (s, 3H), 3.26 (s, 2H), 3.62-3.64 (m, 2H), 3.93-3.95 (d, 1H), 4.11-4.14 (m, 2H), 7.00 (s, 1H), 7.22-7.25 (m, 2H), 7.31 (s, 1H), 7.35-7.39 (m, 1H), 7.58-7.60 (d, 1H), 7.60 (s, 1H), 7.66 (s, 1H).

Example 337. Synthesis of Compound 337



247c 337

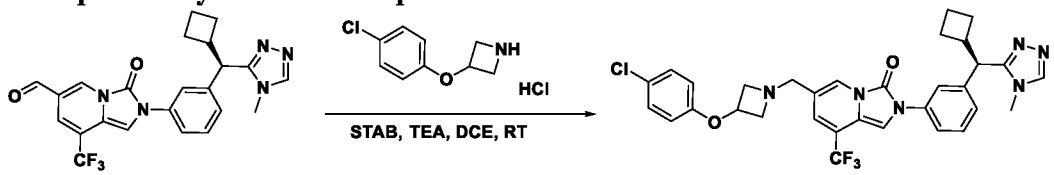
Synthesis of 337

[1181] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and (3-methylazetidin-3-yl)methylium hydrochloride (158.88 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.317 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 64% B in 8 min, Wave Length: 220 nm; RT1(min): 7.53) to afford 337

(124.9 mg, 36.00%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 525. H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 1.18 (s, 6H), 1.67-1.87 (m, 5H), 2.07-2.12 (m, 1H), 2.91 (s, 6H), 3.18-3.25 (m, 1H), 3.35 (s, 2H), 3.42 (s, 3H), 4.24-4.27 (d, 1H), 6.97 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.45 (m, 1H), 7.62 (s, 1H), 7.68-7.70 (d, 1H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 338. Synthesis of Compound 338

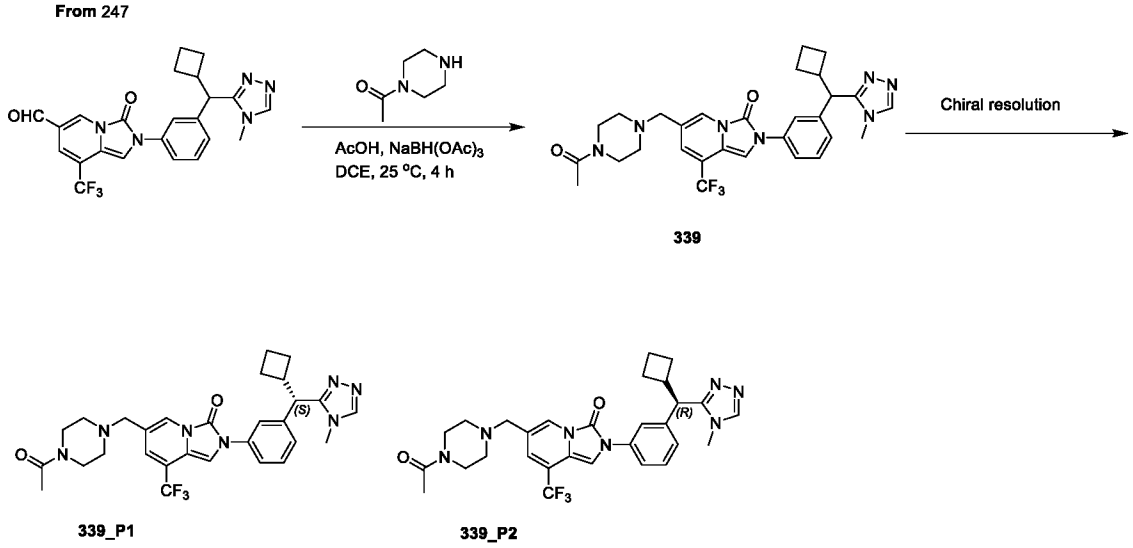


1. Synthesis of 338

[1182] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and 3-(4-chlorophenoxy)azetidine hydrochloride (9.66 mg, 0.044 mmol, 2 equiv) in DCE (5 mL) was added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.317 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred 3h at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by HP-Flash with the following conditions (Column: Welch Utimate AQ-C18, 50*250mm*10μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 45% B to 75% B in 20 min, Wave Length: 220 nm; RT1(min): 20) to afford 338 (125.3 mg, 30.53%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 623. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.67-1.87 (m, 5H), 2.07-2.12 (m, 1H), 3.06-3.10 (m, 2H), 3.20-3.25 (m, 1H), 3.42 (s, 3H), 3.45 (s, 2H), 4.24-4.27 (d, 1H), 4.81-4.84 (m, 1H), 6.85-6.88 (d, 2H), 6.99 (s, 1H), 7.18-7.20 (d, 1H), 7.29-7.33 (m, 3H), 7.42-7.46 (m, 1H), 7.62 (s, 1H), 7.67-7.73 (m, 3H), 8.33 (s, 1H).

Example 339. Synthesis of Compound 339_P1 and 339_P2



1. Synthesis of 339

[1183] To a solution of 2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl) imidazo[1,5-a]pyridine-6-carbaldehyde (200 mg, 439.14 umol, 1.0 equiv) and 1-piperazin-1-ylethanone (168 mg, 1.32 mmol, 3.0 equiv) in DCE (10 mL) was added AcOH (26 mg, 439 umol, 1.0 equiv) at 25°C. After addition, the mixture was stirred at this temperature for 2 hr, and then NaBH(OAc)3 (186 mg, 878 umol, 2.0 equiv) was added. The resulting mixture was stirred at 25 °C for 2 hr. The reaction was poured into water (10 mL) and the resulting mixture was extracted with CH2Cl2 (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um; Mobile Phase A: Water (NH4HCO3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 20% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 5.1) to afford 339 (35 mg, 13% yield) as a yellow solid.

2. Synthesis of 339_P1& P2

[1184] The 339 (35 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [Neu-MeOH]; B%: 20%-45%, 15 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.29; RT2 (min): 1.44) to afford 339_P1 (11.2 mg, 62% yield) as a yellow solid.

MS-339_P1 (ES, m/z): [M+H]+ 568.2.

H-NMR- 339_P1:(400 MHz, DMSO-d6) δ 8.34 (s, 1 H), 7.70-7.74 (m, 3 H), 7.43-7.47 (m, 1 H), 7.33 (s, 1 H), 7.20-7.22 (m, 1 H), 7.04 (s, 1 H), 4.27 (d, J = 5.6 Hz, 1 H), 3.37-3.44 (m, 7

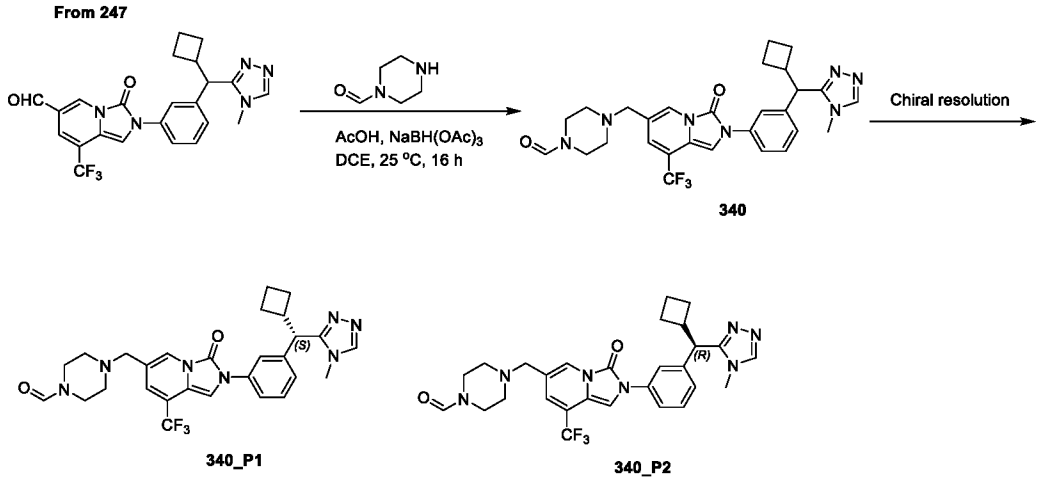
H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.51-2.52 (m, 1 H), 2.35-2.39 (m, 4 H), 2.09-2.13 (m, 1 H), 1.99 (s, 3 H), 1.78-1.81 (m, 5 H).

339_P2-0(11.1 mg, 62% yield) as a yellow solid.

MS-339-P2: (ES, m/z): [M+H]+ 568.2.

H-NMR-339-P2: (400 MHz, DMSO-d6) δ 8.34 (s, 1 H), 7.70-7.74 (m, 3 H), 7.43-7.47 (m, 1 H), 7.33 (s, 1 H), 7.20-7.22 (m, 1 H), 7.04 (s, 1 H), 4.27 (d, J = 5.6 Hz, 1 H), 3.37-3.44 (m, 7 H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.51-2.52 (m, 1 H), 2.35-2.39 (m, 4 H), 2.09-2.13 (m, 1 H), 1.99 (s, 3 H), 1.78-1.81 (m, 5 H).

Example 340. Synthesis of Compound 340_P1 and 340_P2



1. Synthesis of 340

[1185] To a solution of piperazine-1-carbaldehyde (150 mg, 1.32 mmol, 3.0 equiv), 2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridine-6-carbaldehyde (200 mg, 439 umol, 1.0 equiv) in DCE (10 mL) was added AcOH (26 mg, 439 umol, 1.0 equiv) at 25°C. After addition, the mixture was stirred at this temperature for 2 hrs, and then NaBH(OAc)3 (186 mg, 878 umol, 2.0 equiv) was added. The resulting mixture was stirred at 25 °C for 14 hrs. The reaction was poured into water (10 mL) and the resulting mixture was extracted with DCM (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um; Mobile Phase A: Water (NH4HCO3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 25% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 5.1) to afford 340 (30 mg, 11%) as a light yellow solid.

2. Synthesis of 340_P1& P2

[1186] The 340 (30 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [Neu-MeOH]; B%: 35%-35%, 13 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.37; RT2 (min): 1.44) to afford 340_P1 (5.4 mg, 35% yield) as a yellow solid.

MS-340-P1: (ES, m/z): [M+H]+ 554.2.

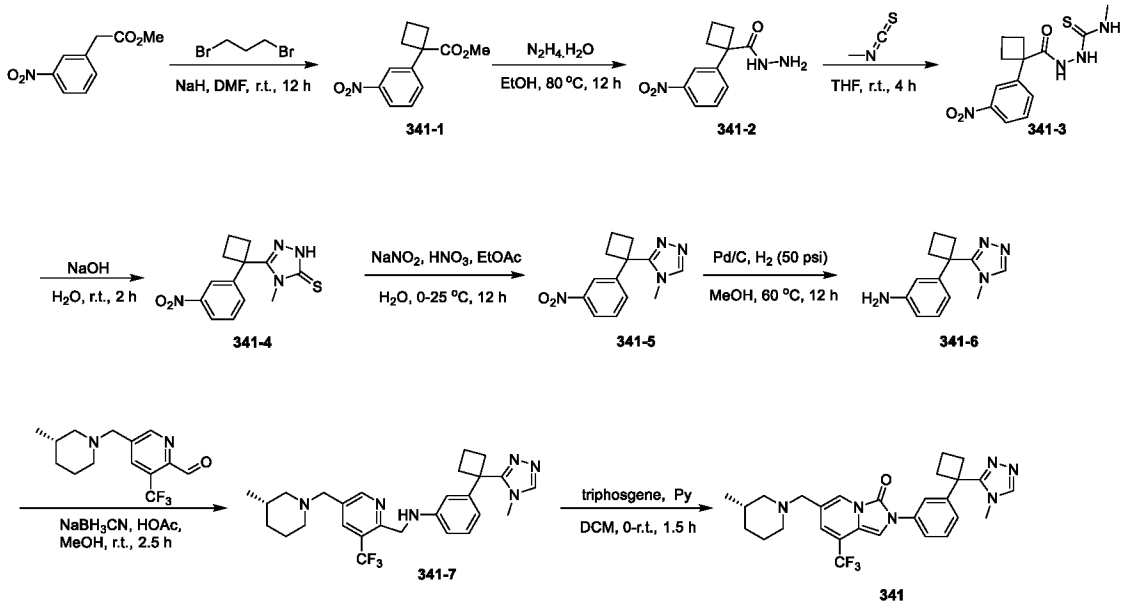
H-NMR-340-P1:(400 MHz, DMSO-d6) δ 8.32 (s, 1 H), 7.99 (s, 1 H), 7.71-7.72 (m, 1 H), 7.69-7.70 (m, 2 H), 7.43-7.45 (m, 1 H), 7.41 (s, 1 H), 7.20-7.21 (m, 1 H), 7.03 (s, 1 H), 4.25 (d, J = 5.2 Hz, 1 H), 3.42 (s, 3 H), 3.38-3.39 (m, 4 H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.41-2.42 (m, 2 H), 2.35-2.39 (m, 2 H), 2.09-2.13 (m, 1 H), 1.76-1.79 (m, 4 H), 1.69-1.70 (m, 1 H).

340_P2 (4.8 mg, 30% yield) as a yellow solid.

MS-340-P2: (ES, m/z): [M+H]+ 554.2.

H-NMR-340-P2:(400 MHz, DMSO-d6) δ 8.32 (s, 1 H), 7.99 (s, 1 H), 7.71-7.72 (m, 1 H), 7.69-7.70 (m, 2 H), 7.43-7.45 (m, 1 H), 7.41 (s, 1 H), 7.20-7.21 (m, 1 H), 7.03 (s, 1 H), 4.25 (d, J = 5.2 Hz, 1 H), 3.42 (s, 3 H), 3.38-3.39 (m, 4 H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.41-2.42 (m, 2 H), 2.35-2.39 (m, 2 H), 2.09-2.13 (m, 1 H), 1.76-1.79 (m, 4 H), 1.69-1.70 (m, 1 H).

Example 341. Synthesis of Compound 341



1. Synthesis of 341-1

[1187] To a solution of methyl 2-(3-nitrophenyl)acetate (10 g, 51.2 mmol, 1 equiv) and 1,3-dibromopropane (5.22 mL, 51.24 mmol, 1 equiv) in DMF (300 mL) was added NaH (4.1 g,

102 mmol, 60% purity, 2 equiv) at room temperature. Then the mixture was stirred at room temperature for 12 hr. The reaction mixture was diluted with water (150 mL), extracted with EtOAc (150 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-5% EtOAc/PE) to afford 341-1 (5 g, 41.48%) as a white solid.

H-NMR-341-1: (400 MHz, CHLOROFORM-d) δ 8.14 (t, J = 2.0 Hz, 1H), 8.11-8.05 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.52-7.44 (m, 1H), 3.64 (s, 3H), 2.94-2.81 (m, 2H), 2.57-2.44 (m, 2H), 2.18-2.04 (m, 1H), 1.97-1.82 (m, 1H)

2. Synthesis of 341-2

[1188] To a solution of 341-1 (4.93 g, 20.9 mmol, 1 equiv) in EtOH (50 mL) was added N2H4.H2O (15.6 mL, 314.37 mmol, 98% purity, 15 equiv) at room temperature. The mixture was heated to 80 °C and stirred for 12 hr. The reaction mixture was cooled to room temperature and concentrated in vacuum to remove EtOH (40 mL), then the mixture was diluted with water (50 mL), and extracted with CH2Cl2 (40 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 341-2 (4.3 g, 87.22%) as a white solid, which was used directly without further purification.

3. Synthesis of 341-3

[1189] To a solution of 341-2 (4.3 g, 18.3 mmol, 1 equiv) in THF (50 mL) was added methylimino(thioxo)methane (2.67 g, 36.5 mmol, 2 equiv) at room temperature. The mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted water (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 341-3 (4.3 g, crude) as a white solid, which was used directly in the next step.

4. Synthesis of 341-4

[1190] To a solution of NaOH (4.46 g, 111 mmol, 8 equiv) in water (45 mL) was added 341-3 (4.3 g, 13.9 mmol, 1 equiv). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with water (50 mL), and adjusted pH to 3 by 1N HCl. Then the mixture was filtered and the filter cake was concentrated in vacuum to afford 341-4 (4 g, 98.8%) as a white solid.

H-NMR-341-4: (400 MHz, DMSO-d6) δ 13.84 (s, 1H), 8.21-8.15 (m, 1H), 8.06 (t, J = 2.0 Hz, 1H), 7.80-.75 (m, 1H), 7.74-7.69 (m, 1H), 3.01 (s, 3H), 2.94-2.85 (m, 2H), 2.73-2.65 (m, 2H), 2.09-1.97 (m, 2H)

5. Synthesis of 341-5

[1191] HNO3 (10.03 mL, 151.55 mmol, 68% purity, 10 equiv) was added to water (140 mL) to afford the diluted HNO3 solution (1 M, 150 mL). To a solution of 341-4 (4.4 g, 15.15 mmol, 1 eq) and NaNO2 (10.46 g, 151.55 mmol, 10 equiv) in water (44 mL) and EtOAc (4.40 mL, 44.94 mmol, 2.97 equiv) was added diluted HNO3 solution (1 M, 150 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 12 hr. The reaction was quenched by the addition of Sat.NaHCO3 (300 mL) The aqueous layer was extracted with CH2Cl2 (150 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 341-5 (3.8 g, crude) as a yellow solid.

6. Synthesis of 341-6

[1192] To a solution of 341-5 (1 g, 3.87 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (1 g, 10% purity). The mixture was degassed and purged with H2 for 3 times, and then the mixture was stirred at 60 °C for 12 hr under H2 (50 psi). The reaction mixture was filtered through celite, and the filtrate was concentrated in vacuum o afford 341-6 (0.78 g, 88.24%) as a gray solid.

H-NMR-341-6: (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.44-6.39 (m, 2H), 6.38-6.36 (m, 1H), 5.06 (s, 2H), 3.17 (s, 3H), 2.88-2.77 (m, 2H), 2.58-2.52 (m, 2H), 1.99-1.88 (m, 2H)

7. Synthesis of 341-7

[1193] To a solution of 341-6 (0.68 g, 2.98 mmol, 1 equiv) and I-2 (767 mg, 2.68 mmol, 0.9 equiv) in MeOH (15 mL) was added AcOH (511 uL, 8.94 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 hr under nitrogen atmosphere, then NaBH3CN (374 mg, 5.96 mmol, 2 equiv) was added to the mixture. The resulted mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. The reaction mixture was concentrated in vacuum to remove MeOH, the residue was diluted with Sat. NaHCO3 (20 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-10% MeOH/ CH2Cl2) to afford 341-7 (1.53 g, 89.5%) as a yellow oil.

H-NMR-341-7: (400 MHz, CHLOROFORM-d) δ 8.58 (s, 1H), 7.94-7.91 (m, 1H), 7.88 (s, 1H), 7.16-7.10 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 6.57-6.53 (m, 2H), 5.35 (s, 1H), 5.23 (s, 2H), 4.46 (s, 2H), 3.11 (s, 3H), 2.92-2.87 (m, 2H), 2.66-2.59 (m, 3H), 2.07-2.00 (m, 2H), 1.92-1.81 (m, 1H), 1.64-1.55 (m, 6H), 0.84-0.75 (m, 4H)

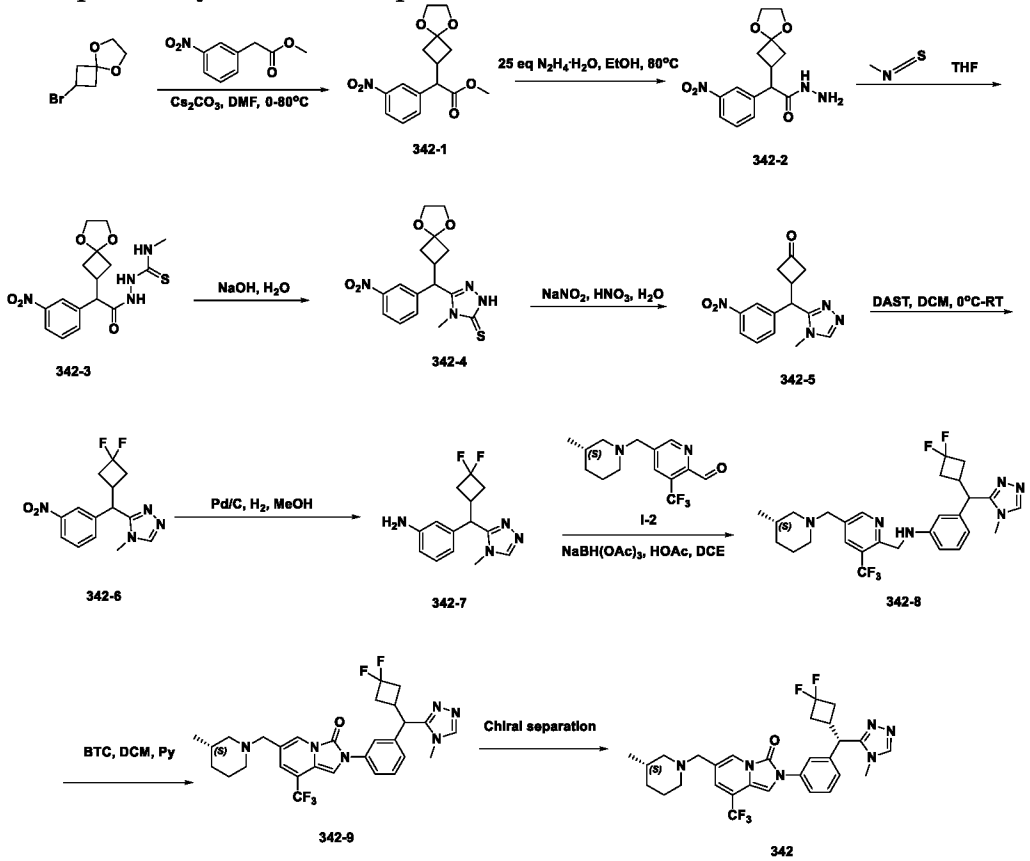
8. Synthesis of 341

[1194] To a solution of 341-7 (0.7 g, 1.40 mmol, 1 equiv) in DCM (10 mL) was added

pyridine (680 uL, 8.42 mmol, 6 equiv) and bis(trichloromethyl) carbonate (208 mg, 702 umol, 0.5 equiv) at 0 °C under nitrogen atmosphere, the mixture was stirred at 0 °C for 1.5 hr under nitrogen atmosphere. The reaction mixture was diluted with Sat. NaHCO3 (20 mL), extracted with CH2Cl2 (15 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by normal phase SiO2 chromatography (0-10% MeOH/ CH2Cl2) to give crude product. The crude product (450 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 15% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 5.5) to afford 341 (110 mg, 14.79%) as a yellow solid.

LCMS-341 (ES, m/z): [M+H]+ 525.2. H-NMR-341 (400 MHz, METHANOL-d4) δ 8.47 (s, 1H), 8.38 (s, 1H), 7.83 (s, 1H), 7.76 (t, J = 2.0 Hz, 1H), 7.64-7.53 (m, 2H), 7.38-7.32 (m, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 3.73 (d, J = 12.4 Hz, 2H), 3.35 (s, 3H), 3.26-3.11 (m, 2H), 3.08-2.98 (m, 2H), 2.89-2.78 (m, 2H), 2.48-2.34 (m, 1H), 2.21-2.07 (m, 3H), 1.82 (s, 3H), 1.77-1.65 (m, 1H), 1.14-1.02 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H).

Example 342. Synthesis of Compound 342



1. Synthesis of 342-1

[1195] Into a 250 mL 3-necked round-bottom flask were added methyl 2-(3-nitrophenyl)acetate (4 g, 20.495 mmol, 1 equiv) , DMF (50 mL) ,Cs2CO3 (33.39 g, 102.475 mmol, 5 equiv) and 2-bromo-5,8-dioxaspiro[3.4]octane (8.3 g, 42.996 mmol, 2.10 equiv) at 0°C. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 342-1 (1.8 g, 28.58%) as a light yellow oil.

2. Synthesis of 342-2

Into a 100 mL round-bottom flask were added 342-1 (1.8 g, 5.857 mmol, 1 equiv), EtOH (22 mL) and Hydrazine (4.69 g, 146.425 mmol, 25 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched by the addition of Water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure to afford 342-2 (1.7 g, 94.44%) as an off-white solid.

3. Synthesis of 342-3

Into a 100 mL round-bottom flask were added 342-2 (1.8 g, 5.857 mmol, 1 equiv), tetrahydrofuran (22 mL) and methyl isothiocyanate (1.07 g, 14.643 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (40 mL) at room temperature. The resulting mixture was filtered; the filter cake was washed with water (3x20 mL). The filtrate was concentrated under reduced pressure to afford 342-3 (1.8 g, 80.78%) as an off-white solid.

4. Synthesis of 342-4

Into a 100 mL round-bottom flask were added NaOH (10 ml, 1M), and 342-3 (1 g, 2.629 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture/residue was acidified to pH 6 with 1M HCl (aq.). The resulting mixture was filtered; the filter cake was washed with water (3x4 mL). The filtrate was concentrated under reduced pressure to afford 342-4 (0.9 g, 94.48%) as an off-white solid.

5. Synthesis of 342-5

To a stirred solution of 342-4 (1.8 g, 4.967 mmol, 1 equiv) in H2O (8 ml) was added NaNO2 (3.43 g, 49.670 mmol, 10 equiv) at room temperature. To the above mixture was added HNO3 (52 ml, 1M) dropwise at 0°C. The resulting mixture was stirred for additional 1 h at 0°C. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer

was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 342-5 (1 g, 70.32%) as an off-white solid.

6. Synthesis of 342-6

Into a 100 mL round-bottom flask were added 342-5 (1 g, 3.493 mmol, 1 equiv), DCM (15 mL) and DAST (2.25 g, 13.972 mmol, 4 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford 342-6 (150 mg, 13.93%) as a light yellow solid.

7. Synthesis of 342-7

[1196] To a solution of 342-6 (150 mg, 0.487 mmol, 1.00 equiv) in 5 mL MeOH was added Pd/C (10%, 51 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 342-7 (110 mg, 81.23%) as a light yellow solid.

8. Synthesis of 342-8

[1197] Into a 100 mL round-bottom flask were added 342-7 (110 mg, 0.395 mmol, 1 equiv), DCE (3 mL), 5-{[(3S)-3-methylpiperidin-1-yl]methyl}-3-(trifluoromethyl)pyridine-2-carbaldehyde (113.16 mg, 0.395 mmol, 1 equiv) , HOAc (23.74 mg, 0.395 mmol, 1 equiv) and NaBH(OAc)3 (167.54 mg, 0.790 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (15 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC, eluted with CH2Cl2 / MeOH (12:1) to afford 342-8 (90 mg, 41.51%) as a light yellow solid.

9. Synthesis of 342-9

[1198] Into a 50 mL round-bottom flask were added 342-8 (90 mg, 0.164 mmol, 1 equiv), Pyridine (77.86 mg, 0.984 mmol, 6 equiv) and d Triphosgene (19.47 mg, 0.066 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 15 min at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel

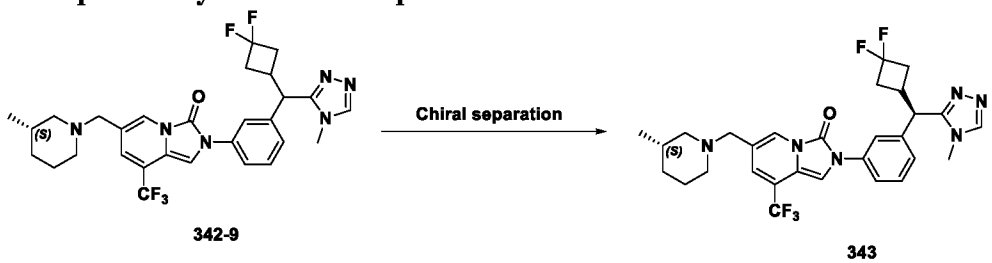
column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 342-9 (60 mg, 63.65%) as a light yellow solid.

10. Synthesis of 342

The 342-9 (60 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 16 min; Wave Length: 220/254 nm; RT1(min): 10.644; RT2(min): 16.675; The first peak was the product. Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 4.4 mL; Number of Runs: 2) to afford 342 (23.8 mg, 39.67%) as a light yellow solid.

H-NMR: 1H NMR (300 MHz, CD3OD-d4) δ 0.90-0.96 (m, 4H), 1.30-1.34 (m, 1H),1.61-1.78 (m, 4H), 1.99-2.04 (m, 1H), 2.33-2.54 (m, 3H), 2.84-2.93 (m, 3H), 3.15-3.17 (m, 1H), 3.32-3.37 (m, 2H), 3.52 (s, 3H), 4.33-4.36 (d, 1H), 6.69 (s, 1H), 7.13-7.16 (m, 2H), 7.28-7.30 (m, 1H), 7.52-7.56 (m, 1H), 7.68-7.73 (m, 3H), 8.45 (s, 1H).

Example 343. Synthesis of Compound 343



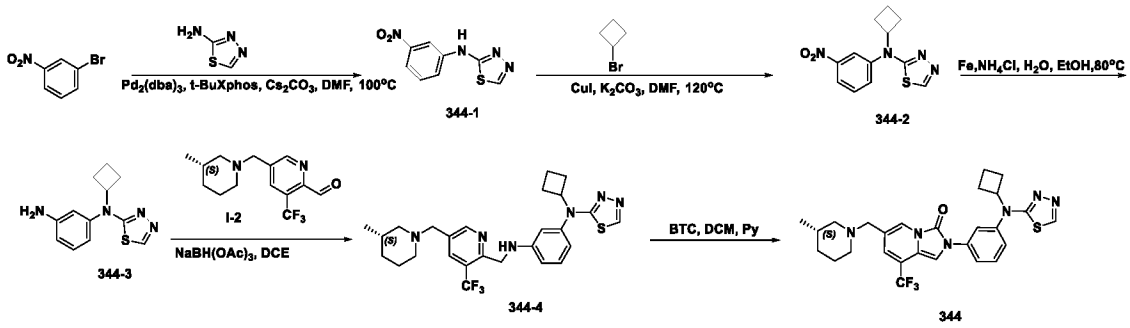
342-9 343

1. Synthesis of 343

[1199] The 342-9 (60 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 16 min; Wave Length: 220/254 nm; RT1(min): 10.644; RT2(min): 16.675; The second peak was the product. Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 4.4 mL; Number of Runs: 2) to afford 343 (24.3 mg, 40.50%) as a light yellow solid.

H-NMR: 1H NMR (300 MHz, CD3OD-d4) δ 0.90-0.96 (m, 4H), 1.62-1.81 (m, 5H), 1.91-2.04 (m, 1H), 2.33-2.48 (m, 1H), 2.50-2.54 (m, 2H), 2.84-2.93 (m, 3H), 3.15-3.17 (m, 1H), 3.32-3.37 (m, 2H), 3.52 (s, 3H), 4.33-4.36 (d, 1H), 6.69 (s, 1H), 7.13-7.16 (m, 2H), 7.28-7.30 (m, 1H), 7.52-7.56 (m, 1H), 7.68-7.73 (m, 3H), 8.45 (s, 1H).

Example 344. Synthesis of Compound 344



1. Synthesis of 344-1

[1200] Into a 500 mL 3-necked round-bottom flask were added 3-bromo-1-nitrobenzene (10 g, 49.503 mmol, 1 equiv), 2-amino-1,3,4-thiadiazole (5.01 g, 49.503 mmol, 1 equiv), Pd2(dba)3 (4.53 g, 4.950 mmol, 0.1 equiv), t-BuXPhos (4.20 g, 9.901 mmol, 0.2 equiv), Cs2CO3 (32.26 g, 99.006 mmol, 2 equiv) and DMF (300 mL) at room temperature. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (3x400 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (100:1) to afford 344-1 (6 g, 51.27%) as an orange solid.

2. Synthesis of 344-2

[1201] Into a 250 mL 3-necked round-bottom flask were added 344-1 (3 g, 13.500 mmol, 1 equiv), bromocyclobutane (5.47 g, 40.500 mmol, 3 equiv), CuI (0.26 g, 1.350 mmol, 0.1 equiv), K2CO3 (3.73 g, 27.000 mmol, 2 equiv) and DMF (50 mL) at room temperature. The resulting mixture was stirred for overnight at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 30:1) to afford 344-2 (300 mg, 7.64%) as a brown oil.

3. Synthesis of 344-3

[1202] Into an 8 mL sealed tube were added 344-2 (130 mg, 0.470 mmol, 1 equiv), EtOH (2 mL), H2O (0.5 mL), NH4Cl (125.83 mg, 2.350 mmol, 5 equiv) and Fe (78.82 mg, 1.410 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 6 h at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 344-3(80 mg, 65.58%) as a light yellow oil.

4. Synthesis of 344-4

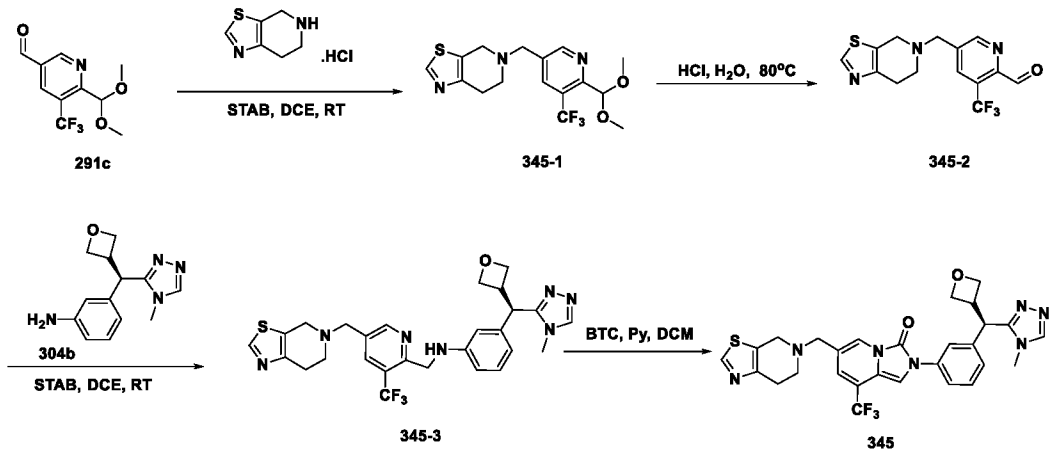
[1203] Into an 8 mL sealed tube were added 344-3 (125 mg, 0.507 mmol, 1 equiv), DCE (1.25 mL), I-2(290.56 mg, 1.014 mmol, 2 equiv) and NaBH(OAc)3 (322.65 mg, 1.521 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 15mL). The combined organic layers were washed with water (2x10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 15:1) to afford 344-4 (130 mg, 47.11%) as a light yellow oil.

5. Synthesis of 344

[1204] Into a 50 mL 3-necked round-bottom flask were added 344-4 (130 mg, 0.252 mmol, 1 equiv), DCM (2.5 mL) and Pyridine (119.42 mg, 1.512 mmol, 6 equiv) at 0°C. To the above mixture was added Triphosgene (33.60 mg, 0.113 mmol, 0.45 equiv) at 0°C. The resulting mixture was stirred for additional 10 min at 0°C. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (5 mL) at 0°C. The resulting mixture was extracted with CH2Cl2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 15:1) to afford crude product (70 mg) as a light yellow oil. The crude product (70 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep EVO C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 60% B to 90% B in 9 min; Wave Length: 220 nm; RT(min): 8.66) to afford 344 (44.4 mg, 24.02%) as a light yellow solid.

LCMS: (ES, m/z): [M+H] + 544. H-NMR: (300 MHz, CD3OD, ppm): δ0.81-0.89 (m, 4H), δ1.46-1.49 (m, 1H), δ1.58-1.66(m, 4H), δ1.76-1.91 (m, 3H), δ2.31-2.42 (m, 2H), δ2.43-2.49 (m, 2H), δ2.67-2.77 (m, 2H), δ3.24-3.30(d, 2H), δ5.09-5.13 (m, 1H), δ6.95-7.00 (m, 2H), δ7.37 (s, 1H), δ7.43-7.45 (m, 1H), δ7.47-7.52 (m, 2H), δ7.66 (s, 1H), δ8.36 (s, 1H).

Example 345. Synthesis of Compound 345



1. Synthesis of 345-1

[1205] Into a 20mL sealed tube were added 291c (600 mg, 2.408 mmol, 1.00 equiv), DCE (8 mL) and 4H,5H,6H,7H-[1,3]thiazolo[5,4-c]pyridine hydrochloride (425.36 mg, 2.408 mmol, 1 equiv) and Et3N(486.41 mg, 4.816 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. To the above mixture was added STAB (1020.62 mg, 4.816 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The reaction was quenched with sat. NaHCO3 (aq.)(20 mL) at room temperature. The aqueous layer was extracted with CH2Cl2/MeOH (10:1) (2x15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CHCl2 / MeOH= 30:1) to afford 345-1 (400 mg, 44.49%) as a yellow oil.

2. Synthesis of 345-2

[1206] Into a 8mL sealed tube were added 345-1 (400 mg, 1.071 mmol, 1 equiv) and HCl (1M, 4 mL) at room temperature. The resulting mixture was stirred for overnight at 80°C. The mixture was allowed to cool down to room temperature. The mixture was basified to pH 7 with saturated NaOH (aq.)(1 M). The aqueous layer was extracted with CH2Cl2/MeOH=10/1 (2x15 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 345-2 (260 mg, 74.15%) as a yellow oil.

3. Synthesis of 345-3

[1207] To a stirred solution of 345-2 (450.20 mg, 1.375 mmol, 1.2 equiv) and 304b (280 mg, 1.146 mmol, 1.00 equiv) in DCE (15 mL) was added STAB (485.83 mg, 2.292 mmol, 2 equiv).The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (20 mL). The resulting mixture was extracted with CH2Cl2/MeOH (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the

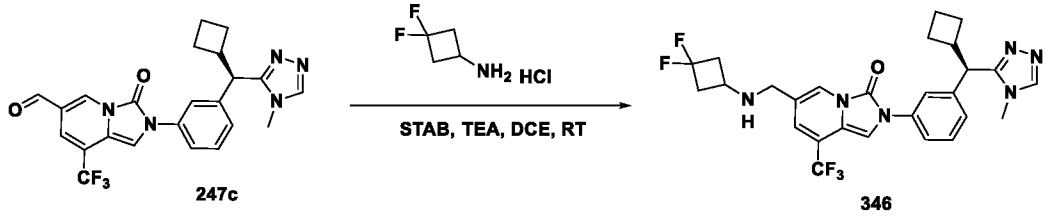
following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH4HCO3), 5% to 55% gradient in 30 min; detector, UV 254 nm. This resulted in 345-3 (200 mg, 31.41%) as a white solid.

4. Synthesis of 345

[1208] To a stirred solution of 345-3 (140 mg, 0.252 mmol, 1 equiv) and Pyridine (119.59 mg, 1.512 mmol, 6 equiv) in DCM (3 mL) was added Triphosgene (29.91 mg, 0.101 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 0.5 h at 0 °C. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (10 mL). The resulting mixture was extracted with CH2Cl2/MeOH=10/1 (3 x 15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH4HCO3), 15% to 65% gradient in 30 min; detector, UV 254 nm. This resulted in 345 (99.8 mg, 68.10%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 582. H-NMR: (400 MHz, DMSO-d6, ppm): δ2.82-2.88 (m, 4H), δ3.38 (s, 3H), δ3.53 (s, 2H), δ3.75 (s, 2H), δ3.90-3.99 (m, 1H), δ4.27-4.30 (t, 1H), δ4.49-4.50 (d, 2H), δ4.73-4.82 (m, 2H), δ7.07 (s, 1H), δ7.18-7.20 (d 1H), δ7.39 (s, 1H), δ7.46-7.50 (t, 1H), δ7.76-7.78 (m, 3H), δ8.38 (s, 1H), δ8.92 (s, 1H).

Example 346. Synthesis of Compound 346



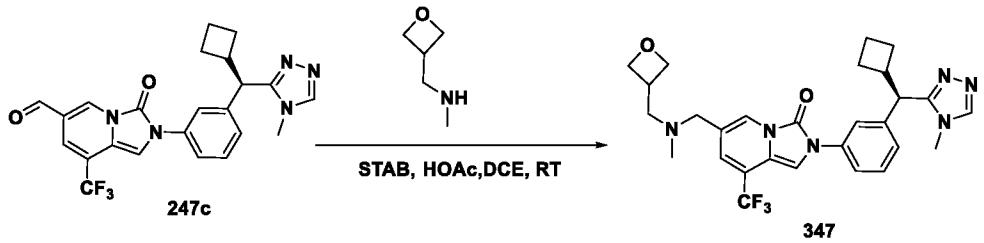
1. Synthesis of 346

[1209] To a stirred solution of 247C(300 mg, 0.659 mmol, 1.00 equiv) and 3,3-difluorocyclobutan-1-amine hydrochloride (189.13 mg, 1.318 mmol, 2 equiv) in DCE (4 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature under air atmosphere. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 15 mL). The resulting mixture was concentrated under reduced pressure. The crude product (98 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A:

Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 55% B in 7 min, 55% B; Wave Length: 220 nm; RT1(min): 8.13) to afford 346 (71.0 mg, 19.13%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :547. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.65-1.89 (m, 5H), δ 2.02-2.16 (m, 1H), δ 2.29-2.56 (m, 2H), δ 3.62-3.81 (m, 3H), δ 3.12-3.23 (m, 1H), δ 3.24-3.26 (m, 1H), δ 3.45-3.51 (m, 5H), δ 4.25-4.27 (d, 1H), δ 7.10 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 1H), δ 7.71-7.78 (m, 3H), δ 8.33 (s, 1H).

Example 347. Synthesis of Compound 347



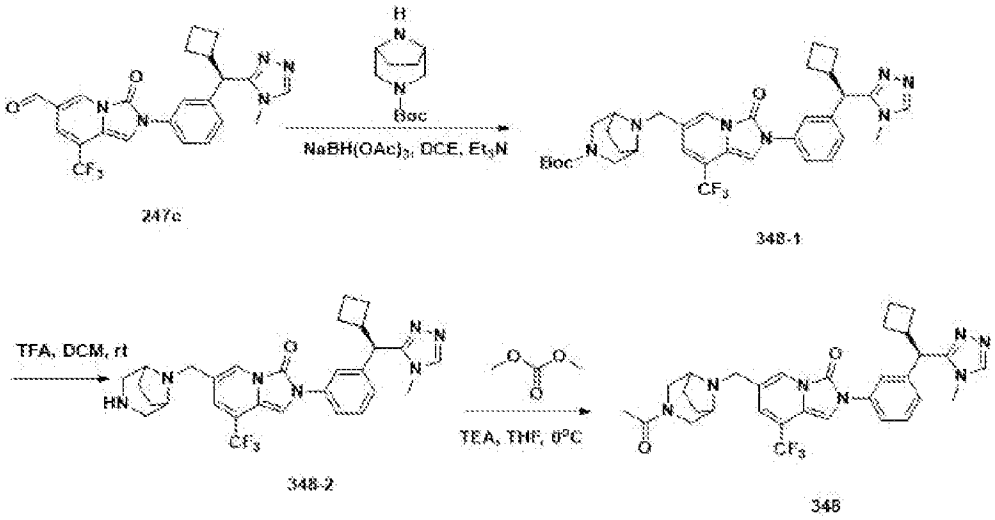
1. Synthesis of 347

[1210] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and methyl(oxetan-3-ylmethyl)amine (133.25 mg, 1.318 mmol, 2 equiv) in DCE (4 mL) were added STAB (279.21 mg, 1.318 mmol, 2 equiv) and HOAc (39.56 mg, 0.659 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The crude product (52 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 53% B in 8 min; Wave Length: 254/220 nm; RT1(min): 6.42) to afford 347 (36.7 mg, 10.00%) as a yellow solid.

LC-MS-347 (ES, m/z): [M+H] + :541

H-NMR-347 (400 MHz, DMSO-d6, ppm): δ 1.62-1.89 (m, 5H), δ 2.01-2.16 (m, 4H), δ 2.63-2.72 (m, 2H), δ 3.12-3.23 (m, 2H), δ 3.33-3.36 (m, 2H), δ 3.45 (s, 3H), δ 4.22-4.31 (m, 3H), δ 4.61-4.64 (m, 2H), δ 7.00 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 1H), δ 7.71-7.78 (m, 3H), δ 8.33 (s, 1H).

Example 348. Synthesis of Compound 348



1. Synthesis of 348-1

[1211] To a stirred mixture of tert-butyl 3,8-diazabicyclo [3.2.1] octane-3-carboxylate (1165.32 mg, 5.490 mmol, 5 equiv) and Et3N (166.64 mg, 1.647 mmol, 1.5 equiv) in DCE (5 mL) were added 247C(500 mg, 1.098 mmol, 1 equiv) and NaBH(OAc)3 (698.03 mg, 3.294 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 348-1 (340 mg, 42.77%) as a yellow oil.

2. Synthesis of 348-2

[1212] A solution of 348-1 (320 mg, 0.442 mmol, 1 equiv, 90%) in TFA (1 mL) and DCM (3 mL) was stirred for overnight at room temperature. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with CH2Cl2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 348-2 (220 mg, 85.74%) as a yellow solid.

3. Synthesis of 348

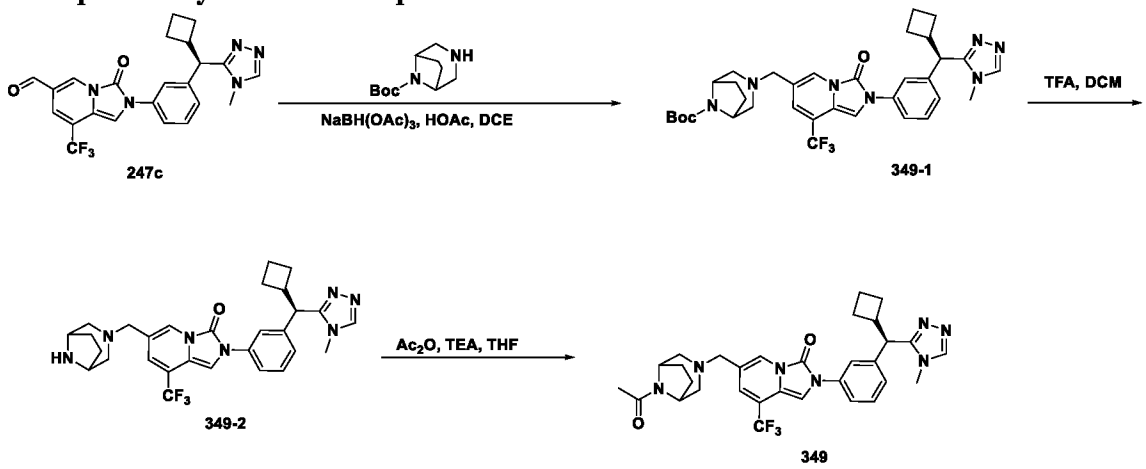
[1213] To a stirred mixture of 348-2 (210 mg, 0.362 mmol, 1 equiv, 95%) and dimethyl carbonate (32.58 mg, 0.362 mmol, 1 equiv) in THF (2 mL) was added TEA (73.20 mg, 0.724 mmol, 2 equiv) at 0°C. The resulting mixture was stirred for 2h at 0°C. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with CH2Cl2: MeOH (10:1) (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following

conditions: Column: C18 Column 40g; Mobile Phase A: Water (0.1% NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 61% B in 8 min to afford 348 (116.9 mg, 52.98%) as a yellow solid.

LC-MS-348 (ES, m/z): [M+H] + 594

H-NMR: (400 MHz, DMSO, ppm): δ 1.25-1.31 (m, 1H),δ 1.31-1.49 (m, 1H), δ1.65-1.75 (m, 1H), δ1.75-1.88 (m, 4H), δ1.88-1.95 (d, 2H), δ1.95-2.01 (d, 3H), δ2.05-2.15 (m, 1H), δ2.66-2.69 (d, 1H), δ3.19-3.26 (m, 4H), δ3.26-3.32 (m, 2H), δ3.40-3.55 (m, 4H), δ3.84-4.15 (d, 1H), δ4.25-4.35 (d, 1H), δ7.10 (s, 1H), δ7.19-7.21 (d, 1H), δ7.32 (s, 1H), δ7.42-7.47 (m, 1H), δ7.68-7.71 (m, 1H), δ7.73-7.76 (d, 2H), δ8.33 (s, 1H),

Example 349. Synthesis of Compound 349



247c 349-1 349-2 349

1. Synthesis of 349-1

[1214] To a stirred solution of 247c (500 mg, 1.09 mmol, 1.0 equiv) and tert-butyl 3,8-diazabicyclo [3.2.1] octane-8-carboxylate (233 mg, 1.09 mmol, 1.0 equiv) in DCE (5 mL) were added HOAc (65 mg, 1.09 mmol, 1.0 equiv) and NaBH(OAc)3 (465 mg, 2.19 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH2Cl2 (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=10:1) to afford 349-1 (380 mg, 48%) as a yellow solid.

2. Synthesis of 349-2

[1215] A solution of 349-1 (380 mg, 0.58 mmol, 1.0 equiv) and TFA (1 mL) in DCM (3 mL) was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. The mixture was neutralized to pH 7 with NH3 in MeOH. The residue was purified by Prep-TLC (CH2Cl2/MeOH=10:1) to afford 349-2 (240 mg, 73%) as a yellow

solid.

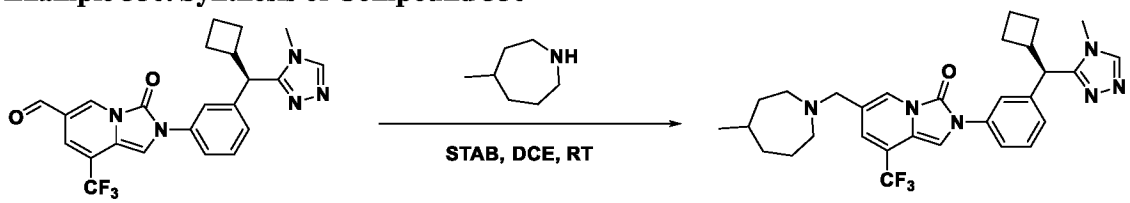
3. Synthesis of 349-0

[1216] To a stirred solution of 349-2 (240 mg, 0.43 mmol, 1.0 equiv) and TEA (88 mg, 0.87 mmol, 2.0 equiv) in THF (2.4 mL) was added Ac2O (44 mg, 0.43 mmol, 1.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=10:1) to afford 349 (189 mg, 72%) as a yellow solid.

LC-MS-349 (ES, m/z): [M/2+H]+ 297

H-NMR: (400 MHz, dmso-d6, δ ppm): 1.58-1.96 (m, 9H), 1.96 (s, 3H), 2.07-2.09 (m, 1H), 2.13-2.22 (m, 2H), 2.65-2.72 (m, 2H), 3.20-3.25 (m, 1H), 3.30-3.33 (m, 2H), 3.43 (s, 3H), 4.16 (s, 1H), 4.25-4.27 (d, 1H), 4.41-4.43 (d, 1H), 7.06 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (t, 1H), 7.67-7.73 (m, 3H), 8.33 (s, 1H).

Example 350. Synthesis of Compound 350



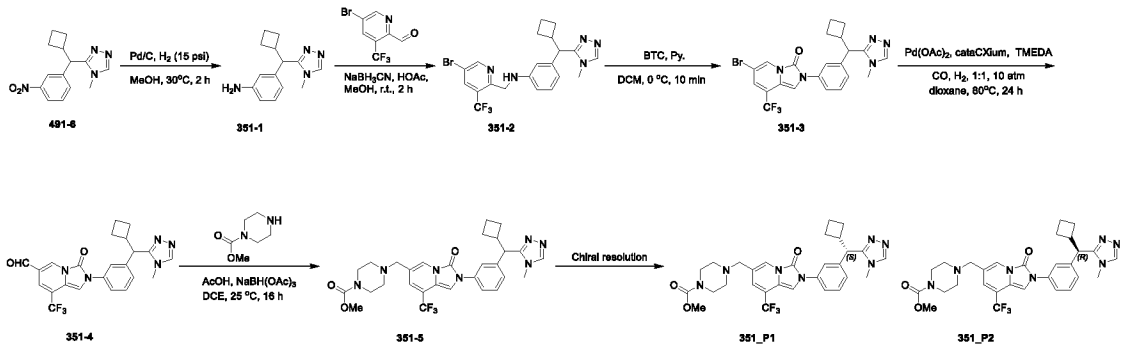
247c 350

1. Synthesis of 350

[1217] To a stirred mixture of 247c (500 mg, 1.098 mmol, 1 equiv) and 4-methylazepane (248.56 mg, 2.196 mmol, 2 equiv) in DCE (5 mL) was added NaBH(OAc)3 (698.03 mg, 3.294 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 350 (64.4 mg, 10.49%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 553. H-NMR: (400 MHz, CD3OD-d4, ppm, δ): 0.97-1.01 (s, 3H), 1.3 (m, 3H), 2.84-2.89 (m, 1H), 3.21-3.29 (s, 3H), 3.55 (s, 2H), 3.80 (s, 2H), 7.07 (s, 1H), 7.25-7.27 (d, 1H), 7.39 (s, 1H), 7.48-7.52 (m, 1H), 7.64-7.66 (m, 1H), 7.77 (s, 1H), 7.82 (s, 1H), 8.30 (m, 3H), 8.92 (s, 1H).

Example 351. Synthesis of Compound 351_P1 and 351_P2



1. Synthesis of 351-1

[1218] To a solution of 491-6 (9 g, 33 mmol, 1 equiv) in MeOH (150 mL) was added Pd/C (3 g, 10% purity) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with H2 several times. The mixture was stirred under H2 (15 psi) at 25°C for 12 hours. The reaction mixture was filtered and the filter was concentrated to give crude product. The crude product was triturated with PE (100 mL) at 25°C for 0.5 h. The mixture was filtered and the filter cake was concentrate in vacuum to afford 351-1 (7 g, crude) as a yellow solid.

H-NMR-351-1: (400 MHz, DMSO-d6) δ 8.29 (s, 1 H), 6.92 (t, J =7.69 Hz, 1 H), 6.29-6.44 (m, 3 H), 5.01 (s, 2 H), 3.92 (d, J =10.4 Hz, 1 H), 3.35 (s, 3 H), 3.10 (t, J =7.6 Hz, 1 H), 1.99-2.16 (m, 1 H), 1.71-1.85 (m, 4 H), 1.57-1.71 (m, 1 H)

2. Synthesis of 351-2

[1219] To a solution of 351-1 (12 g, 49.52 mmol, 1 equiv) in DCE (120 mL) was added HOAc (2.83 mL, 49.5 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (15.1 g, 59.4 mmol, 1.2 equiv) at 25°C. After addition, the mixture was stirred at 25 oC for 2 hrs, and then NaBH(OAc)3 (20.9 g, 99.0 mmol, 2 equiv) was added. The resulting mixture was stirred at 25 °C for 2 hrs. The reaction was poured into Sat.NaHCO3 (100 mL) and extracted with CH2Cl2 (2 x 100 mL). The organic phase was washed with brine (80 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give crude product. The crude product was triturated with PE (100 mL) at 25 °C for 10 min, filtered and the filter cake was concentrated in vacuum to afford 351-2 (17 g, 66%)

H-NMR-351-2: (400 MHz, DMSO-d6) δ 8.91-9.03 (m, 1 H), 8.47 (d, J = 2.0 Hz, 1 H), 8.29 (s, 1 H), 6.93-7.04 (m, 1 H), 6.35-6.52 (m, 3 H), 6.23 (s, 1 H), 4.40-4.51 (m, 2 H), 3.89-4.00 (m, 1 H), 3.04-3.19 (m, 1 H), 2.02-2.15 (m, 1 H), 1.59-1.86 (m, 5 H)

3. Synthesis of 351-3

[1220] To a solution of 351-2 (6 g, 12.49 mmol, 1 equiv) and pyridine (6.05 mL, 74.9 mmol,

6 equiv) in DCM (60 mL) was added TRIPHOSGENE (1.67 g, 5.62 mmol, 0.45 equiv) in DCM (6 mL) at 0 °C. The mixture was stirred at 0°C for 10 min. The reaction was poured into sat NaHCO3 (600 mL) and the resulting mixture was extracted with EtOAc (2x 300 mL). The organic phase was washed with brine (80 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give crude product. The crude product was triturated with PE (50 mL) at 25oC for 10 min, filtered and the filter cake was concentrated in vacuum to afford 351-3 (6 g, 95%).

H-NMR-351-3: (400 MHz, DMSO-d6) δ 8.54-8.65 (m, 1 H), 8.33 (s, 1 H), 8.02 (s, 1 H), 7.73-7.76 (m, 1 H), 7.65-7.71 (m, 1 H), 7.41-7.49 (m, 2 H), 7.19-7.25 (m, 1 H), 7.16 (s, 1 H), 4.19-4.34 (m, 1 H) ,3.43 (s, 3 H), 3.14-3.27 (m, 1 H), 2.03-2.16 (m, 1 H), 1.63-1.89 (m, 5 H)

4. Synthesis of 351-4

[1221] To a solution of 351-3 (340 mg, 671 umol, 1 equiv) in dioxane (20 mL) was added N,N,N', N'-tetramethylethane-1,2-diamine (202 uL, 1.34 mmol, , 2 equiv) and diacetoxypalladium (30.1 mg, 134 umol, 0.2 equiv), bis(1-adamantyl)-butyl-phosphane (48.5 mg, 134 umol, 0.2 equiv). The mixture was stirred at 80 °C for 12 hr under CO/H2 (1:1) (2.5 Mpa). The reaction mixture was concentrated in vacuum to dryness. The reaction was poured into water (50 mL) and the resulting mixture was extracted with EtOAc (2 x 50 mL). The organic phase was washed with sat NaHCO3 (20 mL), brine (20 mL), dried over anhydrous Na2SO4, concentrated in vacuum to afford 351-4 (450 mg, crude) as yellow solid, which was used into the next step without further purification.

5. Synthesis of 351-5

[1222] To a solution of 351-4 (300 mg, 658 umol, 1.0 equiv) and methyl piperazine-1-carboxylate (284 mg, 1.98 mmol, 3.0 equiv) in DCE (10 mL) was added AcOH (39 mg, 658 umol, 1.0 equiv) at. After addition, the mixture was stirred at 25 °C for 2 hrs, and then NaBH(OAc)3 (698 mg, 3.29 mmol, 5.0 equiv) was added. The resulting mixture was stirred at 25 °C for 14 hrs. The reaction was poured into water (10 mL) and the resulting mixture was extracted with CH2Cl2 (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; Mobile Phase A: Water (NH4HCO3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 25% B to 55% B in 8 min; Wave Length: 220 nm; RT1 (min): 5.1) to afford 351-5 (74 mg, 17% yield) as a yellow solid.

6. Synthesis of 351_P1& P2

[1223] 351-5 (74 mg) was purified by Chiral separation with the following conditions

(column: DAICEL CHIRALCEL OD(250mm*30mm,10um); Mobile Phase: [Neu-IPA]; B%: 50%-50%, 10 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.77; RT2 (min): 2.56) to afford 351_P1 (13 mg, 33% yield) as a yellow solid.

MS-351-P1: (ES, m/z): [M+H]+ 584.3.

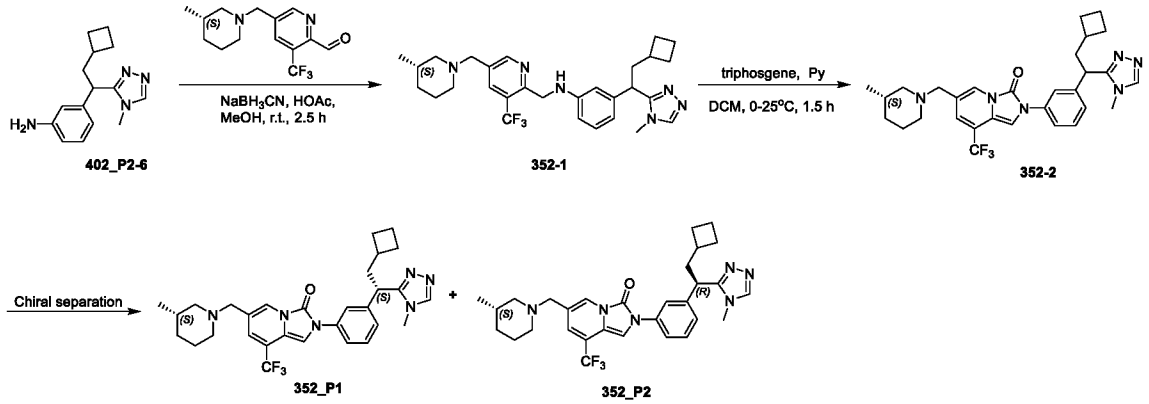
H-NMR-351-P1: (400 MHz, DMSO-d6) δ 8.32 (s, 1 H), 7.72 (s, 1 H), 7.65-7.74 (m, 2 H), 7.42-7.45 (m, 1 H), 7.28-7.32 (m, 1 H), 7.18-7.20 (m, 1 H), 7.01 (s, 1 H), 4.25 (d, J = 5.2 Hz, 1 H), 3.58 (s, 3 H), 3.42 (s, 3 H) 3.30-3.30-3.31 (m, 4 H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.35-2.39 (m, 4 H), 2.09-2.13 (m, 1 H), 1.76-1.79 (m, 4 H), 1.69-1.70 (m, 1 H).

351_P2 (21 mg, 56% yield) as a yellow solid.

MS-351-P2: (ES, m/z): [M+H]+ 584.3.

H-NMR-351-P2: (400 MHz, DMSO-d6) δ 8.32 (s, 1 H), 7.72 (s, 1 H), 7.65-7.74 (m, 2 H), 7.42-7.45 (m, 1 H), 7.28-7.32 (m, 1 H), 7.18-7.20 (m, 1 H), 7.01 (s, 1 H), 4.25 (d, J = 5.2 Hz, 1 H), 3.58 (s, 3 H), 3.42 (s, 3 H) 3.30-3.30-3.31 (m, 4 H), 3.27-3.29 (m, 2 H), 3.24-3.25 (m, 1 H), 2.35-2.39 (m, 4 H), 2.09-2.13 (m, 1 H), 1.76-1.79 (m, 4 H), 1.69-1.70 (m, 1 H).

Example 352. Synthesis of Compound 352_P1 and 352_P2



1. Synthesis of 352-1

[1224] To a solution of 402_P2-6 (1 g, 3.9 mmol, 1 equiv) and I-2 (1.01 g, 3.51 mmol, 0.9 equiv) in MeOH (20 mL) was added AcOH (669 uL, 11.7 mmol, 3 equiv), the mixture was stirred at 25 °C for 1 hr under nitrogen atmosphere, then NaBH3CN (490 mg, 7.8 mmol, 2 equiv) was added to the mixture, the result mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. The reaction mixture was diluted with Sat. NaHCO3 (20 mL), extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine (20 mL x2), dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to afford 352-1 (1.3 g, 57%) as a yellow oil. H-NMR: (400 MHz, METHANOL-d4) 8.69 (s, 1H), 8.31 (s, 1H), 8.13

(s, 1H), 7.19-6.97 (m, 1H), 6.71-6.55 (m, 1H), 6.53-6.45 (m, 2H), 4.55 (s, 2H), 4.02-3.86 (m, 1H), 3.66 (s, 2H), 3.41 (s, 3H), 2.89-2.79 (m, 2H), 2.38-2.12 (m, 4H), 2.10-2.00 (m, 2H), 1.93-1.86 (m, 1H), 1.80-1.62 (m, 8H), 0.99-0.92 (m, 1H), 0.89 (d, J = 6.4 Hz, 3H)

2. Synthesis of 352-2

[1225] To a solution of 352-1 (1.2 g, 2.28 mmol, 1 equiv) in DCM (20 mL) was added pyridine (1.1 mL, 13.6 mmol, 6 equiv) and bis(trichloromethyl) carbonate (676 mg, 2.28 mmol, 1 equiv) at 0°C, then the mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. The reaction mixture was diluted with Sat. NaHCO3 (40 mL), extracted with DCM (25 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to give crude product. The crude product (450 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 25% B to 60% B in 8 min; Wave Length: 220 nm; RT1(min): 6.0) to afford 352-2 (190 mg, 14.6%) as a yellow solid. H-NMR-352-2: (400 MHz, METHANOL-d4) δ 8.37 (s, 1H), 7.77 (s, 1H), 7.70-7.62 (m, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 4.60 (s, 1H), 4.29-4.15 (m, 1H), 3.58 (s, 2H), 3.55

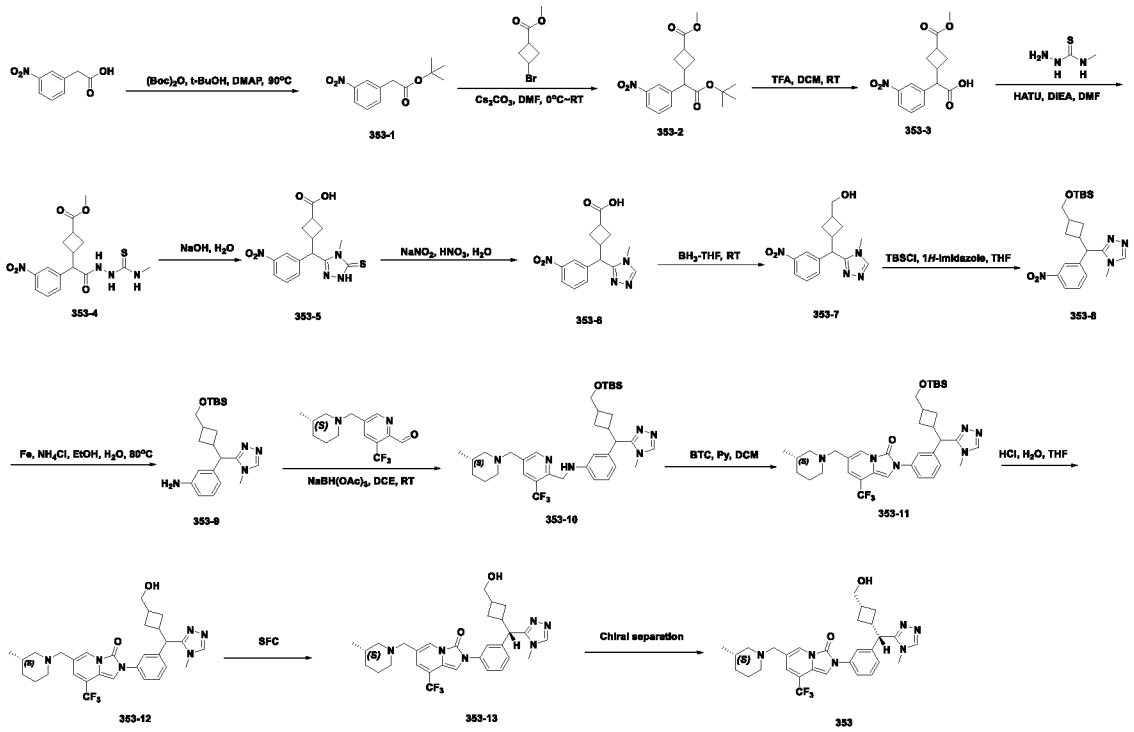
3. Synthesis of 352_P1&P2

[1226] The 332-8 (250 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [IPA]; B%: 50%-50%, 8 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.63; RT2 (min): 4.77) to afford 352_P1 (50.4 mg, 36.4%) and 352_P2 (20.7 mg, 14.7%)

LCMS-352_P1: (ES, m/z): [M+H]+ 553.2. H-NMR-352_P1: (400 MHz, METHANOL-d4) δ 8.37 (s, 1H), 7.68 (d, J = 2.0 Hz, 2H), 7.67-7.63 (m, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 4.26-4.19 (m, 1H), 3.54 (s, 3H), 3.35 (s, 2H), 2.94-2.83 (m, 2H), 2.48-2.39 (m, 1H), 2.33-2.24 (m, 2H), 2.12-2.06 (m, 1H), 2.03-1.90 (m, 2H), 1.88-1.57 (m, 9H), 0.95-0.89 (m, 3H)

LCMS-352_P2: (ES, m/z): [M+H]+ 553.2. H-NMR-352_P2: (400 MHz, METHANOL-d4) δ 8.37 (s, 1H), 7.68 (d, J = 1.2 Hz, 2H), 7.67-7.63 (m, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 4.26-4.18 (m, 1H), 3.54 (s, 3H), 3.35 (s, 2H), 2.98-2.80 (m, 2H), 2.46-2.39 (m, 1H), 2.35-2.22 (m, 2H), 2.13-2.04 (m, 1H), 2.02-1.90 (m, 2H), 1.88-1.58 (m, 9H), 1.00-0.88 (m, 4H)

Example 353. Synthesis of Compound 353



1. Synthesis of 353-1

[1227] To a stirred solution of 2-(3-nitrophenyl)acetic acid (50 g, 276.019 mmol, 1 equiv) and DMAP (3.37 g, 27.602 mmol, 0.1 equiv) in t-BuOH (100 mL) was added (Boc)2O (120.48 g, 552.038 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6h at 90°C under nitrogen atmosphere. The reaction was quenched with water (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 353-1 (60 g, 82.46%) as a light yellow oil.

2. Synthesis of 353-2

[1228] To a stirred solution of 353-1 (8 g, 33.719 mmol, 1 equiv) in DMF (100 mL) was added Cs2CO3 (54.93 g, 168.595 mmol, 5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C. To the above mixture was added methyl 3-bromocyclobutane-1-carboxylate (19.53 g, 101.157 mmol, 3.00 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 353-2

(8 g, 61.12%) as a light yellow oil.

3. Synthesis of 353-3

[1229] To a stirred solution of 353-2 (8 g, 22.898 mmol, 1 equiv) in DCM (60 mL) was added TFA (20 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 353-3 (8 g, 95.31%) as a light brown oil.

4. Synthesis of 353-4

[1230] To a stirred solution of 353-3 (8 g, 27.278 mmol, 1 equiv) and HATU (15.56 g, 40.917 mmol, 1.5 equiv) in DMF (100 mL) were added DIEA (10.58 g, 81.834 mmol, 3 equiv) and 1-amino-3-methylthiourea (3.73 g, 35.461 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 353-4 (4.5 g, 36.86%) as a brown yellow oil.

5. Synthesis of 353-5

[1231] To a stirred solution of NaOH (3.79 g, 94.632 mmol, 8 equiv) in H2O (100 mL) was added 353-4 (4.5 g, 11.829 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 6h at room temperature. The mixture/residue was neutralized to pH 7 with HCl (aq.). The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 353-5 (4 g, 77.65%) as a light brown oil.

6. Synthesis of 353-6

[1232] To a stirred solution of 353-5 (4 g, 11.482 mmol, 1 equiv) and NaNO2 (7.92 g, 114.820 mmol, 10 equiv) in H2O (100 mL) was added HNO3 (114 mL, 114.820 mmol, 10 equiv, 1M) at room temperature. The resulting mixture was stirred for 4h at room temperature. The mixture was aneutralized to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM/MeOH=10:1 (300 mL). The resulting mixture was filtered, the filter cake was washed with DCM (2x50 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 353-6 (2 g, 49.56%) as a yellow solid.

7. Synthesis of 353-7

[1233] To a stirred solution of 353-6 (2 g, 6.323 mmol, 1 equiv) in THF (30 mL) was added BH3-THF (31.61 mL, 31.615 mmol, 5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 353-7 (2 g, 83.70%) as a light yellow solid.

8. Synthesis of 353-8

[1234] To a stirred solution of 353-7 (2 g, 6.615 mmol, 1 equiv) and TBSCl (2.99 g, 19.845 mmol, 3 equiv) in THF (50 mL) was added 1H-imidazole (2.25 g, 33.075 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 6h at room temperature. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 353-8 (1.8 g, 60.74%) as an off-white solid.

9. Synthesis of 353-9

[1235] To a stirred solution of 353-8 (1.8 g, 4.321 mmol, 1 equiv) and Fe (1.21 g, 21.605 mmol, 5 equiv) in EtOH (50 mL)/H2O (10 mL) was added NH4Cl (2.31 g, 43.210 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 4h at 80°C. The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM (100mL). The resulting mixture was filtered, the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 353-9 (1.2 g, 67.53%) as an off-white solid.

10. Synthesis of 353-10

[1236] To a stirred solution of 353-9 (1.2 g, 3.104 mmol, 1 equiv) and I-2(1.07 g, 3.725 mmol, 1.2 equiv) in DCE (30 mL) was added NaBH(OAc)3 (1.97 g, 9.312 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 6h at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 353-10 (1.7 g, 80.87%) as an off-white solid.

11. Synthesis of 353-11

[1237] To a stirred solution of 353-10 (1.7 g, 2.588 mmol, 1 equiv) and Pyridine (2.05 g,

25.880 mmol, 10 equiv) in DCM (40 mL) was added Triphosgene (0.31 g, 1.035 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 353-11 (1.5 g, 78.94%) as a yellow solid.

12. Synthesis of 353-12

[1238] To a stirred solution of 353-11 (1.5 g, 2.196 mmol, 1 equiv) in THF (10 mL) was added HCl in H2O (20 mL, 1M) at room temperature. The resulting mixture was stirred for 1h at room temperature. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 353-12 (1.1 g, 85.43%) as a yellow solid.

13. Synthesis of 353-13

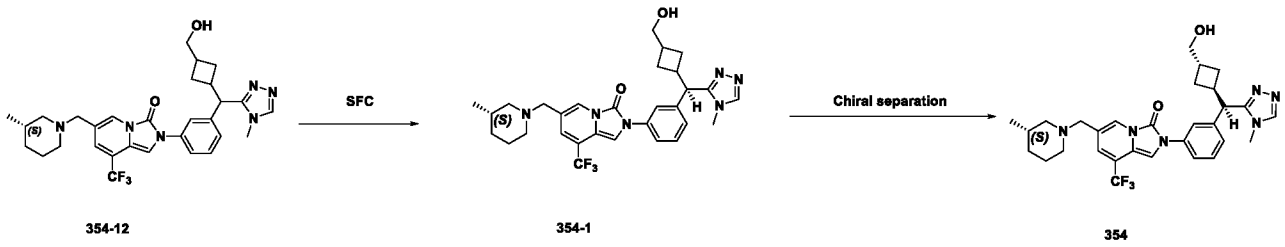
[1239] The 353-12 (1.1 g, 1.934 mmol, 1 equiv) was purified by Prep-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: IPA(0.5% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.58; RT2(min): 6.52; the first peak is product) to afford 353-13 (450 mg, 40.91%) as a yellow solid.

14. Synthesis of 353

[1240] The 353-13 (450 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 8.657; RT2(min): 9.447; the first peak is product) to afford 353 (53.4 mg, 11.80%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.37-1.79 (m, 7H), 1.83-1.95 (m, 3H), 2.28-2.30 (m, 2H), 2.74-2.84 (m, 2H), 3.15-3.32 (m, 3H), 3.42-3.44 (m, 5H), 4.27-4.30 (d, 1H), 4.47-4.50 (m, 1H), 7.01 (s, 1H), 7.19-7.21 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.70 (m, 2H), 7.75 (s, 1H), 8.32 (s, 1H).

Example 354. Synthesis of Compound 354



354-12 354-1 354

1. Synthesis of 354-1

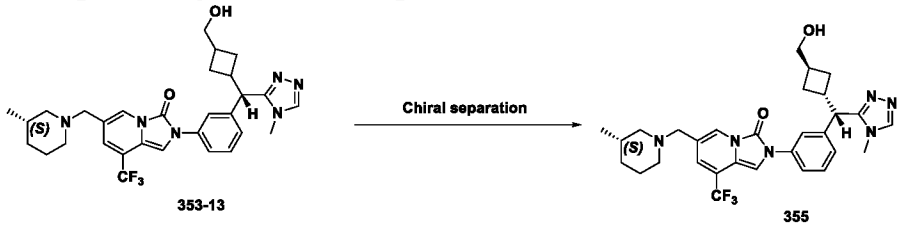
[1241] The 354-12 (1.1 g) was purified by Prep-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: IPA(0.5% 2M NH3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.58; RT2(min): 6.52; the second peak is product) to afford 354-1 (450 mg, 40.91%) as a yellow solid.

2. Synthesis of 354

[1242] The 354-1 (450 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.187; RT2(min): 11.097, the first peak is product) to afford 354 (240.2 mg, 51.99%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 569. H-NMR-354 (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.39-1.48 (m, 2H), 1.48-1.67 (m, 5H), 1.69-1.83 (m, 1H), 1.83-1.95 (m, 1H), 2.08-2.14 (m, 1H), 2.14-2.23 (m, 1H), 2.74-2.84 (m, 2H), 3.01-3.12 (m, 1H), 3.24 (s, 2H), 3.32 (s, 2H), 3.42 (s, 3H), 4.14-4.17 (d, 1H), 4.40-4.42 (m, 1H), 7.01 (s, 1H), 7.17-7.19 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.73 (m, 3H), 8.33 (s, 1H).

Example 355. Synthesis of Compound 355



353-13 355

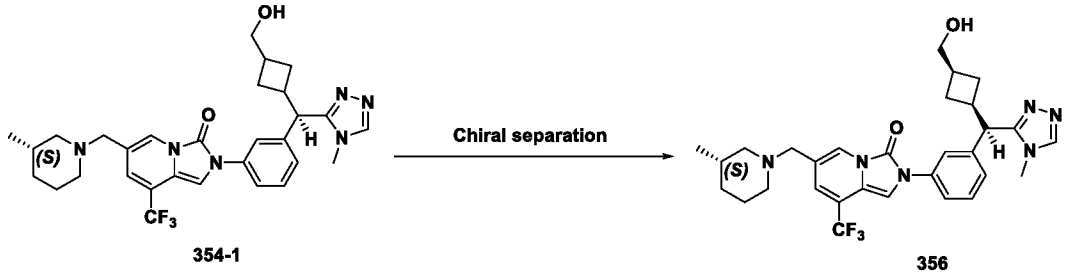
1. Synthesis of 355

[1243] The 353-13 (450 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 8.657; RT2(min): 9.447; the second peak is

product) to afford 355 (229.6 mg, 50.77%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 569. H-NMR-355 (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.35-1.69 (m, 7H), 1.69-1.83 (m, 1H), 1.83-1.95 (m, 1H), 2.08-2.13 (m, 1H), 2.13-2.19 (m, 1H), 2.74-2.84 (m, 2H), 3.01-3.12 (m, 1H), 3.24 (s, 2H), 3.32 (s, 2H), 3.42 (s, 3H), 4.14-4.17 (d, 1H), 4.40-4.42 (m, 1H), 7.01 (s, 1H), 7.17-7.19 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.73 (m, 3H), 8.32 (s, 1H).

Example 356. Synthesis of Compound 356



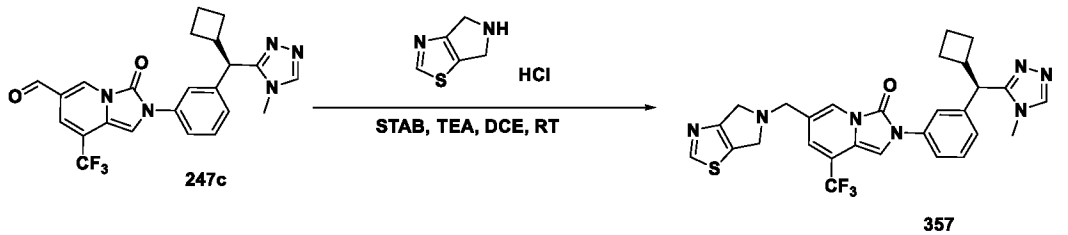
354-1 356

1. Synthesis of 356

[1244] The 354-1 (450 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.187; RT2(min): 11.097, the second peak is product) to afford 356 (51.6 mg, 11.29%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 569. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.93 (m, 4H), 1.37-1.79 (m, 7H), 1.83-1.95 (m, 3H), 2.28-2.35 (m, 2H), 2.65-2.3.01 (m, 2H), 3.15-3.17 (m, 1H), 3.32(s, 2H), 3.34-3.44 (m, 5H), 4.27-4.30 (d, 1H), 4.48-4.51 (m, 1H), 7.07 (s, 1H), 7.20-7.22 (d, 1H), 7.33 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.75 (m, 3H), 8.32 (s, 1H).

Example 357. Synthesis of Compound 357



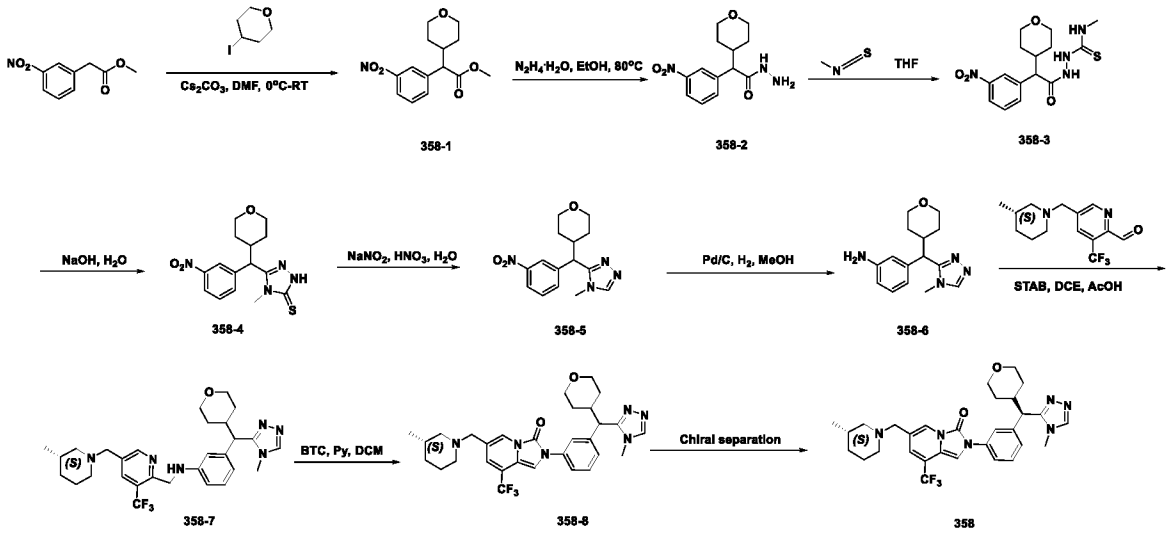
247c 357

1. Synthesis of 357

[1245] To a stirred solution of 247c (300 mg, 0.659 mmol, 1.00 equiv) and 4H,5H,6H-pyrrolo[3,4-d][1,3]thiazole dihydrochloride (262.28 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (266.62 mg, 2.636 mmol, 4 equiv) at room temperature. The mixture

was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The crude product (130mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 55% B in 8 min, 55% B; Wave Length: 220 nm; RT1(min): 7.55) to afford 357 (117.5 mg, 31.00%) as a yellow solid. LC-MS: (ES, m/z): [M+H] + :566. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.80-1.82 (m, 5H), δ 2.01-2.16 (m, 1H), δ 3.15-3.21 (m, 1H), δ 3.33 (s, 3H), δ 3.78 (s, 2H), δ 3.91-3.93 (m, 2H), δ 4.02-4.03 (d, 2H), δ 4.25-4.28 (d, 1H), δ 7.11 (s, 1H), δ 7.09-7.21 (d, 1H), δ 7.33 (s, 1H), δ 7.43-7.46 (m, 1H), δ 7.69-7.74 (m, 2H), δ 7.80 (s, 1H), δ 8.33 (s, 1H), δ 9.00 (s, 1H).

Example 358. Synthesis of Compound 358



1. Synthesis of 358-1

[1246] Into a 250 mL 3-necked round-bottom flask were added methyl,2-(3-nitrophenyl) acetate (10 g, 51.236 mmol, 1 equiv), 4-iodooxane (32.59 g, 153.708 mmol, 3 equiv), DMF (100 mL) and Cs2CO3 (83.47 g, 256.180 mmol, 5 equiv) at 0 °C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. NH4Cl (aq.) (200 ml) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA

(10:1) to afford 358-1 (13 g, 89.03%) as a white solid.

2. Synthesis of 358-2

[1247] Into a 500 mL 3-necked round-bottom flask were added 358-1 (13 g, 46.546 mmol, 1 equiv), NH2NH2H2O (69.90 g, 1396.380 mmol, 30 equiv) and EtOH (130 mL) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched with sat. NH4Cl (aq.) (200 ml) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure to afford 358-2 (10.5 g, 76.73%) as a white solid.

3. Synthesis of 358-3

[1248] Into a 250 mL 3-necked round-bottom flask were added 358-2 (10.5 g, 37.595 mmol, 1 equiv), methyl isothiocyanate (6.87 g, 93.987 mmol, 2.5 equiv) and tetrahydrofuran (110 mL) at room temperature. The mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (200 ml) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford 358-3 (12 g, 86.05%) as a white solid.

4. Synthesis of 358-4

[1249] A mixture of 358-3 (10 g, 28.376 mmol, 1 equiv) in sodium hydroxide (280 ml, 1 M) was stirred for overnight at room temperature. The reaction was diluted with water. And then the pH value of the solution was adjusted to 5 with HCL aq. (1 M). The precipitated solids were collected by filtration and the resulting mixture was concentrated under reduced pressure to afford the title compound 358-4 as a white solid, which was used without purification.

5. Synthesis of 358-5

[1250] To a stirred solution of 358-5 (9 g, 26.915 mmol, 1 equiv) in water (48 ml) was added NaNO2 (18.57 g, 269.150 mmol, 10 equiv). This was followed by addition of HNO3 (269.15 ml, 1 M) dropwise with stirring at 0 °C. The mixture was stirred for overnight at room temperature. And then the pH value of the solution was adjusted to 8 with sat. NaHCO3 (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 358-6 (8 g, 92.41%) as a yellow oil.

6. Synthesis of 358-6

[1251] To a solution of 358-5 (2 g, 6.615 mmol, 1 equiv) in 20 mL MeOH was added Pd/C

(10%, 0.21 g) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 5 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and the mixture was concentrated under reduced pressure. This resulted in 358-6 (1.8 g, 93.91%) as a yellow oil.

7. Synthesis of 358-7

[1252] Into a 100 mL round-bottom flask were added 358-6 (1 g, 3.672 mmol, 1 equiv), DCE (10 mL), I-2(1.37 g, 4.774 mmol, 1.3 equiv) and STAB (2.33 g, 11.016 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (30 ml) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x30 mL) and the mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 15:1) to afford 358-7 (1.5 g, 70.01%) as a yellow oil.

8. Synthesis of 358-8

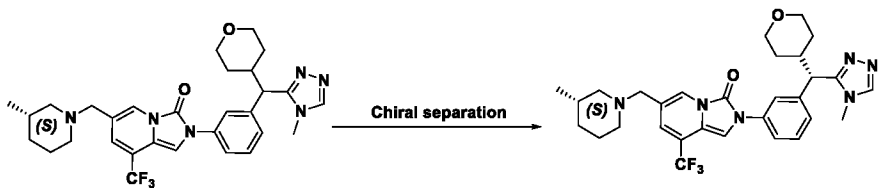
[1253] Into a 100 mL round-bottom flask were added 358-7 (1.5 g, 2.764 mmol, 1 equiv), DCM (30 mL) and pyridine (1.31 g, 16.584 mmol, 6 equiv) at room temperature. To the above mixture was added triphosgene (0.41 g, 1.382 mmol, 0.5 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 358-8 (1 g, 61.71%) as a yellow solid.

9. Synthesis of 358-0

[1254] The 358-9 (250 mg) was purified by Chiral separation with the following conditions Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.381; RT2(min): 8.334; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1 mL; Number of Runs: 7) to afford 358 (105.4 mg, 42.16%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 569. H-NMR: (400 MHz, DMSO, δ ppm): 0.72-0.99 (d, 4H), 1.11-1.37 (m, 3H), 1.37-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.80-1.99 (m, 1H), 2.69-2.88 (d, 2H), 3.15-3.31 (m, 5H), 3.45-3.58 (s, 3H), 3.72-3.88 (m, 2H), 4.02-4.15 (d, 1H), 6.91-7.06 (s, 1H), 7.23-7.36 (d, 2H), 7.38-7.51 (m, 1H), 7.60-7.66 (s, 1H), 7.66-7.75 (d, 1H), 7.76-7.86 (s, 1H), 8.26-8.38 (s, 1H).

Example 359. Synthesis of Compound 359



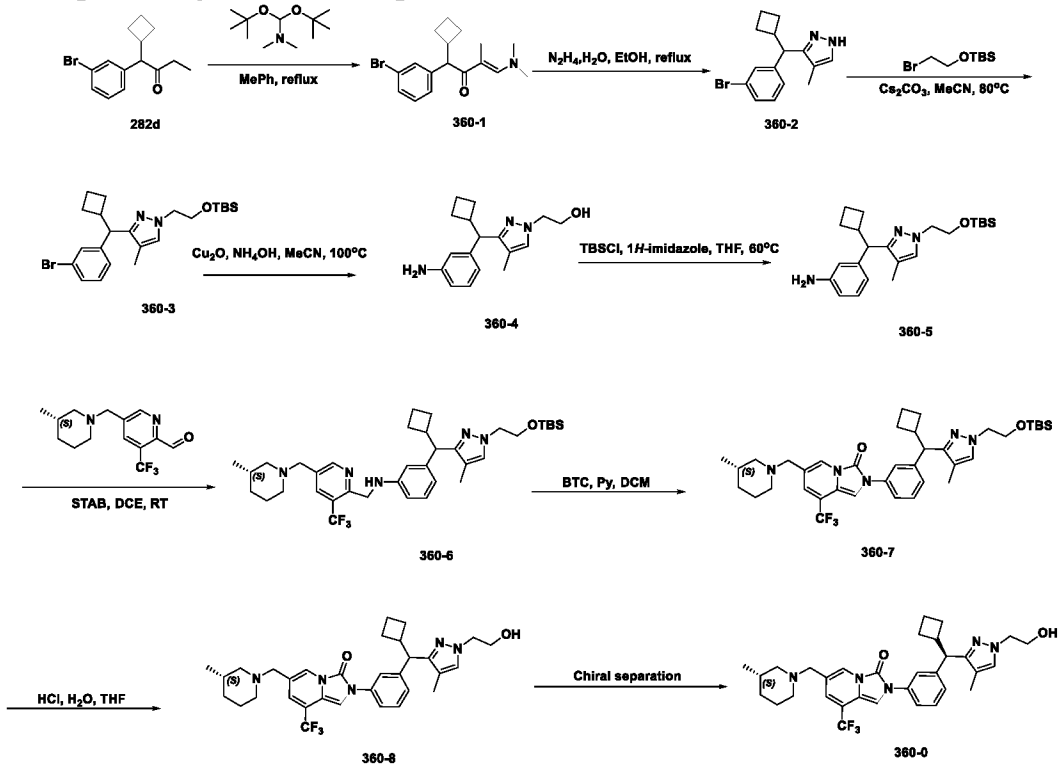
358-8 359

1. Synthesis of 359

[1255] The 358-8 (250 mg) was purified by Chiral separation with the following conditions Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.381; RT2(min): 8.334; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1 mL; Number of Runs: 7) to afford 359 (112.6 mg, 45.04%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 569. H-NMR: (400 MHz, DMSO, δ ppm): 0.72-0.99 (d, 4H), 1.11-1.37 (m, 3H), 1.37-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.80-1.99 (m, 1H), 2.69-2.88 (d, 2H), 3.15-3.31 (m, 5H), 3.45-3.58 (s, 3H), 3.72-3.88 (m, 2H), 4.02-4.15 (d, 1H), 6.91-7.06 (s, 1H), 7.23-7.36 (d, 2H), 7.38-7.51 (m, 1H), 7.60-7.66 (s, 1H), 7.66-7.75 (d, 1H), 7.76-7.86 (s, 1H), 8.26-8.38 (s, 1H).

Example 360. Synthesis of Compound 360



282d 360-1 360-2 360-3 360-4 360-5 360-6 360-7 360-8 360-9

1. Synthesis of 360-1

[1256] To a stirred solution of 282-4 (15 g, 53.344 mmol, 1 equiv) in Toluene (150 mL) was added [bis(tert-butoxy)methyl]dimethylamine (54.23 g, 266.720 mmol, 5 equiv) at room temperature. The resulting mixture was stirred overnight at 110°C. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 360-1 (9 g, 30.10%) as a yellow oil.

2. Synthesis of 360-2

[1257] To a stirred solution of 360-1 (9 g, 26.764 mmol, 1 equiv) in EtOH (100 mL) was added hydrazine hydrate (98%)(13.40 g, 267.640 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 6h at 80°C. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions (Column, C18 silica gel; Mobile Phase A: Water(0.05% FA), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 10% B to 50% B in 20 min, Wave Length: 220 nm) to afford the crude product. The crude product (9 g) was purified by HP-FLASH with the following conditions (Column: Welch Utimate AQ-C18, 50*250mm*10μm; Mobile Phase A: Water(0.05% TFA), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 35% B to 65% B in 30 min, Wave Length: 220 nm) to afford 360-2 (4.1 g, 46.68%) as a light yellow oil.

3. Synthesis of 360-3

[1258] To a stirred solution of 360-2 (2 g, 6.553 mmol, 1 equiv) and (2-bromoethoxy)(tert-butyl)dimethylsilane (3.92 g, 16.383 mmol, 2.5 equiv) in MeCN (100 mL) was added Cs2CO3 (6.40 g, 19.659 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 5:1) to afford 360-4 (2.2 g, 67.36%) as a colorless oil.

4. Synthesis of 360-4

[1259] To a solution of 360-3 (2 g, 4.315 mmol, 1 equiv) and Cu2O (0.12 g, 0.863 mmol, 0.2 equiv) in MeCN (10 mL) was added NH4OH (10 mL) in a pressure tank. The resulting mixture was stirred for overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The

crude product was used in the next step directly without further purification. This resulted in 360-3 (1.2 g, 87.71%) as a light yellow oil.

5. Synthesis of 360-5

[1260] To a stirred solution of 360-4 (1.2 g, 4.205 mmol, 1 equiv) and t-butyldimethylchlorosilane (1.90 g, 12.615 mmol, 3 equiv) in tetrahydrofuran (100 mL) was added 1H-imidazole (1.43 g, 21.025 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 4h at 60°C. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 8:1) to afford 360-5 (1.2 g, 69.98%) as a light yellow oil.

6. Synthesis of 360-6

[1261] To a stirred solution of 360-5 (0.8 g, 2.002 mmol, 1 equiv) and I-2(0.75 g, 2.603 mmol, 1.3 equiv) in DCE (10 mL) was added STAB (0.85 g, 4.004 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The residue was purified by Prep-TLC (PE / EA 2:1) to afford 360-6 (1.2 g, 87.69%) as a light yellow solid.

7. Synthesis of 360-7

[1262] To a stirred solution of 360-6 (1.2 g, 1.791 mmol, 1 equiv) and Pyridine (1.42 g, 17.910 mmol, 10 equiv) in DCM (20 mL) was added Triphosgene (0.21 g, 0.716 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 360-6 (1 g, 74.61%) as a yellow solid.

8. Synthesis of 360-8

[1263] To a stirred solution of 360-7 (1 g, 1.437 mmol, 1 equiv) in THF (10 mL) was added HCl (aq.)(10 mL, 1M) at room temperature. The resulting mixture was stirred for 3h at room temperature. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 360-8 (700 mg, 80.40%) as a yellow solid.

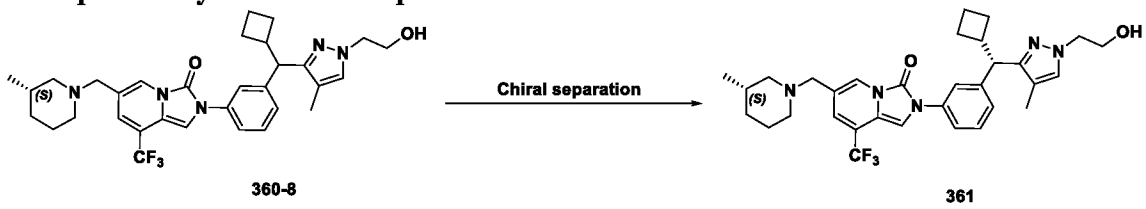
9. Synthesis of 360

[1264] The 360-8 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions

(Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 5.715; RT2(min): 7.05; the second peak is product) to afford 360 (155.5 mg, 38.56%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 582. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.43-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.71-1.80 (m, 4H), 1.80-1.95 (m, 4H), 1.95-2.02 (m, 1H), 2.71-2.85 (m, 2H), 3.09-3.12 (m, 1H), 3.64-3.68 (m, 2H), 3.92-3.95 (d, 1H), 4.01-4.03 (m, 2H), 7.00 (s, 1H), 7.21-7.26 (m, 2H), 7.32 (s, 1H), 7.35-7.39 (m, 1H), 7.58-7.60 (d, 1H), 7.66 (s, 1H), 7.73 (s, 1H).

Example 361. Synthesis of Compound 361



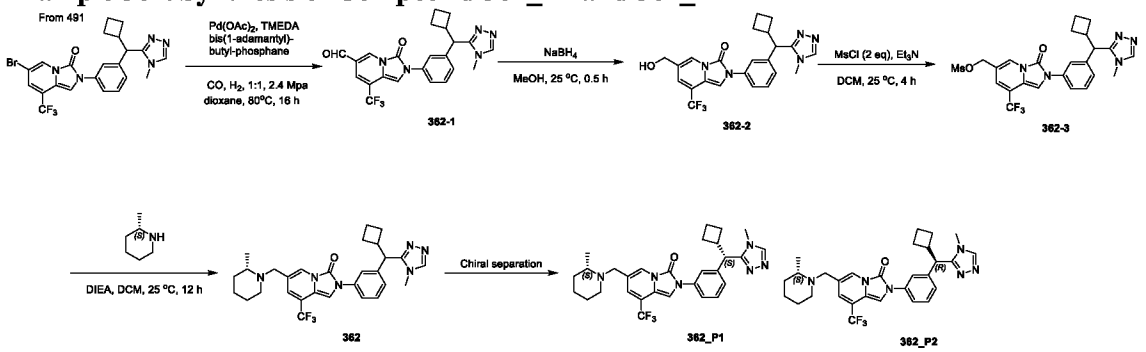
1. Synthesis of 361

[1265] The 360-8 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 5.715; RT2(min): 7.05; the first peak is product) to afford 361 (166.2 mg, 41.13%) as a yellow solid.

LC-MS-361: (ES, m/z): [M+H]+ 582

H-NMR-361: (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.43-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.71-1.80 (m, 4H), 1.80-2.02 (m, 5H), 2.71-2.85 (m, 2H), 3.09-3.12 (m, 1H), 3.64-3.68 (m, 2H), 3.92-3.95 (d, 1H), 4.01-4.03 (m, 2H), 7.00 (s, 1H), 7.21-7.26 (m, 2H), 7.32 (s, 1H), 7.35-7.39 (m, 1H), 7.58-7.60 (d, 1H), 7.66 (s, 1H), 7.73 (s, 1H).

Example 362. Synthesis of Compound 362_P1 and 362_P2



1. Synthesis of 362-1

[1266] To a solution of 6-bromo-2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (1 g, 1.98 mmol, 1 equiv) in dioxane (40 mL) was added N,N,N',N'-tetramethylethane-1,2-diamine (459.02 mg, 3.95 mmol, 2 equiv) and diacetoxypalladium (88.68 mg, 395.01 umol, 0.2 equiv), bis(1-adamantyl)-butyl-phosphane(141.63 mg, 395.01 umol, 0.2 equiv). The mixture was stirred at 80 °C for 16 hr under CO/H2 (1:1) (2.5 Mpa). The reaction was poured into water (50 mL) and the resulting mixture was extracted with EtOAc (2 x 50 mL). The organic phase was washed with sat NaHCO3(20 mL), brine (20 mL), dried over anhydrous Na2SO4, concentrated in vacuum to afford 362-1 (0.65 g, crude) as a light yellow solid.

2. Synthesis of 362-2

[1267] To a solution of 362-1 (3 g, 6.59 mmol, 1 equiv) in MeOH (40 mL) was added NaBH4 (747.62 mg, 19.76 mmol, 3 equiv). The mixture was stirred at 25 °C for 0.5 hr. The reaction was poured into water (50 mL) and the resulting mixture was concentrated in vacuum to remove MeOH, then extracted with EtOAc (2 x 30 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue 362-2 (3 g, crude) as a yellow solid.

3. Synthesis of 362-3

[1268] To a solution of 362-2 (300 mg, 655.81 umol, 1 equiv) in DCM (10 mL) was added Et3N (199.08 mg, 1.97 mmol, 273.84 uL, 3 equiv) and MsCl (150.25 mg, 1.31 mmol, 2 equiv). The mixture was stirred at 25 °C for 1 hr. The reaction was poured into water (30 mL) and the resulting mixture was extracted with DCM (2 x 30 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue 362-3 (330 mg, crude) as a balck solid.

4. Synthesis of 362

[1269] To a solution of 362-3 (270 mg, 504.17 umol, 1 equiv) in DCM (9 mL) was added Et3N (153 mg, 1.51 mmol, 210.52 uL, 3 equiv) and (2S)-2-methylpiperidine (100 mg, 1.01 mmol, 119.19 uL, 2 equiv). The resulting mixture was stirred at 25 °C for 12 hrs. The reaction was poured into water (30 mL) and the resulting mixture was extracted with DCM (2 x 30 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water(NH4HCO3)-ACN]; B%: 40%-70%, 10 min) to afford 362 (22 mg, 8%) as a light yellow solid.

5. Synthesis of 362_P1&P2

[1270] 362 (22 mg) was purified by Chiral separation with the following conditions (column:

REGIS WHELK-O1 (250mm*25mm,10um); Mobile Phase: [Neu-ETOH]; B%: 55%-55%,12min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.47; RT2 (min): 4.77) to afford 362_P1 (6.5 mg, 28% yield) as a yellow solid.

MS-362_P1: (ES, m/z): [M+H]+ 538.2

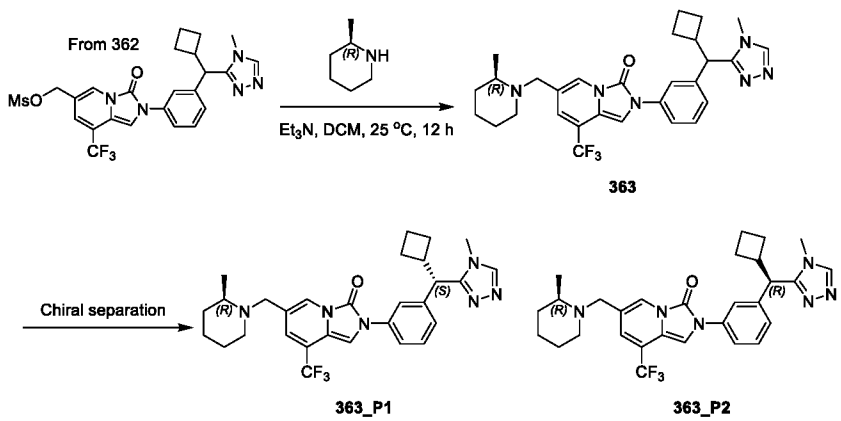
1H-NMR-362_P1: (400 MHz, DMSO-d6) δ ppm 8.33 (s, 1H), 7.75 (s, 1H), 7.69-7.60 (m, 2H), 7.47-7.43 (m, 1H), 7.31 (m, 1H), 7.21-7.19 (d, J = 8 Hz, 1H), 6.99 (s, 1H), 4.31-4.20 (m, 1H), 3.70-3.67 (d, J = 12 Hz, 1H), 3.44 (s, 3H), 3.10-2.99 (m, 1H), 3.16-3.14 (m, 1H), 2.88-2.74 (m, 1H), 2.43-2.40 (m, 2H), 2.19-2.14 (m, 2H), 1.78-1.67 (m, 4H), 1.61-1.59 (m, 3H), 1.50-1.38 (m, 3H), 1.16-1.11 (m, 3H)

362_P2 (5.6 mg, 24% yield) as a yellow solid.

MS-362-P2: (ES, m/z): [M+H]+ 538.2. 1H-NMR-362_P2: (400 MHz, DMSO-d6) δ ppm 8.33 (s, 1H), 7.74 (s, 1H), 7.71-7.66 (m, 2H),

7.46-7.42 (m, 1H), 7.31 (s, 1H), 7.19 (d, J = 8 Hz, 1H), 6.98 (s, 1H), 4.28-4.21 (m, 1H), 3.69-3.66 (d, J = 12 Hz, 1H), 3.43 (s 3H), 3.28-3.25 (m, 1H), 3.04-3.00 (d, J = 12 Hz , 1H), 2.79-2.71 (m, 1H), 2.43-2.33 (m, 2H), 2.04-2.03 (m, 1H), 2.02-2.01 (m, 1H), 1.76-1.74 (m, 4H), 1.64-1.62 (m, 3H), 1.49-1.44 (m, 3H), 1.05-1.01 (m, 3H).

Example 363. Synthesis of Compound 363_P1 and 363_P2



1. Synthesis of 363

[1271] To a solution of [2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridin-6-yl]methyl methanesulfonate (200 mg, 373.46 umol, 1.0 equiv) in DCM (5 mL) was added Et3N (113.3 mg, 1.12 mmol, 3 equiv) and (2R)-2-methylpiperidine (74.07 mg, 746.91 umol, 2 equiv). The mixture was stirred at 25 °C for 12 hr. The reaction was poured into water (30 mL) and the resulting mixture was extracted with DCM (2 x 30 mL). The organic phase was washed with brine (10 mL), dried over

anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC(Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile phase A: [water(NH4HCO3)-ACN]; B%: ACN: Flow rate: 50 mL/min; Gradient: 45% B to 75% B in 8 min. Wave Length: 220 nm; RT1(min): 5.1) to afford 363 (60 mg, 29% yield) as a yellow solid.

2. Synthesis of 363_P1& P2

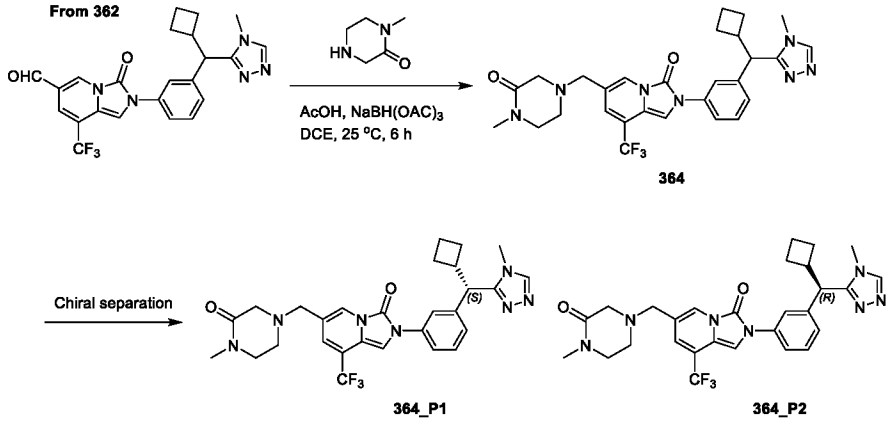
[1272] The 363 (60 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD(250mm*30mm,10um); Mobile Phase A%: [Neu-MeOH]; B%: 40%-40%, 8 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.30; RT2 (min): 1.38) to afford 363_P1 (20.0 mg, 33% yield) as a yellow solid.

MS-363_P1 (ES, m/z): [M+H]+ 539.2. 1H-NMR-363_P1(400 MHz, DMSO-d6) δ=8.33 (s, 1H), 7.75 (s, 1H), 7.73-7.71 (m, 1H), 7.71-7.69 (m, 1H), 7.45-7.38 (m, 1H), 7.20-7.13 (m, 1H), 7.00-6.91 (m, 1H), 6.79-6.72 (m, 1H), 4.26-4.25 (m, 1H), 3.67-3.44 (m, 1H), 3.43 (s, 3H), 3.41-3.33 (m, 2H), 3.05-3.01 (m, 1H), 2.83-2.68 (m, 1H), 2.47-2.45 (m, 1H), 2.25-2.16 (m, 2H), 1.77-1.75 (m, 4H), 1.70-1.68 (m, 2H), 1.50-1.43 (m, 1H), 1.40-1.37 (m, 1H), 1.28-1.25 (m, 2H), 1.10-1.08 (m, 3H)

363_P2 (25.5 mg, 41% yield) as a yellow solid.

363-P2: (ES, m/z): [M+H]+ 539.2. 1H-NMR-363-P2: (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 7.75 (s, 1H), 7.73-7.71 (m, 1H), 7.71-7.69 (m, 1H), 7.45-7.38 (m, 1H), 7.20-7.13 (m, 1H), 7.00-6.91 (m, 1H), 6.79-6.72 (m, 1H), 4.26-4.25 (m, 1H), 3.67-3.44 (m, 1H), 3.50 (s, 3H), 3.41-3.33 (m, 2H), 3.05-3.01 (m, 1H), 2.83-2.68 (m, 1H), 2.47-2.45 (m, 1H), 2.25-2.16 (m, 2H), 1.77-1.75 (m, 4H), 1.70-1.68 (m, 2H), 1.50-1.43 (m, 1H), 1.40-1.37 (m, 1H), 1.28-1.25 (m, 2H), 1.10-1.08 (m, 3H).

Example 364. Synthesis of Compound 364_P1 and 364_P2



1. Synthesis of 364

[1273] To a solution of 2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridine-6-carbaldehyde (400 mg, 878.29 umol, 1.0 equiv.), 1-methylpiperazin-2-one (200 mg, 1.76 mmol, 2.0 equiv.) in DCE (10 mL) was added dropwise AcOH (52 mg, 878.29 umol, 50.23 uL, 1.0 equiv.) at 25 °C. After addition, the mixture was stirred at this temperature for 2 hrs, and then NaBH(OAc)3 (558 mg, 2.63 mmol, 3.0eq) was added dropwise. The resulting mixture was stirred at 25 °C for 14 hrs. The resulting mixture was stirred at 25 °C for 6 hrs. The reaction was poured into sat NaHCO3 (30 mL) and the resulting mixture was extracted with DCM (2 x 20 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 25%-55%,10 min) to afford 364 (466 mg, 87%) as a light yellow solid.

2. Synthesis of 364_P1, P2

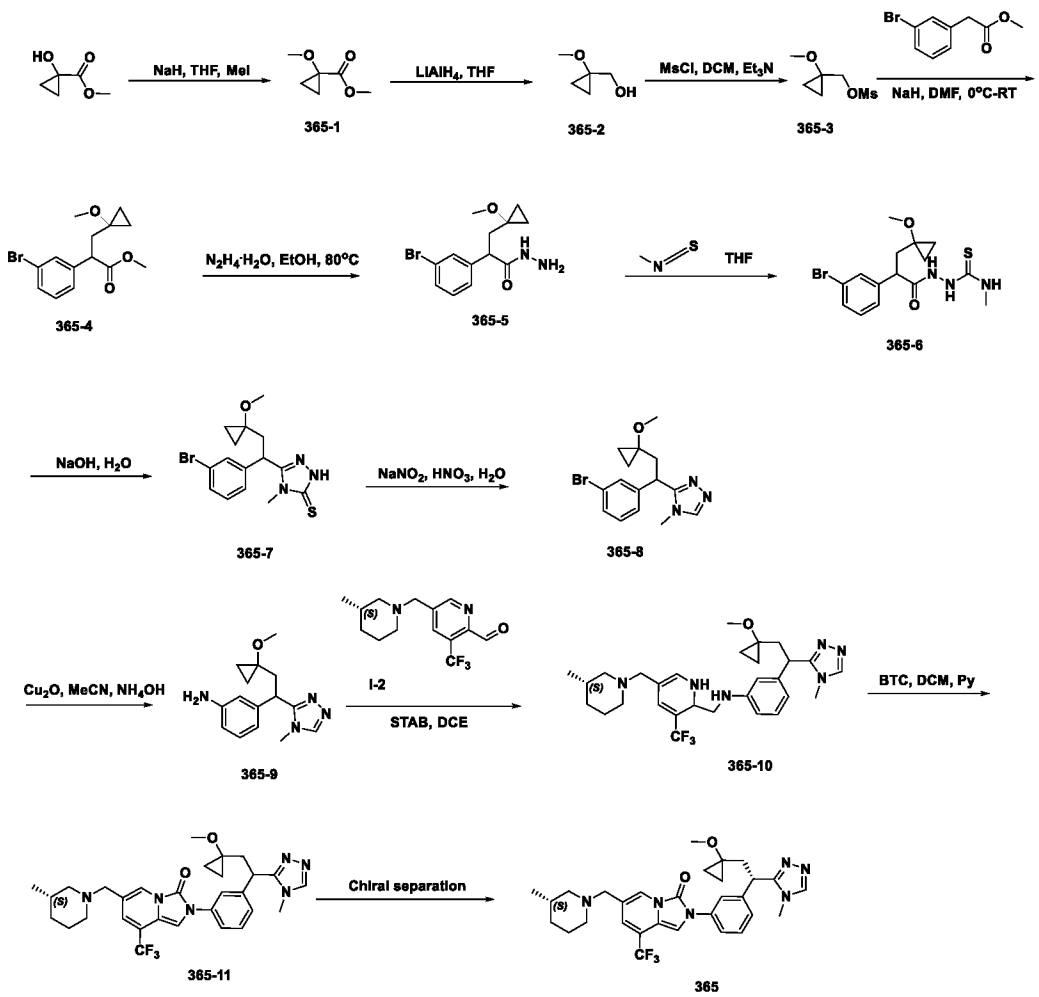
[1274] The 364 (70 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD(250mm*30mm,10um); Mobile Phase: [Neu-IPA]; B%: 45%-45%,7min, Flow rate: 70 mL/min; Wave Length: 254 nm; RT1 (min): 1.54; RT2 (min): 1.69) to afford 364_P1 (17.2 mg, 23% yield) as a yellow solid.

MS-364-P1: (ES, m/z): [M+H]+ 553.2. 1H-NMR-364_P1: (400 MHz, CHLOROFORM-d) δ ppm 8.00 (s, 1H), 7.58-7.52 (m, 2H), 7.50-7.43 (m, 1H), 7.39-7.31 (m, 1H), 7.19-7.17 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.78 (s, 1H), 3.93-3.88 (m, 1H), 3.37 (s, 3H), 3.32-3.25 (m, 5H), 3.15-3.09 (m, 2H), 2.94 (s, 3H), 2.72-2.64 (m, 2H), 2.33-2.21 (m, 1H), 1.82-1.64 (m, 5H)

364_P2 (15.6mg, 21% yield) as a yellow solid.

MS-364-P2: (ES, m/z): [M+H]+ 553.2. 1H-NMR-364_P2: (400 MHz, CHLOROFORM-d) δ ppm 8.05 (s, 1H) 7.66-7.60 (m, 2H) 7.59-7.53 (m, 1H) 7.47-7.40 (m, 1H) 7.21-7.17 (m, 1H) 6.94 (s, 1H) 6.79 (s, 1H), 3.99-3.96 (d, J = 12 Hz, 1 H) 3.32 (s, 3H) 3.38-3.33 (m, 5H), 3.24-3.15 (m, 2H), 2.95 (m, 3H), 2.80-2.71 (m, 2H) 2.41-2.29 (m, 1H), 2.00-1.79 (m, 5H).

Example 365. Synthesis of Compound 365



1. Synthesis of 365-1

[1275] To a stirred solution of methyl 1-hydroxycyclopropane-1-carboxylate (23 g, 198.078 mmol, 1 equiv) in THF (250 mL) was added NaH (11.88 g, 297.117 mmol, 1.5 equiv, 60%) in four portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To the above mixture was added MeI (50.61 g, 356.540 mmol, 1.8 equiv) dropwise over 20min at °C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (750 mL) at 0°C. The resulting mixture was extracted with EtOEt (2 x300 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 365-1 (25 g, 96.98%) as a light yellow oil.

2. Synthesis of 365-2

[1276] To a stirred mixture of LiAlH4 (14.58 g, 384.192 mmol, 2 equiv) in THF (450mL) was added 365-1 (25 g, 192.096 mmol, 1 equiv) in THF(150 mL) dropwise at 0°C under

nitrogen atmosphere. The resulting mixture was stirred for1 h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of NaOH (2M) (75 mL) at 0°C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was dried over anhydrous MgSO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 365-2 (16 g, 81.55%) as a colorless oil.

3. Synthesis of 365-3

[1277] To a stirred solution of 365-2 (5 g, 48.956 mmol, 1 equiv) and Et3N (5.94 g, 58.747 mmol, 1.2 equiv) in DCM (100 mL) was added MsCl (6.17 g, 53.852 mmol, 1.1 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0°C under nitrogen atmosphere. The resulting mixture was diluted with MTBE (100 mL). The DCM was removed under reduced pressure. The resulting mixture was filtered, the filter cake was washed with MTBE (10 mL). To the above filtrate was added DMF (10 mL). The MTBE was removed under reduced pressure. This resulted in 365-3 solution in DMF(10 mL).

4. Synthesis of 365-4

[1278] A solution of 365-3 (16.78 g, 73.243 mmol, 1.5 equiv) in DMF (170 mL) was treated with NaH (2.93 g, 73.256 mmol, 1.50 equiv, 60%) for 30 min at 0 °C under nitrogen atmosphere followed by the addition of (1-methoxycyclopropyl)methyl methanesulfonate (8.8 g, 48.829 mmol, 1 equiv) in DMF(10 mL) dropwise at 0°C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH4Cl (aq.) (600 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (100 mL), then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (25:1) to afford crude product (12 g). The crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(10 mmol/L NH4HCO3), 30% to 90% gradient in 35 min; detector, UV 220 nm. This resulted in 365-4 (2.9 g, 18.96%) as a light yellow oil.

5. Synthesis of 365-5

[1279] To a stirred solution of 365-4 (2.9 g, 9.260 mmol, 1 equiv) in EtOH (30 mL) was added hydrazine hydrate (3.71 g, 74.080 mmol, 8 equiv). The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (120 mL). The resulting mixture was extracted with CH2Cl2 (3 x 100mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 365-5 (3 g, NaN) as a light yellow solid.

6. Synthesis of 365-6

[1280] To a stirred solution of 365-5 (3 g, 9.579 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added methyl isothiocyanate (1.05 g, 14.369 mmol, 1.5 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (50 mL). The THF was removed under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x5 mL). The resulting solid was dried under vacuum. This resulted in 365-6 (3.2 g, 86.48%) as a white solid.

7. Synthesis of 365-7

[1281] To a stirred mixture of 365-6 (3.2 g, 8.284 mmol, 1 equiv) in H2O (40 mL) was added NaOH (1.66 g, 41.420 mmol, 5 equiv). The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 4 with HCl (1M). The resulting mixture was extracted with EtOAc (2 x 50mL). The combined organic layers were concentrated under reduced pressure. This resulted in 365-7 (2.8 g, 91.78%) as a yellow solid.

8. Synthesis of 365-8

[1282] To a stirred mixture of 365-7 (2.8 g, 7.603 mmol, 1 equiv) and NaNO2 (5.25 g, 76.030 mmol, 10 equiv) in H2O (30 mL) and EtOAc (30 mL) was added HNO3 (76.03 mL, 76.030 mmol, 10 equiv, 1M) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (20 mL). The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 365-8 (2.4 g, 93.89%) as a light yellow solid.

9. Synthesis of 365-9

[1283] To a solution of 365-8 (2.35 g, 6.989 mmol, 1 equiv) in MeCN (70 mL) and NH3H2O (70 mL, 25%) was added Cu2O (0.50 g, 3.494 mmol, 0.5 equiv) in a pressure tank. The resulting mixture was stirred for overnight at 100°C. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The MeCN was removed under reduced pressure. The resulting mixture was extracted with CH2Cl2/MeOH=10/1 (2 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 365-9 (1.9 g, 99.81%) as a yellow solid.

10. Synthesis of 365-10

[1284] To a stirred solution of 365-9 (900 mg, 3.305 mmol, 1 equiv) and I-2(1135.30 mg,

3.966 mmol, 1.2 equiv) in DCE (20 mL) was added STAB (1400.73 mg, 6.610 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (30 mL). The resulting mixture was extracted with CH2Cl2 (3 x 40mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 365-10 (1.1 g, 61.12%) as a white solid.

11. Synthesis of 365-11

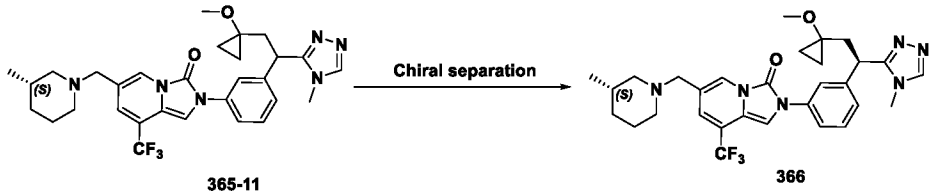
[1285] To a stirred solution of 365-10 (1.1 g, 2.020 mmol, 1 equiv) and Pyridine (0.96 g, 12.120 mmol, 6 equiv) in DCM (30 mL) was added Triphosgene (0.24 g, 0.808 mmol, 0.4 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NaHCO3 (aq.) (30 mL). The resulting mixture was extracted with CH2Cl2/MeOH=10/1 (2 x 30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10mmol/L NH4HCO3), 20% to 80% gradient in 35 min; detector, UV 254 nm. This resulted in 365-11 (720 mg, 62.69%) as a yellow solid.

12. Synthesis of 365

[1286] 365-11(350 mg) was separated by Prep-CHiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 6 min; Wave Length: 220/254 nm; RT1(min): 4.382; RT2(min): 5.07; the first peak is product) to afford 365 (143.6 mg, 41.03%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 569. H-NMR: (400 MHz, DMSO-d6, ppm): δ0.11-0.25 (m, 2H), δ0.50 (s, 2H), δ0.82-0.86 (m, 4H), δ1.43-1.66 (m, 5H), δ1.75-1.92 (m, 1H), δ2.19-2.25 (m, 1H), δ2.59-2.63 (m, 1H), δ2.65-2.75 (m, 2H), δ3.15 (s, 3H), δ3.25 (s, 2H), δ3.53 (s, 3H), δ4.44-4.48 (t, 1H), δ7.01 (s, 1H), δ7.32-7.36 (m, 2H), δ7.43-7.46 (t, 1H), δ7.66 (s, 1H), δ7.70-7.72 (d, 1H), δ7.80 (s, 1H), δ8.35 (s, 1H).

Example 366. Synthesis of Compound 366



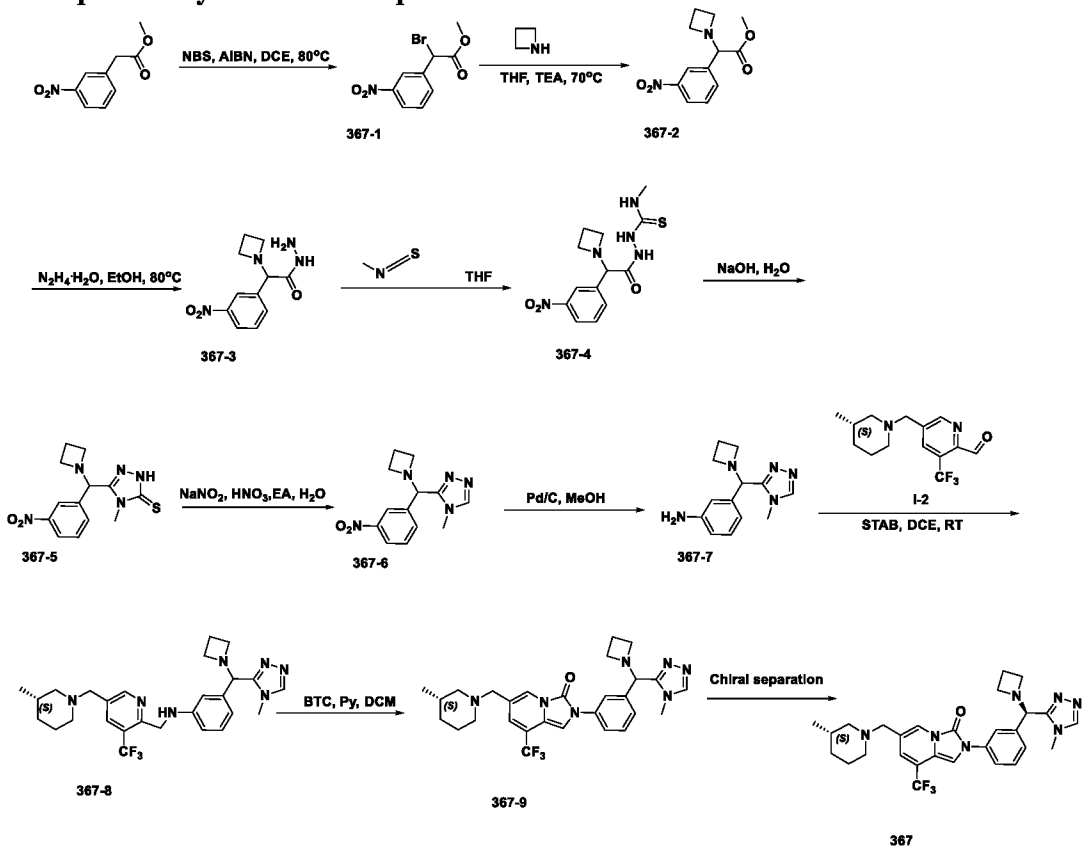
1. Synthesis of 366

[1287] 365-11(350 mg) was separated by Prep-Chiral-HPLC with the following conditions

(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 6 min; Wave Length: 220/254 nm; RT1(min): 4.382; RT2(min): 5.07; the second peak was product) to afford 366 (131.5 mg, 37.57%) as a yellow solid..

LC-MS-366 (ES, m/z): [M+H] + 569. H-NMR-366 (400 MHz, DMSO-d6, ppm): δ0.11-0.25 (m, 2H), δ 0.49 (s, 2H), δ0.82-0.86 (m, 4H), δ1.43-1.48 (m, 5H), δ1.50-1.69 (m, 4H), δ1.75-1.92 (m, 1H), δ2.19-2.25 (m, 1H), δ2.59-2.63 (m, 1H), δ2.65-2.75 (m, 2H), δ3.15 (s, 3H), δ3.25 (s, 2H), δ3.53 (s, 3H), δ4.44-4.48 (t, 1H), δ7.01 (s, 1H), δ7.32-7.36 (m, 2H), δ7.43-7.47 (m, 1H), δ7.66 (s, 1H), δ7.70-7.72 (d, 1H), δ7.80 (s, 1H), δ8.35 (s, 1H).

Example 367. Synthesis of Compound 367



1. Synthesis of 367-1

[1288] Into a 500 mL 3-necked round-bottom flask were added methyl 2-(3-nitrophenyl)acetate (20 g, 102.473 mmol, 1 equiv), DCE (200 mL), NBS (27.36 g, 153.709 mmol, 1.5 equiv) and AIBN (1.68 g, 10.247 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (400 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x300 mL). The

resulting mixture was concentrated under vacuum. The residue was purified by silica gel column

2. Synthesis of 367-2

[1289] Into a 100 mL 3-necked round-bottom flask were added 367-1 (5 g, 18.244 mmol, 1 equiv), THF (50 mL), azetidine (2.08 g, 36.488 mmol, 2 equiv) and TEA (5.54 g, 54.732 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 70°C. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (6:1) to afford 367-2 (3.5 g, 70.53%) as a yellow oil.

3. Synthesis of 367-3

[1290] Into a 100 mL 3-necked round-bottom flask were added 367-2 (3.1 g, 12.387 mmol, 1 equiv), EtOH (30 mL) and NH2NH2.H2O (6.33 g, 123.870 mmol, 10 equiv, 98%) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with CH2Cl2/MeOH (10:1) (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (12:1) to afford 367-3 (3 g, 96.77%) as a yellow oil.

4. Synthesis of 367-4

[1291] Into a 100 mL 3-necked round-bottom flask were added 367-3 (3 g, 11.988 mmol, 1 equiv), tetrahydrofuran (40 mL) and methyl isothiocyanate (1.31 g, 17.982 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 367-4 (4 g, 93.90%) as a yellow oil.

5. Synthesis of 367-5

[1292] Into a 100 mL 3-necked round-bottom flask were added 367-4 (4 g, 12.370 mmol, 1 equiv), H2O (50 mL) and NaOH (1.98 g, 49.480 mmol, 4 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 5 with 1M HCl (aq.). The aqueous layer was extracted with CH2Cl2 (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (40:1) to afford 367-5 (3.4 g, 90.01%)

as a yellow solid.

6. Synthesis of 367-6

[1293] Into a 250 mL 3-necked round-bottom flask was added 367-5 (3.4 g, 11.134 mmol, 1 equiv), EA (34 mL), H2O (30 mL) and NaNO2 (7.68 g, 111.340 mmol, 10 equiv) at room temperature. To the above mixture was added HNO3 (110 mL, 111.340 mmol, 10 equiv, 1M) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH 7 with saturated NaHCO3 (aq.). The aqueous layer was extracted with CH2Cl2 (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 367-6 (1.9 g, 62.44%) as a yellow solid.

7. Synthesis of 367-7

[1294] Into a 100 mL 3-necked round-bottom flask were added 367-6 (1.9 g, 6.952 mmol, 1 equiv), MeOH (60 mL) and Pd/C (0.19 g, 10%) at room temperature. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 367-7 (1 g, 59.12%) as a yellow oil.

8. Synthesis of 367-8

[1295] Into a 50mL 3-necked round-bottom flask were added 367-7 (1 g, 4.110 mmol, 1 equiv), DCE (10 mL), I-2(1.18 g, 4.110 mmol, 1 equiv) and STAB (1.74 g, 8.220 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH2Cl2/MeOH (10:1) (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 367-8 (1 g, 47.37%) as a yellow solid.

9. Synthesis of 367-9

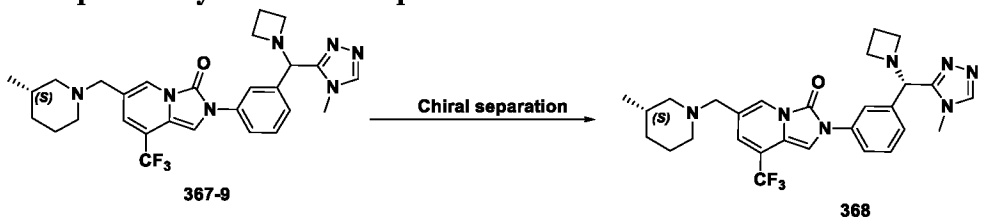
[1296] Into a 100mL 3-necked round-bottom flask were added 367-8 (800 mg, 1.558 mmol, 1 equiv), DCM (24 mL) and Pyridine (1232.05 mg, 15.580 mmol, 10 equiv) at room temperature. To the above mixture was added Triphosgene (415.97 mg, 1.402 mmol, 0.9 equiv) at 0°C. The resulting mixture was stirred for 15min at room temperature. The reaction was quenched with NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH2Cl2/MeOH (10:1) (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 12:1) to afford 367-9 (110 mg, 12.56%) as a yellow solid.

10. Synthesis of 367

[1297] The 367-9 (110 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 23 min; Wave Length: 220/254 nm; RT1(min): 10.586; RT2(min): 16.766; the second peak is product) to afford 367 (24.7 mg, 21.96%) as a yellow solid.

H-NMR-367 (400 MHz, DMSO-d6, δ ppm): 0.83-0.92 (m, 4H), 1.43-1.47 (m, 1H), 1.49-1.66 (m, 4H), 1.89-1.91 (m, 1H), 2.00-2.07 (m, 2H), 2.69-2.82 (m, 2H), 3.08-3.13 (m, 2H), 3.21-3.24 (m, 4H), 3.62 (s, 3H), 4.99 (s, 1H), 7.01 (s, 1H), 7.32-7.36 (m, 2H), 7.46-7.50 (m, 1H), 7.65-7.67 (d, 1H), 7.97 (s, 1H), 8.32 (s, 1H).

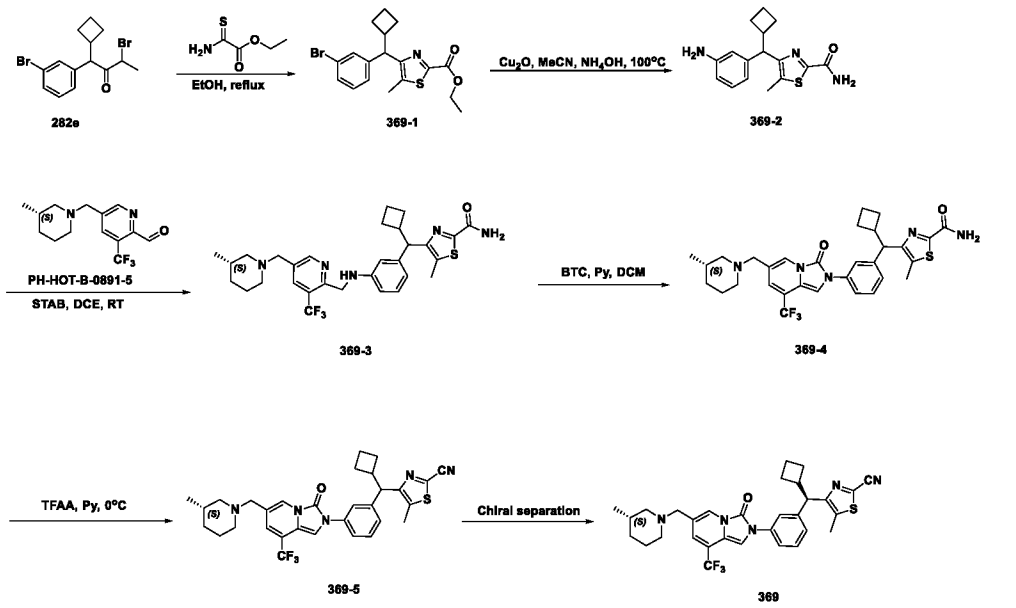
Example 368. Synthesis of Compound 368



1. Synthesis of 368

[1298] The 367-9 (110 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 23 min; Wave Length: 220/254 nm; RT1(min): 10.856; RT2(min): 16.766; the first peak is product) to afford 368 (25.5 mg). H-NMR-368 δ1.16-1.19 (m, 3H), 0.83-0.92 (m, 4H), 1.43-1.47 (m, 1H), 1.49-1.66 (m, 4H), 1.86-1.91 (m, 1H), 2.00-2.07 (m, 2H), 2.69-2.82 (m, 2H), 3.08-3.13 (m, 2H), 3.21-3.24 (m, 4H), 3.62 (s, 3H), 4.99 (s, 1H), 7.01 (s, 1H), 7.32-7.36 (m, 2H), 7.46-7.50 (m, 1H), 7.65-7.67 (d, 1H), 7.97 (s, 1H), 8.32 (s, 1H).

Example 369. Synthesis of Compound 369



1. Synthesis of 369-1

[1299] To a stirred solution of 282e (7 g, 19.440 mmol, 1 equiv) in EtOH (70 mL) was added ethyl carbamothioylformate (3.88 g, 29.160 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=5:1 to afford 369-1 (3 g, 35.61%) as a yellow solid.

2. Synthesis of 369-2

[1300] To a stirred mixture of 369-1 (2 g, 5.072 mmol, 1 equiv) in MeCN (10 mL) and NH4OH (10 mL) were added Cu2O (0.15 g, 1.014 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C. The resulting mixture concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA =1:1) to afford 369-2 (900 mg, 58.87%) as a yellow solid.

3. Synthesis of 369-3

[1301] To a stirred mixture of 369-2 (880 mg, 2.920 mmol, 1 equiv) and I-2(835.88 mg, 2.920 mmol, 1 equiv) in DCE (9 mL) were added STAB (1856.35 mg, 8.760 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=40:1) to afford 369-3 (900 mg, 53.92%) as a yellow solid.

4. Synthesis of 369-4

[1302] To a stirred solution of 369-3 (900 mg, 1.574 mmol, 1 equiv) and Pyridine (747.13 mg, 9.444 mmol, 6 equiv) in DCM (18 mL) was added Triphosgene (163.49 mg, 0.551 mmol, 0.35 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH2Cl2 (2x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=30:1) to 369-4 (560 mg, 59.52%) as a yellow solid.

5. Synthesis of 369-5

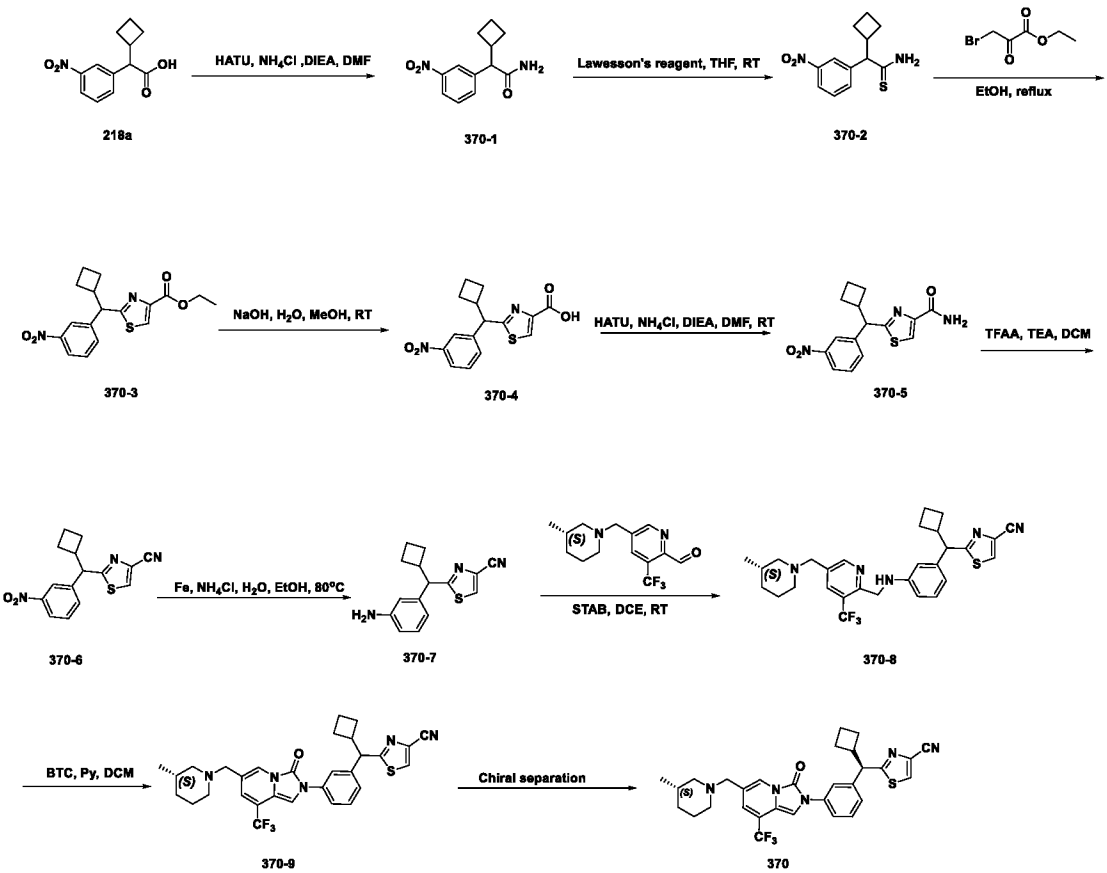
[1303] To a stirred solution of 369-4 (500 mg, 0.837 mmol, 1 equiv) in pyridine (6 mL) was added TFAA (351.4 mg, 1.673 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of NaHCO3 (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=15:1) to afford 369-5 (350 mg, 57.14%) as a yellow solid.

6. Synthesis of 369

[1304] The 369-5 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-C NEO, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 9 min; Wave Length: 220/254 nm; RT1 (min): 5.311; RT2 (min): 6.367; the second peak is product) to afford 369 (112.2 mg, 30.94%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 580. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.80-0.95 (m, 4H), 1.38-1.75 (m, 6H), 1.65-1.94 (m, 6H), 2.57 (s, 3H), 2.75 (s, 2H), 3.24 (s, 3H), 4.29-4.32 (d, 1H), 7.00 (s, 1H), 7.30-7.32 (m, 1H), 7.40-7.44 (m, 1H), 7.62-7.67 (m, 2H), 7.81 (s, 1H).

Example 370. Synthesis of Compound 370



1. Synthesis of 370-1

[1305] To a stirred solution of 218a (90 g, 382.590 mmol, 1 equiv) and HATU (189.12 g, 497.367 mmol, 1.3 equiv) in DMF (200 mL) was added NH4Cl (40.93 g, 765.180 mmol, 2 equiv) and DIEA (148.35 g, 1147.770 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (1000 mL). The aqueous layer was extracted with EtOAc (2x800 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 370-1 (80 g, 80.34%) as an off-white solid.

2. Synthesis of 370-2

[1306] To a stirred solution of 370-1 (79 g, 337.239 mmol, 1 equiv) in THF (200 mL) was added Lawesson Reagent (204.59 g, 505.858 mmol, 1.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with water (1000 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x300 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA

(10:1) to afford 370-2 (60 g, 65.39%) as an off-white solid.

3. Synthesis of 370-3

[1307] To a stirred solution of 370-2 (30 g, 119.847 mmol, 1 equiv) in EtOH (100 mL) was added ethyl 3-bromo-2-oxopropanoate (23.37 g, 119.847 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with water (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x300 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 370-3 (22 g, 49.28%) as a light yellow oil.

4. Synthesis of 370-4

[1308] To a stirred solution of 370-3 (6 g, 17.321 mmol, 1 equiv) and NaOH (2.08 g, 51.963 mmol, 3 equiv) in MeOH (60 mL) was added H2O (20 mL) at room temperature. The resulting mixture was stirred for 6h at room temperature. The resulting mixture was diluted with water (200 mL). The mixture/residue was acidified to pH 5 with HCl (aq.). The aqueous layer was extracted with EtOAc (5x100 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 370-4 (5 g, 77.07%) as an off-white solid.

5. Synthesis of 370-5

[1309] To a stirred solution of 370-4 (5 g, 15.706 mmol, 1 equiv) and HATU (7.76 g, 20.418 mmol, 1.3 equiv) in DMF (100 mL) were added DIEA (6.09 g, 47.118 mmol, 3 equiv) and NH4Cl (2.52 g, 47.118 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 370-5 (2.7 g, 51.46%) as an off-white solid.

6. Synthesis of 370-6

[1310] To a stirred solution of 370-5 (2.7 g, 8.508 mmol, 1 equiv) and TEA (2.58 g, 25.524 mmol, 3 equiv) in DCM (50 mL) was added TFAA (2.68 g, 12.762 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The crude product mixture was used in the next step directly without further purification. This resulted in 370-6 (2.4 g, 85.76%) as an off-white solid.

7. Synthesis of 370-7

[1311] To a stirred solution of 370-6 (2.4 g, 8.017 mmol, 1 equiv) and NH4Cl (4.29 g, 80.170 mmol, 10 equiv) in EtOH (30 mL) was added H2O (10 mL) at room temperature. The resulting mixture was stirred for 4h at room temperature. The resulting mixture was filtered through a Celite pad, the filter cake was washed with EtOAc (2x10 mL). The filtrate was diluted with water (100mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 370-7 (1.7 g, 74.78%) as an off-white solid.

8. Synthesis of 370-8

[1312] To a stirred solution of 370-7 (700 mg, 2.599 mmol, 1 equiv) and I-2(892.79 mg, 3.119 mmol, 1.2 equiv) in DCE (5 mL) was added STAB (1101.52 mg, 5.198 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 370-8 (1 g, 67.74%) as a light yellow oil.

9. Synthesis of 370-9

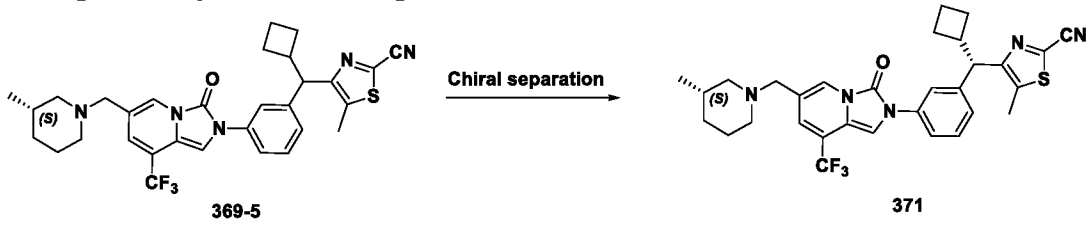
[1313] To a stirred solution of 370-8 (1 g, 1.853 mmol, 1 equiv) and Pyridine (1.47 g, 18.530 mmol, 10 equiv) in DCM (20 mL) was added Triphosgene (0.22 g, 0.741 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated NaHCO3 (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 370-9 (700 mg, 64.78%) as a yellow solid.

10. Synthesis of 370

[1314] The 370-9 (380 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.145; RT2(min): 10.424; the second peak is product) to afford 370 (149.4 mg, 39.12%) as a yellow solid.

LC-MS-370 (ES, m/z): [M+H]+ 566. H-NMR-370 (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.39-1.69 (m, 5H), 1.70-1.93 (m, 6H), 2.07-2.09 (m, 1H), 2.71-2.85 (m, 2H), 3.18-3.31 (m, 3H), 4.58-4.61 (d, 1H), 7.00 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.66 (s, 1H), 7.75-7.78 (d, 1H), 7.85 (s, 1H), 8.75 (s, 1H).

Example 371. Synthesis of Compound 371



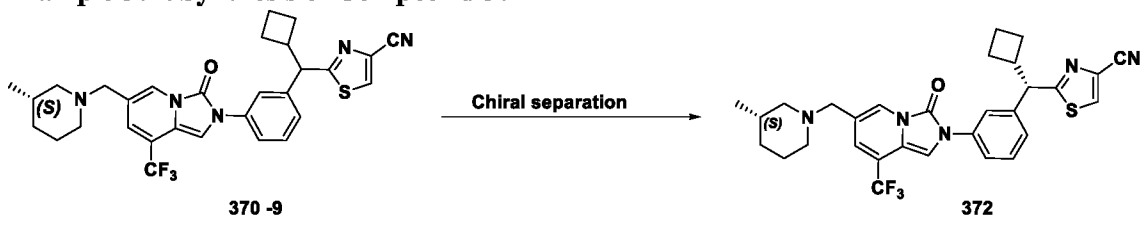
369-5 371

1. Synthesis of 371

[1315] The 369-5 (350 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRAL ART Amylose-C NEO, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 9 min; Wave Length: 220/254 nm; RT1 (min): 5.311; RT2 (min): 6.367; the first peak is product) to afford 371 (113.4 mg, 31.27%) as a yellow solid.

LCMS: (ES, m/z): [M+H]+ 580. H-NMR: (400 MHz, DMSO-d6, ppm, δ): 0.78-0.95 (m, 4H), 1.38-1.75 (m, 6H), 1.65-1.99 (m, 6H), 2.57 (s, 3H), 2.75 (s, 2H), 3.25 (s, 3H), 4.29-4.32 (d, 1H), 7.01 (s, 1H), 7.30-7.32 (m, 2H), 7.40-7.44 (m, 1H), 7.63-7.67 (m, 2H), 7.81 (s, 1H).

Example 372. Synthesis of Compound 372



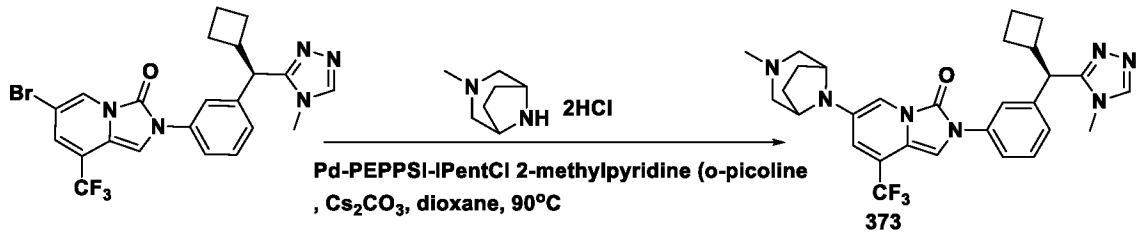
370 -9 372

1. Synthesis of 372

[1316] The 370-9 (380 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.145; RT2(min): 10.424; the first peak is product) to afford 372 (153.4 mg, 39.04%) as a yellow solid.

LC-MS-372 (ES, m/z): [M+H]+ 566. H-NMR-372 (400 MHz, DMSO-d6, δ ppm): 0.82-0.93 (m, 4H), 1.39-1.69 (m, 5H), 1.70-1.93 (m, 6H), 2.07-2.09 (m, 1H), 2.74-2.83 (m, 2H), 3.19-3.31 (m, 3H), 4.58-4.61 (d, 1H), 7.00 (s, 1H), 7.33-7.37 (m, 2H), 7.46-7.50 (m, 1H), 7.66 (s, 1H), 7.75-7.78 (d, 1H), 7.85 (s, 1H), 8.75 (s, 1H).

Example 373. Synthesis of Compound 373



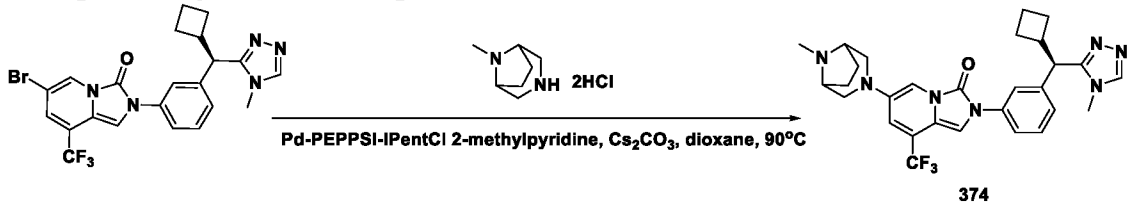
1. Synthesis of 373

[1317] To a stirred solution of 3-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride (471.92 mg, 2.372 mmol, 4 equiv) and 247C(300 mg, 0.593 mmol, 1.00 equiv) in dioxane (5 mL) were added Cs2CO3 (1930.49 mg, 5.930 mmol, 10 equiv) and Pd-PEPPSI-IPentCl 2-methylpyridine (o-picoline (249.19 mg, 0.296 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for overnight at 90°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford crude product (102 mg). The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 8 min; Wave Length: 220 nm; RT1(min): 7.20) to afford 373 (87.1 mg, 28.63%) as a yellow solid.

LC-MS-373 (ES, m/z): [M+H] + :552

H-NMR-373 (400 MHz, DMSO-d6, ppm): δ 1.79-1.86 (m, 9H), δ 2.08-2.12 (m, 4H), δ 2.27-2.30 (m, 2H), δ 2.47-2.50 (m, 2H), δ 3.12-3.22 (m, 1H), δ 3.31 (s, 3H), δ 4.08 (s, 2H), δ 4.24-4.26 (d, 1H), δ 6.93 (s, 1H), δ 7.16-7.18 (m, 1H), δ 7.28 (s, 1H), δ 7.41-7.45 (m, 1H), δ 7.67-7.69 (d, 1H), δ 7.73 (s, 1H), δ 8.33 (s, 1H).

Example 374. Synthesis of Compound 374



Synthesis of 374

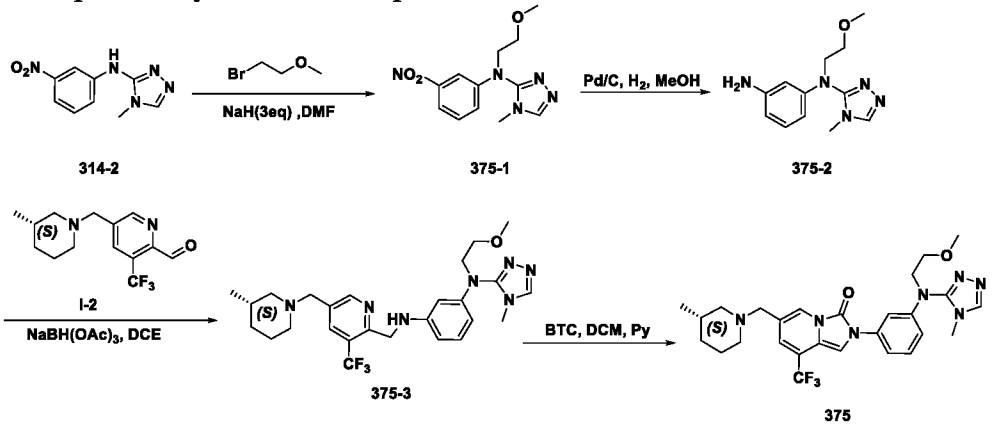
[1318] To a stirred solution of 8-methyl-3,8-diazabicyclo[3.2.1]octane dihydrochloride (471.92 mg, 2.372 mmol, 4 equiv) and 247C(300 mg, 0.593 mmol, 1.00 equiv) in dioxane (5 mL) were added Cs2CO3 (1930.49 mg, 5.930 mmol, 10 equiv) and Pd-PEPPSI-IPentCl 2-methylpyridine (o-picoline) (249.19 mg, 0.296 mmol, 0.5 equiv) at room temperature. The

resulting mixture was stirred for overnight at 90°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford crude product (90 mg). The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 59% B in 8 min; Wave Length: 220 nm; RT1(min): 7.34) to afford 374 (75.3 mg, 25.85%) as a yellow solid.

LC-MS-374 (ES, m/z): [M+H] + :552

H-NMR-374 (400 MHz, DMSO-d6, ppm): δ 1.67-1.71 (m, 3H), δ 1.72-1.82 (m, 4H), δ 2.89-1.96 (m, 2H), δ 2.01-2.12 (m, 1H), δ 2.20 (s, 3H), δ 2.67-2.72 (m, 2H), δ 3.11-3.20 (m, 5H), δ 3.45 (s, 3H), δ 4.24-4.26 (d, 1H), δ 6.75 (s, 1H), δ 7.16-7.18 (d, 1H), δ 7.24 (s, 1H), δ 7.26-7.28 (d, 1H), δ 7.69-7.71 (d, 1H), δ 7.74 (s, 1H), δ 8.32 (s, 1H).

Example 375. Synthesis of Compound 375



1. Synthesis of 375-1

[1319] To a stirred solution of 314-2 (1.5 g, 6.843 mmol, 1 equiv) and DMF (20 mL) was added NaH (0.82 g, 20.529 mmol, 3 equiv, 60%) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added 2-bromoethyl methyl ether (4.76 g, 34.215 mmol, 5 equiv) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=40:1) to afford 375-1 (480 mg, 23.53%) as a brown oil.

2. Synthesis of 375-2

[1320] To a solution of 375-1 (450 mg, 1.623 mmol, 1 equiv) in 10 mL MeOH was added Pd/C (20%, 90 mg) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH=40:1) to afford 375-2 (350 mg, 81.97%) as a white solid.

3. Synthesis of 375-3

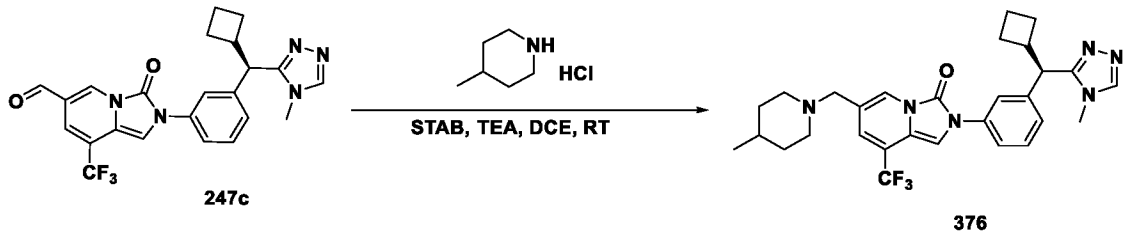
[1321] Into a 25 mL round-bottom flask were added 375-2 (350 mg, 1.415 mmol, 1 equiv), I-2(486.23 mg, 1.698 mmol, 1.2 equiv), STAB (599.91 mg, 2.830 mmol, 2 equiv) and DCE (5 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=30:1) to afford 375-3 (300 mg, 38.50%) as a brown oil.

4. Synthesis of 375-0

[1322] Into a 50 mL round-bottom flask were added 375-3 (300 mg, 0.580 mmol, 1 equiv), pyridine (366.77 mg, 4.640 mmol, 8 equiv) and DCM (10 mL) at room temperature. To the above mixture was added Triphosgene (137.60 mg, 0.464 mmol, 0.8 equiv) at 0 °C. The resulting mixture was stirred for additional 5 min at 0 °C. The reaction was quenched with sat. NaHCO3 (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under vacuum. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 67% B in 8 min, 67% B; Wave Length: 220 nm;

H-NMR: 1H NMR (400 MHz, DMSO-d6) δ0.81-0.92 (m, 4H), δ1.41-1.46 (m, 1H), δ1.49-1.66 (m, 4H), δ1.85-1.90 (m, 1H), δ2.72-2.77 (m, 2H), δ3.22 (s, 3H), δ3.23 (s, 2H), δ3.27-3.34 (m, 3H), δ3.56-3.59 (m, 2H), δ3.95-3.98 (m, 2H), δ6.60-6.63 (m, 1H), δ6.99 (s, 1H), δ7.22-7.26 (m, 2H), δ7.31 (s, 1H), δ7.35-7.39 (m, 2H), δ7.65 (s, 1H), δ8.48 (s, 1H).

Example 376. Synthesis of Compound 376



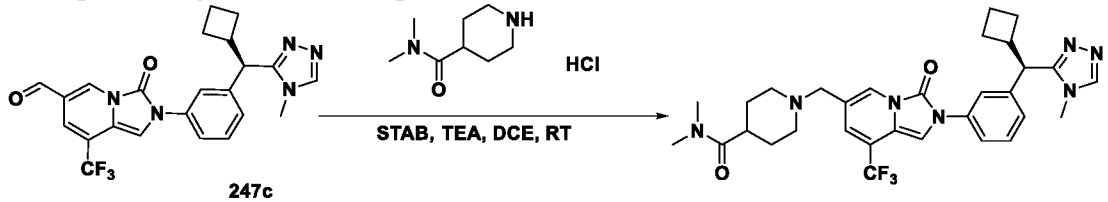
247c 376

1. Synthesis of 376

[1323] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and piperidine, 4-methyl-hydrochloride (130.66 mg, 1.318 mmol, 2 equiv) in DCE (5 mL) were added TEA (39.56 mg, 0.659 mmol, 1 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 18mL). The resulting mixture was concentrated under reduced pressure. The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43% B to 73% B in 8 min; Wave Length: 220 nm; RT1(min): 7.60) to afford 376 (93.6 mg, 26.22%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :539. H-NMR: (400 MHz, DMSO-d6, ppm): δ 0.91-0.93 (d, 3H), δ 1.07-1.15 (m, 2H), δ 1.21-1.25 (m, 1H), δ 1.51-1.53 (m, 2H), δ 1.70-1.83 (m, 5H), δ 1.85-1.93 (m, 2H), δ 2.08-2.09 (d, 1H), δ 2.81-2.83 (d, 2H), δ 3.25 (s, 3H), δ 3.46 (s, 3H), δ 4.24-4.27 (m, 1H), δ 7.00 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 1H), δ 7.64-7.73 (m, 3H), δ 8.33 (s, 1H).

Example 377. Synthesis of Compound 377



247c 377

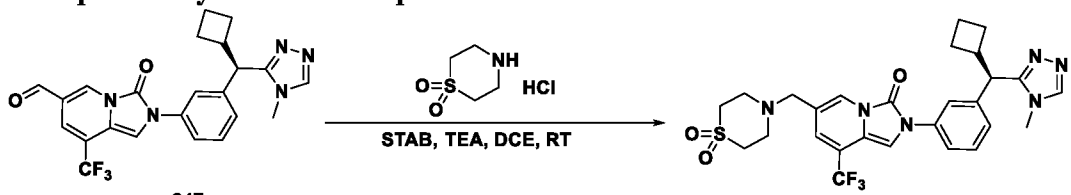
Synthesis of 377

[1324] To a stirred solution of N,N-dimethylpiperidine-4-carboxamide hydrochloride (253.85 mg, 1.318 mmol, 2 equiv) and 247c (300 mg, 0.659 mmol, 1.00 equiv) in DCE (5 mL) were added TEA (133.31 mg, 1.318 mmol, 2 equiv) at room temperature. The mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (279.21 mg, 1.318

mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 18mL). The resulting mixture was concentrated under reduced pressure. The crude product (68 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 7.60) to afford 377 (47.3 mg, 18.65%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + :596. H-NMR: (400 MHz, DMSO-d6, ppm): δ 1.51-1.62 (m, 4H), δ 1.71-1.83 (m, 5H), δ 1.92-2.15 (m, 3H), δ 2.51-2.53 (d, 1H), δ 2.80 (s, 3H), δ 2.81-2.85 (m, 2H), δ 3.00 (s, 3H), δ 3.31 (s, 1H), δ 3.33-3.35 (d, 2H), δ 3.46 (s, 3H), δ 4.24-4.27 (m, 1H), δ 7.00 (s, 1H), δ 7.18-7.20 (d, 1H), δ 7.31 (s, 1H), δ 7.42-7.46 (m, 1H), δ 7.64-7.73 (m, 3H), δ 8.33 (s, 1H).

Example 378. Synthesis of Compound 378

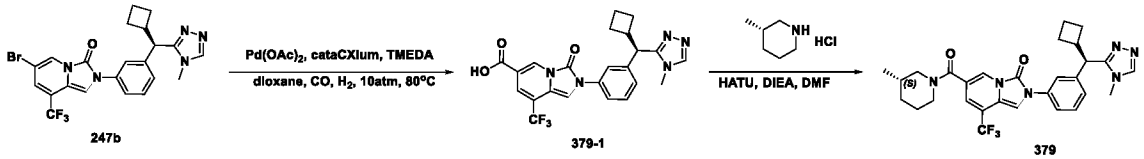


1. Synthesis of 378

[1325] To a stirred solution of 247c (300 mg, 0.659 mmol, 1 equiv) and thiomorpholine-1,1-dioxide hydrochloride (339.18 mg, 1.977 mmol, 3 equiv) in DCE (5 mL) was added TEA (199.97 mg, 1.977 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (279.21 mg, 1.318 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 8 min, Wave Length: 220 nm; RT1(min): 7.60) to afford 378 (66.6 mg, 17.37%) as a yellow solid.

LC-MS: (ES, m/z): [M+H]+ 575. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.67-1.87 (m, 5H), 2.08-2.10 (m, 1H), 2.95-2.96 (m, 4H), 3.11-3.12 (m, 4H), 3.20-3.23 (m, 1H), 3.43 (s, 3H), 3.50 (s, 2H), 4.25-4.27 (d, 1H), 7.05 (s, 1H), 7.19-7.21 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.72 (m, 2H), 7.78 (s, 1H), 8.33 (s, 1H).

Example 379. Synthesis of Compound 379



1. Synthesis of 379-1

[1326] Into a 1L pressure tank reactor were added 247b (20 g, 19.750 mmol, 1 equiv), dioxane (600 mL), TMEDA (6.89 g, 59.250 mmol, 3 equiv), bis(adamantan-1-yl)(butyl)phosphane (1.42 g, 3.950 mmol, 0.2 equiv) and Pd(OAc)2 (0.44 g, 1.975 mmol, 0.1 equiv) at room temperature. After flushing the autoclave three times with CO/H2 (1:1), the mixture was pressurized to 10 atm with CO/H2 (1:1) at 80 °C for overnight. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 379-1 (3 g, 16.11%) as a yellow solid.

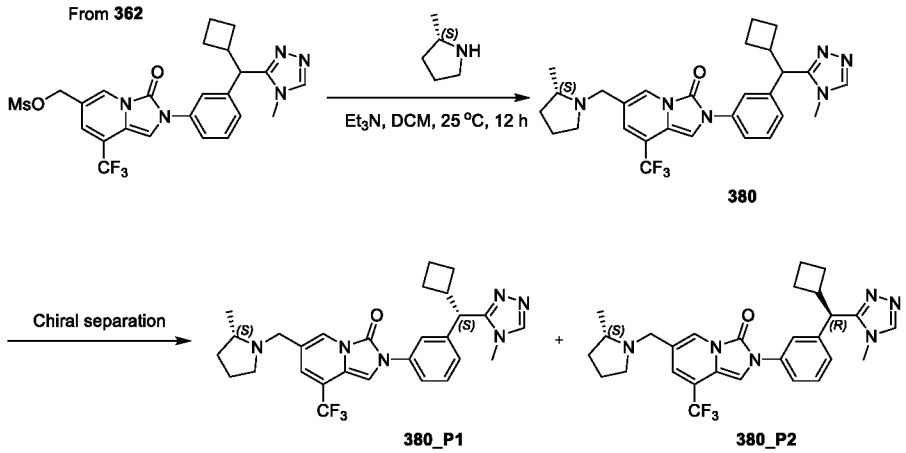
2. Synthesis of 379

[1327] Into a 50mL 3-necked round-bottom flask were added DMF (20 mL), 379-1 (2 g, 4.242 mmol, 1.00 equiv), HATU (2.42 g, 6.363 mmol, 1.5 equiv), (3S)-3-methylpiperidine hydrochloride (0.86 g, 6.363 mmol, 1.5 equiv) and DIEA (1.64 g, 12.726 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (40 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, A: water (10mmol/L NH4HCO3), B: MeCN, 20% B to 80% B gradient in 20 min; detector, UV 254 nm. This resulted in 379 (110 mg, 4.50%) as a yellow solid.

H-NMR: (400 MHz, dmso-d6, δ ppm): 0.86-0.88 (d, 3H), 1.15-1.17 (m, 1H), 1.44-1.47 (m, 1H), 1.58-1.72 (m, 3H), 1.70-1.85 (m, 5H), 2.07-2.10 (m, 1H), 2.51-2.66 (m, 1H), 2.90-3.04 (m, 1H), 3.20-3.23 (m, 1H), 3.43 (s, 3H), 3.90-4.08 (m, 2H), 4.25-4.28 (d, 1H), 7.03 (s, 1H),

7.20-7.22 (d, 1H), 7.41-7.43 (d, 1H), 7.45-7.47 (m, 1H), 7.67-7.69 (d, 1H), δ7.75 (s, 1H), δ7.82 (s, 1H), δ8.33 (s, 1H).

Example 380. Synthesis of Compound 380_P1 and 380_P2



1. Synthesis of 380

[1328] To a solution of (2S)-2-methylpyrrolidine (64 mg, 746.91 umol, 2 equiv) and [2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridin-6-yl]methyl methanesulfonate (200 mg, 373.46 umol, 1 equiv) in DCM (4 mL) was added Et3N (113 mg, 1.12 mmol, 160 uL, 3 equiv) at 25 °C. After addition, the mixture was stirred at this temperature for 12 h. The reaction was poured into saturated NaHCO3 (15 mL) and the resulting mixture was extracted with DCM (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile Phase A: water (NH4HCO3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 40% B to 70% B in 8 min) to afford 380 (50 mg, 17%) as a yellow solid.

2. Synthesis of 380_P1&P2

[1329] The 380 (50 mg) was purified by Chiral separation with the following conditions (column: Phenomenex-Cellulose-2 (250mm*30mm,10um); Mobile Phase: [Neu-ETOH]; B%: 50%-50%, 5min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 6.7; RT2 (min): 9.2) to afford 380_P1 (21.8 mg, 43.1%) and 380_P2 (23.2 mg, 45.9%).

MS-380_P1: (ES, m/z): [M+H]+ 525.25.

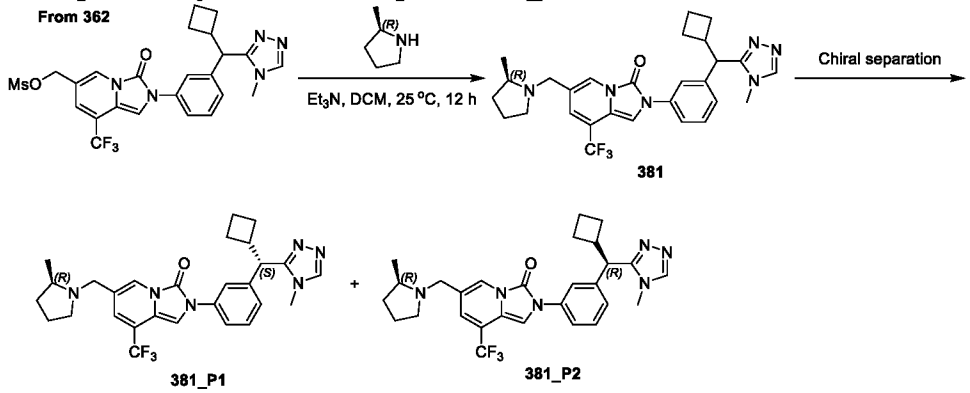
1H-NMR-380_P1: (400 MHz, DMSO-d6) δ 8.37-8.27 (m, 1 H), 7.78-7.59 (m, 3 H), 7.48-7.39 (m, 1 H), 7.34-7.28 (m, 1 H), 7.22-7.14 (m, 1 H), 7.02-6.92 (m, 1 H), 4.29-4.22 (m, 1

H), 3.77-3.64 (m, 1 H), 3.46-3.39 (m, 3 H), 3.22-3.16 (m, 1 H), 3.07-2.99 (m, 1 H), 2.13 (br d, J = 8.0 Hz, 1 H), 2.01-1.57 (m, 9 H), 1.40-1.29 (m, 1 H), 1.12-1.05 (m, 3 H).

LCMS-380_P2: (ES, m/z): [M+H]+ 525.25.

1H-NMR-380_P2: (400 MHz, CHLOROFORM-d) δ 8.05-8.01 (m, 1 H), 7.67 (s, 2 H), 7.58-7.52 (m, 1 H), 7.46-7.38 (m, 1 H), 7.20-7.13 (m, 1 H), 6.98-6.94 (m, 1 H), 6.79-6.72 (m, 1 H), 4.01-3.91 (m, 1 H), 3.78 (s, 1 H), 3.45-3.34 (m, 4 H), 3.07-2.87 (m, 2 H), 2.50-2.29 (m, 2 H), 2.17-2.08 (m, 1 H), 2.02-1.89 (m, 3 H), 1.86-1.68 (m, 5 H), 1.50-1.44 (m, 1 H), 1.20-1.12 (m, 3 H).

Example 381. Synthesis of Compound 381_P1 & P2



1. Synthesis of 381

[1330] To a solution of (2R)-2-methylpyrrolidine (90.83 mg, 746.91 umol, 2 equiv, HCl) and [2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridin-6-yl]methyl methanesulfonate (200 mg, 373.46 umol, 1 equiv) in DCM (4 mL) was added Et3N (151.16 mg, 1.49 mmol, 207.92 uL, 4 equiv) at 25 °C. After addition, the mixture was stirred at this temperature for 12 h. The reaction was poured into saturated NaHCO3 (15 mL) and the resulting mixture was extracted with DCM (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile phase A: water (NH4HCO3), Mobile phase B: ACN; Flow rate: 50 mL/min; Gradient: 40% B to 70% B in 8 min; Wave Length: 220 nm) to afford 381 (40 mg, 20%) as a yellow solid.

2. Synthesis of 381_P1&P2

[1331] The 381 (40 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALPAK IC(250mm*30mm,10um); Mobile phase: [Neu-ETOH];

B%: 65%-65%, 50min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 15.5; RT2 (min): 21.4) to afford 381_P1 (16.7 mg, 37.1%) and 381_P2 (17.7 mg, 38.9%).

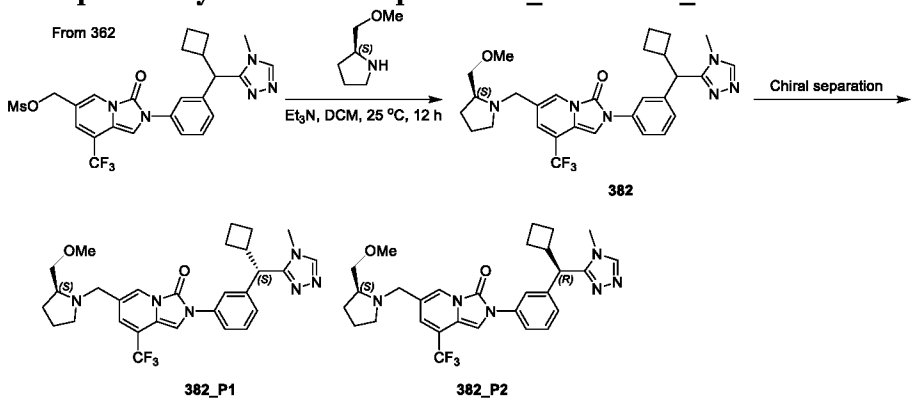
MS-381_P1: (ES, m/z): [M+H]+ 525.25.

1H-NMR-381_P1: (400 MHz, DMSO-d6) δ 8.33 (s, 1 H), 7.74-7.71 (m, 1 H), 7.69-7.68 (m, 2 H), 7.47-7.43 (m, 1 H), 7.32 (s, 1 H), 7.21-7.19 (m, 1 H), 6.98 (s, 1 H), 4.26 (d, J = 10.0 Hz, 1 H), 3.76-3.66 (m, 1 H), 3.43 (s, 3 H), 3.21 (br s, 2 H), 3.04 (d, J = 14.0 Hz, 1 H), 2.92-2.82 (m, 1 H), 2.18-2.05 (m, 2 H), 2.13-1.65 (m, 8 H), 1.41-1.30 (m, 1 H), 1.09-1.02 (m, 3 H).

MS-381_P2: (ES, m/z): [M+H]+ 525.25.

1H-NMR-381_P2: (400 MHz, DMSO-d6) δ 8.29 (s, 1 H), 7.74 (s, 1 H), 7.72-7.65 (m, 2 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.31 (s, 1 H), 7.20 (d, J = 8.0 Hz, 1 H), 6.98 (s, 1 H), 4.26 (d, J = 12.0 Hz, 1 H), 3.71 (br d, J = 12.0 Hz, 1 H), 3.48-3.40 (s, 3 H), 3.28-3.12 (m, 2 H), 3.10-2.99 (m, 1 H), 2.96-2.79 (m, 1 H), 2.32-2.05 (m, 2 H), 2.00-1.73 (m, 1 H), 1.73-1.54 (m, 7 H), 1.24 (m, 1 H), 1.09-1.02 (m, 3 H).

Example 382. Synthesis of Compound 382_P1 and 382_P2



1. Synthesis of 382

[1332] To a solution of [2-[3-[cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-3-oxo-8-(trifluoromethyl)imidazo[1,5-a]pyridin-6-yl]methyl methanesulfonate (450 mg, 420.14 umol, 50% purity, 1 equiv.) in DCM (5 mL) was added Et3N (127.54 mg, 1.26 mmol, 3 equiv.) and (2S)-2-(methoxymethyl)pyrrolidine (96.78 mg, 840.28 umol, 103.84 uL, 2 equiv.). The mixture was stirred at 25 °C for 12 hr. The reaction was poured into water (30 mL) and the resulting mixture was extracted with DCM (2 x 30 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC(Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile phase A: [water(NH4HCO3)-ACN]; B%: ACN: Flow rate: 50 mL/min; Gradient: 40% B to 70% B in 8 min. Wave Length: 220 nm; RT1(min): 5.1) to afford 382 (25 mg, 10% yield) as a yellow solid.

2. Synthesis of 382_P1&P2

[1333] 382 (25 mg) was purified by Chiral separation with the following conditions (column: REGIS WHELK-O1 (250mm*30mm,5um); Mobile Phase: [Neu-IPA]; B%: 55%-55%, 18min, Flow rate: 70 mL/min; Wave Length: 254 nm; RT1 (min): 2.38; RT2 (min): 3.00) to afford 382_P1 (5.0 mg, 20% yield) as a yellow solid

382-P1: (ES, m/z): [M+H]+ 554.2

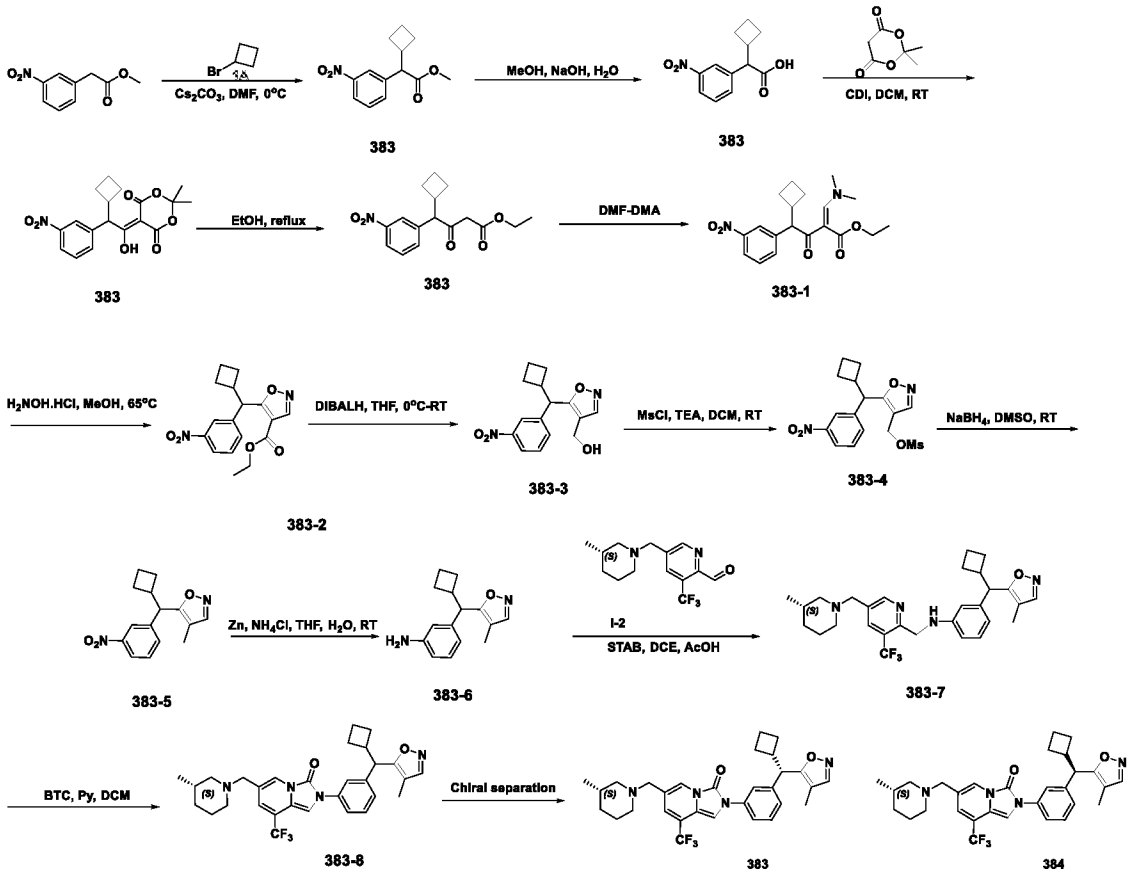
1H-NMR-382_P1: (400 MHz, DMSO-d6) δ ppm 8.32 (s, 1H), 7.77-7.66 (m, 3H), 7.48-7.42 (m, 1H), 7.32 (s, 1H), 7.23-7.18 (m, 1H), 7.00 (s, 1H), 4.27-4.25 (d, J = 8.0 Hz, 1H), 3.81-3.78 (m, 1H) 3.35 (s, 3H), 3.86-3.75 (m, 1H), 3.48-3.42 (m, 2H), 3.29-3.23 (m, 3H), 3.25-3.23 (m, 1H), 2.94-2.83 (m, 1H), 2.76-2.74 (m, 1H), 2.56-2.54 (m, 1H), 2.22-2.21 (m, 1H), 1.96-1.46 (m, 8H), 1.32-1.11 (m, 1H)

382_P2 (4.7 mg, 19% yield) as a yellow solid.

382-P2: (ES, m/z): [M+H]+ 554.2

1H-NMR-382_P2: (400 MHz, DMSO-d6) δ ppm 8.32 (s, 1H), 7.74 (s, 1H), 7.71-7.39 (m, 2H), 7.49-7.41 (m, 1H), 7.32 (s, 1H), 7.24-7.17 (m, 1H), 7.04-6.99 (m, 1H), 4.27-4.25 (m, 1H), 3.81-3.78 (m, 1H), 3.44 (s, 3H), 3.46-3.45 (m, 1H), 3.38-3.33 (m, 2H), 3.31-3.30 (m, 3H), 3.30-3.29 (m, 1H), 2.74-2.73 (m, 1H), 2.66-2.64 (m, 1H), 2.46-2.44 (m, 1H), 2.19-2.11 (m, 1H), 1.66-1.36 (m, 8H), 1.51-1.49 (m, 1H).

Example 383. Synthesis of Compound 383 & 384



1. Synthesis of 383-1

[1334] Into a 2L 3-necked round-bottom flask were added methyl 2-(3-nitrophenyl)acetate (100 g, 512.363 mmol, 1 equiv), DMF (1 L) and Cs_2CO_3 (834.69 g, 2561.815 mmol, 5 equiv) at 0°C. The resulting mixture was stirred for 3h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (207.51 g, 1537.089 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 3 days at room temperature. The mixture acidified to pH 7 with saturated NH_4Cl (aq.) (1L). The resulting mixture was extracted with EtOAc (3 x 1L). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 383-1 (100 g, 74.38%) as a light yellow oil.

2. Synthesis of 383-2

[1335] Into a 500 mL round-bottom flask were added 383-1 (30 g, 120.353 mmol, 1 equiv), MeOH (100 mL) and THF (100 mL) at room temperature. To the above mixture was added NaOH (9.63 g, 240.706 mmol, 2 equiv) and H_2O (100 mL) at room temperature. The resulting mixture was stirred for additional 3 h at 50 °C. The mixture was acidified to pH 5 with 1M HCl (aq.) 400 ml. The aqueous layer was extracted with EtOAc (3x200 mL). The

resulting mixture was concentrated under vacuum. This resulted in 383-2 (25 g, 83.89%) as a white solid.

3. Synthesis of 383-3

[1336] Into a 500 mL 3-necked round-bottom flask were added 383-2 (25 g, 106.275 mmol, 1 equiv), CDI (20.68 g, 127.530 mmol, 1.2 equiv) and DCM (300 mL) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added meldrum's acid (18.38 g, 127.530 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with 1M HCl (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3x200 mL). The resulting mixture was concentrated under vacuum. The resulting mixture was washed with 300 mL of NH_4HCO_3 (aq). The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under vacuum. The crude product 383-3 (35 g) as colorless oil was used in the next step directly without further purification.

4. Synthesis of 383-4

[1337] Into a 500 mL round-bottom flask were added 383-3 (35 g, 96.859 mmol, 1 equiv) and EtOH (350 mL) at room temperature. The resulting mixture was stirred for overnight at 80°C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (1000 mL). The aqueous layer was extracted with EtOAc (3x400 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 383-4 (12 g, 38.55%) as a colorless oil.

5. Synthesis of 383-5

[1338] Into a 500 mL 3-necked round-bottom flask were added 383-4 (13.3 g, 43.559 mmol, 1 equiv) and DMF-DMA (150 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under reduced pressure to afford 383-5 (15 g, 95.55%) as a Brown yellow oil. The crude product was used in the next step directly without further purification.

6. Synthesis of 383-6

[1339] Into a 500 mL 3-necked round-bottom flask were added 383-5 (15 g, 41.619 mmol, 1 equiv), MeOH (160 mL) and $NH_2OH.HCl$ (4.34 g, 62.428 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1 h at 65°C under nitrogen atmosphere. The reaction was quenched by the addition of Water (100 mL) at room temperature. The

aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (15:1) to afford 383-6 (8 g, 58.19%) as a Brown yellow oil.

7. Synthesis of 383-7

[1340] Into a 250 mL 3-necked round-bottom flask were added 383-6 (4 g, 12.109 mmol, 1 equiv), THF (50 mL) and DIBALH (4.31 g, 30.273 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x60 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 383-7 (2.3 g, 65.88%) as a light brown oil.

