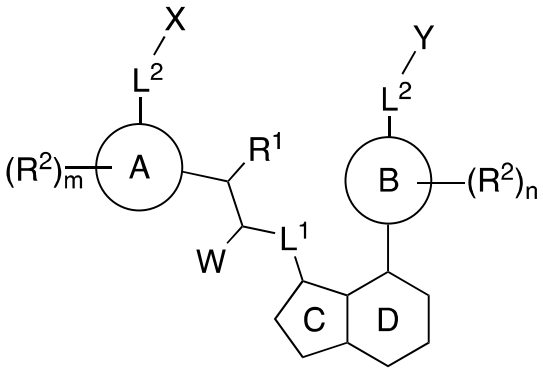
CLAIMS

~~We claim:~~

1. A compound having the structure of Formula I:



(Formula I)

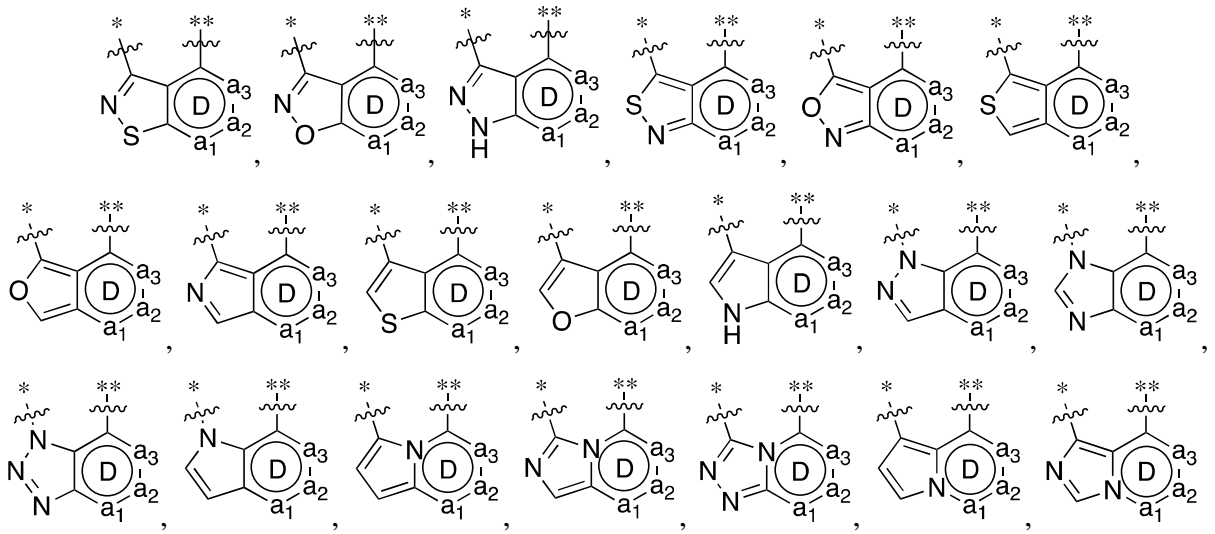
or a pharmaceutically acceptable salt thereof,

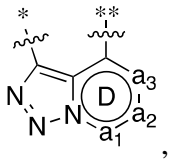
wherein:

A is aryl or heteroaryl;

B is a bond, aryl or heteroaryl;

the 5,6-membered bicyclic heteroaryl represented by C and D is selected from:



or  , where ~ represents the points of attachment, * represents the point attaching to L^1, and ** represents the point attaching to B;

a_1 is CH, N or NH;

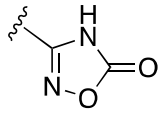
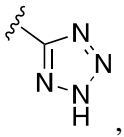
a_2 is $C(Z^1)$, N or $N(Z^2)$;

a_3 is $C(Z^1)$, N or $N(Z^2)$,

provided that a_1, a_2, and a_3 are selected such that ring D is aromatic;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-N(R^{X1})-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-S(O)$_2$-(C_1-C_6 alkyl)$_p$-;

W is C(O)OR^{W1}, C(O)N(H)S(O)$_2R^{W2}$, S(O)$_2$N(H)C(O)R^{W2}, S(O)$_2$N(H)R^{W3},  , or  , where ~ represents the point of attachment;

X is absent, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, or N(R^{X1})(R^{X2}), wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Y is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, N(R^{X1})(R^{X2}), or hydroxyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

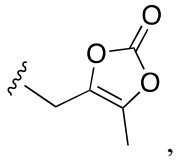
Z^2 is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W2} is C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{W3} is aryl or heteroaryl;

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, aryl, heteroaryl, or heterocyclyl, wherein each of aryl, heteroaryl, or heterocyclyl are optionally substituted with one, two, three or four R^{X3}; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -C(O)N(R^{X3c})(R^{X3d}), amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, N(R^{Z2})(R^{Z2}), C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl,

hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3 or 4, with the proviso that n is 0 when B is a bond; and

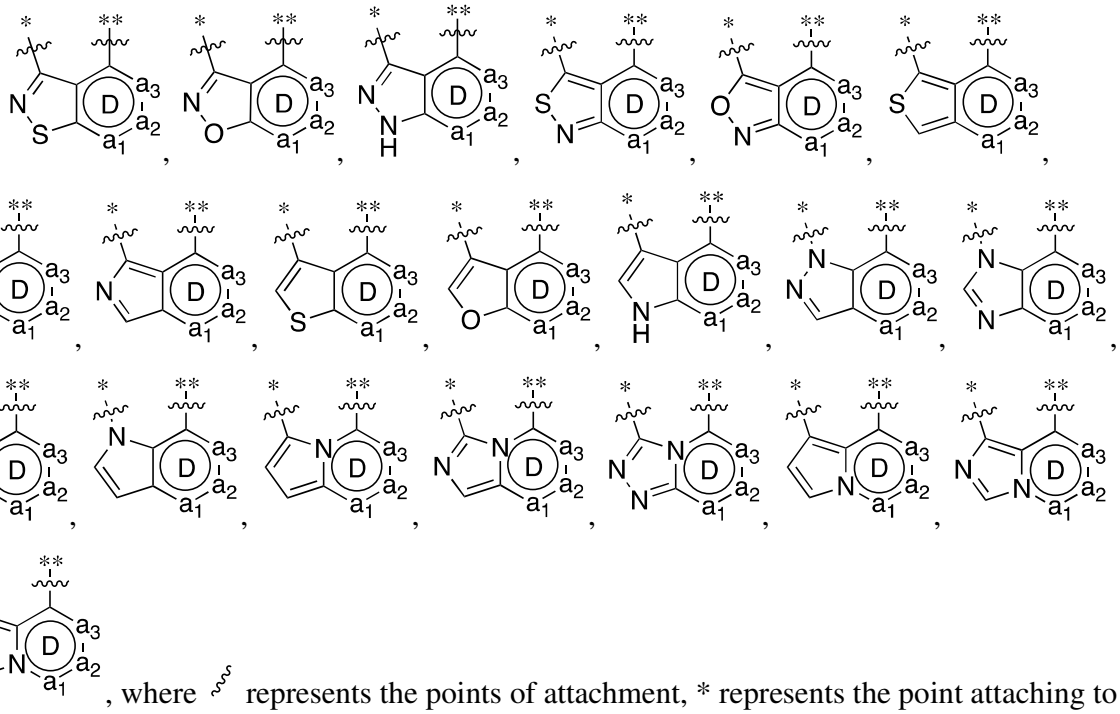
p in each instance is independently 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

A is aryl or heteroaryl;

B is aryl or heteroaryl;

the 5,6-membered bicyclic heteroaryl represented by C and D is selected from:



or , where represents the points of attachment, * represents the point attaching to L^1, and ** represents the point attaching to B;

a_1 is CH, N or NH;

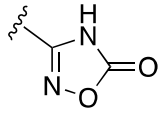
a_2 is $C(Z^1)$, N or $N(Z^2)$;

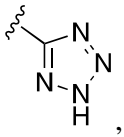
a_3 is $C(Z^1)$, N or $N(Z^2)$,

provided that a_1, a_2, and a_3 are selected such that ring D is aromatic;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-N(R^{X1})-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-$S(O)_2$-(C_1-C_6 alkyl)$_p$-;

W is $C(O)OR^{W1}$, $C(O)N(H)S(O)_2R^{W2}$, $S(O)_2N(H)C(O)R^{W2}$, $S(O)_2N(H)R^{W3}$, 

, or  , where ~ represents the point of attachment;

X is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, or $N(R^{X1})(R^{X2})$, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Y is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, $N(R^{X1})(R^{X2})$, or hydroxyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Z^2 is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W2} is C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{W3} is aryl or heteroaryl;

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, aryl, heteroaryl, or heterocyclyl, wherein each of aryl, heteroaryl, or heterocyclyl are optionally substituted with one, two, three or four R^{X3}; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, $-C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-

C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

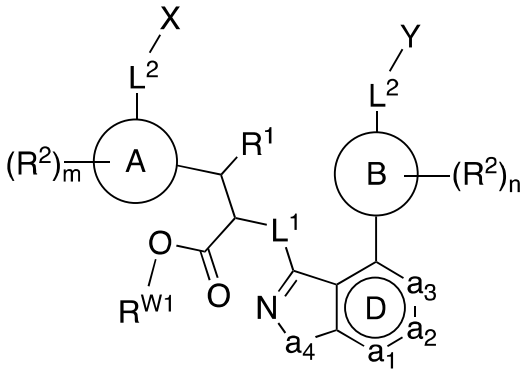
R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1.

3. A compound having the structure of Formula II:



(Formula II)

or a pharmaceutically acceptable salt thereof,

wherein:

A is aryl or heteroaryl;

B is a bond, aryl or heteroaryl;

a_1 is CH, N or NH;

a_2 is $C(Z^1)$, N or $N(Z^2)$;

a_3 is $C(Z^1)$, N or $N(Z^2)$;

a_4 is S, O or NH,

provided that a_1, a_2, and a_3 are selected such that ring D is aromatic;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-$N(R^{X1})$-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-$S(O)_2$-(C_1-C_6 alkyl)$_p$-;

X is absent, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, or $N(R^{X1})(R^{X2})$, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Y is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, $N(R^{X1})(R^{X2})$, or hydroxyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

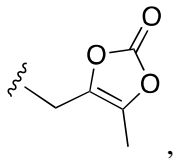
Z^2 is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, aryl, heteroaryl, or heterocyclyl, wherein each of aryl, heteroaryl, or heterocyclyl are optionally substituted with one, two, three or four R^{X3}; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -C(O)N(R^{X3c})(R^{X3d}), amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, N(R^{Z2})(R^{Z2}), C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3 or 4, with the proviso that n is 0 when B is a bond; and

p in each instance is independently 0 or 1.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein:

A is aryl or heteroaryl;

B is aryl or heteroaryl;

a_1 is CH, N or NH;

a_2 is $C(Z^1)$, N or $N(Z^2)$;

a_3 is $C(Z^1)$, N or $N(Z^2)$;

a_4 is S, O or NH,

provided that a_1, a_2, and a_3 are selected such that ring D is aromatic;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-$N(R^{X1})$-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-$S(O)_2$-(C_1-C_6 alkyl)$_p$-;

X is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, or $N(R^{X1})(R^{X2})$, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Y is aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, $N(R^{X1})(R^{X2})$, or hydroxyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Z^2 is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, aryl, heteroaryl, or heterocyclyl, wherein each of aryl, heteroaryl, or heterocyclyl are optionally substituted with one, two, three or four R^{X3}; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -C(O)N(R^{X3c})(R^{X3d}), amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, N(R^{Z2})(R^{Z2}), C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl,

cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1.

5. ~~A~~ The compound of any of claims 1-3, wherein A is phenyl, pyridine, pyridazine, pyrimidine, pyrazine or thiophene; and/or B is phenyl, pyridine or thiophene.

~~6. A compound of any of claims 1-5, wherein B is phenyl, pyridine or thiophene.~~

~~7.~~6. ~~A~~ The compound of any of claims 1 – ~~6~~5, wherein:

L^1 is O;

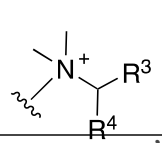
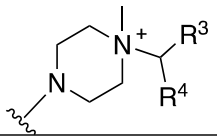
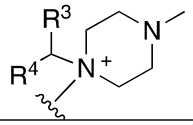
R^1 is H;

R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2.

~~8. A compound of any of claims 1 – 7, wherein:~~

~~Y is~~  ~~,~~  ~~or~~  ~~, where~~ ~~represents the point of attachment;~~

~~R^3 is H or C_1-C_6 alkyl;~~

~~R^4 is -O-P(O)(O^-)(O^-), -O-P(O)(O^-)(OR^5), -O-P(O)(OR^5)(OR^5), -O-$S(O_2)$-O^-, -O-$S(O_2)$-OR^5, Cy^a, -O-C(O)-R^6, -O-C(O)-OR^6, or -O-C(O)-N(R^6)(R^6);~~

~~Cy^a is cycloalkyl, heterocyclyl, aryl or heteroaryl;~~

~~R^5 in each instance is independently H, C_1-C_6 alkyl, or aralkyl(C_1-C_6); and~~

~~R^6 in each instance is independently H, C_1-C_6 alkyl, or C_1-C_6 aminoalkyl.~~

~~9.~~7. The compound of claim 3, wherein:

A is aryl;

B is aryl;

a_1 is CH;

a_2 is C(H) or N;

a_3 is C(Z^1);

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond or -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-;

X is aryl or heteroaryl, wherein each of said aryl and heteroaryl is optionally substituted with one, two, three or four R^{X3};

Y is heterocyclyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, N(R^{X1})(R^{X2}), or hydroxyl, wherein heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, $-C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide,

sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, nitro or cyano, wherein each of said C_1-C_6 alkyl, C_1-C_6 aminoalkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl and heteroaryl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1.

~~10.~~8. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein:

A is aryl;

B is aryl;

a_1 is CH;

a_2 is $C(Z^1)$;

a_3 is C(H);

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond or -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-;

X is aryl or heteroaryl, wherein each of said aryl and heteroaryl is optionally substituted with one, two, three or four R^{X3};

Y is heterocyclyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, N(R^{X1})(R^{X2}), or hydroxyl, wherein heterocyclyl is optionally substituted with one, two, three or four R^{X3};

Z^1 is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or N(R^{2a})(R^{2b});

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, CH(R^{W1a})(R^{W2a}), heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is OC(O)OR^{W2b}, OC(O)N(R^{W2b})(R^{W2b}) or OP(O)(OR^{W2b})$_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is OC(O)N(R^{W2b})(R^{W2b}), the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X1} and R^{X2} are in each instance each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl; or

R^{X1} and R^{X2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{X3};

R^{X3} in each instance is independently aryl, heteroaryl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl and heteroaryl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Z1} in each instance is independently halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, nitro or cyano, wherein each of said C_1-C_6 alkyl, C_1-C_6 aminoalkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl and heteroaryl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1.

~~11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein:~~

~~Z^1 is an indazolyl, benzoimidazolyl, benzoimidazolonyl, indolyl, pyrrolopyridinyl or isoquinolinyl, wherein each of indazolyl, benzoimidazolyl, benzoimidazolonyl, indolyl, pyrrolopyridinyl and isoquinolinyl optionally substituted with one, two or three groups independently selected from C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano.~~

~~12. The compound of any one of claims 1-11, wherein L^2 is a bond and Y is hydroxyl.~~

~~13.~~9. The compound of any one of claims 1-~~12~~8, wherein:

R^{W1} is H;

L^1 is O;

R^1 is H;

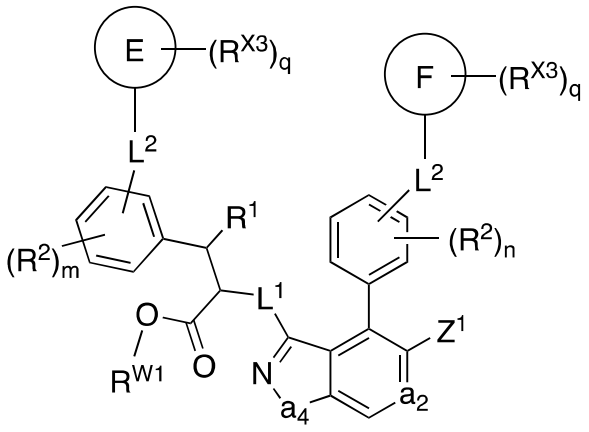
R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2.

~~14. The compound of any one of claims 1-13, wherein a_2 is C(H) or N.~~

~~15.~~10. A compound having the structure of Formula III:



(Formula III)

or a pharmaceutically acceptable salt thereof,

wherein:

a_2 is $C(Z^1)$ or N;

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-N(R^{X1})-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-S(O)$_2$-(C_1-C_6 alkyl)$_p$-;

E is absent, aryl, heteroaryl, cycloalkyl or heterocyclyl;

F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

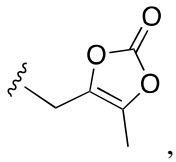
Z^1 in each instance is independently H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -$C(O)N(R^{X3c})(R^{X3d})$, amino,

nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1; and

q in each instance is independently 0, 1, 2, 3 or 4, with the proviso that q is 0 in $-(R^{X3})_q$ when E is absent.

~~16.~~11. The compound of claim ~~15~~10, or a pharmaceutically acceptable salt thereof, wherein:

a_2 is $C(Z^1)$ or N;

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-$N(R^{X1})$-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-$S(O)_2$-(C_1-C_6 alkyl)$_p$-;

E is aryl, heteroaryl, cycloalkyl or heterocyclyl;

F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

Z^1 in each instance is independently H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, $-C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1; and

q in each instance is independently 0, 1, 2, 3 or 4.

~~17.~~12. The compound of claim 10~~15~~, wherein:

a_2 is C(H) or N;

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond or -$(C_1$-C_6 alkyl$)_p$-O-$(C_1$-C_6 alkyl$)_p$-;

E is aryl or heteroaryl;

F is cycloalkyl or heterocyclyl;

Z^1 is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or, when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -C(O)N(R^{X3c})(R^{X3d}), amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently halogen, hydroxy, N(R^{Z2})(R^{Z2}), C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, nitro or cyano, wherein each of said C_1-C_6 alkyl, C_1-C_6 aminoalkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

m is 0, 1, 2 or 3;

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

p in each instance is independently 0 or 1; and

q in each instance is independently 0, 1, 2, 3 or 4.

~~18.~~13. The compound of claim ~~15~~10, wherein:

R^{W1} is H;

L^1 is O;

R^1 is H;

R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2; or

R^1 is H;

R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2; or

L^1 is O;

R^1 is H;

R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2.

~~19. The compound of claim 15, wherein a_2 is C(H) or N.~~

~~20. The compound of claim 15, wherein:~~

~~R^1 is H;~~

~~R^2 in each instance is independently C_1-C_6 alkyl or halogen;~~

~~m is 0; and~~

~~n is 2.~~

~~21. The compound of claim 15 wherein:~~

~~L^1 is O;~~

~~R^1 is H;~~

~~R^2 in each instance is independently C_1-C_6 alkyl or halogen;~~

~~m is 0; and~~

~~n is 2.~~

~~22. The compound of any one of claims 15-21, wherein Z^1 in each instance is independently H or halogen.~~

~~23. The compound of any one of claims 5-21, wherein Z^1 in each instance is independently H, Br or Cl.~~

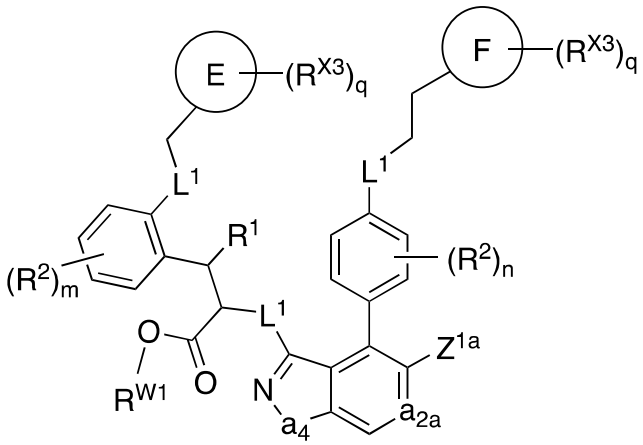
~~24.~~14. The compound of any one of claims ~~5-21~~5-13, wherein:

Z^1 in each instance is independently H, phenyl, pyridine, thiophene, furan, pyrrole, cyclopropyl, or cyclobutyl, wherein each of phenyl, pyridine, thiophene, furan, pyrrole, cyclopropyl, and cyclobutyl is optionally substituted with one or two R^{Z1}; and

R^{Z1} in each instance is independently halogen or C_1-C_6 alkyl, preferably independently methyl, ethyl, F or C.

~~25. The compound of claim 24, wherein R^{Z1} in each instance is independently methyl, ethyl, F or Cl.~~

~~26.~~15. A compound having the structure of Formula IV:



(Formula IV)

or a pharmaceutically acceptable salt thereof,

wherein:

a_{2a} is CH or N;

a_4 is S, O or NH;

L^1 in each instance is independently a bond, CH_2, O, NH, S, SO, or SO_2;

E is absent, aryl, heteroaryl, cycloalkyl or heterocyclyl;

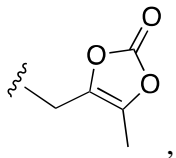
F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

Z^{1a} is H, halogen, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or, when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, $-C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl,

amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

m is 0, 1, 2, or 3;

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

q in each instance is independently 0, 1, 2, 3 or 4, with the proviso that q is 0 in

–$(R^{X3})_q$ when E is absent.

~~27.~~16. The compound of claim ~~26~~15, or a pharmaceutically acceptable salt thereof, wherein:

a_{2a} is CH or N;

a_4 is S, O or NH;

L^1 in each instance is independently a bond, CH_2, O, NH, S, SO, or SO_2;

E is aryl, heteroaryl, cycloalkyl or heterocyclyl;

F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

Z^{1a} is H, halogen, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, or heteroaryl, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -C(O)N(R^{X3c})(R^{X3d}), amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, N(R^{Z2})(R^{Z2}), C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

m is 0, 1, 2, or 3;

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

q in each instance is independently 0, 1, 2, 3 or 4.

~~28.~~17. The compound of claim ~~26~~15 or 16, wherein:

R^1 is H;

R^2 in each instance is independently C_1-C_6 alkyl or halogen;

m is 0; and

n is 2; and/or

Z^{1a} is phenyl, pyridine, thiophene, furan, pyrrole, cyclopropyl, or cyclobutyl, wherein each is optionally substituted with one or two R^{Z1}; and R^{Z1} in each instance is independently halogen or C_1-C_6 alkyl, preferably independently methyl, ethyl, F or Cl.

~~29. The compound of any one of claims 26-28, wherein Z^{1a} is halogen.~~

~~30. The compound of claim 27, wherein the halogen is Br or Cl.~~

~~31. The compound of any one of claims 26-28, wherein:~~

~~Z^{1a} is phenyl, pyridine, thiophene, furan, pyrrole, cyclopropyl, or cyclobutyl, wherein each is optionally substituted with one or two R^{Z1}; and~~

~~R^{Z1} in each instance is independently halogen or C_1-C_6 alkyl.~~

~~32. The compound of claim 31, wherein R^{Z1} in each instance is independently methyl, ethyl, F or Cl.~~

~~33.~~18. The compound of any of claims ~~15-32~~10-17, wherein:

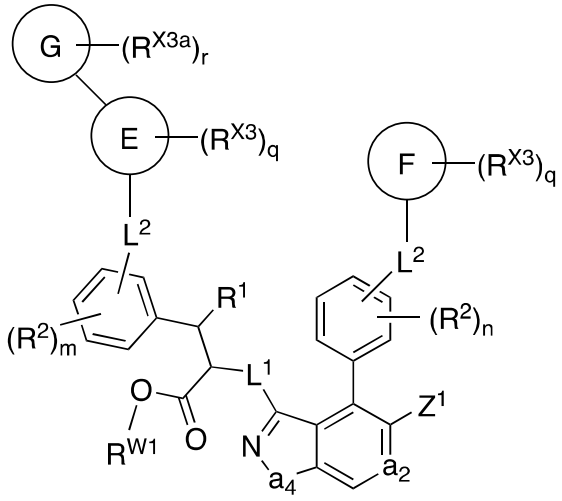
E is phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, furan, thiophene, pyrrole, pyrazole, imidazole or triazole;

F is pyrrolidine, piperidine, piperazine, tetrahydropyran, morpholine, 2,6-diazaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-azaspiro[3.3]heptanyl, or 2-oxaspiro[3.3]heptanyl;

R^{X3} in each instance is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano; and

q in each instance is independently 0, 1 or 2.

~~34.~~19. A compound having the structure of Formula V:



(Formula V)

or a pharmaceutically acceptable salt thereof,

wherein:

a_2 is $C(Z^1)$ or N;

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, -(C_1-C_6 alkyl)$_p$-O-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-N(R^{X1})-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S-(C_1-C_6 alkyl)$_p$-, -(C_1-C_6 alkyl)$_p$-S(O)-(C_1-C_6 alkyl)$_p$-, or -(C_1-C_6 alkyl)$_p$-S(O)$_2$-(C_1-C_6 alkyl)$_p$-;

E is aryl, heteroaryl, cycloalkyl or heterocyclyl;

F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

G is aryl, heteroaryl, cycloalkyl or heterocyclyl;

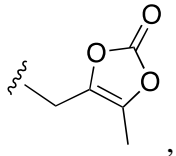
Z^1 in each instance is independently H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, $-C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl, amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

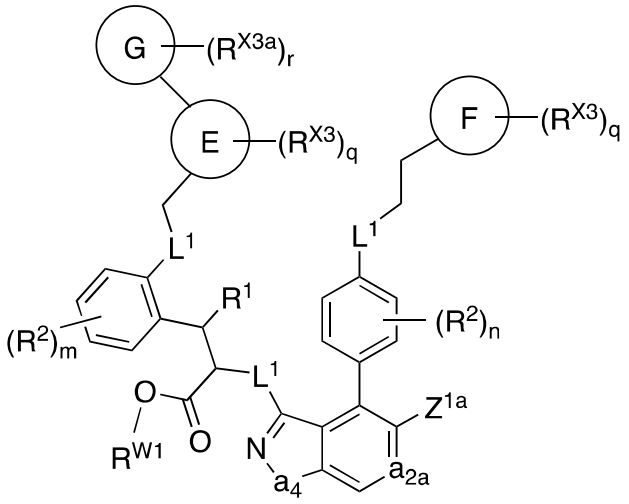
n is 0, 1, 2, 3 or 4;

p in each instance is independently 0 or 1;

q in each instance is independently 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.; or having the structure of Formula VI:

~~35. A compound having the structure of Formula VI:~~



(Formula VI)

or a pharmaceutically acceptable salt thereof,

wherein:

a_2 is $C(Z^1)$ or N;

a_4 is S, O or NH;

L^1 in each instance is independently a bond, CH_2, O, NH, S, SO, or SO_2;

E is aryl, heteroaryl, cycloalkyl or heterocyclyl;

F is aryl, heteroaryl, cycloalkyl or heterocyclyl;

G is aryl, heteroaryl, cycloalkyl or heterocyclyl;

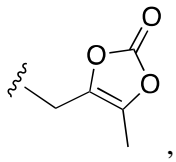
Z^1 in each instance is independently H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -$C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl,

amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

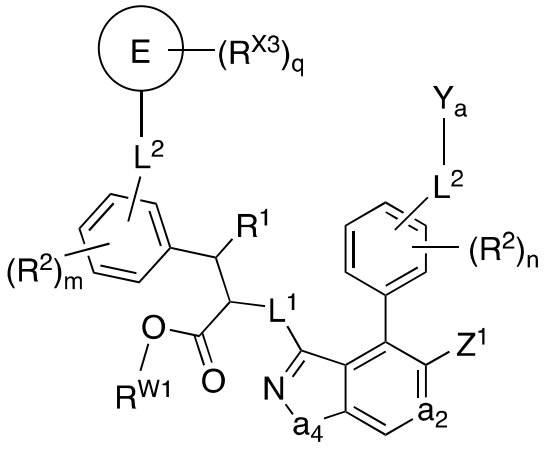
m is 0, 1, 2, or 3;

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

q in each instance is independently 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4. ; or having the structure of Formula VII:

~~36. A compound having the structure of Formula VII:~~



(Formula VII)

or a pharmaceutically acceptable salt thereof,

wherein:

a_2 is $C(Z^1)$ or N;

a_4 is S, O or NH;

L^1 is a bond, CH_2, O, NH, S, SO, or SO_2;

L^2 in each instance is independently a bond, optionally substituted C_1-C_6 alkyl, $-(C_1\text{-}C_6\text{ alkyl})_p\text{-}O\text{-}(C_1\text{-}C_6\text{ alkyl})_p-$, $-(C_1\text{-}C_6\text{ alkyl})_p\text{-}N(R^{X1})\text{-}(C_1\text{-}C_6\text{ alkyl})_p-$, $-(C_1\text{-}C_6\text{ alkyl})_p\text{-}S\text{-}(C_1\text{-}C_6\text{ alkyl})_p-$, $-(C_1\text{-}C_6\text{ alkyl})_p\text{-}S(O)\text{-}(C_1\text{-}C_6\text{ alkyl})_p-$, or $-(C_1\text{-}C_6\text{ alkyl})_p\text{-}S(O)_2\text{-}(C_1\text{-}C_6\text{ alkyl})_p-$;

E is absent, aryl, heteroaryl, cycloalkyl or heterocyclyl;

Y_a is C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, $N(R^{X1})(R^{X2})$, or hydroxyl;

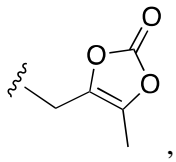
Z^1 in each instance is independently H, halogen, -L^2-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four R^{Cy1};

R^1 is H, hydroxy, C_1-C_3 alkyl, C_1-C_2 haloalkyl, C_1-C_2 hydroxyalkyl, or C_1-C_2 alkoxy;

R^2 in each instance is independently cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 aminoalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, nitro or $N(R^{2a})(R^{2b})$;

R^{2a} and R^{2b} are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

R^{W1} is H, C_1-C_6 alkyl, $CH(R^{W1a})(R^{W2a})$, heterocyclyl, aryl, heteroaryl, or  , where ≈ represents the point of attachment, wherein each of said heterocyclyl, aryl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W1a} is H or C_1-C_6 alkyl;

R^{W2a} is $OC(O)OR^{W2b}$, $OC(O)N(R^{W2b})(R^{W2b})$ or $OP(O)(OR^{W2b})_2$;

R^{W2b} in each instance is independently H, C_1-C_6 alkyl, cycloalkyl or C_1-C_6 alkoxy; or,

when R^{W2a} is $OC(O)N(R^{W2b})(R^{W2b})$, the two R^{W2b}, together with the N to which they are connected, form a heterocyclyl or heteroaryl, wherein each of said heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R^{W3a};

R^{W3a} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{X3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, -$C(O)N(R^{X3c})(R^{X3d})$, amino, nitro, sulfonamide, sulfoxide, sulfonyl, or cyano, wherein each of heteroaryl, heterocyclyl,

amino, nitro, sulfonamide, sulfoxide, sulfonyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 hydroxyalkyl is optionally substituted with one, or two R^{X3b};

R^{X3b} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano, wherein each of aryl, heteroaryl and heterocyclyl is optionally substituted with one, two, three or four groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl, halogen, amino, nitro, sulfonamide, sulfoxide, sulfonyl or cyano;

R^{X3c} and R^{X3d} is each independently selected from H, C_1-C_6 cycloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl; or

R^{X3c} and R^{X3d}, together with the N to which they are connected, form a 4 – 6 membered heterocycle optionally substituted with one or two groups each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyl or halogen;R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Cy1} is aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, hydroxy, $N(R^{Cy2})(R^{Cy2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano;

R^{Cy2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl;

m is 0, 1, 2, or 3;

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

p in each instance is independently 0 or 1; and

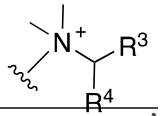
q in each instance is independently 0, 1, 2, 3 or 4, with the proviso that q is 0 in $-(R^{X3})_q$ when E is absent.

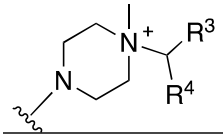
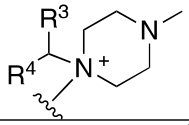
~~37.~~20. The compound of claim ~~36~~19, or a pharmaceutically acceptable salt thereof, wherein:

E is phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, furan, thiophene, pyrrole, pyrazole, imidazole or triazole;

Y_a is $N(R^{X1})(R^{X2})$; and

q in each instance is independently 0, 1 or 2.