8. Synthesis of 383-8

[1341] Into a 100 mL 3-necked round-bottom flask were added 383-7 (2.3 g, 7.978 mmol, 1 equiv), DCM (30 mL), TEA (2.42 g, 23.934 mmol, 3 equiv) and MsCl (1.37 g, 11.967 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of Water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure to afford 383-8 (2.5 g, 85.53%) as a light brown oil. The crude product was used in the next step directly without further purification.

9. Synthesis of 383-9

[1342] Into a 100 mL 3-necked round-bottom flask were added 383-8 (2.5 g, 6.823 mmol, 1 equiv), DMSO (30 mL) and $NaBH_4$ (0.52 g, 13.646 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 383-9 (1.2 g, 64.58%) as a light yellow solid.

10. Synthesis of 383-10

[1343] Into a 100 mL 3-necked round-bottom flask were added 383-9 (700 mg, 2.571 mmol, 1 equiv), THF (12 mL), NH_4Cl (687.52 mg, 12.855 mmol, 5 equiv) in H_2O (4 mL) and Zn (2521.04 mg, 38.565 mmol, 15 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with THF (3x7 mL). The filtrate was concentrated under

reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 383-10 (500 mg, 80.27%) as a light yellow solid.

11. Synthesis of 383-11

[1344] Into a 100 mL round-bottom flask were added 383-10 (480 mg, 1.981 mmol, 1 equiv), DCE (10 mL), I-2 (567.11 mg, 1.981 mmol, 1 equiv), AcOH (59.48 mg, 0.991 mmol, 0.5 equiv) and STAB (839.64 mg, 3.962 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 383-11 (500 mg, 49.24%) as a light yellow solid.

12. Synthesis of 383-12

[1345] Into a 100 mL round-bottom flask were added 383-11 (400 mg, 0.780 mmol, 1 equiv), DCM (10 mL), pyridine (370.33 mg, 4.680 mmol, 6 equiv) and triphosgene (92.62 mg, 0.312 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 383-12 (250 mg, 59.48%) as a light yellow solid.

13. Synthesis of 383

[1346] The 383-12 (250 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.41; RT2(min): 13.28; The first peak was 383. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1.2 mL; Number of Runs: 5) to afford 383 (89.7 mg, 35.88%) as a light yellow solid.

LC-MS-383 (ES, *m/z*): $[M+H]^+$ 539

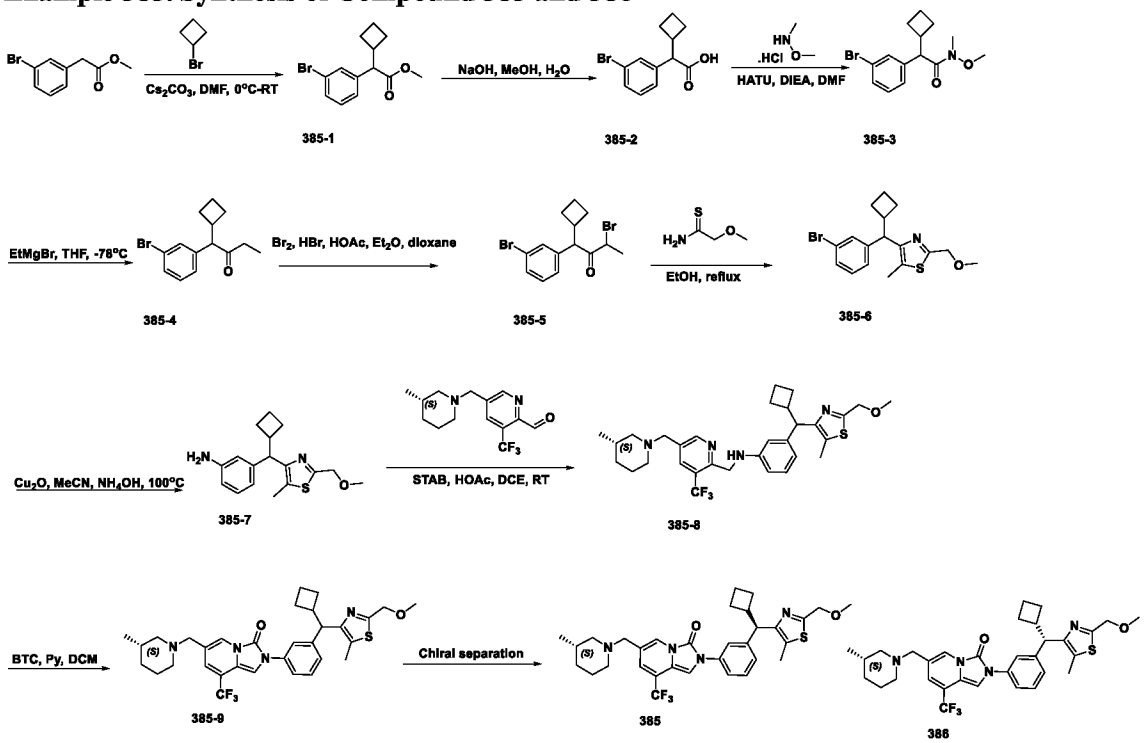
H-NMR-383 1H NMR (300 MHz, DMSO-d6, *ppm*) δ 0.82-0.86 (m, 4H), 1.58 (s, 1H), 1.60-1.63 (m, 1H), 1.66-1.76 (m, 5H), 1.78-1.82 (m, 3H), 1.84-1.97 (m, 3H), 1.99 (s, 3H), 2.73-2.77 (m, 2H), 3.15-3.18 (m, 1H), 3.25-3.32 (d, 2H), 4.34-4.37 (d, 1H), 7.01 (s, 1H), 7.29-7.34 (m, 2H), 7.37-7.48 (m, 1H), 7.66-7.77 (m, 2H), δ 7.82 (s, 1H), 8.32 (s, 1H).

LC-MS-384 (ES, *m/z*): $[M+H]^+$ 539

H-NMR-384 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 0.81-0.83 (m, 4H), 1.57-1.62 (m, 1H), 1.65-1.80 (m, 5H), 1.81-1.97 (m, 6H), 1.98 (s, 3H), 2.72-2.77 (m, 2H), 3.15-3.18 (m, 1H),

3.24-3.32 (d, 2H), 4.34-4.37 (d, 1H), 7.01 (s, 1H), 7.29-7.34 (m, 2H), 7.37-7.48 (m, 1H), 7.66-7.71 (m, 2H), δ 7.84 (s, 1H), 8.32 (s, 1H).

Example 385. Synthesis of Compound 385 and 386



1. Synthesis of 385-1

[1347] To a stirred mixture of methyl 2-(3-bromophenyl)acetate (48 g, 209.540 mmol, 1 equiv) in DMF (700 mL) was added Cs_2CO_3 (341.36 g, 1047.700 mmol, 5 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 0 °C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (84.87 g, 628.620 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 2 days at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x200 mL). The filtrate was quenched with saturated NH_4Cl (aq.) (2 L) at room temperature. The aqueous layer was extracted with EtOAc (2x1 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=100:1 to afford 385-1 (48 g, 72.81%) as a yellow solid.

2. Synthesis of 385-2

[1348] To a stirred solution of 385-1 (48 g, 169.512 mmol, 1 equiv) in MeOH (600 mL)/ H_2O (200 mL) was added NaOH (20.34 g, 508.536 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 6 with 1 M HCl (aq.). The aqueous layer was extracted with EtOAc (3x1000 mL). The

resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=1:1 to afford 385-2 (50 g, 98.64%) as a yellow solid.

3. Synthesis of 385-3

[1349] To a stirred solution of 385-2 (50 g, 185.778 mmol, 1 equiv) and methoxy(methyl)amine hydrochloride (36.24 g, 371.556 mmol, 2 equiv) in DMF (550 mL) was added DIEA (72.03 g, 557.334 mmol, 3 equiv) and HATU (77.70 g, 204.356 mmol, 1.1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (2 L) at room temperature. The aqueous layer was extracted with EtOAc (2x1 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=5:1 to afford 385-3 (50 g, 77.58%) as a yellow oil.

4. Synthesis of 385-4

[1350] To a stirred solution of 385-3 (20 g, 64.060 mmol, 1 equiv) in THF (200 mL) was added EtMgBr (256 mL, 256.240 mmol, 4 equiv, 1M) dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at -78°C under nitrogen atmosphere. The reaction was quenched with saturated NH_4Cl (aq.) (1 L) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=6:1 to afford 385-4 (18 g, 90.93%) as a yellow oil.

5. Synthesis of 385-5

[1351] To a stirred solution of 385-4 (15 g, 53.344 mmol, 1 equiv) in Et_2O (80 mL) and dioxane (80 mL) were added Br_2 (5.97 g, 37.341 mmol, 0.7 equiv) and HBr in AcOH (40%)(3.02 g, 37.341 mmol, 0.7 equiv) at 0 °C. The resulting mixture was stirred for 3 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (aq.) (400 mL) at room temperature. The aqueous layer was extracted with EtOAc (200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=100:1 to afford 385-5 (12 g, 62.47%) as a colorless oil.

6. Synthesis of 385-6

[1352] To a stirred solution of 385-5 (5 g, 13.885 mmol, 1 equiv) in EtOH (50 mL) was added 2-methoxyethanethioamide (2.92 g, 27.770 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The reaction was quenched with water (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica

gel column chromatography, eluted with PE/EA=5:1 to afford 385-6 (3 g, 52.49%) as a yellow solid.

7. Synthesis of 385-7

[1353] To a stirred mixture of 385-6 (3.1 g, 8.463 mmol, 1 equiv) in NH_4OH (6 mL) and MeCN (6 mL) were added Cu_2O (0.24 g, 1.693 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C. The resulting mixture was filtered, the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=200:1 to afford 385-7 (1.4 g, 54.70%) as a yellow solid.

8. Synthesis of 385-8

[1354] To a stirred mixture of 385-7 (700 mg, 2.315 mmol, 1 equiv) and I-2 (795.17 mg, 2.778 mmol, 1.2 equiv) in DCE (7 mL) were added HOAc (138.99 mg, 2.315 mmol, 1 equiv) and STAB (1471.61 mg, 6.945 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 385-8 (900 mg, 67.89%) as a yellow solid.

9. Synthesis of 385-9

[1355] To a stirred solution of 385-8 (880 mg, 1.536 mmol, 1 equiv) and pyridine (729.21 mg, 9.216 mmol, 6 equiv) in DCM (10 mL) were added Triphosgene (159.57 mg, 0.538 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 385-9 (480 mg, 52.18%) as a yellow solid.

10. Synthesis of 385

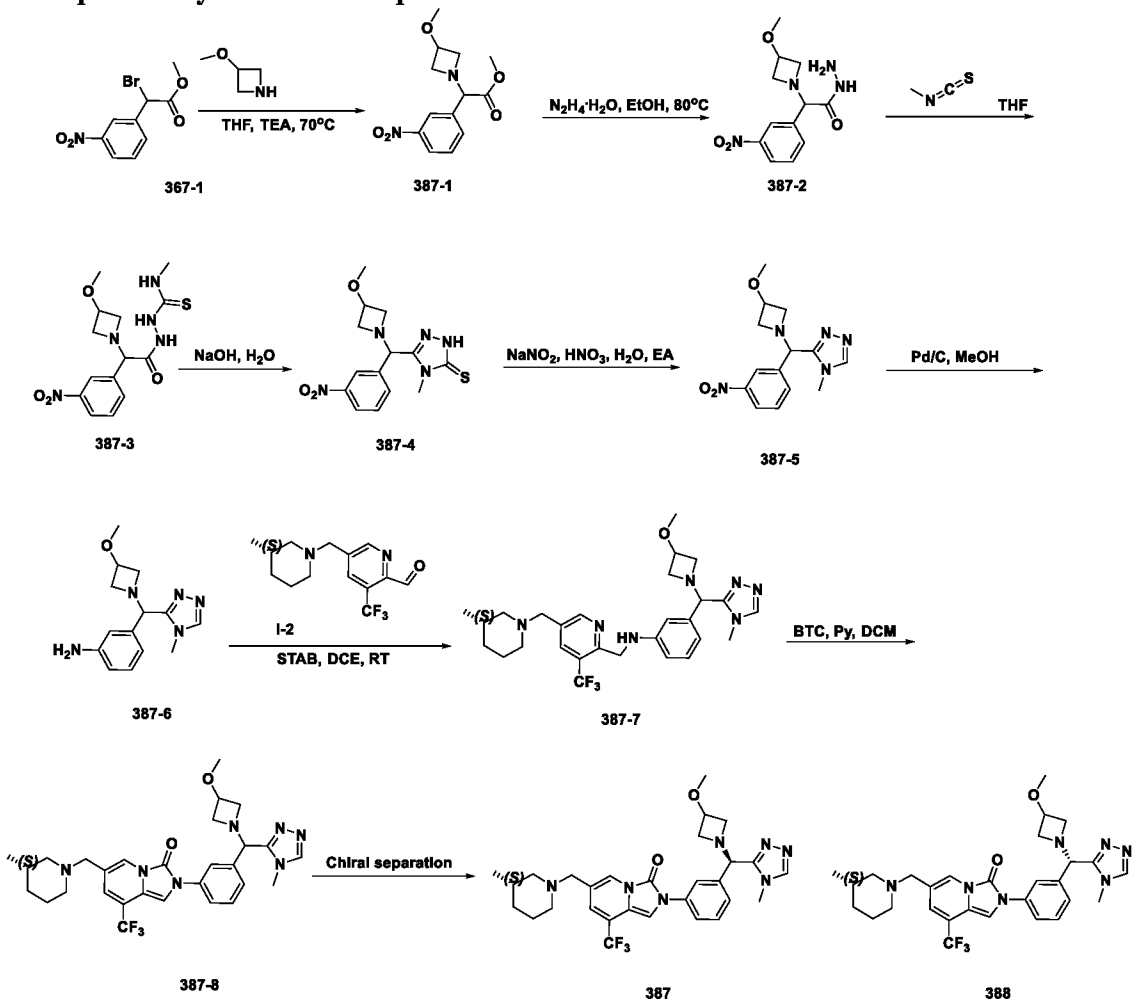
[1356] The 385-9 (480 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 9.5 min; Wave Length: 220/254 nm; RT1 (min): 5.79; RT2 (min): 7.66; the first peak is 386 the second peak is LC-MS-385-0) to afford 386 (62.6 mg, 12.61%) as a yellow solid and 385 (188.4 mg, 37.52%) as a yellow solid.

LC-MS-385 (ES, *m/z*): $[M+H]^+$ 599. H-NMR-385 (400 MHz, DMSO-d6, δ *ppm*): 0.70-0.93 (m, 4H), 1.33-1.58 (m, 1H), 1.58-1.71 (m, 5H), 1.71-1.85 (m, 6H), 2.40-2.44 (m, 3H), 2.75-

2.90 (m, 2H), 3.18-3.25 (m, 3H), 3.25 (s, 3H), 4.10-4.13 (s, 1H), 4.61 (s, 2H), 7.00 (s, 1H), 7.26 (s, 1H), 7.33-7.37 (m, 1H), 7.39-7.41 (m, 1H), 7.59-7.61 (m, 1H), 7.66 (s, 1H), 7.80 (s, 1H).

LC-MS-386 (ES, *m/z*): $[M+H]^+$ 599. H-NMR-386 (400 MHz, DMSO-d6, δ *ppm*): 0.70-0.93 (m, 4H), 1.33-1.60 (m, 1H), 1.60-1.71 (m, 5H), 1.71-1.92 (m, 6H), 2.44 (s, 3H), 2.73-2.77 (m, 2H), 3.18-3.25 (m, 3H), 3.30 (s, 3H), 4.10-4.13 (m, 1H), 4.58 (s, 2H), 7.00 (s, 1H), 7.25 (s, 1H), 7.33-7.41 (m, 2H), 7.59-7.61 (m, 1H), 7.66 (s, 1H), 7.80 (s, 1H).

Example 387. Synthesis of Compound 387 and 388



1. Synthesis of 387-1

[1357] A solution of 367-1 (5 g, 18.244 mmol, 1 equiv), 3-methoxyazetidine (3.18 g, 36.488 mmol, 2 equiv) and TEA (5.54 g, 54.732 mmol, 3 equiv) in THF (50 mL) was stirred for overnight at 70°C under nitrogen atmosphere. The reaction was quenched by the addition of water (20 mL) at room temperature. The aqueous layer was extracted with DCM/MeOH:10/1 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The crude

product 387-1 (3.36 g, 65.71%) as a yellow oil was used in the next step directly without further purification.

2. Synthesis of 387-2

[1358] A solution of 387-1 (3.36 g, 11.988 mmol, 1 equiv) and hydrazine hydrate (98%) (6.00 g, 119.880 mmol, 10 equiv) in EtOH (40 mL) was stirred for overnight at 80°C. The reaction was quenched with water (100 mL) at room temperature. The precipitated solids were collected by filtration. The resulting mixture was concentrated under vacuum. The crude product 387-2 (3.3 g, 98.21%) as a yellow powder was used in the next step directly without further purification.

3. Synthesis of 387-3

[1359] A solution of 387-2 (3.36 g, 11.988 mmol, 1 equiv) and methyl isothiocyanate (1.31 g, 17.982 mmol, 1.5 equiv) in tetrahydrofuran (40 mL) was stirred for overnight at room temperature. The reaction was quenched with water (100 mL). The aqueous layer was extracted with DCM/MeOH:10/1(3x30 mL). The resulting mixture was concentrated under reduced pressure. The crude product 387-3 (4.2 g, 99.14%) as a yellow powder was used in the next step directly without further purification.

4. Synthesis of 387-4

[1360] Into a 100 mL 3-necked round-bottom flask were added 387-3 (4.8 g, 13.582 mmol, 1 equiv) and NaOH(aq,1mol/L) (2.17 g, 54.328 mmol, 4 equiv) stirred for overnight at room temperature. The mixture was acidified to pH 6 with HCl (1 M, 46 mL). The aqueous layer was extracted with DCM/MeOH:10/1 (3x150 mL). The resulting mixture was concentrated under reduced pressure. The crude product 387-4 (3.96 g, 86.93%) as a yellow powder was used in the next step directly without further purification.

5. Synthesis of 387-5

[1361] To a stirred mixture of 387-4 (3.96 g, 11.808 mmol, 1 equiv) and $NaNO_2$ (aq.1mol/L,8.15 g, 118.080 mmol, 10 equiv) in EtOAc (19.6 mL) was added HNO_3 (aq.1mol/L,8.43 mL, 118.080 mmol, 10 equiv) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature.The mixture was acidified to pH 8 with saturated $NaHCO_3$ (aq. 10 mL). The aqueous layer was extracted with DCM (3x20 mL). The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 387-5 (3.56 g, 99.40%) as a yellow oil.

6. Synthesis of 387-6

[1362] To a solution of 387-5 (3.6 g, 11.869 mmol, 1 equiv) in 120 mL MeOH was added Pd/C (10%, 0.4 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture

was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a filter paper pad and concentrated under reduced pressure. The crude product 387-6 (1.2 g, 36.99%) as a yellow oil was used in the next step directly without further purification.

7. Synthesis of 387-7

[1363] Into a 100mL 3-necked round-bottom flask were added 387-6 (1.2 g, 4.390 mmol, 1 equiv), DCE (20 mL) and I-2 (1.26 g, 4.390 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. To the above mixture was added STAB (1.86 g, 8.780 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq. 20 mL) at room temperature. The aqueous layer was extracted with DCM / MeOH (10:1) (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (30:1) to afford 387-7 (1.2 g, 50.28%) as a yellow solid.

8. Synthesis of 387-8

[1364] Into a 20mL sealed tube were added 555-7 (880 mg, 1.619 mmol, 1 equiv), DCM (6.5 mL) and pyridine (1280.41 mg, 16.190 mmol, 10 equiv) at room temperature. To the above mixture was added triphosgene (432.29 mg, 1.457 mmol, 0.9 equiv) at 0°C. The resulting mixture was stirred for additional 15min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq. 10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (2x4 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 387-8 (120 mg, 13.01%) as a yellow solid.

9. Synthesis of 387

[1365] The 387-8 (130 mg) was purified by Chiral separation with the following conditions (Column: Lux 5um Cellulose-2, 2.12*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 29 min; Wave Length: 220/254 nm; RT1(min): 18.68; RT2(min): 23.04; The first peak is 388, and the second peak is 387-0; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number of Runs: 8) to afford 387-8 (120 mg, 13.01%) as a yellow solid and 387 (25.4 mg, 18.93%) as a yellow solid.

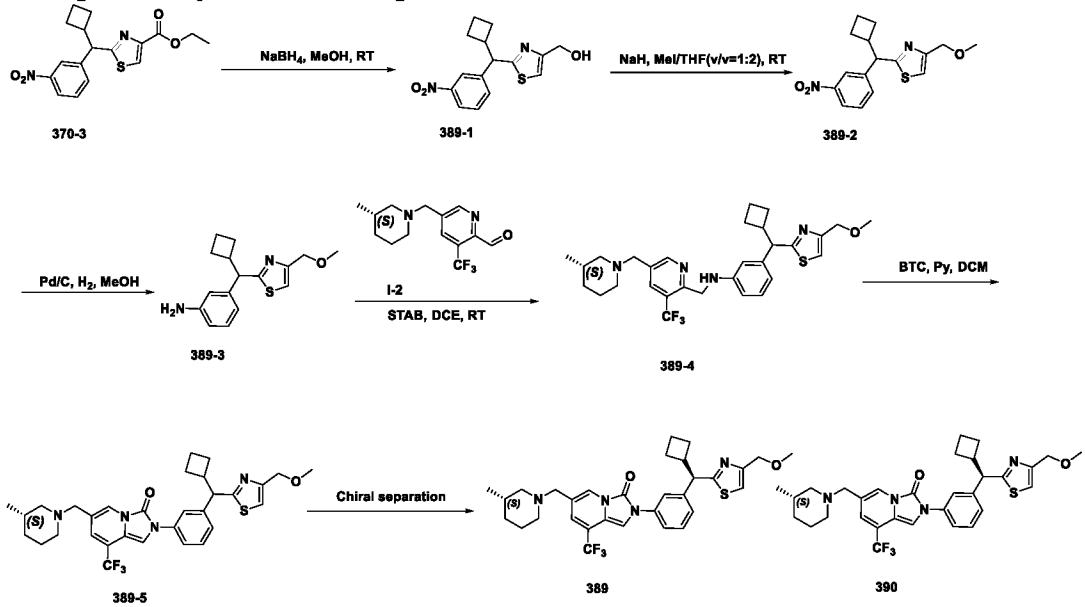
LC-MS-387 (ES, *m/z*): $[M+H]^+$ 570. H-NMR-387 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.82-0.86 (d, 4H), δ1.44-1.47 (d, 1H), δ1.58-1.66 (m, 4H), δ1.87-1.92 (t, 1H), δ2.67-2.77 (m, 2H), δ2.90-2.94 (t, 1H), δ2.95-2.99 (t, 1H), δ3.15 (s, 3H), δ3.25 (s, 2H), δ3.41-3.45 (m,

1H), δ3.50-3.57 (m, 1H), δ3.59 (s, 3H), δ4.01-4.05 (m, 1H), δ5.02 (s, 1H), δ7.01-7.03 (d, 1H), δ7.32-7.36 (m, 2H), δ7.47-7.49 (m, 1H), δ7.67-7.69 (m, 2H), δ7.96 (s, 1H), δ8.33 (s, 1H).

LC-MS-388 (ES, *m/z*): $[M+H]^+$ 570

H-NMR-388 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.82-0.86 (m 4H), δ1.44-1.47 (d, 1H), δ1.58-1.66 (m, 4H), δ1.87-1.92 (m, 1H), δ2.67-2.77 (m, 2H), δ2.90-2.94 (m, 1H), δ2.95-2.99 (m, 1H), δ3.15 (s, 3H), δ3.25 (s, 2H), δ3.41-3.45 (m, 1H), δ3.50-3.56 (m, 1H), δ3.59 (s, 3H), δ4.03-4.06 (m, 1H), δ5.02 (s, 1H), δ7.01 (s, 1H), δ7.32-7.36 (m, 2H), δ7.47-7.51 (t, 1H), δ7.67-7.70 (d, 2H), δ7.96 (s, 1H), δ8.33 (s, 1H).

Example 388. Synthesis of Compound 389 and 390



1. Synthesis of 389-1

[1366] To a stirred solution of 389-1 (12 g, 34.642 mmol, 1 equiv) in MeOH (150 mL) was added $NaBH_4$ (6.55 g, 173.210 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 389-1 (7 g, 63.07%) as a light yellow oil.

2. Synthesis of 389-2

[1367] To a stirred solution of 389-1 (3 g, 9.857 mmol, 1 equiv) in THF (30 mL) was added NaH (1.97 g, 49.285 mmol, 5 equiv, 60%) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added MeI (15

mL) at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 389-2 (1 g, 29.63%) as a light yellow oil.

3. Synthesis of 389-3

[1368] To a solution of 389-2 (1 g, 3.141 mmol, 1 equiv) in MeOH (30 mL) was added Pd/C (100 mg, 0.940 mmol, 0.30 equiv) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 389-3 (620 mg, 61.60%) as a light yellow oil.

4. Synthesis of 389-4

[1369] To a stirred solution of 389-3 (600 mg, 2.080 mmol, 1 equiv) and I-2 (714.73 mg, 2.496 mmol, 1.2 equiv) in DCE (8 mL) was added STAB (881.83 mg, 4.160 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 40:1) to afford 389-4 (600 mg, 49.04%) as a light yellow solid.

5. Synthesis of 389-5

[1370] To a stirred solution of 389-4 (600 mg, 1.074 mmol, 1 equiv) and Pyridine (849.46 mg, 10.740 mmol, 10 equiv) in DCM (20 mL) was added Triphosgene (127.46 mg, 0.430 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 389-5 (400 mg, 61.16%) as a yellow solid.

6. Synthesis of 389 and 390

[1371] The 389-5 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.39; RT2(min): 10.01, the first peak is 390; the

second peak is 389-0) and Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 72% B to 93% B in 8 min, Wave Length: 254 nm; RT1(min): 7.38) to afford 390 (58.8 mg, 14.60%) as a yellow solid and 389 (63.6 mg, 15.84%) as a yellow solid.

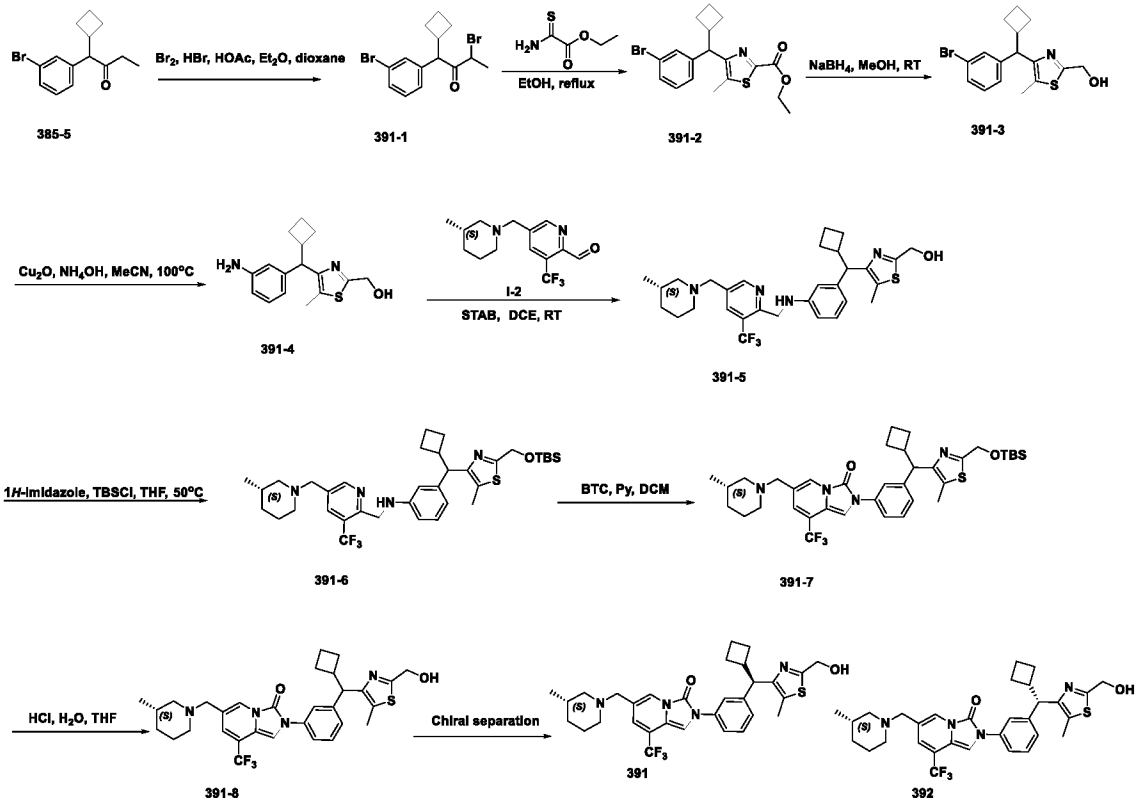
LC-MS-389 (ES, *m/z*): $[M+H]^+$ 585

H-NMR-389 (400 MHz, DMSO-d6, δ *ppm*): 0.83-0.93 (m, 4H), 1.43-1.49 (m, 1H), 1.49-1.66 (m, 4H), 1.71-1.98 (m, 6H), 2.06-2.13 (m, 1H), 2.67-2.74 (m, 2H), 3.15-3.24 (m, 1H), 3.29 (s, 2H), 3.32 (s, 3H), 4.43-4.46 (m, 3H), 7.00 (s, 1H), 7.31-7.33 (m, 2H), 7.41-7.47 (m, 2H), 7.66 (s, 1H), 7.72-7.74 (d, 1H), 7.83 (s, 1H).

LC-MS-390 (ES, *m/z*): $[M+H]^+$ 585

H-NMR-390 (400 MHz, DMSO-d6, δ *ppm*): 0.83-0.93 (m, 4H), 1.43-1.53 (m, 1H), 1.58-1.98 (m, 10H), 2.01-2.12 (m, 1H), 2.67-2.77 (m, 2H), 3.15-3.24 (m, 1H), 3.29 (s, 2H), 3.32 (s, 3H), 4.43-4.46 (m, 3H), 7.00 (s, 1H), 7.31-7.33 (m, 2H), 7.41-7.47 (m, 2H), 7.66 (s, 1H), 7.72-7.74 (d, 1H), 7.83 (s, 1H).

Example 389. Synthesis of Compound 391 and 392



1. Synthesis of 391-1

[1372] To a stirred solution of 1-(3-bromophenyl)-1-cyclobutylbutan-2-one (10 g, 35.563

mmol, 1 equiv) in Et_2O (100 mL) and dioxane (100 mL) were added Br_2 (3.98 g, 24.894 mmol, 0.7 equiv) and HBr in AcOH(40%)(2.01 g, 24.894 mmol, 0.7 equiv) at 0 °C. The resulting mixture was stirred for 3 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (aq.) (400 mL) at room temperature. The aqueous layer was extracted with EtOAc (200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA =100:1 to afford 391-1 (7 g, 54.66%) as a colorless oil.

2. Synthesis of 391-2

[1373] To a stirred solution of 391-1 (7 g, 19.440 mmol, 1 equiv) in EtOH (70 mL) were added ethyl carbamothioylformate (5.18 g, 38.880 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (2x150 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=10:1 to afford 391-2 (3 g, 39.14%) as a yellow solid.

3. Synthesis of 391-3

[1374] To a stirred mixture of 391-2 (3 g, 7.608 mmol, 1 equiv) in MeOH (30 mL) was added $NaBH_4$ (0.58 g, 15.216 mmol, 2 equiv) in portions at 0°C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (150 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=5:1 to afford 391-3 (2.5 g, 93.28%) as a yellow solid.

4. Synthesis of 391-4

[1375] To a stirred mixture of 391-3 (2.4 g, 6.813 mmol, 1 equiv) in MeCN (10 mL) and NH_4OH (10 mL) was added Cu_2O (0.19 g, 1.363 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C. The resulting mixture was filtered, the filter cake was washed with MeOH (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 391-4 (700 mg, 35.63%) as a yellow solid.

5. Synthesis of 391-5

[1376] To a stirred mixture of 391-4 (680 mg, 2.358 mmol, 1 equiv) and I-2 (810.02 mg, 2.830 mmol, 1.2 equiv) in DCE (7 mL) was added STAB (1499.11 mg, 7.074 mmol, 3 equiv) at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (20 mL). The resulting

mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 391-5 (910 mg, 69.08%) as a yellow solid.

6. Synthesis of 391-6

[1377] To a stirred solution of 391-5 (890 mg, 1.593 mmol, 1 equiv) and 1H-imidazole (216.89 mg, 3.186 mmol, 2 equiv) in THF (10 mL) were added TBSCl (480.18 mg, 3.186 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 391-6 (1 g, 93.28%) as a yellow solid.

7. Synthesis of 391-7

[1378] To a stirred solution of 391-6 (1 g, 1.486 mmol, 1 equiv) and pyridine (0.71 g, 8.916 mmol, 6 equiv) in DCM (12 mL) were added Triphosgene (0.15 g, 0.520 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 5 min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 391-7 (800 mg, 77.02%) as a yellow solid.

8. Synthesis of 391-8

[1379] To a stirred solution of 391-7 (800 mg, 1.145 mmol, 1 equiv) in THF (4 mL) was added HCl (4 mL, 2M) at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 391-8 (250 mg, 37.36%) as a yellow solid.

9. Synthesis of 391

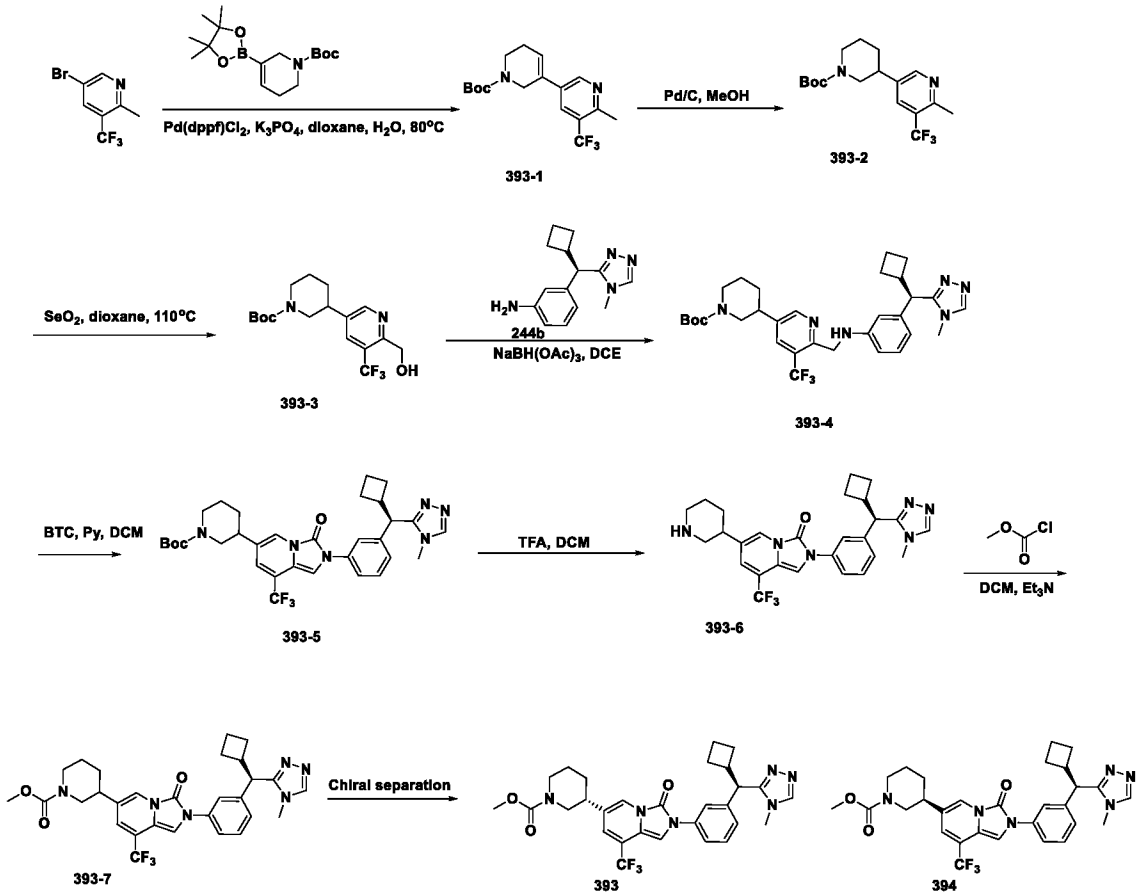
[1380] The 391-8 (260 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 8.5 min; Wave Length: 220/254 nm; RT1 (min): 4.967; RT2 (min): 7.185; the first peak is 392; the second peak is 391-0) to afford 391 (111.7 mg, 42.19%) as a yellow solid.

LC-MS-391: (ES, *m/z*): $[M+H]^+$ 585. H-NMR-391: (400 MHz, DMSO-d6, δ *ppm*): 0.70-0.93 (m, 4H), 1.33-1.48 (m, 1H), 1.48-1.88 (m, 11H), 2.43 (s, 3H), 2.73-2.77 (m, 2H), 3.17-3.24

(m, 3H), 4.08-4.11 (m, 1H), 4.59-4.62 (m, 2H), 5.86-5.89 (m, 1H), 7.00 (s, 1H), 7.27 (s, 1H), 7.32-7.37 (m, 1H), 7.37-7.41 (m, 1H), 7.58-7.60 (m, 1H), 7.66 (s, 1H), 7.80 (s, 1H).

LC-MS-392: (ES, *m/z*): $[M+H]^+$ 585. H-NMR-392: (400 MHz, DMSO-d6, δ *ppm*): 0.70-0.93 (m, 4H), 1.33-1.48 (m, 1H), 1.48-1.88 (m, 11H), 2.43 (s, 3H), 2.73-2.77 (m, 2H), 3.17-3.24 (m, 3H), 4.08-4.11 (m, 1H), 4.59-4.62 (m, 2H), 5.86-5.89 (m, 1H), 7.00 (s, 1H), 7.27 (s, 1H), 7.32-7.37 (m, 1H), 7.37-7.41 (m, 1H), 7.58-7.60 (m, 1H), 7.66 (s, 1H), 7.80 (s, 1H).

Example 390. Synthesis of Compound 393 and 394



1. Synthesis of 393-1

[1381] A solution of 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (3.88 g, 16.170 mmol, 1 equiv) and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate (5 g, 16.170 mmol, 1.00 equiv) in dioxane (40 mL) and H2O (10 mL) was treated with K3PO4 (10.30 g, 48.510 mmol, 3 equiv), and Pd(dppf)Cl2 (1.77 g, 2.425 mmol, 0.15 equiv) at room temperature, The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of water (100mL) at room temperature. The resulting mixture was extracted with DCM (3 x 100mL).

The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 393-1 (5.03 g, 85.41%) as a light yellow solid.

[1382] 2. Synthesis of 393-2

To a solution of 393-1 (5 g, 14.604 mmol, 1 equiv) in MeOH (150 mL) was added Pd/C (10%, 1.5g) under nitrogen atmosphere in a 1L round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere by using a hydrogen balloon. The resulting mixture was filtered, the filter cake was washed with MeOH (100 mL). The filtrate was concentrated under reduced pressure to afford 393-2 (3.6 g, 68.00%) as a light yellow solid.

3. Synthesis of 393-3

[1383] A solution of 393-2 (3.6 g, 10.454 mmol, 1 equiv) in dioxane (36 mL) was treated with SeO_2 (3.48 g, 31.362 mmol, 3 equiv), The resulting mixture was stirred for overnight at 110°C. The reaction was quenched with water(50ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 393-3 (2.91 g, 62.57%) as a white solid.

4. Synthesis of 393-4

[1384] A solution of 393-3 (2.93 g, 8.122 mmol, 1.2 equiv) in DCE (30 mL) was treated with 244b (1.64 g, 6.768 mmol, 1.00 equiv) for 2h at room temperature followed by the addition of STAB (2.15 g, 10.152 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 6 h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.)(100ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (10 mmol/L NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 254 nm. This resulted in 393-4(2.7 g, 68.23%) as a white solid.

5. Synthesis of 393-5

[1385] A solution of 393-4 (2.7 g, 4.618 mmol, 1 equiv) in DCM (27 mL) was treated with Pyridine (2.19 g, 27.708 mmol, 6 equiv) at room temperature followed by the addition of Triphosgene (0.55 g, 1.847 mmol, 0.4 equiv) at 0°C. The solution was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of $NaHCO_3$(100mL) at room temperature. The resulting mixture was extracted with

DCM/MeOH(10:1)(2 x 50mL).The resulting solution was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water(0.1% NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 254 nm. This resulted in 393-5 (1.83 g, 64.89%) as a yellow solid.

6. Synthesis of 393-6

[1386] A solution of 393-5 (1.83 g, 2.997 mmol, 1 equiv) in TFA (3.8 mL) and DCM (15.2 mL) was stirred for 2h at room temperature under air atmosphere. The resulting mixture was concentrated under vacuum to afford 393-6(2.7 g, NaN) as a yellow solid.

[1387] 7. Synthesis of 393-7

A solution of 393-6 (1.5 g, 2.938 mmol, 1 equiv) in DCM (15 mL) was treated with methyl chloroformate (0.31 g, 3.232 mmol, 1.1 equiv) and Et_3N (0.89 g, 8.814 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The resulting mixture was washed with 20 mL of water. The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure.The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 393-7(392 mg, 23.47%) as a yellow solid.

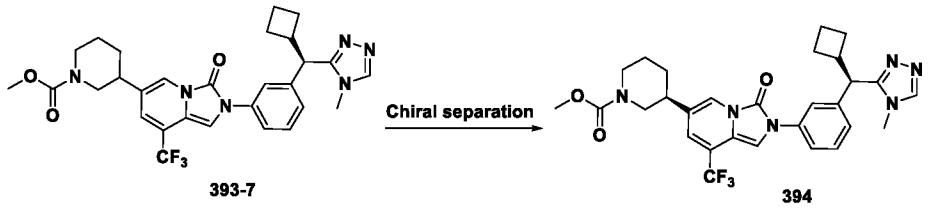
8. Synthesis of 393-0

The 393-7 (350 mg, 0.616 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 12 min; Wave Length: 220/254 nm; RT_1(min): 7.21; RT_2(min): 9.46; the first peak was product) to afford 393 (117.5 mg, 32.06%) as a yellow solid.

LC-MS-393 (ES, m/z): $[M+H]^+$ 569/ H-NMR-393 (400 MHz, DMSO, δ ppm): 1.43-1.47 (m, 1H), 1.73-1.88 (m, 8H), 2.09-2.19 (m, 1H), 2.61-2.68 (m, 1H), 2.67-2.87 (m, 2H), 3.13-3.19 (m, 1H), 3.44 (s, 3H), 3.61 (s, 3H), 3.96-4.25 (m, 2H), 4.25-4.28 (d, 1H), 7.13 (s, 1H), 7.19-7.21 (d, 1H), 7.30 (s, 1H), 7.42-7.44 (t, 1H), 7.61 (s, 1H), 7.69-7.70 (m, 1H), 7.71 (s, 1H), 8.34 (s, 1H).

LC-MS-394: (ES, m/z): $[M+H]^+$ 569. H-NMR- 394: (400 MHz, DMSO, δ ppm): 1.43-1.47 (m, 1H), 1.73-1.88 (m, 8H), 2.08-2.10 (m, 1H), 2.61-2.67 (m, 1H), 2.68-2.87 (m, 2H), 3.13-3.19 (m, 1H), 3.44 (s, 3H), 3.61 (s, 3H), 3.93-4.09 (m, 2H), 4.25-4.28 (d, 1H), 7.13 (s, 1H), 7.19-7.21 (d, 1H), 7.30 (s, 1H), 7.42-7.44 (t, 1H), 7.61 (s, 1H), 7.69-7.71 (m, 1H), 7.73 (s, 1H), 8.34 (s, 1H).

Example 391. Synthesis of Compound 394



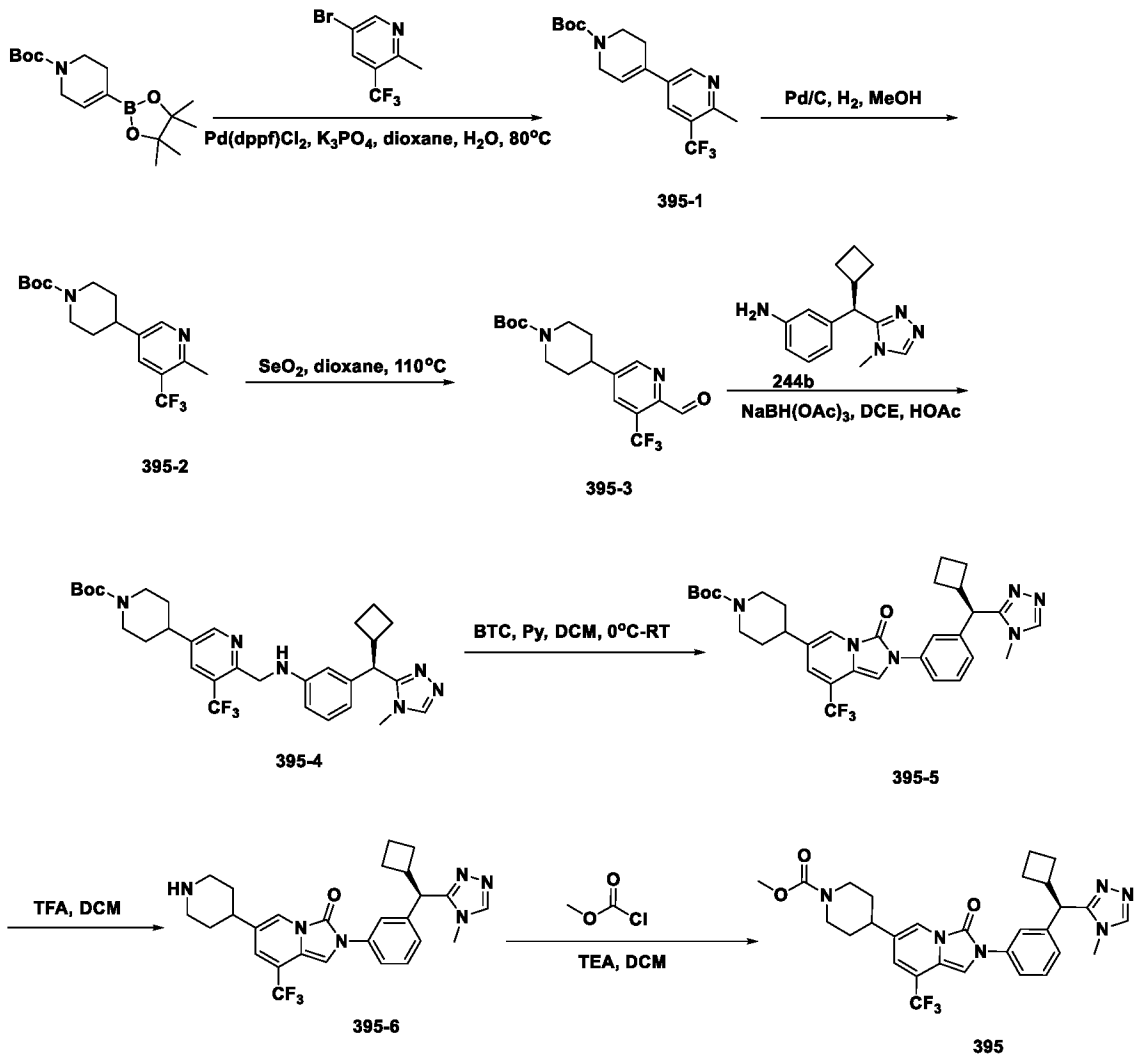
393-7 394

1. Synthesis of 394-0

[1388] The 393-7 (350 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 12 min; Wave Length: 220/254 nm; RT_1(min): 7.21; RT_2(min): 9.46; the second peak was product) to afford 394 (116 mg, 32.61%) as yellow solid.

LC-MS-394 (ES, m/z): $[M+H]^+$ 569. H-NMR-394 (400 MHz, DMSO, δ ppm): 1.43-1.47 (m, 1H), 1.73-1.88 (m, 8H), 2.08-2.10 (m, 1H), 2.61-2.67 (m, 1H), 2.68-2.87 (m, 2H), 3.13-3.19 (m, 1H), 3.44 (s, 3H), 3.61 (s, 3H), 3.93-4.09 (m, 2H), 4.25-4.28 (d, 1H), 7.13 (s, 1H), 7.19-7.21 (d, 1H), 7.30 (s, 1H), 7.42-7.44 (t, 1H), 7.61 (s, 1H), 7.69-7.71 (m, 1H), 7.73 (s, 1H), 8.34 (s, 1H).

Example 392. Synthesis of Compound 395



1. Synthesis of 395-1

[1389] A solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (4 g, 12.936 mmol, 1 equiv) and 5-bromo-2-methyl-3-(trifluoromethyl) pyridine (3.10 g, 12.936 mmol, 1 equiv) in dioxane (32 mL) and H_2O (8 mL) was added K_3PO_4 (8.24 g, 38.808 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (1.42g, 1.940 mmol, 0.15 equiv) at room temperature under nitrogen atmosphere. The reaction was quenched with Water (30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 395-1 (4 g, 83.99%) as a yellow solid.

2. Synthesis of 395-2

[1390] To a solution of 395-1 (4 g, 11.684 mmol, 1 equiv) in 40 mL MeOH was added Pd/C

(10%, 400 mg) under nitrogen atmosphere in a 250 mL round-bottom flask. The mixture was hydrogenated at room temperature for 4h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. This resulted 395-2 (3.5 g, 80.90%) as a yellow solid.

3. Synthesis of 395-3

[1391] A solution of 395-2 and SeO_2 (4.51 g, 40.652 mmol, 4 equiv) in dioxane (35 mL) was stirred for overnight at 110°C under nitrogen atmosphere. The reaction was quenched with Water (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 395-3 (1.5 g, 38.71%) as a yellow solid.

4. Synthesis of 395-4

[1392] Into a 100mL round-bottom flask were added 395-3 (250 mg, 0.698 mmol, 1 equiv) 244b (202.86 mg, 0.838 mmol, 1.2 equiv), $NaBH(OAc)_3$ (443.56 mg, 2.094 mmol, 3 equiv) and DCE (4 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with Water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 395-4 (230 mg, 51.21%) as a yellow solid.

5. Synthesis of 395-5

[1393] The solution of compound 395-4 (1.4 g, 2.394 mmol, 1 equiv) and Pyridine (1.14 g, 14.364 mmol, 6 equiv) in DCM (20 mL) was stirred for 5 min at 0°C. Into the mixture was added Triphosgene (0.46 g, 1.556 mmol, 0.65 equiv) at 0°C. The resulting mixture was stirred for 10 min at 0°C. The reaction was quenched with sat. $NaHCO_3$ (aq.) (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 395-5 (700 mg, 45.48%) as a yellow solid.

6. Synthesis of 395-6

[1394] Into a 8mL sealed tube were added 395-5 (700 mg, 1.146 mmol, 1 equiv) TFA (2 mL) and DCM (4 mL) at room temperature. The resulting mixture was stirred for 2h at room temperature. The mixture/residue was acidified to pH 7 with saturated $NaHCO_3$ (aq.) (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 /

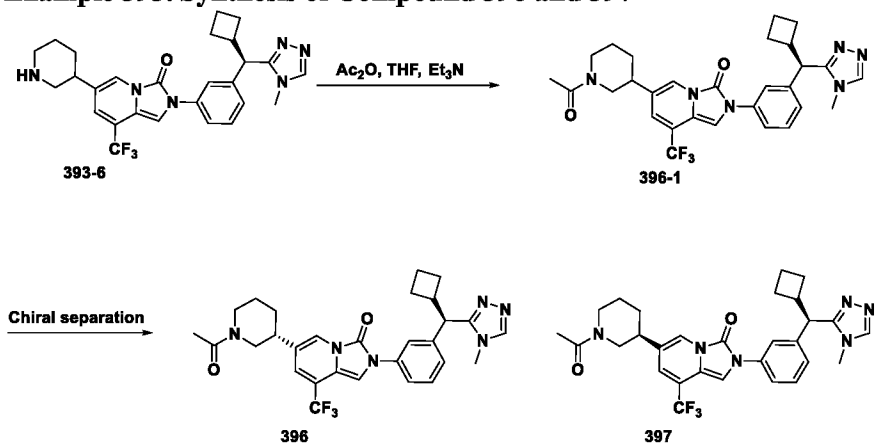
MeOH 10:1) to afford 395-6 (350 mg, 56.81%) as a yellow solid.

7. Synthesis of 395

[1395] A solution of 395-6 (150 mg, 0.294 mmol, 1 equiv) and TEA (89.19 mg, 0.882 mmol, 3 equiv) in DCM (2 mL) was stirred for 5 min at 0°C. The resulting mixture was added methyl chloroformate (30.54 mg, 0.323 mmol, 1.1 equiv) and stirred for 2.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (5 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford the crude product. The crude product (90 mg) was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 51% B in 8 min; Wave Length: 220 nm; RT1(min): 7.9) to afford 395 (55.5 mg, 33.02%) as a yellow solid.

LC-MS-395: (ES, m/z): $[M+H]^+$ 569. H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 1.48-1.52 (m, 2H), 1.75-1.80 (m, 7H), 2.08-2.15 (s, 1H), 2.57-2.61 (m, 1H), 2.71-3.06 (s, 2H), 3.11-3.30 (s, 1H), 3.40-3.52 (s, 3H), 3.58-3.71 (s, 3H), 4.05-4.21 (d, 1H), 7.12-7.26 (m, 2H), 7.27-7.39 (s, 1H), 7.40-7.50 (m, 1H), 7.50-7.58 (s, 1H), 7.61-7.73 (d, 1H), 7.73-7.80 (d, 1H), 8.19-8.48 (s, 1H).

Example 393. Synthesis of Compound 396 and 397



1. Synthesis of 396-1

[1396] A solution of 393-6 (1.2 g, 2.350 mmol, 1 equiv) in THF (12 mL) was treated with acetic anhydride (0.36 g, 3.525 mmol, 1.5 equiv) and Et_3N (0.71 g, 7.050 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was quenched with water (100mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 200mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse

flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1%NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 254 nm to afford 396-1(531 mg, 38.84%) as a yellow solid.

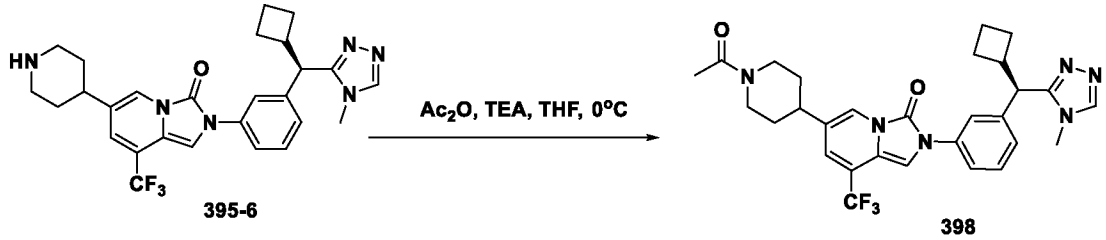
2. Synthesis of 396 and 397

[1397] The 396-1(500 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 12 min; Wave Length: 220/254 nm; RT_1(min): 7.566; RT_2(min): 9.486; the first peak was 396-0; the second peak 397) to afford 396 (162.3 mg, 31.10%)as a light yellow solid and 397 (191.5 mg, 37.50%) as a light yellow solid.

LC-MS-396 (ES, m/z): $[M+H]^+$ 553. H-NMR-396 (400 MHz, DMSO, δ ppm): 1.33-1.53 (m, 1H), 1.68-1.87 (m, 9H), 2.03-2.08 (m, 4H), 2.50-2.61 (m, 1H), 3.01-3.27 (m, 2H), 3.44 (s, 3H), 3.71-3.84 (d, 1H), 4.25-4.28 (d, 1H), 4.31-4.44(t,1H),7.11-7.32 (m, 3H), 7.45-7.46 (t, 1H), 7.59-7.74 (m, 3H), 8.34 (s, 1H).

LC-MS-397 (ES, m/z): $[M+H]^+$ 553. H-NMR-397: (400 MHz, DMSO, δ ppm): 1.33-1.53 (m, 1H), 1.68-1.87 (m, 9H), 2.03-2.08 (m, 4H), 2.62-2.72 (m, 1H), 3.01-3.27 (m, 2H), 3.44 (s, 3H), 3.78-3.81 (m, 1H), 4.26-4.28 (d, 1H), 4.33-4.41 (t,1H),7.11-7.22 (m, 2H), 7.32 (s, 1H), 7.43-7.46 (t, 1H), 7.60-7.74 (m, 3H), 8.34 (s, 1H).

Example 394. Synthesis of Compound 398-0



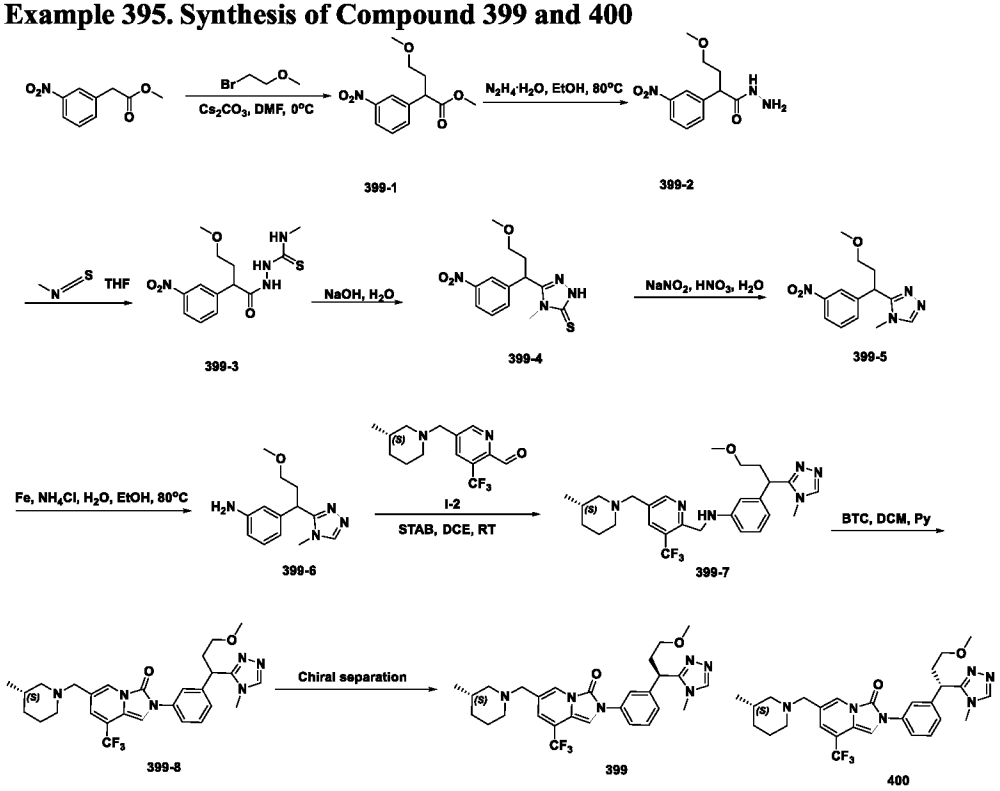
1. Synthesis of 398

[1398] A solution of 395-6 (150 mg, 0.294 mmol, 1 equiv) and Ac_2O (44.99 mg, 0.441 mmol, 1.5 equiv) in THF (2 mL) was stirred for 5 min at 0°C. The resulting mixture was added TEA (89.19 mg, 0.882 mmol, 3 equiv) and stirred for 2.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford the crude product. The crude product (90 mg) was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 51% B in 8 min; Wave Length: 254 nm; RT1(min): 7.9

to afford 398 (52.0 mg, 31.77%) as a yellow solid.

LC-MS-398: (ES, m/z): $[M+H]^+$ 553. H-NMR-398: (400 MHz, DMSO, δ ppm): 1.32-1.49 (m,1H), 1.55-1.68 (m, 1H), 1.68-1.94 (m, 7H), 1.97-2.07 (s, 3H), 2.07-2.15 (s, 1H), 2.52-2.61 (s, 1H), 2.62-2.75 (m, 1H), 3.02-3.16 (m, 1H), 3.16-3.27 (s, 1H), 3.41-3.49 (s, 3H), 3.83-4.00 (d, 1H), 4.18-4.38 (d, 1H), 4.42-4.69 (d, 1H), 7.10-7.26 (m, 2H), 7.26-7.39 (s, 1H), 7.39-7.50 (m, 1H), 7.50-7.67 (s, 1H), 7.70-7.87(m,2H), 8.25-8.41(s,1H).

Example 395. Synthesis of Compound 399 and 400



1. Synthesis of 399-1

[1399] A solution of methyl 2-(3-nitrophenyl) acetate (10 g, 51.236 mmol, 1 equiv) and Cs_2CO_3 (83.47 g, 256.180 mmol, 5 equiv) in DMF (100 mL) was stirred for 3h at 0°C under nitrogen atmosphere. To the above mixture was added 2-bromoethyl methyl ether (21.36 g, 153.708 mmol, 3 equiv) room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (300 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1) to afford 399-1 (7 g, 48.55%) as a yellow oil.

2. Synthesis of 399-2

[1400] A solution of 399-1 (6.9 g, 27.245 mmol, 1 equiv) and $NH_2NH_2.H_2O$ (8.73 g, 272.450

mmol, 10 equiv) in EtOH (70 mL) was stirred overnight at 80°C. The reaction was quenched with saturated NH_4Cl (aq.) (200 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3x50 mL). This resulted in 399-2 (6.8 g, 88.69%) as a yellow solid.

3. Synthesis of 399-3

[1401] A solution of 399-2 (6.8 g, 26.850 mmol, 1 equiv) and methyl isothiocyanate (2.94 g, 40.275 mmol, 1.5 equiv) in tetrahydrofuran (80 mL) was stirred for 5h at room temperature. The resulting mixture was washed with water (40 mL). The reaction was diluted with saturated water (100 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3x40 mL). This resulted in 399-3 (8.2 g, 84.22%) as a yellow solid.

4. Synthesis of 399-4

[1402] A solution of 399-3 (8.7 g, 26.657 mmol, 1 equiv) and NaOH (10.66 g, 266.570 mmol, 10 equiv) in H_2O (200 mL) was stirred for 5h at room temperature under air atmosphere. The mixture was neutralized to pH 6 with HCl (aq.). The precipitated solids were collected by filtration and washed with water (2x30 mL). This resulted in 399-4 (8.2 g, 89.78%) as a yellow solid.

5. Synthesis of 399-5

[1403] To a stirred solution of 399-4(8.2 g, 26.592 mmol, 1 equiv) and $NaNO_2$ (18.35 g, 265.920 mmol, 10 equiv) in H_2O (82 ml) was added HNO_3 (265.92 mL, 265.920 mmol, 10 equiv, 1M) dropwise at at room temperature. The result mixture was stirred for 5h at room temperature. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.) (300 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (80:1) to afford 399-5 (8 g, 97.99%) as a yellow solid.

6. Synthesis of 399-6

[1404] To a stirred solution of 399-5 (4 g, 14.477 mmol, 1 equiv) and Fe (2.43 g, 43.431 mmol, 3 equiv) in EtOH (40 mL) were added NH_4Cl (7.74 g, 144.770 mmol, 10 equiv) in H_2O (40 mL) at room temperature. The resulting mixture was stirred for 3h at 80°C. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x50 mL). The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1)

to afford 399-6 (2 g, 50.48%) as a brown solid.

7. Synthesis of 399-7

[1405] A solution of 399-6 (600 mg, 2.436 mmol, 1 equiv) and I-2 (767.14 mg, 2.680 mmol, 1.1 equiv) and STAB (1032.54 mg, 4.872 mmol, 2 equiv) in DCE (10 mL) was stirred for 5h at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (80 mL). The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 399-7 (900 mg, 67.94%) as a yellow solid.

8. Synthesis of 399-8

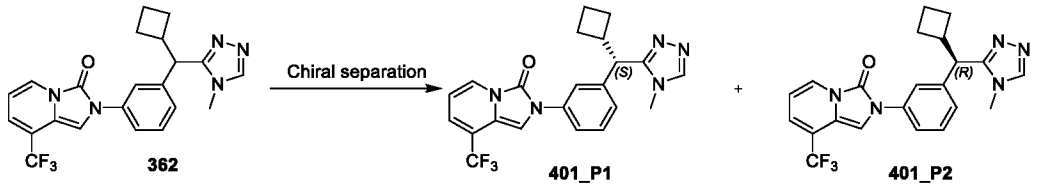
[1406] To a stirred solution of 399-7 (600 mg, 1.161 mmol, 1 equiv) and Pyridine (551.20 mg, 6.966 mmol, 6 equiv) in DCM (15 ml) was added Triphosgene (127.52 mg, 0.430 mmol, 0.37 equiv) at 0°C. The result mixture was stirred for 10min at 0°C. The mixture was quenched with saturated $NaHCO_3$ (aq.) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 399-8 (400 mg, 60.30%) as a yellow solid.

9. Synthesis of 399

[1407] The 399-8 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 4.96; RT2(min): 8.87; the first peak is 400; the second peak is 399) to afford 400 (155 mg,38.47%) as a yellow solid and 399 (139.1 mg, 34.33%) as a yellow solid.

LC-MS-400 (ES, m/z): $[M+H]^+$543. H-NMR-400 (400 MHz, DMSO-d6, δ *ppm*): 0.86-0.97 (d, 4H), 1.41-1.51 (m, 1H), 1.51-1.71 (m, 4H), 1.87-1.92 (m, 1H), 2.20-2.34 (m, 1H), 2.47-2.50 (m, 1H), 2.50-2.52 (m, 1H), 2.68-2.75 (m, 2H), 3.21 (s, 3H), 3.27-3.29 (m, 3H), 3.43 (s, 3H), 4.36-4.40 (m, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.34 (s, 1H), 7.44-7.48 (m, 1H), 7.65 (s, 1H), 7.71-7.75 (m, 2H), 8.36 (s, 1H). LC-MS-399 (ES, m/z): $[M+H]^+$ 543
H-NMR-399 (400 MHz, DMSO-d6, δ *ppm*): 0.86-0.97 (d, 4H), 1.41-1.71 (m, 5H), 1.87-1.92 (m, 1H), 2.20-2.34 (m, 1H), 2.48-2.51 (m, 2H), 2.68-2.75 (m, 2H), 3.21 (s, 3H), 3.27-3.29 (m, 3H), 3.43 (s, 3H), 4.36-4.40 (m, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.34 (s, 1H), 7.44-7.48 (m, 1H), 7.65 (s, 1H), 7.72-7.75 (m, 2H), 8.35 (s, 1H).

Example 396. Synthesis of Compound 401_P1&P2



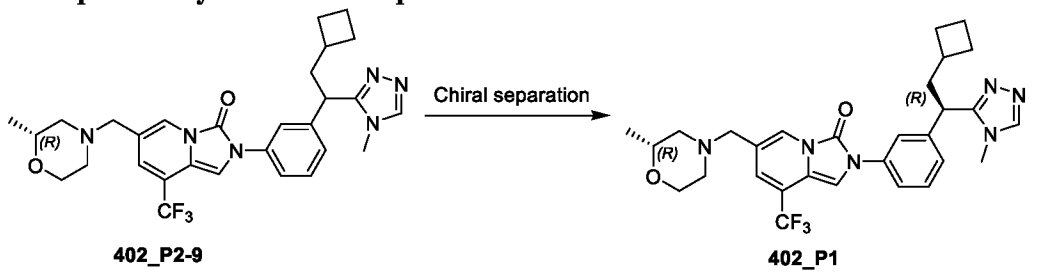
1. Synthesis of 401_P1, P2

[1408] The crude 362 was purified by prep-HPLC(column: Phenomenex C18 75*30mm*3um; Mobile phase A: water (NH_3H_2O+NH_4HCO_3), Mobile phase B: ACN; Flow rate: 70 mL/min; Gradient: 20% B to 50% B in 8 min; Wave Length: 220 nm) to afford pure 362 (30 mg) as a yellow solid. 362 was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD(250mm*30mm,10um); Mobile phase: [Neu-IPA]; B%: 50%-50%, 15min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 7.85; RT2 (min): 10.1) to afford 401_P1 (6.1 mg, 19.3%) and 401_P2 (7.7 mg, 24.6%).

MS-401_P1: (ES, m/z): $[M+H]^+$ 428.17. H-NMR-401_P1: (400 MHz, DMSO-d6) δ 8.34 (s, 1 H), 7.80-7.77 (m, 2 H), 7.71-7.69 (m, 1 H), 7.45-7.31 (m, 1 H), 7.21 (s, 1 H), 7.19-7.10 (m, 1 H), 7.12-7.05 (m, 1 H), 6.31-6.28 (m, 1 H), 4.29-4.26 (m, 1 H), 3.44-3.41 (m, 3 H), 3.27-3.22 (m, 1 H), 2.09 (s, 1 H), 1.82-1.69 (m, 5 H).

MS-401_P2: (ES, m/z): $[M+H]^+$ 428.17. H-NMR-401_P2: (400 MHz, DMSO-d6) δ 8.34 (s, 1 H), 7.80-7.76 (m, 2 H), 7.76-7.69 (m, 1 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.33-7.28 (m, 1 H), 7.22-7.17 (m, 1 H), 7.12-7.07 (m, 1 H), 6.31-6.28 (m, 1 H), 4.26 (d, J = 10.0 Hz, 1 H), 3.46-3.39 (m, 3 H), 3.25-3.22 (m, 1 H), 2.14-2.04 (m, 1 H), 1.87-1.66 (m, 5 H).

Example 397. Synthesis of Compound 402



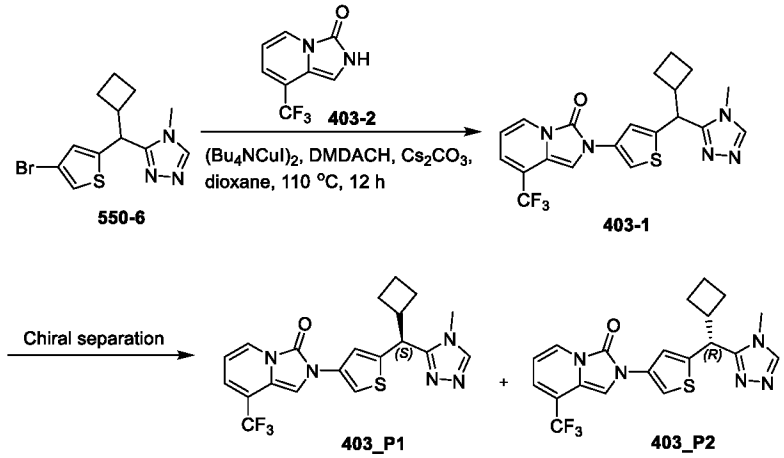
1. Synthesis of 402

[1409] The 402_P2-9 (68.7 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD(250mm*30mm,10um);mobile phase: [Neu-IPA];B%: 50%-50%,10min, Flow rate: 60 mL/min; Wave Length: 220/254 nm; RT1 (min): 4.71; RT2 (min): 6.03) to afford 402 (24 mg, 34.44%) as a yellow solid.

MS-402: (ES, m/z): $[M+H]^+$ 555.2. ^{1}H-NMR-402: (400 MHz, METHANOL-d4) δ 8.35 (s, 1H), 7.67 (d, J = 4.4 Hz, 2H), 7.65-7.61 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 7.6 Hz,

1H), 7.11 (d, J = 14.8 Hz, 2H), 4.20 (t, J = 7.6 Hz, 1H), 3.87-3.82 (m, 1H), 3.69-3.62 (m, 2H), 3.52 (s, 3H), 3.33 (s, 2H), 2.80 (d, J = 11.6 Hz, 1H), 2.74 (d, J = 11.6 Hz, 1H), 2.46-2.37 (m, 1H), 2.32-2.23 (m, 2H), 2.21-2.14 (m, 1H), 2.10-2.03 (m, 1H), 1.94-1.89 (m, 1H), 1.87-1.78 (m, 3H), 1.76-1.64 (m, 2H), 1.13 (d, J = 6.4 Hz, 3H).

Example 398. Synthesis of Compound 403_P1&P2



1. Synthesis of 403-1

[1410] To a solution of 550-6 (0.18 g, 576.50 umol, 1 equiv) and 403-2 (128 mg, 634 umol, 1.1 equiv) in dioxane (1 mL) was added iodocopper;tetrabutylammonium;diiodide (64.5 mg, 57.6 umol, 0.1 equiv), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (16.4 mg, 115 umol, 0.2 equiv) and Cs_2CO_3 (375 mg, 1.15 mmol, 2 equiv) under nitrogen atmosphere, the mixture was stirred at 110 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (10 mL x2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give crude product. The crude product (140 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 75*30mm*3um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 8 min; Wave Length: 220 nm; RT1(min): 6.5) afford 403-1 (25 mg, 8.3%) as a yellow solid.

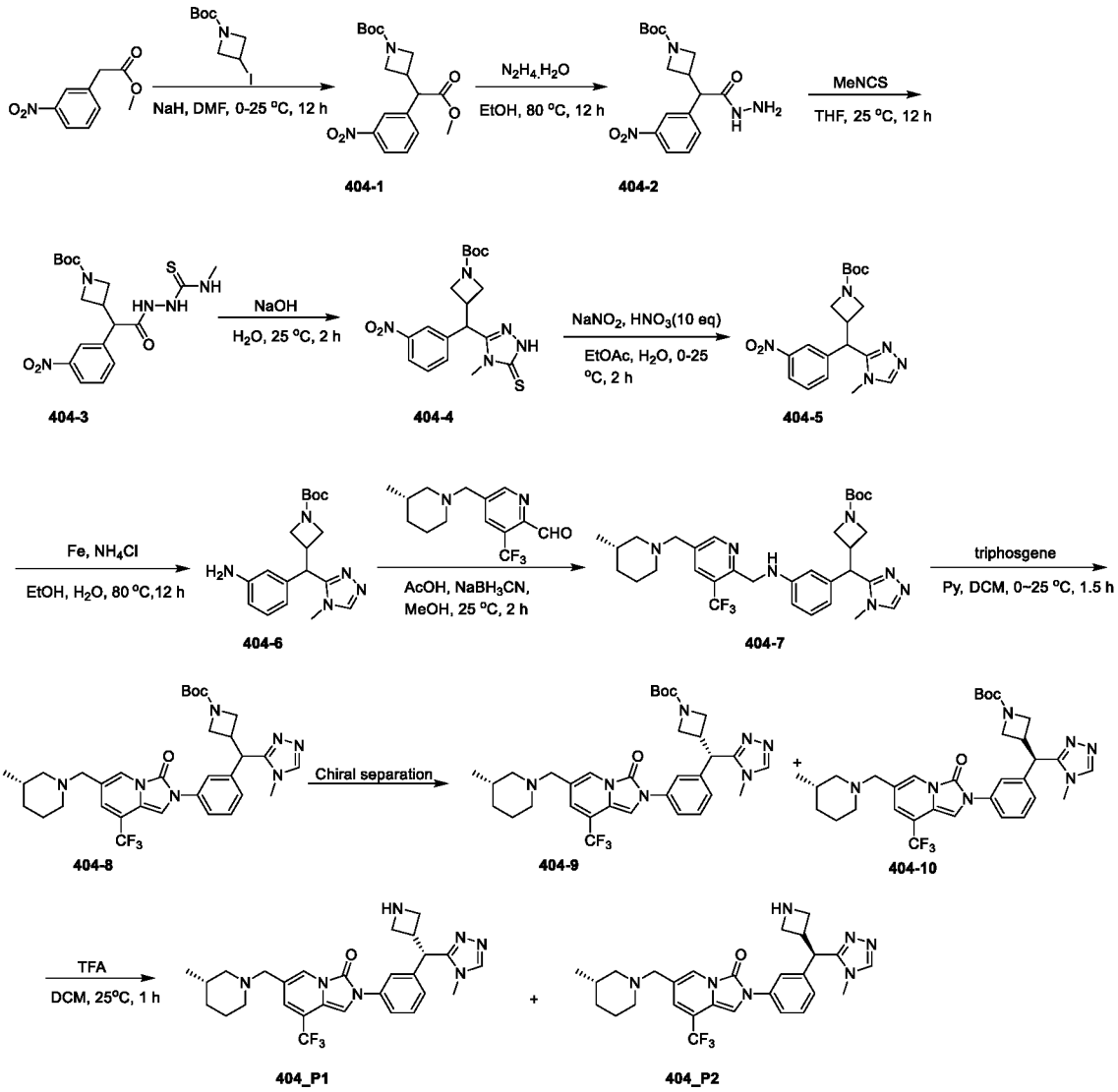
2. Synthesis of 403_P1&P2

[1411] The 403-1 (25 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [IPA]; B%: 50%-50%, 10 min, Flow rate: 27 mL/min; Wave Length: 220/254 nm; RT1 (min): 5.77; RT2 (min): 6.50) to afford 403_P1 (4 mg, 15%) and 403_P2 (8 mg, 30%) as yellow solid.

MS-403_P1: (ES, m/z): $[M+H]^+$ 434.0. H-NMR-403_P1: (400 MHz, CHLOROFORM-d) δ 8.07 (s, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 6.76 (s, 1H), 6.15 (t, J = 6.8 Hz, 1H), 4.24 (d, J = 10.4 Hz, 1H), 3.54 (s, 3H), 3.41-3.30 (m, 1H), 2.30-2.20 (m, 1H), 2.17-2.10 (m, 1H), 1.98-1.82 (m, 3H), 1.79-1.71 (m, 1H)

MS-403_P2: (ES, m/z): $[M+H]^+$ 434.1. H-NMR-403_P2: (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.27 (d, J = 0.8 Hz, 1H), 6.89 (d, J = 6.8 Hz, 1H), 6.79 (s, 1H), 6.19 (t, J = 6.8 Hz, 1H), 4.27 (d, J = 10.4 Hz, 1H), 3.57 (s, 3H), 3.47-3.32 (m, 1H), 2.34-2.24 (m, 1H), 2.22-2.13 (m, 1H), 2.03-1.86 (m, 3H), 1.81-1.74 (m, 1H).

Example 399. Synthesis of Compound 404_P1 & P2



1. Synthesis of 404-1

[1412] To a solution of NaH (2.07 g, 51.8 mmol, 60% purity, 1.1 equiv) in DMF (90 mL) was added methyl 2-(3-nitrophenyl)acetate (9.2 g, 47.1 mmol, 1 equiv). The mixture was cooled to 0 °C, then tert-butyl 3-iodoazetidine-1-carboxylate (22.6 g, 80.1 mmol, 1.7 equiv) was added at 0 °C. The mixture was stirred at 25 °C for 12 h under nitrogen atmosphere. The reaction mixture was quenched by Sat.NH4Cl (800 mL), extracted with EtOAc (250 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (5:1) to afford 404-1 (13 g, 78%) as a yellow solid.

2. Synthesis of 404-2

[1413] To a solution of 404-1 (13 g, 37.1 mmol, 1 equiv) in EtOH (80 mL) was added N2H4.H2O (17.1 mL, 346 mmol, 98% purity, 9.4 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrate in vacuum to remove EtOH (80 mL), then the mixture was diluted with water (800 mL), and extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 404-2 (12.5 g, crude) as a yellow solid.

3. Synthesis of 404-3

[1414] To a solution of 404-2 (12.5 g, 12.96 mmol, 1 equiv) in THF (250 mL) was added methylimino(thioxo)methane (4.88 mL, 71.3 mmol, 2 equiv). The mixture was stirred at 25 °C for 4 hr. The reaction mixture was diluted water (800 mL), extracted with EtOAc (350 mL x2). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 404-3 (15 g, crude) as a brown solid.

11H-NMR-404-3: (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 9.21 (s, 1H), 8.22 (s, 1H), 8.18-8.13 (m, 1H), 7.90 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 4.61 (s, 1H), 4.11-4.07 (m, 1H), 3.98-3.87 (m, 3H), 3.69 (d, J = 16.0 Hz, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.92-2.80 (m, 3H), 1.36 (s, 9H)

4. Synthesis of 404-4

[1415] To a solution of NaOH (22.6 g, 566 mmol, 16 equiv) in water (220 mL) was added 404-3 (15 g, 35.4 mmol, 1 equiv). The mixture was stirred at 25°C for 2 hr. The reaction mixture was adjusted pH to 3 by 1N HCl. Then the mixture was filtered and the filter cake was concentrated in vacuum to afford 404-4 (14.7 g, crude) as a brown solid.

1H-NMR-404-4: (400 MHz, DMSO-d6) δ 13.80 (s, 1H), 8.20-8.15 (m, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.72-7.64 (m, 1H), 4.84 (d, J = 11.2 Hz, 1H), 4.61 (s, 1H), 3.97 (s, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 1.35 (s, 9H)

5. Synthesis of 404-5

[1416] HNO3 (8.16 mL, 123 mmol, 68% purity, 10 equiv) was added to water (124 mL) to afford the diluted HNO3 solution (1 M, 132 mL). To a solution of 404-4 (5 g, 12.3 mmol, 1 equiv) and NaNO2 (8.51 g, 123 mmol, 10 equiv) in EtOAc (20 mL) and water (100 mL) was added diluted HNO3 solution (1 M, 132 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 2 hr. The reaction was quenched by the addition of Sat.NaHCO3 (800 mL). The aqueous phase was extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum to afford 404-5 (3.55 g, crude) as a yellow oil.

1H-NMR-404-5: (400 MHz, CHLOROFORM-d) δ 8.13-8.07 (m, 2H), 8.03 (s, 1H), 7.56-7.45 (m, 2H), 4.24-4.19 (m, 2H), 3.85-3.74 (m, 1H), 3.63-3.57 (m, 1H), 3.56-3.44 (m, 2H), 3.37 (s, 3H), 1.35 (s, 9H)

6. Synthesis of 404-6

[1417] To a solution of 404-5 (3.55 g, 9.51 mmol, 1 equiv) in EtOH (50 mL) was added Fe (2.65 g, 47.5 mmol, 5 equiv) and NH4Cl (5.09 g, 95 mmol, 10 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered through celite, and the filtrate was concentrated in vacuum to give a residue. The residue was diluted with water (300 ml) and extracted with EtOAc (80 ml x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc /MeOH (10:1) to afford 404-6 (1.16 g, 35.5%) as a white solid.

1H-NMR-404-6: (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.48-6.27 (m, 3H), 5.10 (s, 2H), 4.29 (d, J = 10.8 Hz, 1H), 3.95 (d, J = 4.0 Hz, 1H), 3.71 (s, 1H), 3.65-3.58 (m, 1H), 3.48 (s, 1H), 3.33 (s, 4H), 1.36 (s, 9H)

7. Synthesis of 404-7

[1418] To a solution of 404-6 (1.16 g, 3.38 mmol, 1 equiv) and I-2 (967 mg, 3.38 mmol, 0.9 equiv) in MeOH (20 mL) was added AcOH (579 uL, 10.1 mmol, , 3 equiv), the mixture was stirred at 25 °C for 1 h under nitrogen atmosphere, then NaBH3CN (424 mg, 6.76 mmol, 2 equiv) was added to the mixture, the result mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuum to remove MeOH, the residue was diluted with Sat. NaHCO3 (200 mL), extracted with EtOAc (50 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to afford 404-7 (1.8 g, 86% yield) as a gray solid.

1H-NMR-404-7: (400 MHz, DMSO-d6) δ 8.69 (s, 1H), 8.36-8.27 (m, 1H), 8.03 (s, 1H), 7.01 (t, J = 7.8 Hz, 1H), 6.60-6.47 (m, 2H), 6.38 (d, J = 7.6 Hz, 1H), 6.21 (t, J = 5.6 Hz, 1H), 4.44 (d, J = 4.8 Hz, 2H), 4.31 (d, J = 10.8 Hz, 1H), 3.95 (s, 1H), 3.70-3.41 (m, 6H), 3.28 (s, 3H), 2.68 (s, 2H), 1.95-1.84 (m, 1H), 1.67-1.55 (m, 4H), 1.55-1.39 (m, 2H), 1.36 (s, 9H), 0.81 (d, J = 6.0 Hz, 3H)

8. Synthesis of 404-8

[1419] To a solution of 404-7 (0.9 g, 1.47 mmol, 1 equiv) in DCM (7 mL) was added pyridine (710 uL, 8.8 mmol, 6 equiv) and bis(trichloromethyl) carbonate (630 mg, 2.12 mmol, 1.45 equiv) at 0 °C. The mixture was stirred at 25 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat. NaHCO3 (100 mL), extracted with CH2Cl2 (50 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to afford 404-8 (926 mg, 98%) as a yellow solid.

1H-NMR-404-8: (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.81-7.72 (m, 2H), 7.65 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.57 (s, 1H), 4.05-3.92 (m, 1H), 3.71 (d, J = 5.6 Hz, 2H), 3.57-3.48 (m, 2H), 3.39 (s, 3H), 3.25 (s, 2H), 2.81-2.69 (m, 2H), 1.96-1.84 (m, 1H), 1.67-1.56 (m, 4H), 1.45 (d, J = 12.4 Hz, 1H), 1.36 (s, 9H), 0.82 (d, J = 6.0 Hz, 3H)

9. Synthesis of 404-9&10

The 404-8 (0.2 g) was purified by Chiral separation with the following conditions (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [Neu-ETOH];B%: 50%-50%,20min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 4.71; RT2 (min): 6.03) to afford 404-9 (50.3 mg, 89%) as a white solid and 404-10 (52.9 mg,95%) as a white solid.

1H-NMR-404-9: (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.81-7.73 (m, 2H), 7.65 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.37 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.07-3.94 (m, 1H), 3.77-3.64 (m, 2H), 3.57-3.46 (m, 2H), 3.38 (s, 2H), 3.24 (s, 3H), 2.80-2.70 (m, 2H), 1.89 (t, J = 10.4 Hz, 1H), 1.68-1.56 (m, 4H), 1.45 (d, J = 12.4 Hz, 1H), 1.36 (s, 9H), 1.23 (s, 1H), 0.83 (d, J = 6.0 Hz, 3H)

1H-NMR-404-10: (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.82-7.72 (m, 2H), 7.67 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 3.99 (d, J = 1.2 Hz, 1H), 3.70 (d, J = 5.5 Hz, 2H), 3.52 (s, 5H), 2.78 (s, 2H), 2.03-

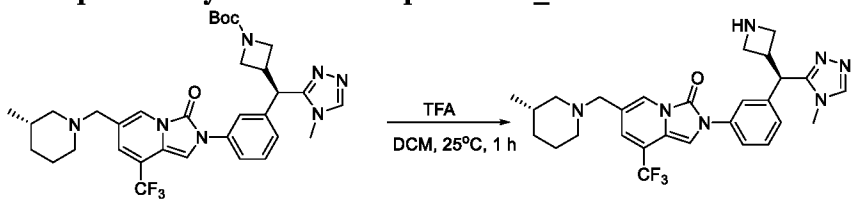
1.86 (m, 1H), 1.71-1.55 (m, 4H), 1.51-1.44 (m, 1H), 1.36 (s, 9H), 1.23 (s, 1H), 0.83 (d, J = 6.0 Hz, 3H)

10. Synthesis of 404

[1420] To a solution of 404-9 (50.3 mg, 78.6 umol, 1 equiv) in DCM (1 mL) was added HCl/dioxane (78.6 ul, 4 M, 4 equiv). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 75*30mm*3um; Mobile Phase A: water (NH4HCO3)), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 1% B to 25% B in 8 min; Wave Length: 220 nm; RT1 (min): 8.2) to afford 404 (9.6 mg, 22%) as a yellow solid.

MS-404: (ES, m/z): [M+H]+ 540.2. 1H-NMR-404: (400 MHz, METHANOL-d4) δ 8.54 (s, 1H), 8.47-8.39 (m, 1H), 7.81-7.63 (m, 3H), 7.57 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 16.4 Hz, 2H), 4.75 (d, J = 10.0 Hz, 1H), 4.28 (s, 1H), 4.14-3.87 (m, 4H), 3.56 (s, 2H), 3.52-3.44 (m, 3H), 3.13-2.96 (m, 2H), 2.23 (t, J = 10.8 Hz, 1H), 1.93 (t, J = 10.8 Hz, 1H), 1.85-1.65 (m, 4H), 1.07-0.96 (m, 1H), 0.92 (d, J = 6.0 Hz, 3H).

Example 400. Synthesis of Compound 404_P2



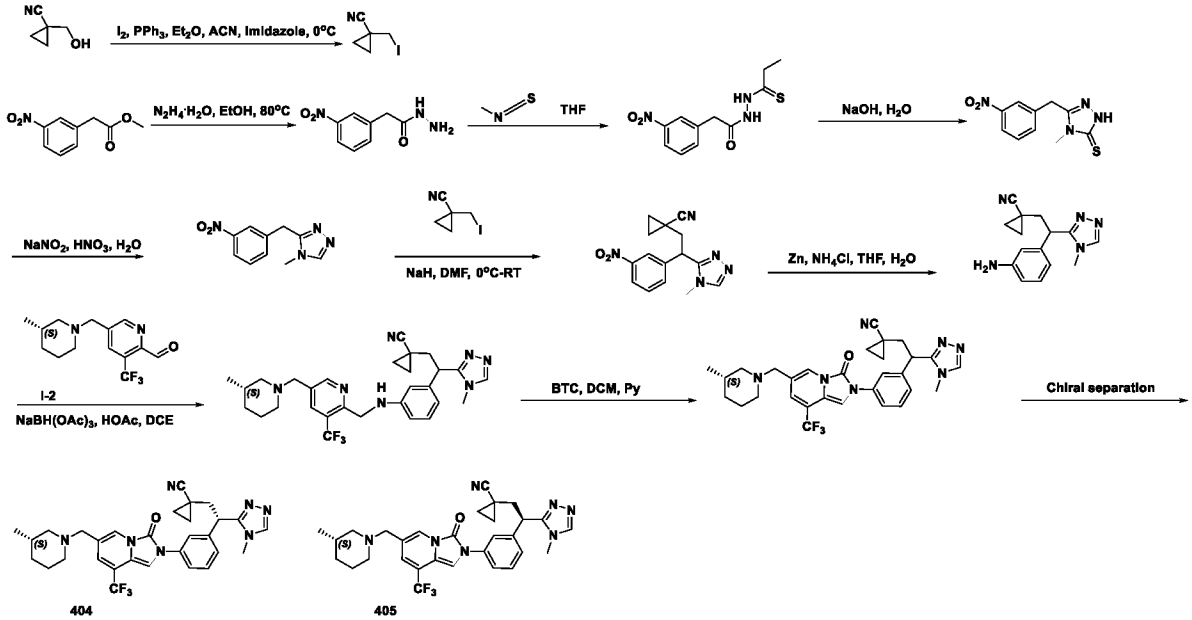
404-10 404_P2

1. Synthesis of 404

[1421] To a solution of 404-10 (42.9 mg, 67 umol, 1 equiv) in DCM (1 mL) was added HCl/dioxane (67 ul, 4 M, 4 equiv). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 75*30mm*3um; Mobile Phase A: water (NH4HCO3)), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 1% B to 25% B in 8 min; Wave Length: 220 nm; RT1 (min): 8.4) to afford 403 (6 mg, 15%) as a yellow solid.

MS-404: (ES, m/z): $[M+H]^+$ 540.1. ^{1}H-NMR-404: (400 MHz, METHANOL-d4) δ 8.51 (s, 1H), 8.46-8.39 (m, 1H), 7.86-7.64 (m, 3H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 16.8 Hz, 2H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.27 (t, *J* = 8.0 Hz, 1H), 4.16-3.85 (m, 4H), 3.55-3.49 (m, 2H), 3.46 (s, 3H), 3.11-2.90 (m, 2H), 2.27-2.11 (m, 1H), 1.89 (t, *J* = 10.0 Hz, 1H), 1.82-1.62 (m, 4H), 0.99 (d, *J* = 9.2 Hz, 1H), 0.92 (d, *J* = 6.0 Hz, 3H).

Example 401. Synthesis of Compound 404 and 405



1. Synthesis of 404-1

[1422] Into a 500 mL 3-necked round-bottom flask were added 1-(hydroxymethyl)cyclopropane-1-carbonitrile (10 g, 102.969 mmol, 1 equiv), Et_2O (150 mL),ACN (75 mL), imidazole (9.81 g, 144.157 mmol, 1.4 equiv), I_2 (39.20 g, 154.453 mmol, 1.5 equiv) and PPh_3 (35.11 g, 133.860 mmol, 1.3 equiv) at 0°C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Na_2SO_3 (500 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 404-1 (16 g, 75.06%) as a yellow oil.

2. Synthesis of 404-2

[1423] Into a 500 mL 3-necked round-bottom flask were added methyl 2-(3-nitrophenyl)acetate (30 g, 153.709 mmol, 1 equiv) and hydrazine hydrate (98%) (77.8 g, 1554.104 mmol, 10.11 equiv) in EtOH (300mL) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was quenched with water(200mL) at room temperature. The aqueous layer was extracted with EA (3 x300 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 404-2(28 g, 83.06%) as a white solid.

3. Synthesis of 404-3

[1424] Into a 1000mL 3-necked round-bottom flask were added methyl isothiocyanate (25.59

g, 350.040 mmol, 2.44 equiv), tetrahydrofuran (280 mL) and 404-2 (28 g, 143.459 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with Water (200mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3 x 20 mL). This resulted in 404-3 (35 g, 90.96%) as a yellow solid.

4. Synthesis of 404-4

[1425] Into a 500mL 3-necked round-bottom flask were added 1M NaOH (1300 mL, aq) and 404-3 (35 g, 130.46 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 5 with 1M HCl (1300 mL). The precipitated solids were collected by filtration and washed with water (3x10 mL). This resulted in 404-4 (30 g, 91.86%) as a yellow solid.

5. Synthesis of 404-5

[1426] To a stirred solution of 404-4 (30 g, 120 mmol, 1 equiv) and $NaNO_2$ (82.8 g, 1200 mmol, 10 equiv) in water (250mL) was added HNO_3 (75.6 g, 1200 mmol, 10 equiv) dropwise at 0°C. The resulting mixture was stirred for overnight at room temperature. The mixture neutralized to pH 7 with sat. $NaHCO_3$ (1000 mL). The aqueous layer was extracted with EA (3 x 500 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 404-5 (25.8g, 98.72%) as a yellow solid.

6. Synthesis of 404-6

[1427] Into a 250mL 3-necked round bottom flask were added 404-5 (5 g, 22.913 mmol, 1 equiv), DMF (60 mL) and NaH (0.66 g, 27.496 mmol, 1.2 equiv) at 0°C. The resulting mixture was stirred for 1 h at 0°C. To the above mixture was added 404-1 (4.74 g, 22.913 mmol, 1 equiv) at 0°C. The resulting mixture was stirred for additional 3 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (300 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (100:1) to afford 404-6 (420 mg, 6.18%) as a light yellow soild.

7. Synthesis of 404-7

[1428] Into a 30 mL sealed tube were added 404-6 (420 mg, 1.413 mmol, 1 equiv), THF (8 mL), NH_4Cl (377.91 mg, 7.065 mmol, 5 equiv), H_2O (2 mL) and Zn (1385.73 mg, 21.195 mmol, 15 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered; the filter cake was washed with THF (3 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-

TLC (DCM/MeOH=15:1) to afford 404-7 (300mg, 79.45%) as a light yellow solid.

8. Synthesis of 404-8

[1429] Into a 50 mL round bottom flask were added 404-7 (300 mg, 1.122 mmol, 1 equiv), DCE (3 mL), I-2 (321.28 mg, 1.122 mmol, 1 equiv) and $NaBH(OAc)_3$ (475.67 mg, 2.244 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with DCM/MeOH=10:1 (3 x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=15:1) to afford 404-8 (300 mg, 49.72%) as a yellow oil.

9. Synthesis of 404-9

[1430] Into a 100 mL round-bottom flask were added 404-8 (300 mg, 0.558 mmol, 1 equiv), DCM (12 mL) and pyridine (264.83 mg, 3.348 mmol, 6 equiv) and triphosgene (66.23 mg, 0.223 mmol, 0.4 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched by the addition of sat. $NaHCO_3$ (50 mL) at room temperature. The aqueous layer was extracted with DCM (3 x 20 mL). The residue was purified by Prep-TLC (DCM/MeOH 15:1) to afford 404-9 (190 mg, 60.41%) as a yellow soild.

10. Synthesis of 404-0

[1431] The 404-9 (190 mg, 0.320 mmol, 1 equiv, 95%) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 5.09; RT2(min): 6.74; The first peak was the 404; the second peak was 405. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.8 mL; Number of Runs: 6) to afford 404 (46.6 mg, 24.53%) as a yellow solid and 405 (55.9 mg, 29.42%) as a yellow solid.

LC-MS-404 (ES, *m/z*): $[M+H]^+$ 564

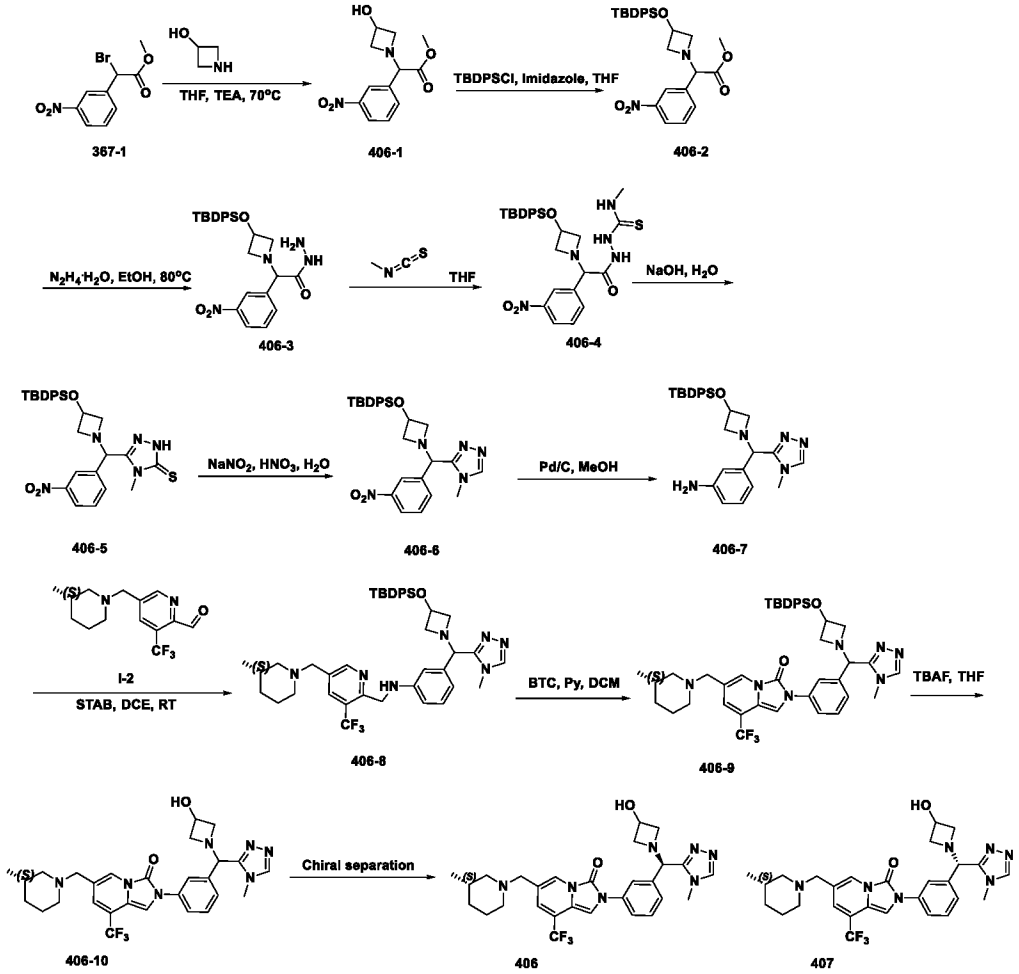
H-NMR-404 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 0.65-0.70(m, 1H), 0.96-1.00(m, 4H), 1.09-1.11(m, 2H), 1.20-1.23(m, 1H), 1.32-1.48(m, 1H), 1.58-12.63(m, 4H), 1.88-1.92(m, 1H), 2.24-2.30(m, 1H), 2.50-2.57(m, 1H), 2.73-2.75(m, 2H), 3.25-3.33(m, 2H), 3.51(s, 3H), 4.48-4.52(m, 1H), 7.01(s, 1H), 7.30-7.33(m, 2H), 7.47-7.51(m, 1H), 7.66(s, 1H), 7.77-7.80(m, 2H), 8.39(s, 1H).

LC-MS-405 (ES, *m/z*): $[M+H]^+$ 564

H-NMR-405 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 0.65-0.70(m, 1H), 0.99-1.02(m, 4H),1.09-1.11(m,2H), 1.32-1.48(m, 1H), 1.58-1.65(m, 1H), 1.85-1.90(m, 4H), 1.90-2.08(m, 1H), 2.24-2.30(m, 1H), 2.50-2.57(m, 1H), 2.73-2.75(m, 2H), 3.25-3.44(m, 2H),3.51(s, 3H),

4.48-4.52(m, 1H), 7.01(s, 1H), 7.30-7.33(m, 2H), 7.47-7.51(m, 1H), 7.66(s, 1H), 7.77-7.80(m, 2H), 8.39(s, 1H).

Example 402. Synthesis of Compound 406 and 407



367-1 406-1 406-2 406-3 406-4 406-5 406-6 406-7 406-8 406-9 406-10 406 407

1. Synthesis of 406-1

[1432] To a stirred solution of 367-1 (5 g, 18.244 mmol, 1 equiv), THF (50 mL), and azetidin-3-ol (1.60 g, 21.893 mmol, 1.2 equiv) was added TEA (3.69 g, 36.488 mmol, 2 equiv). The resulting mixture was stirred for overnight at 70°C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (1x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford 406-1 (3.4 g, 70.00%) as a yellow oil.

2. Synthesis of 406-2

[1433] To a stirred solution of 406-1 (3.4 g, 12.770 mmol, 1 equiv), THF (10 mL) and

Imidazole (2.61 g, 38.310 mmol, 3 equiv) was added TBDPSCl (14.04 g, 51.080 mmol, 4 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (20mL) at room temperature. The aqueous layer was extracted with EtOAc (1x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford 406-2 (4.2 g, 65.17%) as a yellow oil.

3. Synthesis of 406-3

[1434] To a stirred solution of 406-2 (4 g, 7.926 mmol, 1 equiv) and EtOH (40 mL) was added $NH_2NH_2.H_2O$ (3.17 g, 63.408 mmol, 8 equiv). The resulting mixture was stirred for overnight at 80°C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (1x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 406-3 (3.6 g, 90.00%) as a yellow oil.

4. Synthesis of 406-4

[1435] To a stirred solution of 406-3 (3.6 g, 7.133 mmol, 1 equiv) and tetrahydrofuran (50 mL) was added methyl isothiocyanate (1.30 g, 17.832 mmol, 2.5 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum and wash with water (50 mL). The precipitated solids were collected by filtration and washed with water (1x100 mL). The resulting solid was dried under vacuum. This resulted in 406-4 (3.7 g, 89.77%) as a yellow solid.

5. Synthesis of 406-5

[1436] Into a 100 mL 3-necked round-bottom flask were added 406-4 (3.7 g, 6.404 mmol, 1 equiv) and NaOH (aq.1mol/L) (1.02 g, 25.616 mmol, 4 equiv). The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 4 with conc. HCl (1 M, 44 mL). The aqueous layer was extracted with EtOAc (1x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 406-5 (3.3 g, 92.06%) as a yellow solid.

6. Synthesis of 406-6

[1437] To a stirred mixture of 406-5 (3.3 g, 5.895 mmol, 1 equiv) and $NaNO_2$ (aq.1mol/L, 4.07 g, 58.950 mmol, 10 equiv) in EtOAc (60 mL) was added HNO_3 (aq.1mol/L,3.71 g, 58.832 mmol, 10 equiv) dropwise at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 8 with saturated $NaHCO_3$ (aq. 40 mL). The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture

was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 406-6 (2.6 g, 83.57%) as a yellow solid.

7. Synthesis of 406-7

[1438] To a solution of 406-6 (2.6 g, 4.927 mmol, 1 equiv) in 30 mL MeOH was added Pd/C (10%, 0.52 g) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product 406-7 (2.4 g, 97.87%) as a yellow solid was used in the next step directly without further purification.

8. Synthesis of 406-8

[1439] To a stirred solution of 406-7 (2.2 g, 4.420 mmol, 1 equiv) and DCE (25 mL) was added I-2 (1.52 g, 5.304 mmol, 1.2 equiv) room temperature. The resulting mixture was stirred for overnight at room temperature. To the above mixture was added STAB (1.87 g, 8.840 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq. 30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (1x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 406-8 (1.7 g, 50.08%) as a yellow oil.

9. Synthesis of 406-9

[1440] To a stirred solution of 406-8 (1.6 g, 2.083 mmol, 1 equiv), DCM (20 mL) and pyridine (1.65 g, 20.830 mmol, 10 equiv) was added triphosgene (0.22 g, 0.729 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 15min at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10/1) (2x10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to afford 406-9 (410 mg, 24.79%) as a yellow solid.

10. Synthesis of 406-10

[1441] To a stirred solution of 406-9 (400 mg, 0.504 mmol, 1 equiv) and THF (5 mL) was added TBAF (197.58 mg, 0.756 mmol, 1.5 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (5mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting

mixture was concentrated under vacuum. The crude product was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, A: water (10mmol/L NH_4HCO_3), B: CH_3CN, 20% B to 80% B gradient in 20 min; detector, UV 254 nm. This resulted in product. The residue was dried by lyophilization to afford 406-10 (120 mg, 42.87%) as a yellow oil.

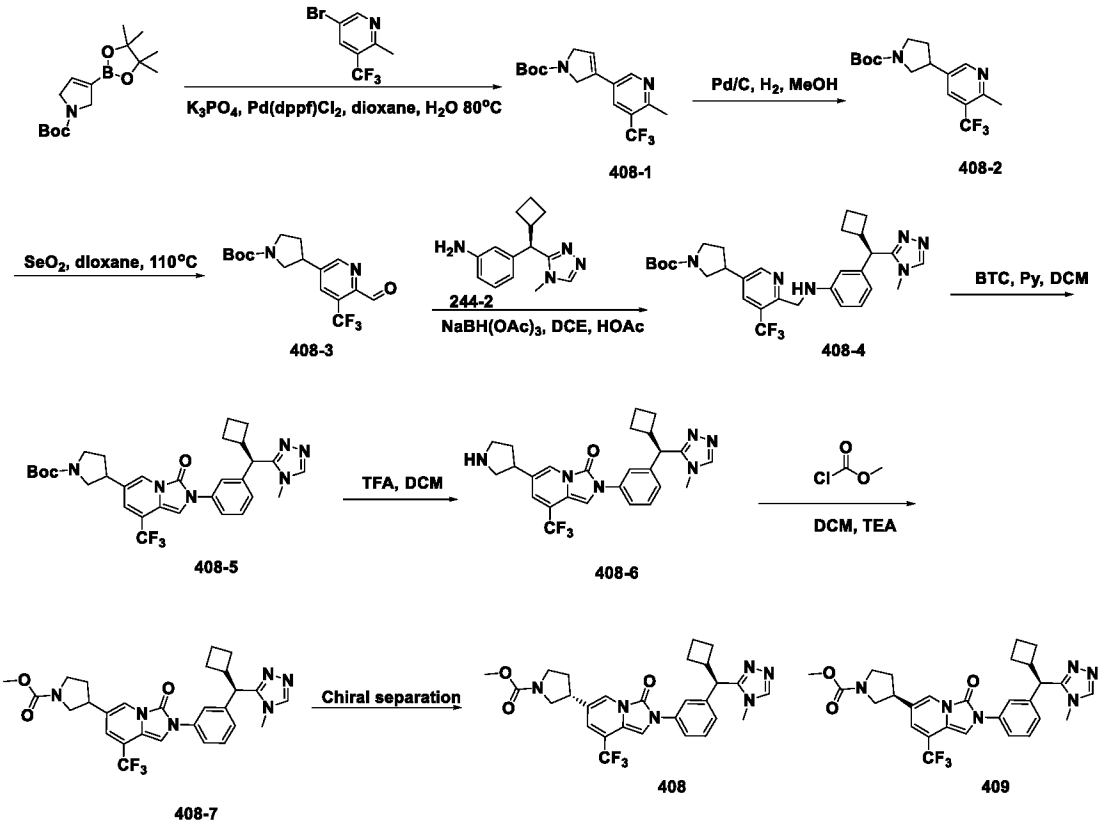
11. Synthesis of 406 and 407

[1442] The 406-10 (120 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: IPA: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 15 min; Wave Length: 220/254 nm; RT1(min): 8.82; RT2(min): 11.41; The first peak is 407; the second peak is 406; Sample Solvent: IPA: DCM=1: 1--HPLC; Injection Volume: 0.6 mL; Number of Runs: 5) to afford crude prodcut. The crude product (21 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 15% B in 7 min; Wave Length: 254; 220 nm; RT1(min): 5.65;) to afford 407 (13.0 mg, 9.95%) as a yellow solid and 406 (11.6 mg, 8.89%) as a yellow solid.

LC-MS-407 (ES, *m/z*): $[M+H]^+$ 556. H-NMR-407 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.82-0.89 (m, 4H), δ1.41-1.50 (m, 1H), δ1.58-1.63 (m, 4H), δ1.87-1.92 (t, 1H), δ2.67-2.78 (m, 2H), δ2.80-2.87 (m, 1H), δ2.87-2.89 (t, 1H), δ3.25 (s, 2H), δ3.38 (s, 1H), δ3.57 (s, 4H), δ4.25-4.28 (t, 1H), δ4.97 (s, 1H), δ5.40 (s, 1H), δ7.01 (s, 1H), δ7.33-7.36 (m, 2H), δ7.46-7.50 (t, 1H), δ7.66 (s, 2H), δ7.95 (s, 1H), δ8.21 (s, 1H), δ8.32 (s, 1H).

LC-MS-406 (ES, *m/z*): $[M+H]^+$ 556. H-NMR-406 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.82-0.86 (m, 4H), δ1.41-1.50 (m, 1H), δ1.58-1.66 (m, 4H), δ1.87-1.92 (t, 1H), δ2.73-2.80 (m, 2H), δ2.81-2.83 (t, 1H), δ2.86-2.89 (t, 1H), δ3.22 (s, 2H), δ3.38-3.42 (m, 1H), δ3.52-3.77 (m, 4H), δ4.24-4.28 (t, 1H), δ4.97 (s, 1H), δ7.01 (s, 1H), δ7.32-7.36 (m, 2H), δ7.46-7.50 (t, 1H), δ7.67 (s, 2H), δ7.95 (s, 1H), δ8.20 (s, 1H), δ8.33 (s, 1H).

Example 403. Synthesis of Compound 408 and 409



1. Synthesis of 408-1

[1443] Into a 250 mL 3-necked round-bottom flask were added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate (5 g, 16.938 mmol, 1 equiv), dioxane (50 mL), H_2O (12.5 mL), 5-bromo-2-methyl-3-(trifluoromethyl)pyridine (4.07 g, 16.938 mmol, 1 equiv) , K_3PO_4 (10.79 g, 50.814 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (1.24 g, 1.694 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x80 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 408-1 (5 g, 89.91%) as a grey solid.

2. Synthesis of 408-2

[1444] To a solution of 408-1 (5 g, 15.228 mmol, 1 equiv) in 60 mL MeOH was added Pd/C (10%, 1.62 g) in a pressure tank. The mixture was hydrogenated at room temperature under 30 psi of hydrogen pressure for 2 h, filtered through a Celite pad and concentrated under reduced pressure to afford 408-2 (4.2 g, 83.49%) as a light brown solid.

3. Synthesis of 408-3

[1445] Into a 250 mL 3-necked round-bottom flask were added 408-2 (4 g, 12.108 mmol, 1 equiv), dioxane (50 mL) and SeO_2 (6.72 g, 60.540 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 408-3 (1.1 g, 26.38%) as a light yellow solid.

4. Synthesis of 408-4

[1446] Into a 100 mL 3-necked round-bottom flask were added 408-3 (1 g, 2.904 mmol, 1 equiv), DCE (15 mL), 244b (0.70 g, 2.904 mmol, 1 equiv), HOAc (0.17 g, 2.904 mmol, 1 equiv) and $NaBH(OAc)_3$ (1.23 g, 5.808 mmol, 2 equiv) at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 408-4 (1 g, 60.34%) as a light yellow solid.

5. Synthesis of 408-5

[1447] Into a 100 mL 3-necked round-bottom flask were added 408-4 (1 g, 1.752 mmol, 1 equiv), DCM (15 mL), pyridine (0.83 g, 10.512 mmol, 6 equiv) and triphosgene (0.21 g, 0.701 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (15 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (80:1) to afford 408-5 (800 mg, 76.51%) as a light yellow solid.

6. Synthesis of 408-6

[1448] Into a 100 mL round-bottom flask were added 408-5 (780 mg, 1.307 mmol, 1 equiv), DCM (9 mL) and TFA (3 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 408-6 (500 mg, 77.03%) as a light yellow solid.

7. Synthesis of 408-7

[1449] Into a 100 mL round-bottom flask were added 408-6 (230 mg, 0.463 mmol, 1 equiv), DCM (5 mL), TEA (140.62 mg, 1.389 mmol, 3 equiv) and methyl chloroformate (43.77 mg, 0.463 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 2 h at room

temperature. The reaction was quenched by the addition of water (15 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 408-7 (250 mg, 97.32%) as a light yellow solid.

8. Synthesis of 408 and 409

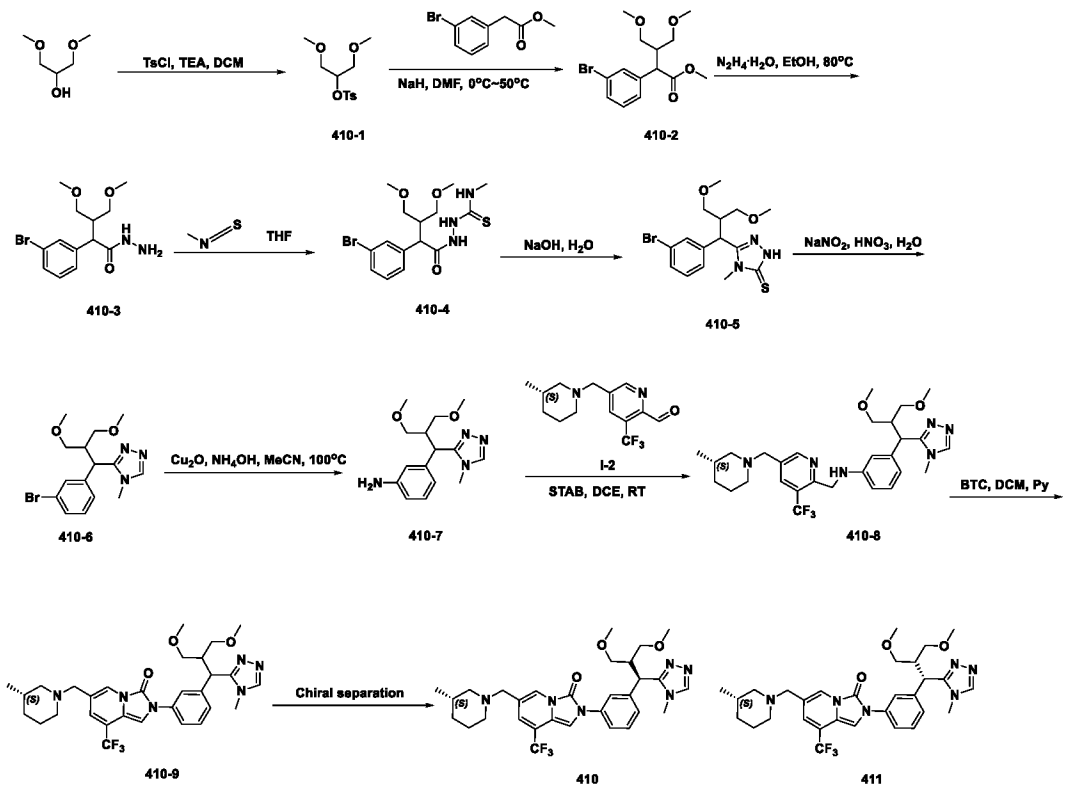
[1450] The 408-7 (250 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.97; RT2(min): 10.97; The first peak was the 408; the second peak was 409. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.3 mL; Number of Runs: 15) to afford 408 (101.4 mg, 40.56%) as a light yellow solid and 409 (94.5 mg, 37.80%) as a light yellow solid..

LC-MS-408 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-408 1H NMR (300 MHz, DMSO-d6 *ppm*) δ1.60-1.89 (m, 5H), 1.90-2.09 (m, 1H), 2.06-2.13 (m, 2H), 3.18-3.33 (m, 4H), 3.43-3.48 (m, 3H), 3.50 (s, 1H), 3.52-3.60 (m, 3H), 3.66-3.70 (m, 1H), 4.25-4.27 (d, 1H), 7.18-7.20 (d, 2H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.60 (s, 1H), 7.68-7.70 (m, 1H), 7.74 (s, 1H), 8.32 (s, 1H).

LC-MS-409 (ES, *m/z*): $[M+H]^+$ 555

H-NMR-409 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 1.60-1.89 (m, 5H), 1.90-2.09 (m, 1H), 2.06-2.13 (m, 2H), 3.18-3.32 (m, 4H), 3.43-3.48 (m, 3H), 3.50 (s, 1H), 3.52-3.60 (m, 3H), 3.66-3.70 (m, 1H), 4.25-4.27 (d, 1H), 7.18-7.20 (d, 2H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.60 (s, 1H), 7.68-7.70 (m, 1H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 404. Synthesis of Compound 410 and 411



1. Synthesis of 410-1

[1451] To a stirred mixture of glycerin dimethyl ether (30 g, 249.692 mmol, 1 equiv) and TsCl (95.20 g, 499.384 mmol, 2 equiv) in DCM (300 mL) was added TEA (75.80 g, 749.076 mmol, 3 equiv) dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (500 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 410-1 (20 g, 29.20%) as a white solid.

2. Synthesis of 410-2

[1452] To a stirred mixture of methyl 2-(3-bromophenyl)acetate (25.05 g, 109.354 mmol, 1.50 equiv) and DMF (216.21 mL, 2793.720 mmol, 38.32 equiv) was added NaH (3.50 g, 145.810 mmol, 2 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C under nitrogen atmosphere. To the above mixture was added 410-1 (20 g, 72.905 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at 50°C. The mixture was allowed to cool down to room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (1000mL) at room temperature. The resulting mixture was extracted with EtOAc (4 x300 mL). The combined organic layers were concentrated

under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 55 min; detector, UV 220 nm. This resulted in methyl 4102-2 (7 g, 28.99%) as a yellow oil.

3. Synthesis of 410-3

[1453] To a stirred mixture of methyl 410-2 (7 g, 21.135 mmol, 6.9 equiv) in EtOH (70 mL) was added $NH_2NH_2.H_2O$ (1.53 g, 30.630 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 410-3 (6.1 g, 87.14%) as a yellow solid.

4. Synthesis of 410-4

[1454] To a stirred mixture of 410-3 (3 g, 9.058 mmol, 1 equiv) and tetrahydrofuran (40 mL) was added methyl isothiocyanate (3.31 g, 45.290 mmol, 5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (4x40 mL). The resulting mixture was concentrated under vacuum. This resulted in 410-4 (2.6 g, 71.00%) as a yellow solid.

5. Synthesis of 410-5

[1455] To a stirred mixture of NaOH (1.29 g, 32.219 mmol, 5.01 equiv) in H_2O (100 mL) was added 410-4 (2.6 g, 6.431 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 7 with HCl (1M). The aqueous layer was extracted with CH_2Cl_2 (4x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with PE: EA=20:1 (25 mL). This resulted in 410-5 (2.1 g, 84.53%) as a white solid.

6. Synthesis of 410-6

[1456] To a stirred mixture of 410-6 (2.1 g, 5.436 mmol, 1 equiv) and $NaNO_2$ (1.13 g, 16.308 mmol, 3 equiv) in H_2O (40 mL) was added HNO_3 (20 mL, 1mol/L) dropwise at room temperature. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (5x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 410-6 (1.5 g, 77.89%) as a white solid.

7. Synthesis of 410-7

[1457] Into a pressure tank reactor was added 410-6 (1.45 g, 4.093 mmol, 1 equiv) and Cu_2O

(0.59 g, 4.093 mmol, 1 equiv) in NH_4OH (0.75 mL) and MeCN (0.75 mL) at room temperature. The resulting mixture was stirred overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 410-7 (600 mg, 50.48%) as a brown solid.

8. Synthesis of 410-8

[1458] To a stirred mixture of 410-7 (600.00 mg, 2.066 mmol, 1 equiv) and I-2 (650.75 mg, 2.273 mmol, 1.1 equiv) in DCE (10 mL) was added STAB (875.88 mg, 4.132 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 410-8 (900 mg, 77.68%) as a yellow solid.

9. Synthesis of 410-9

[1459] To a stirred mixture of 410-8 (600 mg, 1.070 mmol, 1 equiv) and Pyridine (507.90 mg, 6.420 mmol, 6 equiv) in DCE (6 mL) was added Triphosgene (123.85 mg, 0.417 mmol, 0.39 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 410-9 (360 mg, 57.34%) as a yellow solid.

10. Synthesis of 410 and 411

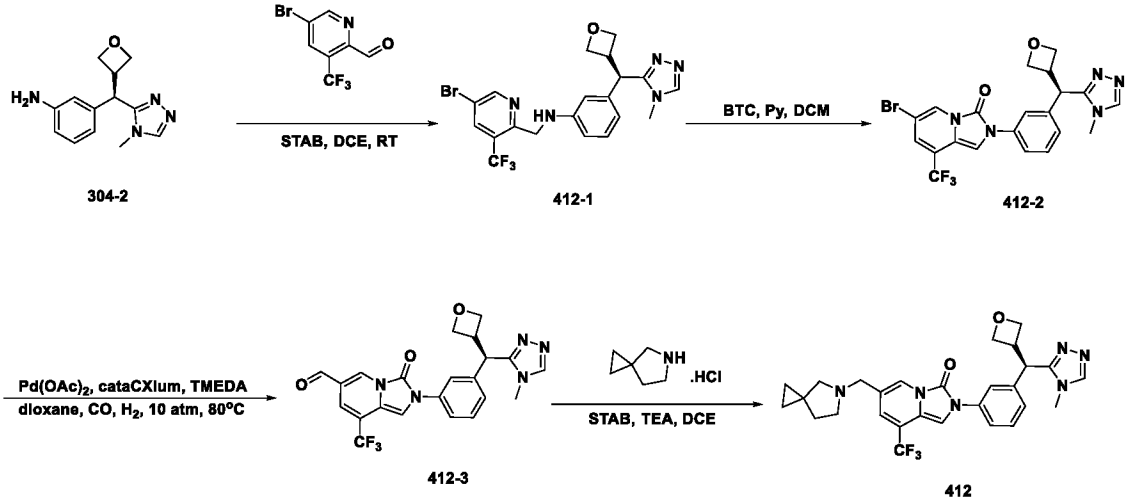
[1460] The 410-9 (300mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.14; RT2(min): 13.09; the first peak is 411; the second peak is 410) to afford 410 (128.8 mg, 42.93%) as a yellow solid.

LC-MS-411: (ES, *m/z*): $[M+H]^+$ 558. H-NMR-411: (400 MHz, DMSO-d_6, δ *ppm*): 0.80-0.91 (m, 4H), 1.44-1.98 (m, 6H), 2.74-2.83 (m, 3H), 3.10-3.14 (m, 1H), 3.17 (s, 3H), 3.24 (s, 3H), 3.26-3.30 (m, 3H), 3.33-3.40 (m, 2H), 3.41 (s, 3H), 4.26-4.29 (d, 1H), 7.02 (s, 1H), 7.32-7.34 (m, 2H), 7.45-7.48 (m, 1H), 7.66-7.70 (m, 1H), 7.74-7.76 (d, 1H), 7.83 (s, 1H), 8.34 (s, 1H).

LC-MS-410: (ES, *m/z*): $[M+H]^+$ 558. H-NMR-410: (400 MHz, DMSO-d_6, δ *ppm*): 0.80-0.91 (m, 4H), 1.44-1.98 (m, 6H), 2.74-2.83 (m, 3H), 3.10-3.14 (m, 1H), 3.17 (s, 3H), 3.24 (s, 3H),

3.26-3.30 (m, 3H), 3.33-3.40 (m, 2H), 3.41 (s, 3H), 4.26-4.29 (d, 1H), 7.02 (s, 1H), 7.32-7.34 (m, 2H), 7.45-7.48 (m, 1H), 7.66-7.70 (m, 1H), 7.74-7.76 (d, 1H), 7.83 (s, 1H), 8.34 (s, 1H).

Example 405. Synthesis of Compound 412



1. Synthesis of 412-1

[1461] To a stirred solution of 304-2 (3.4 g, 13.917 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (4.24 g, 16.700 mmol, 1.2 equiv) in DCE (100 mL) was added STAB (5.90 g, 27.834 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (300 mL) at room temperature. The aqueous layer was extracted with DCM/MeOH=10:1(3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 412-1 (4 g, 57.80%) as a Brown yellow solid.

2. Synthesis of 412-2

[1462] To a stirred solution of 412-2 (4 g, 8.294 mmol, 1 equiv) and Pyridine (6.56 g, 82.933 mmol, 10.00 equiv) in DCM (100 mL) was added Triphosgene (0.98 g, 3.318 mmol, 0.40 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (200 mL) at room temperature. The aqueous layer was extracted with DCM (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MTBE (100 mL). This resulted in 412-2 (3.5 g, 75.55%) as a reddish brown solid.

3. Synthesis of 412-3

[1463] To a solution of 412-2 (3.4 g, 6.689 mmol, 1 equiv) in dioxane (100 mL) was added $Pd(OAc)_2$ (0.15 g, 0.669 mmol, 0.1 equiv) and bis(adamantan-1-yl)(butyl)phosphane (0.48 g, 1.338 mmol, 0.2 equiv) in a pressure tank. The mixture was purged with nitrogen for 3min

and then was pressurized to 15atm with CO/H_2=1:1 at 80°C for overnight. The reaction mixture was cooled to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 412-2 (1.1 g, 32.36%) as a reddish brown solid.

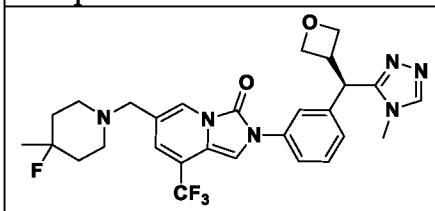
4. Synthesis of 412

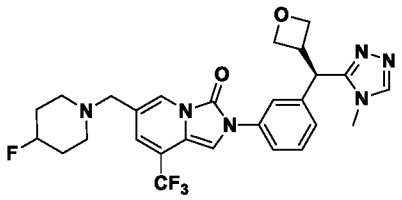
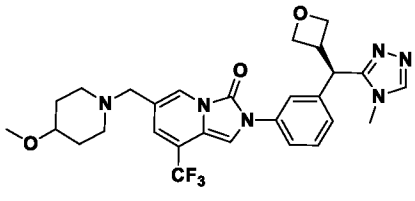
[1464] To a stirred solution of 412-3 (250 mg, 0.547 mmol, 1 equiv) and 5-azaspiro[2.4]heptane hydrochloride (219.09 mg, 1.641 mmol, 3 equiv) in DCE (5 mL) was added TEA (165.92 mg, 1.641 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (231.67 mg, 1.094 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 46% B in 8 min; Wave Length: 220 nm; RT1(min): 7.07) to afford 412 (24.9 mg, 8.33%) as a yellow solid.

LC-MS-412: (ES, *m/z*): $[M+H]^+$ 539. H-NMR-412: (400 MHz, DMSO-d6, δ *ppm*): 0.41-0.63 (d, 4H), 1.71-1.81 (m, 2H), 2.47-2.49 (m, 2H), 2.67-2.71 (m, 2H), 3.38-3.41 (m, 5H), 3.89-3.95 (m, 1H), 4.27-4.30 (m, 1H), 4.48-4.49 (d, 2H), 4.72-4.80 (m, 2H), 7.04 (s, 1H), 7.17-7.19 (d, 1H), 7.37 (s, 1H), 7.45-7.49 (m, 1H), 7.67 (s, 1H), 7.75-7.76 (m, 2H), 8.37 (s, 1H).

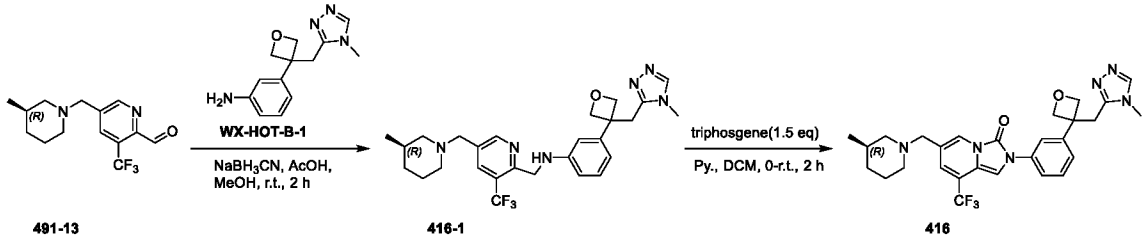
Example 406. Synthesis of Compounds 413-415

[1465] The following compounds were prepared in a similar manner to 412-0, replacing and 5-azaspiro[2.4]heptane hydrochloride with the appropriate amine.

Compound	Yield and Characterization Data
 413	8.88% yield (ES, *m/z*): $[M+H]^+$ 559 (400 MHz, DMSO-d_6, δ *ppm*): 1.28-1.37 (m, 4H), 1.66-1.70 (m, 1H), 1.70-1.81 (m, 3H), 2.24-2.29 (m, 2H), 2.59-2.62 (m, 2H), 3.30-3.32 (m, 2H), 3.38 (s, 3H), 3.89-3.95 (m, 1H), 4.27-4.30 (m, 1H), 4.48-4.51 (d, 2H), 4.72-4.81 (m, 2H), 7.01 (s, 1H), 7.17-7.19 (d, 1H), 7.37 (d, 1H), 7.45-7.49 (m,1H), 7.67 (s, 1H), 7.75-7.77 (m, 2H), 8.37 (s, 1H).

 414	14.01% yield (ES, *m/z*): $[M+H]^+$ 545 (400 MHz, DMSO-d_6, δ *ppm*): 1.61-1.79 (m, 2H), 1.80-1.91 (m, 2H), 2.34-2.36 (m, 2H), 2.50-2.54 (m, 2H), 3.30-3.32 (m, 2H), 3.38 (s, 3H), 3.89-3.95 (m, 1H), 4.27-4.30 (m, 1H), 4.48-4.51 (d, 2H), 4.62-4.81 (m, 3H), 7.01 (s, 1H), 7.17-7.19 (d, 1H), 7.37 (d, 1H), 7.45-7.49 (m,1H), 7.67 (s, 1H), 7.75-7.77 (m, 2H), 8.37 (s, 1H).
 415	24.91% yield (ES, *m/z*): $[M+H]^+$ 557 (400 MHz, DMSO-d6, δ *ppm*): 1.35-1.47 (m, 2H), 1.74-1.89 (m, 2H), 2.05-2.15 (m, 2H), 2.60-2.66 (m, 2H), 3.09-3.22 (m, 4H), 3.27 (s, 2H), 3.38 (s, 3H), 3.89-3.93 (m, 1H), 4.27-4.30 (m, 1H), 4.48-4.49 (d, 2H), 4.72-4.80 (m, 2H), 7.00 (s, 1H), 7.17-7.18 (d, 1H), 7.37 (s, 1H), 7.45-7.48 (m, 1H), 7.65 (s, 1H), 7.75-7.76 (m, 2H), 8.37 (s, 1H).

Example 407. Synthesis of Compound 416



491-13 416-1 416

1. Synthesis of 416-1

To a solution of 491-13 (554 mg, 2.27 mmol, 1 equiv) and 491-13 (520 mg, 1.82 mmol, 0.8 equiv) in MeOH (10 mL) was added HOAc (130 uL, 2.27 mmol, 1 equiv). The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. Then $NaBH_3CN$ (142 mg, 2.27 mmol, 1 equiv) was added. The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The mixture adjusted pH to 8 by Sat.$NaHCO_3$ (50 ml) and extracted with EtOAc (20 ml x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to afford 416-1 (320 mg, 27%) as a yellow solid.

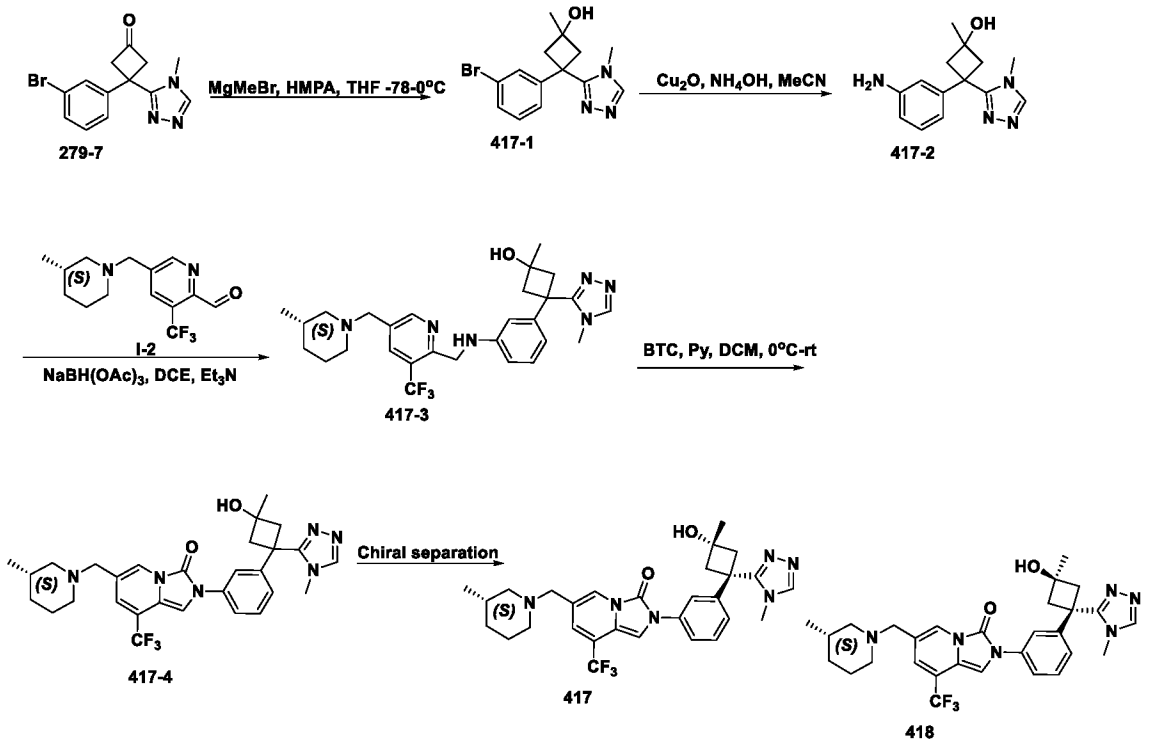
2. Synthesis of 416

To a solution of 416-1 (0.13 g, 252 umol, 1 equiv) in DCM (10 mL) was added Py (122 uL, 1.52 mmol, 6 equiv) and bis(trichloromethyl) carbonate (150 mg, 505 umol, 2 equiv) at 0 °C. The mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.$NaHCO_3$ (100 mL), extracted with DCM (50 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in

vacuum. The residue was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 150*40mm*10um; Mobile Phase A: water (NH_3H_2O+NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 35% B in 8 min; Wave Length: 220 nm; RT1 (min): 7.2) to afford 416 (32 mg, 24%) as a yellow solid.

MS-416: (ES, m/z): $[M+H]^+$ 541.2. ^{1}H-NMR-416: (400 MHz, METHANOL-d4) δ 8.21 (s, 1H), 7.68-7.62 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 1.6 Hz, 1H), 7.12 (d, J = 4.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 1H), 5.09 (s, 5H), 3.68 (s, 2H), 2.96 (s, 3H), 2.92-2.84 (m, 2H), 2.03-1.94 (m, 1H), 1.79-1.57 (m, 6H), 1.01-0.93 (m, 1H), 0.91 (d, J = 5.6 Hz, 3H).

Example 408. Synthesis of Compound 417 and 418



1. Synthesis of 417-1

To a stirred solution of 279-7 (10 g, 32.66 mmol, 1.0 equiv) and MeMgBr (11.7 g, 97.98 mmol, 3.0 equiv) in THF (100 mL) was added HMPA (17.6 g, 97.98 mmol, 3.0 equiv) at -78°C. The resulting mixture was stirred for 3 h at -78°C. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=20:1 to afford 417-1 (4.5 g, 43%) as an off-white solid.

2. Synthesis of 417-2

To a stirred solution of 417-1 (2.4 g, 7.44 mmol, 1.0 equiv) and Cu_2O (0.43 g, 2.98 mmol, 0.4 equiv) in MeCN (15 mL) was added $NH_3.H_2O$ (15 mL) at room temperature. The resulting mixture was stirred for overnight at 100 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH=20:1 to afford 417-2 (1.6 g, 77 %) as a colorless oil.

3. Synthesis of 417-3

To a stirred solution of 417-2 (1 g, 3.87 mmol, 1.0 equiv) and I-2 (1.1 g, 3.87 mmol, 1.0 equiv) in DCE (10 mL) was added Et_3N (392 mg, 3.87 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1.6 g, 7.74 mmol, 2.0 equiv). The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 417-3 (630 mg, 31%) as an off-white solid.

4. Synthesis of 417-4

To a stirred solution of 417-3 (630 mg, 1.19 mmol, 1.0 equiv) and pyridine (565 mg, 7.15 mmol, 6.0 equiv) in DCM (7 mL) was added triphosgene (124 mg, 0.41 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 417-4 (220 mg, 33%) as a yellow solid.

5. Synthesis of 417 and 418

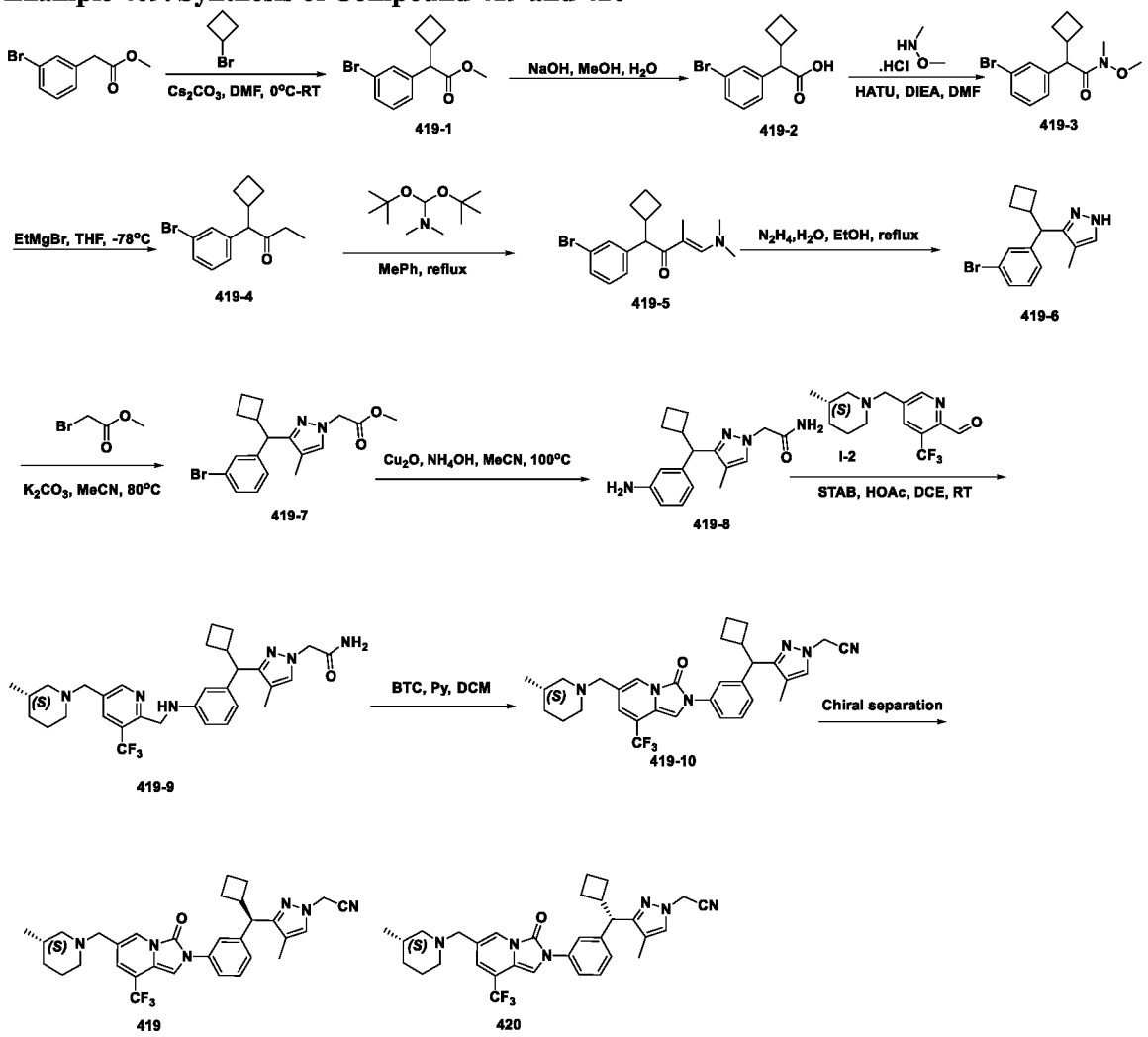
The 417-4 (220 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 11 min; Wave Length: 220/254 nm; RT1(min): 5.24; RT2(min): 7.90; The first peak was the 417-0; the second peak was 418-0. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 1 mL; Number of Runs: 4) to afford 417 (54 mg, 25%) as a yellow solid and 418 (54 mg, 25%) as a yellow solid.

LC-MS-417: (ES, m/z): $[M+H]^+$ 555. H-NMR-417 (400 MHz, *DMSO*, δ ppm): 0.85 (s, 4H), 1.12 (s, 3H), 1.40-1.50 (m, 1H), 1.58-1.68 (m, 4H), 1.87-1.92 (t, 1H), 2.74-2.77 (m, 2H), 2.92-2.95 (m, 2H), 3.05-3.08 (m, 2H), 3.17-3.25 (m, 2H), 3.32 (s, 3H), 5.10-5.12 (d, 1H),

7.00 (s, 1H), 7.34-7.36 (m, 2H), 7.47-7.51 (t, 1H), 7.60-7.62 (d, 1H), 7.66 (s, 1H), 7.91 (s, 1H), 8.24 (s, 1H).

LC-MS-418: (ES, m/z): [M+H] + 555. H-NMR-418: (400 MHz, DMSO, δ ppm): 0.82-0.85 (m, 4H), 1.13 (s, 3H), 1.40-1.49 (m, 1H), 1.58-1.66 (m, 4H), 1.86-1.91 (t, 1H), 2.72-2.85 (m, 4H), 3.03-3.10 (m, 2H), 3.16-3.24 (m, 2H), 3.32 (s, 3H), 5.08-5.12 (d, 1H), 7.00 (s, 1H), 7.14-7.16 (d, 1H), 7.32 (s, 1H), 7.45-7.49 (t, 1H), 7.60-7.70 (m, 3H), 8.28 (s, 1H).

Example 409. Synthesis of Compound 419 and 420



1. Synthesis of 419-1

A solution of methyl 2-(3-bromophenyl)acetate (100 g, 436.542 mmol, 1 equiv) in DMF (1000 mL) was treated with Cs_2CO_3 (166.17 g, 2182.710 mmol, 5 equiv) for 3h at 0°C under nitrogen atmosphere followed by the addition of bromocyclobutane (176.80 g, 1309.626 mmol, 3 equiv). The resulting mixture was stirred for 20 h at room temperature. The reaction was quenched with water(3000ml) at room temperature. The aqueous layer was extracted

with EtOAc (2x2 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford methyl 419-1 (94 g, 76.04%) as a yellow solid.

2. Synthesis of 419-2

A solution of methyl 419-1 (94 g, 331.962 mmol, 1 equiv) in MeOH (3000 mL) was treated with NaOH (995.89 mL, 995.886 mmol, 3 equiv,1M). The resulting mixture was stirred for 2h at room temperature. The MeOH was removed under reduced pressure. The mixture was acidified to pH 5 with HCl (1 M). The precipitated solids were collected by filtration and washed with water (150 mL). This resulted in 419-2 (80 g, 89.54%) as a yellow oil.

3. Synthesis of 419-3

To a stirred mixture of 419-2 (80 g, 297.245 mmol, 1 equiv), DIEA (115.25 g, 891.735 mmol, 3 equiv) and methoxy(methyl)amine hydrochloride (57.99 g, 594.490 mmol, 2 equiv) in DMF (800 mL) was added HATU (124.33 g, 326.970 mmol, 1.1 equiv). The resulting mixture was stirred for 12h at room temperature. The reaction was quenched with water(2500ml) at room temperature. The aqueous layer was extracted with EtOAc (2 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (12:1) to afford 419-3 (63 g, 59.06%) as a yellow solid.

4. Synthesis of 419-4

To a stirred solution of 419-3(63 g, 201.789 mmol, 1 equiv) in THF(600 mL) was added EtMgBr (807 mL, 807.156 mmol, 4 equiv) at -78°C. The resulting mixture stirred for 5 h at room temperature. The reaction was quenched with sat. NH_4Cl (aq.)(2000ml) at room temperature. The aqueous layer was extracted with EtOAc (3x800 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 419-4 (42.4 g, 66.7%) as a yellow oil.

5. Synthesis of 419-5

A solution of 419-4 (28.5 g, 101.354 mmol, 1 equiv) in toluene (300 mL) was treated with [bis(tert-butoxy)methyl]dimethylamine (51.52 g, 253.385 mmol, 2.5 equiv) .The resulting mixture was stirred for 5h at room temperature. The resulting mixture was concentrated under vacuum to afford 419-6 (38.3 g, crude) as a yellow oil.

6. Synthesis of 419-6

A solution of 419-5 (38.5 g, 114.490 mmol, 1 equiv) in EtOH (385 mL) was treated for hydrazine (36.69 g, 1144.900 mmol, 10 equiv). The resulting mixture was stirred for 8h at 80°C. The reaction was quenched by the addition of water (1000mL) at room temperature.

The aqueous layer was extracted with CH_2Cl_2/MeOH(10:1) (3x1000 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water（0.1%NH_4HCO_3）, 25% to 85% gradient in 30 min; detector, UV 220 nm. This resulted in 419-6 (15 g, 37.77%) as a yellow solid.

7. Synthesis of 419-7

A solution of 419-6 (3 g, 9.829 mmol, 1 equiv) in MeCN (30 mL) was treated formethyl 2-bromoacetate (4.51 g, 29.487 mmol, 3 equiv) and K_2CO_3 (2.72 g, 19.658 mmol, 2 equiv) , The resulting mixture was stirred for 4h at 80°C. The resulting mixture was filtered, the filter cake was washed with MeCN (2x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 419-7 (2.92 g, 72.44%) as a light yellow solid.

8. Synthesis of 419-8

To a solution of methyl 419-7 (2.86 g, 7.581 mmol, 1 equiv) in NH_3 (7M in MeOH) (100 mL) was added Cu_2O (0.43 g, 3.032 mmol, 0.4 equiv) in a pressure tank. The resulting mixture was stirred for overnight at 100°C. The resulting mixture was filtered, the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1%NH_4HCO_3),20% to 70% gradient in 30 min; detector, UV220 nm to afford 419-8 (568 mg, 22.60%) as a white solid.

9. Synthesis of 419-9

A solution of 419-8 in DCE (6 mL, 75.796 mmol, 39.82 equiv) was treated with I-2 (599.48 mg, 2.094 mmol, 1.1 equiv) for 2h at room temperature under nitrogen atmosphere followed by the addition of STAB (605.16 mg, 2.856 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$(aq.)(20ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1)(2 x 30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 254 nm to afford 419-9(1.13 g, 62.63%) as a yellow solid.

10. Synthesis of 419-10

A solution of 419-9 (1.13 g, 1.987 mmol, 1 equiv)in DCM (12 mL) was treated with Pyridine (943.04 mg, 11.922 mmol, 6 equiv) at room temperature followed by the addition of Triphosgene (17.72 mg, 0.060 mmol, 0.4 equiv). The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of $NaHCO_3$(20mL) at room temperature. The resulting mixture was extracted with DCM/MeOH(10:1)(2 x 40mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water (0.1% NH_4HCO_3), 20% to 80% gradient in 30 min; detector, UV 254 nm. This resulted in 419-10 as a yellow solid.

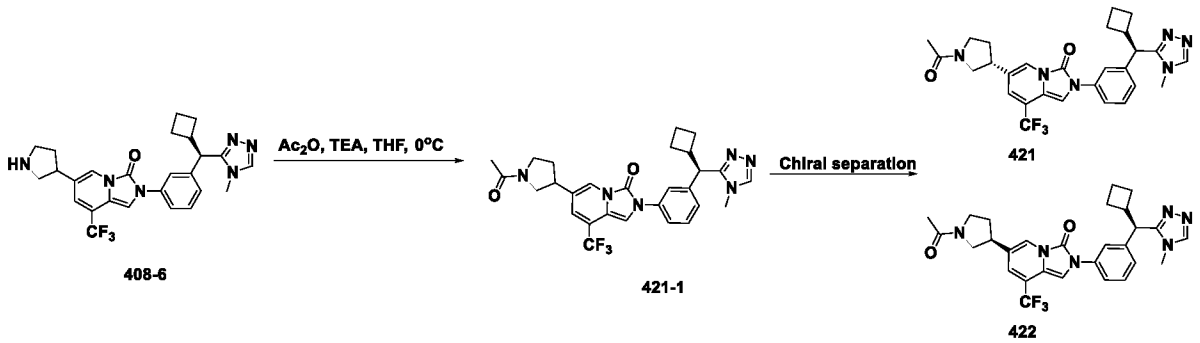
11. Synthesis of 419 and 420

The 419-10 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: ACN(0.1% IPAmine); Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 16 min; Wave Length: 220/254 nm; RT_1(min): 8.93; RT_2(min): 11.44; the first peak was 419-0; the second peak was 420-0) to afford 419 (104.2 mg, 29.77%) as a yellow solid and 420 (110.8 mg, 30.80%) as a yellow solid.

LC-MS-419: (ES, m/z): $[M+H]^+$ 577. H-NMR-419: (400 MHz, DMSO, δ ppm): 0.83-0.84 (m, 4H), 1.42-1.53 (m, 1H), 1.58-1.61 (m, 5H), 1.62-1.84(m, 4H), 1.86 (s, 3H), 1.88-1.98 (m, 1H),1.99-2.10 (m, 1H), 2.77-2.85 (m, 2H), 3.11-3.17 (m, 1H), 3.27(s,2H), 3.99-4.01 (d, 1H), 5.36 (s, 2H), 7.00 (s, 1H), 7.27-7.28 (d, 1H), 7.30 (s, 1H), 7.39-7.42 (m, 1H), 7.47 (s, 1H), 7.65 -7.66(m, 1H), 7.67(s, 1H), 7.73 (s, 1H).

LC-MS-420: (ES, m/z): $[M+H]^+$ 577. H-NMR- 420: (400 MHz, DMSO, δ ppm): 0.83-0.84 (m, 4H), 1.42-1.53 (m, 1H), 1.58-1.62 (m, 5H), 1.64-1.87(m, 4H), 1.86-1.98 (m, 4H),1.99-2.10 (m, 1H), 2.75-2.85 (m, 2H), 3.11-3.17 (m, 1H), 3.27(s,2H), 3.99-4.01 (d, 1H), 5.36 (s, 2H), 7.01 (s, 1H), 7.21-7.22 (d, 1H), 7.28 (s, 1H), 7.38-7.42 (t, 1H), 7.47 (s, 1H), 7.61 - 7.66(m, 1H), 7.67(s, 1H), 7.74 (s, 1H).

Example 410. Synthesis of Compound 421 and 422



1. Synthesis of 421-1

[1466] Into a 100 mL 3-necked round-bottom flask were added 408-6 (230 mg, 0.463 mmol, 1 equiv), THF (5 mL), Ac_2O (94.58 mg, 0.926 mmol, 2 equiv) and TEA (140.62 mg, 1.389 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for 4 h at 0°C. The reaction was quenched by the addition of Water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 421-1 (200 mg, 80.17%) as a light yellow solid.

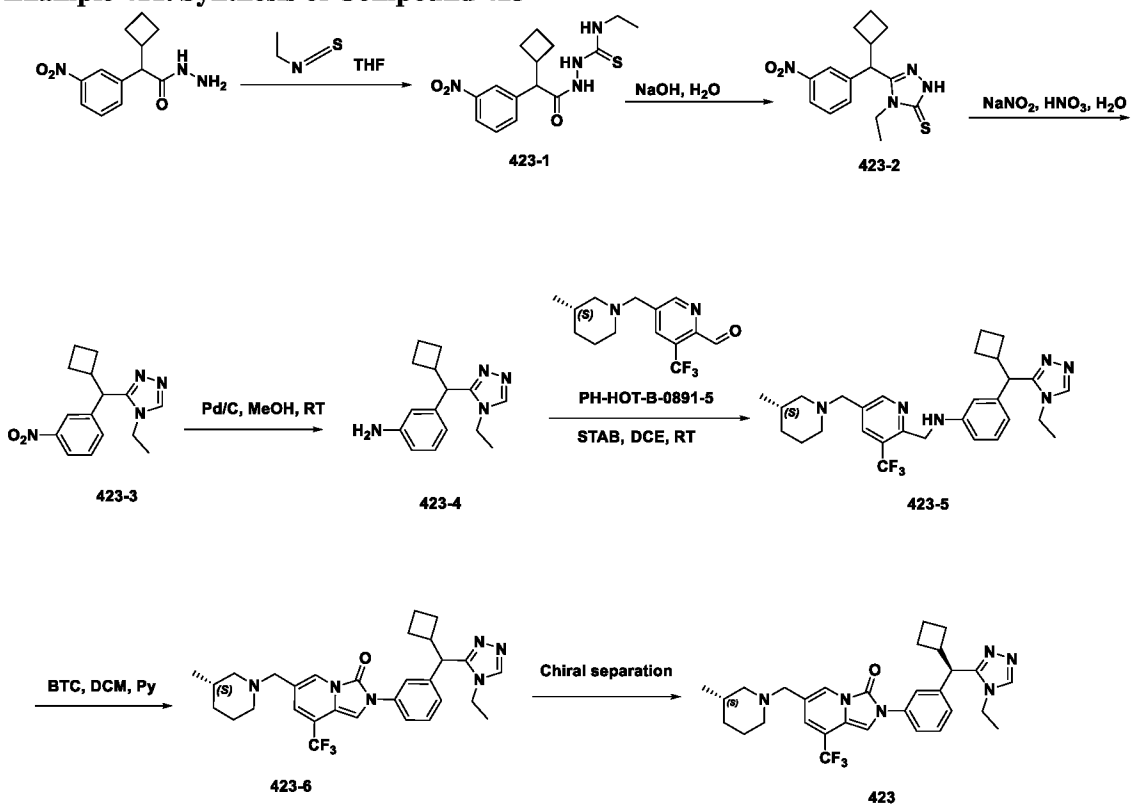
2. Synthesis of 421 and 422

[1467] The 421-1 (200 mg) was purified by Chiral separation with the following conditions (Column: Exsil Chiral-NR, 3*25 cm, 8 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: ACN=1: 1(0.1% 2M NH_3-MeOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B; Column Temperature (35°C); Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 8.33; RT2(min): 9.93; The first peak was 421-0; the second peak was 421-0. Sample Solvent: MeOH-Preparative; Injection Volume: 4 mL; Number of Runs: 8) to afford crude product (60 mg). The residue was purified by Prep-TLC eluted with CH_2Cl_2 / MeOH (10:1) to afford 421 (46.5 mg, 23.25%) as a light yellow solid and 422 (47.2 mg, 23.60%) as a light yellow solid.

LC-MS-421: (ES, *m/z*): $[M+H]^+$ 539. H-NMR-421: 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 1.61-1.89 (m, 5H), 1.90-2.28 (m, 6H), 3.15-3.25 (m, 3H), 3.35-3.41 (m, 4H), 3.50-3.81 (m, 2H), 4.25-4.27 (d, 1H), 7.17-7.18 (m, 2H), 7.32-7.33 (d, 1H), 7.42-7.46 (m, 1H), 7.59-7.74 (m, 3H), 8.33 (s, 1H).

LC-MS-422: (ES, *m/z*): $[M+H]^+$ 539. H-NMR-422: 1H NMR (300 MHz, DMSO-d6 *ppm*) δ1.61-1.89 (m, 5H), 1.90-2.28 (m, 6H), 3.15-3.25 (m, 3H), 3.35-3.41 (m, 4H), 3.50-3.61 (m, 1H), 3.61-3.81 (m, 1H), 4.25-4.27 (d, 1H), 7.17-7.18 (m, 2H), 7.32-7.33 (d, 1H), 7.42-7.46 (m, 1H), 7.59-7.74 (m, 3H), 8.33 (s, 1H).

Example 411. Synthesis of Compound 423



1. Synthesis of 423-1

[1468] To a stirred solution of 2-cyclobutyl-2-(3-nitrophenyl)acetohydrazide (10 g, 40.117 mmol, 1.00 equiv) in tetrahydrofuran (200 mL) was added isothiocyanatoethane (10.49 g, 120.351 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (150 mL). The precipitated solids were collected by filtration and washed with water (20 mL). This resulted in 423-1(12 g, 91%) as an off-white solid.

2. Synthesis of 423-2

[1469] To a stirred solution of 423-1 (12 g, 35.671 mmol, 1 equiv) in H_2O (120.00 mL) was added NaOH (14.27 g, 356.710 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 50 °C. The mixture was neutralized to pH 7 with HCl (aq). The precipitated solids were collected by filtration and washed with water (4x50 mL). This resulted in 423-2 (11 g, 96.85%) as a white solid.

3. Synthesis of 423-3

[1470] To a stirred solution of 423-2 and $NaNO_2$ (23.84 g, 345.480 mmol, 10 equiv) in H_2O (440.00 mL) was added HNO_3 (21.77 g, 345.480 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH

7 with saturated $NaHCO_3$ (aq.). The precipitated solids were collected by filtration and washed with water (3x50 mL). This resulted in 423-3 (8.5 g, 83.35%) as a white solid.

4. Synthesis of 423-4

[1471] To a solution of 423-3 (2 g, 6.985 mmol, 1 equiv) in MeOH (40 mL) was added Pd/C (200 mg, 10%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 423-4 (1.6 g, 80.42%) as a yellow oil.

5. Synthesis of 423-5

[1472] To a stirred solution of 423-4 (500 mg, 1.950 mmol, 1 equiv) and I-2 (558.41 mg, 1.950 mmol, 1 equiv) in DCE (25.00 mL) was added STAB (826.75 mg, 3.900 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 423-5 (860 mg, 77.02%) as a yellow oil.

6. Synthesis of 423-6

[1473] To a stirred solution of 423-5 (860 mg, 1.633 mmol, 1 equiv) and Pyridine (1.29 g, 16.330 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (193.82 mg, 0.653 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 423-6 (420 mg, 46.07%) as a yellow oil.

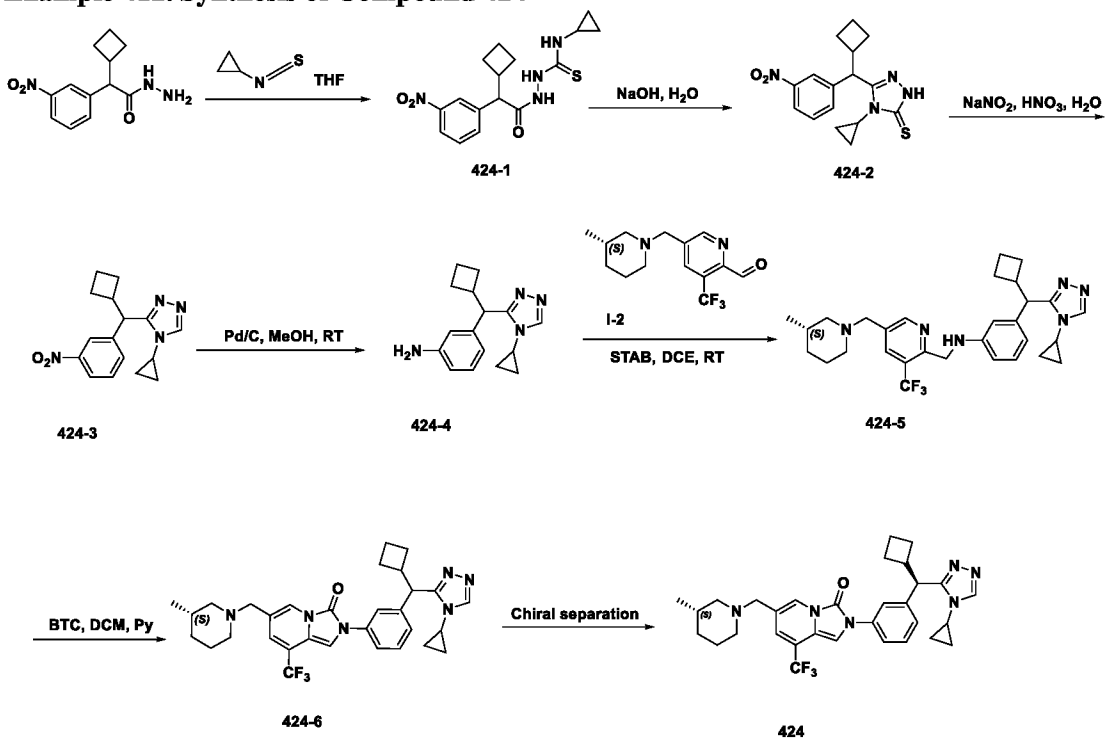
7. Synthesis of 423-0

[1474] The 423-6 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 26 min; Wave Length: 220/254 nm; RT1(min): 10.04; RT2(min): 19.42; the second peak is product) to afford 423 (103.1 mg, 25.54%) as a yellow solid.

LC-MS-423: (ES, *m/z*): $[M+H]^+$ 553. H-NMR-423: (400 MHz, DMSO-d6, δ *ppm*): 0.81-0.83 (m, 4H), 1.03-1.07 (m, 3H), 1.57-1.62 (m, 1H), 1.62-1.68 (m, 5H), 1.68-1.98 (m, 5H), 2.01-2.08 (m, 1H), 2.74-2.76 (m, 2H), 3.20-3.24 (m, 3H), 3.83-3.89 (m, 2H), 4.24-4.27 (d, 1H),

7.01 (s, 1H), 7.21-7.23 (d, 1H), 7.29 (s, 1H), 7.41-7.45 (m, 1H), 7.65-7.70 (m, 1H), 7.70(s, 1H), 8.42(s, 1H).

Example 412. Synthesis of Compound 424



2. Synthesis of 424-1

[1475] To a stirred mixture of 2-cyclobutyl-2-(3-nitrophenyl)acetohydrazide (5 g, 20.059 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added isothiocyanatocyclopropane (5.97 g, 60.177 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (4x50mL). The resulting mixture was concentrated under vacuum. This resulted in 424-1 (6 g, 85.85%) as a white solid.

2. Synthesis of 424-2

[1476] To a stirred mixture of NaOH (6.89 g, 172.210 mmol, 10 equiv) in H_2O (172 mL) was added 424-1 (6 g, 17.221 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at 50 °C. The mixture was neutralized to pH 7 with HCl (1M). The aqueous layer was extracted with CH_2Cl_2 (5x50mL). The resulting mixture was concentrated under vacuum. This resulted in 424-2 (5.2 g, 91.39%) as a yellow solid.

3. Synthesis of 424-3

[1477] To a stirred mixture of 424-2 (5 g, 15.133 mmol, 1 equiv) and $NaNO_2$ (10.44 g, 151.330 mmol, 10 equiv) in H_2O (50 ml) was added HNO_3 (150 mL, 151.330 mmol, 10

equiv, 1M) dropwise at room temperature. The resulting mixture was stirred for 8h at room temperature. The mixture was neutralized to pH 7 with NaOH (aq.). The aqueous layer was extracted with CH_2Cl_2 (5x50 mL). The resulting mixture was concentrated under vacuum. This resulted in 424-3 (3 g, 66.45%) as a yellow solid.

4. Synthesis of 424-4

[1478] To a solution of 424-3 (3.2 g, 10.726 mmol, 1 equiv) in 100 mL MeOH was added Pd/C (10%, 0.11g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressur. This resulted in 424-4(1.5 g, 52.11%) as a yellow solid.

5. Synthesis of 424-5

[1479] To a stirred mixture of 424-4 (500 mg, 1.864 mmol, 1.2 equiv) and I-2 (640.10 mg, 2.236 mmol, 1.2 equiv) in DCE (5 mL) was added STAB (1184.62 mg, 5.589 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 424-5 (600 mg, 59.78%) as a white solid.

6. Synthesis of 424-6

[1480] To a stirred mixture of 242-5 (600 mg, 1.114 mmol, 1 equiv) and Pyridine (528.64 mg, 6.684 mmol, 6 equiv) in DCM (15 mL) was added Triphosgene (132.22 mg, 0.446 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (3x40 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 424-6 (380 mg, 60.42%) as a yellow solid.

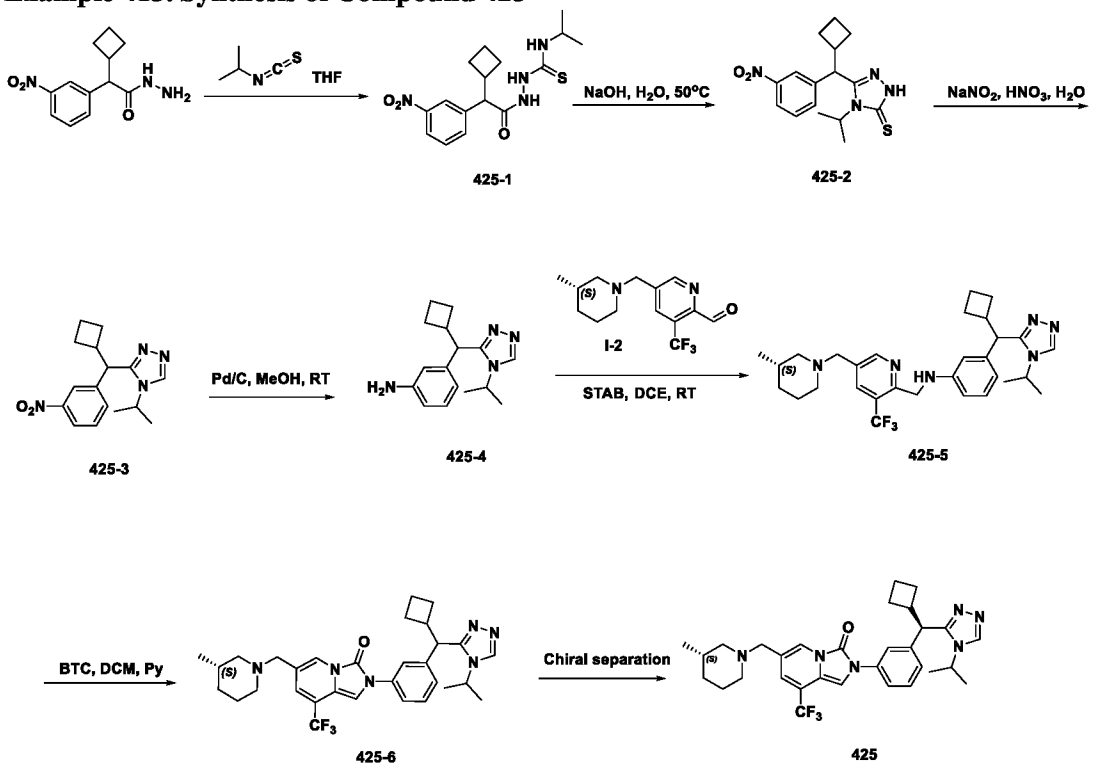
7. Synthesis of 424

[1481] 424-6 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.14; RT2(min): 13.09; the second peak is product) to afford 424 (143.2 mg, 47.73%) as a yellow solid.

LC-MS-424: (ES, *m/z*): $[M+H]^+$ 558. H-NMR-424: (400 MHz, DMSO-d_6, δ *ppm*): 0.58-0.59 (m, 1H),0.81-0.87(m, 5H), 0.94-0.92 (m, 2H), 1.57-1.59 (m, 1H), 1.61-1.79 (m, 4H), 1.80-

1.88 (m, 6H), 2.10-2.21 (m, 1H), 2.72-2.76 (m, 2H),2.97--3.00 (m, 1H), 3.24-3.33 (m, 3H), 4.34 (d, 1H), 7.00 (s, 1H), 7.20-7.22 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.68 (m, 2H), 7.78 (s, 1H), 8.35 (s, 1H).

Example 413. Synthesis of Compound 425



1. Synthesis of 425-1

[1482] A solution of 2-cyclobutyl-2-(3-nitrophenyl)acetohydrazide (5 g, 20.059 mmol, 1 equiv) and 2-isothiocyanatopropane (3.04 g, 30.089 mmol, 1.5 equiv) in tetrahydrofuran (50 mL) was stirred for 5h at room temperature. The resulting mixture was diluted with water (80 mL). The precipitated solids were collected by filtration and washed with water (3x20 mL). This resulted in 425-1 (6 g, 76.82%) as a yellow solid.

2. Synthesis of 425-2

[1483] A solution of 425-1 (6 g, 17.121 mmol, 1 equiv) and NaOH (6.85 g, 171.210 mmol, 10 equiv) in H_2O (170 mL) was stirred overnight at 50 °C. The mixture was neutralized to pH 6 with 1M HCl(aq.). The precipitated solids were collected by filtration and washed with water (3x20 mL). This resulted in 425-2 (4 g, 63.25%) as a yellow solid,

3. Synthesis of 425-3

[1484] To a stirred solution of 425-2 (4 g, 12.033 mmol, 1 equiv) and $NaNO_2$ (8.30 g, 120.330 mmol, 10 equiv) in H_2O (40 mL) was added HNO_3 (120 mL, 120.33 mmol, 10

equiv, 1M) dropwise at room temperature. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 425-3 (3.2 g, 79.68%) as a yellow solid.

4. Synthesis of 425-4

[1485] To a solution of 425-3 (3.8 g, 12.651 mmol, 1 equiv) in MeOH (100 mL) was added Pd/C (380 mg, 10%) under nitrogen atmosphere in a 250mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 425-4 (3.2 g, 84.19%) as a light yellow solid.

5. Synthesis of 425-5

[1486] A solution of 425-4 (500 mg, 1.849 mmol, 1 equiv) and I-2 (635.32 mg, 2.219 mmol, 1.2 equiv) and STAB (783.86 mg, 3.698 mmol, 2 equiv) in DCE (5 mL) was stirred for 4h at room temperature under air atmosphere. The mixture was quenched with saturated $NaHCO_3$ (aq.) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 425-5 (600 mg, 57.01%) as a yellow solid.

6. Synthesis of 425-6

[1487] To a stirred solution of 425-5 (580 mg, 1.073 mmol, 1 equiv) and Pyridine (509.11 mg, 6.438 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (117.77 mg, 0.397 mmol, 0.37 equiv) at room temperature. The result mixture was stirred for 10min at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 12:1) to afford 425-6 (350 mg, 54.70%) as a yellow solid.

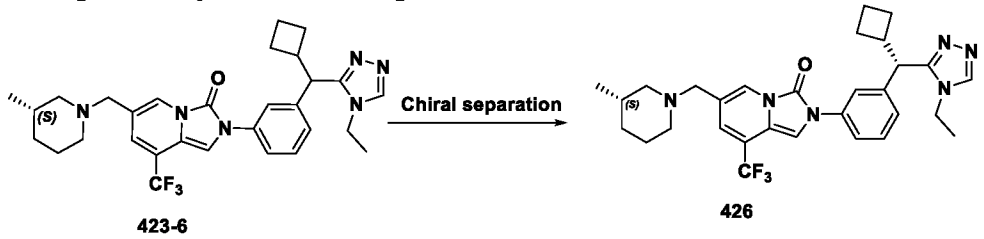
7. Synthesis of 425-7

[1488] The 425-6 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 7.13; RT2(min): 9.28; the second peak is product) to afford 425 (115.0 mg, 32.85%) as a yellow solid.

LC-MS-425 (ES, m/z): $[M+H]^+$ 567

H-NMR-425 (400 MHz, DMSO-d6, δ *ppm*): 0.84-0.92 (m, 4H), 0.92-0.94 (d, 3H), 1.38-1.40 (d, 3H), 1.59-1.89 (m, 11H), 2.08-2.12 (m, 1H), 2.68-2.75 (m, 2H), 3.21-3.33 (m, 3H), 4.27-4.36 (m, 2H), 7.01 (s, 1H), 7.19-7.21 (d, 1H), 7.28 (s, 1H), 7.41-7.45 (m, 1H), 7.65-7.69 (m, 2H), 7.75 (s, 1H), 8.59 (s ,1H).

Example 414. Synthesis of Compound 426



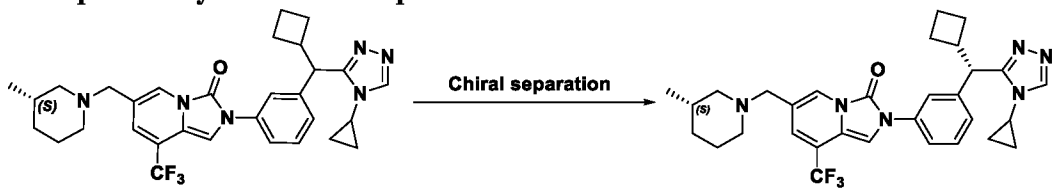
423-6 426

1. Synthesis of 426

[1489] The 423-6 (420 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 26 min; Wave Length: 220/254 nm; RT1(min): 10.04; RT2(min): 19.42; the first peak is product) to afford 426 (137.3 mg, 34.25%) as a yellow solid.

LC-MS-426: (ES, *m/z*): $[M+H]^+$ 553. H-NMR-426: (400 MHz, DMSO-d6, δ ppm): 0.81-0.83 (m, 4H), 1.03-1.07 (m, 3H), 1.57-1.62 (m, 1H), 1.62-1.68 (m, 5H), 1.68-1.98 (m, 5H), 2.01-2.08 (m, 1H), 2.74-2.76 (m, 2H), 3.20-3.24 (m, 3H), 3.83-3.89 (m, 2H), 4.24-4.27 (d, 1H), 7.01 (s, 1H), 7.21-7.23 (d, 1H), 7.29 (s, 1H), 7.41-7.45 (m, 1H), 7.65-7.70 (m, 1H), 7.70(s, 1H), 8.42(s, 1H).

Example 415. Synthesis of Compound 427



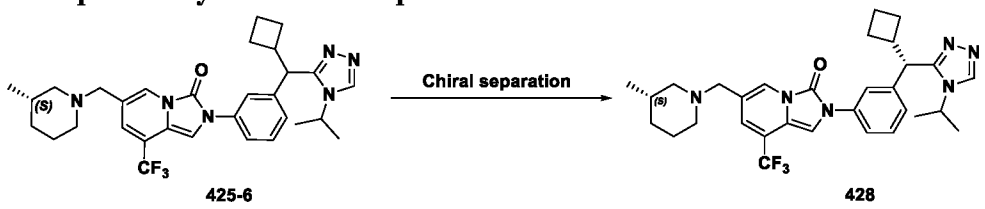
424-6 427

1. Synthesis of 427

[1490] 424-6 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18 min; Wave Length: 220/254 nm; RT1(min): 8.14; RT2(min): 13.09; the frist peak is product) to afford 427 (151.0 mg, 50.33%) as a yellow solid.

LC-MS-427: (ES, *m/z*): $[M+H]^+$ 565. H-NMR-427: (400 MHz, DMSO-d_6, δ *ppm*): 0.58-0.59 (m, 1H),0.81-0.87 (m, 5H), 0.94-0.92 (m, 2H), 1.57-1.59 (m, 1H), 1.61-1.79 (m, 4H), 1.80-1.88 (m, 6H), 2.10-2.21 (m, 1H), 2.72-2.76 (m, 2H),2.97--3.00 (m, 1H), 3.24-3.33 (m, 3H), 4.34 (d, 1H), 7.00 (s, 1H), 7.20-7.22 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.68 (m, 2H), 7.78 (s, 1H), 8.35 (s, 1H).

Example 416. Synthesis of Compound 428



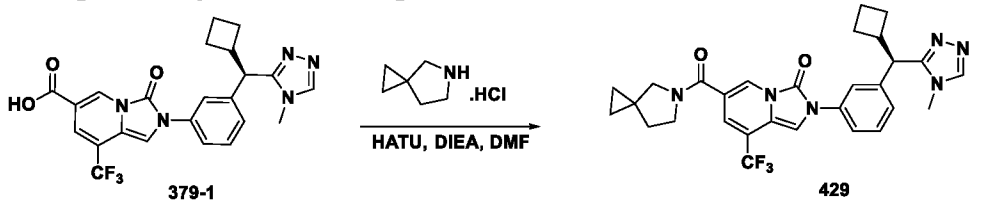
425-6 428

1. Synthesis of 428

[1491] The 425-6 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)-, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 7.13; RT2(min): 9.28; the first peak is product) to afford 428 (99.5 mg, 28.24%) as a yellow solid.

LC-MS-428: (ES, *m/z*): $[M+H]^+$ 567. H-NMR-428: (400 MHz, DMSO-d6, δ *ppm*): 0.84-0.92 (m, 4H), 0.92-0.94 (d, 3H), 1.38-1.40 (d, 3H), 1.41-1.89 (m, 11H), 2.08-2.12 (m, 1H), 2.68-2.75 (m, 2H), 3.21-3.33 (m, 3H), 4.27-4.36 (m, 2H), 7.01 (s, 1H), 7.19-7.21 (d, 1H), 7.28 (s, 1H), 7.41-7.45 (m, 1H), 7.65-7.69 (m, 2H), 7.75 (s, 1H), 8.59 (s ,1H).

Example 417. Synthesis of Compound 429



379-1 429

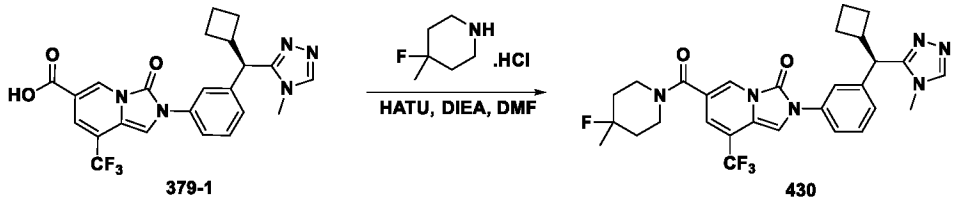
1. Synthesis of 429

[1492] To a stirred solution of 379-1 (200 mg, 0.424 mmol, 1.00 equiv), HATU (241.96 mg, 0.636 mmol, 1.5 equiv), DIEA (164.49 mg, 1.272 mmol, 3 equiv) and DMF (2 mL) was added 5-azaspiro [2.4] heptane hydrochloride (68.02 mg, 0.509 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (4 mL) at room temperature. The aqueous layer was extracted with EtOAc (1x4 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions

(Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 52% B in 8 min; Wave Length: 254 nm; RT1(min): 7.57;) to afford 429 (81.2 mg, 34.49%) as a yellow solid.

LC-MS-429: (ES, *m/z*): $[M+H]^+$ 551. H-NMR-429: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.65 (s, 4H), δ1.70-1.83 (m, 7H), δ2.07-2.09 (d, 1H), δ3.21-3.22 (m, 1H), δ3.37 (s, 1H), δ3.42 (s, 3H), δ3.56-3.60 (d, 2H), δ3.79 (s, 1H), δ4.25-4.28 (d, 1H), δ7.15-7.22 (m, 2H), δ7.41-7.47 (m, 2H), δ7.66-7.68 (d, 1H), δ7.76 (s, 1H), δ8.00-8.02 (d, 1H), δ8.33 (s, 1H).

Example 418. Synthesis of Compound 430

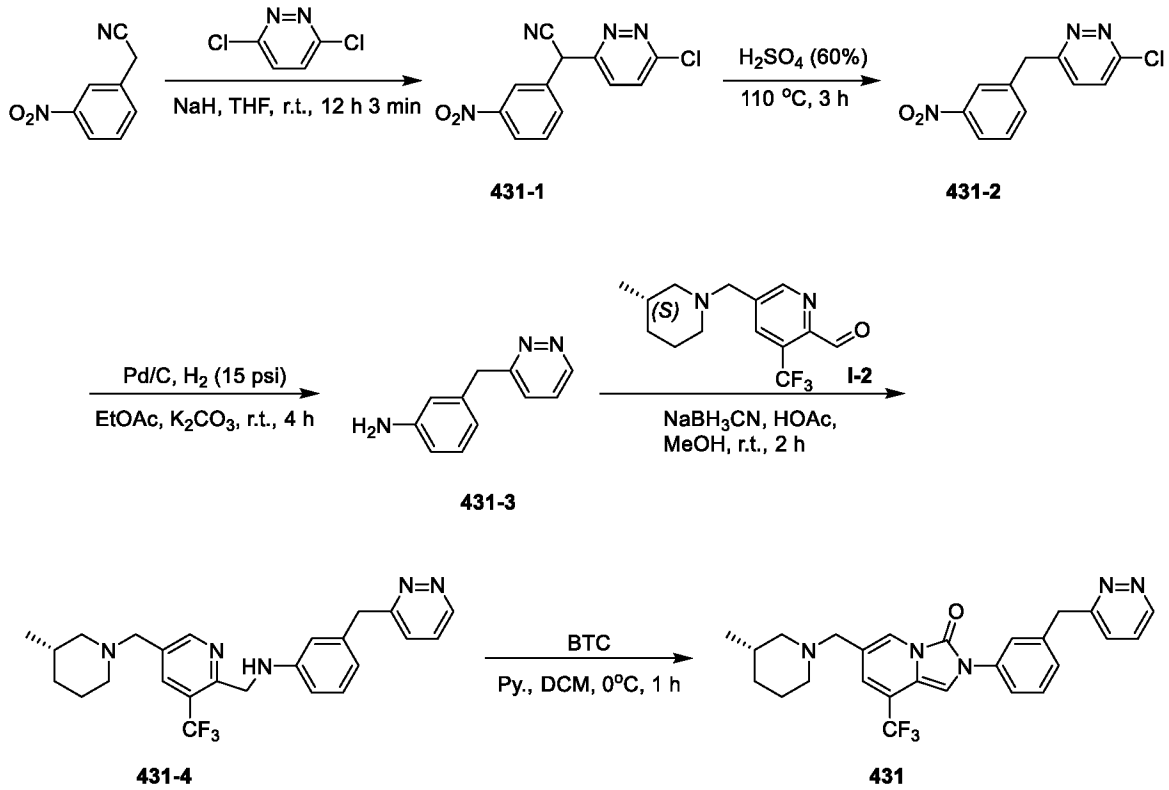


1. Synthesis of 430

[1493] To a stirred solution of 379-1 (200 mg, 0.424 mmol, 1.00 equiv), HATU (241.96 mg, 0.636 mmol, 1.5 equiv), DIEA (164.49 mg, 1.272 mmol, 3 equiv) and DMF (2 mL) was added 4-fluoro-4-methylpiperidine hydrochloride (78.21 mg, 0.509 mmol, 1.2 equiv). The resulting mixture was stirred for overnight at room temperature under. The reaction was quenched by the addition of water (4 mL) at room temperature. The aqueous layer was extracted with EtOAc (1x4 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 53% B in 8 min; Wave Length: 220 nm; RT1(min): 7.23) to afford 430 (128.2 mg, 52.01%) as a yellow solid.