~~38. The compound of any of claims 15, 26, 34, and 35, wherein F is~~  ~~,~~

 ~~or~~  ~~, where~~ ~~represents the point of attachment;~~

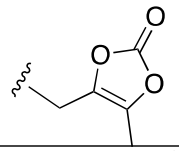
~~R_3 is H or C_1-C_6 alkyl;~~

~~R^4 is $-O-P(O)(O^-)(O^-)$, $-O-P(O)(O^-)(OR^5)$, $-O-P(O)(OR^5)(OR^5)$, $-O-S(O_2)-O^-$, $-O-S(O_2)-OR^5$, $-Cy^a$, $-O-C(O)-R^6$, $-O-C(O)-OR^6$, or $-O-C(O)-N(R^6)(R^6)$;~~

~~R^5 in each instance is independently H, C_1-C_6 alkyl, or aralkyl(C_1-C_6);~~

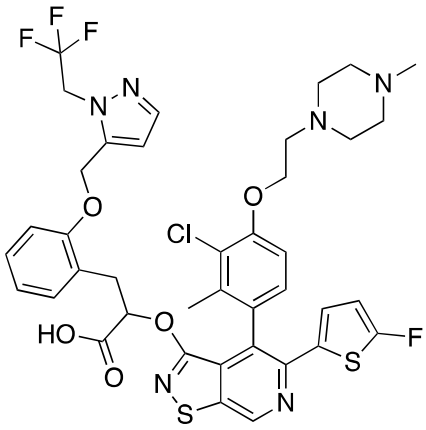
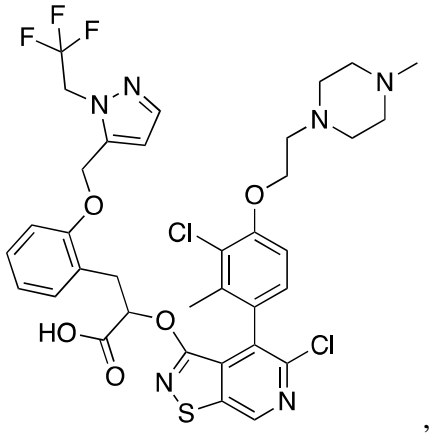
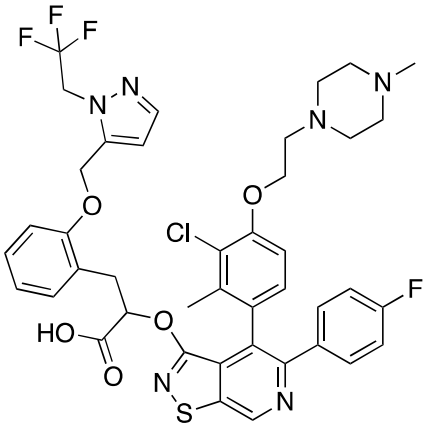
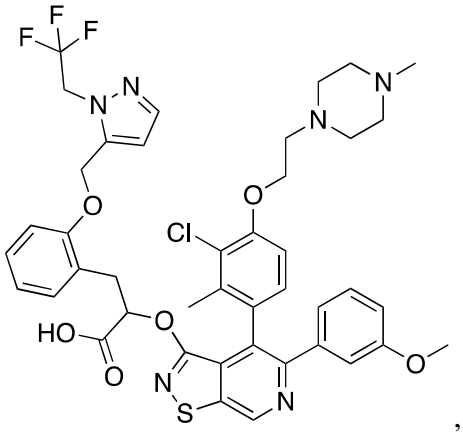
~~R^6 in each instance is independently H, C_1-C_6 alkyl, or C_1-C_6 aminoalkyl; and~~

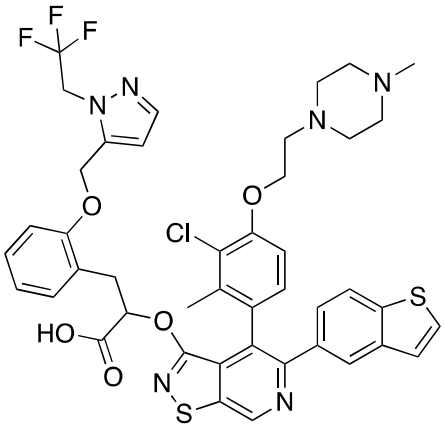
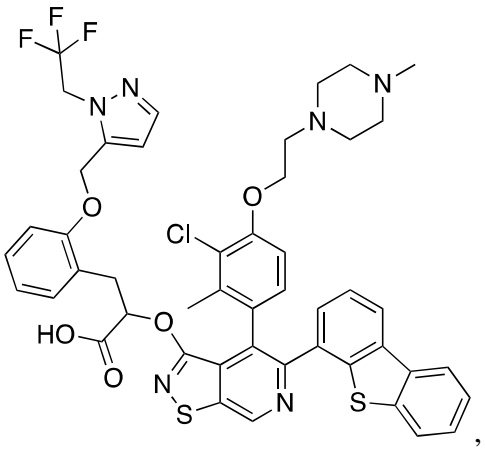
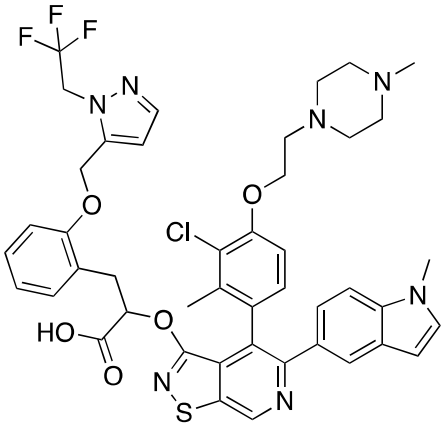
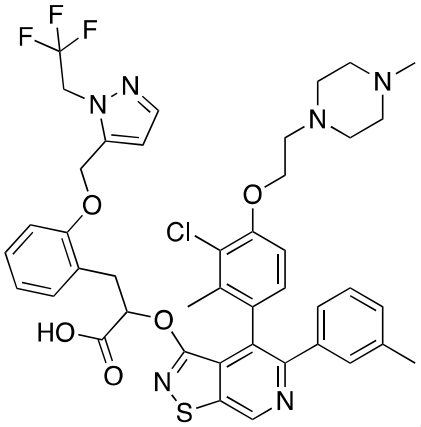
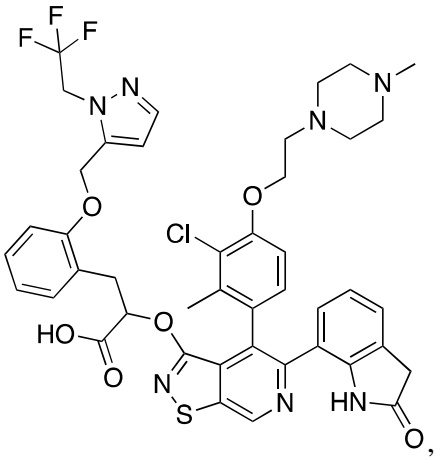
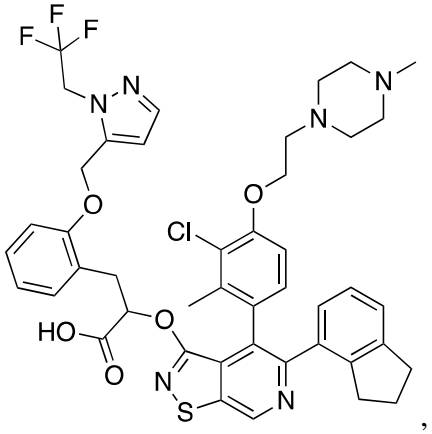
~~q, in the instance of F substitution with R^{X3}, is 0.~~

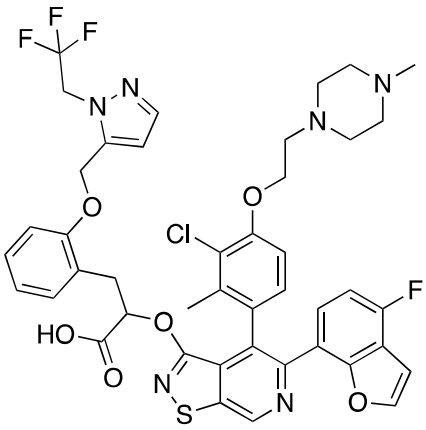
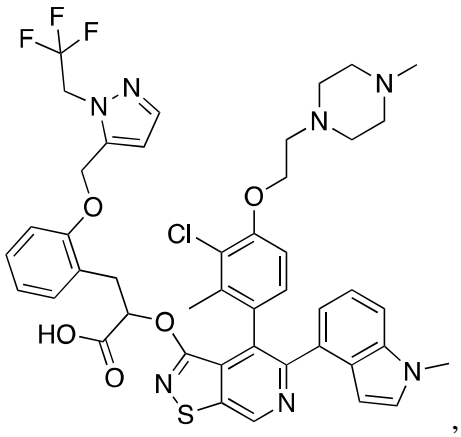
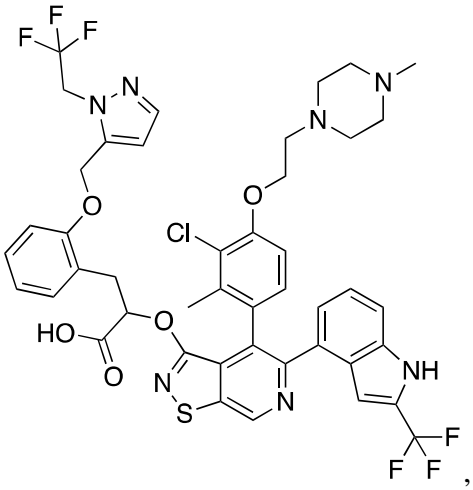
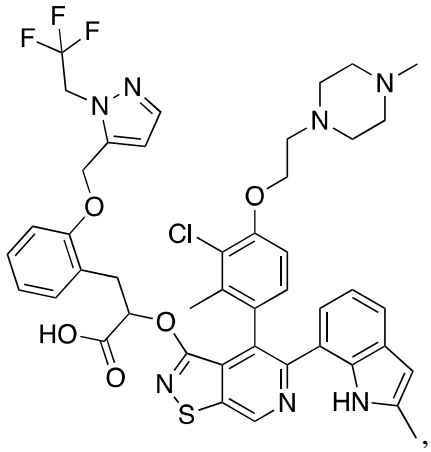
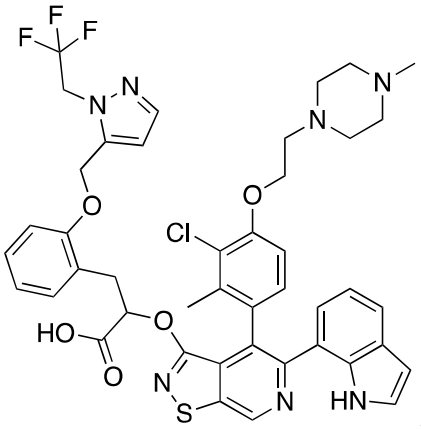
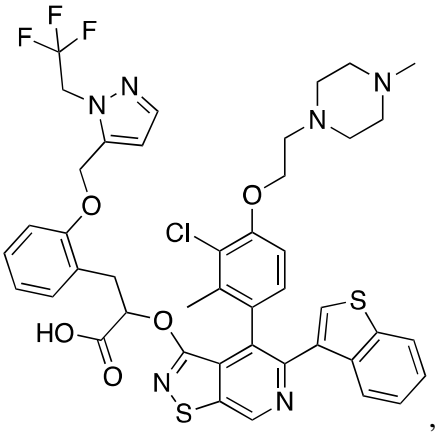
~~39. The compound of any of claims 1, 3, 15, 26, 34, 35 and 36, wherein R^{W1} is~~  ~~.~~

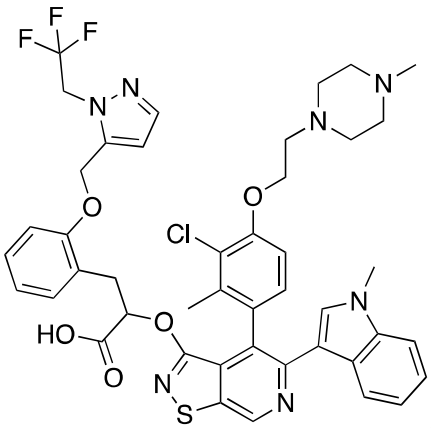
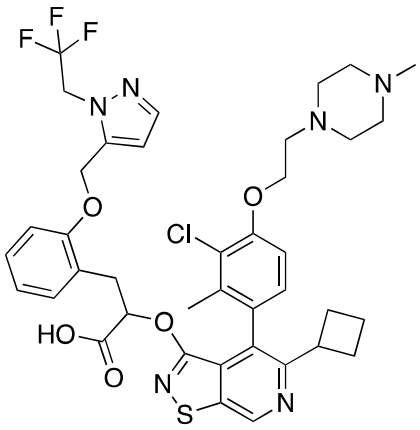
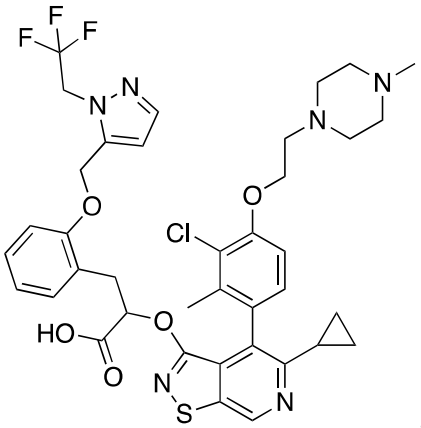
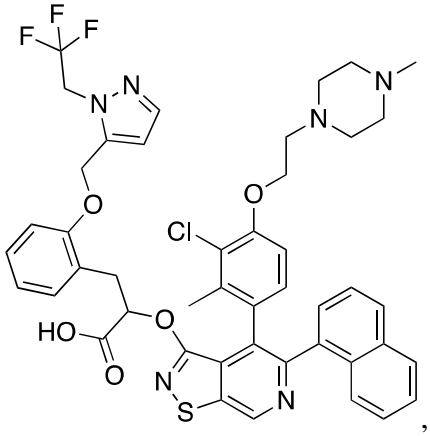
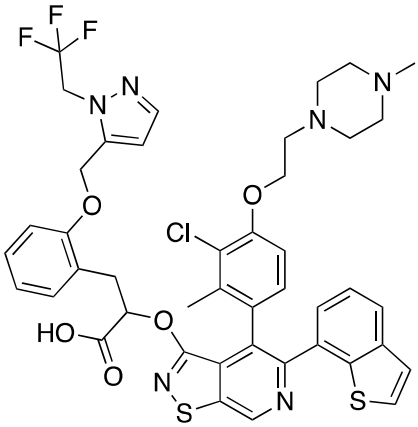
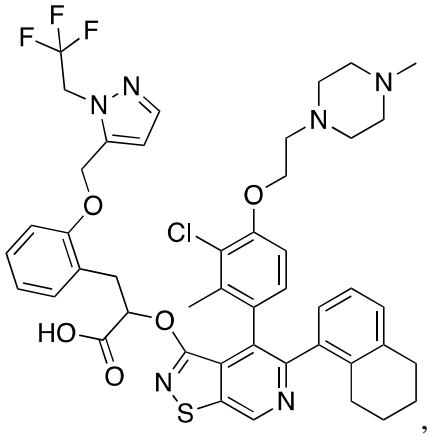
~~40.~~21. The compound of any of claims ~~1—39~~1-20, wherein C_1-C_6 haloalkyl is trifluoromethane or trifluoroethane.

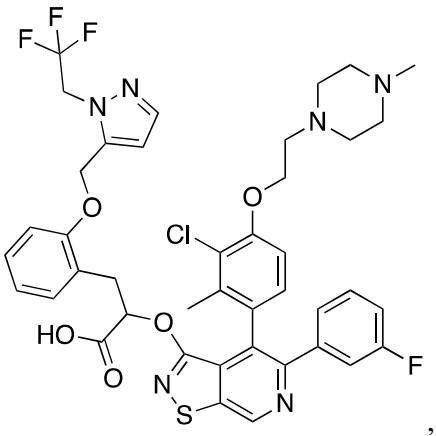
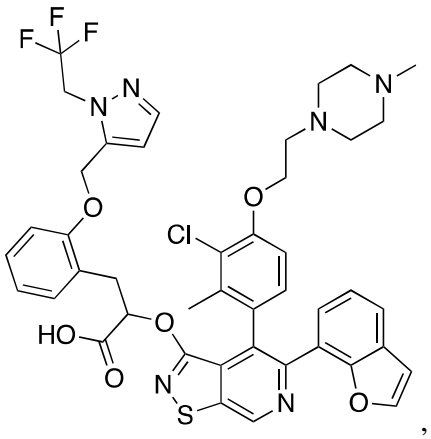
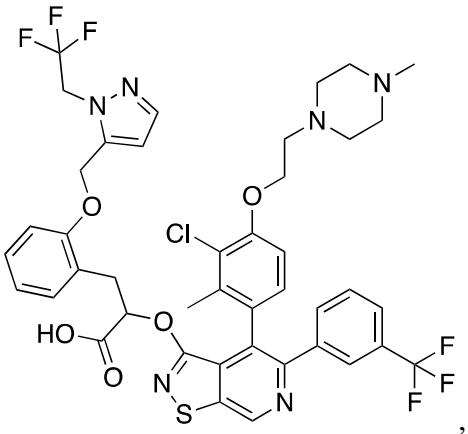
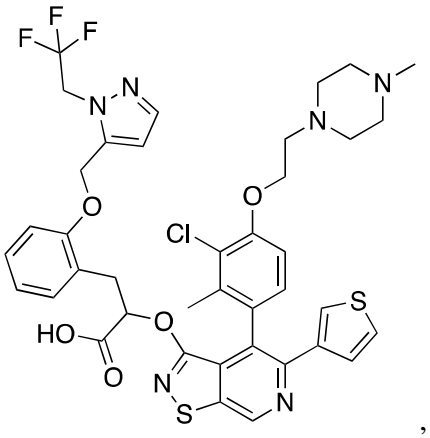
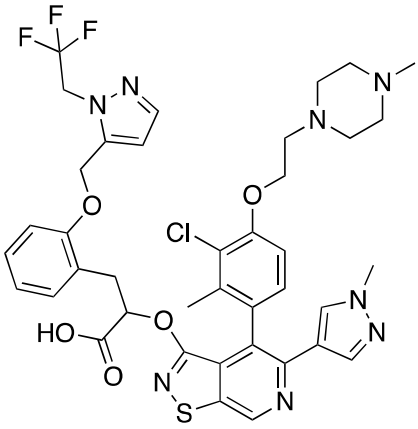
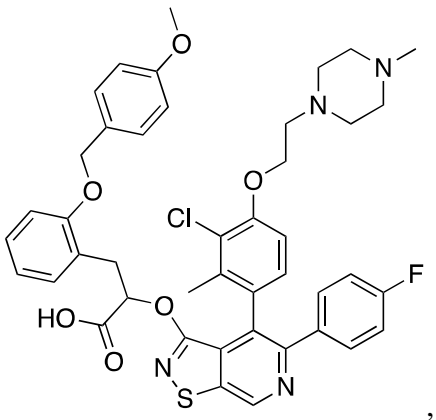
~~41.~~22. A compound selected from:

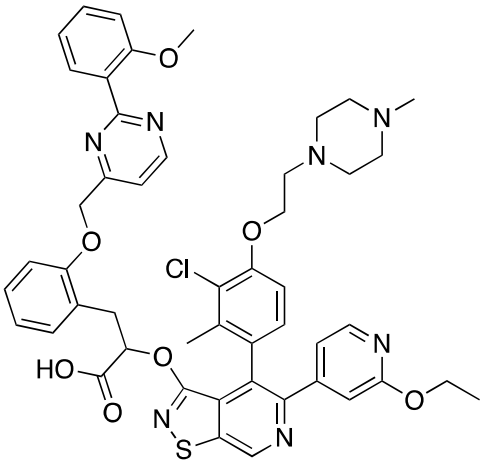
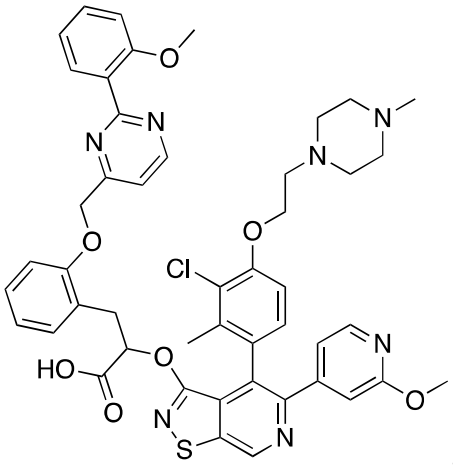
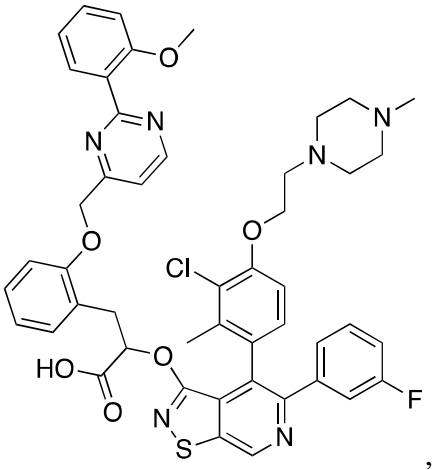
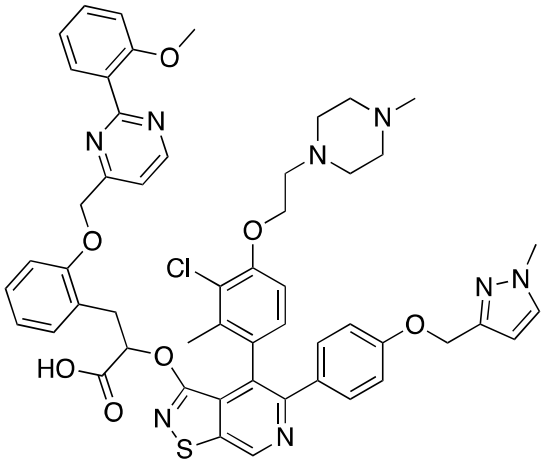
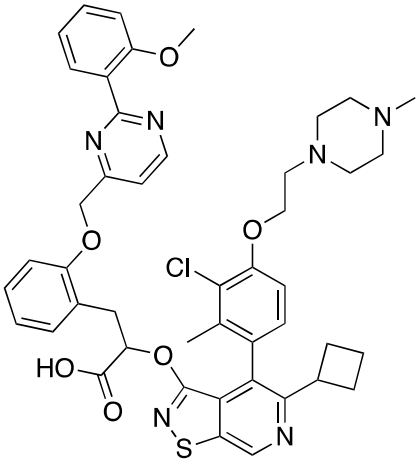
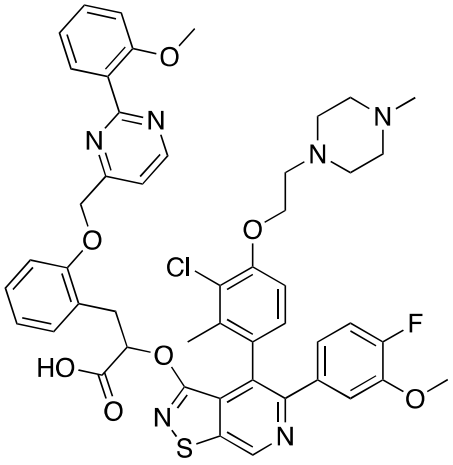

,

,

,

,

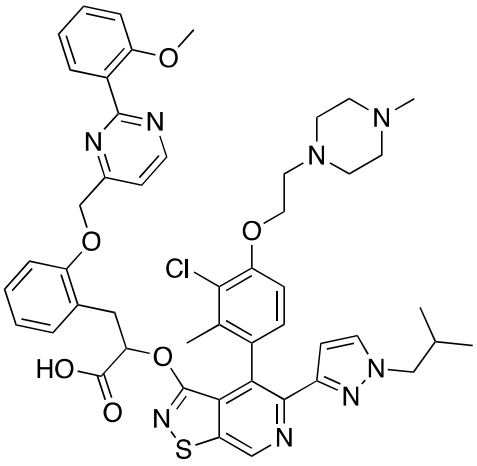
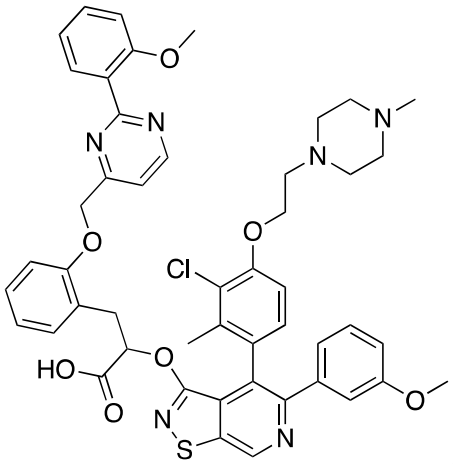
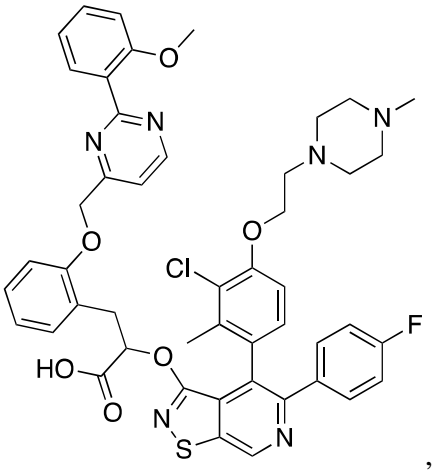
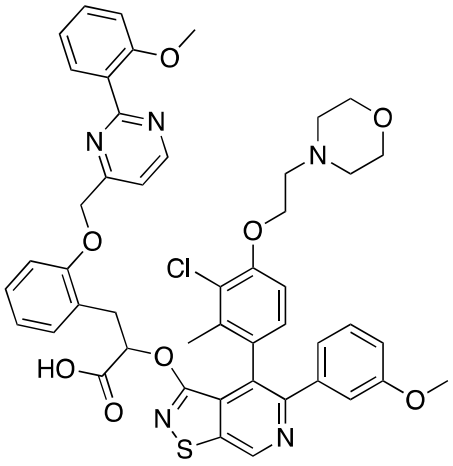
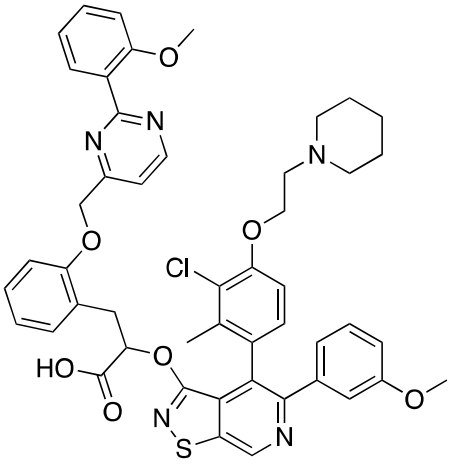
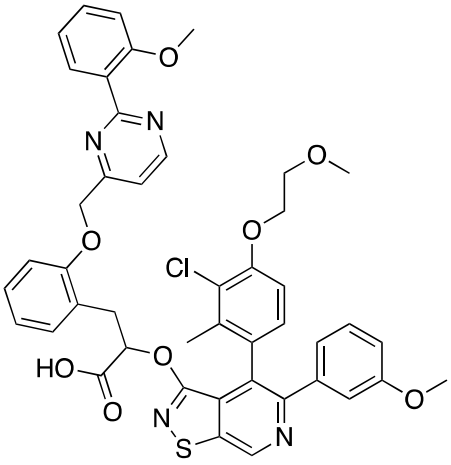

,

,

,

,

,

,

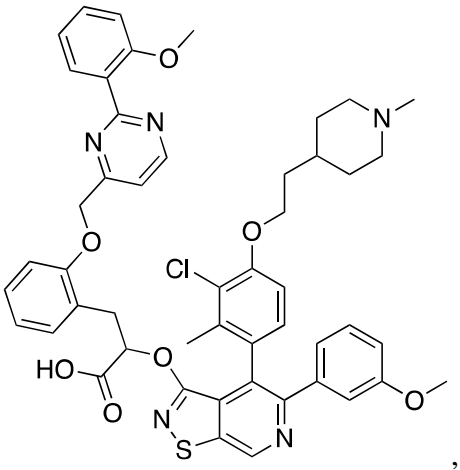
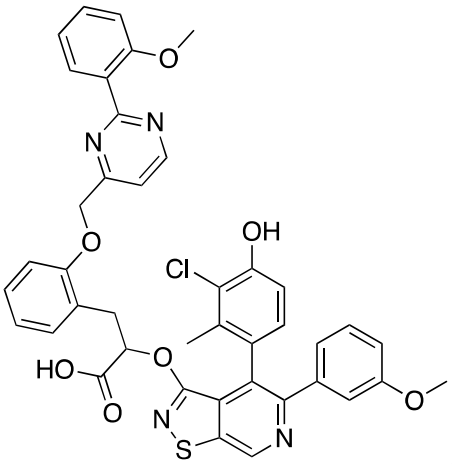
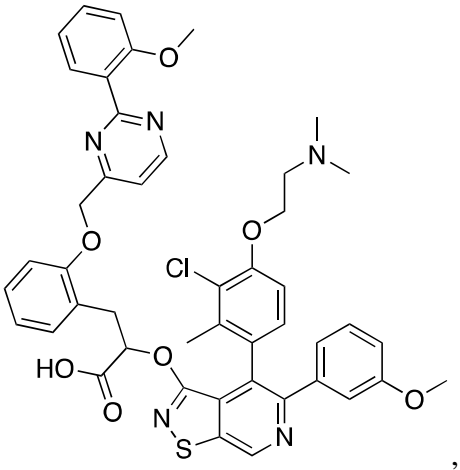
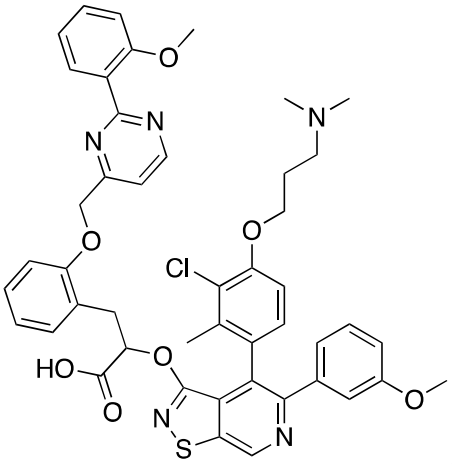

,

,

,

,

,

,

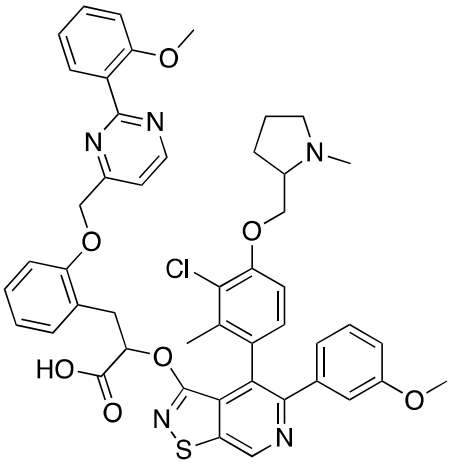

,

,

,

,

,

,

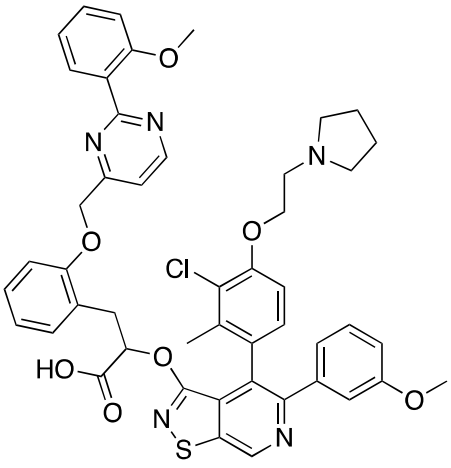

,

,

,

,

,

,

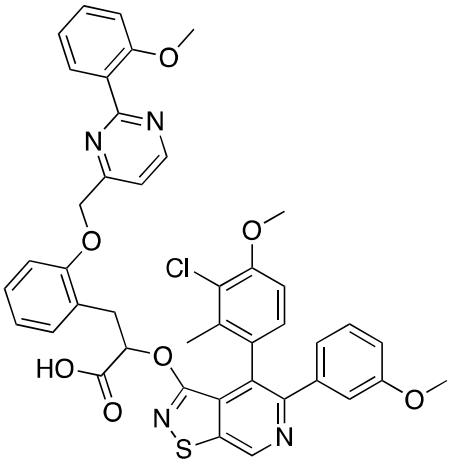

,

,

,

,

,

,


,

,

,

,

,

,


,

,

,

,

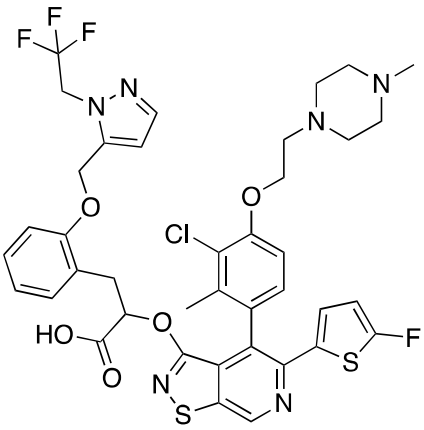
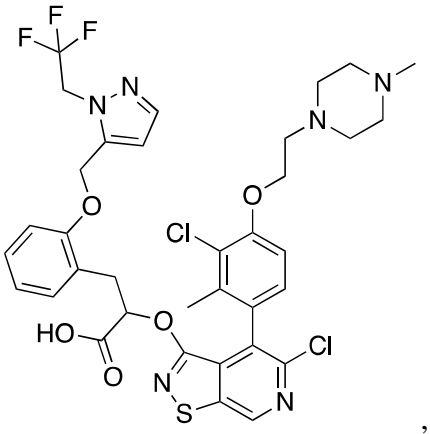
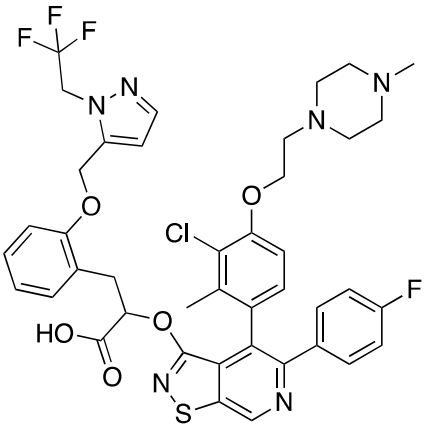
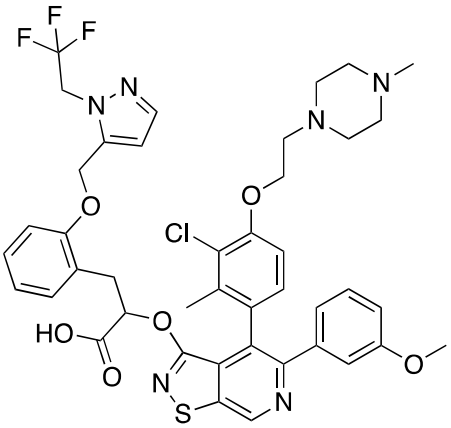
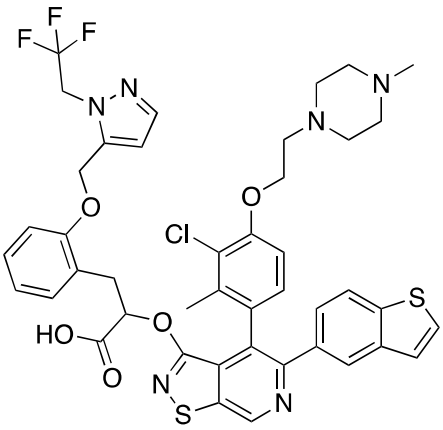
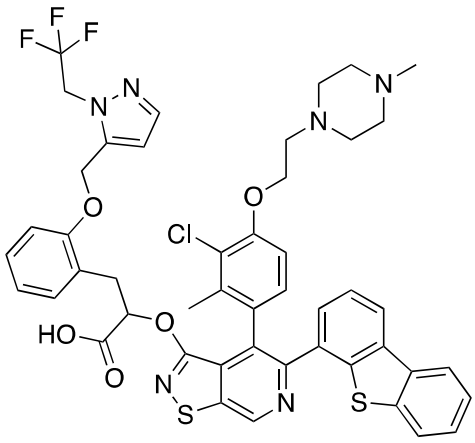


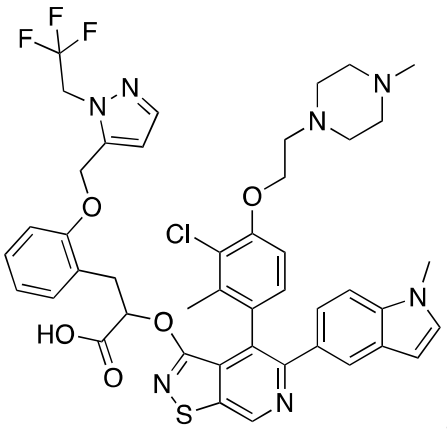
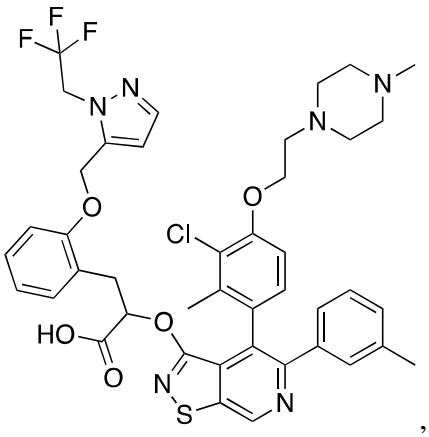
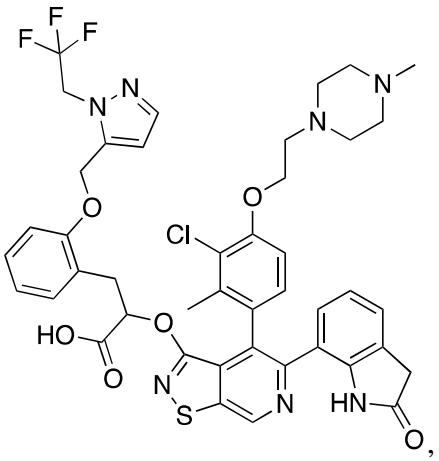
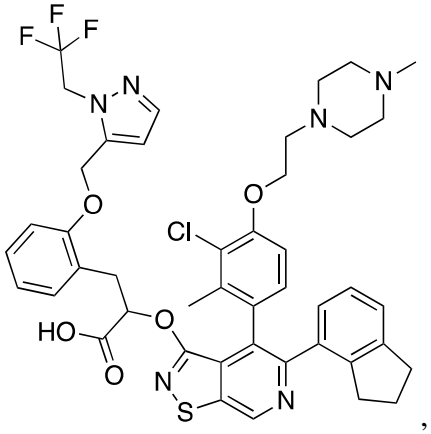
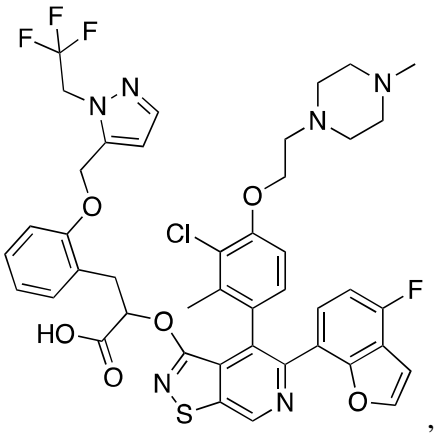
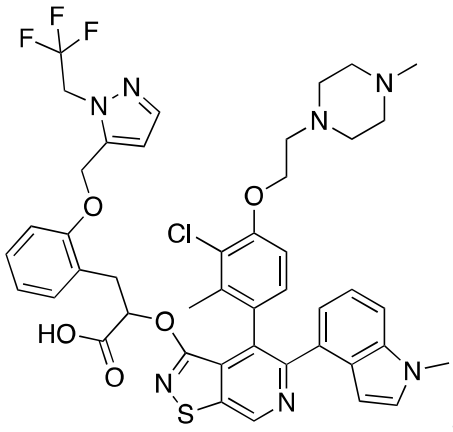
, 

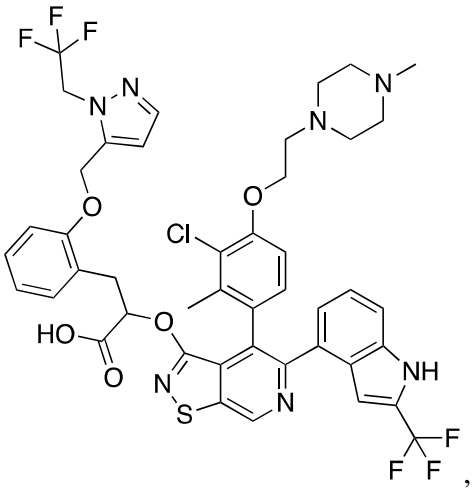
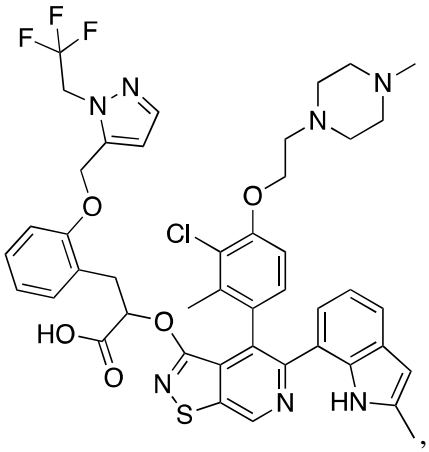
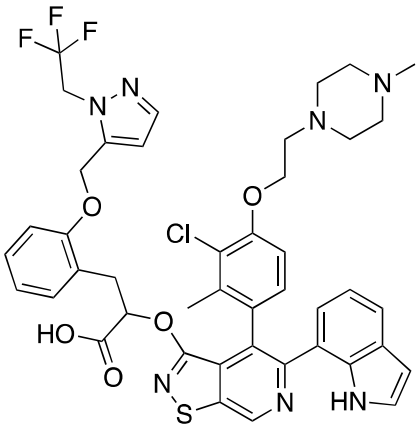
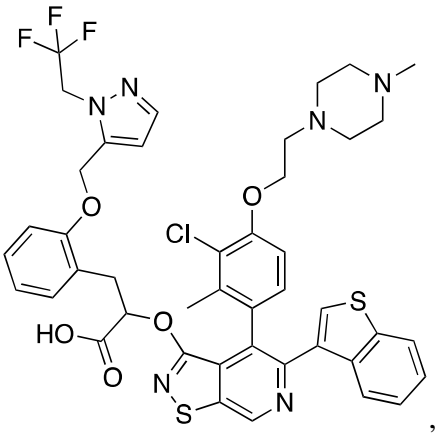
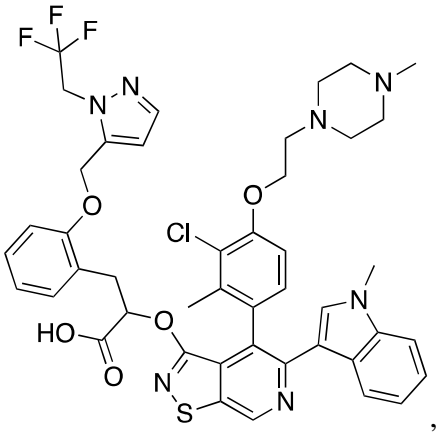
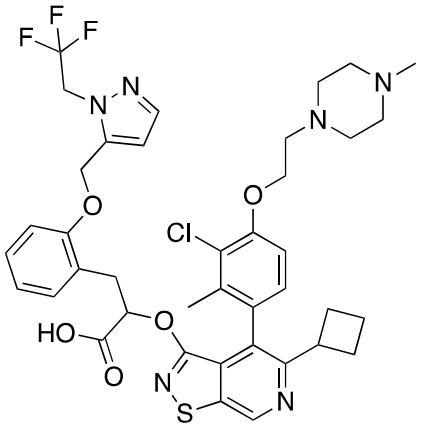
, and 

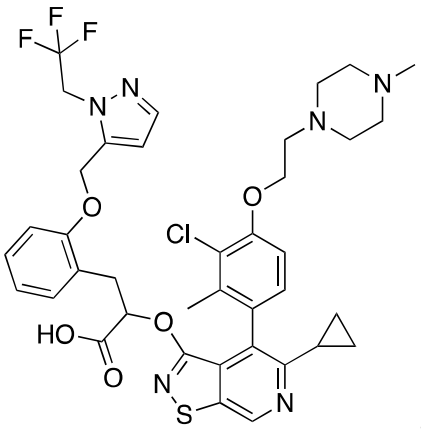
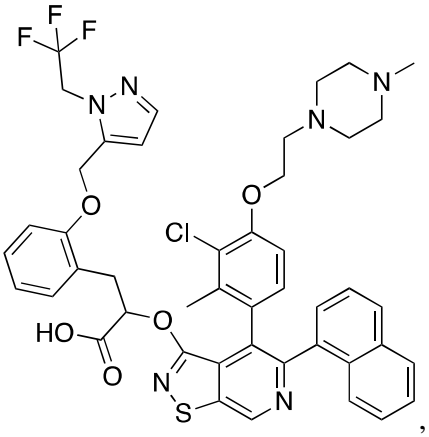
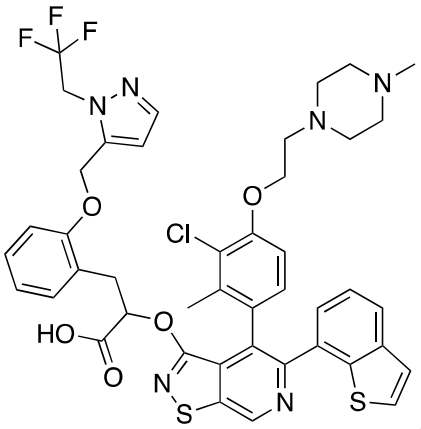
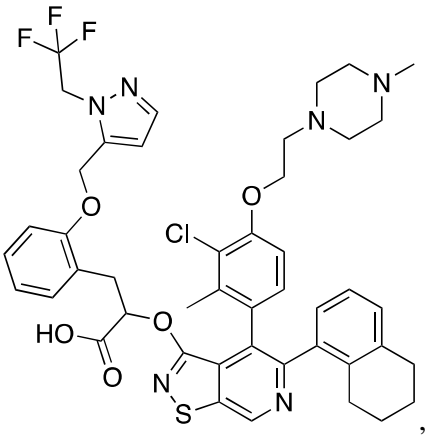
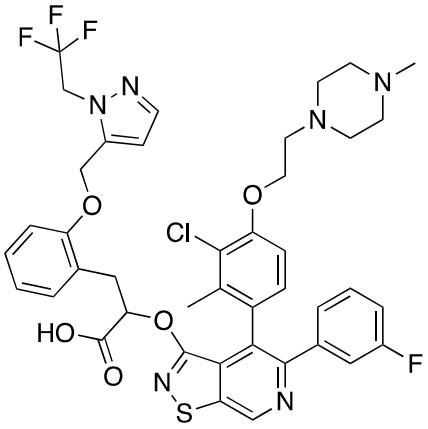
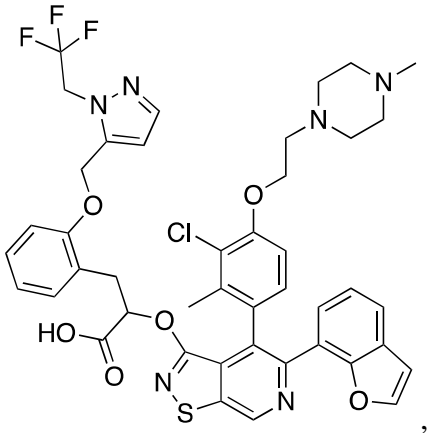
, or a pharmaceutically acceptable salt thereof.

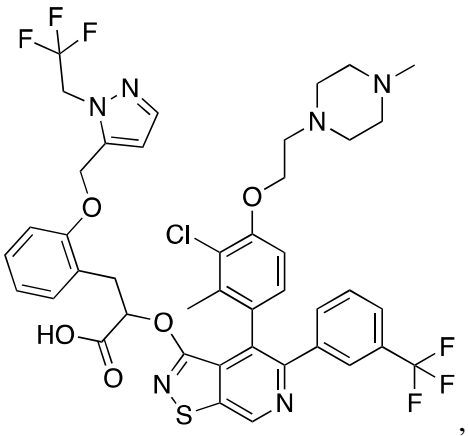
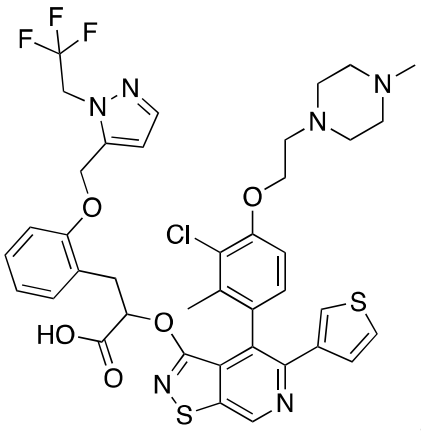
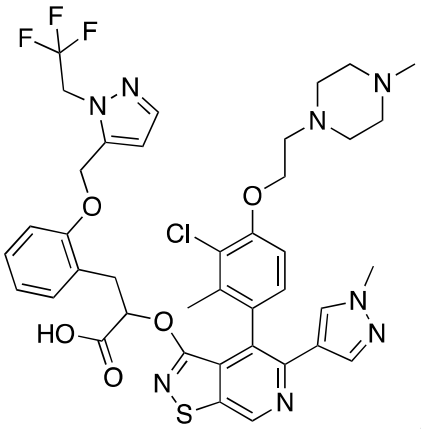
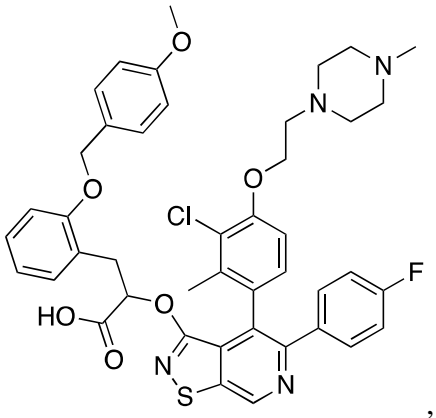
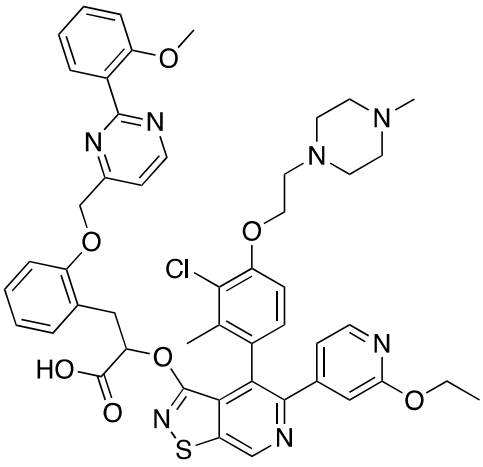
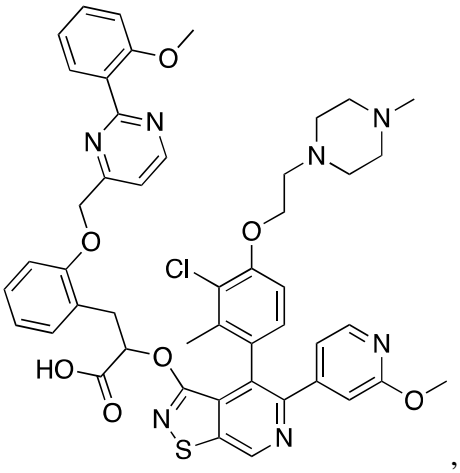
~~42.~~23. A compound selected from:

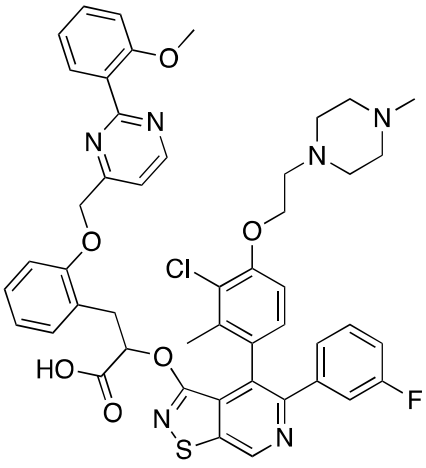
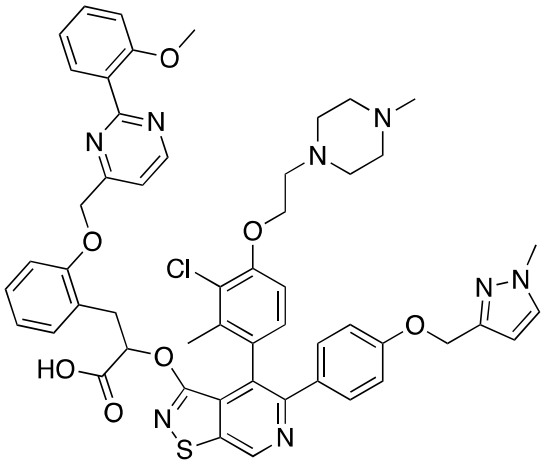
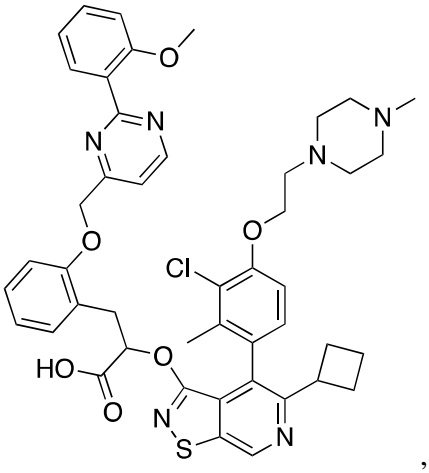
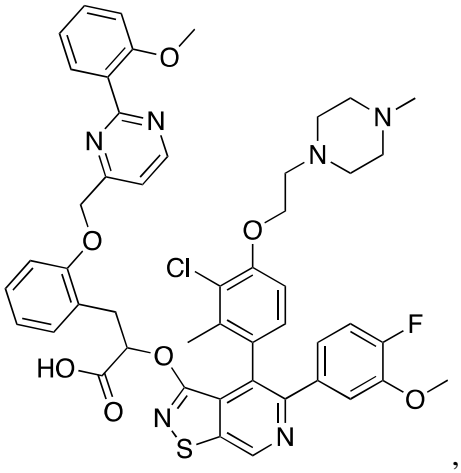
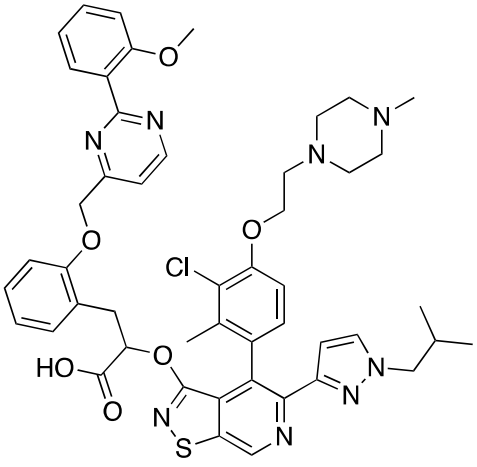
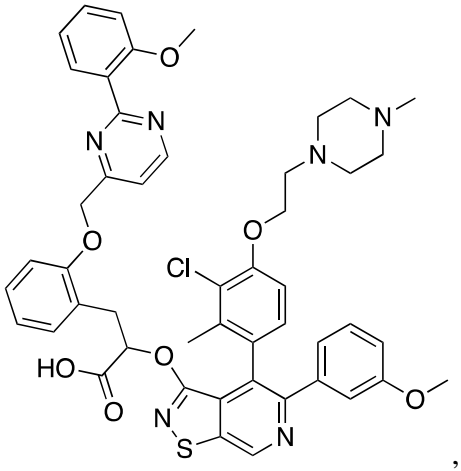

,

,

,

,

,

,

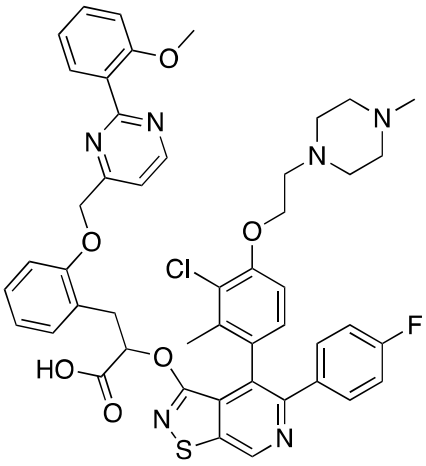
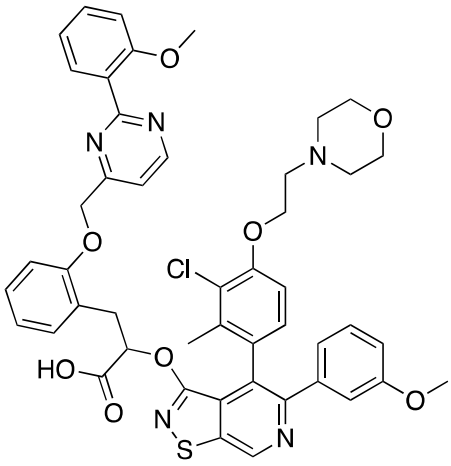
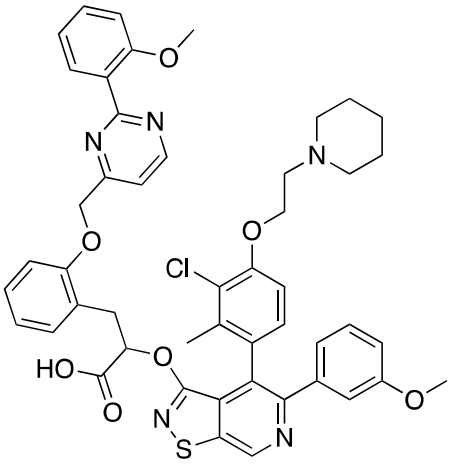
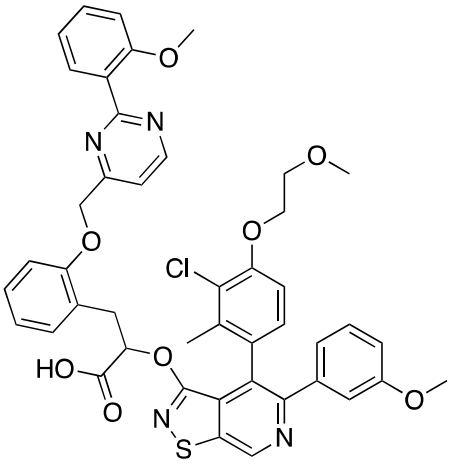
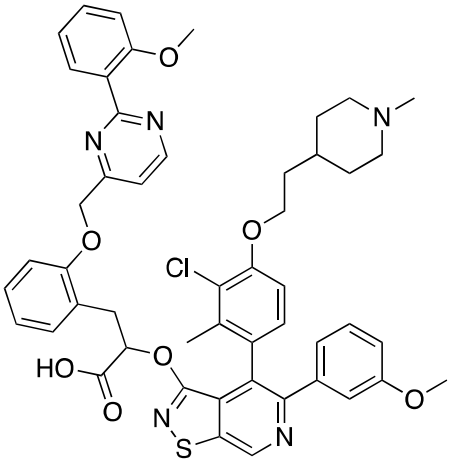
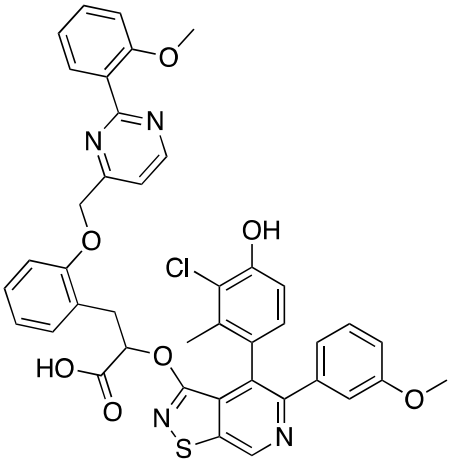

,

,

,

,

,

,

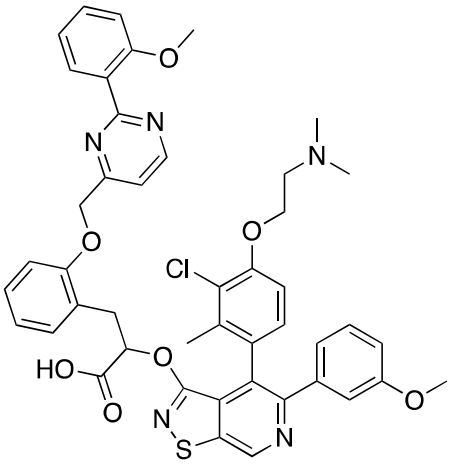
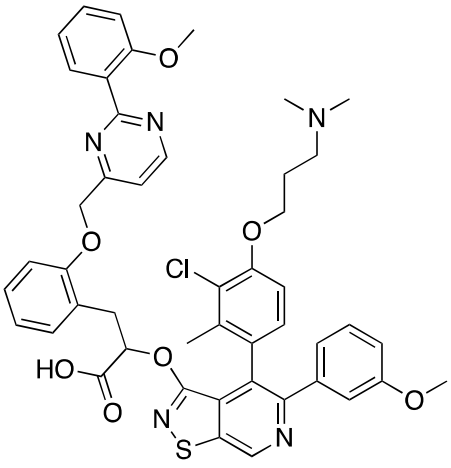
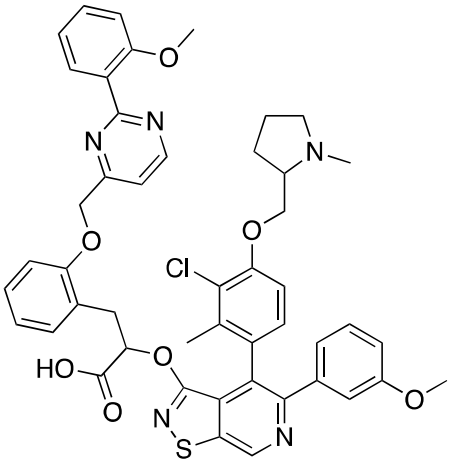
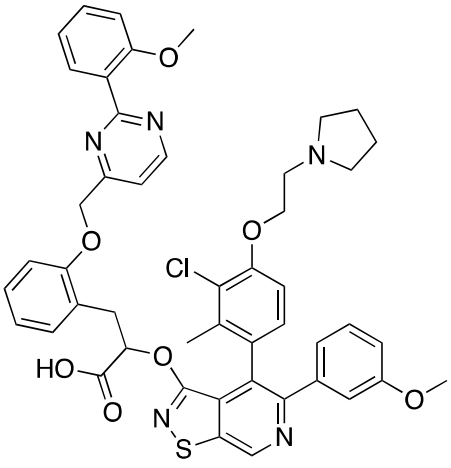
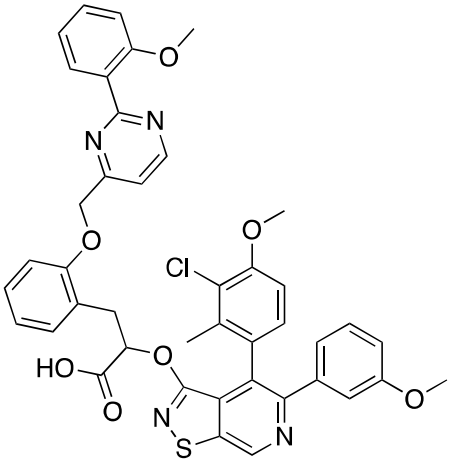
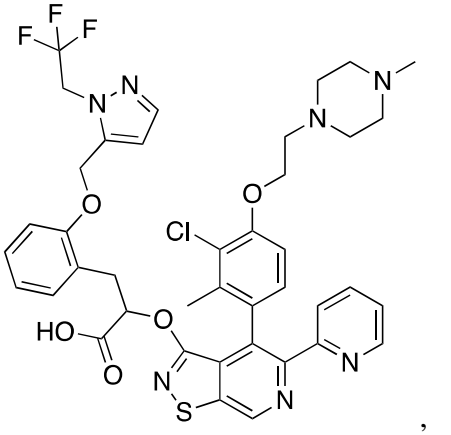

,

,

,

,

,

,

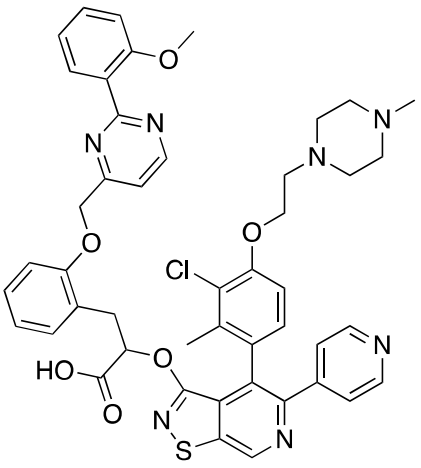
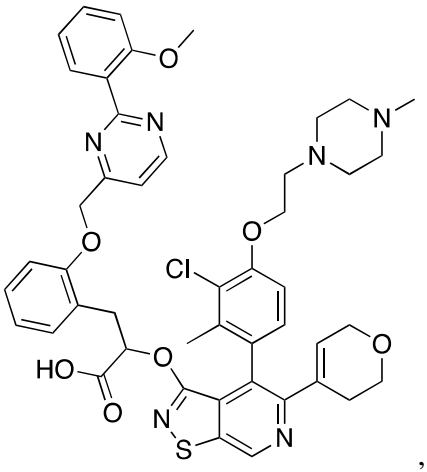
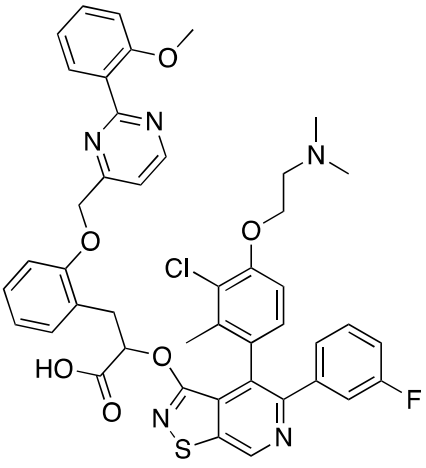
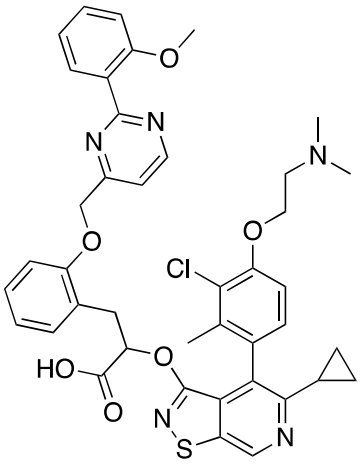
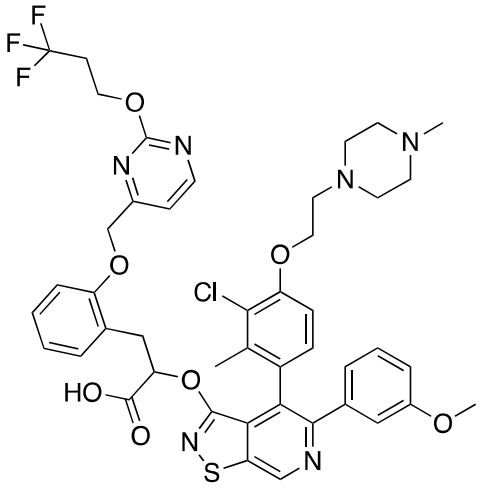
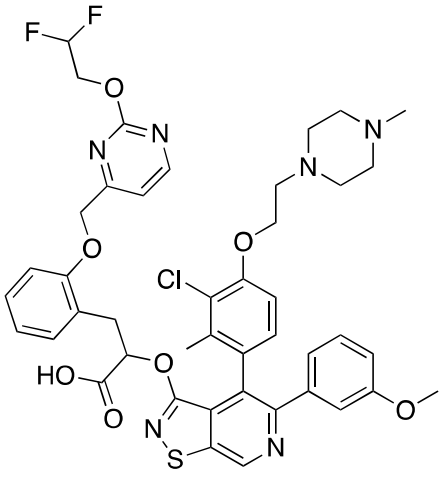