LC-MS-430: (ES, *m/z*): $[M+H]^+$ 571. H-NMR-430: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.31-1.41 (d, 3H), δ1.70-1.80 (m, 9H), δ2.08-2.10 (d, 1H), δ3.19-3.25 (m, 3H), δ3.43 (s, 3H), δ3.90 (s, 2H), δ4.25-4.28 (d, 1H), δ7.06 (s, 1H), δ7.21-7.23 (d, 1H), δ7.41-7.47 (m, 2H), δ7.67-7.69 (d, 1H), δ7.75 (s, 1H), δ7.88 (s, 1H), δ8.35 (s, 1H).

Example 419. Synthesis of Compound 431



1. Synthesis of 431-1

[1494] To a solution of 2-(3-nitrophenyl)acetonitrile (5 g, 30.8 mmol, 1 equiv) in THF (150 mL) was added NaH (1.85 g, 46.2 mmol, 60% purity, 1.5 equiv) and stirred for 3 min until no bubbles are formed. And then a solution of 3,6-dichloropyridazine (4.59 g, 30.8 mmol, 1 equiv) in THF (50 mL) was added to reaction mixture dropwise. The result mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (300 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with PE/EtOAc (1:1) to afford 431-1 (2.6 g, 31%) as a brown solid.

^{1}H NMR-431-1: (400 MHz, CHLOROFORM-d) δ 8.30 (t, J = 2.0 Hz, 1H), 8.22-8.16 (m, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.63-7.52 (m, 3H), 5.71 (s, 1H)

2. Synthesis of 431-2

[1495] A mixture of 431-1 (2 g, 7.28 mmol, 1 equiv) in H_2SO_4 (20 mL, 60% purity) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 110 °C for 3 h under nitrogen atmosphere. The reaction mixture was poured into ice, and then adjusted pH to 9 by ammonia and extracted with DCM (30 mL x3). The combined organic layers were

dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with PE/EtOAc (1:2) to afford 431-2 (1.57 g, 86%) as a pink solid.

^{1}H NMR-431-2: (400 MHz, CHLOROFORM-d) δ 8.10-8.05 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.48-7.37 (m, 2H), 7.23 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H)

3. Synthesis of 431-3

[1496] To a solution of 431-2 (1 g, 4.01 mmol, 1 equiv) in EtOAc (10 mL) was added K_2CO_3 (553 mg, 4.01 mmol, 1 equiv) and Pd/C (1 g, 1.6 mmol, 10% purity). The mixture was stirred at 25 °C for 3 h under hydrogen atmosphere(15 psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford 431-3 (620 mg, crude) as a white solid.

4. Synthesis of 431-4

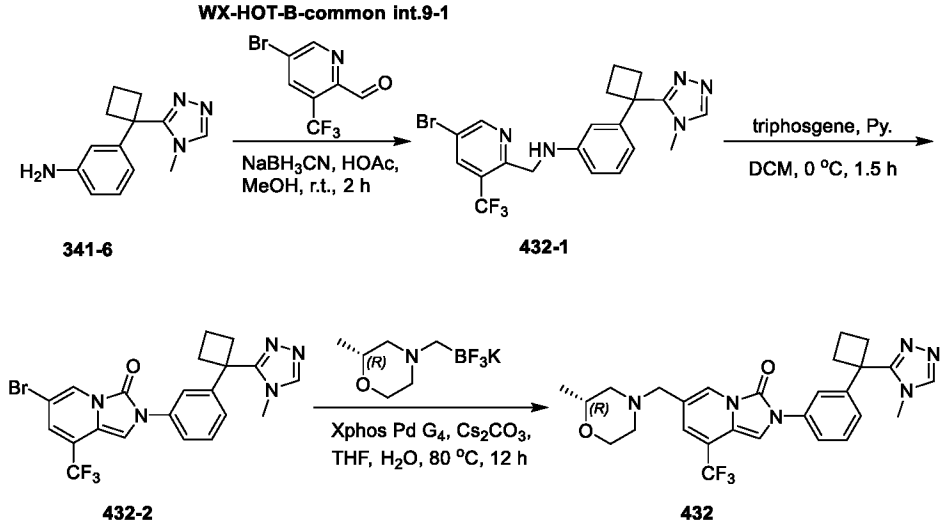
[1497] To a solution of 431-3 (620 mg, 3.35 mmol, 1 equiv) and I-2 (958 mg, 3.35 mmol, 1 equiv) in MeOH (8 mL) was added HOAc (574 uL, 10.0 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. And then $NaBH_3CN$ (420 mg, 6.69 mmol, 2 equiv) was added to reaction mixture. The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was adjusted pH to 8 with saturated $NaHCO_3$ and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with DCM/ MeOH (10:1) to afford 431-4 (890 mg, 58%) as a yellow solid.

5. Synthesis of 431

[1498] To a solution of 431-4 (660 mg, 1.45 mmol, 1 equiv) in DCM (5 mL) was added Py. (701 uL, 8.69 mmol, 6 equiv). And bis(trichloromethyl) carbonate (860 mg, 2.9 mmol, 2 equiv) was added to reaction solution at 0 °C. The mixture was stirred at 25°C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with saturated.$NaHCO_3$ (10 mL), extracted with DCM (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with DCM/MeOH (10:1) to give crude product. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm; RT(min): 8.4) afford 431 (30 mg, 4.3%) as a yellow solid.

MS-431: (ES, m/z): $[M+H]^+$ 482.2. ^{1}H-NMR-431: (400 MHz, METHANOL-d_4) δ 9.11-9.06 (m, 1H), 8.48-8.30 (m, 1H), 7.86 (s, 1H), 7.77-7.70 (m, 2H), 7.70-7.63 (m, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.13 (s, 1H), 4.44 (s, 2H), 3.79 (s, 2H), 3.28-3.14 (m, 2H), 2.53-2.43 (m, 1H), 2.25-2.15 (m, 1H), 1.78 (s, 3H), 1.76-1.65 (m, 1H), 1.17-1.04 (m, 1H), 1.00-0.92 (m, 3H).

Example 420. Synthesis of Compound 432



1. Synthesis of 432-1

[1499] To a solution of 341-6 (1.5 g, 6.57 mmol, 1 equiv) and I-2 (1.5 g, 5.91 mmol, 0.9 equiv) in MeOH (20 mL) was added AcOH (1.13 mL, 19.7 mmol, 3 equiv), the mixture was stirred at 25 °C for 1 h under nitrogen atmosphere, then $NaBH_3CN$ (825 mg, 13.1 mmol, 2 equiv) was added, the result mixture was stirred at 25 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuum. The residue was diluted with Sat. $NaHCO_3$ (25 mL), extracted with EtOAc (25 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 432-1 (1.83 g, 60%) as a yellow solid.

^{1}H-NMR-432-1: (400 MHz, METHANOL-d_4) δ = 8.84 (d, J = 1.5 Hz, 1H), 8.35-8.27 (m, 2H), 7.14 (t, J = 7.9 Hz, 1H), 6.64-6.57 (m, 2H), 6.50 (d, J = 1.8 Hz, 1H), 4.52 (s, 2H), 3.19 (s, 3H), 2.93-2.85 (m, 2H), 2.73 - 2.65 (m, 2H), 2.13-2.04 (m, 2H)

2. Synthesis of 432-2

[1500] To a solution of 432-1 (0.5 g, 1.07 mmol, 1 equiv) in DCM (8 mL) was added pyridine (519 uL, 6.43 mmol, 6 equiv) and bis(trichloromethyl) carbonate (318 mg, 1.07 mmol, 1 equiv) at 0 °C, the result mixture was stirred at 25 °C for 1 h under nitrogen

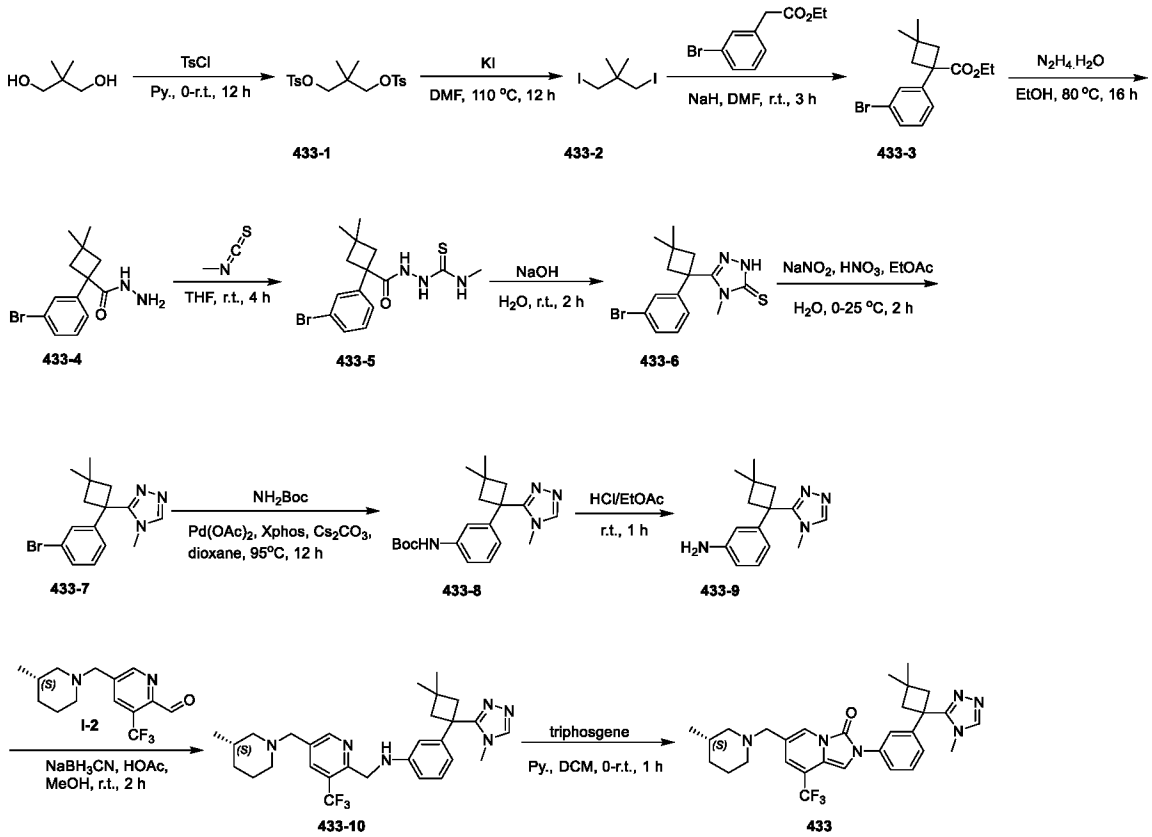
atmosphere. The reaction mixture was diluted with Sat.$NaHCO_3$ (10 mL), extracted with DCM (8 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 432-2 (500 mg, 94.7%) as a yellow solid. ^{1}H-NMR-432-2: (400 MHz, METHANOL-d_4) δ 8.37 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.63-7.55 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.08 (s, 1H), 3.34 (s, 3H), 3.07-2.99 (m, 2H), 2.87-2.78 (m, 2H), 2.20-2.09 (m, 2H)

3. Synthesis of 432

[1501] To a solution of a BF_3 salt (0.25 g, 1.13 mmol, 2 equiv) and 432-2 (278 mg, 565 umol, 1 equiv) in THF (4 mL) and H_2O (1 mL) was added Cs_2CO_3 (552 mg, 1.7 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (48.6 mg, 56.5 umol, 0.1 equiv), the mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give crude product. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 15% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 8.0) to afford 432 (101 mg, 33.5%) as a yellow solid.

MS-432: (ES, m/z): $[M+H]^+$ 527.2. ^{1}H-NMR-432: (400 MHz, METHANOL-d_4) δ 8.36 (s, 1H), 7.76 (t, J = 2.0 Hz, 1H), 7.69 (s, 1H), 7.63-7.50 (m, 2H), 7.34-7.27 (m, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 3.90-3.82 (m, 1H), 3.71-3.60 (m, 2H), 3.37 (s, 2H), 3.33 (s, 3H), 3.07-2.95 (m, 2H), 2.88-2.73 (m, 4H), 2.27-2.07 (m, 3H), 1.95-1.87 (m, 1H), 1.13 (d, J = 6.4 Hz, 3H).

Example 421. Synthesis of Compound 433



1. Synthesis of 433-1

[1502] To a solution of 2,2-dimethylpropane-1,3-diol (20 g, 192 mmol, 1 equiv) in Py. (120 mL) was added a solution of 4-methylbenzenesulfonyl chloride (109 g, 576 mmol, 3 equiv) in Py. (120 mL) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was quenched with ice and water (500 mL), then the mixture was filtered. The filter cake was concentrated under reduced pressure to afford 433-1 (79 g, 99%) as a white solid.

H-NMR-433-1: (400 MHz, DMSO-d6) δ 7.74 (d, J = 8.4 Hz, 4H), 7.48 (d, J = 8.0 Hz, 4H), 3.73 (s, 4H), 2.44 (s, 6H), 0.79 (s, 6H)

2. Synthesis of 433-2

[1503] A solution of 433-1 (27 g, 65.4 mmol, 1 equiv) and KI (65.19 g, 392.71 mmol, 6 equiv) in DMF (270 mL) was stirred at 110 °C for 12 hr. The reaction mixture was extracted with water (450 mL) and EtOAc (150 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with EA/PE=0:1 to afford 433-2 (16.5 g, 78%) as a colorless oil.

3. Synthesis of 433-3

[1504] To a solution of 433-2 (12 g, 37.0 mmol, 0.9 equiv) and ethyl 2-(3-

bromophenyl)acetate (10 g, 41.1 mmol, 1 equiv) in DMF (120 mL) was added NaH (3.29 g, 82.3 mmol, 60% purity, 2 equiv), the mixture was stirred at 25 °C for 3 hr. The reaction mixture was diluted with water (150 mL), extracted with EtOAc (90 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=1:9 to afford 433-3 (7 g, 55%) as a colorless oil.

H-NMR-433-3: (400 MHz, CHLOROFORM-d) δ 7.37 (t, J = 2.0 Hz, 1H), 7.29-7.25 (m, 1H), 7.20-7.14 (m, 1H), 7.12-7.07 (m, 1H), 4.05-3.98 (m, 2H), 2.78-2.57 (m, 2H), 2.37-2.14 (m, 2H), 1.10 (t, J = 7.1 Hz, 3H), 1.07 (s, 3H), 0.94 (s, 3H)

4. Synthesis of 433-4

[1505] To a solution of ethyl 433-3 (6.9 g, 22.1 mmol, 1 equiv) in EtOH (35 mL) was added N2H4.H2O (27.5 mL, 554 mmol, 98% purity, 25 equiv), the mixture was stirred at 80 °C for 16 hr. The reaction mixture was concentrated in vacuum to remove EtOH. The residue was diluted with water (50 mL) and brine (10 mL), extracted with DCM (50 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 433-4 (6.5 g, crude) as a colorless oil.

H-NMR-433-4: (400 MHz, DMSO-d6) δ 9.12-9.07 (m, 1H), 7.46-7.45 (m, 1H), 7.37-7.32 (m, 1H), 7.28-7.20 (m, 2H), 4.14 (d, J = 4.4 Hz, 2H), 2.62 (s, 1H), 2.58 (s, 1H), 2.16 (d, J = 12.8 Hz, 2H), 1.02 (s, 3H), 0.90 (s, 3H)

5. Synthesis of 433-5

[1506] To a solution of 433-4 (6.5 g, 21.8 mmol, 1 equiv) in THF (65 mL) was added methylimino(thioxo)methane (2.99 mL, 43.7 mmol, 2 equiv), the mixture was stirred at 25 °C for 4 hr. The reaction mixture was diluted with water (70 mL) and EtOAc (50 mL). The mixture was filtered and the filter cake was concentrated in vacuum to afford 433-5 (7.5 g, 93%) as a white solid.

H-NMR-433-5: (400 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.21 (s, 1H), 7.58 (s, 1H), 7.46-7.37 (m, 2H), 7.35-7.27 (m, 1H), 7.24-6.99 (m, 1H), 2.89-2.75 (m, 5H), 2.25 (d, J = 12.4 Hz, 2H), 1.13 (s, 3H), 0.94 (s, 3H)

6. Synthesis of 433-6

[1507] To a solution of NaOH (6.48 g, 162.03 mmol, 8 equiv) in H2O (65 mL) was added 433-5 (7.5 g, 20.2 mmol, 1 equiv), the mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with water (70 mL), adjusted pH to 3 by 1N HCl. The mixture was filtered and the filter cake was concentrated in vacuum to afford 433-6 (7 g, 98%) as a white solid.

H-NMR-433-6: (400 MHz, DMSO-d6) δ 13.75 (s, 1H), 7.51-7.46 (m, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.38-7.30 (m, 2H), 3.02 (s, 3H), 2.78 (d, J = 12.8 Hz, 2H), 2.54 (d, J = 12.8 Hz, 2H), 1.08 (d, J = 6.8 Hz, 6H)

7. Synthesis of 433-7

[1508] HNO3 (13.1 mL, 198 mmol, 68% purity, 10 equiv) was added to H2O (184 mL) to afford the diluted HNO3 solution (1M, 197 mL). To a solution of 433-6 (7 g, 19.87 mmol, 1 equiv) and NaNO2 (13.7 g, 198 mmol, 10 equiv) in H2O (70 mL) and EtOAc (7.0 mL, 71.5 mmol, 3.6 equiv) was added diluted HNO3 solution (1 M, 197 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 2 hr. The reaction mixture was quenched by the addition of Sat.NaHCO3 (600 mL). The aqueous layer was extracted with EtOAc (150 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 433-7 (5 g, 78%) as a yellow solid.

H-NMR-433-7: (400 MHz, METHANOL-d4) δ 8.32 (s, 1H), 7.47-7.43 (m, 1H), 7.43-7.39 (m, 1H), 7.36-7.32 (m, 1H), 7.32-7.26 (m, 1H), 3.34-3.32 (m, 3H), 2.96-.88 (m, 2H), 2.72-2.62 (m, 2H), 1.15 (s, 3H), 1.11 (s, 3H)

8. Synthesis of 433-8

[1509] To a solution of 433-7 (1 g, 3.12 mmol, 1 equiv) and NH2Boc (439 mg, 3.75 mmol, 1.2 equiv) in dioxane (15 mL) was added Cs2CO3 (1.42 g, 4.37 mmol, 1.4 equiv), Pd(OAc)2 (35.1 mg, 156 umol, 0.05 equiv) and XPhos (149 mg, 312 umol, 0.1 equiv), the mixture was stirred at 95 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (15 mL * 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with CH2Cl2/MeOH=10:1 to afford 433-8 (800 mg, 72%) as a yellow oil.

9. Synthesis of 433-9

[1510] To a solution of 433-8 (800 mg, 2.24 mmol, 1 equiv) in EtOAc (10 mL) was added HCl/EtOAc (10 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was adjusted pH to 8 with saturated NaHCO3 and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 433-9 (410 mg, crude) as a white solid.

10. Synthesis of 433-10

To a solution of 433-9 (360 mg, 1.40 mmol, 1 equiv) and I-2 (402 mg, 1.4 mmol, 1 equiv) in MeOH (5 mL) was added HOAc (241 uL, 4.21 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 hr. Add then NaBH3CN (176 mg, 2.81 mmol, 2 equiv) was added to reaction

mixture. The result mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was adjusted pH to 8 with saturated NaHCO3 and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with CH2Cl2/MeOH=10:1 to afford 433-10 (730 mg, 87%) as a yellow solid

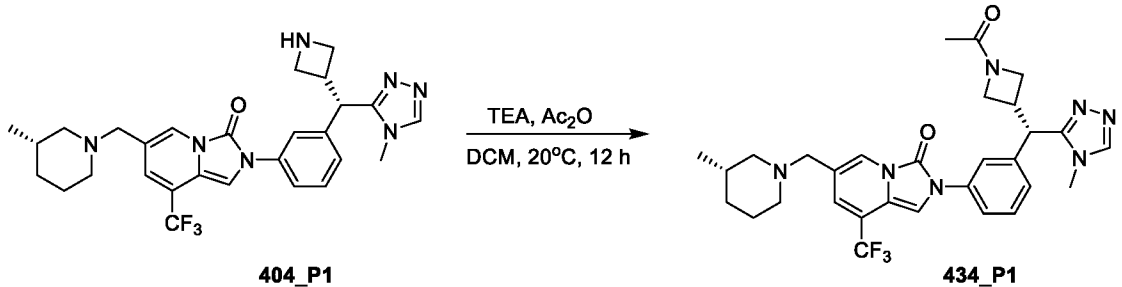
11. Synthesis of 433

[1511] To a solution of 433-10 (330 mg, 626 umol, 1 equiv) in DCM (5 mL) was added Py (303 uL 3.76 mmol, , 6 equiv). And bis(trichloromethyl) carbonate (186 mg, 626 umol, 1 equiv) was added to reaction solution at 0 °C. The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with saturated.NaHCO3 (10 mL), extracted with CH2Cl2 (10 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with CH2Cl2/MeOH=10:1 to give crude product. The crude product (340 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 15% B to 55% B in 8 min; Wave Length: 220 nm; RT1(min): 6.5) to afford 433 (151.7mg, 44%) as a yellow solid.

MS-433: (ES, m/z): [M+H]+ 553.3

1H NMR-433: (400 MHz, METHANOL-d4) δ 8.42 (s, 1H), 8.34 (s, 1H), 7.79 (s, 2H), 7.62-7.51 (m, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.23-7.07 (m, 2H), 4.60 (s, 1H), 3.65 (s, 2H), 3.41 (s, 3H), 3.14-3.08 (m, 1H), 2.99 (d, J = 12.8 Hz, 2H), 2.78 (d, J = 12.8 Hz, 2H), 2.39-2.26 (m, 1H), 2.10-1.97 (m, 1H), 1.82 (d, J = 12.0 Hz, 3H), 1.73-1.64 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.09-1.01 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H).

Example 422. Synthesis of Compound 434_P1



404_P1 434_P1

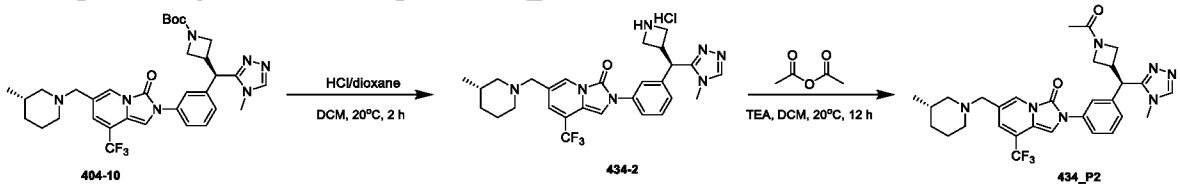
1. Synthesis of 434_P1

[1512] To a solution of 404_P1 (150 mg, 277 umol, 1 equiv) in DCM (2 mL) was added TEA (116 uL, 833 umol, 3 equiv) and Ac_2O (52 uL, 556 umol, 2 equiv). The mixture was

concentrated under reduced pressure (20 °C). The residue was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: water (FA), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 5% B to 35% B in 8 min; Wave Length: 220 nm; RT1 (min): 8.2) to afford 434_P1 (50.9 mg, 29%) as a yellow solid.

MS-434_P1: (ES, m/z): $[M+H]^+$ 582.2. ^{1}H-NMR-434_P1: (400 MHz, METHANOL-d4) δ 8.45 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 7.87 (s, 1H), 7.76-7.66 (m, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.35-7.29 (m, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 4.68-4.61 (m, 1H), 4.46 (t, J = 8.8 Hz, 0.5H), 4.26-4.06 (m, 1.5H), 3.94-3.89 (m, 1H), 3.85 (d, J = 5.2 Hz, 2H), 3.73-3.58 (m, 2H), 3.51 (s, 3H), 3.23 (d, J = 11.2 Hz, 2H), 2.60-2.47 (m, 1H), 2.32-2.19 (m, 1H), 1.81-1.67 (m, 7H), 1.15-1.04 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H).

Example 423. Synthesis of Compound 434_P2



1. Synthesis of 434-2

[1513] To a solution of 404-10 (0.13 g, 203 umol, 1 equiv) in DCM (1 mL) was added HCl/dioxane (4 M, 305 uL, 6 equiv). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure to afford 434-2 (0.13 g, crude) as a yellow solid.

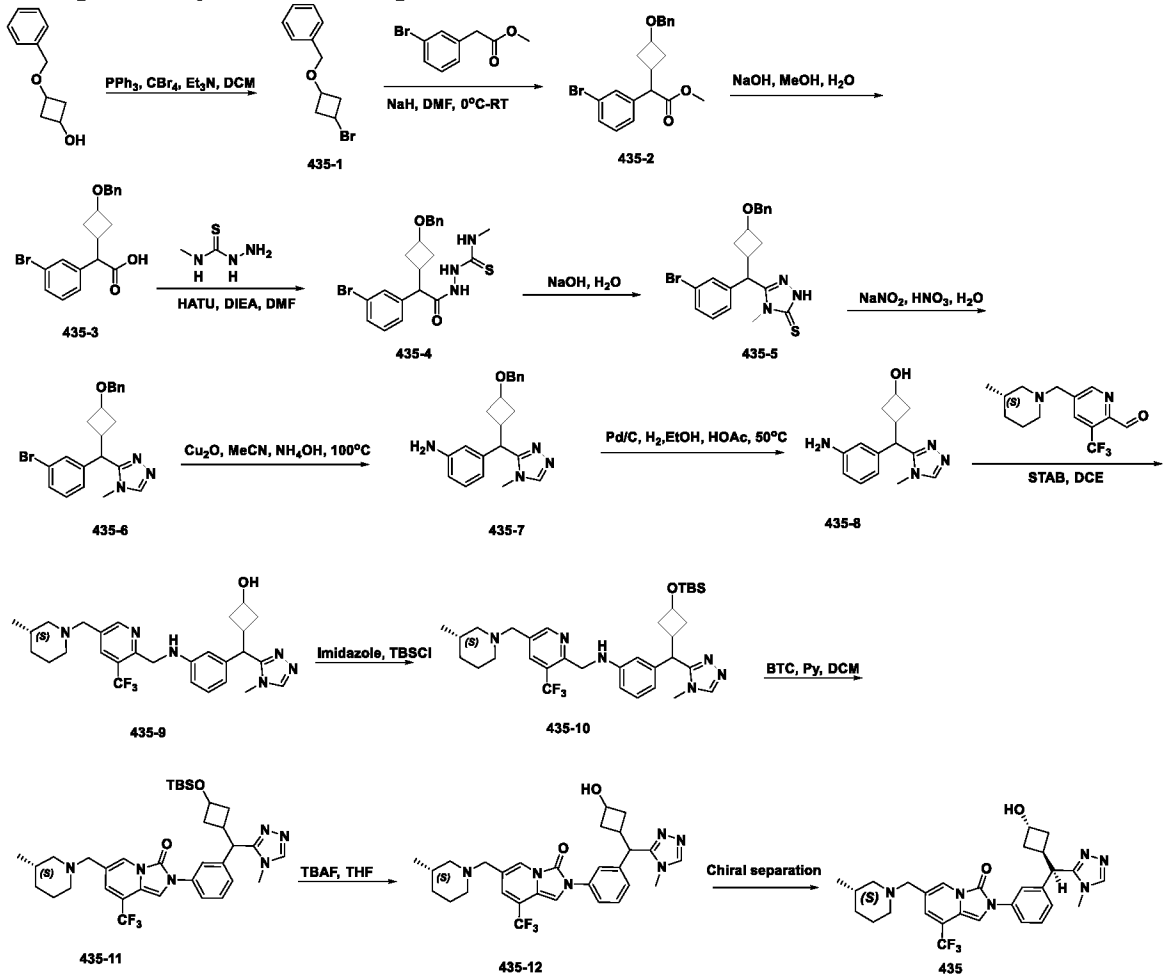
2. Synthesis of 434_P2

[1514] To a solution of 434-2 (0.1 g, 173.59 umol, 1 equiv, HCl) in DCM (2 mL) was added Ac_2O (35.44 mg, 347.19 umol, 32.52 uL, 2 equiv), TEA (52.70 mg, 520.78 umol, 72.49 uL, 3 equiv). The mixture was stirred at 20 °C for 12 h. It worked up with a small test scale (20 mg) together. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 15%-55%, 8 min, Wave Length: 220 nm; RT1 (min): 6.5 min) to afford 434_P2 (31 mg, 25.61% yield) as a yellow solid.

MS-434_P2: (ES, m/z): $[M+H]^+$ 582.2. ^{1}H-NMR-434_P2: (400 MHz, MeOH) δ 8.40 (d, J = 2.8 Hz, 2H), 7.84 (s, 1H), 7.73-7.70 (m, 2H), 7.68 (t, J = 1.6 Hz, 1H), 7.33-7.30 (m, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 4.65-4.61 (m, 1H), 4.46 (t, J = 8.4 Hz, 0.5H), 4.25-4.20 (m, 0.5H), 4.18-4.07 (m, 1H), 3.93-3.90 (m, 1H), 3.79-3.76 (m, 2H), 3.68-3.65 (m, 2H), 3.50 (s, 3H), 3.30-

3.17 (m, 2H), 2.51-2.42 (m, 1H), 2.23-2.14 (m, 1H), 1.85-1.69 (m, 7H), 1.12-1.03 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H).

Example 424. Synthesis of Compound 435



1. Synthesis of 435-1

[1515] Into a 2L 3-necked round-bottom flask were added 3-(benzyloxy)cyclobutan-1-ol (29 g, 162.710 mmol, 1 equiv) ,PPh_3 (106.69 g, 406.775 mmol, 2.5 equiv) ,CBr_4 (134.90 g, 406.775 mmol, 2.5 equiv) and DCM (1006 mL) at 0°C. To the above mixture was added Et_3N (37.05 g, 366.098 mmol, 2.25 equiv) dropwise over 50min at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was diluted with sat. $NaHCO_3$(aq.)(1000 mL). The resulting mixture was extracted with DCM (2 x500 mL). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 435-1 (32 g, 79.12%) as a yellow oil.

2. Synthesis of 435-2

[1516] Into a 1L 3-necked round-bottom flask were added 435-1 (32.01 g, 132.744 mmol, 1.2 equiv) and DMF (320 mL) at 0°C.To the above mixture was added NaH (5.31 g, 132.744 mmol, 1.2 equiv, 60%) in portions at 0°C. The resulting mixture was stirred for additional 0.5h at 0°C.To the above mixture was added methyl 2-(3-bromophenyl)acetate (25.34 g, 110.620 mmol, 1.00 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.960ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x320 mL). The combined organic layers were washed with brine (320 mL). The combined organic layers was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 435-2 (40 g, 83.60%) as a yellow oil.

3. Synthesis of 435-3

[1517] Into a 1L 3-necked round-bottom flask were added 435-2 (40 g, 102.751 mmol, 1 equiv) MeOH (720 mL) and H_2O (360 mL) and NaOH (16.44 g, 411.004 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The MeOH was removed under vacuum. The mixture was acidified to pH 5 with HCl (aq.)(1 M).The aqueous layer was extracted with EtOAc (3x400 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 435-3 (32.5 g, 81.76%) as a white solid.

4. Synthesis of 435-4

[1518] Into a 250mL 3-necked round-bottom flask were added 435-3 (10 g, 26.648 mmol, 1 equiv), DMF (100 mL), DIEA (6.89 g, 53.296 mmol, 2 equiv) and HATU (12.16 g, 31.978 mmol, 1.2 equiv) at room temperature .The resulting mixture was stirred for 2h at room temperature . To the above mixture was added 4-methyl-3-thiosemicarbazide (3.64 g, 34.642 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with water (300 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (2x30 mL). This resulted in 435-4 (8.6 g, 69.79%) as a white solid.

5. Synthesis of 435-5

[1519] Into a 250mL round-bottom flask were added 435-4 (8.6 g, 18.598 mmol, 1 equiv), H_2O (75 mL) and NaOH (2.98 g, 74.392 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 5 with HCl (aq.). The precipitated solids were collected by filtration and washed with water (3x20 mL).This resulted in 435-5 (8.1 g, 93.11%) as a white solid.

6. Synthesis of 435-6

[1520] Into a 500mL 3-necked round-bottom flask were added 435-5 (8.1 g, 18.227 mmol, 1 equiv) , $NaNO_2$ (12.58 g, 182.270 mmol, 10 equiv) and H_2O (100 mL) at room temperature. To the above mixture was added HNO_3 (91 mL, 91.135 mmol, 5 equiv, 1M) dropwise over 0.5 h at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The mixture was basified to pH 7 with sat. $NaHCO_3$(aq.). The resulting mixture was extracted with EtOAc (3 x 100mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 435-6 (7 g, 88.48%) as a white solid.

7. Synthesis of 435-7

[1521] Into a 500 mL ammonolysis kettle were added 435-6 (7 g, 16.977 mmol, 1 equiv), Cu_2O (4.86 g, 33.954 mmol, 2 equiv) ,MeCN (300 mL) and NH_4OH (300 mL) at room temperature. The resulting mixture was stirred for overnight at 100°C. The resulting mixture was extracted with CH_2Cl_2 / MeOH (10:1) (5 x 300ml). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 435-7 (2.5 g, 38.04%) as a green oil.

8. Synthesis of 435-8

[1522] To a solution of 435-7 (2.14 g, 6.141 mmol, 1 equiv) in EtOH (20 mL) and HOAc (20 mL) was added Pd/C (321 mg, 10%) under nitrogen atmosphere in a 100mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 435-8 (500 mg, 28.36%) as a white solid.

9. Synthesis of 435-9

[1523] To a stirred solution of 435-8 (500 mg, 1.936 mmol, 1 equiv) and I-2 (664.97 mg, 2.323 mmol, 1.2 equiv) in DCE (10 mL) was added STAB (820.44 mg, 3.872 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 435-9 (750 mg, 73.30%) as a white solid.

10. Synthesis of 435-10

[1524] To a stirred solution of 435-9 (750 mg, 1.419 mmol, 1 equiv) and Imidazole (193.18 mg, 2.838 mmol, 2 equiv) in THF (15 mL) was added TBSCl (427.68 mg, 2.838 mmol, 2

equiv). The resulting mixture was stirred for 5 h at room temperature. The resulting mixture was diluted with water (45 mL). The resulting mixture was extracted with EtOAc (4 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 435-10 (640 mg, 70.17%) as a white solid.

11. Synthesis of 435-11

[1525] To a stirred solution of 435-10 (640 mg, 0.996 mmol, 1 equiv) and Pyridine (393.72 mg, 4.980 mmol, 5 equiv) in DCM (20 mL) was added Triphosgene (118.16 mg, 0.398 mmol, 0.4 equiv) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C under. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 435-11 (507 mg, 76.14%) as a yellow solid.

[1526] **12. Synthesis of 435-12**

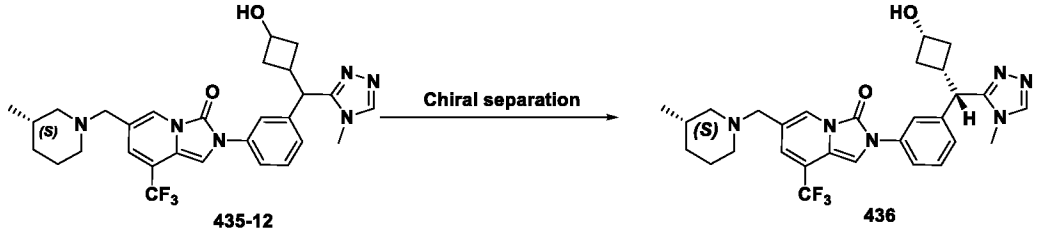
To a stirred solution of 435-11 (507 mg, 0.758 mmol, 1 equiv) in THF (5 mL) was added TBAF (2.27 mL, 2.274 mmol, 3 equiv, 1 M). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1). The crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 5% to 60% gradient in 25 min; detector, UV 254 nm. This resulted in 435-12 (400 mg, 95.15%) as a yellow solid.

13. Synthesis of 435

[1527] 435-12 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 4.75; RT2(min): 8.50; RT3(min): 10.90; first peak was product) The crude product (140 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 35% B to 35% B in 12 min; Wave Length: 220/254 nm; RT1(min): 8.04; RT2(min): 10.09; first peak was desired product) to afford 435 (61.6 mg, 15.40%) as a yellow solid.

LCMS-435:(ES, m/z): $[M+H]^+$ 555. NMR-435: (400 MHz, CD_3OD, δ ppm): 0.90-0.96 (m, 4H), 1.64-1.78 (m, 5H), 1.97-2.08 (m, 3H), 2.20-2.29 (m, 2H), 2.86-2.92 (m, 2H), 3.24-3.28 (m, 1H), 3.32 (s, 2H), 3.56 (s, 3H), 4.30-4.33 (d, 1H), 4.41-4.44 (t, 1H), 7.13 (s, 2H), 7.29-7.30 (d, 1H), 7.50-7.53 (t, 1H), 7.65-7.71 (m 3H), 8.37 (s,1H).

Example 425. Synthesis of Compound 436

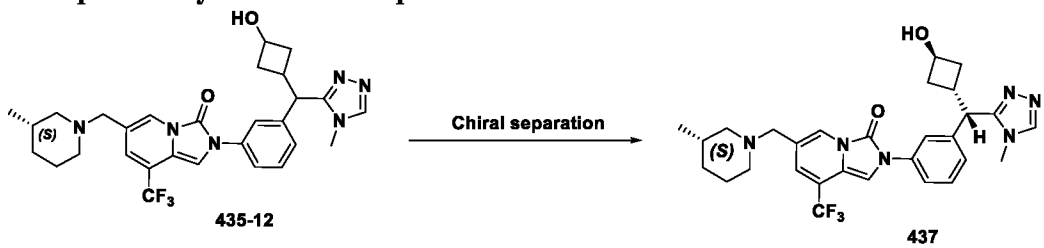


[1528] 1. Synthesis of 436

435-12 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 4.75; RT2(min): 8.50; RT3(min): 10.90; the first peak was product) to afford crude product (140 mg). The crude product (140 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 35% B to 35% B in 12 min; Wave Length: 220/254 nm; RT1(min): 8.04; RT2(min): 10.09; the second peak was product) to afford 436 (41.9 mg, 10.47%) as a yellow solid.

LCMS-436:(ES,m/z): $[M+H]^+$ 555. NMR-436: (400 MHz, CD_3OD, δ ppm): 0.90-0.96 (m, 4H), 1.31-1.85 (m, 7H), 1.96-2.01 (t, 1H), 2.22-2.25 (m, 1H), 2.57-2.61 (m, 1H), 2.74-2.85 (m, 1H), 2.87-2.91 (m, 2H), 3.24-3.26 (m, 1H), 3.28 (s, 2H), 3.54 (s, 3H), 4.11-4.15 (t, 1H), 4.22-4.25 (t, 1H), 7.12 (s, 2H), 7.25-7.27 (d, 1H), 7.49-7.53 (t, 1H), 7.66-7.72 (m 3H), 8.37 (s,1H).

Example 426. Synthesis of Compound 437



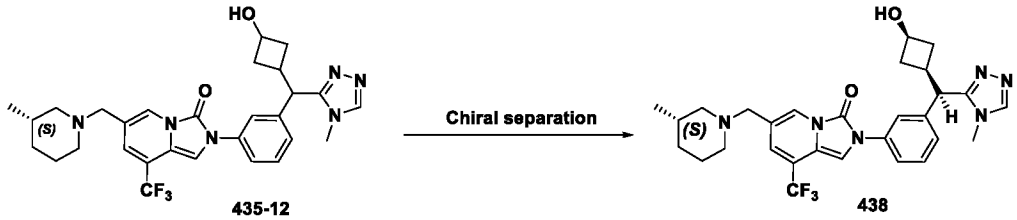
1. Synthesis of 437

[1529] 435-12 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions

(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 4.75; RT2(min): 8.50; RT3(min): 10.90; second peak was desired product) to afford 437 (76.3 mg, 19.07%) as a yellow solid.

LCMS-437:(ES,m/z): $[M+H]^+$ 555. NMR-437: (400 MHz, CD_3OD, δ ppm): 0.90-0.96 (m, 4H), 1.64-1.78 (m, 5H), 1.97-2.08 (m, 3H), 2.20-2.27 (m, 2H), 2.87-2.93 (m, 2H), 3.24-3.28 (m, 1H), 3.36 (s, 2H), 3.56 (s, 3H), 4.30-4.33 (d, 1H), 4.41-4.44 (t, 1H), 7.13 (s, 2H), 7.29-7.31 (d, 1H), 7.50-7.54 (t, 1H), 7.66-7.71 (m 3H), 8.37 (s,1H).

Example 427. Synthesis of Compound 438

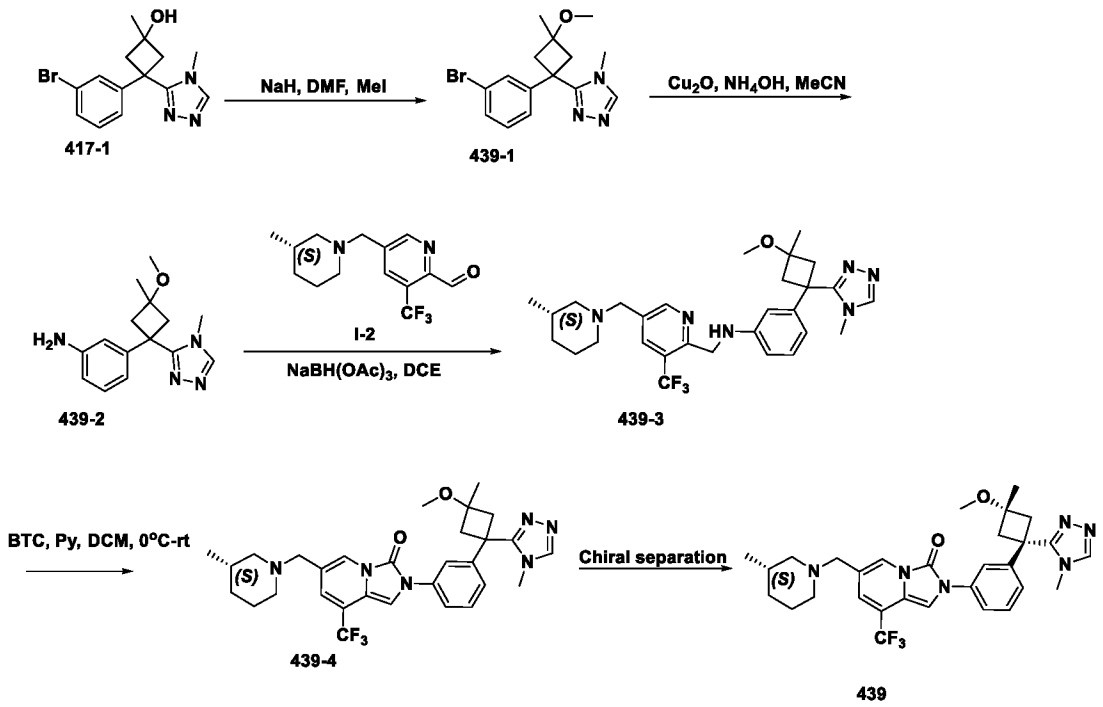


1. Synthesis of 438

[1530] 435-12 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 4.75; RT2(min): 8.50; RT3(min): 10.90; the third peak was product) to afford 438 (48.8 mg, 12.20%) as a yellow solid.

LCMS-438:(ES, m/z): $[M+H]^+$ 555. NMR-438: (400 MHz, CD_3OD, δ ppm): 0.90-0.96 (m, 4H), 1.60-1.85 (m, 7H), 1.96-2.01 (t, 1H), 2.22-2.25 (m, 1H), 2.57-2.61 (m, 1H), 2.74-2.85 (m, 1H), 2.87-2.91 (m, 2H), 3.24-3.26 (m, 1H), 3.28 (s, 2H), 3.54 (s, 3H), 4.11-4.15 (t, 1H), 4.22-4.25 (t, 1H), 7.12 (s, 2H), 7.25-7.27 (d, 1H), 7.49-7.53 (t, 1H), 7.66-7.72 (m 3H), 8.37 (s,1H).

Example 428. Synthesis of Compound 439



1. Synthesis of 439-1

[1531] To a solution of 417-1 (2 g, 6.20 mmol, 1.0 equiv) in DMF (20 mL) was added sodium hydride (60% in oil, 297 mg) at 0 degrees C. The mixture was stirred for 15 min. MeI (1.3 g, 9.31 mmol, 1.5 equiv) was added and the mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was quenched by water and extracted with DCM (3*25 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 439-1 (800 mg, 38%) as a colorless oil.

2. Synthesis of 439-2

[1532] To a stirred solution of 439-1 (1.5 g, 4.69 mmol, 1.0 equiv) and Cu_2O (268 mg, 1.88 mmol, 0.4 equiv) in MeCN (10 mL) was added $NH_3.H_2O$ (10 mL) at room temperature. The resulting mixture was stirred for overnight at 100°C. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x30 mL). The combined organic layers were washed with water (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 439-2 (1 g, 72%) as a colorless oil.

3. Synthesis of 439-3

[1533] To a stirred solution of 439-2 (1 g, 3.67 mmol, 1.0 equiv) and I-2 (1 g, 3.67 mmol, 1.0 equiv) in DCE (10 mL) was added $NaBH(OAc)_3$ (1.6 g, 7.34 mmol, 2.0 equiv) at room

temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 439-3 (1.4 g, 70%) as an off-white solid.

4. Synthesis of 439-4

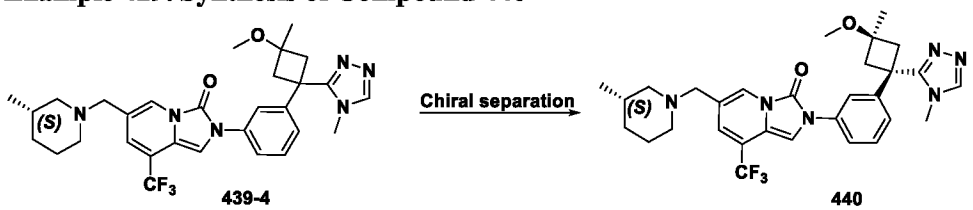
[1534] To a stirred solution of 439-3 (1 g, 1.84 mmol, 1.0 equiv) and pyridine (0.9 g, 11.05 mmol, 6.0 equiv) in DCM (10 mL) was added triphosgene (0.2 g, 0.64 mmol, 0.35 equiv) at room temperature. The resulting mixture was stirred for 1 h at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 439-4 (520 mg, 50%) as a yellow solid.

5. Synthesis of 439

[1535] The 439-4 (450 mg, 0.75 mmol, 1.0 equiv, 95%) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 5.12; RT2(min): 6.49; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 14) to afford 439 (48 mg, 11%) as a yellow solid.

LC-MS-439: (ES, m/z): $[M+H]^+$ 569. H-NMR-439: (400 MHz, *CD_3OD*, δ ppm): 0.90-0.96 (m, 4H), 1.32 (s, 3H), 1.57-1.78 (m, 4H), 1.93-2.02 (m, 1H), 2.84-2.97 (m, 4H), 3.13-3.25 (m, 5H), 3.42-3.48 (m, 2H), 3.50 (s, 3H), 7.13-7.16 (d, 2H), 7.43-7.45 (d, 1H), 7.54-7.63 (m, 2H), 7.68 (s, 1H), 7.89 (s, 1H), 8.30 (s, 1H).

Example 429. Synthesis of Compound 440



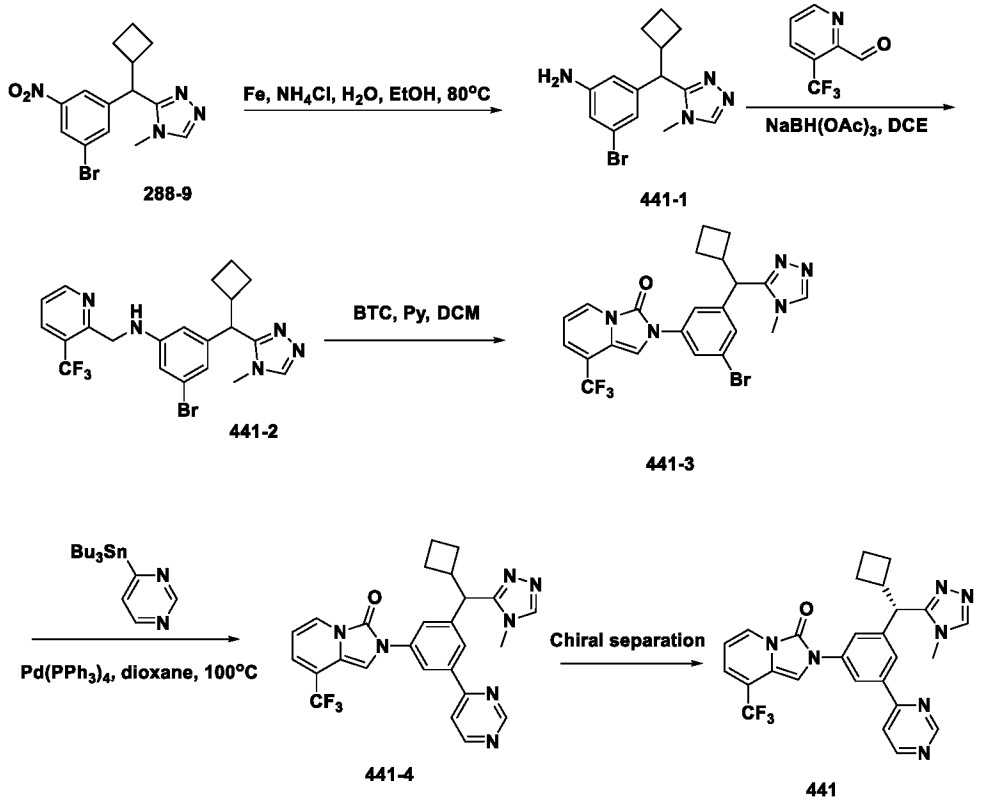
1. Synthesis of 440

[1536] The 439-4 (450 mg, 0.75 mmol, 1.0 equiv, 95%) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate:

20 mL/min; Gradient: 40% B to 40% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 5.12; RT2(min): 6.49; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.5 mL; Number of Runs: 14) to afford 440 (328 mg, 73%) as a yellow solid.

LC-MS-440: (ES, m/z): $[M+H]^+$ 569. H-NMR-440: (400 MHz, *CD_3OD*, δ ppm): 0.90-0.98 (m, 4H), 1.26-1.30 (m, 3H), 1.57-1.77 (m, 4H), 1.95-2.00 (m, 1H), 2.85-2.91 (m, 2H), 2.96-2.99 (m, 2H), 3.11-3.18 (m, 2H), 3.20(s, 3H), 3.33-3.36 (m, 2H), 3.41 (s, 3H), 7.12-7.15 (d, 2H), 7.25-7.27 (d, 1H), 7.54-7.63 (m, 2H), 7.67 (s, 1H), 7.74 (s, 1H), 8.41(s, 1H).

Example 430. Synthesis of Compound 441



1. Synthesis of 441-1

[1537] To a stirred solution of 288-9 (2.75 g, 7.830 mmol, 1 equiv) and Fe (1.31 g, 23.490 mmol, 3 equiv) in EtOH (60 mL)/H_2O (20 mL) was added NH_4Cl (4.19 g, 78.300 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for 3h at 80°C. The resulting mixture was filtered, the filter cake was washed with DCM (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (30:1) to afford 441-1 (2.4 g, 95.42%) as an off-white solid.

2. Synthesis of 441-2

[1538] To a stirred solution of 441-2 (2.4 g, 7.471 mmol, 1 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (1.44 g, 8.218 mmol, 1.1 equiv) in DCE (30 mL) was added $NaBH(OAc)_3$ (3.17 g, 14.942 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (200 mL) at room temperature. The aqueous layer was extracted with DCM (3x80 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with MTBE (100 mL). This resulted in 441-2 (3.1 g, 82.92%) as an off-white solid.

3. Synthesis of 441-3

[1539] To a stirred solution of 441-2 (3.1 g, 6.454 mmol, 1 equiv) and Pyridine (5.10 g, 64.540 mmol, 10 equiv) in DCM (60 mL) were added Triphosgene (0.77 g, 2.582 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (200 mL) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The product was precipitated by the addition of MTBE. This resulted in 441-3 (3 g, 86.30%) as a yellow solid.

4. Synthesis of 441-4

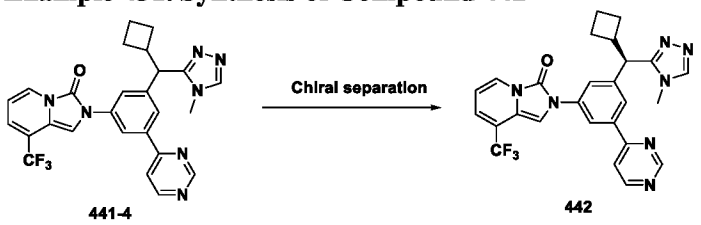
[1540] To a stirred solution of 441-3 (400 mg, 0.790 mmol, 1 equiv) and 4-(tributylstannyl)pyrimidine (583.24 mg, 1.580 mmol, 2 equiv) in dioxane (6 mL) were added $Pd(PPh_3)_4$ (136.94 mg, 0.118 mmol, 0.15 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 441-4 (300 mg, 72.12%) as a yellow solid.

5. Synthesis of 441

[1541] The 441-4 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.18; RT2(min): 11.04; the first peak is product) to afford 441 (70.8 mg, 23.08%) as a yellow solid.

LC-MS-441: (ES, *m/z*): $[M+H]^+$ 506. H-NMR-441: (400 MHz, DMSO-d6, δ *ppm*): 1.73-1.84 (m, 5H), 2.11-2.13 (m, 1H), 3.28-3.30 (m, 1H), 3.48 (s, 3H), 4.40-4.43 (d, 1H), 6.29-6.32 (m, 1H), 7.11-7.13 (d, 1H), 7.52 (s, 1H), 7.79-7.81 (d, 1H), 8.04 (s, 1H), 8.09 (s, 1H), 8.16-8.17 (d, 1H), 8.35 (s, 1H), 8.41 (s, 1H), 8.82-8.93 (d, 1H), 9.29 (s, 1H).

Example 431. Synthesis of Compound 442

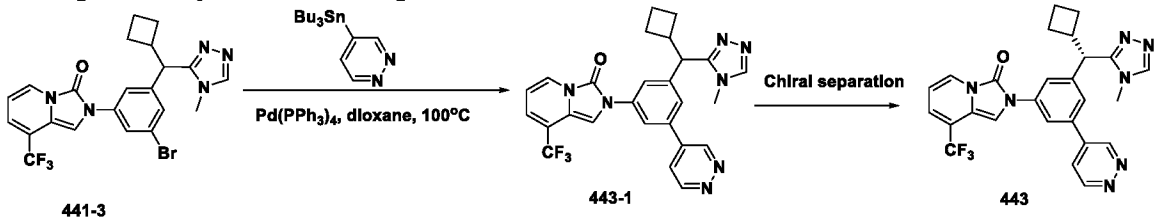


1. Synthesis of 442

[1542] The 441-4 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.18; RT2(min): 11.04; the second peak is product) to afford 442 (66.9 mg, 21.90%) as a yellow solid.

LC-MS-442: (ES, *m/z*): $[M+H]^+$ 506. H-NMR-442: (400 MHz, DMSO-d6, δ *ppm*): 1.73-1.83 (m, 5H), 2.10-2.12 (m, 1H), 3.28-3.30 (m, 1H), 3.48 (s, 3H), 4.40-4.43 (d, 1H), 6.29-6.32 (m, 1H), 7.11-7.13 (d, 1H), 7.53 (s, 1H), 7.79-7.81 (d, 1H), 8.04 (s, 1H), 8.09 (s, 1H), 8.16-8.17 (d, 1H), 8.35 (s, 1H), 8.41 (s, 1H), 8.82-8.93 (d, 1H), 9.29 (s, 1H).

Example 432. Synthesis of Compound 443



1. Synthesis of 443-1

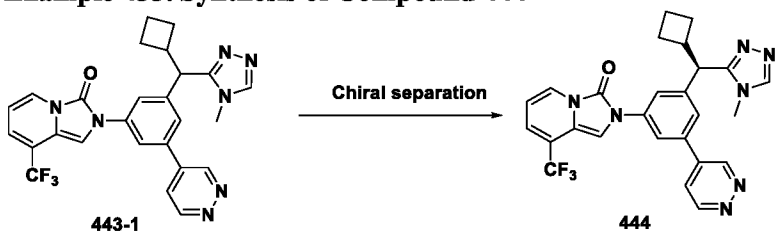
[1543] To a stirred solution of 441-3 (400 mg, 0.790 mmol, 1 equiv) and 4-(tributylstannyl)pyridazine (583.24 mg, 1.580 mmol, 2 equiv) in dioxane (6 mL) was added $Pd(PPh_3)_4$ (136.94 mg, 0.118 mmol, 0.15 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 443-1 (250 mg, 60.10%) as a yellow solid.

2. Synthesis of 443-0

[1544] The 443-1 (250 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 22 min; Wave Length: 220/254 nm; RT1(min): 11.27; RT2(min): 16.99; the first peak is product) to afford 443 (88.9 mg, 34.71%) as a yellow solid.

LC-MS-443: (ES, *m/z*): $[M+H]^+$ 506. H-NMR-443: (400 MHz, DMSO-d6, δ *ppm*): 1.71-1.90 (m, 5H), 2.08-2.12 (m, 1H), 3.28-3.33 (m, 1H), 3.49 (s, 3H), 4.37-4.39 (d, 1H), 6.28-6.32 (m, 1H), 7.10-7.12 (d, 1H), 7.59 (s, 1H), 7.78-7.80 (d, 2H), 8.05-8.09 (d, 2H), 8.10 (s, 1H), 8.34 (s, 1H), 9.33-9.34 (d, 1H), 9.71 (s, 1H).

Example 433. Synthesis of Compound 444

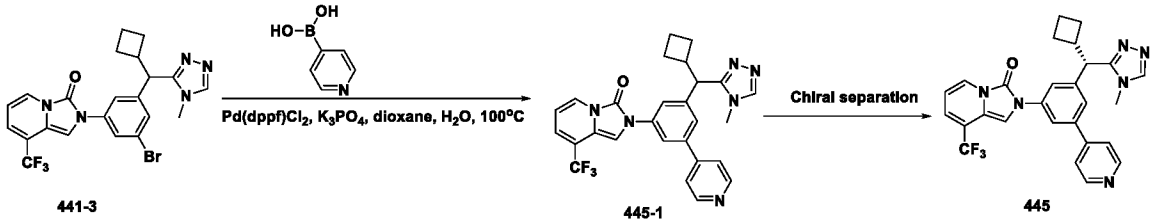


1. Synthesis of 444

[1545] The 443-1 (250 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 90% B to 90% B in 22 min; Wave Length: 220/254 nm; RT1(min): 11.27; RT2(min): 16.99; the second peak is product) to afford 444 (87.0 mg, 34.35%) as a yellow solid.

LC-MS-444: (ES, *m/z*): $[M+H]^+$ 506. H-NMR-444: (400 MHz, DMSO-d6, δ *ppm*): 1.73-1.89 (m, 5H), 2.08-2.12 (m, 1H), 3.28-3.33 (m, 1H), 3.49 (s, 3H), 4.37-4.39 (d, 1H), 6.28-6.32 (m, 1H), 7.10-7.12 (d, 1H), 7.59 (s, 1H), 7.78-7.80 (d, 2H), 8.05-8.10 (m, 3H), 8.35 (s, 1H), 9.33-9.34 (d, 1H), 9.71 (s, 1H).

Example 434. Synthesis of Compound 445



1. Synthesis of 445-1

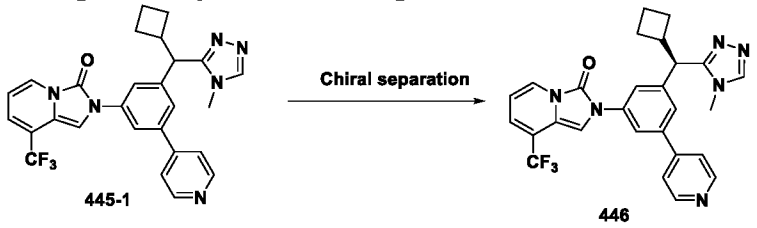
[1546] To a stirred solution of 441-3 (400 mg, 0.790 mmol, 1 equiv) and pyridin-4-ylboronic acid (194.21 mg, 1.580 mmol, 2 equiv) in dioxane (6 mL)/H_2O (1.5 mL) was added K_3PO_4 (419.23 mg, 1.975 mmol, 2.5 equiv) and $Pd(dppf)Cl_2$ (57.81 mg, 0.079 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 100°C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 445-1 (320 mg, 77.08%) as a yellow solid.

2. Synthesis of 445

[1547] The 445-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 4.50; RT2(min): 6.70; the first peak is product) to afford 445 (130.0 mg, 39.73%) as a yellow solid.

LC-MS-445: (ES, *m/z*): $[M+H]^+$ 505. H-NMR-445: (400 MHz, DMSO-d6, δ *ppm*): 1.71-1.89 (m, 5H), 2.08-2.11 (m, 1H), 3.29-3.33 (m, 1H), 3.49 (s, 3H), 4.37-4.39 (d, 1H), 6.28-6.31 (m, 1H), 7.10-7.12 (d, 1H), 7.54 (s, 1H), 7.66 (s, 1H), 7.74-7.80 (m, 3H), 7.93 (s, 1H), 8.03 (s, 1H), 8.35 (s, 1H), 8.68-8.69 (d, 2H).

Example 435. Synthesis of Compound 446

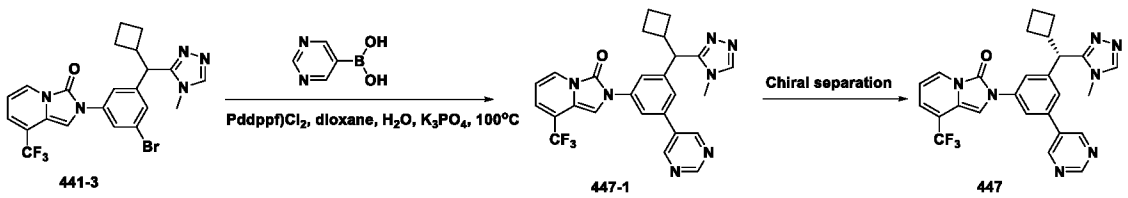


1. Synthesis of 446

[1548] The 445-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 4.50; RT2(min): 6.70; the second peak is product) to afford 446 (129.3 mg, 40.04%) as a yellow solid.

LC-MS-446: (ES, *m/z*): $[M+H]^+$ 505. H-NMR-446: (400 MHz, DMSO-d6, δ *ppm*): 1.71-1.89 (m, 5H), 2.08-2.13 (m, 1H), 3.29-3.33 (m, 1H), 3.49 (s, 3H), 4.37-4.39 (d, 1H), 6.28-6.31 (m, 1H), 7.10-7.12 (d, 1H), 7.54 (s, 1H), 7.66 (s, 1H), 7.74-7.80 (m, 3H), 7.93 (s, 1H), 8.02 (s, 1H), 8.34 (s, 1H), 8.67-8.69 (d, 2H).

Example 436. Synthesis of Compound 447



1. Synthesis of 447-1

[1549] To a stirred mixture of 441-3 (400 mg, 0.790 mmol, 1 equiv) and pyrimidin-5-

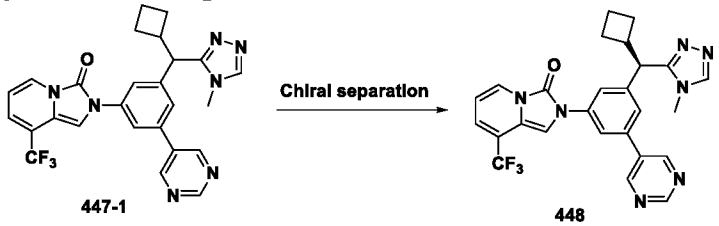
ylboronic acid (195.78 mg, 1.580 mmol, 2 equiv) in dioxane (4 mL) and H_2O (1 mL) were added K_3PO_4 (335.38 mg, 1.580 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (57.81 mg, 0.079 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 447-1 (260 mg, 65.11%) as a yellow solid.

2. Synthesis of 447

[1550] 447-1 (260 mg, 0.514 mmol, 1 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 19 min; Wave Length: 220/254 nm; RT1(min): 11.1; RT2(min): 14.82; the first peak was product) to afford 447 (92.3 mg, 35.50%) as a yellow solid.

LCMS-447:(ES,m/z): $[M+H]^+$ 506. NMR-447: (400 MHz, DMSO, ppm): δ 1.71-1.86 (m, 5H), 2.08-2.13 (m, 1H), 3.30-3.32 (m, 1H), 3.50 (s, 3H), 4.35-4.38 (d, 1H), 6.28-6.32 (t, 1H), 7.10-7.12 (d, 1H), 7.57 (s, 1H), 7.69 (s, 1H), 7.78-7.80 (d, 1H), 8.01 (s, 1H), 8.34 (s, 1H), 9.21-9.24 (m, 3H).

Example 437. Synthesis of Compound 448

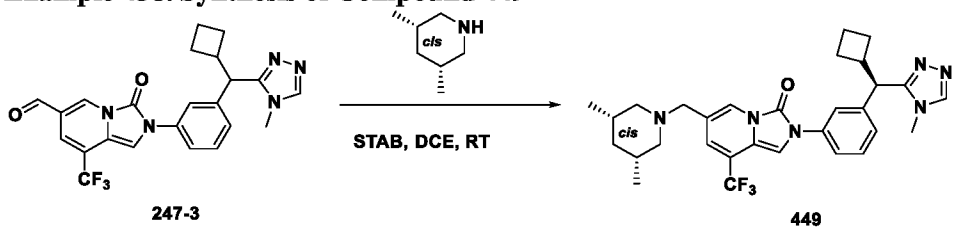


1. Synthesis of 448

[1551] 447-1 (260 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 19 min; Wave Length: 220/254 nm; RT1(min): 11.1; RT2(min): 14.82; the second peak was product) to afford 448 (94 mg, 36.15%) as a yellow solid.

LCMS-448:(ES, m/z): $[M+H]^+$ 506. NMR-448: (400 MHz, DMSO, ppm): δ 1.71-1.85 (m, 5H), 2.08-2.12 (m, 1H), 3.32-3.36 (m, 1H), 3.50 (s, 3H), 4.35-4.38 (d, 1H), 6.28-6.32 (t, 1H), 7.10-7.12 (d, 1H), 7.57 (s, 1H), 7.69 (s, 1H), 7.78-7.80 (d, 1H), 8.01 (s, 1H), 8.34 (s, 1H), 9.21-9.24 (m, 3H).

Example 438. Synthesis of Compound 449

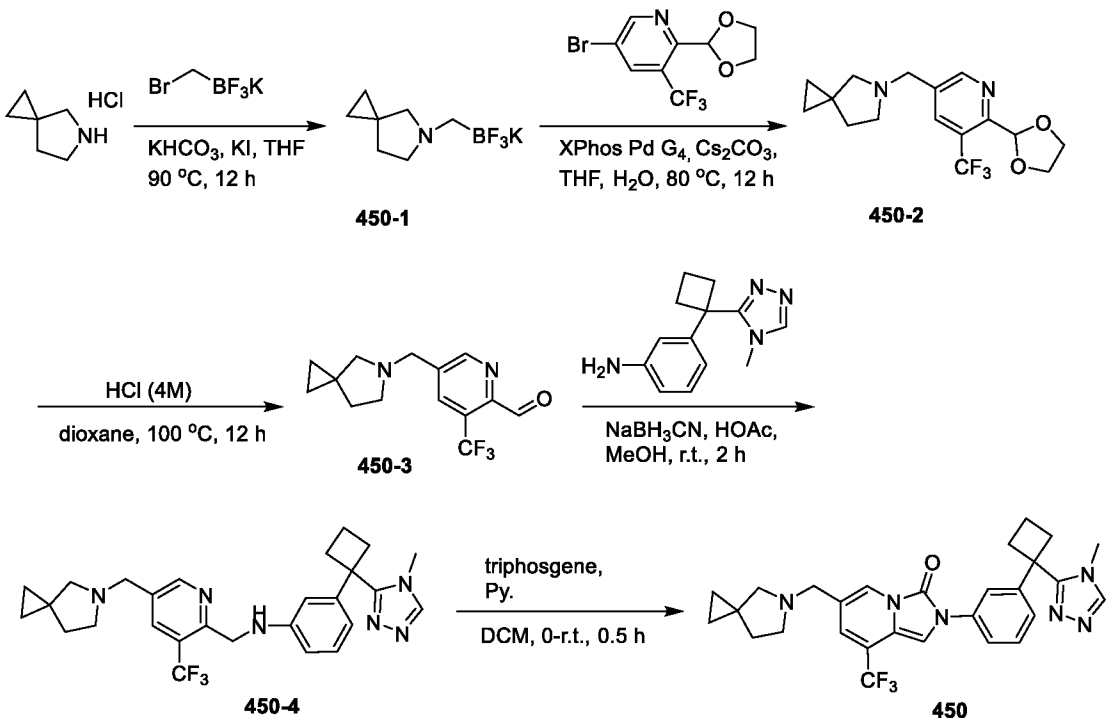


Synthesis of 449

[1552] To a stirred solution of 247-3 (300 mg, 0.659 mmol, 1 equiv) and (3R,5S)-3,5-dimethylpiperidine (223.70 mg, 1.977 mmol, 3 equiv) in DCE (5 mL) was added STAB (279.21 mg, 1.317 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for additional 6h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 54% B to 74% B in 8 min, 74% B; Wave Length: 254 nm; RT1(min): 7.1) to afford 449 (80.2 mg, 21.81%) as a yellow solid.

LC-MS-449: (ES, *m/z*): $[M+H]^+$ 553. H-NMR-449: (400 MHz, DMSO-d6, δ *ppm*): 0.44-0.55 (m, 1H), 0.80-0.82 (d, 6H), 1.43-1.48 (m, 2H), 1.59-1.81 (m, 8H), 2.08-2.10 (m, 1H), 2.75-2.80 (m, 2H), 3.25-3.29 (m, 3H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.42-7.46 (m, 1H), 7.65-7.74 (m, 3H), 8.32 (s, 1H).

Example 439. Synthesis of Compound 450



1. Synthesis of 450-1

[1553] A mixture of potassium;bromomethyl(trifluoro)boranuide (826.67 mg, 4.12 mmol, 1.1 equiv), 5-azaspiro[2.4]heptane (0.5 g, 3.74 mmol, 1 equiv, HCl salt), $KHCO_3$ (749 mg, 7.48 mmol, 2 equiv) and KI (62.1 mg, 374 umol, 0.1 equiv) in THF (8 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuum. The residue was triturated with acetone (15 mL) at 40 °C for 1 hr. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 450-1 (650 mg, crude) as a yellow oil.

2. Synthesis of 450-2

[1554] To a solution of 450-1 (550 mg, 2.53 mmol, 2 equiv) and I-2 (377 mg, 1.27 mmol, 1 equiv) in THF (4 mL) and H_2O (1 mL) was added Cs_2CO_3 (1.24 g, 3.80 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (109 mg, 126 umol, 0.1 equiv), the mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The combined mixture was diluted with water (10 mL), extracted with EtOAc (10 mL x3). The combined organic layers dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc/PE (3:1) to afford 450-2 (360 mg, 86.5%) as a yellow oil.

^{1}H-NMR-450-2: (400 MHz, METHANOL-d_4) δ 8.80 (s, 1H), 8.19 (s, 1H), 6.18 (d, J = 0.8 Hz, 1H), 4.31-4.22 (m, 2H), 4.10-4.02 (m, 2H), 3.80 (s, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.54 (s, 2H), 1.87 (t, J = 6.9 Hz, 2H), 0.57 (d, J = 7.6 Hz, 4H)

3. Synthesis of 450-3

[1555] To a solution of 450-2 (0.36 g, 1.1 mmol, 1 equiv) in dioxane (3.6 mL) was added HCl (4 M, 3.6 mL, 13.13 equiv), the mixture was stirred at 100 °C for 12 hr. The reaction mixture was adjusted pH to 8 by Sat.$NaHCO_3$, extracted with DCM (8 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc/PE (1:3) to afford 450-3 (230 mg, 74%) as a light yellow oil.

^{1}H-NMR-450-3: (400 MHz, CHLOROFORM-d) δ 10.01 (d, J = 1.2 Hz, 1H), 8.69 (s, 1H), 7.95 (s, 1H), 3.57 (s, 2H), 2.55 (t, J = 6.8 Hz, 2H), 2.29 (s, 2H), 1.68-1.60 (m, 2H), 0.34 (d, J = 3.2 Hz, 4H)

4. Synthesis of 450-4

[1556] To a solution of 450-3 (0.23 g, 809 umol, 1 equiv) and 3-(1-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)aniline (184 mg, 809 umol, 1 equiv) in MeOH (3 mL) was added AcOH (139 uL, 2.43 mmol, 3 equiv), the mixture was stirred at 20 °C for 1 hr, then $NaBH_3CN$ (101 mg, 1.62 mmol, 2 equiv) was added to the mixture, the result mixture was stirred at 20 °C for 1 hr under nitrogen atmosphere. The reaction mixture was diluted with Sat.$NaHCO_3$ (20 mL), extracted with EtOAc (15 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 450-4 (350 mg, 87%) as a yellow solid.

^{1}H-NMR-450-4: (400 MHz, CHLOROFORM-d) δ 8.60 (s, 1H), 7.96-7.89 (m, 2H), 7.12 (t, J = 8.0 Hz, 1H), 6.64-6.48 (m, 3H), 4.46 (s, 2H), 3.67 (s, 2H), 3.11 (s, 3H), 2.95-2.84 (m, 2H), 2.78-2.70 (m, 2H), 2.66-2.57 (m, 2H), 2.47 (s, 2H), 2.06-2.00 (m, 2H), 1.79 (t, J = 6.8 Hz, 2H), 0.49 (s, 4H)

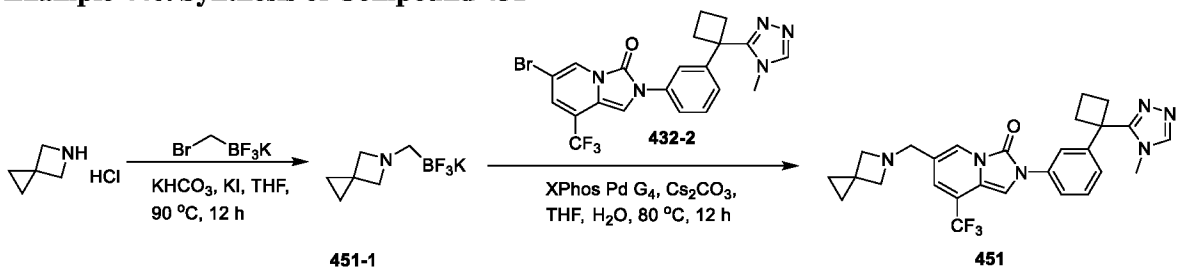
5. Synthesis of 450

[1557] To a solution of 450-4 (0.27 g, 543 umol, 1 equiv) in DCM (3.5 mL) was added pyridine (263 uL, 3.26 mmol, 6 equiv), then the mixture was cooled to 0 °C, bis(trichloromethyl) carbonate (80.6 mg, 271 umol, 0.5 equiv) was added to the mixture at 0 °C, the mixture was stirred at 20 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat. $NaHCO_3$ (15 mL), extracted with DCM (8 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in

vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give crude product. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 8.5) to afford 450 (81 mg, 28%) as a yellow solid.

MS-450: (ES, m/z): $[M+H]^+$ 523.3. ^{1}H-NMR-450: (400 MHz, METHANOL-d_4) δ 8.38 (s, 1H), 8.37 (s, 1H), 7.90 (s, 1H), 7.77-7.72 (m, 1H), 7.65-7.53 (m, 2H), 7.37 (d, J = 7.2 Hz, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 3.97 (s, 2H), 3.35 (s, 3H), 3.31-3.26 (m, 2H), 3.08-2.99 (m, 4H), 2.89-2.78 (m, 2H), 2.23-2.10 (m, 2H), 2.04 (t, J = 7.2 Hz, 2H), 0.73 (d, J = 8.4 Hz, 4H).

Example 440. Synthesis of Compound 451



1. Synthesis of 451-1

[1558] To a solution of potassium;bromomethyl(trifluoro)boranuide (839 mg, 4.18 mmol, 1 equiv), 5-azaspiro[2.3]hexane;hydrochloride (500 mg, 4.18 mmol, 1 equiv), $KHCO_3$ (837 mg, 8.36 mmol, 2 equiv) and KI (69.4 mg, 418. umol, 0.1 equiv) in THF (13 mL) was stirred at 90 °C for 12 h under N_2. The mixture was concentrated under reduced pressure to give a residue. The residue was triturated with acetone at 40 °C for 2 h, then the mixture was filtered and filtrate was concentrated under reduced pressure to afford 451-1 (700 mg, crude) as a white solid.

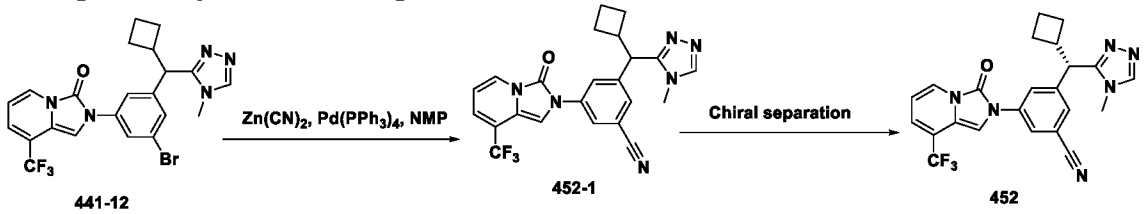
2. Synthesis of 451

[1559] To a solution of 432-2 (300 mg, 609 umol, 1 equiv) and 451-1 (309 mg, 1.52 mmol, 2.5 equiv) in THF (8 mL) and H_2O (2 mL) was added Cs_2CO_3 (595.66 mg, 1.83 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl] phenyl]palladium(1+) (52.4 mg, 60.9 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was extracted with water (120 mL) and EtOAc (40 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was

purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give a crude product. The crude product (170 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 8.3) to afford 451 (51 mg, 16.3%) as a yellow solid.

MS-451: (ES, m/z): $[M+H]^+$ 509.2. H-NMR-451: (400 MHz, METHANOL-d4) δ=8.51 (s, 1H), 8.36 (s, 1H), 7.87 (s, 1H), 7.75-7.73 (m, 1H), 7.60-7.52 (m, 2H), 7.32 (br d, J = 7.6 Hz, 1H), 7.18 (s, 1H), 7.08 (s, 1H), 3.97 (s, 2H), 3.87 (s, 4H), 3.33 (s, 3H), 3.04-2.97 (m, 2H), 2.84-2.77 (m, 2H), 2.18-2.07 (m, 2H), 0.71 (s, 4H).

Example 441. Synthesis of Compound 452



1. Synthesis of 452-1

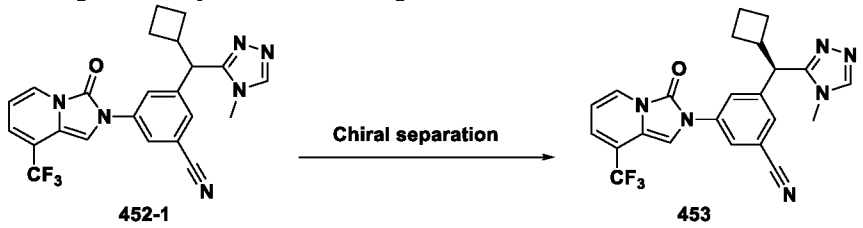
[1560] To a stirred solution of 441-12 (400 mg, 0.790 mmol, 1 equiv) and $Zn(CN)_2$ (371.05 mg, 3.160 mmol, 4 equiv) in NMP (5 mL) was added $Pd(PPh_3)_4$ (91.29 mg, 0.079 mmol, 0.1 equiv) under argon atmosphere. The resulting mixture was stirred for 4h at 140°C under argon atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (15mL) at room temperature. The resulting mixture was extracted with EtOAc (1 x15 mL). The combined organic layers were washed with sat. LiCl (aq.) (15mL) at room temperature, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 452-1 (290 mg, 81.13%) as a yellow solid.

2. Synthesis of 452

[1561] The 452-1 (290 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 17 min; Wave Length: 220/254 nm; RT1(min): 12.43; RT2(min): 14.79; The first peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.25 mL; Number of Runs: 18) to afford 452 (29.8 mg, 9.77%) as a yellow solid.

LC-MS-452: (ES, *m/z*): $[M+H]^+$ 454. H-NMR-452: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.69-1.85 (m, 5H), δ2.06-2.07 (d, 1H), δ3.21-3.23 (m, 1H), δ3.48 (s, 3H), δ4.38-4.40 (d, 1H), δ6.28-6.31 (t, 1H), δ7.11-7.13 (d, 1H), δ7.51 (s, 1H), δ7.69 (s, 1H), δ7.78-7.80 (d, 1H), δ8.25-8.26 (d, 2H), δ8.36 (s, 1H).

Example 442. Synthesis of Compound 453



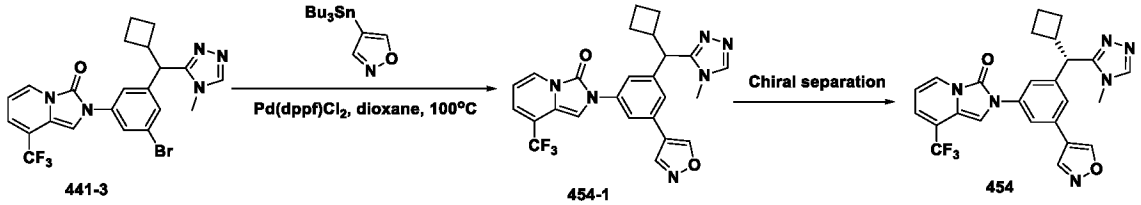
452-1 453

1. Synthesis of 453

[1562] The 452-1 (290 mg) was purified by Chiral separation with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 17 min; Wave Length: 220/254 nm; RT1(min): 12.43; RT2(min): 14.79; The second peak is product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.25 mL; Number of Runs: 18) to afford 453 (11.6 mg, 3.92%) as a yellow solid.

LC-MS-453: (ES, *m/z*): $[M+H]^+$ 454. H-NMR-453: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.71-1.80 (m, 5H), δ2.06-2.07 (d, 1H), δ3.22-3.23 (m, 1H), δ3.48 (s, 3H), δ4.38-4.40 (d, 1H), δ6.28-6.31 (t, 1H), δ7.11-7.13 (d, 1H), δ7.51 (s, 1H), δ7.69 (s, 1H), δ7.78-7.80 (d, 1H), δ8.24-8.25 (d, 2H), δ8.36 (s, 1H).

Example 443. Synthesis of Compound 454



441-3 454-1 454

1. Synthesis of 454-1

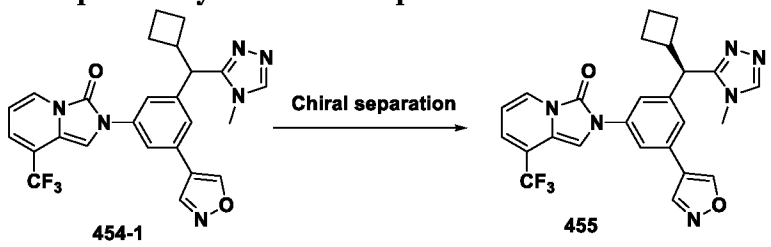
[1563] To a stirred solution of 441-3 (850 mg, 1.68 mmol, 1.0 equiv) and 4-(tributylstannyl)-1,2-oxazole (902 mg, 2.52 mmol, 1.5 equiv) in dioxane (15 mL) was added Pd(dppf)Cl2 (137 mg, 0.17 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH=20:1) to afford 454-1 (230 mg, 28%) as a yellow solid.

2. Synthesis of 454

[1564] The 454-1 (230 mg, 0.47 mmol, 1.0 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 11.39; RT2(min): 14.18; the first peak was product) to afford 454 (64 mg, 27%) as a yellow solid.

LC-MS-454: (ES, m/z): [M+H] + 495. H-NMR-454: (400 MHz, DMSO-d6, δ ppm): 1.70-1.82 (m, 5H), 2.08-2.12 (m, 1H), 3.28-3.30 (m, 1H), 3.45 (s, 3H), 4.23-4.28 (d, 1H), 6.28-6.32 (t, 1H), 7.09-7.13 (d, 1H), 7.43 (s, 1H), 7.57 (s, 1H), 7.76-7.80 (m, 1H), 7.83 (s, 1H), 7.89 (s, 1H), 8.34 (s,1H), 9.22 (s,1H), 9.52 (s, 1H).

Example 444. Synthesis of Compound 455

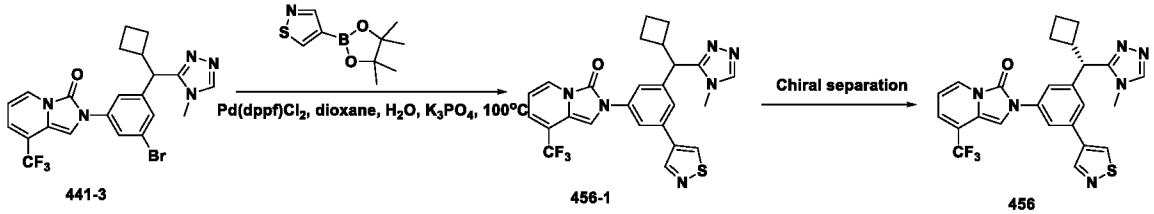


1. Synthesis of 455

[1565] The 454-1 (230 mg, 0.47 mmol, 1.0 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 16.5 min; Wave Length: 220/254 nm; RT1(min): 11.39; RT2(min): 14.18; the second peak was product) to afford 455 (36 mg, 15%) as a yellow solid.

LC-MS-455: (ES, m/z): $[M+H]^+$ 495. H-NMR-455: (400 MHz, DMSO-*d6*, δ ppm): 1.70-1.74 (m, 5H), 1.75-1.82 (m, 4H), 2.08-2.12 (m, 1H), 3.28-3.30 (m, 1H), 3.47 (s, 3H), 4.25-4.28 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.43 (s, 1H), 7.58 (s, 1H), 7.78-7.80 (d, 1H), 7.83 (s, 1H), 7.89 (s, 1H), 8.34 (s,1H), 9.21 (s,1H), 9.52 (s, 1H).

Example 445. Synthesis of Compound 456



1. Synthesis of 456-1

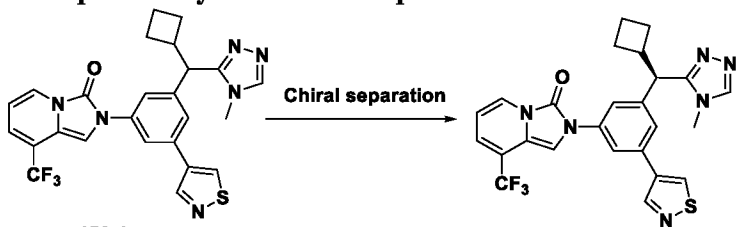
[1566] To a stirred mixture of 441-3 (400 mg, 0.790 mmol, 1 equiv) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-thiazole (250.14 mg, 1.185 mmol, 1.5 equiv) in dioxane (4 mL) and H_2O (1 mL) were added K_3PO_4 (335.38 mg, 1.580 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (57.81 mg, 0.079 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 456-1 (320 mg, 79.34%) as a yellow solid.

2. Synthesis of 456

[1567] 456-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 17 min; Wave Length: 220/254 nm; RT1(min): 9.53; RT2(min): 12.25; the first peak was product) to afford 456 (114.6 mg, 35.81%) as a yellow solid.

LCMS-456:(ES, m/z): $[M+H]^+$ 511. NMR-456: (400 MHz, DMSO, ppm): δ 1.71-1.84 (m, 5H), 2.08-2.13 (m, 1H), 3.26-3.28 (m, 1H), 3.53 (s, 3H), 4.30-4.32 (d, 1H), 6.28-6.32 (t, 1H), 7.10-7.12 (d, 1H), 7.49 (s, 1H), 7.66 (s, 1H), 7.78-7.80 (d, 1H), 7.84 (s, 1H), 7.99 (s, 1H), 8.34 (s, 1H), 9.09 (s, 1H), 9.43 (s, 1H).

Example 446. Synthesis of Compound 457



456-1 457

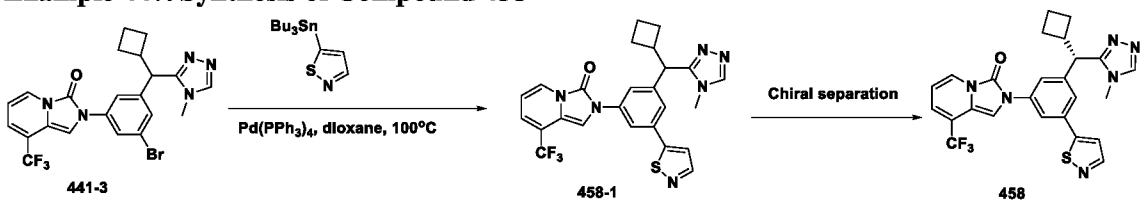
1. Synthesis of 457

[1568] 456-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 17 min; Wave Length: 220/254 nm; RT1(min): 9.53; RT2(min): 12.25; the second peak was product) to afford 457 (103.0 mg, 32.19%) as a yellow solid.

LCMS-457(ES, m/z): $[M+H]^+$ 511. NMR-457 (400 MHz, DMSO, ppm): δ 1.71-1.84 (m, 5H), 2.08-2.13 (m, 1H), 3.34-3.43 (m, 1H), 3.49 (s, 3H), 4.30-4.33 (d, 1H), 6.28-6.32 (t, 1H),

7.10-7.12 (d, 1H), 7.49 (s, 1H), 7.66 (s, 1H), 7.78-7.80 (d, 1H), 7.84 (s, 1H), 7.99 (s, 1H), 8.34 (s, 1H), 9.09 (s, 1H), 9.43 (s, 1H).

Example 447. Synthesis of Compound 458



1. Synthesis of 458-1

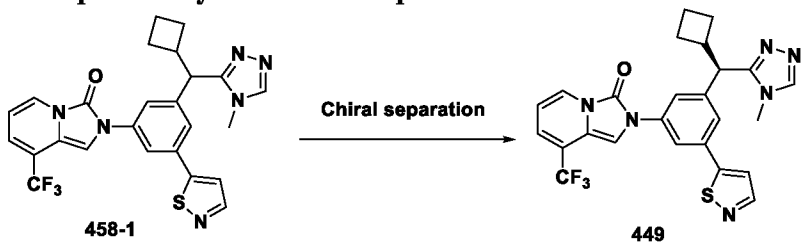
[1569] To a stirred solution of 441-3 (400 mg, 0.790 mmol, 1 equiv) and 5-(tributylstannyl)-1,2-thiazole (443.39 mg, 1.185 mmol, 1.5 equiv) in dioxane (4 mL) was added $Pd(PPh_3)_4$ (91.29 mg, 0.079 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 458-1 (360 mg, 89.26%) as a yellow solid.

2. Synthesis of 458

[1570] 458-1 (360 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH, Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 17 min; Wave Length: 220/254 nm; RT1(min): 9.53; RT2(min): 12.25; The first peak was product) to afford 458 (132.6 mg, 36.83%) as a yellow solid.

LCMS-458 (ES, m/z): $[M+H]^+$ 511. NMR-458 (400 MHz, DMSO, ppm): δ 1.73-1.84 (m, 5H), 2.08-2.12 (m, 1H), 3.27-3.29 (m, 1H), 3.50 (s, 3H), 4.37-4.40 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.51 (s, 1H), 7.60 (s, 1H), 7.79-7.81 (d, 1H), 7.87 (s, 1H), 7.92 (s, 1H), 8.06 (s, 1H), 8.37 (s, 1H), 8.64 (s, 1H).

Example 448. Synthesis of Compound 459



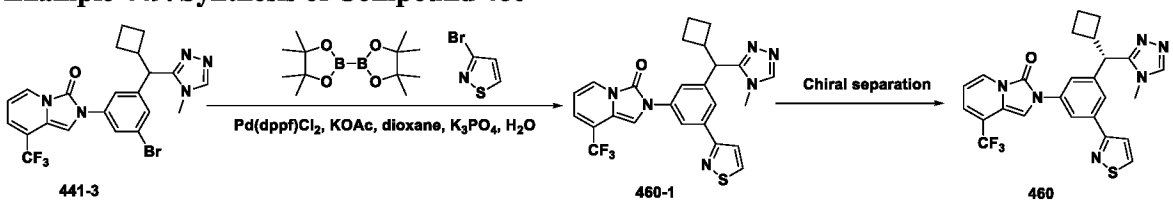
Synthesis of 459

[1571] 458-1 (360 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 17

min; Wave Length: 220/254 nm; RT1(min): 9.53; RT2(min): 12.25; the second peak was product) to afford 459 (69.3 mg, 19.25%) as a yellow solid.

LCMS-459 (ES, m/z): $[M+H]^+$ 511. NMR-459 (400 MHz, DMSO, ppm): δ 1.71-1.83 (m, 5H), 2.08-2.11 (m, 1H), 3.27-3.30 (m, 1H), 3.50 (s, 3H), 4.37-4.40 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.51 (s, 1H), 7.60 (s, 1H), 7.79-7.80 (d, 1H), 7.87 (s, 1H), 7.92 (s, 1H), 8.06 (s, 1H), 8.35 (s, 1H), 8.64 (s, 1H).

Example 449. Synthesis of Compound 460



1. Synthesis of 460-1

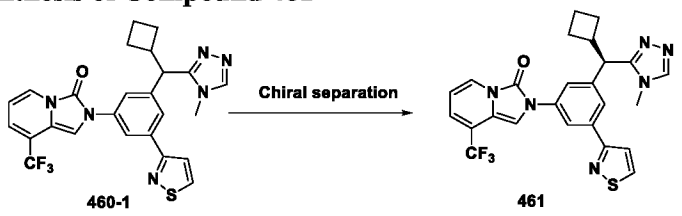
[1572] To a stirred mixture of 441-3 (1 g, 1.97 mmol, 1.0 equiv) and bis(pinacolato)diboron (0.5 g, 1.97 mmol, 1.0 equiv) in dioxane (10 mL) was added KOAc (190 mg, 1.97 mmol, 1.0 equiv) and $Pd(dppf)Cl_2$ (140 mg, 0.20 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. To the above mixture was added H_2O (3 mL),3-bromo-1,2-thiazole (490 mg, 2.96 mmol, 1.5 equiv), K_3PO_4 (840 mg, 3.95 mmol, 2.0 equiv) and $Pd(dppf)Cl_2$ (140 mg, 0.20 mmol, 0.1 equiv) was added under nitrogen atmosphere. The resulting mixture was stirred \overnight at 80°C. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=25:1) to afford 460-1 as a yellow solid.

2. Synthesis of 460

[1573] The 460-1 (350 mg, 0.69 mmol, 1.0 equiv) was purified by Prep-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 15 min; Wave Length: 220/254 nm; RT1(min): 8.90; RT2(min): 11.87; the first peak was product) to afford 460 (102.5 mg, 28%) as a yellow solid.

LC-MS-460 (ES, m/z): $[M+H]^+$ 511. H-NMR-460 (400 MHz, DMSO-*d6*, δ ppm): 1.76-1.88 (m, 5H), 2.11-2.14 (m, 1H), 3.25-3.27 (m, 1H), 3.47 (s, 3H), 4.36-4.39 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.49 (s, 1H), 7.79-7.81 (d, 1H), 7.90-7.91 (d, 1H), 8.01 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H), 9.20-9.21 (d, 1H).

Example 450. Synthesis of Compound 461

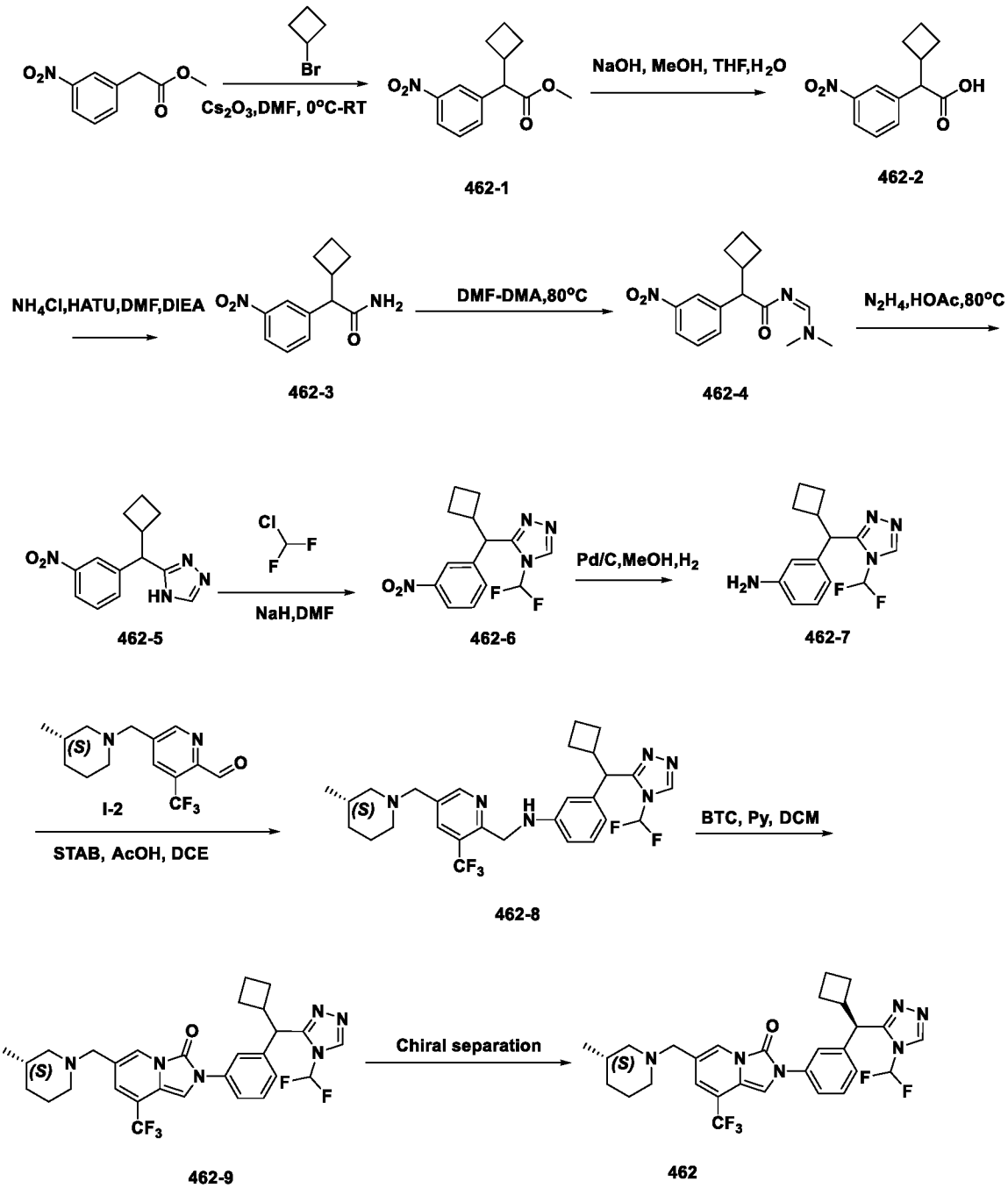


1. Synthesis of 461

[1574] The 460-1 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 15 min; Wave Length: 220/254 nm; RT1(min): 8.90; RT2(min): 11.87; the second peak was product) to afford crude product. The crude product (74 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 57% B in 8 min, 57% B; Wave Length: 220 nm; RT1(min): 7.28;) to 461 (28 mg, 8%) as a yellow solid.

LC-MS-461 (ES, m/z): $[M+H]^+$ 511. H-NMR-461 (400 MHz, DMSO-*d6*, δ ppm): 1.76-1.88 (m, 5H), 2.11-2.14 (m, 1H), 3.25-3.27 (m, 1H), 3.47 (s, 3H), 4.36-4.39 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.49 (s, 1H), 7.79-7.81 (d, 1H), 7.90-7.91 (d, 1H), 8.01 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H), 9.20-9.21 (d, 1H).

Example 451. Synthesis of Compound 462



1. Synthesis of 462-1

[1575] A solution of methyl 2-(3-nitrophenyl) acetate (70 g, 358.654 mmol, 1 equiv) in DMF (700 mL) was treated with Cs_2CO_3 (584.28 g, 1793.270 mmol, 5 equiv) for 1h at 0°C under nitrogen atmosphere. To the above mixture was added bromocyclobutane (145.26 g, 1075.962 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was

filtered the filter cake was washed with MTBE (2x500 mL). The filtrate was concentrated under reduced pressure. The crude product was re-crystallized from Heptane/MTBE (5:1 600mL) to afford 462-1 (61 g, 68.23%) as a Brown yellow solid.

2. Synthesis of 462-2

[1576] To a stirred mixture of H_2O (120 mL) and THF (120 mL) in MeOH (360 mL) were added 462-1 (61 g, 244.718 mmol, 1 equiv) and NaOH (19.58 g, 489.436 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The mixture was acidified to pH 7 with conc.HCl(100mL). The aqueous layer was extracted with EtOAc (3x500 mL). The resulting liquid was dried over anhydrous Na_2SO_4. The resulting mixture was concentrated under reduced pressure. This resulted in 462-2 (56 g, 94.36%) as a light red solid.

3. Synthesis of 462-3

[1577] To a stirred mixture of 462-2 (56 g, 238.056 mmol, 1 equiv) and DIEA (61.54 g, 476.112 mmol, 2 equiv) in DMF (600 mL) were added HATU (181.03 g, 476.112 mmol, 2 equiv) and NH_4Cl (38.20 g, 714.168 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (2L). The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 462-3 (55 g, 91.72%) as a Brown yellow solid.

4. Synthesis of 462-4

[1578] To a stirred solution of 462-3 (55 g, 234.787 mmol, 1 equiv) in DMF-DMA (550 mL) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 462-4 (50 g, 67.71%) as a Brown yellow solid.

5. Synthesis of 462-5

[1579] To a stirred solution of 462-4 (50 g, 172.810 mmol, 1 equiv) in HOAc (500 mL) at room temperature. To the above mixture was added hydrazine hydrate (400 mL, 8065.360 mmol, 46.67 equiv, 98%) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water

(500 mL). The aqueous layer was extracted with EtOAc (3x300 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 462-5 (40 g, 86.93%) as a Brown yellow solid.

6. Synthesis of 462-6

[1580] A solution of 462-5 (10 g, 38.718 mmol, 1 equiv) in DMF (100 mL) was treated with NaH (4.65 g, 193.590 mmol, 5 equiv) for 1h at 0°C. To the above mixture was added chlorodifluoromethane (6.70 g, 77.436 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The resulting mixture was diluted with water (500mL). The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 462-6 (5 g, 40.21%) as a yellow green solid.

7. Synthesis of 462-7

[1581] To a solution of 462-6 (5 g, 16.219 mmol, 1 equiv) in 100mL MeOH was added Pd/C (10%, 1g) under nitrogen atmosphere in a 250 mL round-bottom flask. The mixture was hydrogenated at room temperature for 3h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 462-7 (3 g, 64.47%) as a yellow green solid.

8. Synthesis of 462-8

[1582] A solution of 462-7 (1 g, 3.593 mmol, 1 equiv) in DCE (10 mL) was treated with I-2 (1.03 g, 3.593 mmol, 1 equiv) at room temperature under nitrogen atmosphere followed by the addition of AcOH (0.22 g, 3.593 mmol, 1 equiv) and STAB (2.28 g, 10.779 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with CH_3Cl (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 462-8 (1.2 g, 60.88%) as a yellow solid.

9. Synthesis of 462-9

[1583] A solution of 462-8 (600 mg, 1.094 mmol, 1 equiv) in DCM (6 mL) was treated with pyridine (519.06 mg, 6.564 mmol, 6 equiv) at 0°C followed by the addition of triphosgene (194.72 mg, 0.656 mmol, 0.6 equiv) at room temperature. The resulting mixture was stirred for 10 min at room temperature. The residue was acidified to pH 7 with saturated $NaHCO_3$ (aq.) (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x3 mL). The residue was

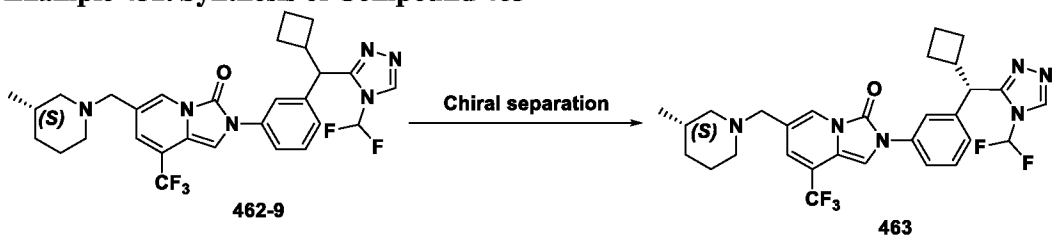
purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 462-9 (250 mg, 38.59%) as a yellow solid.

10. Synthesis of 462

[1584] The 462-9 (250 mg, 0.435 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 11 min; Wave Length: 220/254 nm; RT1(min): 8.34; RT2(min): 9.85; The second peak was product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.1 mL; Number of Runs: 18) to afford 462 (100 mg, 39.20%) as a yellow solid.

LC-MS-462 (ES, m/z): $[M+H]^+$ 575. H-NMR-462 (400 MHz, DMSO-d6, *ppm*): δ0.82-0.84 (m, 4H), δ1.58-1.67 (d, 1H), δ1.67-1.82 (m, 5H), δ1.82-1.99 (m, 5H), δ2.00-2.15 (d, 1H), δ2.75-2.87 (s, 2H), δ3.18-3.33 (m, 3H), δ4.41-4.43 (d, 1H), δ7.01 (d, 1H), δ7.09-7.23 (d, 1H), δ7.31 (s, 1H), δ7.39-7.41(d, 1H), δ7.47-7.65 (d, 1H), δ7.71 (d, 1H), δ7.75-7.82 (d, 1H), δ7.85-8.02 (d, 1H), δ8.89-8.94 (d, 1H).

Example 452. Synthesis of Compound 463



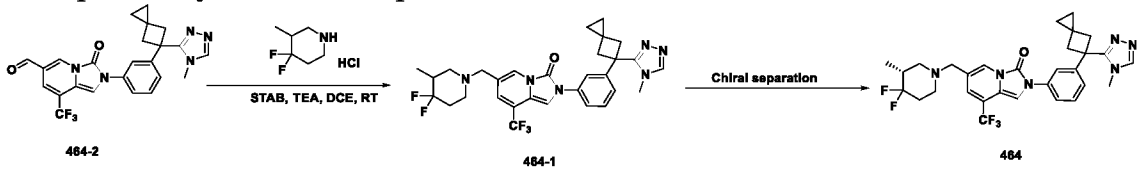
462-9 463

1. Synthesis of 463

[1585] The 462-9 (250 mg, 0.435 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 11 min; Wave Length: 220/254 nm; RT1(min): 8.34; RT2(min): 9.85; The first peak was product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.1 mL; Number of Runs: 18) to afford 463 (77.4 mg, 30.34%) as a yellow solid.

LC-MS-463 (ES, m/z): $[M+H]^+$ 575/ H-NMR-463 (400 MHz, DMSO-d6, *ppm*): δ0.76-0.94 (m, 4H), δ1.41 (d, 1H), δ1.52-1.85 (m, 5H), δ1.86-1.94 (m, 5H), δ1.96-2.05 (d, 1H), δ2.72-2.85 (s, 2H), δ3.12-3.30 (m, 3H), δ4.32-4.51 (d, 1H), δ6.93-7.01 (d, 1H), δ7.08-7.15 (d, 1H), δ7.29 (d, 1H), δ7.35-7.51 (d, 1H), δ7.66-7.71 (d, 1H), δ7.72-7.81 (d, 1H), δ7.82-7.85 (d, 1H), δ7.86-8.08 (d, 1H), δ8.94 (d, 1H).

Example 453. Synthesis of Compound 464



1. Synthesis of 464-1

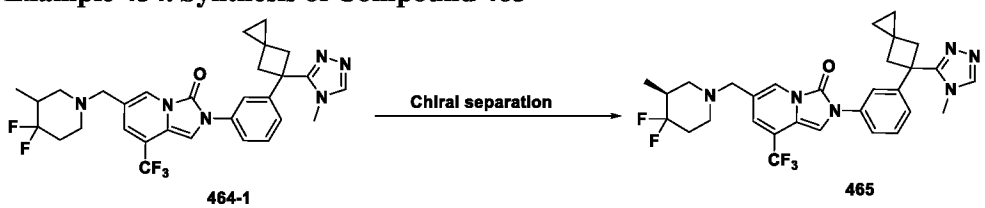
[1586] To a stirred solution of 464-2 (700 mg, 1.497 mmol, 1 equiv) and 4,4-difluoro-3-methylpiperidine hydrochloride (385.50 mg, 2.246 mmol, 1.5 equiv) in DCE (10 mL) were added TEA (303.07 mg, 2.994 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (634.75 mg, 2.994 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with with saturated NH_4Cl (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 464-1 (430 mg, 47.48%) as a yellow solid.

2. Synthesis of 464

[1587] The 464-1 (430 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 14 min; Wave Length: 220/254 nm; RT1(min): 6.86; RT2(min): 9.75, the first peak is product) to afford 464 (170.6 mg, 38.37%) as a yellow solid.

LC-MS-464 (ES, *m/z*): $[M+H]^+$ 587. H-NMR-464 (400 MHz, DMSO-d6, δ *ppm*): 0.45-0.49 (m, 2H), 0.55-0.59 (m, 2H), 0.92-0.94 (d, 3H), 1.88-2.18 (m, 4H), 2.26-2.31 (m, 1H), 2.75-2.82 (m, 4H), 3.17-3.22 (m, 2H), 3.24 (s, 3H), 3.35 (s, 2H), 7.02 (s, 1H), 7.18-7.21 (d, 1H), 7.36 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.65 (d, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 454. Synthesis of Compound 465



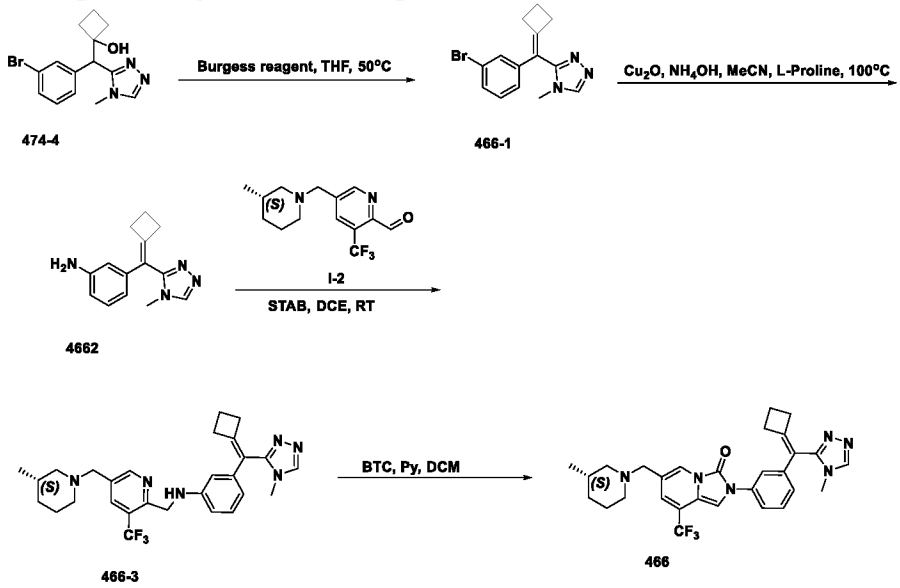
1. Synthesis of 465

[1588] 464-1 (430 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 14

min; Wave Length: 220/254 nm; RT1(min): 6.86; RT2(min): 9.75, the second peak is product) to afford 465 (143.6 mg, 32.86%) as a yellow solid.

LC-MS-465 (ES, *m/z*): $[M+H]^+$ 587. H-NMR-465 (400 MHz, DMSO-d6, δ *ppm*): 0.45-0.49 (m, 2H), 0.55-0.59 (m, 2H), 0.92-0.94 (d, 3H), 1.88-2.18 (m, 4H), 2.26-2.31 (m, 1H), 2.75-2.82 (m, 4H), 3.17-3.22 (m, 2H), 3.24 (s, 3H), 3.35 (s, 2H), 7.02 (s, 1H), 7.18-7.21 (d, 1H), 7.36 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.65 (d, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 455. Synthesis of Compound 466



1. Synthesis of 466-1

[1589] To a stirred solution of 474-4 (500 mg, 1.552 mmol, 1 equiv) in THF (10 mL) was added Burgess reagent (369.79 mg, 1.552 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at 50°C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 466-1 (300 mg, 57.20%) as a light yellow solid.

2. Synthesis of 466-2

[1590] Into a 20mL pressure tank reactor were added 466-1 (300 mg, 0.986 mmol, 1 equiv), Cu_2O (28.22 mg, 0.197 mmol, 0.2 equiv), NH_4OH (3 mL), MeCN (3 mL) and L-Proline (11.35 mg, 0.099 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 466-2 (180 mg, 68.35%) as a yellow oil.

3. Synthesis of 466-3

[1591] To a stirred solution of 466-2 (180 mg, 0.749 mmol, 1 equiv) and I-2 (235.89 mg, 0.824 mmol, 1.1 equiv) in DCE (5 mL) were added STAB (317.50 mg, 1.498 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 5h at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 466-3 (240 mg, 59.61%) as an off-white solid.

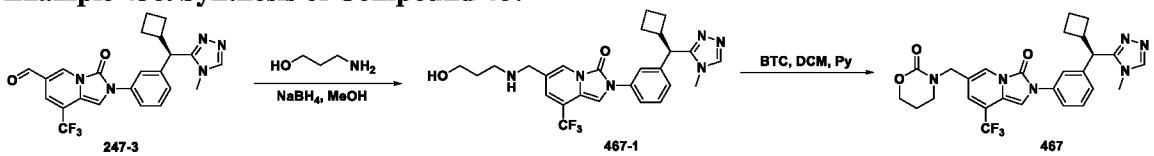
4. Synthesis of 466

[1592] To a stirred solution of 466-3 (220 mg, 0.431 mmol, 1 equiv) and Pyridine (340.81 mg, 4.310 mmol, 10 equiv) in DCM (5 mL) was added Triphosgene (51.14 mg, 0.172 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x20 mL). The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 466 (141.3 mg, 59.89%) as a yellow solid.

LC-MS-466 (ES, *m/z*): $[M+H]^+$ 537

H-NMR-466 (400 MHz, DMSO-d6, δ *ppm*): 0.81-0.95 (m, 4H), 1.41-1.51 (m, 1H), 1.53-1.73 (m, 4H), 1.86-1.91 (m, 1H), 2.04-2.12 (m, 2H), 2.67-2.78 (m, 4H), 3.14-3.17 (m, 2H), 3.24 (s, 2H), 3.32 (s, 3H), 7.00 (s, 1H), 7.02-7.04 (d, 1H), 7.32 (s, 1H), 7.46-7.50(m, 1H), 7.62-7.70 (m, 2H), 7.71 (s, 1H), 8.51 (s, 1H).

Example 456. Synthesis of Compound 467



1. Synthesis of 467-1

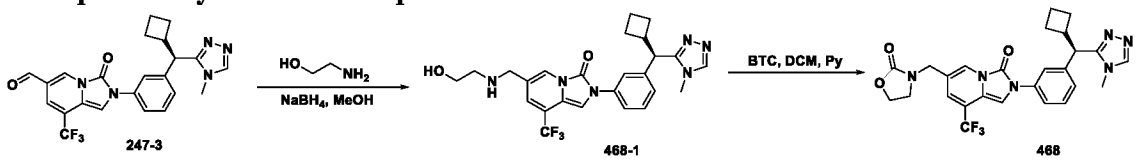
[1593] Into a 100 mL round-bottom flask were added 247-3 (1 g, 2.196 mmol, 1 equiv), propanolamine (0.49 g, 6.588 mmol, 3 equiv) and MeOH (20 mL) at room temperature. The mixture was stirred for overnight at room temperature. To the above mixture was added $NaBH_4$ (0.25 g, 6.588 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=10:1) to afford 467-1 (300 mg, 24.43%) as a yellow solid.

2. Synthesis of 467

[1594] Into a 100 mL round-bottom flask were added 467-1 (650 mg, 1.263 mmol, 1 equiv), DCM (20 mL) and pyridine (799.37 mg, 10.104 mmol, 8 equiv) at room temperature. To the above mixture was added triphosgene (187.42 mg, 0.631 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 3 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x60 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=10:1) to afford crud product. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 40% B to 70% B in 8 min; Wave Length: 254 nm; RT1(min): 7.83) to afford 467 (43.6 mg, 6.33%) as a yellow solid.

LC-MS-467 (ES, *m/z*): $[M+H]^+$ 541. H-NMR-467 1H NMR (400 MHz, MeOD *ppm*) δ1.71-1.78 (m, 1H), δ1.82-1.99 (m, 4H), δ2.06-2.11 (m, 2H), δ2.25-2.27 (m, 1H), δ3.27-3.29 (m, 1H), δ3.33-3.39 (m, 2H), δ3.58 (s, 3H), δ4.28-4.34 (m, 3H), δ4.35-4.38 (m, 2H), δ7.07 (s, 1H), δ7.15 (s, 1H), δ7.27-7.29 (d, 1H), δ7.48-7.52 (t, 1H), δ7.64-7.66 (m, 2H), δ7.75 (s, 1H), δ8.37 (s, 1H).

Example 457. Synthesis of Compound 468



1. Synthesis of 468-1

[1595] Into a 100 mL round-bottom flask were added 247-3 (600 mg, 1.317 mmol, 1 equiv) propanolamine (0.49 g, 6.588 mmol, 3 equiv), ethanolamine (241.42 mg, 3.951 mmol, 3 equiv) and MeOH (15 mL) at room temperature. The mixture was stirred for overnight at room temperature. To the above mixture was added $NaBH_4$ (149.51 mg, 3.951 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=10:1) to afford 468-1 (200 mg, 27.90%) as a yellow solid.

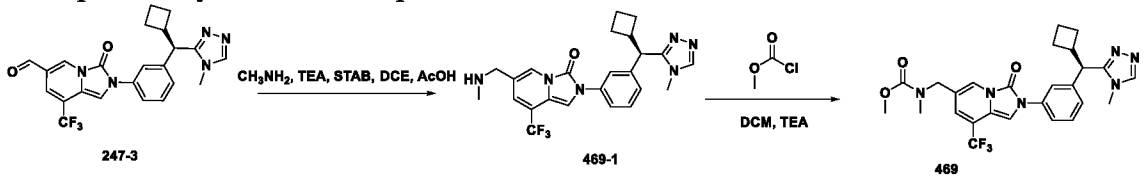
2. Synthesis of 468

[1596] Into a 100 mL round-bottom flask were added 468-1 (300 mg, 0.599 mmol, 1 equiv), DCM (10 mL) and pyridine (379.28 mg, 4.792 mmol, 8 equiv) at room temperature. To the

above mixture was added triphosgene (88.93 mg, 0.299 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 3 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=10:1) to afford crud product. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 46% B to 65% B in 8 min; Wave Length: 254 nm; RT1(min): 7.83) to afford 468 (24.7 mg, 7.62%) as a yellow solid.

LC-MS-468 (ES, *m/z*): $[M+H]^+$ 527. H-NMR-468: 1H NMR (400 MHz, MeOD *ppm*) δ1.75-1.82 (m, 1H), δ1.86-1.96 (m, 4H), δ2.24-2.29 (m, 1H), δ3.56 (s, 3H), δ3.60-3.64 (m, 2H), δ4.28-4.31 (m, 3H), δ4.38-4.43 (m, 2H), δ6.99 (s, 1H), δ7.17 (s, 1H), δ7.27-7.29 (d, 1H), δ7.48-7.52 (t, 1H), δ7.64-7.66 (m, 2H), δ7.78 (s, 1H), δ8.37 (s, 1H).

Example 458. Synthesis of Compound 469



1. Synthesis of 469-1

[1597] Into a 100 mL 3-necked round-bottom flask were added 247-3 (1 g, 2.196 mmol, 1 equiv), CH_3NH_2 (0.20 g, 6.588 mmol, 3 equiv), STAB (1.40 g, 6.588 mmol, 3 equiv), AcOH (0.13 g, 2.196 mmol, 1 equiv) and DCE (10 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 469-1 (500 mg, 45.50%) as a yellow solid.

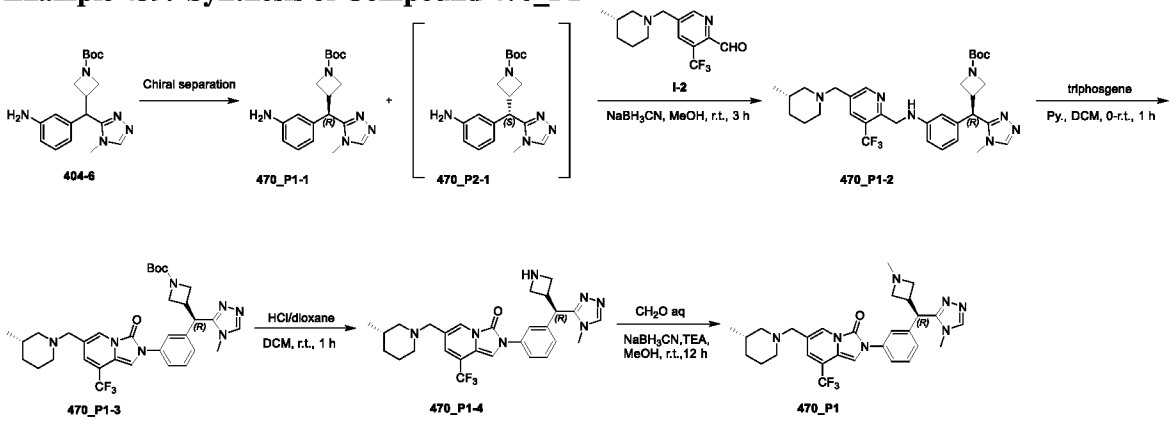
2. Synthesis of 469

[1598] Into a 20 mL sealed tube were added 469-1 (240 mg, 0.510 mmol, 1 equiv), DCM (4 mL), TEA (154.85 mg, 1.530 mmol, 3 equiv) and methyl chloroformate (53.02 mg, 0.561 mmol, 1.1 equiv) at room temperature. The final reaction mixture was irradiated with microwave radiation for 2 h at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The resulting

mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1). The crude product (180 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 7.42) to afford 469 (115.1 mg, 42.35%) as a yellow solid.

LC-MS-469 (ES, m/z): $[M+H]^+$ 529. H-NMR- 469 (400 MHz, DMSO, δ ppm): 1.50-1.89 (m, 5H), 2.04-2.23 (s, 1H), 2.78-2.90 (s, 3H), 3.14-3.30 (s, 1H), 3.41-3.48 (s, 3H), 3.59-3.69 (s, 3H), 4.23-4.38 (m, 3H), 6.69-6.99 (s, 1H), 7.12-7.28 (d, 1H), 7.31-7.42 (s, 1H), 7.42-7.51 (m, 1H), 7.68-7.81 (m, 3H), 8.27-8.42(s, 1H).

Example 459. Synthesis of Compound 470_P1



1. Synthesis of 470_P1-1

[1599] 404-6 (1.3 g) was purified by Chiral separation with the following conditions(column: REGIS(S,S)WHELK-O1 (250mm*50mm, 10 um); Mobile Phase: [Neu-IPA]; B%: 50%-50%, 6 min, Flow rate: 75 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.24) to afford 470_P1-1 (650 mg, 43%) as a white solid.

2. Synthesis of 470_P1-2

[1600] To a solution of 470_P1-1 (649 mg, 1.89 mmol, 1 equiv) and I-2 (541 mg, 1.89 mmol, 1 equiv) in MeOH (15 mL) was added AcOH (324 uL, 5.67 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 h. Then $NaBH_3CN$ (237 mg, 3.78 mmol, 2 equiv) was added, the mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The reaction mixture was adjusted to pH=8 with sat.$NaHCO_3$ (30 mL) and extracted with DCM (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH=10:1 to afford 470_P1-2 (920 mg,

79%) as a yellow solid.

H-NMR-470_P1-2: (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.31 (s, 1H), 8.02 (s, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.57-6.51 (m, 2H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.21 (t, *J* = 5.6 Hz, 1H), 4.44 (d, *J* = 5.2 Hz, 2H), 4.31 (d, *J* = 10.8 Hz, 1H), 3.95 (s, 1H), 3.62 (d, *J* = 6.4 Hz, 2H), 3.56-3.54 (m, 2H), 3.49 (s, 1H), 3.29 (s, 3H), 2.67 (d, *J* = 6.8 Hz, 2H), 1.93-1.87 (m, 1H), 1.66-1.55 (m, 5H), 1.45 (d, *J* = 12.0 Hz, 1H), 1.36 (s, 9H), 0.90-0.83 (m, 1H), 0.81 (d, *J* = 6.0 Hz, 3H)

3. Synthesis of 470_P1-3

[1601] To a solution of 470_P1-2 (0.2 g, 325.88 umol, 1 equiv) in DCM (10 mL) was added Py (315 uL, 3.91 mmol, 12 equiv) and bis(trichloromethyl) carbonate (72.5 mg, 244 umol, 0.75 equiv) at 0 °C. The mixture was stirred at 25 °C for 0.5 h under nitrogen atmosphere. The same scale reaction was conducted with in parallel for 2 batches in total and work up together. The reaction mixture was quenched with $NaHCO_3$ (aq. 50 mL). The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH=10:1 to afford 470_P1-3 (300 mg, 72%) as a yellow solid.

H-NMR-470_P1-3: (400 MHz, CHLOROFORM-d) δ 7.97 (s, 1H), 7.61-7.48 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.67 (s, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 3.67-3.60 (m, 1H), 3.56-3.47 (m, 2H), 3.42 (s, 1H), 3.36 (s, 3H), 3.15 (s, 2H), 2.75-2.64 (m, 2H), 1.84 (t, *J* = 10.0 Hz, 1H), 1.67-1.48 (m, 6H), 1.35 (s, 9H), 0.88-0.81 (m, 1H), 0.79 (d, *J* = 5.6 Hz, 3H)

4. Synthesis of 470_P1-4

[1602] To a solution of 470_P1-3 (200 mg, 312 umol, 1 equiv) in DCM (3 mL) was added HCl/dioxane (4 M, 1.00 mL, 12.7 equiv). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to afford 470_P1-4 (200 mg, crude) as a yellow solid.

5. Synthesis of 470_P1

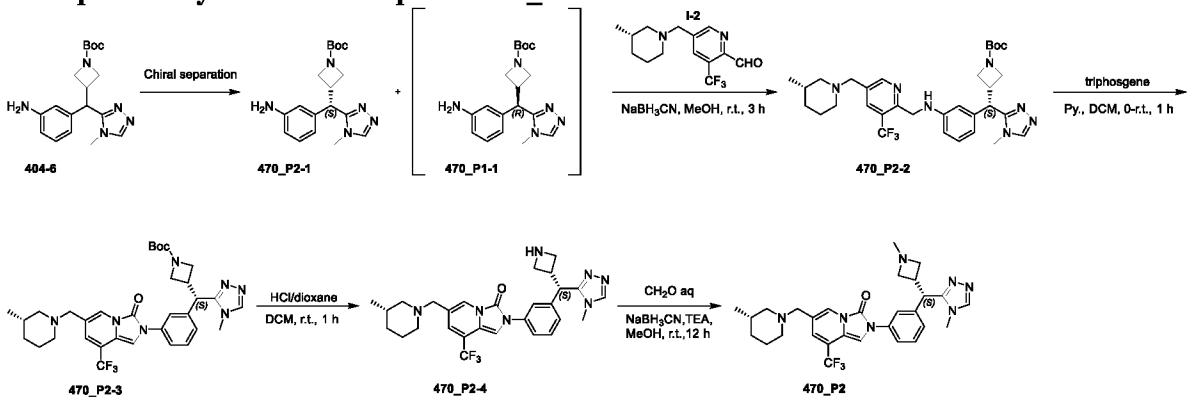
[1603] To a solution of 470_P1-4 (200 mg, 370 umol, 1 equiv) in MeOH (2 mL) was added TEA (103 uL, 741.30 umol, 2 equiv) and HCHO (90.2 mg, 1.11 mmol, 37% purity, 3 equiv). The mixture was stirred at 20 °C for 0.5 h. Then $NaBH_3CN$ (46.6 mg, 741 umol, 2 equiv) was added. The mixture was stirred at 20 °C for 12 h under nitrogen atmosphere. The reaction mixture was adjusted to pH=8 with sat.$NaHCO_3$ (180 mL) and extracted with DCM (60 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a crude product. The residue was purified by

silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give a crude product. The crude product (160 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 25% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5) to afford 470_P1 (74 mg, 11.9%) as a yellow solid.

LCMS-470_P1: (ES, m/z): $[M+H]^+$ 554.2

H-NMR-470_P1: (400 MHz, METHANOL-d4) δ 8.56 (s, 1H), 8.45 (s, 1H), 7.77-7.69 (m, 3H), 7.58 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 17.6 Hz, 2H), 4.76 (d, J = 10.4 Hz, 1H), 4.30 (t, J = 8.4 Hz, 1H), 4.14-3.95 (m, 3H), 3.82 (d, J = 6.8 Hz, 1H), 3.53 (s, 2H), 3.49 (s, 3H), 3.10-2.95 (m, 2H), 2.89 (s, 3H), 2.25-2.13 (m, 1H), 1.95-1.85 (m, 1H), 1.77 (d, J = 3.2 Hz, 3H), 1.71-1.60 (m, 1H), 1.07-0.97 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H).

Example 460. Synthesis of Compound 470_P2



1. Synthesis of 470_P2-1

[1604] 404-6 (1.3 g) was purified by Chiral separation with the following conditions(column: REGIS(S,S)WHELK-O1 (250mm*50mm, 10 um); Mobile Phase: [Neu-IPA]; B%: 50%-50%, 6 min, Flow rate: 75 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.60) to afford 470_P2-1 (650 mg, 43%) as a white solid.

2. Synthesis of 470_P2-2

[1605] To a solution of I-2 (523.91 mg, 1.83 mmol, 1 equiv) and 470_P2-1 (628.46 mg, 1.83 mmol, 1 equiv) in MeOH (7 mL) was added HOAc (314 uL, 5.49 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 hr. And then $NaBH_3CN$ (345 mg, 3.66 mmol, 3 equiv) was added to reaction mixture. The mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction mixture was adjusted pH to 8 with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH (10:1) to give crude product.

The crude product (940 mg) was purified by Prep-HPLC with the following conditions (Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 50% B to 80% B in 8 min; Wave Length: 220 nm; RT1(min): 8.5) to afford 470_P2-2 (410 mg, 46%) as a white solid.

^{1}H-NMR-470_P2-2: (400 MHz, METHANOL-d_4) δ 8.68 (s, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.68-6.60 (m, 1H), 6.56-6.50 (m, 2H), 4.54 (s, 2H), 4.33 (d, J = 12.0 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 3.86-3.73 (m, 2H), 3.64-3.57 (m, 3H), 3.41 (s, 4H), 2.89-2.72 (m, 2H), 1.99 (s, 1H), 1.81-1.52 (m, 6H), 1.44 (s, 9H), 0.97-0.91 (m, 1H), 0.88 (d, J = 6.0 Hz, 3H)

3. Synthesis of 470_P2-3

[1606] To a solution of 470_P2-2 (390 mg, 634 umol, 1 equiv) in CH_2Cl_2 (10 mL) was added Py (308 uL, 3.82 mmol, 6 equiv). And bis(trichloromethyl) carbonate (376 mg, 1270 umol, 2 equiv) was added to reaction mixture at 0 °C. The result mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with saturated $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (20 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 470_P2-3 (470 mg, 96%) as a yellow solid.

^{1}H-NMR-470_P2-3: (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.71 (d, J = 18.4 Hz, 3H), 7.55 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 10.8 Hz, 2H), 4.63 (d, J = 12.0 Hz, 1H), 3.94-3.77 (m, 3H), 3.68-3.59 (m, 2H), 3.52 (s, 3H), 3.00-2.76 (m, 3H), 2.06-1.97 (m, 1H), 1.81-1.65 (m, 6H), 1.44 (s, 9H), 0.91 (d, J = 5.6 Hz, 4H)

4. Synthesis of 470_P2-4

[1607] To a solution 470_P2-3 (370 mg, 156 umol, 1 equiv) in DCM (2.5 mL) was added HCl/dioxane (4 M, 235 uL, 6 equiv). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated at room temperature to afford 470_P2-4 (300 mg, crude) as a yellow solid.

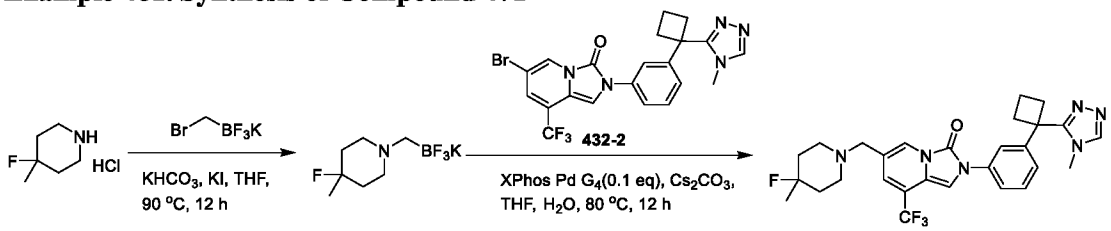
5. Synthesis of 470_P2

[1608] To a solution of 470_P2-4 (78 mg, 145 umol, 1 equiv) and formaldehyde (35.2 mg, 434 mmol, 37% purity, 3 equiv) in MeOH (2 mL) was added TEA (29.3 mg, 289 umol, 2 equiv). The reaction mixture was stirred at 20 °C for 1 h. Then $NaBH_3CN$ (18.2 mg, 289 umol, 2 equiv) was added to reaction mixture. The mixture was stirred at 20 °C for 11 h. The same scale reaction was conducted with in parallel for 3 batches in total and work up with a

small test scale (50 mg) together. The reaction mixture was adjusted pH to 8 with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography, eluted with CH_2Cl_2/MeOH=10:1 to give crude product. The crude product (450 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 5% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 9.5) to afford 470_P2 (77 mg, 26%) as a yellow solid.

MS-470_P2: (ES, m/z): $[M+H]^+$ 554.2. ^{1}H-NMR-470_P2: (400 MHz, METHANOL-d_4) δ 8.53 (s, 1H), 8.45 (s, 1H), 7.77 (s, 1H), 7.74-7.70 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.15 (s, 1H), 4.75 (d, *J* = 10.4 Hz, 1H), 4.41-4.27 (m, 1H), 4.18-3.97 (m, 3H), 3.83 (d, *J* = 9.6 Hz, 1H), 3.57 (s, 2H), 3.48 (s, 3H), 3.14-2.98 (m, 2H), 2.90 (s, 3H), 2.23 (d, *J* = 2.0 Hz, 1H), 1.99-1.89(m, 1H),1.84-1.58(m, 4H),1.09-0.98 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H).

Example 461. Synthesis of Compound 471



1. Synthesis of 471-1

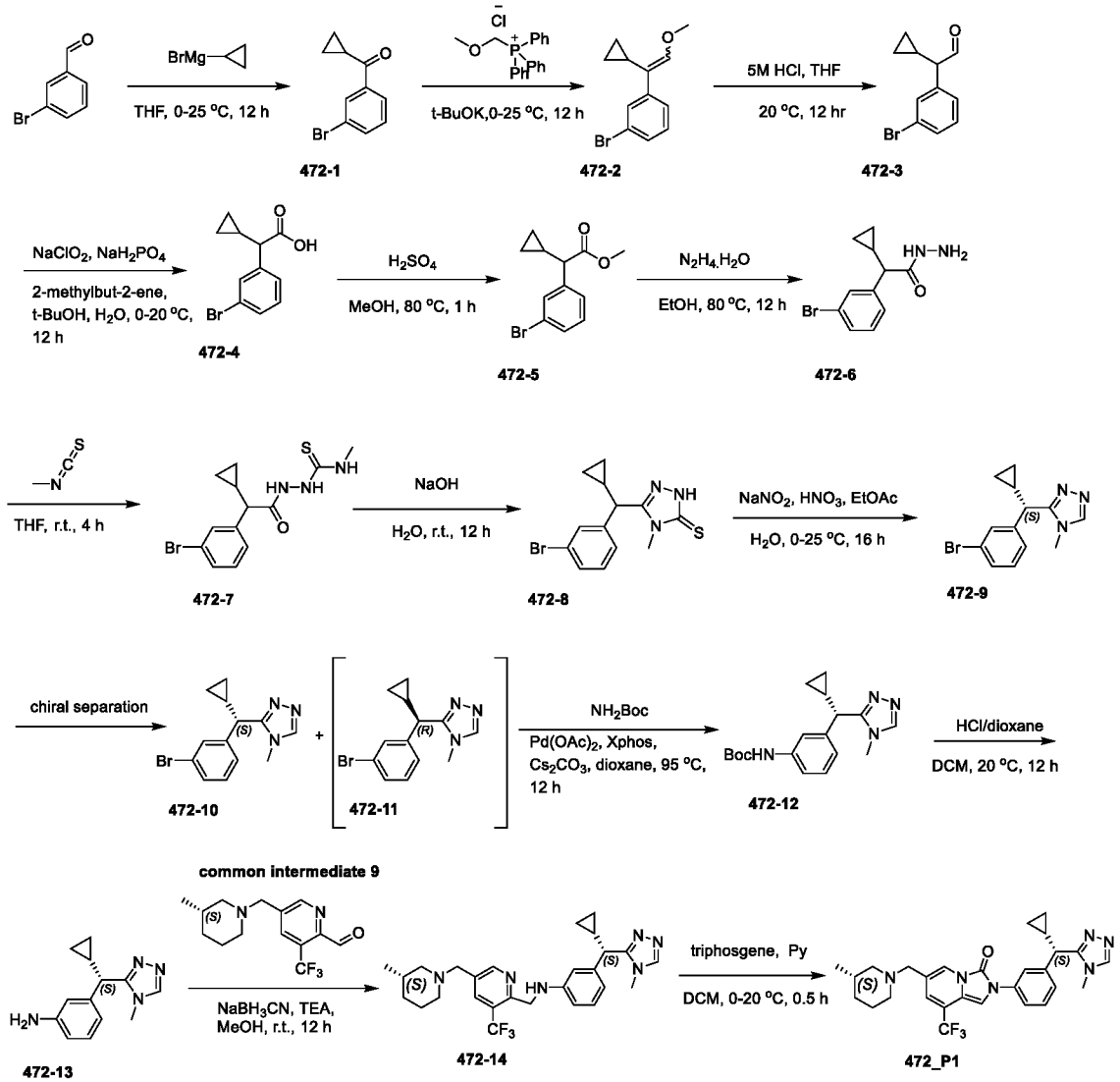
[1609] To a solution of 4-fluoro-4-methyl-piperidine (400 mg, 2.6 mmol, 1 equiv, HCl) and potassium; bromomethyl(trifluoro)boranuide (523 mg, 2.6 mmol, 1 equiv) in THF (10 mL) was added $KHCO_3$ (521 mg, 5.21 mmol, 2 equiv) and KI (43.2 mg, 260 umol, 0.1 equiv). The mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The crude product was triturated with acetone (50 ml) at 35 °C for 1 h. Then the mixture was filtered and the filtrate was concentrated under reduced pressure to afford 471-1 (400 mg, 64%) as a white solid.

2. Synthesis of 471

[1610] To a solution of 471-1 (241 mg, 1.02 mmol, 2 equiv) and 432-2 (250 mg, 508 umol, 1 equiv) in THF (8 mL) and H_2O (2 mL) was added Cs_2CO_3 (496 mg, 1.52 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-

(methylamino)phenyl] phenyl]palladium(1+) (43.7 mg, 50.8 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was extracted with water (50 ml) and EtOAc (30 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1) to give a crude product (0.3 g). The crude product (0.3 g) was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: water (FA), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 40% B in 8 min; Wave Length: 220 nm; RT1 (min): 6.2) to afford 471 (120.6 mg, 44%) as a yellow solid.
MS-471: (ES, m/z): $[M+H]^+$ 543.1. ^{1}H-NMR-471: (400 MHz, METHANOL-d4) δ 8.37-8.33 (m, 1H), 7.77-7.71 (m, 2H), 7.62-7.51 (m, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.11 (s, 1H), 3.52 (s, 2H), 3.33 (s, 3H), 3.06-2.97 (m, 2H), 2.87-2.78 (m, 4H), 2.61-2.49 (m, 2H), 2.22-2.06 (m, 2H), 1.94-1.81 (m, 3H), 1.80-1.70 (m, 1H), 1.40-1.32 (m, 3H).

Example 462. Synthesis of Compound 472_P1



1. Synthesis of 472-1

[1611] To a solution of 3-bromobenzaldehyde (50.0 g, 270 mmol, 31.5 mL, 1.0 equiv) in THF (500.0 mL) at 0°C. After addition, then bromo(cyclopropyl)magnesium (1 M, 351.3 mL, 1.3 equiv) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 12 hours. The reaction was poured into water (300.0 mL) and the resulting mixture was extracted with EtOAc (2 x 150.0 mL). The organic phase was washed with brine (70.0 mL x 2), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 1/1) to afford 472-1 (13.7 g, 22.62% yield) as yellow oil.

2. Synthesis of 472-2

[1612] To a solution methoxymethyl(triphenyl)phosphonium;chloride (8.4 g, 24.5 mmol, 2.4

equiv) and t-BuOK (2.3 g, 20.4 mmol, 2 equiv) in THF (400.0 mL) was added dropwise DMSO (1.6 g, 20.4 mmol, 1.6 mL, 2.0 equiv) at 0 °C. After addition, the mixture was stirred at this temperature for 30 minutes, and then 472-1 (2.3 g, 10.22 mmol, 1.0 equiv) was added at 0 °C. The resulting mixture was stirred at 25 °C for 11.5 hours. The reaction was poured into water (150.0 mL) and the resulting mixture was extracted with EtOAc (2 x 100.0 mL). The organic phase was washed with brine (60.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1) to afford 472-2 (2.3 g, 90.21% yield) as colorless oil.

3. Synthesis of 472-3

[1613] To a solution of 472-2 (12.0 g, 47.4 mmol, 1.0 equiv) in THF (120.0 mL) was added HCl (5 M, 36.0 mL, 3.8 equiv). The mixture was stirred at 20 °C for 12 hours. The reaction was poured into water (100.0 mL) and the resulting mixture was extracted with EtOAc (2 x 90.0 mL). The organic phase was washed with brine (60.0 mL x 2), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The crude product was used directly into next step. Compound 472-3 (13.8 g, crude) was obtained as colorless oil.

4. Synthesis of 472-4

[1614] To a solution of 472-3 (11.5 g, 48.1 mmol, 1.0 equiv) in t-BuOH (180.0 mL) and 2-methylbut-2-ene (90.0 mL) and then sodium;hypochlorite (7.2 g, 96.2 mmol, 5.9 mL, 2.0 equiv) and NaH_2PO_4 (11.5 g, 96.2 mmol, 2.0 equiv) in H_2O (20.0 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 2 hour. The mixture was added $NaHCO_3$ (50.0 mL) to adjust pH = 8. Then the mixture was partitioned between H_2O (50.0 mL) and EtOAc (100.0 mL). The aqueous phase was separated and added HCl (2M, 40.0 mL) to adjust pH = 5, then the aqueous phase was added EtOAc (80.0 mL). The organic phase was separated, washed with brine (40.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly into next step. Compound 472-4 (9.8 g, 79.87% yield) was obtained as yellow oil.

5. Synthesis of 472-5

[1615] To a solution of 472-4 (8.5 g, 33.3 mmol, 1.0 equiv) in MeOH (120.0 mL) was added H_2SO_4 (653 mg, 6.7 mmol, 0.2 equiv). The mixture was stirred at 80 °C for 1 hour. The reaction was poured into water (100.0 mL) and the resulting mixture was extracted with EtOAc (2 x 80.0 mL). The organic phase was washed with brine (50.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The crude product was used directly into next step. Compound 472-5 (9.0 g, 85.31% yield) was obtained as colorless oil.

H-NMR-472-5: (400 MHz, DMSO-d6) δ ppm 7.44-7.58 (m, 2 H), 7.22-7.39 (m, 2 H), 3.57-3.69 (m, 3 H), 2.93-3.06 (m, 1 H), 1.27-1.43 (m, 1 H), 0.53-0.67 (m, 1 H), 0.27-0.50 (m, 2 H), 0.10-0.24 (m, 1 H).

6. Synthesis of 472-6

[1616] To a solution of 472-5 (8.0 g, 29.7 mmol, 1.0 equiv) in EtOH (80.0 mL) was added $N_2H_4.H_2O$ (60.7 g, 1.2 mol, 58.9 mL, 98% purity, 40.0 equiv). The mixture was stirred at 80 °C for 12 hours. The reaction was poured into water (160.0 mL) and the resulting mixture was extracted with EtOAc (2 x 160.0 mL). The organic phase was washed with brine (20.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The crude product was used directly into next step. Compound 472-6 (9.0 g, crude) was obtained as colorless oil.

H-NMR-472-6: (400 MHz, DMSO-d_6) δ ppm 9.16 (br s, 1 H), 7.52-7.61 (m, 1 H), 7.40-7.47 (m, 1 H), 7.32-7.38 (m, 1 H), 7.22-7.30 (m, 1 H), 4.25 (br s, 2 H), 2.59 (d, J = 10.0 Hz, 1 H), 1.32-1.47 (m, 1 H), 0.42-0.58 (m, 2 H), 0.23-0.34 (m, 1 H), 0.01-0.17 (m, 1 H).

7. Synthesis of 472-7

[1617] To a solution of 472-6 (8.0 g, 29.7 mmol, 1.0 equiv) in THF (80.0 mL) was added methylimino(thioxo)methane (4.3 g, 59.4 mmol, 4.0 mL, 2.0 equiv). The mixture was stirred at 20 °C for 4 hours. The reaction was poured to water (60.0 mL) to form solid. The solid was filtered and concentrated. The crude product was used directly into next step. Compound 472-7 (11.5 g, crude) was obtained as a white solid.

8. Synthesis of 472-8

[1618] To a solution of NaOH (9.8 g, 245.4 mmol, 8.0 equiv) in H_2O (110.0 mL) was added 472-7 (10.5 g, 30.7 mmol, 1.0 equiv). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was added 1M HCl to pH = 3-4 to form solid, the solid was filtered and the filter cake was concentrated under reduced pressure. The crude product was used directly into next step. Compound 472-8 (10.0 g, crude) was obtained as a white solid.

9. Synthesis of 472-9

[1619] HNO_3 (28.6 g, 308.4 mmol, 20.4 mL, 68% purity, 10.0 equiv) was added to H_2O (290.0 mL) to afford the diluted HNO_3 solution (1M, 310.0 mL). To a solution of 472-8 (10.0 g, 30.8 mmol, 1.0 equiv) and $NaNO_2$ (21.3 g, 308.4 mmol, 10.0 equiv) in H_2O (100.0 mL) and EtOAc (10.0 mL) was added was added diluted HNO_3 solution (1 M, 6.2 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 16 hours. The reaction mixture was added a.q. $NaHCO_3$ to pH =7-8, and the resulting mixture was extracted with EtOAc (2 x 100.0 mL). The organic phase was washed with brine (80.0 mL), dried over anhydrous Na_2SO_4,

concentrated in vacuum to give a residue. The crude product was used directly into next step. Compound 472-9 (9.0 g, 87.89% yield) was obtained as yellow solid.

H-NMR-472-9: (400 MHz, DMSO-d_6) δ ppm 9.16 (br s, 1 H), 7.52-7.61 (m, 1 H), 7.40-7.47 (m, 1 H), 7.32-7.38 (m, 1 H), 7.22-7.30 (m, 1 H), 4.25 (br s, 2 H), 2.59 (d, J = 10.0 Hz, 1 H), 1.32-1.47 (m, 1 H), 0.42-0.58 (m, 2 H), 0.23-0.34 (m, 1 H), 0.01-0.17 (m, 1 H).

10. Synthesis of 472-10&11

[1620] The 472-9 (4.9 g) was separated by chiral separation with the following condition (column: DAICEL CHIRALPAK IC (250mm*50mm,10um); mobile phase: [0.1%NH_3H_2O MEOH]; B%: 50%-50%, 7 min) to afford 472-10 (2.2 g, 43.42% yield) as a yellow solid and 472-11 (2.6 g, 49.08% yield) as a yellow solid.

H-NMR-472-10: (400 MHz, DMSO-d_6) δ ppm 8.29-8.41 (m, 1 H), 7.48-7.52 (m, 1 H), 7.42-7.47 (m, 1 H), 7.22-7.33 (m, 2 H), 3.53-3.63 (m, 1 H), 3.36-3.43 (m, 3 H), 3.14-3.19 (m, 1 H), 1.48-1.66 (m, 1 H), 0.45-0.63 (m, 2 H), 0.26-0.38 (m, 2 H).

H-NMR-472-11: (400 MHz, DMSO-d_6) δ ppm 8.18-8.27 (m, 1 H), 7.36-7.40 (m, 1 H), 7.28-7.35 (m, 1 H), 7.13-7.22 (m, 2 H), 3.41-3.51 (m, 1 H), 3.24-3.32 (m, 3 H), 3.01-3.09 (m, 2 H), 1.39-1.51 (m, 1 H), 0.34-0.52 (m, 2 H), 0.13-0.26 (m, 2 H).

11. **Synthesis of 472-12**

[1621] A mixture of 472-10 (470 mg, 1.6 mmol, 1.0 equiv), NH_2Boc (226 mg, 1.9 mmol, 1.2 equiv), Cs_2CO_3 (1.0 g, 3.2 mmol, 2.0 equiv) and $Pd(OAc)_2$ (36 mg, 0.1 equiv), Xantphos (186 mg, 0.2 equiv) in dioxane (10.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 95 °C for 12 hours under N_2 atmosphere. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with EtOAc (2 x 10.0 mL). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 50/1 to 5/1) to afford 472-12 (420 mg, 79.43% yield) as a yellow solid.

12. Synthesis of 472-13

[1622] To a solution of 472-12 (420 mg, 1.3 mmol, 1.0 equiv) in DCM (8.0 mL) was added HCl/dioxane (4 M, 1.6 mL, 5.0 equiv). The mixture was stirred at 20 °C for 12 hours. The reaction was concentrated in reduced pressure. The crude product was used directly into next step. Compound 472-13 (450 mg, crude, HCl) was obtained as a yellow solid.

13. **Synthesis of 472-14**

[1623] To a solution of 472-13 (210 mg, 1.0 equiv, HCl) and 5-[[(3S)-3-methyl-1-piperidyl]methyl]-3-(trifluoromethyl)pyridine-2-carbaldehyde (272 mg, 1.2 equiv) in MeOH

(8.0 mL) was added dropwise TEA (160 mg, 1.6 mmol, 2.0 equiv) at 20 °C. After addition, the mixture was stirred at this temperature for 1 hour, and then $NaBH_3CN$ (99 mg, 1.6 mmol, 2.0 equiv) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 11 hours. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with EtOAc (2 x 10.0 mL). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 30/1 to 1/1) to afford 472-14 (450 mg, 91.03% yield) as yellow oil.

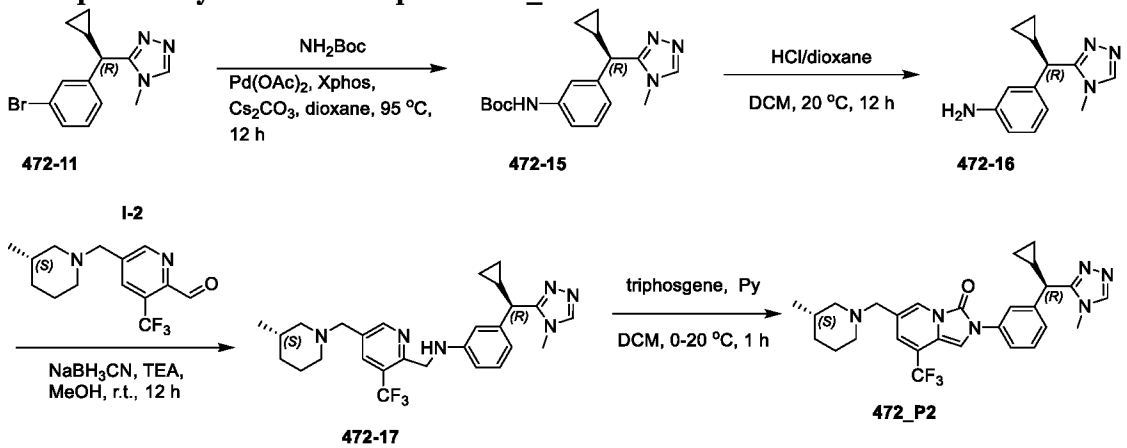
14. Synthesis of 472_P1

[1624] To a solution of 472-14 (200 mg, 1.0 equiv) in DCM (4.0 mL) was added dropwise pyridine (190 mg, 2.4 mmol, 6.0 equiv) at 0 °C. And then triphosgene (119 mg, 1.0 equiv) in DCM (0.8 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 0.5 hour. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with EtOAc (2 x 15.0 mL). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(FA)-ACN];B%: 1%-30%, 8 min) to afford 472-P1 (170 mg, 40.36% yield) as a yellow solid.

MS-472_P1: (ES, m/z): [M+H]+ 525.3.

H-NMR-472_P1: (400 MHz, DMSO-d6) δ ppm 8.30-8.43 (m, 1 H), 8.11-8.19 (m, 1 H), 7.75 (s, 1 H), 7.61-7.73 (m, 2 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.28-7.33 (m, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 6.93-7.07 (m, 1 H), 3.60 (d, J = 9.6 Hz, 1 H), 3.37-3.49 (m, 3 H), 3.22-3.32 (m, 2 H), 2.70-2.83 (m, 2 H), 1.85-1.99 (m, 1 H), 1.53-1.75 (m, 5 H), 1.37-1.50 (m, 1 H), 0.75-0.94 (m, 4 H), 0.56-0.66 (m, 1 H), 0.45-0.55 (m, 1 H), 0.27-0.42 (m, 2 H).

Example 463. Synthesis of Compound 472_P2



1. Synthesis of 472-15

[1625] A mixture of 472-11 (619 mg, 2.1 mmol, 1.0 equiv), NH_2Boc (298 mg, 2.5 mmol, 1.2 equiv), Cs_2CO_3 (1.4 g, 4.2 mmol, 2.0 equiv) and $Pd(OAc)_2$ (48 mg, 0.1 equiv), Xantphos (245 mg, 0.2 equiv) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 95 °C for 12 hours under N_2 atmosphere. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 10.0 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 50/1 to 5/1) to afford 472-15 (470 mg, 67.51% yield) as a yellow solid.

2. Synthesis of 472-16

[1626] To a solution of 472-15 (470 mg, 1.4 mmol, 1.0 equiv) in DCM (8.0 mL) was added HCl/dioxane (4 M, 1.8 mL, 5.0 equiv). The mixture was stirred at 20 °C for 12 hours. The reaction was concentrated in reduced pressure. The crude product was used directly into next step. Compound 472-16 (420 mg, crude, HCl) was obtained as a yellow solid.

3. Synthesis of 472-17

[1627] To a solution of 472-16 (210.00 mg, 793.19 umol, 1 equiv, HCl) and 5-[[(3S)-3-methyl-1-piperidyl]methyl]-3-(trifluoromethyl)pyridine-2-carbaldehyde (272.50 mg, 951.83 umol, 1.2 equiv) in MeOH (8 mL) was added dropwise TEA (160.52 mg, 1.59 mmol, 220.80 uL, 2 equiv) at 20°C. After addition, the mixture was stirred at this temperature for 1 hr, and then $NaBH_3CN$ (99.69 mg, 1.59 mmol, 2 equiv) was added dropwise at 20°C. The resulting mixture was stirred at 20°C for 11 hr. The residue was purified by column chromatography (SiO_2, Dichloromethane : Methanol = 30/1 to 1/1). Compound 472-17 (230 mg, 461.30 umol, 52.66% yield, 80% purity) was obtained as yellow oil.

4. Synthesis of 472_P2

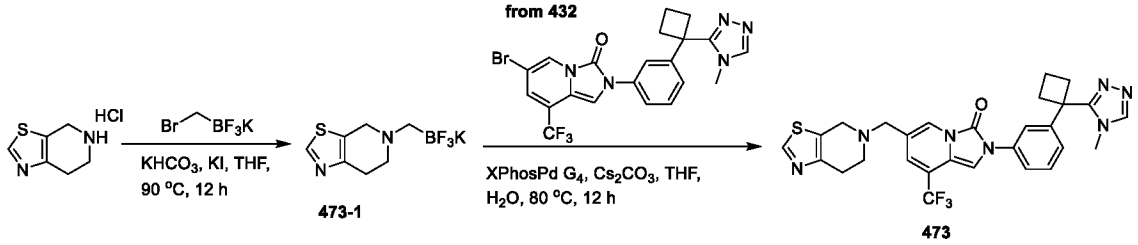
[1628] To a solution of 472-17 (0.23 g, 461.31 umol, 1 equiv) in DCM (4 mL) was added Py (218.94 mg, 2.77 mmol, 223.40 uL, 6 equiv). Then a solution of triphosgene (68.45 mg, 230.65 umol, 0.5 equiv) in DCM (2 mL) was added to the above mixture at 0°C. The mixture was stirred at 20°C for 1 hr under N_2. The same scale reaction was conducted with in parallel for 2 batches in total and work up with a small test scale (50 mg) together. The reaction mixture was quenched by addition water 10 mL at 0°C, and then diluted with DCM 30 mL and extracted with DCM (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give part 1:

0.29 g product with 86% LCMS purity; part 2: 0.19 g product with 56% LCMS purity. Two parts of product was further purified by prep-HPLC(FA condition; column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(FA)-ACN];B%: 5%-40%,7 min). 179.7 mg 472-P1 (99% purity) was obtained as yellow solid.

MS-472_P2: (ES, m/z): [M+H]+ 525.3.

H-NMR-472_P2: (400 MHz, METHANOL-d4) δ = 8.46-8.37 (m, 2H), 7.85 (s, 1H), 7.68 (s, 1H), 7.64 (br d, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 3.83 (s, 2H), 3.63 (d, *J* = 9.8 Hz, 1H), 3.53-3.40 (m, 3H), 3.29-3.18 (m, 2H), 2.57-2.46 (m, 1H), 2.24 (s, 1H), 1.90-1.64 (m, 5H), 1.16-1.03 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.80-0.62 (m, 2H), 0.51-0.36 (m, 2H).

Example 464. Synthesis of Compound 473



1. Synthesis of 473-1

[1629] To a solution of 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (400 mg, 2.26 mmol, 1 equiv, HCl) in THF (8 mL) was added potassium;hydrogen carbonate (453.35 mg, 4.53 mmol, 2 equiv) and potassium;iodide (37.59 mg, 226.41 umol, 0.1 equiv), potassium;bromomethyl(trifluoro)boranuide (454.72 mg, 2.26 mmol, 1 equiv). The mixture was heated to 90°C and stirred at 90°C for 12 hr. The mixture was concentrated under reduced pressure to give a crude. Then the crude was triturated with acetone (60 mL) at 40°C for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 473-1 (0.27 g, crude) as a light yellow solid.

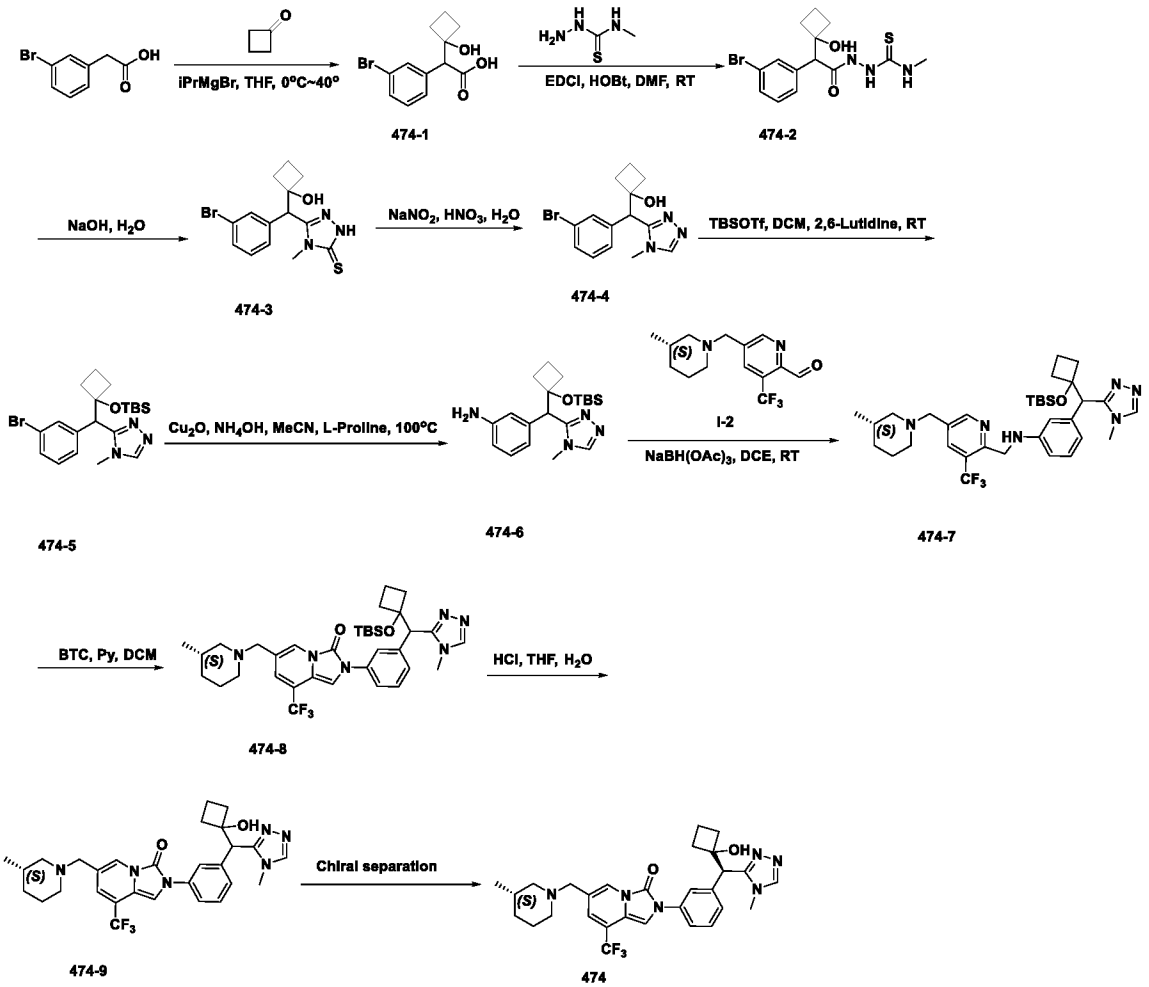
2. Synthesis of 473

[1630] To a solution of 473-1 (220 mg, 845.73 umol, 2 equiv) in THF (6 mL) and H_2O (1.5 mL) was added 473-2 (208.17 mg, 422.87 umol, 1 equiv), dicesium;carbonate (413.33 mg, 1.27 mmol, 3 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2(methylamino)phenyl]phenyl]palladium(1+) (36.39 mg, 42.29 umol, 0.1 equiv). The suspension was degassed and purged with N_2 for 3 times. Then the mixture was heated to 80 °C and stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction mixture was poured into water (10 mL), extracted with EtOAc (15 mL x3). The combined organic layer was washed

with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1) and (DCM: Methanol=100/1 to 0/1) to afford 473 (0.17 g, crude) as a brown solid. The crude product (170 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(FA)-ACN];B%: 5%-45%,7min; Wave Length: 220 nm; RT1(min): 8) to afford 473 (60.6 mg) as a yellow solid.

MS-473: (ES, m/z): [M+H]+ 566.1. ^{1}H-NMR-473: (400 MHz, METHANOL-d4) δ 8.85 (s, 1H), 8.35 (s, 1H), 7.77-7.73 (m, 2H), 7.61-7.58 (m, 1H), 7.56-7.52 (m, 1H), 7.31-7.29 (d, *J* = 8 Hz, 1H), 7.14-7.14 (m, 2H), 3.82 (s, 2H), 3.60 (s, 2H), 3.33 (s, 3H), 3.05-2.97 (m, 4H), 2.94-2.93 (m, 2H), 2.85-2.78 (m, 2H), 2.19-2.09 (m, 2H).

Example 465. Synthesis of Compound 474



1. Synthesis of 474-1

[1631] To a stirred solution of M-bromophenylacetic acid (50 g, 232.508 mmol, 1 equiv) in THF (500 mL) was added iPrMgBr (232.5 mL, 465.016 mmol, 2 equiv, 2M) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. To the above mixture was added cyclobutanone (32.59 g, 465.016 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 1 h at 40 °C. The reaction was quenched with saturated NH_4Cl (aq.) (2000 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x1 L). The resulting mixture was concentrated under reduced pressure to afford 474-1 (40 g, 60.33%) as a yellow oil. The crude product was used in the next step directly without further purification.

2. Synthesis of 474-2

[1632] To a stirred solution of 474-1 (40 g, 140.283 mmol, 1 equiv) and 1-amino-3-methylthiourea (22.13 g, 210.424 mmol, 1.5 equiv) in DMF (400 mL) were added EDCI (53.78 g, 280.566 mmol, 2 equiv) and HOBt (37.91 g, 280.566 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (2000 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x1000 mL). The resulting mixture was concentrated under reduced pressure to afford 474-2 (60 g, 114.89%) as a yellow oil. The crude product was used in the next step directly without further purification.

3. Synthesis of 474-3

[1633] To a stirred mixture of NaOH (16.1 g, 402.530 mmol, 2.50 equiv) in H_2O (600 mL) was added 474-2 (60 g, 161.169 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The mixture neutralized to pH 7 with 1M HCl (aq.). The aqueous layer was extracted with EtOAc (2x600 mL). The resulting mixture was concentrated under reduced pressure to afford 474-3 (22 g, 38.53%) as a yellow solid. The crude product was used in the next step directly without further purification.

4. Synthesis of 474-4

[1634] To a stirred solution of 474-3 (22 g, 62.100 mmol, 1.00 equiv) and $NaNO_2$ (42.85 g, 621.000 mmol, 10 equiv) was added HNO_3 (41.4 mL, 621.000 mmol, 10 equiv) in H_2O (620 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) (2000 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x1 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=1:1 to afford 474-4 (8 g, 39.98%) as a yellow solid.

5. Synthesis of 474-5

[1635] To a stirred solution of 474-4 (3 g, 9.311 mmol, 1 equiv) and 2,6-Lutidine (2.00 g, 18.622 mmol, 2 equiv) in DCM (50 mL) were added TBSOTf (3.69 g, 13.966 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=2:1 to afford 474-5 (3.2 g, 78.74%) as a yellow solid.

6. Synthesis of 474-6

[1636] To a stirred mixture of 474-5 (3.2 g, 7.332 mmol, 1 equiv) and L-Proline (0.17 g, 1.466 mmol, 0.2 equiv) in MeCN (8 mL) were added NH_4OH (8 mL) and Cu_2O (0.21 g, 1.466 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C. The resulting mixture was filtered, the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 474-6 (1.5 g, 54.91%) as a yellow solid.

7. Synthesis of 474-7

[1637] To a stirred mixture of 474-6 (900 mg, 2.416 mmol, 1 equiv) and I-2 (829.88 mg, 2.899 mmol, 1.2 equiv) in DCE (10 mL) were added $NaBH(OAc)_3$ (1535.85 mg, 7.248 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 474-7 (950 mg, 61.18%) as a yellow solid.

8. Synthesis of 474-8

[1638] To a stirred solution of 474-7 (960 mg, 1.493 mmol, 1 equiv) and pyridine (708.70 mg, 8.958 mmol, 6 equiv) in DCM (12 mL) were added Triphosgene (155.08 mg, 0.523 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 474-8 (800 mg, 80.09%) as a yellow solid.

9. Synthesis of 474-9

[1639] To a stirred solution of 474-8 (780 mg, 1.166 mmol, 1 equiv) in THF (8 mL) were added HCl (8 mL, 2M) at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc

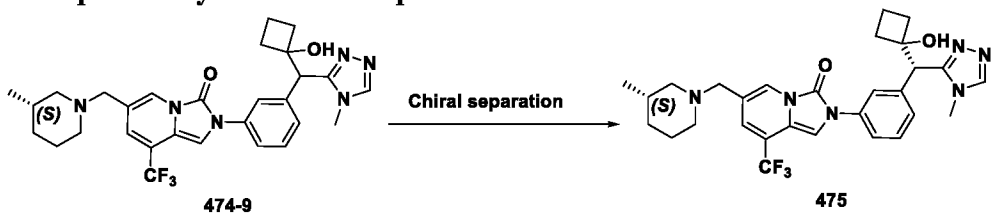
(2x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 474-9 (450 mg) as a yellow solid.

10. Synthesis of 474

[1640] The 474-9 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14.5 min; Wave Length: 220/254 nm; RT1 (min): 8.25; RT2 (min): 11.98; the second peak is product) to afford 474 (186.6 mg, 41.22%) as a yellow solid.

LC-MS-474 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-474 (400 MHz, DMSO-d6, δ *ppm*): 0.82-0.86 (m, 4H), 1.47-1.50 (m, 1H), 1.50-1.66 (m, 5H), 1.66-1.89 (m, 3H), 1.89-2.14 (m, 2H), 2.14-2.26 (m, 1H), 2.73-2.77 (m, 2H), 3.25-3.30 (m, 2H), 3.45 (s, 3H), 4.56 (s, 1H), 5.50 (s, 1H), 7.01 (s, 1H), 7.24-7.26 (s, 1H), 7.34-7.36 (m, 1H), 7.44-7.46 (m, 1H), 7.65 (s, 1H), 7.65-7.70 (m, 1H), 7.70-7.72 (m, 1H), 7.88 (s, 1H), 8.44(s, 1H).

Example 466. Synthesis of Compound 475



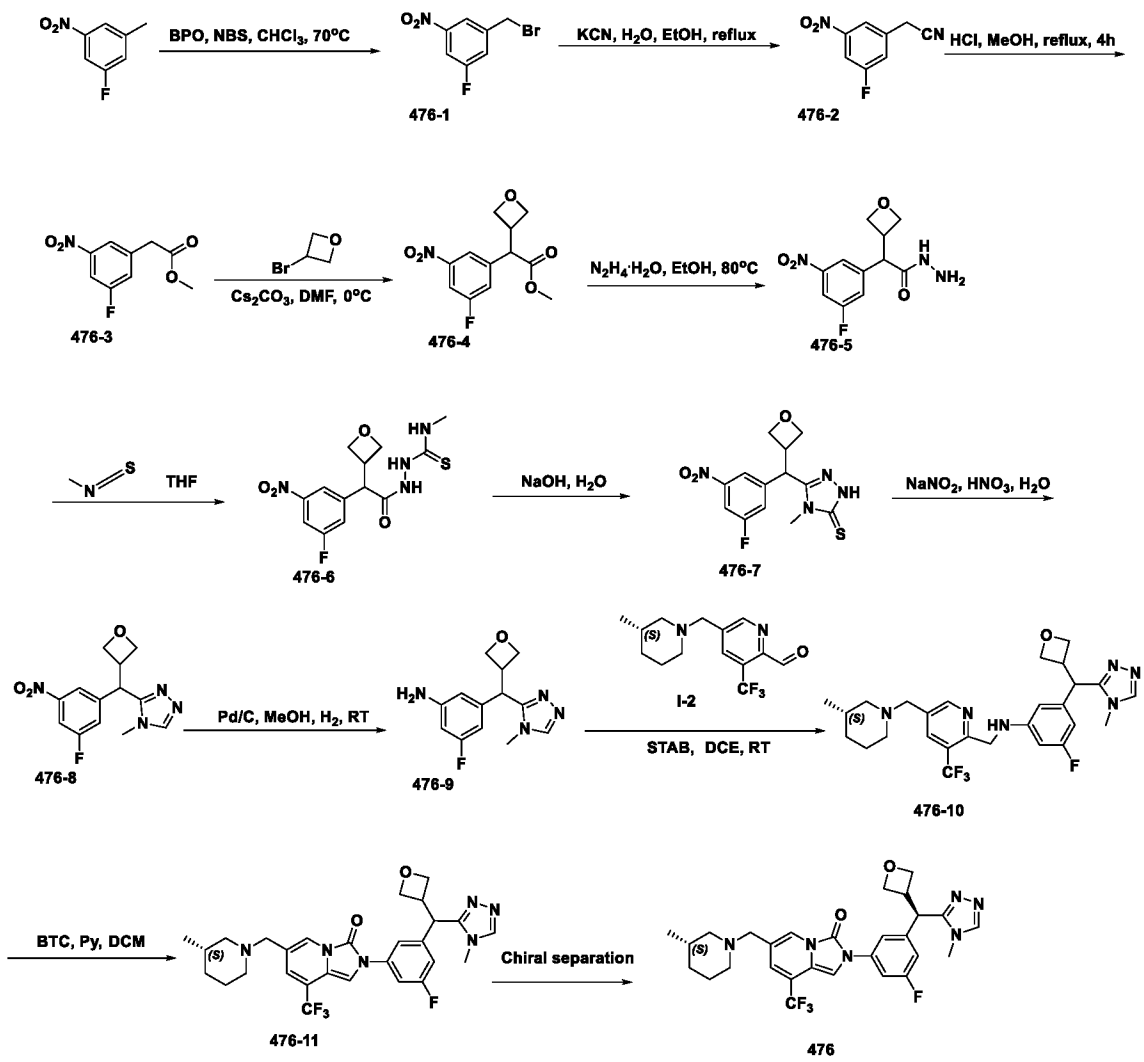
474-9 475

1. Synthesis of 475

[1641] The 474-9 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14.5 min; Wave Length: 220/254 nm; RT1 (min): 8.25; RT2 (min): 11.98; the first peak is product) to afford 475 (175.1 mg, 38.68%) as a yellow solid.

LC-MS-475 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-475 (400 MHz, CD_3OD-d4, δ *ppm*): 1.73-1.93 (m, 1H), 1.93-1.98 (m, 4H), 2.22-2.29 (m, 1H), 2.62 (s, 2H), 3.08 (s, 3H), 3.23-3.30 (m, 1H), 3.34-3.47 (m, 2H), 4.54 (s, 3H), 3.83 (s, 2H), 4.28-4.31 (m, 1H), 3.83 (s, 2H), 7.11 (s, 1H), 7.15 (s, 1H), 7.27-7.29 (m, 1H), 7.48-7.52 (m, 1H), 7.64-7.66 (m, 1H), 7.82 (s, 1H), 8.38(s, 1H).

Example 467. Synthesis of Compound 476



1. Synthesis of 476-1

[1642] To a stirred mixture of 1-fluoro-3-methyl-5-nitrobenzene (100 g, 644.629 mmol, 1 equiv) and NBS (229.47 g, 1289.258 mmol, 2 equiv) in $CHCl_3$ (1000 mL) was added BPO (24.78 g, 96.694 mmol, 0.15 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched with saturated NH_4Cl (aq.) (500 mL) at room temperature. The resulting mixture was diluted with water (1.5 L). The aqueous layer was extracted with CH_2Cl_2 (2x1 L).The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 476-1 (21 g, 13.92%) as a yellow oil.

2. Synthesis of 476-2

[1643] To a stirred mixture of 476-1 (21 g, 89.734 mmol, 1 equiv) in H_2O (50 mL) and EtOH

(200 mL) were added KCN (11.69 g, 179.468 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with saturated $NaHCO_3$ (aq.) (300 mL) at room temperature. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2x500 mL). The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (2x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 476-2 (2.5 g, 15.47%) as a yellow oil.

3. Synthesis of 476-3

[1644] To a stirred solution of 476-2 (2.5 g, 13.878 mmol, 1 equiv) in MeOH (30 mL) was added HCl(g) over 1h at room temperature. The resulting mixture was stirred for 2h at 80 °C. The reaction was quenched with $NaHCO_3$ (aq.) (200mL) at room temperature. The aqueous layer was extracted with EtOAc (2x80 mL).The resulting mixture was concentrated under reduced pressure. This resulted in 476-3 (2.7 g, 91.27%) as a yellow solid.

4. Synthesis of 476-4

[1645] To a stirred mixture of methyl 476-3 (2.2 g, 10.321 mmol, 1 equiv) in DMF (40 mL) was added Cs_2CO_3 (11.77 g, 36.123 mmol, 3.5 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 3h at °C under nitrogen atmosphere. To the above mixture was added 3-bromooxetane (3.53 g, 25.802 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (100:1) to afford 476-4 (1.7 g, 61.18%) as a yellow solid.

5. Synthesis of 476-5

[1646] To a stirred solution of 476-4 (1.6 g, 5.943 mmol, 1 equiv) in EtOH (16 mL) were added $NH_2NH_2.H_2O$ (3.04 g, 59.430 mmol, 10 equiv, 98%) at room temperature. The resulting mixture was stirred overnight at 80 °C. The reaction was quenched with saturated NH_4Cl (aq.) (100 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (2x50 mL). This resulted in 476-5 (1.5 g, 93.75%) as a yellow solid.

6. Synthesis of 476-6

[1647] To a stirred mixture of 476-5 (1.4 g, 5.200 mmol, 1 equiv) in tetrahydrofuran (20 mL) were added methyl isothiocyanate (0.95 g, 13.000 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was

diluted with water (20 mL). The resulting mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water (2x30 mL). This resulted in 476-6 (1.8 g, 91.00%) as a white solid.

7. Synthesis of 476-7

[1648] To a stirred mixture of NaOH (2.1 g, 52.580 mmol, 10 equiv) in H_2O (50 mL) was added 476-6 (1.8 g, 5.258 mmol, 1 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was neutralized to pH 7 with 1M HCl (aq.). The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. This resulted in 476-7 (1.2 g, 70.37%) as a yellow solid

8. Synthesis of 476-8

[1649] To a stirred mixture of 476-7 (1.2 g, 3.700 mmol, 1 equiv) and $NaNO_2$ (2.55 g, 37.000 mmol, 10 equiv) were added HNO_3 (37 mL, 37.000 mmol, 10 equiv, 1M) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 476-8 (700 mg, 64.73%) as a yellow solid.

9. Synthesis of 476-9

[1650] To a solution of 476-8 (680 mg, 2.327 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (10%, 68 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 476-9 (620 mg, 101.60%) as a yellow solid.

10. Synthesis of 476-10

[1651] A solution of 476-9 (600 mg, 2.290 mmol, 1 equiv) and I-2 (982.41 mg, 3.435 mmol, 1.5 equiv) in DCE (10 mL) was stirred overnight at room temperature. To the above mixture was added STAB (808.04 mg, 3.812 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 476-10 (600 mg, 59.10%) as a white solid.

11. Synthesis of 476-11

[1652] To a stirred mixture of 476-10 (600 mg, 1.127 mmol, 1 equiv) and Pyridine (534.67

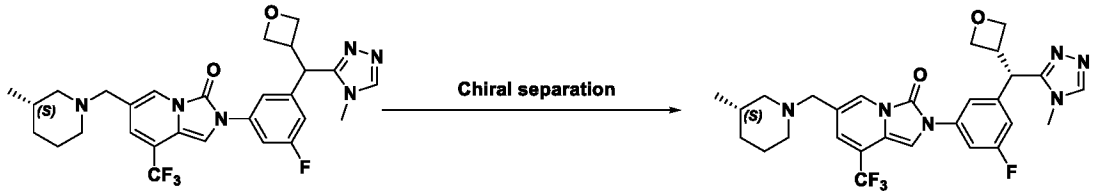
mg, 6.762 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (133.72 mg, 0.451 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL).The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 476-11 (300 mg, 47.67%) as a yellow solid.

12. Synthesis of 476

[1653] The 476-9 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 6.05; RT2(min): 6.92; the second peak is product) to afford 476 (84.3 mg, 28.10%) as a yellow solid.

LC-MS-476 (ES, *m/z*): $[M+H]^+$ 559. H-NMR-476 (400 MHz, DMSO-d_6, δ *ppm*): 0.83-0.91 (m, 4H), 1.43-1.51 (m, 1H), 1.53-1.73 (m, 4H), 1.89-1.95 (m, 1H), 2.74-.277 (m, 2H), 3.24-3.29 (m, 2H), 3.42 (s, 3H), 3.92-3.95 (m, 1H), 4.26-4.29 (m, 1H), 4.49-4.50 (m, 2H), 4.72-4.75 (m, 1H), 4.83-4.85(m,1H),7.02-7.06(m, 2H),7.46 (s, 1H),7.64-7.71(m, 2H),7.75-7.78(d, 1H),8.39 (s, 1H).

Example 468. Synthesis of Compound 477

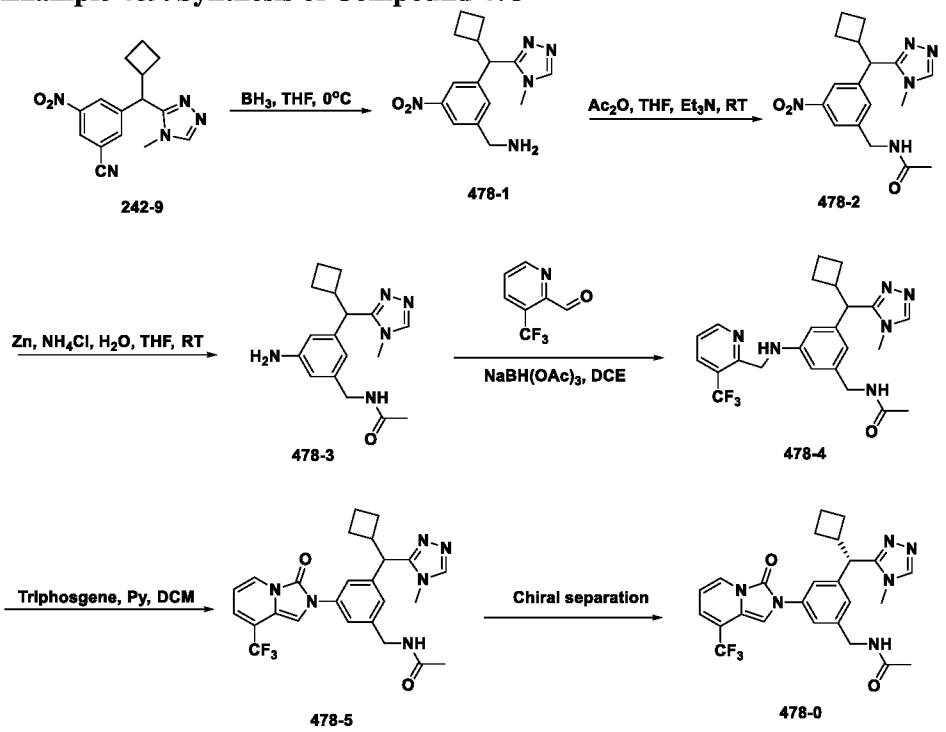


1. Synthesis of 477

[1654] The 476-11 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 6.05; RT2(min): 6.92; the first peak is product) to afford 476 (113.0 mg, 37.66%) as a yellow solid..