,

,

,

,

,

,

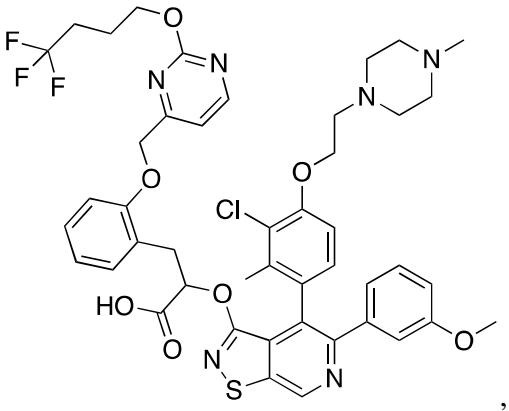
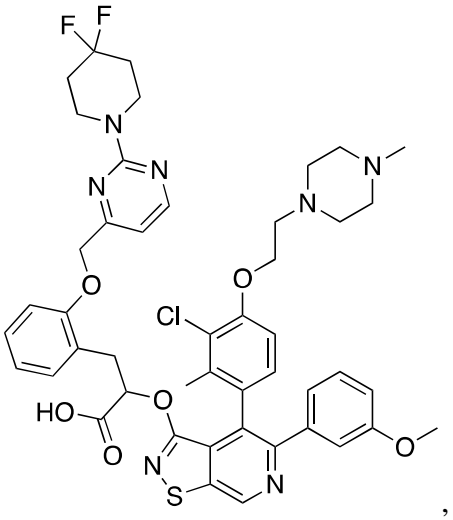
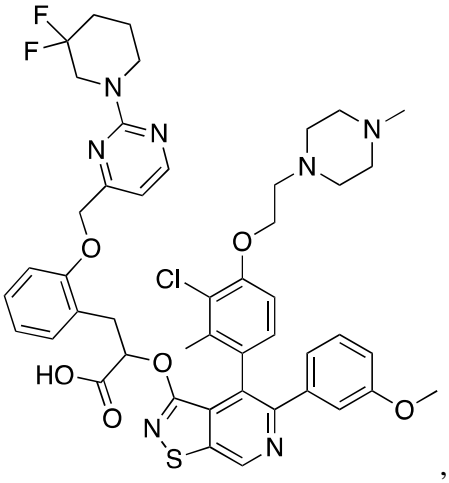
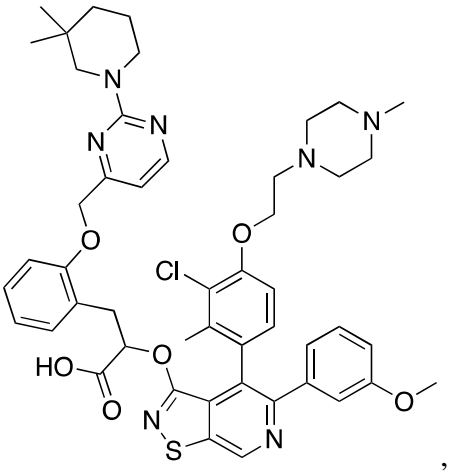
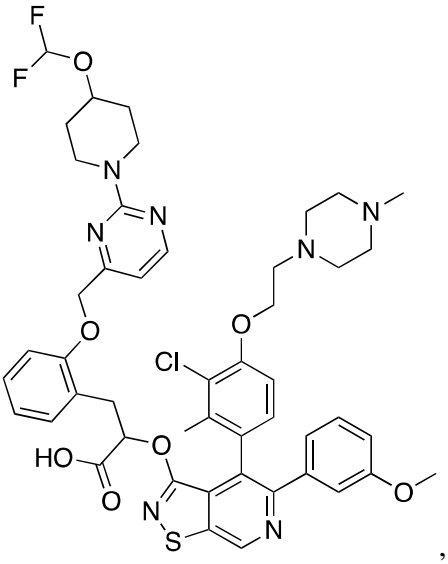
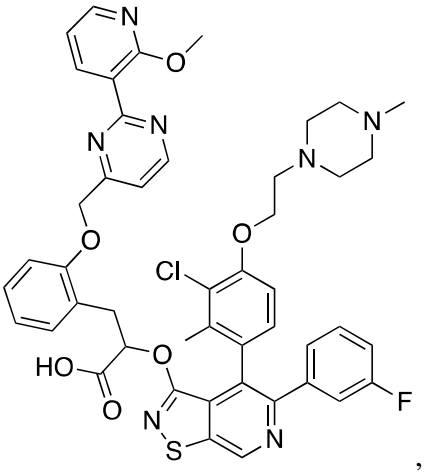

,

,

,

,

,

,

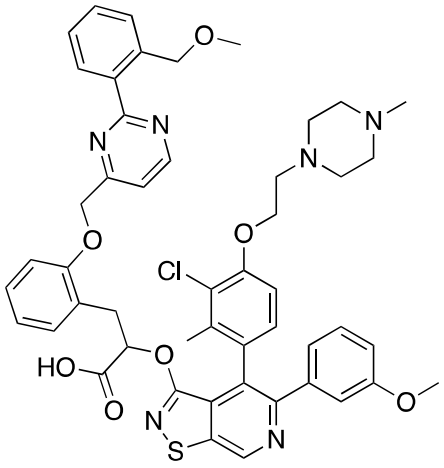
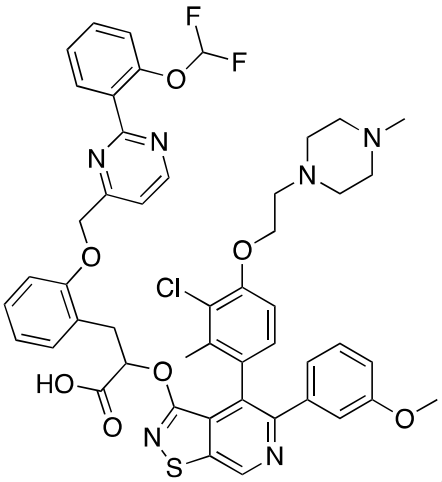
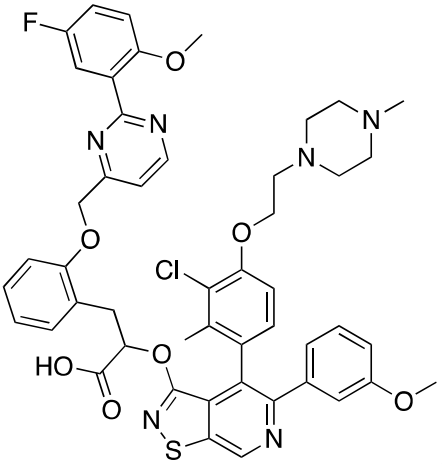
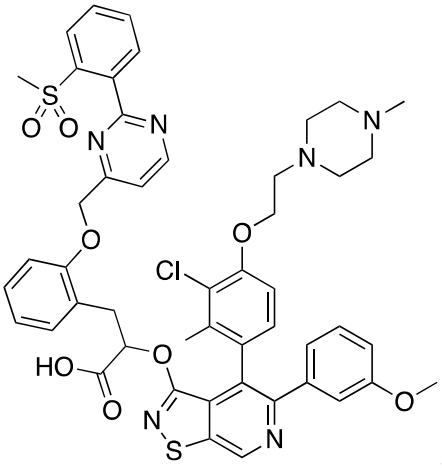
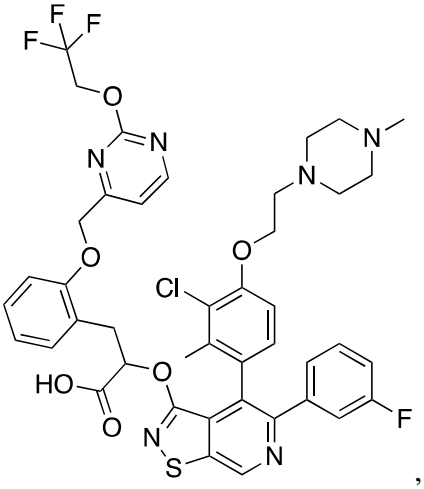
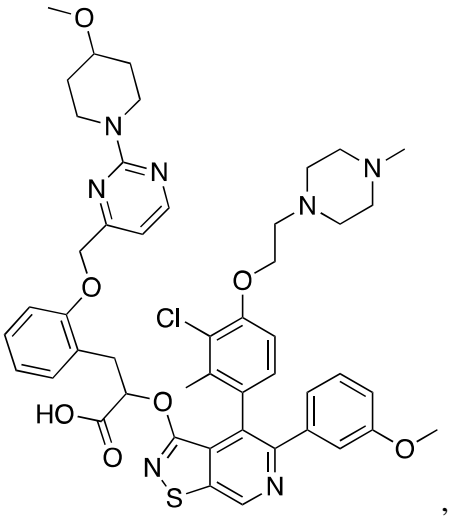

,

,

,

,

,

,

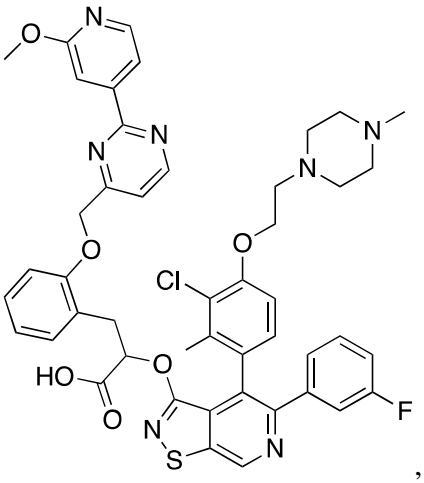
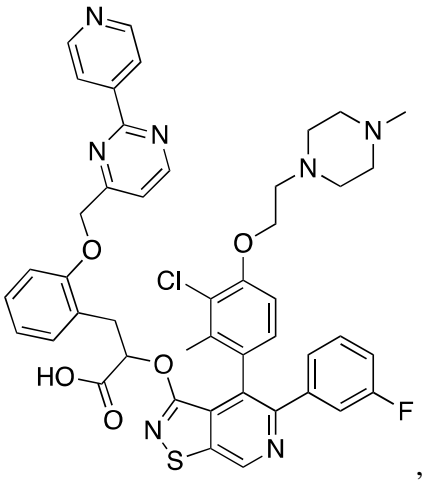
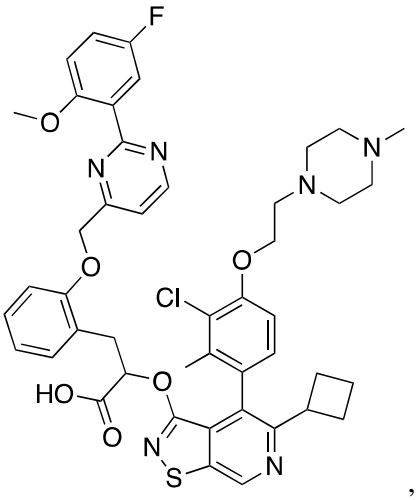
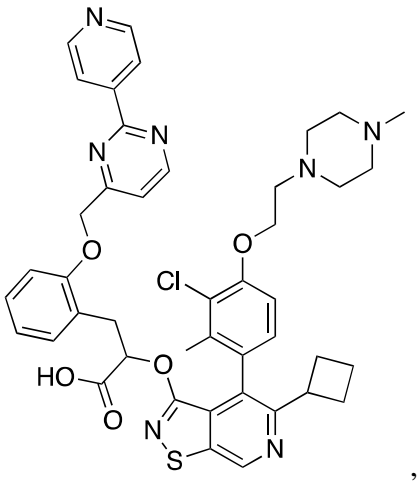
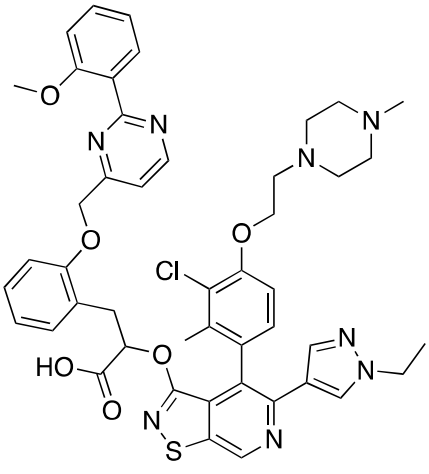
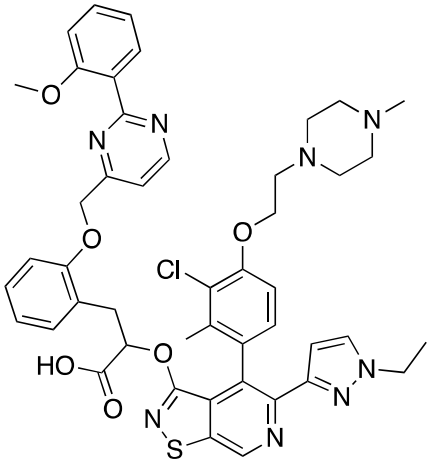

,

,

,

,

,

,

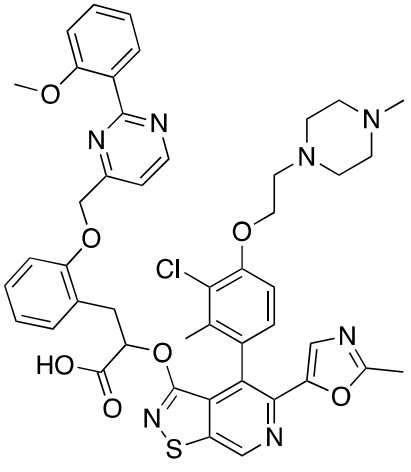
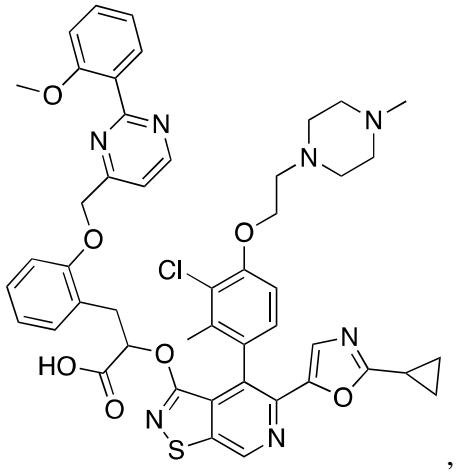
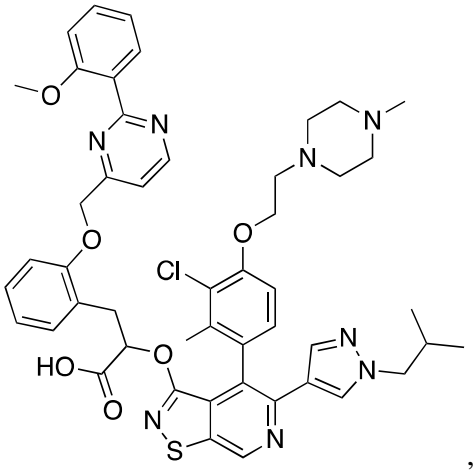
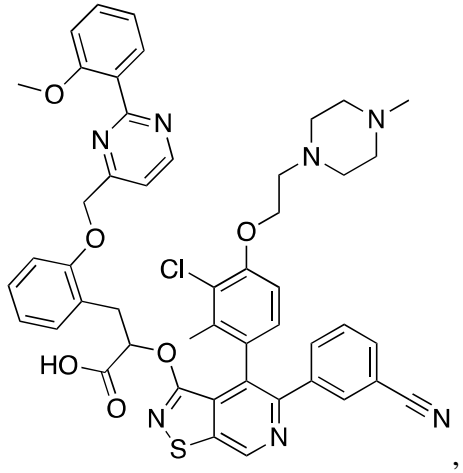
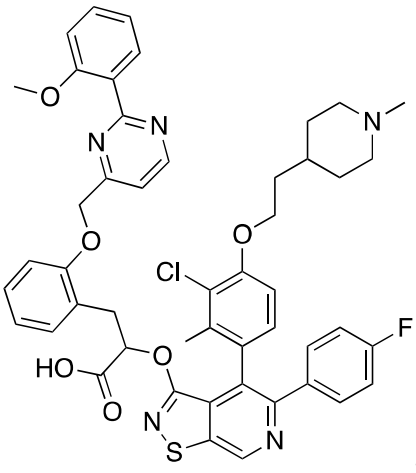
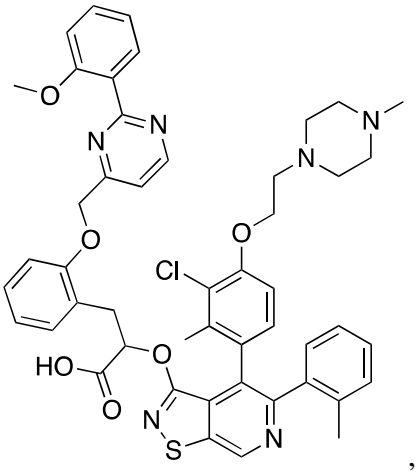

,

,

,

,

,

,

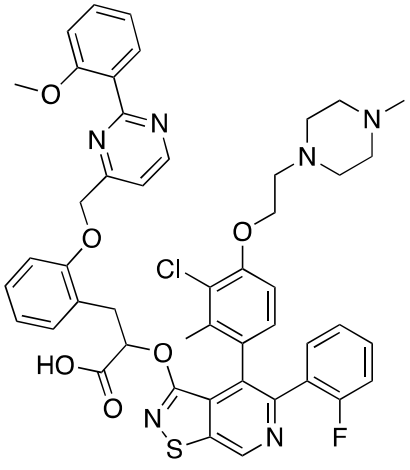
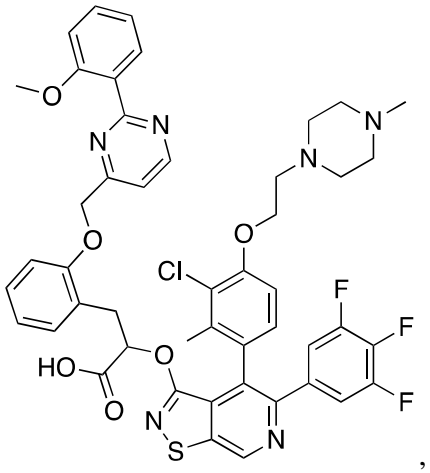
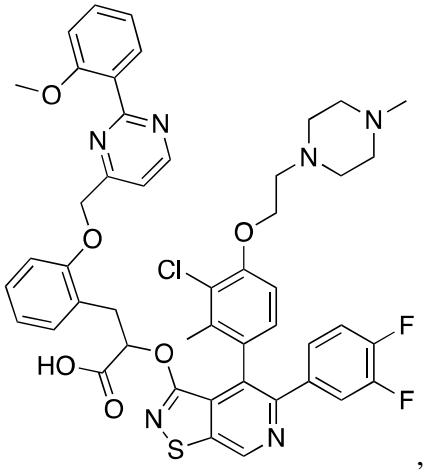
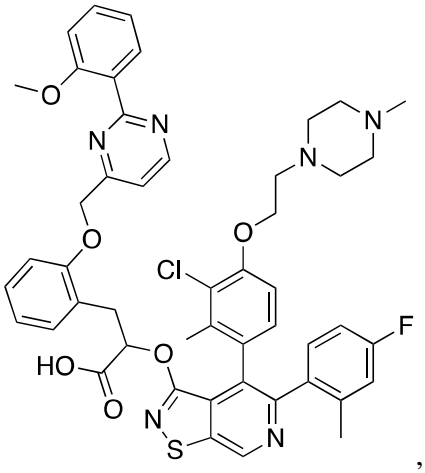
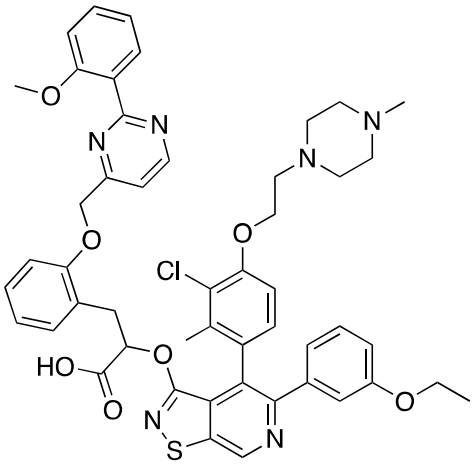
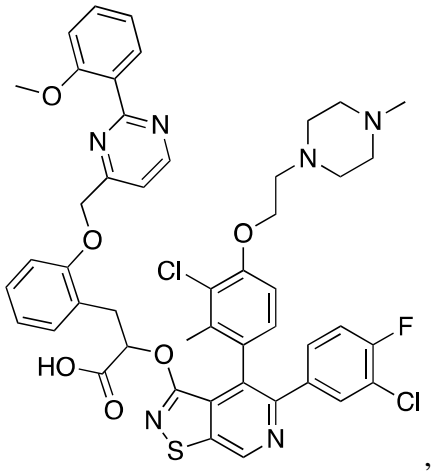

,

,

,

,

,

,

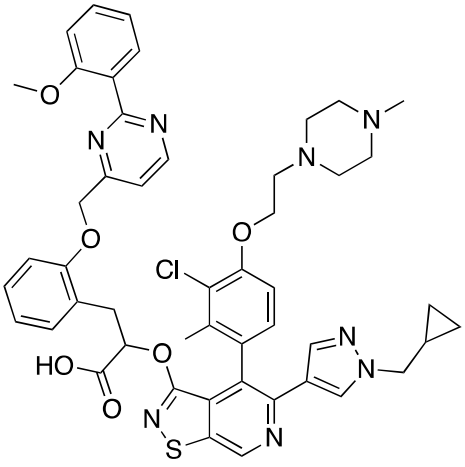
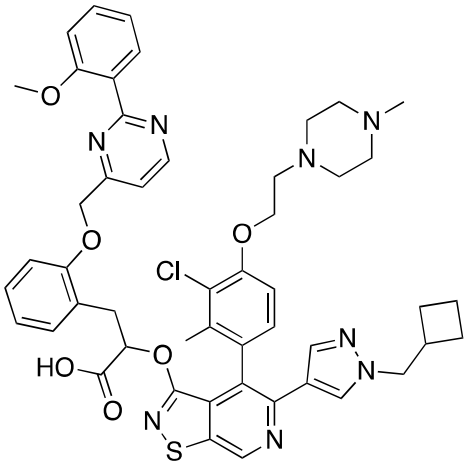
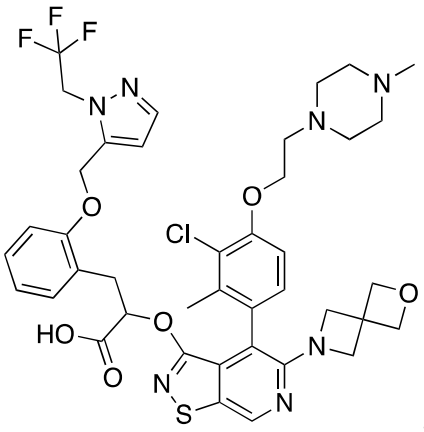
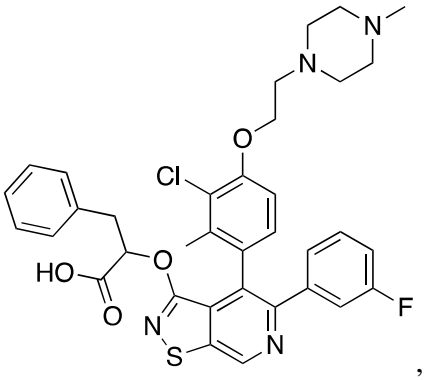
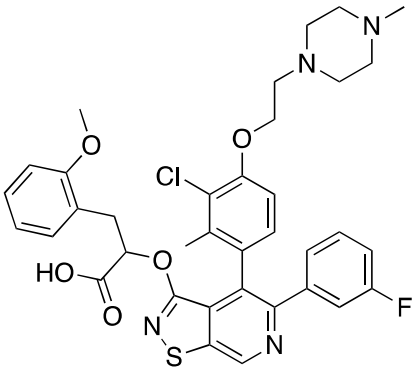
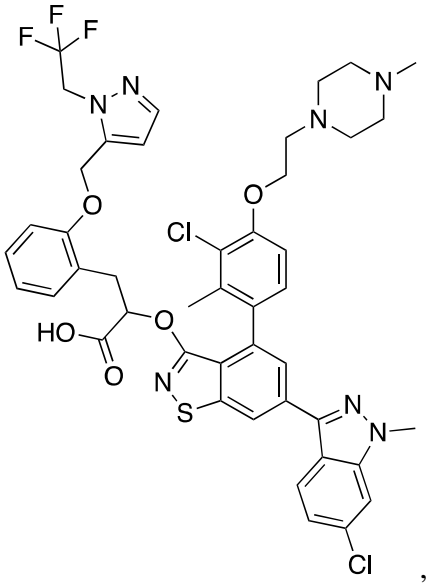

,

,

,

,

,

,

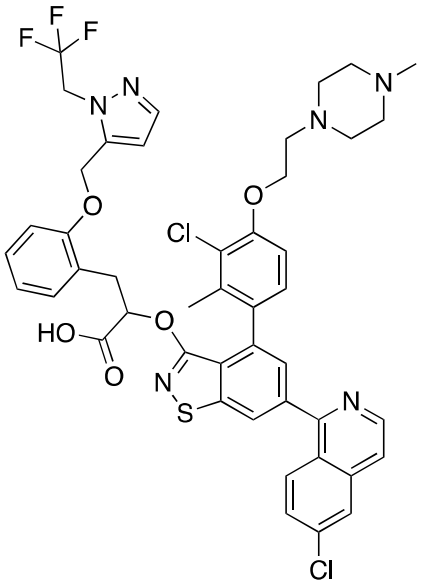
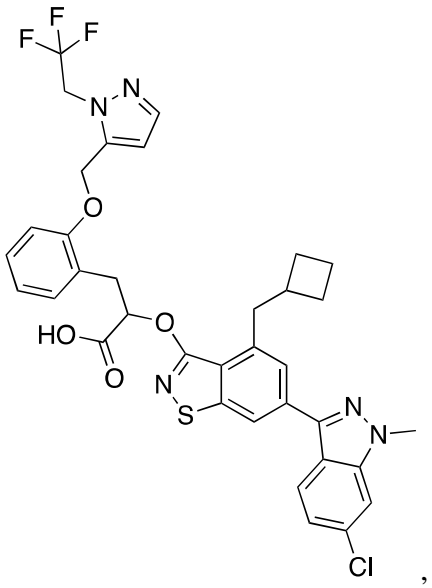
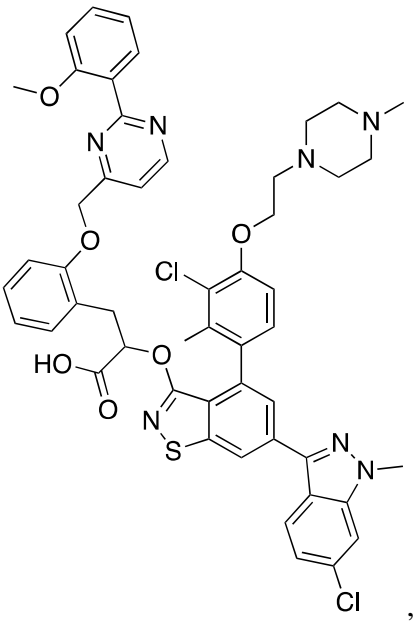
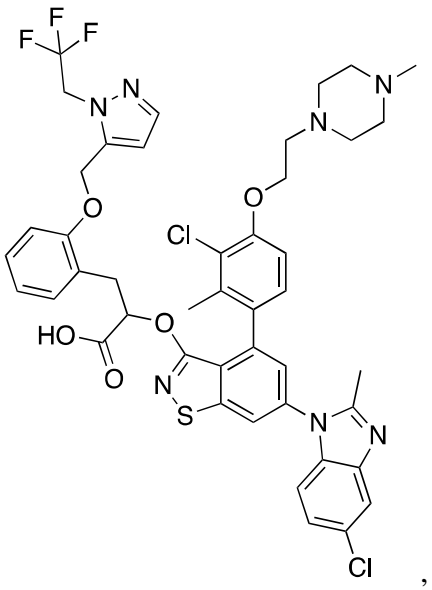

,

,

,

,

,

,

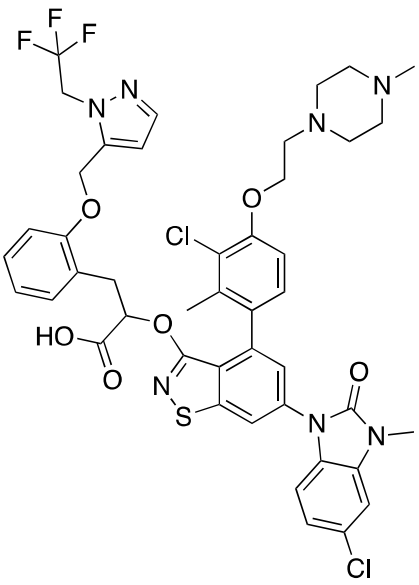
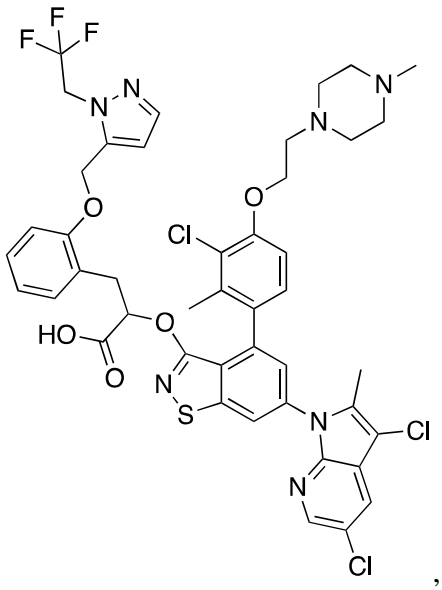
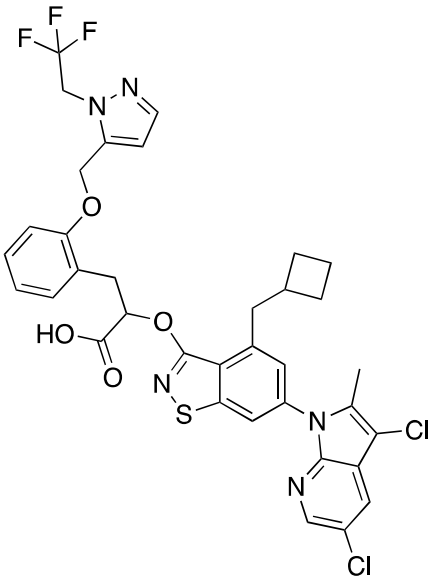
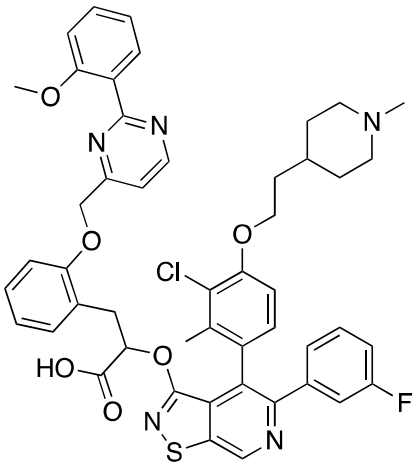

,

,

,

,

,

,


,

,

,

,

,

,

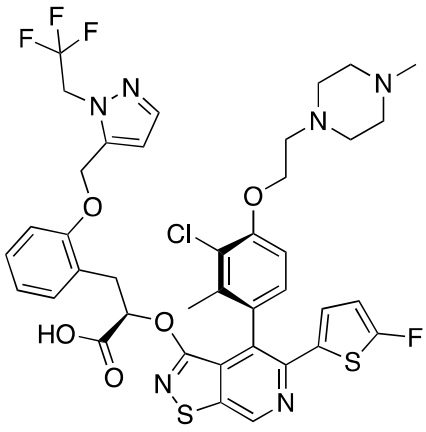
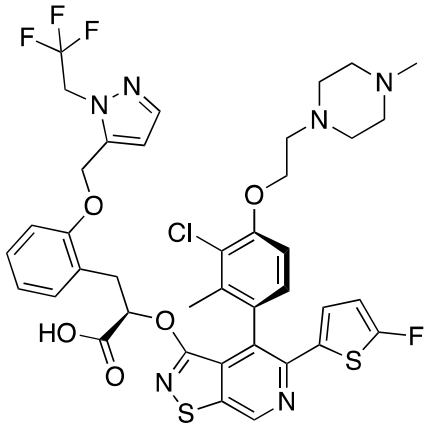
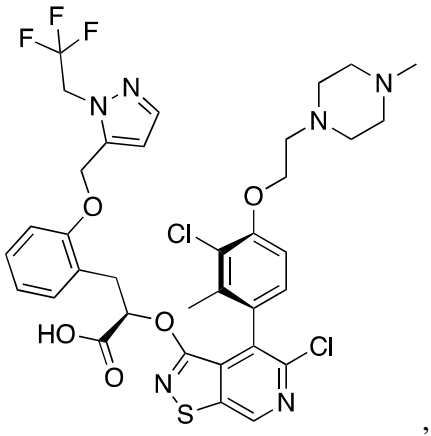
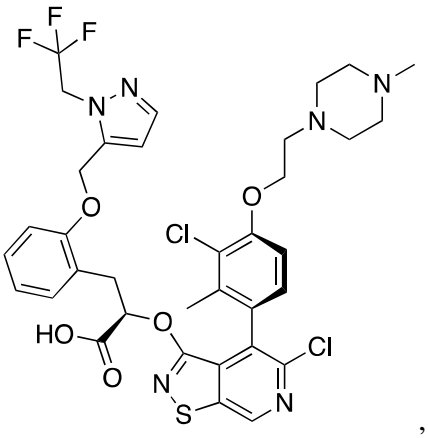
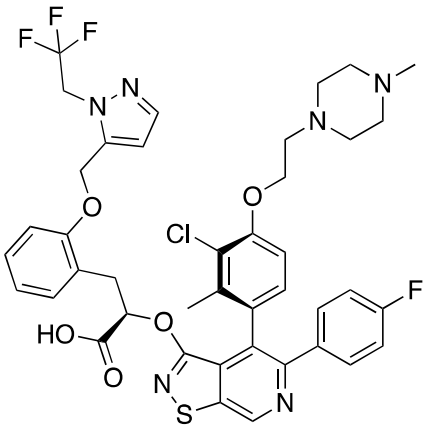
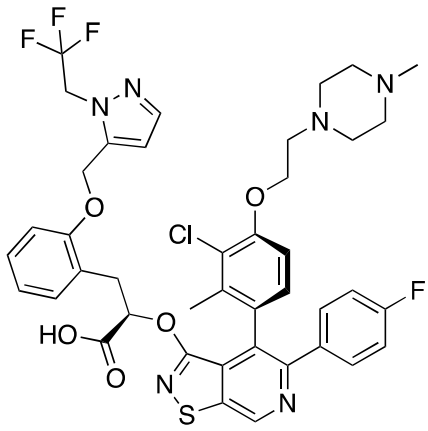

,

,

,

,

,

,

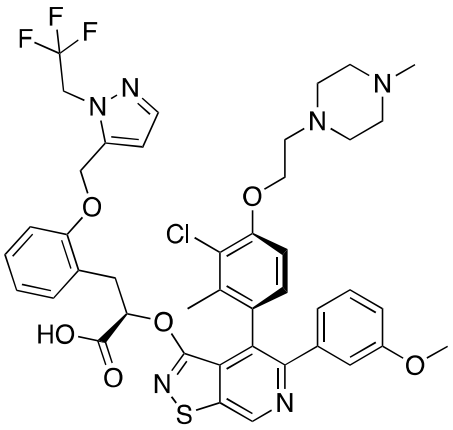
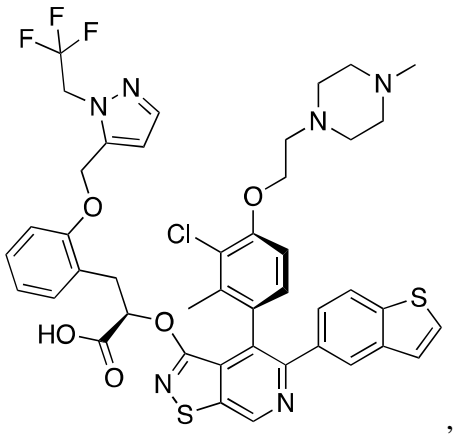
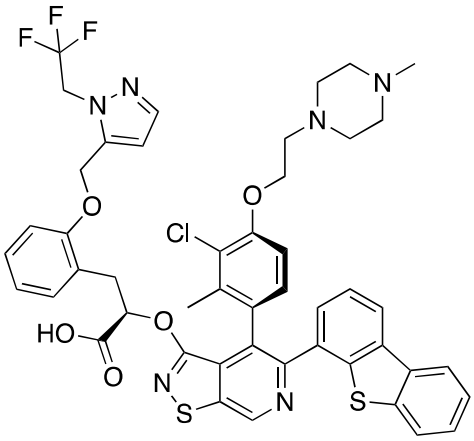
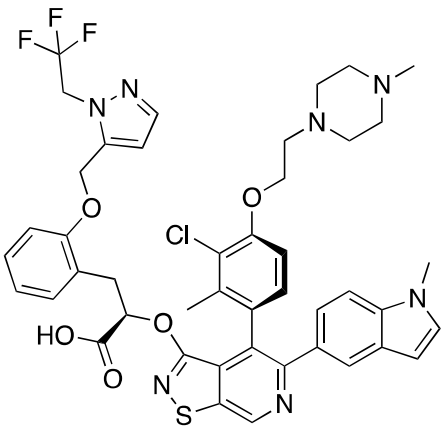
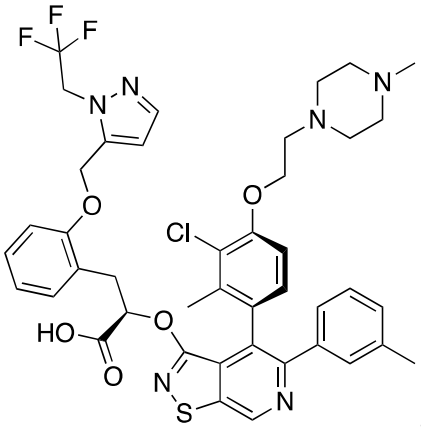
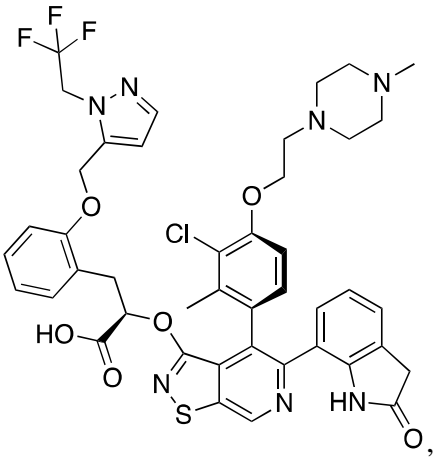

,

,

,

,

,

,

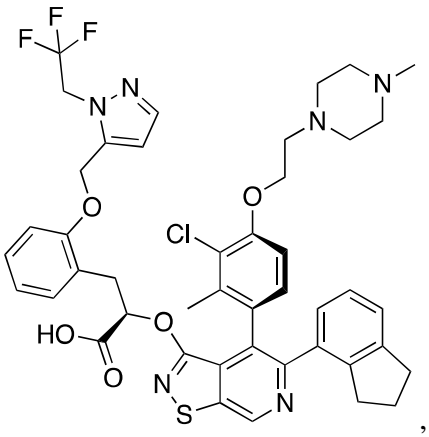
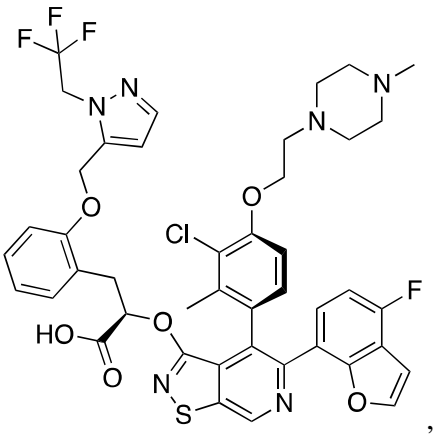
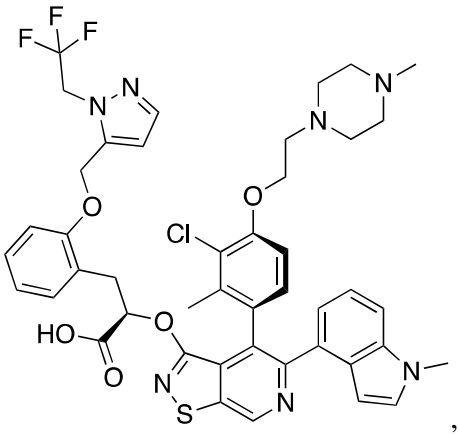
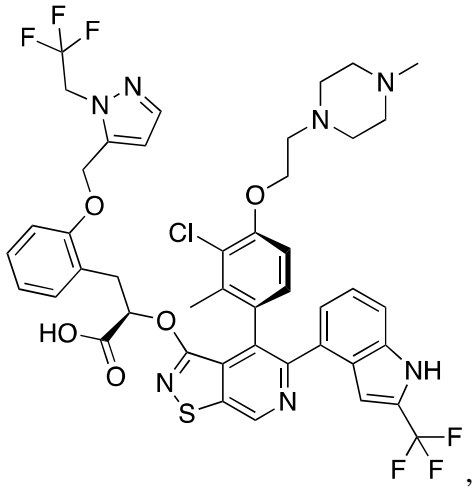
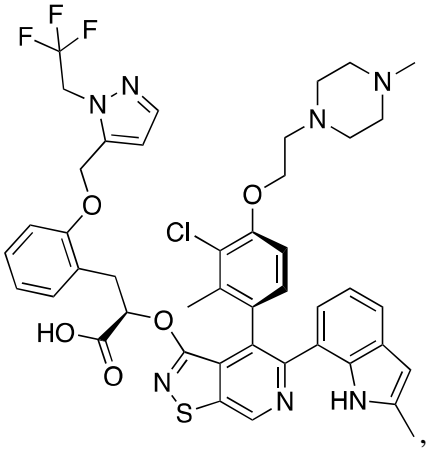
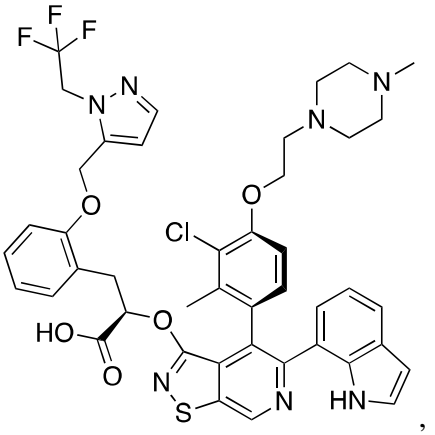

,

,

,

,

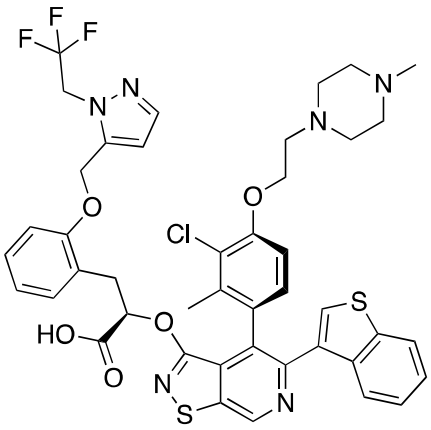
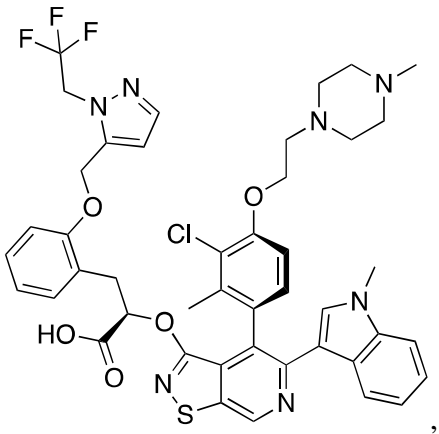
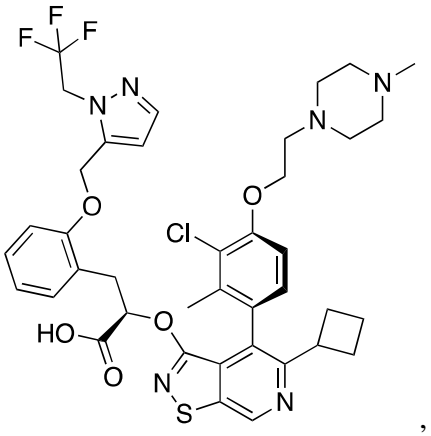
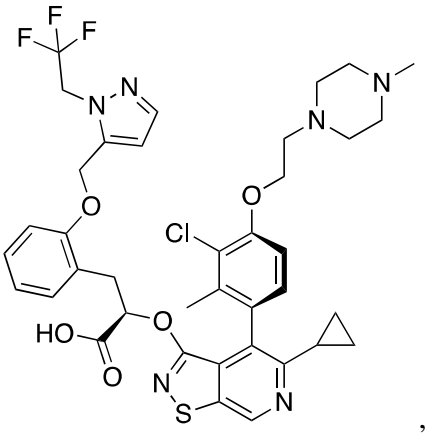
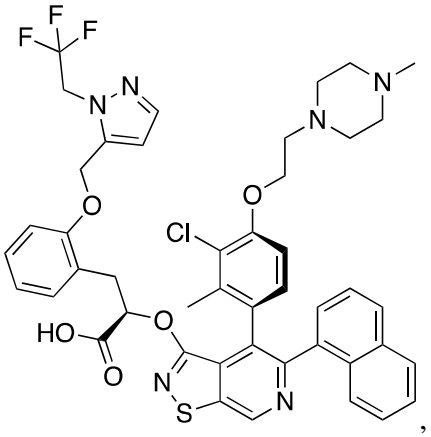
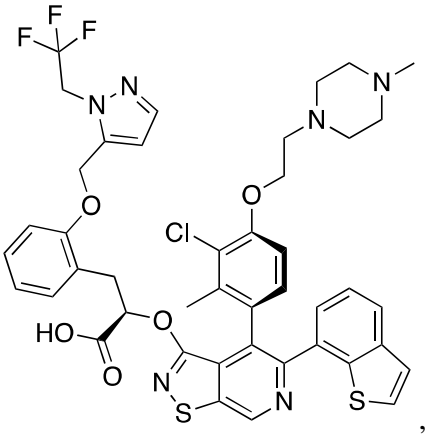

,

,

, and

, or a pharmaceutically acceptable salt thereof.

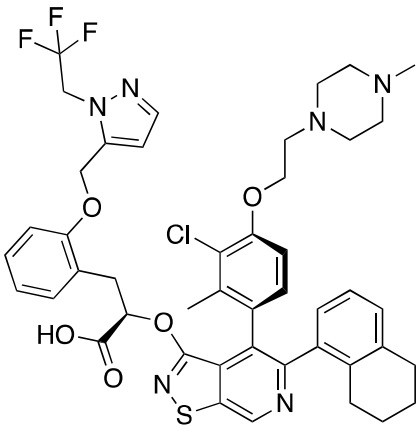
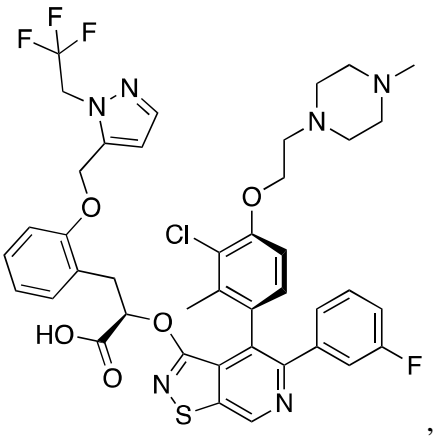
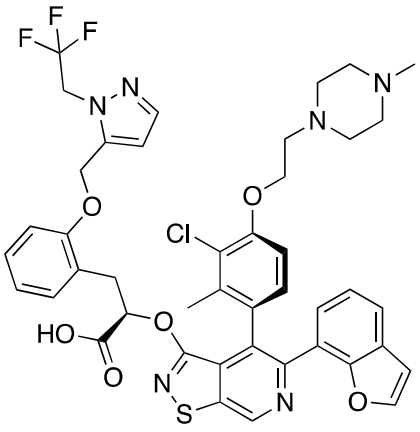
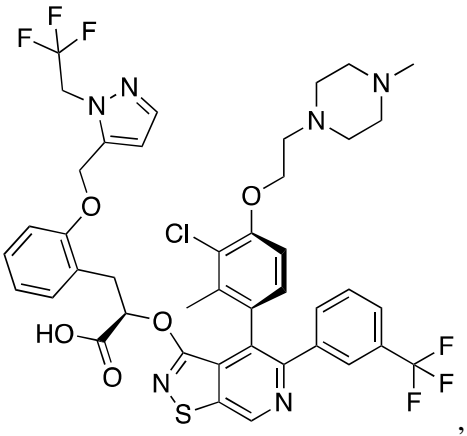
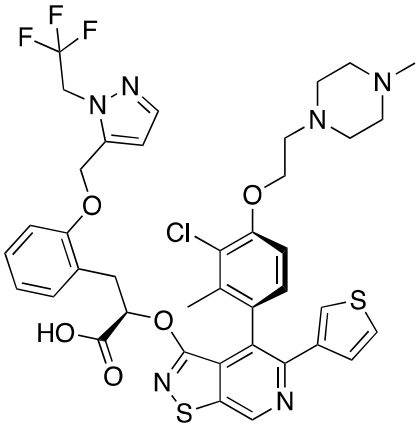
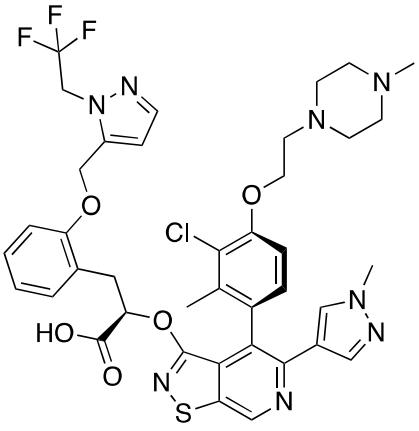
~~43.~~24. A compound selected from:

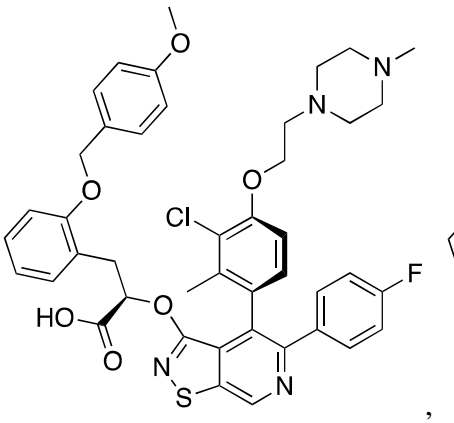
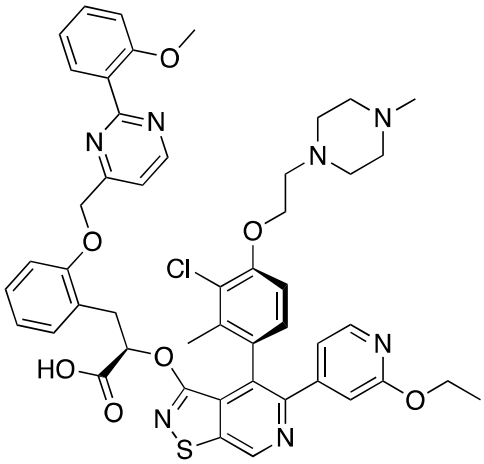
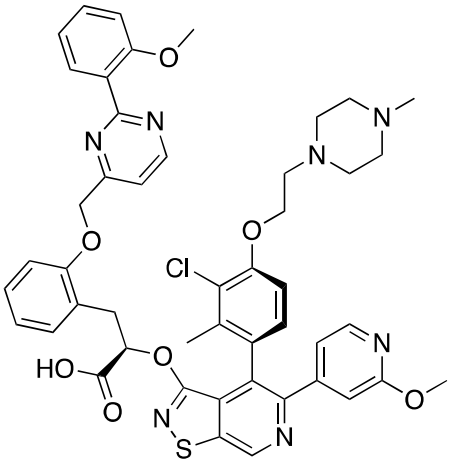
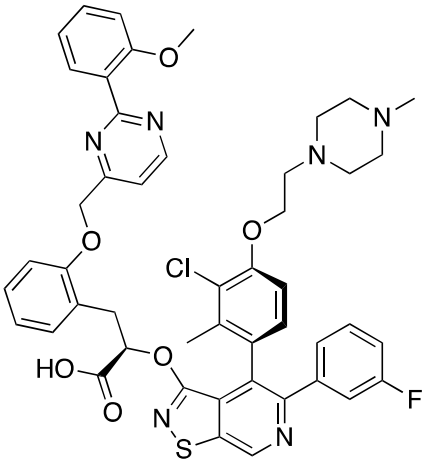
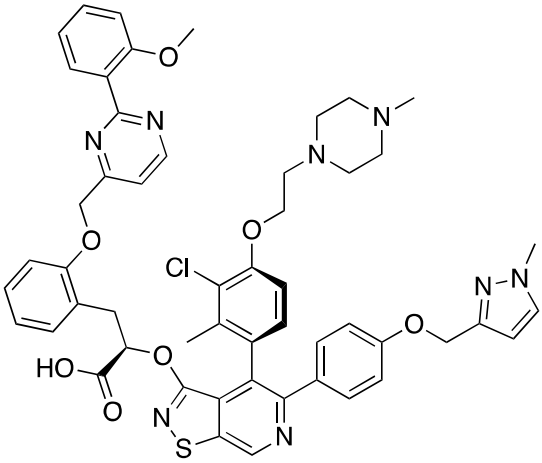
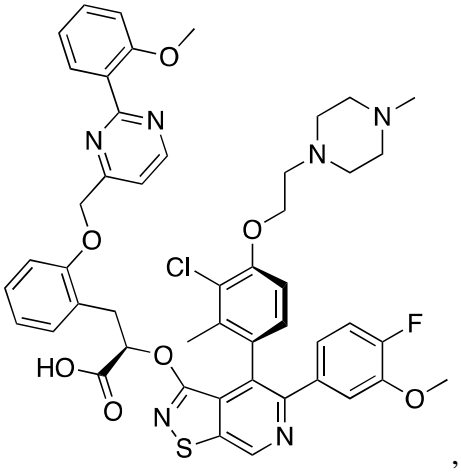

,

,

,

,

,

,

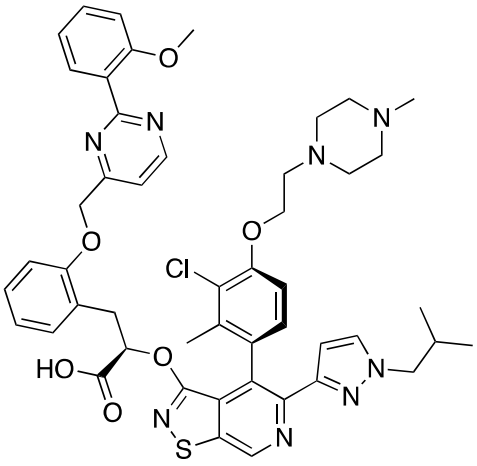
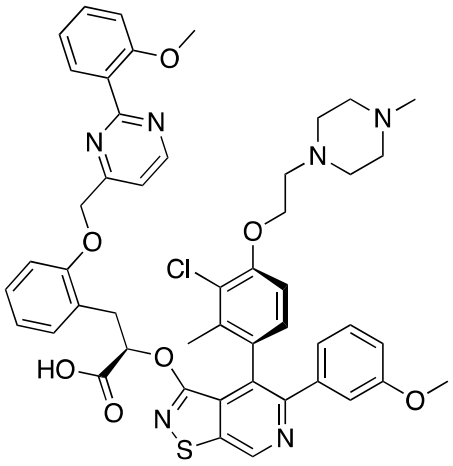
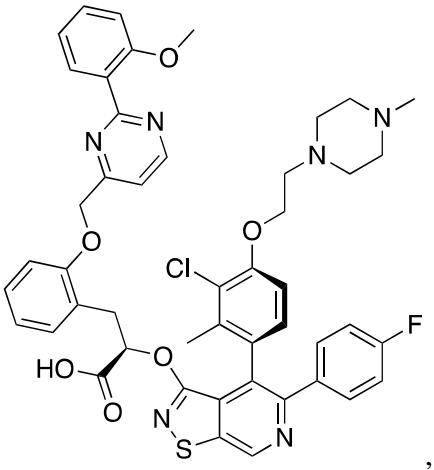
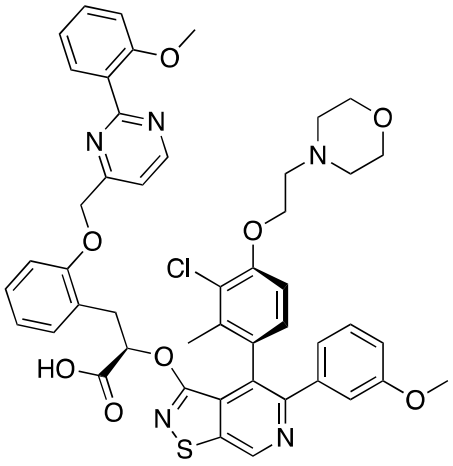
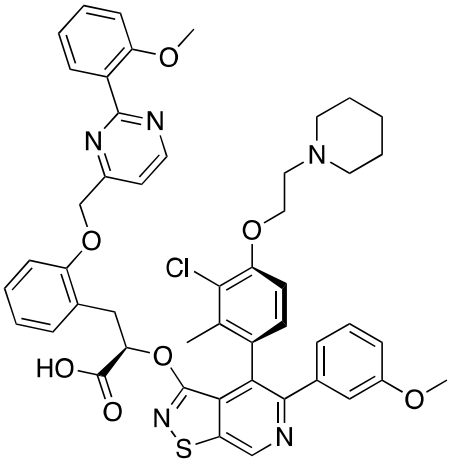
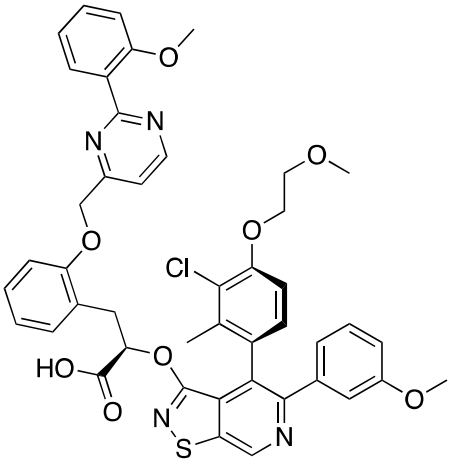

,

,

,

,

,

,

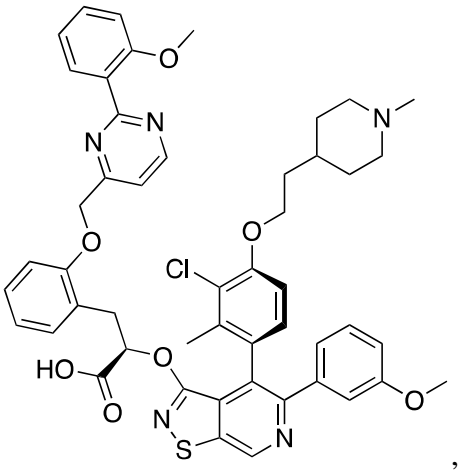
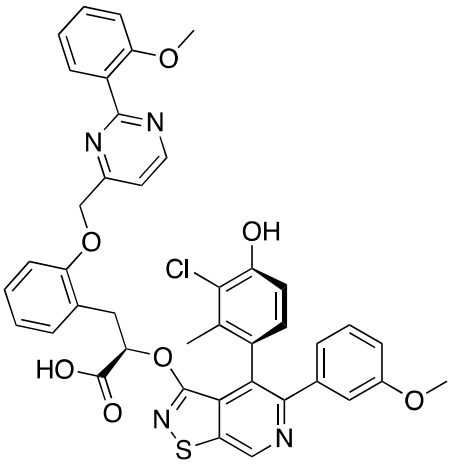
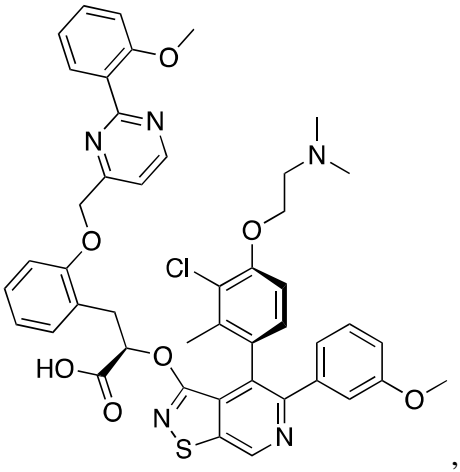
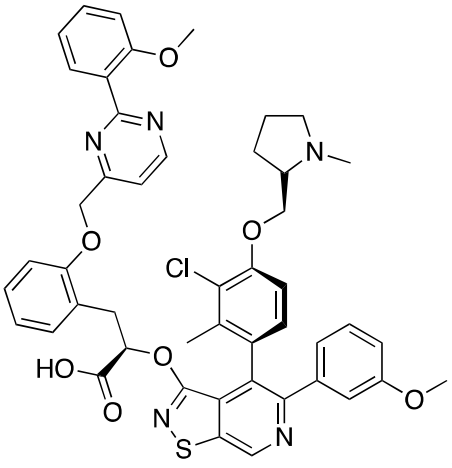
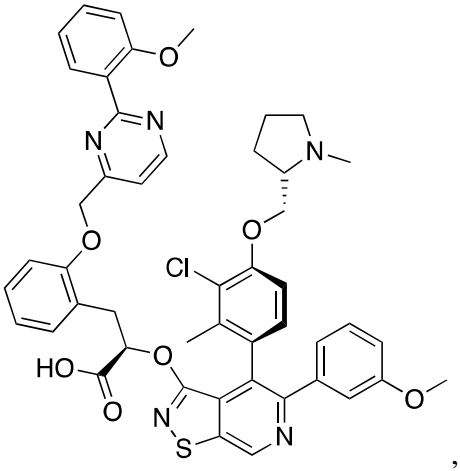
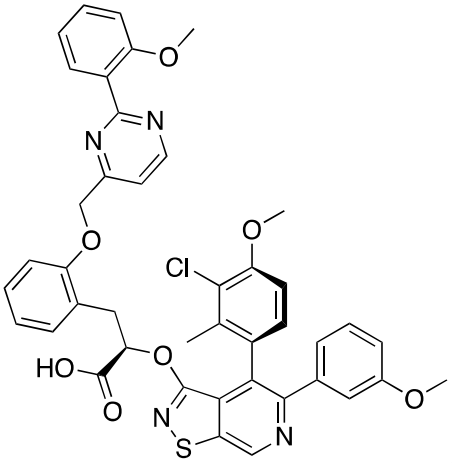

,

,

,

,

,

,

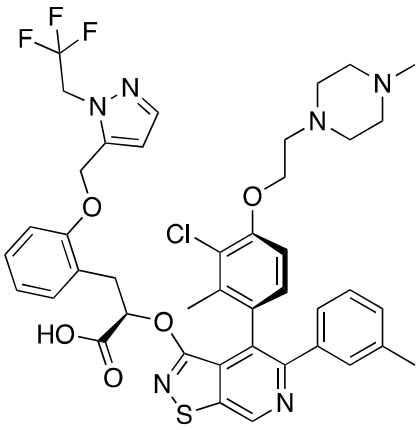
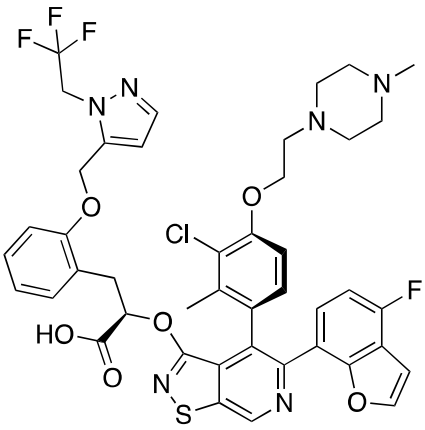
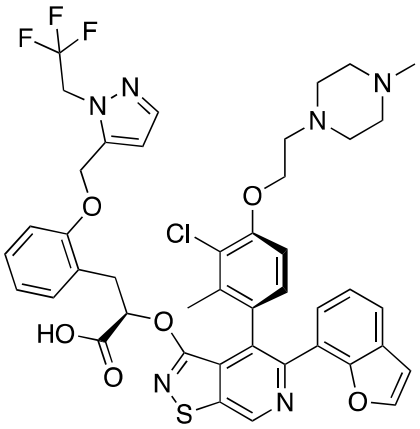