LC-MS-477 (ES, *m/z*): $[M+H]^+$ 559. H-NMR-477 (400 MHz, DMSO-d_6, δ *ppm*): 0.83-0.91 (m, 4H), 1.43-1.51 (m, 1H), 1.53-1.73 (m, 4H), 1.89-1.95 (m, 1H), 2.74-.277 (m, 2H), 3.24-3.29 (m, 2H), 3.42 (s, 3H), 3.92-3.95 (m, 1H), 4.26-4.29 (m, 1H), 4.49-4.50 (m, 2H), 4.72-4.75 (m, 1H), 4.83-4.85 (m,1H), 7.02-7.06 (m, 2H), 7.46 (s, 1H), 7.64 (s, 1H), 7.71 (s, 1H), 7.75-7.78 (d, 1H), 8.39 (s, 1H).

Example 469. Synthesis of Compound 478



1. Synthesis of 478-1

[1655] To a stirred solution of 242-9 (2 g, 6.727 mmol, 1 equiv) in THF (20 mL) was added BH3-THF (13.45 mL, 13.454 mmol, 2.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with HCl (aq.) at room temperature. The mixture was basified to pH 9 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with DCM/MeOH(10:1) (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 478-1 (600 mg, 27.53%) as an off-white solid.

2. Synthesis of 478-2

[1656] To a stirred solution of 478-1 (600 mg, 1.991 mmol, 1 equiv) and Et_3N (604.44 mg, 5.973 mmol, 3 equiv) in THF (10 mL) was added Ac_2O (406.53 mg, 3.982 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 478-2 (550 mg, 72.40%) as an off-white solid.

3. Synthesis of 478-3

[1657] To a stirred solution of 478-2 (480 mg, 1.398 mmol, 1 equiv) and NH_4Cl (747.70 mg, 13.980 mmol, 10 equiv) in THF (15 mL)/H_2O (5 mL) was added Zn (274.17 mg, 4.194

mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (2x10 mL). The filtrate was diluted with saturated $NaHCO_3$(aq) (100 mL) and extracted with DCM/MeOH(10:1) (3x50 mL). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 478-3 (350 mg, 74.30%) as an off-white solid.

4. Synthesis of 478-4

[1658] To a stirred solution of 478-3 (330 mg, 1.053 mmol, 1 equiv) and 3-(trifluoromethyl)pyridine-2-carbaldehyde (202.82 mg, 1.158 mmol, 1.1 equiv) in DCE (5 mL) was added $NaBH(OAc)_3$ (446.32 mg, 2.106 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (60 mL) at room temperature. The aqueous layer was extracted with DCM (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 478-4 (420 mg, 80.20%) as an off-white solid.

5. Synthesis of 478-5

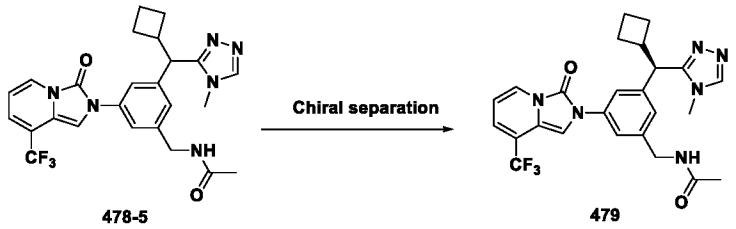
[1659] To a stirred solution of 478-4 (400 mg, 0.847 mmol, 1 equiv) and Pyridine (669.61 mg, 8.465 mmol, 10.00 equiv) in DCM (10 mL) were added Triphosgene (100.48 mg, 0.339 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated $NaHCO_3$(aq.)(60 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 478-5 (300 mg, 68.25%) as a yellow solid.

6. Synthesis of 478

[1660] The 478-5 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 8.37; RT2(min): 10.19; the first peak is product) to afford 478 (87.0 mg, 27.55%) as a yellow solid.

LC-MS-478 (ES, *m/z*): $[M+H]^+$ 499. H-NMR-478 (400 MHz, DMSO-d6, δ *ppm*): 1.65-1.76 (m, 1H), 1.76-1.84 (m, 4H), 1.85 (s, 3H), 2.07-2.10 (m, 1H), 3.18-3.25 (m, 1H), 3.43 (s, 3H), 4.23-4.28 (m, 3H), 6.27-6.30 (m, 1H), 7.06-7.11 (m, 2H), 7.26 (s, 1H), 7.58 (s, 1H), 7.64 (s, 1H), 7.77-7.79 (d, 1H), 8.33-8.38 (m, 1H).

Example 470. Synthesis of Compound 479

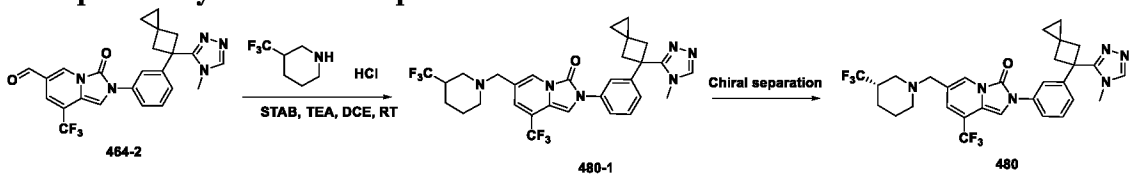


1. Synthesis of 479

[1661] The 478-5 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 12.5 min; Wave Length: 220/254 nm; RT1(min): 8.37; RT2(min): 10.19; the second peak is product) to afford 479 (87.0 mg, 27.55%) as a yellow solid.

LC-MS-479 (ES, *m/z*): $[M+H]^+$ 499. H-NMR-479 (400 MHz, DMSO-d6, δ *ppm*): 1.65-1.76 (m, 1H), 1.76-1.84 (m, 4H), 1.85 (s, 3H), 2.07-2.10 (m, 1H), 3.18-3.25 (m, 1H), 3.43 (s, 3H), 4.23-4.26 (m, 3H), 6.27-6.30 (m, 1H), 7.06-7.11 (m, 2H), 7.26 (s, 1H), 7.58 (s, 1H), 7.64 (s, 1H), 7.77-7.79 (d, 1H), 8.33-8.38 (m, 1H).

Example 471. Synthesis of Compound 480



1. Synthesis of 480-1

[1662] To a stirred solution of 464-2 (700 mg, 1.497 mmol, 1 equiv) and 3-(trifluoromethyl)piperidine hydrochloride (567.87 mg, 2.994 mmol, 2 equiv) in DCE (10 mL) were added TEA (303.07 mg, 2.994 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (634.75 mg, 2.994 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 480-1 (370 mg, 39.23%) as a yellow solid.

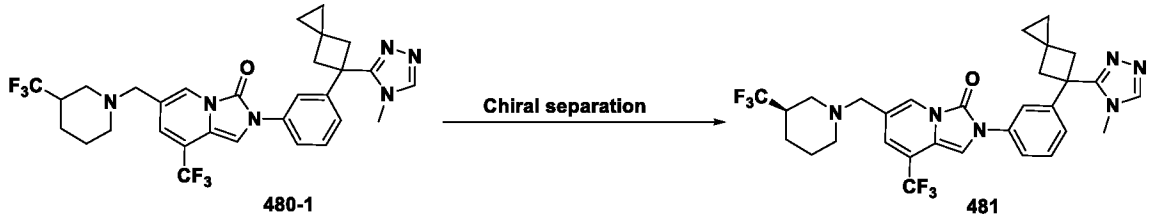
2. Synthesis of 480

[1663] The 480-1 (370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 15

min; Wave Length: 220/254 nm; RT1(min): 9.83; RT2(min): 12.67; the first peak is product) to afford the crude product. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 480 (54.6 mg, 14.05%) as a yellow solid.

LC-MS-480 (ES, *m/z*): $[M+H]^+$ 605. H-NMR-480 (400 MHz, DMSO-d6, δ *ppm*): 0.43-0.49 (m, 2H), 0.55-0.59 (m, 2H), 1.24-1.34 (m, 1H), 1.47-1.58 (m, 1H), 1.83-1.91 (m, 1H), 1.97-2.05 (m, 2H), 2.51-2.61 (m, 1H), 2.75-2.80 (m, 3H), 2.97-3.03 (m, 1H), 3.17-3.24 (m, 2H), 3.32 (s, 3H), 3.40 (s, 2H), 7.02 (s, 1H), 7.18-7.20 (d, 1H), 7.35 (s, 1H), 7.49-7.53 (m, 1H), 7.63-7.65 (d, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 472. Synthesis of Compound 481



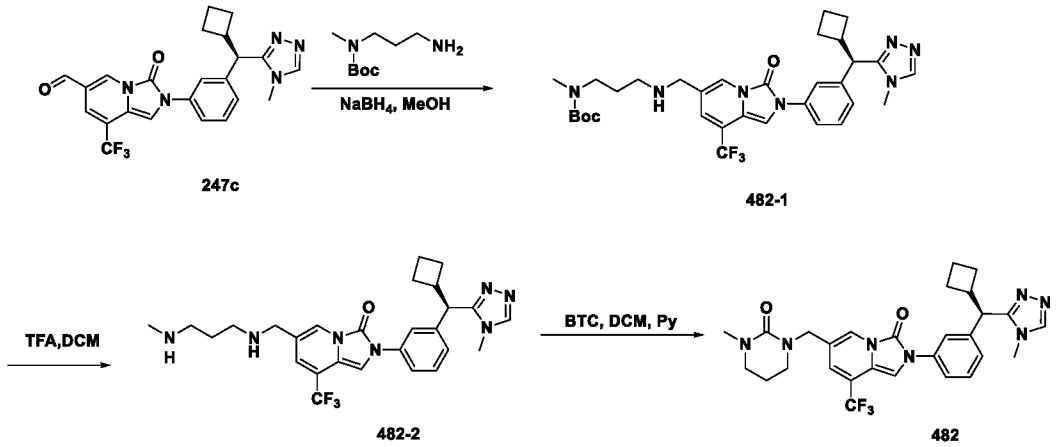
480-1 481

Synthesis of 481

[1664] 480-1 (370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 15 min; Wave Length: 220/254 nm; RT1(min): 9.83; RT2(min): 12.67; the second peak is product) to afford 481 (145.8 mg, 38.85%) as a yellow solid.

LC-MS-481 (ES, *m/z*): $[M+H]^+$ 605. H-NMR-481 (400 MHz, DMSO-d6, δ *ppm*): 0.43-0.49 (m, 2H), 0.55-0.59 (m, 2H), 1.24-1.34 (m, 1H), 1.47-1.58 (m, 1H), 1.83-1.91 (m, 1H), 1.97-2.05 (m, 2H), 2.51-2.61 (m, 1H), 2.75-2.80 (m, 3H), 2.97-3.03 (m, 1H), 3.17-3.24 (m, 2H), 3.32 (s, 3H), 3.40 (s, 2H), 7.02 (s, 1H), 7.17-7.19 (d, 1H), 7.35 (s, 1H), 7.49-7.52 (m, 1H), 7.63-7.65 (d, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 8.39 (s, 1H).

Example 473. Synthesis of Compound 482



247c 482-1 482-2 482

1. Synthesis of 482-1

[1665] To a stirred solution of 247-3 (800 mg, 1.757 mmol, 1 equiv) in MeOH (7 mL) was added tert-butyl N-(3-aminopropyl)-N-methylcarbamate (661.41 mg, 3.514 mmol, 2 equiv) was stirred for overnight at room temperature. To the above mixture was added $NaBH_4$ (332.25 mg, 8.785 mmol, 5 equiv). The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with sat. NH_4Cl (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford 482-1 (380 mg, 27.57%) as a brown oil.

2. Synthesis of 482-2

[1666] A solution of tert-butyl 482-1 (380 mg, 0.605 mmol, 1 equiv) and TFA (3 mL) in DCM (9 mL) was stirred for 3 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford 482-2 (100 mg, 29.12%) as a brown oil.

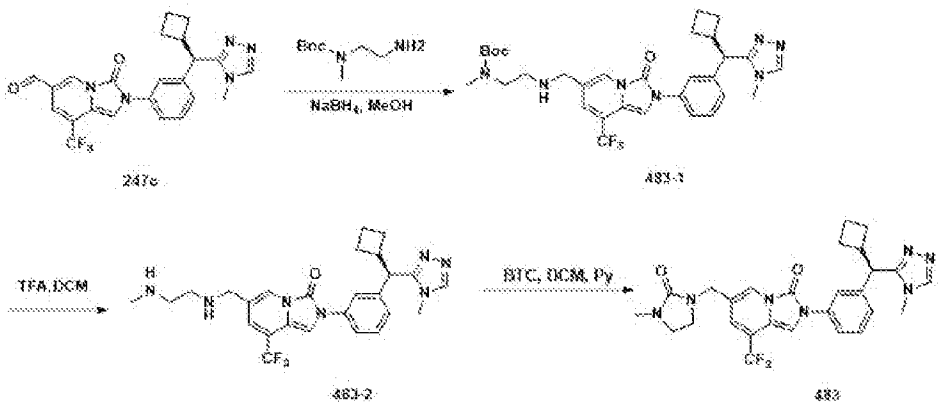
3. Synthesis of 482

[1667] To a stirred solution of 482-2 (100 mg, 0.152 mmol, 1 equiv) and pyridine (71.96 mg, 0.912 mmol, 6 equiv) in DCM (10 mL) were added triphosgene (18.00 mg, 0.061 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 5 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford crude product. The crude product (60 mg) was purified by Prep-HPLC with the following

conditions (Column: X Bridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 47% B in 8 min; Wave Length: 220 nm; RT1(min): 7.37) to afford 482 (21.0 mg, 24.84%) as a light yellow solid.

LC-MS-482 (ES, *m/z*): $[M+H]^+$ 554. H-NMR-482 (400 MHz, CD_3OD, *ppm*): δ1.75-1.80 (m, 1H), δ1.86-1.92 (m, 4H), δ1.93-2.04 (m, 2H), δ2.24-2.28 (m, 1H), δ2.97 (s, 3H), δ3.14-3.16 (m, 1H), δ3.32-3.38 (m, 4H), δ3.35-3.56 (m, 3H), δ4.28-4.36 (d, 1H), δ4.87 (s, 2H), δ7.04-7.14 (d, 1H), δ7.26-7.29 (d, 1H), δ7.48-7.50 (d, 1H), δ7.52 (m, 1H), δ7.63-7.67 (m, 3H), δ8.38 (s, 1H).

Example 474. Synthesis of Compound 483



1. Synthesis of 483-1

[1668] To a stirred solution of 247c (800 mg, 1.757 mmol, 1 equiv) in MeOH (7 mL) was added tert-butyl N-(2-aminoethyl)-N-methylcarbamate (612.13 mg, 3.514 mmol, 2 equiv) was stirred for overnight at room temperature. To the above mixture was added $NaBH_4$ (332.25 mg, 8.785 mmol, 5 equiv) The resulting mixture was stirred for additional 1h at room temperature. The reaction was quenched with sat. NH_4Cl (20mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 483-1 (330 mg, 26.94%) as a brown oil.

2. Synthesis of 483-2

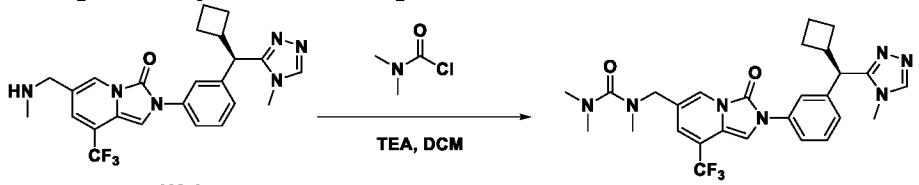
[1669] A solution of 483-1 (330 mg, 0.538 mmol, 1 equiv) and TFA (2 mL) in DCM (6 mL) was stirred for 3h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 8:1) to afford 483-2 (120 mg, 34.76%) as a brown oil.

3. Synthesis of 483

[1670] To a stirred solution of 483-2 (120 mg, 0.234 mmol, 1 equiv) and pyridine (110.89 mg, 1.404 mmol, 6 equiv) in DCM (10 mL) was added triphosgene (27.73 mg, 0.094 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 5min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 8:1) to afford the crude product (80mg). The crude product (80mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 46% B in 8 min; Wave Length: 220 nm; RT1(min): 7.35) to afford 483 (41.9 mg, 32.95%) as a light yellow solid.

LC-MS-483 (ES, *m/z*): $[M+H]^+$ 541. H-NMR-483 (400 MHz, CD_3OD, *ppm*): δ 1.75-1.81 (m, 1H), δ1.86-1.97 (m, 4H), δ2.24-2.28 (m, 1H), δ2.84 (s, 3H), δ3.15 (s, 1H), δ3.27-3.34 (m, 4H), δ3.34-3.56 (m, 3H), δ4.19 (s, 2H), δ4.28-4.31 (d, 1H), δ6.98 (s, 1H), δ7.14 (s, 1H), δ7.26-7.28 (d, 1H), δ7.29 (s, 1H), δ7.48-7.52 (m, 2H), δ7.63-7.71 (m, 1H), δ8.38 (s, 1H).

Example 475. Synthesis of Compound 484

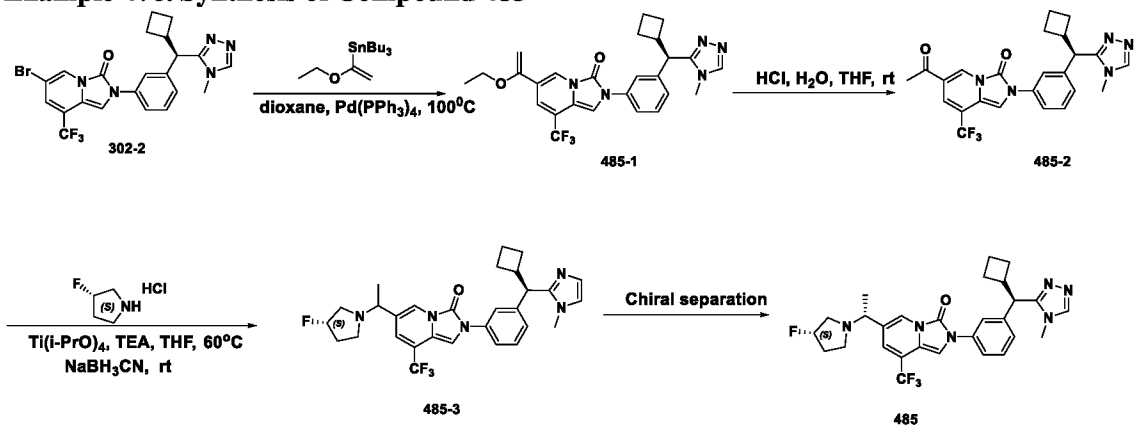


1. Synthesis of 484

[1671] Into a 20 mL sealed tube were added 469-1 (160 mg, 0.340 mmol, 1 equiv), DCM (3 mL), TEA (103.24 mg, 1.020 mmol, 3 equiv) and dimethylcarbamyl chloride (73.14 mg, 0.680 mmol, 2 equiv) at room temperature. The final reaction mixture was irradiated with microwave radiation for 2 h at room temperature. The reaction was quenched with water (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 48% B in 8 min; Wave Length: 220 nm; RT1(min): 7.33) to afford 484 (59.4 mg, 31.90%) as a yellow solid.

LC-MS-484 (ES, m/z): $[M+H]^+$ 542. H-NMR-484 (400 MHz, DMSO, δ *ppm*): 1.52-1.90 (m, 5H), 1.99-2.18 (s, 1H), 2.64-2.75 (s, 3H), 2.75-2.80 (s, 6H), 3.15-3.30 (m, 1H), 3.39-3.51 (s, 3H), 3.91-4.21 (s, 2H), 4.21-4.35 (d, 1H), 6.80-7.12 (s, 1H), 7.12-7.28 (d, 1H), 7.28-7.40 (d, 1H), 7.40-7.65 (m, 1H), 7.65-7.80(m, 3H), 8.21-8.40 (s, 1H).

Example 476. Synthesis of Compound 485



1. Synthesis of 485-1

[1672] Into a 250 mL 3-necked round-bottom flask were added 302-2 (10 g, 19.750 mmol, 1 equiv), tributyl(1-ethoxyethenyl) stannane (10.70 g, 29.625 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (2.28 g, 1.975 mmol, 0.1 equiv) and dioxane (100 mL) at room temperature. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (500 mL). The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 485-1 (8 g, 76.53%) as a yellow solid.

2. Synthesis of 485-2

[1673] Into a 250 mL round-bottom flask were added 485-1 (8 g, 16.080 mmol, 1 equiv), THF (20 mL) and 1M HCl (20 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 485-2 (7 g, 86.24%) as a yellow solid.

3. Synthesis of 485-3

[1674] Into a 40 mL vial were added 485-2 (500 mg, 1.065 mmol, 1 equiv), (3S)-3-fluoropyrrolidine hydrochloride (160.49 mg, 1.278 mmol, 1.2 equiv), TEA (431.10 mg, 4.260

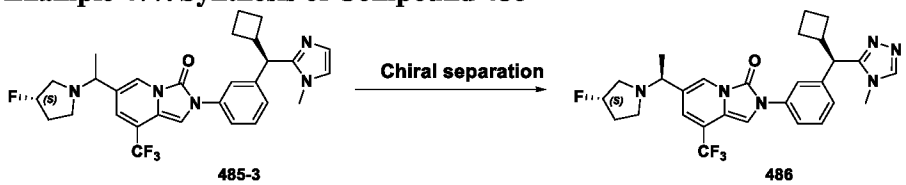
mmol, 4 equiv), $Ti(Oi\text{-}Pr)_4$ (605.41 mg, 2.130 mmol, 2 equiv) and THF (10 mL) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added $NaBH_3CN$ (133.85 mg, 2.130 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at 60 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford crude product. The crude product (250 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 53% B in 8 min; Wave Length: 254 nm; RT1(min): 7.37) to afford 485-3 (120 mg, 20.60%) as a yellow solid.

4. Synthesis of 485

[1675] The 485-3 (150 mg, 0.276 mmol, 1 equiv) was purified by Chiral seperation with the following conditions (Column: CHIRALPAK IG, 7*25cm, 10 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 19 min; Wave Length: 220/254 nm; RT1(min): 12.72; RT2(min): 15.97; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 8) to afford 485 (42.4 mg, 28.01%) as a yellow solid.

LC-MS-485 (ES, *m/z*): $[M+H]^+$ 543. H-NMR-485 (400 MHz, DMSO-d6, *ppm*): δ 1.30 (s, 3H), δ1.60-1.97 (m, 6H), δ2.05-2.12 (m, 2H), δ2.40-2.50 (m, 1H), δ2.65-2.67 (m, 2H), δ2.80-2.95 (m, 1H), δ3.20-3.28 (m, 2H), δ3.43 (s, 3H), δ4.25-4.28 (d, 1H), δ5.13-5.28 (d, 1H), δ7.05 (s, 1H), δ7.19-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.46 (m, 1H), δ7.67-7.70 (m, 3H), δ8.33 (s, 1H).

Example 477. Synthesis of Compound 486



485-3 486

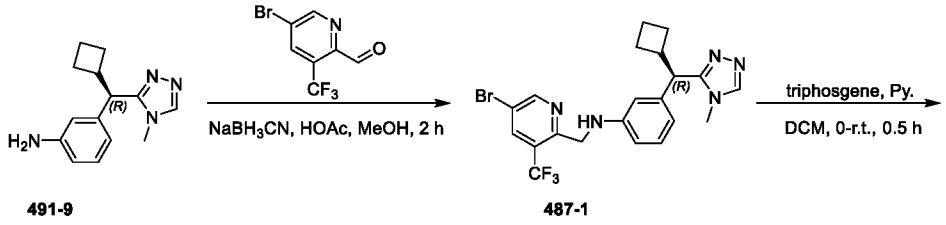
1. Synthesis of 486

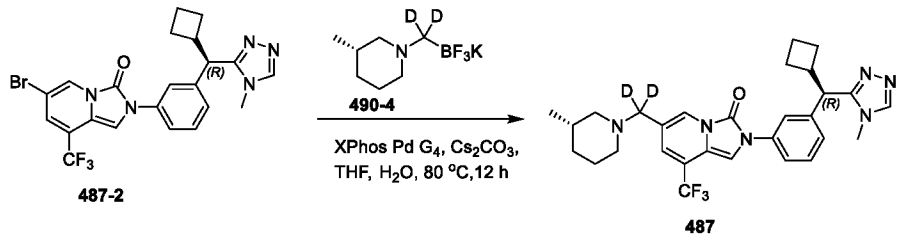
[1676] The 485-3 (150 mg, 0.276 mmol, 1 equiv) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IG, 7*25cm, 10 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 19 min; Wave Length: 220/254 nm; RT1(min): 12.72;

RT2(min): 15.97; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 8) to afford 486 (40.4 mg, 26.69%) as a yellow solid.

LC-MS-485 (ES, *m/z*): $[M+H]^+$ 543. H-NMR-485 (400 MHz, DMSO-d6, *ppm*): δ 1.28-1.30 (d, 3H), δ1.77-1.81 (m, 6H), δ2.08-2.29 (m, 3H), δ2.65-2.67 (m, 2H), δ2.80-2.95 (m, 1H), δ3.20-3.28 (m, 2H), δ3.43 (s, 3H), δ4.25-4.27 (d, 1H), δ5.11-5.25 (d, 1H), δ7.06 (s, 1H), δ7.19-7.21 (d, 1H), δ7.31 (s, 1H), δ7.42-7.46 (m, 1H), δ7.67-7.72 (m, 3H), δ8.33 (s, 1H).

Example 478. Synthesis of Compound 487





1. Synthesis of 487-1

[1677] To a solution of 491-9 (3.9 g, 16.1 mmol, 1 equiv) and 5-bromo-3-(trifluoromethyl)picolinaldehyde (4.09 g, 16.1 mmol, 1 equiv) in MeOH (50 mL) was added HOAc (2.76 mL, 48.28 mmol, 3 equiv). The mixture was stirred at 20 °C for 1 hr. Then $NaBH_3CN$ (2.02 g, 32.2 mmol, 2 equiv) was added. The mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction mixture was extracted with water (120 mL) and EtOAc (40 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 487-1 (6.64 g, 85.89%) as a yellow solid.

^{1}H-NMR-487-1: (400 MHz, CHLOROFORM-d) δ 8.80 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.01 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.58 (t, J = 7.6 Hz, 2H), 6.52 (s, 1H), 4.49 (s, 2H), 3.80 (d, J = 10.4 Hz, 1H), 3.35 (s, 3H), 2.39-2.29 (m, 1H), 1.94-1.76 (m, 6H)

2. Synthesis of 487-2

[1678] To a solution of 487-1 (6.64 g, 13.8 mmol, 1 equiv) in DCM (66 mL) was added Py. (6.69 mL, 82.94 mmol, 6 equiv) and bis(trichloromethyl) carbonate (2.05 g, 6.91 mmol, 0.5

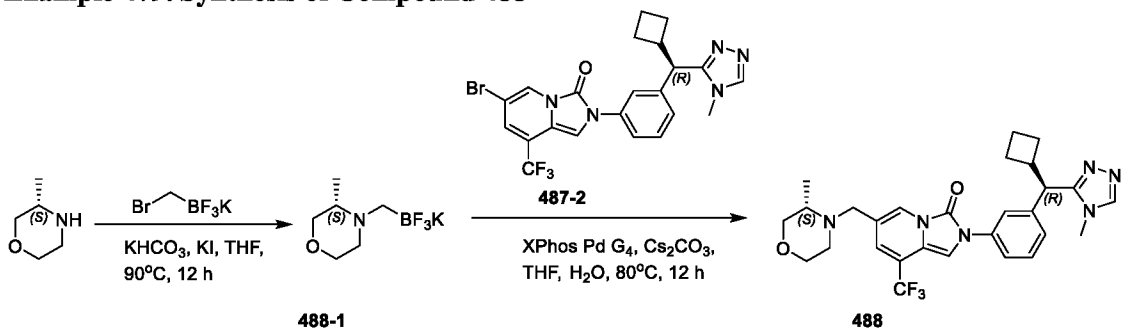
equiv) at 0 °C. Then the mixture was stirred at 20 °C for 0.5 hr. The reaction was quenched with Sat. $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 487-2 (5.34 g, 76.29%) as a yellow solid.

3. Synthesis of 487

[1679] To a solution of 487-2 (450 mg, 888 umol, 1 equiv) and 487-3 (393 mg, 1.78 mmol, 2 equiv) in THF (8 mL) and H_2O (2 mL) was added Xphos Pd G_4 (76.5 mg, 88.8 umol, 0.1 equiv) and Cs_2CO_3 (868 mg, 2.67 mmol, 3 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was extracted with water (120 mL) and EtOAc (40 mL x3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give a crude product. The crude product (500 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 5% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5) to afford 487 (183.5 mg, 38.01%) as a yellow solid.

MS-487: (ES, m/z): $[M+H]^+$ 541.3. ^{1}H-NMR-487: (400 MHz, METHANOL-d4) δ 8.48 (s, 1H), 8.36 (s, 1H), 7.82 (s, 1H), 7.66-7.61 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.12 (s, 1H), 4.28 (d, J = 10.8 Hz, 1H), 3.54 (s, 3H), 3.23-3.13 (m, 2H), 2.47-2.39 (m, 1H), 2.27-2.21 (m, 1H), 2.14 (t, J = 11.2 Hz, 1H), 1.95-1.68 (m, 9H), 1.12-1.00 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H).

Example 479. Synthesis of Compound 488



1. Synthesis of 488-1

[1680] A mixture of (3S)-3-methylmorpholine (2 g, 19.77 mmol, 1 equiv),

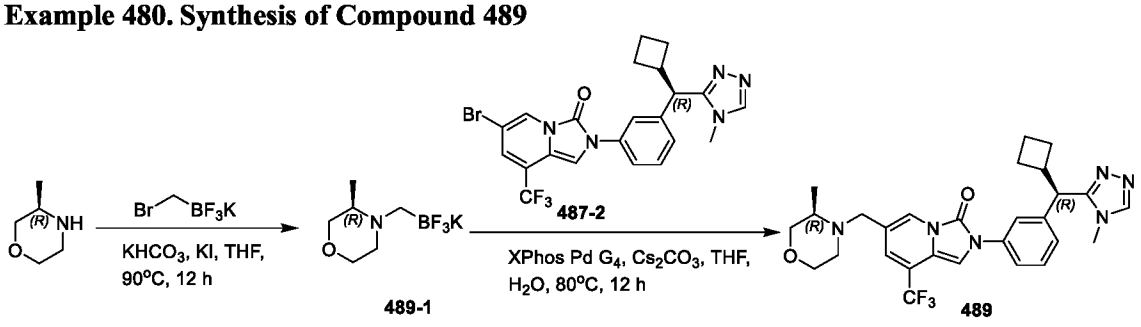
potassium;bromomethyl (trifluoro)boranuide (3.97 g, 19.7 mmol, 1 equiv), KI (328 mg, 1.98 mmol, 0.1 equiv), $KHCO_3$ (3.96 g, 39.5 mmol, 2 equiv) in THF (20 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with acetone (40 mL) at 40 °C for 1 hr. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 488-1 (680 mg, crude) as a yellow solid.

2. Synthesis of 488

[1681] To a solution of 487-2 (260 mg, 513 umol, 1 equiv) and 488-1 (227 mg, 1.03 mmol, 2 equiv) in THF (4 mL) and water (1 mL) was added Cs_2CO_3 (501.94 mg, 1.54 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl] phenyl]palladium(1+) (44.19 mg, 51.35 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water 10 mL and extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH=10:1 to give crude product. The crude product (230 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 75*30mm*3um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm; RT1(min): 10.0) to afford 488 (85.4 mg, 31%) as a yellow solid.

MS-488: (ES, m/z): $[M+H]^+$ 541.3. ^1H NMR-488 (400 MHz, METHANOL-d_4) δ 8.38 (s, 1H), 7.70 (s, 1H), 7.68-7.63 (m, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.30-7.25 (m, 1H), 7.12 (s, 1H), 7.07 (s, 1H), 4.30 (d, J = 10.8 Hz, 1H), 3.90 (d, J = 13.6 Hz, 1H), 3.81-3.71 (m, 2H), 3.67-3.59 (m, 1H), 3.56 (s, 3H), 3.30 (s, 1H), 3.07 (d, J = 13.6 Hz, 1H), 2.79-2.69 (m, 1H), 2.62-2.51 (m, 1H), 2.34-2.22 (m, 2H), 2.00-1.83 (m, 5H), 1.83-1.73 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H).

Example 480. Synthesis of Compound 489



1. Synthesis of 489-1

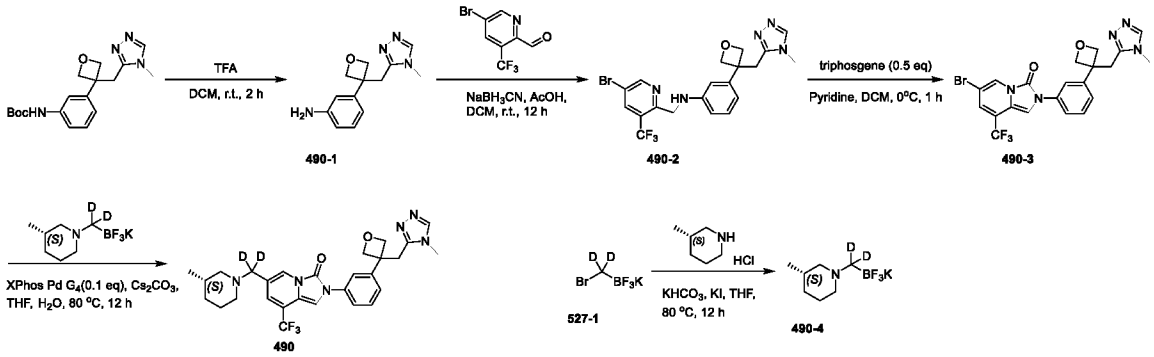
[1682] A solution of potassium;bromomethyl(trifluoro)boranuide (3.97 g, 19.7 mmol, 1 equiv), (3R)-3-methylmorpholine (2 g, 19.7 mmol, 1 equiv), $KHCO_3$ (3.96 g, 39.5 mmol, 2 equiv) and KI (328 mg, 1.98 mmol, 0.1 equiv) in THF (30 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure to give a residue. Then the residue was triturated with acetone at 40 °C for 2 h and filtered. The filtrate was concentrated under reduced pressure to afford 489-1 (1.28 g, crude) as a white solid.

2. Synthesis of 489

[1683] To a solution of 489-1 (294 mg, 1.33 mmol, 2 equiv) and 487-2 (337 mg, 665 umol, 1 equiv) in THF (8 mL) and H_2O (2 mL) was added Cs_2CO_3 (650 mg, 2.00 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl] phenyl]palladium(1+) (57.2 mg, 66.5 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was extracted with water (120 mL) and EtOAc (40 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to give a crude product. The crude product (315 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm; RT1(min): 8.0) to afford 489 (102.1 mg, 28.03%) as a yellow solid.

MS-489: (ES, m/z): $[M+H]^+$ 541.3. ^{1}H-NMR-489: (400 MHz, METHANOL-d4) δ 8.37 (s, 1H), 8.23 (s, 1H), 7.70 (s, 1H), 7.67-7.61 (m, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.28 (d, J = 11.2 Hz, 1H), 3.90 (d, J = 13.6 Hz, 1H), 3.79-3.70 (m, 2H), 3.65-3.57 (m, 1H), 3.54 (s, 3H), 3.31-3.24 (m, 1H), 3.08 (d, J = 13.6 Hz, 1H), 2.78-2.71 (m, 1H), 2.62-2.52 (m, 1H), 2.35-2.20 (m, 2H), 1.99-1.81 (m, 5H), 1.81-1.69 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H).

Example 481. Synthesis of Compound 490



490-1 490-2 490-3 490 527-1 490-4

1. Synthesis of 490-1

[1684] To a solution of tert-butyl N-[3-[3-[(4-methyl-1,2,4-triazol-3-yl)methyl]oxetan-3-yl]phenyl]carbamate (2 g, 5.81 mmol, 1 equiv) in CH2Cl2 (20 mL) was added TFA (5 mL) at 25 °C and stirred for 2 hr. The mixture was concentrated in vacuum to get a crude(4.6 g). The crude (4 g) was dissolved with MeOH (200 mL) and adjust pH=7 with Amberlyst 21(basic). The mixture was filtered and washed with MeOH (500 mL). The filtrate was concentrated in vacuum to get 490-1(1.4 g, crude) as a yellow solid.

2. Synthesis of 490-2

[1685] To a solution of 490-1 (1.3 g, 5.32 mmol, 1.00 equiv) in MeOH (20 mL) was added common int.9 (1.22 g, 4.79 mmol, 0.9 equiv), AcOH (319.57 mg, 5.32 mmol, 1 equiv) at 25°C and stirred for 1 hr. NaBH3CN (668.83 mg, 10.64 mmol, 2 equiv) was added and stirred for 11 h. The mixture was concentrated in vacuum to get a residue. The residue was diluted with EtOAc (20 mL) and H2O (20 mL), extracted with EtOAc (20 mLx3). The combined organic layers were washed with brine (20 mLx2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2) with petroleum ether/EtOAc = 1:1 to 0:1 to EtOAc:MeOH=1:0 to 5:1 to get 490-2 (1.3 g, crude) as a yellow solid.

3. Synthesis of 490-3

[1686] To a solution of 490-2 (400 mg, 829.37 umol, 1 equiv) in DCM (10 mL) was added Py. (393.62 mg, 4.98 mmol, 6 equiv), bis(trichloromethyl) carbonate (0.12 g, 414.68 umol, 0.5 equiv) at 0°C and stirred for 1 h. The reaction mixture was diluted with Sat.NaHCO3 (100 mL), extracted with DCM (100 mLx3). The combined organic layers were dried over Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column chromatography (SiO2) with petroleum ether/EtOAc= 5:1 to 0:1 to DCM/MeOH=1:0 to 1:1 to afford 490-3(950 mg, crude) as a yellow solid.

4. Synthesis of 490-3

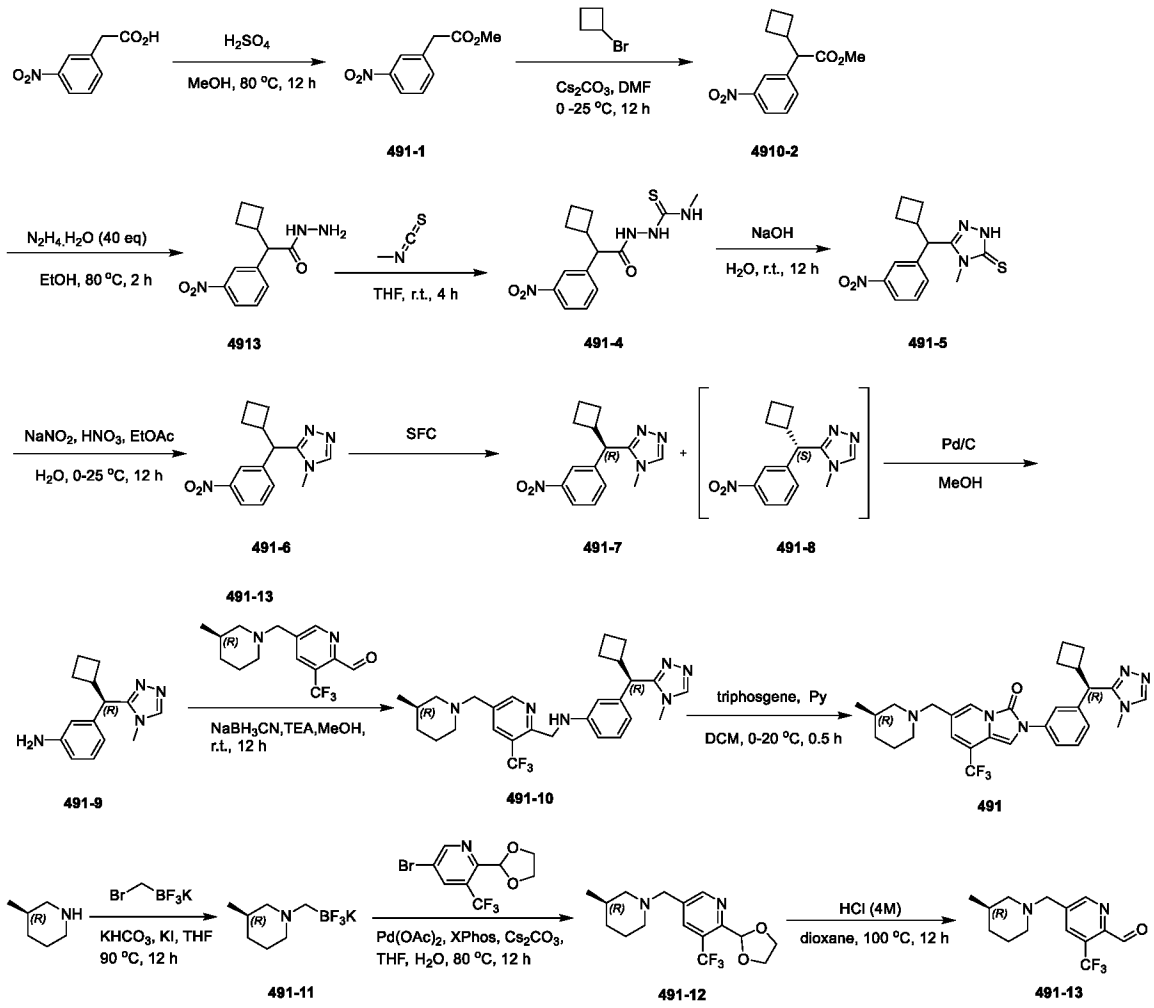
[1687] To a solution of (3S)-3-methylpiperidine;hydrochloride (668 mg, 4.93 mmol, 1 equiv) in THF (10 mL) was added [bromo(dideuterio)methyl]-trifluoro-boron;potassium hydride (1 g, 4.93 mmol, 1 equiv), KHCO3 (987 mg, 9.86 mmol, 2 equiv), KI (81.8 mg, 492 umol, 0.1 equiv). Then the mixture was heated to 80°C and stirred for 12 h under N2 atmosphere. The mixture was concentrated in vacuum to get a residue. The residue was dissolved with acetone (150 mL). Then the mixture was heated to 50°C and stirred for 3 h. The mixture was filtered, the filtrate was concentrated and get 490-4 (1.4 g, crude) was obtained as a light yellow solid.

5. Synthesis of 490

[1688] To a solution of 490-3 (300 mg, 590.21 umol, 1 equiv) in THF (10 mL), H2O (2.5 mL) was added [dideuterio-[(3S)-3-methyl-1-piperidyl]methyl]-trifluoro-boron;potassium hydride (275.52 mg, 1.25 mmol, 2 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (53.78 mg, 62.50 umol, 0.1 eq), dicesium;carbonate (610.91 mg, 1.88 mmol, 3 equiv) under N2. The suspension was degassed and purged with N2 for 3 times. The mixture was heated to 80 °C and stirred for 12 h under N2. The mixture was poured into H2O (20 mL), extracted with DCM (20 mLx3). The combined organic layer was dried by Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc= 5:1 to 0:1 to DCM:MeOH= 1:0 to 10:1 to get a crude. The crude was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(FA)-ACN];B%: 5%-45%, 8min, Wave Length: 220 nm; RT(min): 7.8 min) to get 490 (127.5 mg) as a light yellow solid.

MS-490: (ES, m/z): [M+H]+ 543.2. 1H-NMR-490: (400 MHz, MeOD) δ 8.39 (s, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.63-7.60 (m, 1H), 7.46 (t, J = 8Hz, 1H), 7.29-7.28 (m, 1H), 7.16-7.12 (m, 2H), 6.93-6.91 (m, 1H), 5.08-5.05 (m, 4H), 3.66 (s, 2H), 3.28-3.21 (m, 2H), 2.96 (s, 3H), 2.58-2.52 (m, 1H), 2.30-2.24 (m, 1H), 1.89-1.82 (m, 3H), 1.79-1.71(m, 1H), 1.14-1.05 (m, 1H), 0.97 (d, J= 6.4Hz, 3H).

Example 482. Synthesis of Compound 491



1. Synthesis of 491-1

[1689] To a solution of 2-(3-nitrophenyl)acetic acid (100.0 g, 552.1 mmol, 1 equiv) in MeOH (1000.0 mL) was added H2SO4 (10.9 g, 110.4 mmol, 5.9 mL, 0.2 equiv). The mixture was stirred at 80 °C for 12 hours. The reaction was poured into water (1000.0 mL) and the resulting mixture was extracted with EtOAc (700.0 mLx2). The organic phase was washed with NaHCO3 (300.0 ml) and brine (300.0 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue to afford 491-1 (104.0 g, 96.53% yield) was as yellow oil.

H-NMR-491-1: (400 MHz, DMSO-d6) δ ppm 8.17-8.22 (m, 1 H), 8.11-8.16 (m, 1 H), 7.71-7.78 (m, 1 H), 7.59-7.67 (m, 1 H), 3.86-3.95 (s, 2 H), 3.58-3.68 (s, 3 H).

2. Synthesis of 491-2

[1690] To a solution of 491-1 (30.0 g, 153.7 mmol, 1.0 equiv) in DMF (300.0 mL) was added Cs2CO3 (250.4 g, 768.5 mmol, 5.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 3 hours. Then the mixture was added bromocyclobutane (62.3 g, 461.1 mmol, 43.5 mL, 3.0

equiv) at 25 °C. The mixture was stirred at 25 °C for 9 hours. The reaction was poured into water (500.0 mL) and the resulting mixture was extracted with EtOAc (300.0 mLx2). The organic phase was washed with brine (300.0 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate = 0/1 to 3/1) to afford 491-2 (35.0 g, 91.35% yield) as colorless oil.

3. Synthesis of 491-3

[1691] To a solution of 491-2 (76.0 g, 304.9 mmol, 1.0 equiv) in EtOH (800.0 mL) was added hydrazine;hydrate (622.9 g, 12.2 mol, 604.8 mL, 98% purity, 40.0 equiv). The mixture was stirred at 80 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The mixture was added H2O (800.0 mL) and EtOAc (800.0 mL). The organic phase was washed with NaHCO3 (300.0 ml) and brine (300.0 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. 491-3 (38.0 g, 40.00% yield) was obtained as a yellow solid.

4. Synthesis of 491-4

[1692] To a solution of 491-3 (35.0 g, 140.4 mmol, 1.0 equiv) in THF (350.0 mL) was added methylimino(thioxo)methane (20.5 g, 280.8 mmol, 19.2 mL, 2.0 equiv). The mixture was stirred at 25 °C for 4 hours. The reaction was poured to water (600.0 mL) to give white solid. The solid was filtered and concentrated to afford 491-4 (39.0 g, 86.16% yield) as a white solid.

5. Synthesis of 491-5

[1693] To a solution of NaOH (36.7 g, 918.1 mmol, 8.0 equiv) in H2O (500.0 mL) was added 491-4 (37.0 g, 114.8 mmol, 1.0 equiv). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was acidified by 1M HCl to pH=3~4 to form solid. The solid was filtered and the filter cake was concentrated under reduced pressure to afford 491-5 (39.0 g, crude) as a white solid.

6. Synthesis of 491-6

[1694] HNO3 (112.6 g, 1.2 mol, 80.5 mL, 68% purity, 10.0 equiv) was added to H2O (599.0 mL) to afford the diluted HNO3 solution (2M, 690.0 mL). To a solution of 491-5 (37.0 g, 121.6 mmol, 1.0 equiv) and NaNO2 (83.8 g, 1.2 mol, 10.0 equiv) in H2O (420.0 mL) and EtOAc (42.0 mL) was added diluted HNO3 solution (1 M, 6.2 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 12 hours. The reaction mixture was neutralized by a.q. NaHCO3 to pH=7-8, and the resulting mixture was extracted with EtOAc (800.0 mLx2). The organic phase was washed with brine (500.0 mL), dried over anhydrous Na2SO4,

concentrated in vacuum to give 491-6 (34.0 g, 98.19% yield) as a white solid.

H-NMR-491-6: (400 MHz, DMSO-d6) 8.36 (s, 1 H), 8.14-8.20 (m, 1 H), 8.06-8.13 (m, 1 H), 7.76 (br d, J = 7.6 Hz, 1 H), 7.58-7.67 (m, 1 H), 4.42-4.54 (m, 1 H), 3.45(s, 3 H), 3.05-3.21 (m, 1 H), 1.99-2.12 (m, 1 H), 1.65-1.88 (m, 5 H).

7. Synthesis of 491-7&8

[1695] The racemate was purified by SFC(column: DAICEL CHIRALPAK IC(250mm*50mm,10um);mobile phase: [0.1% NH3H2O MEOH]; B%: 55%-55%, 9.5 min) to afford 491-7 (29 g, 48.00% yield) as a yellow solid and 491-8 (29 g, 48.00% yield) as a yellow solid.

H-NMR-491-7: (400 MHz, DMSO-d6) δ ppm 8.32-8.42 (m, 1 H), 8.13-8.19 (m, 1 H), 8.07-8.13 (m, 1 H), 7.72-7.80 (m, 1 H), 7.58-7.68 (m, 1 H), 4.43-4.52 (m, 1 H), 3.39-3.51 (m, 3 H), 3.07-3.16 (m, 1 H), 1.99-2.11 (m, 1 H), 1.67 - 1.86 (m, 5 H).

H-NMR-491-8: (400 MHz, DMSO-d6) δ ppm 8.34-8.42 (m, 1 H), 8.14-8.19 (m, 1 H), 8.06-8.13 (m, 1 H), 7.72-7.79 (m, 1 H), 7.58-7.67 (m, 1 H), 4.39-4.53 (m, 1 H), 3.45 (s, 3 H), 3.07-3.17 (m, 1 H), 1.98-2.13 (m, 1 H), 1.64-1.83 (m, 5 H).

8. Synthesis of 491-9

[1696] A mixture of 491-7 (2.0 g, 7.3 mmol, 1.0 equiv), Pd/C (1.0 g, 10% purity) in MeOH (15.0 mL) was degassed and purged with H2 for 3 times, and then the mixture was stirred at 30 °C for 12 hours under H2 atmosphere (50 psi). The reaction mixture was filtered and the filtrate was concentrated to afford 491-9 (1.7 g, 95.52% yield) as a black solid.

H-NMR-491-9: (400 MHz, DMSO-d6) δ ppm 8.22-8.33 (m, 1 H), 6.86-6.96 (m, 1 H), 6.28-6.43 (m, 3 H), 4.90-5.10 (m, 2 H), 3.85-3.95 (m, 1 H), 3.31-3.35 (m, 3 H), 3.01-3.16 (m, 1 H), 1.95-2.16 (m, 1 H), 1.71-1.80 (m, 4 H), 1.58-1.68 (m, 1 H).

9. Synthesis of 491-10

[1697] To a solution of 491-9 (450 mg, 1.8 mmol, 1.0 equiv) in MeOH (10.0 mL) was added HOAc(223 mg, 3.7 mmol, 2.0 equiv) dropwise and 5-[[(3R)-3-methyl-1-piperidyl]methyl]-3-(trifluo romethyl)pyridine-2-carbaldehyde (532 mg, 1.8 mmol, 1.0 equiv) at 20 °C. After addition, the mixture was stirred at this temperature for 1 hour, and then NaBH3CN (233 mg, 3.7 mmol, 2.0 equiv) was added at 20 °C. The resulting mixture was stirred at 20 °C for 11 hours. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with DCM (10.0 mL x2). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, Dichloromethane: Methanol = 30/1 to 1/1) to afford (680 mg, 71.32% yield) as a white solid.

10. Synthesis of 491

[1698] To a solution of 491 (170 mg, 1.0 equiv) in DCM (5.0 mL) was added dropwise pyridine (157 mg, 1.9 mmol, 6.0 equiv) at 0°C. And then triphosgene (49 mg, 0.5 equiv) in DCM (0.5 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 0.5 hour. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with EtOAc (2 x 15.0 mL). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 5%-45%, 8 min) to afford 491 (114 mg, 62.23% yield) as a yellow solid.

LCMS-491 (ES, m/z): [M+H]+ 539.3. H-NMR-491 (400 MHz, METHANOL-d4) δ ppm 8.41-8.50 (m, 1 H), 8.32-8.39 (m, 1 H), 7.77-7.88 (m, 1 H), 7.59-7.68 (m, 2 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.24-7.32 (m, 1 H), 7.14 (br d, J = 14.6 Hz, 2 H), 4.23-4.34 (m, 1 H), 3.67-3.80 (m, 2 H), 3.50-3.59 (m, 3 H), 3.25-3.30 (m, 1 H), 3.10-3.24 (m, 2 H), 2.36-2.48 (m, 1 H), 2.19-2.30 (m, 1 H), 2.08-2.18 (m, 1 H), 1.86-1.99 (m, 4 H), 1.64-1.84 (m, 5 H), 1.01-1.12 (m, 1 H), 0.90-0.98 (m, 3 H).

11. Synthesis of 491-11

[1699] To a solution of (3R)-3-methylpiperidine (1.5 g, 15.1 mmol, 1 equiv) and potassium;bromomethyl (trifluoro)boranuide (3.04 g, 15.1 mmol, 1 equiv) in THF (30 mL) was added KHCO3 (3.03 g, 30.2 mmol, 2 equiv) and KI (251 mg, 1.51 mmol, 0.1 equiv). The mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was triturated with acetone (50 ml) at 35 oC for 30 min. Then the mixture was filtered, and the filtrate was concentrated under reduced pressure to afford 491-11 (2.5 g, crude) as a yellow oil.

12. Synthesis of 491-12

[1700] To a solution of 5-bromo-2-(1,3-dioxolan-2-yl)-3-(trifluoromethyl)pyridine (1.68 g, 5.64 mmol, 1 equiv) and 491-11 (2.47 g, 11.2 mmol, 2 equiv) in THF (32 mL) and water (8 mL) was added dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (485 mg, 563 umol, 0.1 equiv), Cs2CO3 (5.51 g, 16.9 mmol, 3 equiv), the mixture was stirred at 80 °C for 12 hr under nitrogen atmosphere. The reaction mixture was diluted with water (40 mL), extracted with EtOAc (35 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography,

eluted with PE/EA=1:1 to afford 491-12 (1.7 g, 91% yield) as a yellow oil.

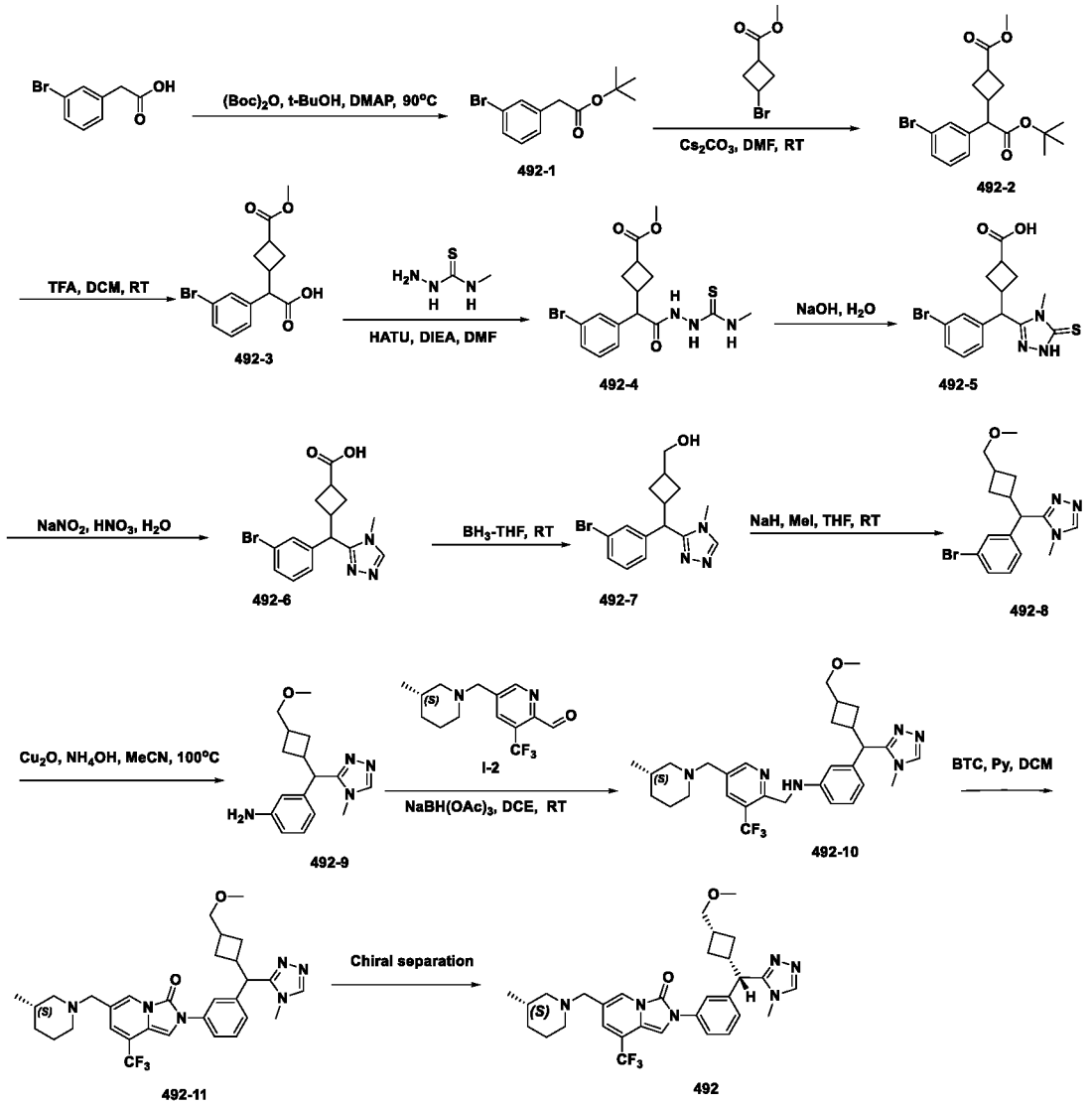
H-NMR-491-12: (400 MHz, CHLOROFORM-d) δ 8.78 (s, 1H), 7.98 (s, 1H), 6.28 (d, J = 1.2 Hz, 1H), 4.41-4.33 (m, 2H), 4.18-4.10 (m, 2H), 3.55 (d, J = 2.0 Hz, 2H), 2.81-2.64 (m, 2H), 2.00-1.89 (m, 1H), 1.75-1.56 (m, 5H), 0.93-0.83 (m, 4H)

13. Synthesis of 491-13

[1701] To a solution of 491-12 (1.7 g, 5.15 mmol, 1 equiv) in dioxane (17 mL) was added HCl (4 M, 17 mL, 13.21 equiv), the mixture was stirred at 100 °C for 12 hr. The reaction mixture was diluted with Sat.NaHCO3 (50 mL), extracted with EtOAc (30 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc=6:1 to afford 491-13 (1 g, 68%) as a yellow oil.

H-NMR-491-13: (400 MHz, CHLOROFORM-d) δ 10.21 (s, 1H), 8.87 (s, 1H), 8.12 (s, 1H), 3.59 (s, 2H), 2.76-2.64 (m, 2H), 2.02-1.90 (m, 1H), 1.75-1.60 (m, 5H), 1.59-1.51 (m, 1H), 0.94-0.86 (m, 1H), 0.84 (d, J = 6.0 Hz, 3H).

Example 483. Synthesis of Compound 492



1. Synthesis of 492-1

[1702] To a stirred solution of M-bromophenylacetic acid (20 g, 93.003 mmol, 1 equiv) and DMAP (1.14 g, 9.300 mmol, 0.1 equiv) in t-BuOH (300 mL) was added $(Boc)_2O$ (40.60 g, 186.006 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6h at 90°C under nitrogen atmosphere. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford tert-butyl 2-(3-bromophenyl)acetate (16 g, 57.10%) as a light yellow oil.

2. Synthesis of 492-2

[1703] To a stirred solution of 492-1 (8 g, 29.504 mmol, 1 equiv) in DMF (100 mL) was

added Cs_2CO_3 (48.06 g, 147.520 mmol, 5 equiv) at 0°C under nitrogen atmosphere. To the above mixture was added methyl 3-bromocyclobutane-1-carboxylate (17.09 g, 88.512 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford 492-2 (7.4 g, 58.90%) as a light yellow oil.

3. Synthesis of 492-3

[1704] To a stirred solution of 492-2 (7.4 g, 19.307 mmol, 1 equiv) in DCM (50 mL) was added TFA (10 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 492-3 (7.4 g, 97.23%) as a brown oil.

4. Synthesis of 492-4

To a stirred solution of 492-3 (7.3 g, 22.312 mmol, 1 equiv) and HATU (12.73 g, 33.468 mmol, 1.5 equiv) in DMF (100 mL) were added DIEA (8.65 g, 66.936 mmol, 3 equiv) and 1-amino-3-methylthiourea (3.05 g, 29.006 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 492-4 (6 g, 51.92%) as a brown yellow oil.

5. Synthesis of 492-5

[1705] To a stirred solution of NaOH (4.63 g, 115.856 mmol, 8 equiv) in H_2O (100 mL) was added 492-4 (6 g, 14.482 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 6h at room temperature. The mixture was neutralized to pH 7 with HCl (aq.). The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. This resulted in 492-5 (5 g, 72.25%) as a yellow solid.

6. Synthesis of 492-6

[1706] To a stirred solution of 492-5 (5 g, 13.079 mmol, 1 equiv) and $NaNO_2$ (9.02 g, 130.790 mmol, 10 equiv) in H_2O (200 mL) was added HNO_3 (130.7 mL g, 130.790 mmol, 10.00 equiv, 1 M) at room temperature. The resulting mixture was stirred for 4h at room temperature. The mixture was aneutralized to pH 7 with saturated $NaHCO_3$ (aq.). The

resulting mixture was concentrated under vacuum. The residue was dissolved in DCM/MeOH=10:1 (300 mL). The resulting mixture was filtered, the filter cake was washed with DCM (2x50 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 492-6 (4 g, 69.86%) as a yellow solid.

7. Synthesis of 492-7

[1707] To a stirred solution of 492-6 (3 g, 9.484 mmol, 1 equiv) in THF) was added BH_3-THF (42.83 mL, 42.830 mmol, 5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 20 min; detector, UV 220 nm. This resulted in 492-7 (1.3 g, 43.52%) as a off-white solid.

8. Synthesis of 492-8

[1708] To a stirred silution of 492-7 (1.27 g, 3.777 mmol, 1 equiv) in THF (20 mL) was added NaH (0.18 g, 4.532 mmol, 1.2 equiv, 60%) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. To the above mixture was added MeI (0.80 g, 5.665 mmol, 1.5 equiv). The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (60 mL). The resulting mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 492-8 (920 mg, 69.54%) as a white solid.

9. Synthesis of 492-9

[1709] To a solution of 492-8 (920 mg, 2.627 mmol, 1 equiv) in MeCN (18 mL) and NH_4OH (6 mL) was added Cu_2O (150.34 mg, 1.051 mmol, 0.4 equiv) in a pressure tank. The resulting mixture was stirred for overnight at 100 °C. The resulting mixture was diluted with water (60 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (25:1) to afford 492-9 (750 mg, 99.71%) as a white solid.

10. Synthesis of 492-10

[1710] A solution of 492-9 (750 mg, 2.619 mmol, 1 equiv) and I-2 (899.75 mg, 3.143

mmol, 1.2 equiv) in DCE (15 mL) was stirred for overnight at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1110.10 mg, 5.238 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 6 h at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 492-10 (1 g, 68.59%) as a white solid.

11. Synthesis of 492-11

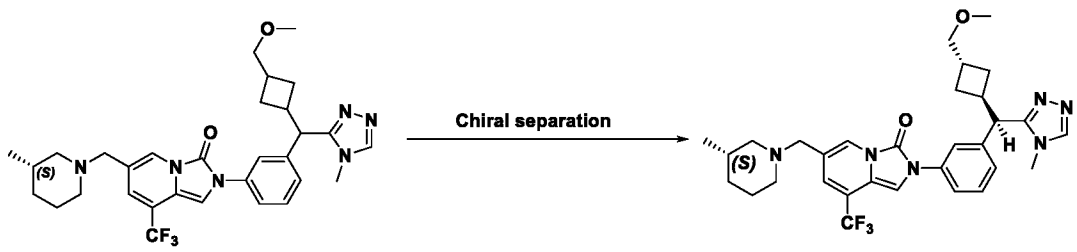
[1711] To a stirred solution of 492-10 (0.98 g, 1.760 mmol, 1 equiv) and Pyridine (0.84 g, 10.560 mmol, 6 equiv) in DCM (20 mL) was added Triphosgene (0.21 g, 0.704 mmol, 0.4 equiv). The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (40 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 5% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in 492-11 (700 mg, 68.24%) as a yellow solid.

12. Synthesis of 492

[1712] 492-11 (700 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: UniChiral OD-5H, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH3); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.56; RT2(min): 5.92; first peak was product) to afford crude product (350 mg). The crude product (350 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 9 min; Wave Length: 220/254 nm; RT1(min): 4.78; RT2(min): 7.00; first peak was product) to afford 492 (151.2 mg, 21.60%) as a yellow solid.

LCMS-492(ES, m/z): $[M+H]^+$ 583. NMR-492 (400 MHz, CD_3OD, δ ppm): 0.92-0.99 (m, 4H), 1.53-1.79 (m, 7H), 1.96-1.99 (m, 1H), 2.01-2.13 (m, 1H), 2.33-2.36 (m, 1H), 2.45-2.47 (m, 1H), 2.94-3.02 (m, 2H), 3.15-3.18 (m, 1H), 3.37 (s, 5H), 3.43 (s, 2H),3.54 (s, 3H), 4.22-4.25 (d, 1H), 7.13-7.14 (d, 2H), 7.26-7.28 (d, 1H), 7.51-7.53 (t, 1H), 7.65-7.71 (m, 3H), 8.38 (s,1H).

Example 484. Synthesis of Compound 493



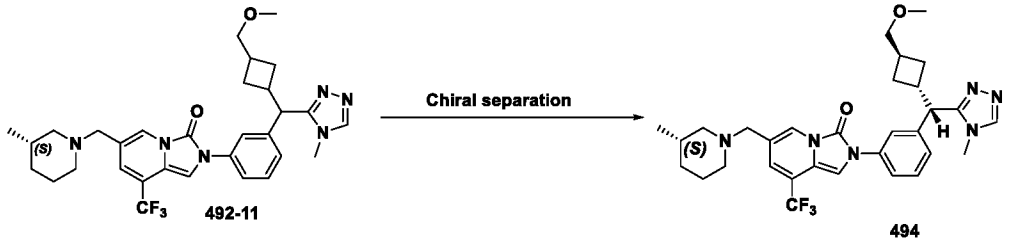
492-11 493

1. Synthesis of 493

[1713] 492-11 (700 mg, 1.201 mmol, 1 equiv) was purified by Prep-Chiral-SFC with the following conditions (Column: UniChiral OD-5H, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.56; RT2(min): 5.92; the first peak was product) to afford crude product (350 mg). The crude product (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 9 min; Wave Length: 220/254 nm; RT1(min): 4.78; RT2(min): 7.00; the second peak was product) to afford 493 (151.2 mg, 21.60%) as a yellow solid.

LCMS-493(ES, m/z): $[M+H]^+$ 583. NMR-493 (400 MHz, CD_3OD, δ ppm): 0.91-0.98 (m, 4H), 1.53-1.89 (m, 7H), 1.99-2.12 (m, 3H), 2.56-2.57 (m, 1H), 2.89-3.95 (m, 2H), 3.35-3.47 (m, 6H), 3.48-3.49 (d, 2H),3.56 (s, 3H), 4.35-4.37 (d, 1H), 7.13 (s, 2H), 7.28-7.30 (d, 1H), 7.51-7.53 (t, 1H), 7.65-7.70 (m, 3H), 8.38 (s,1H).

Example 485. Synthesis of Compound 494



492-11 494

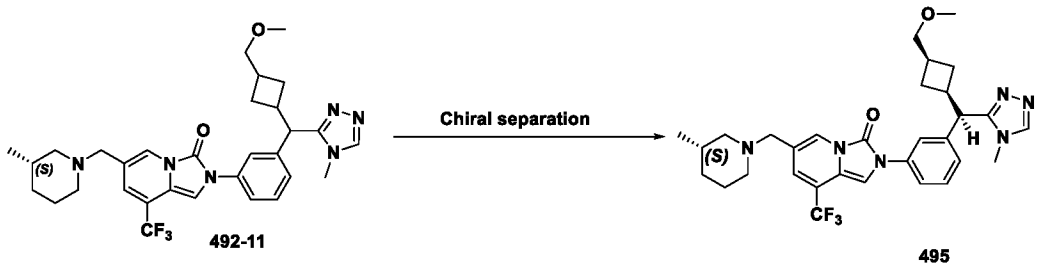
1. Synthesis of 494

[1714] 492-11(700 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: UniChiral OD-5H, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.56; RT2(min): 5.92; the second peak was product) to afford crude product (270 mg). The crude product (270 mg) was purified by Prep-HPLC with the following conditions (Column:

CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 9.5 min; Wave Length: 220/254 nm; RT1(min): 5.73; RT2(min): 6.76; the second peak was product) to afford 494 (104.7 mg, 14.96%) as a yellow solid.

LCMS-494(ES,m/z): $[M+H]^+$ 583. NMR-494 (400 MHz, CD_3OD, δ ppm): 0.90-0.95 (m, 4H), 1.53-1.78 (m, 6H), 1.84-1.87 (m, 1H), 2.01-2.10 (m, 3H), 2.55-2.56 (m, 1H), 2.89-2.96 (m, 2H), 3.30-3.32 (m, 1H), 3.35-3.39 (m, 5H), 3.47-3.49 (d, 2H),3.56 (s, 3H), 4.35-4.37 (d, 1H), 7.13-7.14 (d, 2H), 7.28-7.30 (d, 1H), 7.51-7.53 (t, 1H), 7.65-7.70 (m, 3H), 8.38 (s,1H).

Example 486. Synthesis of Compound 495

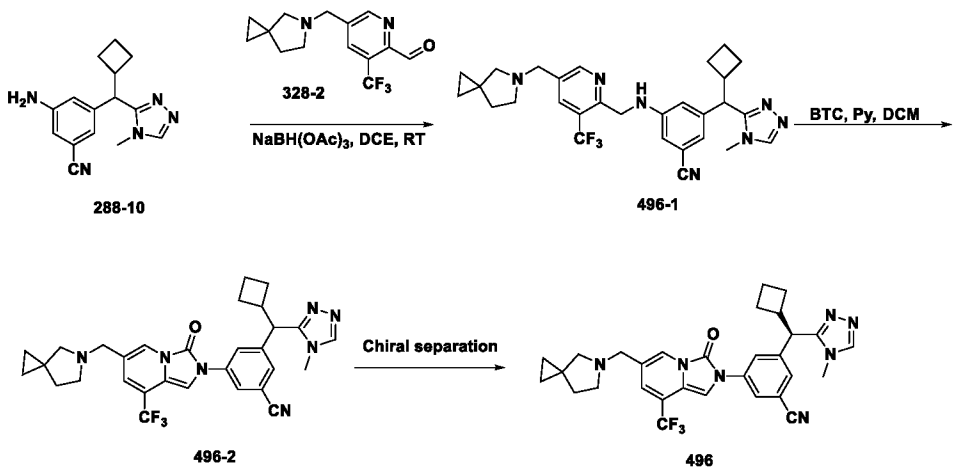


1. Synthesis of 495

[1715] 492-11 (700 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: UniChiral OD-5H, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.56; RT2(min): 5.92; the second peak was product) to afford crude product (350 mg). The crude product (350 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 9.5 min; Wave Length: 220/254 nm; RT1(min): 5.73; RT2(min): 6.76; the first peak was product) to afford 495 (104.7 mg, 14.96%) as a yellow solid.

LCMS-495(ES, m/z): $[M+H]^+$ 583. NMR-495 (400 MHz, CD_3OD, δ ppm): 0.91-0.96 (m, 4H), 1.53-1.55 (m, 1H),1.66-1.79 (m, 6H), 1.96-2.13 (m, 2H), 2.33-2.35 (m, 1H), 2.45-2.47 (m, 1H), 2.93-3.02 (m, 2H), 3.15-3.18 (m, 1H), 3.37-3.47 (m, 5H), 3.50-3.55 (m, 5H), 4.22-4.25 (d, 1H), 7.13-7.14 (d, 2H), 7.26-7.28 (d, 1H), 7.51-7.53 (t, 1H), 7.65-7.70 (m, 3H), 8.38 (s,1H).

Example 487. Synthesis of Compound 496



1. Synthesis of 496-1

[1716] To a stirred solution of 288-10 (500 mg, 1.870 mmol, 1 equiv) in DCE (10 mL) was added 328-2 (691.20 mg, 2.431 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1189.18 mg, 5.610 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 496-1 (470 mg, 44.57%) as an off-white solid.

2. Synthesis of 496-2

[1717] To a stirred solution of 496-1 (450 mg, 0.840 mmol, 1 equiv) and Pyridine (664.56 mg, 8.400 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (99.72 mg, 0.336 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 496-2 (300 mg, 61.67%) as a yellow solid.

3. Synthesis of 496

[1718] The 496-2 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 11 min; Wave Length: 220/254 nm; RT1(min): 5.50; RT2(min): 8.07; the second peak is product) to afford 496 (139.7 mg, 46.10%) as a yellow solid.

LC-MS-496 (ES, *m/z*): $[M+H]^+$ 562. H-NMR-496 (400 MHz, DMSO-d6, δ *ppm*): 0.51-0.58 (m, 4H), 1.75-1.84 (m, 7H), 2.03-2.09 (m, 1H), 2.47-2.50 (m, 2H), 2.64-2.74 (m, 2H), 3.19-3.23 (m, 1H), 3.25 (s, 2H), 3.48 (s, 3H), 4.40-4.42 (d, 1H), 7.07 (s, 1H), 7.51 (s, 1H), 7.68-7.69 (m, 2H), 8.22-8.25 (d, 2H), 8.36 (s, 1H).

Example 488. Synthesis of Compound 497



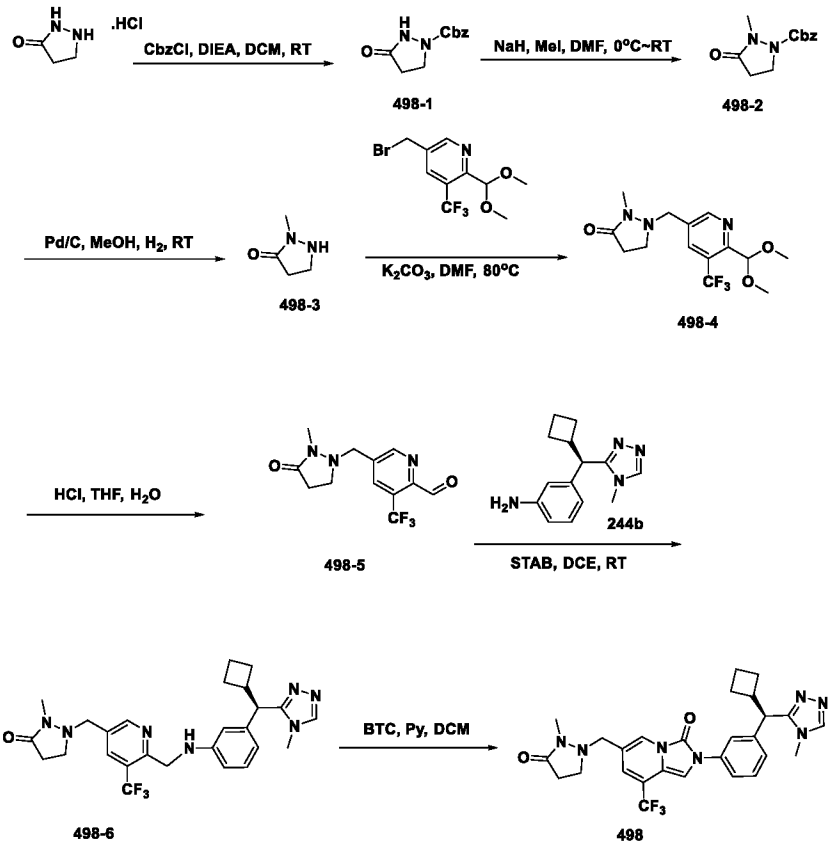
496-2 497

1. Synthesis of 497

[1719] The 496-2 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 11 min; Wave Length: 220/254 nm; RT1(min): 5.50; RT2(min): 8.07; the first peak is product) to afford 497 (135.1 mg, 44.63%) as a yellow solid.

LC-MS-497 (ES, *m/z*): $[M+H]^+$ 562. H-NMR-497 (400 MHz, DMSO-d6, δ *ppm*): 0.51-0.58 (m, 4H), 1.75-1.84 (m, 4H), 2.03-2.09 (m, 1H), 2.47-2.50 (m, 2H), 2.64-2.74 (m, 2H), 3.19-3.23 (m, 1H), 3.25 (s, 2H), 3.48 (s, 3H), 4.40-4.42 (d, 1H), 7.07 (s, 1H), 7.51 (s, 1H), 7.69 (s, 1H), 8.22-8.25 (d, 2H), 8.36 (s, 1H).

Example 489. Synthesis of Compound 498



1. Synthesis of 498-1

[1720] To a stirred solution of pyrazolidin-3-one hydrochloride (2 g, 16.320 mmol, 1 equiv) and DIEA (4.22 g, 32.640 mmol, 2 equiv) in DCM (20 mL) was added CbzCl (4.18 g, 24.480 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 498-1 (1.2 g, 33.39%) as a yellow oil.

2. Synthesis of 498-2

[1721] To a stirred mixture of 498-1 (1.1 g, 4.995 mmol, 1 equiv) in DMF (11 mL) were added NaH (0.40 g, 9.990 mmol, 2 equiv, 60%) at 0°C. The resulting mixture was stirred for 1 h at 0°C. To the above mixture was added MeI (1.42 g, 9.990 mmol, 2 equiv) at 0°C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=5:1) to afford 498-2 (800 mg, 68.37%) as a yellow oil.

3. Synthesis of 498-3

[1722] To a solution of 498-2 (800 mg, 3.415 mmol, 1.00 equiv) in 20 mL MeOH was added Pd/C (10%, 80 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The resulting mixture was filtered, the filter cake was washed with MeOH (3x20 mL). The filtrate was concentrated under reduced pressure to afford 498-3 (250 mg, 73.12%) as a yellow oil.

4. Synthesis of 498-4

[1723] To a stirred mixture of 498-3 (250 mg, 2.497 mmol, 1 equiv) and 541-2 (1176.46 mg, 3.745 mmol, 1.5 equiv) in DMF (8 mL) were added K_2CO_3 (690.19 mg, 4.994 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The reaction was quenched with saturated NH_4Cl (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 498-4 (450 mg, 54.07%) as a yellow solid.

5. Synthesis of 498-5

[1724] To a stirred solution of 498-4 (430 mg, 1.290 mmol, 1.00 equiv) in THF (1.5 mL) were added HCl (1.5 mL, 1M) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (20 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 498-5 (300 mg, 80.96%) as a yellow oil.

6. Synthesis of 498-6

[1725] To a stirred mixture of 498-5 (280 mg, 0.975 mmol, 1 equiv) and 244b (283.46 mg, 1.170 mmol, 1.2 equiv) in DCE (5 mL) were added STAB (619.79 mg, 2.925 mmol, 3 equiv) at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 498-6 (400 mg, 79.90%) as a yellow solid.

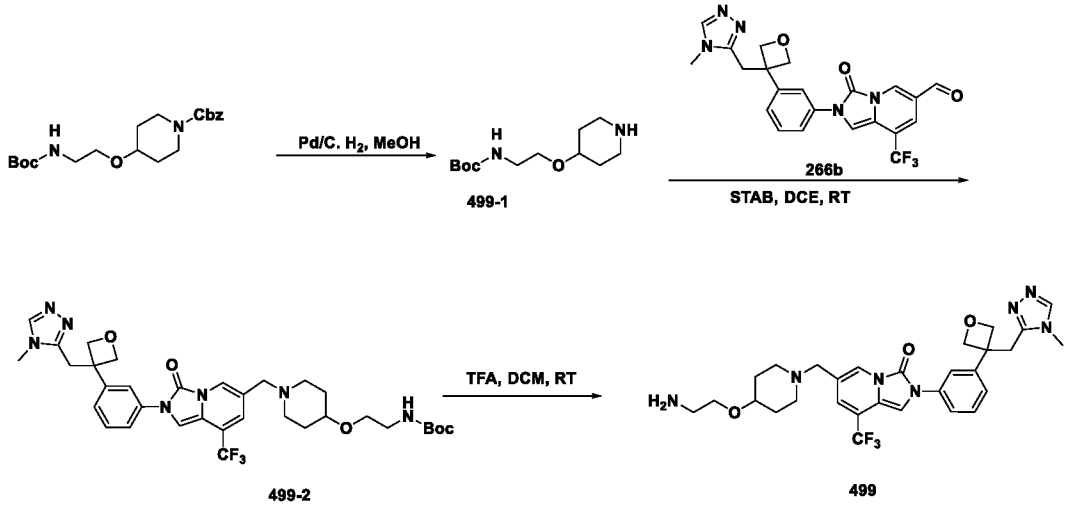
7. Synthesis of 498

[1726] To a stirred solution of 498-6 (380 mg, 0.740 mmol, 1 equiv) and pyridine (351.17 mg, 4.440 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (76.84 mg, 0.259 mmol, 0.35 equiv) at 0 °C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (30 mL) at room temperature. The

aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 498 (236.3 mg, 58.48%) as a yellow solid.

LC-MS-498 (ES, *m/z*): $[M+H]^+$ 540. H-NMR-498 (400 MHz, CD_3OD-d4, δ *ppm*): 0.82-0.93 (m, 4H), 1.43-1.53 (m, 1H), 1.53-1.71 (m, 5H), 1.71-1.80 (m, 4H), 1.80-1.95 (m, 4H), 1.95-2.02 (m, 1H), 2.71-2.85 (m, 2H), 3.09-3.12 (m, 1H), 3.64-3.68 (m, 2H), 3.92-3.95 (d, 1H), 4.01-4.03 (m, 2H), 7.00 (s, 1H), 7.21-7.26 (m, 2H), 7.32 (s, 1H), 7.35-7.39 (m, 1H), 7.58-7.60 (d, 1H), 7.66 (s, 1H), 7.73 (s, 1H).

Example 490. Synthesis of Compound 499



1. Synthesis of 499-1

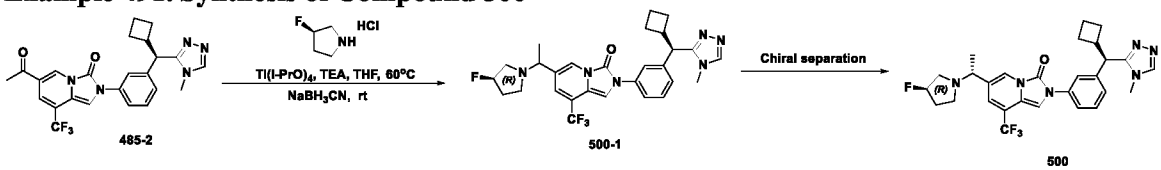
[1727] To a solution of benzyl 4-(2-((tert-butoxycarbonyl)amino)ethoxy)piperidine-1-carboxylate (12 g, 31.70 mmol, 1.0 equiv) in 360 mL MeOH was added Pd/C (10%, 2g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 499-1 (7 g, 90 %) as a colorless oil.

2. Synthesis of 499-2

[1728] To a stirred solution of 499-1 (1 g, 4.09 mmol, 1.0 equiv) and 266b (1.8 g, 4.09 mmol, 1.0 equiv) in DCE (10 mL) was added STAB (1.7 g, 8.18 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with water (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC

(CH_2Cl_2/MeOH=10:1) to afford 499-2 (900 mg, 32%) as a yellow solid.

Example 491. Synthesis of Compound 500



1. Synthesis of 500-1

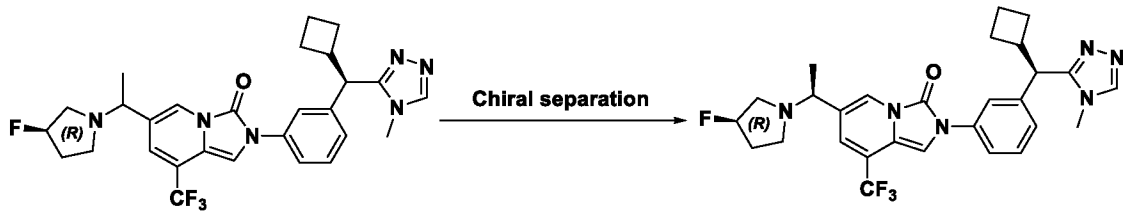
[1729] Into a 40 mL vial were added 485-2 (500 mg, 1.065 mmol, 1 equiv), (3S)-3-fluoropyrrolidine hydrochloride (113.89 mg, 1.278 mmol, 1.2 equiv), TEA (431.10 mg, 4.260 mmol, 4 equiv), Ti(Oi-Pr)$_4$ (605.41 mg, 2.130 mmol, 2 equiv) and THF (10 mL) at room temperature. The mixture was stirred for 1 h at room temperature. To the above mixture was added $NaBH_3CN$ (133.85 mg, 2.130 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at 60 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=15:1) to afford crude product. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 57% B in 8 min; Wave Length: 220 nm; RT1(min): 6.83) to afford 500-1 (200 mg, 34.26%) as a yellow solid

2. Synthesis of 500

[1730] 500-1 (200 mg, 0.369 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 7*25cm, 10 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 19 min; Wave Length: 220/254 nm; RT1(min): 12.72; RT2(min): 15.97; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 8) to afford 500 (52.9 mg, 25.82%) as a yellow solid.

LC-MS-500 (ES, *m/z*): $[M+H]^+$ 543. H-NMR-500 1H NMR (400 MHz, MeOD *ppm*) δ1.40-1.42 (d, 3H), δ1.75-1.77 (m, 1H), δ1.80-2.15 (m, 5H), δ2.22-2.29 (m, 2H), δ2.41-2.43 (m, 1H), δ2.65-2.87 (m, 2H), δ2.02-3.04 (m, 1H), δ3.26-3.29 (m, 2H), δ3.48 (s, 3H), δ4.28-4.31 (d, 1H), δ5.11-5.25 (m, 1H), δ7.14 (s, 1H), δ7.19 (s, 1H), δ7.26-7.28 (d, 1H), δ7.48-7.52 (t, 1H), δ7.64-7.67 (m, 2H), δ7.71 (s, 1H), δ8.37 (s, 1H).

Example 492. Synthesis of Compound 501



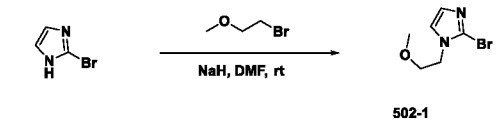
500-1 501

1. Synthesis of 501

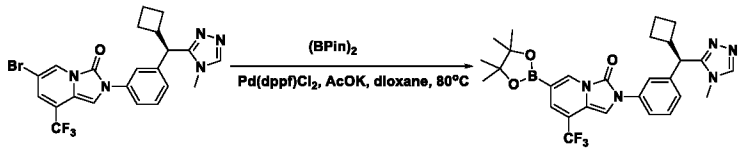
[1731] The 500-1 (200 mg, 0.369 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 7*25cm, 10 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 19 min; Wave Length: 220/254 nm; RT1(min): 12.72; RT2(min): 15.97; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 8) to afford 501 (62 mg, 30.66%) as a yellow solid.

LC-MS-501 (ES, *m/z*): $[M+H]^+$ 543. H-NMR-501 1H NMR (400 MHz, MeOD *ppm*) δ1.40-1.42 (d, 3H), δ1.75-1.77 (m, 1H), δ1.80-2.15 (m, 5H), δ2.22-2.29 (m, 2H), δ2.41-2.43 (m, 1H), δ2.65-2.87 (m, 2H), δ2.02-3.04 (m, 1H), δ3.26-3.29 (m, 2H), δ3.48 (s, 3H), δ4.28-4.31 (d, 1H), δ5.11-5.25 (m, 1H), δ7.14 (s, 1H), δ7.19 (s, 1H), δ7.26-7.28 (d, 1H), δ7.48-7.52 (t, 1H), δ7.64-7.67 (m, 2H), δ7.71 (s, 1H), δ8.37 (s, 1H).

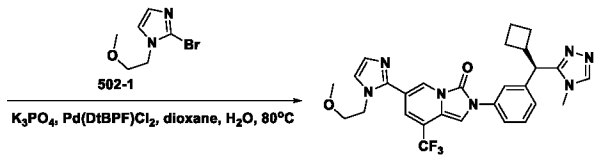
Example 493. Synthesis of Compound 502



502-1



502-2 502-2



502

1. Synthesis of 502-1

[1732] A mixture of 2-bromo-1H-imidazole (5 g, 34.019 mmol, 1 equiv) and NaH (2.04 g, 85.047 mmol, 2.5 equiv) in DMF (50 mL) was stirred for 1h at 0°C. To the above mixture was added 2-bromoethyl methyl ether (14.19 g, 102.057 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The mixture was acidified to pH 7 with saturated NH_4Cl (aq.) (100 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (200:1) to afford 502-1 (5.5 g, 70.96%) as a yellow oil.

2. Synthesis of 502-2

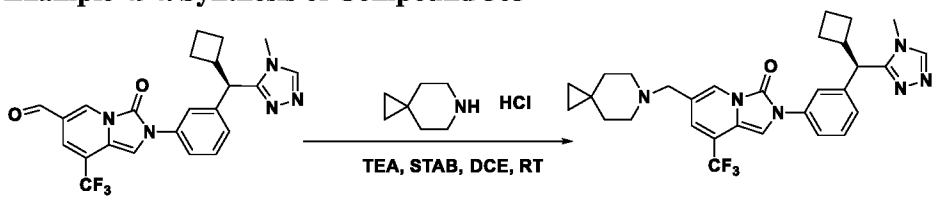
[1733] Into a 250mL round-bottom flask were added 502-1 (1.3 g, 2.568 mmol, 1 equiv) and dioxane (130 mL), KOAc (503.96 mg, 5.136 mmol, 2 equiv) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.61 g, 10.272 mmol, 4 equiv) and $Pd(dppf)Cl_2$ (281.80 mg, 0.385 mmol, 0.15 equiv) at room temperature. The resulting mixture was stirred for 8h at 80°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 502-2 (750 mg, 47.51%) as a yellow oil.

3. Synthesis of 502

[1734] To a stirred mixture of 502-2 (750 mg, 3.658 mmol, 2 equiv) and 502-1 (1012.03 mg, 1.829 mmol, 1 equiv) in dioxane (8 mL) H_2O (2 mL) were added K_3PO_4 (1164.56 mg, 5.487 mmol, 3 equiv) and $Pd(DtBPF)Cl_2$ (178.79 mg, 0.274 mmol, 0.15 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford the crude product. The crude product (350mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 7 min; Wave Length: 220 nm; RT1(min): 5.88) to afford 502 (166.4 mg, 16.40%) as a yellow solid.

LC-MS-502 (ES, *m/z*): $[M+H]^+$ 552. H-NMR-502 (400 MHz, CD_3OD, *ppm*): δ 1.75-1.81 (m, 1H), δ1.88-1.95 (m, 4H), δ2.24-2.29 (m, 1H), δ3.30-3.35 (m, 1H), δ3.38 (s, 3H), δ3.56 (s, 3H), δ3.78-3.81 (m, 2H), δ4.26-4.89 (m, 3H), δ7.12-7.13 (d, 1H), δ7.23 (s, 1H), δ7.27-7.29 (d, 1H), δ7.33-7.36 (m, 2H), δ7.49-7.54 (m, 1H), δ7.66-7.71 (m, 2H), δ7.29(s, 1H), δ8.38 (s, 1H).

Example 494. Synthesis of Compound 503



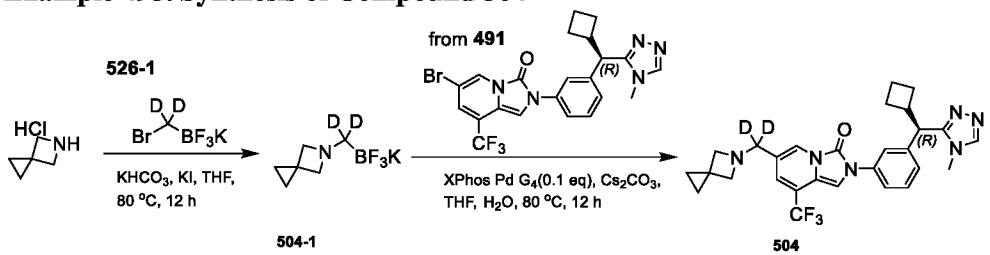
247c 503

1. Synthesis of 503

[1735] To a stirred solution of 247c (400 mg, 0.878 mmol, 1 equiv) and 6-azaspiro[2.5]octane hydrochloride (372.28 mg, 1.756 mmol, 2 equiv) in DCE (40 mL) were added TEA (177.75 mg, 1.756 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added STAB (372.28 mg, 1.756 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 30% to 65% gradient in 30 min; detector, UV 254 nm. The resulting mixture was concentrated under reduced pressure. This resulted in 503 (98.8 mg, 20.02%) as a yellow solid.

LC-MS-503 (ES, *m/z*): $[M+H]^+$ 551 . H-NMR-503 (400 MHz, DMSO-d6, δ *ppm*): 0.25 (s, 4H), 1.23-1.34 (d, 4H), 1.68-1.81 (m, 5H), 2.08-2.10 (s, 1H), 2.33-2.67 (m, 4H), 3.21-3.23 (s, 1H), 3.31-3.32 (s, 2H), 3.41-3.43 (s, 3H), 4.24-4.27 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (m, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.73 (m, 3H), 8.32 (s, 1H).

Example 495. Synthesis of Compound 504



1. Synthesis of 504-1

[1736] To a solution of [bromo(dideuterio)methyl]-trifluoro-boron;potassium hydride (339 mg, 1.7 mmol, 1.0 equiv) and 5-azaspiro[2.3]hexane (200 mg, 1.7 mmol, 1.0 equiv, HCl) in THF (4.0 mL) was added $KHCO_3$ (334 mg, 3.4 mmol, 2.0 equiv) and KI (27 mg, 0.1 equiv). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was

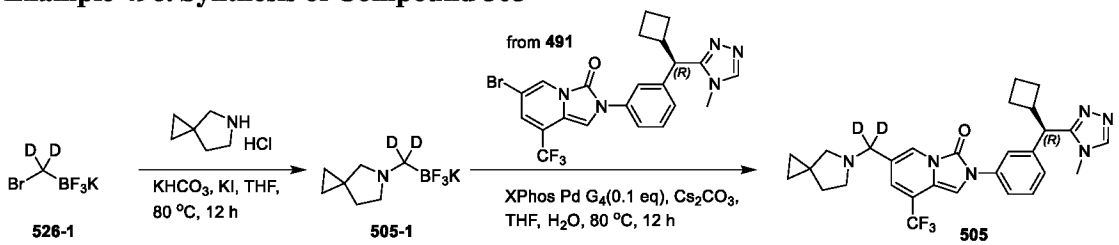
concentrated in vacuum. The residue was triturated with acetone (5 mL) at 35 °C for 1 hour. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 504-1 (270 mg, 78.73% yield) was obtained as colorless oil.

2. Synthesis of 504

[1737] A mixture of 504-1 (170 mg, 2.0 equiv), 6-bromo-2-[3-[(R)-cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (210 mg, 1.0 equiv), Cs_2CO_3 (405 mg, 1.2 mmol, 3.0 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (35 mg, 0.1 equiv) in THF (10 mL) and H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Column: Phenomenex Luna C18 75*30mm*3um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 20% B to 60% B in 8 min; Wave Length: 220 nm; RT1 (min): 8.3) to afford 504 (62 mg, 28.41% yield) as a yellow solid.

MS-504: (ES, m/z): [M+H]+ 525.2. H-NMR-504: (400 MHz, METHANOL-d4) δ ppm 8.42 (s, 1 H), 8.35 (s, 1 H), 7.89 (s, 1 H), 7.65-7.59 (m, 2 H), 7.52-7.45 (m, 1 H), 7.28 (d, J = 2.4 Hz 1 H), 7.17 (s, 1 H), 7.08 (s, 1 H), 4.28 (d, J = 3.2 Hz, 1 H), 3.92 (s, 4 H), 3.55 (s, 3 H), 3.30-3.23 (m, 1 H), 2.30-2.19 (m, 1 H), 1.96-1.83 (m, 4 H), 1.82-1.71 (m, 1 H), 0.73 (s, 4 H).

Example 496. Synthesis of Compound 505



1. Synthesis of 505-1

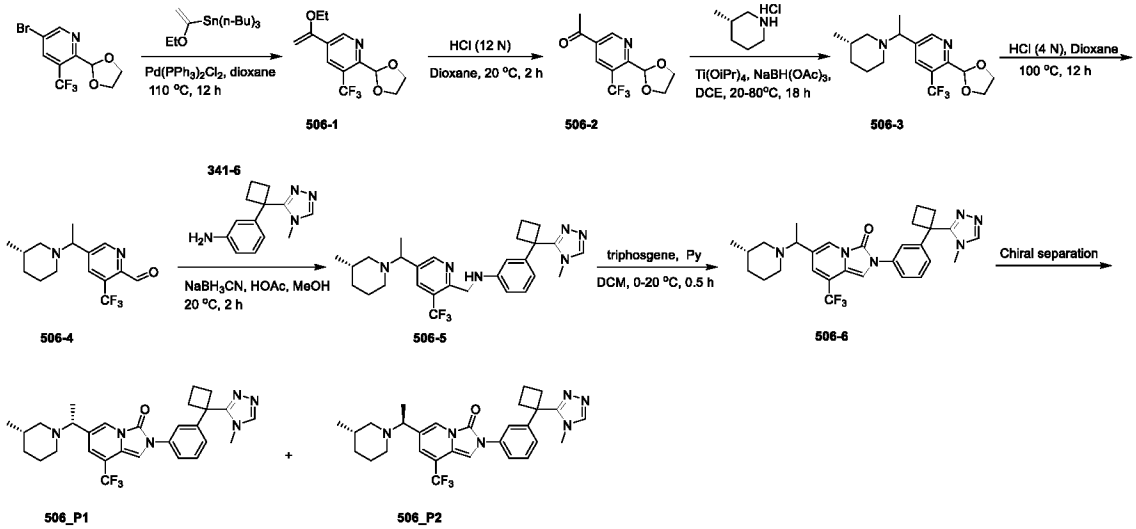
[1738] A mixture of 526-1 (303.62 mg, 1.50 mmol, 1 equiv), 5-azaspiro[2.4]heptane (200 mg, 1.50 mmol, 1 equiv, HCl), $KHCO_3$ (299.70 mg, 2.99 mmol, 2 equiv), KI (24.85 mg, 149.68 umol, 0.1 equiv) in THF (4 mL) and then the mixture was stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction was concentrated in reduced pressure, then the residue was triturated with acetone (20 mL) at 35 °C for 1 hr. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 505-1 (0.28 g, 85%) as a yellow oil. NN

2. Synthesis of 505

[1739] To a solution of 505-1 (0.22 g, 1.00 mmol, 1 equiv) in THF (5 mL) /H_2O (1 mL) was added Xphos Pd G4 (86.40 mg, 100.41 umol, 0.1 equiv), 6-bromo-2-[3-[(R)-cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (305.05 mg, 602.48 umol, 0.6 equiv) and Cs_2CO_3 (981.51 mg, 3.01 mmol, 3 equiv). The resulting mixture was stirred at 80 °C for 12 hr. The reaction was poured into water (10 mL) and the resulting mixture was extracted with EtOAc (10 mLx2). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by normal phase SiO_2 chromatography (10-100% MeOH/ DCM) to give crude product. The crude product (157 mg) was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile phase A: Water (FA), Mobile phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 30% B in 8 min; Wave Length: 220 nm) to afford 505(79.1 mg, 49.8%) as a yellow solid.

MS-505: (ES, m/z): [M+H]+ 539.27. H-NMR-505: (400 MHz, METHANOL-d4) δ 8.35 (s, 1 H), 7.84-7.75 (m, 1 H), 7.69-7.58 (m, 2 H), 7.54-7.43 (m, 1 H), 7.32-7.22 (m, 1 H), 7.20-7.07 (m, 2 H), 4.33-4.22 (m, 1 H), 3.53 (s, 3 H), 3.30-3.25 (m, 1H), 3.11-2.98 (m, 2 H), 2.80 (s, 2 H), 2.31-2.18 (m, 1 H), 2.01-1.67 (m, 7 H), 0.70-0.59 (m, 4 H).

Example 497. Synthesis of Compound 506_P1&P2



1. Synthesis of 506-1

[1740] A mixture of 5-bromo-2-(1,3-dioxolan-2-yl)-3-(trifluoromethyl)pyridine (5 g, 16.78 mmol, 1 equiv), tributyl(1-ethoxyvinyl)stannane (6.23 mL, 18.4 mmol, 1.1 equiv) and $Pd(PPh_3)_2Cl_2$ (589 mg, 839 umol, 0.05 equiv) in dioxane (100 mL) was stirred at 110 °C for 12 h under nitrogen atmosphere. The reaction mixture was quenched by addition Sat. KF

(aq.400 mL), and then diluted with water (100 mL) and extracted with EtOAc (150 mL x3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (5:1) to afford 506-1 (4.4 g, 90%) as a yellow oil.

^{1}H-NMR-506-1: (400 MHz, CHLOROFORM-d) δ 8.97 (d, J = 1.6 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 6.21 (s, 1H), 4.71 (d, J = 3.2 Hz, 1H), 4.34-4.24 (m, 3H), 4.07-4.01 (m, 2H), 3.92-3.84 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H)

2. Synthesis of 506-2

[1741] To a solution of 506-1 (4.4 g, 15.21 mmol, 1 equiv) in HCl (0.7 mL) and dioxane (45 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was adjusted to pH=8 with sat.$NaHCO_3$ (600 mL) and extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (3:1) to afford 506-2 (3.8 g, 95%) as a yellow oil.

3. Synthesis of 506-3

[1742] To a solution of 506-2 (3.8 g, 14.5 mmol, 1 equiv) and (3S)-3-methylpiperidine (2.96 g, 21.8 mmol, 1.5 equiv, HCl) in DCE (70 mL) was added tetraisopropoxytitanium (17.2 mL, 58.2 mmol, 4 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. Then $NaBH(OAc)_3$ (9.25 g, 43.6 mmol, 3 equiv) was added at 20 °C, The mixture was stirred at 80 °C for 6 h under nitrogen atmosphere. The mixture was adjust to pH = 8 by sat.$NaHCO_3$ (300 ml) and extracted with EtOAc (100 ml x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with DCM/ MeOH (10:1) to afford 506-3 (3.2 g, 63%) as a yellow oil.

^{1}H-NMR-506-3: (400 MHz, CHLOROFORM-d) δ 8.72 (s, 1H), 7.87 (d, J = 1.2 Hz, 1H), 6.18 (s, 1H), 4.33-4.23 (m, 2H), 4.07-4.03 (m, 2H), 3.53-3.43 (m, 1H), 2.84-2.67 (m, 1H), 2.62-2.48 (m, 1H), 1.88-1.77 (m, 1H), 1.62-1.41 (m, 5H), 1.32-1.25 (m, 3H), 0.80-0.70 (m, 4H)

4. Synthesis of 506-4

[1743] To a solution of 506-3 (3.2 g, 9.29 mmol, 1 equiv) in HCl (30 mL) and dioxane (30 mL) was stirred at 100 °C for 12 h. The mixture was adjust to pH = 8 by sat.$NaHCO_3$ (200 ml) and extracted with EtOAc (100 ml x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography eluted with DCM/ MeOH (10:1) to afford 506-4 (2.1 g, 75%) as a yellow oil.

^{1}H-NMR-506-4: (400 MHz, CHLOROFORM-d) δ 10.17 (s, 1H), 8.86 (s, 1H), 8.06 (s, 1H), 3.52 (s, 1H), 2.81-2.68 (m, 1H), 2.59-2.49 (m, 1H), 1.96-1.83 (m, 1H), 1.63-1.55 (m, 4H), 1.36-1.30 (m, 3H), 0.82-0.71 (m, 5H)

5. Synthesis of 506-5

[1744] To a solution of 506-4 (0.9 g, 3.0 mmol, 1 equiv) and 341-6 (684 mg, 3.0 mmol, 1 equiv) in MeOH (15 mL) was added HOAc (514 uL, 8.99 mmol, 3 equiv). The mixture was stirred at 20 °C for 1 h. Then $NaBH_3CN$ (376 mg, 5.99 mmol, 2 equiv) was added. The mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The mixture was adjust to pH = 8 by Sat.$NaHCO_3$ (150 ml) and extracted with DCM (50 ml x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with DCM/ MeOH (10:1) to afford 506-5 (0.9 g, 58%) as a yellow solid.

6. Synthesis of 506-6

[1745] To a solution of 506-5 (370 mg, 721 umol, 1 equiv) in DCM (5 mL) was added Py (349 uL, 4.33 mmol, 6 equiv) and bis(trichloromethyl) carbonate (107 mg, 361 umol, 0.5 equiv) at 0 °C. The mixture was stirred at 20 °C for 0.5 h under nitrogen atmosphere. The same scale reaction was conducted in parallel for 3 batches in total and work up together. The reaction was quenched with sat.$NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (50 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc /MeOH (10:1) to afford 506-6 (0.9 g, 35.5%) as a yellow solid.

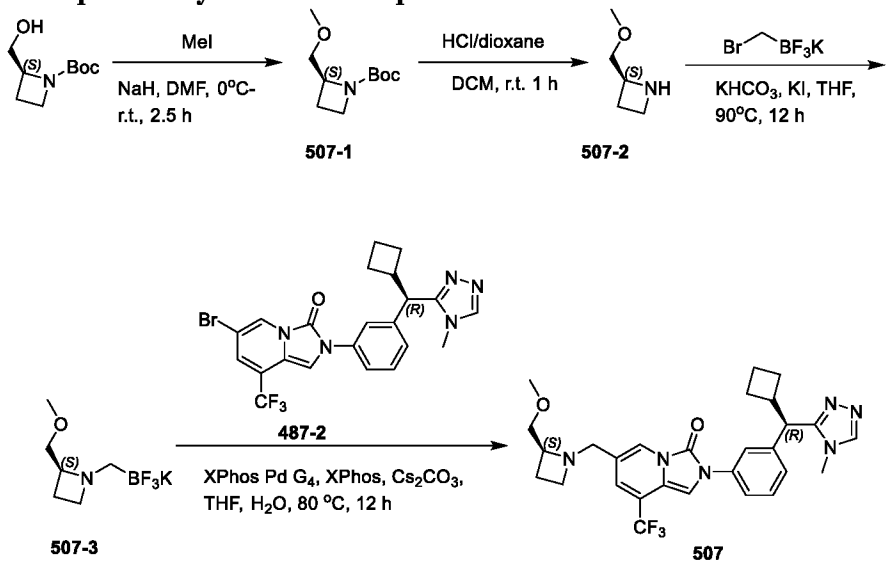
7. Synthesis of 506-P1&P2

[1746] The 506-6 (0.9 g) was purified by Chiral separation with the following conditions (column: REGIS(S,S)WHELK-O1(250mm*30mm,10um);mobile phase: [Neu-ETOH];B%: 27%-27%,6min, Flow rate: 55 mL/min; Wave Length: 220/254 nm; RT1 (min): 4.71; RT2 (min): 6.03) to afford 506_P1 (206 mg, 26%) as a yellow solid and 506_P2 (239.6mg, 30%) as a yellow solid.

MS-506_P1: (ES, m/z): $[M+H]^+$ 539.3 ^{1}H-NMR-506_P1: (400 MHz, METHANOL-d4) δ 8.35 (s, 1H), 7.76 (t, J = 1.6 Hz, 1H), 7.60 (s, 2H), 7.57-7.51 (m, 1H), 7.32-7.27 (m, 1H), 7.15 (d, J = 12.0 Hz, 2H), 3.42-3.36 (m, 1H), 3.33 (s, 3H), 3.05-2.98 (m, 2H), 2.94 (d, J =

10.8 Hz, 1H), 2.85-2.78 (m, 3H), 2.21-2.08 (m, 2H), 2.02-1.94 (m, 1H), 1.75-1.67 (m, 3H), 1.66-1.52 (m, 2H), 1.36 (d, J = 6.8 Hz, 3H), 0.96-0.88 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H) MS-506-P2: (ES, m/z): $[M+H]^+$ 539.3 ^{1}H-NMR-506_P2: (400 MHz, METHANOL-d4) δ 8.36 (s, 1H), 7.76 (t, J = 1.6 Hz, 1H), 7.63-7.57 (m, 2H), 7.56-7.52 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 10.4 Hz, 2H), 3.42-3.37 (m, 1H), 3.33 (s, 3H), 3.05-2.98 (m, 2H), 2.89 (d, J = 8.0 Hz, 1H), 2.87-2.78 (m, 3H), 2.20-2.02 (m, 3H), 1.75-1.65 (m, 4H), 1.60-1.53 (m, 1H), 1.37 (d, J = 6.8 Hz, 3H), 0.92-0.86 (m, 4H).

Example 498. Synthesis of Compound 507



1. Synthesis of 507-1

[1747] A solution of NaH (469.14 mg, 60% purity, 1.22 equiv) in DMF (10 mL) was cooled to 0°C under nitrogen atmosphere. Then a solution of tert-butyl (2S)-2-(hydroxymethyl) azetidine-1-carboxylate (1.8 g, 9.61 mmol, 1 equiv) in DMF (5 mL) was added to the mixture dropwise. The mixture was stirred at 0°C for 0.5 hr. Then iodomethane (897 uL, 14.4 mmol, 1.5 equiv) was added to reaction mixture at 0°C. The mixture was stirred at 20°C for 2 hr. The mixture was quenched by saturated NH_4Cl (50 ml) and extracted with EtOAc (3 x50 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with PE/EA=1:1 to afford 507-1 (1.45 g, 75%) as a white oil.

^{1}H-NMR-507-1: (400 MHz, CHLOROFORM-d) δ 4.24 (s, 1H), 3.94-2.95 (m, 7H), 2.13 (s, 2H), 1.38 (s, 9H)

2. Synthesis of 507-2

[1748] To a solution of 507-1 (1.13 g, 5.61 mmol, 1 equiv) in DCM (10 mL) was added

HCl/dioxane (4 M, 8.42 mL, 6 equiv). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated at room temperature to afford 507-2 (560 mg, crude) as a white oil.

3. Synthesis of 507-3

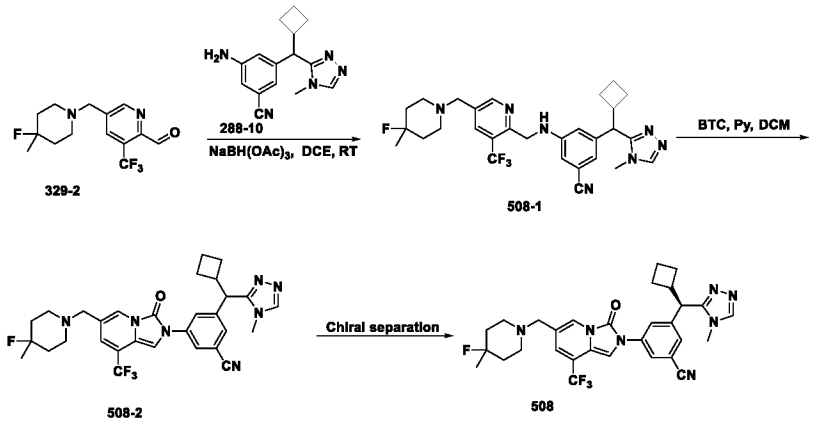
[1749] A mixture of 507-2 (560 mg, 5.54 mmol, 1 equiv), potassium; bromomethyl (trifluoro) boranuide (1.11 g, 5.54 mmol, 1 equiv), KI (91.9 mg, 553 umol, 0.1 equiv), $KHCO_3$ (1.11 g, 11.1 mmol, 2 equiv) in THF (8 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with acetone at 40 °C for 60 min. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 507-3 (1.2 g, crude) as a yellow solid.

4. Synthesis of 507

[1750] To a solution of 507-3 (655 mg, 2.96 mmol, 5 equiv) and 487-2 (300 mg, 592 umol, 1 equiv) in THF (4 mL) and water (1 mL) was added XPhos (28.2 mg, 59.25 umol, 0.1 equiv) and Cs_2CO_3 (579 mg, 1.78 mmol, 3 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (51 mg, 59.2 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water 10 mL and extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography, eluted with CH_2Cl_2/MeOH=10:1 to give crude product. The crude product (230 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile phase A: Water (0.2% formic acid), B: ACN; Flow rate: 50ml/min Gradient: 1% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5 min) to afford 507 (41 mg, 13%) as a yellow solid.

MS-507: (ES, m/z): $[M+H]^+$ 541.1. ^{1}H-NMR-507 (400 MHz, ACETONITRILE-d_3) δ 8.08 (s, 1H), 7.71-7.60 (m, 2H), 7.56 (s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 4.16 (d, J = 10.4 Hz, 1H), 3.53 (d, J = 13.2 Hz, 1H), 3.42 (s, 3H), 3.41-3.36 (m, 2H), 3.35-3.27 (m, 4H), 3.26 (s, 3H), 2.96-2.87 (m, 1H), 2.24-2.16 (m, 1H), 2.08-2.00 (m, 1H), 1.95-1.82 (m, 5H), 1.80-1.72 (m, 1H).

Example 499. Synthesis of Compound 508



1. Synthesis of 508-1

[1751] A solution of 329-2 (1001.64 mg, 3.291 mmol, 1.1 equiv) and 288-10 (800 mg, 2.992 mmol, 1.00 equiv) in DCE (10 mL) was stirred overnight at room temperature. To the above mixture was added STAB (1268.46 mg, 5.984 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 508-1 (650 mg, 37.14%) as a light yellow oil.

2. Synthesis of 508-2

[1752] To a stirred solution of 508-1 (650 mg, 1.170 mmol, 1 equiv) and Pyridine (555.21 mg, 7.020 mmol, 6 equiv) in DCM (10 mL) were added Triphosgene (121.50 mg, 0.409 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (60 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 508-2 (300 mg, 43.65%) as a yellow solid.

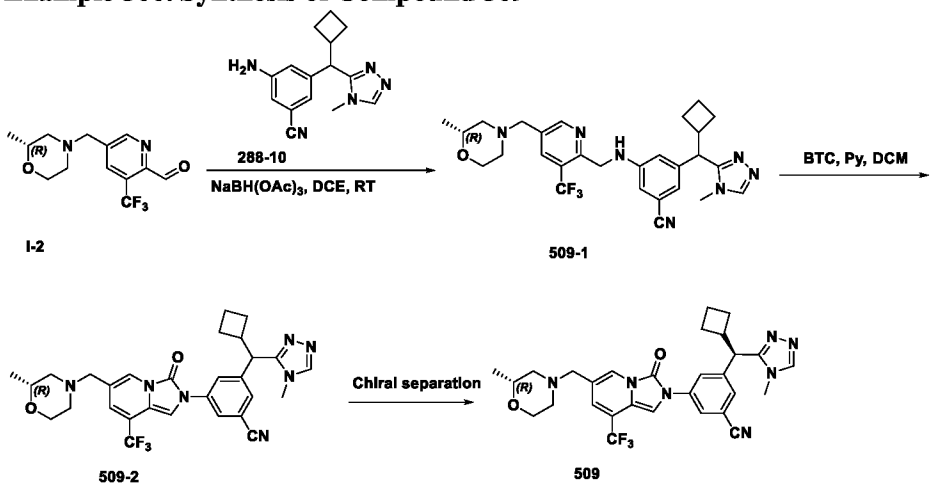
3. Synthesis of 508

The 508-2 (300 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 5.87; RT2(min): 8.06; the first peak is product) to afford 508 (114.0 mg, 37.16%) as a yellow solid.

LC-MS-508 (ES, *m/z*): $[M+H]^+$ 582. H-NMR-508 (400 MHz, DMSO-d6, δ *ppm*): 1.25-1.39 (d, 3H), 1.52-1.60 (m, 1H), 1.61-1.85 (m, 8H), 2.07-2.08 (m, 1H), 2.23-2.31 (m, 1H), 2.67-

2.68 (m, 2H), 3.18-3.22 (m, 1H), 3.32 (s, 2H), 3.48 (s, 3H), 4.38-4.40 (d, 1H), 7.04 (s, 1H), 7.52 (s, 1H), 7.70-7.75 (d, 2H), 8.23-8.24 (d, 2H), 8.37 (s, 1H).

Example 500. Synthesis of Compound 509



1. Synthesis of 509-1

[1753] A solution of 288-10 (500 mg, 1.870 mmol, 1.00 equiv) and I-2 (593.07 mg, 2.057 mmol, 1.1 equiv) in DCE (10 mL) was stirred overnight at room temperature. To the above mixture was added STAB (792.79 mg, 3.740 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (60 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 509-1 (470 mg, 43.31%) as a light yellow solid.

2. Synthesis of 509-2

[1754] To a stirred solution of 509-1 (470 mg, 0.871 mmol, 1 equiv) and Pyridine (413.38 mg, 5.226 mmol, 6 equiv) in DCM (10 mL) were added Triphosgene (90.46 mg, 0.305 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 30% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 509-2 (260 mg, 49.08%) as a yellow solid.

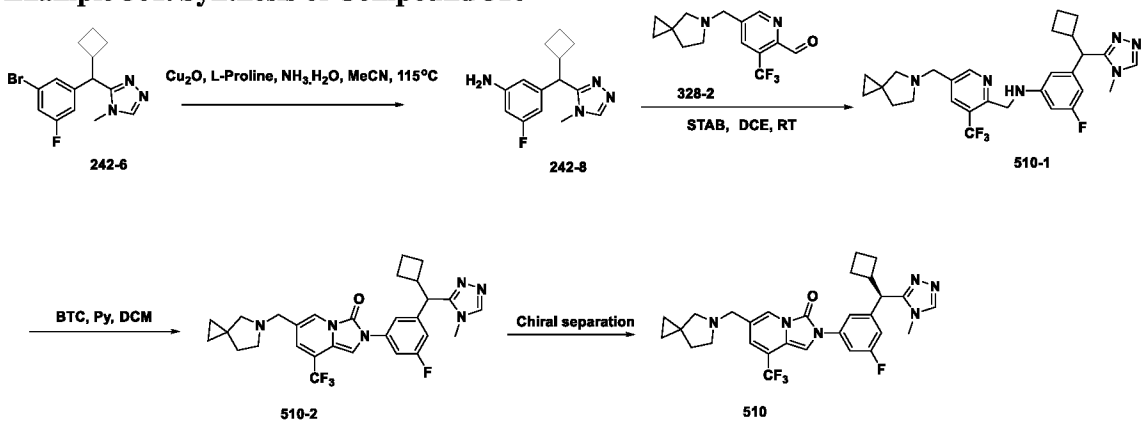
3. Synthesis of 509

[1755] The 509-2 (260 mg) was purified by Chiral separation with the following conditions

(Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 11 min; Wave Length: 220/254 nm; RT1(min): 6.67; RT2(min): 8.16; the first peak is product) to afford 509 (92.6 mg, 35.15%) as a yellow solid.

LC-MS-509 (ES, *m/z*): $[M+H]^+$ 566. H-NMR-509 (400 MHz, DMSO-d6, δ *ppm*): 1.00-1.10 (d, 3H), 1.63-1.85 (m, 6H), 2.03-2.11 (m, 2H), 2.61-2.75 (m, 2H), 3.18-3.30 (m, 3H), 3.41-3.53 (m, 5H), 3.73-3.75 (d, 1H), 4.35-4.40 (m, 1H), 7.04 (s, 1H), 7.52 (s, 1H), 7.68-7.70 (d, 2H), 8.23-8.24 (d, 2H), 8.37 (s, 1H).

Example 501. Synthesis of Compound 510



1. Synthesis of 242-8

[1756] Into a pressure tank reactor was added 242-6 (10 g, 30.845 mmol, 1 equiv), L-Proline (0.07 g, 0.617 mmol, 0.1 equiv) and Cu_2O (0.88 g, 6.150 mmol, 0.20 equiv) in NH_4OH (150 mL) and MeCN (150 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (50:1) to afford 242-8 (4.7 g, 52.68%) as a yellow solid.

2. Synthesis of 510-1

[1757] To a stirred solution/mixture of 242-8 (600 mg, 2.305 mmol, 1 equiv) and 328-2 (786.29 mg, 2.766 mmol, 1.2 equiv) in DCE (6 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. To the above mixture was added STAB (977.00 mg, 4.610 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 17:1) to afford 510-3 600 mg, 49.25%) as a white solid.

3. Synthesis of 510-2

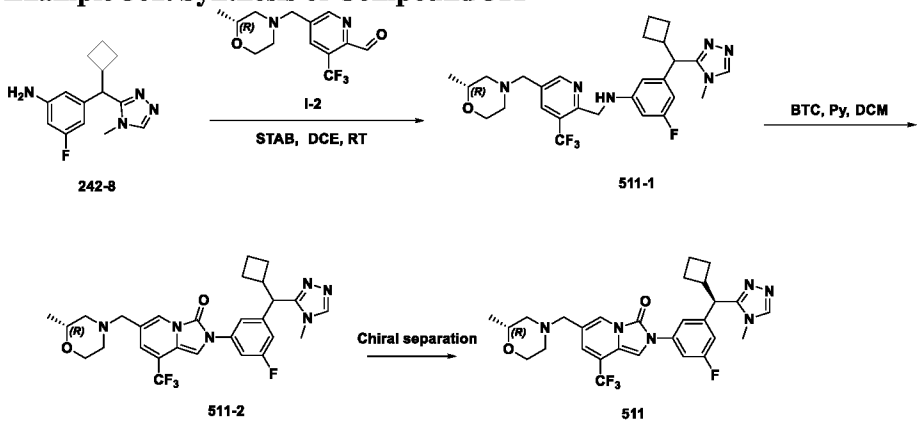
[1758] To a stirred mixture of 510-1 (600 mg, 1.135 mmol, 1 equiv) and Pyridine (538.71 mg, 6.810 mmol, 6 equiv) in DCM (6 mL) was added Triphosgene (131.36 mg, 0.443 mmol, 0.39 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80mL) at room temperature. The aqueous layer was extracted with DCM (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 510-4 (320 mg, 50.83%) as a yellow solid.

4. Synthesis of 510-0

[1759] The 510-4 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 10 min; Wave Length: 220/254 nm; RT1(min): 7.24; RT2(min): 8.45; the second peak is product) to afford 510 (114.3 mg, 35.71%) as a yellow solid.

LC-MS-510 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-510 (400 MHz, DMSO-d_6, δ *ppm*): 0.48-0.58 (d, 4H), 1.68-1.82 (m, 7H), 2.06-2.08 (m, 1H), 2.45-2.50 (m, 2H), 2.63-2.73 (m, 2H), 3.18-3.24 (m, 1H), 3.39 (s, 2H), 3.46 (s, 3H), 4.30-4.33 (d, 1H), 7.04-7.06 (m, 2H), 7.42 (s, 1H), 7.69-7.72 (m, 3H), 8.35 (s, 1H).

Example 502. Synthesis of Compound 511



1. Synthesis of 511-1

[1760] To a stirred solution of 242-8 (500 mg, 1.921 mmol, 1.00 equiv) in DCE (20 mL) was added I-2 (664.43 mg, 2.305 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. To the above mixture was added STAB (814.16 mg, 3.842 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 6h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.)

at room temperature. The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 18:1) to afford 511-1 (500 mg, 46.43%) as a white solid.

2. Synthesis of 511-2

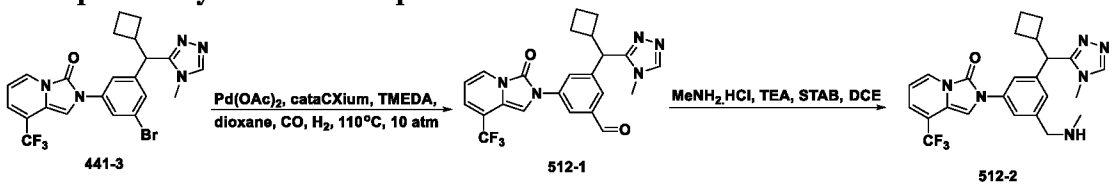
[1761] To a stirred solution of 511-1 (480 mg, 0.901 mmol, 1 equiv) and Pyridine (712.90 mg, 9.010 mmol, 10 equiv) in DCM (10 mL) was added Triphosgene (106.97 mg, 0.360 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 511-2 (350 mg, 66.74%) as a yellow solid.

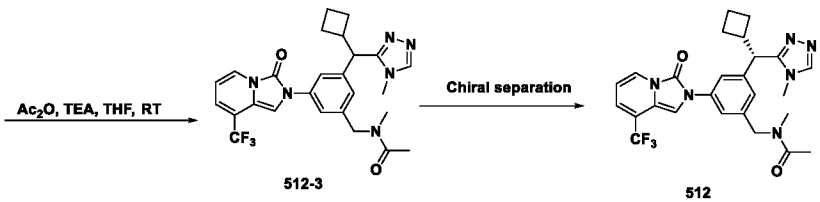
3. Synthesis of 511

[1762] The 511-2 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 10 min; Wave Length: 220/254 nm; RT1(min): 5.61; RT2(min): 8.01; the second peak is product) to afford 511 (124.2 mg, 35.49%) as a yellow solid.

LC-MS-511 (ES, *m/z*): $[M+H]^+$ 559. H-NMR-511 (400 MHz, DMSO-d6, δ *ppm*): 1.03-1.04 (d, 3H), 1.70-1.84 (m, 6H), 2.03-2.12 (m, 2H), 2.65-2.67 (m, 1H), 2.72-2.74 (m, 1H), 3.20-3.27 (m, 1H), 3.27 (s, 2H), 3.45-3.51 (m, 5H), 3.72-3.75 (m, 1H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.41 (s, 1H), 7.68-7.71 (m, 3H), 8.35 (s, 1H).

Example 503. Synthesis of Compound 512





1. Synthesis of 512-1

[1763] To a solution of 441-3 (1.2 g, 2.370 mmol, 1 equiv) in dioxane (30 mL) was added $Pd(OAc)_2$ (0.05 g, 0.237 mmol, 0.1 equiv); bis(adamantan-1-yl)(butyl)phosphane (0.17 g,

0.474 mmol, 0.2 equiv) and TMEDA (0.55 g, 4.733 mmol, 2.00 equiv) in a pressure tank. The mixture was purged with nitrogen for 2min and then was pressurized to 15atm with CO/H_2=1:1 at 110°C for overnight. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 512-1 (800 mg, 68.93%) as a yellow solid.

2. Synthesis of 512-2

[1764] To a stirred solution of 512-1 (780 mg, 1.713 mmol, 1 equiv) and Methylamine hydrochloride (346.90 mg, 5.139 mmol, 3 equiv) in DCE (20 mL) was added TEA (519.92 mg, 5.139 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for h at room temperature. To the above mixture was added STAB (1088.92 mg, 5.139 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 512-2 (580 mg, 64.78%) as a yellow solid.

3. Synthesis of 512-3

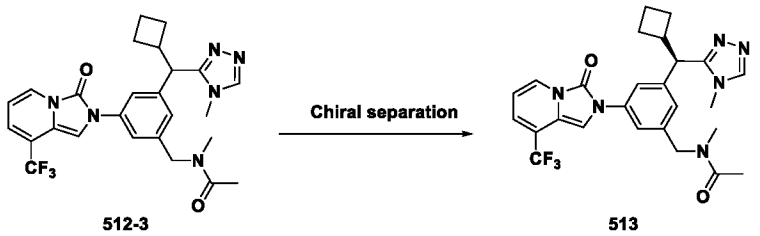
[1765] To a stirred solution of 512-2 (560 mg, 1.190 mmol, 1 equiv) and TEA (361.33 mg, 3.570 mmol, 3 equiv) in THF (10 mL) was added Ac_2O (364.53 mg, 3.570 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 12:1) to afford 512-3 (450 mg, 71.55%) as a yellow solid.

4. Synthesis of 512

[1766] The 512-3 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.23; RT2(min): 10.39; the first peak is product) to afford 512 (150.7 mg, 32.58%) as a yellow solid.

LC-MS-512 (ES, *m/z*): $[M+H]^+$ 513. H-NMR-512 (400 MHz, DMSO-d6, δ *ppm*): 1.68-1.91 (m, 5H), 2.02-2.13 (m, 4H), 2.78-2.89 (s, 3H), 3.18-3.25 (m, 1H), 3.43 (s, 3H), 4.24-4.31 (m, 1H), 4.51-4.58 (s, 2H), 6.26-6.30 (m, 1H), 7.04-7.09 (m, 1H), 7.10-7.12 (m, 1H), 7.28-7.31 (m, 1H), 7.54-7.63 (m, 2H), 7.76-7.78 (d, 1H), 8.33 (s, 1H).

Example 504. Synthesis of Compound 513



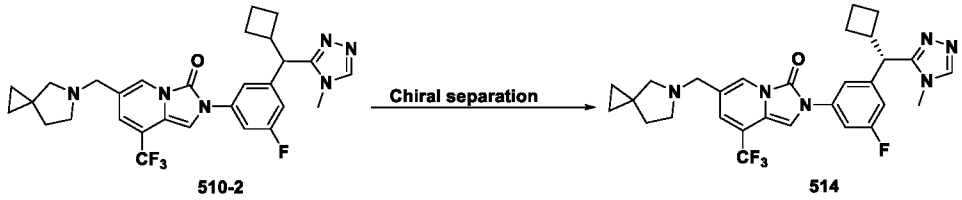
512-3 513

1. Synthesis of 513

[1767] The 512-3 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13 min; Wave Length: 220/254 nm; RT1(min): 8.23; RT2(min): 10.39; the second peak is product) to afford 513 (147.3 mg, 32.00%) as a yellow solid.

LC-MS-513 (ES, *m/z*): $[M+H]^+$ 513. H-NMR-513 (400 MHz, DMSO-d6, δ *ppm*): 1.68-1.91 (m, 5H), 2.02-2.13 (m, 4H), 2.78-2.89 (s, 3H), 3.18-3.25 (m, 1H), 3.43 (s, 3H), 4.24-4.31 (m, 1H), 4.51-4.58 (s, 2H), 6.26-6.30 (m, 1H), 7.04-7.09 (m, 1H), 7.10-7.12 (m, 1H), 7.28-7.31 (m, 1H), 7.54-7.63 (m, 2H), 7.76-7.78 (d, 1H), 8.33 (s, 1H).

Example 505. Synthesis of Compound 514



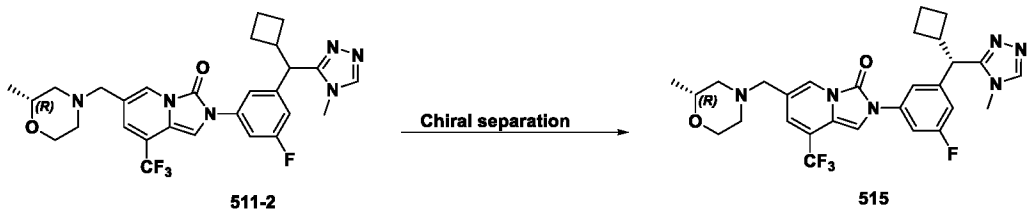
510-2 514

1. Synthesis of 514

[1768] The 510-2 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 10 min; Wave Length: 220/254 nm; RT1(min): 7.24; RT2(min): 8.45; 18 the first peak is product) to afford 514 (112.2 mg, 35.06%) as a yellow solid.

LC-MS-514 (ES, *m/z*): $[M+H]^+$ 555. H-NMR-510 (400 MHz, DMSO-d_6, δ *ppm*): 0.48-0.58 (d, 4H), 1.68-1.82 (m, 7H), 2.06-2.08 (m, 1H), 2.45-2.50 (m, 2H), 2.63-2.73 (m, 2H), 3.18-3.24 (m, 1H), 3.39 (s, 2H), 3.46 (s, 3H), 4.30-4.33 (d, 1H), 7.04-7.06 (m, 2H), 7.42 (s, 1H), 7.69-7.72 (m, 3H), 8.35 (s, 1H).

Example 506. Synthesis of Compound 515



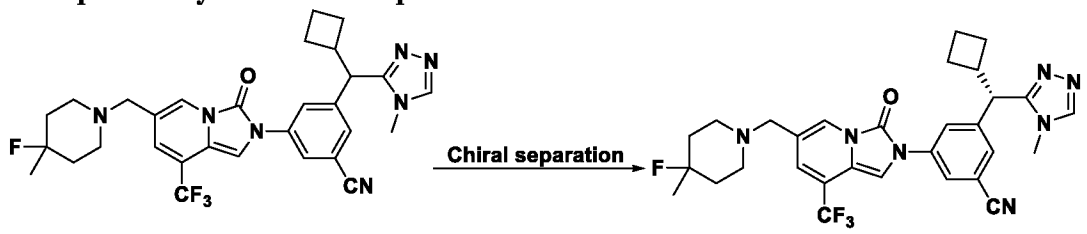
511-2 515

1. Synthesis of 515

[1769] 511-2 (350 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 10 min; Wave Length: 220/254 nm; RT1(min): 5.61; RT2(min): 8.01; the first peak is product) to afford 515 (136.9 mg, 38.25%) as a yellow solid.

LC-MS-515 (ES, *m/z*): $[M+H]^+$ 559. H-NMR-515 (400 MHz, DMSO-d6, δ *ppm*): 1.03-1.04 (d, 3H), 1.70-1.84 (m, 6H), 2.03-2.12 (m, 2H), 2.65-2.67 (m, 1H), 2.72-2.74 (m, 1H), 3.20-3.27 (m, 1H), 3.27 (s, 2H), 3.45-3.51 (m, 5H), 3.72-3.75 (m, 1H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.41 (s, 1H), 7.68-7.71 (m, 3H), 8.35 (s, 1H).

Example 507. Synthesis of Compound 516



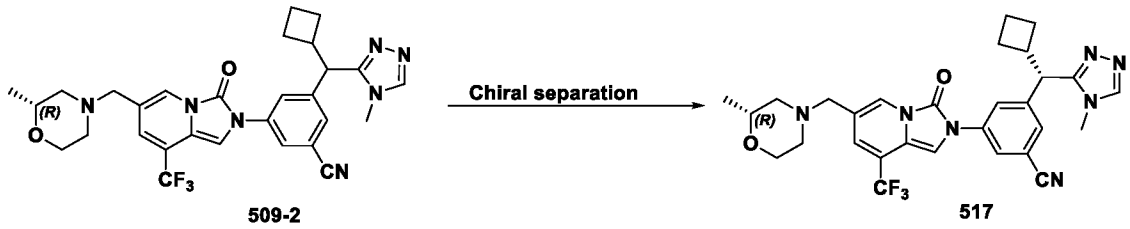
508-2 516

1. Synthesis of 516

[1770] The 508-2 (300 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 5.87; RT2(min): 8.06; the second peak is product.) to afford 516 (113.8 mg, 37.25%) as a yellow solid.

LC-MS-516 (ES, *m/z*): $[M+H]^+$ 582. H-NMR-516 (400 MHz, DMSO-d6, δ *ppm*): 1.25-1.39 (d, 3H), 1.52-1.86 (m, 9H), 2.07-2.08 (m, 1H), 2.26-2.32 (m, 2H), 2.62-2.65 (m, 2H), 3.18-3.22 (m, 1H), 3.32 (s, 2H), 3.48 (s, 3H), 4.38-4.40 (d, 1H), 7.04 (s, 1H), 7.52 (s, 1H), 7.68-7.70 (d, 2H), 8.23-8.24 (d, 2H), 8.37 (s, 1H).

Example 508. Synthesis of Compound 517



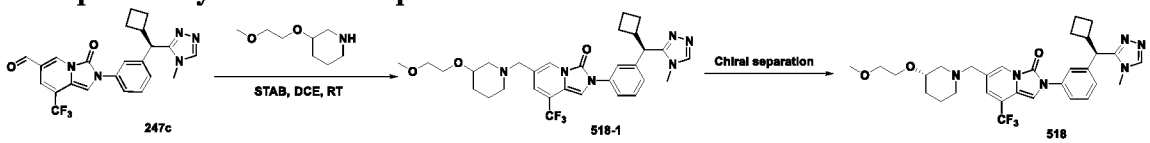
509-2 517

1. Synthesis of 517

[1771] 509-2 (260 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 11 min; Wave Length: 220/254 nm; RT1(min): 6.67; RT2(min): 8.16; the second peak is product) to afford 517 (96.6 mg, 36.67%) as a yellow solid.

LC-MS-517 (ES, *m/z*): $[M+H]^+$566. H-NMR-517 (400 MHz, DMSO-d6, δ *ppm*): 1.00-1.10 (d, 3H), 1.63-1.85 (m, 6H), 2.03-2.11 (m, 2H), 2.61-2.75 (m, 2H), 3.18-3.30 (m, 3H), 3.41-3.51 (m, 5H), 3.73-3.75 (d, 1H), 4.38-4.40 (m, 1H), 7.04 (s, 1H), 7.52 (s, 1H), 7.69-7.70 (d, 2H), 8.23-8.24 (d, 2H), 8.37 (s, 1H).

Example 509. Synthesis of Compound 518



247c 518-1 518

1. Synthesis of 518-1

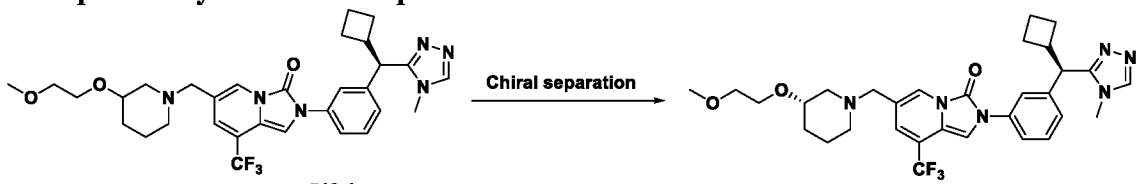
[1772] To a stirred solution of 247c (700 mg, 1.537 mmol, 1 equiv) in DCE (10 mL) was added 3-(2-methoxyethoxy)piperidine (489.46 mg, 3.074 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added STAB (651.49 mg, 3.074 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 70% gradient in 30 min; detector, UV 254 nm. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 518-1 (300 mg, 31.63%) as a yellow solid.

2. Synthesis of 518

[1773] The 518-1 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH),

Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 20 min; Wave Length: 220/254 nm; RT1(min): 6.27; RT2(min): 11.95; the first peak is product) to afford the crude product. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the 518 (82.2 mg, 26.55%) as a yellow solid. LC-MS-518 (ES, *m/z*): $[M+H]^+$ 599. H-NMR-518 (400 MHz, DMSO-d6, δ *ppm*): 1.08-1.23 (m, 1H), 1.37-1.53 (m, 1H), 1.64-1.74 (m, 2H), 1.74-1.88 (m, 4H), 1.88-1.91 (m, 2H), 1.91-2.03 (m, 1H), 2.03-2.10 (m, 1H), 2.63-2.66 (m, 1H), 2.88-2.93 (m, 1H), 3.20-3.30 (m, 4H), 3.32 (s, 2H), 3.33-3.35 (m, 1H), 3.35-3.40 (m, 2H), 3.43 (s, 3H), 3.50-3.53 (m, 2H), 4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.70 (m, 2H), 7.73 (s, 1H), 8.32 (s, 1H).

Example 510. Synthesis of Compound 519

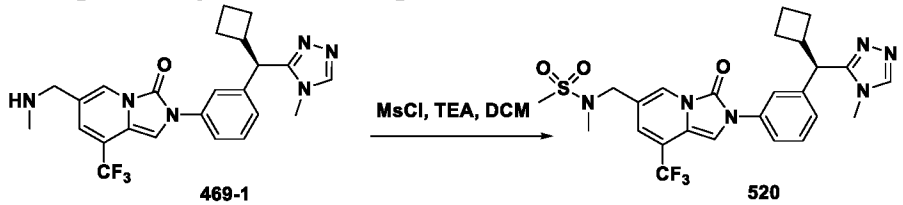


1. Synthesis of 519

[1774] 518-1 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 20 min; Wave Length: 220/254 nm; RT1(min): 6.27; RT2(min): 11.95; the second peak is product) to afford 519 (125.1 mg, 41.49%) as a yellow solid.

LC-MS-519 (ES, *m/z*): $[M+H]^+$ 599. H-NMR-519 (400 MHz, DMSO-d6, δ *ppm*): 1.08-1.23 (m, 1H), 1.37-1.53 (m, 1H), 1.64-1.74 (m, 2H), 1.74-2.03 (m, 7H), 2.03-2.10 (m, 1H), 2.63-2.66 (m, 1H), 2.88-2.93 (m, 1H), 3.20-3.30 (m, 4H), 3.32 (s, 2H), 3.33-3.35 (m, 1H), 3.35-3.40 (m, 2H), 3.43 (s, 3H), 3.50-3.53 (m, 2H), 4.25-4.27 (d, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.67-7.70 (m, 2H), 7.73 (s, 1H), 8.32 (s, 1H).

Example 511. Synthesis of Compound 520



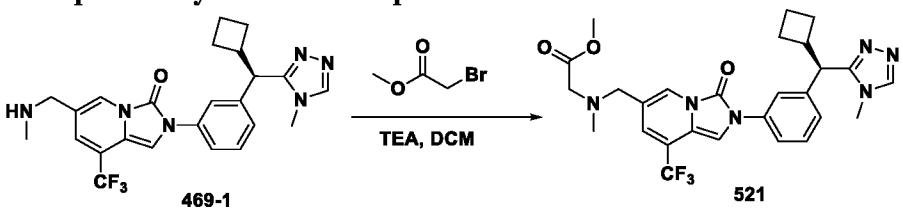
1. Synthesis of 520

[1775] Into a 40 mL sealed tube were added 469-1 (380 mg, 0.808 mmol, 1 equiv), DCM (5 mL), TEA (245.19 mg, 2.424 mmol, 3 equiv) and MsCl (101.76 mg, 0.889 mmol, 1.1 equiv) at room temperature. The final reaction mixture was irradiated with microwave radiation for

1.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1). The crude product (180 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 48% B in 8 min; Wave Length: 254 nm; RT1(min): 7.57) to afford 520 (81.6 mg, 18.25%) as a yellow solid.

LC-MS-520 (ES, m/z): $[M+H]^+$ 549. H-NMR- 520 (400 MHz, DMSO, δ *ppm*): 1.65-1.93 (m, 5H), 2.04-2.20 (s, 1H), 2.69-2.80 (s, 3H), 2.94-3.08 (s, 3H), 3.18-3.29 (m, 1H), 3.39-3.50 (s, 3H), 4.02-4.17 (s, 2H), 4.21-4.38 (d, 1H), 6.87-6.99 (s, 1H), 7.16-7.27 (d, 1H), 7.31-7.41 (s, 1H), 7.41-7.55 (m, 1H), 7.62-7.73 (m, 1H), 7.73-7.80 (s, 1H), 7.80-7.87 (s, 1H), 8.26-8.42 (s, 1H).

Example 512. Synthesis of Compound 521



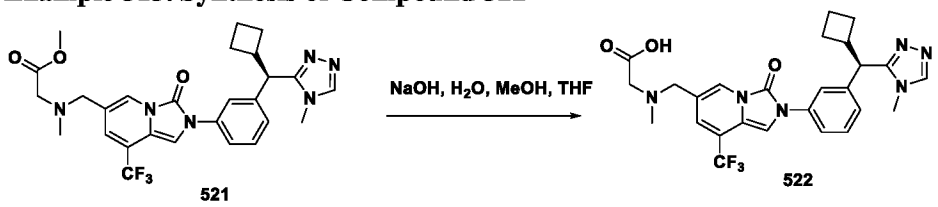
1. Synthesis of 521

[1776] Into a 20 mL sealed tube were added 469-1 (350 mg, 0.744 mmol, 1 equiv), DCM (4 mL), TEA (225.83 mg, 2.232 mmol, 3 equiv) and methyl 2-bromoacetate (136.56 mg, 0.893 mmol, 1.2 equiv) at room temperature. The final reaction mixture was irradiated with microwave radiation for 1.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1). The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 51% B in 8 min; Wave Length: 254 nm; RT1(min): 7.57) to afford 521 (100.3 mg, 24.53%) as a yellow solid.

LC-MS-521 (ES, m/z): $[M+H]^+$ 543. H-NMR-521-1724 (400 MHz, DMSO, δ *ppm*): 1.60-1.91 (m, 5H), 2.01-2.16 (s, 1H), 2.22-2.35 (s, 3H), 3.14-3.30 (m, 1H), 3.36-3.39 (s, 2H), 3.40-

3.46 (s, 5H), 3.58-3.71 (s, 3H), 4.18-4.31 (d, 1H), 6.99-7.12 (s, 1H), 7.12-7.29 (d, 1H), 7.29-7.37 (s, 1H), 7.37-7.52 (m, 1H), 7.62-7.74 (m, 2H), 7.74-7.83 (s, 1H), 8.25-8.41 (s, 1H).

Example 513. Synthesis of Compound 522



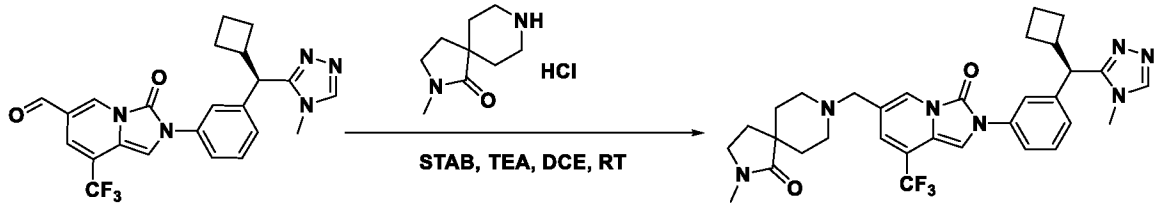
521 522

1. Synthesis of 522

[1777] Into a 20 mL sealed tube were added 521 (280 mg, 0.516 mmol, 1 equiv), MeOH (1 mL), THF (1 mL), H_2O (3 mL) and NaOH (61.92 mg, 1.548 mmol, 3 equiv) at room temperature. The final reaction mixture was irradiated with microwave radiation for 4 h at room temperature. The reaction was quenched with 1 M HCl (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1). The crude product (190 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 36% B in 8 min; Wave Length: 254 nm; RT1(min): 7.45) to afford 522 (92.1 mg, 33.70%) as a yellow solid.

LC-MS-522 (ES, m/z): $[M+H]^+$ 529. H-NMR-522 (400 MHz, DMSO, δ *ppm*): 1.65-1.90 (m, 5H), 2.00-2.17 (s, 1H), 2.23-2.34 (s, 3H), 3.15-3.30 (s, 3H), 3.43-3.46 (s, 3H), 3.46-3.51 (d, 2H), 4.12-4.43 (d, 1H), 7.06-7.15 (s, 1H), 7.15-7.27 (m, 1H), 7.27-7.40 (s, 1H), 7.40-7.51 (m, 1H), 7.64-7.73 (m, 2H), 7.73-7.86 (s, 1H), 8.28-8.41 (s, 1H).

Example 514. Synthesis of Compound 523



247c 523

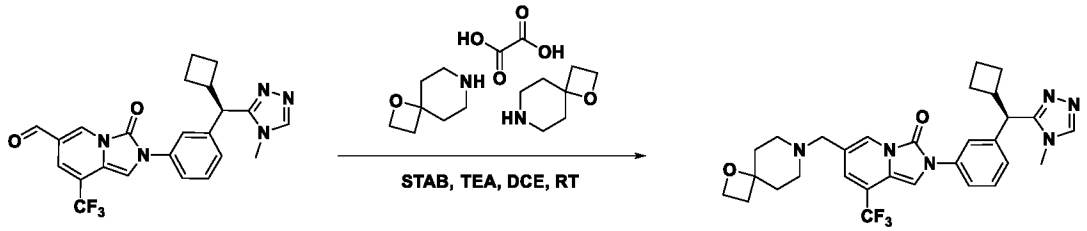
1. Synthesis of 523

[1778] To a stirred solution of 247c (500 mg, 1.098 mmol, 1.00 equiv) and 2-methyl-2,8-diazaspiro [4.5] decan-1-one hydrochloride (337.09 mg, 1.647 mmol, 1.5 equiv) in DCE (10 mL) were added TEA (222.19 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB

(465.35 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 523 (124.2 mg, 18.39%) as a yellow solid.

LC-MS-523 (ES, *m/z*): $[M+H]^+$ 608. H-NMR-523 (400 MHz, DMSO-d6, δ *ppm*): 1.25-1.35 (m, 2H), 1.61-1.70 (m, 3H), 1.71-1.78 (m, 4H), 1.79-1.83 (m, 2H), 2.01-2.13 (m, 3H), 2.71 (s, 3H), 2.72-2.83 (m, 2H), 3.18-3.31 (m, 5H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.66-7.73 (m, 1H), 8.33 (s, 1H).

Example 515. Synthesis of Compound 524



1. Synthesis of 524

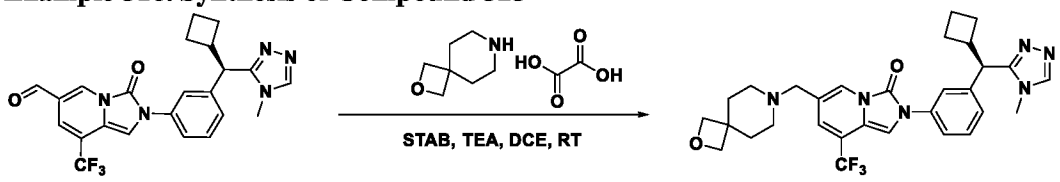
[1779] To a stirred solution of 247c (500 mg, 1.098 mmol, 1.00 equiv) and 1-Oxa-7-azaspiro[3.5]nonane hemioxalate (378.10 mg, 1.098 mmol, 1 equiv) in DCE (10 mL) were added TEA (166.64 mg, 1.647 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (465.35 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (80 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under reduced pressure. The crude product (178 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 54% B in 8 min, Wave Length: 254 nm; RT1(min): 7.9) to afford 524 (145.9 mg, 23.01%) as a yellow solid.

LC-MS-524: (ES, *m/z*): $[M+H]^+$ 567

H-NMR-524: (400 MHz, DMSO-d6, δ *ppm*): δ 1.61-1.85 (m, 9H), 2.07-2.09 (m, 1H), 2.29-2.32 (m, 4H), 2.46-2.51 (m, 2H), 3.19-3.25 (m, 3H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 4.34-

4.38 (m, 2H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.66 (s, 1H), 7.66-7.70 (d, 1H), 7.73 (s, 1H), 8.33 (s, 1H).

Example 516. Synthesis of Compound 525



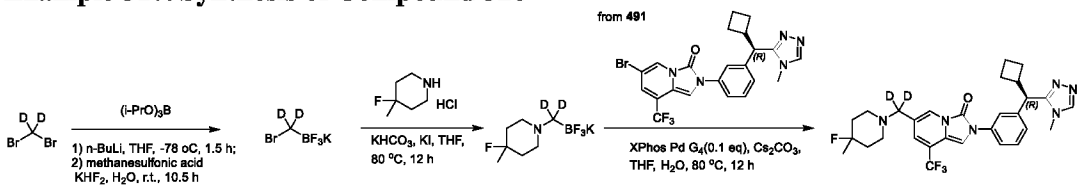
247c 525

1. Synthesis of 525

[1780] To a stirred mixture of 247c (500 mg, 1.098 mmol, 1 equiv) and 2-oxa-7-azaspiro[3.5]nonane oxalate (209.45 mg, 1.647 mmol, 1.5 equiv) in DCE (6 mL) was added TEA (333.28 mg, 3.294 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added STAB (698.03 mg, 3.294 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x30 mL). The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 525 (213.6 mg, 33.65%) as a yellow solid.

LC-MS-525: (ES, *m/z*): $[M+H]^+$ 567. H-NMR-525: (400 MHz, DMSO-d6, δ *ppm*): 1.71-1.91 (m, 9H), 1.99-2.08 (m, 2H), 2.08-2.41 (m, 3H), 3.13-3.23 (m, 4H), 3.23 (s, 3H), 4.17-4.37 (m, 5H), 7.00 (s, 1H), 7.19-7.21 (m, 1H), 7.21-7.31 (s, 1H), 7.31-7.38 (m, 1H), 7.38-7.42 (m, 1H), 7.65-7.73 (m, 3H), 8.33 (s, 1H).

Example 517. Synthesis of Compound 526



526-1 526-2 526

1. Synthesis of 526-1

[1781] To a solution of dibromo(dideuterio)methane (5 g, 28.43 mmol, 1 equiv) and triisopropyl borate (5.3 g, 28.43 mmol, 6.54 mL, 1 equiv) in THF (39 mL) was added n-BuLi (2.5 M, 11.37 mL, 1 equiv) dropwise at -78 °C. Then the reaction was stirred for 1.5 hr. Methanesulfonic acid (1.37 g, 14.22 mmol, 1.01 mL, 0.5 equiv) was added to the mixture at this temperature. After addition, the mixture was stirred at 0 °C for 30 min. Then KHF_2 (6.66 g, 85.30 mmol, 2.81 mL, 3 equiv) and H_2O (7.8 mL) was added dropwise to the reaction

mixture at 0 °C for 30 min. Then the mixture was stirred at 25 °C for 9.5 hr. The crude product was triturated with acetone (40 mL) at 35 °C for 1 hr to afford 526-1 (5 g, 41%) as a white solid.

2. Synthesis of 526-2

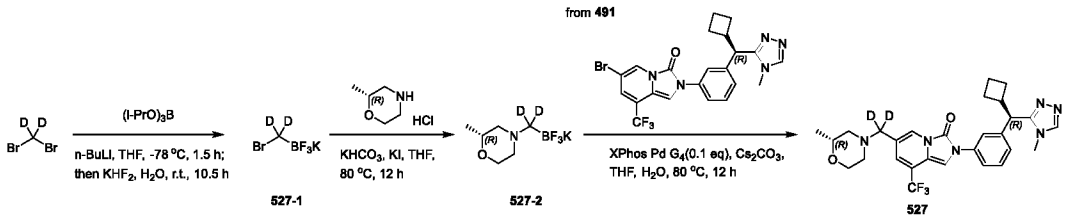
[1782] To a solution of [bromo(dideuterio)methyl]-trifluoro-boron;potassium hydride (130 mg, 640.88 umol, 1 equiv) and 4-fluoro-4-methyl-piperidine (98.45 mg, 640.88 umol, 1 equiv, HCl) in THF (3 mL) was added $KHCO_3$ (128.32 mg, 1.28 mmol, 2 equiv), 4-fluoro-4-methyl-piperidine (98.45 mg, 640.88 umol, 1 equiv, HCl) and KI (10.64 mg, 64.09 umol, 0.1 equiv). The resulting mixture was stirred at 80 °C for 12 hr. The reaction was concentrated under reduced pressure, then the residue was trituated with acetone (20 mL) at 35 °C for 1 hr. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 526-2 (0.111 g, 72.4%) as a yellow oil.

3. Synthesis of 526

[1783] A mixture of 526-2 (225 mg, 941.03 umol, 1 equiv), 6-bromo-2-[3-[(R)-cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (285.88 mg, 564.62 umol, 0.6 equiv), Xphos Pd G4 (80.97 mg, 94.10 umol, 0.1 equiv), Cs_2CO_3 (919.82 mg, 2.82 mmol, 3 equiv) in THF (5 mL) / H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hr under N_2 atmosphere. The reaction was poured into water (10 mL) and the resulting mixture was extracted with EtOAc (10 mLx2). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by normal phase SiO_2 chromatography (10-100% MeOH/ DCM) to give crude product. The crude product (250 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile phase A: Water (FA), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 40% B in 8 min; Wave Length: 220 nm) to afford 526 (96.8 mg, 37.5%) as a yellow solid.

MS: (ES, m/z): [M+H]+ 559.27. H-NMR (400 MHz, METHANOL-d4) δ 8.36 (s, 1 H), 7.72-7.68 (m, 1 H), 7.68-7.60 (m, 2 H), 7.52-7.44 (m, 1 H), 7.29-7.23 (m, 1 H), 7.13-7.08 (m, 2 H), 4.32-4.25 (m, 1 H), 3.54 (s, 3 H), 2.77-2.74 (m, 2 H), 2.52-2.39 (m, 2 H), 2.30-2.19 (m, 1 H), 2.01-1.63 (m, 10 H), 1.40-1.31 (m, 3 H).

Example 518. Synthesis of Compound 527



1. Synthesis of 527-1

[1784] To a solution of dibromo(dideuterio)methane (5.0 g, 28.4 mmol, 1.0 equiv) and triisopropyl borate (5.3 g, 28.4 mmol, 6.5 mL, 1.0 equiv) in THF (39.0 mL) was added n-BuLi (2.5 M, 11.4 mL, 1.0 equiv) dropwise at -78 °C. Then the reaction was stirred for 1.5 hour, methanesulfonic acid (1.4 g, 14.2 mmol, 1.0 mL, 0.5 equiv) was added to the mixture at this temperature. After addition, the mixture was stirred at 0 °C for 30 minutes. Then KHF_2 (6.7 g, 85.3 mmol, 2.8 mL, 3.0 equiv) and H_2O (7.8 mL) was added dropwise to the reaction mixture at 0 °C for 30 minutes. Then the mixture was stirred at 25 °C for 9.5 hours. The reaction was concentrated in reduced pressure. The crude product was triturated with acetone (40.0 mL) at 35 °C for 1 hour to afford 527-1 (3.0 g, 52.01% yield) was obtained as a white solid.

2. Synthesis of 527-2

[1785] To a solution of 527-1 (294 mg, 1.4 mmol, 1.0 equiv) and (2R)-2-methylmorpholine (200 mg, 1.4 mmol, 1.0 equiv, HCl) in THF (5.0 mL) was added $KHCO_3$ (291 mg, 2.9 mmol, 2.0 equiv) and KI (24 mg, 0.1 equiv). The mixture was stirred at 80 °C for 12 hours. The reaction was concentrated in reduced pressure. The residue was triturated with acetone (5.0 mL) at 35 °C for 1 hour. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 527-2 (300 mg, 92.53% yield) was obtained as a white solid.

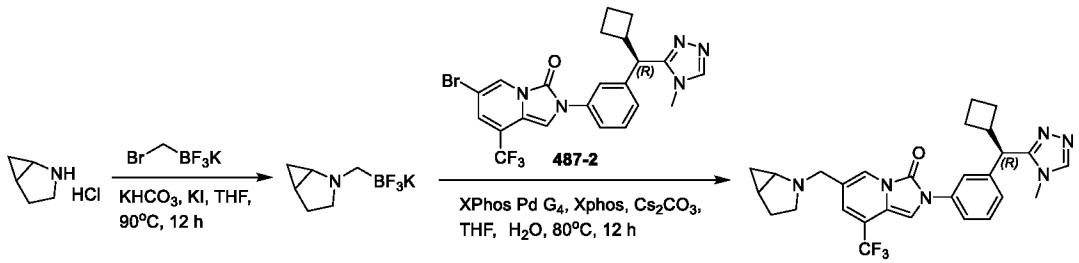
3. Synthesis of 527

[1786] mixture of 527-2 (165 mg, 1.5 equiv), 6-bromo-2-[3-[(R)-cyclobutyl-(4-methyl-1,2,4-triazol-3-yl)methyl]phenyl]-8-(trifluoromethyl)imidazo[1,5-a]pyridin-3-one (250 mg, 1.0 equiv), CS_2CO_3 (482 mg, 3.0 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (42 mg, 0.1 equiv) in THF (6.0 mL) and H_2O (1.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. The reaction was poured into water (20.0 mL) and the resulting mixture was extracted with EtOAc (2 x 15.0 mL). The organic phase was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Column: Phenomenex Luna C18

75*30mm*3um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 20% B to 60% B in 8 min; Wave Length: 220 nm;) to afford 527 (85 mg, 31.36% yield) was obtained as a yellow solid.

MS: (ES, m/z): [M+H]+ 543.3. H-NMR: (400 MHz, METHANOL-d4) δ ppm 8.38 (s, 1 H), 7.69 (s, 1 H), 7.68-7.62 (m, 2 H), 7.54-7.46 (m, 1 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 7.12 (br d, *J* = 5.2 Hz, 2 H), 4.29 (d, *J* = 10.8 Hz, 1 H), 3.92-3.82 (m, 1 H), 3.71-3.62 (m, 2 H), 3.59-3.51 (m, 3 H), 3.31-3.23 (m, 1 H), 2.88-2.71 (m, 2 H), 2.30-2.17 (m, 2 H), 1.96-1.85 (m, 5 H), 1.82-1.74 (m, 1 H), 1.15 (d, *J* = 6.4 Hz, 3 H).

Example 519. Synthesis of Compound 528



1. Synthesis of 528-1

[1787] A mixture of 2-azabicyclo[3.1.0]hexane (0.3 g, 2.51 mmol, 1 equiv, HCl), potassium;bromomethyl (trifluoro)boranuide (504 mg, 2.51 mmol, 1 equiv), $KHCO_3$ (502.31 mg, 5.02 mmol, 2 equiv) and KI (41.6 mg, 251 umol, 0.1 equiv) in THF (5 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The crude product was triturated with acetone (50 mL) at 35 °C for 1 h. Then the mixture was filtered and the filtrate was concentrated under reduced pressure to afford 528-1 (410 mg, crude) as a yellow oil.

2. Synthesis of 528

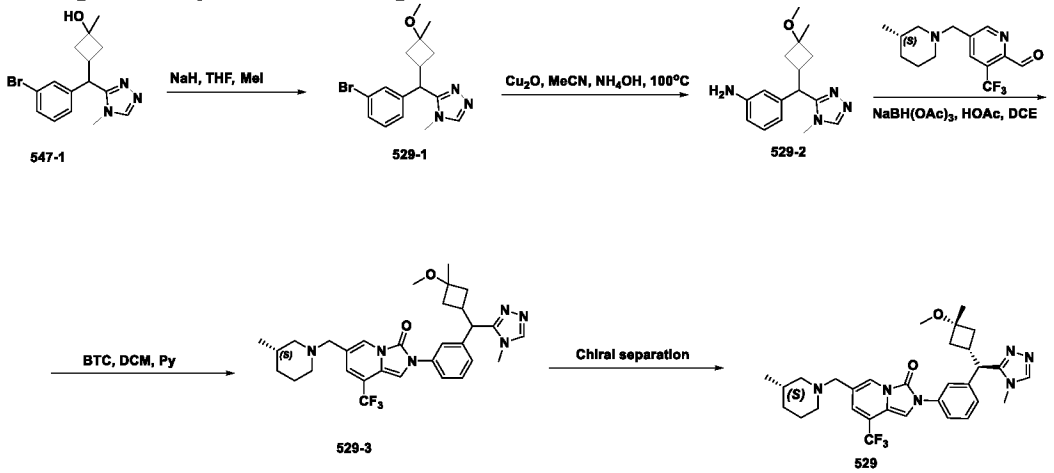
[1788] To a solution of 487- 2 (0.3 g, 592 umol, 1 equiv) and 528-1 (361 mg, 1.78 mmol, 3 equiv) in THF (8 mL) and H_2O (2 mL) was added XPhos (28.2 mg, 59.2 umol, 0.1 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]- phenyl]palladium(1+) (50.9 mg, 59.2 umol, 0.1 equiv) and Cs_2CO_3 (579 mg, 1.78 mmol, 3 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was extracted with water (50 ml) and EtOAc (30 ml x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with DCM/MeOH (10:1). The crude product (230 mg) was purified by Prep-HPLC

with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: water (FA), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 1% B to 35% B in 8 min; Wave Length: 220 nm; RT1 (min): 6.2) to afford 528 (32 mg, 10%) as a yellow solid.

MS-528: (ES, m/z): $[M+H]^+$ 523.2.

^{1}H-NMR-528: (400 MHz, METHANOL-d4) δ 8.44-8.40 (m, 1H), 8.36 (s, 1H), 7.76 (s, 1H), 7.66-7.60 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 2H), 4.28 (d, *J* = 10.8 Hz, 1H), 3.66-3.56 (m, 2H), 3.54 (s, 3H), 3.29-3.21 (m, 1H), 2.98 (*J* = 9.2 Hz, 1H), 2.84-2.77 (m, 1H), 2.29-2.15 (m, 2H), 2.11-2.00 (m, 1H), 1.99-1.85 (m, 5H), 1.81-1.70 (m, 1H), 1.60-1.51 (m, 1H), 0.91-0.83 (m, 1H), 0.36-0.28 (m, 1H).

Example 520. Synthesis of Compound 529



1. Synthesis of 529-1

[1789] A solution of 574-1 (1.11 g, 3.301 mmol, 1 equiv) in THF (11 mL) was treated with NaH (0.24 g, 5.942 mmol, 1.8 equiv, 60%) for 1h at 0°C under nitrogen atmosphere followed by the addition of MeI (1.08 g, 7.592 mmol, 2.3 equiv) at 0°C. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. The resulting mixture was diluted with 30 mL of sat.NH_4Cl(aq.). The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 20mL). The combined organic layers was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 529-1 (1.22 g, 94.96%) as a yellow solid.

2. Synthesis of 529-2

[1790] Into a 50mL pressure tank reactor were added 529-1 (1.22 g, 3.483 mmol, 1 equiv) , Cu2O (0.35 g, 2.438 mmol, 0.7 equiv), MeCN (18 mL) and NH_4OH (18 mL) at room temperature. The mixture was stirred for overnight at 105°C under nitrogen atmosphere. The

resulting mixture was diluted with 100 mL of water.The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 529-2 (400 mg, 38.10%) as a yellow solid.

[1791] **3. Synthesis of 529-3**

A solution of 529-2 (400 mg, 1.397 mmol, 1 equiv) in DCE (4 mL) was treated with I-2 (519.85 mg, 1.816 mmol, 1.3 equiv) for 2h at room temperature under nitrogen atmosphere followed by the addition of $NaBH(OAc)_3$ (444.04 mg, 2.095 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 529-3 (470 mg, 57.42%) as a yellow solid.

[1792] **4. Synthesis of 529-4**

To a stirred solutio of 529-3 (460 mg, 0.826 mmol, 1 equiv) and Pyridine (392.18 mg, 4.956 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (98.08 mg, 0.330 mmol, 0.4 equiv) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (15 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 529-4 (270 mg, 56.08%) as a yellow solid.

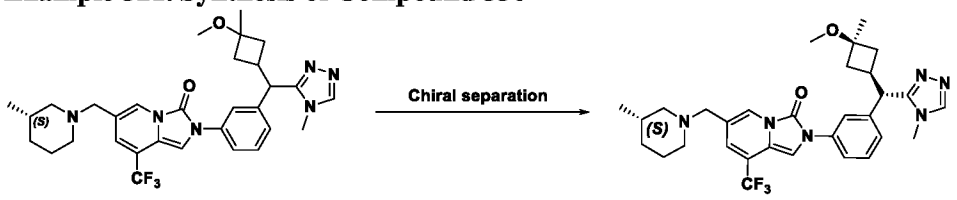
5. Synthesis of 529

[1793] 529-4 (270 mg, 0.463 mmol, 1 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 27 min; Wave Length: 220/254 nm; RT1(min): 5.42; RT2(min): 25.02; Sample Solvent: EtOH: DCM=1: 1; the first peak was product) to afford - 529 (113.4 mg, 42.00%) as a yellow solid.

LCMS-529:(ES, m/z): $[M+H]^+$ 583

NMR-529: (400 MHz, CD_3OD, δ ppm): 0.91-0.96 (m, 4H), 1.37 (s, 3H), 1.60-1.78 (m, 5H), 1.81-1.90 (m, 2H), 1.96-2.01 (m, 2H), 2.23-2.28 (m, 1H), 2.89-2.96 (m, 3H), 3.17 (s, 3H), 3.38 (s, 2H), 3.54 (s, 3H), 4.24-4.26 (d, 1H), 7.13-7.14 (d, 2H), 7.27-7.29 (d, 1H), 7.50-7.54 (t, 1H), 7.66-7.70 (m, 3H), 8.38 (s,1H).

Example 521. Synthesis of Compound 530



529-4 530

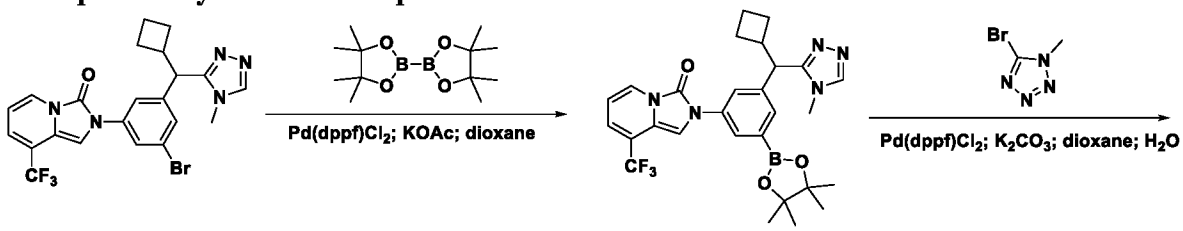
1. Synthesis of 530

[1794] 529-4 (270 mg, 0.463 mmol, 1 equiv) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 65% B to 65% B in 27 min; Wave Length: 220/254 nm; RT1(min): 5.42; RT2(min): 25.02; Sample Solvent: EtOH: DCM=1: 1; the second peak was product) to afford 530 (91.1 mg, 33.74%) as a yellow solid.

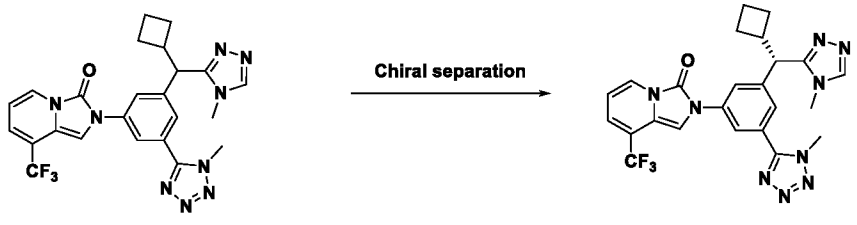
LCMS-530:(ES,m/z): $[M+H]^+$ 583

NMR-530: (400 MHz, CD_3OD, δ ppm): 0.91-0.97 (m, 4H), 1.36 (s, 3H), 1.61-1.78 (m, 5H), 1.81-1.89 (m, 2H), 1.96-2.03 (m, 2H), 2.23-2.28 (m, 1H), 2.89-2.96 (m, 3H), 3.17 (s, 3H), 3.38 (s, 2H), 3.54 (s, 3H), 4.24-4.26 (d, 1H), 7.13-7.14 (d, 2H), 7.27-7.29 (d, 1H), 7.50-7.54 (t, 1H), 7.66-7.70 (m, 3H), 8.38 (s,1H).

Example 522. Synthesis of Compound 531



441-3 531-1



531-2 531

1. Synthesis of 531-1

[1795] To a stirred mixture of 441-3 (1 g, 1.975 mmol, 1 equiv) and bis(pinacolato)diboron (0.50 g, 1.975 mmol, 1 equiv) indioxane (10 mL) was added KOAc (0.23 g, 2.370 mmol, 1.2

equiv) and $Pd(dppf)Cl_2$ (0.29 g, 0.395 mmol, 0.2 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The resulting mixture was used in the next step directly without further purification.

2. Synthesis of 531-2

[1796] To a stirred mixture of 531-1 (1.09 g, 1.970 mmol, 1 equiv) and 5-bromo-1-methyl-1,2,3,4-tetrazole (0.48 g, 2.955 mmol, 1.5 equiv) indioxane (10 mL) and H_2O (2 mL) was added K_2CO_3 (0.54 g, 3.940 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (0.14 g, 0.197 mmol, 0.1 equiv) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (40 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 531-2 (450 mg, 44.84%) as a yellow solid.

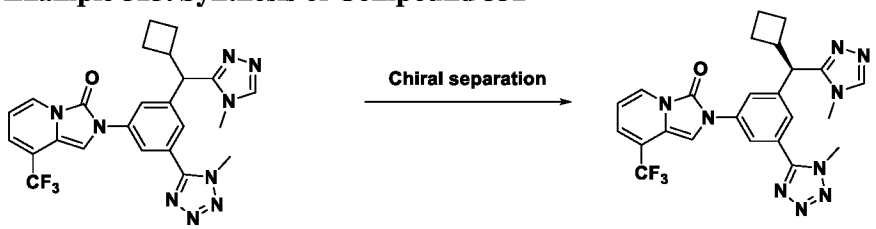
3. Synthesis of 531

[1797] 531-2 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 10 min; Wave Length: 220/254 nm; RT1(min): 7.03; RT2(min): 9.47; the first peak was product) to afford 531 (197.2 mg, 43.82%) as a yellow solid.

LCMS-531:(ES, m/z): $[M+H]^+$ 510

NMR-531: (400 MHz, DMSO, ppm): δ 1.74-1.84 (m, 5H), 2.08-2.12 (m, 1H), 3.26-3.30 (m, 1H), 3.51 (s, 3H), 4.19 (s, 3H), 4.43-4.46 (d, 1H), 6.29-6.33 (t, 1H), 7.12-7.14 (d, 1H), 7.48 (s, 1H), 7.74 (s, 1H), 7.81-7.82 (d, 1H), 8.06 (s, 1H), 8.23 (s, 1H), 8.37 (s, 1H).

Example 523. Synthesis of Compound 532



531-2 532

1. Synthesis of 532-0

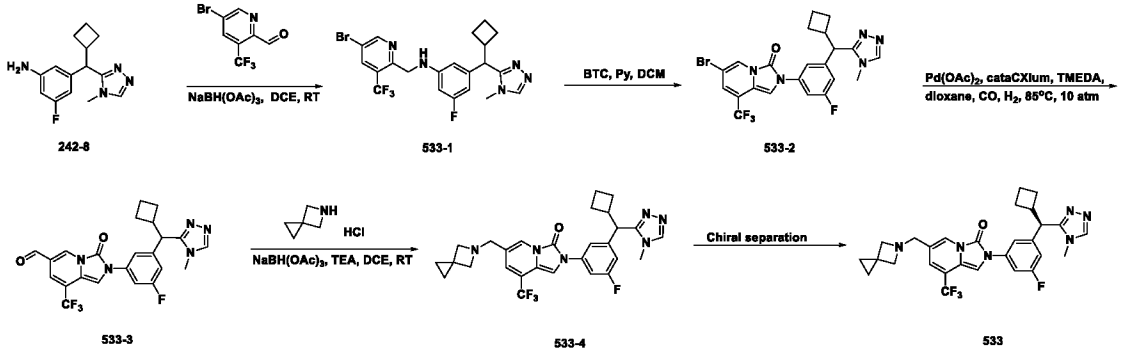
[1798] 531-2 (450 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 10 min; Wave Length: 220/254 nm; RT1(min): 7.03; RT2(min): 9.47; the second peak was product)

to afford 532 (190.5 mg, 42.33%) as a yellow solid.

LCMS-532:(ES, m/z): $[M+H]^+$ 510

NMR-532: (400 MHz, DMSO, ppm): δ 1.72-1.84 (m, 5H), 2.08-2.13 (m, 1H), 3.26-3.28 (m, 1H), 3.51 (s, 3H), 4.19 (s, 3H),4.43-4.46 (d, 1H), 6.29-6.33 (t, 1H), 7.12-7.14 (d, 1H), 7.48 (s, 1H), 7.74 (s, 1H), 7.81-7.82 (d, 1H), 8.06 (s, 1H), 8.22 (s, 1H), 8.37 (s, 1H).

Example 524. Synthesis of Compound 533



1. Synthesis of 533-1

[1799] To a stirred solution of 242-8 (1 g, 3.841 mmol, 1 equiv) in DCE (30 mL) was added 5-bromo-3-(trifluoromethyl)picolinaldehyde (1.17 g, 4.609 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. To the above mixture was added $NaBH(OAc)_3$ (1.63 g, 7.682 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 533-1 (1.1 g, 56.31%) as a white solid.

2. Synthesis of 533-2

[1800] To a stirred solution of 533-1 (1.1 g, 2.207 mmol, 1 equiv) and Pyridine (1.75 g, 22.070 mmol, 10 equiv) inDCM (30 mL) was added Triphosgene (0.26 g, 0.883 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 533-2 (950 mg, 77.98%) as an orange solid.

3. Synthesis of 533-3

[1801] To a solution of 533-2 (900 mg, 1.717 mmol, 1 equiv) and TMEDA (398.95 mg, 3.433 mmol, 2.00 equiv) in 1,4-dioxane (30 mL) were added bis(adamantan-1-

yl)(butyl)phosphane (123.09 mg, 0.343 mmol, 0.2 equiv) and $Pd(OAc)_2$ (38.54 mg, 0.172 mmol, 0.1 equiv) in a pressure tank. The mixture was purged with nitrogen for 3min and then was pressurized to 15atm with CO/H_2=1:1 at 85°C for overnight. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 533-3 (650 mg, 74.39%) as a yellow solid.

4. Synthesis of 533-4

[1802] To a stirred solution of 533-3 (630 mg, 1.331 mmol, 1 equiv) and 5-azaspiro[2.3]hexane hydrochloride (318.28 mg, 2.662 mmol, 2 equiv) in DCE (8 mL) were added TEA (269.32 mg, 2.662 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (564.06 mg, 2.662 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 533-4 (320 mg, 43.60%) as a yellow solid.

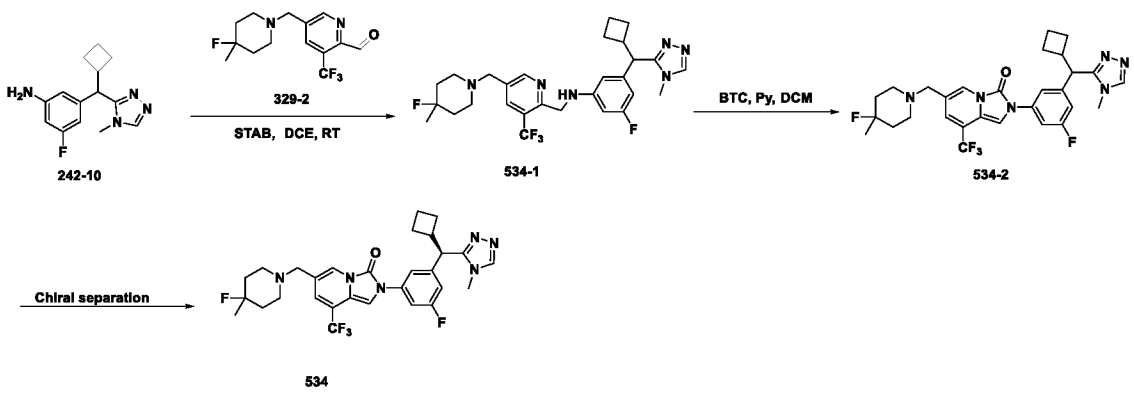
5. Synthesis of 533

[1803] The 533-4 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 6.67; RT2(min): 9.59; the second peak is product) to afford 533 (122.4 mg, 38.10%) as a yellow solid.

LC-MS-533: (ES, *m/z*): $[M+H]^+$ 541

H-NMR-533: (400 MHz, DMSO-d6, δ *ppm*): 0.50 (s, 4H), 1.67-1.82 (m, 5H), 2.04-2.08 (m, 1H), 3.18-3.24 (m, 1H), 3.24-29 (m, 4H), 3.46 (s, 5H), 4.30-4.33 (d, 1H), 7.02-7.05 (m, 2H), 7.41 (s, 1H), 7.68-7.71 (m, 3H), 8.35 (s, 1H).

Example 525. Synthesis of Compound 534



1. Synthesis of 534-1

[1804] A mixture of 329-2 (600 mg, 1.972 mmol, 1.2 equiv) and 242-10 (427.74 mg, 1.643 mmol, 1 equiv) in DCE (20 mL) was stirred overnight at room temperature. To the above mixture was added STAB (1044.76 mg, 4.930 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL).The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 534-1 (600 mg, 66.56%) as a white solid.

2. Synthesis of 534-2

[1805] To a stirred mixture of 534-1 (600 mg, 1.094 mmol, 1 equiv) and Pyridine (519.06 mg, 6.564 mmol, 6 equiv) in DCE (15 mL) was added Triphosgene (126.57 mg, 0.427 mmol, 0.39 equiv) at room temperature. The resulting mixture was stirred for 30min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 534-2 (320 mg, 50.92%) as a yellow solid.

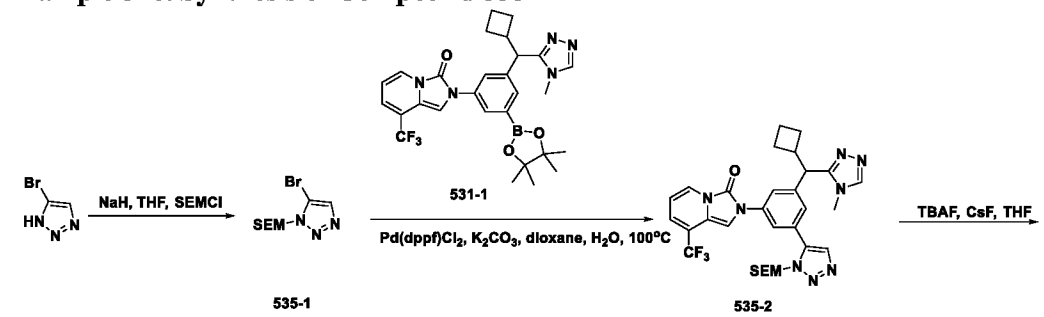
3. Synthesis of 534

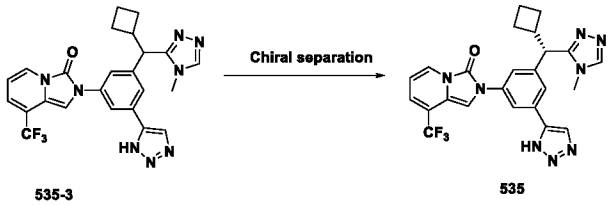
[1806] The 534-2 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 m; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.43; RT2(min): 8.34; the second peak is product) to afford 534 (117.5 mg, 39.17%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 558. H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.71-1.74 (m, 3H), 1.60-1.82 (m, 9H), 2.02-2.08 (m, 1H), 2.24-2.33 (m, 2H), 2.51-2.62 (m, 2H), 3.15-3.22 (m,

1H), 3.22(s, 2H), 3.46 (s, 3H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.41 (s, 1H), 7.68-7.71 (m, 3H), 8.35 (s, 1H).

Example 526. Synthesis of Compound 535





1. Synthesis of 535-1

[1807] To a stirred solution of 4-bromo-3H-1,2,3-triazole (1 g, 6.758 mmol, 1 equiv) in THF (20 mL) was added NaH (0.32 g, 8.110 mmol, 1.2 equiv, 60%) in three portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To the above mixture was added SEMCl (1.35 g, 8.110 mmol, 1.2 equiv) at 0 °C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH4Cl (aq.) (60 mL). The resulting mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH4HCO3), 115% to 70% gradient in 30 min; detector, UV 254 nm. This resulted in 535-1 (1.1 g, 58.50%) as a colorless oil.