,

,

,

,

,

,


,

,

,

,

,

,

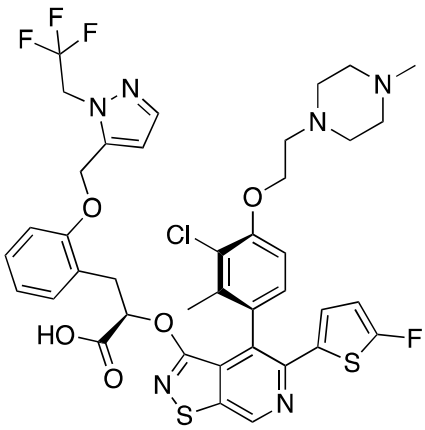
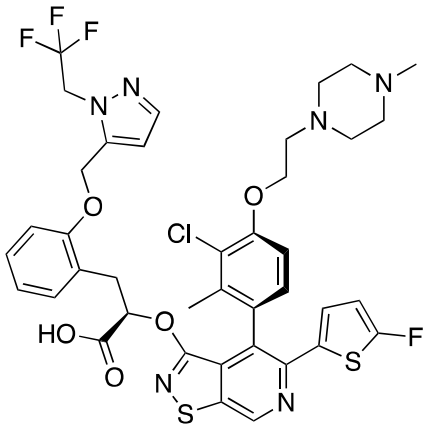

,

,

,

,

,

,

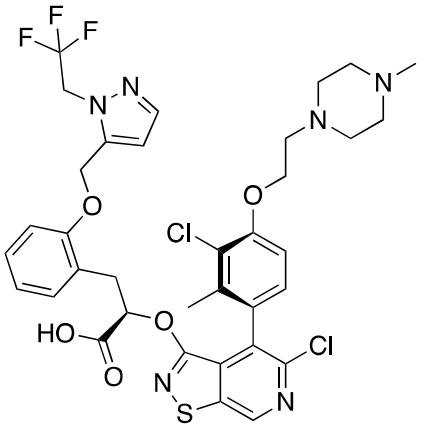
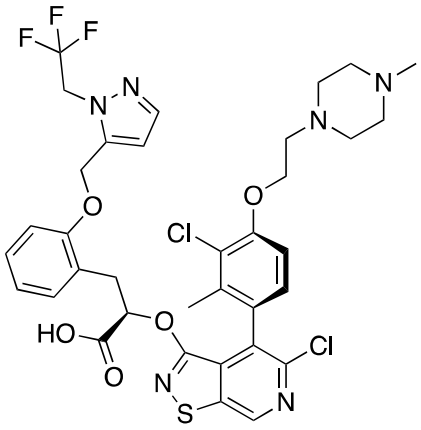
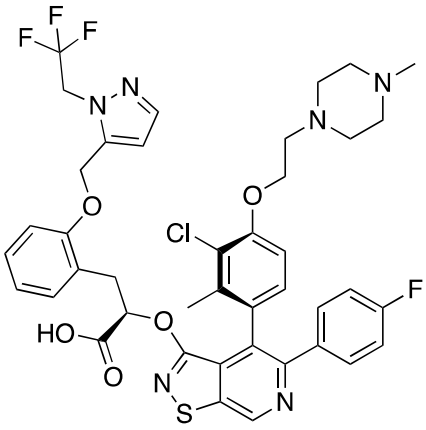
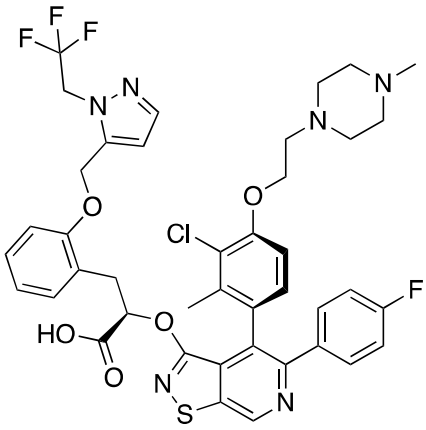
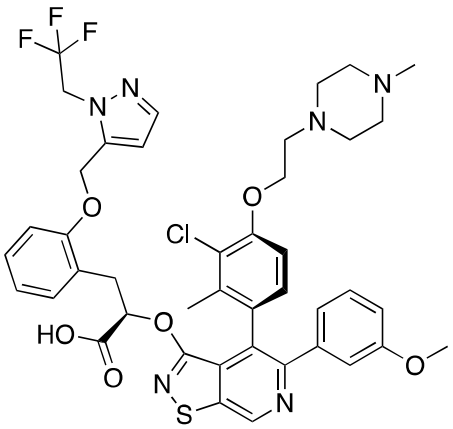
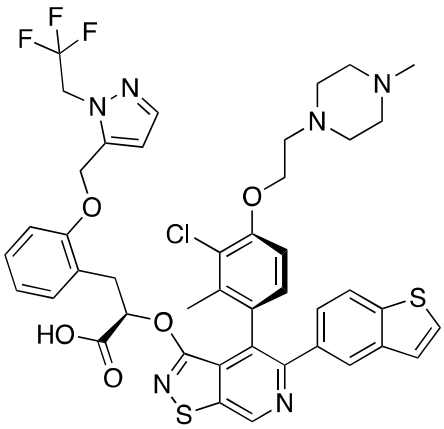

,

,

,

,

,

,

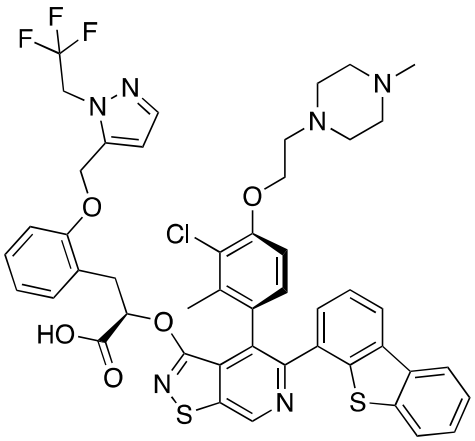
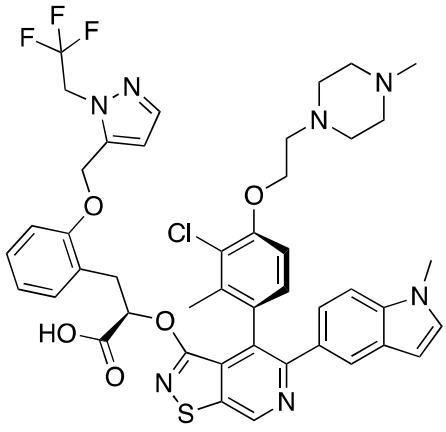
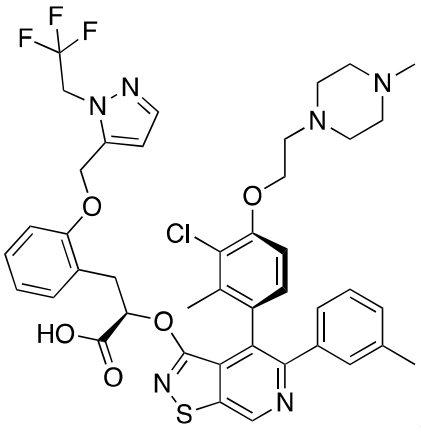
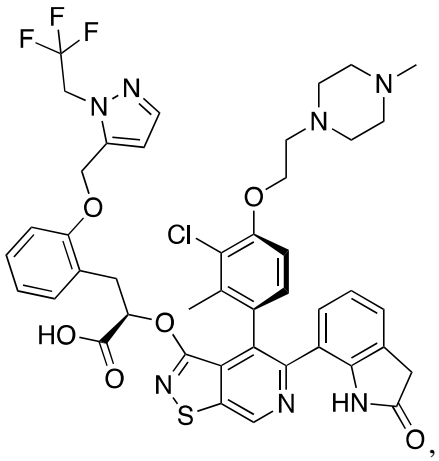
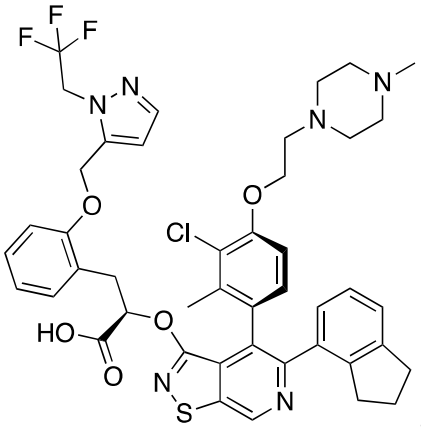
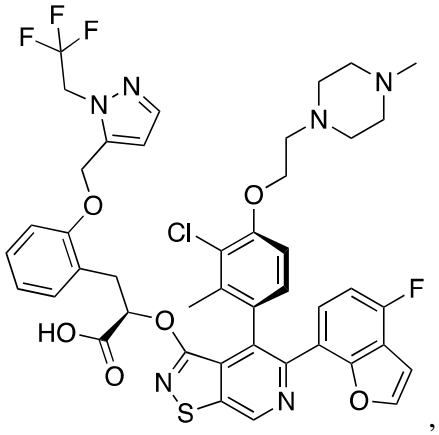

,

,

,

,

,

,

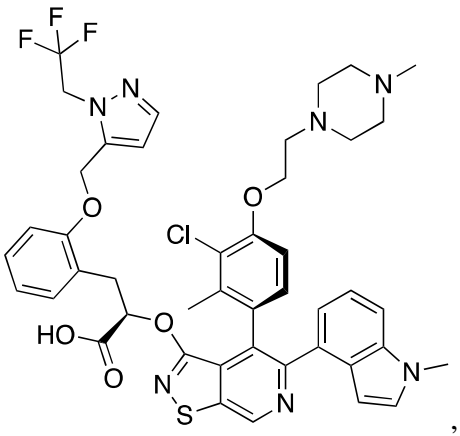
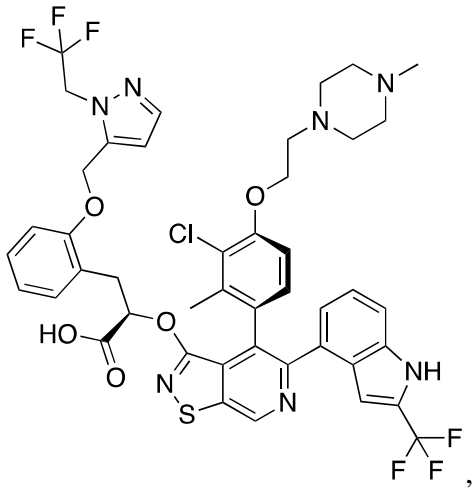
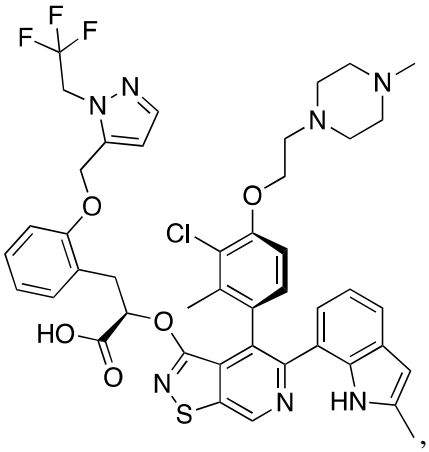
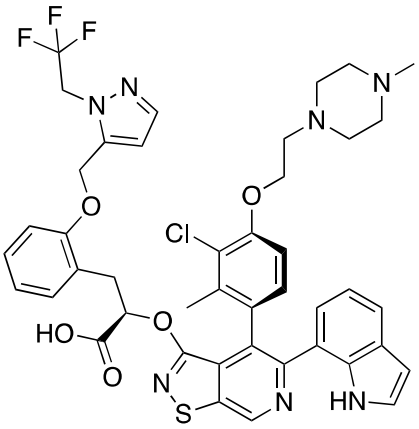
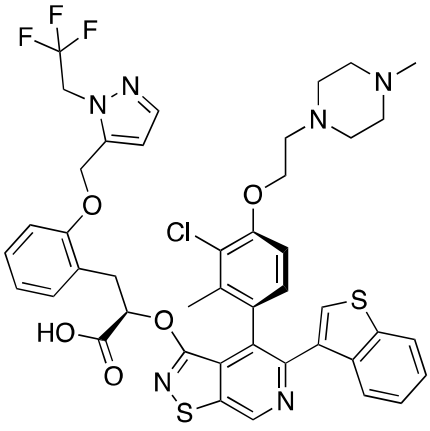
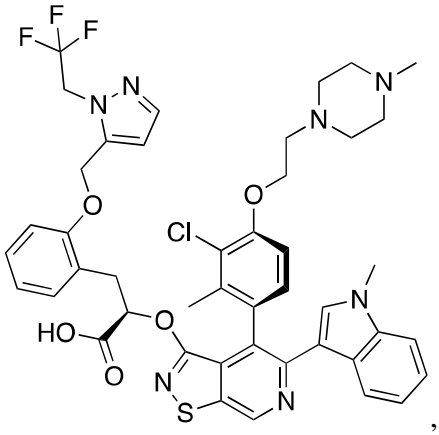

, 
, and 
, or a pharmaceutically acceptable salt thereof.

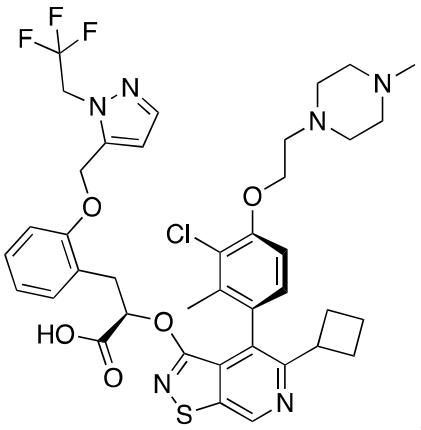
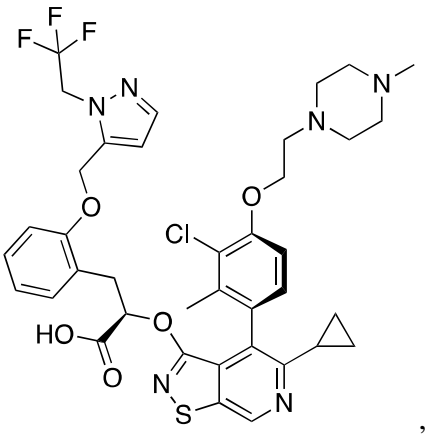
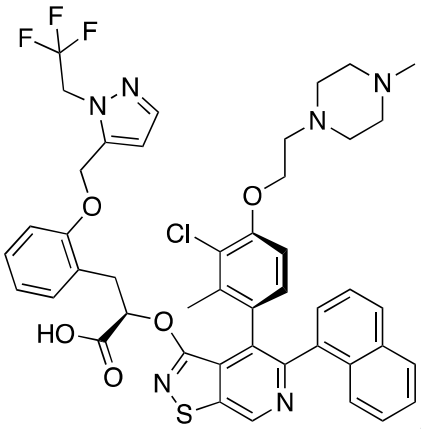
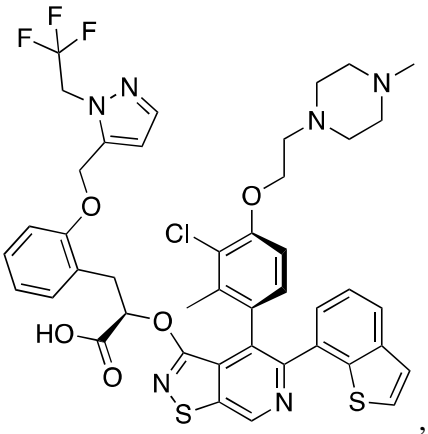
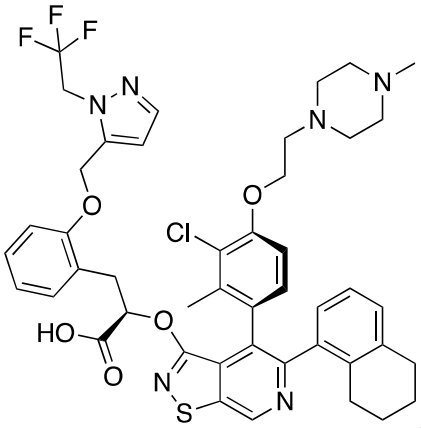
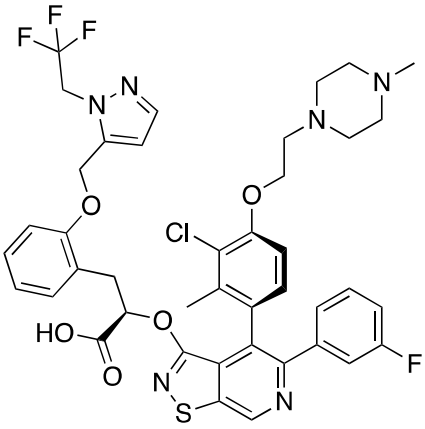
~~44.~~25. A compound selected from:

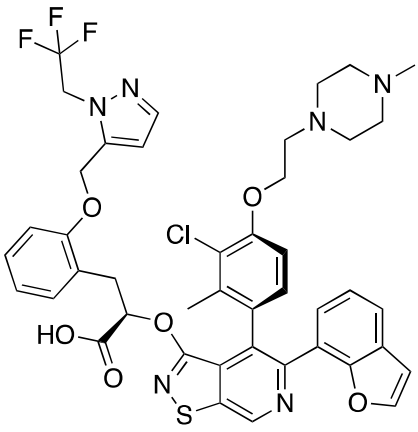
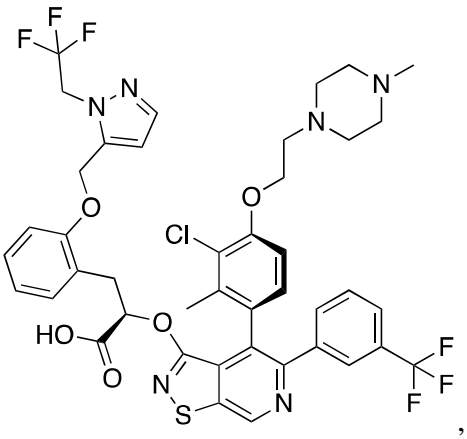
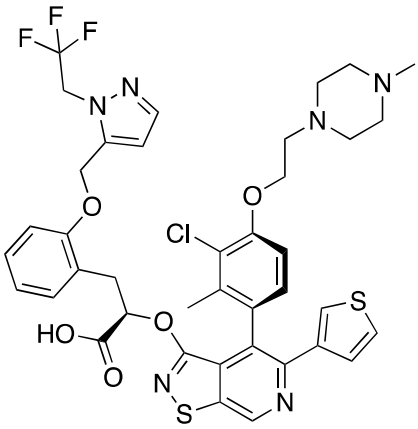
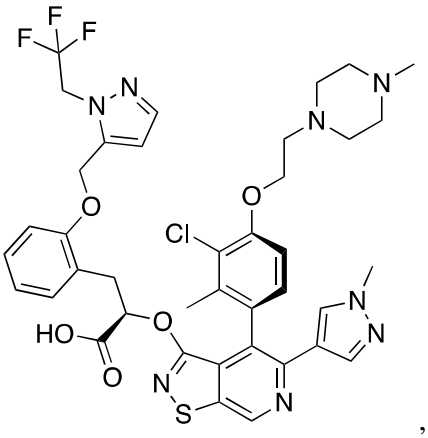
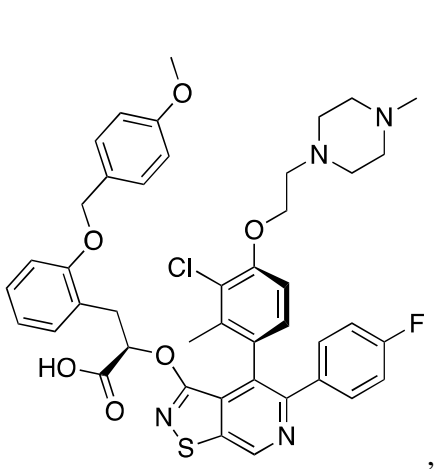
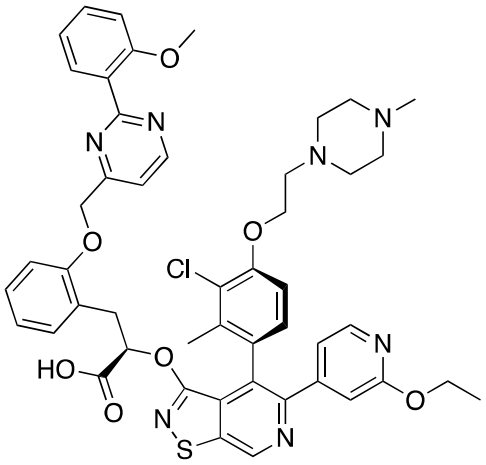

, 
,

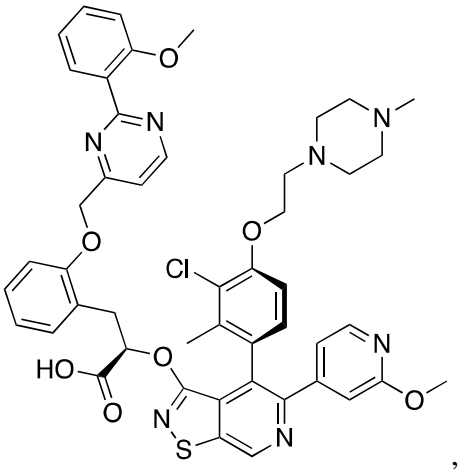
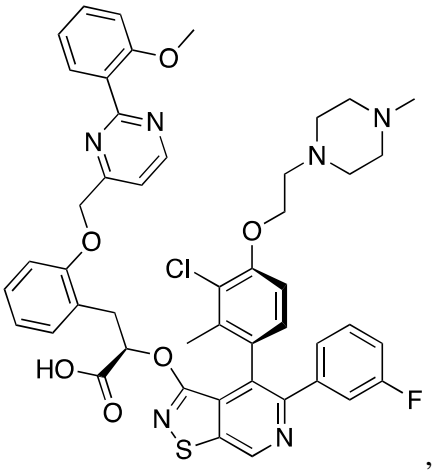
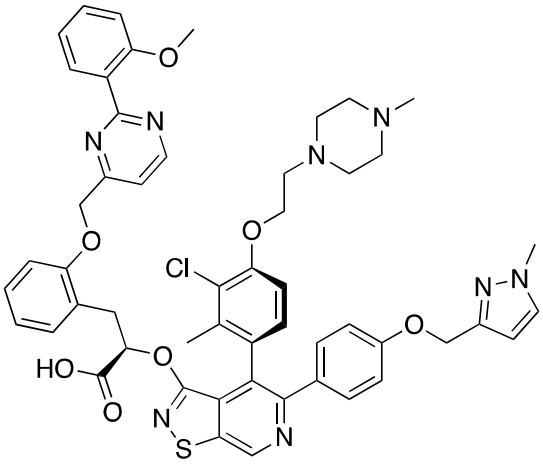
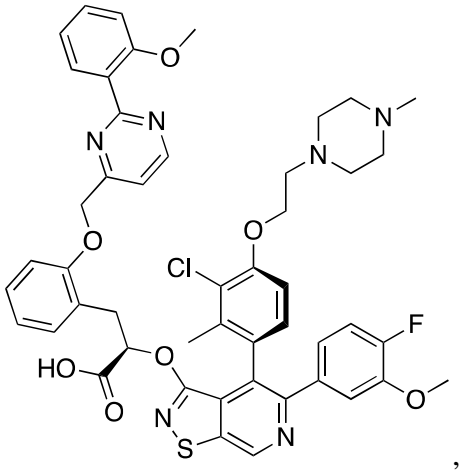
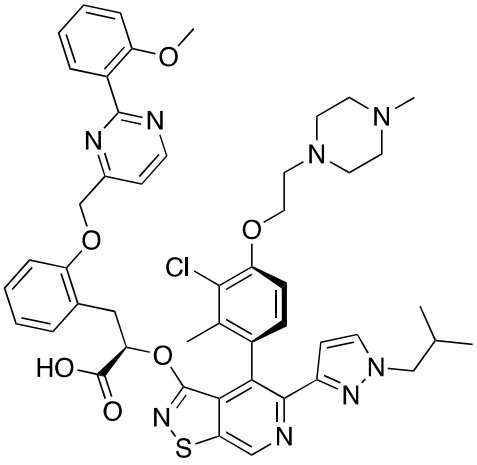
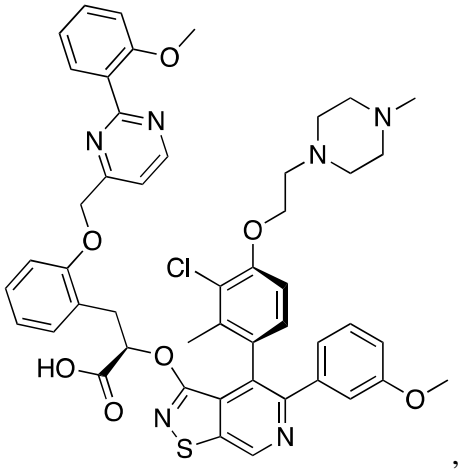

,

,

,

,

,

,

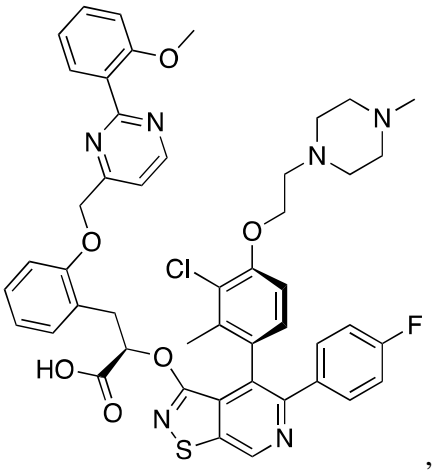
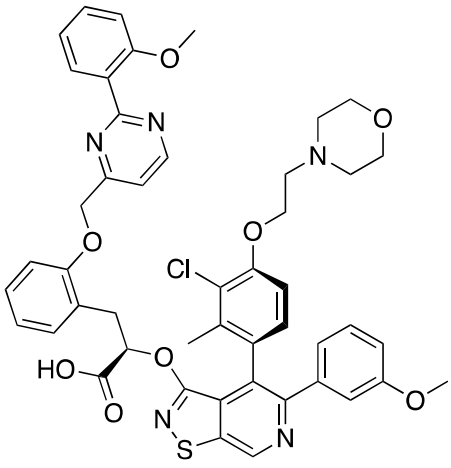
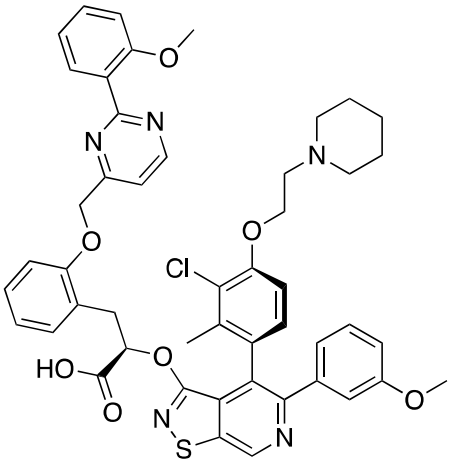
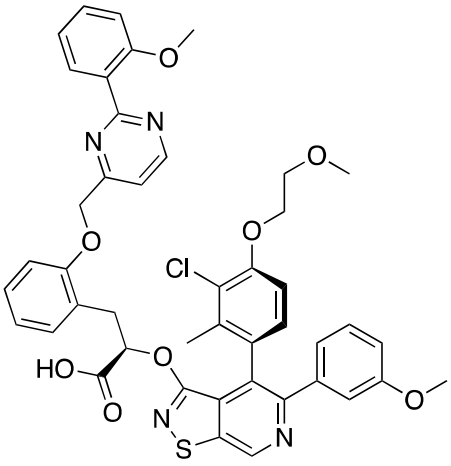
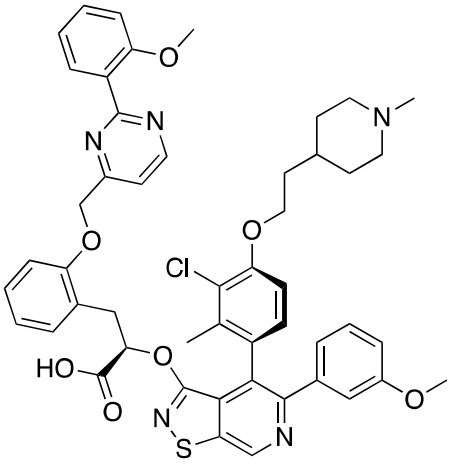
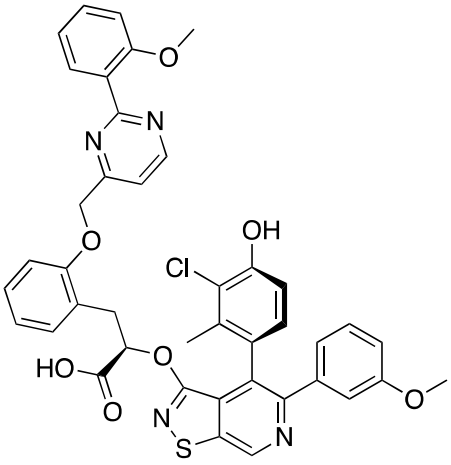

,

,

,

,

,

,

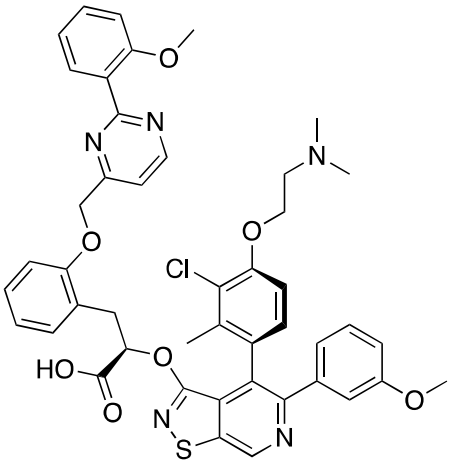
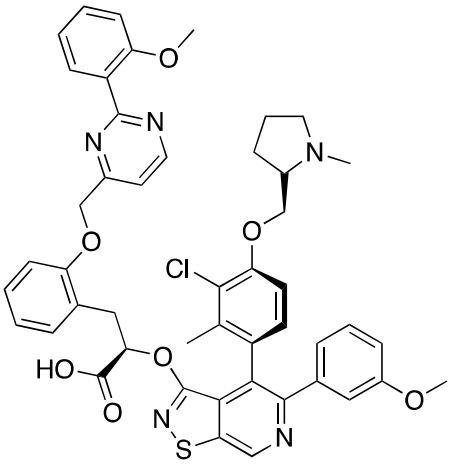
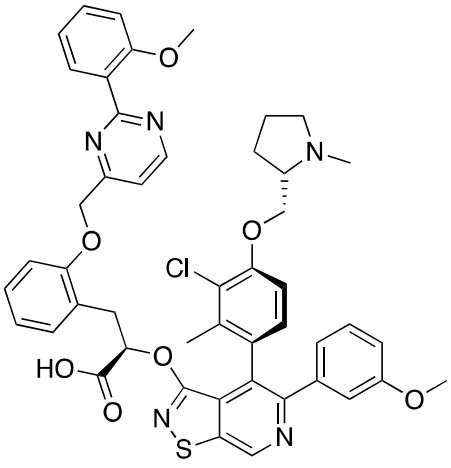
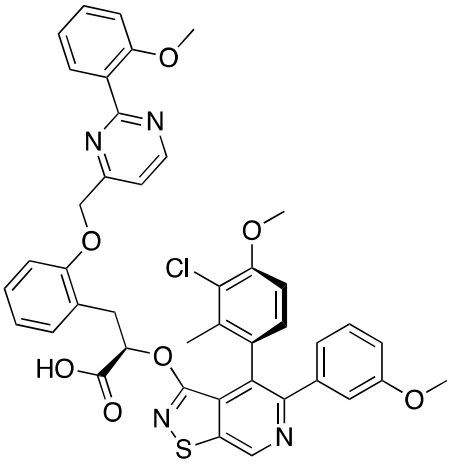
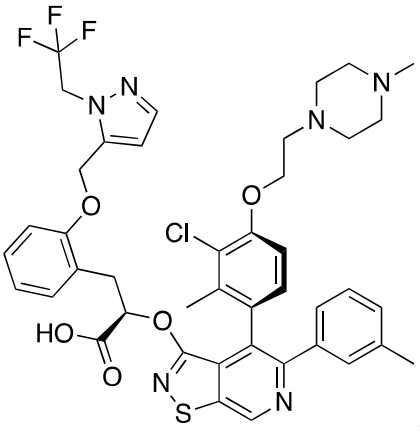
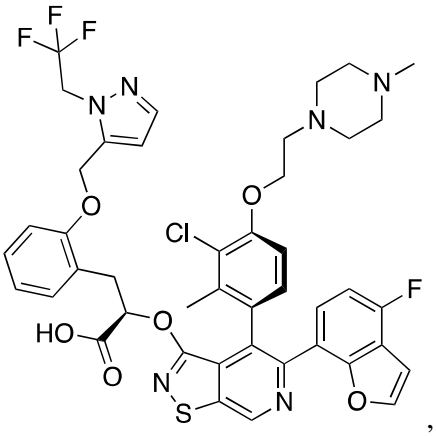

,

,

,

,

,

,

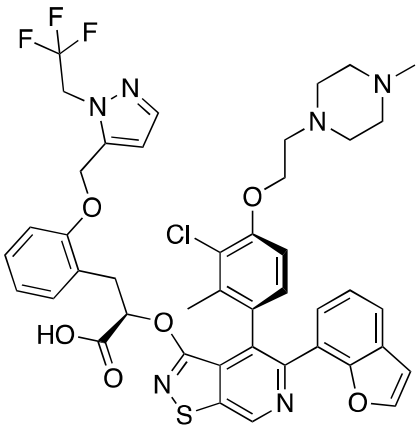
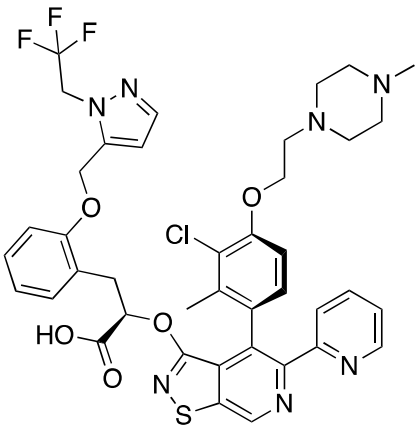
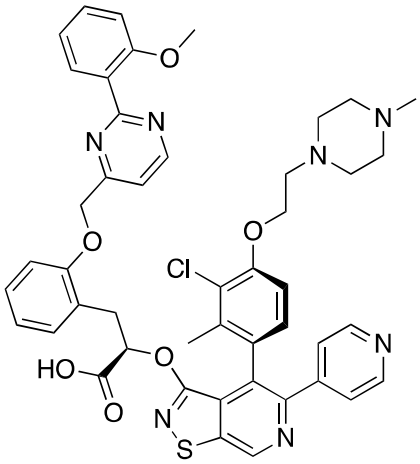
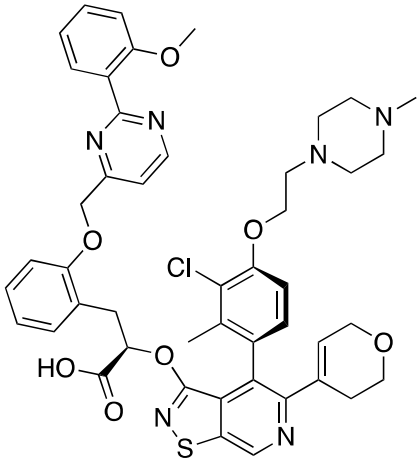
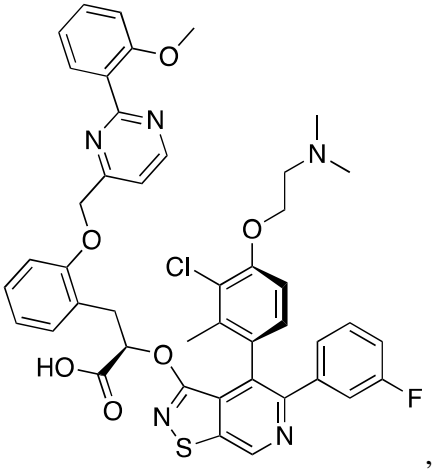
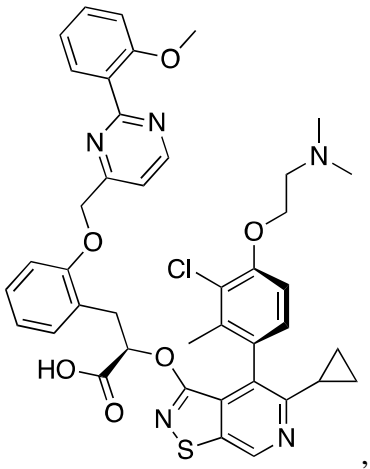

,

,

,

,

,

,

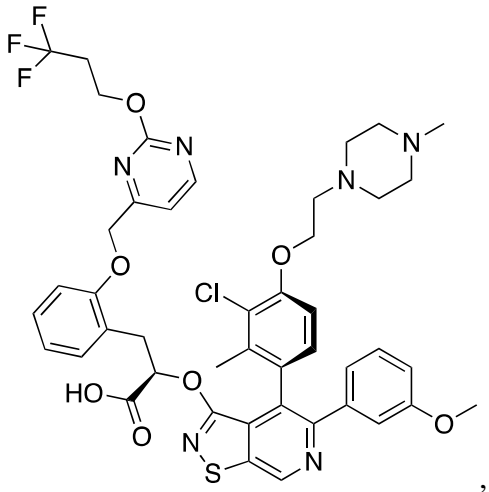
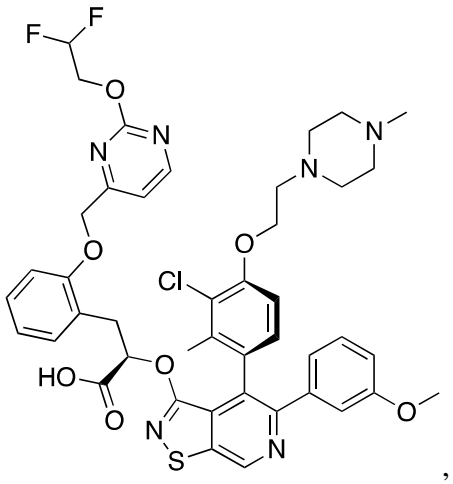
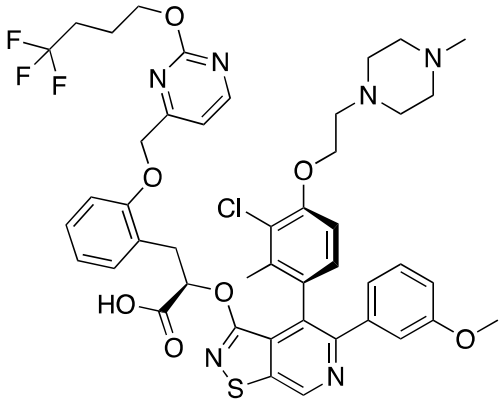
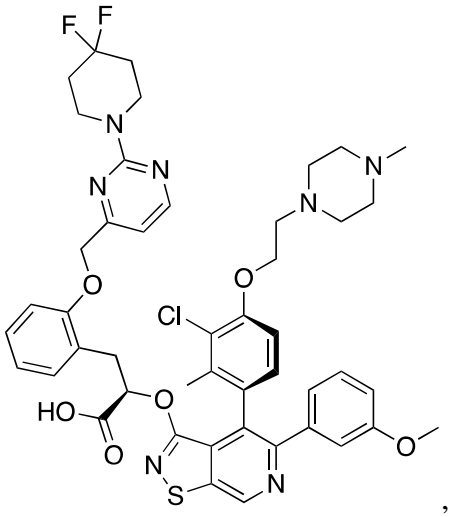
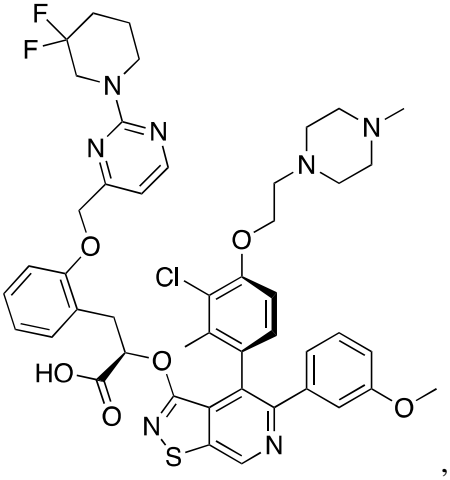
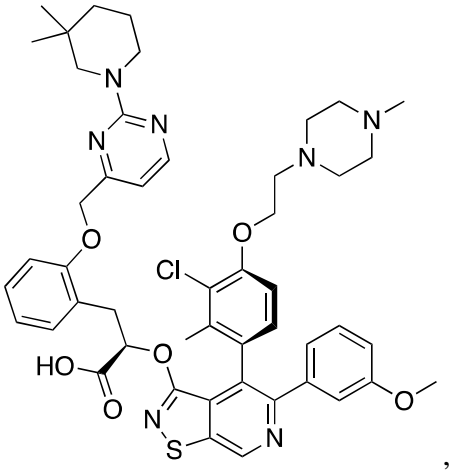

,

,

,

,

,

,

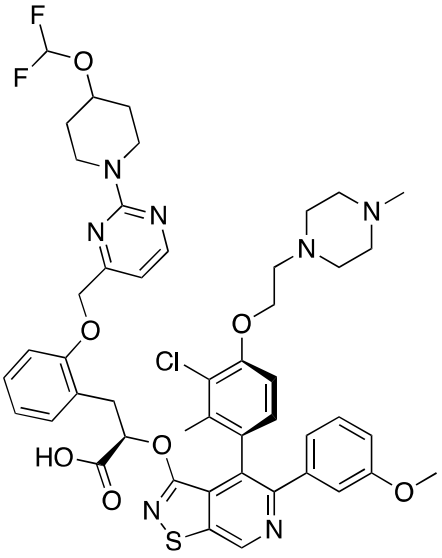
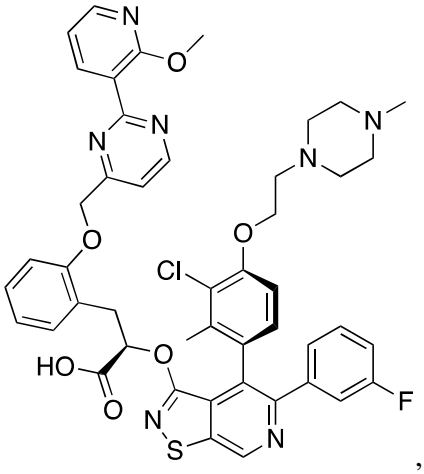
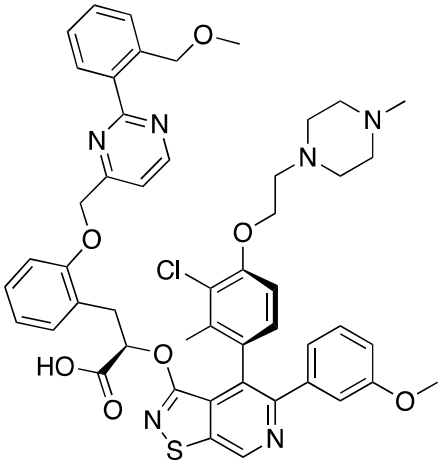
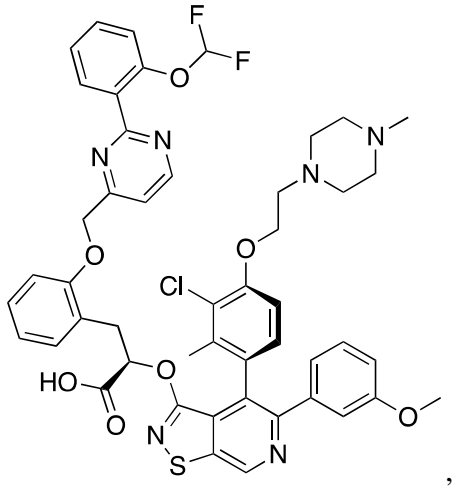
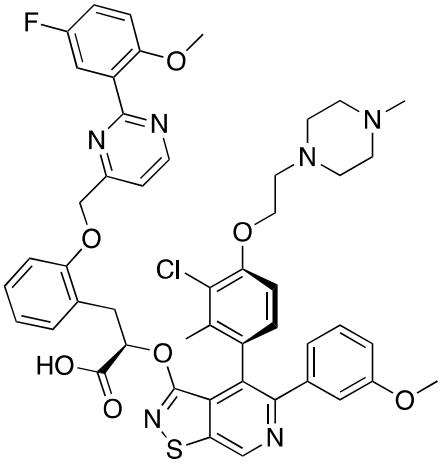
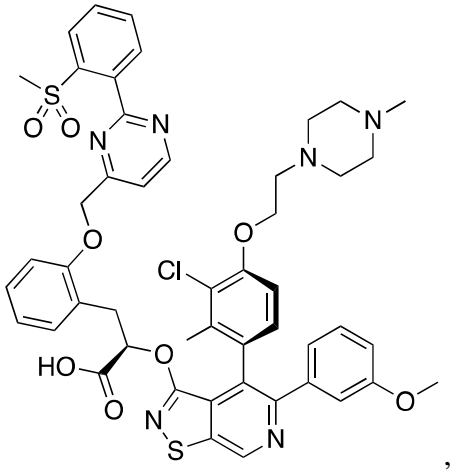

,

,

,

,

,

,

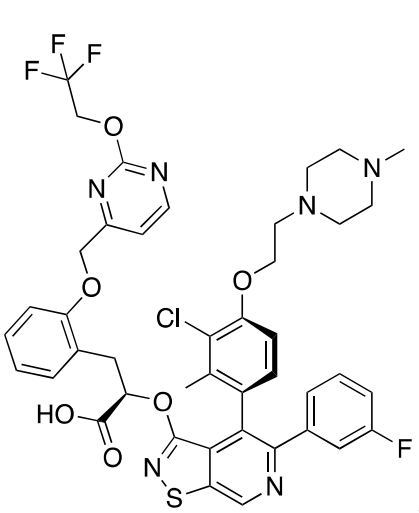
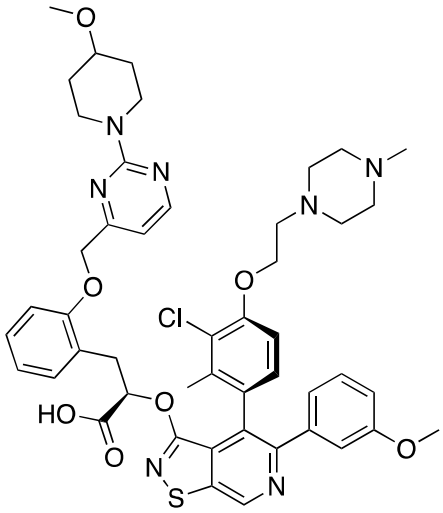
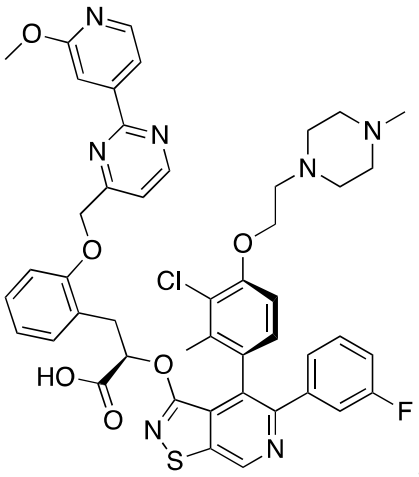
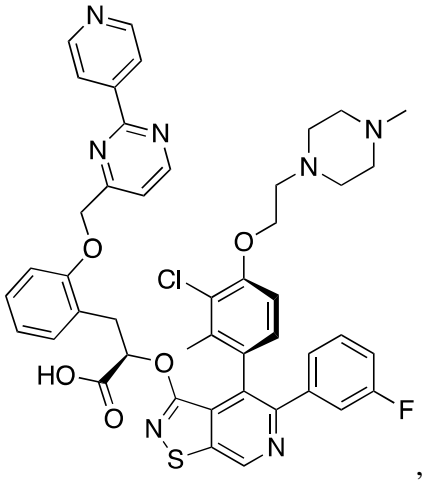
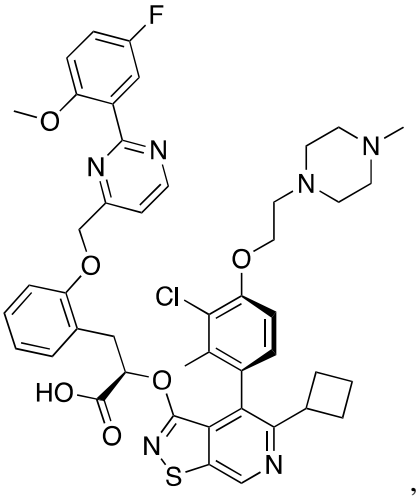
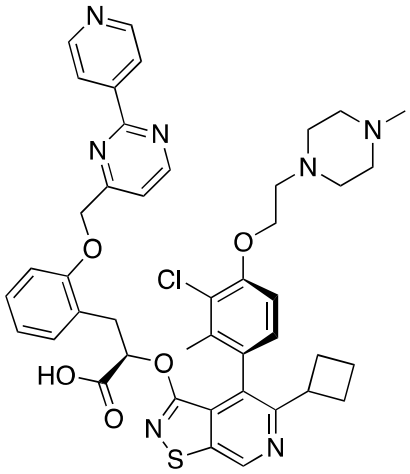

,

,

,

,

,

,

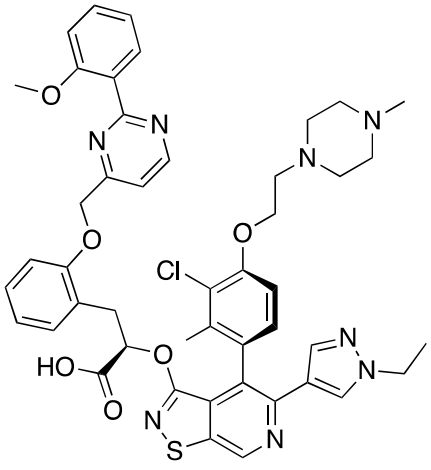
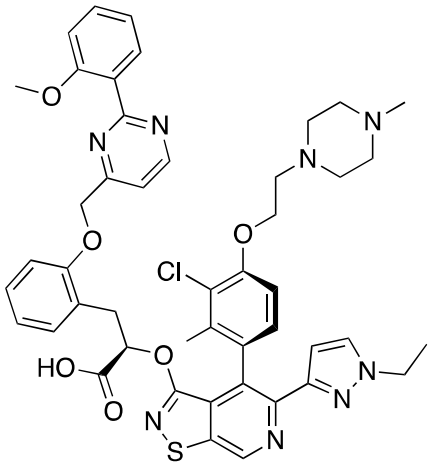
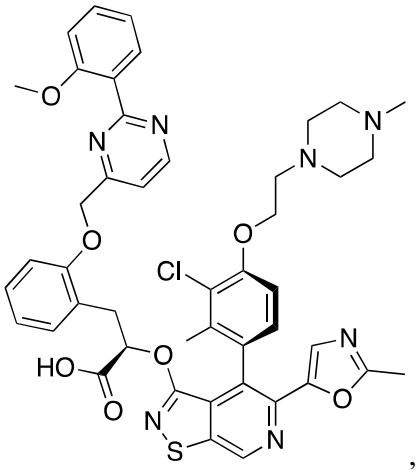
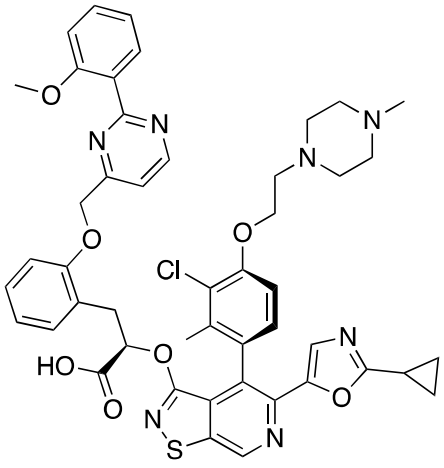
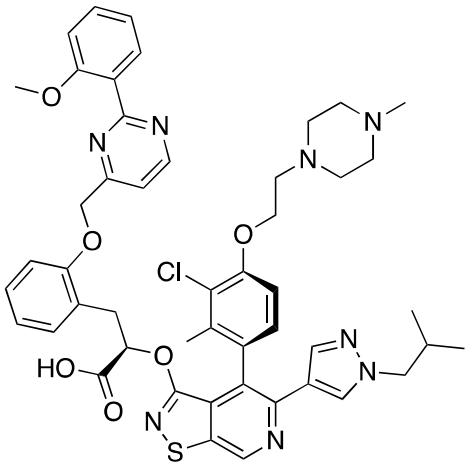
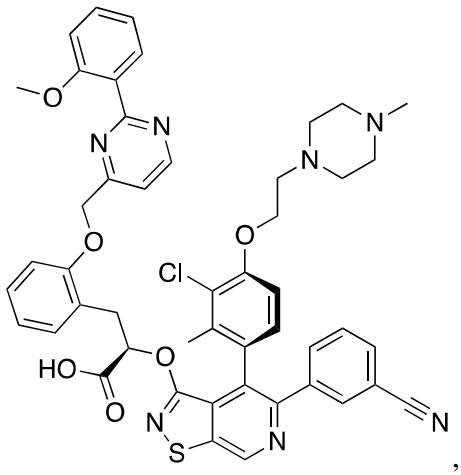

,

,

,

,

,

,

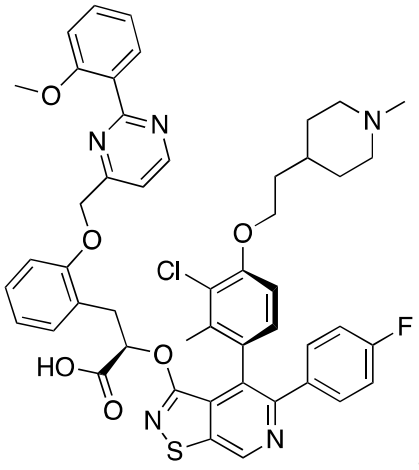
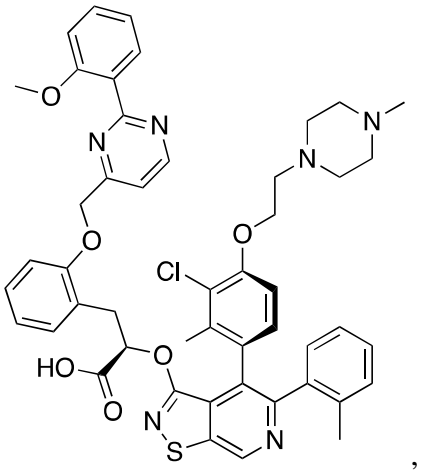
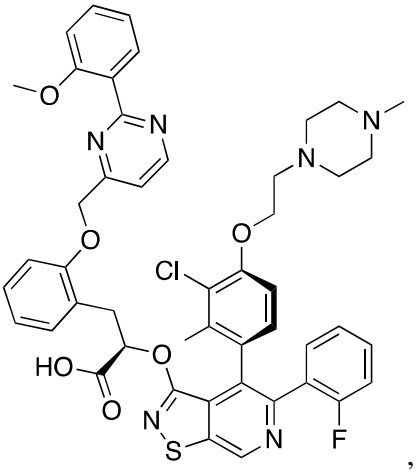
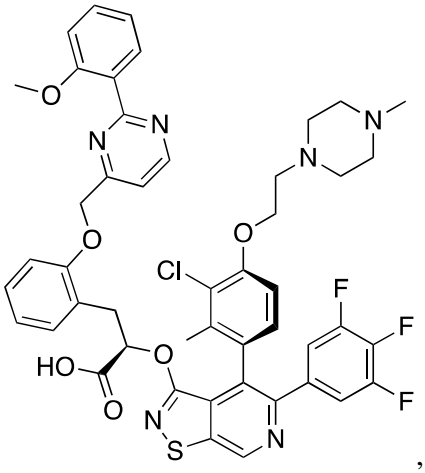
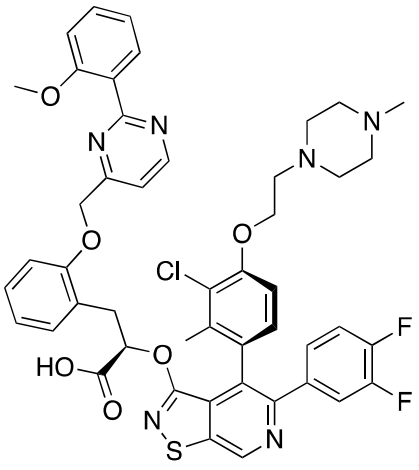
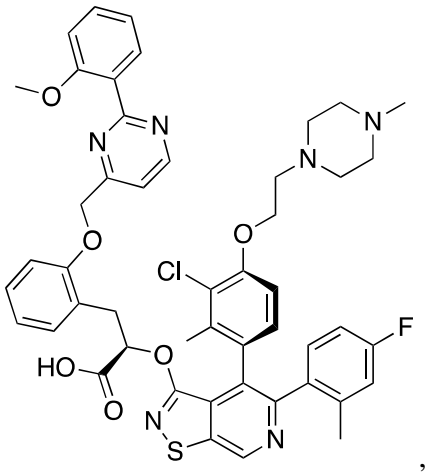

,

,

,

,

,

,

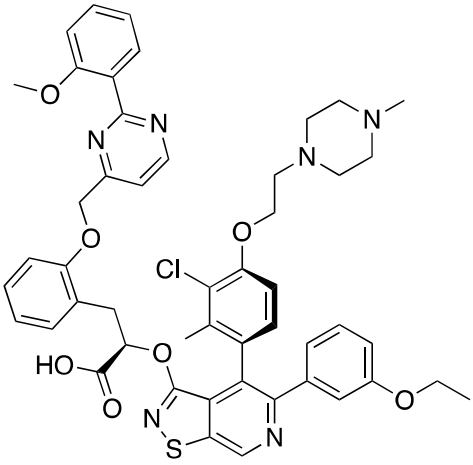
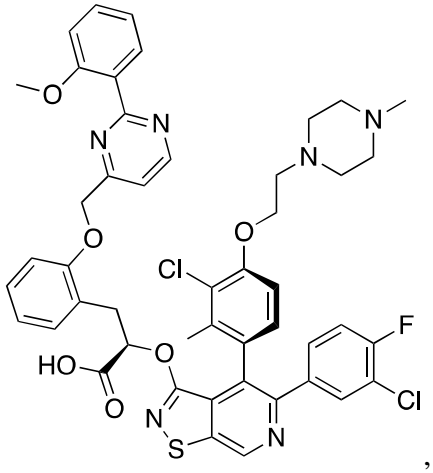
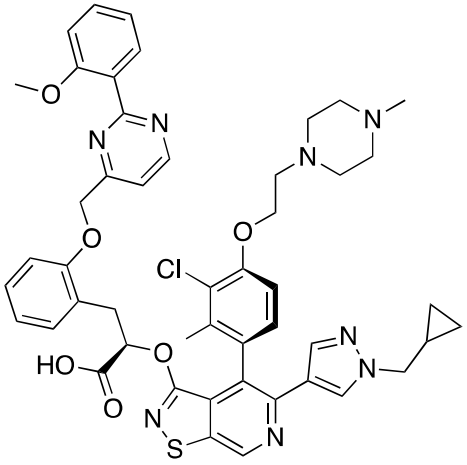
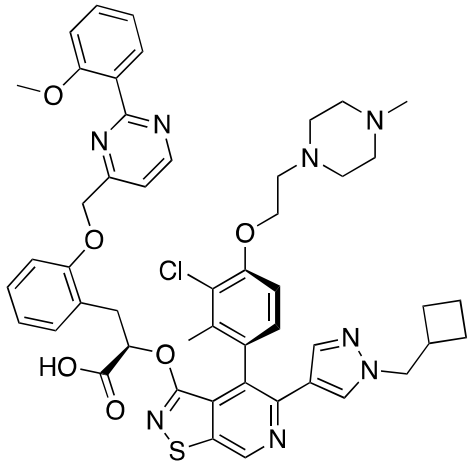
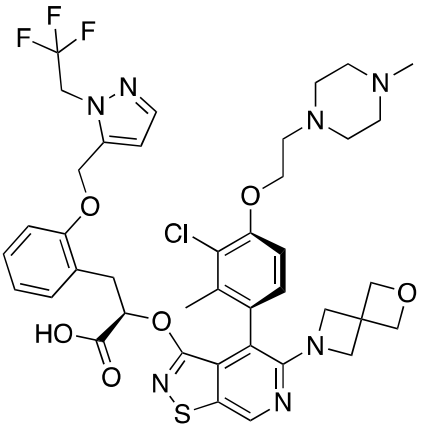
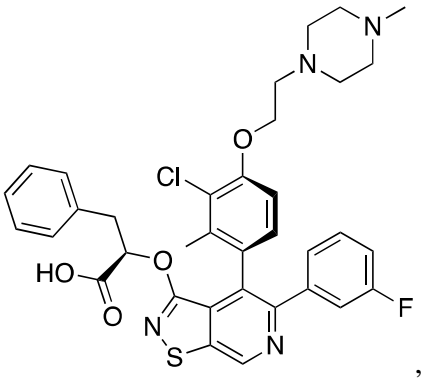

,

,

,

,

,

,

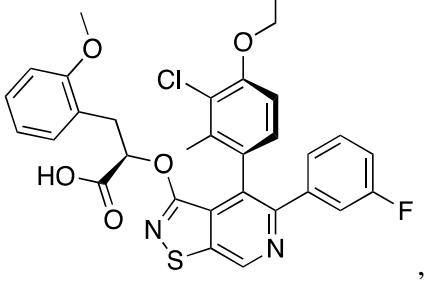
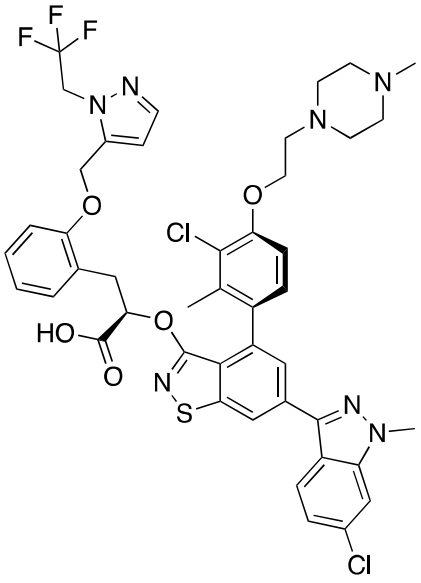
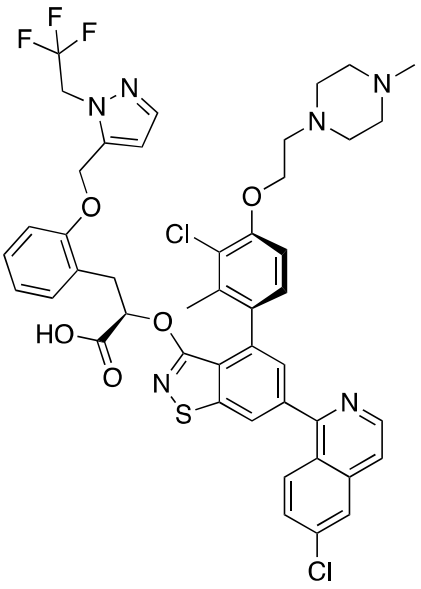
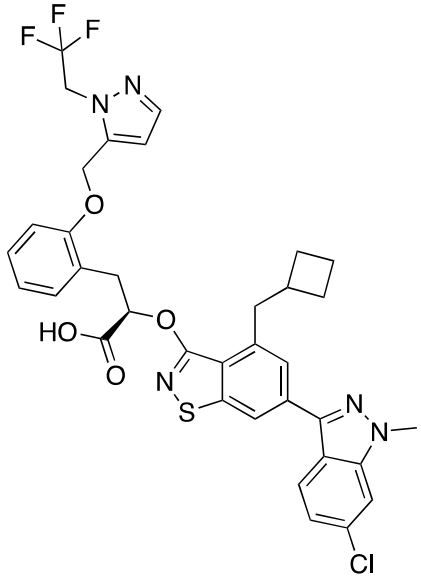

,

,

,

,

,

,

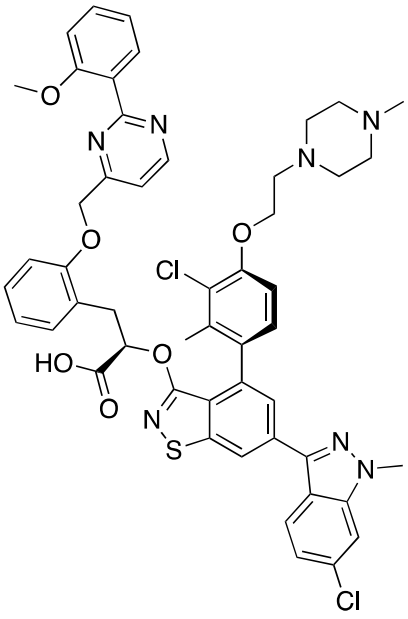
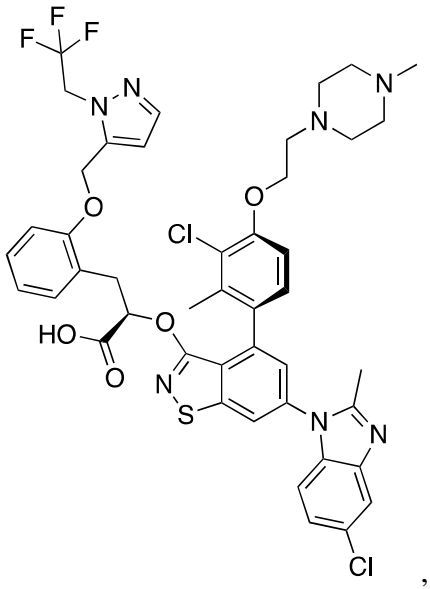
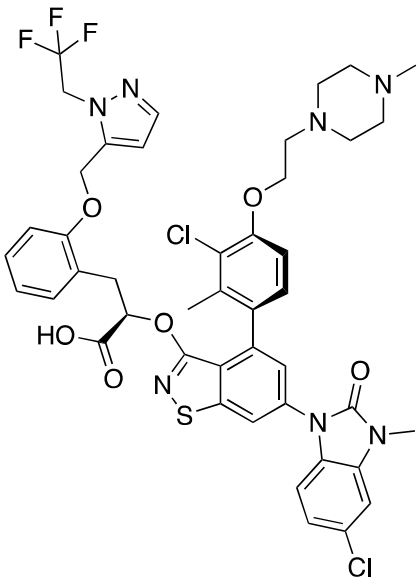
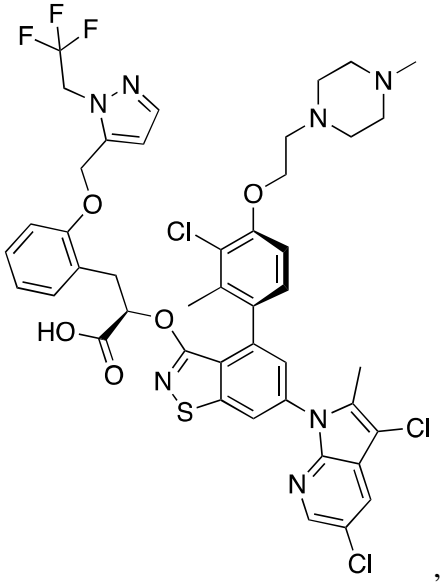