[1808] 2. Synthesis of 535-2

To a stirred solution of 535-1 (1.01 g, 3.614 mmol, 2 equiv) and 531-1 (1 g, 1.807 mmol, 1.00 equiv) indioxane (20 mL) and H_2O (4 mL) were added K_2CO_3 (0.50 g, 3.614 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (0.13 g, 0.181 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100°C under nitrogen

atmosphere. The resulting mixture was diluted with water (60 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 535-2 (950 mg, 84.15%) as a yellow solid.

[1809] **3. Synthesis of 535-3**

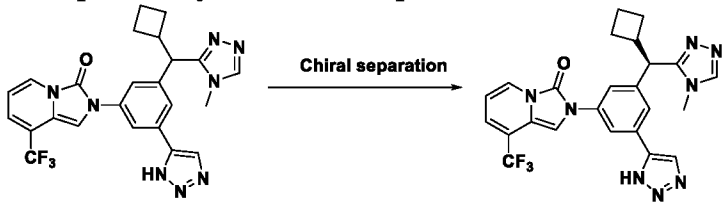
To a stirred solution of 535-2 (890 mg, 1.425 mmol, 1 equiv) in THF (10 mL) was added TBAF (2.85 mL, 2.850 mmol, 2 equiv, 1M) and CsF (432.80 mg, 2.850 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with EtOAc (30 mL). The resulting mixture was washed with 3x30 mL of water. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 5% to 75% gradient in 30 min; detector, UV 254 nm. This resulted in 535-3 as a yellow solid.

4. Synthesis of 535

[1810] 535-3 (410 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: MeOH(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 15 min; Wave Length: 220/254 nm; RT1(min): 7.65; RT2(min): 11.85; the first peak was product) to afford 535 (141.2 mg, 34.44%) as a yellow solid.

LCMS:(ES, m/z): $[M+H]^+$ 495. NMR: (400 MHz, DMSO, ppm): δ 1.71-1.83 (m, 5H), 2.08-2.13 (m, 1H), 3.21-3.27 (m, 1H), 3.48 (s, 3H), 4.33-4.36 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.12 (d, 1H), 7.43 (s, 1H), 7.73 (s, 1H), 7.79-7.81 (m, 2H), 8.12 (s, 1H), 8.31-8.64 (m, 2H), 15.09 (d, 1H).

Example 527. Synthesis of Compound 536



535-3 536

1. Synthesis of 536

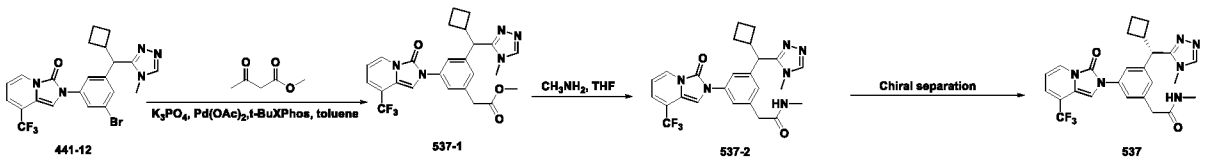
[1811] 535-3 (410 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: MeOH(0.5% 2M NH_3-MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 15 min; Wave Length: 220/254 nm; RT1(min): 7.65; RT2(min): 11.85; the second

peak was product) to afford 536 (137.6 mg, 33.56%) as a yellow solid

LCMS-536:(ES, m/z): $[M+H]^+$ 495

NMR-536: (400 MHz, DMSO, ppm): δ 1.71-1.83 (m, 5H), 2.08-2.13 (m, 1H), 3.27-3.30 (m, 1H), 3.48 (s, 3H), 4.33-4.36 (d, 1H), 6.29-6.32 (t, 1H), 7.11-7.13 (d, 1H), 7.44 (s, 1H), 7.73 - 7.81 (m, 3H), 8.12 (s, 1H), 8.31-8.65 (m, 2H), 15.09 (d, 1H).

Example 528. Synthesis of Compound 537



1. Synthesis of 537-1

[1812] Into a 100mL 3-necked round-bottom flask were added 441-12 (2 g, 3.950 mmol, 1 equiv), toluene (20 mL), methyl acetoacetate (1.38 g, 11.850 mmol, 3 equiv), K_3PO_4 (2.52 g, 11.850 mmol, 3 equiv), $Pd(OAc)_2$ (0.09 g, 0.395 mmol, 0.1 equiv) and t-BuXPhos (0.34 g, 0.790 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 5:1) to afford 537-1 (980 mg, 49.67%) as a yellow oil.

2. Synthesis of 537-2

[1813] Into a 20mL sealed tube were added 537-1 (800 mg, 1.602 mmol, 1 equiv) and CH_3NH_2 (1M in THF) (8 mL) at room temperature. The resulting mixture was stirred for 2 days at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 537-2 (220 mg, 27.55%) as a yellow oil.

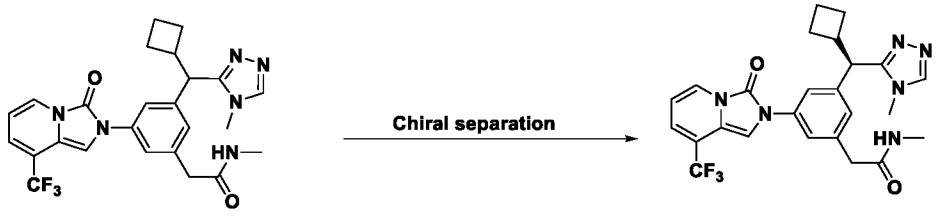
3. Synthesis of 537

[1814] The 537-2 (120 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 9 min; Wave Length: 220/254 nm; RT1(min): 6.78; RT2(min): 8.01;The first peak is product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.2 mL; Number of Runs: 10) to afford 537 (31.1 mg, 24.62%) as a yellow solid.

LC-MS-537: (ES, *m/z*): $[M+H]^+$ 499

H-NMR-537: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.64-1.65 (d, 1H), δ1.80 (s, 4H), δ2.05-2.09 (d, 1H), δ2.55-2.57 (d, 3H), δ3.16-3.26 (m, 1H), δ3.37-3.57 (m, 5H), δ4.22-4.24 (d, 1H), δ6.27-6.30 (t, 1H), δ7.01-7.23 (m, 2H), δ7.26 (s, 1H), δ7.57-7.64 (d, 2H), δ7.77-7.79 (d, 1H), δ7.88-7.97 (m, 1H), δ8.32 (s, 1H).

Example 529. Synthesis of Compound 538



537-2 537

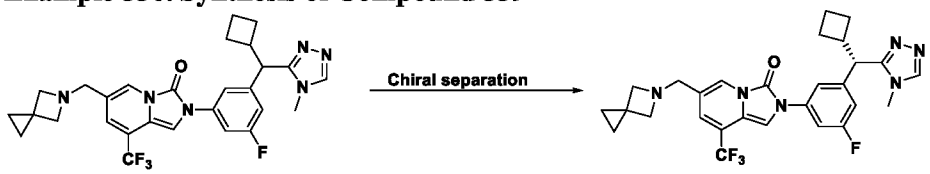
1. Synthesis of 538

[1815] The 537-2 (120 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 9 min; Wave Length: 220/254 nm; RT1(min): 6.78; RT2(min): 8.01; The second peak was the product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.2 mL; Number of Runs: 10) to afford 538 (31.8 mg, 25.18%) as a yellow solid.

LC-MS-538: (ES, *m/z*): $[M+H]^+$ 499

H-NMR-538: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.77-1.79 (d, 1H), δ1.80-1.86 (m, 4H), δ2.05-2.09 (d, 1H), δ2.55-2.57 (d, 3H), δ3.16-3.26 (m, 1H), δ3.37-3.43 (m, 5H), δ4.22-4.24 (d, 1H), δ6.27-6.30 (t, 1H), δ7.11-7.23 (m, 2H), δ7.25 (s, 1H), δ7.57-7.63 (d, 2H), δ7.77-7.79 (d, 1H), δ7.96-7.97 (m, 1H), δ8.32 (s, 1H).

Example 530. Synthesis of Compound 539



533-4 539

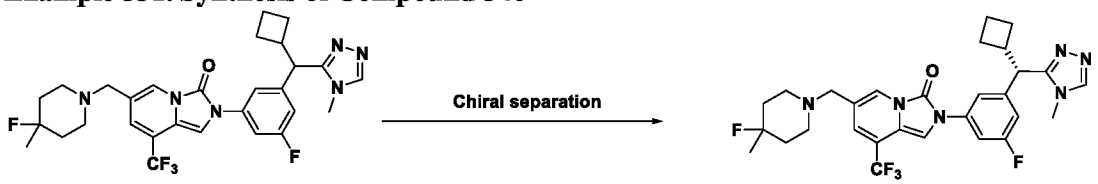
1. Synthesis of 539

[1816] The 533-4 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 13.5 min; Wave Length: 220/254 nm; RT1(min): 6.67; RT2(min): 9.59; the first peak is product) to afford 539 (130.3 mg, 40.07%) as a yellow solid.

LC-MS-539: (ES, *m/z*): $[M+H]^+$ 541

H-NMR-539: (400 MHz, DMSO-d6, δ *ppm*): 0.52 (s, 4H), 1.67-1.82 (m, 5H), 2.04-2.08 (m, 1H), 3.18-3.24 (m, 1H), 3.37 (s, 4H), 3.43 (s, 3H), 3.54-3.64 (m, 2H), 4.30-4.33 (d, 1H), 7.04-7.06 (m, 2H), 7.42 (s, 1H), 7.69-7.72 (m, 3H), 8.35 (s, 1H).

Example 531. Synthesis of Compound 540



534-2 540

1. Synthesis of 540

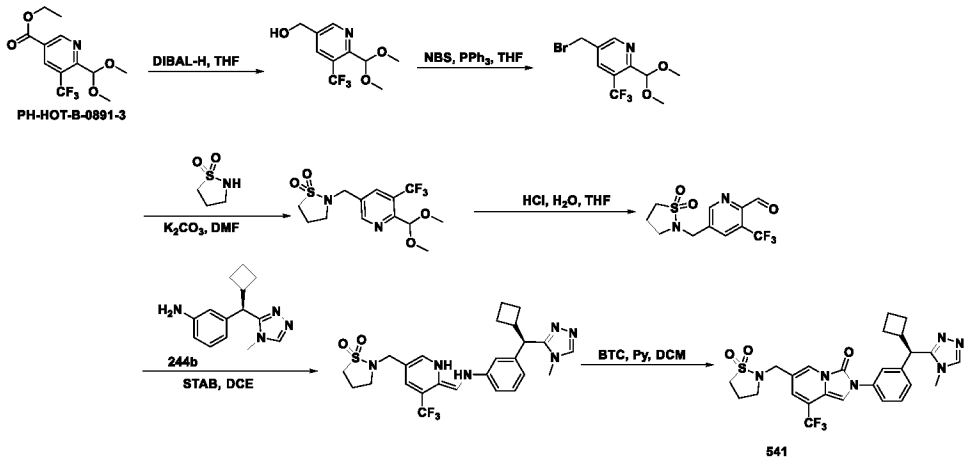
[1817] The 534-2 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 m; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.43; RT2(min): 8.34; the frist peak is product) to afford 540 (52.1 mg, 17.37%) as a yellow solid.

LC-MS-540: (ES, *m/z*): $[M+H]^+$ 559

H-NMR-540: (400 MHz, DMSO-d_6, δ *ppm*): 1.71-1.74 (m, 3H), 1.60-1.82 (m, 9H), 2.02-2.08 (m, 1H), 2.24-2.33 (m, 2H), 2.51-2.62 (m, 2H), 3.15-3.22 (m, 1H), 3.22(s, 2H), 3.46 (s, 3H), 4.30-4.33 (d, 1H), 7.03-7.06 (m, 2H), 7.42 (s, 1H), 7.68-7.71 (m, 3H), 8.35 (s, 1H).

Example 532. Synthesis of Compound 541

1. Synthesis of 541-1



541

[1818] Into a 1 L 3-necked round-bottom flask were added I-2 (25 g, 85.254 mmol, 1 equiv) and THF (250 mL) at 0°C. To the above mixture was added DIBAL-H (170.51 mL, 255.762

mmol, 3 equiv) dropwise over 5min at 0°C. The resulting mixture was stirred for additional 2h at room temperature. The reaction was quenched with sat. NH4Cl (aq.) (300 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 541-1(15.5 g, 68.76%) as a light brown oil.

2. Synthesis of 541-2

[1819] Into a 250 mL 3-necked round-bottom flask were added 541-1 (5 g, 19.904 mmol, 1 equiv), THF (100 mL) and PPh3 (10.44 g, 39.808 mmol, 2 equiv) at 0°C. To the above mixture was added NBS (7.09 g, 39.808 mmol, 2 equiv) in portions over 10 min at 0°C. The resulting mixture was stirred for additional 5h at room temperature. The reaction was quenched with water (15 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 541-2 (6.8 g, 97.89%) as a yellow oil.

3. Synthesis of 541-3

[1820] Into a 40 mL sealed tube were added 541-2 (500 mg, 1.592 mmol, 1 equiv), DMF (5 mL), 1lambda6,2-thiazolidine-1,1-dione (482.13 mg, 3.980 mmol, 2.5 equiv) and K2CO3 (660.00 mg, 4.776 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with water (40 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford 541-3 (510 mg, 85.90%) as a light yellow oil.

4. Synthesis of 541-4

[1821] Into an 8 mL sealed tube were added 541-3 (450 mg, 1.270 mmol, 1 equiv), (1 M) HCl (5 mL) and THF (2 mL) at room temperature. The resulting mixture was stirred for 2h at 80°C. The mixture was basified to pH 7 with saturated NaHCO3 (aq.) (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 50:1) to afford 541-4 (410 mg, 99.49%) as a light yellow oil.

5. Synthesis of 541-5

[1822] Into a 20 mL sealed tube were added 541-4 (400 mg, 1.298 mmol, 1 equiv), DCE (5 mL), PH-244b (399.32 mg, 1.648 mmol, 1.27 equiv) and STAB (599.49 mg, 2.830 mmol,

2.18 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 541-5 (300 mg, 38.35%) as a light yellow oil.

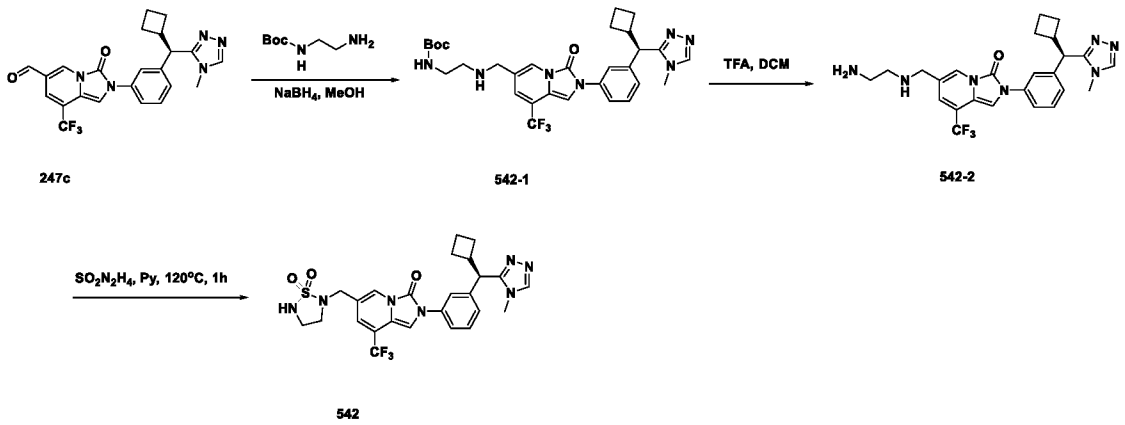
6. Synthesis of 541-0

[1823] Into a 40 mL sealed tube were added 541-5 (300 mg, 0.561 mmol, 1 equiv), pyridine (266.33 mg, 3.366 mmol, 6 equiv) and DCM (10 mL) at 0°C. To the above mixture was added triphosgene (66.61 mg, 0.224 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for additional 5min at 0°C. The mixture was basified to pH 7 with saturated NaHCO3 (aq.) (10 mL). The resulting mixture was extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 44% B in 8 min; Wave Length: 254 nm; RT1(min): 7.7) to afford 541 (50.9 mg, 16.15%) as a light yellow solid.

LCMS137-541: (ES, m/z): [M+H] + 561

H-NMR17-541: (300 MHz, DMSO-d6, ppm): δ1.70-1.81 (m, 5H), δ2.08-2.09 (m, 1H), δ2.20-2.27 (m, 2H), δ3.16-3.28 (m, 5H), δ3.31-3.43 (m, 3H), δ3.96 (s, 2H), δ4.25-4.28 (m, 2H), δ6.97 (s, 1H), δ7.19-7.21 (m, 1H), δ7.36 (s, 1H), δ7.42-7.46 (m, 1H), δ7.69-7.73 (m, 2H), δ7.84 (s, 1H), δ8.33 (s, 1H).

Example 533. Synthesis of Compound 542



1. Synthesis of 542-1

[1824] A solution of 247c (3.5 g, 7.685 mmol, 1 equiv) in MeOH (35 mL) was treated with tert-butyl N-(2-aminoethyl) carbamate (6.16 g, 38.425 mmol, 5 equiv) for overnight at room temperature followed by the addition of $NaBH_4$ (0.87 g, 23.055 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (50mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 542-1 (1.15 g, 22.96%) as a yellow oil.

2. Synthesis of 542-2

[1825] Into a 80mL sealed tube were added 542-1(1.15 g, 1.918 mmol, 1 equiv), TFA (3 mL) and DCM (9 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 542-2 (520 mg, 50.48%) as a yellow oil.

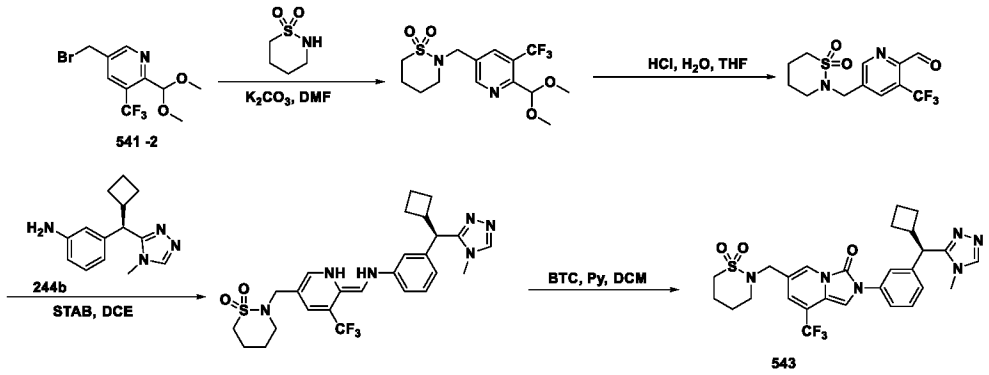
3. Synthesis of 542

[1826] Into a 40mL sealed tube were added 542-2 (440 mg, 0.881 mmol, 1 equiv), sulfamide (101.57 mg, 1.057 mmol, 1.2 equiv) and pyridine (5 mL) at room temperature. The resulting mixture was stirred for 1 h at 120°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford the crude product (80 mg).The crude product (80mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 45% B in 8 min; Wave Length: 254 nm; RT1(min): 8.12) to afford 542-0(26 mg, 5.24%) as a yellow solid.

LC-MS-542: (ES, *m/z*): $[M+H]^+$ 562

H-NMR-542: (400 MHz, $CDCl_3$, *ppm*): δ 1.83-1.86 (m, 1H), δ1.90-1.93 (m, 2H), δ1.94-1.96 (d, 2H), δ2.32-2.39 (m, 1H), δ3.34-3.42 (m, 3H), δ3.48 (s, 3H), δ3.56-3.58 (m, 2H), δ3.94-4.02 (m, 3H), δ4.71 (s, 1H), δ6.81 (s, 1H), δ6.94 (s, 1H), δ7.20-7.22 (d, 1H), δ7.28 (s, 1H), δ7.42-7.46 (m, 1H), δ7.54-7.60(s, 1H), δ7.71 (s, 1H), δ8.20 (s, 1H).

Example 534. Synthesis of Compound 543



1. Synthesis of 543-1

[1827] Into a 40 mL sealed tube were added 541-2 (500 mg, 1.592 mmol, 1 equiv), DMF (5 mL), 1,2-thiazinane 1,1-dioxide (537.96 mg, 3.980 mmol, 2.5 equiv) and K_2CO_3 (660.00 mg, 4.776 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 543-1(520 mg, 84.24%) as a light yellow oil.

2. Synthesis of 543-2

[1828] Into a 20 mL sealed tube were added 543-1 (500 mg, 1.357 mmol, 1 equiv), (1 M) HCl (5 mL) and THF (2 mL) at room temperature. The resulting mixture was stirred for 2h at 80°C. The mixture was basified to pH 7 with saturated $NaHCO_3$ (aq.) (20 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 50:1) to afford 543-2(420 mg, 91.21%) as a light yellow oil.

3. Synthesis of 543-3

[1829] Into a 20 mL sealed tube were added 543-3 (400 mg, 1.298 mmol, 1 equiv), DCE (5 mL), PH-244b (399.32 mg, 1.648 mmol, 1.27 equiv) and STAB (599.49 mg, 2.830 mmol, 2.18 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with water (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 543-4 (200 mg, 38.35%) as a light yellow oil.

4. Synthesis of 543

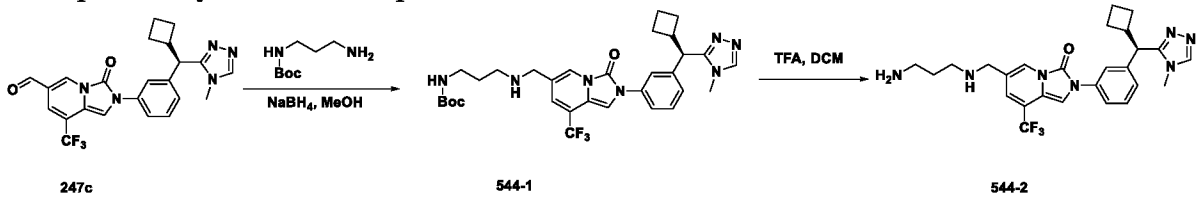
[1830] Into a 20 mL sealed tube were added 543-4 (200 mg, 0.365 mmol, 1 equiv), pyridine

(173.01 mg, 2.190 mmol, 6 equiv) and DCM (6 mL) at 0°C. To the above mixture was added triphosgene (43.27 mg, 0.146 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for additional 5min at 0°C. The mixture was basified to pH 7 with saturated $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 52% B in 8 min; Wave Length: 220 nm; RT1(min): 7.52) to afford 543 (53.1 mg, 25.27%) as a light yellow solid.

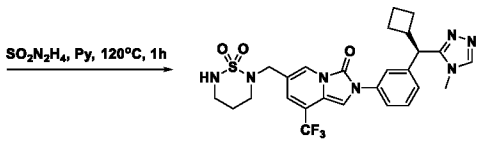
LCMS137-543: (ES, m/z): $[M+H]^+$ 575

H-NMR17-543: (300 MHz, DMSO-d6, *ppm*): δ1.68-1.70 (m, 2H), δ1.70-1.81 (m, 5H), δ2.01-2.09 (m, 3H), δ3.16-3.31 (m, 5H), δ3.43 (s, 3H), δ4.10 (s, 2H), δ4.25-4.28 (m, 1H), δ6.92 (s, 1H), δ7.19-7.21 (m, 1H), δ7.37 (s, 1H), δ7.43-7.46 (m, 1H), δ7.69-7.73 (m, 2H), δ7.85 (s, 1H), δ8.33 (s, 1H).

Example 535. Synthesis of Compound 544



247c 544-1 544-2



544

1. Synthesis of 544-1

[1831] A solution of 247c (3 g, 6.587 mmol, 1 equiv) in MeOH (30 mL) was treated with tert-butyl N-(3-aminopropyl) carbamate (5.74 g, 32.935 mmol, 5 equiv) for overnight at room temperature followed by the addition of $NaBH_4$ (0.75 g, 19.761 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (50mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1) (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 544-1 (1.05 g, 23.90%) as a yellow oil.

2. Synthesis of 544-2

[1832] Into a 80mL sealed tube were added 544-1 (1.05 g, 1.711 mmol, 1 equiv) TFA (3 mL) and DCM (9 mL) at room temperature. The resulting mixture was stirred for 4h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 544-2 (550 mg, 58.21%) as a yellow oil.

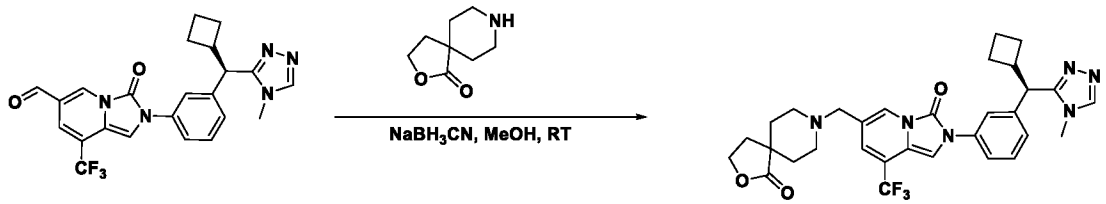
3. Synthesis of 544

[1833] Into a 40mL sealed tube were added 544-2 (550 mg, 1.071 mmol, 1 equiv), sulfamide (123.50 mg, 1.285 mmol, 1.2 equiv) and pyridine (5 mL) at room temperature. The resulting mixture was stirred for 1h at 120°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford the crude product (100 mg).The crude product (100mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 54% B in 8 min; Wave Length: 220 nm; RT1(min): 7.07) to afford 544 (38.1 mg, 6.16%) as a yellow solid.

LC-MS-544: (ES, *m/z*): $[M+H]^+$ 576

H-NMR-544: (400 MHz, $CDCl_3$, *ppm*): δ 1.71-1.86 (m, 5H), δ1.90-1.96 (m, 2H), δ2.32-2.39 (m, 1H), δ3.29-3.32 (m, 2H), δ3.34-3.38 (m, 1H), δ3.40-3.49 (m, 3H), δ3.53-3.58 (d, 2H), δ4.00-4.04 (m, 3H), δ4.41 (s, 1H), δ6.80 (s, 1H), δ6.92 (s, 1H), δ7.20-7.22 (d, 1H), δ7.28 (s, 1H), δ7.42-7.46 (m, 1H), δ7.54-7.56(d, 1H), δ7.60-7.65 (d, 1H), δ7.60 (s, 1H).

Example 536. Synthesis of Compound 545



247c 545

1. Synthesis of 545

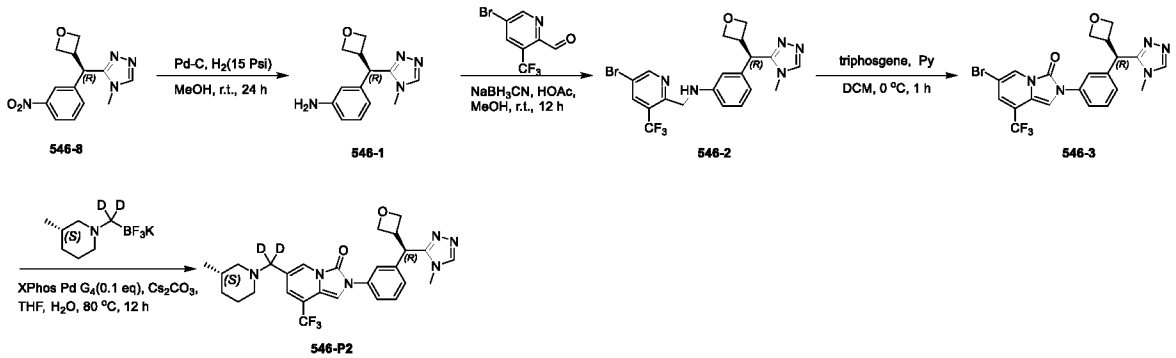
[1834] To a stirred solution of 247c (1000 mg, 2.196 mmol, 1 equiv) and 2-oxa-8-azaspiro[4.5]decan-1-one (681.52 mg, 4.392 mmol, 2 equiv) in MeOH (20 mL) were added $NaBH_3CN$ (275.96 mg, 4.392 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (50 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x30

mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 30% to 60% gradient in 20 min; detector, UV 254 nm. This resulted in 545 (42.6 mg, 6.26%) as a yellow solid.

LC-MS-545: (ES, *m/z*): $[M+H]^+$ 595

H-NMR-545: (400 MHz, DMSO-d6, δ *ppm*): 1.60-1.70 (m, 2H), 1.70-1.81 (m, 7H), 2.09-2.33 (m, 5H), 2.77-2.80 (m, 2H), 3.19-3.21 (m, 1H), 3.21-3.27 (m, 2H), 3.63 (s, 3H), 4.25-4.28 (m, 3H), 7.03 (s, 1H), 7.19-7.20 (m, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.70 (m, 1H), 7.70-7.73 (m, 1H), 8.33 (s, 1H).

Example 537. Synthesis of Compound 546



1. Synthesis of 546-1

[1835] To a solution of 546-8 (320 mg, 1.17 mmol, 1 equiv) in EtOAc (10 mL) was added Pd/C (50 mg, 10% purity) at 25°C. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25°C for 24 h. The mixture was filtered and washed with MeOH (100 mL) and THF (100 mL). The filtrate was concentrated in vacuum to get 546-1 (320 mg, crude) as a light yellow oil.

2. Synthesis of 546-2

[1836] To a solution of 546-1 (340 mg, 1.39 mmol, 1 equiv) in MeOH (5 mL) was added 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (353 mg, 1.39 mmol, 1 equiv), AcOH (83.5 mg, 1.39 mmol, 1 equiv) at 25 °C and stirred for 1 h. $NaBH_3CN$ (174 mg, 2.78 mmol, 2 equiv) was added and stirred for 11 h. The mixture was poured into H_2O (50 mL) at 0°C, extracted with EtOAc (80 mL x3). The combined organic layer was washed by brine (50 mL x3), dried by Na_2SO_4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO_2) with petroleum ether/EtOAc=3:1 to 0:1, then with DCM:MeOH=1:0 to 0:1 to give 546-2 (450 mg, 66%) as a light yellow solid.

3. Synthesis of 546-3

[1837] To a solution of 546-2 (200 mg, 414 umol, 1 equiv) in DCM (10 mL) was added Py (196 mg, 2.49 mmol, 6 equiv), bis(trichloromethyl) carbonate (62 mg, 208 umol, 0.5 equiv) at 0°C and stirred for 1 h. The reaction mixture was diluted with Sat.$NaHCO_3$ (50 mL), extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to get a residue. The combined residue was purified by column (SiO_2) with petroleum ether/EtOAc=3:1 to 0:1, then with DCM:MeOH=1:0 to 0:1 to afford 546-3 (190 mg, 90%) as a light yellow solid.

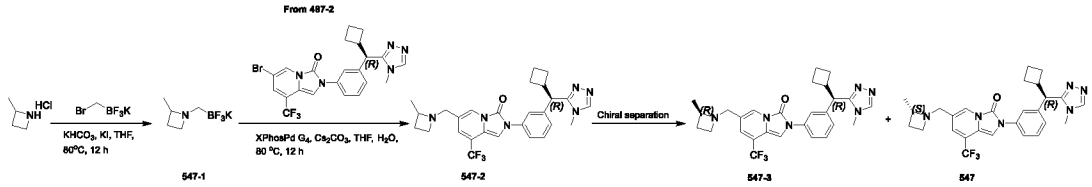
4. Synthesis of 546

[1838] To a solution of 546-3 (390 mg, 767 umol, 1 equiv) in THF (6 mL), H_2O (1.5 mL) was added [dideuterio-[(3S)-3-methyl-1-piperidyl]methyl]-trifluoro-boron;potassium hydride (339 mg, 1.53 mmol, 2 equiv), Cs_2CO_3 (749 mg, 2.30 mmol, 3 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)-phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (66.02 mg, 76.73 umol, 0.1 *eq*) under N_2. The suspension was degassed and purged with N_2 for 3 times. The mixture was heated to 80 °C and stirred for 12 h under N_2. The same scale reaction was conducted with in parallel for 2 batches in total and work up with a small test scale (50 mg) together. The mixture was poured into H_2O (20 mL), extracted with DCM/MeOH (10:1, 20 mLx3). The combined organic layers were washed with brine (20 mL x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2) with petroleum ether/EtOAc = 1:1 to 0:1, then with DCM:MeOH=1:0 to 3:1 to get a crude product. The crude product was further purified by prep-HPLC (FA) (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 1%-40%, 8min, Wave Length: 220 nm; RT (min): 7.0 min) to get 546 (124.4 mg) as a light yellow solid.

MS-546: (ES, m/z): $[M+H]^+$ 543.1

^{1}H-NMR-546: (400 MHz, MeOD) δ 8.39 (d, *J* = 4.8Hz, 2H), 7.86 (s, 1H), 7.69-7.65 (m, 2H), 7.53 (t, *J*= 7.6 Hz, 1H), 7.30-7.28 (m, 1H), 7.20 (m, 1H), 7.12 (s, 1H), 4.95-4.92 (m, 1H), 4.83-4.81 (m, 1H), 4.67-4.61 (m, 2H), 4.43-4.40 (m, 1H), 4.01-3.97 (m, 1H), 3.50 (s, 3H), 3.26-3.20 (m, 2H), 2.56-2.53 (m, 1H), 2.28-2.23 (m, 1H), 1.89-1.67 (m, 4H), 1.15-1.11 (m, 1H), 0.97-0.95 (m, 3H).

Example 538. Synthesis of Compound 547



1. Synthesis of 547-1

[1839] To a solution of 2-methylazetidine (0.5 g, 4.65 mmol, 1 equiv, HCl) in THF (5 mL) was added bromomethyl(trifluoro)boron;potassium hydride (933 mg, 4.65 mmol, 1 equiv), KI (77 mg, 464.76 umol, 0.1 equiv), KHCO3 (93 mg, 9.30 mmol, 2 equiv). The mixture was heated to 80°C and stirred at 80°C for 12 hr. The mixture was concentrated under reduced pressure to give a crude. Then the crude was triturated with acetone (50 mL) at 50oC for 2 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 547-1 (0.7 g, crude) as a light yellow solid.

2. Synthesis of 547-2

[1840] To a solution of 487-2 (400 mg, 790.02 umol, 1 equiv) in THF (6 mL) and H2O (1.5 mL) was added 547-1 (302 mg, 1.58 mmol, 2 equiv), dicesium;carbonate (772 mg, 2.37 mmol, 3 equiv), XPhosPd G4 (68 mg, 79.00 umol, 0.1 equiv). The suspension was degassed and purged with N2 for 3 times. Then the mixture was heated to 80 °C and stirred at 80 °C for 12 hr under N2 atmosphere. The reaction mixture was poured into water (20 mL), extracted with EtOAc (10 mL x3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=10/1 to 0/1) and (DCM: Methanol=100/1 to 0/1) to afford 547-2 (0.39 g, 96.53%) as a brown solid.

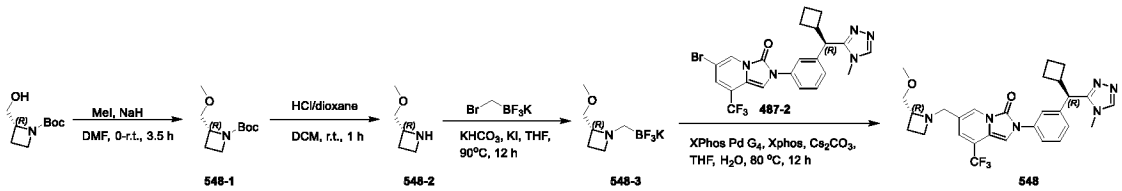
3. Synthesis of 547

[1841] 547-2 (390 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALPAK IC (250mm*30mm,10um); mobile phase: [MeOH (0.1%IPAm)]; B%: 66%-66%, 30min. Flow rate: 4mL/min; Wave Length: 220/254 nm; RT2 (min): 2.342) to afford 547 (77 mg, 19.74%) as a yellow solid.

MS-547: (ES, m/z): [M+H]+ 511.3.

1H-NMR-547: (400 MHz, CDCl3) δ 8.02 (s, 1H), 7.62-7.60 (m, 2H), 7.55-7.53 (m, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.17-7.15 (m, 1H), 6.96 (s, 1H), 6.75 (s, 1H), 3.98-3.95 (m, 1H), 3.49-3.35 (m, 6H), 3.25(s, 2H), 2.81-2.78 (m, 1H), 2.38-2.31 (m, 1H), 2.10-2.09 (m, 1H), 1.95-1.69 (m, 5H), 1.26 (s, 1H), 1.16-1.15 (m, 3H).

Example 539. Synthesis of Compound 548



1. Synthesis of 548-1

[1842] To a solution of NaH (468 mg, 11.7 mmol, 60% purity, 1.22 equiv) in DMF (20 mL) was cooled to 0 °C under nitrogen atmosphere. Then a solution of tert-butyl (2R)-2-(hydroxymethyl)azetidine-1-carboxylate (1.8 g, 9.61 mmol, 1 equiv) in DMF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. Then MeI (900 uL, 14.46 mmol, 1.5 equiv) was added at 0 °C. The mixture was stirred at 20 °C for 3 h under nitrogen atmosphere. The mixture was quenched by saturated NH4Cl (300 mL) and extracted with EtOAc (100 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (10:1) to afford 548-1 (1.8 g, 93%) as a colorless oil.

1H-NMR-548-1: (400 MHz, CHLOROFORM-d) δ 4.29-4.18 (m, 1H), 3.79-3.70 (m, 2H), 3.63-3.55 (m, 1H), 3.50-3.44 (m, 1H), 3.34 (s, 3H), 2.20-2.03 (m, 2H), 1.37 (s, 9H)

2. Synthesis of 548-2

[1843] To a solution of 548-1 (1.2 g, 5.96 mmol, 1 equiv) in DCM (12 mL) was added HCl/dioxane (4 M, 8.94 mL, 6 equiv). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under N2 (20 °C) to afford 548-2 (603 mg, crude) as a yellow oil.

3. Synthesis of 548-3

[1844] A mixture of 548-2 (603 mg, 5.96 mmol, 1 equiv), potassium;bromomethyl(trifluoro) boranuide (1.2 g, 5.96 mmol, 1 equiv), KHCO3 (1.19 g, 11.9 mmol, 2 equiv) and KI (98.9 mg, 596 umol, 0.1 equiv) in THF (10 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was triturated with acetone (50 ml) at 35oC for 30 min. Then the mixture was filtered, and the filtrate was concentrated under reduced pressure to afford 548-3 (1 g, crude) as a white solid.

4. Synthesis of 548

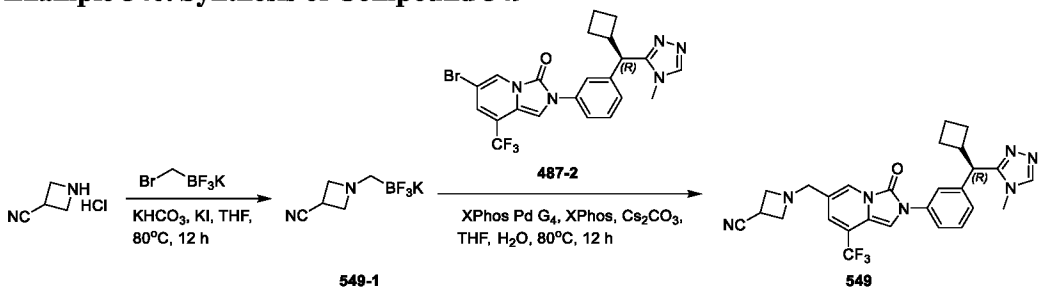
[1845] To a solution of 487-2 (300 mg, 592 umol, 1 equiv) and 548-3 (655 mg, 2.96 mmol, 5 equiv) in THF (8 mL) and H2O (2 mL) was added XPhos (28.2 mg, 59.2 umol, 0.1 equiv), Cs2CO3 (579 mg, 1.78 mmol, 3 equiv) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (50.98 mg, 59.25 umol, 0.1 equiv). The mixture

was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was extracted with water (120 mL) and EtOAc (40 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The crude product (100 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 5% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5) to afford 548 (39.5 mg, 39.29%) as a yellow solid.

MS-548: (ES, m/z): [M+H]+ 541.3

1H-NMR-548: (400 MHz, METHANOL-d4) δ 8.36 (s, 1H), 7.71-7.59 (m, 3H), 7.48 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 12.8 Hz, 2H), 4.28 (d, J = 10.8 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.55-3.48 (m, 4H), 3.44 (d, J = 4.4 Hz, 1H), 3.42-3.39 (m, 1H), 3.37-3.33 (m, 2H), 3.28 (s, 3H), 3.07-2.99 (m, 1H), 2.29-2.19 (m, 1H), 2.15-1.81 (m, 7H), 1.80-1.71 (m, 1H), 1.36-1.20 (m, 0.4H).

Example 540. Synthesis of Compound 549



1. Synthesis of 549-1

[1846] To a solution of azetidine-3-carbonitrile;hydrochloride (1 g, 8.43 mmol, 1 equiv) and bromomethyl(trifluoro)boron;potassium hydride (1.69 g, 8.43 mmol, 1 equiv) in THF (10 mL) was added KHCO3 (1.69 g, 16.8 mmol, 2 equiv) and KI (140. mg, 843 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure to give a residue. Then the residue was triturated with acetone at 35 °C for 2 h and filtered and filtrate was concentrated under reduced pressure to afford 549-1 (460 mg, crude) as a white solid.

2. Synthesis of 549

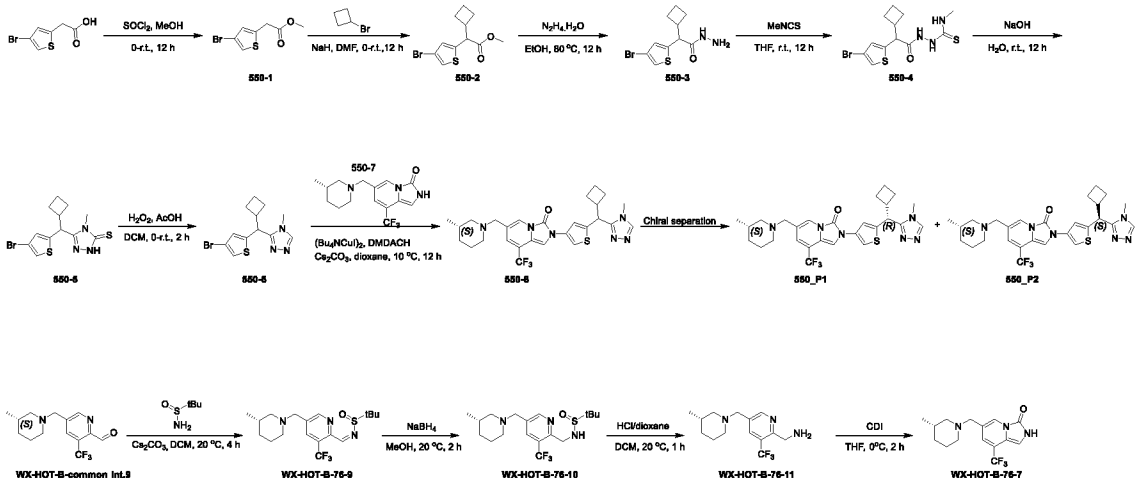
[1847] To a solution of 549-1 (399 mg, 1.98 mmol, 4 equiv) and 487-2 (250 mg, 493 umol, 1 equiv) in THF (16 mL) and H2O (4 mL) was addded XPhos (23.5 mg, 49.4 umol, 0.1 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-

(methylamino)phenyl] phenyl]palladium(1+) (42.5 mg, 49.4 umol, 0.1 equiv) and Cs2CO3 (482.6 mg, 1.48 mmol, 3 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was extracted with NaHCO3 (90mL) and EtOAc (30 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (10:1) to give a crude product. The crude product (225 mg) was purified by prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 5% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5) to afford 549 (37.3 mg, 14.19%) as a yellow solid.

MS-549: (ES, m/z): [M+H]+ 522.2

1H-NMR-549: (400 MHz, METHANOL-d4) δ 8.36 (s, 1H), 7.68 (s, 1H), 7.65-7.61 (m, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.10 (s, 1H), 7.01 (s, 1H), 4.28 (d, J = 10.8 Hz, 1H), 3.63-3.58 (m, 2H), 3.54 (s, 3H), 3.47-3.41 (m, 5H), 2.28-2.21 (m, 1H), 1.97-1.84 (m, 5H), 1.79-1.73 (m, 1H).

Example 541. Synthesis of Compound 550_P1&P2



1. Synthesis of 550-1

[1848] To a solution of 2-(4-bromo-2-thienyl)acetic acid (9 g, 40.7 mmol, 1 equiv) in MeOH (120 mL) was added SOCl2 (14.7 mL, 203 mmol, 5 equiv) at 0 °C, the mixture was stirred at 25 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc/PE (5:1) to afford 550-1 (8.8 g, 92%) as a red oil.

1H-NMR-550-1: (400 MHz, CHLOROFORM-d) δ 7.04 (d, J = 1.6 Hz, 1H), 6.80 (s, 1H), 3.72 (s, 2H), 3.66 (s, 3H)

2. Synthesis of 550-2

[1849] To a solution of NaH (1.68 g, 42.1 mmol, 60% purity, 1.1 equiv) in DMF (90 mL) was added 550-1 (9 g, 38.2 mmol, 1 equiv). The mixture was cooled to 0 °C, then bromocyclobutane (10.8 mL, 114 mmol, 3 equiv) was added to the mixture at 0 °C. The result mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. The reaction mixture was diluted with Sat. NH4Cl (100 mL), extracted with EtOAc (2x 80 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with EtOAc/PE (5:1) to afford 550-2 (8.4 g, 76%) as a yellow oil.

1H-NMR-550-2: (400 MHz, CHLOROFORM-d) δ 7.02 (d, J = 1.6 Hz, 1H), 6.77 (d, J = 0.8 Hz, 1H), 3.73-3.69 (m, 1H), 3.62 (s, 3H), 2.88-2.72 (m, 1H), 2.12-2.00 (m, 1H), 1.97-1.87 (m, 1H), 1.81-1.70 (m, 3H), 1.66-1.57 (m, 1H)

3. Synthesis of 550-3

[1850] To a solution of 550-2 (2 g, 6.92 mmol, 1 equiv) in EtOH (20 mL) was added N2H4.H2O (10.3 mL, 207 mmol, 98% purity, 30 equiv), the mixture was stirred at 80 °C for 12 hr. The reaction mixture was concentrate in vacuum to remove EtOH (20 mL). Then the mixture was diluted with water (20 mL), and extracted with CH2Cl2 (20 mL x3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue to afford 550-3 (1.6 g, crude) as a white solid.

4. Synthesis of 550-4

[1851] To a solution of 550-3 (1.6 g, 5.53 mmol, 1 equiv) in THF (20 mL) was added methylimino (thioxo)methane (756 uL, 11.0 mmol, 2 equiv). The mixture was stirred at 25 °C for 4 hr. The reaction mixture was diluted with water (15 mL), extracted with EtOAc (15 mL x3). The mixture was filtered and the filter cake was concentrated in vacuum to afford 550-4 (1 g, 50%) as a white solid.

1H-NMR-550-4: (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 9.32 (s, 1H), 7.69 (s, 1H), 7.50 (d, J = 1.6 Hz, 1H), 6.97 (d, J = 1.2 Hz, 1H), 3.77 (d, J = 10.4 Hz, 1H), 2.86 (d, J = 4.0 Hz, 3H), 2.74-2.64 (m, 1H), 1.98-1.89 (m, 2H), 1.87-1.80 (m, 1H), 1.79-1.73 (m, 2H), 1.72-1.66 (m, 1H)

5. Synthesis of 550-5

[1852] To a solution of NaOH (883 mg, 22.1 mmol, 8 equiv) in H2O (5.3 mL) was added 550-4 (1 g, 2.76 mmol, 1 equiv). The mixture was stirred at 25 °C for 2 hr. The reaction

mixture was diluted with water (10 mL), adjusted pH to 3 by 1N HCl. The mixture was filtered and the filter cake was concentrated in vacuum to afford 550-5 (900 mg, 95%) as a white solid.

6. Synthesis of 550-6

[1853] A solution of 550-5 (0.9 g, 2.61 mmol, 1 equiv) in DCM (30 mL) was cooled to 0 °C. Then a solution of H2O2 (1.00 mL, 10.46 mmol, 30% purity, 4 equiv) in AcOH (1.2 mL, 20.9 mmol, 8 equiv) was added to the mixture at 0 °C. The result mixture was stirred at 25 °C for 2 hr. The solvent was removed under reduced pressure, and then diluted with water (30 mL) and adjusted pH to 12 by 2N NaOH. The mixture was then extracted with CH2Cl2 (25 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 550-6 (800 mg, crude) as a yellow oil.

1H-NMR-550-6: (400 MHz, METHANOL-d4) δ 8.38 (s, 1H), 7.30 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 0.8 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 3.59 (s, 3H), 3.28-3.17 (m, 1H), 2.21-2.12 (m, 1H), 2.08-2.02 (m, 1H), 1.97-1.84 (m, 4H)

7. Synthesis of 550-9

[1854] To a solution of I-2 (6 g, 20.96 mmol, 1 equiv) in DCM (80 mL) was added 2-methylpropane-2-sulfinamide (2.54 g, 20.96 mmol, 1 equiv), Cs2CO3 (13.66 g, 41.92 mmol, 2 equiv). The mixture was stirred at 20 °C for 4 h. The reaction mixture was poured into water (60 mL), extracted with CH2Cl2 (20 ml x3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na2SO4, filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (10:1) to afford 550-9 (6 g, 73.51%) as a yellow oil.

1H-NMR-550-9: (400 MHz, CHLOROFORM-d) δ 8.96-8.95 (m, 1H), 8.87 (s, 1H), 8.09 (s, 1H), 3.59 (s, 2H), 2.77-2.70 (m, 2H), 2.01-1.95 (m, 1H), 1.73-1.56 (m, 5H), 1.30 (s, 9H), 0.94-0.85 (m, 4H).

8. Synthesis of 550-10

[1855] To a solution of 550-9 (3 g, 7.70 mmol, 1 equiv) in MeOH (40 mL) was added NaBH4 (1.55 g, 40.9 mmol, 5.32 equiv). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into water (100 ml), extracted with EtOAc (50 mL x3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (5:1) to afford 550-10 (2.8 g, 92.8%) as a yellow oil.

1H-NMR: (400 MHz, CHLOROFORM-d) δ 8.63 (s, 1H), 7.93 (s, 1H), 5.04 (t, J = 5.2 Hz, 1H), 4.57 (d, J = 5.2 Hz, 2H), 3.51 (s, 2H), 2.75-2.69 (m, 2H), 1.95-1.90 (m, 1H), 1.72-1.60 (m, 4H), 1.27 (s, 9H), 0.92-0.84 (m, 4H).

9. Synthesis of 550-11

To a solution of 550-10 (5.3 g, 13.5 mmol, 1 equiv) in DCM (60 mL) was added HCl/dioxane (4 M, 16.9 mL, 5 equiv). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue and adjusted pH=8 with ion resin. The mixture was filtered and filtrated concentrated in vacuum to afford 550-11 (3.9 g, crude) as a red oil.

1H-NMR: (400 MHz, METHANOL-d4) δ 8.76 (s, 1H), 8.13 (s, 1H), 4.26 (s, 2H), 3.62 (s, 2H), 2.79-2.76 (m, 2H), 2.02-1.95 (m, 1H), 1.75-1.57 (m, 5H), 0.93-0.85 (m, 4H).

10. Synthesis of 550-7

[1856] To a solution of 550-11 (3.9 g, 13.5 mmol, 1 equiv) in THF (40 mL) was added CDI (2.2 g, 13.5 mmol, 1 equiv) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into water (60 mL), extracted with EtOAc (30 mL x3). The combined organic layer was washed with brine (80 ml), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (5:1) to afford 550-7 (2.7 g, 63.5%) as a yellow solid.

1H-NMR 8: (400 MHz, METHANOL-d4) δ 7.59 (s, 1H), 7.01 (s, 1H), 6.68 (s, 1H), 3.29 (s, 2H), 2.87-2.80 (m, 2H), 1.97-1.90 (m, 1H), 1.74-1.53 (m, 5H), 0.96-0.86 (m, 4H).

11. Synthesis of 550-8

[1857] To a solution of 550-7 (188 mg, 599 umol, 1.1 equiv) in dioxane (10 mL) was added 550-6 (170 mg, 545 umol, 1 equiv), Cs2CO3 (355 mg, 1.09 mmol, 2 equiv), iodocopper; tetrabutylammonium;diiodide (61 mg, 54.45 umol, 0.1 equiv), N1,N2-dimethylcyclohexane-1,2-diamine (15.49 mg, 108.89 umol, 0.2 equiv) in glove box. The mixture was heated to 110°C and stirred for 12 h at 110°C. The same scale reaction was conducted with in parallel for 2 batches in total and work up together. The mixture was washed with NaHCO3 (20 mL) and extracted with DCM (10 mL x3). The combined organic layer was washed with brine (40 mL) and dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH2Cl2/MeOH (10:1) to afford 550-8 (350 mg, 59.02%) as a yellow solid.

12. Synthesis of 550_P1&P2

[1858] 550-8 (350 mg) was purified by Chiral separation with the following

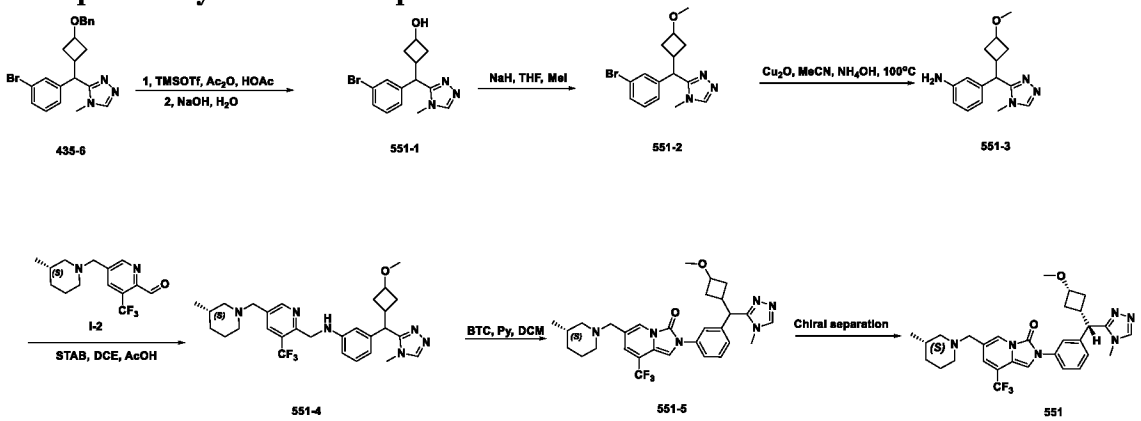
conditions(column: DAICEL CHIRALCEL OD (250mm*30mm,10um); mobile phase: [Neu-IPA]; B%: 38%-38%,9min, Flow rate: 2.5 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.961; RT2 (min): 4.249) to afford 550_P1 (117.3 mg, 33.51%) as a yellow solid and 550_P2 (118.9 mg, 33.97%) as a yellow solid .

MS-550_P1: (ES, m/z): [M+H]+ 545.2.

1H-NMR-550_P1: (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.65-7.63 (m, 2H), 7.40 (s, 1H), 6.99 (s, 1H), 4.57 (d, J = 10.4 Hz, 1H), 3.53 (s, 3H), 3.23-3.13 (m, 3H), 2.75-2.71 (m, 2H), 2.03-1.79 (m, 6H), 1.77-1.57 (m, 5H), 1.44 (d, J = 12.0 Hz, 1H), 0.85-0.81 (m, 4H).

MS-550_P2: (ES, m/z): [M+H]+ 545.2. 1H-NMR-550_P2: (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.65-7.63 (m, 2H), 7.41 (s, 1H), 6.99 (s, 1H), 4.57 (d, J = 10.4 Hz, 1H), 3.53 (s, 3H), 3.23-3.13 (m, 3H), 2.75-2.66 (m, 2H), 2.02-1.81 (m, 6H), 1.75-1.59 (m, 5H), 1.59-1.45(m, 1H), 0.85-0.81 (m, 4H).

Example 542. Synthesis of Compound 551



1. Synthesis of 551-1

[1859] To a stirred solution of 435-6 (6.7 g, 16.249 mmol, 1 equiv) in HOAc (70 mL) and Ac_2O (15 mL) was added TMSOTf (7222.72 mg, 32.498 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (20 mL). To the above mixture was added NaOH (65.00 mL, 64.996 mmol, 4 equiv, 1M). The resulting mixture was stirred for additional 4 h at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (3x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 551-1 (4.4 g, 84.04%) as a white solid.

2. Synthesis of 551-2

[1860] To a stirred solution of 551-1 (2 g, 6.207 mmol, 1 equiv) in THF (20 mL) was added NaH (0.30 g, 7.448 mmol, 1.2 equiv, 60%) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at 0 °C under nitrogen atmosphere. To the above mixture was added MeI (1.32 g, 9.310 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (60 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 551-2 (1.8 g, 86.25%) as a white solid.

3. Synthesis of 551-3

[1861] Into a 50 mL pressure tank reactor were added 551-2 (1.8 g, 5.353 mmol, 1 equiv), MeCN (30 mL), NH4OH (15 mL) and Cu_2O (0.31 g, 2.141 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for overnight at 100°C.The resulting mixture was diluted with DCM (100 mL). The resulting mixture was filtered, the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 551-3 (1.2 g, 82.30%) as a grey solid.

4. Synthesis of 551-4

[1862] To a stirred solution of 551-3 (1.2 g, 4.406 mmol, 1 equiv) and I-2 (1.51 g, 5.287 mmol, 1.2 equiv) in DCE (20 mL) was added STAB (1.87 g, 8.812 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 551-5 (1.6 g, 66.92%) as a white solid.

5. Synthesis of 551-6

[1863] To a stirred solution of 551-5 (1.58 g, 2.912 mmol, 1 equiv) and Pyridine (1.15 g, 14.560 mmol, 5 equiv) in DCM (40 mL) was added Triphosgene (0.30 g, 1.019 mmol, 0.35 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (50 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 65% gradient in 30 min;

detector, UV 254 nm. This resulted in 551-5 (1 g, 60.40%) as a yellow solid.

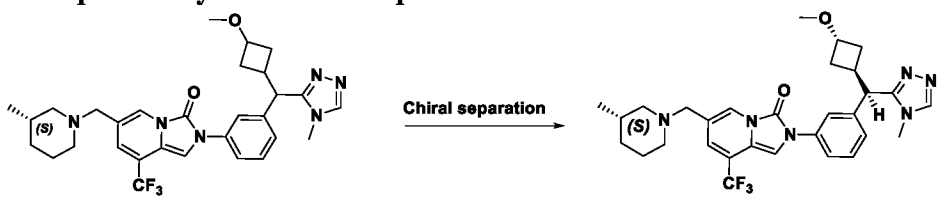
6. Synthesis of 551

[1864] 551-5 (1 g) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: ETOH(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.42; RT2(min): 4.47; the first peak was desired product) to affordcrude product (420 mg). The crude product (420 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 4.83; RT2(min): 6.49; the first peak was product) to afford 551 (305.3 mg, 30.53%) as a yellow solid.

LCMS-551:(ES, m/z): $[M+H]^+$ 569

NMR-551: (400 MHz, CD_3OD, δ ppm): 0.90-0.99 (m, 4H), 1.61-1.81 (m, 7H), 1.96-2.01 (m, 1H), 2.19-2.27 (m, 1H), 2.58-2.63 (m, 1H), 2.79-2.92 (m, 3H), 3.24 (s, 3H), 3.32 (s, 2H), 3.54 (s, 3H), 3.79-3.84 (t, 1H), 4.24-4.26 (d, 1H), 7.13 (s, 2H), 7.26-7.28 (d, 1H), 7.49-7.51 (t, 1H), 7.65-7.70 (m, 3H), 8.38 (s,1H).

Example 543. Synthesis of Compound 552



551-5 552

1. Synthesis of 552

[1865] 551-5 (1 g) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: ETOH(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.42; RT2(min): 4.47; the first peak was product) to afford crude product (380 mg). The crude product (380 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 29 min; Wave Length: 220/254 nm; RT1(min): 18.19; RT2(min): 26.89; the second peak was product) to afford 552 (24.3 mg, 2.43%) as a yellow solid

LCMS-552:(ES, m/z): $[M+H]^+$ 569

NMR-552: (400 MHz, CD_3OD, δ ppm): 0.90-0.97 (m, 4H), 1.61-1.79 (m, 5H), 1.99-2.01 (m, 3H), 2.15-2.17 (m, 1H), 2.32-2.35 (m, 1H), 2.87-2.93 (m, 3H), 3.24 (s, 3H), 3.28-3.32 (m, 1H), 3.36 (s, 2H), 3.55 (s, 3H), 4.09-4.11 (t, 1H), 4.31-4.34 (d, 1H), 7.13-7.15 (d, 2H), 7.28-7.30 (d, 1H), 7.50-7.54 (t, 1H), 7.66-7.72 (m, 3H), 8.38 (s,1H).

Example 544. Synthesis of Compound 553



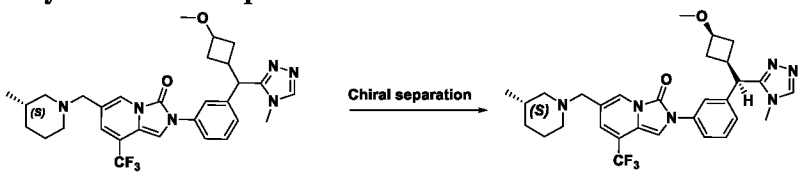
551-5 553

1. Synthesis of 553

[1866] 551-5 (1 g) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: ETOH(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.42; RT2(min): 4.47; the second peak was product) to afford crude product (380 mg). The crude product (380 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 29 min; Wave Length: 220/254 nm; RT1(min): 18.19; RT2(min): 26.89; the second peak was product) to afford 553 (25.6 mg, 2.56%) as a yellow solid

LCMS:(ES,m/z): $[M+H]^+$ 569. NMR: (400 MHz, CD_3OD, δ ppm): 0.90-0.97 (m, 4H), 1.61-1.78 (m, 5H), 1.01-2.03 (m, 3H), 2.15-2.18 (m, 1H), 2.28-2.35 (m, 1H), 2.87-2.93 (m, 3H), 3.24 (s, 3H), 3.28-3.32 (m, 1H), 3.36 (s, 2H), 3.55 (s, 3H), 4.06-4.10 (m, 1H), 4.31-4.34 (d, 1H), 7.13-7.15 (d, 2H), 7.28-7.30 (d, 1H), 7.50-7.54 (t, 1H), 7.66-7.71 (m, 3H), 8.38 (s,1H).

Example 545. Synthesis of Compound 554



551-5 554

1. Synthesis of 554

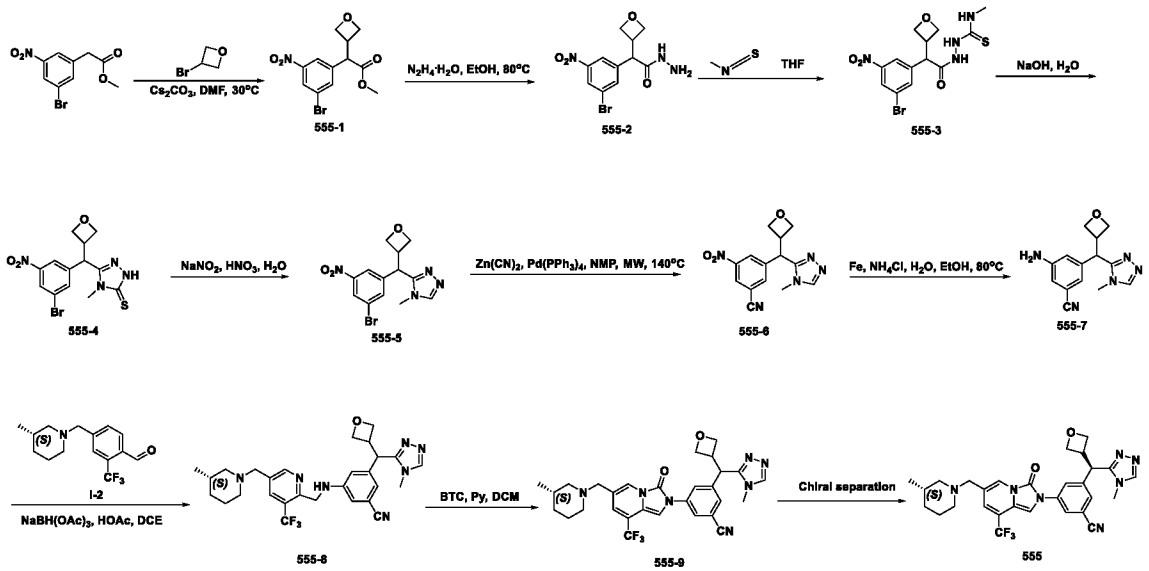
[1867] 551-5 (1 g) was purified by Prep-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B:

ETOH(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 45% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.42; RT2(min): 4.47; second peak was desired product) to affordcrude product (420 mg). The crude product (420 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 7.5 min; Wave Length: 220/254 nm; RT1(min): 4.83; RT2(min): 6.49; first peak was product) to afford 554 (285.7 mg, 28.57%) as a yellow solid

LCMS-554:(ES, m/z): $[M+H]^+$ 569

NMR-554: 0.90-0.99 (m, 4H), 1.61-1.81 (m, 7H), 1.96-2.01 (m, 1H), 2.21-2.24 (m, 1H), 2.58-2.62 (m, 1H), 2.81-2.91 (m, 3H), 3.24 (s, 3H), 3.32 (s, 2H), 3.54 (s, 3H), 3.81-3.84 (t, 1H), 4.24-4.26 (d, 1H), 7.13 (s, 2H), 7.26-7.28 (d, 1H), 7.49-7.53 (t, 1H), 7.66-7.68 (m, 3H), 8.38 (s,1H).

Example 546. Synthesis of Compound 555



1. Synthesis of 555-1

[1868] Into a 250mL 3-necked round-bottom flask was added 555-1 (9 g, 32.838 mmol, 1 equiv), DMF (100 mL) and Cs_2CO_3 (53.50 g, 164.190 mmol, 5 equiv) at 0°C. The resulting mixture was stirred for 1h at 0°C under nitrogen atmosphere. To the above mixture was added 3-bromooxetane (13.50 g, 98.514 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (500 mL) at room temperature. The resulting mixture was extracted with EtOAc

(3x500 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (50:1) to afford methyl 555-2 (6.2 g, 54.33%) as a light yellow solid.

2. Synthesis of 555-2

[1869] Into a 100mL 3-necked round-bottom flask was added 555-1 (6.2 g, 18.780 mmol, 1 equiv), EtOH (70 mL) and $NH_2NH_2.H_2O$ (9.40 g, 187.800 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was quenched with water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (50:1) to afford 555-2 (3.2 g, 49.03%) as a brown solid.

3. Synthesis of 555-3

[1870] Into a 100mL 3-necked round-bottom flask were added 555-2 (3.2 g, 9.693 mmol, 1 equiv), tetrahydrofuran (35 mL) and methyl isothiocyanate (1.77 g, 24.232 mmol, 2.5 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The precipitated solids were collected by filtration and washed with water (2x20 mL). This result in 555-3 (3.3 g, 80.21%) as a light yellow solid.

4. Synthesis of 555-4

[1871] Into a 100mL 3-necked round-bottom flask were added 555-3 (3.3 g, 8.184 mmol, 1 equiv), H_2O (80 mL) and NaOH (3.27 g, 81.840 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture was acidified to pH 6 with HCl (aq.). The precipitated solids were collected by filtration and washed with water (3x20 mL). This result in 555-4 (3 g, 90.40%) as a light yellow solid.

5. Synthesis of 555-5

[1872] Into a 100mL 3-necked round-bottom flask were added 555-4 (3 g, 7.787 mmol, 1 equiv), H_2O (35 mL), $NaNO_2$ (5.37 g, 77.870 mmol, 10 equiv) at 0°C. To the above mixture was added HNO_3 (78 mL, 77.870 mmol, 10 equiv, 1M) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The mixture was basified to pH 7 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford 555-5 (2 g, 69.08%) as a light yellow solid.

6. Synthesis of 555-6

[1873] To a solution of 555-5 (2 g, 5.663 mmol, 1 equiv) and $Zn(CN)_2$ (1.99 g, 16.948 mmol, 2.99 equiv) in NMP (30 mL) was added $Pd(PPh_3)_4$ (0.65 g, 0.562 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The final reaction mixture was irradiated with microwave radiation for 3h at 140°C. The reaction was quenched with 1M LiCl (aq.) (200 mL) at room temperature. The resulting mixture was extracted with EtOAc (6x50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 555-6 (1 g, 56.05%) as a light yellow oil.

7. Synthesis of 555-7

[1874] Into a 100mL 3-necked round-bottom flask were added 555-6 (1 g, 3.341 mmol, 1 equiv), EtOH (20 mL), H_2O (5 mL), NH_4Cl (1.79 g, 33.410 mmol, 10 equiv) and Fe (0.56 g, 10.023 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x10 mL). The filtrate was diluted with water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (5 x 50mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 555-7 (500 mg, 52.79%) as a light yellow solid.

8. Synthesis of 555-8

[1875] To a stirred 555-7 (500 mg, 1.856 mmol, 1 equiv) and I-2 (637.85 mg, 2.228 mmol, 1.2 equiv) in DCE (10.00 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. To the above mixture was added STAB (1573.96 mg, 7.426 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80mL) at room temperature. The aqueous layer was extracted with DCM (3x50 mL).The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 555-8 (300 mg, 39.96%) as a white solid.

9. Synthesis of 555-9

[1876] To a stirred solution of 555-8 (300 mg, 0.556 mmol, 1 equiv) and Pyridine (263.86 mg, 3.336 mmol, 6.00 equiv) in DCM (4 mL) was added Triphosgene (64.34 mg, 0.217 mmol, 0.39 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80mL) at room temperature. The aqueous layer was extracted with DCM (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 555-9 (220 mg, 67.16%) as a yellow solid.

10. Synthesis of 555

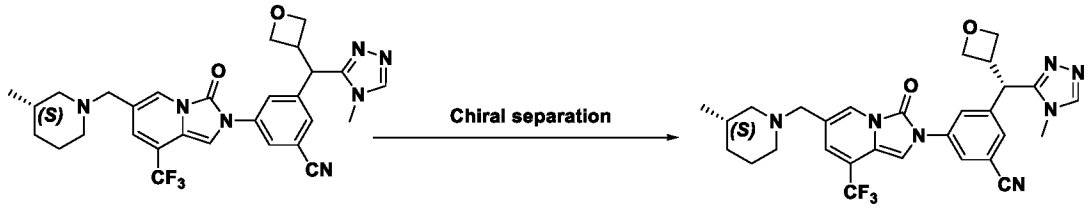
[1877] The 555-9 (220 mg) was purified by Prep-Chiral-HPLC with the following conditions

(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 10 min; Wave Length: 220/254 nm; RT1(min): 5.93; RT2(min): 7.87; the second peak is product) to afford 555 (58.7 mg, 26.68%) as a yellow solid.

LC-MS-555: (ES, *m/z*): $[M+H]^+$ 558

H-NMR-555: (400 MHz, DMSO-d_6, δ *ppm*): 0.80-0.93 (m, 4H), 1.44-1.78 (m, 5H), 1.94-1.98 (m, 1H), 2.74-2.83 (m, 2H), 3.21-3.30 (m, 2H), 3.46 (s, 3H), 3.93-4.01 (m, 1H), 4.27-4.30 (m, 1H), 4.46-4.52 (m, 2H), 4.71-4.75 (m, 1H), 4.90-4.93 (d, 1H), 7.03 (s, 1H), 7.56 (s, 1H), 7.65-7.70 (m, 2H), 8.20 (s, 1H), 8.30 (s, 1H), 8.40 (s, 1H).

Example 547. Synthesis of Compound 556



555-9 556

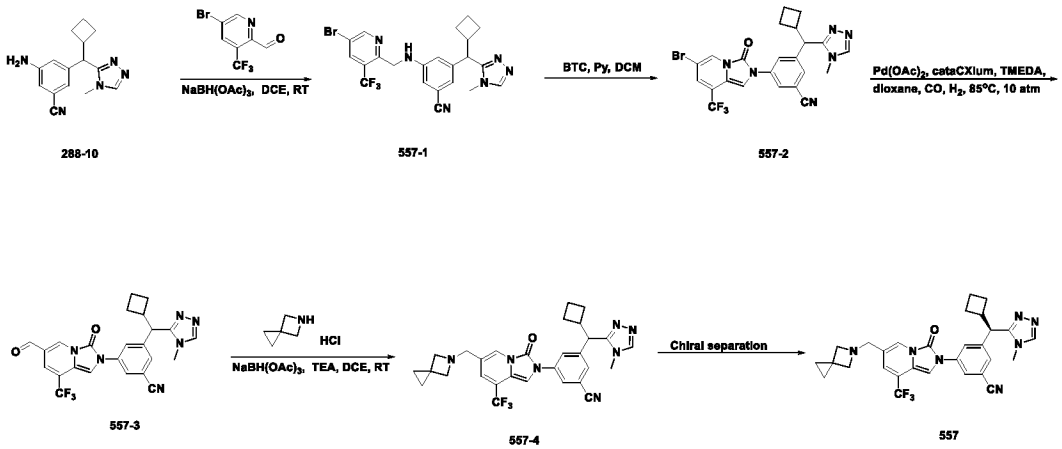
1. Synthesis of 556

[1878] The 555-9 (220 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 10 min; Wave Length: 220/254 nm; RT1(min): 5.93; RT2(min): 7.87; the frist peak is product) to afford 556 (51.6 mg, 23.45%) as a yellow solid.

LC-MS-556: (ES, *m/z*): $[M+H]^+$ 559

H-NMR-556: (400 MHz, DMSO-d_6, δ *ppm*): 0.80-0.93 (m, 4H), 1.44-1.78 (m, 5H), 1.94-1.98 (m, 1H), 2.74-2.83 (m, 2H), 3.21-3.30 (m, 2H), 3.46 (s, 3H), 3.93-4.01 (m, 1H), 4.27-4.30 (m, 1H), 4.46-4.52 (m, 2H), 4.71-4.75 (m, 1H), 4.90-4.93 (d, 1H), 7.03 (s, 1H), 7.56 (s, 1H), 7.65-7.70 (m, 2H), 8.20 (s, 1H), 8.30 (s, 1H), 8.40 (s, 1H).

Example 548. Synthesis of Compound 557



1. Synthesis of 557-1

[1879] To a stirred solution of 288-10 (1 g, 3.741 mmol, 1 equiv) in DCE (30 mL, 378.979 mmol, 101.31 equiv) was added 5-bromo-3-(trifluoromethyl)picolinaldehyde (1.14 g, 4.488 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. To the above mixture was added $NaBH(OAc)_3$ (2.38 g, 11.223 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 557-1 (1 g, 51.84%) as a white solid.

2. Synthesis of 557-2

[1880] To a stirred solution of 557-1 (1 g, 1.979 mmol, 1 equiv) and Pyridine (1.57 g, 19.790 mmol, 10 equiv) in DCM (30 mL) was added Triphosgene (0.23 g, 0.792 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 557-2 (850 mg, 76.80%) as an orange solid.

3. Synthesis of 557-3

[1881] To a solution of 557-2 (800 mg, 1.506 mmol, 1 equiv) and TMEDA (349.93 mg, 3.012 mmol, 2 equiv) in 1,4-dioxane (25 mL) were added bis(adamantan-1-yl)(butyl)phosphane (107.97 mg, 0.301 mmol, 0.2 equiv) and $Pd(OAc)_2$ (33.80 mg, 0.151 mmol, 0.1 equiv) in a pressure tank. The mixture was purged with nitrogen for 3min and then was pressurized to 15atm with CO/H_2=1:1 at 85°C for overnight. The reaction mixture was

cooled to room temperature and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 557-3 (540 mg, 67.18%) as a yellow solid.

4. Synthesis of 557-4

[1882] To a stirred solution of 557-3 (520 mg, 1.082 mmol, 1 equiv) and 5-azaspiro[2.3]hexane hydrochloride (258.87 mg, 2.164 mmol, 2 equiv) in DCE (8 mL) were added TEA (219.05 mg, 2.164 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. To the above mixture was added $NaBH(OAc)_3$ (458.77 mg, 2.164 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (30 mL) at room temperature. The aqueous layer was extracted with DCM (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 557-4 (150 mg, 24.30%) as a yellow solid.

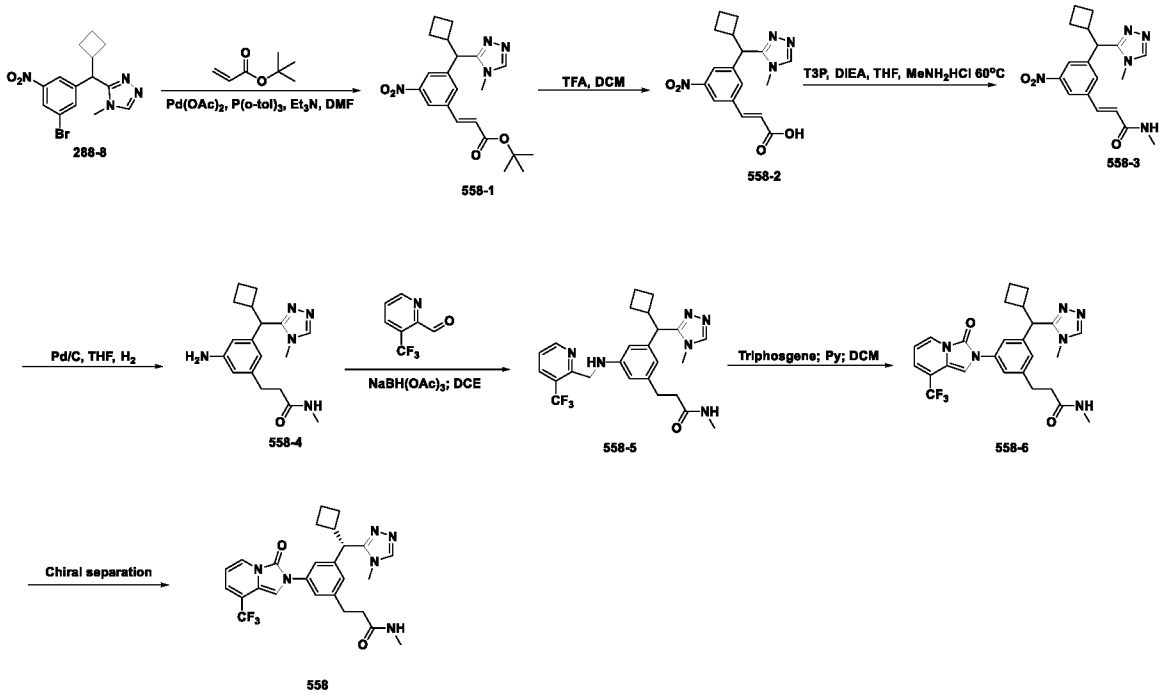
5. Synthesis of 557

[1883] The 557-4 (150 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8 min; Wave Length: 220/254 nm; RT1(min): 3.91; RT2(min): 6.07; the second peak is product) to afford 557 (39.2 mg, 26.08%) as a yellow solid.

LC-MS-557: (ES, *m/z*): $[M+H]^+$ 548

H-NMR-557: (400 MHz, DMSO-d6, δ *ppm*): 0.51 (s, 4H), 1.67-1.84 (m, 5H), 2.03-2.08 (m, 1H), 3.21-3.31 (m, 5H), 3.45 (s, 2H), 3.47 (s, 3H), 4.37-4.40 (d, 1H), 7.02 (s, 1H), 7.51 (s, 1H), 7.67-7.69 (m, 2H), 8.23-8.24 (d, 2H), 8.36 (s, 1H).

Example 549. Synthesis of Compound 558



1. Synthesis of 558-1

[1884] To a stirred solution of 288-8 (2 g, 5.69 mmol, 1.0 equiv) and tert-butyl prop-2-enoate (1.5 g, 11.39 mmol, 2.0 equiv) in DMF (20 mL) were added Et_3N (2.3 g, 22.78 mmol, 4.0 equiv), $Pd(OAc)_2$ (127 mg, 0.57 mmol, 0.1 equiv) and $P(o\text{-}tol)_3$ (346.66 mg, 1.139 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. The reaction was quenched by the addition of water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (3x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford 558-1 (2 g, 72%) as an off-white solid.

2. Synthesis of 558-2

[1885] A solution of 558-1 (2 g, 5.01 mmol, 1.0 equiv) and TFA (5 mL) in DCM (15 mL) was stirred for overnight at room temperature. The mixture was neutralized to pH 8 with NH_3 in MeOH. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford 558-2 (1.5 g, 87%) as an off-white solid.

3. Synthesis of 558-3

[1886] To a stirred solution of 558-2 (980 mg, 2.86 mmol, 1.0 equiv) and methylamine (88

mg, 2.86 mmol, 1.0 equiv) in THF (10 mL) were added T_3P (2.7 g, 8.59 mmol, 3.0 equiv) and DIEA (1.5 g, 11.45 mmol, 4.0 equiv) at room temperature. The resulting mixture was stirred for 3 h at 60 °C. The reaction was quenched by the addition of water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 558-3 (400 mg, 39%) as an off-white solid.

4. Synthesis of 558-4

[1887] To a solution of 558-3 (540 mg, 1.51 mmol, 1.0 equiv) in 20 mL THF was added Pd/C (10%, 100 mg) under nitrogen atmosphere in a 50 mL round-bottom flask. The mixture was hydrogenated at room temperature for overnight under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 558-4 (400 mg, 80%) as an off-white solid.

5. Synthesis of 558-5

[1888] To a stirred solution of 558-4 (380 mg, 1.16 mmol, 1.0 equiv) and 3-(trifluoromethyl) pyridine-2-carbaldehyde (203 mg, 1.16 mmol, 1.0 equiv) in DCE (4 mL) was added $NaBH(OAc)_3$ (491 mg, 2.32 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with water (3x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 558-5 (320 mg, 57%) as an off-white solid.

6. Synthesis of 558-6

[1889] To a stirred solution of 558-5 (320 mg, 0.65 mmol, 1.0 equiv) and pyridine (312 mg, 3.94 mmol, 6.0 equiv) in DCM (3 mL) was added triphosgene (68 mg, 0.23 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 1h at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with water (3x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 558-6 (40 mg, 12%) as a yellow solid.

7. Synthesis of 558

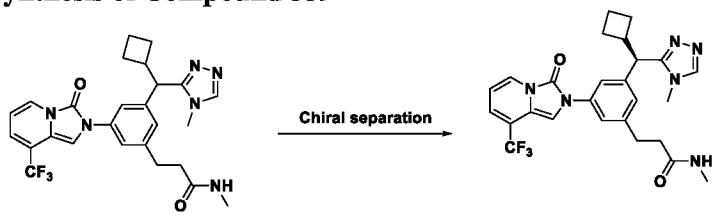
[1890] The 558-6 (280 mg) was purified by chiral separation with the following conditions

(Prep-HPLC-037): Column: Lux 5um Cellulose-2, 2.12*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 20 min; Wave Length: 220/254 nm; RT1(min): 12.61; RT2(min): 16.64; the first peak was the product. Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number of Runs: 11. This resulted in 558 (92 mg, 33%) as a yellow solid.

LC-MS-558: (ES, m/z): $[M+H]^+$ 513

H-NMR-558: (400 MHz, DMSO-d6, δ *ppm*): 1.73-1.78 (m, 1H), 1.79-1.84 (m, 4H), 2.05-2.09 (m, 1H), 2.33-2.37 (t, 2H), 2.54 (s, 3H), 2.80-2.84 (t, 2H), 3.17-3.25 (m, 1H), 3.41 (s, 3H), 4.18-4.21 (m, 1H), 6.27-6.30 (t, 1H), 7.02 (s, 1H), 7.09-7.10 (d, 1H), 7.30 (s, 1H), 7.51 (s, 1H), 7.62 (s, 1H), 7.76-7.78 (d, 1H), 8.32 (s, 1H).

Example 550. Synthesis of Compound 559



558-6 559

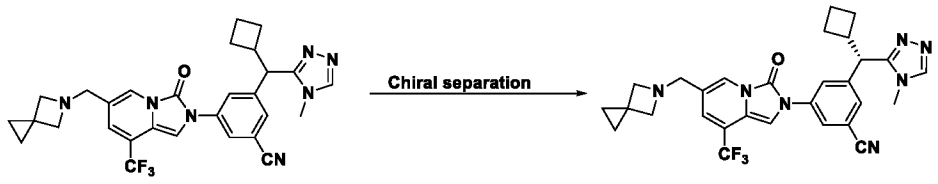
1. Synthesis of 559

[1891] The 558-6 (280 mg) was purified by chiral separation with the following conditions (Prep-HPLC-037): Column: Lux 5um Cellulose-2, 2.12*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 20 min; Wave Length: 220/254 nm; RT1(min): 12.61; RT2(min): 16.64; The second peak was the product. Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number of Runs: 11. This resulted in 559 (94.7 mg, 33.89%) as a yellow solid.

LC-MS-559: (ES, m/z): $[M+H]^+$ 513

H-NMR- 559: (400 MHz, DMSO-d6, δ *ppm*): 1.73-1.84 (m, 5H), 2.05-2.09 (m, 1H), 2.33-2.37 (t, 2H), 2.54 (s, 3H), 2.80-2.84 (t, 2H), 3.17-3.25 (m, 1H), 3.41 (s, 3H), 4.18-4.21 (m, 1H), 6.27-6.30 (t, 1H), 7.02 (s, 1H), 7.09-7.10 (d, 1H), 7.30 (s, 1H), 7.51 (s, 1H), 7.62 (s, 1H), 7.76-7.78 (d, 1H), 8.32 (s, 1H).

Example 551. Synthesis of Compound 560



557-4 560

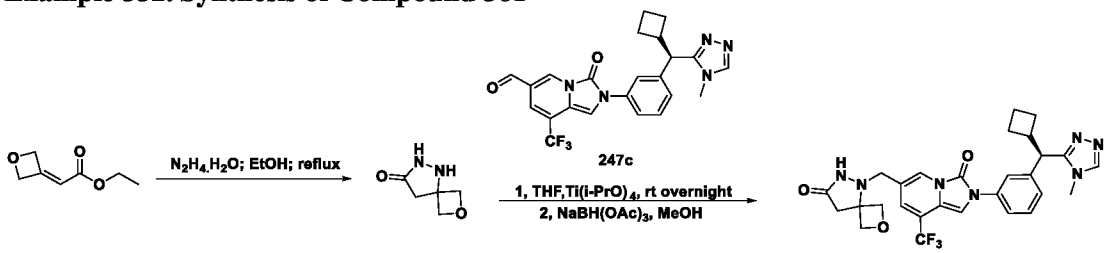
1. Synthesis of 560

[1892] The 557-4 (150 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8 min; Wave Length: 220/254 nm; RT1(min): 3.91; RT2(min): 6.07; the first peak is product) to afford 560 (44.2 mg, 29.08%) as a yellow solid.

LC-MS-560: (ES, *m/z*): $[M+H]^+$ 548

H-NMR-560: (400 MHz, DMSO-d6, δ *ppm*): 0.51 (s, 4H), 1.67-1.84 (m, 5H), 2.03-2.08 (m, 1H), 3.21-3.31 (m, 5H), 3.45 (s, 2H), 3.47 (s, 3H), 4.37-4.40 (d, 1H), 7.02 (s, 1H), 7.51 (s, 1H), 7.67-7.69 (m, 2H), 8.23-8.24 (d, 2H), 8.36 (s, 1H).

Example 552. Synthesis of Compound 561



561-1 PH-HOT-B-1622-0

1. Synthesis of 561-1

[1893] To a stirred solution of ethyl 2-(oxetan-3-ylidene)acetate (3 g, 21.104 mmol, 1 equiv) inEtOH (50 mL) was added hydrazine hydrate (98%) (1.58 g, 31.656 mmol, 1.5 equiv). The resulting mixture was stirred for overnight at80 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 561-1 (1.4 g, 51.77%) as a white solid.

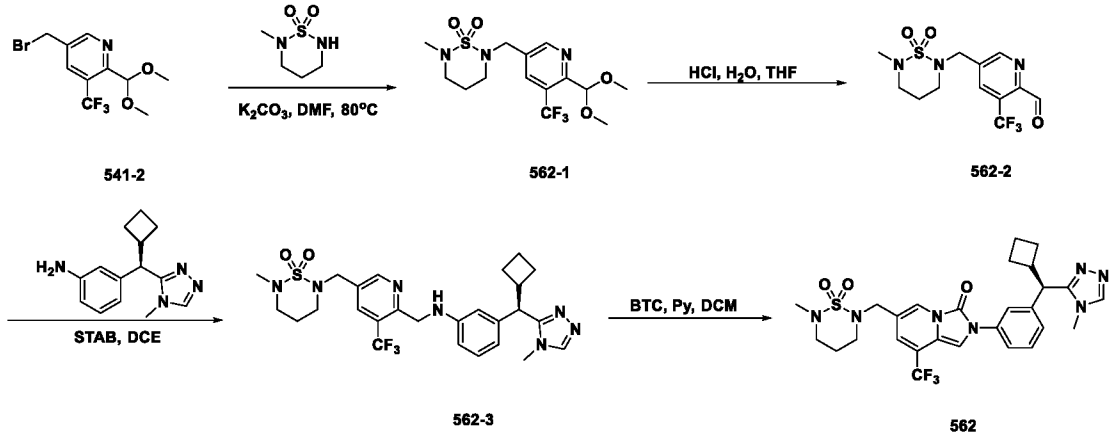
2. Synthesis of 561

[1894] To a stirred solution of 247c (1 g, 2.196 mmol, 1 equiv) and 561-1 (0.56 g, 4.392 mmol, 2 equiv) in THF was added $Ti(Oi\text{-}Pr)_4$ (1.25 g, 4.392 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in

MeOH (20 mL). To the above mixture was added $NaBH(OAc)_3$ (1.40 g, 6.588 mmol, 3 equiv). The resulting mixture was stirred for additional 3 h at room temperature. The resulting mixture was diluted with water (80 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford -561 (79.8 mg, 6.40%) as a yellow solid.

LCMS:(ES, m/z): $[M+H]^+$ 506 NMR: (400 MHz, DMSO, ppm): δ 1.71-1.85 (m, 5H), 2.07-2.10 (m, 1H), 2.82 (s, 2H), 3.21-3.25 (m, 1H), 3.44 (s, 3H), 3.66 (s, 2H), 4.26-4.29 (d, 1H), 4.50-4.52 (d, 2H), 4.78-4.80 (d, 2H), 7.11 (s, 1H), 7.20-7.22 (d, 1H), 7.33 (s, 1H), 7.43-7.47 (m, 3H), 8.34 (s, 1H), 9.43 (s, 1H).

Example 553. Synthesis of Compound 562



1. Synthesis of 562-1

[1895] Into a 40 mL vial were added 541-2 (1.3 g, 1.757 mmol, 1 equiv), 2-methyl-1lambda6,2,6-thiadiazinane-1,1-dione (0.93 g, 6.209 mmol, 1.5 equiv), K_2CO_3 (1.14 g, 8.278 mmol, 2 equiv) and DMF (15 mL) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=50:1) to afford 562-1 (800 mg, 47.39%) as yellow oil.

2. Synthesis of 562-2

[1896] Into a 40 mL vial were added 562-1 (770 mg, 2.008 mmol, 1 equiv) 1M HCl (7 mL) and H_2O (2 mL) at room temperature. The resulting mixture was stirred for 2 h at 80 °C. The residue was basified to pH 8 with sat. NH_4HCO_3 (aq.) (100 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=60:1) to afford 562-2 (600 mg, 84.14%)

as a yellow oil.

3. Synthesis of 562-3

[1897] Into a 50 mL round-bottom flask were added 608-2 (580 mg, 1.719 mmol, 1 equiv), 244b (625.00 mg, 2.579 mmol, 1.5 equiv), STAB (728.83 mg, 3.438 mmol, 2 equiv) and DCE (10 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 562-3 (600 mg, 59.43%) as a yellow oil.

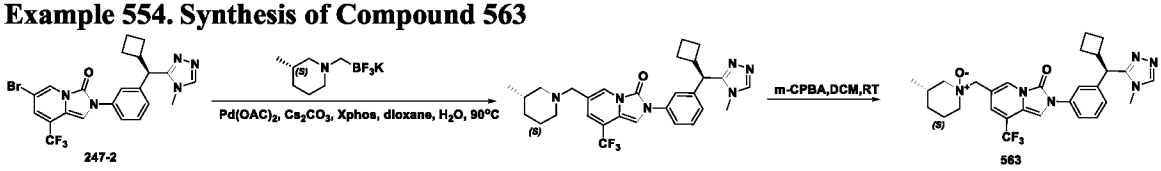
4. Synthesis of 562

[1898] Into a 100 mL round-bottom flask were added 562-3 (500 mg, 0.887 mmol, 1 equiv), pyridine (561.35 mg, 7.096 mmol, 8 equiv) and DCM (20 mL) at room temperature. To the above mixture was added triphosgene (131.61 mg, 0.444 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 3 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The crude product (500 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 54% B in 8 min; Wave Length: 254 nm; RT1(min): 7.52) to afford 562 (206.7 mg, 39.48%) as a yellow solid.

LC-MS-562: (ES, *m/z*): $[M+H]^+$ 590

H-NMR-562: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.82-1.90 (m, 1H), δ1.91-1.99 (m, 6H), δ2.24-2.29 (m, 1H), δ2.83 (s, 3H), δ3.27-3.29 (m, 1H), δ3.39-3.45 (m, 4H), δ3.56 (s, 3H), δ4.11 (s, 2H), δ4.28-4.31 (d, 1H), δ7.03 (s, 1H), δ7.15 (s, 1H), δ7.26-7.28 (d, 1H), δ7.48-7.52 (t, 1H), δ7.64-7.67 (m, 2H), δ7.78 (s, 1H), δ8.38 (s, 1H).

Example 554. Synthesis of Compound 563



1. Synthesis of 563-1

[1899] Into a 40 mL sealed tube were added 247-2 (1 g, 1.975 mmol, 1 equiv) and dioxane (8 mL) and H_2O (2 mL) at room temperature. To the above mixture was added (3S)-3-methyl-1-[(trifluoro-lambda4-boranyl)methyl]piperidine potassium (649.09 mg, 2.963 mmol, 1.5

equiv), Xphos (188.31 mg, 0.395 mmol, 0.2 equiv), Cs_2CO_3 (1.93 g, 5.925 mmol, 3 equiv) and $Pd(OAC)_2$ (22.17 mg, 0.099 mmol, 0.05 equiv) at room temperature. The resulting mixture was stirred for overnight at 90°C under nitrogen atmosphere. The reaction was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 563-1(800 mg, 71.44%) as a light yellow oil.

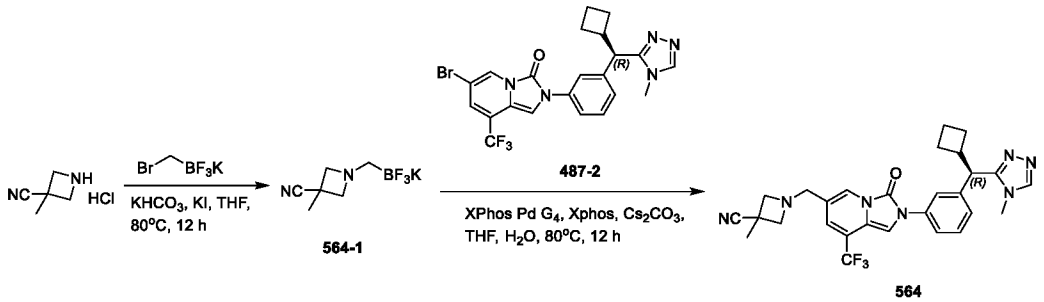
2. Synthesis of 563

[1900] Into a 40 mL sealed tube were added 563-1 (500 mg, 0.928 mmol, 1 equiv) and DCM (10 mL) at 0°C. To the above mixture was added m-CPBA (400.47 mg, 2.320 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at 0°C. The mixture was basified to pH 7 with saturated $NaHCO_3$ (aq.) (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 40% B to 55% B in 7 min; Wave Length: 254; 220 nm; RT1(min): 5.98, 6.05(min).) to afford 563 (100.4 mg, 17.54%) as a light yellow solid.

LCMS137-563: (ES, m/z): $[M+H]^+$ 555

H-NMR18-563: (300 MHz, DMSO-d6, *ppm*): δ0.85-0.91 (m, 3H), δ0.99-1.02 (m, 1H), δ1.64-1.80 (m, 7H), δ2.01-2.17 (m, 3H), δ2.89-2.95 (m, 1H), δ3.19-3.21 (m,2H), δ3.31-3.33 (m, 2H), δ3.33-3.43 (m, 2H), δ3.63 (s, 1H), δ4.25-4.28 (m, 1H), δ4.28-4.49 (m, 2H), δ7.20-7.22 (m, 1H), δ7.35-7.42 (m, 2H), δ7.44-7.46 (m, 1H), δ7.67-7.73 (m, 2H), δ8.02-8.25 m, 1H), δ8.25-8.32 (s, 1H), δ8.32-8.33 (s, 1H).

Example 555. Synthesis of Compound 564



1. Synthesis of 564-1

[1901] A mixture of potassium;bromomethyl(trifluoro)boranuide (757 mg, 3.77 mmol, 1

equiv), 3-methylazetidine-3-carbonitrile;hydrochloride (500 mg, 3.77 mmol, 1 equiv), KI (62.6 mg, 377 umol, 0.1 equiv), $KHCO_3$ (755 mg, 7.54 mmol, 2 equiv) in THF (10 mL) was degassed and purged with nitrogen atmosphere for 3 times, and then the mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The residue was triturated with acetone (20 mL) at 40 °C for 1 hr. Then the mixture was filtered and the filtrate was concentrated in vacuum to afford 564-1 (510 mg, crude) as a yellow oil.

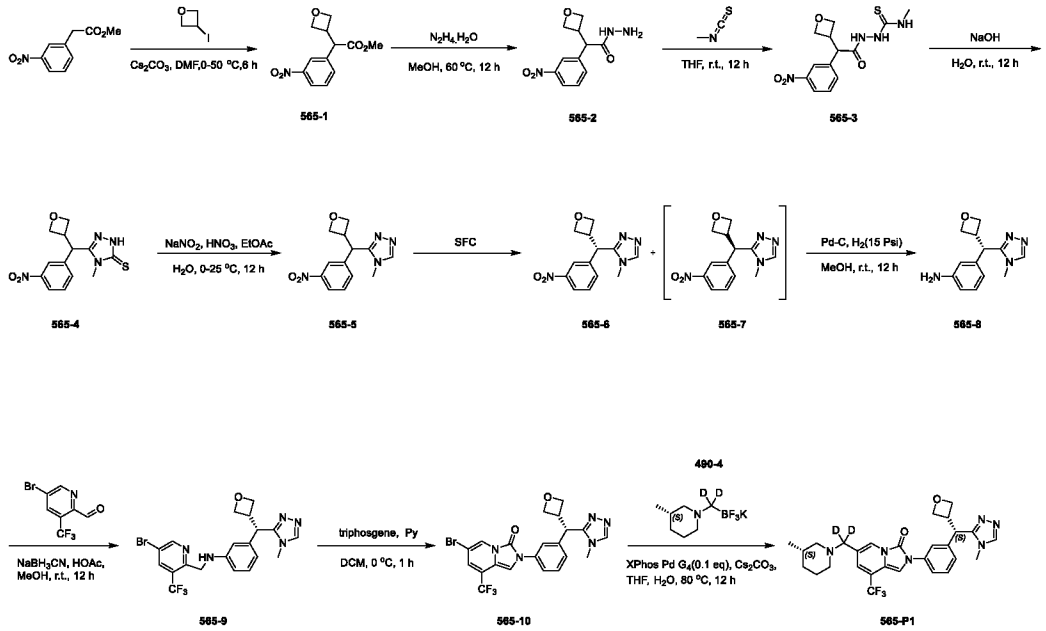
2. Synthesis of 564

[1902] To a solution of 487-2 (300 mg, 592.51 umol, 1 equiv) and 564-1 (512 mg, 2.37 mmol, 4 equiv) in THF (4 mL) and H_2O (1 mL) was added XPhos (28.2 mg, 59.2 umol, 0.1 equiv) and Cs_2CO_3 (579.16 mg, 1.78 mmol, 3 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane; methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (50.9 mg, 59.2 umol, 0.1 equiv). The mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water 20 mL and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with DCM/MeOH (10:1) to give crude product. The crude product (230 mg) was purified by Prep-HPLC with the following conditions (Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile Phase A: Water (10 mmol/L.NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 35% B to 65% B in 8 min; Wave Length: 220 nm; RT1(min): 7.5) to afford 564 (40 mg, 12%) as a yellow solid.

LCMS-564: (ES, m/z): $[M+H]^+$ 536.3.

^{1}H-NMR-564: (400 MHz, ACETONITRILE-d_3) δ 8.08-8.06 (m, 1H), 7.69-7.61 (m, 2H), 7.56 (s, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 4.16 (d, J = 10.8 Hz, 1H), 3.56 (d, J = 7.6 Hz, 2H), 3.44-3.40 (m, 5H), 3.37-3.26 (m, 1H), 3.21 (d, J = 7.6 Hz, 2H), 2.14-2.11 (m, 1H), 1.91-1.83 (m, 4H), 1.80-1.74 (m, 1H), 1.60 (s, 3H).

Example 556. Synthesis of Compound 565_P1



1. Synthesis of 565-1

[1903] To a solution of methyl 2-(3-nitrophenyl)acetate (25 g, 128.09 mmol, 1 *eq*) in DMF (300 mL) was added Cs_2CO_3 (208.67 g, 640.46 mmol, 5 equiv). Then 3-iodooxetane (70.70 g, 384.28 mmol, 3 equiv) was added to the reaction mixture at 0 °C. Then the mixture was stirred for 3 h at 25 °C. Then the mixture was heated to 50 °C and stirred for 3 h at 50 °C under nitrogen atmosphere. The reaction mixture was diluted with H_2O (400 mL) and extracted with EtOAc 1800 mL (600 mL x 3). The combined organic layers were washed with brine 1500 mL (500 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1to1:10) to afford 565-1 (10.9 g, 32%) as a brown solid.

^{1}H-NMR-565-1: (400 MHz, CHLOROFORM-d) δ 8.21-8.12 (m, 2H), 7.64-7.58 (m, 1H), 7.58-7.51 (m, 1H), 4.96 (dd, *J* = 6.8, 7.6 Hz, 1H), 4.62 (dd, *J* = 6.8, 7.6 Hz, 1H), 4.52 (t, *J* = 6.4 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 1H), 4.20 (d, *J* = 12 Hz, 1H), 3.70 (s, 4H)

2. Synthesis of 565-2

[1904] To a solution of 565-1 (4.5 g, 17.91 mmol, 1 equiv) in MeOH (25 mL) was added $N_2H_4.H_2O$ (5 g, 97.88 mmol, 98% purity, 5.46 equiv). The mixture was heated to 45 °C and stirred for 12 h at 45 °C. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (30 mL), and extracted with DCM (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 565-2 (3.7 g, crude) as a white solid.

3. Synthesis of 565-3

[1905] To a solution of 565-2 (3.2 g, 12.74 mmol, 1 equiv) in THF (35 mL) was added isothiocyanatomethane (2.05 g, 28.02 mmol, 1.91 mL, 2.2 equiv). The mixture was stirred at 20 °C for 12 h. The mixture was diluted with H_2O (30 mL). The mixture was concentrated under reduced pressure to remove THF. Then the mixture was filtered to get a filter cake and the filter cake was concentrated in vacuum to afford 565-3 (4.2 g, crude) as a white solid.

4. Synthesis of 565-4

[1906] To a solution of NaOH (2.47 g, 61.66 mmol, 8 equiv) in H_2O (30 mL) was added 565-3 (2.5 g, 7.71 mmol, 1 equiv). The mixture was stirred at 20 °C for 12 h. The mixture was adjusted to pH =2 by HCl (2 M) and filtered. The filter cake was concentrated in vacuum to afford 565-4 (2.7 g, crude) as a white solid.

5. Synthesis of 565-5

[1907] To a solution of 565-4 (4.2 g, 13.71 mmol, 1 equiv) in DCM (70 mL) was cooled to 0 °C. Then a solution of H_2O_2 (6.49 g, 57.24 mmol, 30% purity, 4.17 equiv) in AcOH (6.59 g, 109.68 mmol, 8 equiv) was added to the mixture at 0 °C. The result mixture was stirred at 25 °C for 12 h. The solvent was diluted with H_2O 30 mL and adjusted pH to 12 by 2N NaOH, and extracted with DCM (90 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 5/1) to afford 565-5 (1.2 g, 33%) as a yellow solid.

^{1}H-NMR-565-5: (400 MHz, METHANOL-d_4) δ = 8.41 (s, 1H), 8.23-8.11 (m, 2H), 7.74-7.56 (m, 2H), 4.99-4.89 (m, 2H), 4.67-4.55 (m, 2H), 4.41 (t, *J* = 6.4 Hz, 1H), 4.05-3.93 (m, 1H), 3.49 (s, 3H)

6. Synthesis of 565-6&7

[1908] The 565-5 (3.3 g) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD(250mm*50mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 45%-45%,8.5min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 4.71; RT2 (min): 6.03) to afford 565-6 (1.5 g) as a yellow solid and 565-7 (1.5 g) as a yellow solid.

^{1}H-NMR-565-6: (400 MHz, METHANOL-d_4) δ 8.41 (s, 1H), 8.23-8.13 (m, 2H), 7.75-7.57 (m, 2H), 5.00-4.88 (m, 2H), 4.67-4.54 (m, 2H), 4.41 (t, *J* = 6.4 Hz, 1H), 3.99 (td, *J* = 6.4, 12 Hz, 1H), 3.50 (s, 3H)

^{1}H-NMR-565-7: (400 MHz, METHANOL-d_4) δ 8.41 (s, 1H), 8.23-8.13 (m, 2H), 7.75-7.57 (m, 2H), 5.00-4.88 (m, 2H), 4.67-4.54 (m, 2H), 4.41 (t, J = 6.4 Hz, 1H), 3.99 (td, J = 6.4, 11.6 Hz, 1H), 3.50 (s, 3H)

7. Synthesis of 565-8

[1909] To a solution of 565-6 (500 mg, 1.82 mmol, 1 equiv) in EA (5 mL) was added Pd/C (500 mg, 10% purity, 0.25 equiv) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 15 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to afford 565-8 (450 mg, crude) as a yellow oil.

8. Synthesis of 565-9

[1910] To a solution of 5-bromo-3-(trifluoromethyl)picolinaldehyde (467.89 mg, 1.84 mmol, 1 equiv) in MeOH (10 mL) was added 565-8 (450 mg, 1.84 mmol, 1 equiv), AcOH (110.62 mg, 1.84 mmol, 1 equiv). The mixture was stirred for 30 min at 15 °C.

Then sodium;cyanoboranuide (231.52 mg, 3.68 mmol, 2 equiv) was added to the reaction mixture and stirred for 11.5 h at 15 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to DCM: MeOH = 1:3) to afford 565-9 (650 mg, 59.9%) as a brown solid.

^{1}H-NMR-565-9: (400 MHz, CHLOROFORM-d) δ 8.81 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.65-6.56 (m, 2H), 6.51 (s, 1H), 5.27 (s, 1H), 5.08 (t, J = 7.2 Hz, 1H), 4.69 (t, J = 7.2 Hz, 1H), 4.57-4.46 (m, 3H), 4.39-4.27 (m, 2H), 4.03-3.91 (m, 1H), 3.40-3.32 (m, 3H)

9. Synthesis of 565-10

[1911] To a solution of 565-9 (300 mg, 622.02 umol, 1 equiv) in DCM (6 mL) was added pyridine (295.21 mg, 3.73 mmol, 6 equiv), bis(trichloromethyl) carbonate (60.00 mg, 202.19 umol, 0.25 equiv) at 0°C and stirred for 30 min. The reaction mixture was diluted with Sat.$NaHCO_3$ (10 mL), extracted with DCM (20 mL x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to get a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to DCM: MeOH = 1:1) to afford 565-10 (310 mg, 78.4%) as a yellow solid.

^{1}H-NMR-565-10: (400 MHz, CHLOROFORM-d) δ 8.07 (s, 1H), 7.87 (s, 1H), 7.63 (s, 1H), 7.57 (d, J = 1.2 Hz, 1H), 7.49-7.44 (m, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 6.79 (s,

1H), 5.06 (d, J = 7.2 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.54-4.47 (m, 2H), 4.34 (d, J = 6.0 Hz, 1H), 4.05 (td, J = 5.9, 11.2 Hz, 1H), 3.44 (s, 3H)

10. Synthesis of 565_P1

[1912] A mixture of 490-4 (256.65 mg, 1.16 mmol, 2 equiv), 565-10 (295 mg, 580.38 umol, 1 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (49.94 mg, 58.04 umol, 0.1 equiv), dicesium;carbonate (567.29 mg, 1.74 mmol, 3 equiv) in THF (6 mL), H_2O (1.5 mL) was degassed and purged with N_2 for 3 times. Then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The mixture was concentrated under reduced pressure and diluted with H_2O (15 mL), extracted with DCM (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1) then with (DCM: Methanol=100/1 to 0/1) to afford 565_P1 (0.3 g, crude) as a brown solid. The crude product (0.3 g) was further purified by prep-HPLC with the following conditions (Column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 10%-40%, 8min; Wave Length: 220 nm; RT 1(min): 6.5) to afford 565_P1 (54.1 mg, 22%) as a yellow solid.

MS-565_P1: (ES, m/z): [M+H]+ 543.3.

^{1}H-NMR-565_P1: (400 MHz, METHANOL-d_4) δ 8.39 (s, 1H), 8.37 (m, 0.5H), 7.84 (s, 1H), 7.72-7.63 (m, 2H), 7.55-7.51 (t, J = 16 Hz, 1H), 7.30-7.28 (d, J = 8 Hz, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 4.96-4.92 (t, J = 16 Hz, 1H), 4.84 (s, 1H), 4.68-4.61 (m, 2H), 4.43-4.40 (t, J = 12 Hz, 1H), 4.03-3.97 (m, 1H), 3.50 (s, 3H), 3.24-3.15 (m, 2H), 2.49-2.43 (t, J = 24 Hz, 1H), 2.21-2.15 (t, J = 24 Hz, 1H), 1.87-1.75 (m, 3H), 1.71-1.65 (m, 1H), 1.13-1.05 (m, 1H), 0.96-0.95 (d, J = 4 Hz, 3H).

Example 557. Synthesis of Compound 565_P2



547-2 564-P2

1. Synthesis of 565_P2

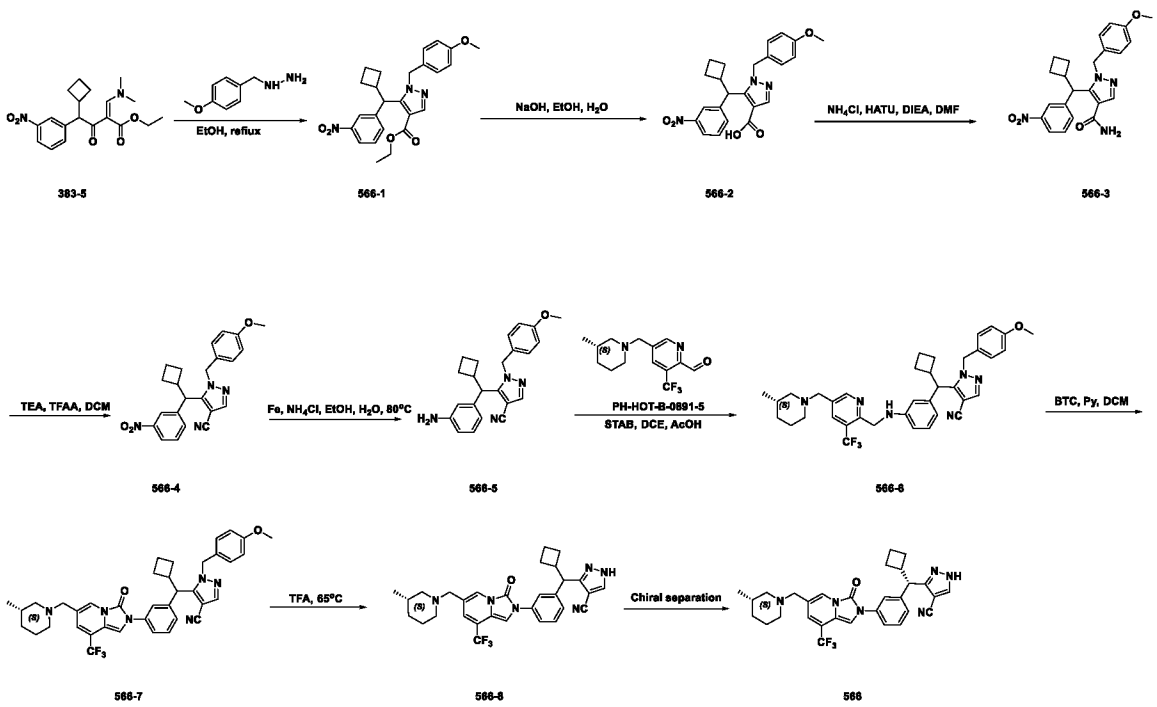
[1913] 547-2 (390 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALPAK IC (250mm*30mm,10um); mobile phase: [MeOH (0.1%IPAm)]; B%: 66%-66%, 30min. Flow rate: 4mL/min; Wave Length: 220/254 nm; RT1

(min): 1.691) to afford crude 565_P2. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(FA)-ACN];B%: 20%-60%, 8 min, Wave Length: 220 nm; RT1 (min): 5.5 min) to afford 565_P2 (50 mg, 12.84%) as a yellow solid.

MS-565_P2: (ES, m/z): [M+H]+ 511.2.

1H-NMR-565_P2: (400 MHz, CHLOROFORM-d) δ 8.04 (s, 1H), 7.79 (s, 1H), 7.62 (s, 1H), 7.52-7.48 (m, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.20-7.18 (m, 1H), 7.12 (s, 1H), 6.77 (s, 1H), 4.09-3.84 (m, 5H), 3.52-3.35 (m, 5H), 2.45-2.27 (m, 3H), 1.98-1.80 (m, 4H), 1.76-1.69 (m, 1H), 1.45 (m, 3H).

Example 558. Synthesis of Compound 566



1. Synthesis of 566-1

[1914] Into a 500 mL round-bottom flask were added 383-5 (17 g, 47.169 mmol, 1 equiv), [(4-methoxyphenyl)methyl]hydrazine (8.61 g, 56.603 mmol, 1.2 equiv) and EtOH (200 mL) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (1000 mL). The aqueous layer was extracted with EtOAc (3x400 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 566-1 (15 g, 65.09%) as a colorless oil.

2. Synthesis of 566-2

[1915] Into a 250 mL round-bottom flask were added 566-1 (7 g, 15.573 mmol, 1 equiv), NaOH (1.25 g, 31.146 mmol, 2 equiv), EtOH (70 mL) and H_2O (20 mL) at room temperature. The resulting mixture was stirred for overnight at 50 °C. The residue was neutralized to pH 7 with 1M HCl (40 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The resulting solid was dried under vacuum. This resulted in 566-2 (6 g, 86.85%) as a white solid.

3. Synthesis of 566-3

[1916] Into a 250 mL round-bottom flask were added 566-2 (6 g, 14.236 mmol, 1 equiv), NH_4Cl (3.81 g, 71.180 mmol, 5 equiv), HATU (10.83 g, 28.472 mmol, 2 equiv), DIEA (5.52 g, 42.708 mmol, 3 equiv) and DMF (70 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (80:1) to afford 566-3 (5 g, 77.68%) as a white oil.

4. Synthesis of 566-4

[1917] Into a 250 mL round-bottom flask were added 566-3 (3 g, 7.135 mmol, 1 equiv), DCM (50 mL) and TEA (3.61 g, 35.675 mmol, 5 equiv) at room temperature. To the above mixture was added TFAA (4.50 g, 21.405 mmol, 3 equiv) dropwise at room temperature. The resulting mixture was stirred for 5 h at room temperature. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (3x150 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (100:1) to afford 566-4 (2 g, 64.08%) as a white oil.

5. Synthesis of 566-5

[1918] Into a 100 mL round-bottom flask were added 566-4 (2 g, 4.970 mmol, 1 equiv), Fe (1.39 g, 24.850 mmol, 5 equiv), NH_4Cl (2.66 g, 49.700 mmol, 10 equiv), EtOH (20 mL) and H_2O (5 mL) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was filtered; the filter cake was washed with DCM (3x30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH=15:1) to afford 566-5 (1.2 g, 60.29%) as a white oil.

6. Synthesis of 566-6

[1919] Into a 100 mL round-bottom flask were added 566-5 (1.2 g, 3.222 mmol, 1 equiv), I-2 (1.11 g, 3.866 mmol, 1.2 equiv), STAB (1.37 g, 6.444 mmol, 2 equiv) and DCE (20 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The

reaction was quenched with sat. NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 566-6 (1.2 g, 53.31%) as a colorless oil.

7. Synthesis of 566-7

[1920] Into a 100 mL round-bottom flask were added 566-6 (1.2 g, 1.867 mmol, 1 equiv), pyridine (1.18 g, 14.936 mmol, 8 equiv) and DCM (30 mL) at room temperature. To the above mixture was added triphosgene (0.28 g, 0.933 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 3 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 566-7 (700 mg, 52.14%) as a yellow solid.

8. Synthesis of 566-8

[1921] Into a 50 mL round-bottom flask were added 566-7 (660 mg, 0.987 mmol, 1 equiv) and TFA (10 mL) at room temperature. The resulting mixture was stirred for overnight at 65 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The crude product (440 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 60% B to 85% B in 8 min; Wave Length: 254 nm; RT1(min): 7.77) to afford 566-8 (140 mg, 25.60%) as a yellow solid.

9. Synthesis of 566

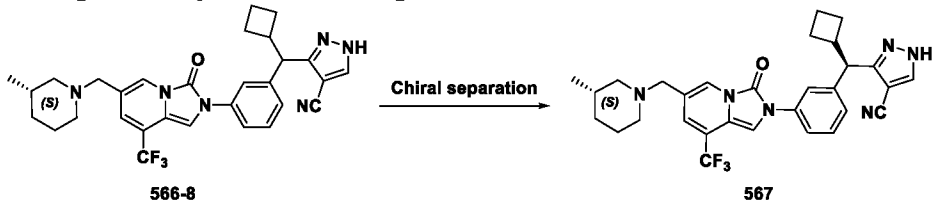
[1922] The 566-8 (140 mg, 0.255 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: HeX=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 21 min; Wave Length: 220/254 nm; RT1(min): 10.04; RT2(min): 12.22; The first peak was the product. Sample Solvent: EtOH: HeX=1: 1; Injection Volume: 0.4 mL; Number of Runs: 8) to afford 566 (52.8 mg, 37.64%) as a yellow solid.

LC-MS-566: (ES, *m/z*): $[M+H]^+$ 549

H-NMR-566: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.79-0.94 (m, 4H), δ1.44-1.47 (m, 1H), δ1.58-1.70 (m, 5H), δ1.76-1.88 (m, 5H), δ1.90-2.01 (m, 1H), δ2.76 (s, 2H), δ3.26 (s, 3H),

δ4.21-4.24 (d, 1H), δ7.01 (s, 1H), δ7.25-7.27 (d, 1H), δ7.31 (s, 1H), δ7.43-7.47 (t, 1H), δ7.67-7.72 (m, 2H), δ7.77 (s, 1H), δ8.31 (s, 1H), δ13.59 (s, 1H).

Example 559. Synthesis of Compound 567



566-8 567

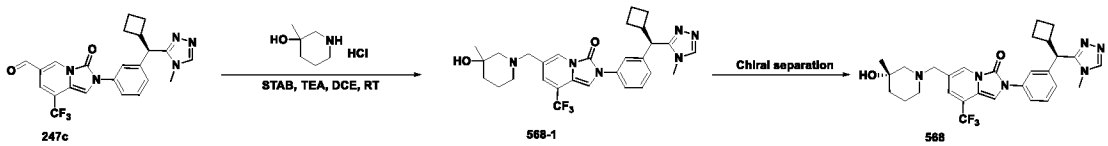
1. Synthesis of 567

[1923] The 566-8 (140 mg, 0.255 mmol, 1 equiv) was purified by chiral separation with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: HeX=1: 1; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 21 min; Wave Length: 220/254 nm; RT1(min): 10.04; RT2(min): 12.22; The second peak was the product. Sample Solvent: EtOH: HeX=1: 1; Injection Volume: 0.4 mL; Number of Runs: 8) to afford 567 (56.0 mg, 39.64%) as a yellow solid.

LC-MS-567: (ES, *m/z*): $[M+H]^+$ 549

H-NMR-567: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ0.79-0.94 (m, 4H), δ1.44-1.47 (m, 1H), δ1.58-1.70 (m, 5H), δ1.76-1.88 (m, 5H), δ1.90-2.01 (m, 1H), δ2.76 (s, 2H), δ3.26 (s, 3H), δ4.21-4.24 (d, 1H), δ7.01 (s, 1H), δ7.25-7.27 (d, 1H), δ7.31 (s, 1H), δ7.43-7.47 (t, 1H), δ7.67-7.72 (m, 2H), δ7.77 (s, 1H), δ8.31 (s, 1H), δ13.58 (s, 1H).

Example 560. Synthesis of Compound 568



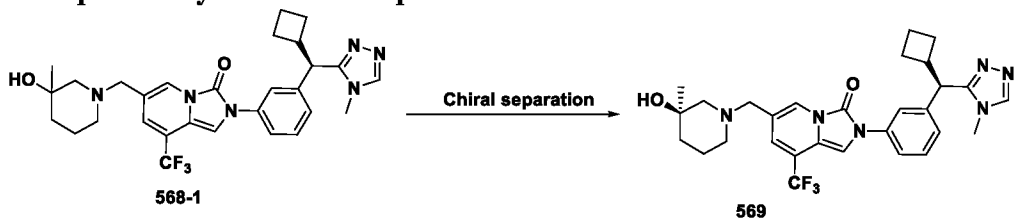
247c 568-1 568

1. Synthesis of 568-1

[1924] To a stirred solution/mixture of 247c (1 g, 2.197 mmol, 1 equiv) and 3-methylpiperidin-3-ol hydrochloride (0.50 g, 3.296 mmol, 1.5 equiv) in DCE (15 mL) was added TEA (1.00 g, 9.882 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (1.40 g, 6.588 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 /

MeOH 20:1) to afford 568-1 (300 mg, 24.65%) as a yellow solid.

Example 561. Synthesis of Compound 569



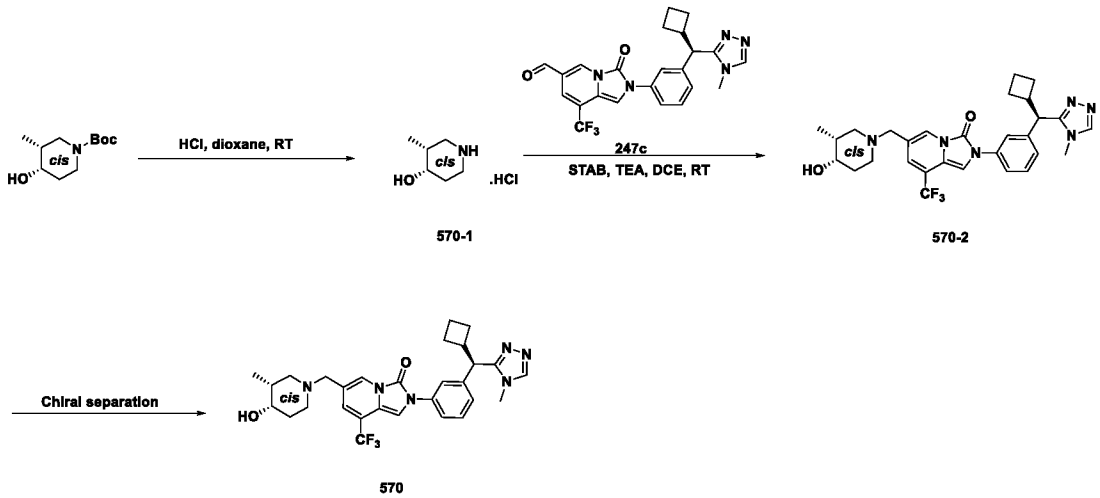
1. Synthesis of 569

[1925] The 568-1 (300 mg) was purified by chiral separation with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 12 min; Wave Length: 220/254 nm; RT1(min): 7.83; RT2(min): 9.70; the second peak is product) to afford 569 (114.7 mg, 58.57%) as a yellow solid.

LC-MS-569: (ES, *m/z*): $[M+H]^+$ 555

H-NMR-569: (400 MHz, DMSO-d_6, δ *ppm*): 1.12 (s, 3H), 1.31-1.58 (m, 3H), 1.61-1.73 (m, 2H), 1.73-1.87 (m, 4H), 2.08-2.10 (m, 2H), 2.21-2.23 (m, 2H), 2.33-2.39 (m, 1H), 3.19-3.25 (m, 2H), 3.25-3.33 (m, 1H), 3.46 (s, 3H), 4.24-4.27 (m, 2H), 7.07 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.71 (d, 1H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 562. Synthesis of Compound 570



1. Synthesis of 570-1

[1926] Into a 100mL round-bottom flask were added tert-butyl 4-hydroxy-3-methylpiperidine-1-carboxylate (1 g, 4.645 mmol, 1 equiv) and HCl(gas) in 1,4-dioxane (20 mL) at room temperature. The resulting mixture was stirred overnight at room temperature.

The resulting mixture was concentrated under vacuum. This resulted in 570-1 (1 g, 99.39%) as a light yellow solid. The crude product was used in the next step directly without further purification.

2. Synthesis of 570-2

[1927] To a stirred solution of 570-1 (1000 mg, 6.595 mmol, 1 equiv) and 247c (1501.82 mg, 3.297 mmol, 0.5 equiv) in DCE (10 mL) was added TEA (1334.74 mg, 13.190 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. To the above mixture was added STAB (2795.49 mg, 13.190 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (5x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford 570-2 (270 mg, 7.09%) as a yellow solid.

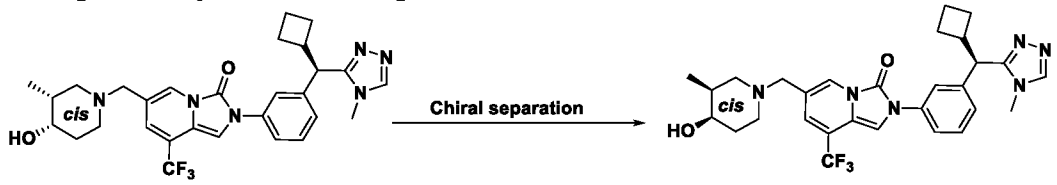
3. Synthesis of 570

[1928] The 570-1 (270 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 21 min; Wave Length: 220/254 nm; RT1(min): 13.65; RT2(min): 17.62; the first peak is product) to afford 570 (88.5 mg, 32.29%) as a yellow solid.

LC-MS-570: (ES, *m/z*): $[M+H]^+$ 555

H-NMR-570: (400 MHz, DMSO-d6, δ *ppm*): 0.79-0.86 (d, 3H), 1.59-1.68 (m, 2H), 1.70-1.91 (m, 6H), 2.00-2.45 (m, 5H), 3.19-3.33 (m, 3H), 3.20-3.43 (s, 3H), 3.59-3.60 (m, 1H), 4.25-4.27 (d, 1H), 4.38-4.40 (m, 1H), 7.01 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.66-7.70 (m, 2H), 7.74 (s, 1H), 8.34 (s, 1H).

Example 563. Synthesis of Compound 571



570-2 571

1. Synthesis of 571

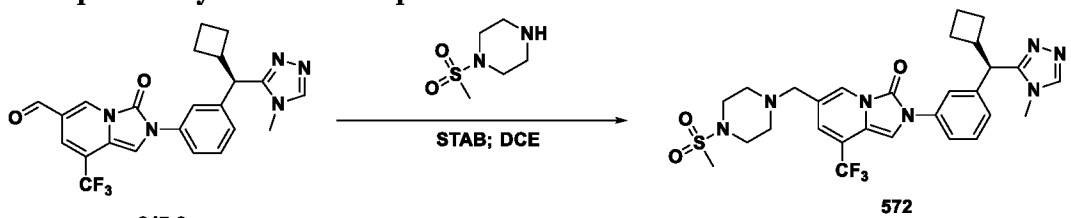
[1929] The 570-2 (270 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 21

min; Wave Length: 220/254 nm; RT1(min): 13.65; RT2(min): 17.62; the second peak is product) to afford 571 (82.1 mg, 29.83%) as a yellow solid.

LC-MS-571: (ES, *m/z*): $[M+H]^+$ 555

H-NMR-571: (400 MHz, DMSO-d6, δ *ppm*): 0.79-0.86 (d, 3H), 1.59-1.91 (m, 8H), 1.95-2.15 (m, 2H), 2.15-2.49 (m, 3H), 3.19-3.33 (m, 3H), 3.20-3.43 (s, 3H), 3.59-3.60 (m, 1H), 4.25-4.27 (d, 1H), 4.38-4.40 (m, 1H), 7.02 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.70 (m, 2H), 7.73 (s, 1H), 8.33 (s, 1H).

Example 564. Synthesis of Compound 572



247-3 572

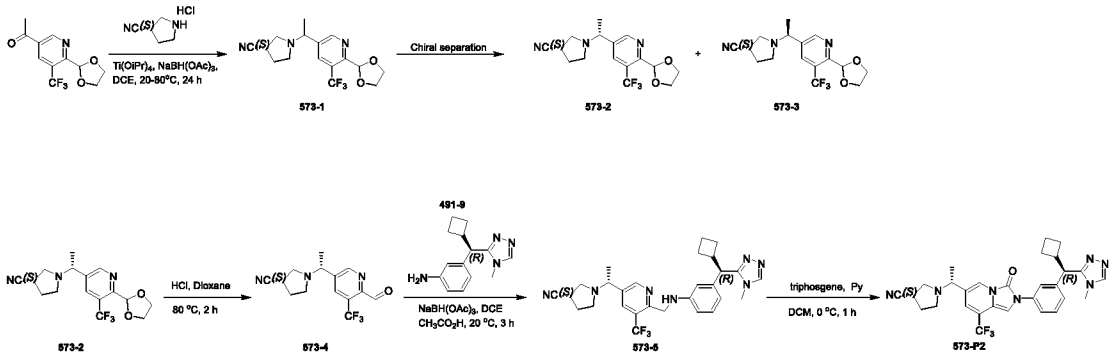
1. Synthesis of 572

[1930] Into a 40 mL sealed tube were added 1-methanesulfonylpiperazine (400 mg, 2.436mmol, 2equiv) DCE (4 mL) and 247-3(554.67 mg, 1.218mmol, 1equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (516.23 mg, 2.436mmol, 2equiv) at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2:MEOH(10:1) (3x10 mL).The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 5% to 65% gradient in 30 min; detector, UV 254 nm. This resulted in 572 (136.5 mg, 18.20%) as a yellow solid.

LC-MS-572: (ES, *m/z*): $[M+H]^+$ 604

H-NMR-572: (400 MHz, CD_3OD, δ *ppm*): 1.73-1.82 (m, 1H), 1.90-1.98 (m, 4H), 2.24-2.29 (m, H), 2.61-2.66 (m, 4H), 2.87 (s, 3H), 3.15-3.28 (m, 5H), 3.42 (s, 2H), 3.53 (s, 3H), 4.29-4.31 (m, 1H), 7.10-7.13 (d, 2H), 7.27-7.29 (d, 1H), 7.48-7.52 (t, 1H), 7.64-7.71 (m, 3H), 8.28 (s, 1H).

Example 565. Synthesis of Compound 573_P1



1. Synthesis of 573-1

[1931] To a solution of 1-(6-(1,3-dioxolan-2-yl)-5-(trifluoromethyl)pyridin-3-yl)ethanone (1.1 g, 4.21 mmol, 1 equiv) and (3S)-pyrrolidine-3-carbonitrile (837 mg, 6.32 mmol, 1.5 equiv, HCl) in DCE (20 mL) was added tetraisopropoxytitanium (3.59 g, 12.63 mmol, 3.73 mL, 3 equiv). The mixture was heated to 80°C and stirred at 80°C for 12 hr. Then sodium;triacetoxyboranuide (3.57 g, 16.85 mmol, 4 equiv) was added to reaction mixture at 20°C. The mixture was stirred at 80 °C for 12 hr under N2. The mixture was poured into NaHCO3 aq. (20 mL), extracted with EtOAc (10 mL x3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a crude. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to afford 573-1 (480 mg, 33.33%) as a yellow oil.

2. Synthesis of 573-2 and 573-3

[1932] 573-1 (480 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm,10um); mobile phase: [Neu-IPA];B%: 26%-26%, 7min Flow rate: 2.5 mL/min; Wave Length: 220/254 nm; RT1 (min): 2.142; RT2 (min): 2.487) to afford 573-2 (155 mg, 32.29%) as a yellow oil and 573-3 (220 mg, 45.83%) as a yellow oil.

1H-NMR-573-2: (400 MHz, METHANOL-d4) δ 8.80 (d, J = 1.6 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 6.17 (d, J = 1.2 Hz, 1H), 4.29-4.21 (m, 2H), 4.11-4.05 (m, 2H), 3.62 (q, J = 6.8 Hz, 1H), 3.21-3.18 (m, 1H), 2.91-2.87 (m, 1H), 2.75-2.71 (m, 1H), 2.67-2.57 (m, 2H), 2.30-2.24 (m, 1H), 2.09-2.02 (m, 1H), 1.44 (d, J = 6.8 Hz, 3H).

1H-NMR-573-3: (400 MHz, METHANOL-d4) δ = 8.80 (d, J = 1.2 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 6.17 (d, J = 0.8 Hz, 1H), 4.27-4.21 (m, 2H), 4.11-4.05 (m, 2H), 3.62 (q, J = 6.4 Hz, 1H), 3.21-3.16 (m, 1H), 2.91-2.82 (m, 2H), 2.66-2.62 (m, 1H), 2.49-2.43 (m, 1H), 2.29-2.24 (m, 1H), 2.11-2.03 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H).

3. Synthesis of 573-4

[1933] To a solution of 573-2 (155 mg, 454 umol, 1 equiv) in dioxane (1 mL) was added HCl (4M, 1 mL). The mixture was heated to 80 °C and stirred at 80 °C for 2 hr. The mixture was poured into NaHCO3 aq. (10 mL) adjust pH to 8-9, extracted with EtOAc (5 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. 573-4 (135 mg, crude) was obtained as a light-yellow oil.

4. Synthesis of 573-5

[1934] To a solution of 573-4 (135 mg, 454 umol, 1 equiv) in DCE (3 mL) was added 491-9 (110 mg, 454 umol, 1 equiv), acetic acid (27 mg, 454 umol, 25.97 uL, 1 equiv) at 20°C. The reaction was stirred for 1 h. Then NaBH(OAc)3 (193 mg, 908 umol, 2 equiv) was added and stirred at 20 °C for 2 hr. The mixture was poured into water (10 ml), extracted with DCM (5 ml *3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=20/1 to 0/1) and (DCM/MeOH=50/1 to 1/1) to afford 573-5 (200 mg, 84.11% yield) as a light-yellow solid..

1H-NMR-573-5: (400 MHz, METHANOL-d4) δ 8.70 (d, J = 1.6 Hz, 1H), 8.31-8.29 (m, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.07-7.03 (m, 1H), 6.59-6.56 (m, 1H), 6.51-6.49 (m, 1H), 6.47-6.45 (m, 1H), 4.52 (s, 2H), 3.98 (d, J = 10.8 Hz, 1H), 3.58-3.53 (m, 1H), 3.42 (s, 3H), 3.22-3.15 (m, 2H), 2.88-2.84 (m, 1H), 2.74- 2.70 (m, 1H), 2.67-2.55 (m, 2H), 2.29-2.19 (m, 2H), 2.08-2.01 (m, 1H), 1.89-1.70 (m, 5H), 1.43 (d, J = 6.8 Hz, 3H).

5. Synthesis of 573_P1

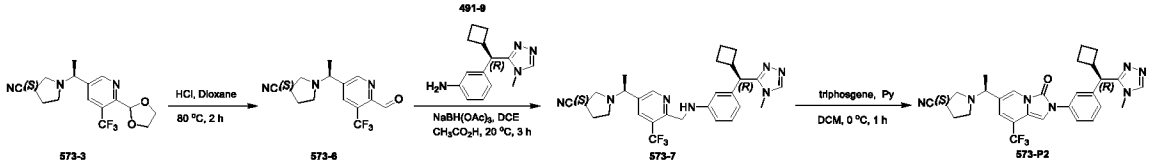
[1935] To a solution of 573-5 (150 mg, 286.48 umol, 1 equiv) in DCM (3 mL) was added Py (135 mg, 1.72 mmol, 139 uL, 6 equiv) and bis(trichloromethyl) carbonate (0.11 g, 370 umol, 1.29 equiv). The mixture was stirred at 0 °C for 1 hr. It was combined with a small test scale (50 mg) together. The reaction mixture was diluted with NaHCO3 aq. (15mL), extracted with DCM (10 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 10%-45%, 8 min, Wave Length: 220 nm; RT1 (min): 7.7 min) to afford 573_P1 (63.8 mg, 30.38% yield) as a yellow solid.

MS-573_P1: (ES, m/z): [M+H]+ 550.2.

1H-NMR-573_P1: (400 MHz, METHANOL-d4) δ 8.37 (d, J = 3.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.65-7.62 (m, 2H), 7.50-7.46 (m, 1H), 7.26-7.24 (m, 1H), 7.13 (d, J = 2.4 Hz, 2H), 4.29-4.26 (m, 1H), 3.54-3.50 (m, 3H), 3.26-3.19 (m, 2H), 2.87-2.83 (m, 2H), 2.70-2.67 (m,

2H), 2.27-2.24 (m, 2H), 2.08-2.04 (m, 1H), 1.95-1.80 (m, 5H), 1.78-1.73 (m, 1H), 1.41-1.35 (m, 3H).

Example 566. Synthesis of Compound 573_P2



1. Synthesis of 573-6

[1936] To a solution of 573-3 (220 mg, 645 umol, 1 equiv) in dioxane (1.5 mL) was added HCl (4M, 1.5 mL). The mixture was heated to 80 °C and stirred at 80 °C for 2 hr. The mixture was poured into NaHCO3 aq. (10 mL) adjust pH to 8-9, extracted with EtOAc (5 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. 573-6 (185 mg, crude) was obtained as a light-yellow oil.

2. Synthesis of 573-7

[1937] To a solution of 573-6 (185 mg, 622 umol, 1 equiv) in DCE (3 mL) was added 491-9 (151 mg, 622 umol, 1 equiv), CH3COOH (37.37 mg, 622.32 umol, 35.63 uL, 1 equiv) at 20°C stirred for 1 hr. Then NaBH(OAc)3 (264 mg, 1.24 mmol, 2 equiv) was added and stirred at 20 °C for 2 hr. The mixture was poured into water (10 ml), extracted with DCM (5 ml *3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=20/1 to 0/1) and (DCM/MeOH=50/1 to 1/1) to afford 573-7 (290 mg, 89.00% yield) as a light-yellow solid.

1H-NMR-573-7: (400 MHz, METHANOL-d4) δ 8.70 (s, 1H), 8.31-8.30 (m, 1H), 8.10 (d, J = 1.2 Hz, 1H), 7.07-7.03 (m, 1H), 6.59-6.57 (m, 1H), 6.51-6.49 (m, 1H), 6.47-6.45 (m, 1H), 4.52 (s, 2H), 3.98 (d, J = 10.8 Hz, 1H), 3.58-3.52 (m, 1H), 3.41 (s, 3H), 3.21-3.14 (m, 2H), 2.89-2.82 (m, 2H), 2.64-2.61 (m, 1H), 2.47-2.41 (m, 1H), 2.31-2.19 (m, 2H), 2.10-2.04 (m, 1H), 1.89-1.70 (m, 5H), 1.42 (d, J = 6.8 Hz, 3H).

3. Synthesis of 573_P2

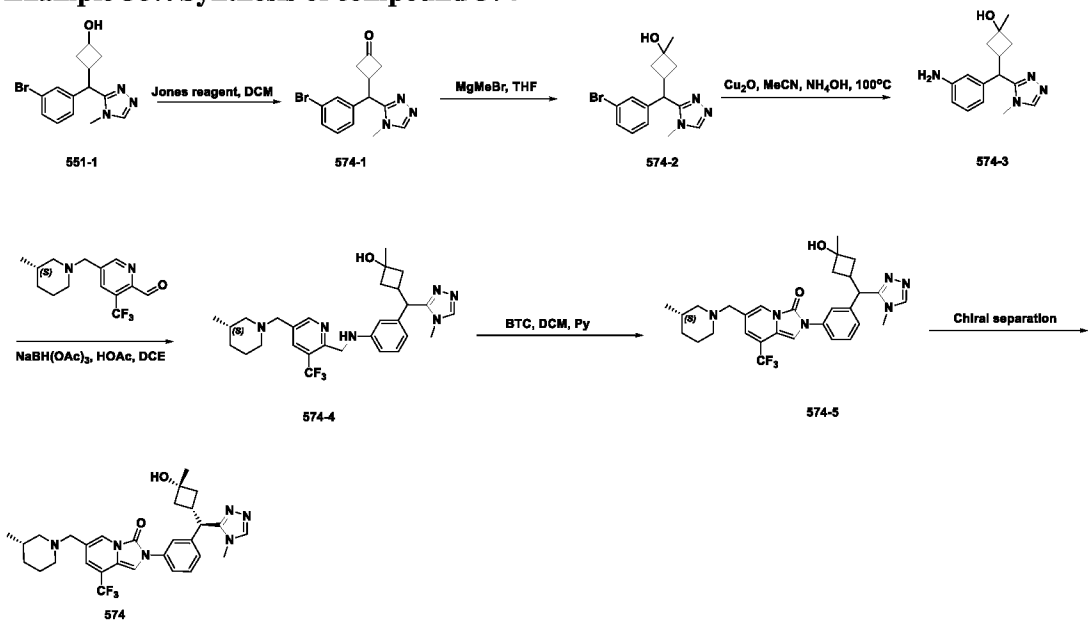
[1938] To a solution of 573-7 (240 mg, 458 umol, 1 equiv) in DCM (4 mL) was added Py (218 mg, 2.75 mmol, 222 uL, 6 equiv) and bis(trichloromethyl) carbonate (0.07 g, 235.89 umol, 0.5 equiv). The mixture was stirred at 0 °C for 1 hr. It was combined with a small test scale (50 mg) together. The reaction mixture was diluted with NaHCO3 aq. (15mL), extracted with DCM (10 mL x3). The combined organic layer was washed with brine (10

mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 10%-45%, 8 min, Wave Length: 220 nm; RT1 (min): 7.7 min) to afford 573_P2 (99.4 mg, 32.65% yield) as a yellow solid.

MS-573_P2: (ES, m/z): [M+H]+ 550.2.

1H-NMR-573_P2: (400 MHz, METHANOL-d4) δ 8.36 (s, 1H), 7.68 (s, 1H), 7.65-7.64 (m, 1H), 7.62 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 4.28 (d, J = 10.4, 1H), 3.53(s, 3H), 3.27-3.17 (m, 2H), 2.95-2.91 (m, 1H), 2.86-2.82 (m, 1H), 2.74-2.70 (m, 1H), 2.57-2.51 (m, 1H), 2.30-2.23 (m, 2H), 2.10-2.05 (m, 1H), 1.95-1.85 (m, 5H), 1.80-1.73 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H).

Example 567. Synthesis of compound 574



1. Synthesis of 574-1

[1939] To a stirred solution of 551-1 (2.4 g, 7.449 mmol, 1 equiv) in DCM (30 mL) was added Jones reagent (7.45 mL, 14.898 mmol, 2 equiv, 2 M) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL). The resulting mixture was filtered, the filter cake was washed with DCM (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 574-1(1.8 g, 75.47%) as a white solid.

2. Synthesis of 574-2

[1940] To a stirred solution of 574-1 (1.8 g, 5.622 mmol, 1 equiv) in THF (20 mL) was

added MeMgBr (6.75 mL, 6.746 mmol, 1.2 equiv, 1M in THF) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (60 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 5% to 70% gradient in 30 min; detector, UV 220 nm. This resulted in 574-2 (1.6 g, 84.65%) as a white solid.

3. Synthesis of 574-3

[1941] To a solution of 574-2 (1.6 g, 4.759 mmol, 1 equiv) in MeCN (48 mL) and NH_4OH (48 mL) was Cu_2O (0.27 g, 1.904 mmol, 0.4 equiv) in a pressure tank. The resulting mixture was stirred for overnight at 100°C. The resulting mixture was diluted with DCM (100 mL). The resulting mixture was filtered, the filter cake was washed with DCM (5 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 574-3 (1.2 g, 92.59%) as a light yellow solid.

4. Synthesis of 574-4

[1942] To a stirred solution of 574-3 (1.1 g, 4.039 mmol, 1 equiv) and I-2 (1.39 g, 4.847 mmol, 1.2 equiv) in DCE (20 mL) was added $NaBH(OAc)_3$ (1.71 g, 8.078 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (15:1) to afford 574-4 (1.2 g, 54.75%) as a white solid.

5. Synthesis of 574-5

[1943] To a stirred solution of 574-4 (1.2 g, 2.211 mmol, 1 equiv) and Pyridine (1.05 g, 13.266 mmol, 6 equiv) in DCM (24 mL) was added Triphosgene (0.26 g, 0.884 mmol, 0.4 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (30 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH (3 x 30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase,

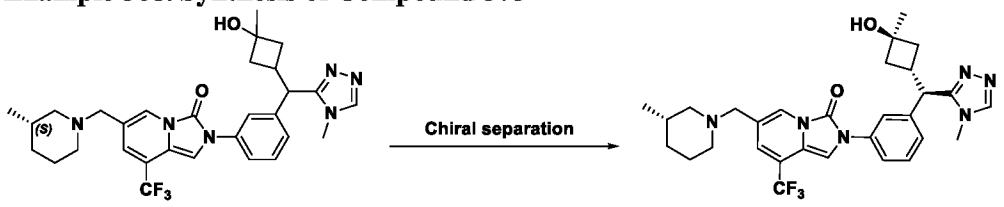
MeCN in Water (10mmol/L NH_4HCO_3), 10% to 75% gradient in 30 min; detector, UV 254 nm. This resulted in 574-5 (605 mg, 48.11%) as a yellow solid.

6. Synthesis of 574

[1944] 574-5 (815 mg, 1.433 mmol, 1 equiv) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.55; RT2(min): 2.68; RT3(min): 3.02; RT4(min): 4.37; the second peak was product) to afford crude product 152 mg. The crude product (152 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 11 min; Wave Length: 220/254 nm; RT1(min): 7.35; RT2(min): 8.72; the second peak was product) to afford 574 (156.2 mg, 19.17%) as a yellow solid.

LCMS:(ES, m/z): $[M+H]^+$ 569. NMR 0: (400 MHz, CD_3OD, δ ppm): 0.90-0.97 (m, 4H), 1.42 (s, 3H), 1.61-1.84 (m, 6H), 1.93-2.01 (m, 3H), 2.32-2.37 (m, 1H), 2.79-2.90 (m, 3H), 3.30 (s, 2H), 3.55 (s, 3H), 4.22-4.25 (d, 1H), 7.12 (s, 2H), 7.26-7.28 (d, 1H), 7.49-7.53 (t, 1H), 7.66-7.72 (m, 3H), 8.38 (s,1H).

Example 568. Synthesis of Compound 575



574-5 575

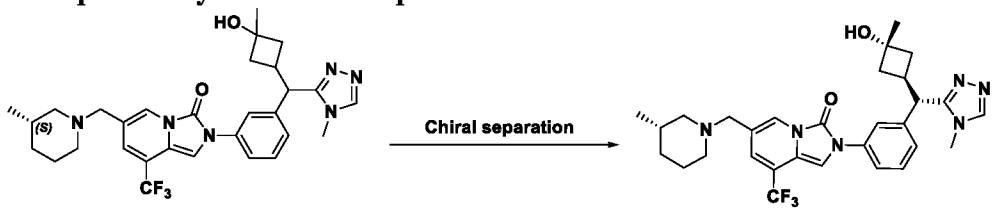
1. Synthesis of 575

[1945] 574-5 (815 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO2, Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.55; RT2(min): 2.68; RT3(min): 3.02; RT4(min): 4.37; the first peak was product) to afford crude product 98 mg. The crude product (98 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 8 min; Wave Length: 220/254 nm; RT1(min): 4.93; RT2(min):

6.56; the first peak was product) to afford 575 (14.0 mg, 1.72%) as a yellow solid.

LCMS-575:(ES, m/z): [M+H] + 569 NMR-575: (400 MHz, CD3OD, δ ppm): 0.90-0.97 (m, 4H), 1.42 (s, 3H), 1.61-1.85 (m, 6H), 1.94-2.06 (m, 3H), 2.34-2.40 (m, 1H), 2.84-2.90 (m, 2H), 3.32 (s, 2H), 3.38-3.42 (m, 1H), 3.55 (s, 3H), 4.24-4.27 (d, 1H), 7.12 (s, 2H), 7.27-7.29 (d, 1H), 7.48-7.52 (t, 1H), 7.65-7.70 (m, 3H), 8.37 (s,1H).

Example 569. Synthesis of Compound 576



574-5 576

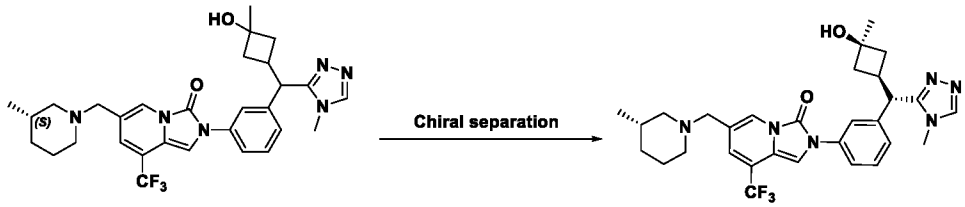
1. Synthesis of 576

[1946] 574-5 (815 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.55; RT2(min): 2.68; RT3(min): 3.02; RT4(min): 4.37; the third peak was product) to afford crude product 20 mg. The crude product (20 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 15 min; Wave Length: 220/254 nm; RT1(min): 9.90; RT2(min): 12.6; Sample Solvent: EtOH: DCM=1: 1; the second peak was product) to afford 2 576 (16.6 mg, 2.04%) as a yellow solid.

LCMS-576:(ES, m/z): $[M+H]^+$ 569

NMR-576: (400 MHz, CD_3OD, δ ppm): 0.89-0.95 (m, 4H), 1.35 (s, 3H), 1.59-1.85 (m, 6H), 1.94-2.04 (m, 3H), 2.34-2.39 (m, 1H), 2.85-2.91 (m, 3H), 3.33 (s, 2H), 3.40-3.43 (m, 1H), 3.55 (s, 3H), 4.24-4.27 (d, 1H), 7.12 (s, 2H), 7.27-7.29 (d, 1H), 7.48-7.52 (t, 1H), 7.66-7.69 (m, 3H), 8.37 (s,1H).

Example 570. Synthesis of Compound 577



574-5 577

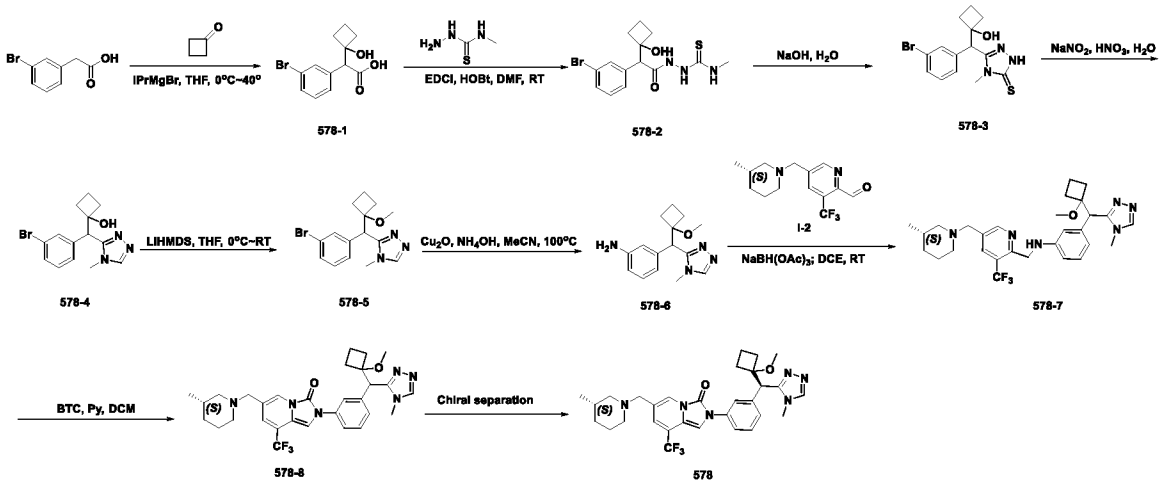
1. Synthesis of 577

[1947] 574-5 (815 mg) was purified by Prep-Chiral-SFC with the following conditions (Column: CHIRAL ART Cellulose-SB, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: DCM=1: 1(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 2.55; RT2(min): 2.68; RT3(min): 3.02; RT4(min): 4.37; the fourth peak was product) to afford 577 (217.5 mg, 26.69%) as a yellow solid.

LCMS-577:(ES,m/z): $[M+H]^+$ 569

NMR-577: (400 MHz, CD_3OD, δ ppm): 0.90-0.97 (m, 4H), 1.37 (s, 3H), 1.60-1.83 (m, 6H), 1.96-2.05 (m, 3H), 2.33-2.37 (m, 1H), 2.79-2.90 (m, 3H), 3.32 (s, 2H), 3.55 (s, 3H), 4.22-4.25 (d, 1H), 7.12 (s, 2H), 7.26-7.28 (d, 1H), 7.49-7.53 (t, 1H), 7.65-7.70 (m, 3H), 8.38 (s,1H).

Example 571. Synthesis of Compound 578



578-1 578-2 578-3 578-4 578-5 578-6 578-7 578-8 578

1. Synthesis of 578-1

[1948] Into a 1L 3-necked round-bottom flask were added m-bromophenylacetic acid (50 g, 232.508 mmol, 1 equiv) and THF (500 mL) at 0 °C. To the above mixture was added cyclobutanone (17.93 g, 255.759 mmol, 1.1 equiv) at 40°C. The resulting mixture was stirred for additional 2h at 40°C.The reaction was quenched with sat. NH_4Cl (aq.)(1500 mL)

at room temperature.The aqueous layer was extracted with EtOAc (3x1 L).The resulting mixture was concentrated under reduced pressure. This resulted in 579-1 (53g, crude) as a yellow solid.

2. Synthesis of 578-2

[1949] Into a 1000mL 3-necked round-bottom flask were added 579-1 (53 g, 185.876 mmol, 1 equiv) ,1-amino-3-methylthiourea (23.46 g, 223.051 mmol, 1.2 equiv), HOBt (37.67 g, 278.814 mmol, 1.5 equiv) and DMF (530 mL) at room temperature.The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere.To the above mixture was added EDCI (53.45 g, 278.814 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature.The reaction was quenched by the addition of sat. NH_4Cl (aq.) (1000mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under vacuum. This resulted in 578-2 (65g, crude) as a yellow solid.

3. Synthesis of 578-3

[1950] Into a 1000mL 3-necked round-bottom flask were added 578-2 (65 g, 174.600 mmol,1 equiv) , H_2O (700 mL) and NaOH (27.93 g, 698.400 mmol, 4 equiv)at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was acidified to pH 7 with HCl(1M). The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 578-3 (33 g, 37.35%) as a white solid.

4. Synthesis of 578-4

[1951] Into a 1L 3-necked round-bottom flask were added 5 578-3 (33 g, 93.149 mmol, 1 equiv), $NaNO_2$ (64.27 g, 931.490 mmol, 10 equiv) and H_2O (200 mL) at room temperature. To the above mixture was added HNO_3 (465.7 mL, 465.745 mmol, 5 equiv, 1M) dropwise over 30min at 0°C. The resulting mixture was stirred for additional 5h at room temperature.The reaction was quenched with sat. $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x1 L). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (30:1) to afford 578-4 (12 g, 37.98%) as a white solid.

5. Synthesis of 578-5

[1952] Into a 250mL 3-necked round-bottom flask were added 578-4(12 g, 37.243 mmol, 1 equiv) and THF (120 mL). To the above solution was added LiHMDS (18.70 g, 111.729 mmol, 3 equiv) at -40°C under nitrogen atmosphere. The resulting mixture was stirred for 1h

at -40°C under nitrogen atmosphere. To the above mixture was added MeI (10.57 g, 74.486 mmol, 2 equiv). The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (300mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 80% gradient in 30 min; detector, UV 220 nm. This resulted in 578-5 (1172 mg, 9.08%) as a white solid.

7. Synthesis of 578-6

[1953] Into a 100 mL pressure tank reactor were added 578-5 (1172 mg, 3.486 mmol, 1 equiv), Cu_2O (249.38 mg, 1.743 mmol, 0.5 equiv) ,NH_4OH (20 mL) and MeCN (20 mL) at room temperature.The resulting mixture was stirred for overnight at 100°C .The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% NH_4HCO_3), 10% to 60% gradient in 40 min; detector, UV 220 nm. This resulted in 578-6 (390 mg, 36.97%) as a white solid.

8. Synthesis of 578-7

[1954] To a stirred solution of 578-6 (370 mg, 1.359 mmol, 1 equiv) and 1-2 (466.74 mg, 1.631 mmol, 1.2 equiv) in DCE (10 mL) was added $NaBH(OAc)_3$ (575.86 mg, 2.718 mmol, 2 equiv). The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 578-7 (510 mg, 69.18%) as a white solid.

9. Synthesis of 578-8

[1955] To a stirred solution of 578-7 (490 mg, 0.903 mmol, 1 equiv) and Pyridine (428.55 mg, 5.418 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (107.18 mg, 0.361 mmol, 0.4 equiv) 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (15 mL). The resulting mixture was extracted with CH_2Cl_2/MeOH=10/1 (2 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 65% gradient in 25 min; detector, UV 254 nm. This resulted in 578-8 (360 mg, 70.11%) as a yellow solid.

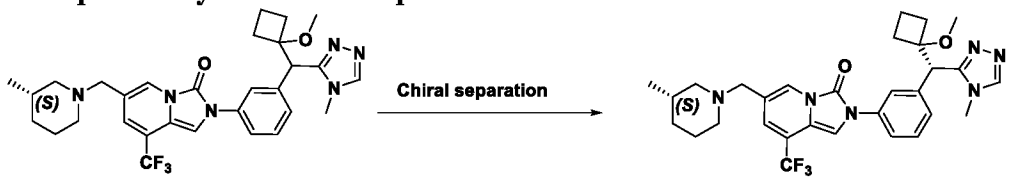
10. Synthesis of 578

[1956] 578-8 (360 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm; RT1(min): 12.04; RT2(min): 16.05; the first peak was product) to afford 578 (126.5 mg, 35.14%) as a yellow solid.

LCMS-578:(ES,m/z): $[M+H]^+$ 569

NMR-578: (400 MHz, DMSO, δ ppm): 0.89-0.99 (m, 4H), 1.12-1.20 (m, 1H), 1.46-1.51 (m, 1H), 1.58-1.74 (m, 5H), 1.80-1.91 (m, 1H), 2.11-2.20 (m, 1H), 2.27-2.36 (m, 3H), 2.71-2.82 (m, 2H), 3.25 (s, 3H), 3.26 (s, 2H), 3.51 (s, 3H), 4.66 (s, 1H), 7.02 (s, 2H), 7.25 (s, 1H), 7.45-7.49 (t, 1H), 7.56-7.57 (d, 1H), 7.67-7.72 (m, 2H), 8.03 (s,1H), 8.36 (s,1H).

Example 572. Synthesis of Compound 579



578-8 579

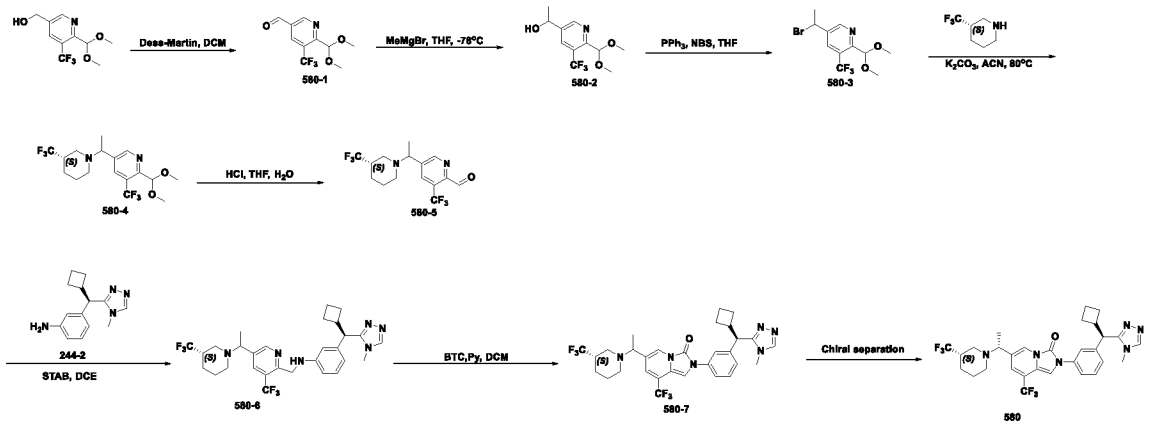
1. Synthesis of 579

[1957] 578-8 (360 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm; RT1(min): 12.04; RT2(min): 16.05; the second peak was product) to afford 579 (126.5 mg, 35.14%) as a yellow solid.

LCMS-579:(ES, m/z): $[M+H]^+$ 569

NMR-579: (400 MHz, DMSO, δ ppm): 0.82-0.99 (m, 4H), 1.10-1.17 (m, 1H), 1.44-1.50 (m, 1H), 1.59-1.67 (m, 5H), 1.90-1.92 (m, 1H), 2.17-2.27 (m, 2H), 2.29-2.38 (m, 2H), 2.76-2.82 (m, 2H), 3.25 (s, 3H), 3.26 (s, 2H), 3.51 (s, 3H), 4.66 (s, 1H), 7.02 (s, 2H), 7.25 (s, 1H), 7.45-7.49 (t, 1H), 7.56-7.58 (d, 1H), 7.68-7.73 (m, 2H), 8.03 (s,1H), 8.36 (s,1H).

Example 573. Synthesis of Compound 580



1. Synthesis of 580-1

[1958] Into a 100mL 3-necked round-bottom flask were added (6-(dimethoxymethyl)-5-(trifluoromethyl)pyridin-3-yl)methanol (5 g, 19.904 mmol, 1 equiv), DCM (50 mL) and Dess-Martin (10.13 g, 23.885 mmol, 1.2 equiv) at 0°C. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (40 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to afford 580-1 (4 g, 80.65%) as a yellow oil.

2. Synthesis of 580-2

[1959] Into a 100mL 3-necked round-bottom flask were added 580-1 (3.8 g, 15.249 mmol, 1 equiv) and THF (30 mL) at room temperature. To the above mixture was added MeMgBr (1M in THF) (15.2 mL) dropwise over 20 min at -78°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (40 mL) at 0°C. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 580-2 (2.7 g, 66.75%) as a yellow oil.

3. Synthesis of 580-3

[1960] Into a 100mL 3-necked round-bottom flask were added 580-2 (2.8 g, 10.557 mmol, 1 equiv), THF (30 mL) and NBS (3.76 g, 21.114 mmol, 2 equiv) at room temperature. To the above mixture was added PPh_3 (5.54 g, 21.114 mmol, 2 equiv) at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched with water (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 580-3 (2.2 g, 63.51%) as a

yellow oil.

4. Synthesis of 580-4

[1961] Into a 50mL 3-necked round-bottom flask were added 580-3 (510 mg, 1.554 mmol, 1 equiv), ACN (5 mL), (3S)-3-(trifluoromethyl)piperidine (261.84 mg, 1.709 mmol, 1.1 equiv) and K_2CO_3 (429.61 mg, 3.108 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched with sat. NH_4Cl (aq.) (5 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 580-4 (450 mg, 72.32%) as a yellow solid.

5. Synthesis of 580-5

[1962] Into a 50mL 3-necked round-bottom flask were added 580-4 (500 mg, 1.249 mmol, 1 equiv), HCl(1M) (2.5 mL) and THF (2.5 mL) at room temperature. The resulting mixture was stirred for overnight at 60°C. The mixture was allowed to cool down to room temperature. The mixture was basified to pH 6 with saturated $NaHCO_3$ (aq.) (5 mL). The aqueous layer was extracted with EtOAc (3x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 580-5 (400 mg, 90.40%) as a yellow oil.

6. Synthesis of 580-6

[1963] Into a 50mL 3-necked round-bottom flask were added 580-5 (380 mg, 1.073 mmol, 1 equiv), DCE (4 mL) and 244-2 (259.91 mg, 1.073 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. To the above mixture was added STAB (454.63 mg, 2.146 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (4 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 580-6 (410 mg, 65.84%) as a yellow solid.

7. Synthesis of 580-7

[1964] Into a 50mL 3-necked round-bottom flask were added 580-6 (410 mg, 0.706 mmol, 1 equiv), DCM (8 mL) and pyridine (558.55 mg, 7.060 mmol, 10 equiv) at room temperature. To the above mixture was added triphosgene (73.34 mg, 0.247 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for additional 30min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (4 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x8 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 580-7 (320 mg, 74.70%)

as a yellow solid.

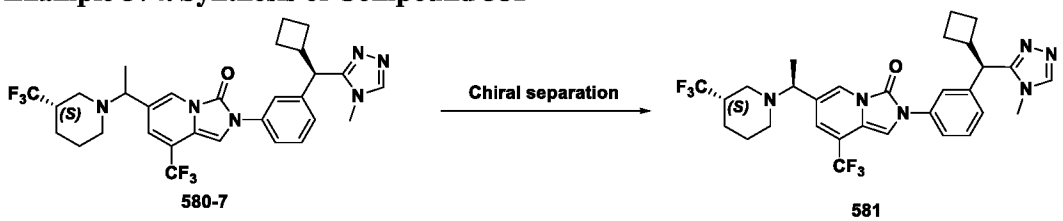
8. Synthesis of 580

[1965] The 580-7 (320 mg) was purified by Chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18 min; Wave Length: 220/254 nm; RT1(min): 9.83; RT2(min): 13.99;The first peak in product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 6) to afford 580 (130.2 mg, 35.96%) as a yellow solid.

LC-MS-580: (ES, *m/z*): $[M+H]^+$ 556

H-NMR-580: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.19-1.26 (m, 4H), δ1.42-1.44 (d, 1H), δ1.63-1.81 (m, 7H), δ2.00-2.09 (m, 3H), δ2.40-2.42 (d, 1H), δ2.82-2.85 (d, 1H), δ2.92-2.95 (d, 1H), δ3.21-3.25 (m, 1H), δ3.43 (s, 3H), δ3.56-3.58 (d, 1H), δ4.25-4.27 (d, 1H), δ7.07 (s, 1H), δ7.18-7.20 (d, 1H), δ7.31 (s, 1H), δ7.42-7.46 (t, 1H), δ7.63-7.73 (m, 3H), δ8.33 (s, 1H).

Example 574. Synthesis of Compound 581



580-7 581

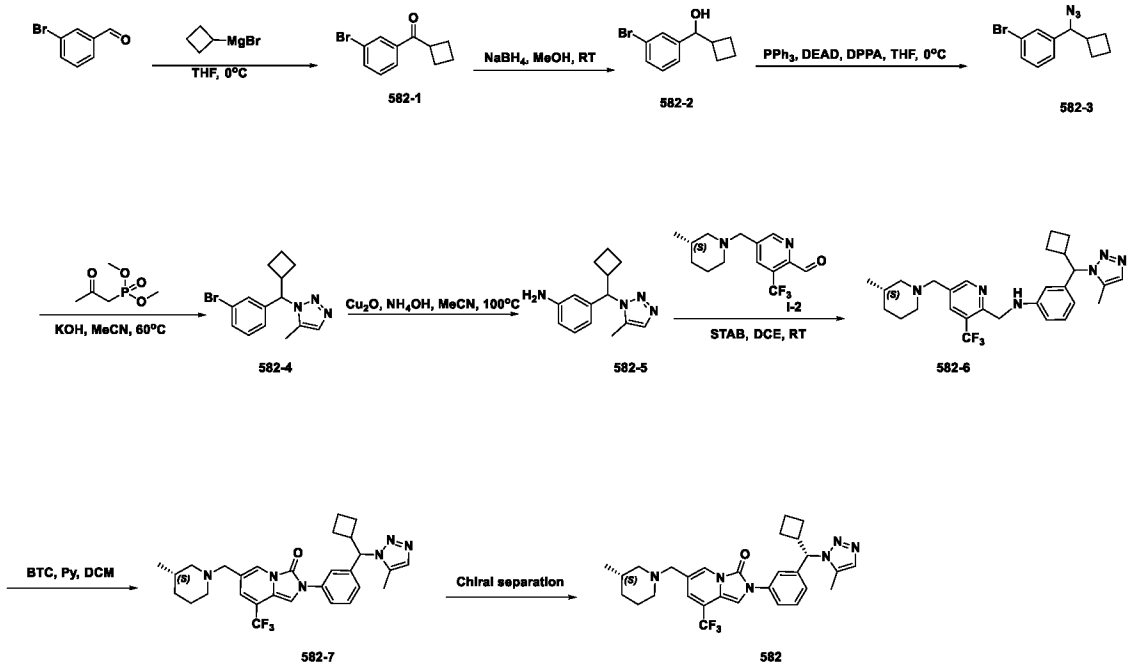
1. Synthesis of 581

[1966] The 580-7 (320 mg) was purified by Chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18 min; Wave Length: 220/254 nm; RT1(min): 9.83; RT2(min): 13.99; The second peak in product; Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 6) to afford 581 (136.9 mg, 41.58%) as a yellow solid.

LC-MS-581: (ES, *m/z*): $[M+H]^+$ 607

H-NMR-581: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.19-1.26 (m, 4H), δ1.42-1.44 (d, 1H), δ1.79-1.85 (m, 7H), δ2.00-2.17 (m, 3H), δ2.45-2.51 (d, 1H), δ2.73-2.75 (d, 1H), δ2.99-3.01 (d, 1H), δ3.18-3.23 (m, 1H), δ3.43 (s, 3H), δ3.60 (s, 1H), δ4.25-4.27 (d, 1H), δ7.11 (s, 1H), δ7.18-7.20 (d, 1H), δ7.31 (s, 1H), δ7.42-7.46 (t, 1H), δ7.59 (s, 1H), δ7.68-7.73 (m, 2H), δ8.33 (s, 1H).

Example 575. Synthesis of Compound 582



1. Synthesis of 582-1

[1967] To a stirred solution of 3-bromobenzaldehyde (45 g, 243.217 mmol, 1.00 equiv) in THF (500 mL) were added bromo(cyclobutyl)magnesium (486 mL, 486.434 mmol, 2 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. The reaction was quenched with saturated NH_4Cl (aq.) (2000 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=100:1 to afford 582-1 (9 g, 15.48%) as a yellow oil.

2. Synthesis of 582-2

[1968] To a stirred mixture of 582-1 (5 g, 20.911 mmol, 1 equiv) in MeOH (50 mL) were added $NaBH_4$ (1.58 g, 41.822 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 582-2 (4 g, 79.33%) as a yellow oil.

3. Synthesis of 582-3

[1969] To a stirred solution of 582-2 (4 g, 16.589 mmol, 1 equiv) and DPPA (6.85 g, 24.883

mmol, 1.5 equiv) in THF (40 mL) was added DEAD (5.78 g, 33.178 mmol, 2 equiv) and PPh_3 (6.53 g, 24.883 mmol, 1.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA=5:1 to afford 582-3 (3 g, 67.95%) as a yellow oil.

4. Synthesis of 582-4

[1970] To a stirred mixture of 582-3 (3 g, 11.272 mmol, 1 equiv) and dimethyl 2-oxopropylphosphonate (2.81 g, 16.908 mmol, 1.5 equiv) in MeCN (30 mL) were added KOH (1.90 g, 33.816 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 4 h at 80°C. The reaction was quenched with water (200 mL) at room temperature. The aqueous layer was extracted with EtOAc (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:1) to afford 582-4 (900 mg, 26.07%) as a yellow solid.

5. Synthesis of 582-5

[1971] To a stirred mixture of 582-4 (1.08 g, 3.527 mmol, 1.00 equiv) and NH_4OH (5.00 mL) in MeCN (5 mL) were added Cu_2O (0.10 g, 0.705 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred overnight at 100°C. The resulting mixture was filtered, the filter cake was washed with MeOH (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=30:1) to afford 582-5 (600 mg, 70.20%) as a yellow solid.

6. Synthesis of 582-6

[1972] To a stirred mixture of 582-5 (580 mg, 2.393 mmol, 1 equiv) and I-2 (822.29 mg, 2.872 mmol, 1.2 equiv) in DCE (6 mL) were added STAB (1521.82 mg, 7.179 mmol, 3 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=20:1) to afford 582-6 (600 mg, 48.90%) as a yellow solid.

7. Synthesis of 582-7

[1973] To a stirred solution of 582-6 (580 mg, 1.131 mmol, 1 equiv) and pyridine (536.98 mg, 6.786 mmol, 6 equiv) in DCM (8 mL) were added Triphosgene (117.51 mg, 0.396 mmol, 0.35 equiv) at 0°C. The resulting mixture was stirred for 10 min at room temperature. The

reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 582-7 (450 mg, 73.84%) as a yellow solid.

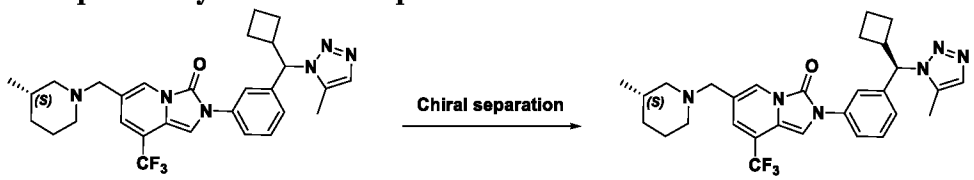
8. Synthesis of 582

[1974] The 582-7 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 10.5 min; Wave Length: 220/254 nm; RT1 (min): 5.97; RT2 (min): 8.25; the first peak is product) to afford 582 (201.8 mg, 44.62%) as a yellow solid.

LC-MS-582: (ES, *m/z*): $[M+H]^+$ 539

H-NMR-582: (400 MHz, DMSO-d6, δ *ppm*): 0.82-0.93 (m, 4H), 1.40-1.49 (m, 1H), 1.49-1.84 (m, 4H), 1.84-1.86 (m, 1H), 1.86-1.98 (m, 6H), 2.24 (s, 3H), 2.72-2.77 (m, 2H), 3.24-3.30 (m, 2H), 3.53-3.59 (m, 1H), 5.60-5.63 (m, 1H), 7.01 (s, 1H), 7.26-7.28 (m, 1H), 7.28-7.32 (m, 1H), 7.47-7.51 (m, 2H), 7.65 (s, 1H), 7.74-7.76 (s, 1H), 7.82 (s, 1H).

Example 576. Synthesis of Compound 583



582-7 583

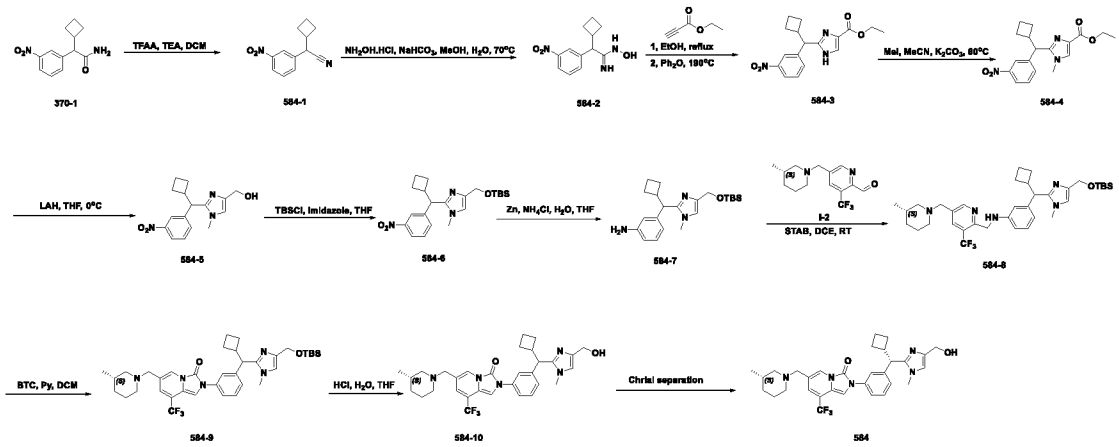
1. Synthesis of 583

[1975] The 582-7 (450 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2 M NH_3-MeOH), Mobile Phase B: EtOH:DCM=1:1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 10.5 min; Wave Length: 220/254 nm; RT1 (min): 5.97; RT2 (min): 8.25; the second peak is product) to afford 583 (201.8 mg, 43.71%) as a yellow solid.

LC-MS-583: (ES, *m/z*): $[M+H]^+$ 539

H-NMR-583: (400 MHz, DMSO-d6, δ *ppm*): 0.82-0.93 (m, 4H), 1.40-1.49 (m, 1H), 1.49-1.84 (m, 4H), 1.84-1.86 (m, 1H), 1.86-1.97 (m, 6H), 2.24 (s, 3H), 2.72-2.77 (m, 2H), 3.24-3.30 (m, 2H), 3.53-3.63 (m, 1H), 5.60-5.63 (m, 1H), 7.01 (s, 1H), 7.26-7.28 (m, 1H), 7.28-7.32 (m, 1H), 7.47-7.51 (m, 2H), 7.65 (s, 1H), 7.74-7.76 (s, 1H), 7.85 (s, 1H).

Example 577. Synthesis of Compound 584



1. Synthesis of 584-1

[1976] To a stirred solution of 370-1 (39 g, 166.485 mmol, 1 equiv) and TEA (42.12 g, 416.213 mmol, 2.5 equiv) in DCM (500 mL, 7865.301 mmol, 47.24 equiv) were added TFAA (41.96 g, 199.782 mmol, 1.2 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 6h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (1000 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 584-1 (32 g, 86.22%) as a light yellow oil.

2. Synthesis of 584-2

[1977] To a stirred solution of 584-1 (10 g, 46.245 mmol, 1 equiv) and $NH_2OH.HCl$ (3.53 g, 50.870 mmol, 1.1 equiv) in MeOH (500 mL)/H_2O (50 mL) were added $NaHCO_3$ (8.55 g, 101.739 mmol, 2.2 equiv) at room temperature. The resulting mixture was stirred overnight at 70°C. The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM (500 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 584-2 (10 g, 69.40%) as a light yellow oil.

3. Synthesis of 584-3

[1978] To a stirred solution of 584-2 (10 g, 40.117 mmol, 1 equiv) in EtOH (200 mL) was added ethyl propiolate (5.90 g, 60.175 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The resulting mixture was concentrated under vacuum. The residue was dissolved in phenoxybenzene (150 mL). The resulting mixture was stirred for 4h at 190°C. The mixture was allowed to cool down to room temperature. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (50:1)

to afford crude product. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 584-3 (3.5 g, 23.84%) as a brown solid.

4. Synthesis of 584-4

[1979] To a stirred solution of 584-3 (3.5 g, 10.627 mmol, 1 equiv) and MeI (2.26 g, 15.941 mmol, 1.5 equiv) in MeCN (80 mL) was added K_2CO_3 (2.94 g, 21.254 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water (300 mL). The aqueous layer was extracted with EtOAc (2x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 3:1) to afford 584-4 (1.2 g, 30.58%) as a brown solid.

5. Synthesis of 584-5

[1980] To a stirred solution of 584-4 (1.2 g, 3.495 mmol, 1 equiv) in THF (50 mL) was added LAH (0.33 g, 8.738 mmol, 2.5 equiv) at 0°C. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (100 mL) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 584-4 (1 g, 75.97%) as a brown yellow solid.

6. Synthesis of 584-6

[1981] To a stirred solution of 584-5 (1 g, 3.318 mmol, 1 equiv) and Imidazole (0.68 g, 9.954 mmol, 3 equiv) in THF (50 mL) were added TBSCl (1.00 g, 6.635 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 3h at 70°C. The reaction was quenched with saturated NH_4Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under vacuum. This resulted in 584-6 (1 g, 58.01%) as a yellow oil. The crude product was used in the next step directly without further purification.

7. Synthesis of 584-7

[1982] To a stirred solution of 584-6 (1 g, 2.406 mmol, 1 equiv) and Zn (0.79 g, 12.030 mmol, 5 equiv) in THF (40 mL)/H_2O (10 mL) was added NH_4Cl (1.29 g, 24.060 mmol, 10 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x10 mL). The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x60 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 584-7 (620 mg, 60.14%) as a light yellow oil.

8. Synthesis of 584-8

[1983] To a stirred solution of 584-7 (600 mg, 1.556 mmol, 1 equiv) in DCE (10 mL) was added I-2 (579.09 mg, 2.023 mmol, 1.3 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added STAB (659.52 mg, 3.112 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was quenched with saturated $NHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 30:1) to afford 584-8 (600 mg, 54.68%) as a light yellow oil.

9. Synthesis of 584-9

[1984] To a stirred solution of 584-8 (600 mg, 0.915 mmol, 1 equiv) and Pyridine (723.56 mg, 9.150 mmol, 10 equiv) in DCM (20 mL) were added Triphosgene (108.57 mg, 0.366 mmol, 0.4 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. This resulted in 584-9 (520 mg, 75.03%) as a yellow solid. The crude product was used in the next step directly without further purification.

10. Synthesis of 584-10

[1985] To a stirred solution of 584-9 (520 mg, 0.763 mmol, 1 equiv) in THF (10 mL) was added HCl (10 mL, 2M) at room temperature. The resulting mixture was stirred for 3h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) at room temperature. The aqueous layer was extracted with DCM (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford 584-10 (400 mg, 89.63%) as a yellow solid.

11. Synthesis of 584

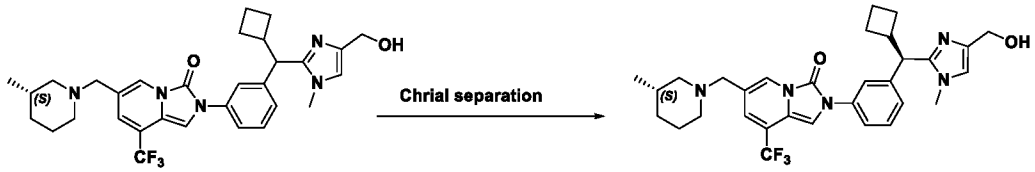
[1986] The 584-10 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 17 min; Wave Length: 220/254 nm; RT1(min): 11.78; RT2(min): 14.16; the first peak is product) to afford 584 (116.1 mg, 28.85%) as a yellow solid.

LC-MS-584: (ES, *m/z*): $[M+H]^+$ 568

H-NMR-584: (400 MHz, DMSO-d6, δ *ppm*): 0.81-0.95 (m, 4H), 1.41-1.55 (m, 1H), 1.55-1.71 (m, 5H), 1.71-1.82 (m, 4H), 1.82-1.98 (m, 1H), 2.02-2.06 (m, 1H), 2.73-2.77 (m, 2H), 3.14-3.25 (m, 3H), 3.44 (s, 3H), 4.12-4.14 (d, 1H), 4.30-4.32 (d, 2H), 4.72-4.75 (m, 1H), 6.81

(s, 1H), 7.01 (s, 1H), 7.21-7.23 (m, 1H), 7.28 (s, 1H), 7.39-7.43 (m, 1H), 7.64-7.66 (m, 2H), 7.76 (s, 1H).

Example 578. Synthesis of Compound 585



584-10 585

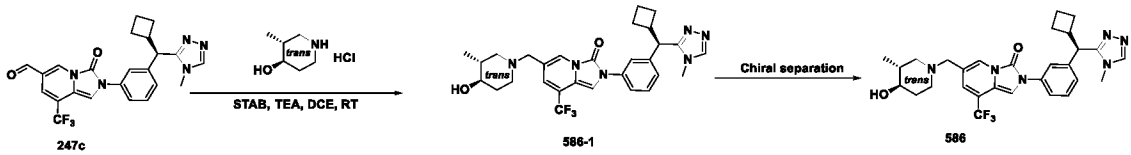
1. Synthesis of 585

[1987] The 584-10 (400 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 17 min; Wave Length: 220/254 nm; RT1(min): 11.78; RT2(min): 14.16; the second peak is product) to afford 585 (102.9 mg, 25.62%) as a yellow solid.

LC-MS-585: (ES, *m/z*): $[M+H]^+$ 568.

H-NMR-585: (400 MHz, DMSO-d6, δ *ppm*): 0.81-0.95 (m, 4H), 1.41-1.55 (m, 1H), 1.55-1.71 (m, 5H), 1.71-1.82 (m, 4H), 1.82-1.98 (m, 1H), 2.02-2.06 (m, 1H), 2.73-2.77 (m, 2H), 3.14-3.25 (m, 3H), 3.44 (s, 3H), 4.12-4.14 (d, 1H), 4.30-4.32 (d, 2H), 4.72-4.75 (m, 1H), 6.81 (s, 1H), 7.01 (s, 1H), 7.21-7.23 (m, 1H), 7.28 (s, 1H), 7.39-7.43 (m, 1H), 7.64-7.66 (m, 2H), 7.76 (s, 1H).

Example 579. Synthesis of Compound 586



247c 586-1 586

1. Synthesis of 586-1

[1988] To a stirred solution of 247c (1 g, 2.196 mmol, 1.00 equiv) and (3R,4R)-3-methylpiperidin-4-ol hydrochloride (0.50 g, 3.294 mmol, 1.5 equiv) in DCE (15 mL) were added TEA (0.44 g, 4.392 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (0.93 g, 4.392 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (aq.) (30mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The resulting

mixture was concentrated under reduced pressure. The crude product (600 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 47% B in 8 min, Wave Length: 254 nm; RT1(min): 7.43) to afford 586-1 (400 mg, 32.19%) as a yellow solid.

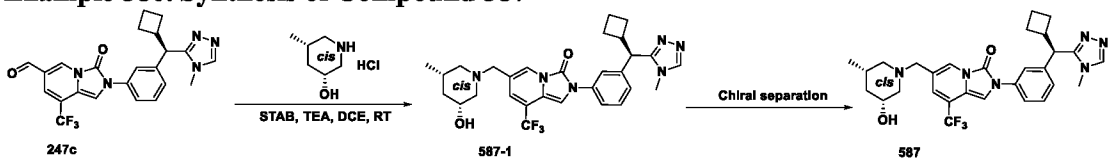
2. Synthesis of 586

[1989] The 586-1 (400 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.32; RT2(min): 8.41; the first peak is product) to afford 586 (49.9 mg, 12.34%) as a yellow solid.

LC-MS-586: (ES, *m/z*): $[M+H]^+$ 555

H-NMR-586: (400 MHz, DMSO-d6, δ *ppm*): 0.81-0.92 (d, 3H), 1.31-1.51 (m, 2H), 1.61-1.87 (m, 7H), 1.92-2.12 (m, 2H), 2.71-2.83 (m, 2H), 2.89-2.98 (m, 1H), 3.19-3.25 (m, 3H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 4.53-4.55 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.64-7.74 (m, 3H), 8.34 (s, 1H).

Example 580. Synthesis of Compound 587



1. Synthesis of 587-1

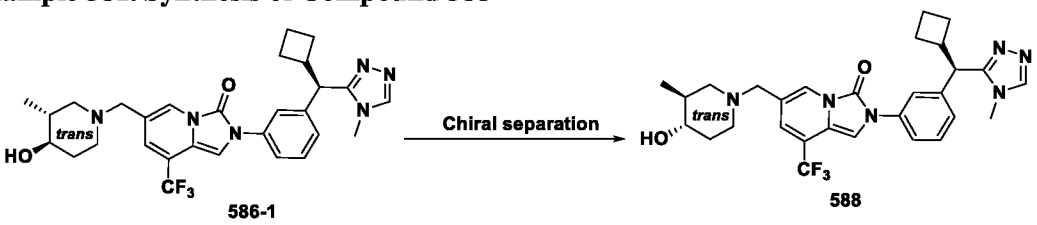
[1990] To a stirred solution of 247c (2.5 g, 5.4945 mmol, 1 equiv) and (3R,5S)-5-methylpiperidin-3-ol (0.95 g, 8.233 mmol, 1.5 equiv) in DCE (25 mL) was added TEA (1.11 g, 10.978 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (2.33 g, 10.978 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 5h at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (200 mL). The aqueous layer was extracted with DCM (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10 mmol/L NH_4HCO_3), 30% to 60% gradient in 20 min; detector, UV 254 nm. This resulted in 587-1 (1 g, 31.20%) as a yellow solid.

2. Synthesis of 587-2

[1991] The 587-1 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.12; RT2(min): 12.20; the first peak is product) to afford 587 (77.9 mg, 25.81%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 555. H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 0.67-0.81 (m, 1H), 0.81-0.94 (d, 3H), 1.88-1.92 (m, 9H), 2.06-2.10 (m, 1H), 2.68-2.73 (m, 1H), 2.67-2.73 (m, 1H), 2.81-2.93 (m, 1H), 3.19-3.30 (m, 2H), 3.30-3.32 (m, 1H), 3.36-3.48 (m, 4H), 4.25-4.28 (d, 1H), 4.61-4.71 (m, 1H), 7.01 (s, 1H), 7.19-7.21 (d, 1H), 7.32 (s, 1H), 7.44-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s,1H).

Example 581. Synthesis of Compound 588

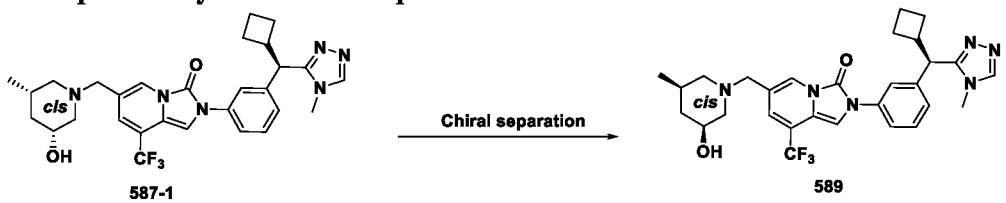


1. Synthesis of 588-0

[1992] The 586-1 (400 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 70% B to 70% B in 10.5 min; Wave Length: 220/254 nm; RT1(min): 6.32; RT2(min): 8.41; the second peak is product) to afford 588 (54.0 mg, 13.14%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 555. H-NMR: (400 MHz, DMSO-d6, δ ppm): 0.81-0.92 (d, 3H), 1.31-1.51 (m, 2H), 1.61-1.87 (m, 7H), 1.92-2.12 (m, 2H), 2.72-2.83 (m, 2H), 2.90-2.98 (m, 1H), 3.19-3.24 (m, 3H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 4.53-4.55 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.64-7.74 (m, 3H), 8.34 (s, 1H).

Example 582. Synthesis of Compound 589



1. Synthesis of 589

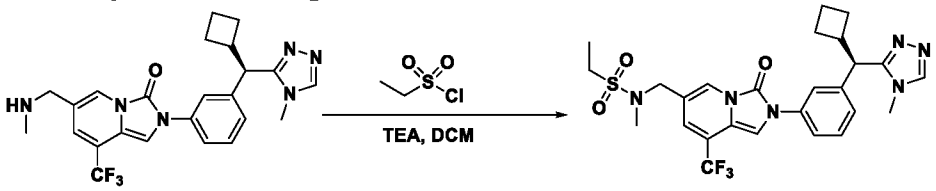
[1993] The 587-1 (300 mg) was purified by Prep-Chiral-HPLC with the following conditions

(Column: CHIRALPAK IG, 2*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.12; RT2(min): 12.20; the second peak is product) to afford 589 (90.7 mg, 30.11%) as a yellow solid.

LC-MS-589: (ES, *m/z*): $[M+H]^+$ 555

H-NMR-589: (400 MHz, DMSO-d6, δ *ppm*): 0.67-0.81 (m, 1H), 0.81-0.94 (d, 3H), 1.48-1.68 (m, 3H), 1.68-1.92 (m, 6H), 2.06-2.10 (m, 1H), 2.68-2.73 (m, 1H), 2.67-2.73 (m, 1H), 2.81-2.93 (m, 1H), 3.19-3.30 (m, 2H), 3.30-3.32 (m, 1H), 3.36-3.48 (m, 4H), 4.25-4.28 (d, 1H), 4.61-4.71 (m, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.44-7.46 (m, 1H), 7.67-7.74 (m, 3H), 8.33 (s,1H).

Example 583. Synthesis of Compound 590



469-1 590

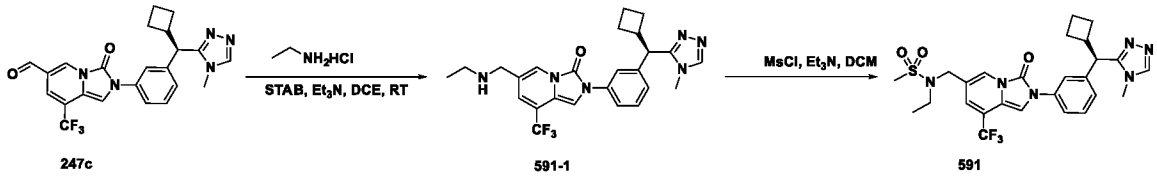
1. Synthesis of 590

[1994] Into a 20 mL sealed tube were added 469-1 (300 mg, 0.638 mmol, 1 equiv), DCM (4 mL, 62.922 mmol, 98.68 equiv), TEA (193.57 mg, 1.914 mmol, 3 equiv) and ethanesulfonyl chloride (81.98 mg, 0.638 mmol, 1 equiv) at room temperature. The solution was stirred for 1.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (160 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 52% B in 8 min; Wave Length: 254 nm; RT1(min): 7.47) to afford 590 (93.4 mg, 25.67%) as a yellow solid.

LC-MS-590: (ES, m/z): $[M+H]^+$ 563

H-NMR- 590: (400 MHz, DMSO, δ *ppm*): 1.15-1.33 (m, 3H), 1.68-1.91 (m, 3H), 2.00-2.18 (s, 1H), 2.71-2.80 (s, 3H), 3.16-3.30 (m, 3H), 3.39-3.52 (s, 3H), 4.08-4.28 (s, 2H), 4.28-4.43 (d, 1H), 6.88-7.00 (s, 1H), 7.17-7.26 (m, 1H), 7.32-7.41 (s, 1H), 7.41-7.52 (m, 1H), 7.63-7.79 (m, 2H), 7.79-7.88 (m, 1H), 8.39-8.51 (s, 1H).

Example 584. Synthesis of Compound 591



1. Synthesis of 591-1

[1995] A solution of 247c (2 g, 4.39 mmol, 1.0 equiv), ethylamine, hydrochloride (1.1 g, 13.17 mmol, 3.0 equiv) and TEA (1.3 g, 13.17 mmol, 3.0 equiv) in DCE (20 mL) was stirred for 30 min at room temperature. To the above mixture was added STAB (1.9 g, 8.78 mmol, 2.0 equiv) at room temperature. The resulting mixture was stirred for additional overnight at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (60 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=10:1) to afford 591-1 (600 mg, 25 %) as a yellow solid.

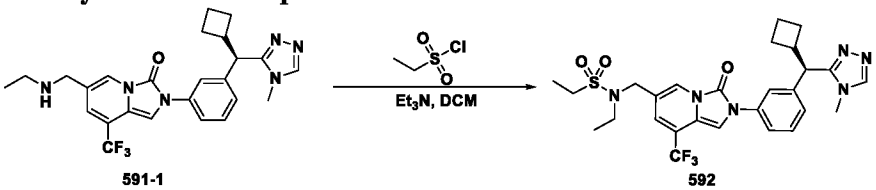
2. Synthesis of 591

[1996] To a stirred solution of 591-1 (300 mg, 0.62 mmol, 1.0 equiv) and TEA (188 mg, 1.86 mmol, 3.0 equiv) in DCM (3 mL) was added MsCl (71 mg, 0.62 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred for additional 6 h at room temperature. The reaction was quenched by the addition of water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford 591 (100 mg, 28%) as a yellow solid.

LC-MS-591: (ES, m/z): $[M+H]^+$ 563

H-NMR- 591: (400 MHz, DMSO-*d6*, δ ppm): 1.00-1.20 (t, 3H), 1.81-1.86 (m, 5H), 2.08-2.10 (m, 1H), 3.02 (s, 3H), 3.18-3.28 (m, 3H), 3.43 (s, 3H), 4.16 (s, 2H), 4.25-4.27 (d, 2H), 7.03 (s, 1H), 7.19-7.21 (d, 1H), 7.32 (s, 1H), 7.43-7.47 (t, 1H), 7.69-7.73 (m, 2H), 7.89 (s, 1H), 8.33 (s, 1H).

Example 585. Synthesis of Compound 592



1. Synthesis of 592

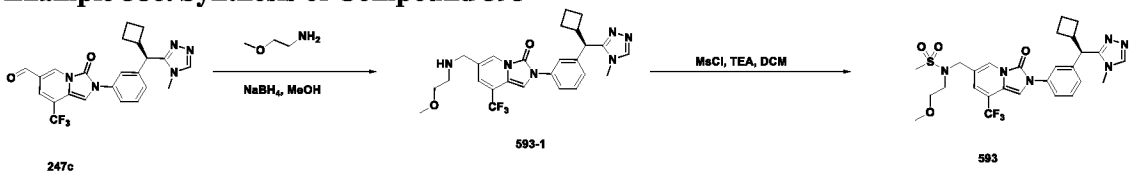
[1997] To a stirred solution of 591-1 (300 mg, 0.62 mmol, 1.0 equiv) and TEA (188 mg, 1.86 mmol, 3.0 equiv) in DCM (3 mL) were added ethanesulfonyl chloride (80 mg, 0.62 mmol,

1.0 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched by the addition of Water (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=15:1) to afford crude product. The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 41% B to 51% B in 8 min, 51% B; Wave Length: 254; 220 nm; RT1(min): 7.98) to afford 592 (23 mg, 6 %) as a yellow solid.

LC-MS-592: (ES, m/z): $[M+H]^+$ 577

H-NMR- 592: (400 MHz, DMSO-*d6*, δ ppm): 1.00-1.15 (t, 3H), 1.22-1.25 (m, 3H), 1.68-1.81 (m, 5H), 2.09-2.10 (m, 1H), 3.16-3.25 (m, 5H), 3.43 (s, 3H), 4.21 (s, 2H), 4.25-4.28 (d, 1H), 7.04 (s, 1H), 7.19-7.21 (d, 1H), 7.36 (s, 1H), 7.43-7.47 (t, 1H), 7.69-7.71 (m, 1H), 7.74 (s, 1H), 7.88 (s, 1H), 8.35 (s, 1H).

Example 586. Synthesis of Compound 593



1. Synthesis of 593-1

[1998] Into a 100 mL 3-necked round-bottom flask were added 247c (500 mg, 1.098 mmol, 1 equiv), ethanamine, 2-methoxy- (82.46 mg, 1.098 mmol, 1 equiv) and MeOH (10 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. To the above mixture was added $NaBH_4$ (83.06 mg, 2.196 mmol, 2 equiv) at 0°C. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x15 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC, eluted with CH_2Cl_2 / MeOH (12:1) to afford 593-1 (210 mg, 37.18%) as a light yellow solid.

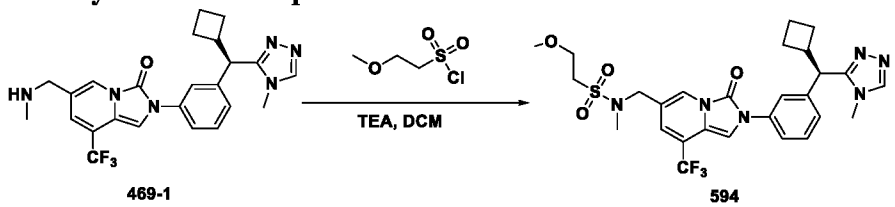
2. Synthesis of 593

[1999] Into a 100 mL round-bottom flask were added 593-1 (200 mg, 0.389 mmol, 1 equiv), DCM (5.00 mL), TEA (118.00 mg, 1.167 mmol, 3 equiv) and MsCl (53.42 mg, 0.467 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for2 h at room temperature. The reaction was quenched by the addition of water (10 mL) at room temperature. The

aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product (150 mg). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 55% B in 7 min; Wave Length: 220 nm; RT1(min): 7.70) to afford 593 (73.0 mg, 31.69%) as a light yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 593. H-NMR: 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 1.62-1.90 (m, 5H), 2.1 (s, 1H), 3.05 (s, 3H), 3.19 (s, 4H), 3.31-3.35 (m, 2H), 3.36-3.47 (m, 5H), 4.19 (s, 2H), 4.25-4.27 (d, 1H), 7.05 (s, 1H), 7.19-7.21 (d, 1H), 7.34 (s, 1H), 7.42-7.46 (m, 1H), δ 7.69-7.74 (m, 1H), 7.86 (s, 1H), 8.32 (s, 1H).

Example 587. Synthesis of Compound 594



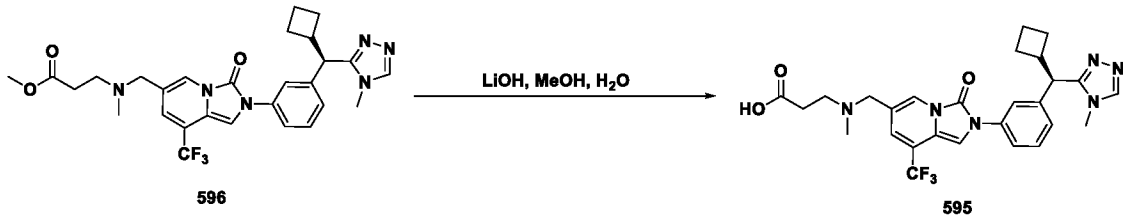
469-1 594

1. Synthesis of 594

[2000] Into a 20 mL sealed tube were added 469-1 (300 mg, 0.614 mmol, 1 equiv), DCM (4 mL, 62.922 mmol, 102.49 equiv), TEA (186.38 mg, 1.842 mmol, 3 equiv) and 2-methoxyethanesulfonyl chloride (97.37 mg, 0.614 mmol, 1 equiv) at room temperature. The mixture was stirred for 1.5 h at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford crude product. The crude product (180 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 51% B in 8 min; Wave Length: 254 nm; RT1(min): 7.47) to afford 594 (112 mg, 30.57%) as a yellow solid.

LC-MS: (ES, m/z): $[M+H]^+$ 593. H-NMR: (400 MHz, DMSO, δ *ppm*): 1.52-1.97 (m, 5H), 2.03-2.19 (s, 1H), 2.70-2.81 (s, 3H), 3.17-3.28 (s, 1H), 3.30-3.35 (s, 3H), 3.41-3.50 (m, 5H), 3.67-3.72 (m, 2H), 4.00-4.15 (s, 2H), 4.20-4.40 (d, 1H), 6.96-7.01 (s, 1H), 7.18-7.23 (m, 1H), 7.35-7.41 (s, 1H), 7.41-7.50 (m, 1H), 7.65-7.78 (m, 2H), 7.82-7.91 (s, 1H), 8.38-8.46 (s, 1H).

Example 588. Synthesis of Compound 595



596 595

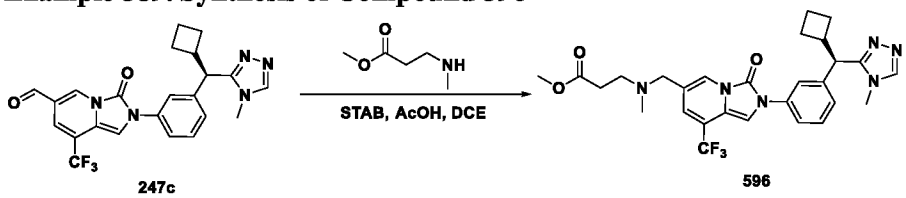
1. Synthesis of 595

[2001] Into a 100 mL round-bottom flask were added 596 (250 mg, 0.449 mmol, 1 equiv), MeOH (6.00 mL), H_2O (1.5 mL) and LiOH (53.79 mg, 2.245 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for overnight at room temperature. The residue was acidified to pH 6 with 1 M HCl (aq.) (2 ml). The reaction was quenched by the addition of water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 35% B in 8 min; Wave Length: 254 nm; RT1(min): 7.27) to afford 595 (85.9 mg, 35.25%) as a light yellow solid.

LC-MS-595: (ES, *m/z*): $[M+H]^+$ 543

H-NMR-595: 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 1.60-1.90 (m, 6H), 2.10 (s, 1H), 2.16 (s, 3H), 2.33-2.42 (m, 2H), 2.63-2.68 (m, 2H), 3.19-3.23 (m, 1H), 3.30 (s, 1H), 3.43 (s, 3H), 4.25-4.27 (d, 1H), 7.00 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), δ 7.69-7.71 (m, 2H), 7.74 (s, 1H), 8.33 (s, 1H).

Example 589. Synthesis of Compound 596



247c 596

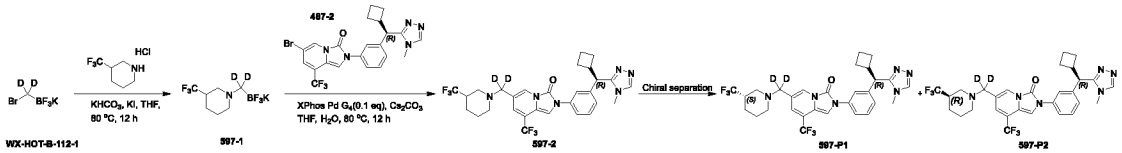
1. Synthesis of 596

[2002] Into a 100 mL round-bottom flask were added 247c (500 mg, 1.098 mmol, 1 equiv), DCE (7 mL), methyl 3-(methylamino)propanoate (257.22 mg, 2.196 mmol, 2 equiv) , STAB (465.35 mg, 2.196 mmol, 2 equiv) and AcOH (65.93 mg, 1.098 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The resulting mixture was concentrated under reduced

pressure. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 53% B in 8 min; Wave Length: 254 nm; RT1(min): 7.53) to afford 596 (300 mg, 49.10%) as a light yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 557. H-NMR: 1H NMR (300 MHz, DMSO-d6 *ppm*) δ 1.60-1.90 (m, 6H), 2.10 (s, 1H), 2.16 (s, 3H), 2.63-2.68 (m, 2H), 3.19-3.23 (m, 1H), 3.30 (s, 1H), 3.43 (s, 3H), 3.59 (s, 3H), 4.25-4.27 (d, 1H), 6.95 (s, 1H), 7.18-7.20 (d, 1H), 7.31 (s, 1H), 7.42-7.46 (m, 1H), 7.68-7.74 (m, 3H), 8.33 (s, 1H).

Example 590. Synthesis of Compound 597_P1&P2



1. Synthesis of 597-1

[2003] To a solution of 527-1 (500 mg, 2.64 mmol, 1 equiv) in THF (20 mL) was added [bromo(dideuterio)methyl]-trifluoro-boron;potassium hydride (534 mg, 2.64 mmol, 1 equiv), $KHCO_3$ (528 mg, 5.27 mmol, 2 equiv), KI (43.78 mg, 263 umol, 0.1 equiv). Then the mixture was heated to 80°C and stirred for 12 h under N_2 atmosphere. The mixture was concentrated in vacuum to get a residue. The residue was dissolved with acetone (50 mL). Then the mixture was heated to 50°C and stirred for 3 h. The mixture was filtered, the filtrate was concentrated and get 597-1 as a light yellow solid.

2. Synthesis of 597-2

[2004] To a solution of 487-2 (400 mg, 790 umol, 1 equiv) in THF (10 mL) and H_2O (2.5 mL) was added 597-1 (869 mg, 3.16 mmol, 4 equiv), Cs_2CO_3 (772 mg, 2.37 mmol, 3 equiv), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (67.98 mg, 79.00 umol, 0.1 equiv) under N_2. The suspension was degassed and purged with N_2 for 3 times. The mixture was heated to 80°C and stirred for 12 h under N_2. The mixture was poured into H_2O (20 mL), extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine (20 mL x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2) with petroleum ether/EtOAc= 2:1 to 0:1, then with DCM:MeOH= 1:0 to 1:1 to obtain 597-2.

^{1}H-NMR-597-2: (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.60-7.53 (m, 3H), 7.41-7.39 (m, 1H), 7.18-7.16 (m, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 4.10-4.08 (m, 1H), 3.98-3.95 (m, 1H), 3.54-3.50 (m, 3H), 3.43 (s, 3H), 3.25-3.23 (m, 1H), 2.34-2.32 (m, 1H), 1.94-1.80 (m, 10 H).

3. Synthesis of 597-P1&P2

[2005] 597-2 (280 mg) was purified by Chiral separation with the following conditions (column: column: DAICEL CHIRALPAK IG (250mm*30mm,10um);mobile phase: [Heptane-EtOH];B%: 40%-80%,15 min, Flow rate: 40 mL/min; Wave Length: 220/254 nm; RT1 (min): 5.01; RT2 (min): 6.00) to afford crude 597-P1 and crude 597-P1. The crude 597-P1 (90 mg) was further purified by column (SiO_2) with DCM:MeOH= 1:0 to 10:1 to obtain 597-P1(53 mg, 18.5%) as a yellow solid.

MS-597_P1: (ES, m/z): $[M+H]^+$ 595.2.

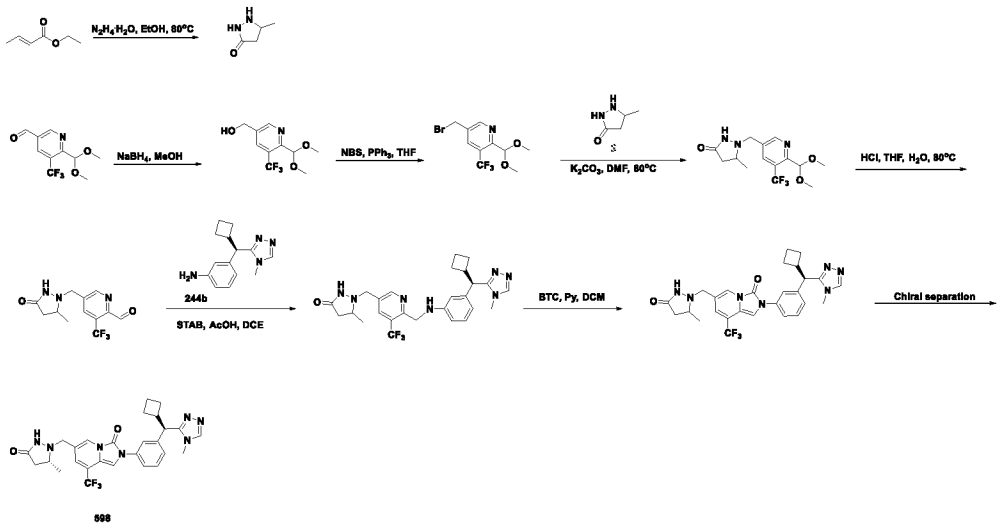
^{1}H-NMR-597_P1: (400 MHz, DMSO) δ 8.32 (s, 1H), 7.73-7.67 (m, 3H), 7.45-7.41 (m, 1H), 7.30 (s, 1H), 7.19-7.17 (m, 1H), 7.01-7.00 (m, 1H), 4.26-4.24 (m, 1H), 3.42 (s, 3H), 3.24-3.20 (m, 1H), 2.98-2.97 (m, 1H), 2.77-2.76 (m, 1H), 2.12-2.10 (m, 1H), 2.00-1.95 (m, 2H), 1.83-1.71 (m, 8H), 1.52-1.50 (m, 1H), 1.25-1.23 (m, 1H).

[2006] The crude 597-P2 (110 mg) was further purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 1%-50%, 8min; Wave Length: 220 nm; RT1 (min): 7.0) to afford 597_P2 (45 mg, 15.5%) as a yellow solid.

MS-597_P2: (ES, m/z): [M+H]+ 595.2.

^{1}H-NMR-597_P2: (400 MHz, DMSO) δ 8.32 (s, 1H), 7.73-7.72 (m, 1H), 7.71-7.69 (m, 1H), 7.68-7.67 (m, 1H), 7.45-7.41 (m, 1H), 7.30 (s, 1H), 7.19-7.17 (m, 1H), 7.01-7.00 (m, 1H), 4.26-4.24 (m, 1H), 3.42 (s, 3H), 3.24-3.20 (m, 1H), 2.98-2.97 (m, 1H), 2.77-2.76 (m, 1H), 2.12-2.10 (m, 1H), 2.00-1.95 (m, 2H), 1.84-1.80 (m, 5H), 1.76-1.71 (m, 3H), 1.52-1.50 (m, 1H), 1.25-1.23 (m, 1H).

Example 591. Synthesis of Compound 598



1. Synthesis of 598-1

[2007] Into a 500 mL round-bottom flask were added ethyl crotonate (15 g, 131.413 mmol, 1 equiv), EtOH (150 mL) and hydrazine hydrate (7.89 g, 157.696 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80°C. The resulting mixture was concentrated under reduced pressure. This resulted in 598-1 (12 g, 91.25%) as a yellow oil.

2. Synthesis of 598-2

[2008] Into a 250 mL round-bottom flask were added 6-(dimethoxymethyl)-5-(trifluoromethyl)pyridine-3-carbaldehyde (5 g, 20.065 mmol, 1 equiv), methanol (50 mL) and $NaBH_4$ (0.38 g, 10.033 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 20 min at room temperature. The reaction was quenched with sat. NH_4Cl (50 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 598-2 (3 g, 56.54%) as a yellow oil.

3. Synthesis of 598-3

[2009] Into a 250 mL round-bottom flask were added 598-2 (3 g, 11.942 mmol, 1 equiv), THF (30 mL), PPh_3 (4.70 g, 17.913 mmol, 1.5 equiv) and NBS (3.19 g, 17.913 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (30 mL) at room temperature. The aqueous layer was extracted with DCM (3 x 40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 598-3 (3 g, 73.58%) as a yellow oil.

4. Synthesis of 598-4

[2010] Into a 50 mL round-bottom flask were added 598-3 (3.0 g, 9.551 mmol, 1 equiv), DMF (15 mL), 598-1 (1.91 g, 19.102 mmol, 2 equiv) and K_2CO_3 (3.96 g, 28.653 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C. The reaction was quenched by the addition of H_2O (60 mL) at room temperature. The aqueous layer was extracted with EA (3 x 40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (50:1) to afford 598-4 (1.3 g, 40.84%) as a yellow oil.

5. Synthesis of 598-5

[2011] Into a 50 mL round-bottom flask were added 598-4 (1.3 g, 3.900 mmol, 1equiv), THF (1mL), 1M HCl (aq. 12 mL) at room temperature. The resulting mixture was stirred for 1 h at 60°C. The mixture was neutralized to pH =7 with sat. NH_4HCO_3(12 mL). The aqueous layer was extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=20:1) to afford 598-5 (250 mg, 21.3%) as a yellow oil.

6. Synthesis of 598-6

[2012] Into a 50 mL round-bottom flask were added 598-5 (250 mg, 0.871 mmol, 1 equiv), DCE (5 mL), 244b (210.80 mg, 0.871 mmol, 1 equiv), STAB (369.30 mg, 1.742 mmol, 2 equiv) and

[2013] AcOH (52.26 mg, 0.871 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at room temperature. The aqueous layer was extracted with DCM/MeOH=10:1 (3 x 10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=15:1) to afford 598-6 (150 mg, 34.30%) as a yellow oil.

7. Synthesis of 598-7

[2014] Into a 100 mL round-bottom flask added 598-6 (150 mg, 0.292 mmol, 1 equiv), DCM (5 mL), pyridine (138.62 mg, 1.752 mmol, 6 equiv) and triphosgene (34.67 mg, 0.117 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 5 min at 0°C. The reaction was quenched with sat. $NaHCO_3$(5 mL) at room temperature. The aqueous layer was extracted with DCM/MeOH=10:1 (3 x 5mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=15:1) to afford 598-7 (50 mg, 31.67%) as a yellow oil.

8. Synthesis of 598

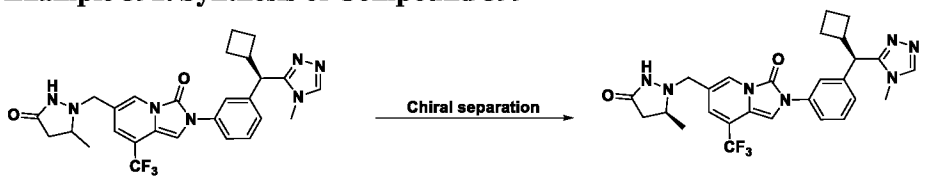
[2015] The 598-7 (50 mg) was purified by Chiral separation with the following conditions

(Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 15 min; Wave Length: 220/254 nm; RT1(min): 4.66; RT2(min): 11.99; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 2.75 mL; Number of Runs: 1) to afford 598 (9.4 mg, 18.44%) as a yellow solid.

LC-MS-598: (ES, *m/z*): $[M+H]^+$ 540

H-NMR-598: 1H NMR (300 MHz, CD_3OD-d4 *ppm*) δ 1.20-1.25(m, 3H), 2.01-2.07(m,1H), 2.24-2.30(m, 4H), 2.98-3.03(m, 1H), 3.15(s, 1H), 3.33(s, 1H), 3.43-3.47(m, 1H), 3.49-3.52(m, 1H), 3.56-3.59(m, 3H), 3.63-3.66(m, 1H), 3.83-3.86(m, 1H), 4.28-4.31(m, 1H), 7.10-7.13(m, 2H), 7.27-7.29(m, 1H), 7.48-7.52(m, 1H), 7.64-7.66(d, 2H), 7.74(s, 1H), 8.37(s, 1H).

Example 592. Synthesis of Compound 599



598-7 599

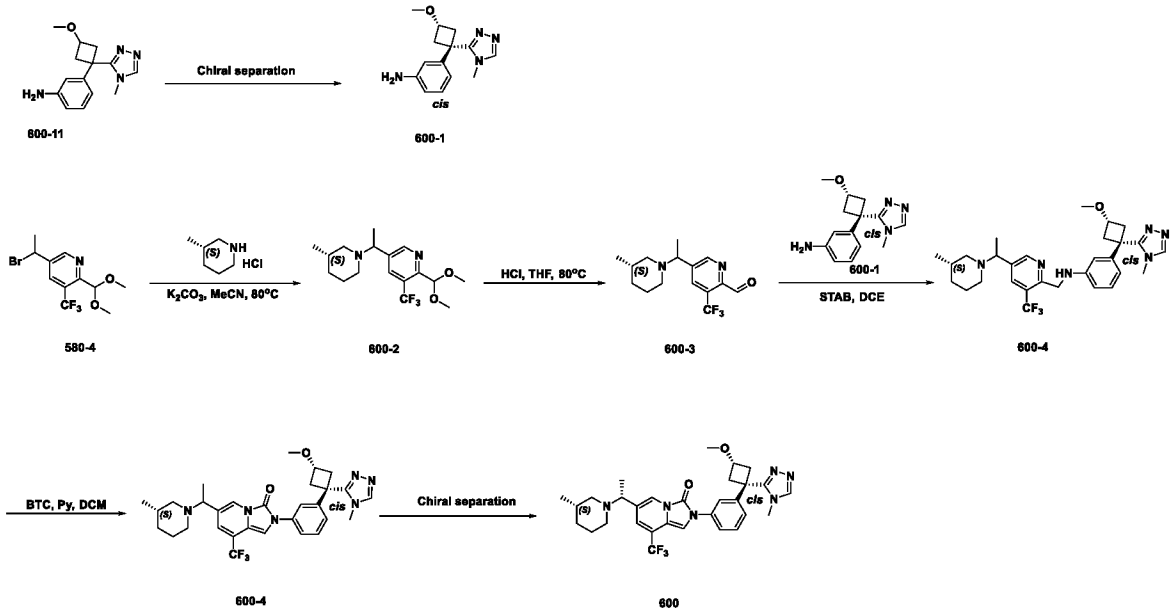
1. Synthesis of 599

[2016] The 598-7 (50 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 60% B to 60% B in 15 min; Wave Length: 220/254 nm; RT1(min): 4.66; RT2(min): 11.99; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 2.75 mL; Number of Runs: 1) to afford 598 (11.0 mg, 22.00%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 540

H-NMR: 1H NMR (300 MHz, CD_3OD-d4 *ppm*) δ 1.26-1.31(m, 3H), 1.75-1.82(m, 1H), 1.88-2.03(m, 4H), 2.06-2.07(m, 1H), 2.25-2.30(m, 1H), 2.98-3.15(m, 1H), 3.28-3.33(m, 1H), 3.45-3.50(m, 1H), 3.52-3.56(m, 3H), 3.62-3.66(m, 1H), 3.83-3.86(m, 1H), 4.28-4.31(m, 1H), 7.09-7.12(m, 2H), 7.27-7.29(m, 1H), 7.48-7.52(m, 1H), 7.64-7.66(m, 2H), 7.74(s, 1H), 8.37(s, 1H).

Example 593. Synthesis of Compound 600



1. Synthesis of 600-1

[2017] The 600-11(10 g) was purified by Prep-SFC with the following conditions (Column: Lux 5um Celluloes-3, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3-MEOH); Flow rate: 70 mL/min; Gradient: isocratic 25% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.5; RT2(min): 6.8; Sample Solvent: MeOH------Preparative; Injection Volume: 1.9 mL; Number Of Runs: 16, the first peak is product) to 600-1 (3.3 g, 33%)as a white solid.

2. Synthesis of 600-2

[2018] To a stirred solution of 580-4 (1.5 g, 4.571 mmol, 1 equiv) and (S)-3-methylpiperidine hydrochloride (1.24 g, 9.142 mmol, 2 equiv) in MeCN (20 mL) was added K_2CO_3 (1.90 g, 13.713 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 5h at 80°C under nitrogen atmosphere. The reaction was quenched with water (80 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 30:1) to afford 600-2 (950 mg, 53.99%) as a light yellow oil.

3. Synthesis of 600-3

[2019] A solution of 600-2 (930 mg, 2.685 mmol, 1 equiv) and HCl (10 mL, 1M) in THF (10 mL) was stirred for 5h at 80°C. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 25:1) to afford 600-3 (730 mg, 81.48%) as a yellow oil.

4. Synthesis of 600-4

[2020] A solution of 600-3 (360 mg, 1.199 mmol, 1 equiv) and 600-1 (309.65 mg, 1.199 mmol, 1 equiv) in DCE (8 mL) was stirred overnight at room temperature. To the above mixture was added STAB (508.11 mg, 2.398 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 5h at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 600-14 (430 mg, 59.49%) as a yellow solid.

5. Synthesis of 600-5

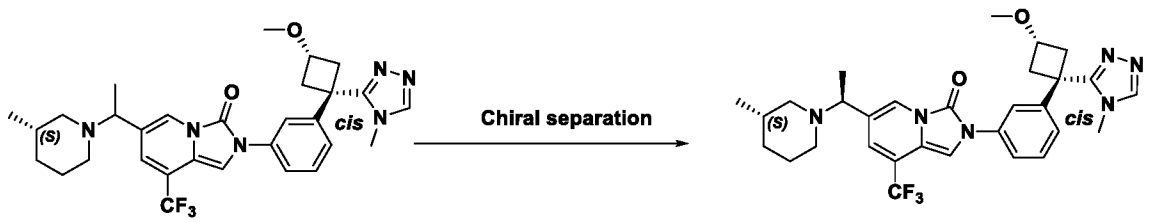
[2021] To a stirred solution of 600-4 (430 mg, 0.792 mmol, 1 equiv) and Pyridine (376.08 mg, 4.752 mmol, 6 equiv) in DCM (10 mL) was added Triphosgene (87.00 mg, 0.293 mmol, 0.37 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (80 mL). The aqueous layer was extracted with DCM (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 600-15 (310 mg, 65.36%) as a yellow solid.

6. Synthesis of 600-0

[2022] The 600-5 (310 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 28 min; Wave Length: 220/254 nm; RT1(min): 18.04; RT2(min): 22.83; the first peak is product) to afford 600 (74.9 mg, 25.14%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 569. H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 0.72-0.98 (m, 4H), 1.20-1.35 (m, 3H), 1.35-1.48 (m, 1H), 1.48-1.72 (m, 4H), 1.98-2.13 (m, 1H), 2.74-2.83 (m, 4H), 3.08-3.13 (m, 2H), 3.16 (s, 3H), 3.24 (s, 3H), 3.41-3.44 (m, 1H), 4.08-4.11 (m, 1H), 7.07 (s, 1H), 7.24-7.26 (d, 1H), 7.39 (s, 1H), 7.48-7.52 (m, 1H), 7.59 (s, 1H), 7.65-7.67 (m, 1H), 7.78 (s,1 H), 8.31 (s,1H).

Example 594. Synthesis of Compound 601



600-5 601

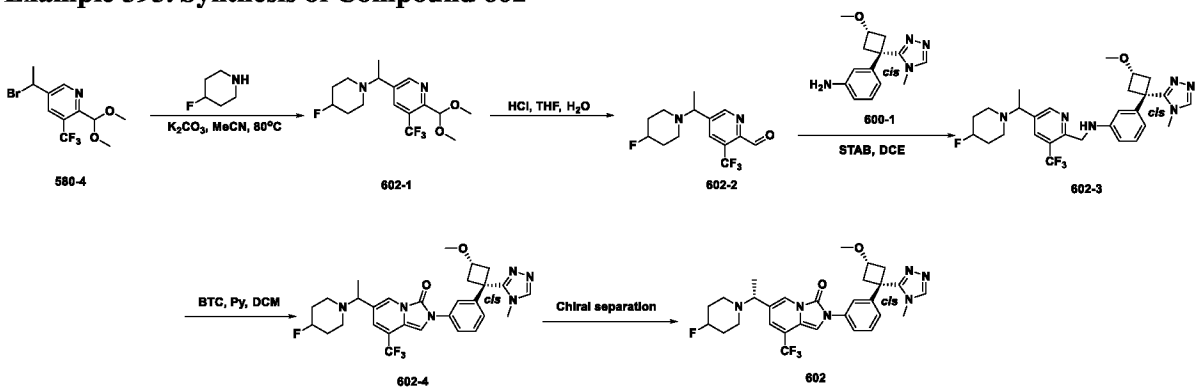
1. Synthesis of 601

[2023] The 600-5 (310 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 28 min; Wave Length: 220/254 nm; RT1(min): 18.04; RT2(min): 22.83, the second peak is product) to afford 601 (92.5 mg, 30.02%) as a yellow solid.

LC-MS-601: (ES, *m/z*): $[M+H]^+$ 569

H-NMR-601: (400 MHz, DMSO-d6, δ *ppm*): 0.72-0.98 (m, 4H), 1.20-1.35 (m, 3H), 1.35-1.48 (m, 1H), 1.48-1.72 (m, 4H), 1.93-2.03 (m, 1H), 2.74-2.83 (m, 4H), 3.08-3.13 (m, 2H), 3.16 (s, 3H), 3.24 (s, 3H), 3.41-3.46 (m, 1H), 4.06-4.11 (m, 1H), 7.08 (s, 1H), 7.24-7.26 (d, 1H), 7.38 (s, 1H), 7.48-7.52 (m, 1H), 7.58 (s, 1H), 7.65-7.67 (m, 1H), 7.79 (s,1 H), 8.31 (s,1H).

Example 595. Synthesis of Compound 602



580-4 602-1 602-2 602-3 602-4 602

1. Synthesis of 602-1

[2024] To a stirred mixture of 580-4 (1.5 g, 4.571 mmol, 1 equiv) and 4-fluoropiperidine (0.57 g, 5.485 mmol, 1.2 equiv) in MeCN (20 mL) was added K_2CO_3 (1.26 g, 9.142 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC

(CH_2Cl_2 / MeOH 35:1) to afford 602-1 (1 g, 62.44%) as a yellow oil.

2. Synthesis of 602-2

[2025] To a stirred mixture of 602-1 (1 g, 2.854 mmol, 1 equiv) in THF (5 mL) was added 1M HCl (10 mL) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x50 mL). The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 30:1) to afford 602-2 (820 mg, 94.41%) as a yellow oil.

3. Synthesis of 602-3

[2026] A solution of 602-2 (450 mg, 1.479 mmol, 1.2 equiv) and 600-1 (318.35 mg, 1.233 mmol, 1 equiv) in DCE (4 mL) was stirred overnight at room temperature. To the above mixture was added STAB (522.38 mg, 2.465 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 602-3 (310 mg, 46.02%) as a white solid.

4. Synthesis of 602-4

[2027] To a stirred mixture of 602-3 (310 mg, 0.567 mmol, 1 equiv) and Pyridine (269.16 mg, 3.402 mmol, 6 equiv) in DCM (3 mL) was added Triphosgene (63.95 mg, 0.215 mmol, 0.38 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL).The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 602-4 (200 mg, 61.59%) as a yellow solid.

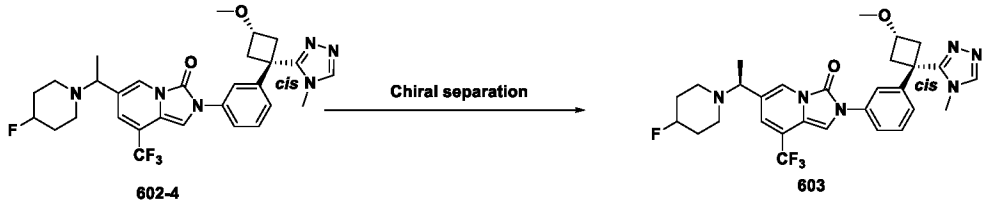
5. Synthesis of 602

[2028] The 602-4 (200 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 14 min; Wave Length: 220/254 nm; RT1(min): 9.69; RT2(min): 11.69; the first peak is product) to afford 602 (34.7 mg, 17.35%) as a yellow solid

LC-MS: (ES, *m/z*): $[M+H]^+$ 558. H-NMR: (400 MHz, DMSO-d_6, δ *ppm*): 1.22-1.27 (m, 3H), 1.64-1.78 (m, 2H), 1.78-1.93 (m, 2H), 2.34-2.36 (m, 2H), 2.50-2.68 (m, 2H), 2.78-2.83 (m, 2H), 3.08-3.15 (m, 2H), 3.17 (s, 3H), 3.24 (s, 3H), 3.49-3.51 (m, 1H), 4.04-4.12 (m, 1H),

4.59-4.72 (m, 1H), 7.07 (s, 1H), 7.24-7.26 (d, 1H), 7.39 (s, 1H), 7.48-7.52 (m, 1H), 7.61 (s, 1H), 7.65-7.67 (d, 1H), 7.78 (s, 1H), 8.34 (s, 1H).

Example 596. Synthesis of Compound 603



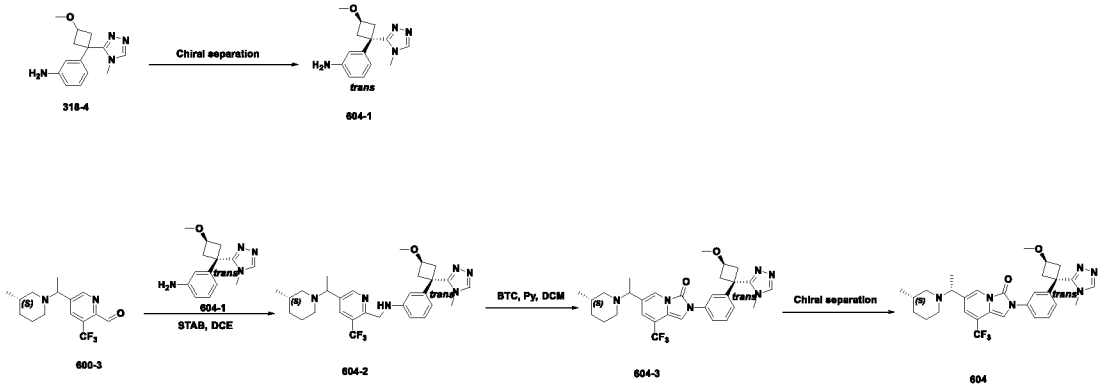
1. Synthesis of 603

[2029] The 602-4 (200 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 14 min; Wave Length: 220/254 nm; RT1(min): 9.69; RT2(min): 11.69; the second peak is product) to afford 602 (30.1 mg, 15.05%) as a yellow solid.

LC-MS-603: (ES, *m/z*): $[M+H]^+$ 573

H-NMR-603: (400 MHz, DMSO-d_6, δ *ppm*): 1.22-1.27 (m, 3H), 1.64-1.78 (m, 2H), 1.78-1.93 (m, 2H), 2.34-2.36 (m, 2H), 2.50-2.68 (m, 2H), 2.78-2.83 (m, 2H), 3.08-3.15 (m, 2H), 3.17 (s, 3H), 3.24 (s, 3H), 3.49-3.51 (m, 1H), 4.04-4.12 (m, 1H), 4.59-4.72 (m, 1H), 7.07 (s, 1H), 7.24-7.26 (d, 1H), 7.39 (s, 1H), 7.48-7.52 (m, 1H), 7.61 (s, 1H), 7.65-7.67 (d, 1H), 7.78 (s, 1H), 8.31 (s, 1H).

Example 597. Synthesis of Compound 604



1. Synthesis of 604-1

[2030] The 318-4 (10 g) was purified by Prep-SFC with the following conditions (Column: Lux 5um Celluloes-3, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MEOH(0.1% 2M NH_3-MEOH); Flow rate: 70 mL/min; Gradient: isocratic 25% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.5;

RT2(min): 6.8; Sample Solvent: MeOH------Preparative; Injection Volume: 1.9 mL; Number Of Runs: 16, the second peak is product) to 604-1 (4.8 g, 48%) as a white solid.

2. Synthesis of 604-2

[2031] A solution of 600-3 (360 mg, 1.199 mmol, 1 equiv) and 604-1 (309.65 mg, 1.199 mmol, 1 equiv) in DCE (3.6 mL) was stirred overnight at room temperature. To the above mixture was added STAB (508.11 mg, 2.398 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 5h at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 604-2 (460 mg, 63.65%) as a yellow solid.

3. Synthesis of 604-3

[2032] To a stirred solution of 604-2 (460 mg, 0.848 mmol, 1 equiv) and Pyridine (402.31 mg, 5.088 mmol, 6 equiv) in DCM (4.3 mL) was added Triphosgene (93.07 mg, 0.314 mmol, 0.37 equiv) at room temperature. The resulting mixture was stirred for 10min at room temperature. The mixture was quenched with saturated $NaHCO_3$ (aq.) (80 mL). The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 /MeOH 20:1) to afford 604-3 (310 mg, 57.88%) as a yellow solid.

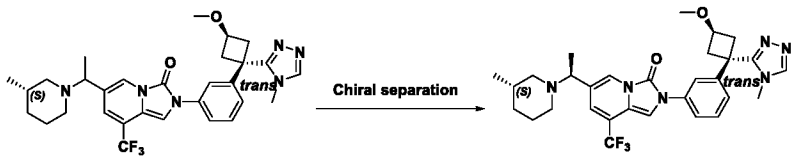
4. Synthesis of 604

[2033] The 604-3 (370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 23 min; Wave Length: 220/254 nm; RT1(min): 14.85; RT2(min): 18.49, the first peak is product) to afford 604 (120.5 mg, 32.73%) as a yellow solid.

LC-MS-604: (ES, *m/z*): $[M+H]^+$ 569

H-NMR-604: (400 MHz, DMSO-d6, δ *ppm*): 0.75-0.92 (m, 4H), 1.21-1.27 (m, 3H), 1.44-1.84 (m, 5H), 1.99-2.04 (m,1H), 2.50-2.55 (m, 2H), 2.69-2.76 (m, 2H), 3.17 (s, 3H), 3.25 (s, 3H), 3.31-3.33 (m, 1H), 3.33-3.35 (m, 1H), 3.42-3.44 (m, 1H), 3.83-3.89 (m, 1H), 7.07-7.10 (m, 2H), 7.39 (s, 1H), 7.46-7.50 (m, 1H), 7.57 (s, 1H), 7.65-7.67 (m, 1H), 7.71 (s,1H), 8.39 (s,1H).

Example 598. Synthesis of Compound 605



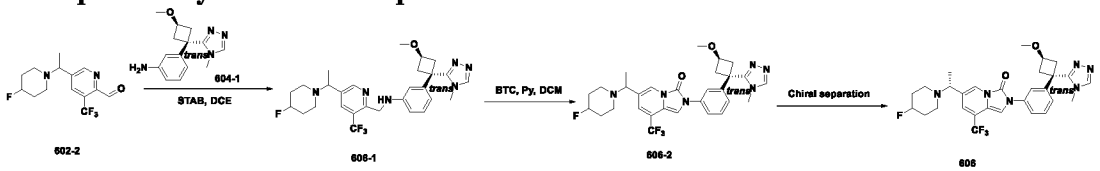
1. Synthesis of 605

[2034] The 604-3 (370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 23 min; Wave Length: 220/254 nm; RT1(min): 14.85; RT2(min): 18.49, the second peak is product) to afford 605 (117.9 mg, 32.39%) as a yellow solid.

LC-MS-605: (ES, *m/z*): $[M+H]^+$ 569

H-NMR-605: (400 MHz, DMSO-d6, δ *ppm*): 0.75-0.92 (m, 4H), 1.21-1.27 (m, 3H), 1.34-1.44 (m, 1H), 1.51-1.78 (m, 4H), 1.81-1.99 (m,1H), 2.50-2.55 (m, 2H), 2.69-2.76 (m, 2H), 3.17 (s, 3H), 3.25 (s, 3H), 3.31-3.33 (m, 1H), 3.33-3.35 (m, 1H), 3.42-3.44 (m, 1H), 3.83-3.89 (m, 1H), 7.07-7.09 (m, 2H), 7.39 (s, 1H), 7.46-7.50 (m, 1H), 7.56 (s, 1H), 7.65-7.67 (m, 1H), 7.70 (s,1H), 8.39 (s,1H).

Example 599. Synthesis of Compound 606



1. Synthesis of 606-1

[2035] A solution of 602-2 (400 mg, 1.316 mmol, 1.067 equiv) and 604-1 (318.35 mg, 1.233 mmol, 1 equiv) in DCE (5 mL) was stirred overnight at room temperature. To the above mixture was added STAB (522.38 mg, 2.465 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for additional 4h at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 606-1 (500 mg, 74.22%) as a white solid.

2. Synthesis of 606-2

[2036] To a stirred mixture of 606-1 (480 mg, 0.878 mmol, 1 equiv) and Pyridine (416.76 mg, 5.268 mmol, 6 equiv) in DCM (5 mL) was added Triphosgene (99.02 mg, 0.334 mmol, 0.38 equiv) at room temperature. The resulting mixture was stirred for 10min at room

temperature. The reaction was quenched with saturated $NaHCO_3$ (aq.) (80 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 606-2 (330 mg, 65.63%) as a yellow solid.

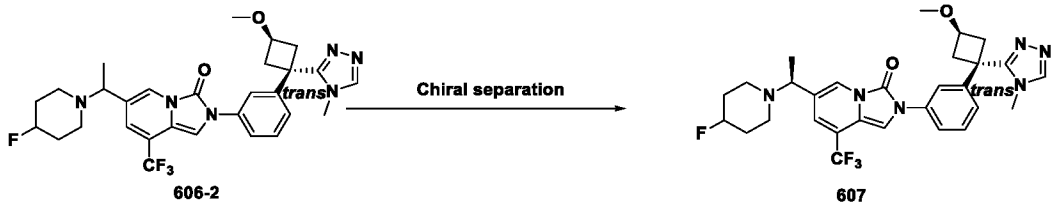
3. Synthesis of 606

[2037] The 606-2 (330 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 15 min; Wave Length: 220/254 nm; RT1(min): 7.49; RT2(min): 10.74; the first peak is product) to afford 606 (109.5 mg, 33.18%) as a yellow solid.

LC-MS-606: (ES, *m/z*): $[M+H]^+$ 558

H-NMR-606: (400 MHz, DMSO-d_6, δ *ppm*): 1.22-1.27 (m, 3H), 1.63-1.78 (m, 2H),1.78-1.93 (m, 2H), 2.34-2.36 (m, 2H), 2.50-2.57 (m, 4H), 3.16 (s, 3H), 3.24 (s, 3H), 3.31-3.35 (m, 2H), 3.49-3.51 (m, 1H), 3.51 (m, 1H), 3.84-3.88 (m, 1H), 4.59-4.72 (m, 1H), 7.07-7.09 (m, 2H), 7.39 (s, 1H), 7.46-7.50 (m, 1H), 7.64 (s, 1H), 7.66-7.69 (d, 1H), 7.70 (s, 1H), 8.39 (s, 1H).

Example 600. Synthesis of Compound 607



606-2 607

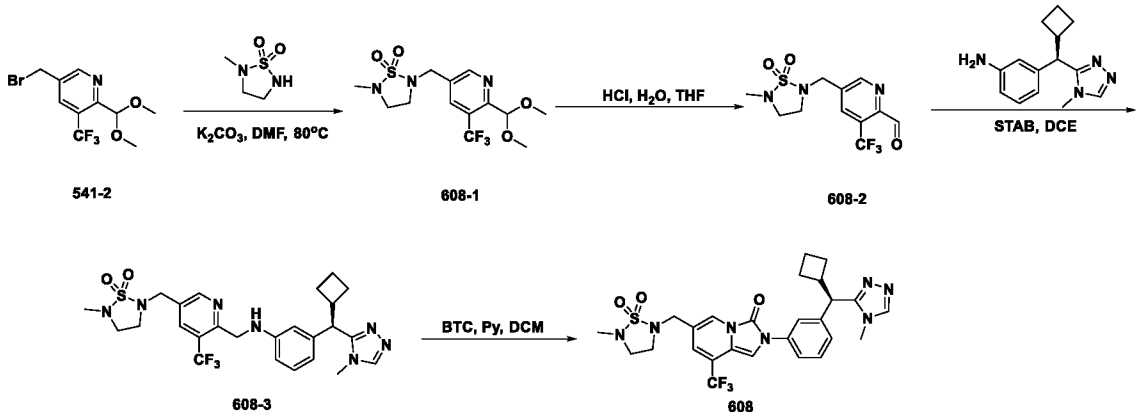
1. Synthesis of 607

[2038] The 606-2 (330 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 55% B to 55% B in 15 min; Wave Length: 220/254 nm; RT1(min): 7.49; RT2(min): 10.74; the second peak is product) to afford 607(143.5 mg, 43.48%) as a yellow solid.

LC-MS-607: (ES, *m/z*): $[M+H]^+$ 573

H-NMR-607: (400 MHz, DMSO-d_6, δ *ppm*): 1.22-1.27 (m, 3H), 1.63-1.78 (m, 2H),1.78-1.93 (m, 2H), 2.34-2.36 (m, 2H), 2.50-2.57 (m, 4H), 3.16 (s, 3H), 3.24 (s, 3H), 3.31-3.35 (m, 2H), 3.49-3.51 (m, 1H), 3.51 (m, 1H), 3.84-3.88 (m, 1H), 4.59-4.72 (m, 1H), 7.07-7.09 (m, 2H), 7.39 (s, 1H), 7.46-7.50 (m, 1H), 7.64 (s, 1H), 7.66-7.69 (d, 1H), 7.70 (s, 1H), 8.39 (s, 1H).

Example 601. Synthesis of Compound 608



1. Synthesis of 608-1

[2039] Into a 40 mL vial were added 541-2 (1.2 g, 3.820 mmol, 1 equiv), 2-methyl-1lambda6,2,5-thiadiazolidine-1,1-dione (0.78 g, 5.730 mmol, 1.5 equiv), K_2CO_3 (1.06 g, 7.640 mmol, 2 equiv) and DMF (15 mL) at room temperature. The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 50:1) to afford 608-1 (700 mg, 46.63%) as a colorless oil.

2. Synthesis of 608-2

[2040] Into a 40 mL vial were added 608-1 (700 mg, 1.895 mmol, 1 equiv) 1M HCl (7 mL) and H_2O (2 mL) at room temperature. The resulting mixture was stirred for 2 h at 80 °C. The residue was basified to pH 8 with sat. NH_4HCO_3 (aq.) (100 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 60:1) to afford 608-2 (400 mg, 61.37%) as a colorless oil.

3. Synthesis of 608-3

[2041] Into a 50 mL round-bottom flask were added 608-2 (400 mg, 1.237 mmol, 1 equiv), I-2 (359.79 mg, 1.484 mmol, 1.2 equiv), STAB (524.46 mg, 2.474 mmol, 2 equiv) and DCE (10 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH=20:1) to afford 608-3 (400 mg, 55.29%) as a colorless oil.

4. Synthesis of 608

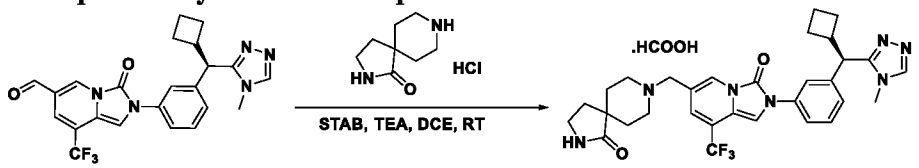
[2042] Into a 50 mL round-bottom flask were added 608-3 (380 mg, 0.691 mmol, 1 equiv),

DCM (10 mL, 157.306 mmol, 227.52 equiv) and pyridine (437.51 mg, 5.528 mmol, 8 equiv) at room temperature. To the above mixture was added triphosgene (102.58 mg, 0.345 mmol, 0.5 equiv) at room temperature. The resulting mixture was stirred for 3 min at room temperature. The reaction was quenched with sat. $NaHCO_3$ (aq.) (50 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 8 min; Wave Length: 254 nm; RT1(min): 7.58) to afford 608 (53.8 mg, 13.42%) as a yellow solid.

LC-MS-608: (ES, *m/z*): $[M+H]^+$ 576

H-NMR-608: 1H NMR (400 MHz, DMSO-d6 *ppm*) δ1.72-1.81 (m, 5H), δ2.06-2.10 (m, 1H), δ2.67 (s, 3H), δ3.19-3.35 (m, 4H), δ3.43 (s, 3H), δ4.02 (s, 2H), δ4.25-4.28 (d, 1H), δ7.01 (s, 1H), δ7.19-7.21 (d, 1H), δ7.35 (s, 1H), δ7.43-7.47 (t, 1H), δ7.69-7.73 (m, 2H), δ7.87 (s, 1H), δ8.32 (s, 1H).

Example 602. Synthesis of Compound 609



247c 609

1. Synthesis of 609

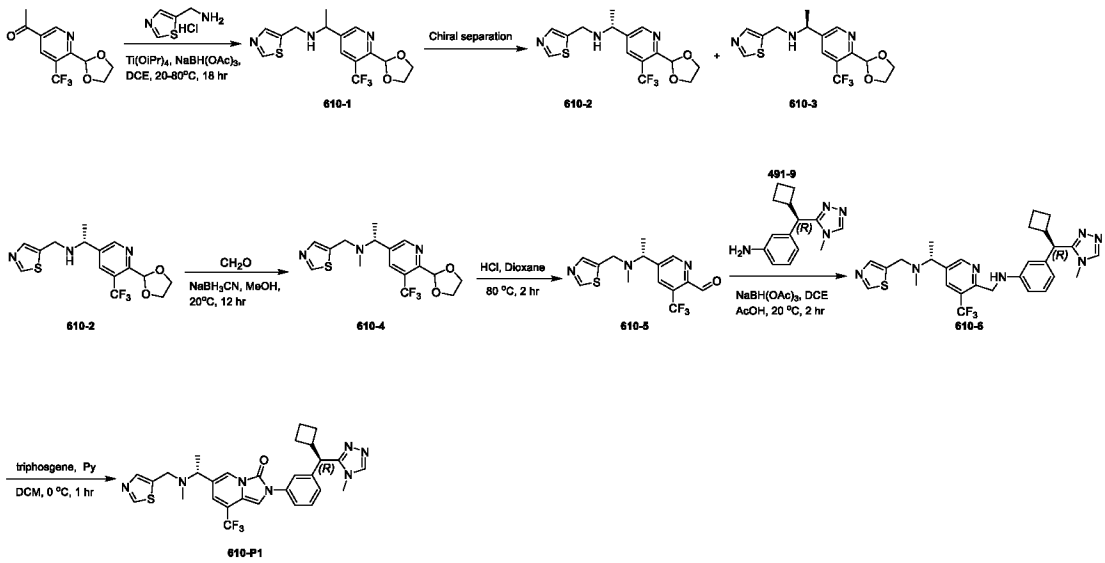
[2043] To a stirred solution of 247c (2 g, 4.391 mmol, 1 equiv) and 2,8-diazaspiro[4.5]decan-1-one hydrochloride (2.51 g, 13.164 mmol, 3.00 equiv) in DCE (40 mL) were added TEA (1.56 g, 15.369 mmol, 3.5 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added STAB (1.86 g, 8.782 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 10% to 55% gradient in 20 min; detector, UV 254 nm. This resulted in 609 (242.5 mg, 8.96%) as a yellow solid.

LC-MS-609: (ES, *m/z*): $[M+H]^+$ 594

H-NMR-609: (400 MHz, DMSO-d6, δ *ppm*): 1.32-1.35 (m, 2H), 1.64-1.88 (m, 7H), 1.90-1.97 (m, 2H), 2.05-2.11 (m, 3H), 2.78-2.81 (m, 2H), 3.13-3.27 (m, 3H), 3.31 (s, 2H), 3.43 (s,

3H), 4.25-4.27 (d, 1H), 7.03 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.55 (s, 1H), 7.68-7.70 (m, 2H), 7.73 (s, 1H), 8.16 (s, 1H), 8.33 (s, 1H).

Example 603. Synthesis of Compound 610_P1



1. Synthesis of 610-1

[2044] To a solution of 1-(6-(1,3-dioxolan-2-yl)-5-(trifluoromethyl)pyridin-3-yl)ethan-1-one (1.3 g, 4.98 mmol, 1 equiv) and thiazol-5-ylmethanamine (1.12 g, 7.47 mmol, 1.5 equiv, HCl) in DCE (15 mL) was added tetraisopropoxytitanium (4.24 g, 14.93 mmol, 4.41 mL, 3 equiv). The mixture was heated to 80 °C and stirred at 80 °C for 12 hr. Then sodium; triacetoxyboranuide (4.22 g, 19.91 mmol, 4 equiv) was added to reaction mixture at 20°C. The mixture was stirred at 80 °C for 6 hr under N_2. The mixture was poured into $NaHCO_3$ aq. (20 mL), extracted with EtOAc (10 mL x3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a crude. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to afford 610-1 (940 mg, 52.56% yield) as a yellow oil.

^{1}H-NMR-610-1: (400 MHz, CHLOROFORM-d) δ 8.83 (d, J = 2.0 Hz, 1H), 8.74 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 6.27 (d, J = 1.2 Hz, 1H), 4.38-4.35 (m, 2H), 4.15-4.12 (m, 2H), 4.02-3.97 (m, 1H), 3.93-3.82 (m, 2H), 1.40 (d, J = 6.8 Hz, 3H).

2. Synthesis of 610-2 and 610-3

[2045] The 610-1 (940 mg) was purified by Chiral separation with the following conditions (column: Phenomenex-Cellulose-2 (250mm*30mm, 10um); mobile phase: [Neu-ETOH]; B%: 20%-20%, 5min Flow rate: 3.4 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.603;

RT2 (min): 1.700) to afford 610-2 (410 mg, 35.96% yield) as a yellow oil and 610-3 (450 mg, 39.47% yield) as a yellow oil.

^{1}H-NMR-610-2: (400 MHz, METHANOL-d_4) δ 8.89 (s, 1H), 8.78 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.66 (s, 1H), 6.16 (d, J = 1.2 Hz, 1H), 4.27-4.23 (m, 2H), 4.08-4.05 (m, 2H), 4.02-3.99 (m, 1H), 3.96-3.83 (m, 2H), 1.41 (d, J = 6.4 Hz, 3H).

^{1}H-NMR-610-3: (400 MHz, METHANOL-d_4) δ 8.89 (s, 1H), 8.78 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.66 (s, 1H), 6.16 (d, J = 1.2 Hz, 1H), 4.27-4.23 (m, 2H), 4.08-4.05 (m, 2H), 4.02-3.99 (m, 1H), 3.96-3.83 (m, 2H), 1.41 (d, J = 6.4 Hz, 3H).

3. Synthesis of 610-4

[2046] To a solution of 610-2 (200 mg, 556 umol, 1 equiv) in MeOH (4 mL) was added HCHO (68 mg, 835 umol, 62 uL, 37% purity, 1.5 equiv) at 20°C stirred for 1 hr. Then $NaBH_3CN$ (69.95 mg, 1.11 mmol, 2 equiv) was added and stirred at 20 °C for 11 hr. The same scale reaction was conducted in parallel for 2 batches in total and work up with a small test scale (20 mg) together. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to afford 610-4 (350 mg, 82.15% yield) as a yellow oil.

^{1}H-NMR-610-4: (400 MHz, METHANOL-d_4) δ 8.94 (s, 1H), 8.85 (s, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.72 (s, 1H), 6.17 (d, J = 1.2 Hz, 1H), 4.27-4.24 (m, 2H), 4.11-4.05 (m, 2H), 3.98 (q, J = 7.2 Hz, 1H), 3.88-3.76 (m, 2H), 2.23 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H).

4. Synthesis of 610-5

[2047] To a solution of 610-4 (0.3 g, 803 umol, 1 equiv) in dioxane (1.5 mL) was added HCl (4M, 1.5 mL). The mixture was heated to 80 °C and stirred at 80 °C for 2 hr. The mixture was poured into $NaHCO_3$ aq. (10 mL) adjust to pH=8-9, extracted with EtOAc (5 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give 610-5 (320 mg, crude) as a yellow oil.

5. Synthesis of 610-6

[2048] To a solution of 610-5 (270 mg, 820 umol, 1 equiv) in DCE (5 mL) was added 491-9 (199 mg, 820 umol, 1 equiv), acetic acid (49.23 mg, 820 umol, 47 uL, 1 equiv) at 20°C stirred for 1 h. Then sodium; triacetoxyboranuide (348 mg, 1.64 mmol, 2 equiv) was added and stirred at 20 °C for 1 hr. The mixture was poured into water (10 ml), extracted with DCM (5 ml x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1) and (DCM/MeOH =50/1 to 1/1) to afford 610-6 (430 mg, crude) as a yellow oil.

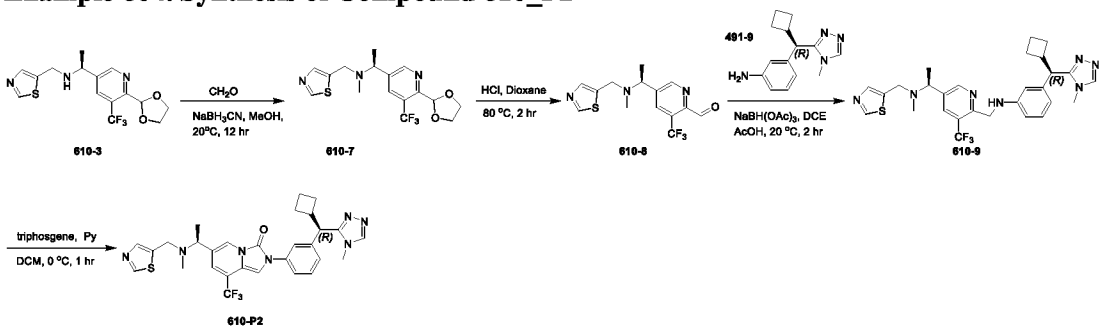
6. Synthesis of 610_P1

[2049] To a solution of 610-6 (380 mg, 684 umol, 1 equiv) in DCM (5 mL) was added Py (325 mg, 4.10 mmol, 331 uL, 6 equiv) and bis(trichloromethyl) carbonate (102 mg, 342 umol, 0.5 equiv). The mixture was stirred at 0 °C for 1 hr. The same scale reaction was conducted and work up with a small test scale (50 mg) together. The reaction mixture was diluted with $NaHCO_3$ aq. (15 mL), extracted with DCM (10 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 10%-45%, 8 min, Wave Length: 220 nm; RT1 (min): 8.5 min) to afford 610_P1 (154.1 mg, 34.24% yield) as a yellow solid.

MS-610_P1: (ES, m/z): $[M+H]^+$ 582.2.

^{1}H-NMR-610_P1: (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.32 (s, 1H), 7.75-7.72 (m, 2H), 7.69-7.67 (m, 1H), 7.59 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.19-7.14 (m, 2H), 4.25 (d, J = 10.8 Hz, 1H), 3.83-3.71 (m, 2H), 3.67-3.62 (m, 1H), 3.42 (s, 3H), 3.24-3.18 (m, 1H), 2.14 (s, 3H), 2.11-2.05 (m, 1H), 1.85-1.67 (m, 5H), 1.30 (d, J = 6.4 Hz, 3H).

Example 604. Synthesis of Compound 610_P2



1. Synthesis of 610-7

[2050] To a solution of 610-3 (240 mg, 667.84 umol, 1 equiv) in MeOH (1 mL) was added HCHO (81.29 mg, 1.00 mmol, 37% purity, 1.5 equiv) at 20°C stirred for 1 hr. Then $NaBH_3CN$ (83.93 mg, 1.34 mmol, 2 equiv) was added and stirred at 20 °C for 11 hr. The same scale reaction was conducted with in parallel for 2 batches in total and work up with a small test scale (180 mg) together. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1) to afford 610-7 (320 mg, 71.74% yield) as a yellow oil.

^{1}H-NMR-610-7: (400 MHz, METHANOL-d_4) δ 8.94 (s, 1H), 8.85 (s, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.72 (s, 1H), 6.17 (d, J = 1.2 Hz, 1H), 4.27-4.24 (m, 2H), 4.11-4.05 (m, 2H), 3.98 (q, J = 7.2 Hz, 1H), 3.88-3.76 (m, 2H), 2.23 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H).

2. Synthesis of 610-8

[2051] To a solution of 610-7 (270 mg, 723.10 umol, 1 equiv) in dioxane (2 mL) was added HCl (4M, 2 mL). The mixture was heated to 80 °C and stirred at 80 °C for 2 hr. The mixture was poured into $NaHCO_3$ aq. (10 mL) to pH=8-9, extracted with EtOAc (5 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give 610-8 (320 mg, crude) as a yellow oil.

3. Synthesis of 610-9

[2052] To a solution of 610-8 (0.27 g, 820 umol, 1 equiv) in DCE (5 mL) was added 491-9 (199 mg, 820 umol, 1 equiv), acetic acid (49.23 mg, 8120 umol, 1 equiv) at 20°C stirred for 1 hr. Then sodium; triacetoxyboranuide (347.51 mg, 1.64 mmol, 2 equiv) was added and stirred at 20 °C for 1 hr. The reaction was combined work up with a small test scale (50 mg) together. The mixture was poured into water (10 mL), extracted with DCM (5 ml x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1) and (DCM/MeOH=50/1 to 1/1) to afford 610-9 (490 mg, crude) as a yellow oil.

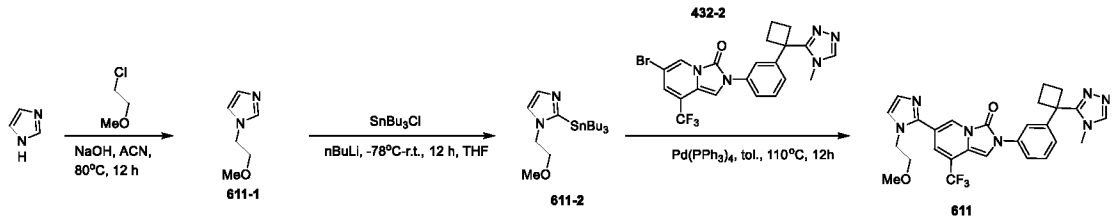
4. Synthesis of 610_P2

[2053] To a solution of 610-9 (440 mg, 791.85 umol, 1 equiv) in DCM (8 mL) was added Py (375.81 mg, 4.75 mmol, 383.48 uL, 6 equiv), bis(trichloromethyl) carbonate (117.49 mg, 395.93 umol, 0.5 equiv). The mixture was stirred at 0 °C for 1 hr. The reaction was combined with a small test scale (50 mg) together. The reaction mixture was diluted with $NaHCO_3$ aq. (15 mL), extracted with DCM (10 mL x3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 45%-65%, 8min, Wave Length: 220 nm; RT1 (min): 10 min) to afford 610_P2 (25.3 mg, 4.94% yield) as a yellow solid.

MS-610_P2: (ES, m/z): $[M+H]^+$ 582.2.

^{1}H-NMR-610_P2: (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.32 (s, 1H), 7.75-7.73 (m, 2H), 7.69-7.67 (m, 1H), 7.59 (s, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.19-7.18 (m, 1H), 7.14 (s, 1H), 4.25 (d, J = 10.8 Hz, 1H), 3.83-3.71 (m, 2H), 3.67-3.63 (m, 1H), 3.42 (s, 3H), 3.24-3.18 (m, 1H), 2.14 (s, 3H), 2.11-2.05 (m, 1H), 1.80-1.67 (m, 5H), 1.30 (d, J = 6.8 Hz, 3H).

Example 605. Synthesis of Compound 611



1. Synthesis of 611-1

[2054] To a solution of imidazole (5 g, 73.45 mmol, 1 equiv) in ACN (150 mL) was added NaOH (58.75 g, 1.47 mol, 20 equiv). The mixture was heated to 80 °C and stirred for 30 min at 80°C. Then 1-chloro-2-methoxy-ethane (6.94 g, 73.45 mmol, 1 equiv) was added dropwise to the mixture and stirred for 11.5 h at 80 °C. The reaction mixture was diluted with 40 mL H2O and extracted with DCM:MeOH=10:1 (50 mL x 3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to afford 611-1 (6.7 g, 70.8%) as a yellow oil.

1H NMR-611-1:(400 MHz, CHLOROFORM-d) δ 7.51 (s, 1H), 7.04 (s, 1H), 6.97-6.96 (m, 1H), 4.09-4.07 (t, J = 8 Hz, 2H), 3.65-3.60 (m, 2H), 3.33 (s, 3H)

2. Synthesis of 611-2

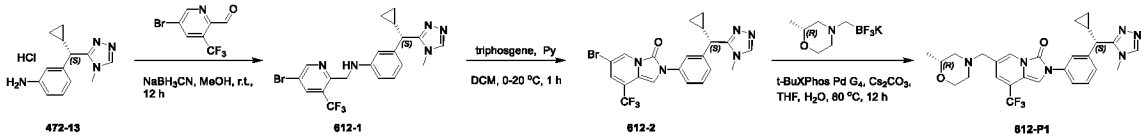
[2055] To a solution of 611-1 (1 g, 7.93 mmol, 1 equiv) in THF (15 mL) was added dropwise butyllithium (2.5 M, 4.75 mL, 1.5 equiv) at -78°C. The mixture was stirred for 1 h at -78°C. Then tributyl(chloro)stannane (2.83 g, 8.69 mmol, 1.10 equiv) was added dropwise to the reaction mixture. Then the mixture was stirred for 11 h at 15°C under N2 atmosphere. The resulting solution was concentrated under vacuum. The residue was diluted with 50 mL of hexane and the solids were filtered out. The filtrate was concentrated under vacuum to afford 611-2 (2.8 g, crude) as a yellow oil.

3. Synthesis of 611

[2056] To a solution of 432-2 (300 mg, 609.40 umol, 1 equiv) in Tol. (10 mL) was added 611-2 (1.52 g, 1.83 mmol, 50% purity, 3 equiv), palladium;triphenylphosphane (70.42 mg, 60.94 umol, 0.1 equiv) under N2. The mixture was heated to 120°C and stirred for 12 h at 120°C. The reaction mixture was diluted with H2O 15 mL and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The crude product (170 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 10%-40%, 8min; Wave Length: 220 nm; RT 1(min): 7.5) to afford 611 (66 mg) as a yellow solid.

1H NMR-611: (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.16 (s, 0.2H), 7.80 (s, 3H), 7.69-7.64 (m, 1H), 7.53-7.47 (m, 2H), 7.21-7.15 (m, 2H), 7.11 (s, 1H), 4.14 (t, J = 8 Hz, 2H), 3.62 (t, J = 8 Hz, 2H), 3.22 (d, J = 4 Hz, 6H), 2.99-2.90 (m, 2H), 2.75-2.66 (m, 2H), 2.07-1.93 (m, 2H).

Example 606. Synthesis of Compound 612_P1



1. Synthesis of 612-1

[2057] A solution of 472-13 (450 mg, 1.9 mmol, 1.0 equiv) and 5-bromo-3-(trifluoromethyl)- pyridine-2-carbaldehyde (500 mg, 1.9 mmol, 1.0 equiv) in MeOH (10.0 mL) was stirred at 20 °C for 1 hour. Then NaBH3CN (247 mg, 3.8 mmol, 2.0 equiv) was added at 20 °C. The resulting mixture was stirred at 20 °C for 11 hours. The reaction was poured into water (30 mL) and the resulting mixture was extracted with EtOAc (2 x 20 mL). The organic phase was washed with brine (15 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM: MeOH = 20:1 to 1:1) to afford 612-1 (530 mg, 57% yield) as a yellow solid.

2. Synthesis of 612-2

[2058] To a solution of 612-1 (470 mg, 1.0 mmol, 1.0 equiv) in DCM (2.0 mL) was added dropwise pyrinide (478 mg, 6.0 mmol, 6.0 equiv) at 0 °C. After addition, the triphosgene (149 mg, 0.5 equiv) was added at 0 °C. The resulting mixture was stirred at 20 °C for 1 hour. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM: MeOH = 50:1 to 1:1) to afford 612-2 (530 mg, 79% yield) as a yellow solid.

3. Synthesis of 612-P1

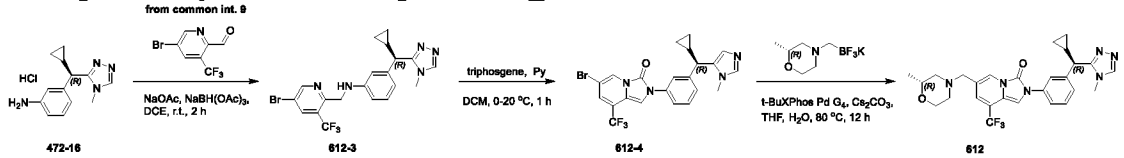
[2059] A mixture of 612-2 (201 mg, 1.0 equiv), potassium hydride;trifluoro-[[(2R)-2-methylmorpholin-4-yl]methyl]boron (270 mg, 1.2 mmol, 3.0 equiv) , Cs2CO3 (399 mg, 1.2 mmol, 3.0 equiv) , dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]-phenyl]palladium(1+) (35 mg, 0.1 equiv) in THF (7.0 mL) and H2O (1.7 mL) was degassed and purged with N2 for 3 times. The mixture was stirred at 80 °C for 12 hours under N2

atmosphere. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 15%-45%, 8 min) to afford 612_P1 (113 mg, 50% yield) as a yellow solid. It was further purified by prep-SFC (column: DAICEL CHIRALCEL OD (250mm*30mm, 10um); mobile phase: [0.1%NH3H2O IPA]; B%: 25%-45%, 12 min) to afford 612_P1 (71 mg, 54% yield) as a yellow solid.

MS-612_P1: (ES, m/z): [M+H]+ 527.2.

H-NMR-612_P1: (400 MHz, DMSO-d6) δ ppm 8.38 (s, 1 H), 7.72-7.62 (m, 3 H), 7.54-7.48 (m, 1 H), 7.28 (d, J = 3.6 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 2 H), 3.85 (d, J = 2.4 Hz, 1 H), 3.60-3.68 (m, 3 H), 3.49 (s, 3 H), 3.33 (s, 2 H), 2.81 (d, J = 2.4 Hz, 1 H), 2.73 (d, J = 2.8 Hz, 1 H), 2.24-2.13 (m, 1 H), 1.92-1.82 (m, 1 H), 1.75-1.63 (m, 1 H), 1.16-1.09 (m, 3 H), 0.80-0.72 (m, 1 H), 0.71-0.63 (m, 1 H), 0.52-0.44 (m, 1 H), 0.43-0.35 (m, 1 H).

Example 607. Synthesis of Compound 612_P2



1. Synthesis of 612-3

[2060] To a solution of 472-16 (550 mg, 2.08 mmol, 1.0 equiv, HCl) and 5-bromo-3-(trifluoromethyl)pyridine-2-carbaldehyde (580 mg, 2.29 mmol, 1.1 equiv) in DCE (15 mL) was added NaOAc (340 mg, 4.15 mmol, 2.0 equiv) at 20 °C. After addition, the mixture was stirred at this temperature for 1 hour, and then NaBH(OAc)3 (880 mg, 4.15 mmol, 2.0 equiv) was added at 20 °C. The resulting mixture was stirred at 20 °C for 1 hour. The reaction was poured into water (30 mL) and the resulting mixture was extracted with EtOAc (2 x 20 mL). The organic phase was washed with brine (15 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM: MeOH = 20:1 to 1:1) to afford 612-3 (520 mg, 53%) as a yellow solid.

1H-NMR-612-3: (400 MHz, DMSO-d6) δ 8.96-8.90 (m, 1 H), 8.48-8.41 (m, 1 H), 8.30-8.25 (m, 1 H), 7.03-6.93 (m, 1 H), 6.51-6.38 (m, 3 H), 6.25-6.16 (m, 1 H), 4.50-4.35 (m, 2 H), 3.33-3.31 (m, 4 H), 1.59-1.47 (m, 1 H), 0.57-0.44 (m, 2 H), 0.28-0.19 (m, 2 H).

2. Synthesis of 612-4

[2061] To a solution of 612-3(330 mg, 1.0 equiv) in DCM (5 mL) was added pyridine (30 mg, 6.0 equiv) at 0 °C. Then triphosgene (105 mg, 0.5 equiv) was added to the mixture at 0 °C. The reaction was stirred for 1 hour at 20 °C. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM: MeOH = 50:1 to 1:1) to afford 612-4 (0.58 g, crude) as a yellow solid.

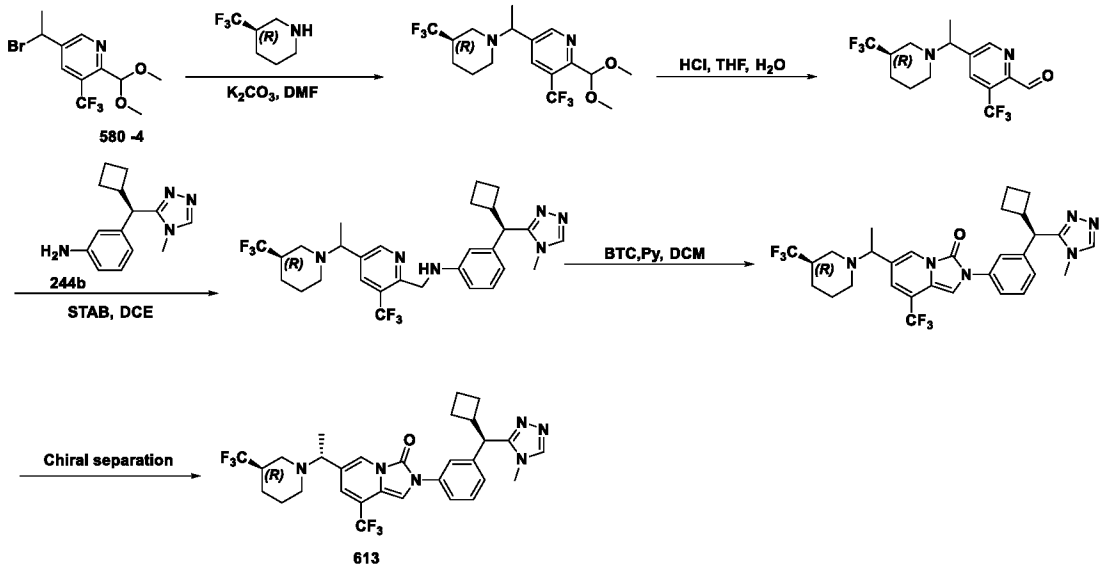
1H-NMR: (400 MHz, DMSO-d6) δ 8.35-8.32 (m, 1 H), 8.03-8.00 (m, 1 H), 7.76-7.72 (m, 1 H), 7.69-7.63 (m, 1 H), 7.49-7.40 (m, 2 H), 7.28-7.23 (m, 1 H), 7.17-7.13 (m, 1 H), 3.62-3.56 (m, 1 H), 3.39 (s, 3 H), 1.71-1.61 (m, 1 H), 0.61-0.47 (m, 2 H), 0.39-0.31 (m, 2 H).

3. Synthesis of 612_P2

[2062] A mixture of 612-4 (210 mg, 1.0 equiv), potassium hydride;trifluoro-[[(2R)-2-methylmorpholin-4-yl]methyl]boron (235 mg, 1.07 mmol, 2.5 equiv), Xphos Pd G4 (36 mg, 0.1 equiv) and Cs2CO3 (416 mg, 1.28 mmol, 3.0 equiv) in THF (5 mL)/H2O (1 mL) was degassed and purged with N2 for 3 times. The mixture was stirred at 80 °C for 12 hours under N2 atmosphere. The reaction was poured into water (20 mL) and the resulting mixture was extracted with EtOAc (2 x 15 mL). The organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO2, DCM: MeOH = 50:1 to 1:1) to give crude product. The crude product (300 mg) was further purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; Mobile phase A: water (FA), Mobile phase B: ACN; Flow rate: 70 mL/min; Gradient: 5% B to 40% B in 8 min; Wave Length: 220 nm) to afford 612_P2 (99.7 mg, 44%) as a yellow solid. It was further purified by prep-SFC (column: DAICEL CHIRALCEL OD (250mm*30mm, 10um); Mobile phase: [Neu-IPA]; B%: 25%-47%, 14min, Flow rate: 70 mL/min; Wave Length: 220/254 nm) to afford 612_P2 (61.2 mg, 62%) as a yellow solid.

MS: (ES, m/z): [M+H]+ 527.55. 1H-NMR: (400 MHz, METHANOL-d4) δ 8.43-8.38 (m, 1 H), 7.73-7.68 (m, 2 H), 7.68-7.64 (m, 1 H), 7.56-7.50 (m, 1 H), 7.33-7.27 (m, 1 H), 7.17-7.13 (m, 1 H), 7.12-7.10 (m, 1 H), 3.91-3.83 (m, 1 H), 3.75-3.61 (m, 3 H), 3.53-3.47 (m, 3 H), 3.37 (s, 2 H), 2.88-2.73 (m, 2 H), 2.27-2.17 (m, 1 H), 1.96-1.86 (m, 1 H), 1.78-1.66 (m, 1 H), 1.18-1.11 (m, 3 H), 0.83-0.63 (m, 2 H), 0.55-0.38 (m, 2 H).

Example 608. Synthesis of Compound 613



1. Synthesis of 613-1

[2063] Into a 40 mL sealed tube were added 580-4 (886.79 mg, 5.790 mmol, 2 equiv), DMF (10 mL) and K2CO3 (1200.39 mg, 8.685 mmol, 3 equiv) at room temperature. To the above mixture was added (R)5-(1-bromoethyl)-2-(dimethoxymethyl)-3-(trifluoromethyl) pyridine (950 mg, 2.895 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for additional overnight at 80°C. The reaction was quenched with sat. NH4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 40:1) to afford 613-1 (800 mg, 65.57%) as a light yellow oil.

2. Synthesis of 613-2

[2064] Into a 40 mL sealed tube were added 613-1 (800 mg, 1.998 mmol, 1 equiv), (1 M) HCl (8 mL) and THF (2 mL) at room temperature. The resulting mixture was stirred for 2h at 80°C. The mixture was basified to pH 7 with saturated NaHCO3 (aq.) (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 40:1) to afford 613-2 (700 mg, 93.93%) as a light yellow oil.

3. Synthesis of 613-3

[2065] Into a 40 mL sealed tube were added 613-2 (450 mg, 1.270 mmol, 1 equiv), DCE (6 mL), 244b (615.57 mg, 2.540 mmol, 2 equiv) and STAB (807.57 mg, 3.810 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was quenched with water (20 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3 x 20 mL). The combined organic layers

were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 613-3 (500 mg, 64.41%) as a light yellow oil.

4. Synthesis of 613-4

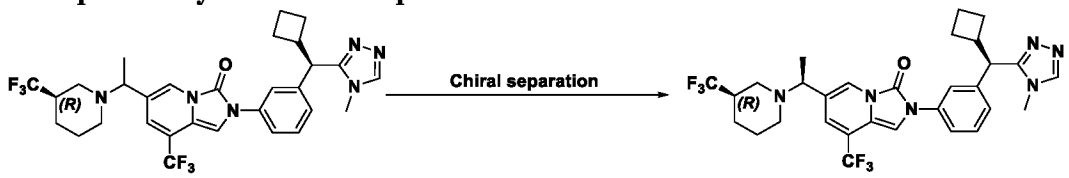
[2066] Into a 100 mL round-bottom flask were added 613-3 (450 mg, 0.775 mmol, 1 equiv), DCM (20 mL) and pyridine (429.13 mg, 5.425 mmol, 7 equiv) at 0°C. To the above mixture was added triphosgene (114.99 mg, 0.388 mmol, 0.50 equiv) at 0°C. The resulting mixture was stirred for additional 10 min at 0°C. The was basified to pH 8 with saturated NaHCO3 (aq.) (40 mL). The resulting mixture was extracted with CH2Cl2 (3 x 40 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 16:1) to afford crude product (350 mg). The crude product (350 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 55% B to 72% B in 7 min; Wave Length: 220 nm; RT1(min): 6.97.) to afford 613-3 (120 mg, 22.97%) as a light yellow solid.

5. Synthesis of 613

[2067] The 613-4 (200mg) was purified by Chiral separation with the following conditions (Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 28 min; Wave Length: 220/254 nm; RT1(min): 16.32; RT2(min): 22.55; The first peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 4) to afford 613 (58.6 mg, 28.98%) as a light yellow solid.

LCMS: (ES, m/z): [M+H] + 607. H-NMR18: (300 MHz, CD3OD, ppm): δ1.30-1.77 (m, 6H), δ1.80-1.83 (m, 2H), δ1.90-1.97 (m, 5H), δ2.05-2.11 (m, 1H), δ2.22-2.25 (d, 2H), δ2.27 (S,1H), δ2.88-2.91 (m, 1H), δ3.05-3.07 (m, 1H), δ3.53-3.57 (m, 4H), δ4.28-4.31(m, 1H), δ7.12-7.16 (m, 2H), δ7.26-7.28 (m, 1H), δ7.48-7.52(m, 1H), δ7.64-7.67 (m,3H), δ8.37 (s, 1H).

Example 609. Synthesis of Compound 614



613-4 614

1. Synthesis of 614

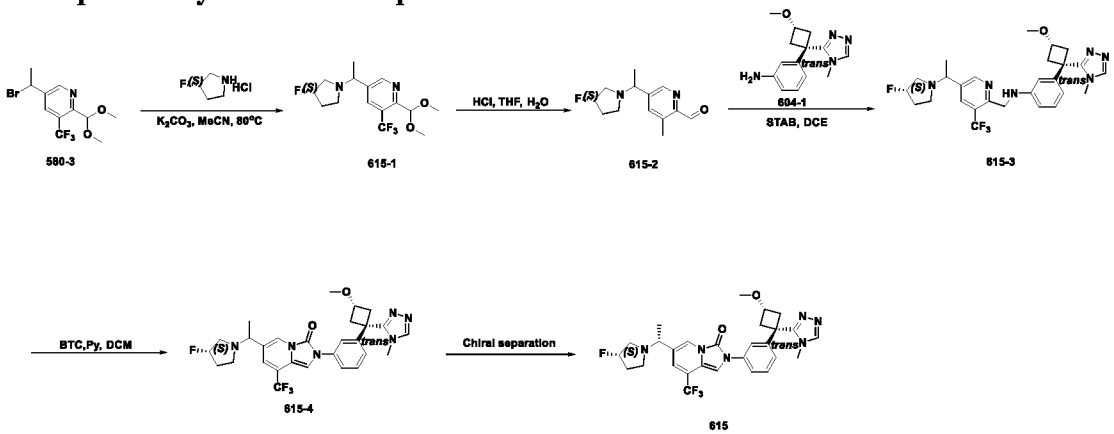
[2068] The 613-4 (200 mg) was purified by Chiral separation with the following conditions

(Column: (R, R)-WHELK-O1-Kromasi, 5*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 28 min; Wave Length: 220/254 nm; RT1(min): 16.32; RT2(min): 22.55; The second peak was the product. Sample Solvent: EtOH: DCM=1: 1--HPLC; Injection Volume: 0.7 mL; Number of Runs: 4) to afford 614 (31.7 mg, 15.36%) as a light yellow solid.

LCMS72-614: (ES, m/z): [M+H] + 607

H-NMR18-614: (300 MHz, CD3OD, ppm): δ1.30-1.77 (m, 6H), δ1.80-1.83 (m, 2H), δ1.90-2.09 (m, 5H), δ2.12-2.25 (m, 3H), δ2.27 (d, 1H), δ2.90-2.93 (m, 2H), δ3.10-3.29 (m, 1H), δ3.53-3.55 (m, 4H), δ4.28-4.31 (m, 1H), δ7.12-7.14(m, 2H), δ7.26-7.28 (m, 1H), δ7.48-7.52 (m, 1H), δ7.64-7.67(m, 3H), δ8.37 (s, 1H).

Example 610. Synthesis of Compound 615



1. Synthesis of 615-1

[2069] A solution of 580-3 in DCM (8mL) in MeCN (12 mL) was treated with(S)-3-fluoropyrrolidine hydrochloride (0.81 g, 9.143 mmol, 2.5 equiv) and K_2CO_3 (1.52 g, 10.971 mmol, 3 equiv) at room temperature. The resulting mixture stirred for 4h at 80°C under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) (30mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 615-1(1.1 g, 78.70%) as a light yellow oil.

2. Synthesis of 615-2

[2070] A solution of 615-1(1.1 g, 3.271 mmol, 1 equiv) in HCl (5.5 mL, 1M) and THF (5.5 ml,) was stirred for 2h at 80°C . The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.) （10ml） . The resulting mixture was extracted with CH_2Cl_2 (3 x 30mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-

TLC (PE / EA 2:1) to afford 615-2 (750 mg, 79.00%) as a yellow oil.

3. Synthesis of 615-3

[2071] A solution of 615-2 (375 mg, 1.292 mmol, 1 equiv) in DCE (4 mL) was treated with 604-1(333.74 mg, 1.292 mmol, 1 equiv) for overnight at room temperature under nitrogen atmosphere followed by the addition of STAB (547.63 mg, 2.584 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.)(20ml). The resulting mixture was extracted with CH_2Cl_2 (3 x 15mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 16:1) to afford 615-3 (388 mg, 55.26%) as a yellow solid.

4. Synthesis of 615-4

[2072] A solution of 615-3 (380 mg, 0.713 mmol, 1 equiv) in DCM (12 mL) was treated with Pyridine (338.63 mg, 4.278 mmol, 6 equiv) at room temperature under nitrogen atmosphere followed by the addition of Triphosgene (84.69 mg, 0.285 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 20min at 0°C under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$(aq.)(30ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 18:1) to afford 615-4 (380 mg, 93.44%) as a yellow solid.

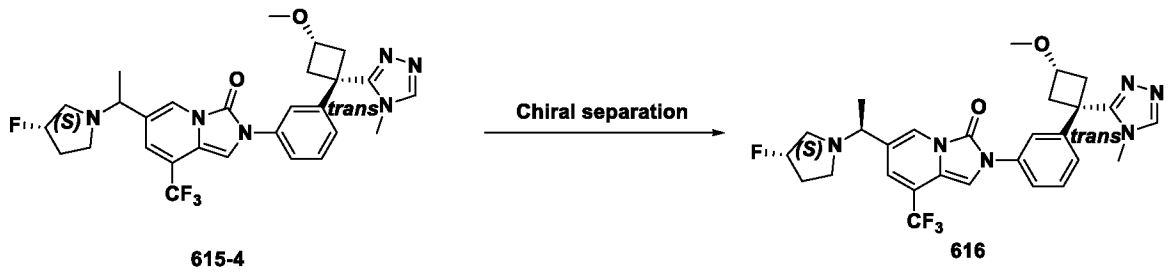
5. Synthesis of 615

[2073] 615-4(370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1-; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 19 min; Wave Length: 220/254 nm; RT_1(min): 12.40; RT_2(min): 15.02; the first peak was the product) to afford 615 (90.9 mg, 23.92%) as a yellow solid.

LCMS-615:(ES, m/z): $[M+H]^+$ 553

NMR-615: (400 MHz, dmso-d6, δ ppm): 1.28-1.30 (d, 3H), 1.77-1.87 (m, 1H), 2.03-2.08 (m, 1H), 2.39-2.41 (m, 1H), 2.59-2.68 (m, 2H), 2.77-2.85 (m, 2H), 2.89-2.92 (m, 1H), 3.08-3.13 (m, 2H), 3.16(s,3H), 3.23 (s, 3H), 3.26-3.29 (m, 1H), 4.06-4.09 (t, 1H), 5.14-5.29 (m, 1H), 7.06 (s, 1H), 7.25-7.27 (d, 1H), 7.41(s, 1H), 7.49-7.52 (t, 1H), 7.65-7.71(m, 2H), 7.77 (s, 1H), 8.34 (s, 1H).

Example 611. Synthesis of Compound 616

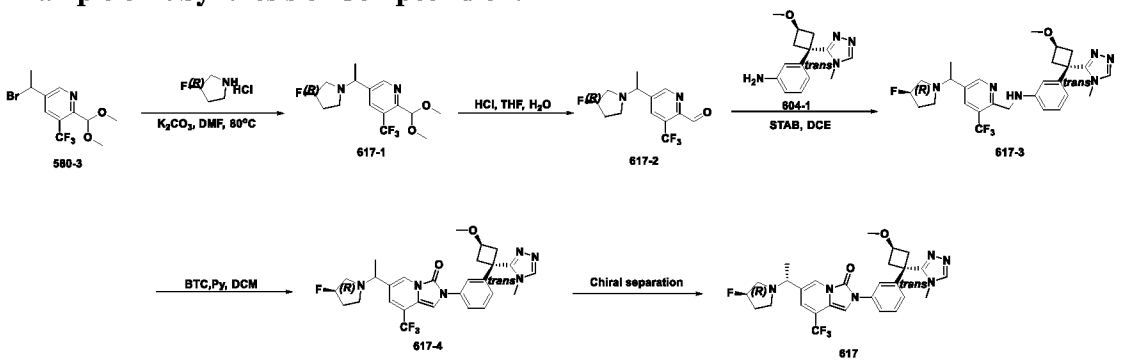


1. Synthesis of 616

[2074] The 615-4 (370 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 19 min; Wave Length: 220/254 nm; RT_1(min): 12.40; RT_2(min): 15.02; the second peak was product) to afford 616 (119.6 mg, 32.32%) as a yellow solid.

LCMS:(ES, m/z): $[M^+H]^+$ 553. NMR: (400 MHz, DMSO, δ ppm): 1.28-1.30 (d, 3H), 1.77-1.95 (m, 1H), 2.03-2.18 (m, 1H), 2.20-2.27 (m, 1H), 2.56-2.66 (m, 1H), 2.73-2.83 (m, 3H), 2.88-2.92 (m, 1H), 3.08-3.13 (m, 2H), 3.17 (s,3H), 3.24 (s, 3H), 3.26-3.28 (m, 1H), 4.04-4.08 (t, 1H), 5.11-5.26 (m, 1H), 7.06 (s, 1H), 7.24-7.26 (d, 1H), 7.41(s, 1H), 7.48-7.52 (t, 1H), 7.66-7.72 (m, 2H), 7.77 (s, 1H), 8.34 (s, 1H).

Example 612. Synthesis of Compound 617



1 .Synthesis of 617-1

[2075] A solution of 580-3 in DMF (20 mL) was treated with (3R)-3-fluoropyrrolidine (1.32 g, 14.780 mmol, 2.5 equiv) and K_2CO_3 (2.45 g, 17.736 mmol, 3 equiv). The resulting mixture was stirred for 4h at 80°C under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) (20mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 617-2 (1.7 g, 77.80%) as a light yellow oil

2. Synthesis of 617-2

[2076] A solution of 617-1(1.7 g, 5.055 mmol, 1 equiv) in HCl (8.5 mL,1M) and THF (8.5 mL) was stirred for 2h at 80°C under nitrogen atmosphere. The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.) (30mL) The resulting mixture was extracted with EtOAc (3 x 40mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 617-2 (800 mg, 49.07%) as a yellow oil.

3. Synthesis of 617-3

[2077] A solution of 617-2 (400 mg, 1.378 mmol, 1 equiv) in DCE (4 mL) was treated with 604-1 (355.99 mg, 1.378 mmol, 1 equiv) for overnight at room temperature under nitrogen atmosphere followed by the addition of STAB (584.13 mg, 2.756 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 4h at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) (20mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 16:1) to afford 617-3 (500 mg, 66.76%) as a yellow solid.

4. Synthesis of 617-4

[2078] A solution of 617-3 (500 mg, 0.939 mmol, 1 equiv) in DCM (15 mL) was treated with Pyridine (445.56 mg, 5.634 mmol, 6 equiv) at room temperature under nitrogen atmosphere followed by the addition of Triphosgene (111.43 mg, 0.376 mmol, 0.4 equiv) at 0°C. The resulting mixture was stirred for 20min at 0°C under nitrogen atmosphere. The reaction was quenched with sat. $NaHCO_3$(aq.) (30ml) at room temperature. The resulting mixture was extracted with CH_2Cl_2/MeOH (10:1) (3 x 20mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 18:1) to afford 617-4 (390 mg, 72.88%) as a yellow solid.

5. Synthesis of 617-0

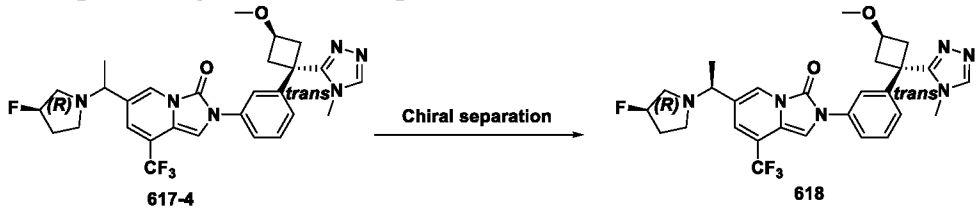
[2079] The 617-4 (390 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm; RT_1(min): 15.55; RT_2(min): 17.97; the first peak was the product) to afford 617 (113.3 mg, 29.05%) as a yellow solid.

LCMS-617:(ES,m/z): $[M+H]^+$ 559

NMR-617: (400 MHz, DMSO, δ ppm): 1.23-1.30 (m, 3H), 1.72-1.92 (m, 1H), 2.03-2.30 (m, 2H), 2.51-2.55 (m, 2H), 2.67-2.72(m, 2H), 2.83-2.89 (m, 1H), 3.16 (s, 3H), 3.24 (s, 3H),

3.26-3.30 (m, 3H), 3.82-3.85(m, 1H), 5.12-5.25 (m, 1H), 7.06-7.09 (m, 2H), 7.42 (s, 1H), 7.46-7.50 (t, 1H) , 7.65-7.71(m, 3H), 8.34 (s, 1H).

Example 613. Synthesis of Compound 618



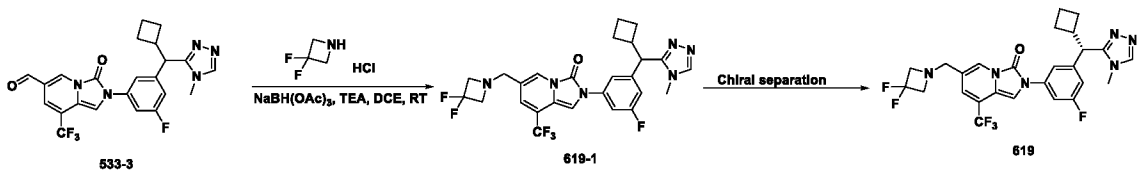
1. Synthesis of 618

[2080] The 617-4(390 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm; RT_1(min): 15.55; RT_2(min): 17.97; the second peak was product) to afford 618 (120 mg, 30.77%) as a yellow solid.

LCMS-618:(ES, m/z): $[M+H]^+$ 559

NMR-618: (400 MHz, DMSO, δ ppm): 1.23-1.30 (m, 3H), 1.72-1.95 (m, 1H), 2.03-2.30 (m, 1H), 2.32-2.45 (m, 2H), 2.67-2.72(m, 2H), 2.80-2.96 (m, 1H), 3.16-3.21 (m, 7H), 3.24 (s, 2H), 3.25-3.30 (m, 2H), 3.82-3.88(m, 1H), 5.16-5.28 (m, 1H),7.08-7.10 (m, 2H), 7.22-7.35 (m, 1H), 7.42 (s, 1H), 7.46-7.50 (t, 1H), 7.65-7.72(m, 2H), 8.38 (s, 1H).

Example 614. Synthesis of Compound 619



1. Synthesis of 619-1

[2081] To a stirred solution of 533-3 (600 mg, 1.267 mmol, 1.00 equiv) and 3,3-difluoroazetidine hydrochloride (246.24 mg, 1.900 mmol, 1.5 equiv) in DCE (10 mL) were added TEA (256.49 mg, 2.534 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (537.20 mg, 2.534 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm,

5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 41% B in 7 min, Wave Length: 254; 220 nm; RT1(min): 5.92) to afford 619-1 (150 mg, 21.07%) as a yellow solid.

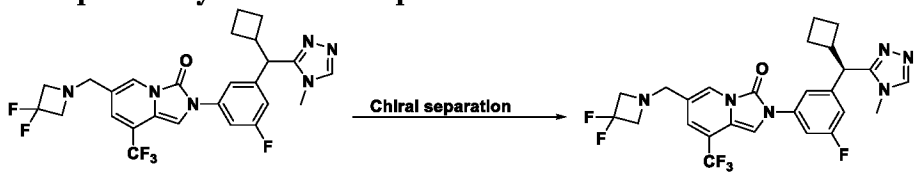
2. Synthesis of 619

[2082] The 619-4 (150 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18.5 min; Wave Length: 220/254 nm; RT1(min): 12.76; RT2(min): 16.08; the first peak is product) to afford 619 (25.3 mg, 16.75%) as a yellow solid.

LC-MS-619: (ES, m/z): [M+H] + 551

H-NMR-619: (400 MHz, DMSO-d6, δ ppm): 1.62-1.65 (m, 1H), 1.66-1.85 (m, 4H), 2.09-2.10 (d, 1H), 3.15-3.24 (m, 1H), 3.46(s, 3H), 3.52 (s, 2H), 3.64-3.70 (m, 4H), 3.30-3.33 (d, 1H), 7.02-7.06 (m, 2H), 7.43 (s, 1H), 7.68-7.70 (d, 2H), 7.77 (s, 1H), 8.35 (s, 1H).

Example 615. Synthesis of Compound 620



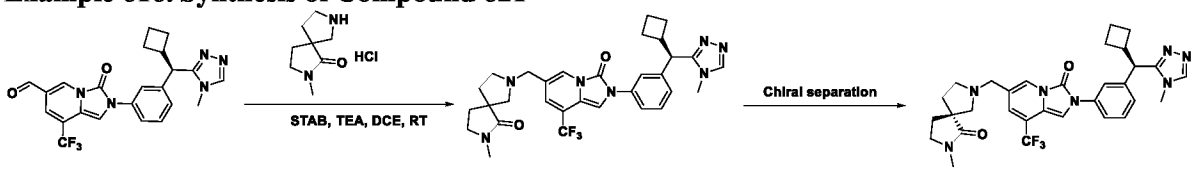
619-1 620

1. Synthesis of 620

[2083] The 619-1 (150 mg) was purified by Chiral separation with the following conditions (Column: CHIRALPAK IC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 18.5 min; Wave Length: 220/254 nm; RT1(min): 12.76; RT2(min): 16.08; the second peak is product) to afford 619 (26.3 mg, 17.36%) as a yellow solid.

LC-MS: (ES, m/z): [M+H] + 551. H-NMR: (400 MHz, DMSO-d6, δ ppm): 1.67-1.69 (m, 1H), 1.70-1.85 (m, 4H), 2.05-2.08 (m, 1H), 3.17-3.19 (m, 1H), 3.46 (s, 3H), 3.52 (s, 2H), 3.60-3.69 (m, 4H), 4.30-4.33 (d, 1H), 7.02-7.06 (m, 2H), 7.43 (s, 1H), 7.68-7.71 (m, 2H), 7.77 (s, 1H), 8.35 (s, 1H).

Example 616. Synthesis of Compound 621



247c 621-1 621

1. Synthesis of 621-1

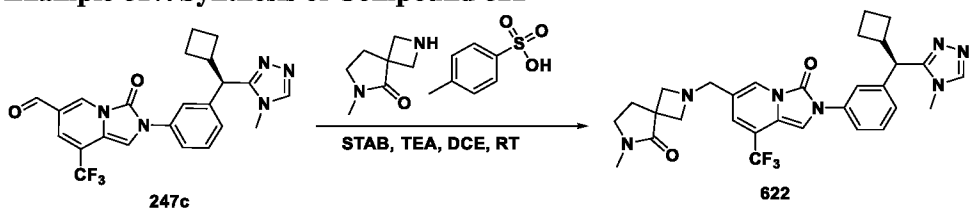
[2084] To a stirred solution of 247c (500 mg, 1.098 mmol, 1 equiv) and 2-methyl-2,7-diazaspiro[4.4]nonan-1-one hydrochloride (418.65 mg, 2.196 mmol, 2 equiv) in DCE (20 mL) were added TEA (222.19 mg, 2.196 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature. To the above mixture was added STAB (1.86 g, 8.782 mmol, 2 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (100 mL) at room temperature. The aqueous layer was extracted with DCM (2x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 621-1 (320 mg, 47.63%) as a yellow solid.

2. Synthesis of 621

[2085] The 621-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.91; RT2(min): 12.05; the first peak is product) to afford 621 (128.5 mg, 38.43%) as a yellow solid.

LC-MS: (ES, *m/z*): $[M+H]^+$ 594. H-NMR: (400 MHz, DMSO-d6, δ *ppm*): 1.65-1.92 (m, 6H), 1.93-2.16 (m, 4H), 2.44-2.50 (m, 2H), 2.61-2.63 (m, 1H), 2.72 (s, 3H), 2.78-2.82 (m, 1H), 3.19-3.25 (m, 3H), 3.43 (s, 5H), 4.25-4.28 (d, 1H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.69-7.74 (m, 3H), 7.73 (s, 1H), 8.33 (s, 1H).

Example 617. Synthesis of Compound 622



247c 622

1. Synthesis of 622

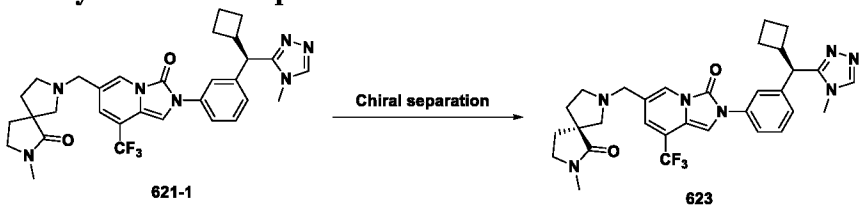
[2086] To a stirred solution of 247c (400 mg, 0.878 mmol, 1.00 equiv) and 6-methyl-2,6-diaza-spiro[3.4]octan-5-one tosylat (411.53 mg, 1.317 mmol, 1.5 equiv) in DCE (5 mL) were added TEA (177.75 mg, 1.756 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 1h at room temperature. To the above mixture was added STAB (372.28 mg, 1.756 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for overnight at

room temperature. The reaction was quenched by the addition of NH4Cl (aq.) (80 mL) at room temperature. The resulting mixture was extracted with CH2Cl2 (3x40 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH4HCO3), 50% to 60% gradient in 10 min; detector, UV 254 nm. This resulted in 622 (122.0 mg, 23.22%) as a yellow solid.

LC-MS-622: (ES, m/z): [M+H] + 580

H-NMR-622: (400 MHz, DMSO-d6, δ ppm): 1.69-1.84 (m, 5H), 2.07-2.09 (m, 1H), 2.25-2.34 (m, 2H), 2.75 (s, 3H), 3.15-3.26 (m, 7H), 3.31 (s, 2H), 3.43 (s, 3H), 4.24-4.27 (d, 1H), 6.99 (s, 1H), 7.18-7.20 (d, 1H), 7.30 (s, 1H), 7.41-7.45 (m, 1H), 7.65-7.69 (m, 1H), 7.74 (s, 1H), 8.32 (s, 1H).

Example 618. Synthesis of Compound 623



621-1 623

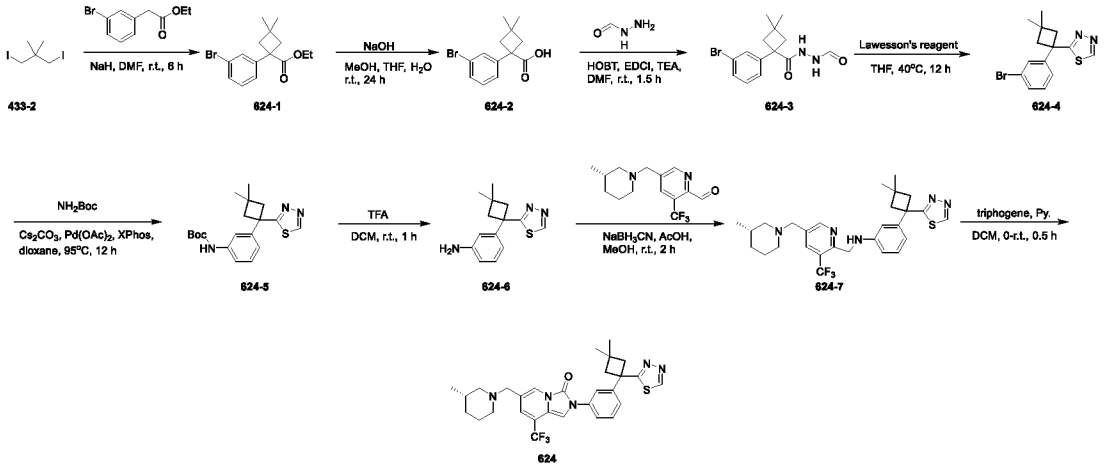
1. Synthesis of 623

[2087] The 621-1 (320 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 16 min; Wave Length: 220/254 nm; RT1(min): 8.91; RT2(min): 12.05; the second peak is product) to afford 623 (110.1 mg, 34.03%) as a yellow solid.

LC-MS-623: (ES, m/z): [M+H]+ 594

H-NMR-623: (400 MHz, DMSO-d6, δ ppm): 1.65-1.92 (m, 6H), 1.93-2.16 (m, 4H), 2.44-2.50 (m, 2H), 2.61-2.63 (m, 1H), 2.72 (s, 3H), 2.78-2.82 (m, 1H), 3.19-3.25 (m, 3H), 3.43 (s, 5H), 4.25-4.28 (d, 1H), 7.04 (s, 1H), 7.18-7.20 (d, 1H), 7.32 (s, 1H), 7.42-7.46 (m, 1H), 7.69-7.74 (m, 3H), 7.73 (s, 1H), 8.33 (s, 1H).

Example 619. Synthesis of Compound 624



1. Synthesis of 624-1

[2088] To a solution of 433-2 (12 g, 37 mmol, 0.9 equiv) and ethyl 2-(3-bromophenyl)acetate (10 g, 41.14 mmol, 1 equiv) in DMF (120 mL) was added NaH (3.29 g, 82.3 mmol, 60% purity, 2 equiv), the mixture was stirred at 20 °C for 6 hr. The reaction mixture was diluted with water (250 mL), extracted with EtOAc (150 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=1:10 to afford 624-1 (7.5 g, 59%) as a colorless oil.

1H-NMR-624-1: (400 MHz, CHLOROFORM-d) δ 7.37 (s, 1H), 7.30-7.24 (m, 1H), 7.18-7.07 (m, 2H), 4.06-3.97 (m, 2H), 2.67 (d, J = 12.8 Hz, 2H), 2.24 (d, J = 12.8 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H), 1.07 (s, 3H), 0.94 (s, 3H)

2. Synthesis of 624-2

[2089] To a solution of ethyl 624-1 (5.5 g, 17.6 mmol, 1 equiv) in MeOH (55 mL) and THF (14 mL) and H2O (14 mL) was added NaOH (1.41 g, 35.3 mmol, 2 equiv). The mixture was stirred at 20 °C for 24 hr. The reaction mixture was concentrated in vacuum to remove MeOH (55 mL) and THF (14 mL). Then the mixture was diluted with water (30 mL), adjusted pH to 2 by 1H HCl. The mixture was filtered and the filter cake was concentrated in vacuum to afford 624-2 (4.6 g, 92%) as a white solid.

1H-NMR-624-2: (400 MHz, METHANOL-d4) δ 7.46 (t, J = 2.0 Hz, 1H), 7.38-7.33 (m, 1H), 7.32-7.28 (m, 1H), 7.25-7.19 (m, 1H), 2.79-2.67 (m, 2H), 2.30 (d, J = 12.8 Hz, 2H), 1.16 (s, 3H), 1.00 (s, 3H)

3. Synthesis of 624-3

[2090] To a solution of 624-2 (5.5 g, 19.4 mmol, 1 equiv) and formohydrazide (1.75 g, 29.1 mmol, 1.5 equiv) in DMF (55 mL) was added EDCI (5.59 g, 29.1 mmol, 1.5 equiv), HOBt

(3.94 g, 29.1 mmol, 1.5 equiv) and TEA (8.11 mL, 58.27 mmol, 3 equiv) under nitrogen atmosphere. The mixture was stirred at 20 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.NH4Cl (100 mL), extracted with EtOAc (50 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=1:3 to afford 624-3 (4.2 g, 66%) as a white solid.

1H-NMR-624-3: (400 MHz, DMSO-d6) δ 9.91-9.69 (m, 2H), 8.00 (s, 1H), 7.54-7.49 (m, 1H), 7.44-7.38 (m, 1H), 7.35-7.26 (m, 2H), 2.73-2.66 (m, 2H), 2.31-2.20 (m, 2H), 1.15-1.07 (m, 3H), 1.02-0.95 (m, 3H)

4. Synthesis of 624-4

[2091] To a solution of 624-3 (2 g, 6.15 mmol, 1 equiv) in THF (32 mL) was added LAWESSON'S REAGENT (4.98 g, 12.3 mmol, 2 equiv). The mixture was stirred at 40 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuum. The residue was dissolved in DCM (40 mL), washed with Sat. Na2CO3 (20 mL x2). The organic phase was dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=1:9 to afford 624-4 (1.2 g, 60%) as a colorless oil.

1H-NMR-624-4: (400 MHz, METHANOL-d4) δ 9.29 (s, 1H), 7.56 (t, J = 2.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.32-7.27 (m, 1H), 2.99 (d, J = 12.8 Hz, 2H), 2.79 (d, J = 12.8 Hz, 2H), 1.15 (s, 3H), 1.09 (s, 3H)

5. Synthesis of 624-5

To a solution of 624-4 (1 g, 3.09 mmol, 1 equiv) and NH2Boc (435 mg, 3.71 mmol, 1.2 equiv) in dioxane (15 mL) was added Pd(OAc)2 (34.7 mg, 154 umol, 0.05 equiv), XPhos (147 mg, 309 umol, 0.1 equiv) and Cs2CO3 (1.41 g, 4.33 mmol, 1.4 equiv). The mixture was stirred at 95 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=1:3 to afford 624-5 (1 g, 90%) as a yellow oil.

1H-NMR-624-5: (400 MHz, METHANOL-d4) δ 9.26 (s, 1H), 7.53 (s, 1H), 7.32-7.24 (m, 2H), 7.10-7.03 (m, 1H), 2.99 (d, J = 12.4 Hz, 2H), 2.82 (d, J = 12.4 Hz, 2H), 1.53 (s, 9H)

6. Synthesis of 624-6

[2092] To a solution of 624-5 (0.9 g, 2.5 mmol, 1 equiv) in DCM (8 mL) was added TFA (8 mL). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated in

vacuum. The residue was dissolved with EtOAc (20 mL), washed with Sat. NaHCO3 (15 mL x2). The separated organic phase was dried over anhydrous Na2SO4, filtered and concentrated in vacuum to afford 624-6 (600 mg, crude) as a brown oil.

7. Synthesis of 624-7

[2093] To a solution of 624-6 (0.4 g, 1.54 mmol, 1 equiv) and I-2 (441 mg, 1.54 mmol, 1 equiv) in MeOH (8 mL) was added AcOH (264 uL, 4.63 mmol, 3 equiv). The mixture was stirred at 20 °C for 0.5 h under nitrogen atmosphere. Then NaBH3CN (193 mg, 3.08 mmol, 2 equiv) was added to the mixture, the result mixture was stirred at 20 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.NaHCO3 (20 mL), extracted with EtOAc (15 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=3:1 to afford 624-7 (0.7 g, 86%) as a yellow oil.

1H-NMR-624-7: (400 MHz, DMSO-d6) δ 9.29 (s, 1H), 8.60 (s, 1H), 7.94 (s, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.54 (s, 1H), 6.47-6.39 (m, 2H), 6.21 (t, J = 5.6 Hz, 1H), 4.38 (d, J = 5.6 Hz, 2H), 3.46 (s, 2H), 2.73 (d, J = 12.4 Hz, 2H), 2.62-2.57 (m, 1H), 2.51 (d, J = 12.4 Hz, 2H), 1.59-1.45 (m, 5H), 1.41-1.33 (m, 1H), 0.98 (s, 3H), 0.89 (s, 3H), 0.79-0.69 (m, 5H)

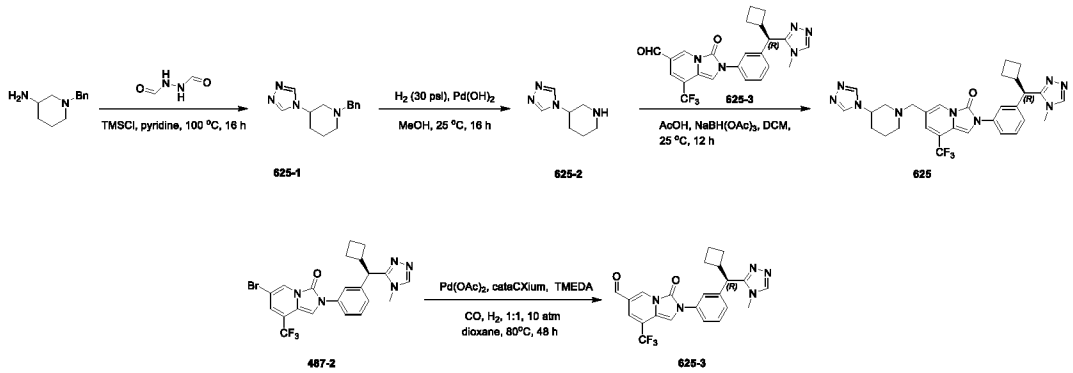
8. Synthesis of 624

[2094] To a solution of 624-7 (0.2 g, 377 umol, 1 equiv) in DCM (1 mL) was added Py (183 uL, 2.27 mmol, 6 equiv) and bis(trichloromethyl) carbonate (56.0 mg, 189 umol, 0.5 equiv) at 0 °C. The mixture was stirred at 20 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.NaHCO3 (20 mL), extracted with DCM (15 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with EA/PE=3:1 give crude product. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: Phenomenex Luna C18 200*40mm*10um; Mobile Phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 15% B to 50% B in 8 min; Wave Length: 220 nm; RT1(min): 8.0) to afford 624 (160 mg, 38%) as a yellow solid.

MS-624: (ES, m/z): [M+H]+ 556.2

1H NMR-624: (400 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.17 (s, 1H), 7.88 (s, 1H), 7.75-7.69 (m, 1H), 7.64 (s, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.43-7.33 (m, 2H), 7.00 (s, 1H), 3.24 (s, 2H), 2.98-2.91 (m, 2H), 2.81 (d, J = 12.4 Hz, 2H), 2.77-2.68 (m, 2H), 1.95-1.83 (m, 1H), 1.69-1.53 (m, 4H), 1.50-1.38 (m, 1H), 1.12 (s, 3H), 1.06 (s, 3H), 0.90-0.77 (m, 4H).

Example 620. Synthesis of Compound 625



1. Synthesis of 625-1

[2095] To a solution of 1-benzylpiperidin-3-amine (1 g, 5.26 mmol, 1 eq) in pyridine (40 mL) was added Et3N (5.46 g, 53.97 mmol, 7.51 mL, 10.27 equiv), TMSCl (8.78 g, 80.83 mmol, 10.26 mL, 15.38 equiv) and N-formamidoformamide (1.53 g, 17.34 mmol, 3.3 equiv). After addition, the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was partitioned between NaHCO3 10 mL and EtOAc 25 mL. The organic phase was separated, washed with brine (5 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Dichloromethane : Methanol=10/1) to give 625-1 (710 mg, 2.93 mmol, 55.75% yield) as a brown yellow liquid.

2. Synthesis of 625-2

[2096] To a solution of 625-1 (500 mg, 2.06 mmol, 1 equiv) in MeOH (20 mL) was added Pd(OH)2 (289.77 mg, 2.06 mmol, 1 equiv). The mixture was stirred at 25 °C for 16 hr under H2 atmosphere. The mixture was filtered and the filtrate concentrated under reduced pressure to give 625-2 (370 mg, crude) as a white solid.

3. Synthesis of 625-3

[2097] To a solution of 487-2 (2 g, 3.95 mmol, 1 equiv) in dioxane (70 mL) was added N,N,N',N'-tetramethylethane-1,2-diamine (918 mg, 7.90 mmol, 2 equiv), Pd(OAc)2 (177 mg, 790 umol, 0.2 equiv), bis(1-adamantyl)-butyl-phosphane (283 mg, 790 umol, 0.2 equiv) under N2. The suspension was degassed and purged with H2 and CO (2.5 MPa) for 3 times. The mixture was heated to 80°C and stirred for 48 h under H2 and CO (2.5 MPa). The mixture was concentrated in vacuum to get a residue. Sat.Na2CO3 (300 mL) was added. The resulting solution was extracted with DCM:MeOH (10:1, 100 mLx3). The combined organic layers were washed with brine (100 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue The residue was purified by column

(SiO2) with petroleum ether/EtOAc= 2:1 to 0:1 to DCM:MeOH= 1:0 to 1:1 to get 625-3 (1 g, 40.5% yield) as a yellow solid.

1H-NMR-625: (400 MHz, CDCl3) δ 9.68 (s, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.56-7.53 (m, 2H), 7.45-7.43 (m, 1H), 7.34-7.33 (m, 1H), 7.26-7.24 (m, 1H), 6.86 (s, 1H), 3.99-3.96 (m, 1H), 3.44 (s, 3H), 2.36-2.34 (m, 1H), 1.94-1.90 (m, 3H), 1.83-1.79 (m, 3H).

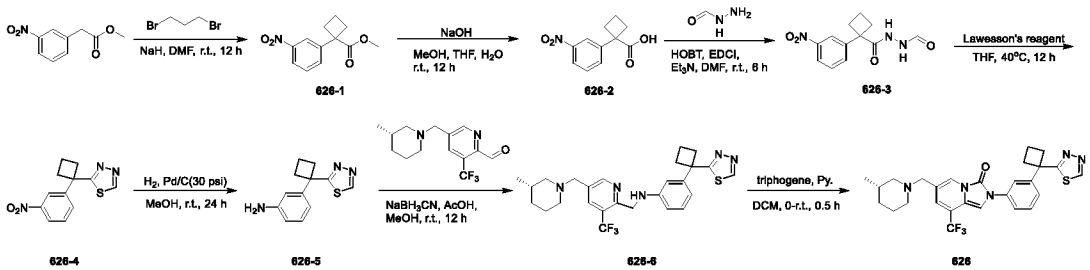
4. Synthesis of 625

[2098] To a solution of 625-2 (100 mg, 658 umol, 1 equiv) in DCM (10 mL) was added 625-3 (300 mg, 658 umol, 1 equiv), AcOH (39.56 mg, 658 umol, 1 equiv) at 25°C and stirred for 1 h. NaBH(OAc)3 (279 mg, 1.32 mmol, 2 equiv) was added and stirred for 11 h. The mixture was poured into H2O (20 mL), extracted with DCM:MeOH (10:1, 20 mL X3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc=1:1 to 0:1 and then with DCM:MeOH=1:0 to 1:1 to get a crude. The crude product was triturated with (DCM:MeOH) : petroleum ether =(20:1, 2 mL):(20 mL) to get a residue. The residue was purified by prep-HPLC (neutral) (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 30%-50%, 8min Wave Length: 220 nm; RT (min): 9.0 min) to get 625 (12 mg, 2.9%) as a yellow solid.

MS-625: (ES, m/z): [M+H]+ 592.3

1H-NMR-625: (400 MHz, DMSO) δ 8.64-8.62 (m, 2H), 8.32 (s, 1H), 7.71-7.67 (m, 3H), 7.45-7.41 (m, 1H), 7.29 (s, 1H), 7.20-7.18 (m, 1H), 7.03 (s, 1H), 4.38-4.36 (m, 1H), 4.26-4.24 (m, 1H), 3.42 (s, 2H), 3.40-3.36 (m, 3H), 3.20-3.18 (m, 1H), 2.96-2.94 (m, 1H), 2.70-2.67 (m, 1H), 2.45-2.43 (m, 1H), 2.25-2.20 (m, 1H), 2.08-2.06 (m, 1H), 1.98-1.96 (m, 1H), 1.78-1.67 (m, 7H), 1.57-1.53 (m, 1H).

Example 621. Synthesis of Compound 626



1. Synthesis of 626-1

[2099] To a solution of methyl 2-(3-nitrophenyl)acetate (10 g, 51.24 mmol, 1 equiv) and 1,3-dibromopropane (10.34 g, 51.24 mmol, 1 equiv) in DMF (360 mL) was added NaH (4.10

g, 102 mmol, 60% purity, 2 equiv) at 25°C and stirred for 12 h. The mixture was poured into H2O (300 mL) at 0°C, extracted with EtOAc (200 mLx3). The combined organic layer was washed by brine (200 mLx3), dried by Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc=100:1 to 3:1 to get 626-1 (8.1 g, 33.6%) as a light yellow solid.

2. Synthesis of 626-2

[2100] To a solution of methyl 626-1 (8.5 g, 36.1 mmol, 1 equiv) in MeOH (80 mL), THF (20 mL) and H2O (20 mL) was added NaOH (2.89 g, 72.2 mmol, 2 equiv) at 25°C and stirred for 12 h. The mixture was acidified to pH = 3 with HCl (aq, 1M). The precipitate solids were collected by filtration and concentrated in vacuum to get 626-2 (7 g, 87.5%) as a white solid.

3. Synthesis of 626-3

[2101] To a solution of 626-2 (6.2 g, 28.0 mmol, 1 equiv) in DMF (80 mL) was added formohydrazide (2.52 g, 42.0 mmol, 1.5 equiv), HOBt (5.68 g, 42.0 mmol, 1.5 equiv), EDCI (8.06 g, 42.0 mmol, 1.5 equiv), TEA (8.51 g, 84.0 mmol, 3 equiv) at 25°C. The reaction mixture was stirred for 6 h at 25°C. The mixture was poured into H2O (300 mL), extracted with DCM:MeOH (20:1, 200 mLx3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO2) with PE/EA= 1:0 to 0:1 to obtain 626-3 (6.5 g, 87.2%) as a light yellow oil.

1H-NMR-626-3: (400 MHz, DMSO), δ 9.85 (brs, 1H), 9.81 (brs, 1H), 8.21-8.20 (m, 1H), 8.13-8.11(m, 1H), 7.99 (s, 1H), 7.82-7.80 (m, 1H), 7.67-7.65 (m, 1H), 2.83-2.80 (m, 2H), 2.49-2.46 (m, 2H), 1.90-1.81 (m, 2H).

4. Synthesis of 626-4

[2102] To a solution of 626-3 (3.3 g, 12.54 mmol, 1 equiv) in THF (80 mL) was added LAWESSON'S REAGENT (10.1 g, 25.0 mmol, 2 equiv). Then the mixture was heated to 40°C and stirred for 12 h. The mixture was poured into sat. Na2CO3 (300 mL) at 0°C, extracted with EtOAc (200 mLx3). The combined organic layer was washed by brine (200 mLx3), dried by Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc=1:0 to 1:1 to get 626-4 (2.5 g, 63.3%) as a light yellow oil.

5. Synthesis of 626-5

[2103] To a solution of 626-4 (2.5 g, 9.57 mmol, 1 equiv) in EtOAc (100 mL) was added Pd/C (2 g, 10% purity) under H2. The suspension was degassed and purged with H2 for 3 times. The mixture was stirred under H2 (30 Psi) at 25 °C and stirred for 24 h. The mixture

was filtered and washed with DCM/MeOH (1:1, 1 L). The filtrate was concentrated in vacuum to get a crude. The crude was purified by column (SiO2) with petroleum ether/EtOAc=10:1 to 1:1 to obtain 626-5 (1.5g, 67.7%) as a light yellow oil.

1H-NMR-626-5 (400 MHz, CDCl3), δ 8.98 (s, 1H), 7.17-7.13 (m, 1H), 6.75-6.73 (m, 1H), 6.63-6.62 (m, 1H), 6.60-6.58 (m, 1H), 3.77 (brs, 2H), 3.00-2.97 (m, 2H), 2.85-2.82 (m, 2H), 2.30-2.27 (m, 1H), 2.01-1.99 (m, 1H).

6. Synthesis of 626-6

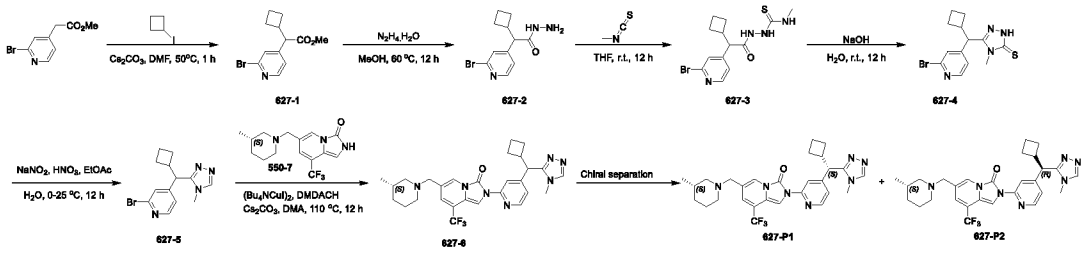
[2104] To a solution of 5-[[(3S)-3-methyl-1-piperidyl]methyl]-3-(trifluoromethyl)pyridine-2-carbaldehyde (198.03 mg, 691.69 umol, 1 equiv) in MeOH (5 mL) was added 626-5 (160 mg, 691 umol, 1 equiv), AcOH (41.54 mg, 691 umol, 1 equiv) at 25 °C and stirred for 1 h. NaBH3CN (86.93 mg, 1.38 mmol, 2 equiv) was added and stirred for 11 h. The mixture was poured into sat. NaHCO3 (100 mL) at 0°C, extracted with DCM (100 mL x3). The combined organic layer was washed by brine (200 mL x3), dried by Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc= 1:0 to 0:1, then with DCM:MeOH= 1:0 to 5:1 to obtain 626-6 (325 mg, 93.67%) as a yellow solid.

7. Synthesis of 626

[2105] To a solution of 626-6 (300 mg, 598 umol, 1 equiv) in DCM (10 mL) was added pyridine (283 mg, 3.59 mmol, 6 equiv), bis(trichloromethyl) carbonate (90 mg, 303 umol, 0.5 equiv) at 0°C and stirred for 1 h. The same scale reaction was conducted with in parallel for 2 batches in total and work up with a small test scale (50 mg) together. The reaction mixture was diluted with Sat.NaHCO3 (50 mL), extracted with DCM (50 mL x3). The combined organic layers were dried over Na2SO4, filtered and concentrated in vacuum to get a residue. The residue was purified by column (SiO2) with petroleum ether/EtOAc= 5:1 to 0:1, then with DCM/MeOH=1:0 to 1:1 to get a crude. The crude was purified by prep-HPLC (neutral) (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 55%-85%,8min;; Wave Length: 220 nm; RT1 (min): 5.2) to obtain 626 (145 mg) as a yellow solid.

1H-NMR-626: (400 MHz, DMSO) δ 9.48 (s, 1H), 7.83 (s, 1H), 7.75-7.73 (m, 1H), 7.64 (s, 1H), 7.51 (t, J = 8 Hz, 1H), 7.41 (s, 1H), 7.33-7.31 (m, 1H), 6.99 (s, 1H), 3.23 (s, 2H), 2.97-2.83 (m, 4H), 2.76-2.71 (m, 2H), 2.17-2.12 (m, 1H), 1.99-1.85 (m, 2H), 1.65-1.57 (m, 4H), 1.48-1.39 (m, 1H), 0.89-0.81 (m, 4H).

Example 622. Synthesis of Compound Synthesis of 627_P1&P2



1. Synthesis of 627-1

[2106] To a solution of methyl 2-(2-bromo-4-pyridyl)acetate (2 g, 8.69 mmol, 1 equiv) in DMF (25 mL) was added iodocyclobutane (2.37 g, 13.04 mmol, 1.5 equiv), Cs2CO3 (5.66 g, 17.39 mmol, 2 equiv). The mixture was stirred for 1 h at 50°C under nitrogen atmosphere. The reaction mixture was diluted with H2O (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (150 mL x 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5:1 to 1:10) to afford 627-1 (2.1 g, 82.4%) as a brown solid.

1H-NMR-627-1: (400 MHz, CHLOROFORM-d) δ 8.30 (d, J = 5.2 Hz, 1H), 7.43 (d, J = 0.4 Hz, 1H), 7.19-7.18 (m, 1H), 3.69 (s, 3H), 3.51 (d, J = 10.4 Hz, 1H), 2.98-2.85 (m, 1H), 2.26-2.15 (m, 1H), 1.93-1.81 (m, 4H), 1.60-1.56 (m, 1H)

2. Synthesis of 627-2

[2107] To a solution of 627-1 (3.96 g, 6.97 mmol, 1 equiv) in MeOH (20 mL) was added N2H4.H2O (7.05 g, 138.01 mmol, 98% purity, 19.81 equiv). The mixture was heated to 60°C and stirred for 12 h at 60°C. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H2O (30 mL), and extracted with DCM (25 mL x 3). The combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure to afford 627-2 (4.1 g, crude) as a white solid.

3. Synthesis of 627-3

[2108] To a solution of 627-2 (3.1 g, 10.91 mmol, 1 equiv) in THF (35 mL) was added methylimino(thioxo)methane (1.75 g, 24.00 mmol, 2.2 equiv). The mixture was stirred for 12 h at 15°C. The mixture was concentrated under reduced pressure to remove THF and diluted with H2O (30 mL), and filtered. Then the mixture was filtered to get a filter cake and the filter cake was concentrated in vacuum to afford 627-3 (3.4 g, crude) as a white solid.

4. Synthesis of 627-4

[2109] To a solution of 627-3 (4.4 g, 12.32 mmol, 1 equiv) in H2O (40 mL) was added

NaOH (3.94 g, 98.53 mmol, 8 equiv). The mixture was stirred for 12 h at 15°C. The mixture was adjusted to pH =2 by HCl (2 M), and filtered. The filter cake was concentrated in vacuum to afford 627-4 (3 g, crude) as a white solid.

5. Synthesis of 627-5

[2110] HNO3 (5.63 g, 60.76 mmol, 68% purity, 10.31 equiv) was added to H2O (60 mL) to afford the diluted HNO3 solution (1M, 64.02 mL). To a solution of 627-4 (2 g, 5.90 mmol, 1 equiv) in H2O (20 mL) was added NaNO2 (4.07 g, 58.95 mmol, 10 equiv), EtOAc (4.16 g, 47.16 mmol, 8 equiv), diluted HNO3 solution (1 M, 64.02 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 12 h. The solvent was diluted with H2O (30 mL) and adjusted pH to 12 by 2N NaOH, and extracted with DCM (150 mL x 3). The combined organic layers were dried over Na2SO4 filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, DCM/MeOH=50/1 to 5/1) to afford 627-5 (1.67 g, 78%) as a yellow oil.

1H-NMR-627-5: (400 MHz, CHLOROFORM-d) δ 8.29-8.28 (d, J = 4 Hz, 1H), 8.08 (s, 1H), 7.37 (s, 1H), 7.14-7.13 (m, 1H), 3.85-3.83 (d, J = 8 Hz, 1H), 3.45 (s, 3H), 3.35-3.21 (m, 1H), 2.31-2.27 (m, 1H), 1.93-1.66 (m, 5H)

6. Synthesis of 627-6-P1

[2111] To a solution of 627-5 (133.70 mg, 435.23 umol, 1 equiv) in dioxane (4 mL) was added 550-7 (150 mg, 478.75 umol, 1.1 equiv), Cs2CO3 (283.61 mg, 870.45 umol, 2 equiv), iodocopper;tetrabutylammonium;diiodide (48.73 mg, 43.52 umol, 0.1 equiv), N1,N2-dimethylcyclohexane-1,2-diamine (12.38 mg, 87.05 umol, 0.2 equiv) in glove box. The same scale reaction was conducted with in parallel for 2 batches in total and work up together. The reaction mixture was diluted with H2O (10 mL) and extracted with EA (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=1/1 to DCM: MeOH = 1:5) to get a product to afford 627-6 (400 mg, crude) as a yellow solid.

1H-NMR-627-6: (400 MHz, CHLOROFORM-d) δ 8.58 (s, 1H), 8.36-8.35 (d, J = 4.0 Hz, 1H), 8.07 (br s, 1H), 7.64-7.49 (m, 2H), 7.05-7.04 (d, J = 4.0 Hz, 1H), 6.96 (s, 1H), 4.05-4.02 (d, J = 12.0 Hz, 1H), 3.47 (s, 3H), 3.43-3.32 (m, 1H), 3.21 (br s, 2H), 2.78-2.73 (m, 2H), 2.33-2.31 (m, 1H), 1.97-1.76 (m, 6H), 1.71-1.50 (m, 6H), 0.87-0.85 (d, J = 8.0 Hz, 3H)

7. Synthesis of 627_P1&P2

[2112] The 627-6 (400 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [Neu-

ETOH];B%: 43%-43%,8min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 1.18; RT2 (min): 1.40) to afford 627_P1 (118.1 mg) as a yellow solid and 627_P2 (157.9 mg) as a yellow solid.

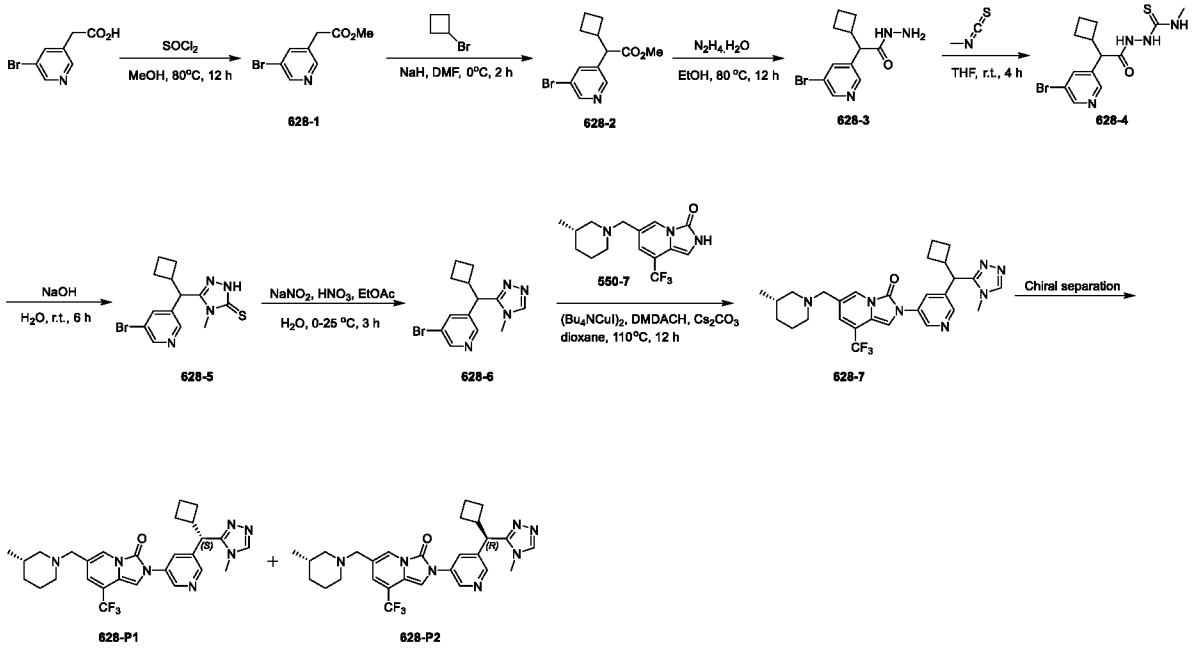
MS-627_P1: (ES, m/z): [M+H]+ 540.3.

1H-NMR-627_P1: (400 MHz, DMSO-d6) δ 8.44-8.43 (d, J = 4.0 Hz, 1H), 8.37-8.36 (d, J = 4.0 Hz, 2H), 7.63 (s, 1H), 7.43 (s, 1H), 7.23-7.22 (d, J = 4.0 Hz, 1H), 7.02 (s, 1H), 4.43-4.40 (d, J = 12 Hz, 1H), 3.45 (s, 3H), 3.26-3.14 (m, 3H), 2.80-2.67 (m, 2H), 2.13-2.02 (m, 1H), 1.99-1.70 (m, 6H), 1.68-1.38 (m, 5H), 0.92-0.75 (m, 4H).

MS-627_P2: (ES, m/z): [M+H]+ 540.3.

1H-NMR-627_P2: (400 MHz, DMSO-d6) δ 8.44-8.43 (d, J = 4.0 Hz, 1H), 8.37-8.36 (d, J = 4.0 Hz, 2H), 7.63 (s, 1H), 7.43 (s, 1H), 7.23-7.22 (d, J = 4.0 Hz, 1H), 7.02 (s, 1H), 4.43-4.40 (d, J = 12 Hz, 1H), 3.45 (s, 3H), 3.26-3.14 (m, 3H), 2.80-2.67 (m, 2H), 2.13-2.02 (m, 1H), 1.99-1.70 (m, 6H), 1.68-1.38 (m, 5H), 0.92-0.75 (m, 4H).

Example 623. Synthesis of Compound 628_P1&P2



1. Synthesis of 628-1

[2113] To a solution of 2-(5-bromo-3-pyridyl)acetic acid (4 g, 18.52 mmol, 1 equiv) in MeOH (50 mL) was added SOCl2 (4 mL, 2.98 equiv). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. And then the residue was adjusted pH to 8 with saturated NaHCO3 and extracted with EtOAc (20

mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (4:1) to afford 628-1 (3.9 g, 92%) as a white solid.

1H-NMR-628-1: (400 MHz, CHLOROFORM-d) δ 8.53 (d, J = 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 3.66 (s, 3H), 3.56 (s, 2H)

2. Synthesis of 628-2

[2114] To a solution of NaH (363 mg, 9.08 mmol, 60% purity, 1.1 equiv) in DMF (20 mL) was added 628-1 (1.9 g, 8.26 mmol, 1 equiv). The mixture was cooled to 0°C under nitrogen atmosphere. And then bromocyclobutane (3.9 mL, 41.3 mmol, 5 equiv) was added to reaction mixture at 0 °C. The mixture was stirred at 0 °C for 2 hr. The reaction mixture was adjusted pH to 1 with 1 N HCl and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with PE/ EtOAc (9:1) to afford 628-2 (560 mg, 18%) as a colorless oil.

1H-NMR-628-2: (400 MHz, CHLOROFORM-d) δ 8.50 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 2.0 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 3.61 (s, 3H), 3.47 (d, J = 10.8 Hz, 1H), 2.92-2.81 (m, 1H), 2.17-2.08 (m, 1H), 1.86-1.73 (m, 4H), 1.55-1.49 (m, 1H)

3. Synthesis of 628-3

[2115] To a solution of 628-2 (0.9 g, 3.17 mmol, 1 equiv) in EtOH (5 mL) was added N2H4.H2O (3.14 mL, 63.3 mmol, 98% purity, 20 equiv). The mixture was stirred at 80 °C for 12 hr. The reaction mixture was concentrated in vacuum to remove EtOH (5 mL). Then the mixture was diluted with water (10 mL), and extracted with DCM (10 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 628-3 (800 mg, crude) as a white solid.

4. Synthesis of 628-4

[2116] To a solution of 628-3 (800 mg, 2.82 mmol, 1 equiv) in THF (8 mL) was added methylimino(thioxo)methane (411 mg, 5.63 mmol, 2 equiv). The mixture was stirred at 20 °C for 4 hr. The reaction mixture was diluted with water 20 mL and extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford 628-4 (977 mg, crude) as a white solid.

5. Synthesis of 628-5

[2117] To a solution of NaOH (875.08 mg, 21.88 mmol, 8 equiv) in water (10 mL) was added 628-4 (977 mg, 2.73 mmol, 1 equiv). The mixture was stirred at 20 °C for 6 hr. The

reaction mixture was filtered and the filter cake was concentrated under reduced pressure to afford 628-5 (800 mg, crude) as a white solid.

1H-NMR-628-5 (400 MHz, DMSO-d6) δ 13.73 (s, 1H), 8.72-8.43 (m, 2H), 7.90 (s, 1H), 4.34 (d, J = 10.8 Hz, 1H), 3.27 (s, 3H), 3.07-2.95 (m, 1H), 2.09 (d, J = 4.0 Hz, 1H), 1.84-1.68 (m, 5H)

6. Synthesis of 628-6

[2118] HNO3 (1.37 mL, 20.63 mmol, 68% purity, 10 equiv) was added to water (19 mL) to afford the diluted HNO3 solution (1 M, 20.37 mL). To a solution of 628-5 (700 mg, 2.06 mmol, 1 equiv) and NaNO2 (1.42 g, 20.6 mmol, 10 equiv) and EtOAc (1.26 g, 14.3 mmol, 1.4 mL) in water (7 mL) was added diluted HNO3 solution (1 M, 20.37 mL) dropwise at 0 °C. Then the mixture was stirred at 25 °C for 3 hr. The reaction was quenched by the addition of saturated NaHCO3 (30 mL). The organic layer was extracted with CH2Cl2 (30 ml x3). The organic phase was concentrated under reduced pressure to afford 628-6 (500 mg, crude) as a yellow solid.

1H-NMR-628-6 (400 MHz, DMSO-d6) δ 8.60 (d, J = 2.4 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.38 (s, 1H), 7.92 (t, J = 2.0 Hz, 1H), 4.34 (d, J = 10.8 Hz, 1H), 3.50 (s, 3H), 3.19-3.06 (m, 1H), 2.01 (s, 1H), 1.81-1.66 (m, 5H)

7. Synthesis of 628

[2119] To a solution of 628-6 (320 mg, 1.04 mmol, 1 equiv) and 550-7 (359 mg, 1.14 mmol, 1.1 equiv) in dioxane (3 mL) was added Cs2CO3 (679 mg, 2.08 mmol, 2 equiv) and N1,N2-dimethylcyclohexane-1,2-diamine (29.6 mg, 208 umol, 0.2 equiv), iodocopper;tetrabutylammonium; diiodide (117 mg, 104 umol, 0.1 equiv). The mixture was stirred at 110 °C for 12 hr. The reaction mixture was diluted with water 30 mL and extracted with EtOAc (30 mL x3). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography eluted with DCM/MeOH (10:1) to afford 628-7 (430 mg, 76%) as a yellow solid.

8. Synthesis of 628_P1&P2

[2120] The 628-7 (430 mg) was purified by Chiral separation with the following conditions (column: DAICEL CHIRALCEL OD (250mm*30mm, 10 um); Mobile Phase: [Neu-ETOH]; B%: 40%-40%, 11 min, Flow rate: 70 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.23; RT2 (min): 6.59) to afford crude product 1 and 628_P2 (92.2 mg, 21%) as a yellow solid. The crude product 1 (120 mg) was further purified by Prep-HPLC with the following conditions (Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile Phase A:

Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 35% B to 65% B in 8 min; Wave Length: 220 nm; RT1 (min): 8.0) to afford 628_P1 (61.4 mg, 51%) as a yellow solid.

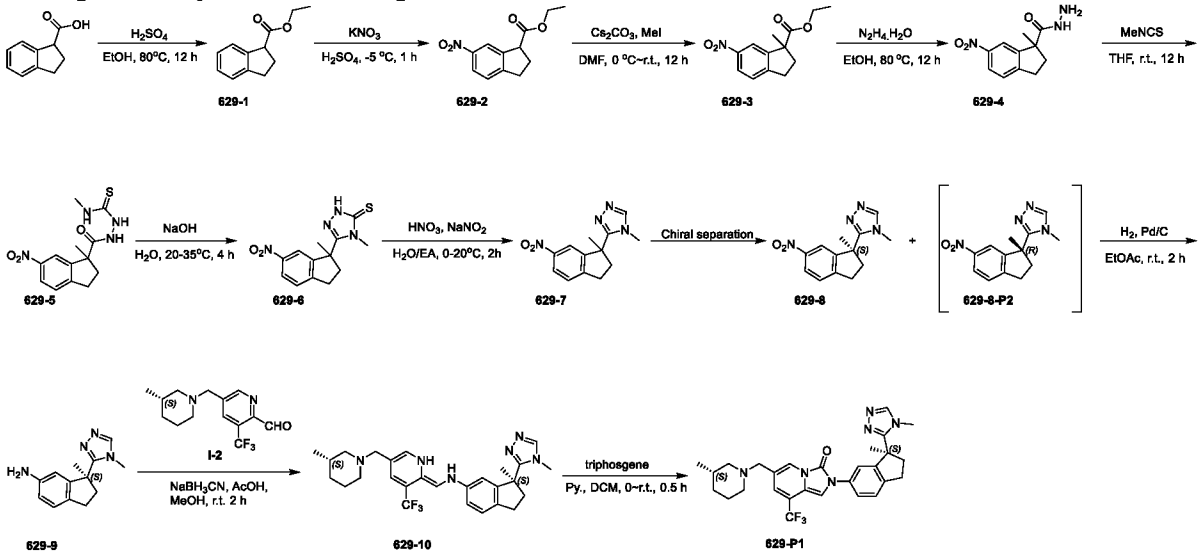
MS-628_P1: (ES, m/z): [M+H]+ 540.3.

1H-NMR-628_P1: (400 MHz, DMSO-d6) δ 8.94 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.36 (s, 1H), 8.15 (t, J = 2.0 Hz, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 7.02 (s, 1H), 4.38 (d, J = 10.4 Hz, 1H), 3.49 (s, 3H), 3.25 (s, 2H), 2.81-2.70 (m, 2H), 2.14-2.03 (m, 1H), 1.94-1.88 (m, 1H), 1.87-1.68 (m, 6H), 1.66-1.51 (m, 4H), 1.51-1.41 (m, 1H), 0.89-0.79 (m, 4H)

MS-628_P2: (ES, m/z): [M+H]+ 540.3.

1H-NMR-628_P2: (400 MHz, DMSO-d6) δ = 8.94 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 1.6 Hz, 1H), 8.36 (s, 1H), 8.15 (t, J = 2.0 Hz, 1H), 7.64 (s, 1H), 7.47 (s, 1H), 7.02 (s, 1H), 4.38 (d, J = 10.4 Hz, 1H), 3.49 (s, 3H), 3.25 (s, 2H), 2.80-2.70 (m, 2H), 2.14-2.02 (m, 1H), 1.94-1.88 (m, 1H), 1.88-1.74 (m, 5H), 1.74-1.52 (m, 5H), 1.48-1.42 (m, 1H), 0.90-0.78 (m, 4H).

Example 624. Synthesis of Compound 629



1. Synthesis of 629-1

[2121] To a solution of indane-1-carboxylic acid (4 g, 24.6 mmol, 1 equiv) in EtOH (40 mL) was added H_2SO_4 (1.31 mL, 24.6 mmol, 1 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography eluted with PE/EA=10:1 to afford 629-1 (4 g, 85%) as a colorless oil.

2. Synthesis of 629-2

[2122] To a solution of 629-1 (15.0 g, 78.8 mmol, 1.0 equiv) in H_2SO_4 (100 mL) was added

KNO_3 (7.9 g, 78.8 mmol, 1.0 equiv) in H_2SO_4 (50 mL) dropwise at -5 °C. The mixture was stirred at -5 °C for 1 hr. The reaction was slowly poured into sat Na_2SO_3 (300 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (100 mL x2). The organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography eluted with PE/EA=5:1 to afford 629-2 (5.2 g, 28% yield) as colorless oil.

3. Synthesis of 629-3

[2123] To a solution of 629-2 (5.2 g, 22.1 mmol, 1 equiv), Cs_2CO_3 (36.0 g, 110 mmol, 5 equiv) in DMF (60 mL) was added MeI (4.13 mL, 66.32 mmol, 3 equiv) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction was poured into water (40 mL) and the resulting mixture was extracted with EtOAc (100 mL x3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography eluted with PE/EA=4:1 to afford 629-3 (3.74 g, 68%) as yellow oil.

4. Synthesis of 629-4

[2124] To a solution of 629-3 (1.3 g, 5.22 mmol, 1 equiv) in EtOH (15 mL) was added $N_2H_4.H_2O$ (7.76 mL, 156.46 mmol, 98% purity, 30 equiv). The mixture was stirred at 80 °C for 12 h. The reaction was poured into water (10 mL) and the resulting mixture was extracted with EtOAc (10 mL x2). The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to afford 629-4 (1.08 g, 88%) as a white solid.
^{1}H-NMR-629-4: (400 MHz, DMSO-d6) δ 8.98-9.15 (m, 1 H) 8.15-8.25 (m, 1 H) 8.08 (d, *J* =8.4, 1 H) 7.48 (d, *J* =8.4 Hz, 1 H) 4.12-4.32 (m, 2 H) 2.90-3.11 (m, 2 H) 2.58-2.73 (m, 1 H) 1.94-2.00 (m, 1 H) 1.42-1.55 (m, 3 H).

5. Synthesis of 629-5

[2125] To a solution of 629-4 (1.08 g, 4.59 mmol, 1 equiv) in THF (15 mL) was added methylimino(thioxo)methane (627 uL, 9.18 mmol, 2 equiv). The mixture was stirred at 20 °C for 12 hr. The reaction was poured to water (50 mL) to form solid. The solid was filtered and the filter cake was concentrated to afford 629-5 (1.32 g, 93%) as a yellow solid.
^{1}H-NMR-629-5: (400 MHz, DMSO-d6) δ 9.59 (s, 1 H), 9.12-9.22 (m, 1 H), 8.25-8.34 (m, 1 H), 8.06 (d, *J* =2.0 Hz, 1 H), 7.65-7.75 (m, 1 H), 7.45-7.55 (m, 1 H), 3.00-3.07 (m, 2 H), 2.82-2.95 (m, 3 H), 2.66-2.75 (m, 1 H), 1.98-2.08 (m, 1 H), 1.51-1.60 (m, 3 H).

6. Synthesis of 629-6

[2126] To a solution of NaOH (1.04 g, 25.9 mmol, 8 equiv) in H_2O (10 mL) was added 629-5 (1.32 g, 4.28 mmol, 1 equiv), the mixture was stirred at 20 °C for 2 h. Then the mixture was

stirred at 35 °C for 2 h. The combined mixture was diluted with water (15 mL), adjusted pH to 3 by 1N HCl. Then the mixture was filtered and the filter cake was concentrated in vacuum to afford 629-6 (950 mg, 77%) as a yellow solid.

^{1}H-NMR-629-6: (400 MHz, METHANOL-d_4) δ 8.21-8.17 (m, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 3.29-3.22 (m, 2H), 3.21 (s, 3H), 2.73-2.61 (m, 1H), 2.40-2.30 (m, 1H), 1.74 (s, 3H)

7. Synthesis of 629-7

[2127] HNO_3 (1.71 mL, 25.8 mmol, 68% purity, 10 equiv) was added to H_2O (23.9 mL) to afford the diluted HNO_3 solution (1M, 25.6 mL). To a solution of 629-6 (0.75 g, 2.58 mmol, 1 equiv) and $NaNO_2$ (1.78 g, 25.8 mmol, 10 equiv) in H_2O (7.5 mL) and EtOAc (750 uL, 7.66 mmol, 3.0 equiv) was added diluted HNO_3 solution (1 M, 25.6 mL) dropwise at 0 °C. Then the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by the addition of $NaHCO_3$ (aq.) (90 mL). The aqueous layer was extracted with DCM (45 mL x3). The aqueous phase was concentrated under reduced pressure to afford 629-7 (620 mg, crude) as a yellow solid.

8. Synthesis of 629-8

[2128] The 629-7 (620 mg) was purified by Chiral separation with the following conditions (column: ChiralPak IH, (250mm*30mm,10um);mobile phase: [Neu-ETOH];B%: 44%-44%,9 min, Flow rate: 72 mL/min; Wave Length: 220/254 nm; RT1 (min): 3.72) to afford 629-8 (230 mg, 33%) as a yellow solid.

^{1}H-NMR-629-8: (400 MHz, METHANOL-d_4) δ 8.39 (s, 1H), 8.22-8.15 (m, 1H), 7.83 (d, J = 1.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 3.33 (s, 3H), 3.29-3.18 (m, 2H), 2.73-2.62 (m, 1H), 2.44-2.32 (m, 1H), 1.82 (s, 3H).

9. Synthesis of 629-9

[2129] To a solution of 629-8 (230 mg, 890 umol, 1 equiv) in EtOAc (5 mL) was added Pd/C (0.2 g, 10% purity), the mixture was stirred at 20 °C for 2 h under H_2 (15 psi). The reaction mixture was filtered through celite, the filtrate was concentrated in vacuum to afford 629-9 (180 mg, crude) as a white solid.

^{1}H-NMR-629-9: (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.65-6.46 (m, 1H), 6.10 (d, J = 2.0 Hz, 1H), 4.95 (s, 2H), 3.18 (s, 3H), 3.06-2.88 (m, 2H), 2.49-2.39 (m, 1H), 2.16-2.06 (m, 1H), 1.67 (s, 3H)

10. Synthesis of 629-10

[2130] To a solution of 629-9 (0.18 g, 788 umol, 1 equiv) and I-2 (226 mg, 788 umol, 1 equiv) in MeOH (4 mL) was added AcOH (135 uL, 2.37 mmol, 3 equiv), the mixture was

stirred at 20 °C for 1 h, then $NaBH_3CN$ (99.1 mg, 1.58 mmol, 2 equiv) was added to the mixture, the result mixture was stirred at 20 °C for 1 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.$NaHCO_3$ (12 mL), extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (10:1) to afford 629-10 (240 mg, 61%) as a white solid.

^{1}H-NMR-629-10: (400 MHz, METHANOL-d_4) δ 8.65 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.70-6.61 (m, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 4.49 (s, 2H), 3.66-3.56 (m, 2H), 3.37 (s, 2H), 3.11 (s, 3H), 3.05-2.95 (m, 1H), 2.85-2.75 (m, 2H), 2.52-2.41 (m, 1H), 2.23-2.14 (m, 1H), 2.03-1.95 (m, 1H), 1.76-1.67 (m, 6H), 1.64-1.52 (m, 1H), 0.98-0.85 (m, 4H)

11. Synthesis of 629_P1

[2131] To a solution of 629-10 (210 mg, 421 umol, 1 equiv) in DCM (2.5 mL) was added Py (204 uL, 2.53 mmol, 6 equiv) and bis(trichloromethyl) carbonate (62.5 mg, 210 umol, 0.5 *eq*) at 0 °C. Then the mixture was stirred at 20 °C for 0.5 h under nitrogen atmosphere. The reaction mixture was diluted with Sat.$NaHCO_3$ (15 mL), extracted with DCM (10 mL x3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography eluted with CH_2Cl_2/MeOH = 10:1 to afford crude product. The crude product (180 mg) was purified by Prep-HPLC with the following conditions (column: Phenomenex Luna C18 200*40mm*10um; mobile phase A: Water (0.2% formic acid), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 10% B to 45% B in 8.0 min; Wave Length: 220 nm; RT1 (min): 7.5) to afford 629_P1 (86 mg, 39%) as a yellow solid.

MS-629_P1: (ES, m/z): $[M+H]^+$ 525.3.

^{1}H-NMR-629_P1: (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.09 (s, 1H), 7.66 (s, 1H), 7.59-7.55 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.17 (s, 1H), 6.75 (s, 1H), 3.55 (d, *J* = 8.0 Hz, 2H), 3.26 (s, 3H), 3.23-3.14 (m, 3H), 3.09-3.04 (m, 1H), 2.59-2.49 (m, 1H), 2.41-2.33 (m, 1H), 2.23-2.13 (m, 1H), 1.90 (s, 4H), 1.88-1.72 (m, 4H), 1.02-0.95 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H).

Example 625. IC50 Screening

Experiment Procedure

a) Thaw UBE1, UBCH5b, CBL-B, Biotin-Ubiquitin, CBL-B assay buffer, and ATP on ice.

Aliquot each protein, CBL-B assay buffer, and ATP into single-use aliquots and stored at -80°C immediately.

b) Transfer 100 nL test compound (10mM stock solution, start at 100uM, 1:3 dilution, 11 points) and then backfill 100 nL DMSO to each well designated for the "Test compound" by Echo.

c) Transfer 200 nL DMSO to each well designated for the "High Control", "Low Control" by Echo.

d) Carefully calculate the amount of proteins needed. Prepare appropriate amounts of diluted proteins; dilute only the amount required for the assay. Do not store diluted proteins. Keep the diluted reagents on ice until use.

e) Add 2.5µl diluted CBL-B (40 nM) for the "High Control" and "Test compound", the final concentration is 10 nM. For the "Low Control", add 2.5 µL buffer each well. Pre-incubate for 15min.

f) Centrifuge at 1000 rpm for 1 minute and shake plate at a speed of 600rpm for 5 minutes.

g) Prepare the Master Mixture (E1E2) using diluted reagents: N wells × (1 µl Biotin-Ub + 0.5 µl diluted UBE1 + 1 µl diluted UBCH5 + 5µl ATP). Pre-incubation for 10min.

h) Add master mixture to each well. Centrifuge at 1000 rpm for 1 minute and shake plate at a speed of 600rpm for 5 minutes.

i) Incubate the reaction at 30°C for 20 minutes. Cover the plate with a plate sealer.

j) Dilute Mab Anti GST-Tb cryptate donor (1:100) and Streptavidin-d2 acceptor (1:100) using PPI-Terbium detection buffer. Prepare only the amount required for the assay Add 5 µL diluted donor and 5 µL acceptor mixture into each well. Centrifuge at 1000 rpm for 1 minute and shake plate at a speed of 600rpm for 5 minutes. Incubate at room temperature for one hour.

k) Read the fluorescent intensity with EnVison2104 (PerkinElmer Life Sciences). Blank value is subtracted from all other values. Tb-donor emission should be measured at 615nM followed by dye-acceptor emission at 665nM.

Plate map for IC50 screen (dose titration of 11 doses for 2 reps)

a) Dilute cpds in 384 well dilution plate according to the dilution plate map

b) Cpds starting conc: 10 mM

c) Final cpd conc in assay: 100000, 33333.3, 11111.1, 3703.7, 1234.57, 411.52, 137.17, 45.72, 15.24, 5.08, 1.69 and 0 nM.

d) High control wells (HC): DMSO vehicle, with Cbl-b

e) Low control wells (LC): DMSO vehicle, No Cbl-b

Data analysis

IC50 screening data analysis

a) Calculate average of HC and LC samples

b) Calculate plate Z' Factor:

$$Z' = 1 - 3 \times \frac{STD_{HC} + STD_{LC}}{AVG_{HC} - AVG_{LC}}$$

The Z' should be >0.5. Otherwise, consider the plate failed QC and repeat the experiment.

c) Calculate percent vehicle of each test well:

$$\%Vehicel = 100 \times \frac{Test\ cpd - Ave_{LC}}{Ave_{HC} - Ave_{LC}}$$

d) Fit the cpd IC50 from non-linear regression equation (Equation:201, XLfit5.3.1.3):

Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope))

X: Log of cpd concentration

Y : Percent inhibition(% inh)

Top and Bottom: Plateaus in same units as Y

logIC50: same log units as X

HillSlope: Slope factor or Hill slope

Compound IC_{50}s were binned into A through F as follows: A indicates <100 nM, B indicates 100 nM-300 nM, C indicates 301 nM-1,000 nM, D indicates 1,001 nM-3,000 nM, E indicates 3,001 nM-10,000 nM, and F indicates >10,000 nM.

Table 2

Cmpd No.	CBL-B TR-FRET activity IC_{50}
1	C
2	C
3	E
4	F
5	F
6	F
7	B
8	B
9	B
10	A
11	A
12	A
13	A
14	A

15	B
16	F
17	F
18	B
19	D
20	E
21	A
22	A
23	A
24	A
25	A
26	B
27	F
28	B
29	A
30	D
31	C
32	A
33	A
34	A
35	E
36	C
37	A
38	C
39	A
40	A
41	A
42	A
43	E
44	A
45	A
46	D
47	F
48	A
49	A
50	A
51	C
52	E
53	A
54	B
55	A
56	A
57	A
58	D
59	A
60	A
61	B
62	A

63	B
64	D
65	C
66	A
67	A
68	A
69	A
70	C
71	B
72	C
73	E
74	B
75	B
76	B
77	A
78	A
79	A
80	C
81	C
82	A
83	F
84	F
85	A
86	C
87	B
88	D
89	B
90	B
91	A
92	C
93	B
94	E
95	C
96	A
97	A
98	B
99	A
100	A
101	D
102	A
103	B
104	B
105	B
106	B
107	A
108	A
109	A
110	A

111	A
112	A
113	C
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	C
123	A
124	A
125	A
126	A
127	C
128	A
129	B
130	B
131	A
132	F
133	F
134	C
135	A
136	C
137	A
138	D
139	B
140	A
141	D
142	F
143	F
144	F
145	B
146	F
147	F
148	F
149	F
150	A
151	C
152	F
153	A
154	A
155	E
156	A
157	A
158	E

159	A
160	D
161	A
162	D
163	A
164	E
165	A
166	A
167	A
168	B
169	E
170	D
171	A
172	A
173	E
174	A
175	D
176	A
177	A
178	C
179	B
180	E
181	F
182	C
183	A
184	A
185	B
186	B
187	B
188	F
189	A
190	A
191	C
192	A
193	A
194	A
195	B
196	C
197	E
198	A
199	A
200	F
201	A
202	A
203	C
204	A
205	A
206	C

207	A
208	F
209	A
210	F
211	D
212	B
213	A
214	A
215	A
216	A
217	A
218	D
219	A
220	E
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223	A
224	F
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226	A
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228	A
229	A
230	F
231	E
232	C
233	A
234	A
235	D
236	A
237	A
238	D
239	A
240	B
241	C
242	F
243	A
244	A
245	A
246	A
247	A
248	A
249	A
250	A
251	A
252	A
253	A
254	D

255	A
256	F
257	F
258	A
259	A
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	F
268	F
269	A
270	F
271	A
272	A
273	A
274	A
275	A
276	A
277	F
278_p1	A
278_p2	A
279	C
280	F
281	F
282	F
283	F
284	C
285	B
286	A
287_P1	A
287_P2	A
288	A
289	F
290	A
291	F
292	B
293	B
294	D
295	A
296	A
297	A
298	A
299	A
300	D

301	B
302	C
303	F
304	A
305	F
306	F
307	A
308	A
309	B
310	A
311	F
312	A
313	A
314	F
315	A
316	A
317	A
318	A
319	A
329	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	D
329	D
330	C
331	C
332_p1	F
332-p2	A
333	B
334	A
335	F
336	F
337	A
338	A
339_P1	A
339_P2	D
340_P1	A
340_P2	D
341	A
342	F
343	B
344	F
345	A

346	F
347	A
348	B
349	A
350	B
351_P1	D
351_P2	A
352_P1	F
352_P2	B
353	F
354	C
355	F
356	A
357	A
358	F
359	F
360	F
361	F
362_P1	A
362_P2	B
363_P1	F
363_P2	A
364_P1	C
364_P2	A
365	D
366	F
367	E
368	A
369	F
370	F
371	F
372	F
373	B
374	C
375	B
376	A
377	A
378	A
379	A
380_P1	D
380_P2	A
381_P1	D
381_P2	A
382_P1	A
382_P2	D
Patent Cmpd No	**Updated Activity**
383	F
384	F

385	F
386	F
387	F
388	F
389	F
390	F
391	F
392	F
393	A
394	B
395	B
396	B
397	B
398	A
399	A
400	F
401_P1	A
401_P2	F
402	F
403_P1	F
403_P2	C
404	F
403	F
404	F
405	F
406	B
407	F
408	A
409	A
410	F
411	F
412	A
413	A
414	A
415	A
416	A
417	A
418	E
419	F
420	F
421	A
422	A
423	F
424	F
425	F
426	F
427	F
428	F

429	B
430	C
431	F
432	F
433	A
434_P1	F
434_P2	D
435	F
436	F
437	A
438	A
439	B
440	F
441	F
442	F
443	F
444	F
445	F
446	F
447	F
448	F
449	A
450	A
451	A
452	F
453	C
454	D
455	F
456	F
457	F
458	E
459	F
460	F
461	F
462	F
463	F
464	A
465	A
466	A
467	A
468	A
469	A
470_P1	F
470_P2	F
471	A
472_P1	B
472_P2	A
473	A

474	A
475	E
476	C
477	A
478	F
479	E
480	A
481	A
482	A
483	A
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485	A
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495	B
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498	A
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504	A
505	A
506_P1	A
506_P2	A
507	A
508	A
509	A
510	C
511	F
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515	F
516	F
517	F
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535	C
536	F
537	F
538	F
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540	C
541	A
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543	A
544	A
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546	A
547	A
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549	A
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550_P2	A
551	C
552	C
553	A
554	A
555	F
556	A
557	F
558	F
559	F
560	A
561	A
562	A
563	A
564	A
565_P1	F
565_P2	A
566	F

567	A
568	A
569	A
570	A
571	A
572	A
573_P1	A
573_P2	A
574	F
575	F
576	F
577	F
578	D
579	C
580	E
581	E
582	F
583	E
584	F
585	F
586	A
587	A
588	A
589	A
590	A
591	A
592	A
593	A
594	A
595	A
596	A
597_P1	E
597_P2	A
598	A
599	A
600	A
601	A
602	C
603	A
604	A
605	A
606	B
607	A
608	A
609	A
610_P1	A
610_P2	A
611	B

612_P1	F
612_P2	A
613	A
614	A
615	C
616	A
617	B
618	B
619	F
620	B
621	A
622	A
623	A
624	C
625	A
626	A
627_P1	A
627_P2	D
628_P1	A
628_P2	E

References:

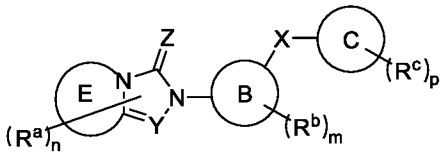
1: Bachmaier, et. al. Nature (2000) 403:211-216

2. Chiang, et. al. Nature (2000) 403:216-220

3: Ronchi and Haas, Methods Mol Biol. (2012) 832: 197

Claims

1. A compound of formula (A):



(A)

or pharmaceutically acceptable salts thereof,

wherein

Y is selected from the group =C(H)-, =C(R^a)- or =N-;

Z is =O or =S;

E is optionally substituted 5-6 membered heterocyclyl;

B is optionally substituted phenyl, optionally substituted 8-10 membered bicyclyl, or optionally substituted 5-6 membered heteroaryl;

C is optionally substituted 5-6 membered heterocyclyl;

X is an optionally substituted C_1-C_3 alkylene chain, wherein one or more methylene units is optionally replaced by -N(H)-, -N(R^1)-, -O-, -S-, -SO-, -SO_2-, optionally substituted 3-6-membered carbocyclyl, and optionally substituted 3-6-membered heterocylyl, wherein X is optionally substituted with an optionally substituted group selected from the group consisting of halogen, C_1-C_3 aliphatic, phenyl, 3-6-membered heteroaryl, 3-6-membered heterocylyl, and -(CH_2)(3-6-membered carbocyclyl);

each R^a is independently selected from the group consisting of L-Y, halogen, -CN, -OH, -OR^1, -NH_2, -NR^1R^2, -SH, -SR^1, -SF_5, -CO_2H, -CO_2R^1, -C(O)R^1, -$CONH_2$, -$CONR^1R^2$, -SO_2NH_2, -$SO_2NR^1R^2$, -SO_2OH, -SO_2OR^1, -S(O)R^1, -$S(O)_2R^1$, -S(O)(NH)R^1, -S(O)(NR^1)R^1, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein R^a is optionally substituted with 1-5 instances of R^{a1};

L is an optionally substituted C_1-C_3 alkylene chain;

A is selected from the group consisting of optionally substituted C_3-C_7 carbocylyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, wherein A is optionally substituted with 1-5 instances of R^{a1};

each R^{a1} is independently selected from the group consisting of halogen, -CN, -OH, $-OR^1$, $-NH_2$, $-NR^1R^2$, -SH, $-SR^1$, $-SF_5$, $-CO_2H$, $-CO_2R^1$, $-CONH_2$, $-CONR^1R^2$, $-SO_2NH_2$, $-SO_2NR^1R^2$, $-SO_2OH$, $-SO_2OR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-S(O)(NH)R^1$, $-S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^b is independently selected from the group consisting of, halogen, -CN, -OH, $-OR^1$, $-NH_2$, $-NR^1R^2$, -SH, $-SR^1$, $-SF_5$, $-CO_2H$, $-CO_2R^1$, $-CONH_2$, $-CONR^1R^2$, $-SO_2NH_2$, $-SO_2NR^1R^2$, $-SO_2OH$, $-SO_2OR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-S(O)(NH)R^1$, $-S(O)(NR^1)R^1$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

each R^c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, OR^1, $-NH_2$, $-NR^1R^2$, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$;

each R^1 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted phenyl, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S, $-C(O)R^3$, $-CO_2R^3$, $-C(O)NHR^3$, and $-SO_2R^3$;

each R^2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, and optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

or R^1 and R^2 are taken together with their intervening atom(s) to form a 3-8-membered heterocyclyl ring containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or an optionally substituted 5-6-membered heteroaryl ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S.

each R^3 is independently selected from the group consisting of optionally substituted C_1-C_6 aliphatic, optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S, optionally substituted phenyl, optionally substituted 5-6-membered heteroaryl containing 1-4 heteroatoms each selected from the group consisting of N, O and S;

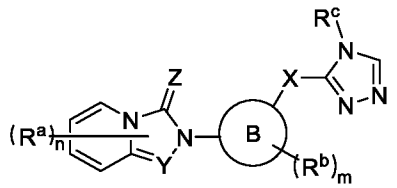
n is 0, 1, 2, 3, 4, or 5;

m is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein C is selected from the group consisting of optionally substituted triazolyl, optionally substituted pyrazolyl, optionally substituted isoxazolyl, optionally substituted thiazolyl, optionally substituted thiadizolyl, optionally substituted pyridinyl, optionally substituted pyrazinyl, optionally substituted pyrimidinyl, and optionally substituted pyridazinyl.

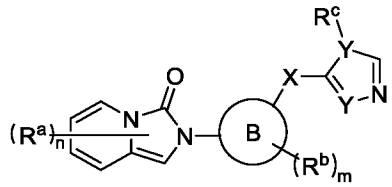
3. The compound of any of claims 1-2, wherein the compound is of Formula (B):



(B),

or pharmaceutically acceptable salts thereof.

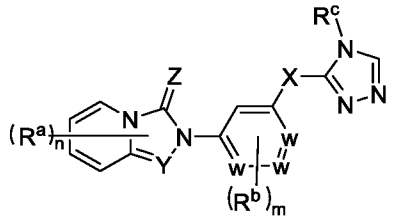
4. The compound of any of claims 1-2, wherein the compound is of Formula (I):



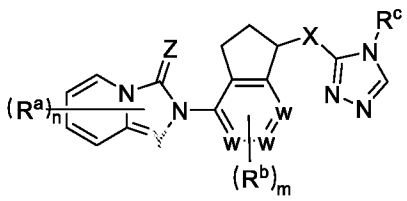
(I),

or pharmaceutically acceptable salts thereof.

5. The compound of any of claims 1-4, wherein the compound is of Formula (Ia) or (IIa):



(Ia)

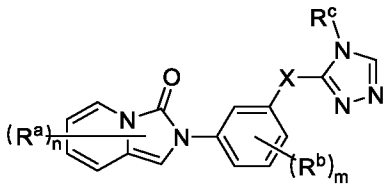


(IIa),

or a pharmaceutically acceptable salt thereof,

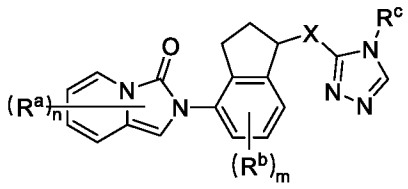
wherein each W is independently selected from N or C.

6. The compound of any of claims 1-5, wherein the compound is of formula (Ia1) or (IIa1):



(Ia1)

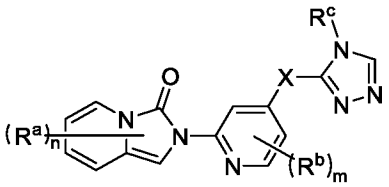
or



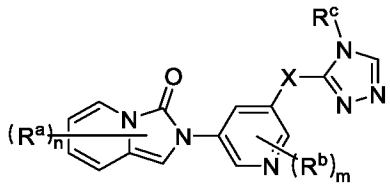
(IIa1)

or a pharmaceutically acceptable salt thereof.

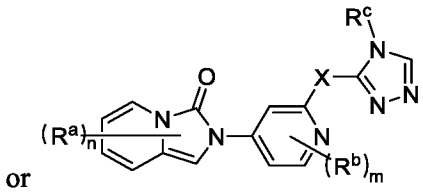
7. The compound of any of claims 1-5, wherein the compound is of Formula (Ia2), (Ia3), or (Ia4):



(Ia2)



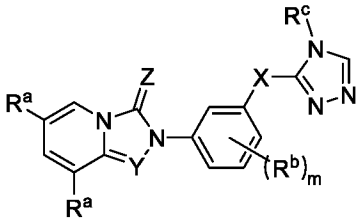
(Ia3)



(Ia3)

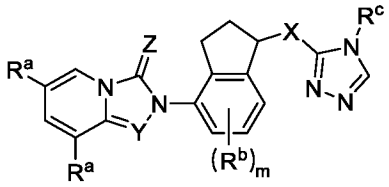
or a pharmaceutically acceptable salt thereof.

8. The compound of any of claims 1-5, wherein the compound is of formula (Ib) or (IIb):



(Ib)

or

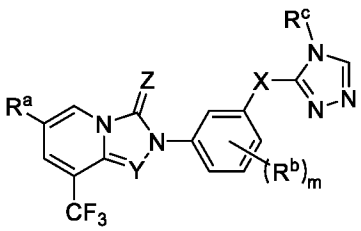


(IIb),

or pharmaceutically acceptable salts thereof,

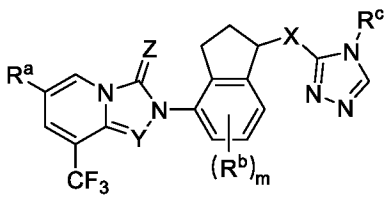
wherein each W is independently selected from N or C.

9. The compound of any of claims 1-5, wherein the compound is of formula (Ic) or (IIc):



(Ic)

or



(IIc),

or pharmaceutically acceptable salts thereof.

10. The compound of any of claims 1-9, wherein R^c is optionally substituted C_1-C_3 aliphatic.

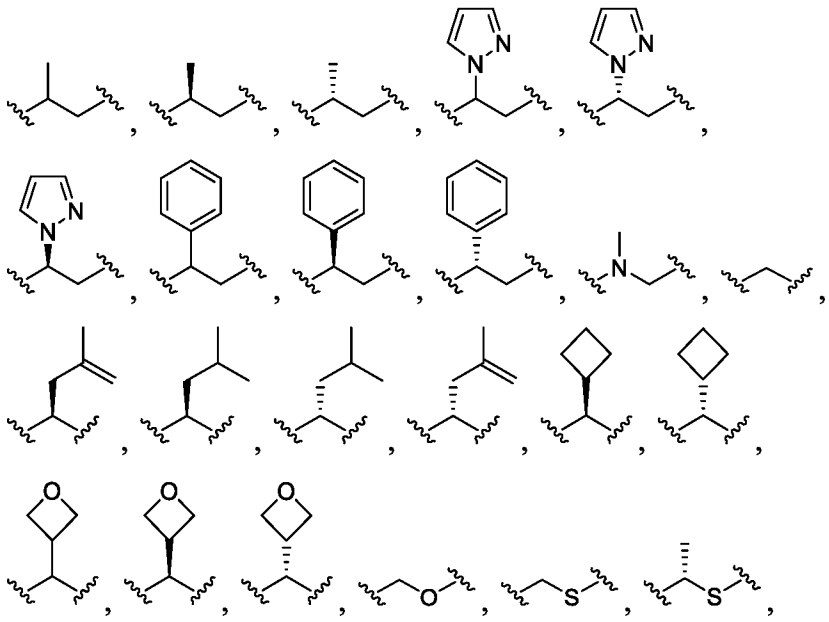
11. The compound of claim 10, wherein each R^c is independently selected from the group consisting of methyl, $-CD_3$, $-CHF_2$

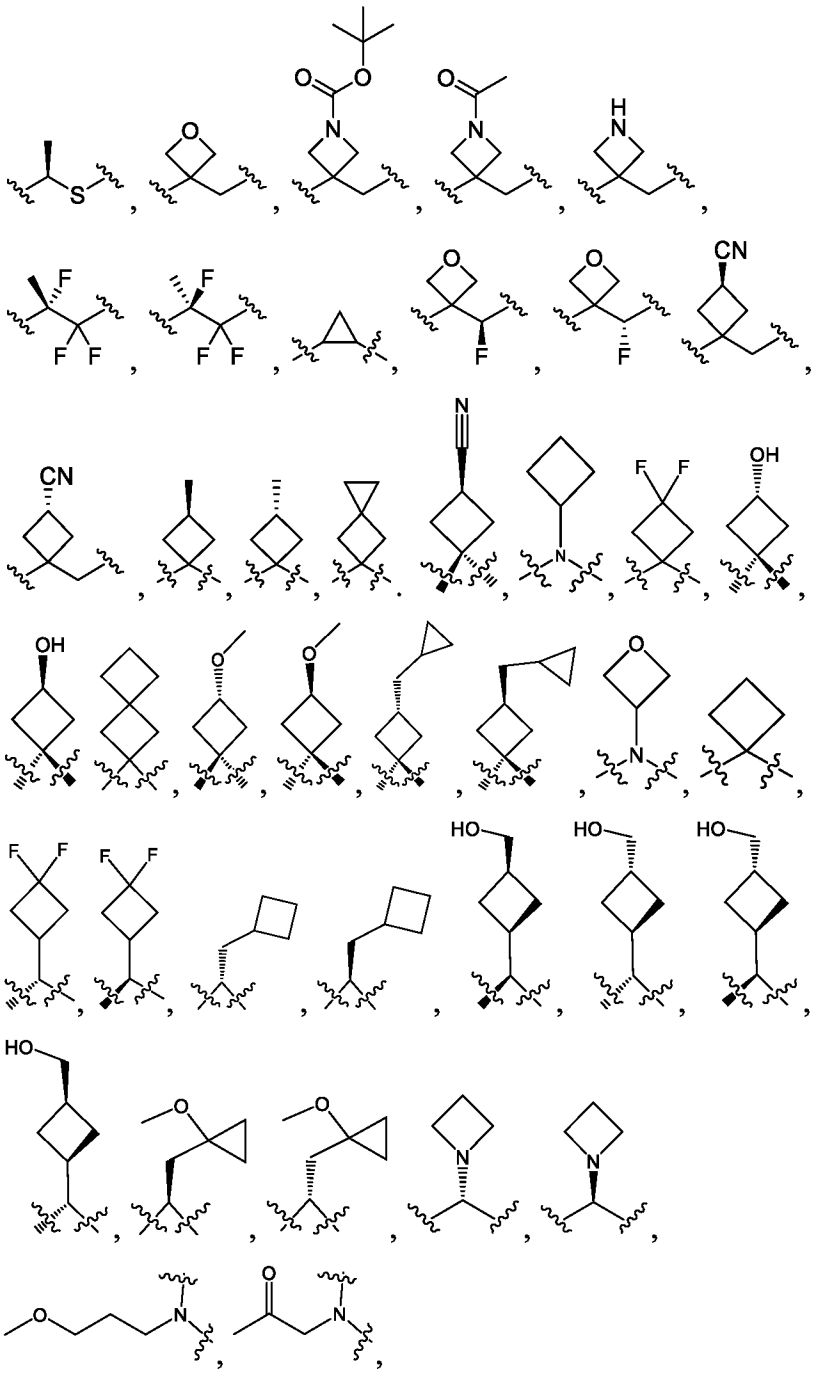
12. The compound of claim 11, wherein R^c is methyl.

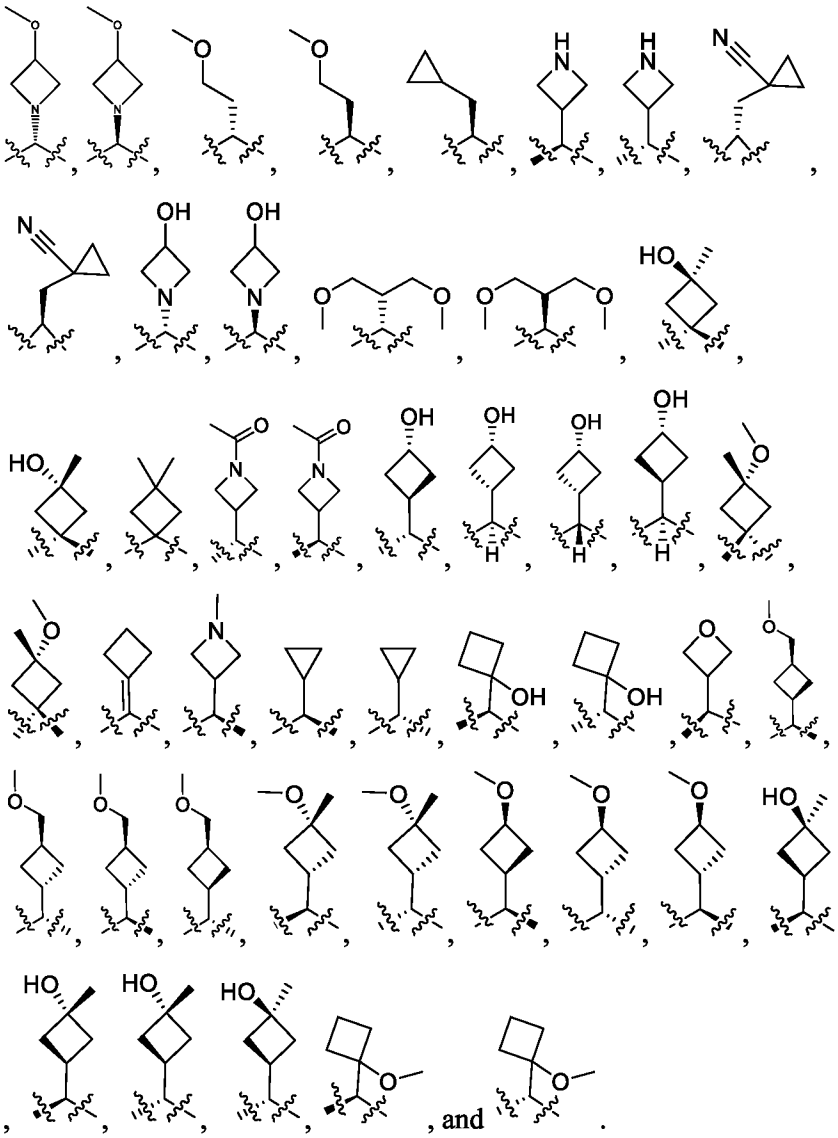
13. The compound of any of claims 1-12, wherein X is optionally substituted C_1-C_2 alkylene.

14. The compound of any of claims 1-12, wherein X is  or optionally substituted C_2 alkylene, wherein one methylene unit is replaced with  .

15. The compound of any of claims 1-12, wherein X is selected from the group consisting of







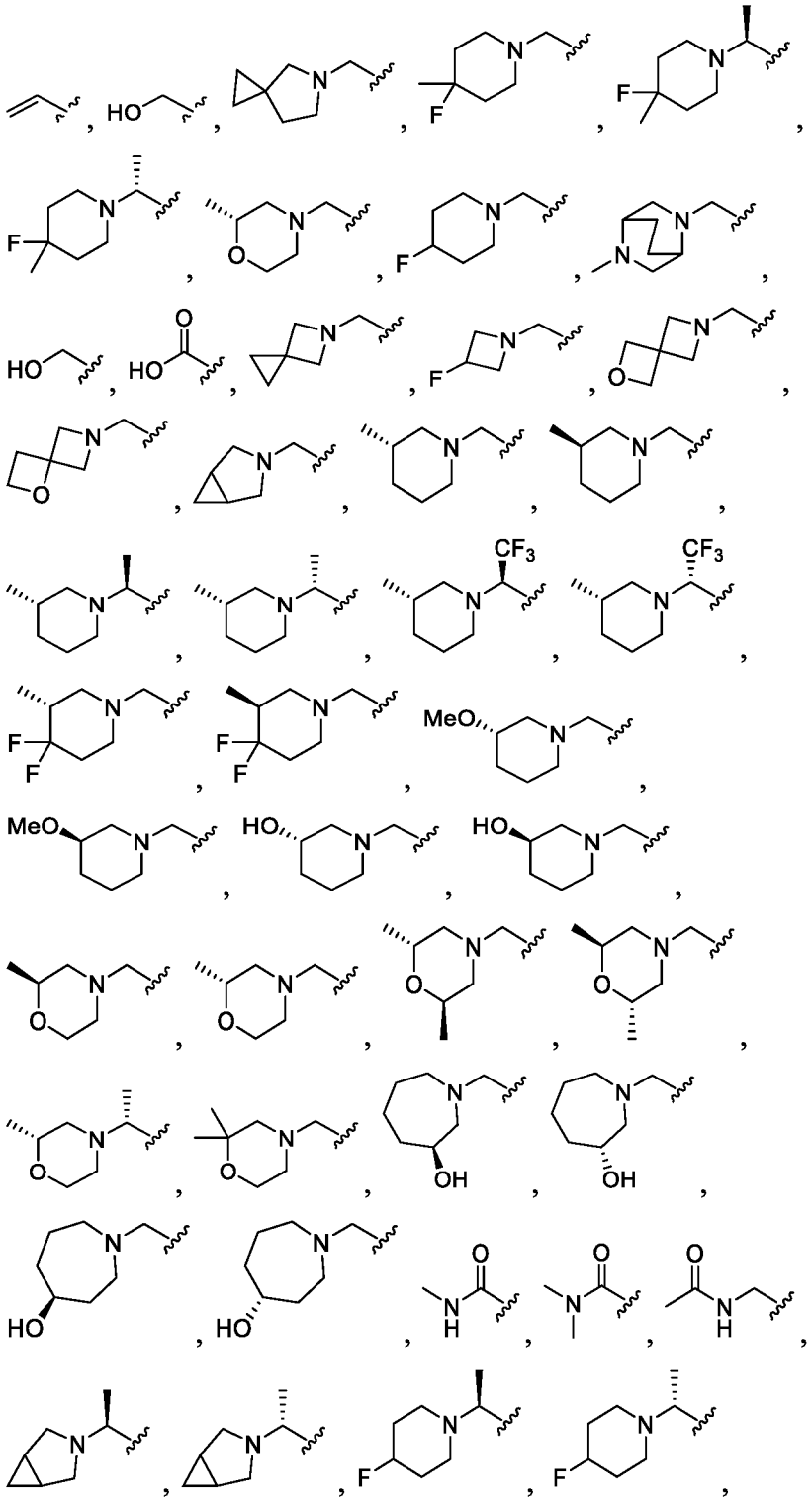
16. The compound of any of claims 1-15, wherein R^a is L-A.

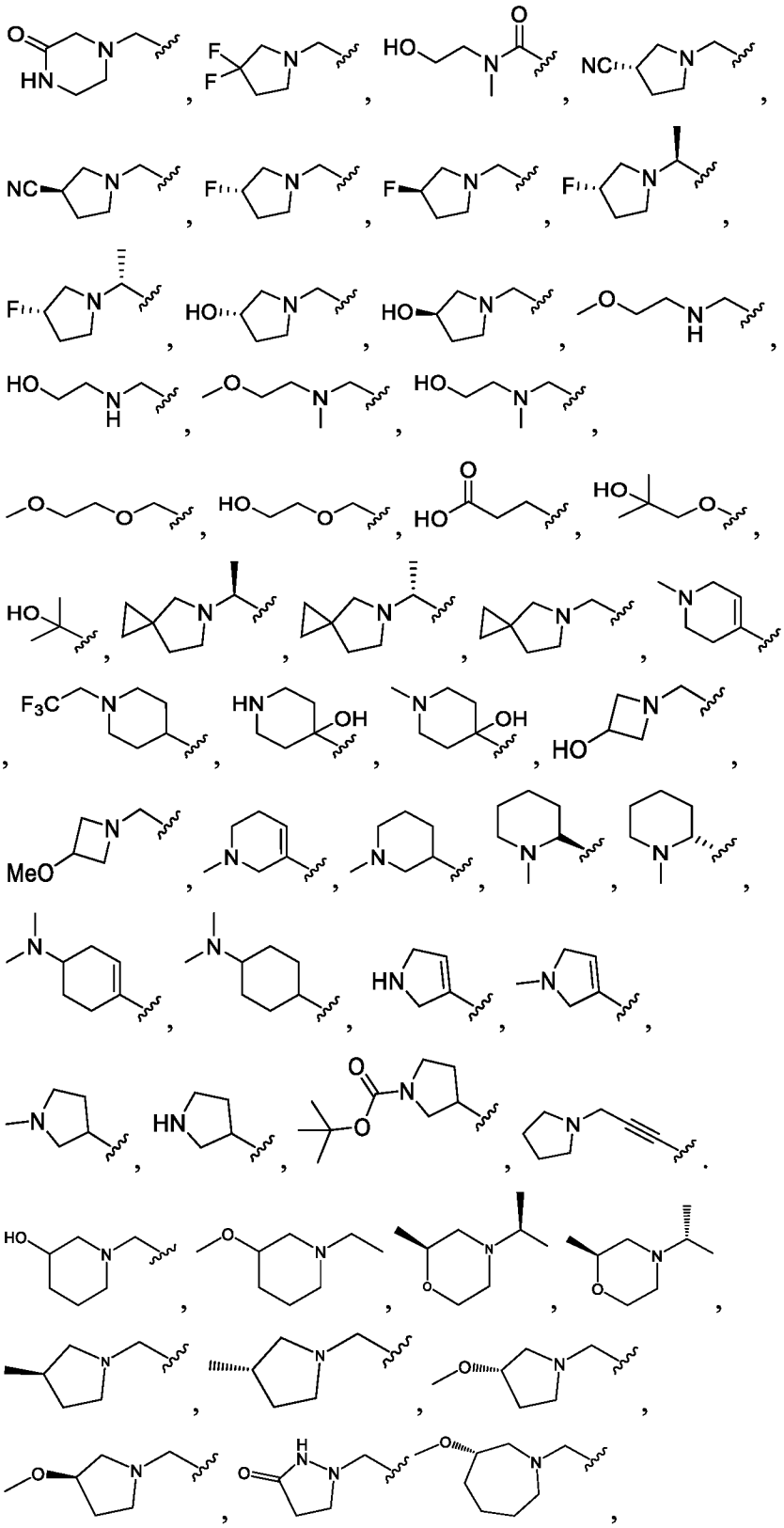
17. The compound of claim 16, wherein L is $-CH_2-$ or $-CH(CH_3)-$.

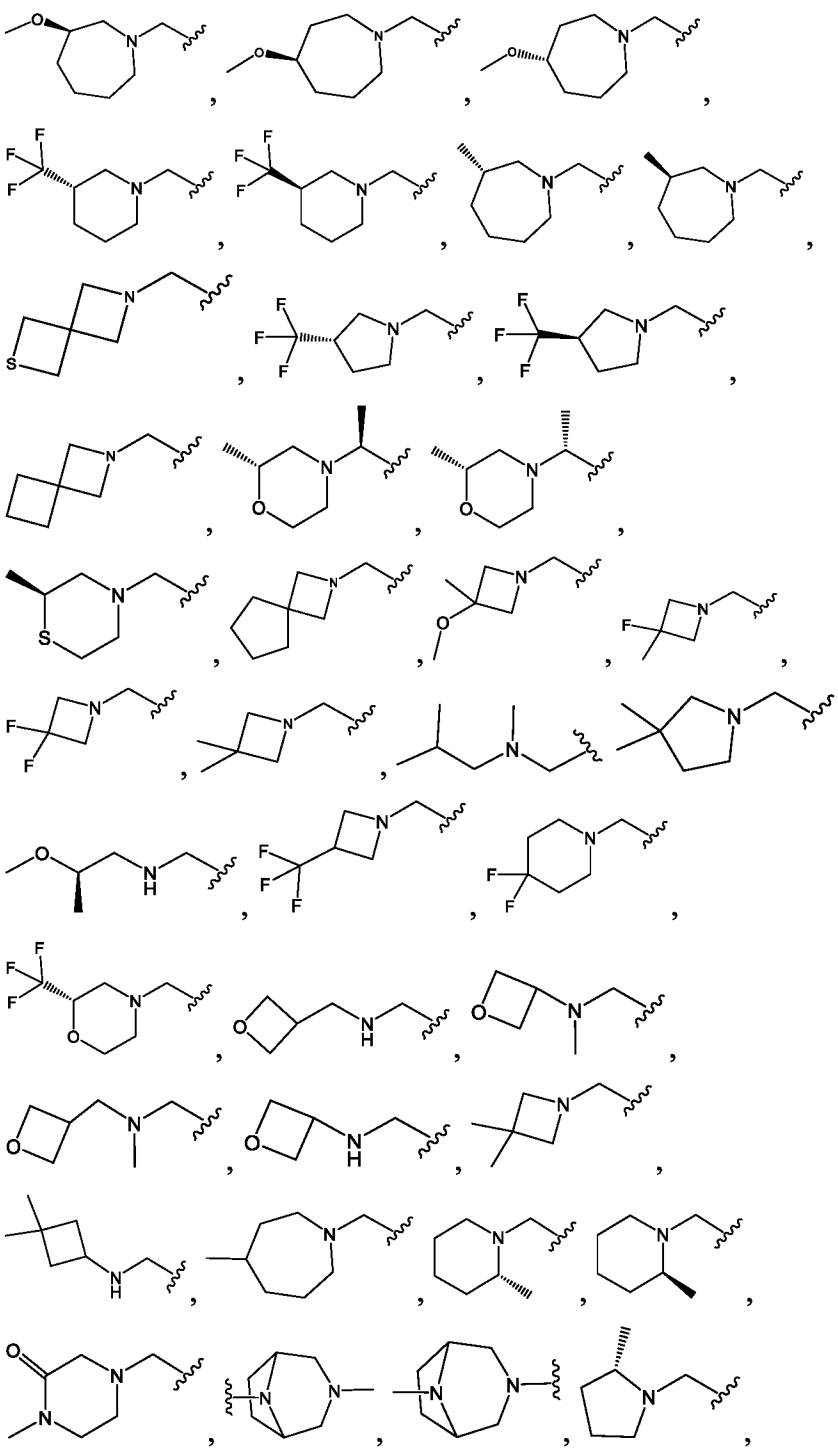
18. The compound of any of claims 16-17, wherein A is optionally substituted 3-6 membered heterocyclyl containing 1-4 heteroatoms each selected from the group consisting of N, O, and S.

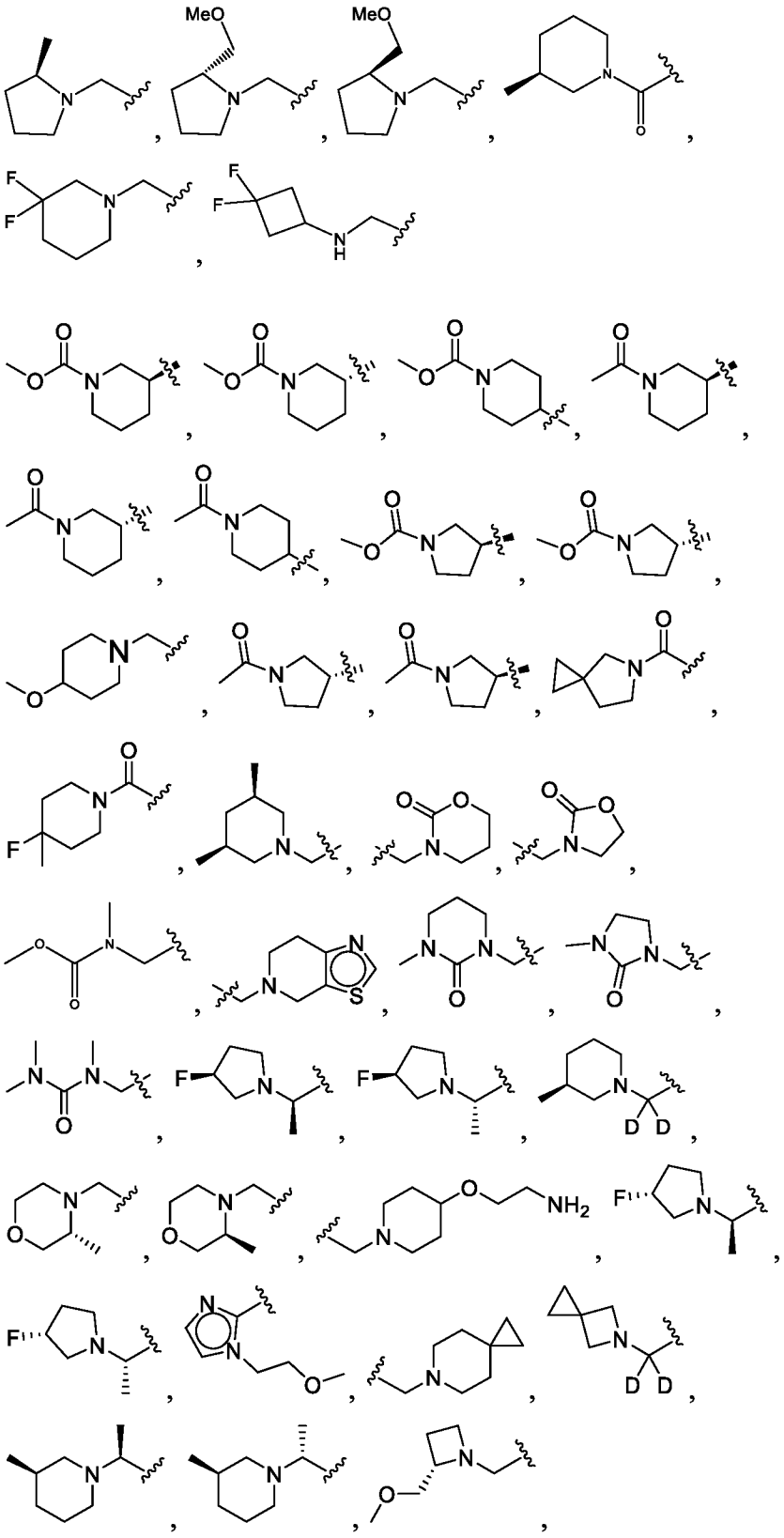
19. The compound of any of claims 1-16, wherein R^a is selected from halogen, -CN, $-C(O)R^1$, $-CO_2H$, $-CONR^1R^2$, optionally substituted C_1-C_6 aliphatic, and optionally substituted C_1-C_6 heteroalkyl.

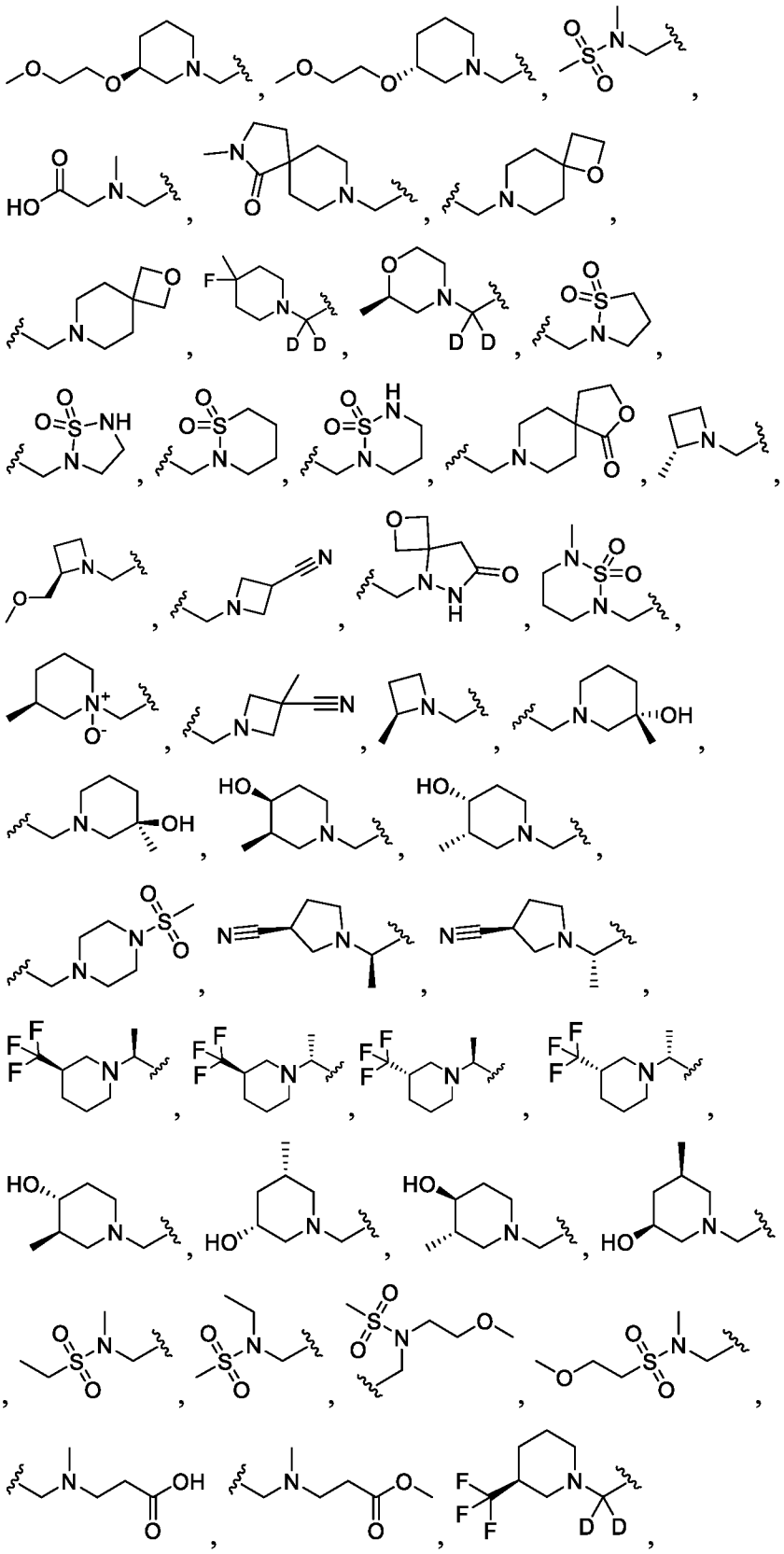
20. The compound of any of claims 1-16, wherein each R^a is independently selected from the group consisting of halogen, -CN, $-CO_2H$, -CHO, $-CHF_2$, $-CF_3$, -OMe, $-S(O)_2NHMe$,

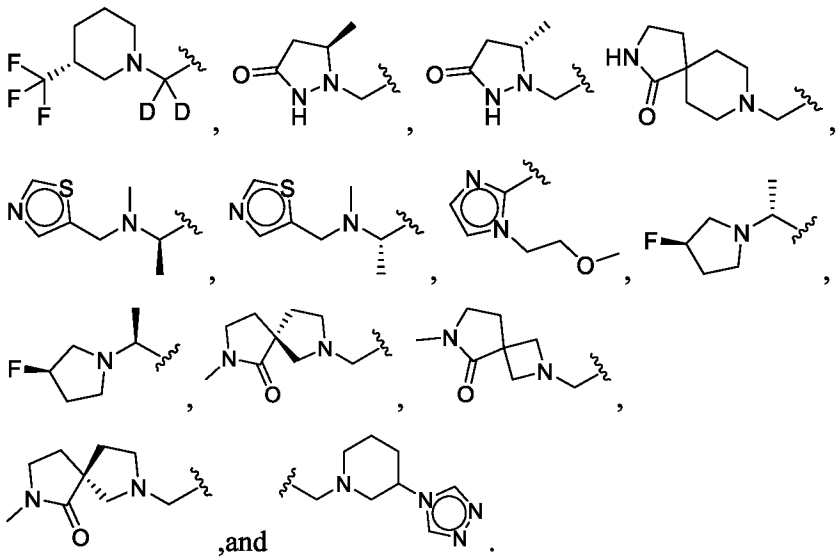




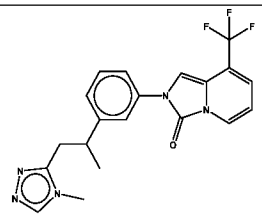
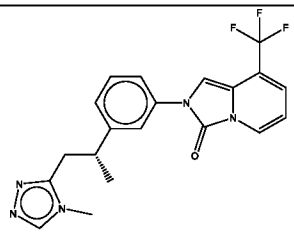
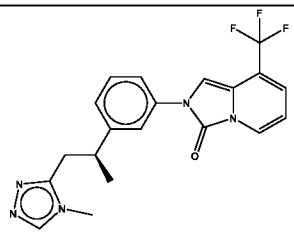
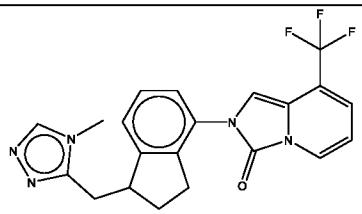


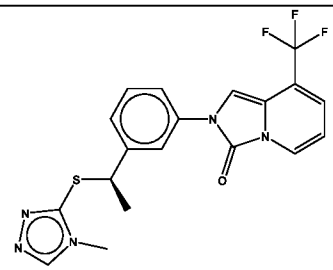
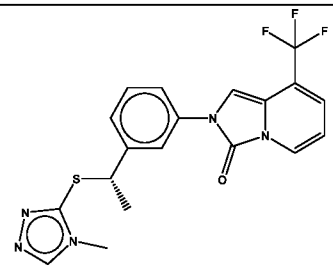
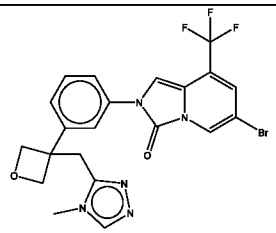
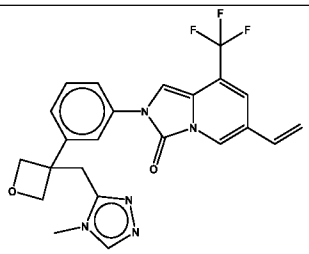
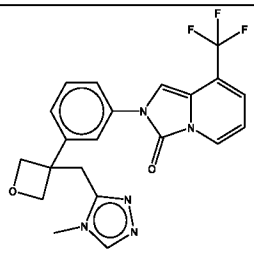
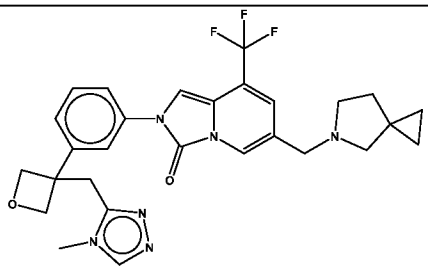


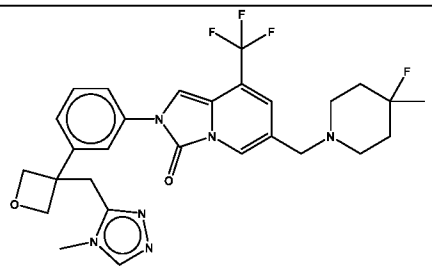
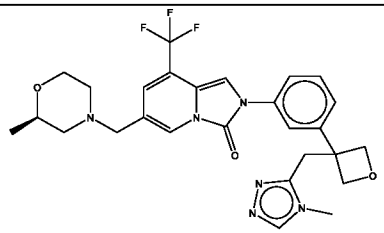
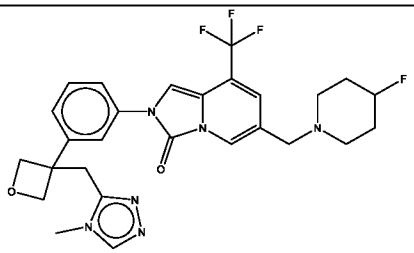
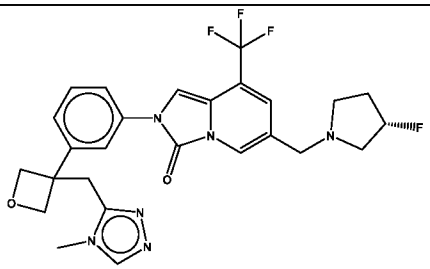
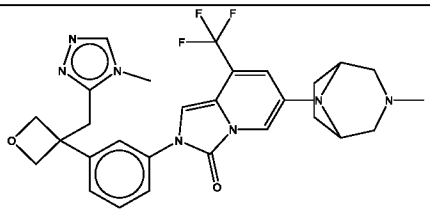
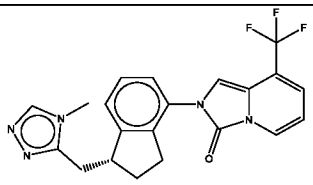


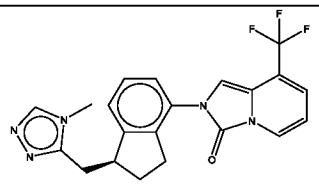
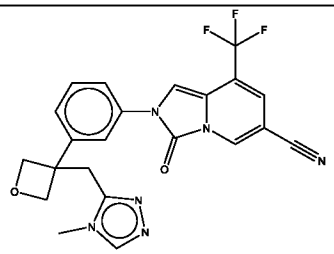
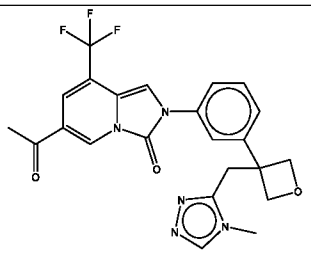
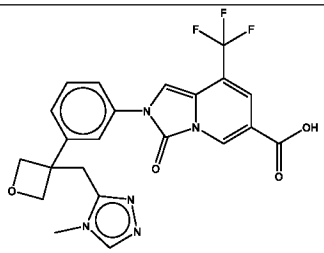
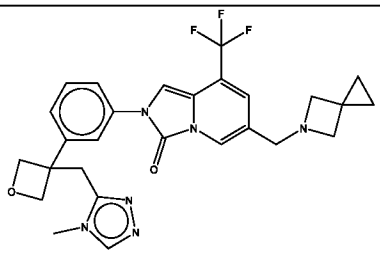
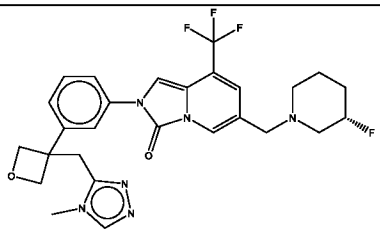


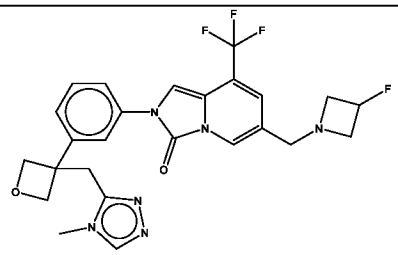
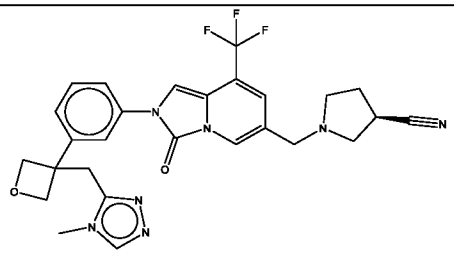
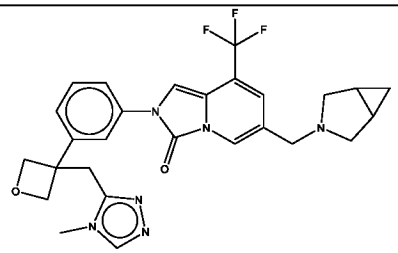
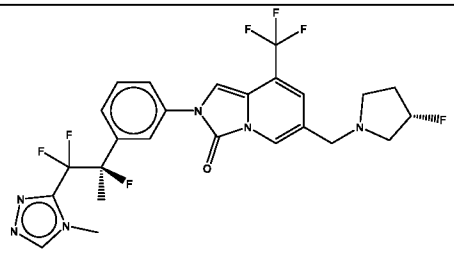
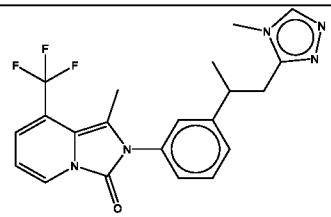
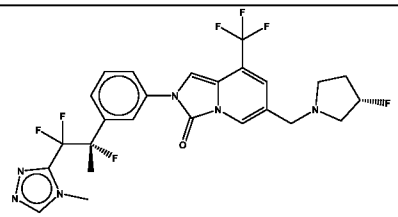
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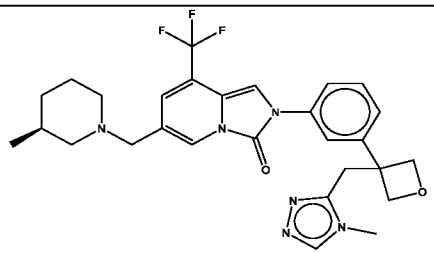
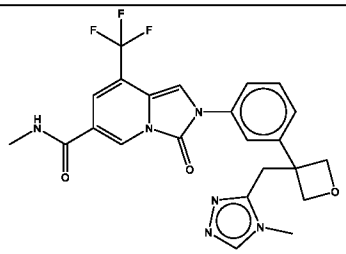
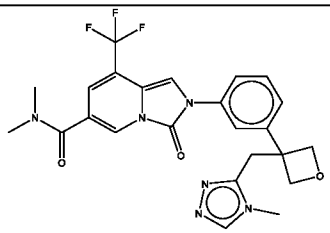
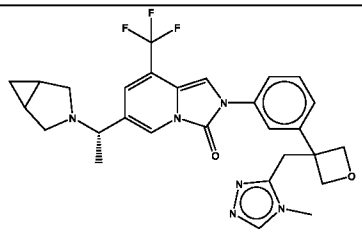
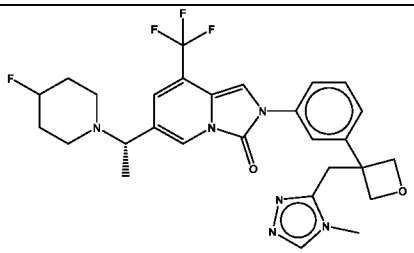
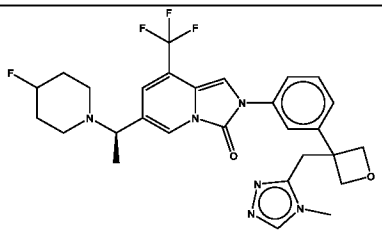
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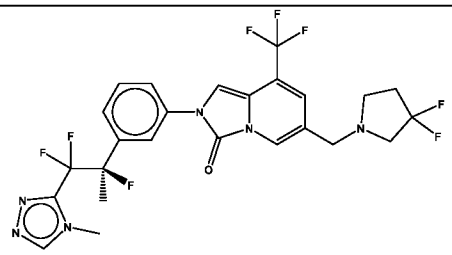
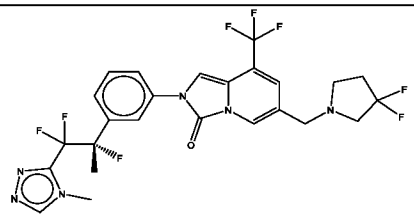
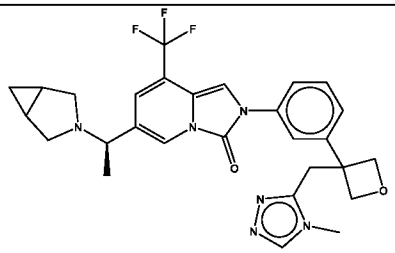
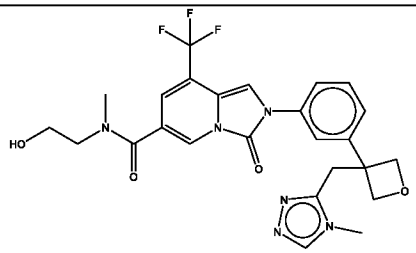
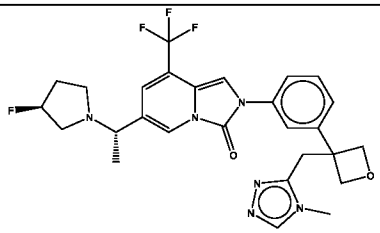
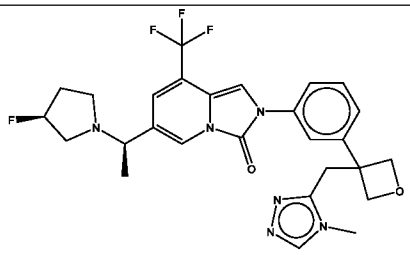
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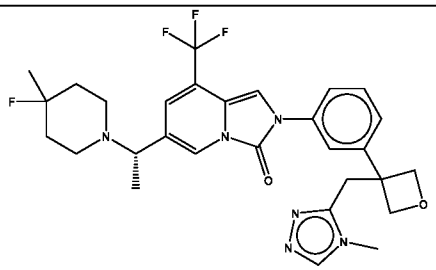
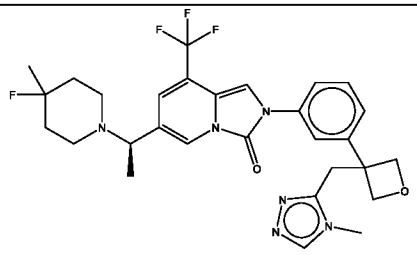
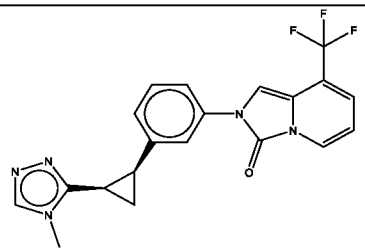
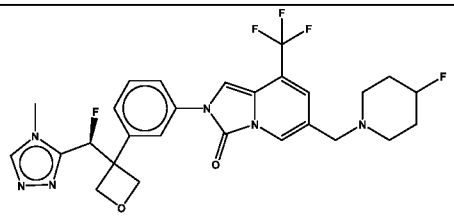
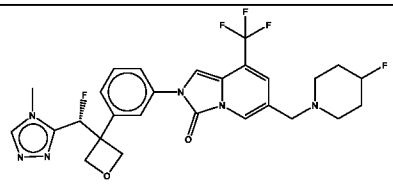
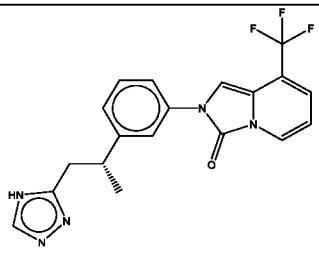
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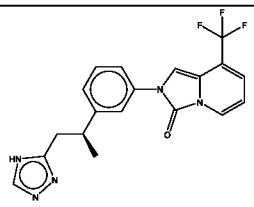
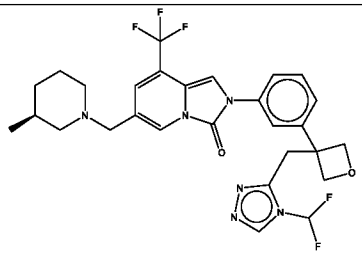
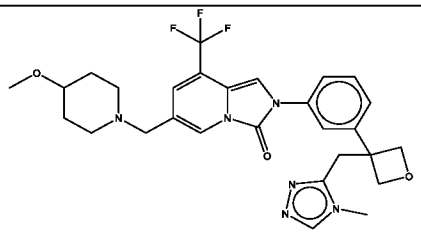
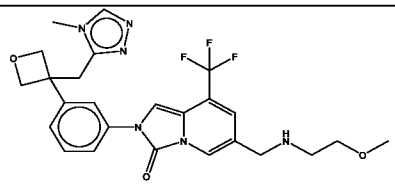
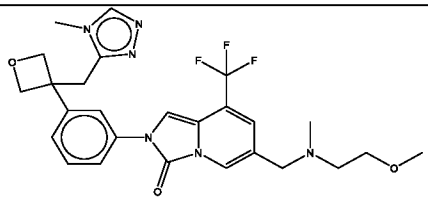
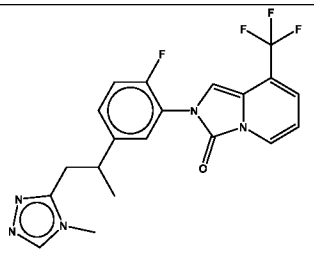
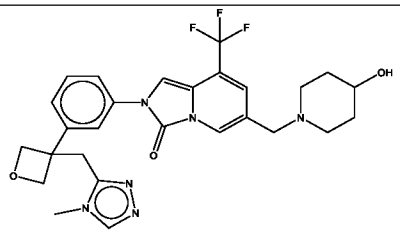
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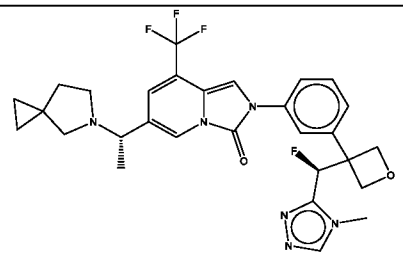
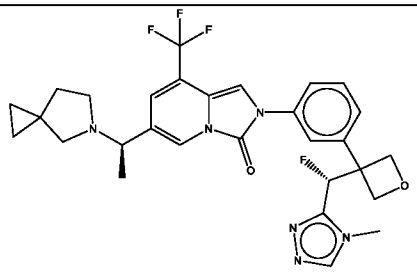
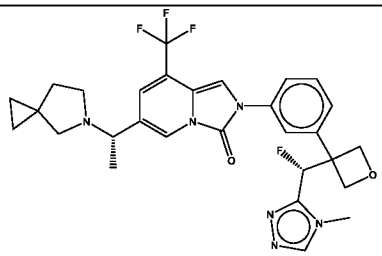
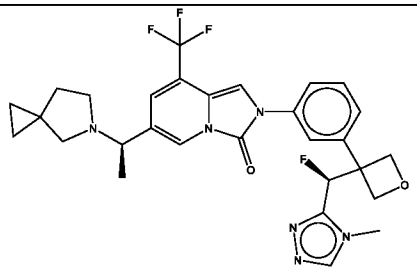
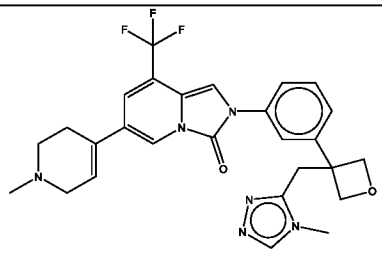
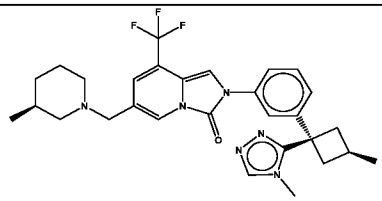
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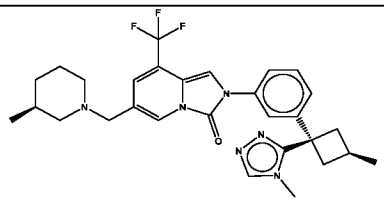
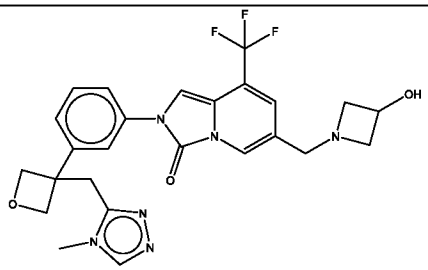
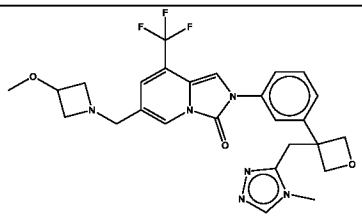
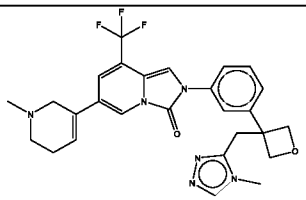
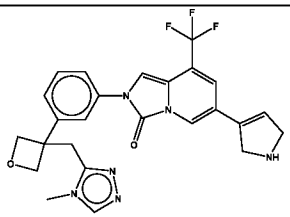
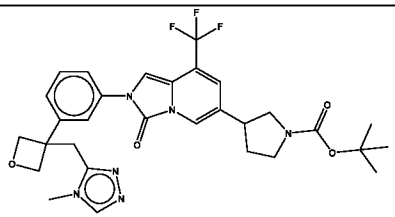
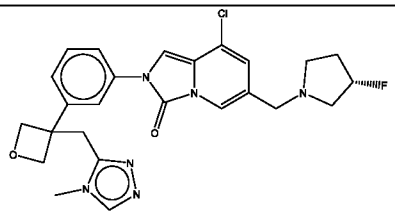
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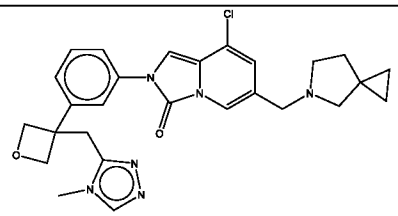
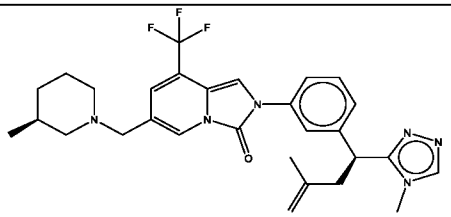
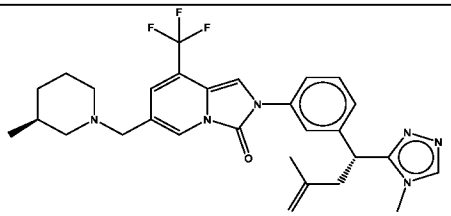
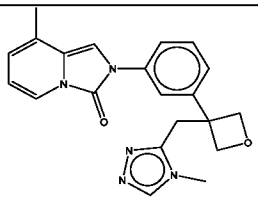
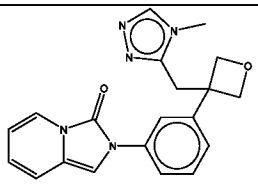
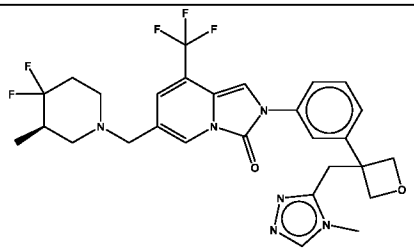
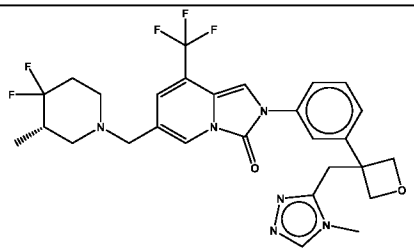
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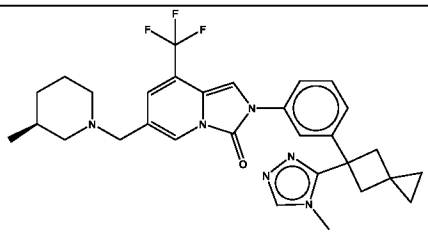
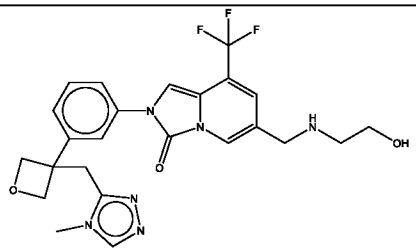
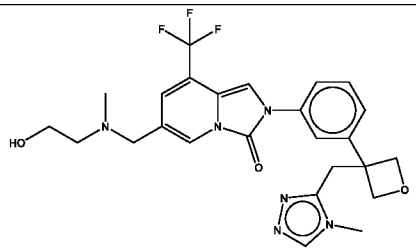
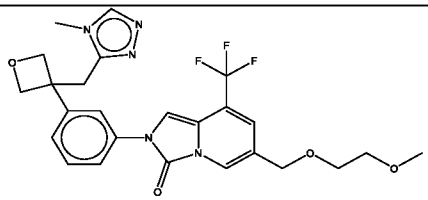
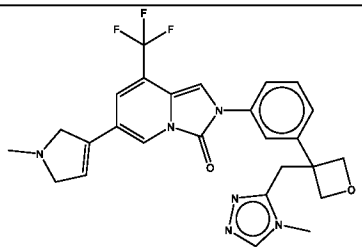
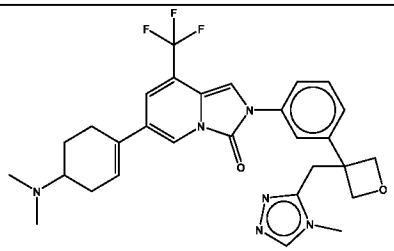
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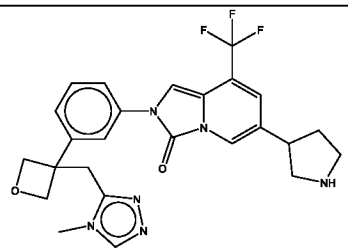
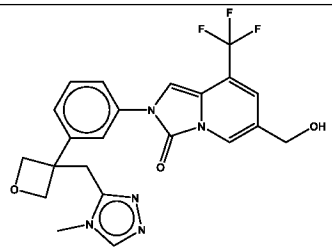
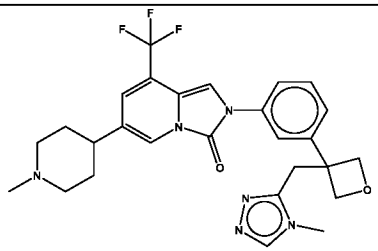
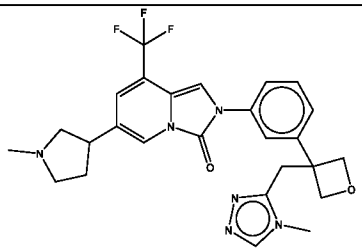
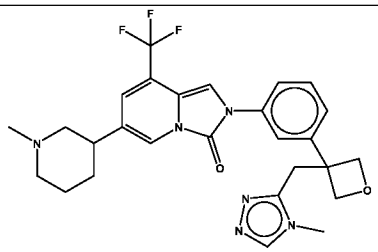
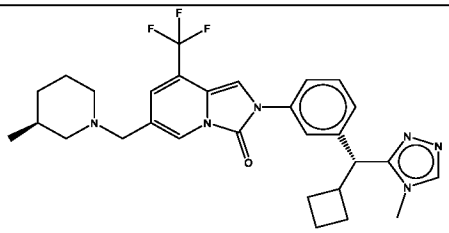
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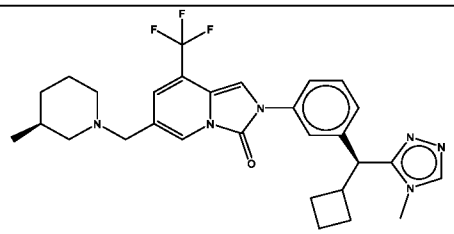
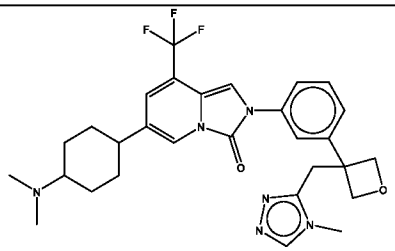
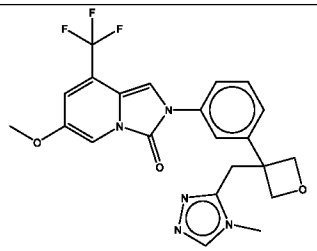
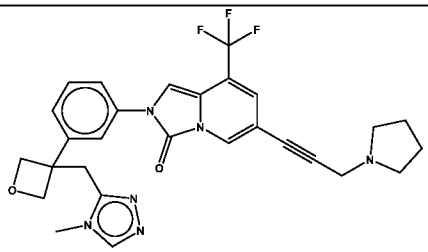
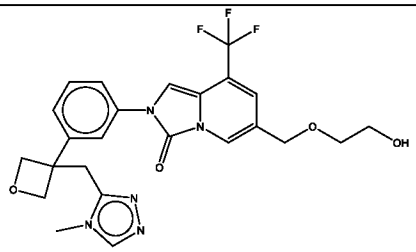
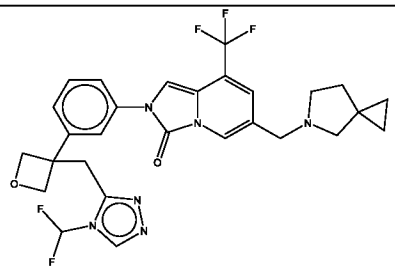
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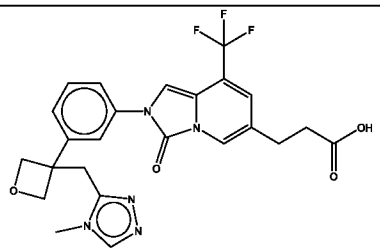
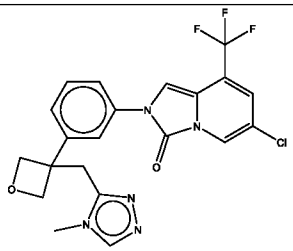
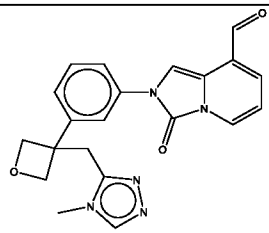
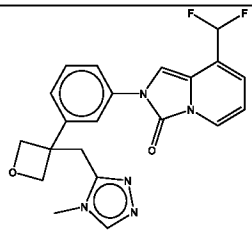
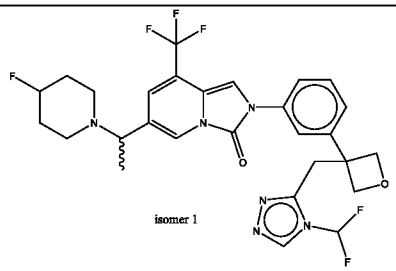
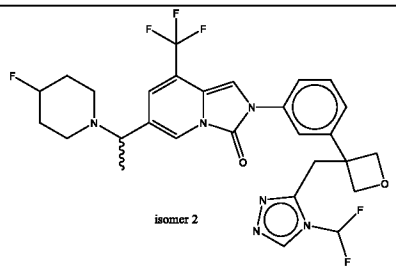
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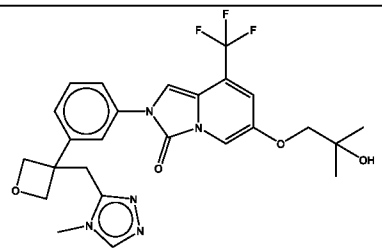
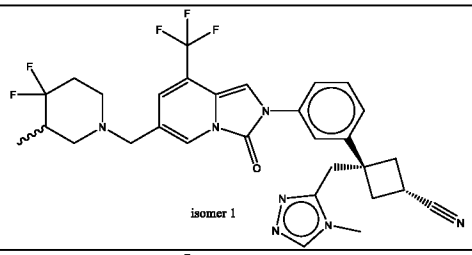
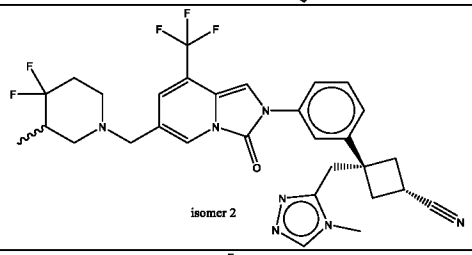
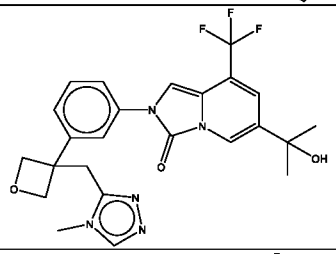
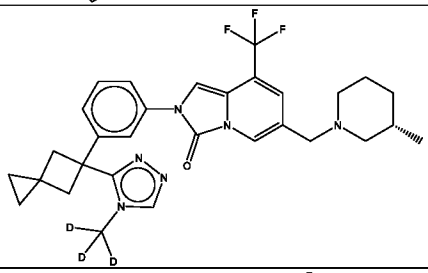
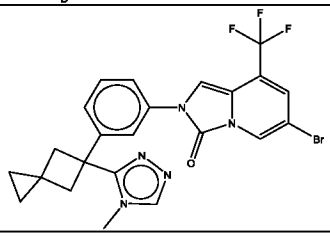
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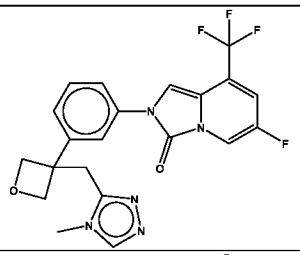
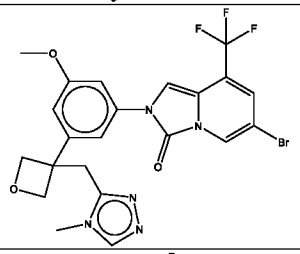
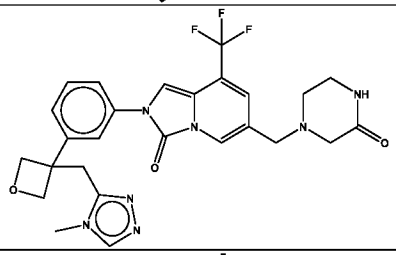
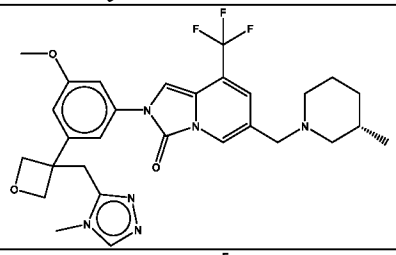
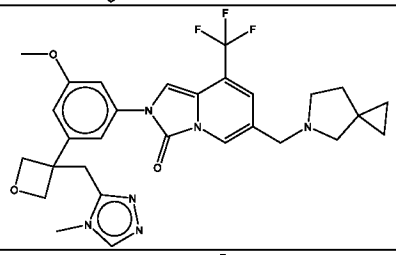
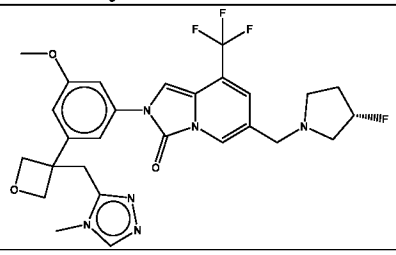
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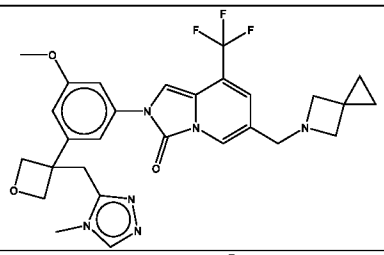
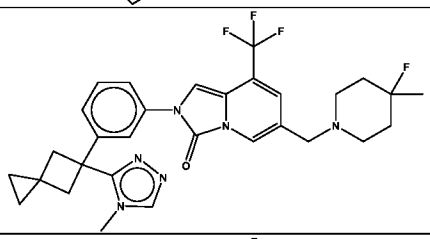
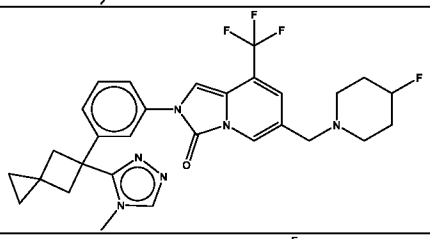
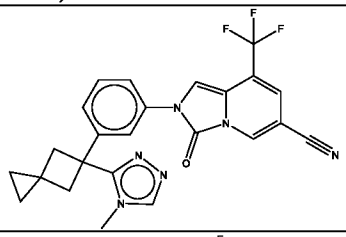
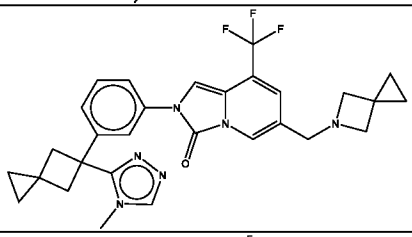
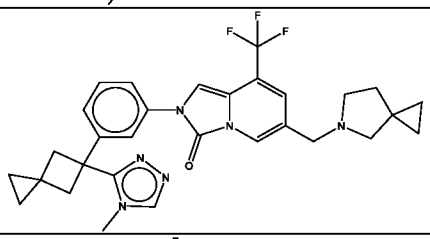
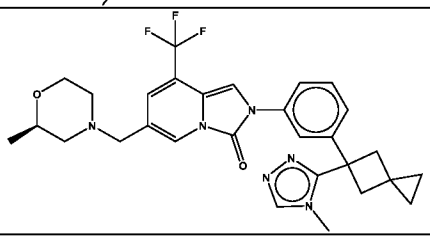
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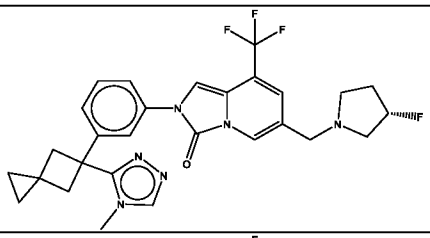
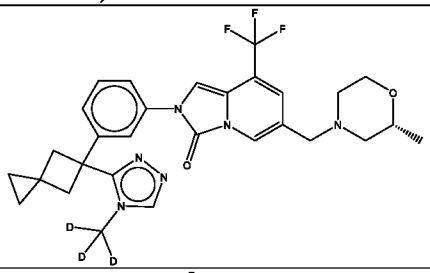
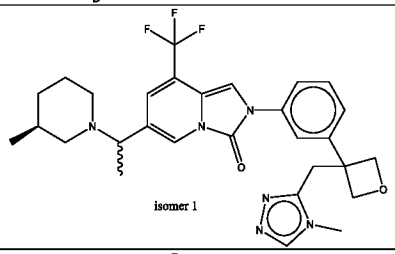
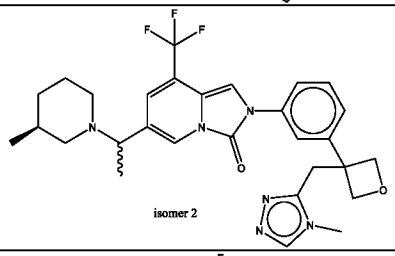
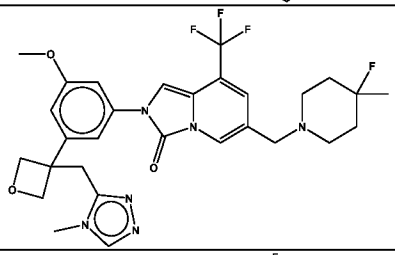
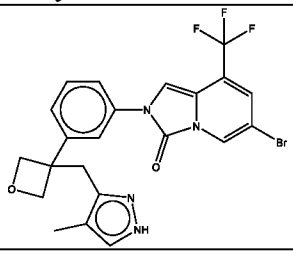
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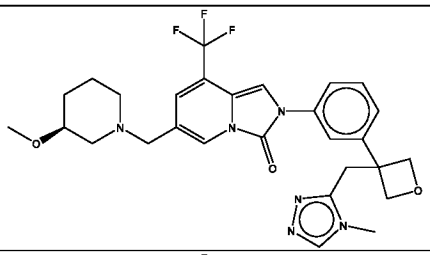
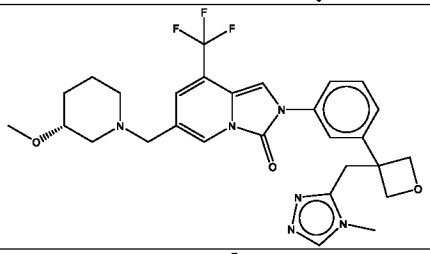
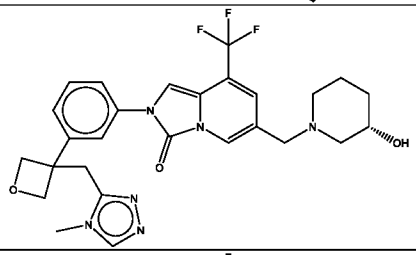
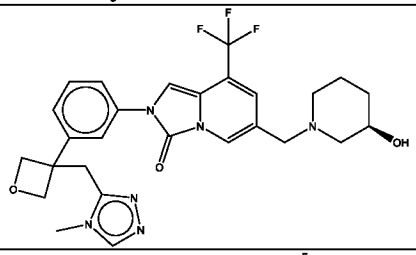
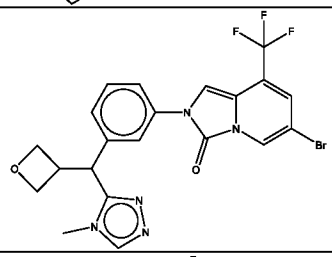
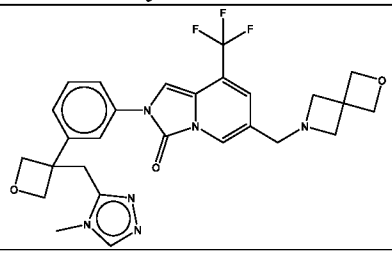
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97	 isomer 2

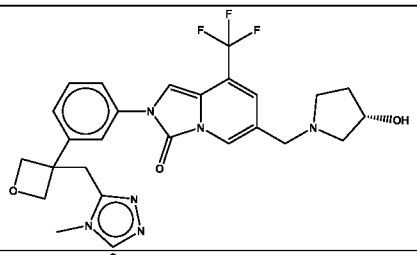
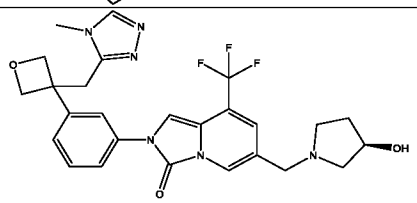
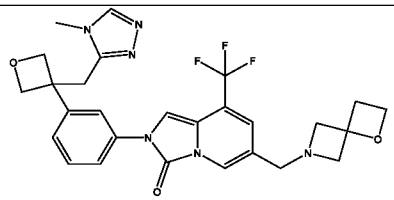
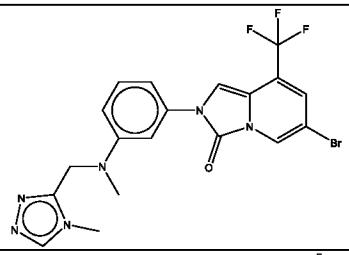
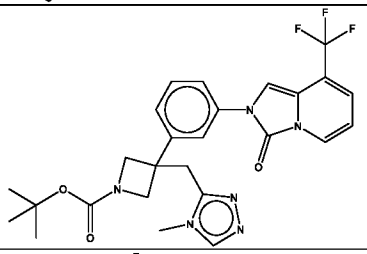
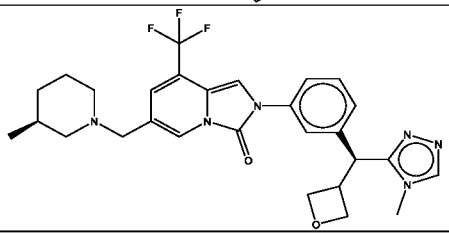
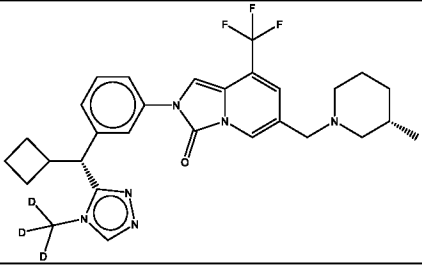
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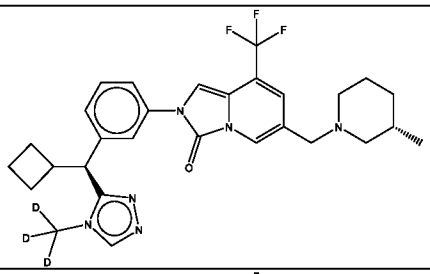
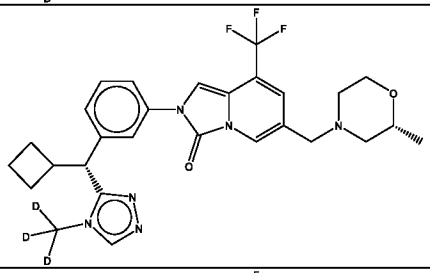
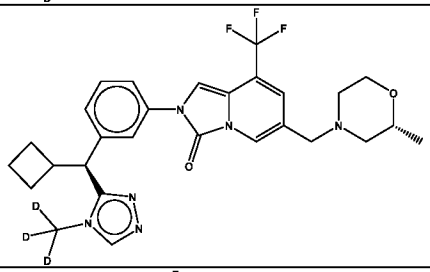
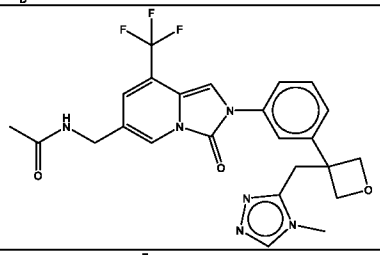
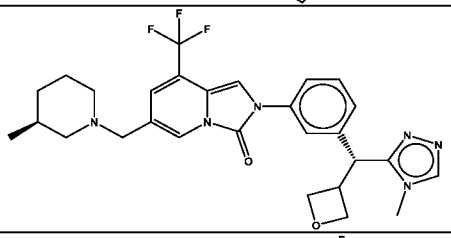
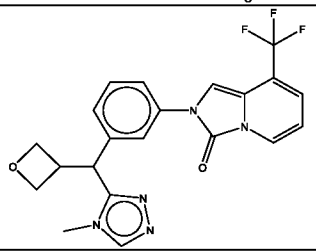
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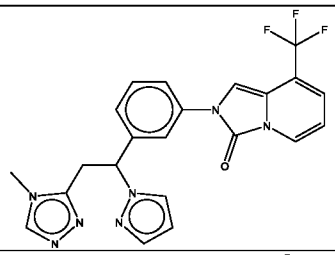
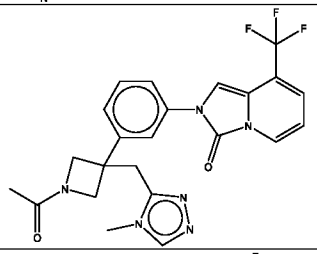
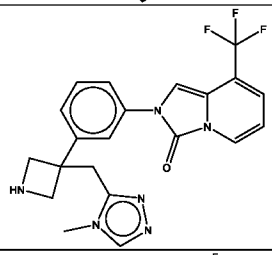
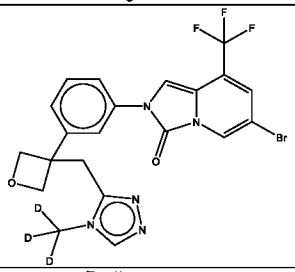
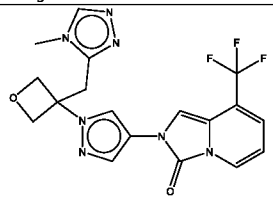
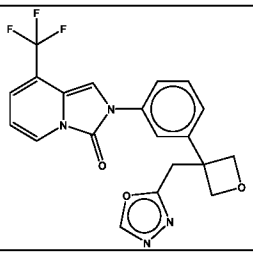
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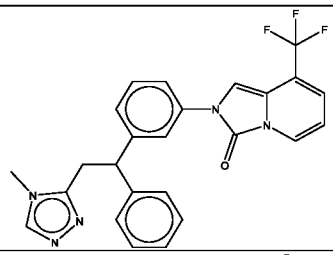
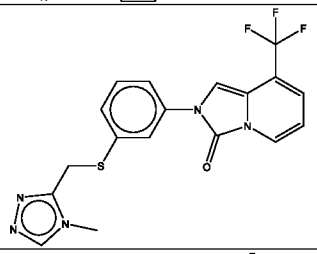
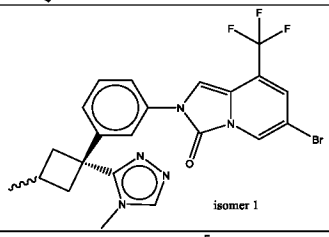
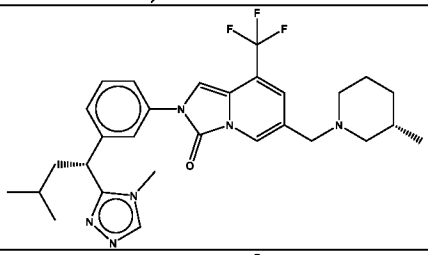
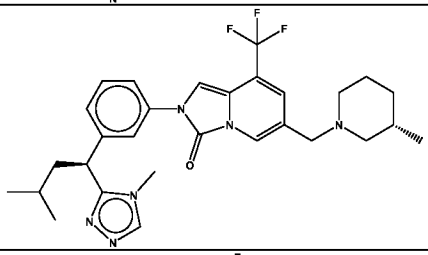
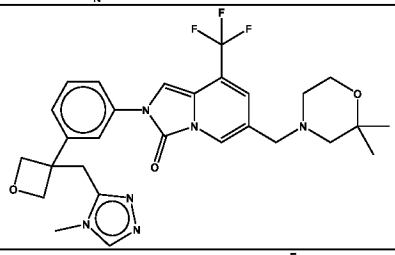
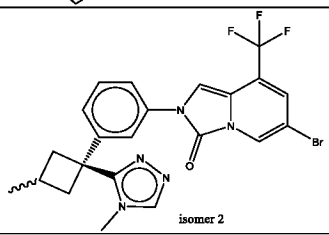
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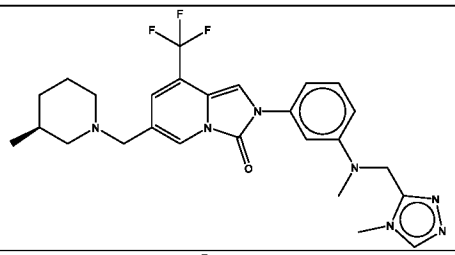
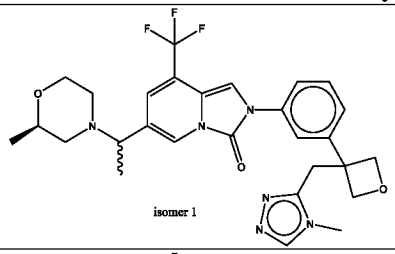
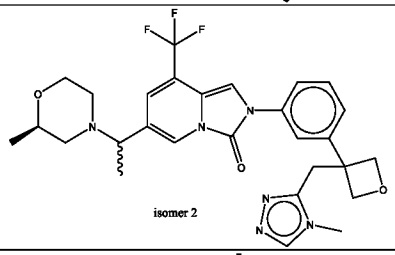
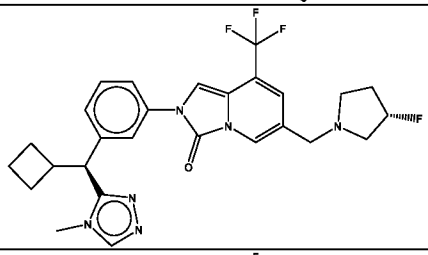
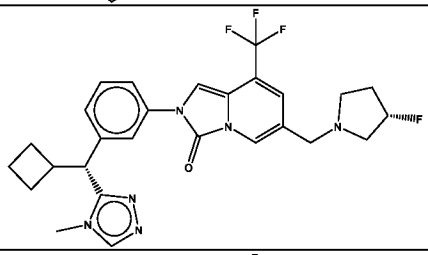
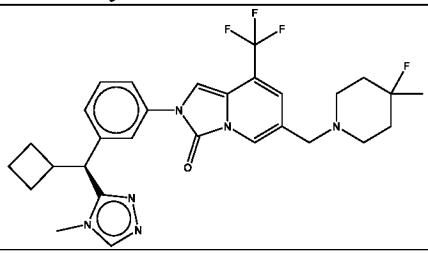
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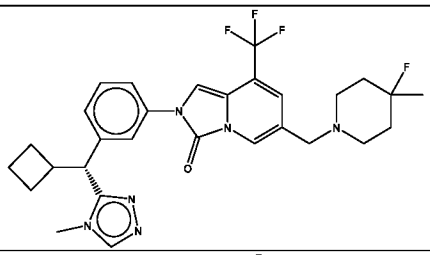
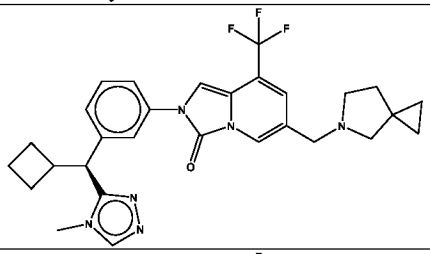
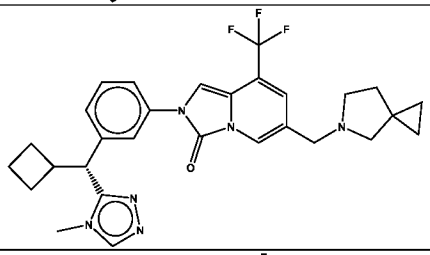
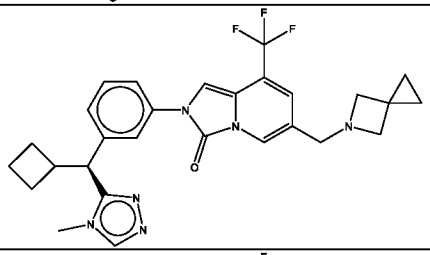
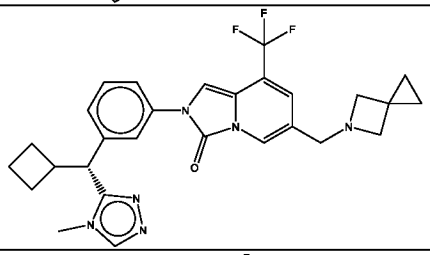
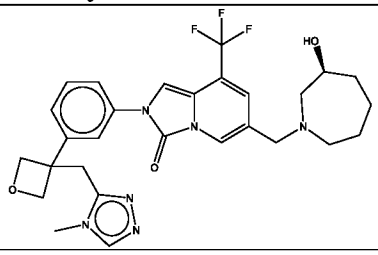
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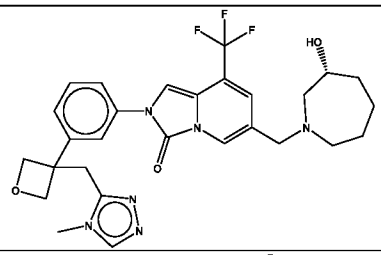
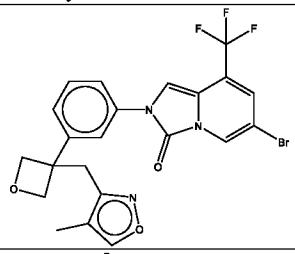
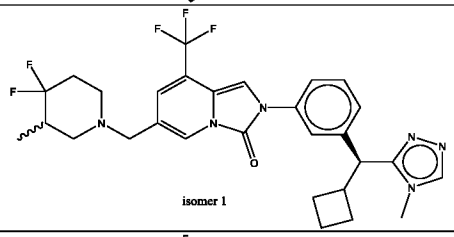
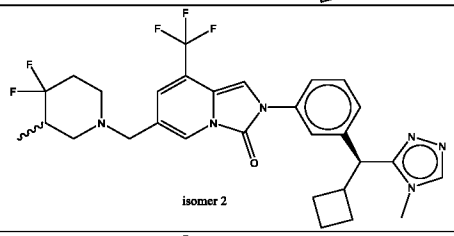
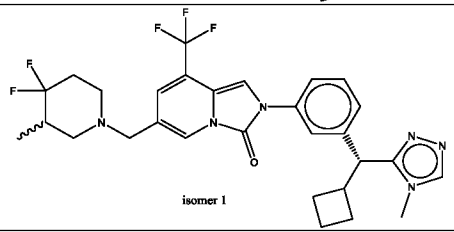
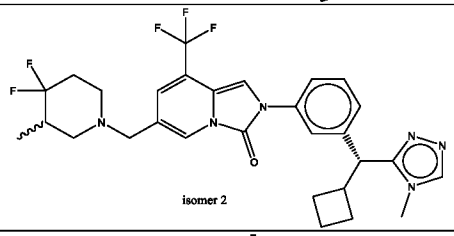
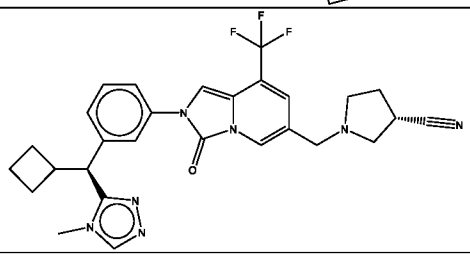
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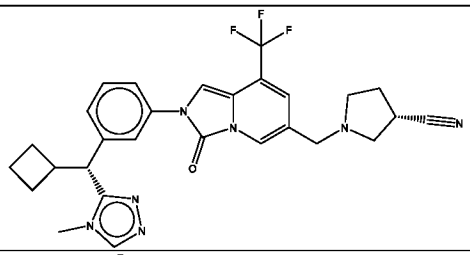
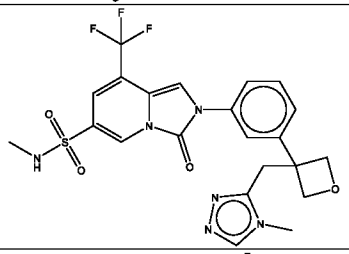
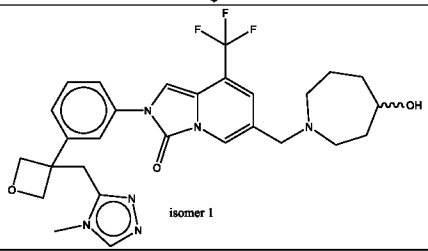
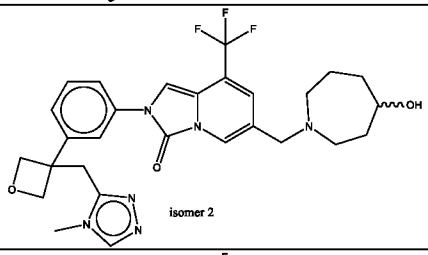
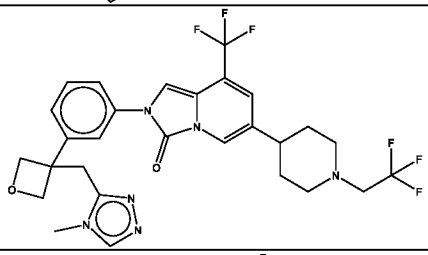
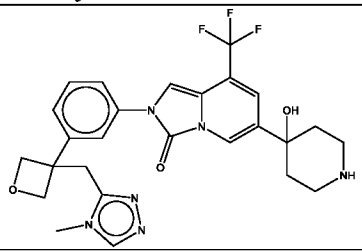
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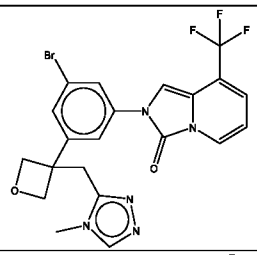
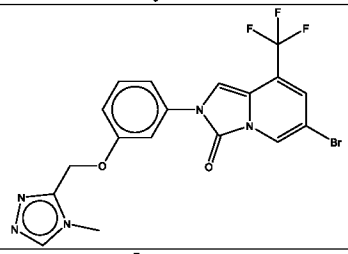
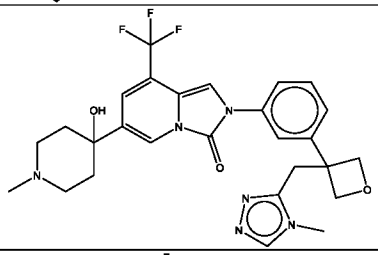
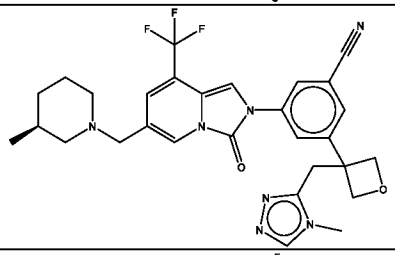
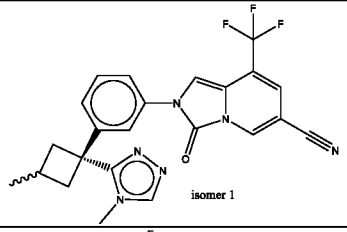
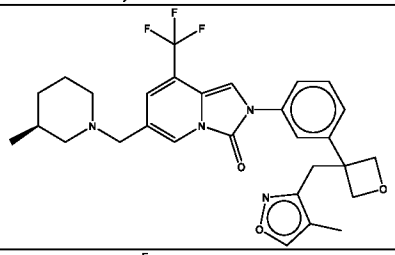
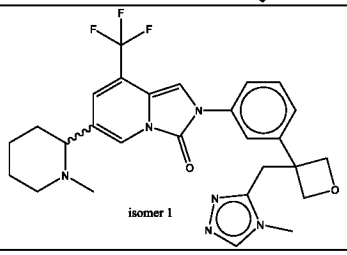
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154	 isomer 2

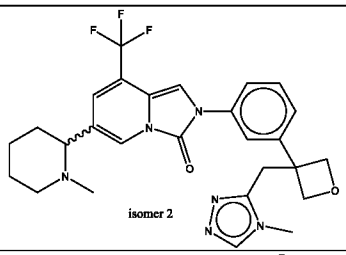
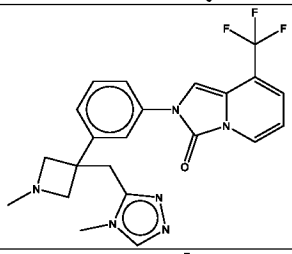
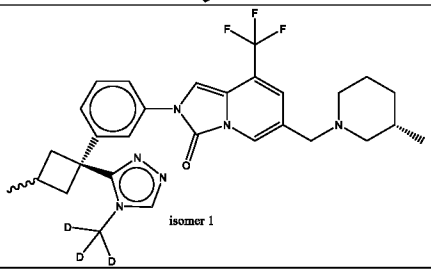
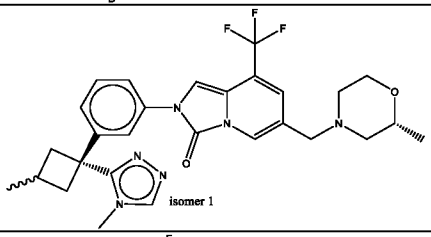
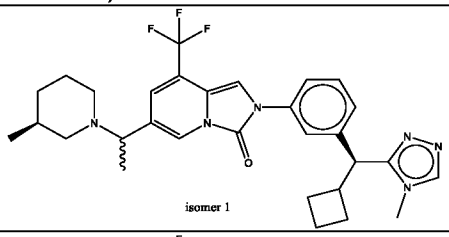
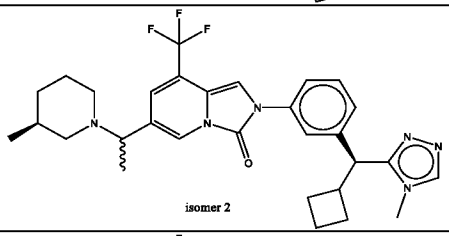
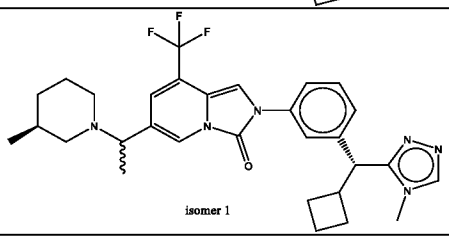
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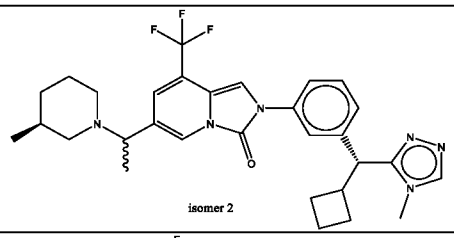
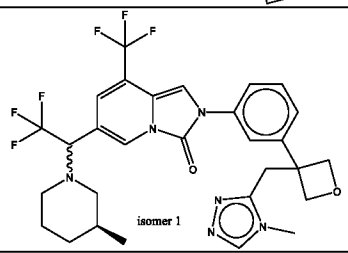
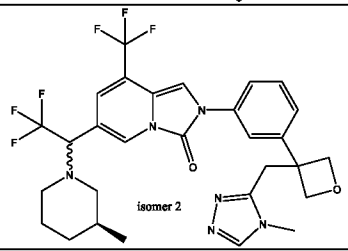
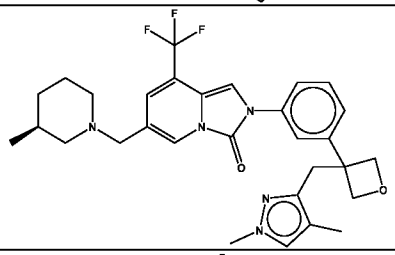
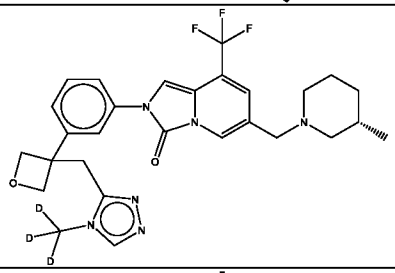
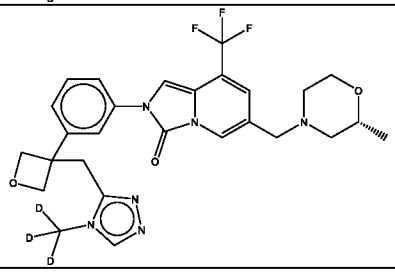
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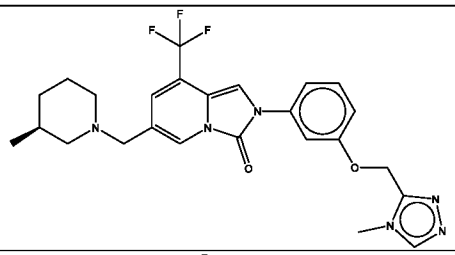
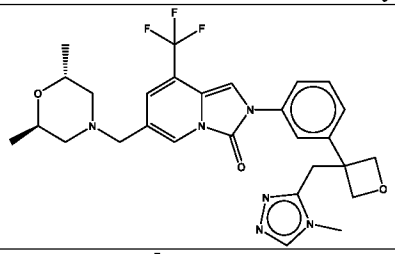
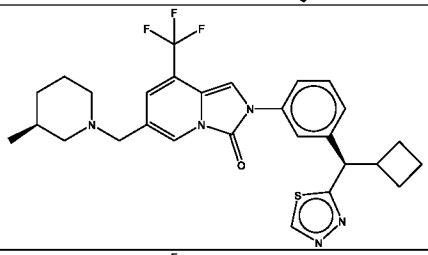
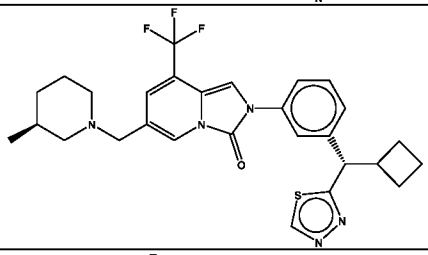
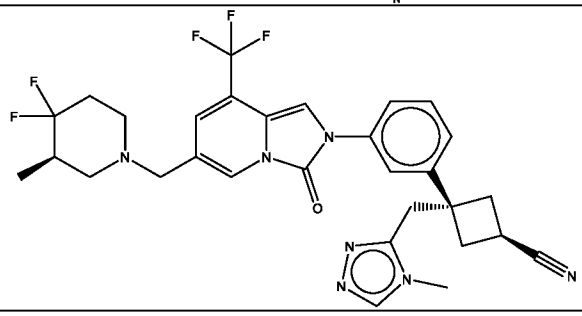
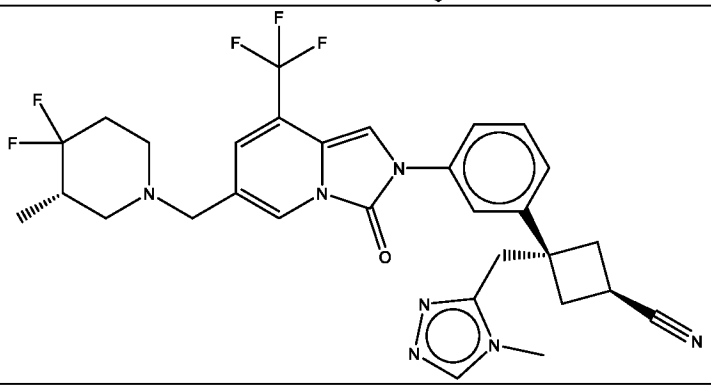
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172	 isomer 2
173	

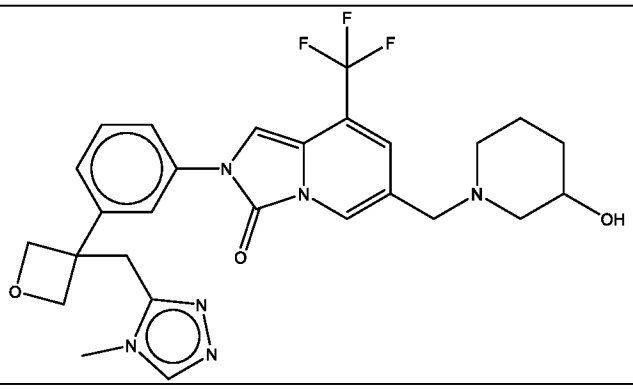
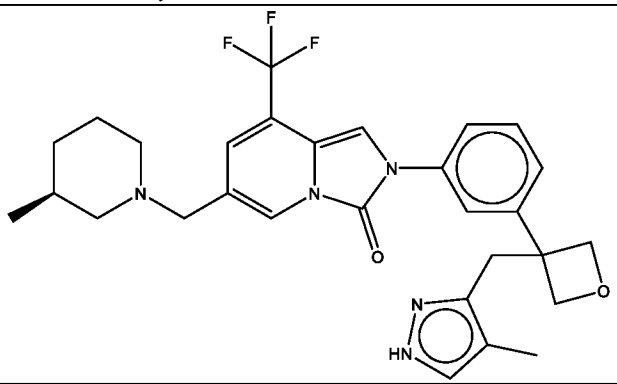
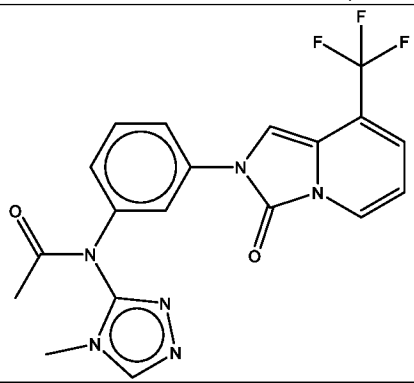
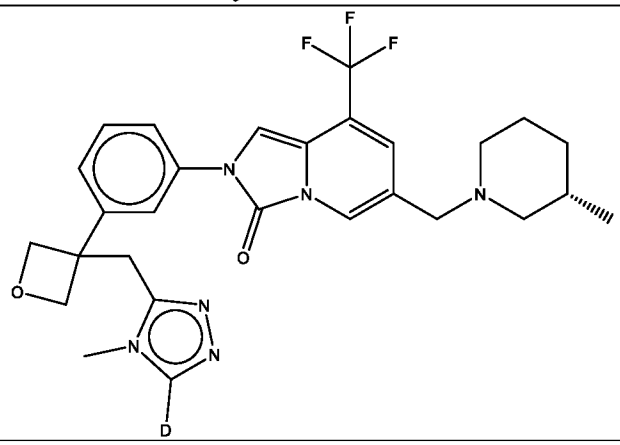
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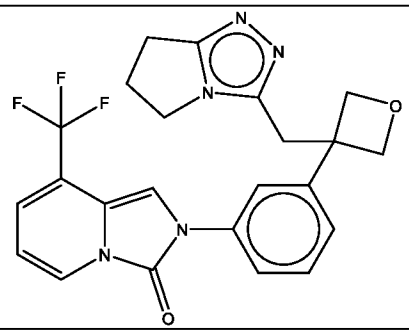
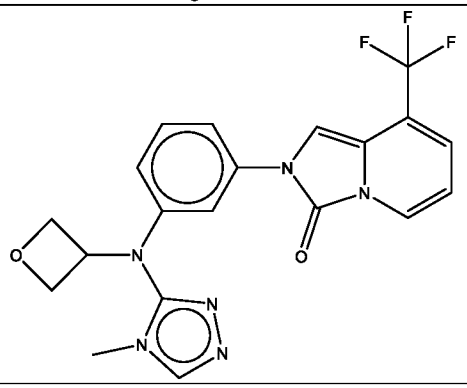
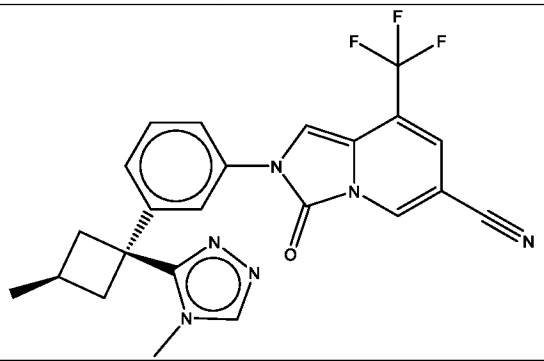
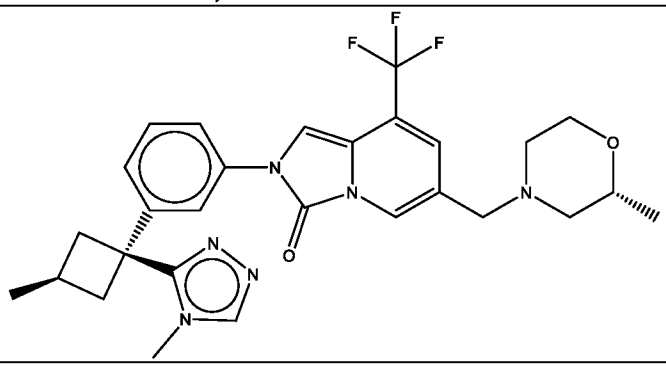
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186	 isomer 1

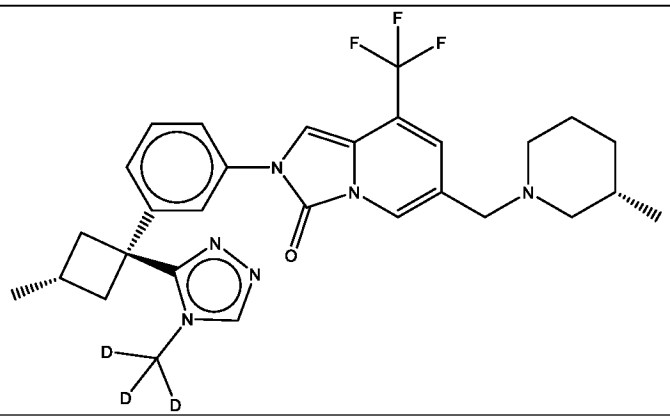
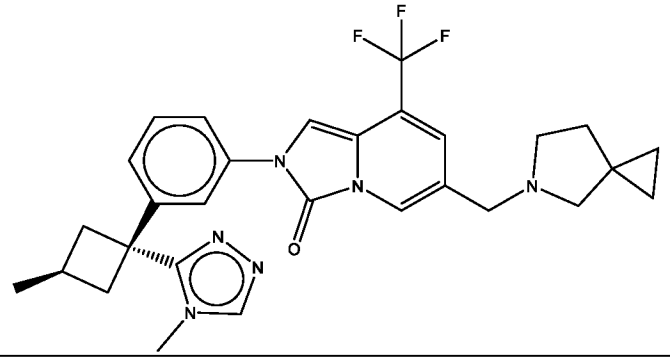
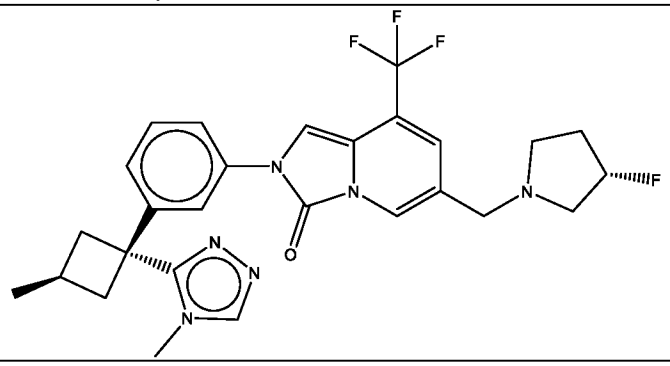
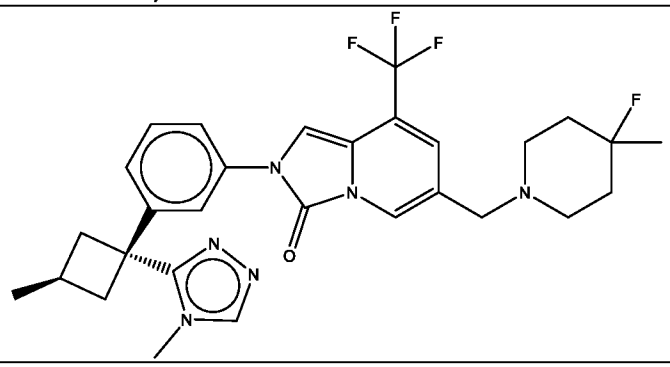
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192	 isomer 2
193	 isomer 1

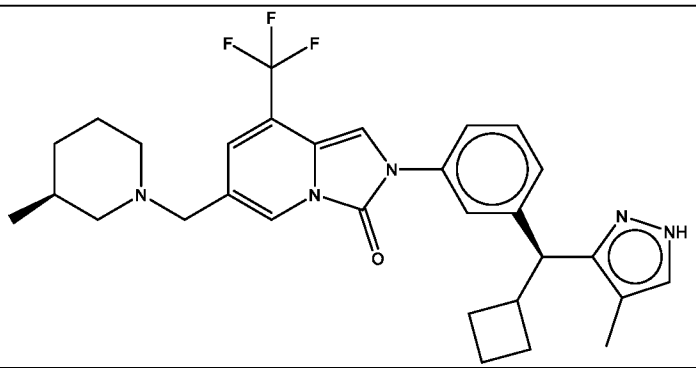
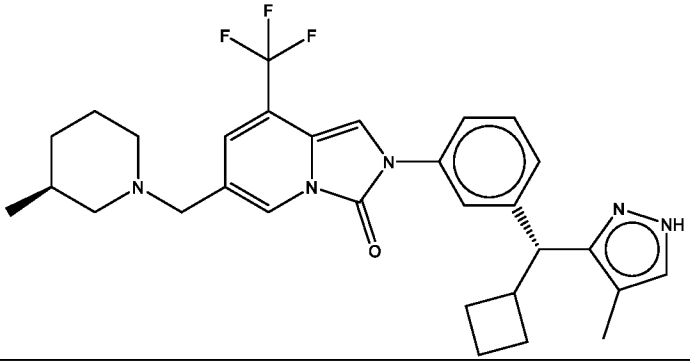
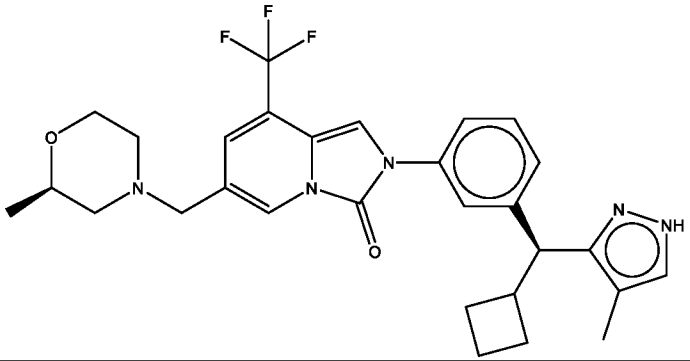
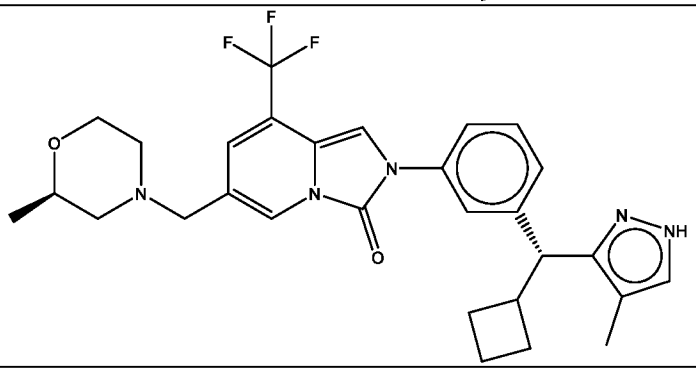
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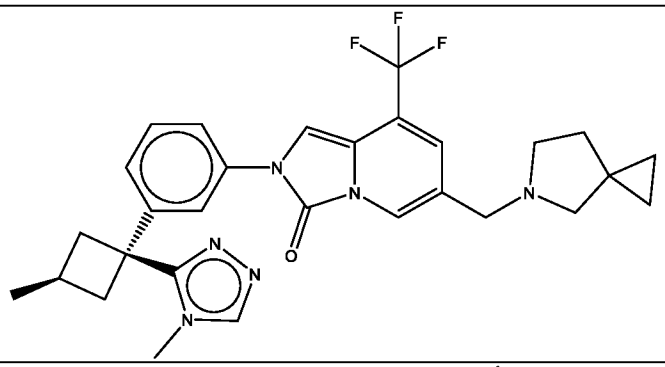
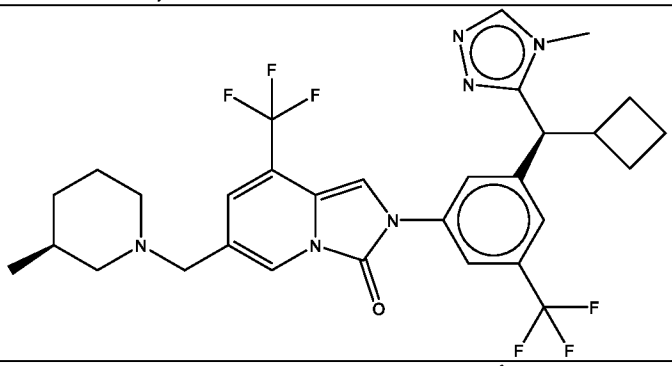
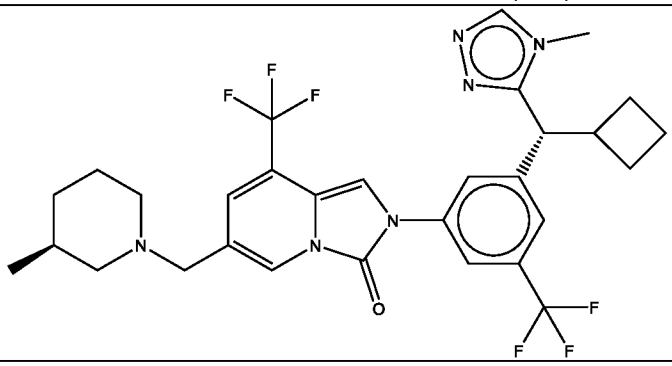
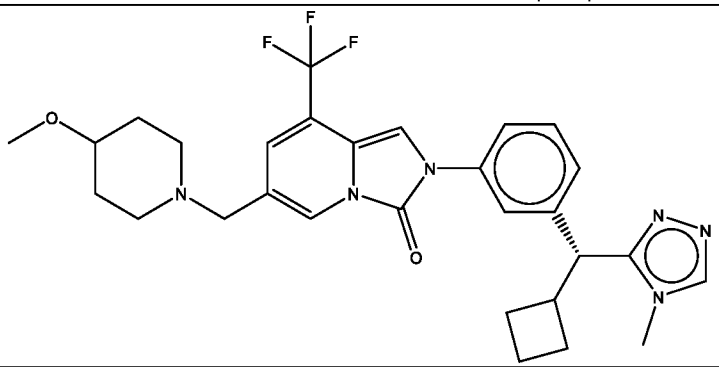
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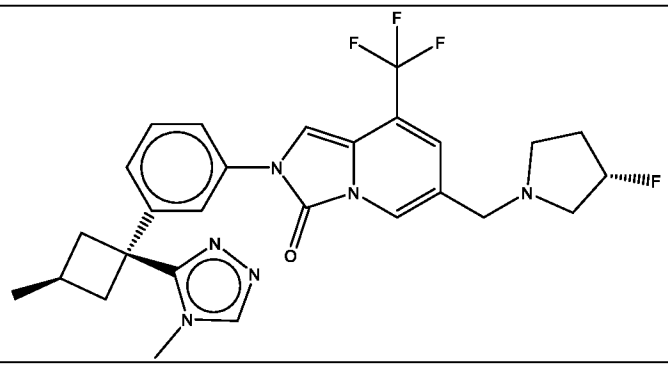
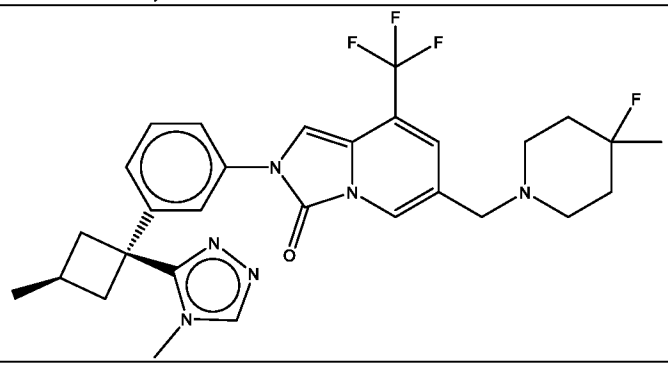
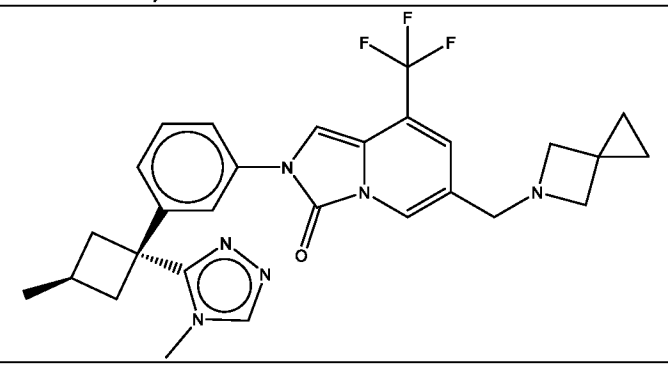
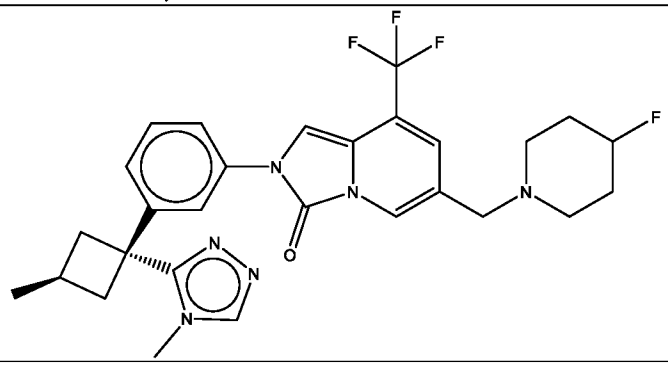
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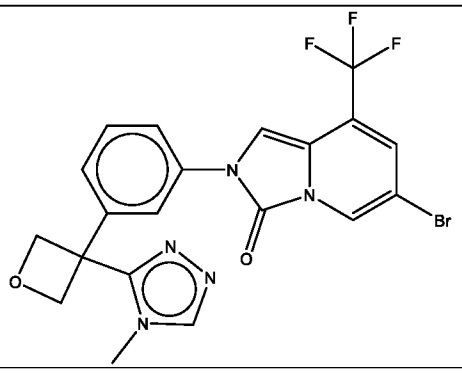
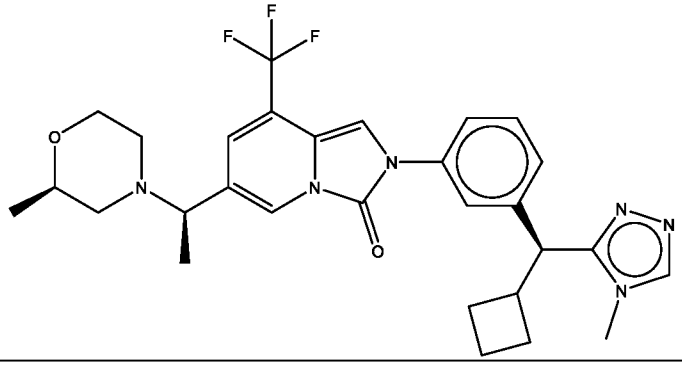
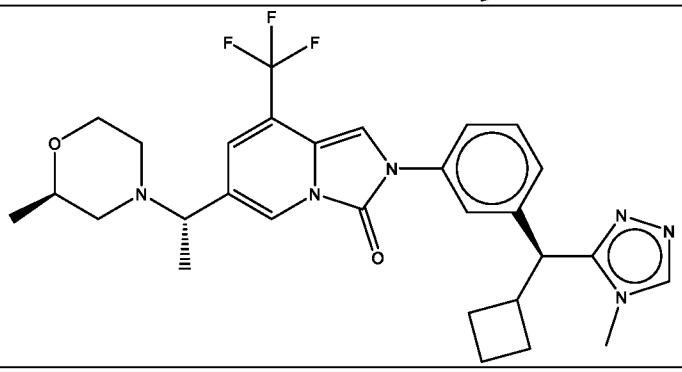
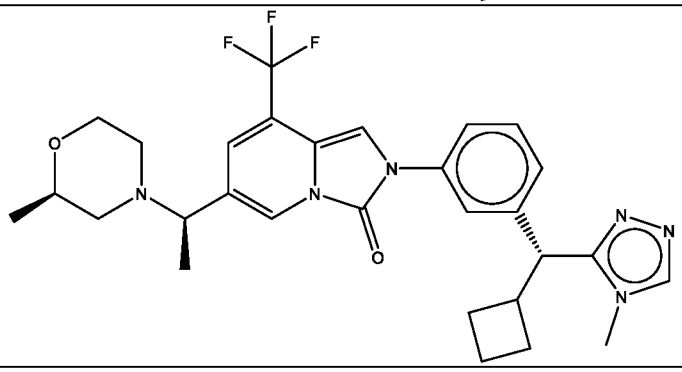
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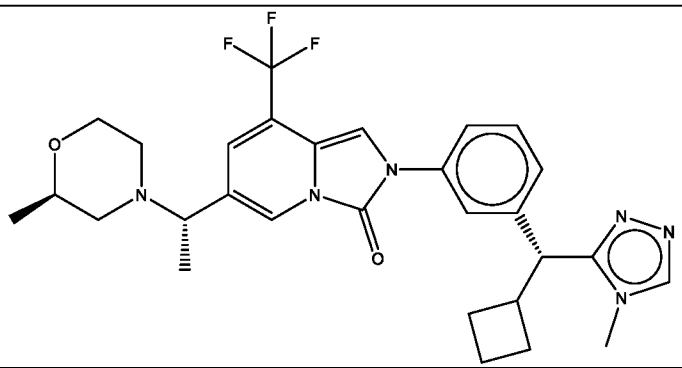
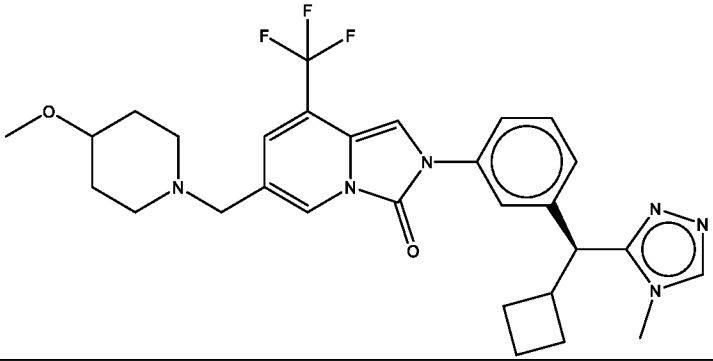
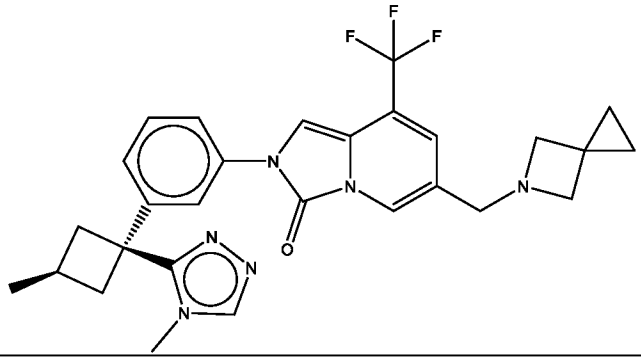
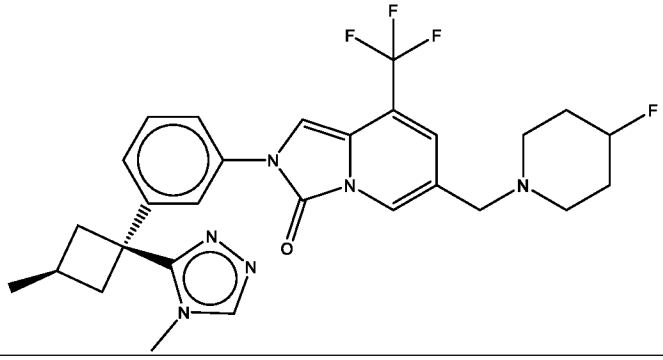
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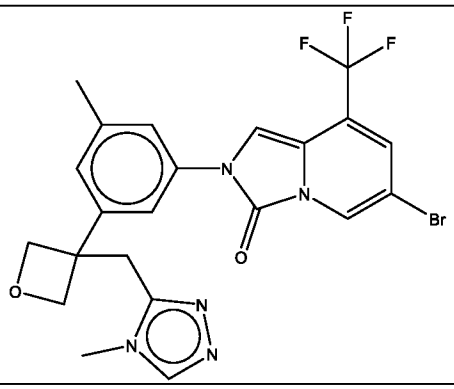
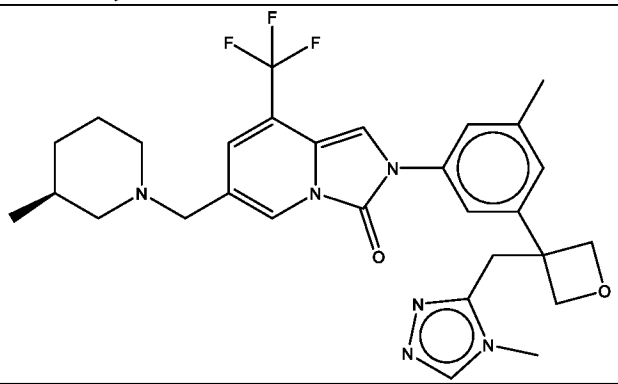
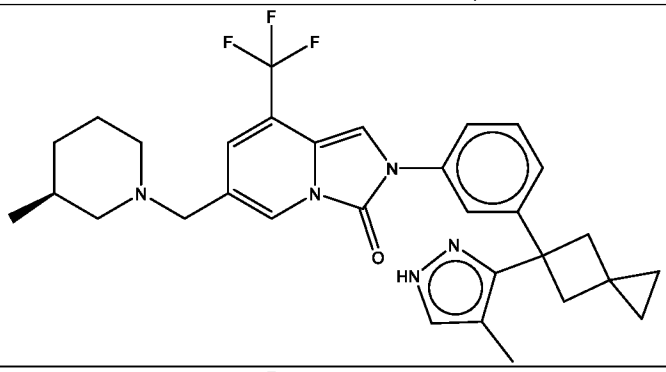
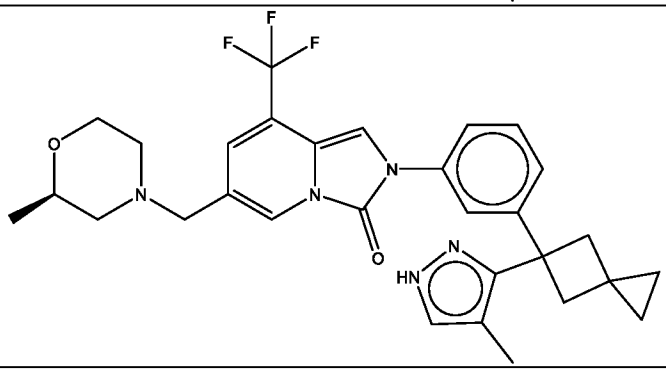
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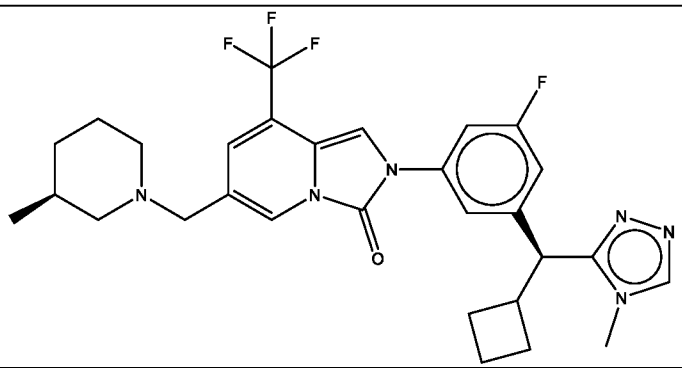
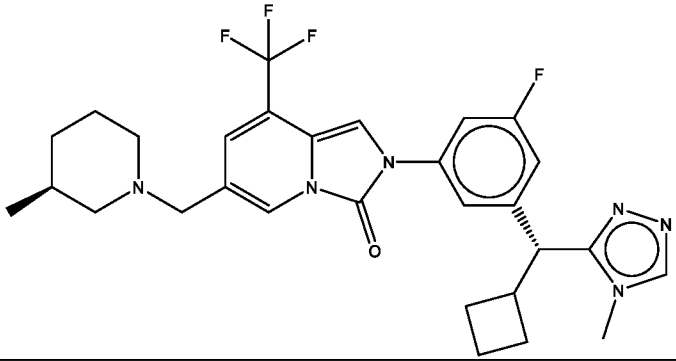
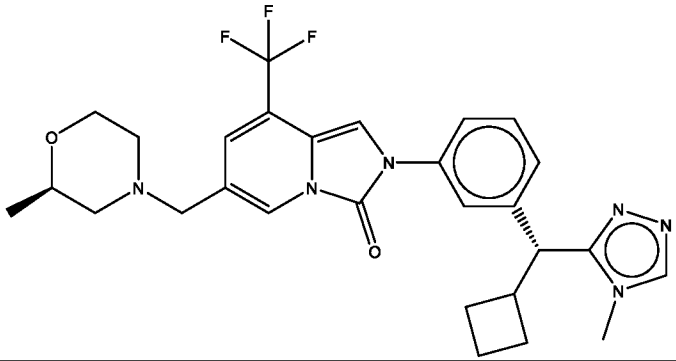
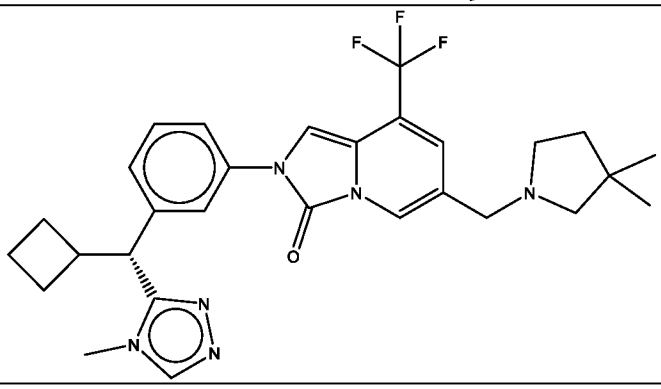
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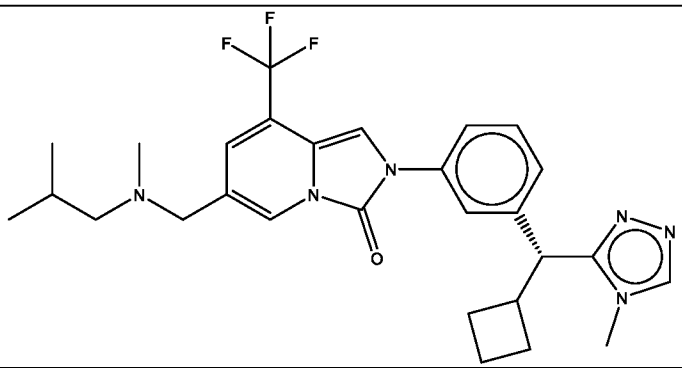
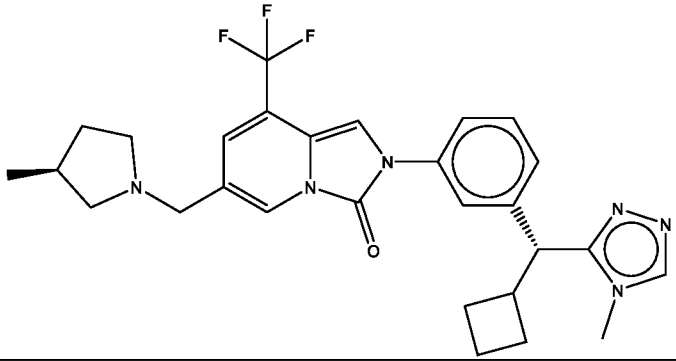
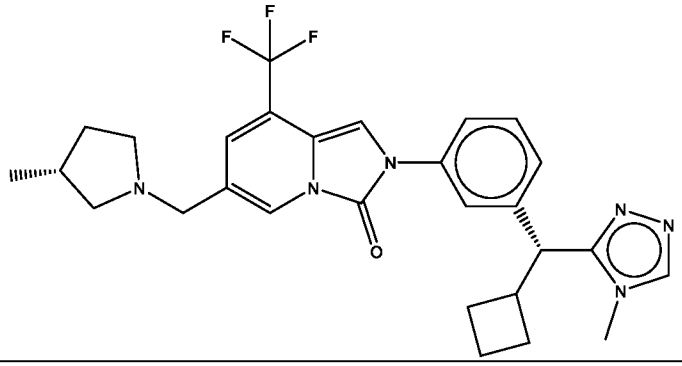
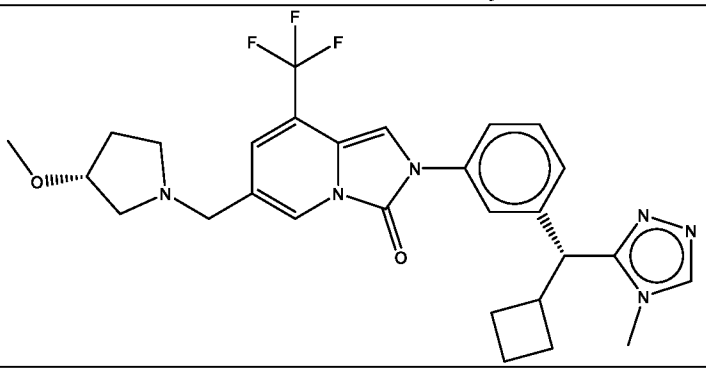
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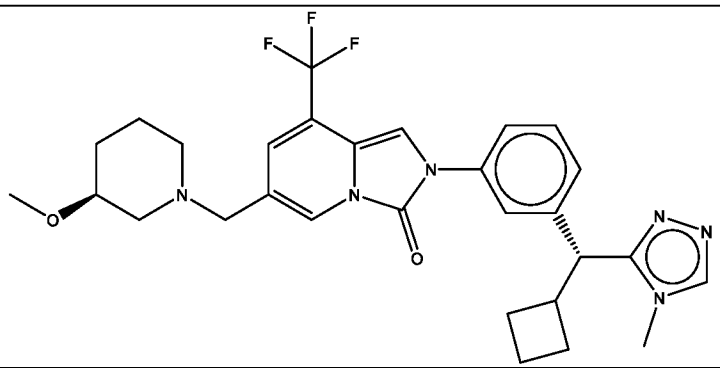
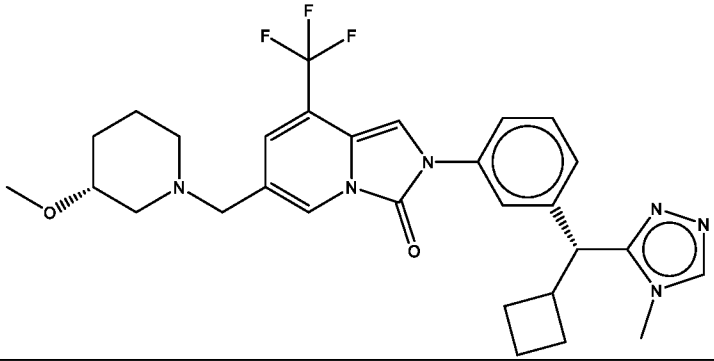
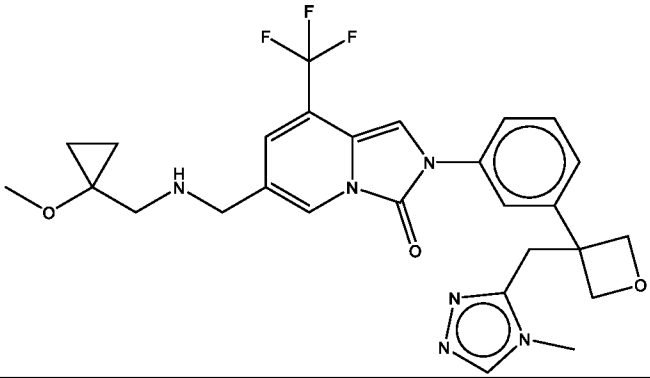
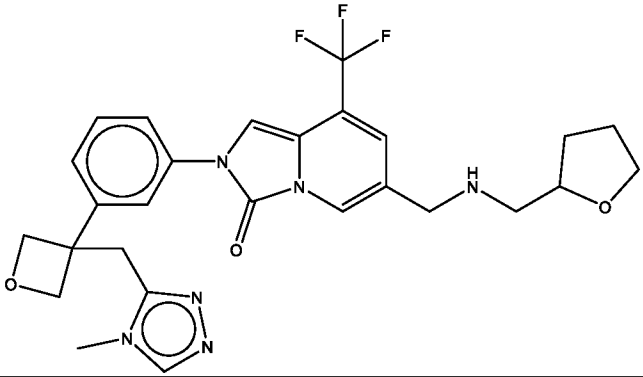
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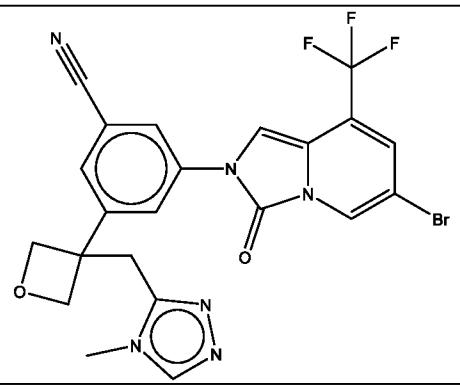
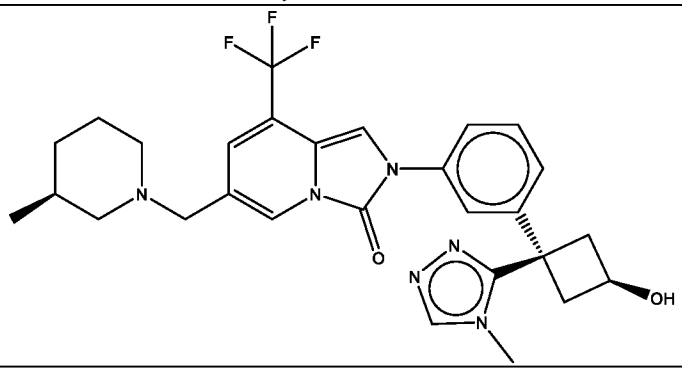
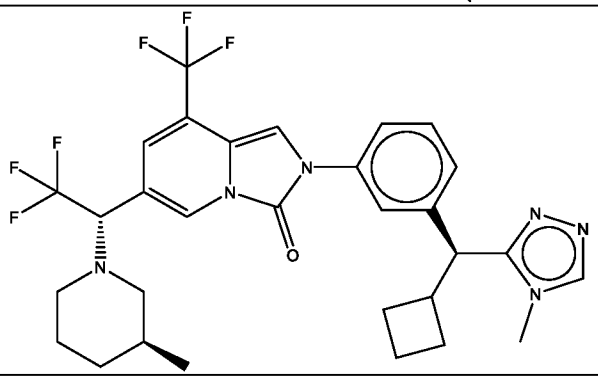
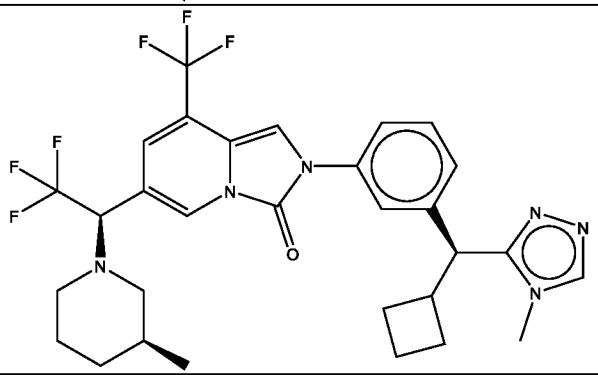
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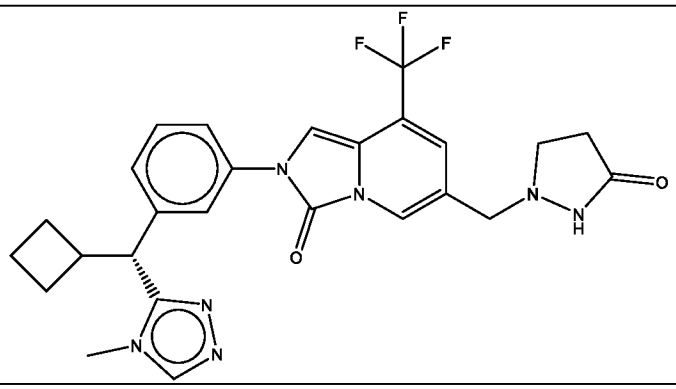
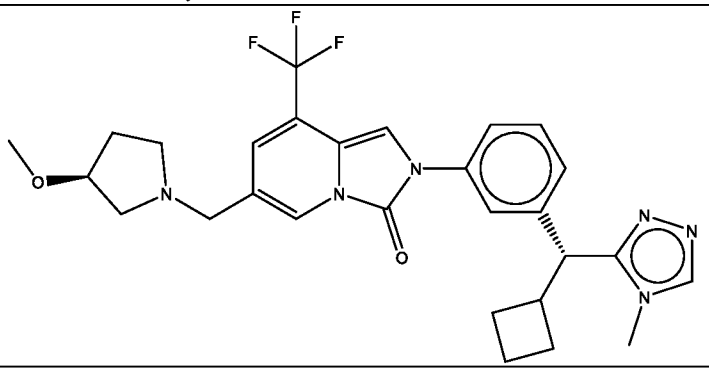
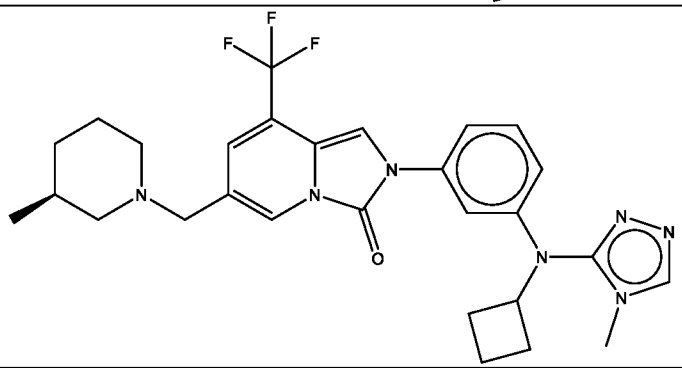
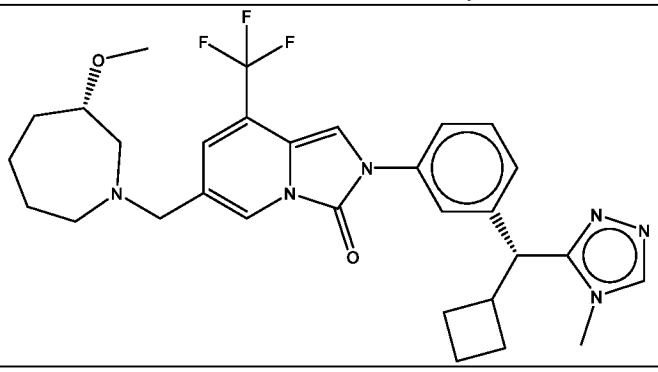
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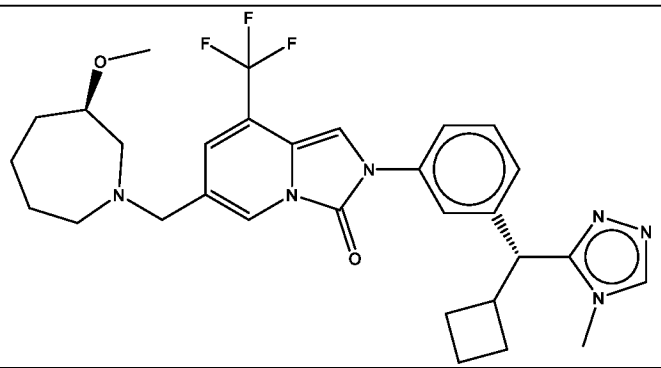
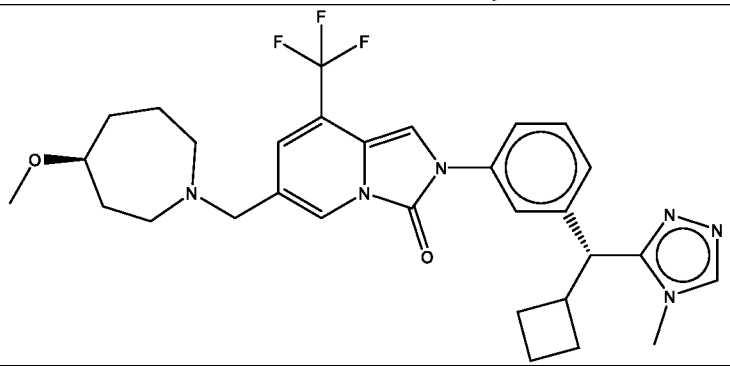
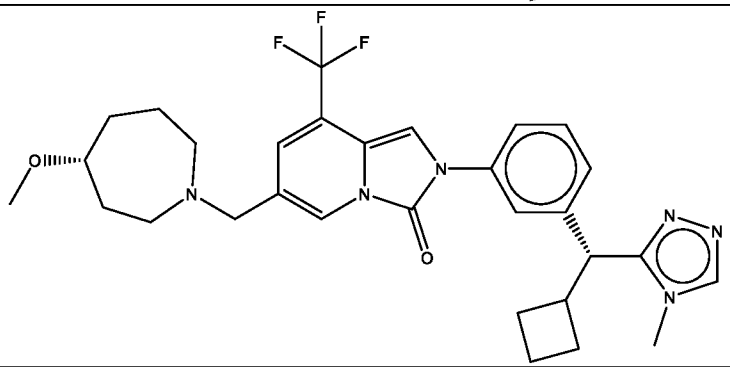
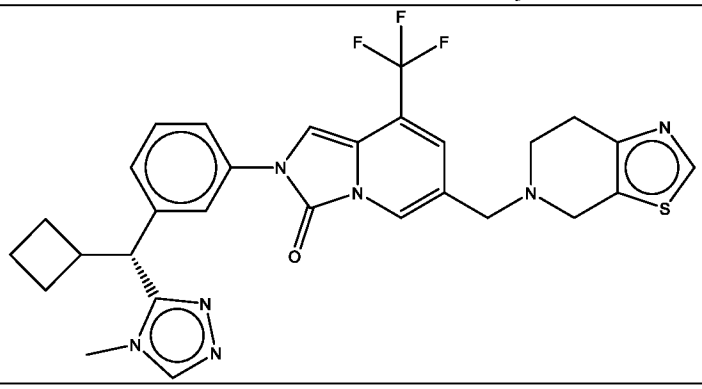
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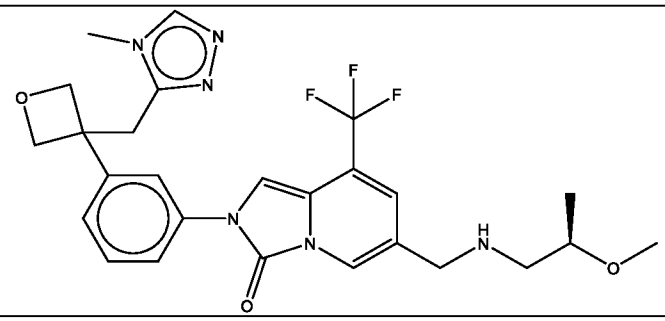
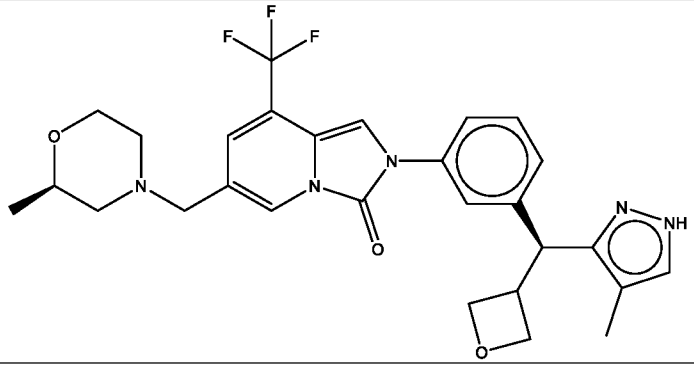
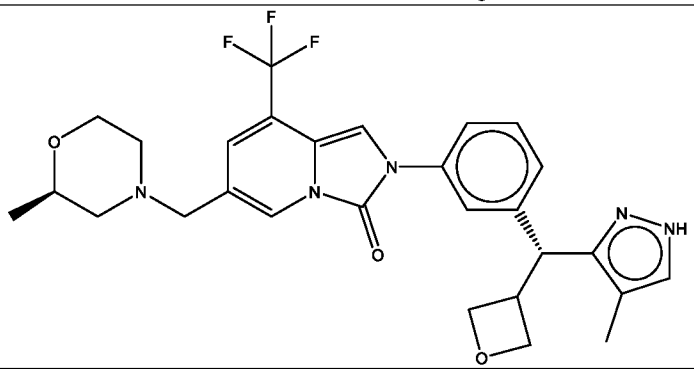
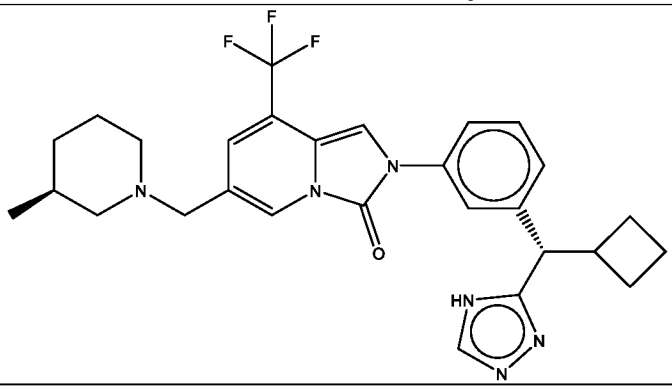
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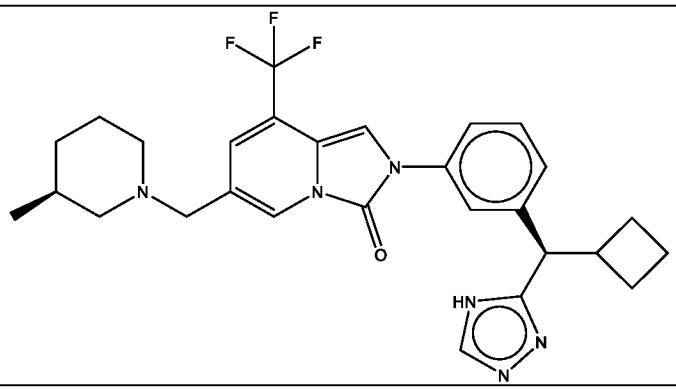
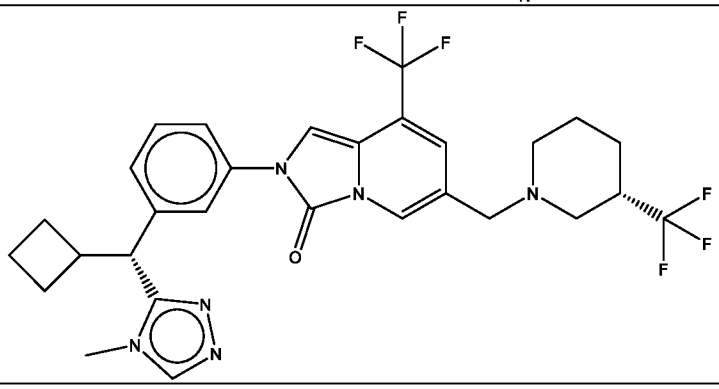
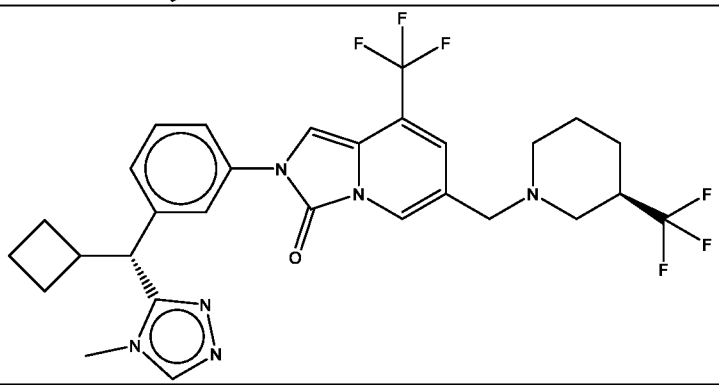
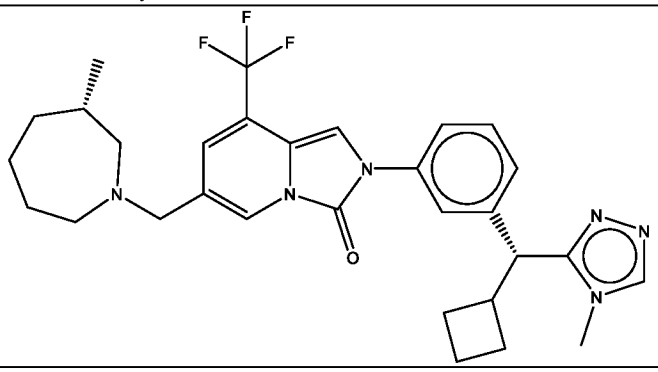
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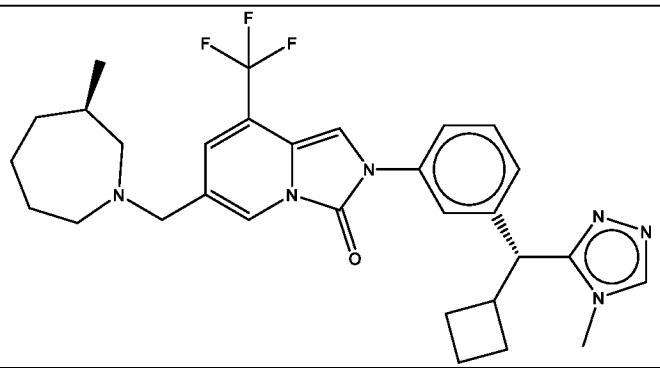
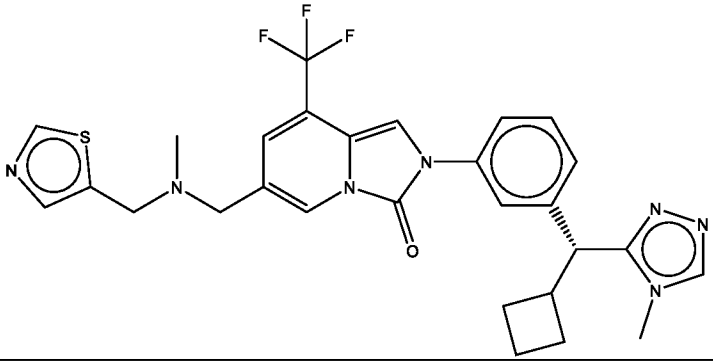
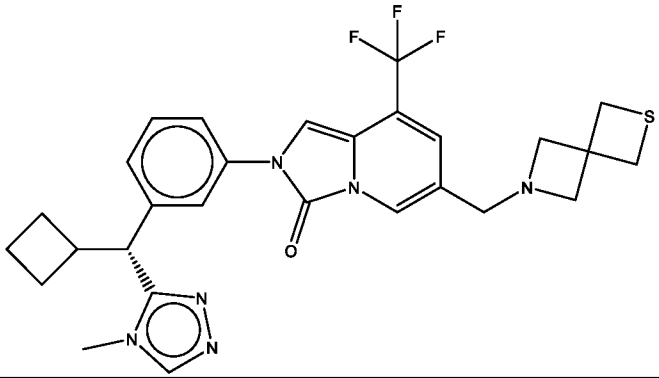
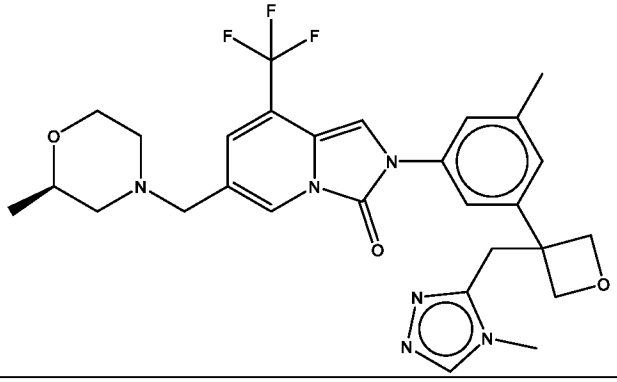
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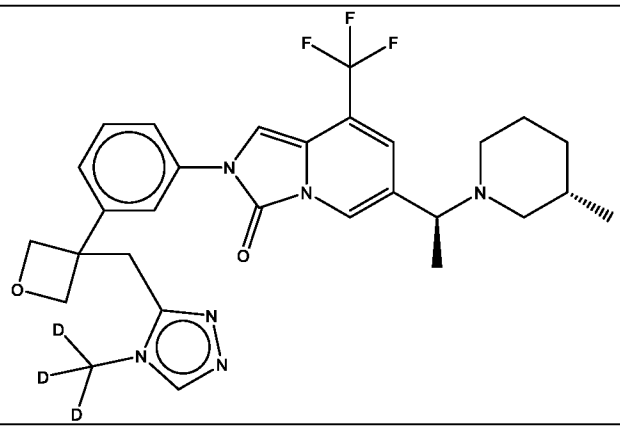
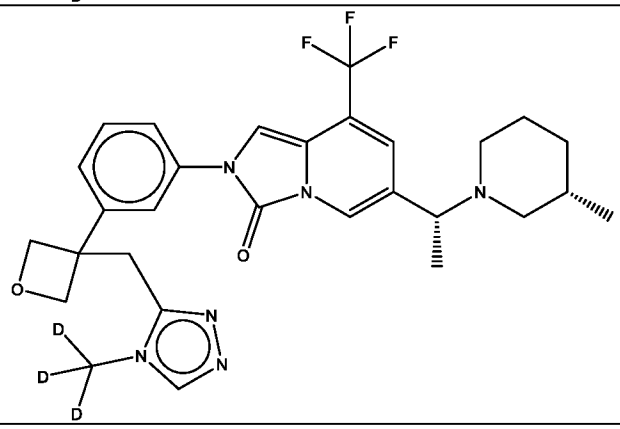
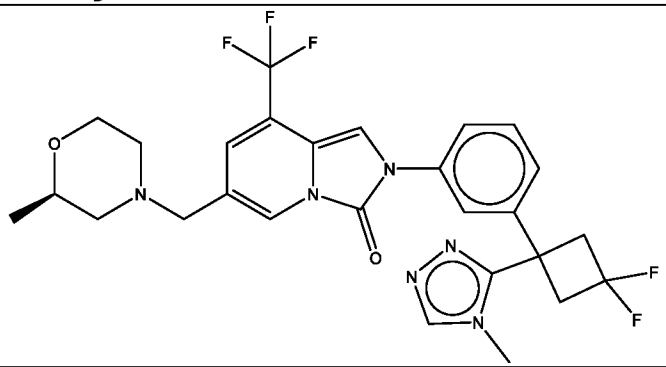
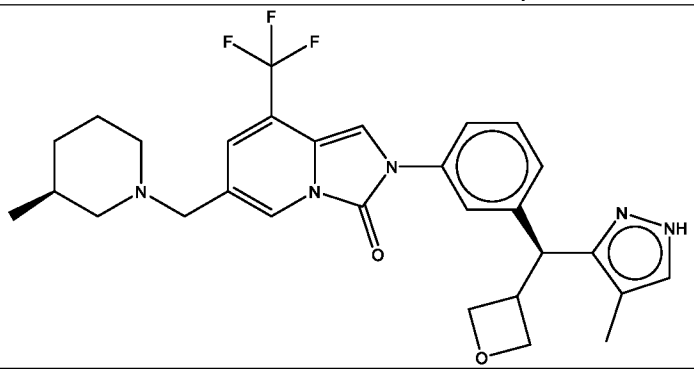
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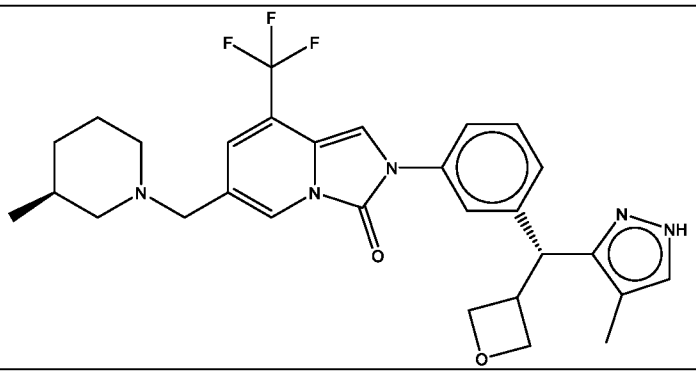
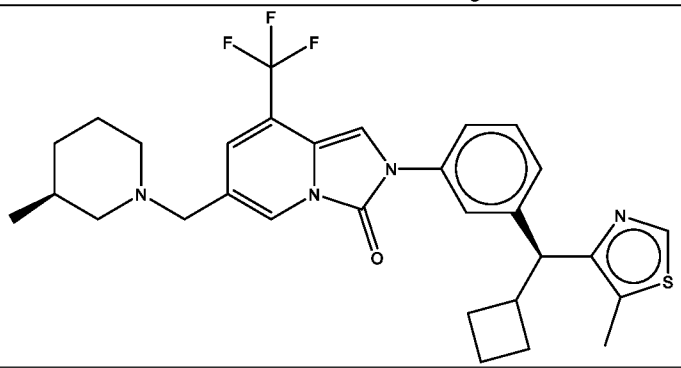
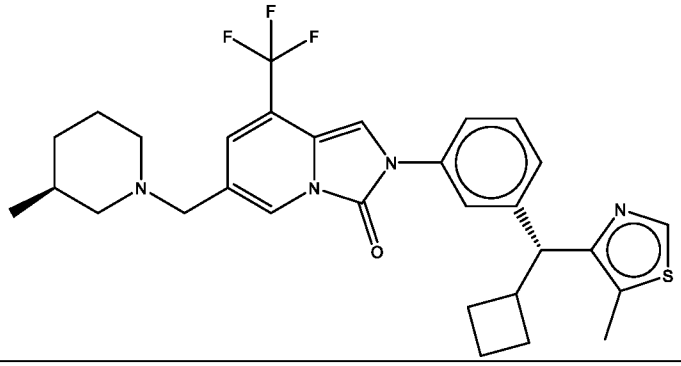
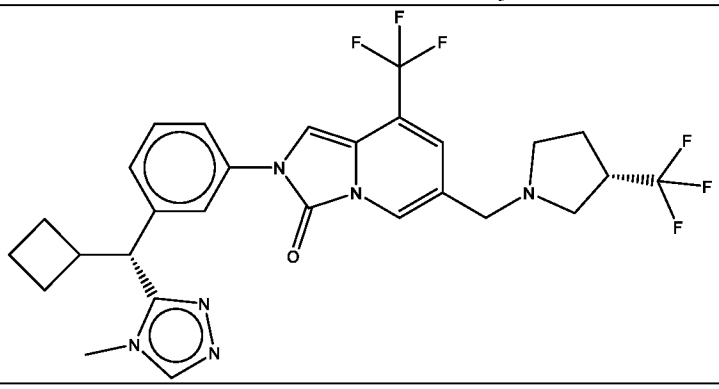
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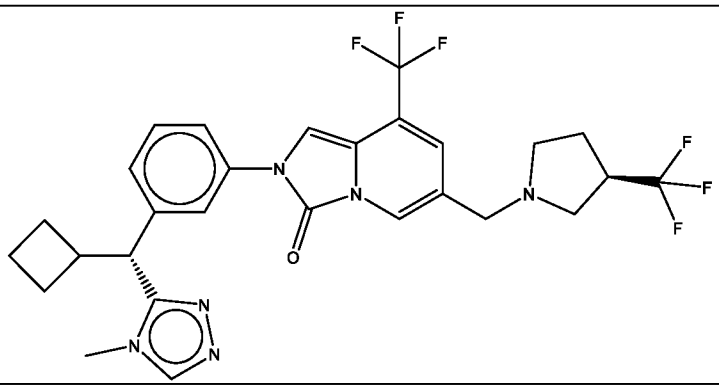
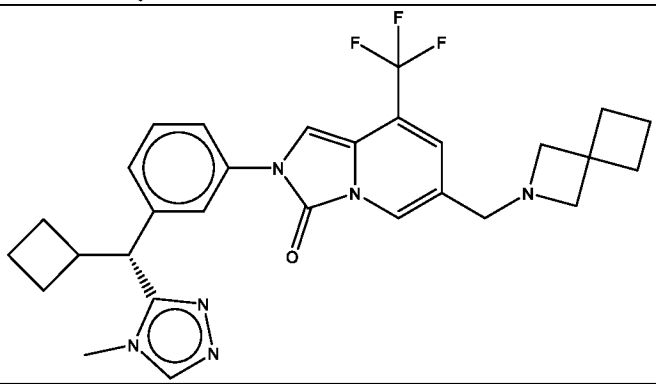
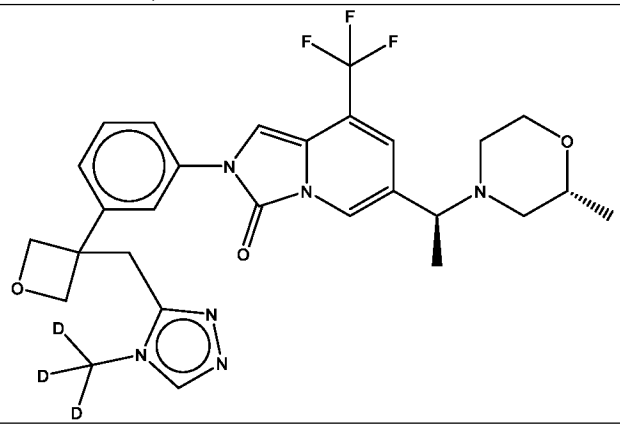
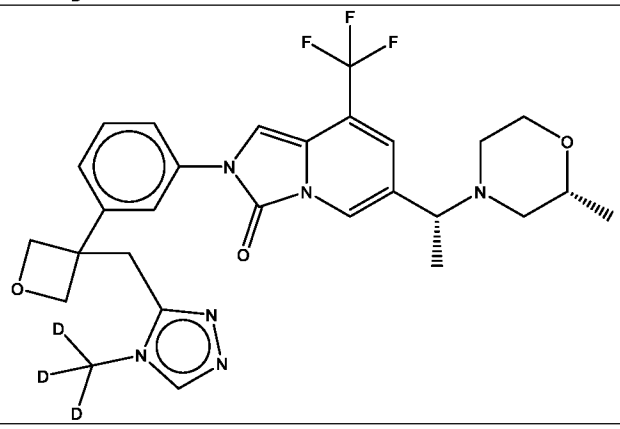
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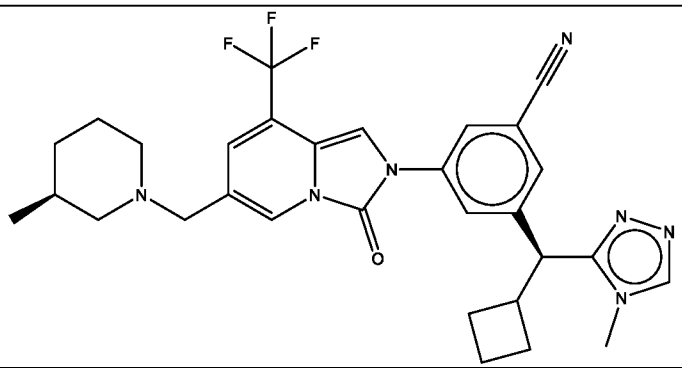
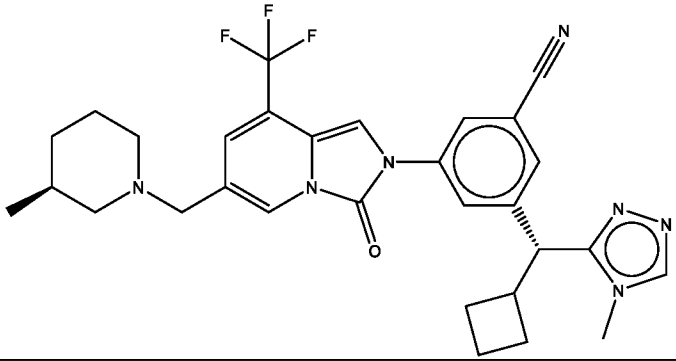
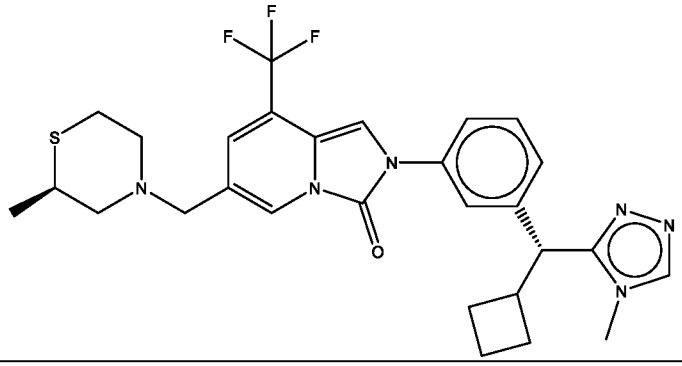
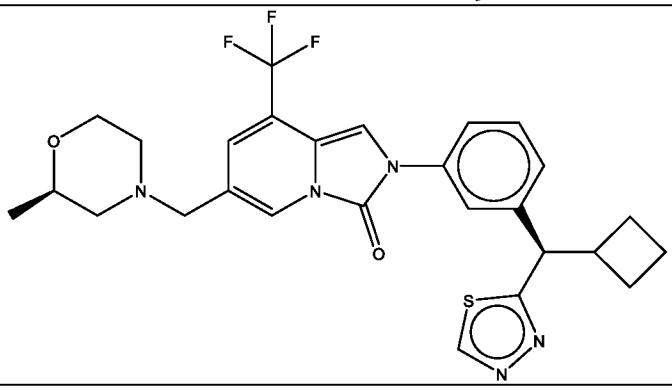
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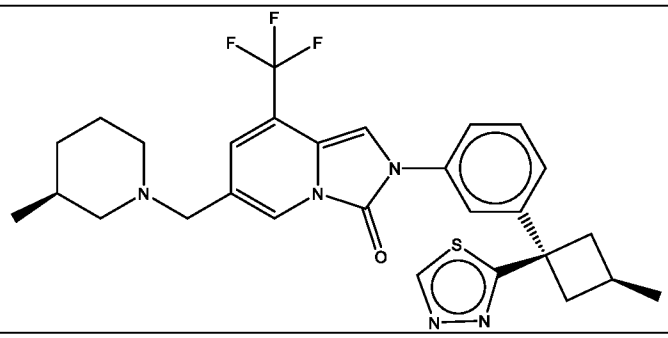
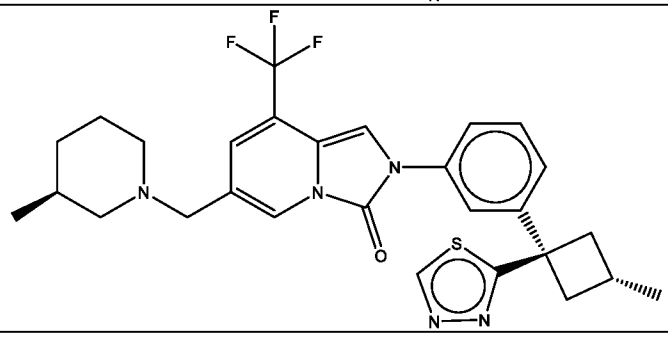
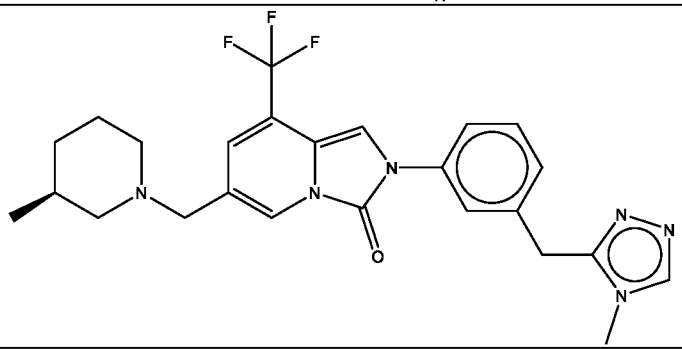
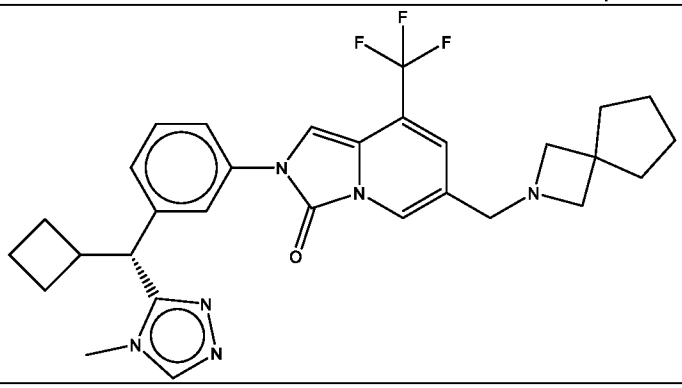
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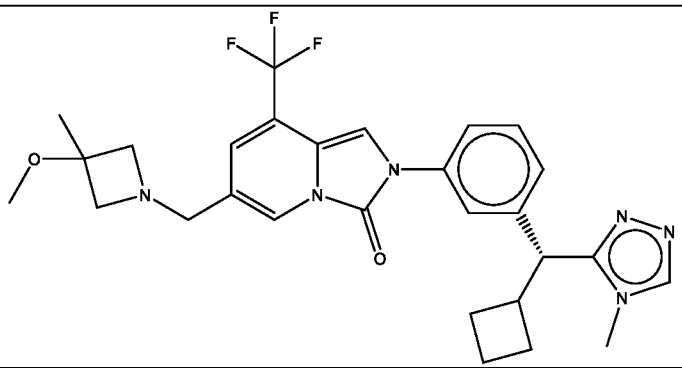
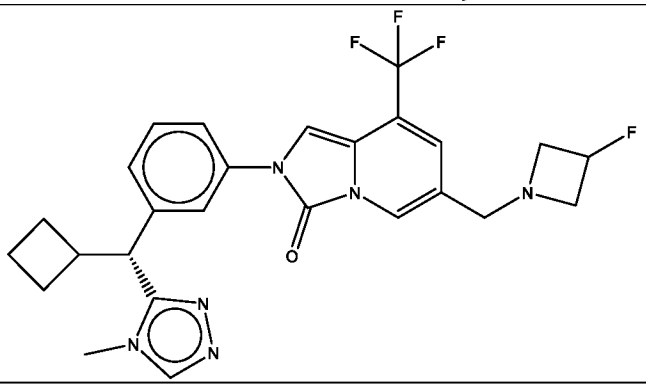
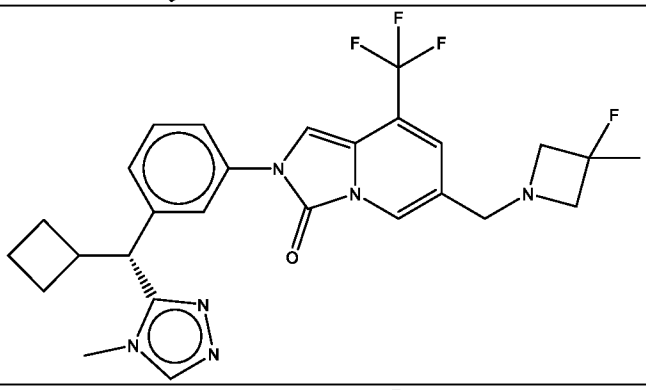
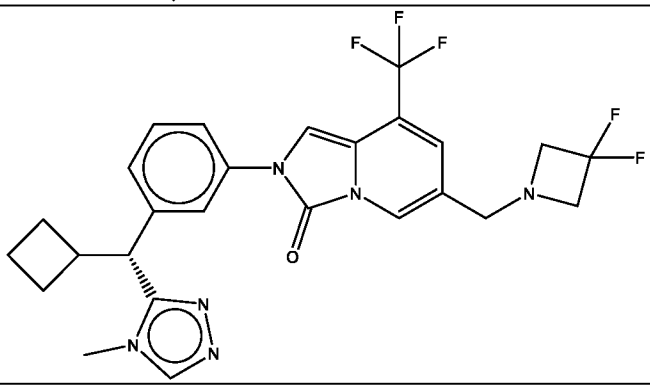
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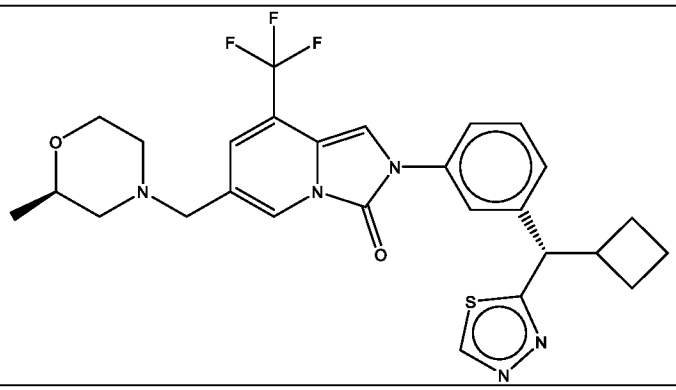
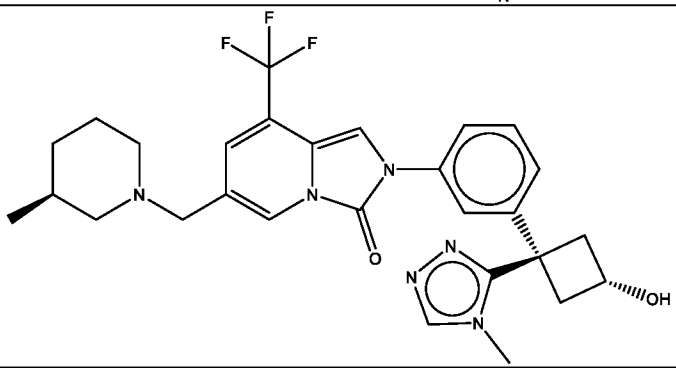
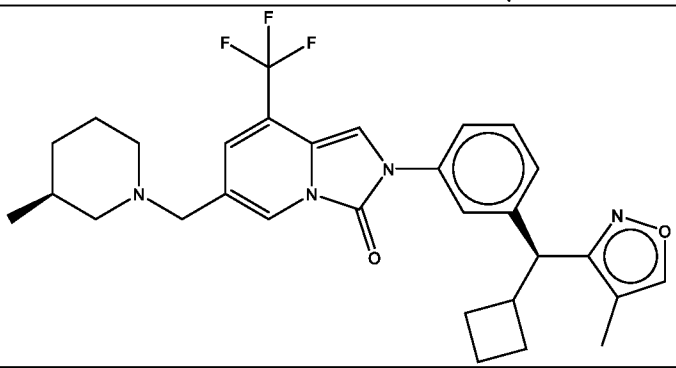
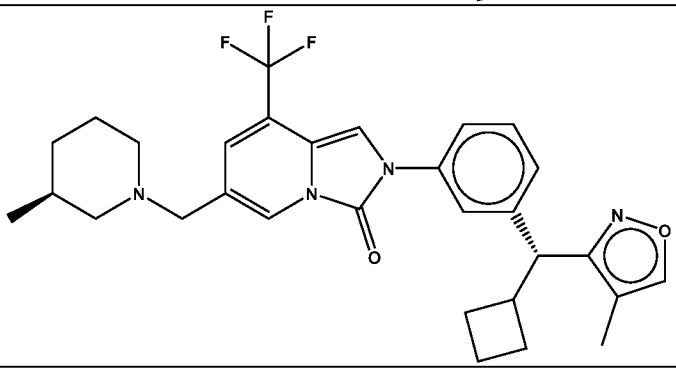
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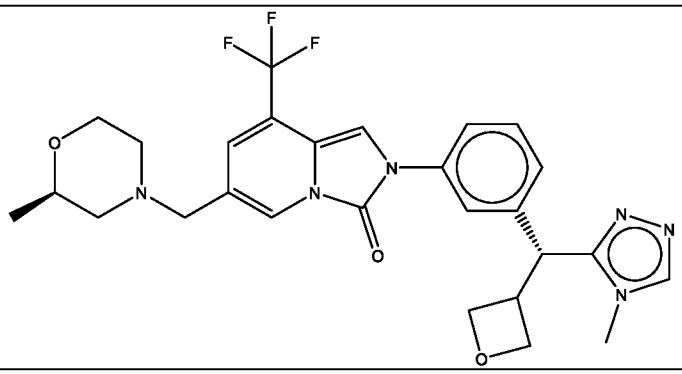
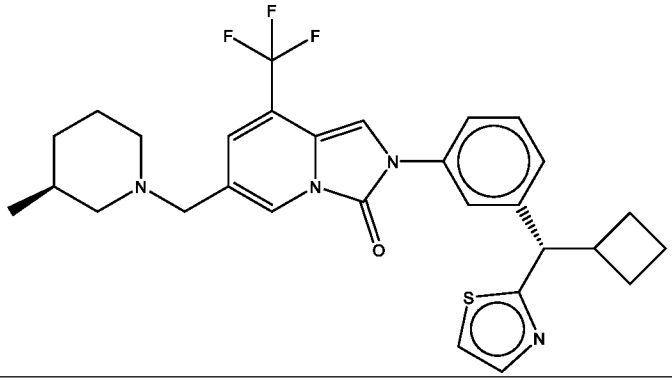
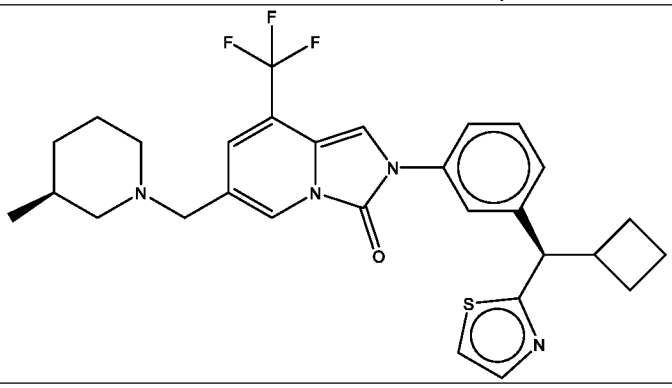
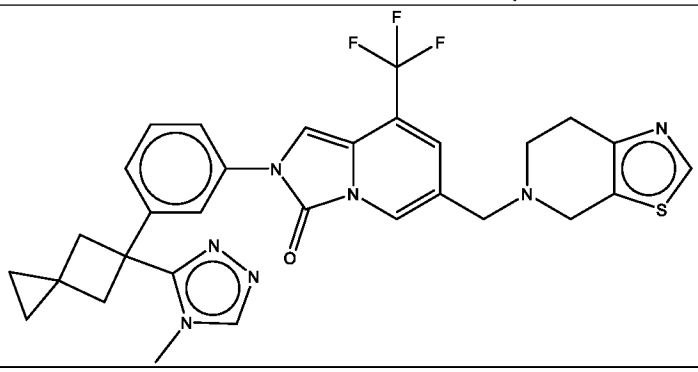
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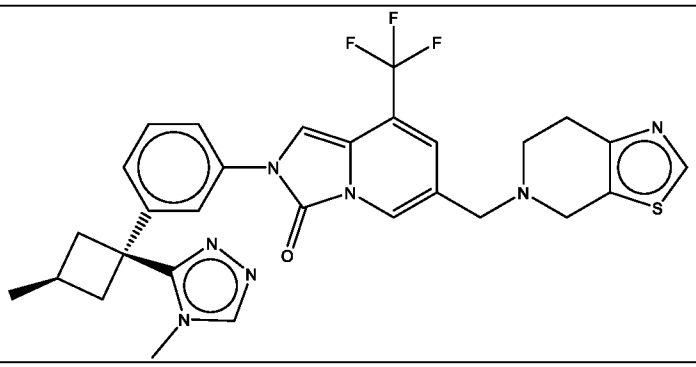
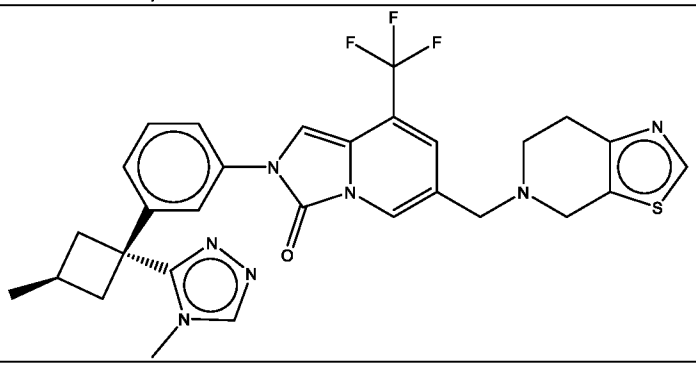
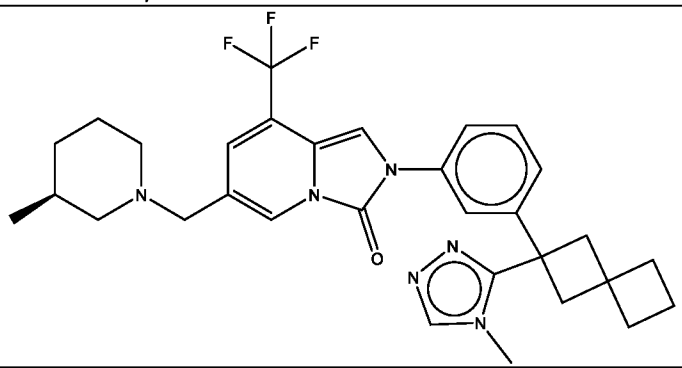
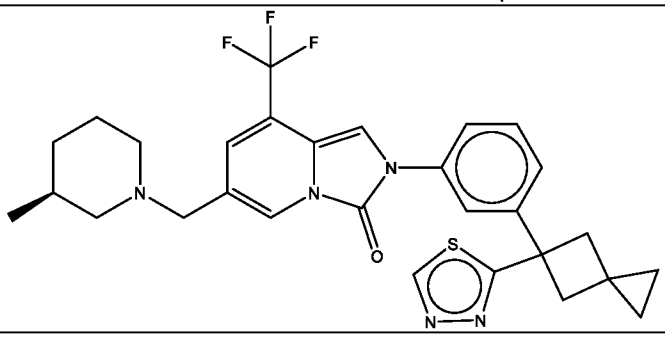
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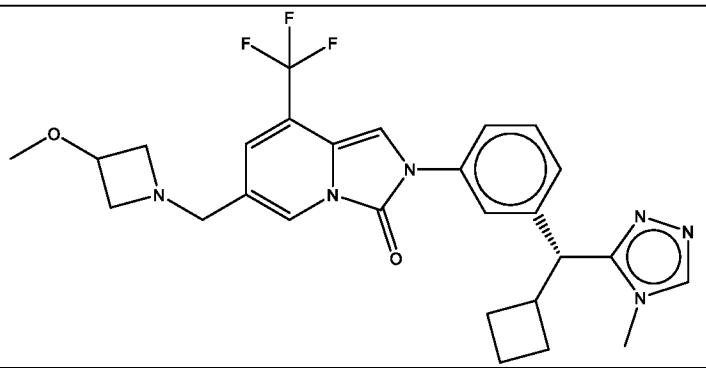
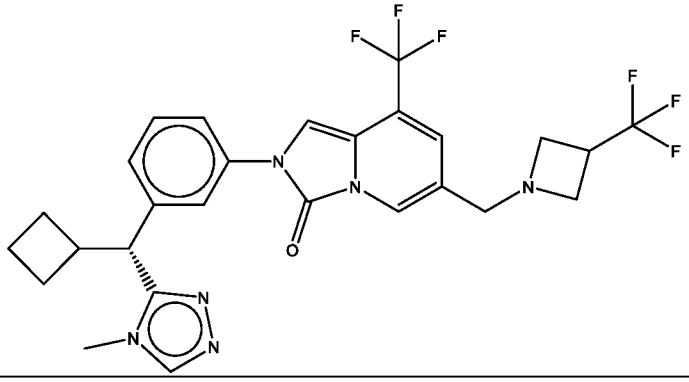
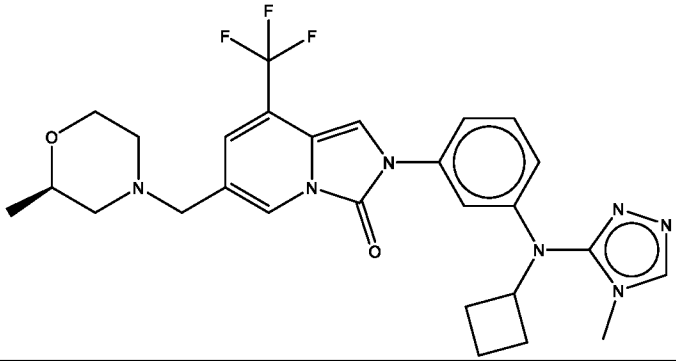
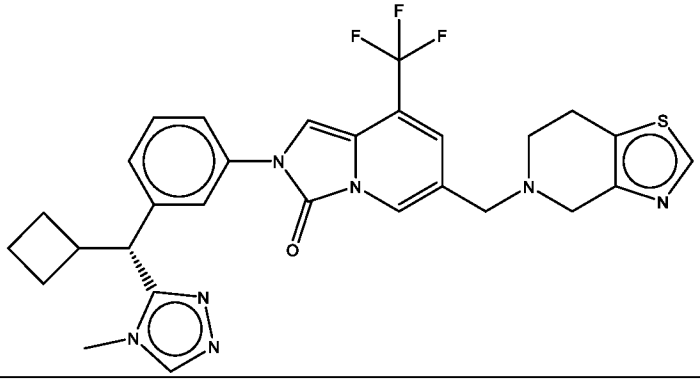
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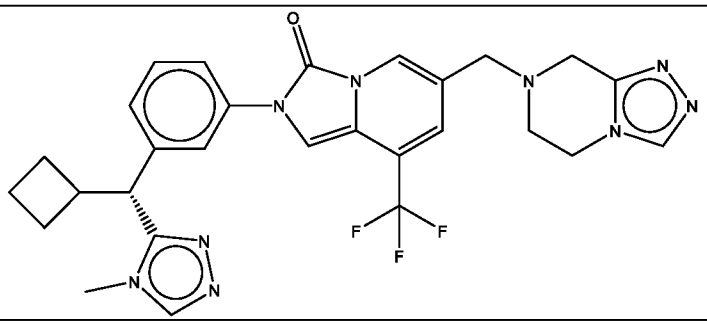
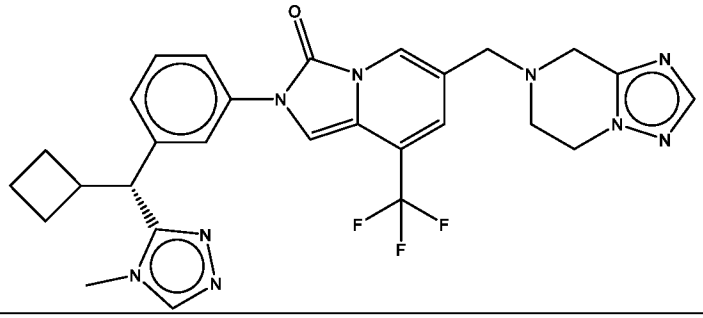
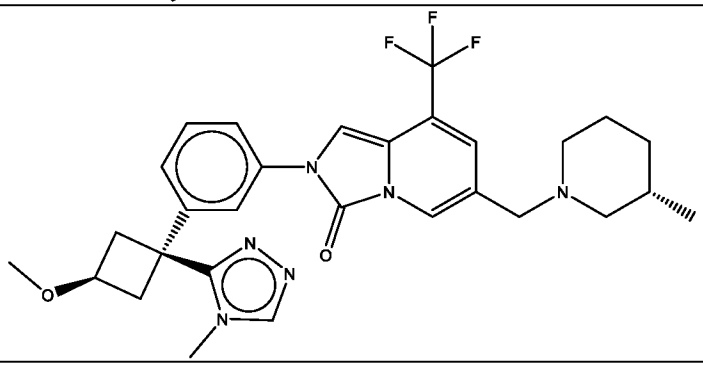
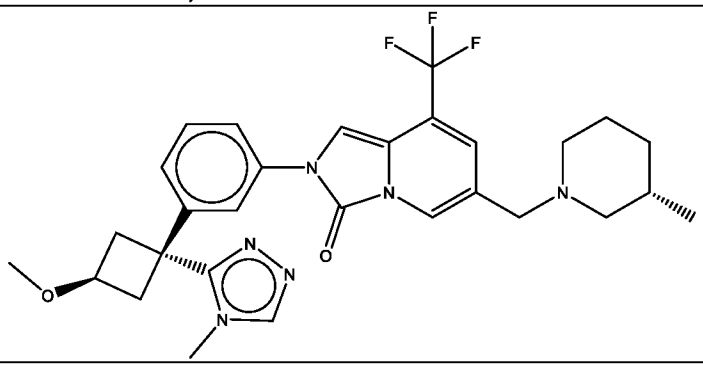
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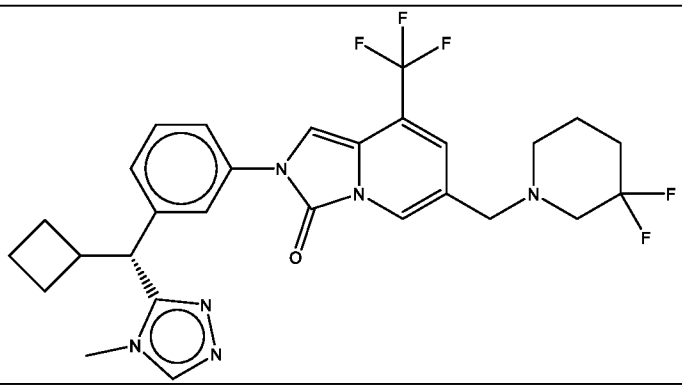
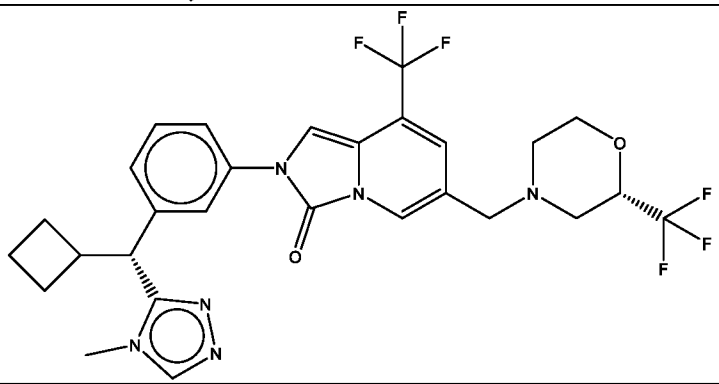
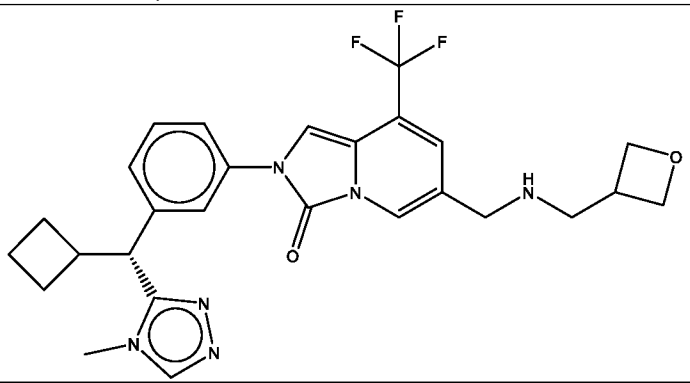
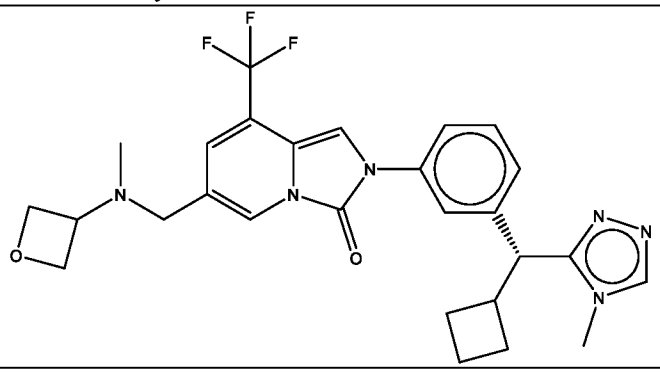
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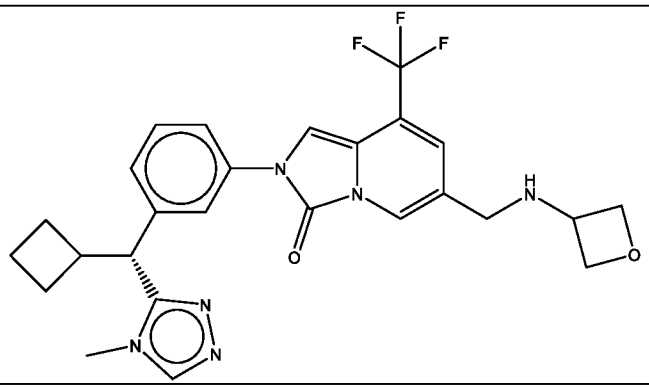
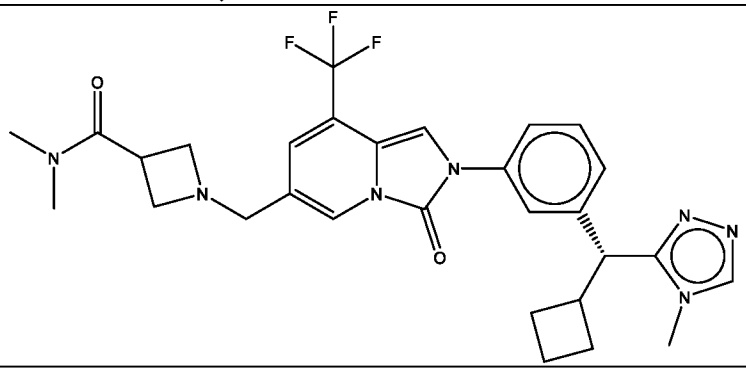
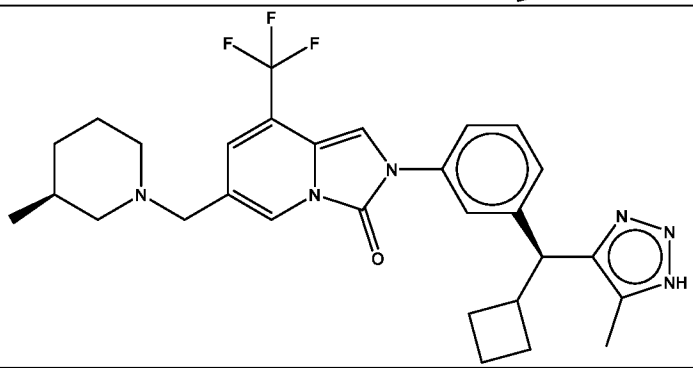
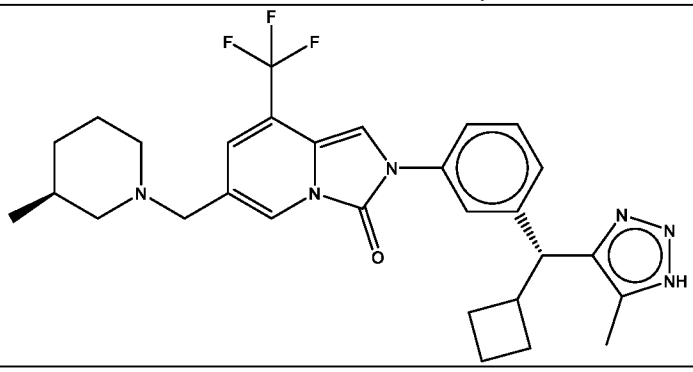
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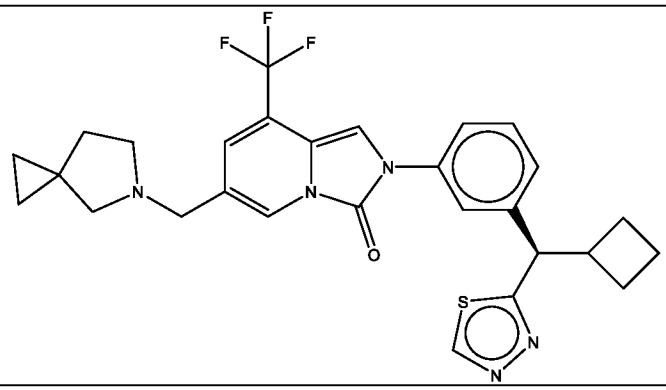
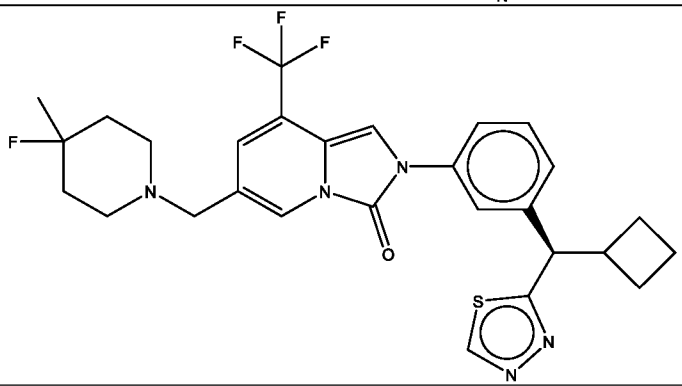
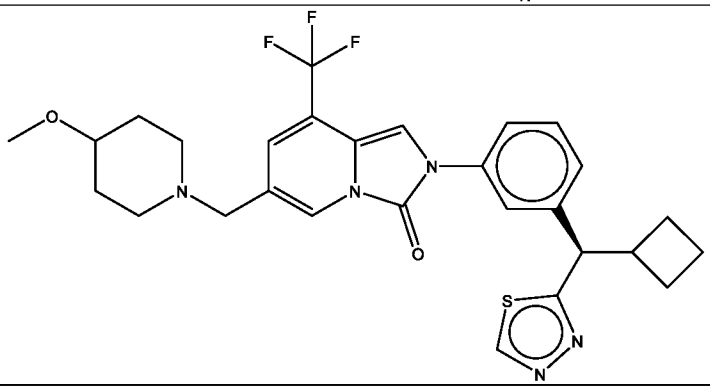
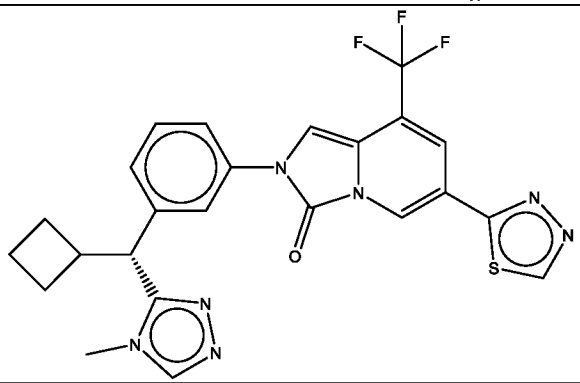
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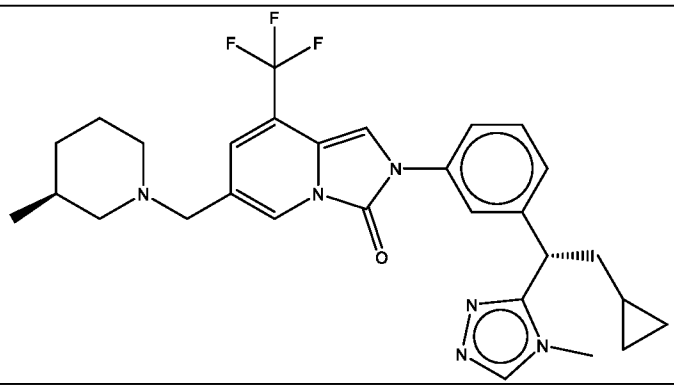
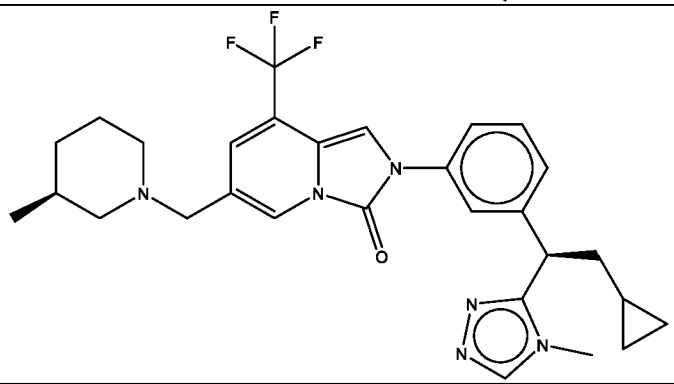
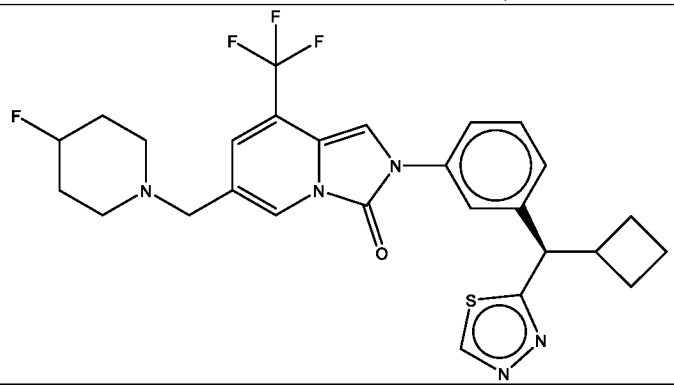
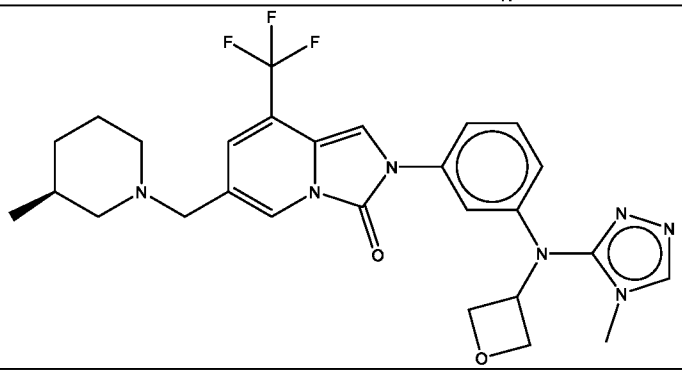
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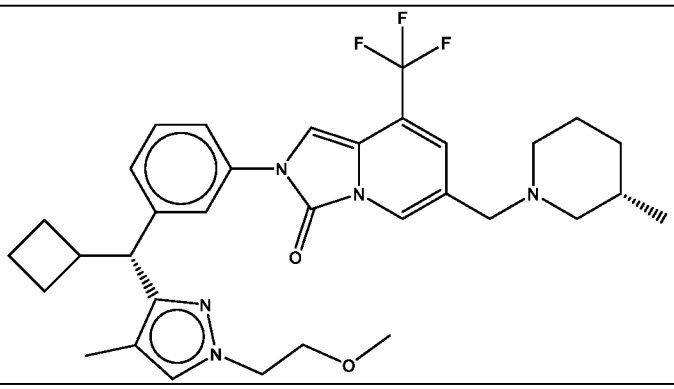
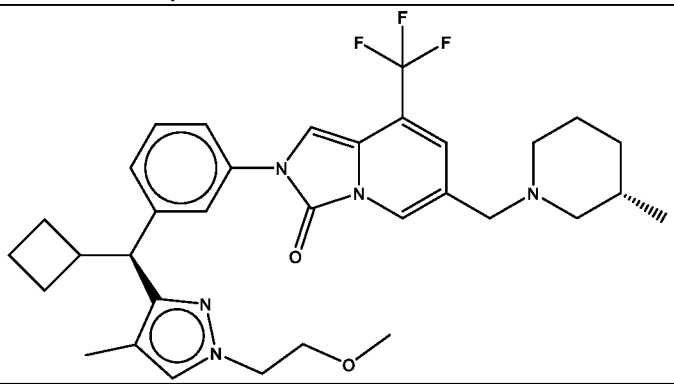
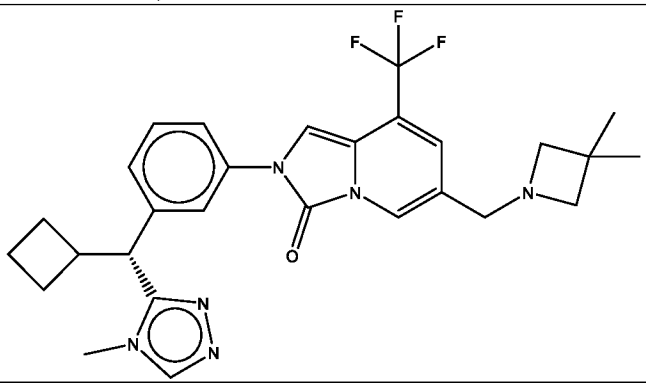
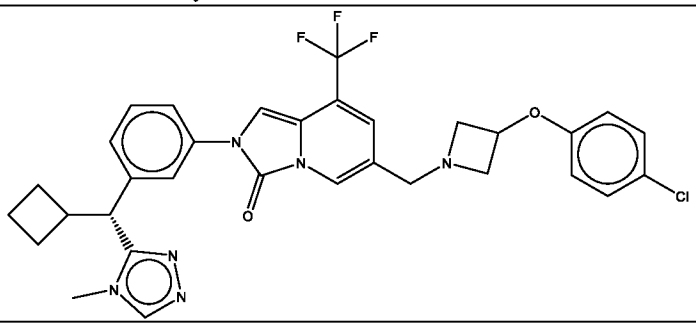
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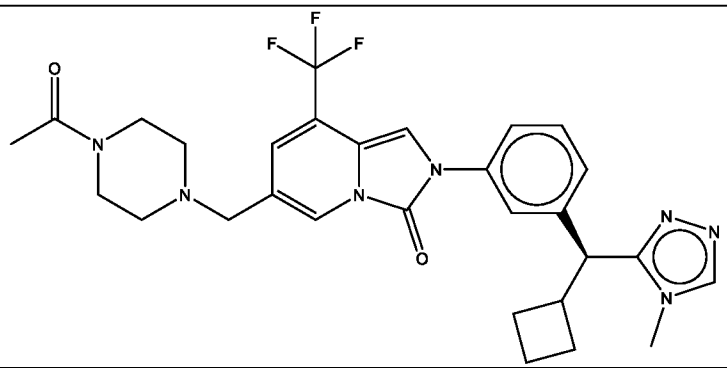
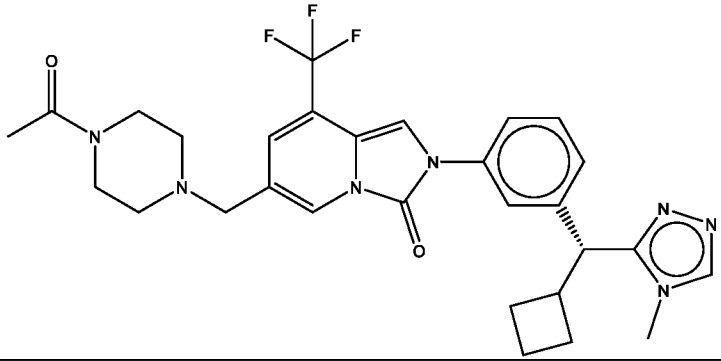
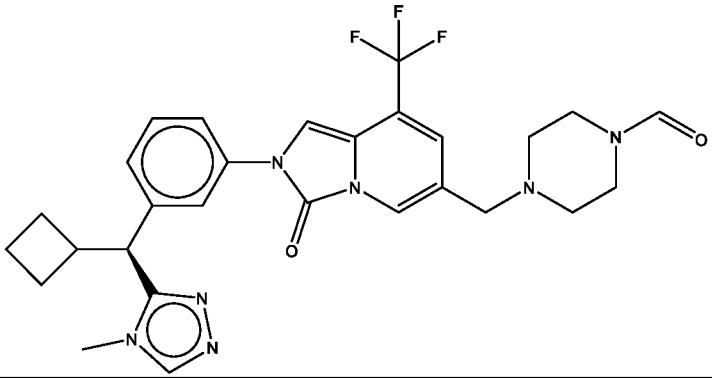
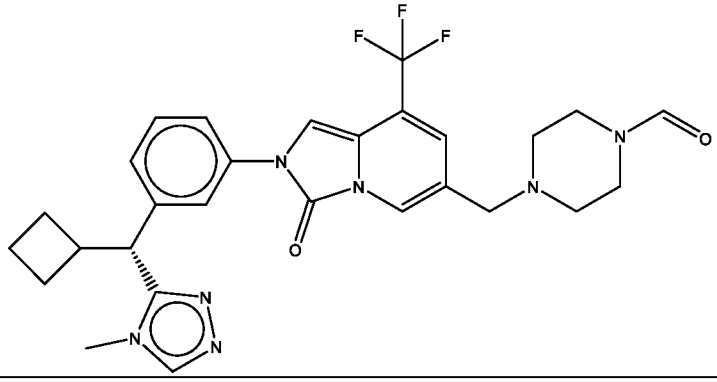
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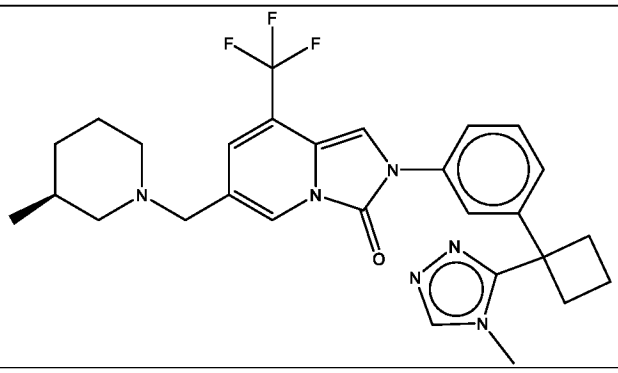
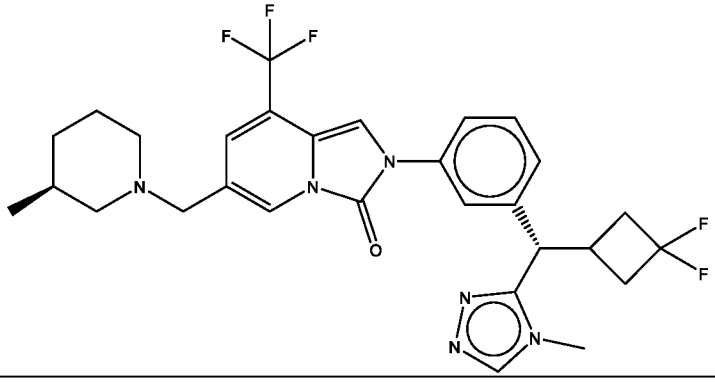
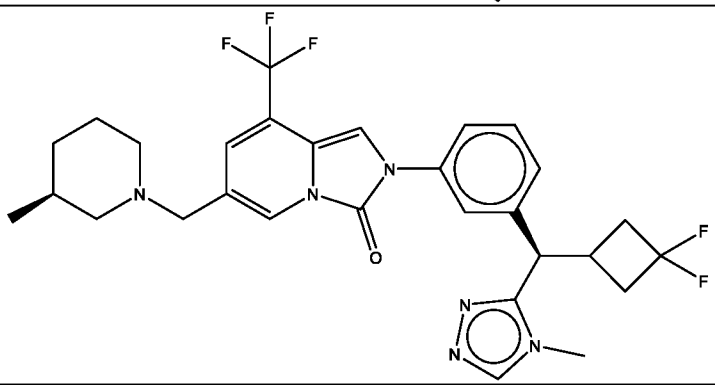
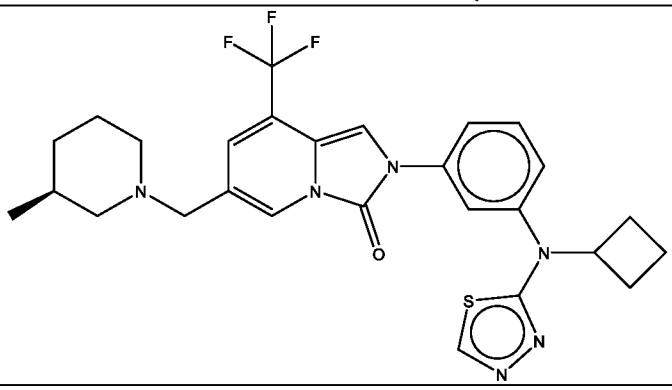
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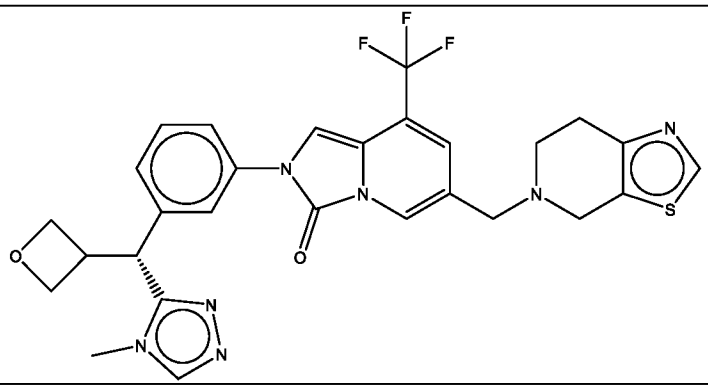
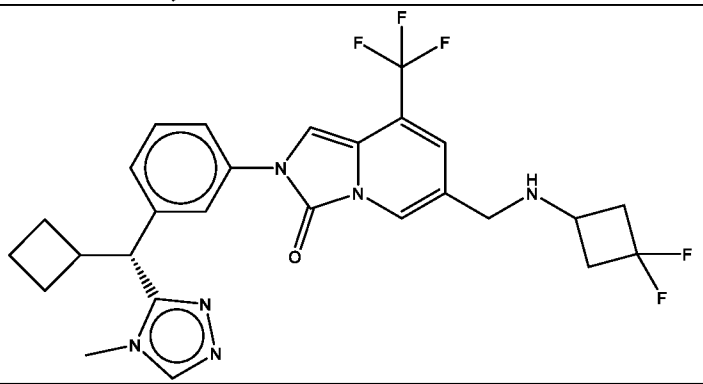
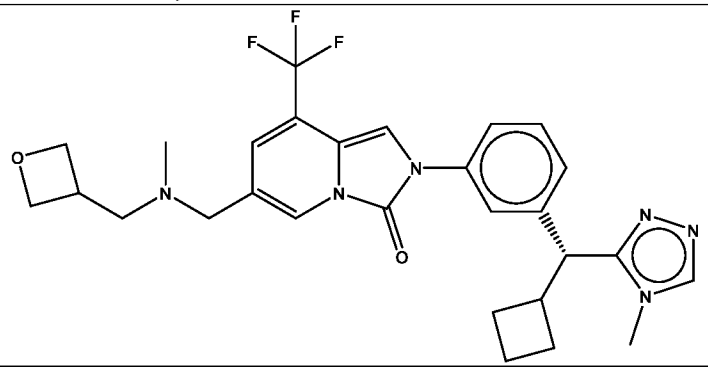
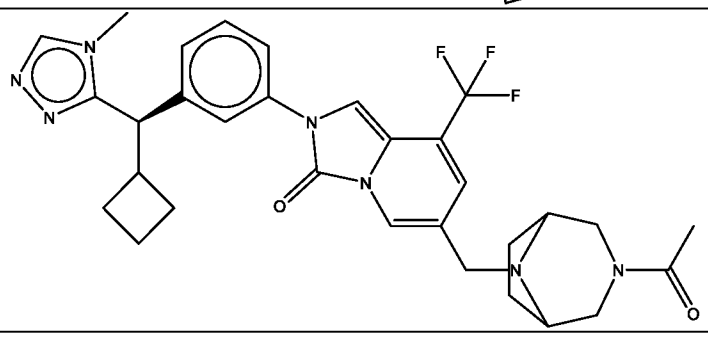
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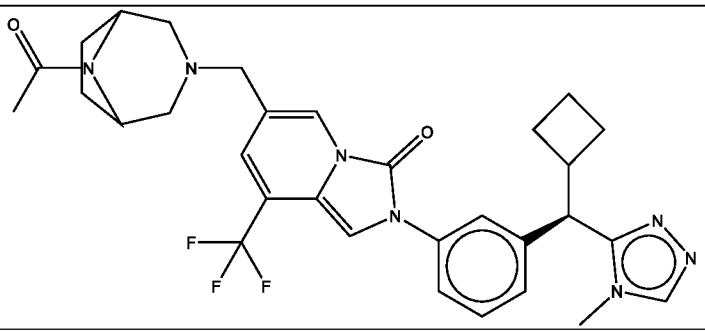
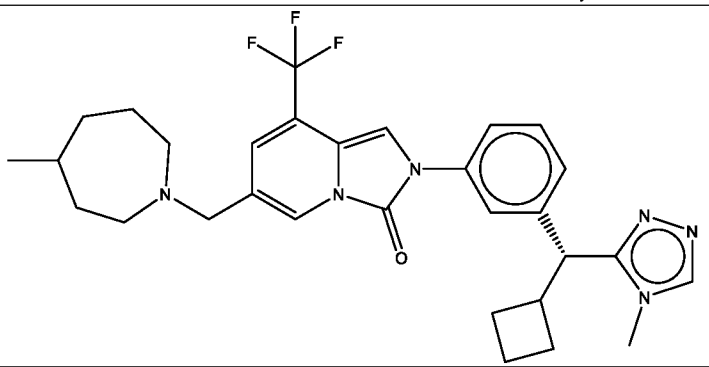
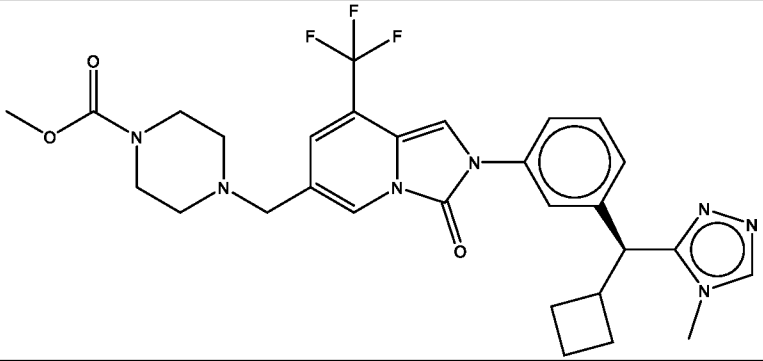
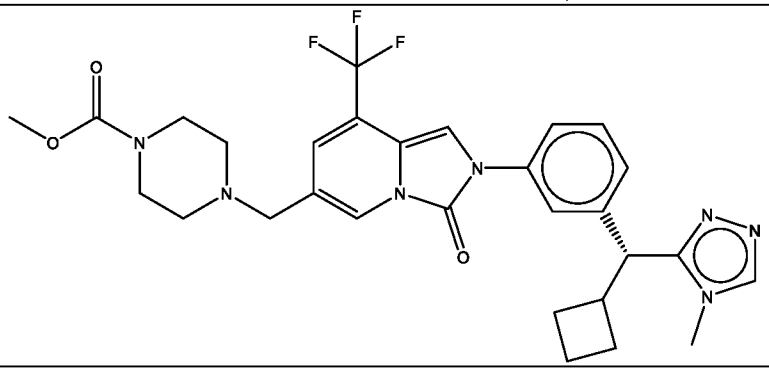
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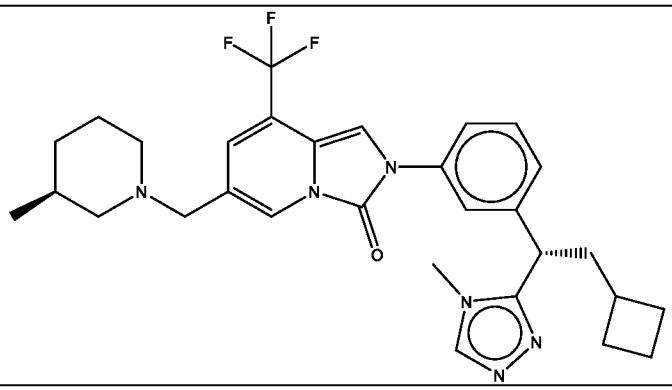
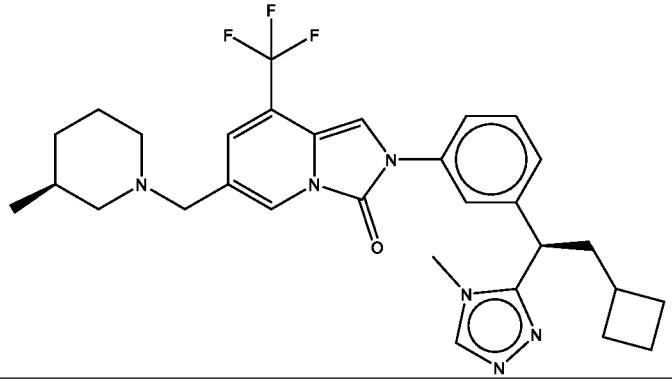
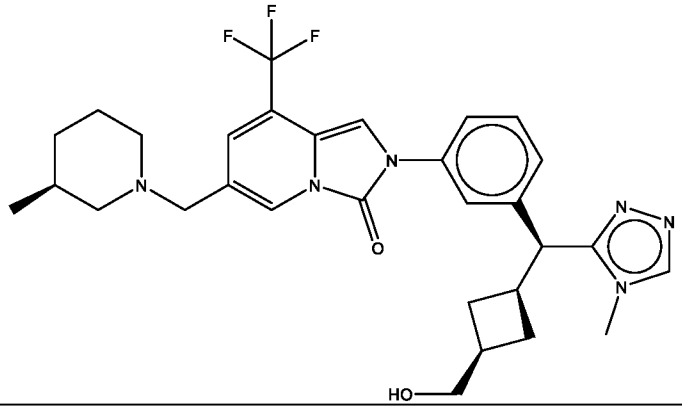
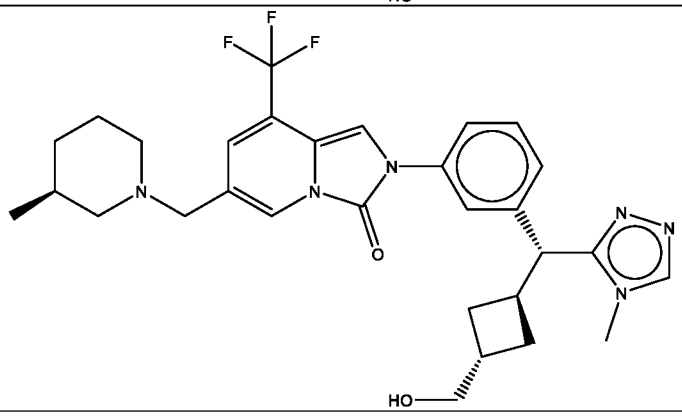
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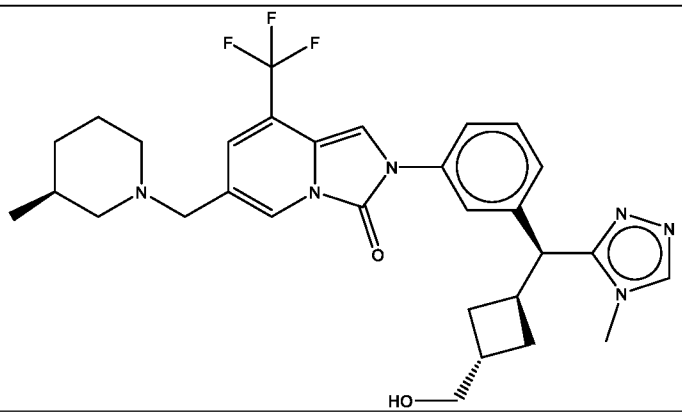
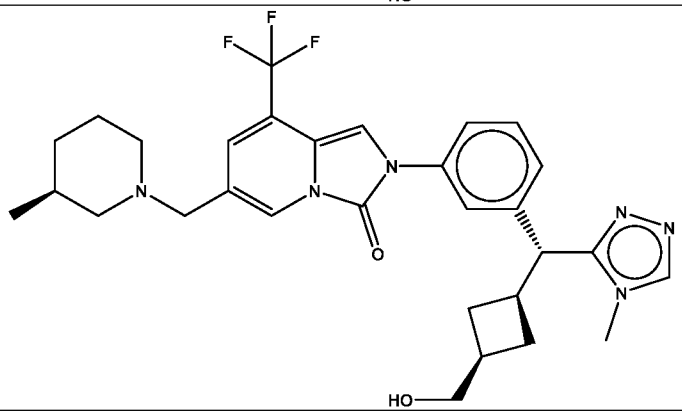
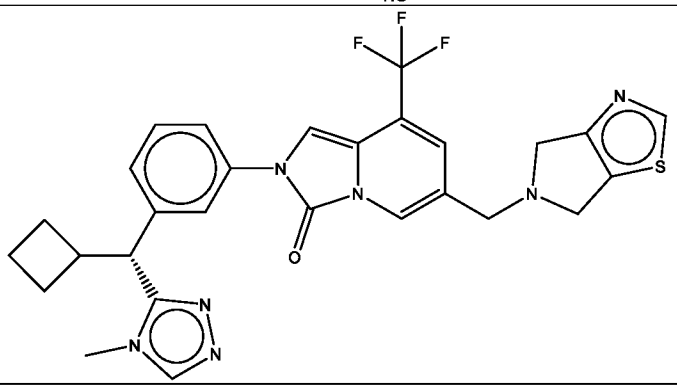
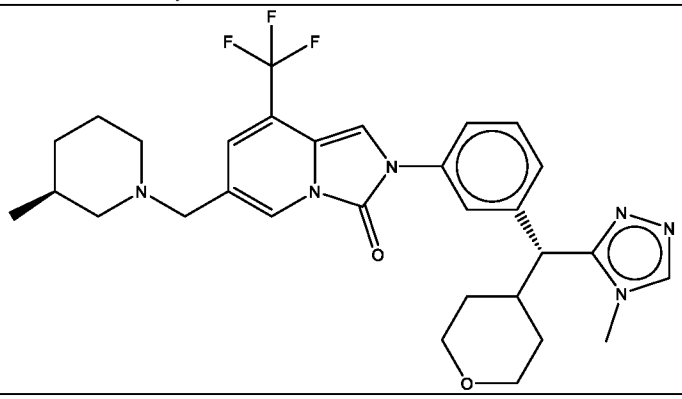
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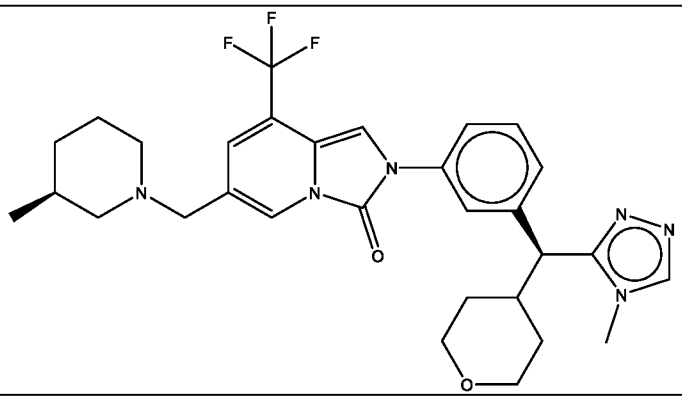
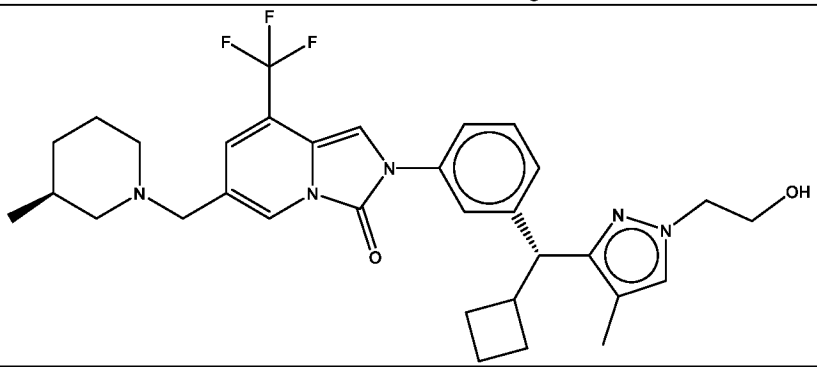
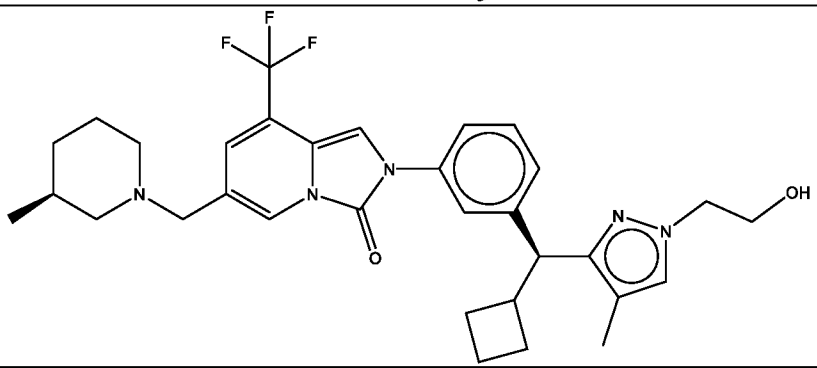
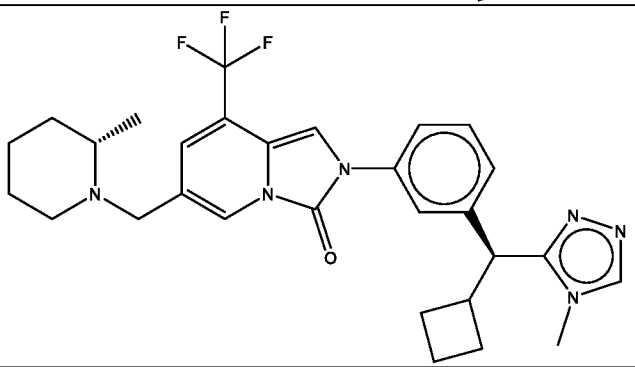
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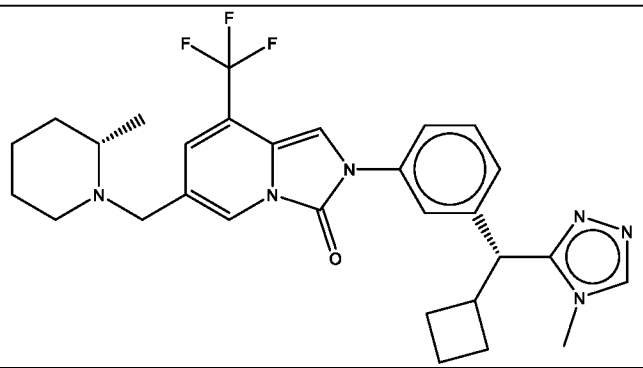
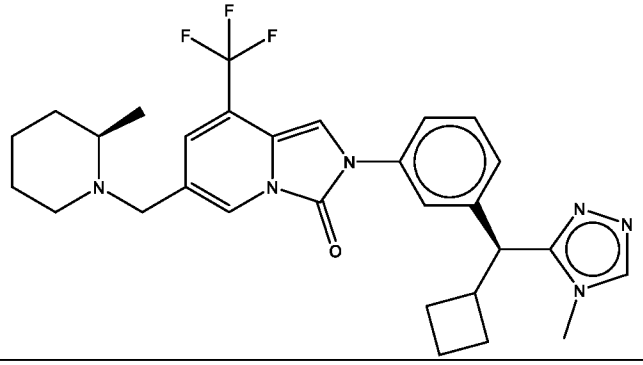
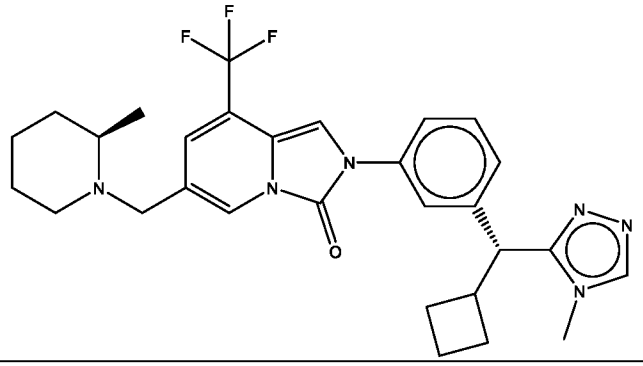
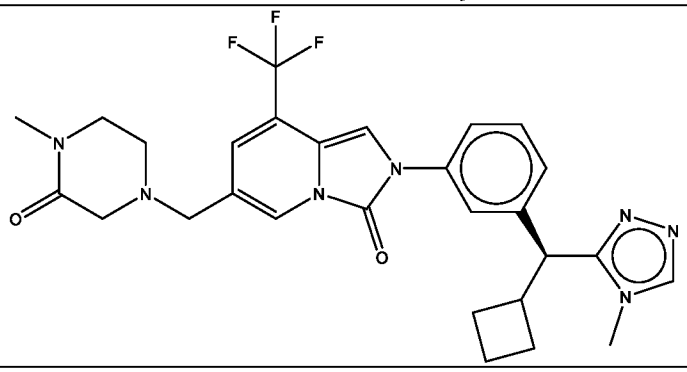
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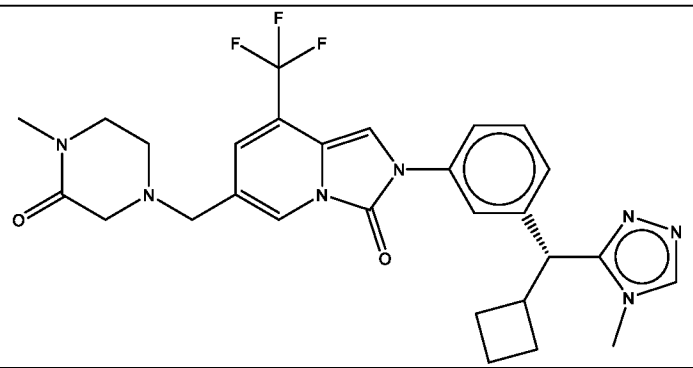
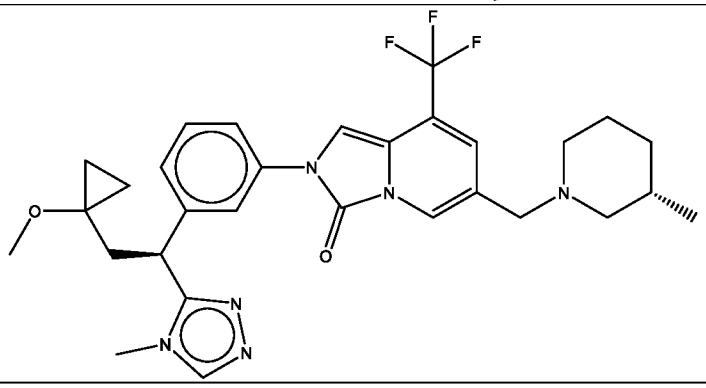
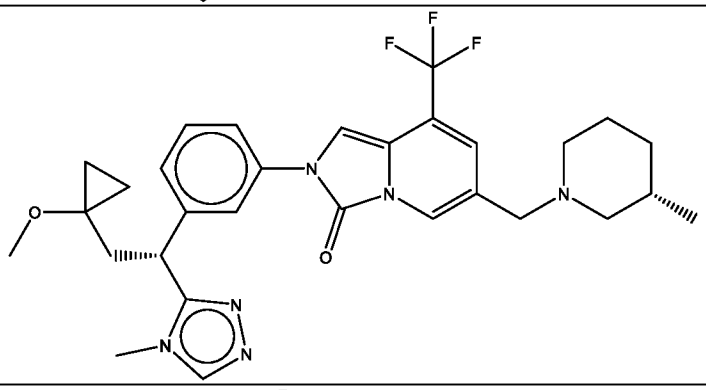
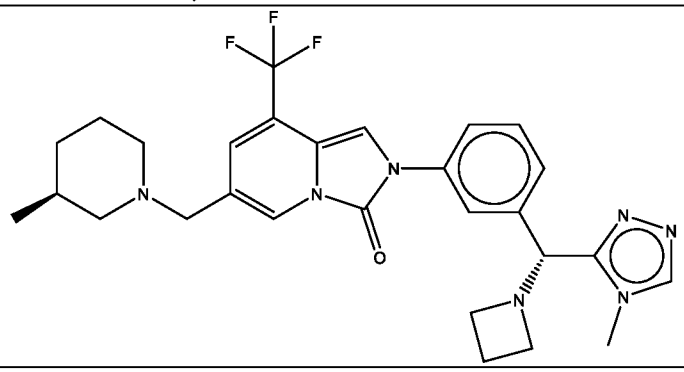
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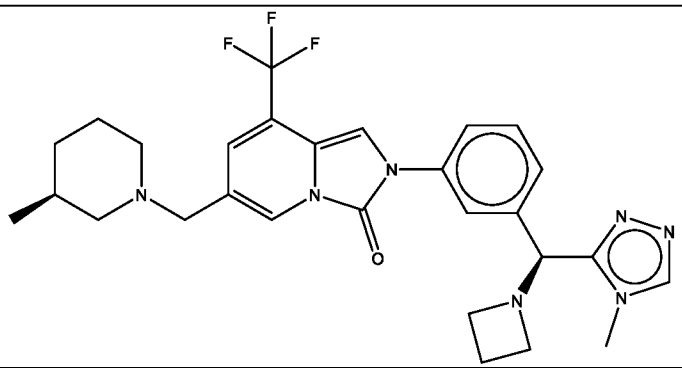
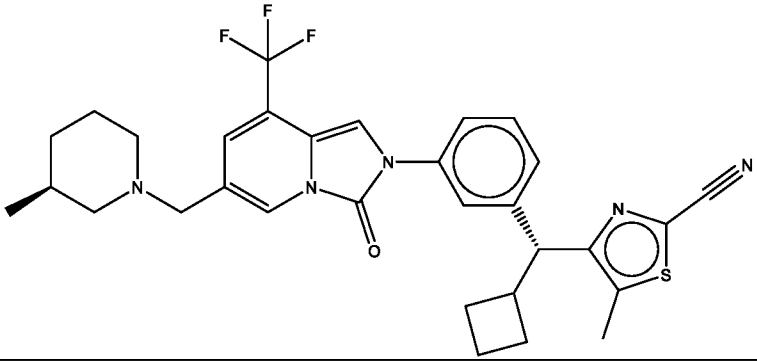
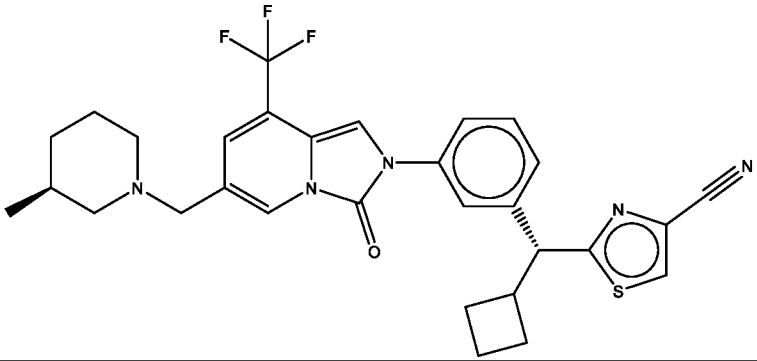
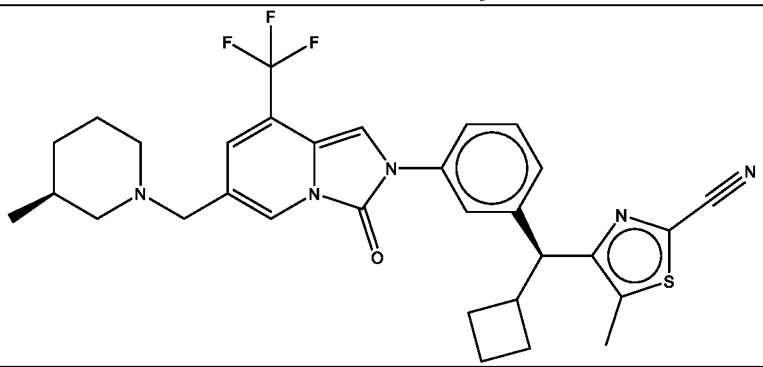
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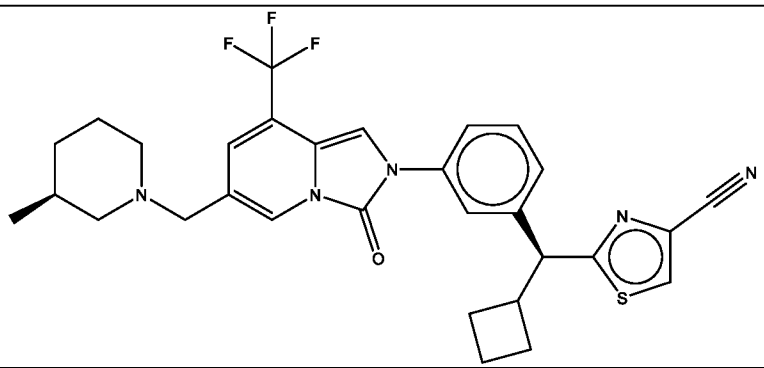
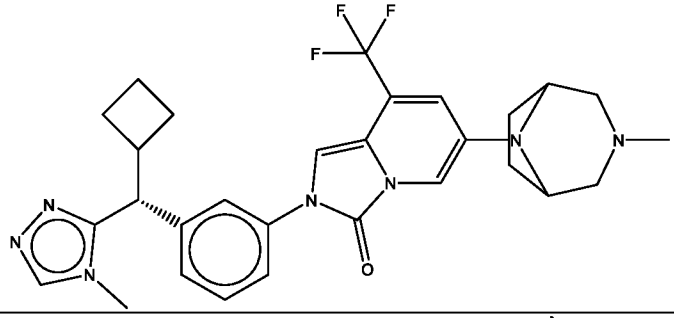
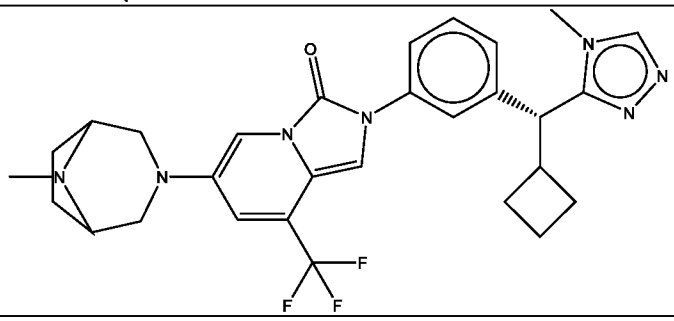
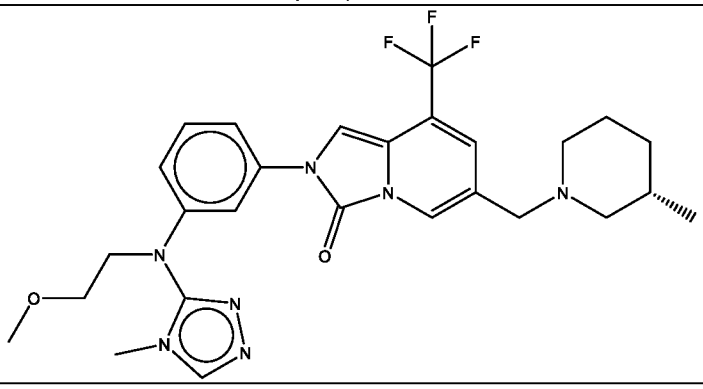
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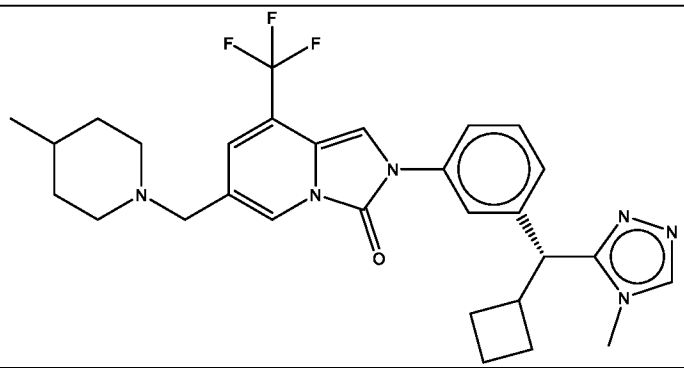
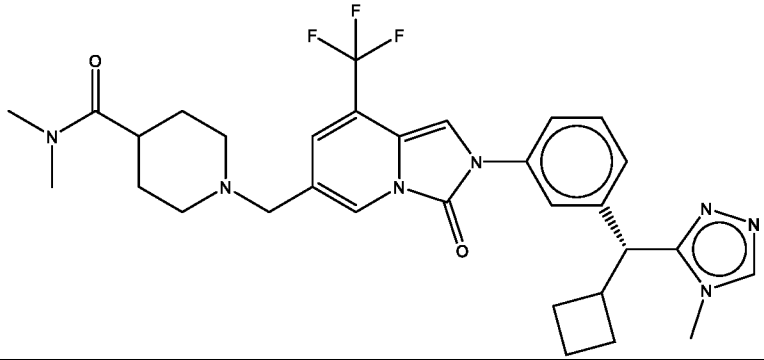
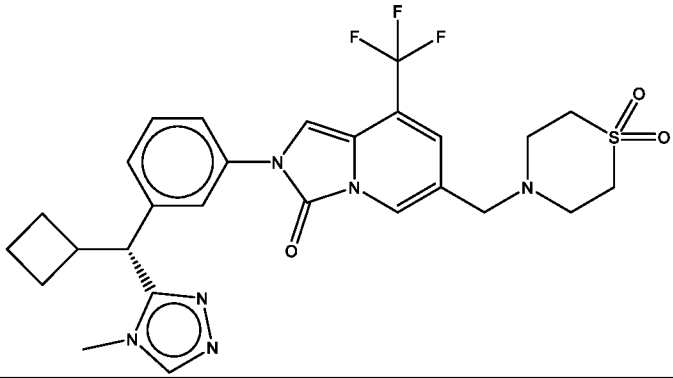
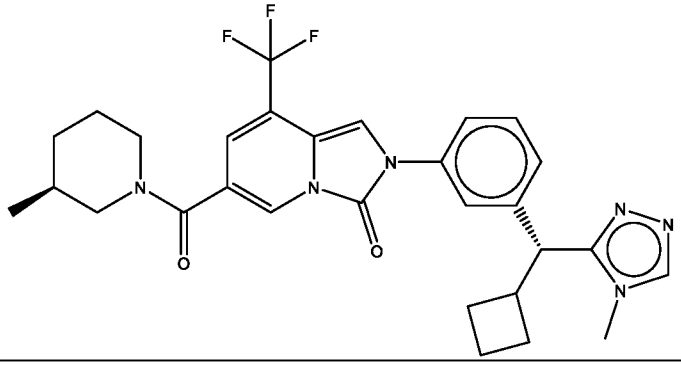
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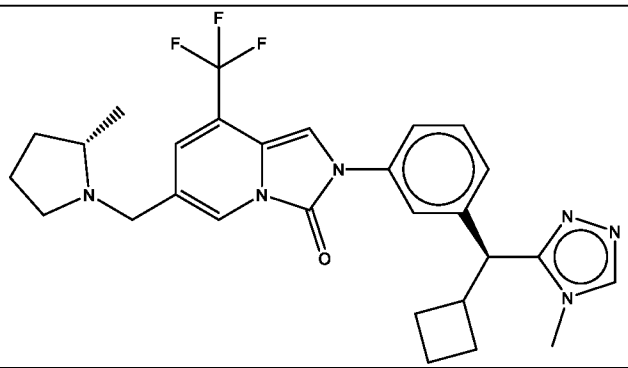
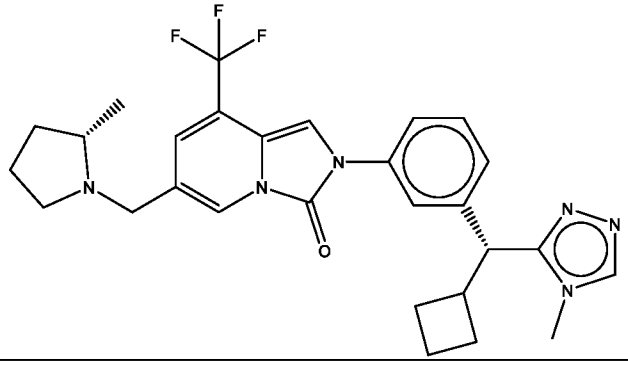
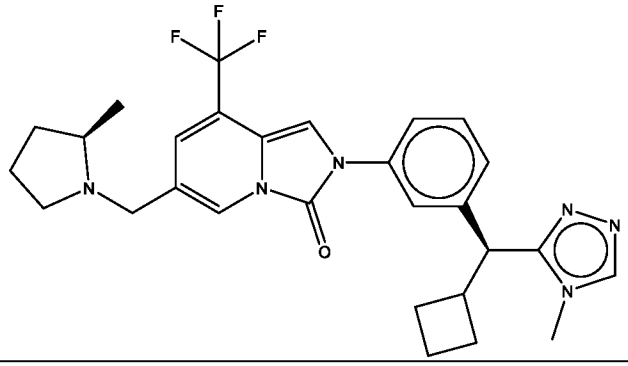
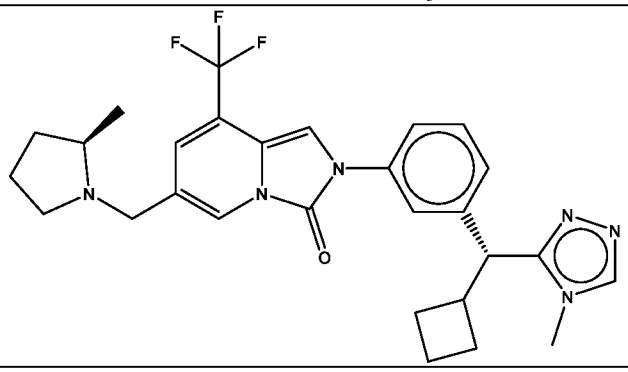
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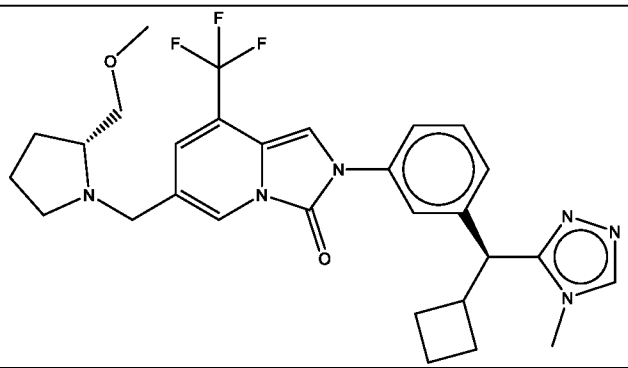
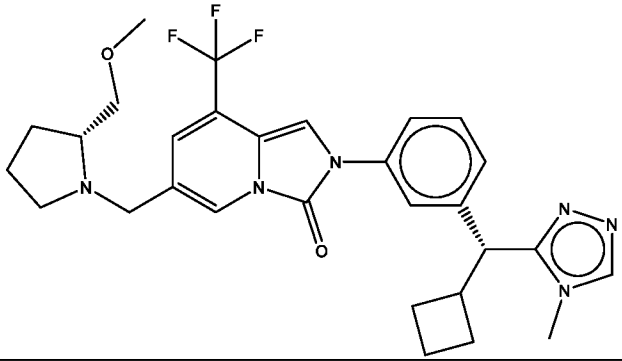
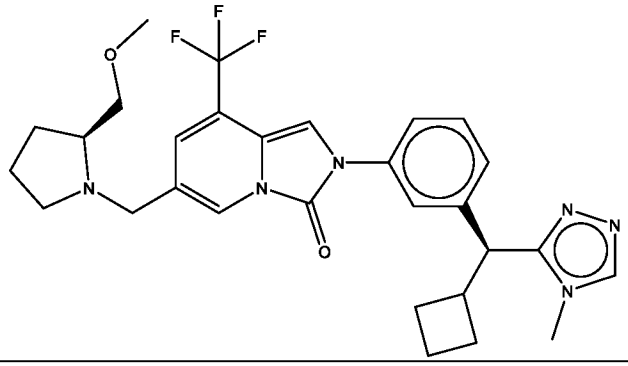
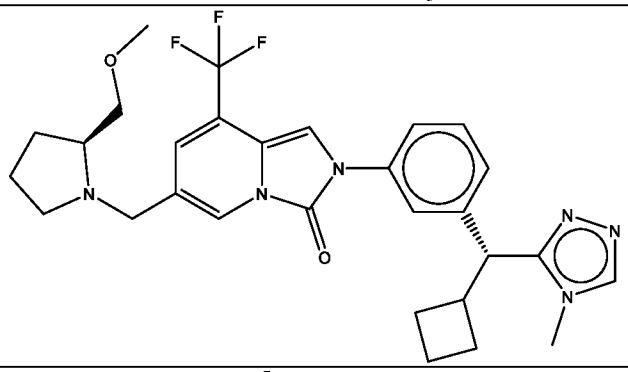
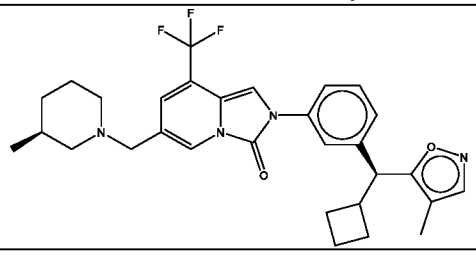
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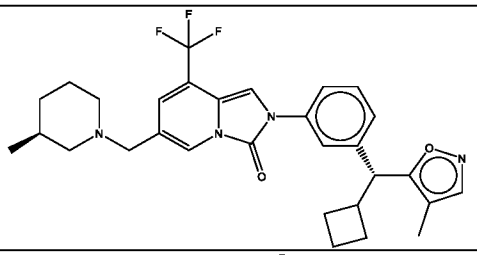
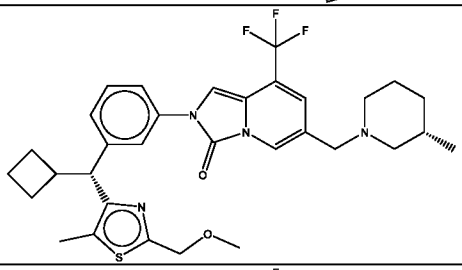
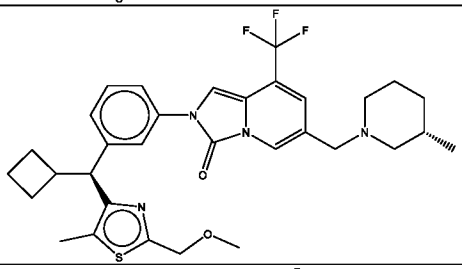
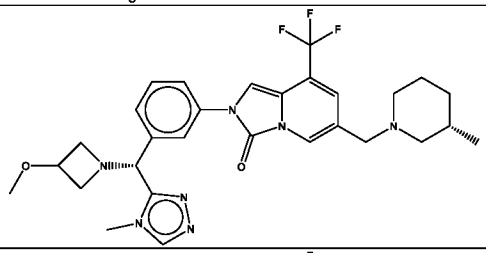
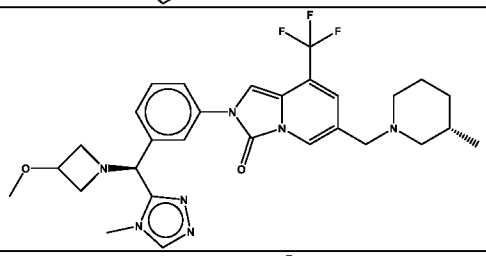
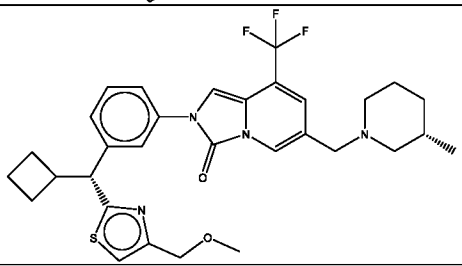
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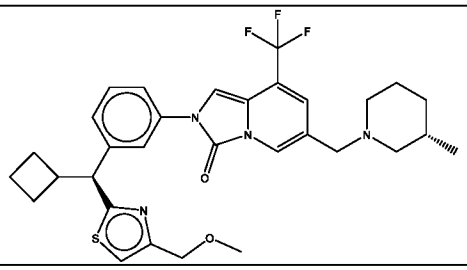
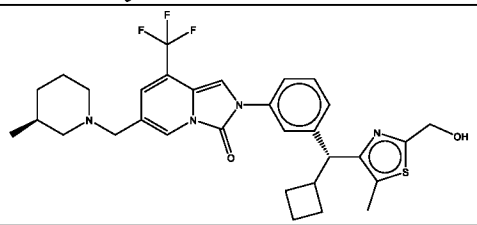
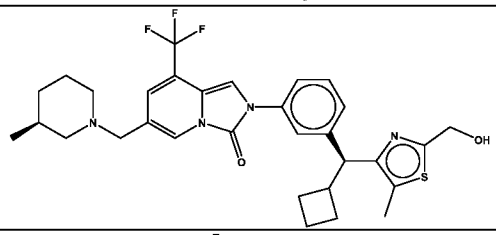
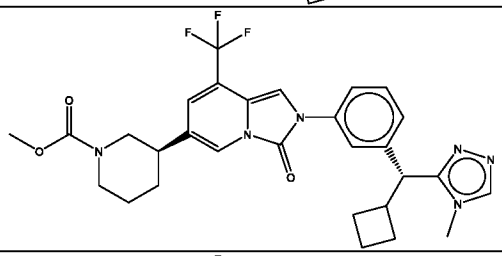
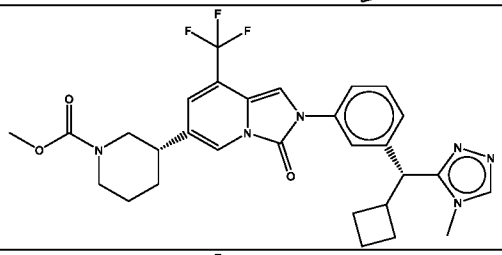
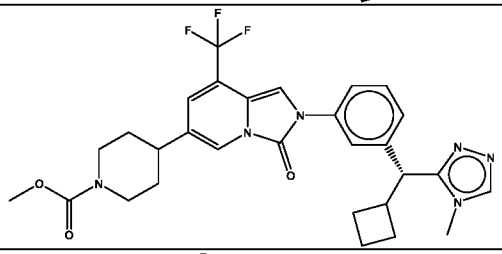
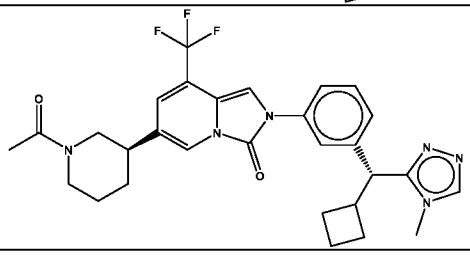
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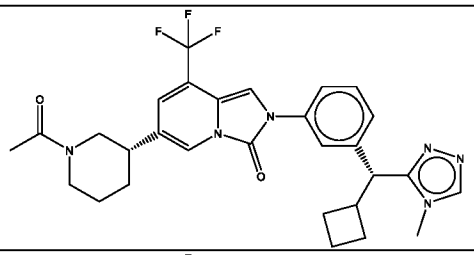
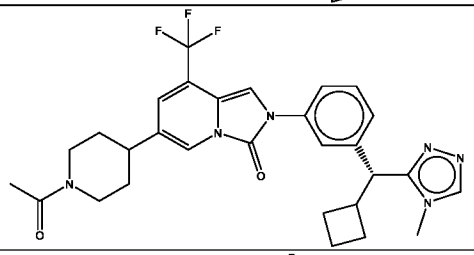
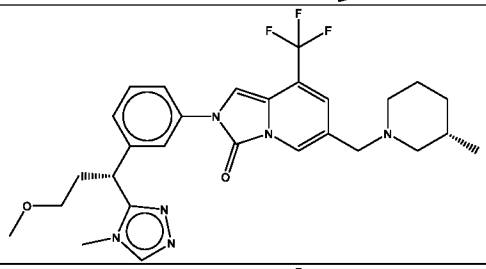
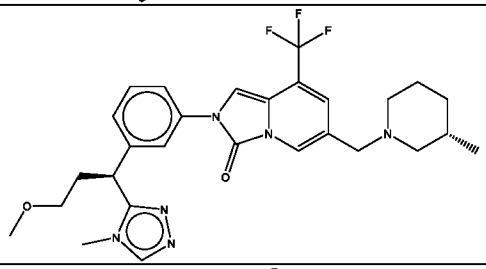
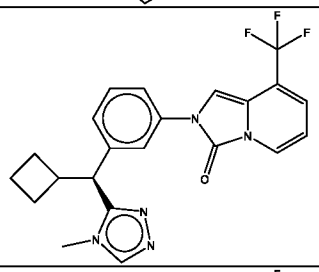
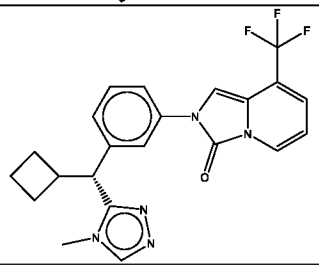
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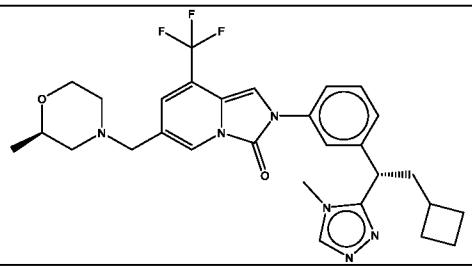
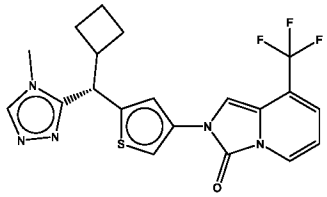
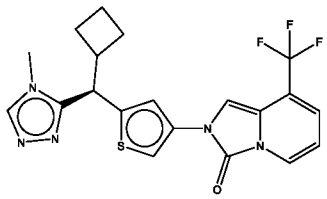
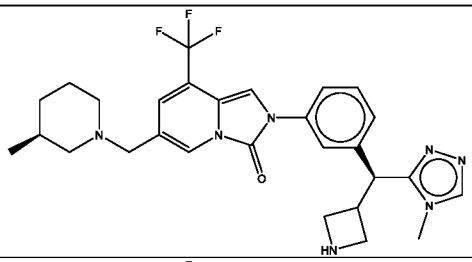
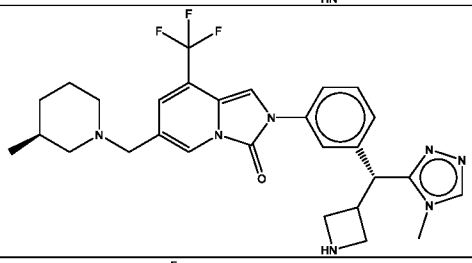
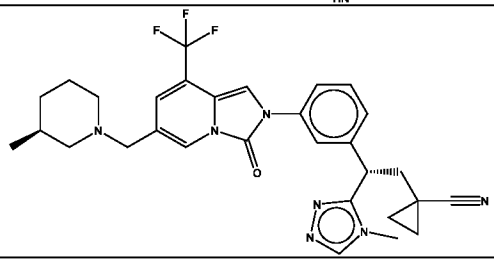
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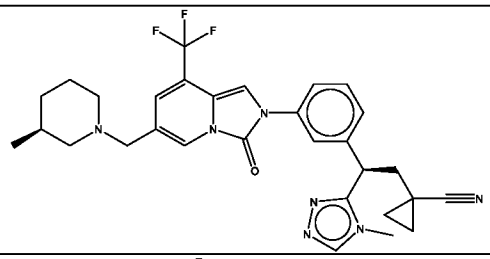
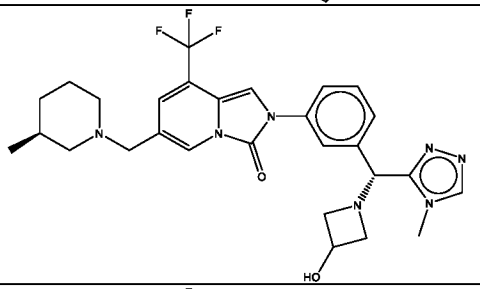
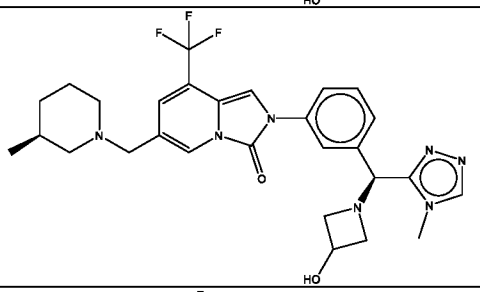
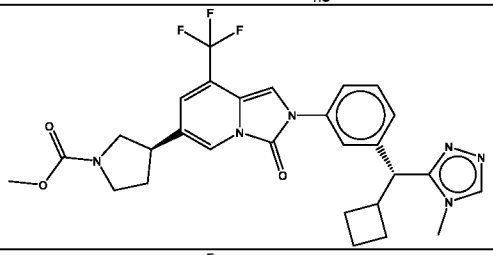
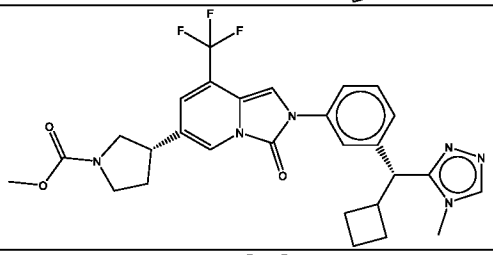
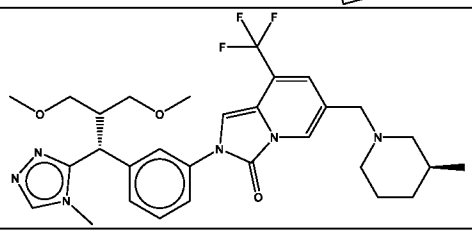
	
	
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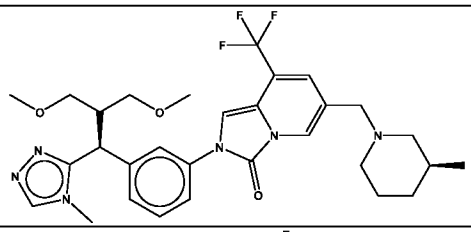
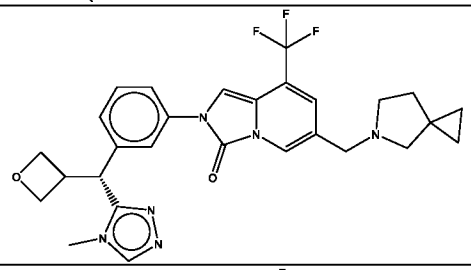
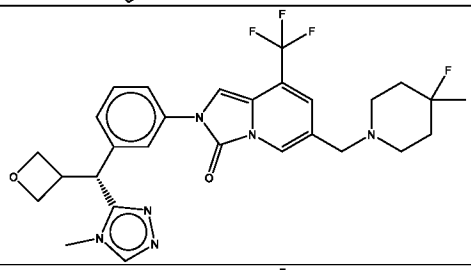
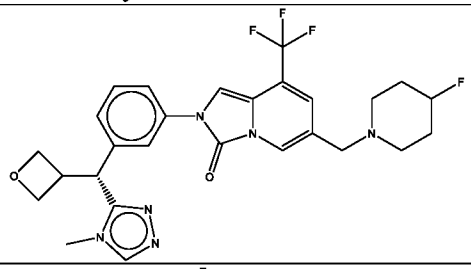
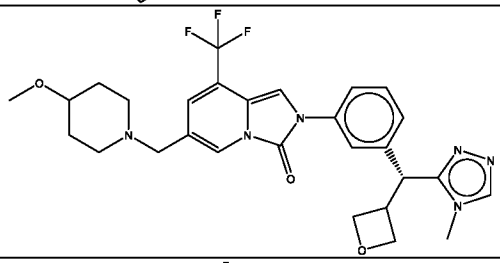
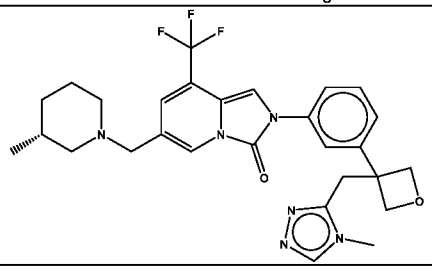
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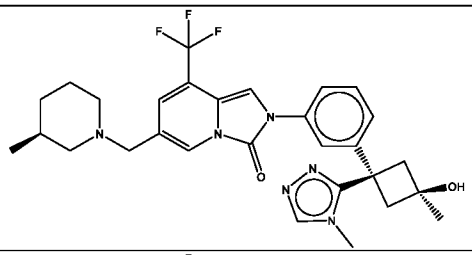
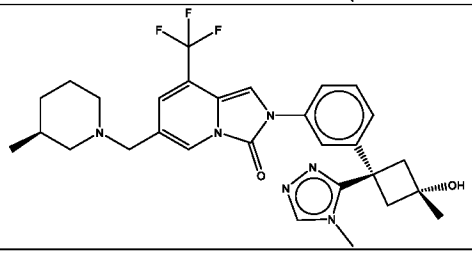
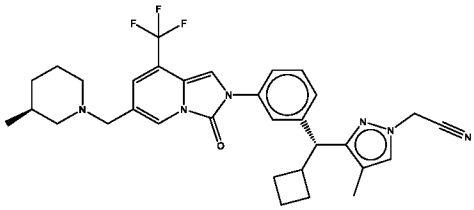
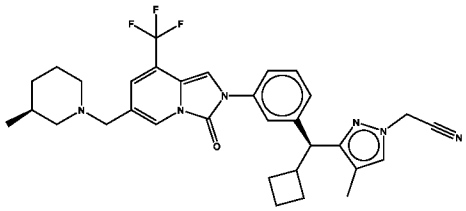
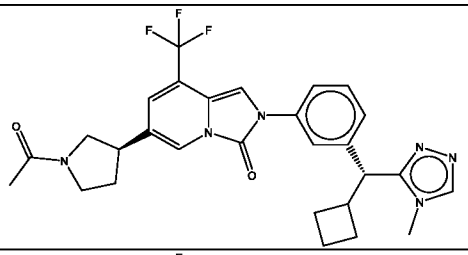
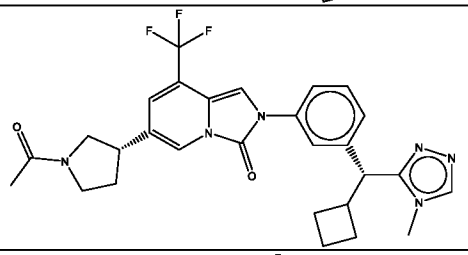
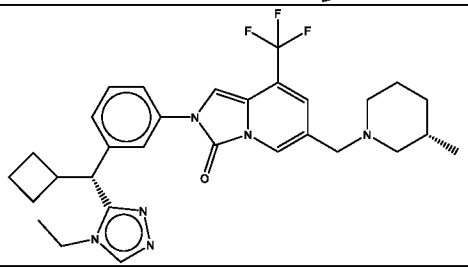
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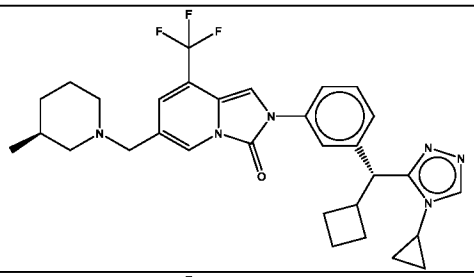
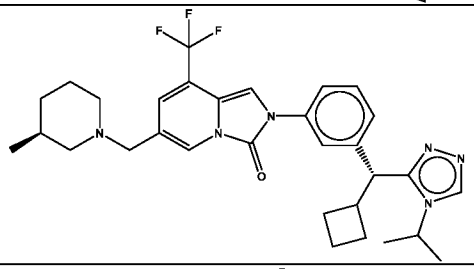
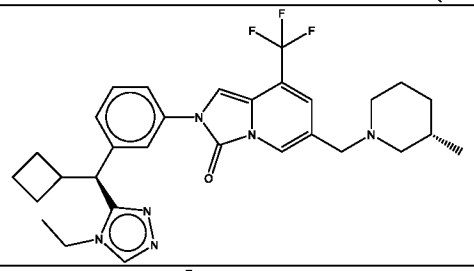
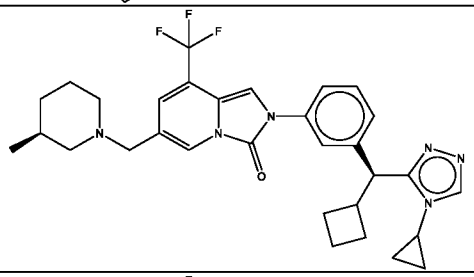
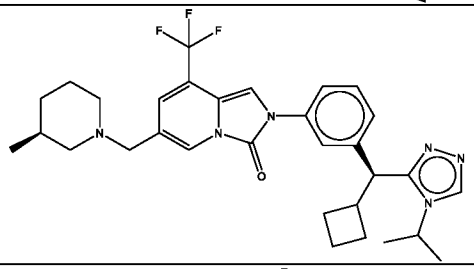
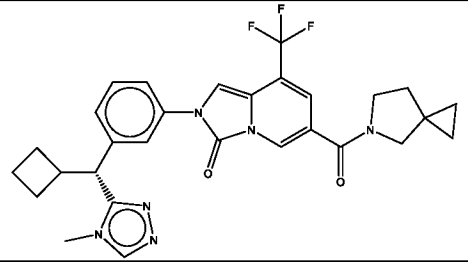
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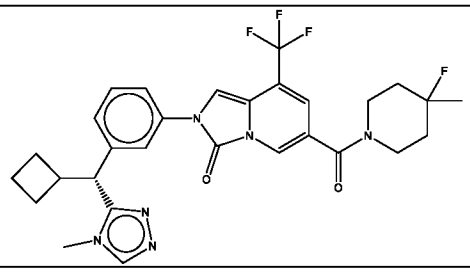
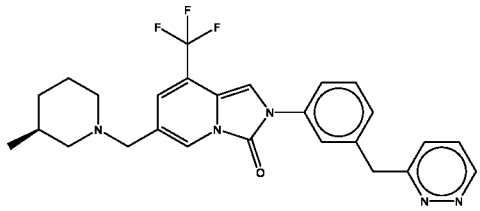
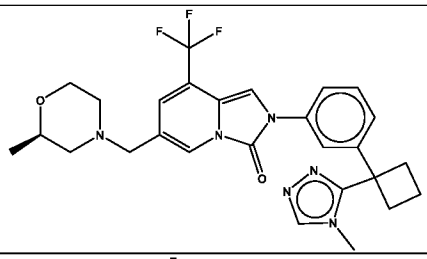
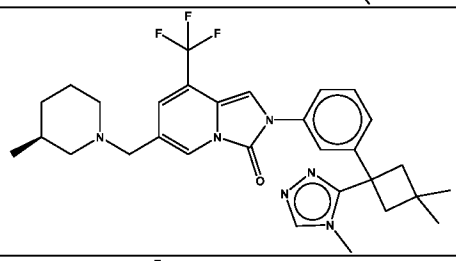
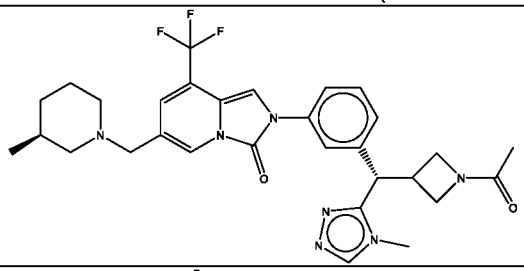
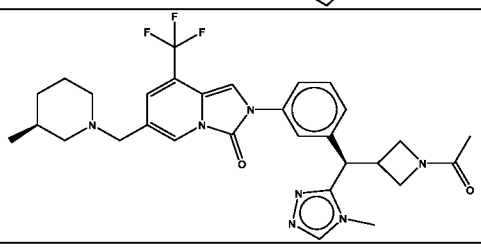
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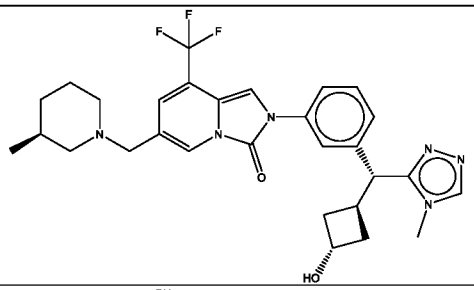
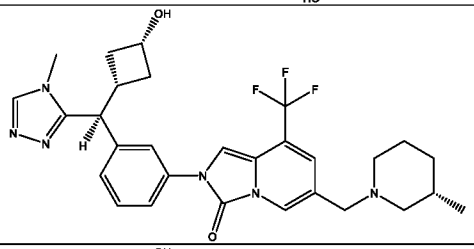
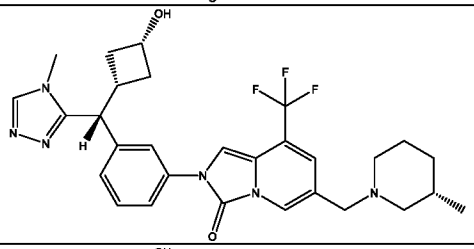
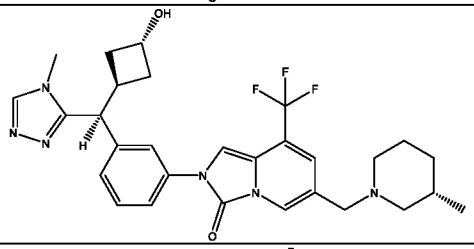
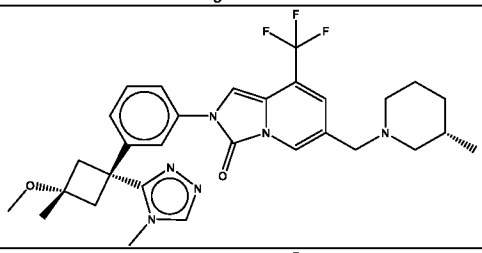
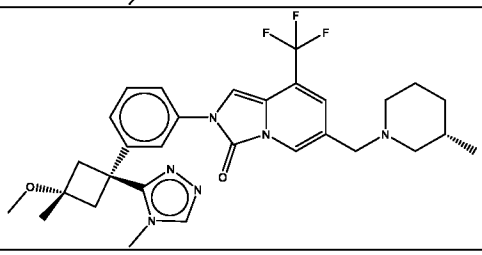
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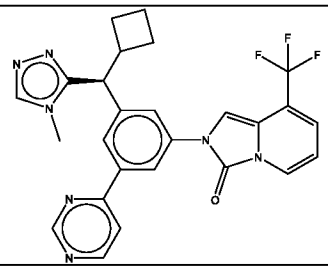
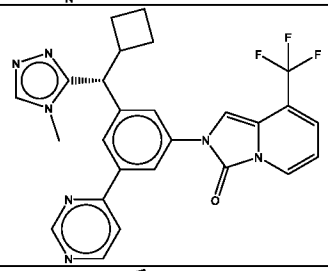
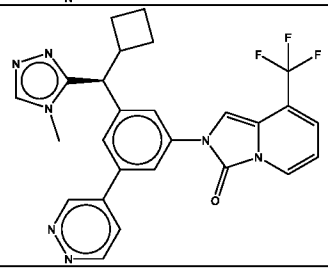
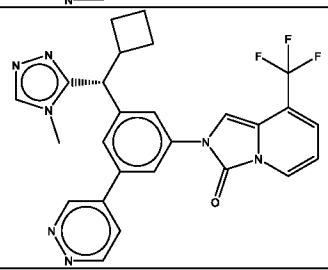
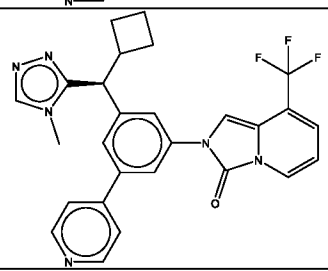
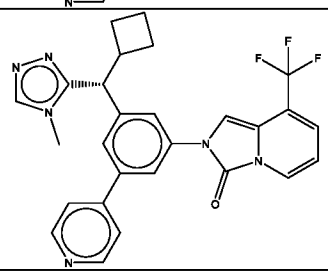
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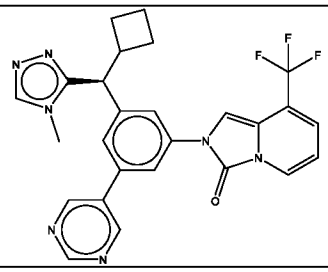
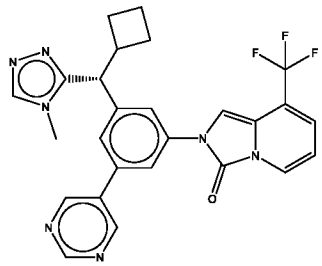
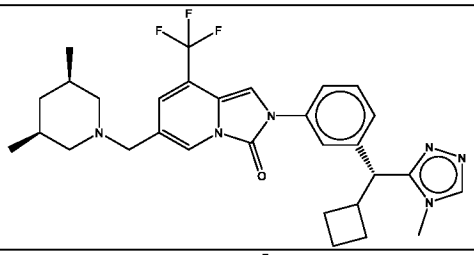
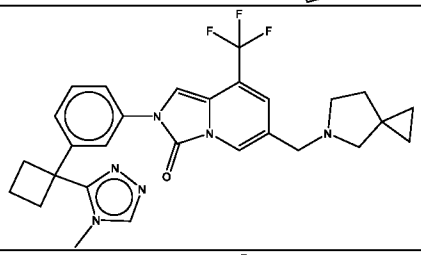
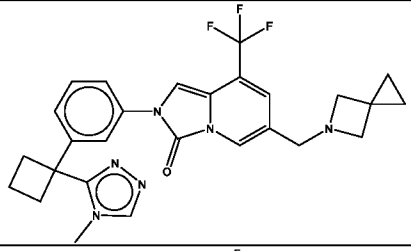
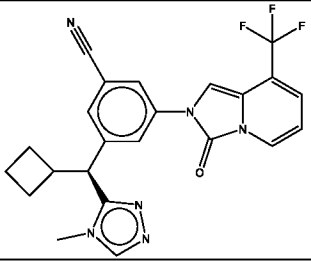
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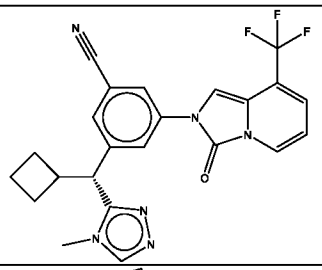
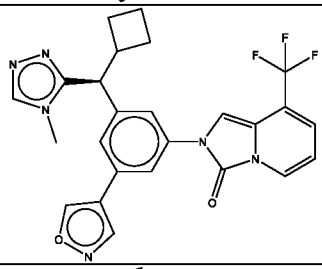
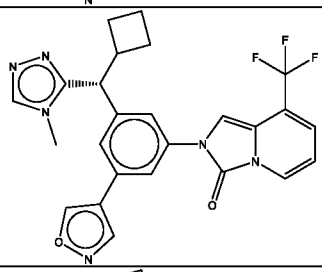
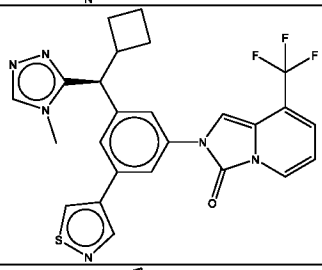
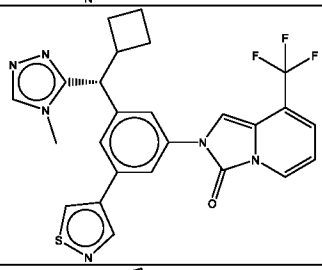
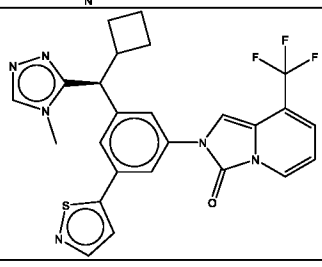
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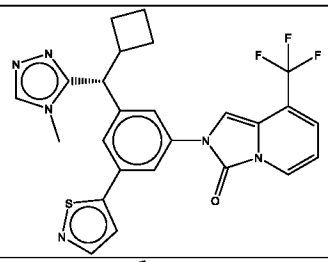
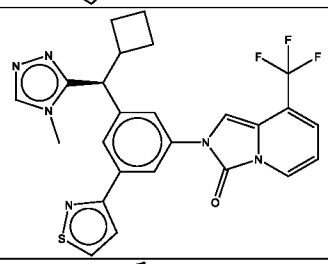
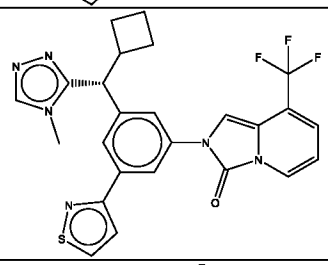
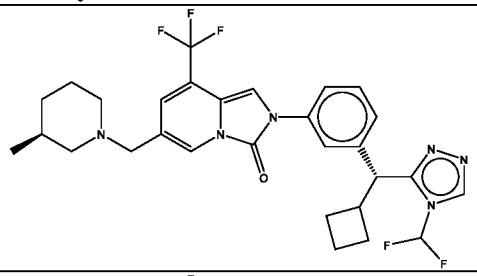
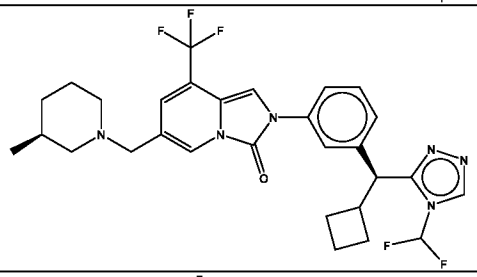
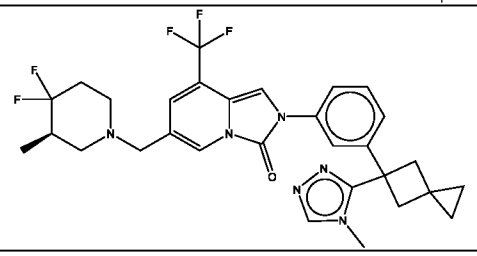
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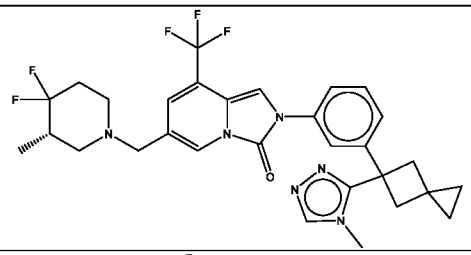
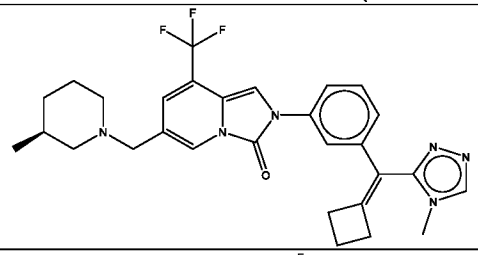
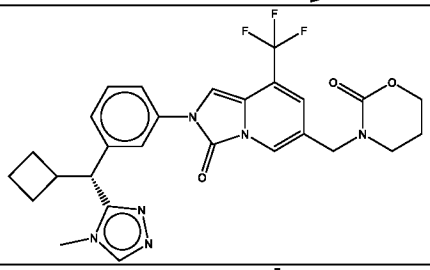
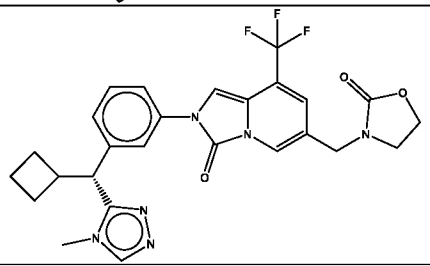
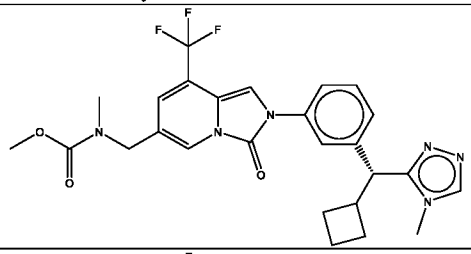
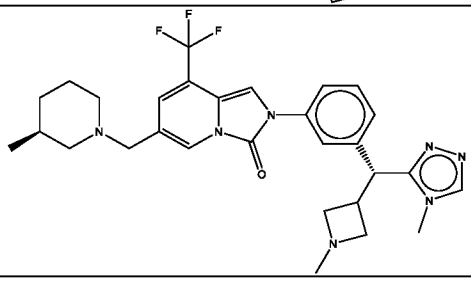
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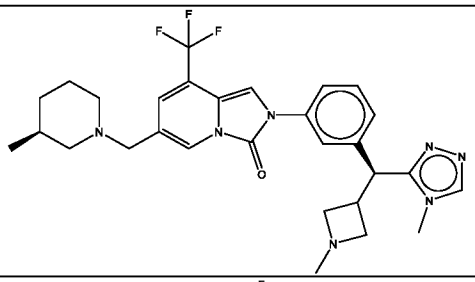
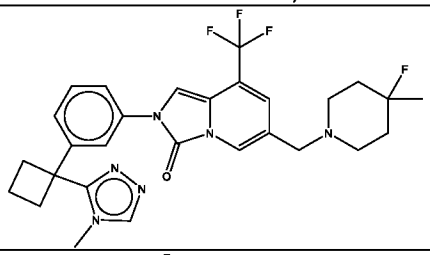
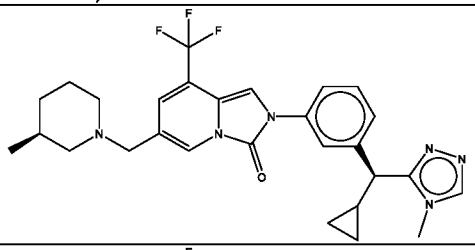
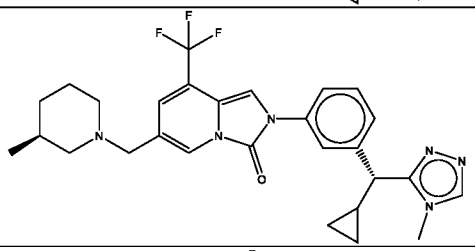
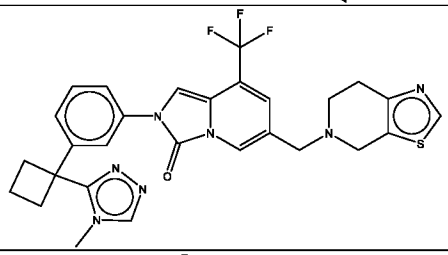
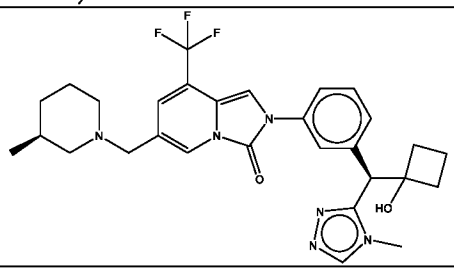
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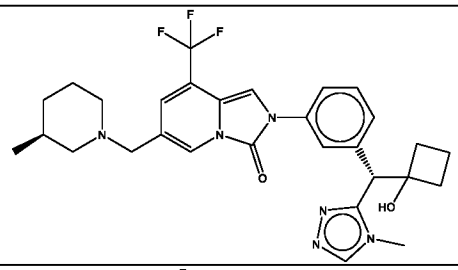
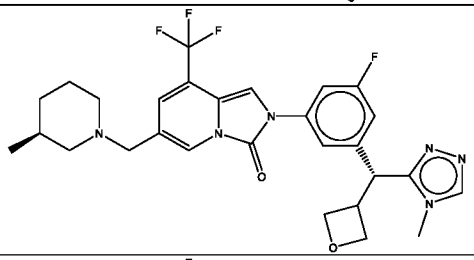
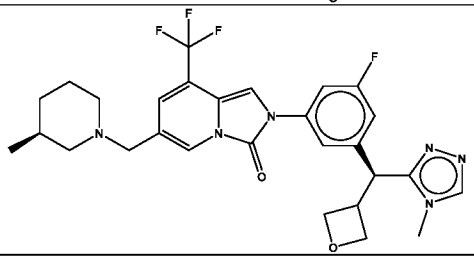
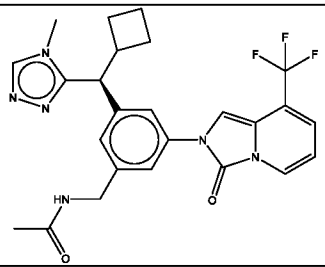
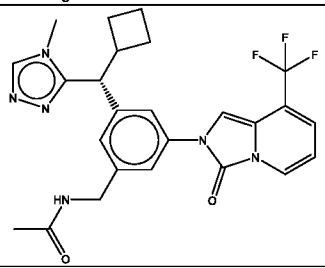
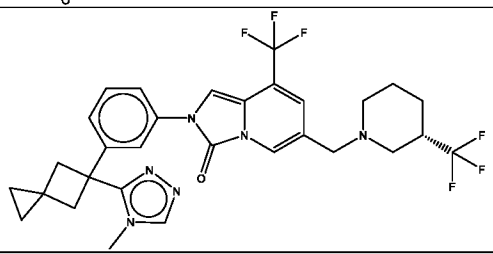
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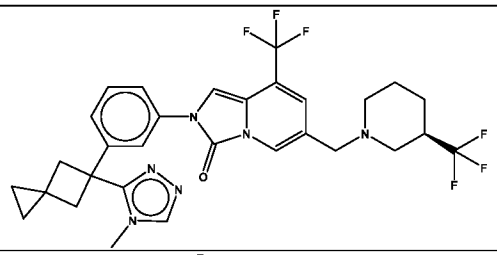
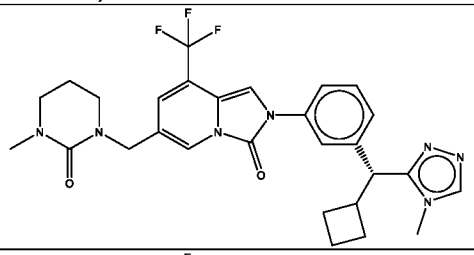
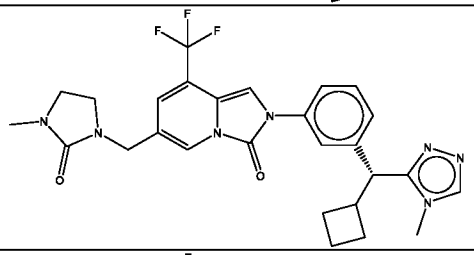
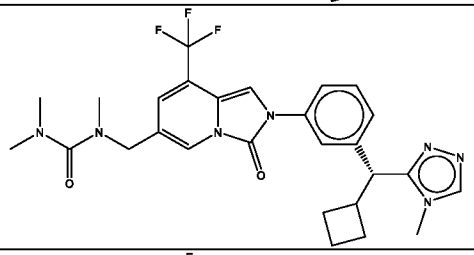
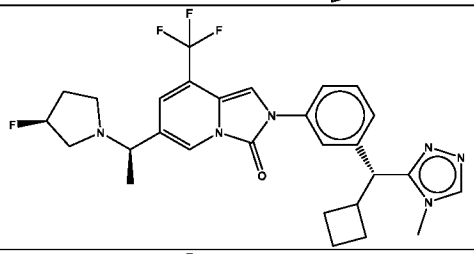
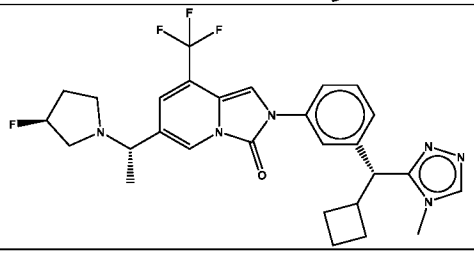
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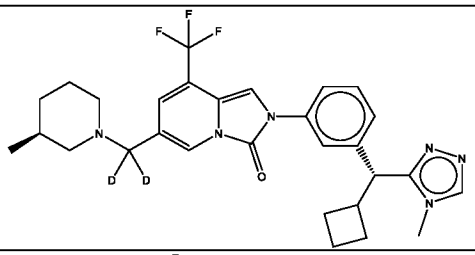
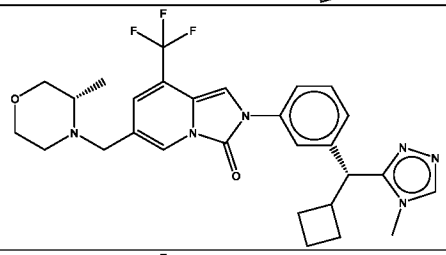
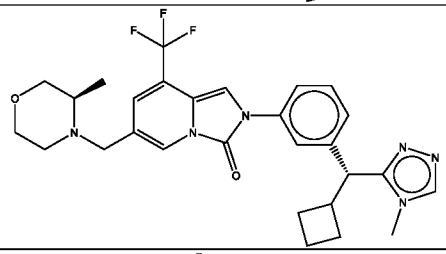
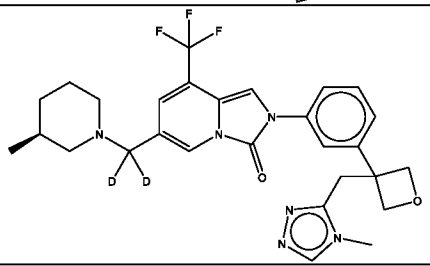
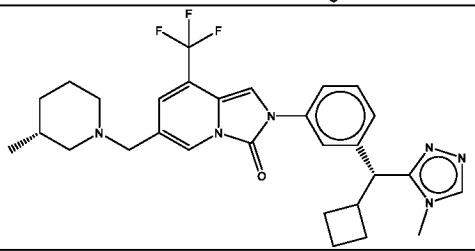
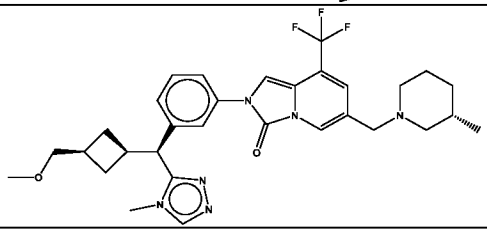
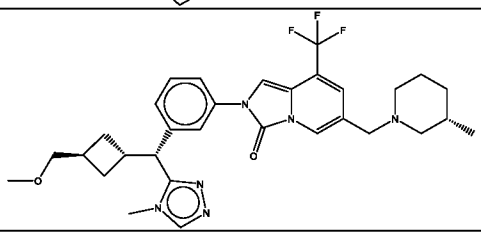
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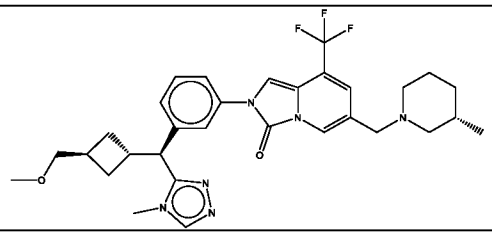
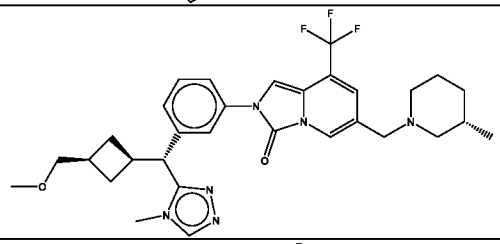
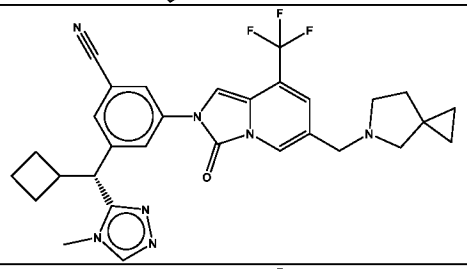
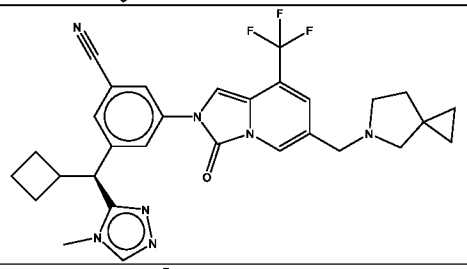
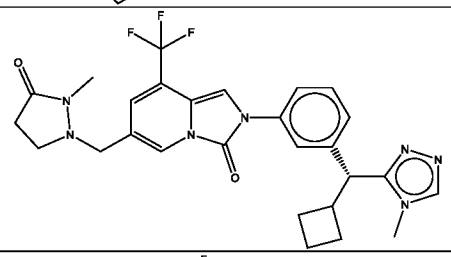
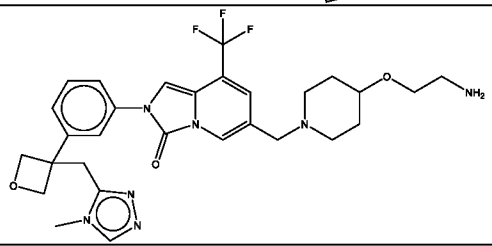
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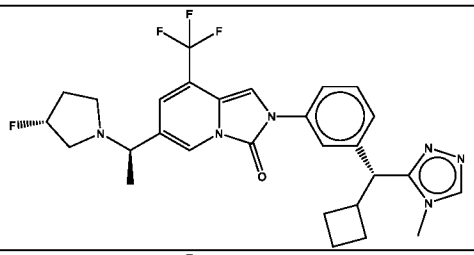
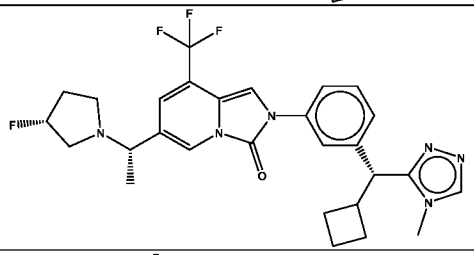
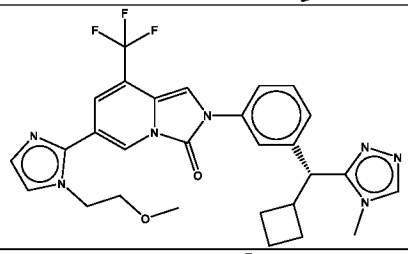
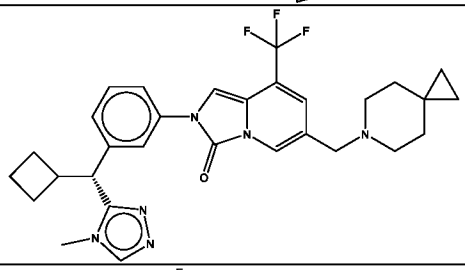
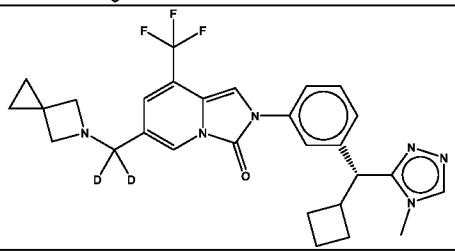
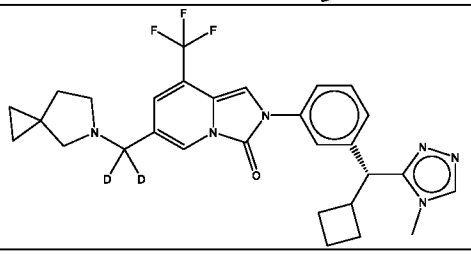
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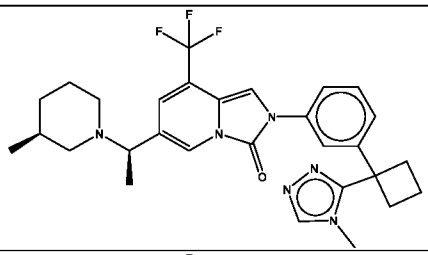
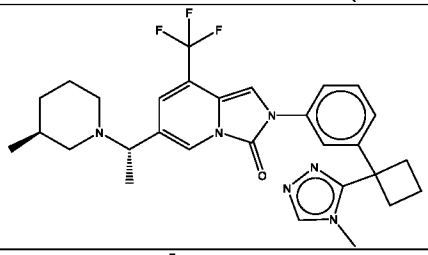
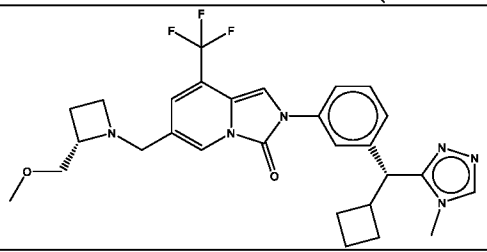
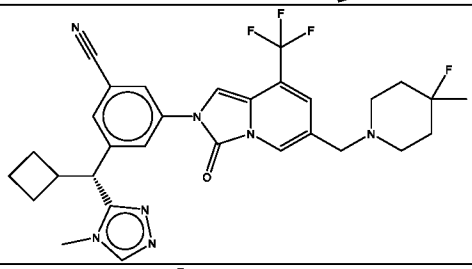
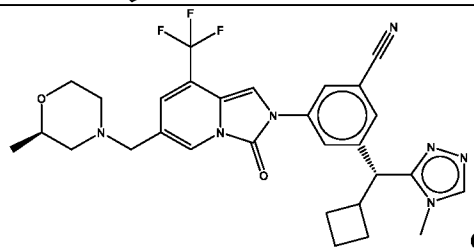
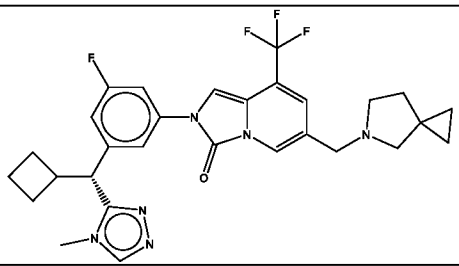
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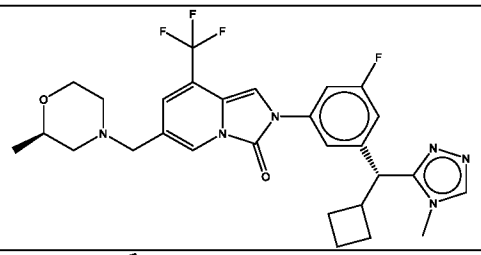
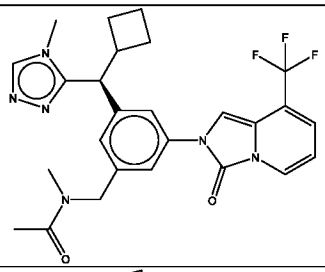
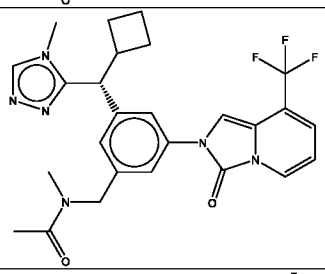
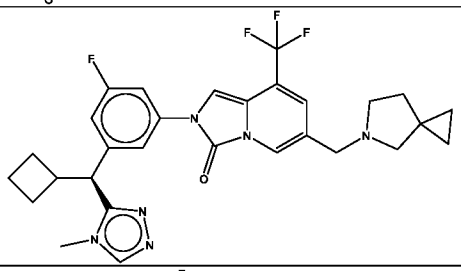
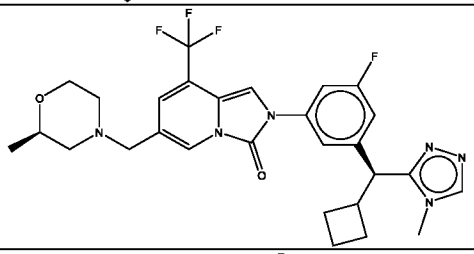
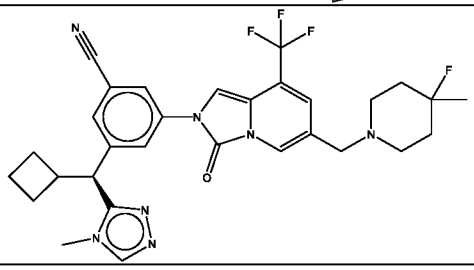
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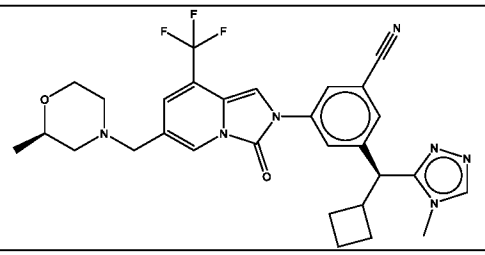
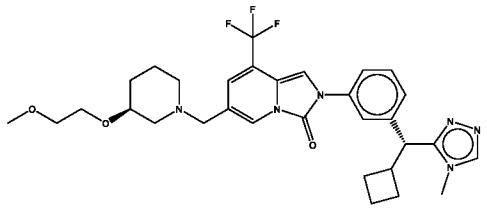
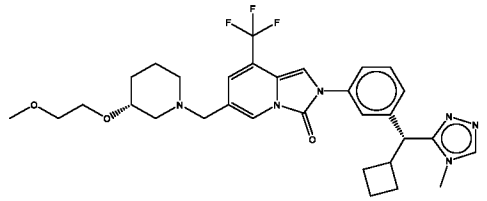
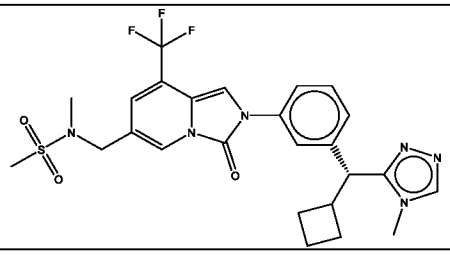
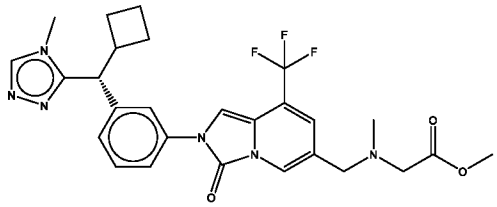
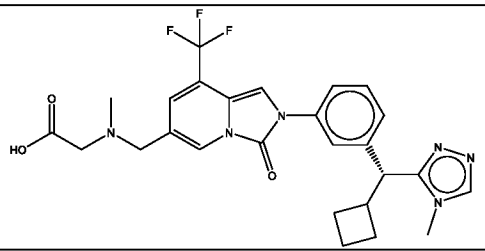
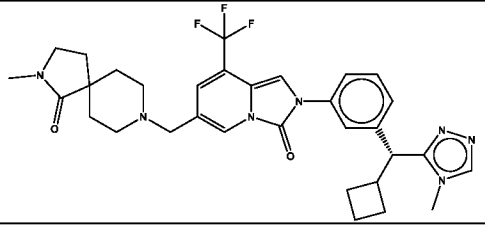
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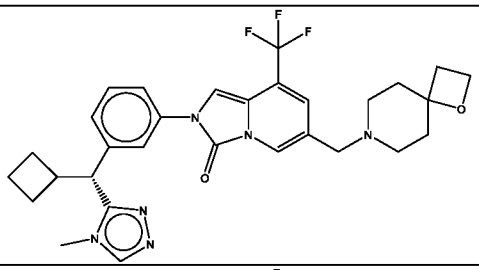
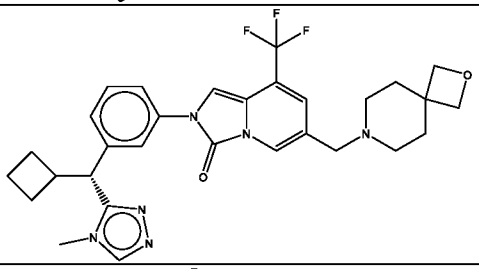
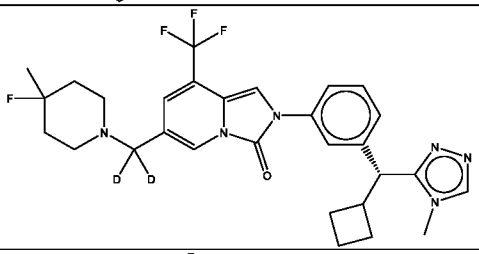
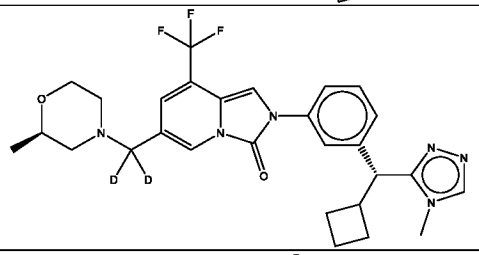
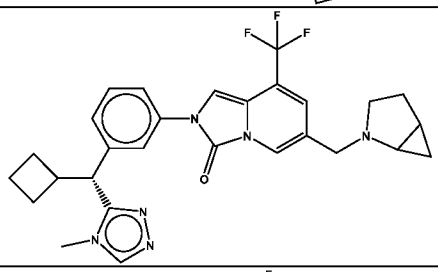
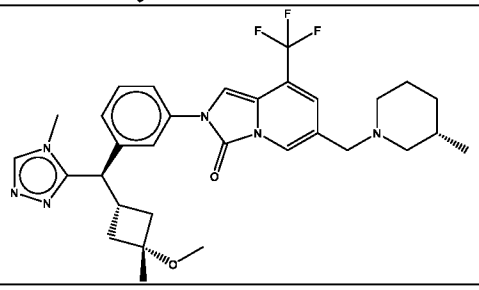
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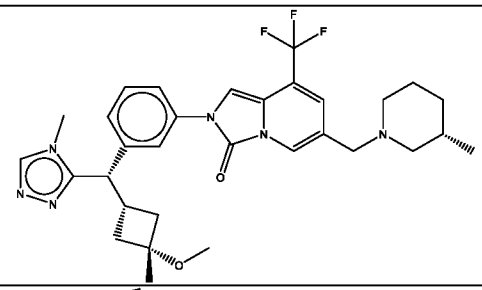
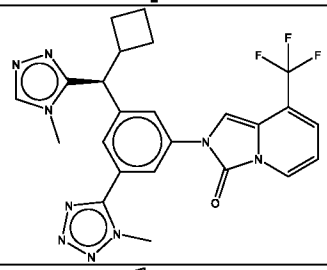
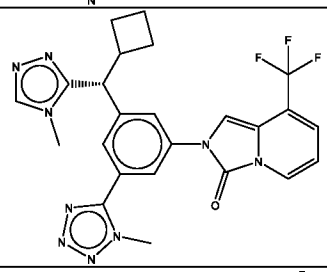
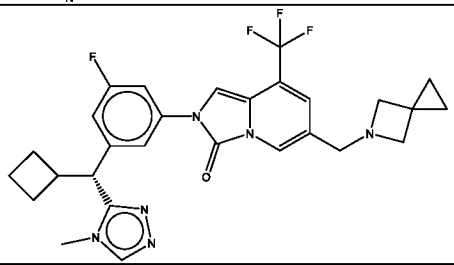
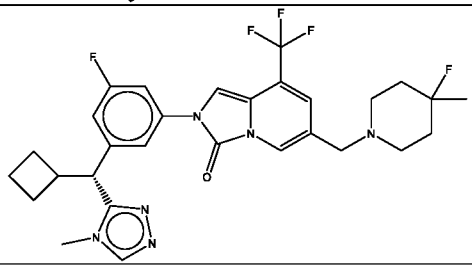
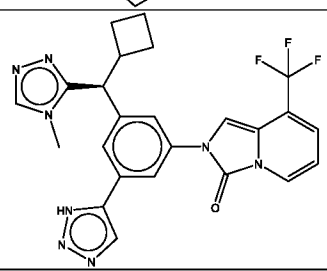
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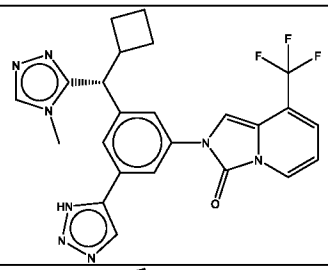
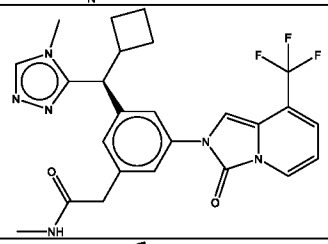
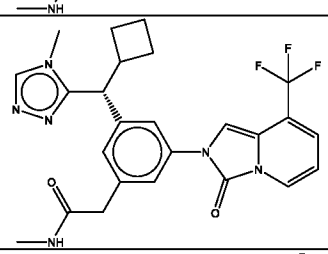
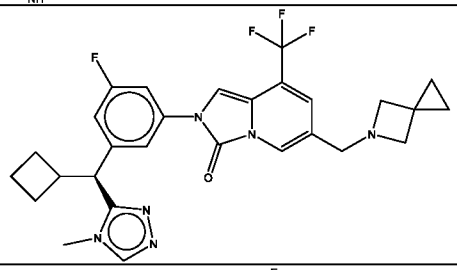
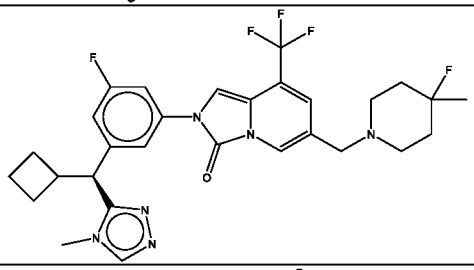
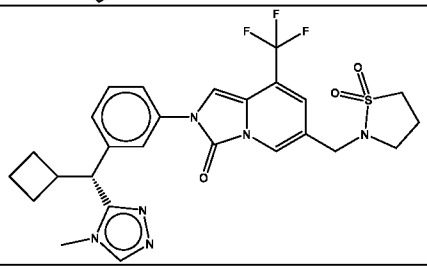
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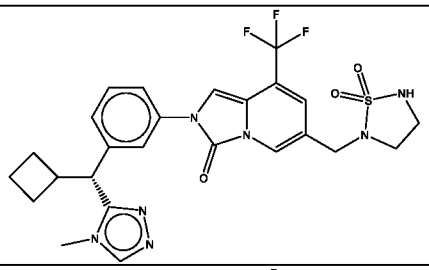
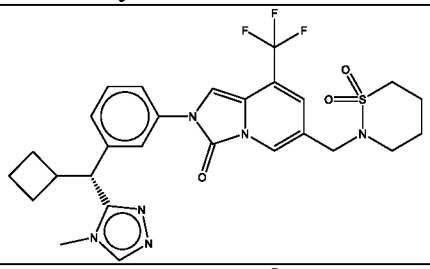
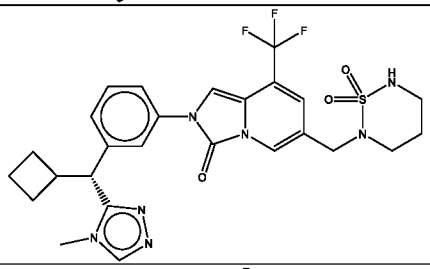
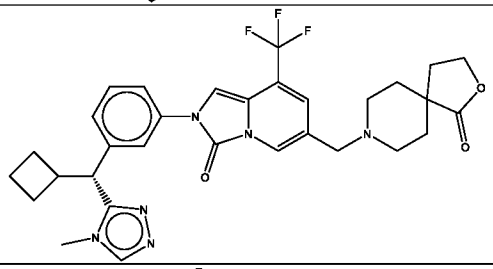
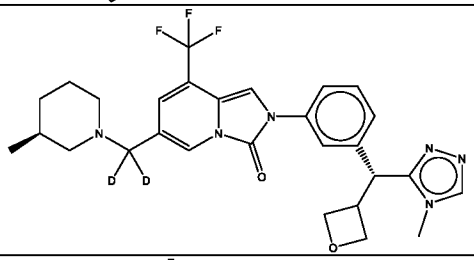
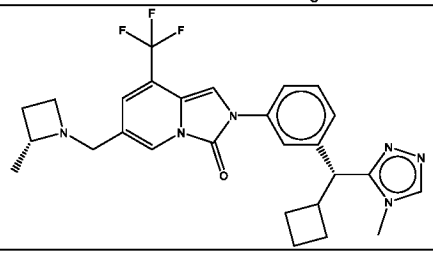
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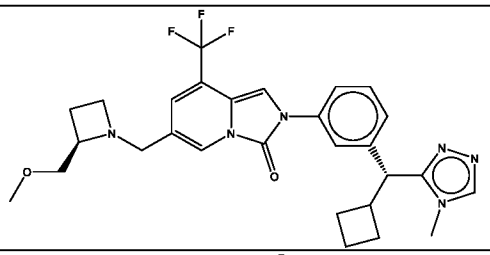
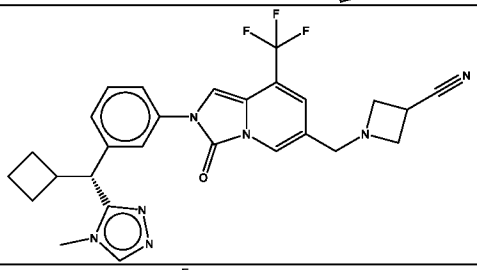
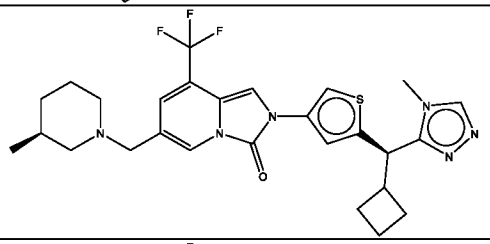
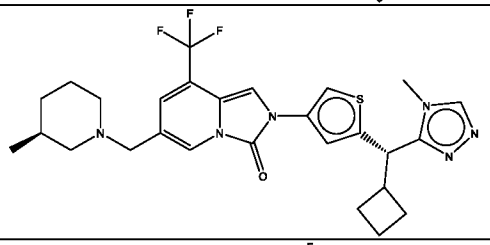
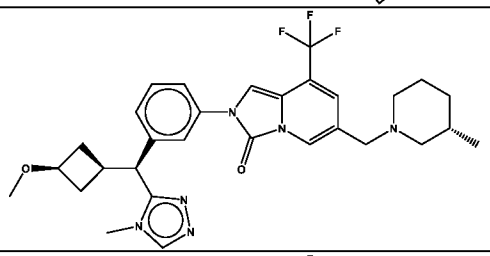
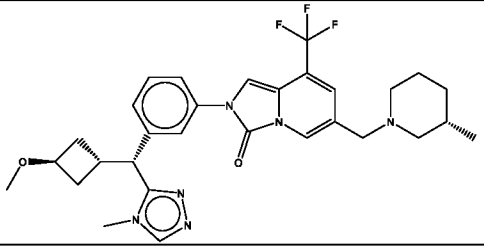
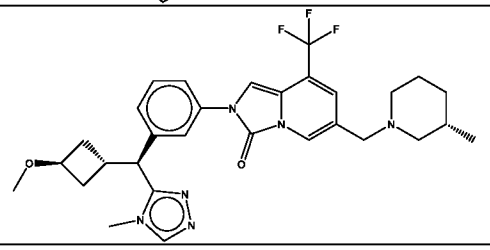
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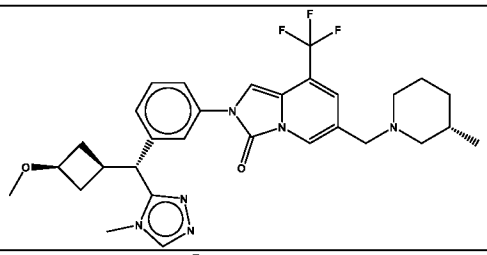
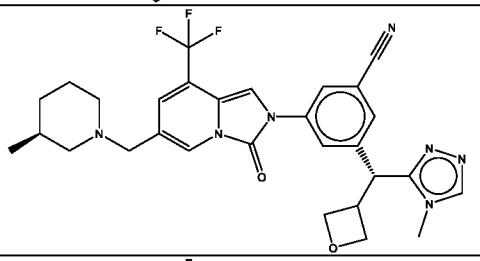
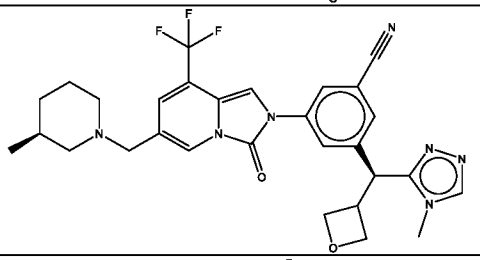
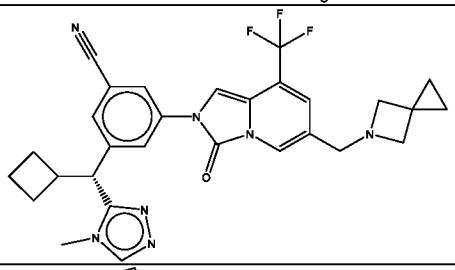
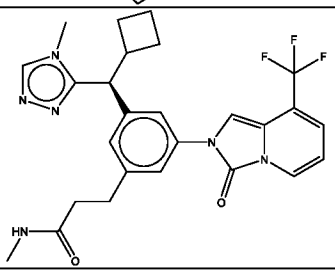
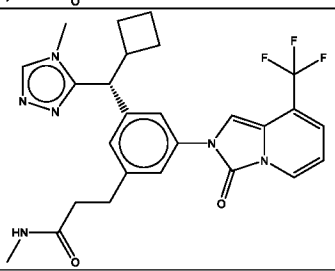
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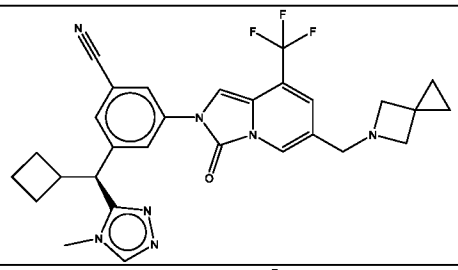
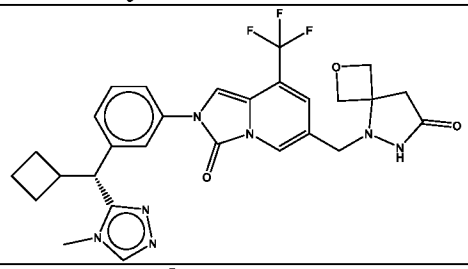
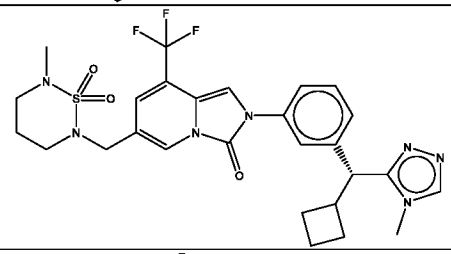
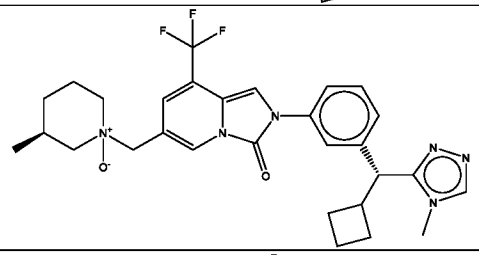
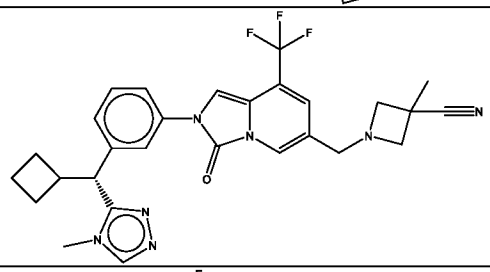
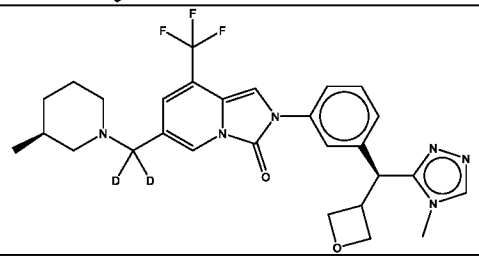
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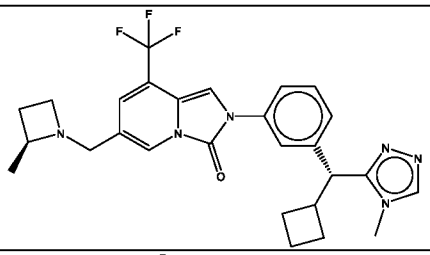
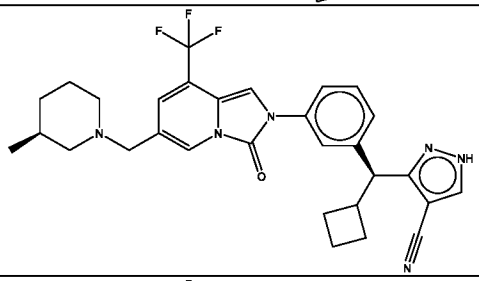
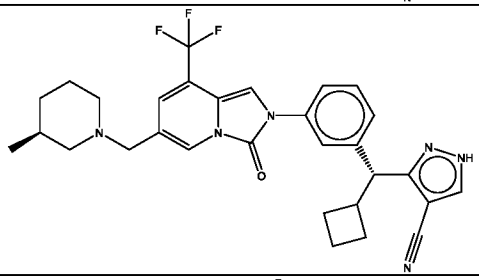
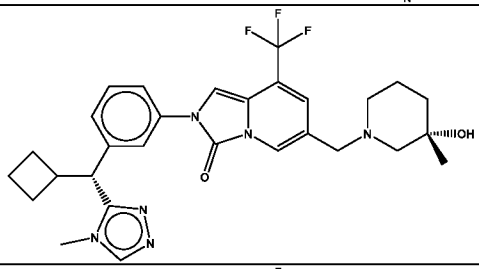
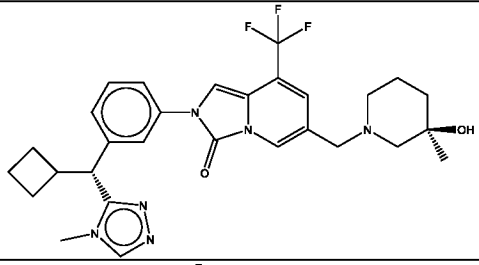
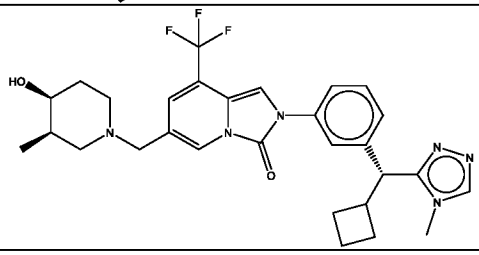
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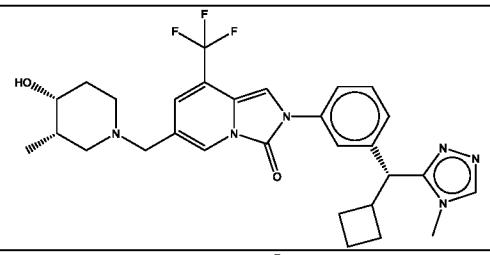
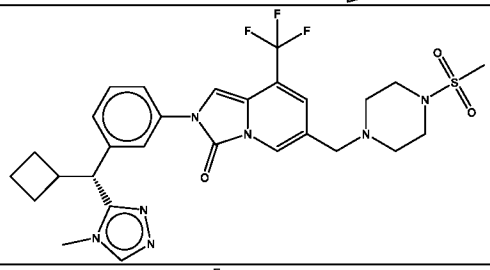
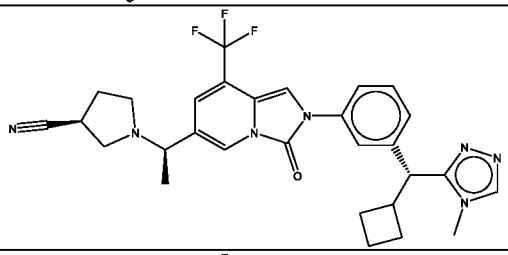
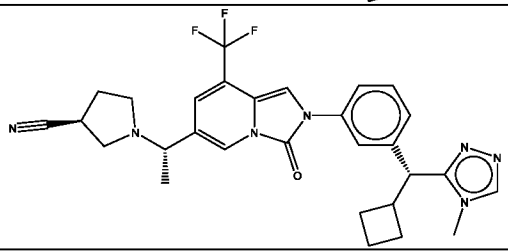
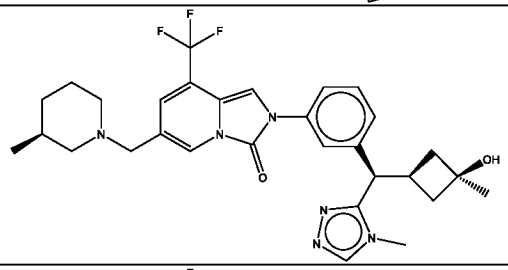
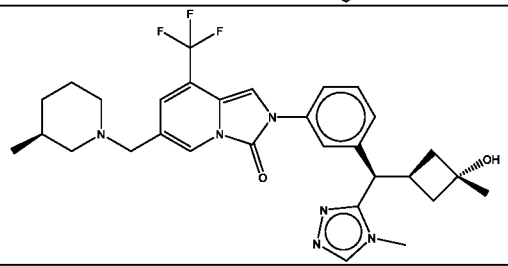
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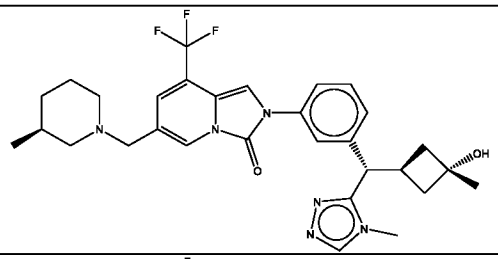
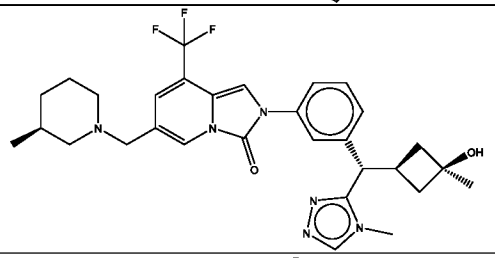
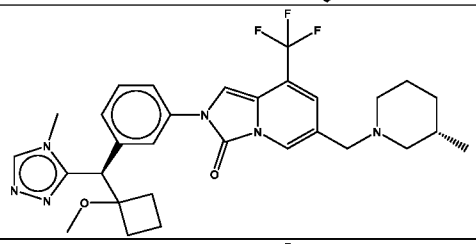
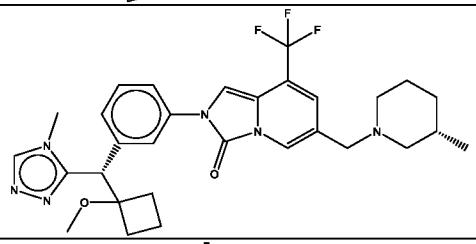
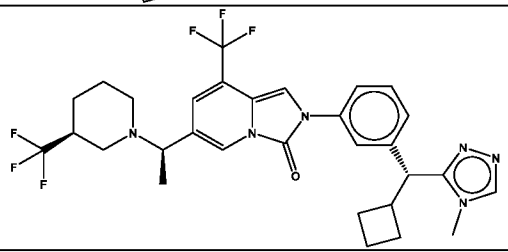
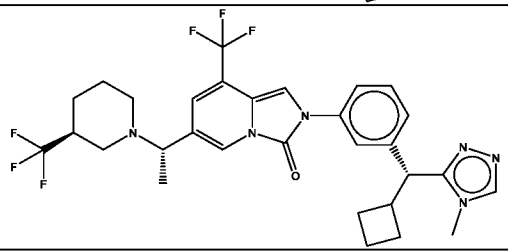
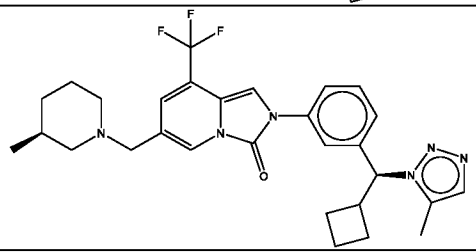
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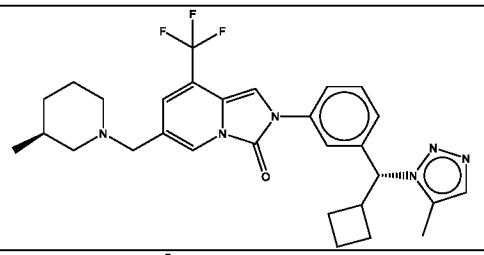
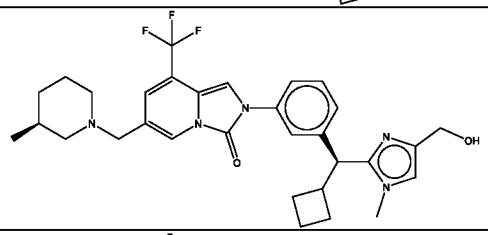
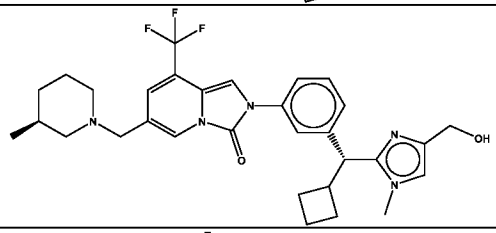
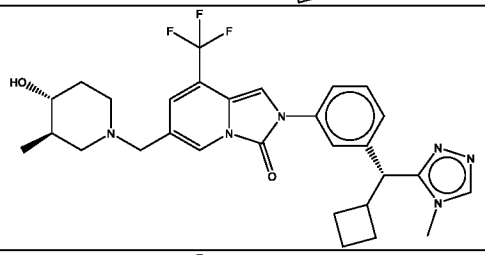
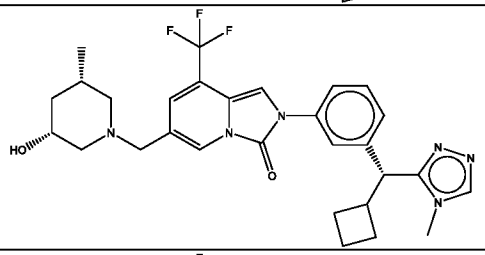
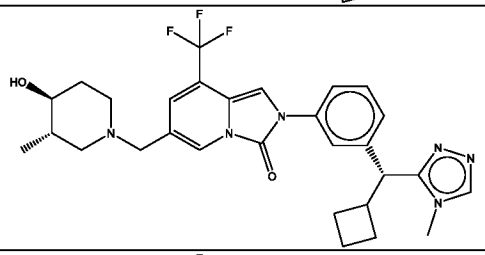
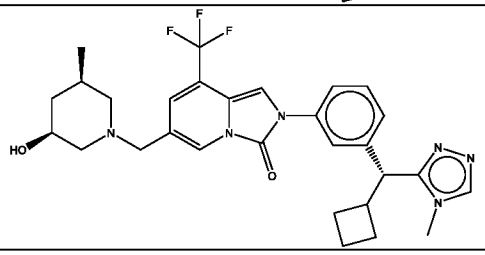
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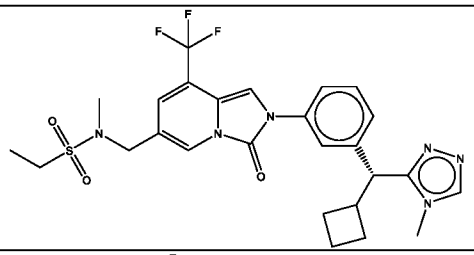
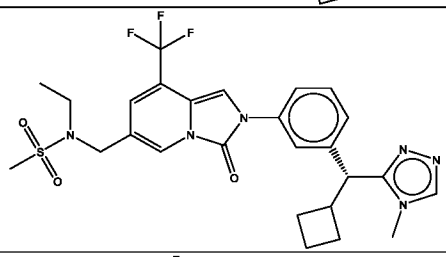
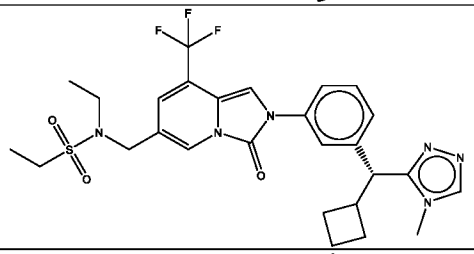
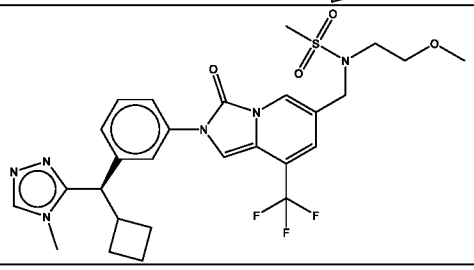
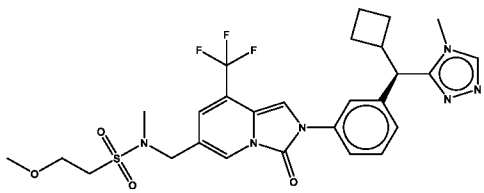
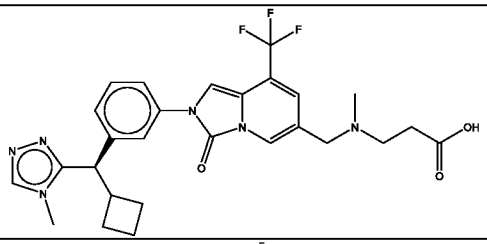
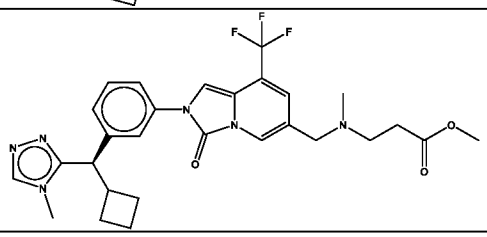
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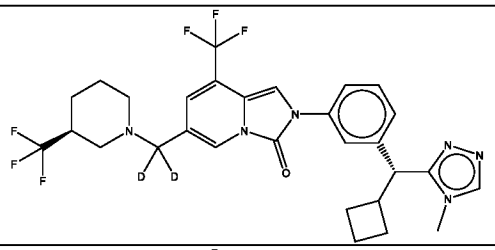
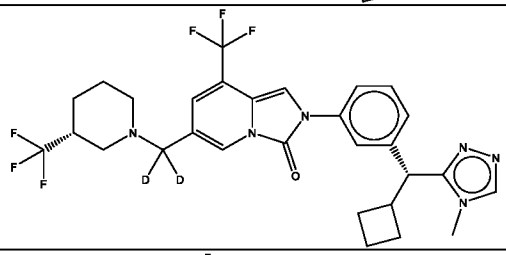
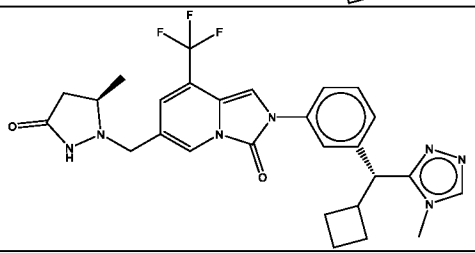
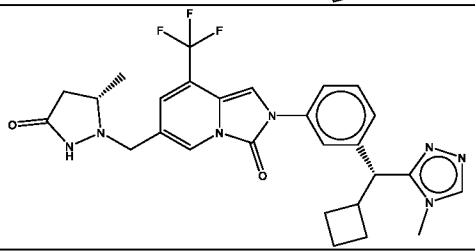
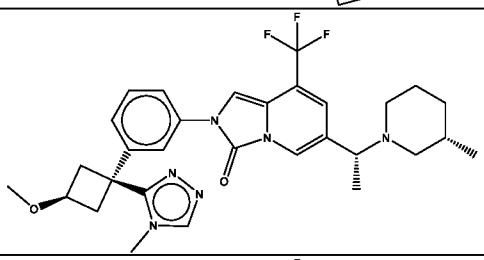
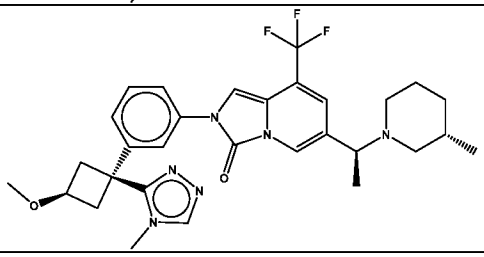
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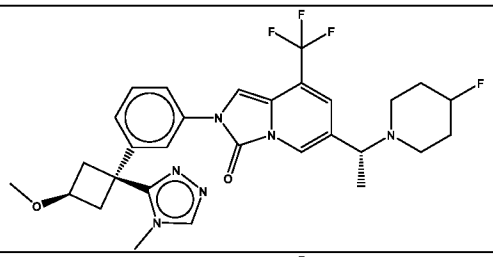
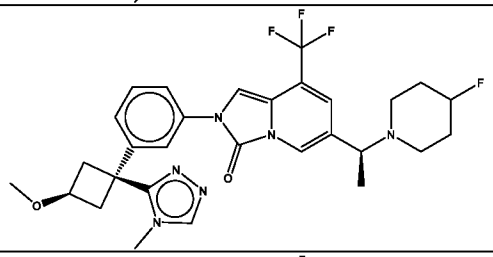
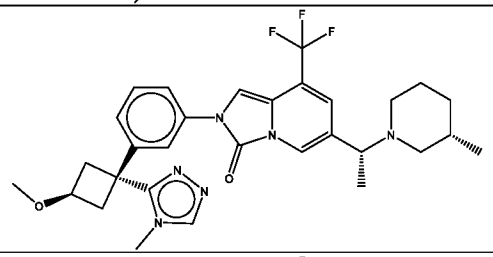
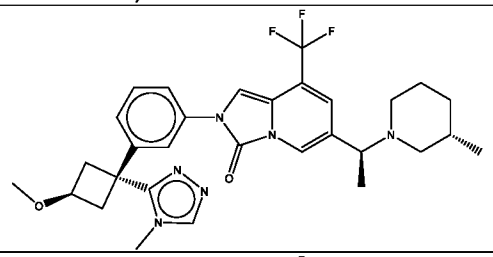
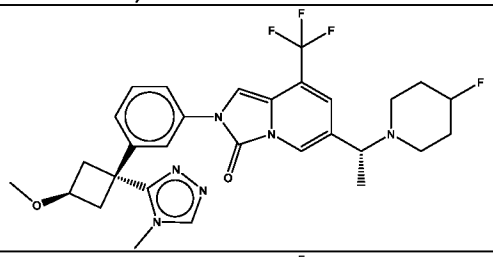
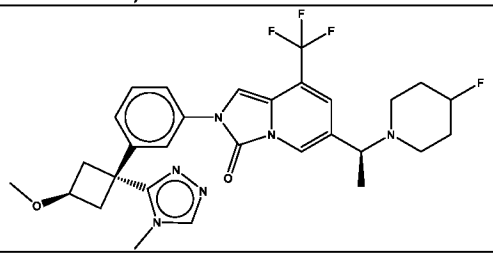
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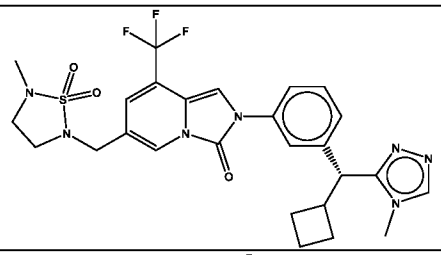
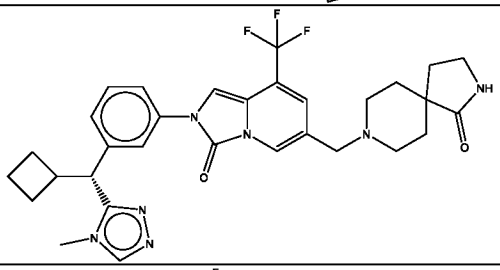
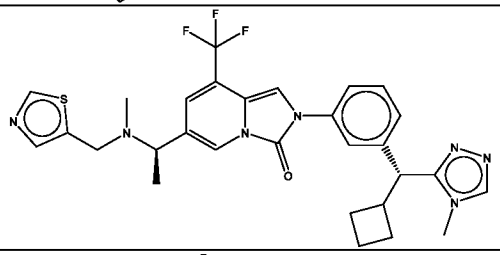
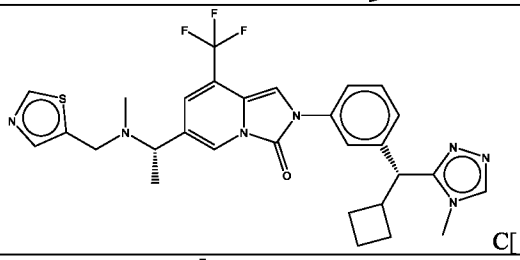
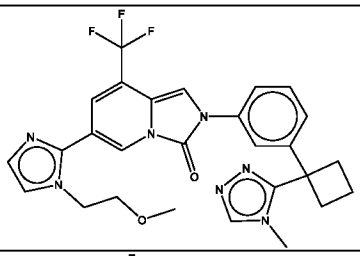
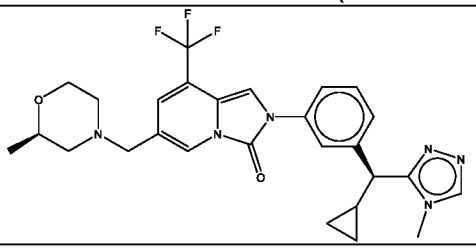
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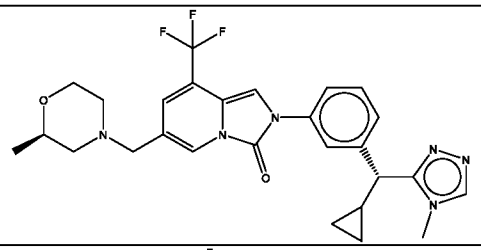
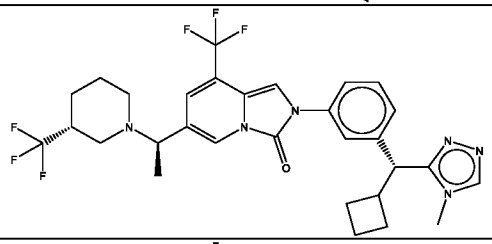
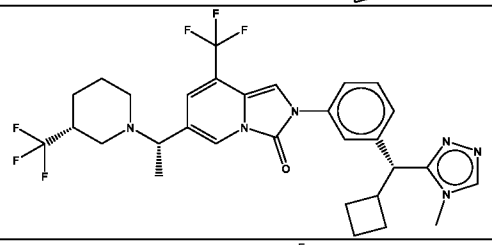
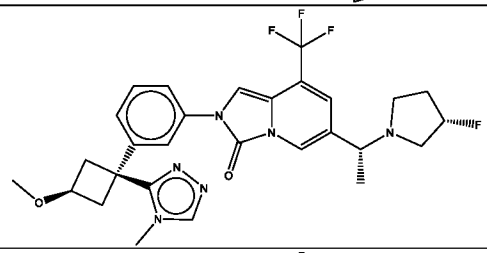
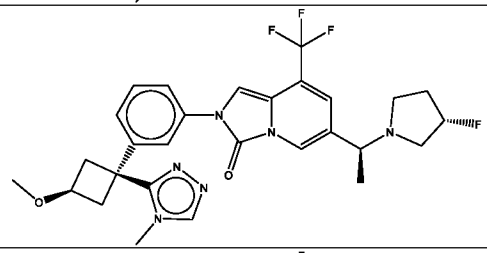
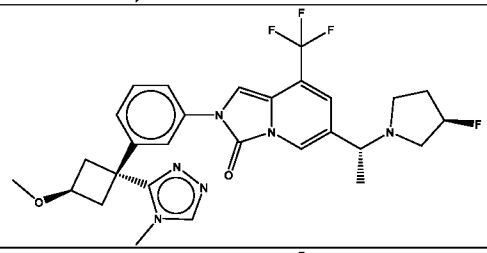
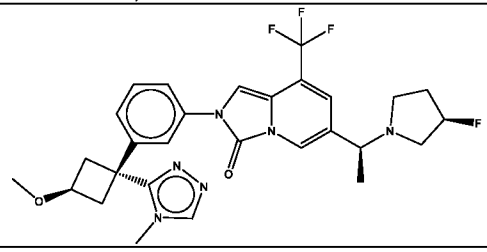
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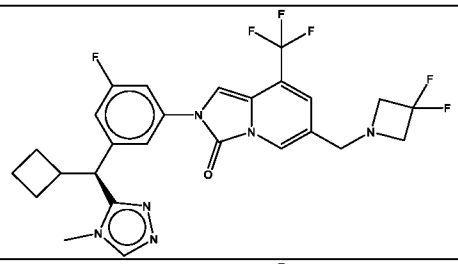
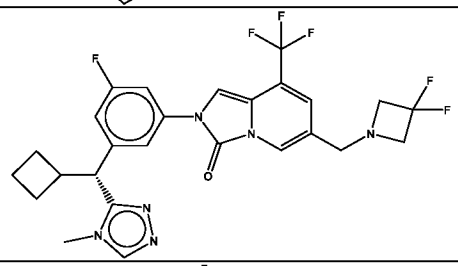
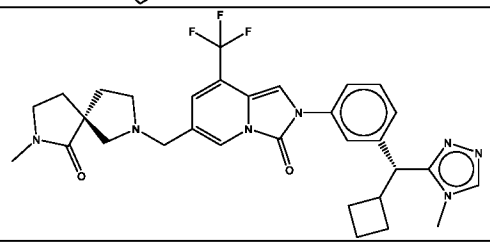
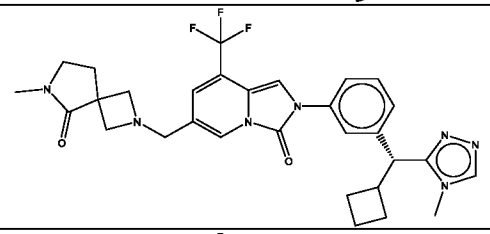
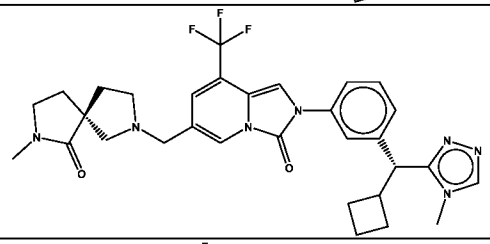
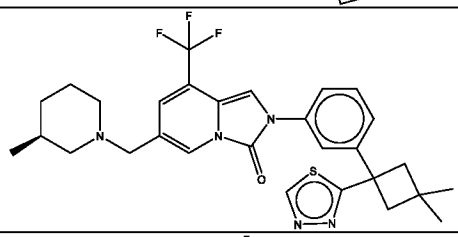
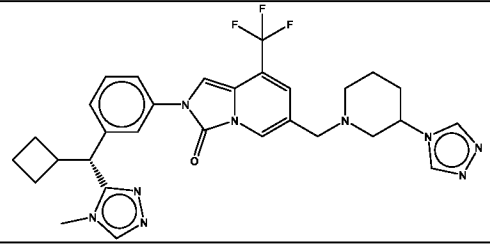
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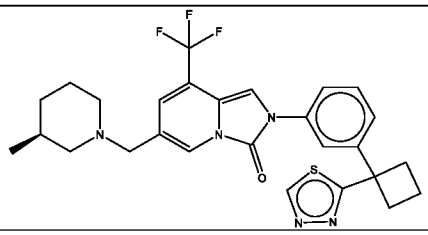
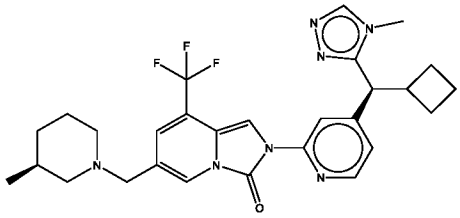
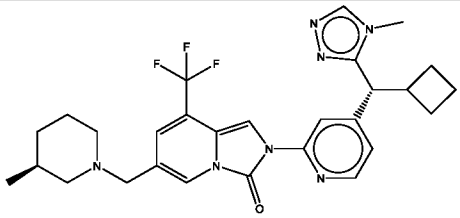
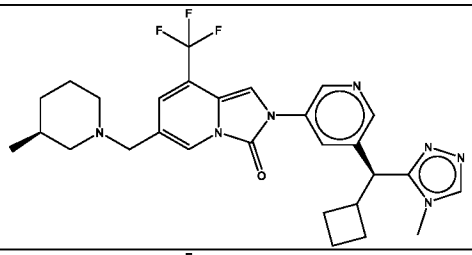
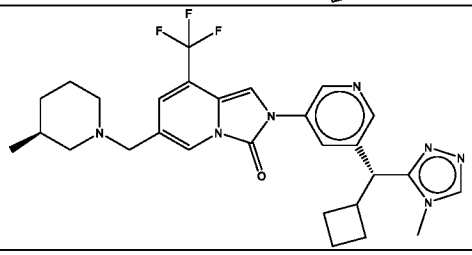
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or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of any of claims 1-21 and a pharmaceutically acceptable adjuvant or carrier.

23. A method of treating a disease or condition associated with cell proliferation comprising administering a therapeutically effective amount of a compound of any of claims 1-21 or a pharmaceutical composition of claim 22 to a subject in need thereof.

24. The method of claim 23, wherein the disease or condition associated with cell proliferation is hyperplasia or cancer.

25. The method of claim 24, wherein cancer is a hematologic cancer.

26. The method of claim 25, wherein the hematologic cancer is selected from a group consisting of lymphoma, leukemia, and myeloma.

27. The method of claim 26, wherein cancer is a non-hematologic cancer.

28. The method of claim 27, wherein the non-hematologic cancer is a sarcoma or a carcinoma.

29. The method of any one of claims 23-28, wherein the subject has one or more of increased T-cell activation, increased T-cell proliferation, decreased T-cell exhaustion, decreased T-cell anergy and decreased T-cell tolerance after administration of compound of any of claims 1-15 or a pharmaceutical composition of claim 16.

30. The method of claim 29, wherein increased T-cell activation comprises increased production of a cytokines.

31. The method of claims 23-28, wherein the subject has increased NK-cell activation.

32. The method of 31, the increased NK-cell activation comprises increased production of cytokines.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/025083

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/077944 A2 (BAYER AG [DE]; BAYER PHARMA AG [DE] ET AL.) 3 May 2018 (2018-05-03) page 263	1-32
X	WO 2009/054984 A1 (MERCK & CO INC [US]; BARROW JAMES C [US] ET AL.) 30 April 2009 (2009-04-30) page 51	1-32
X	WO 2009/014637 A2 (SCHERING CORP [US]; REDDY PANDURANGA ADULLA P [US] ET AL.) 29 January 2009 (2009-01-29) page 101	1-32
X	EP 0 317 947 A2 (SCHERING AG [DE]) 31 May 1989 (1989-05-31) example 7	1-32

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2022	30/06/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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