,

,

,

,

,

,

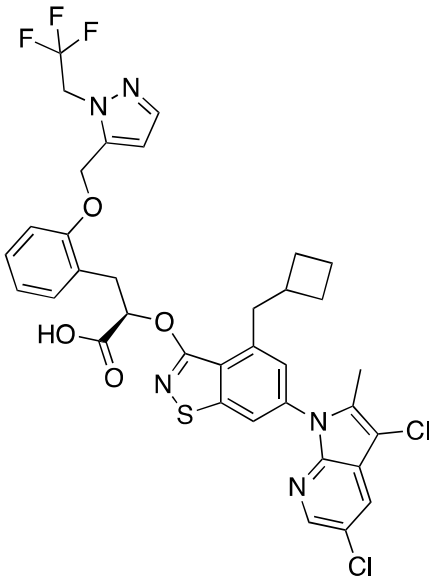
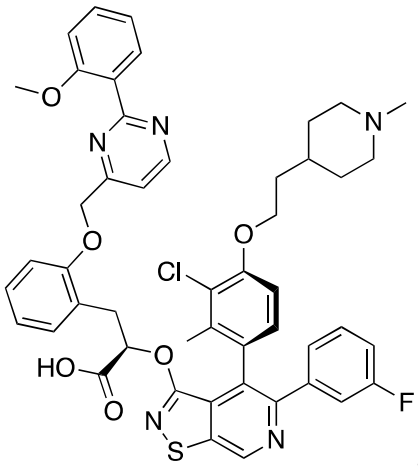

,

,

,

,

,

,


,

,

,

,

,

,

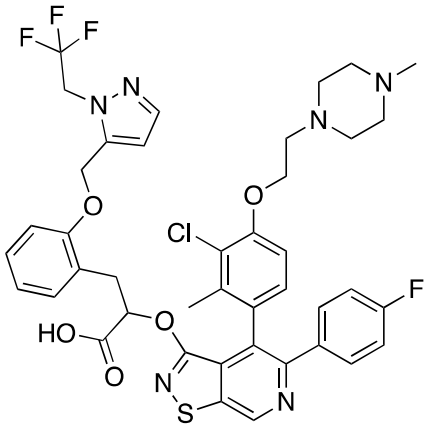
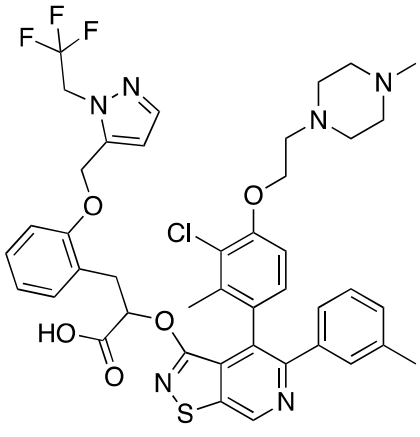

,

,

,

,

,

,

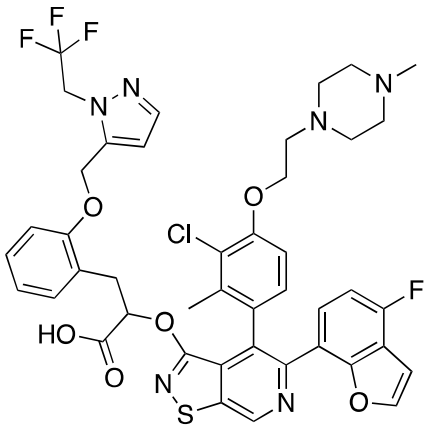
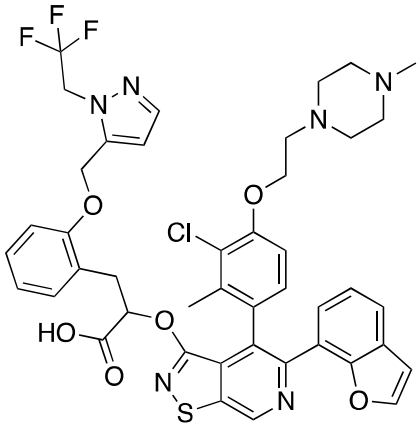

,

,

,

,

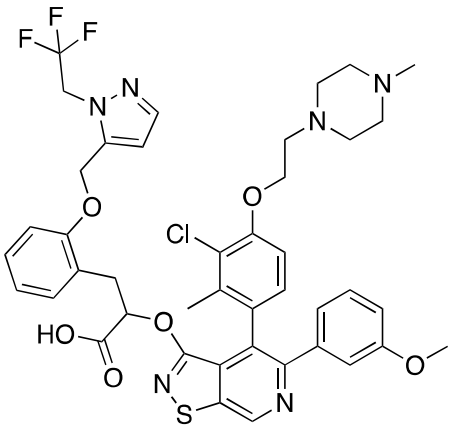
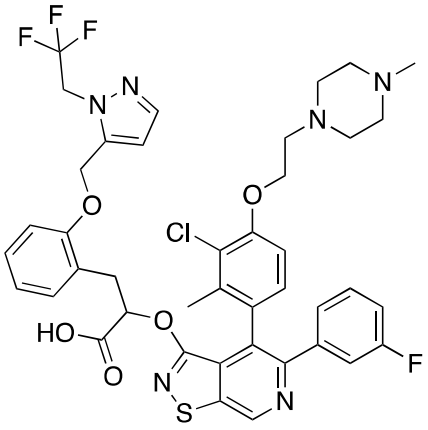
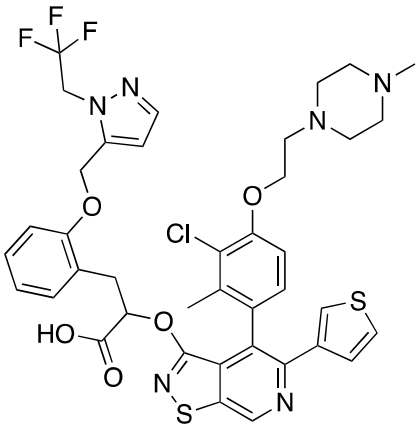
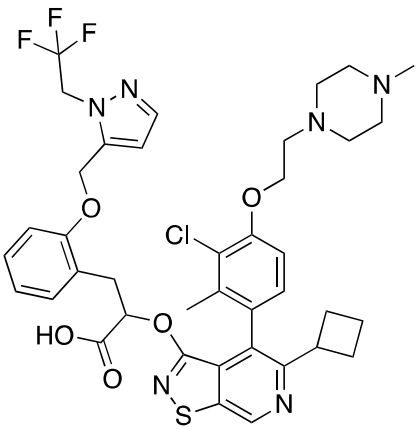
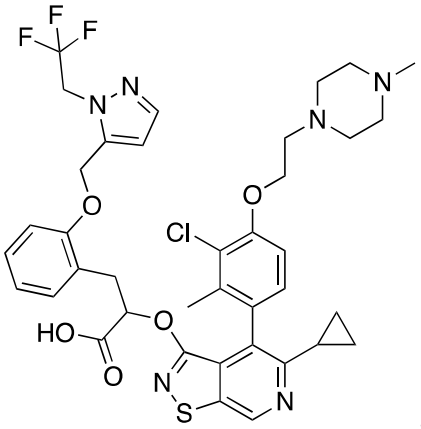
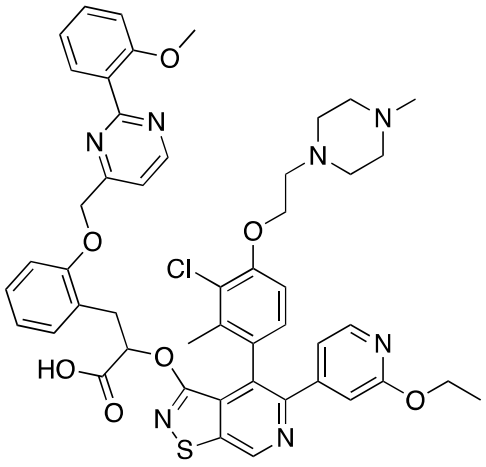

,

,

,

,

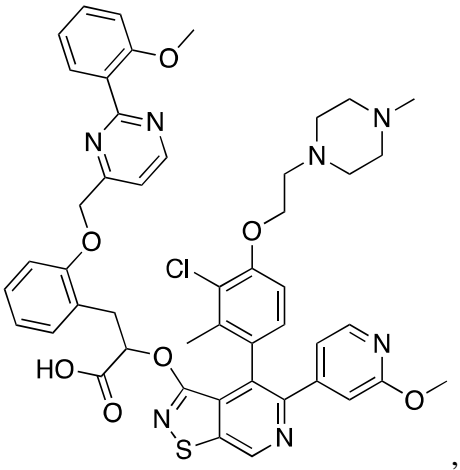
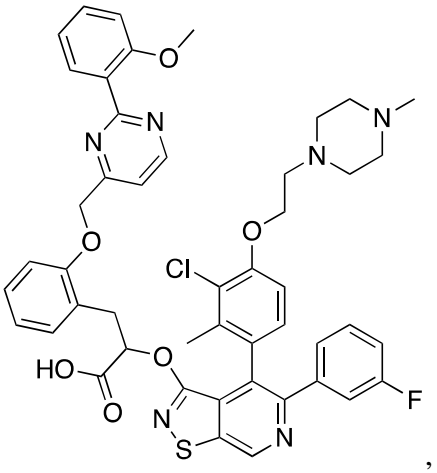
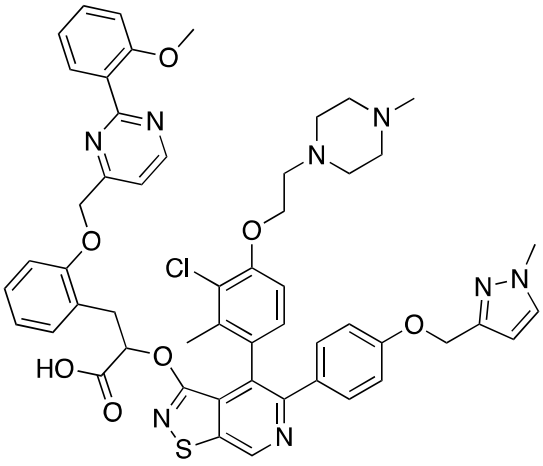
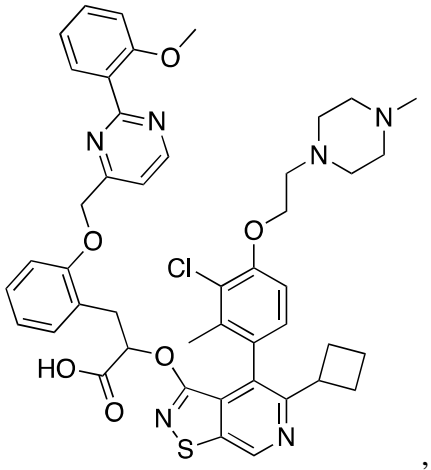
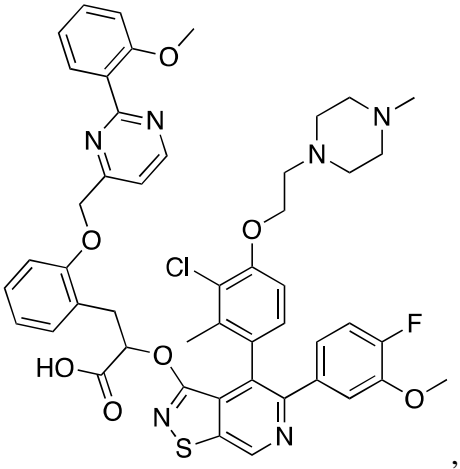
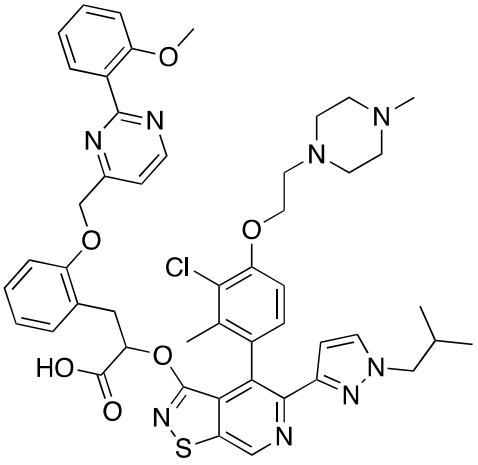
 and  , or a pharmaceutically acceptable salt thereof.

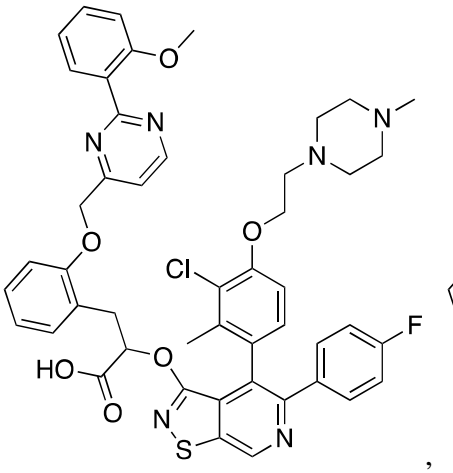
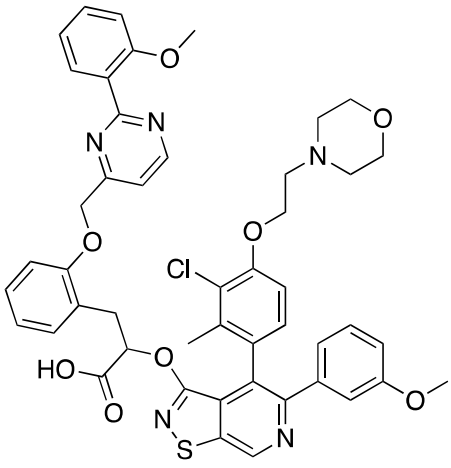
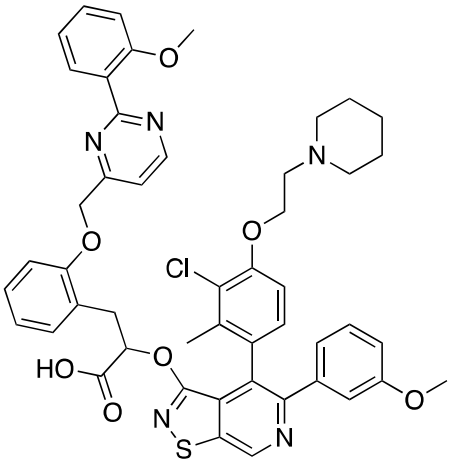
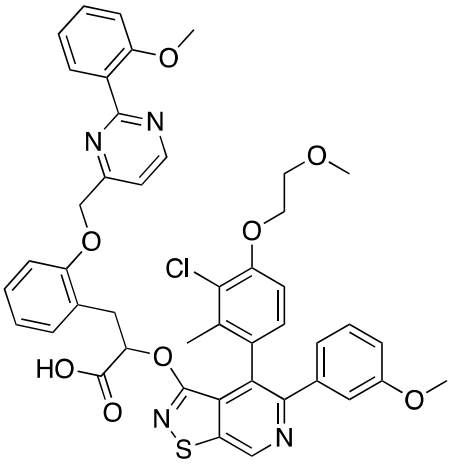
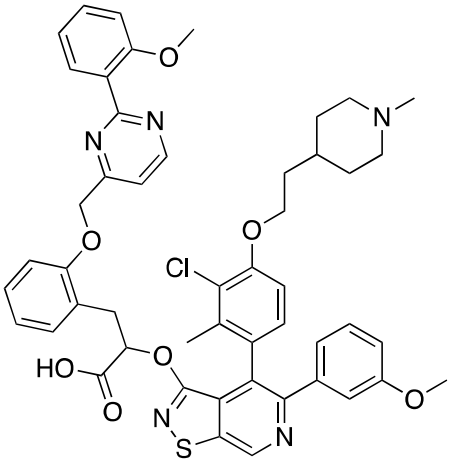
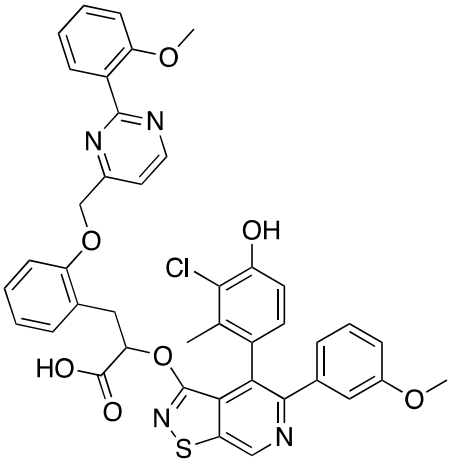
~~45.~~26. A compound selected from:

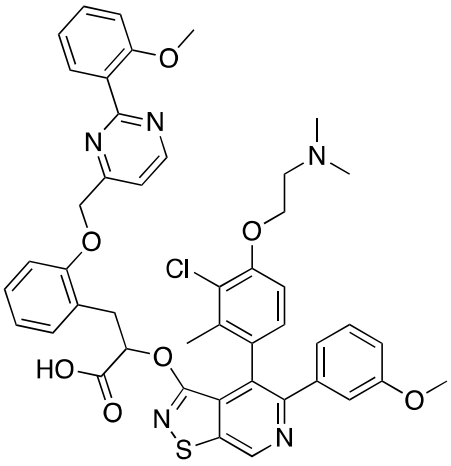
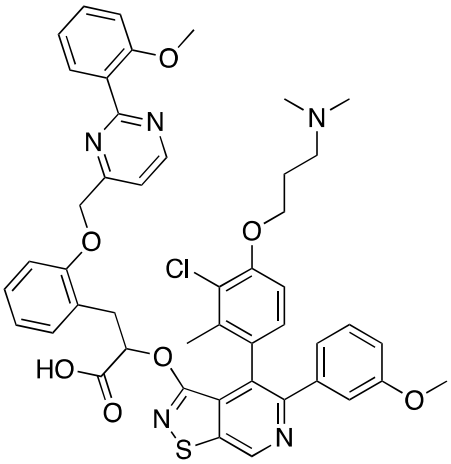
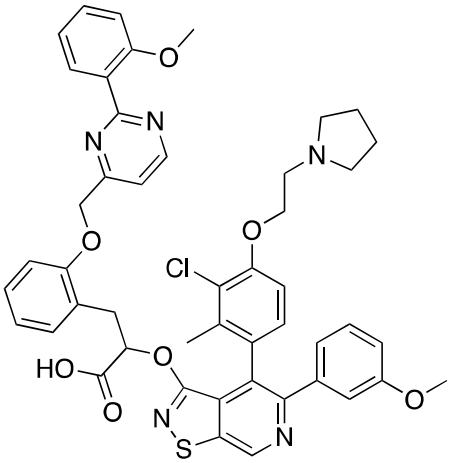
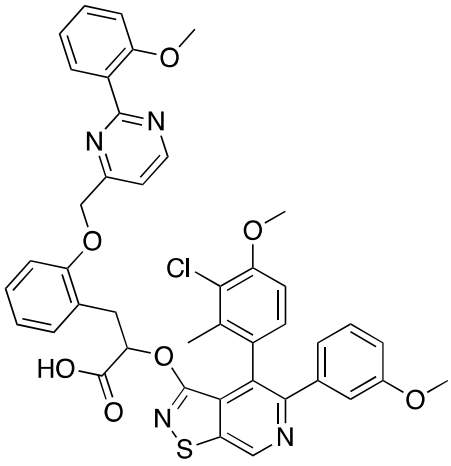
 ,  ,

 ,  ,

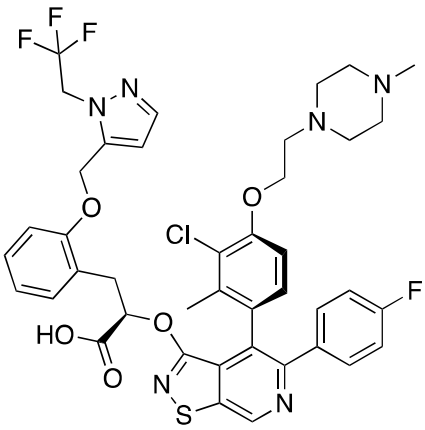
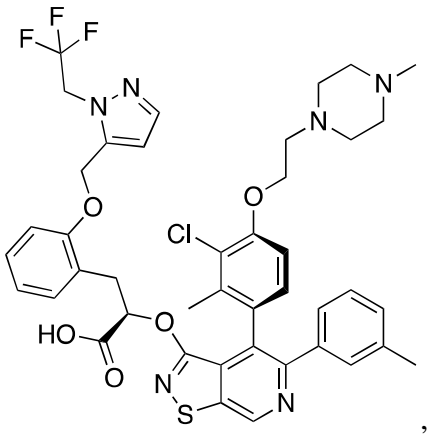
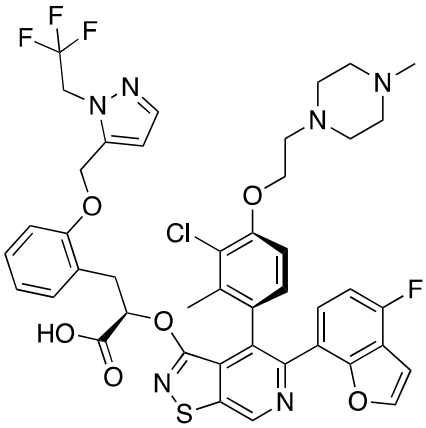
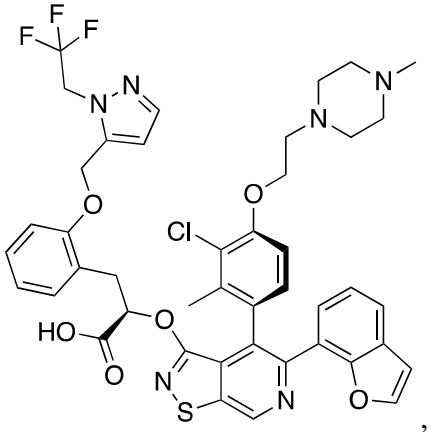
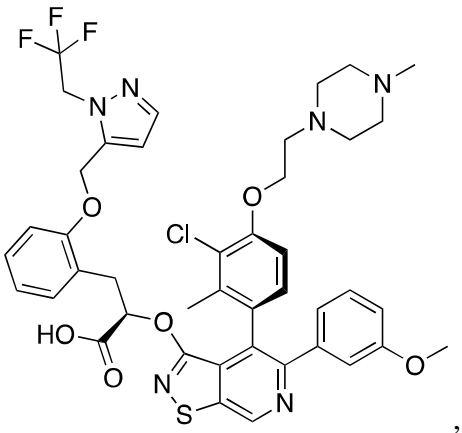
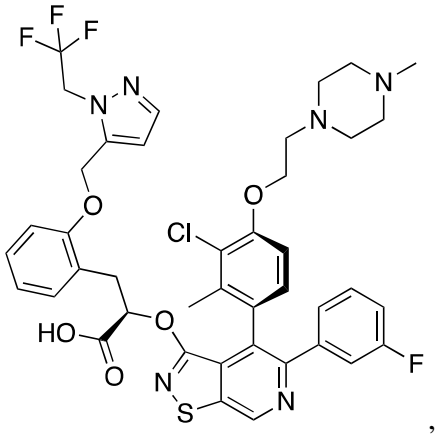

,

,

,

,

,

,

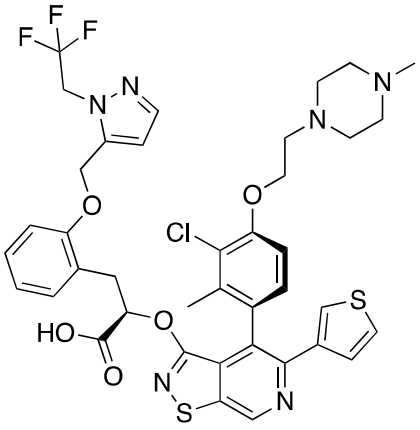
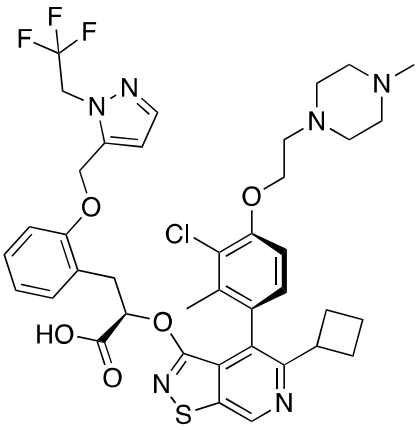
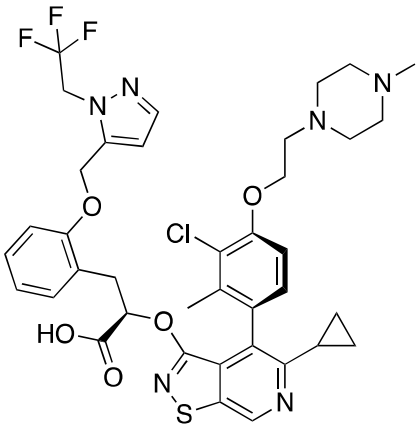
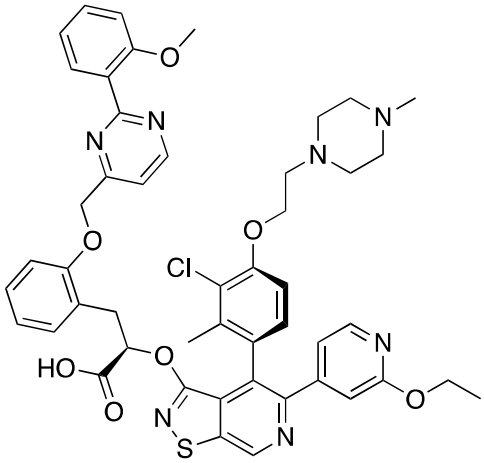
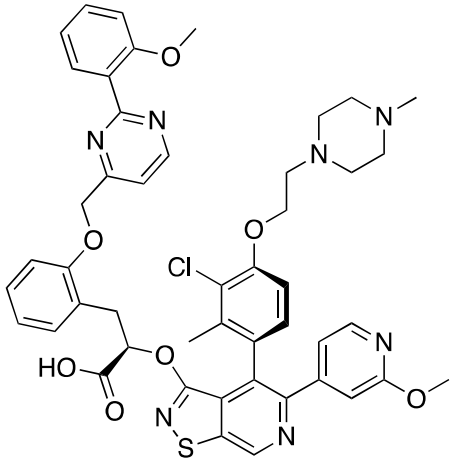
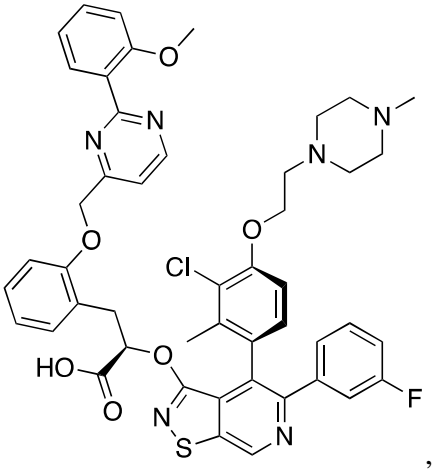

,

,

,

,

,

,

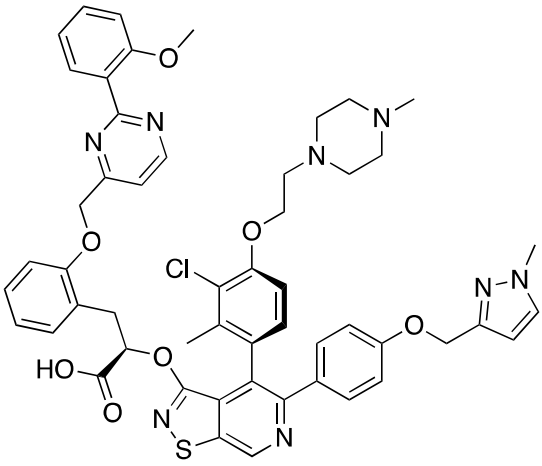
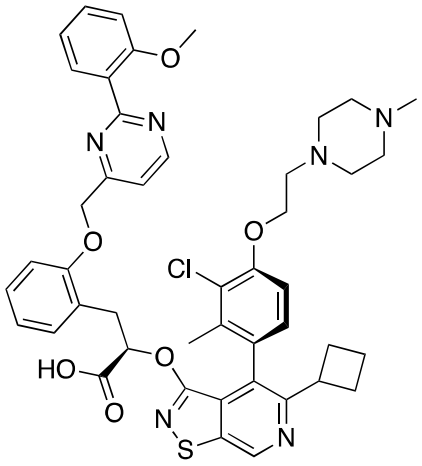
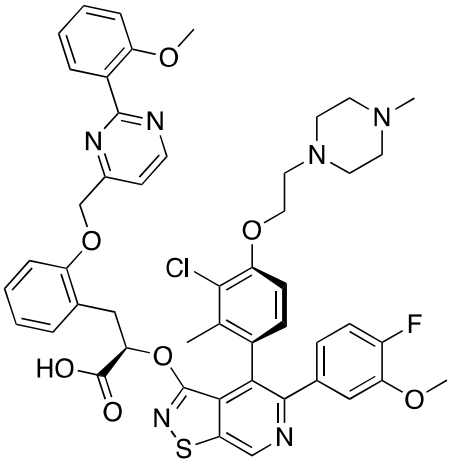
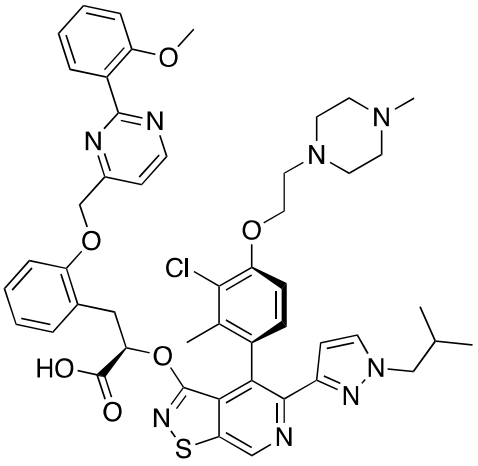
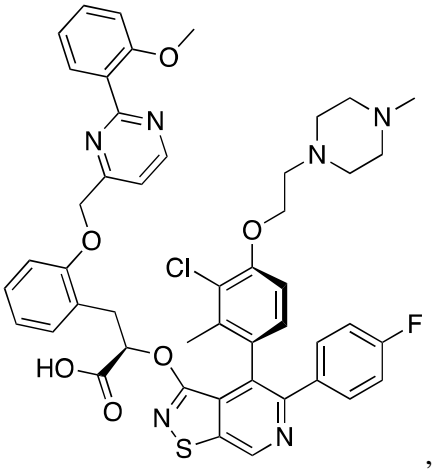
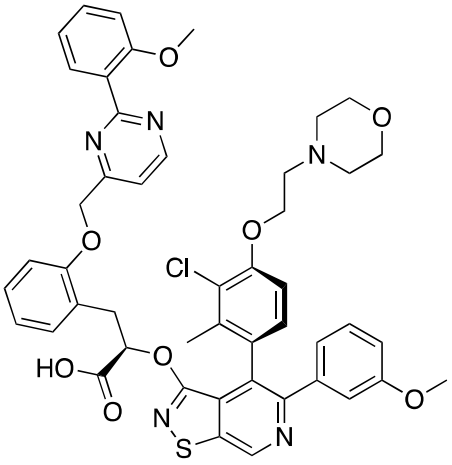

,

,

,

,

,

,

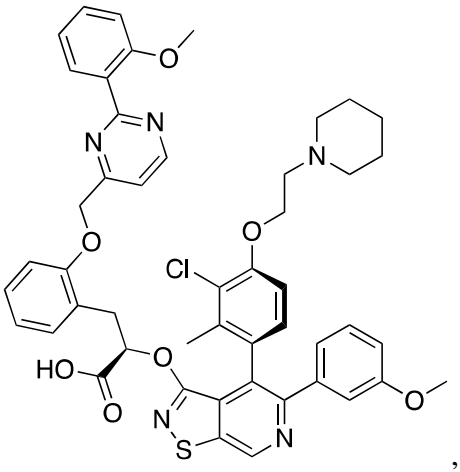
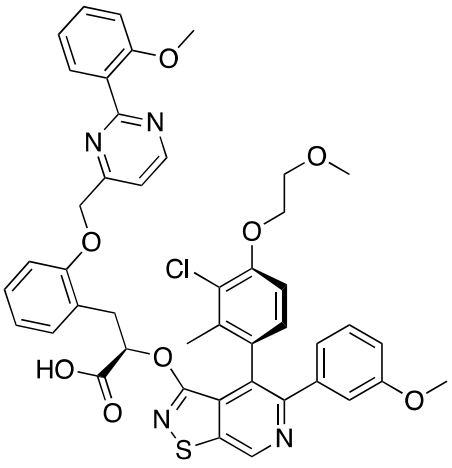
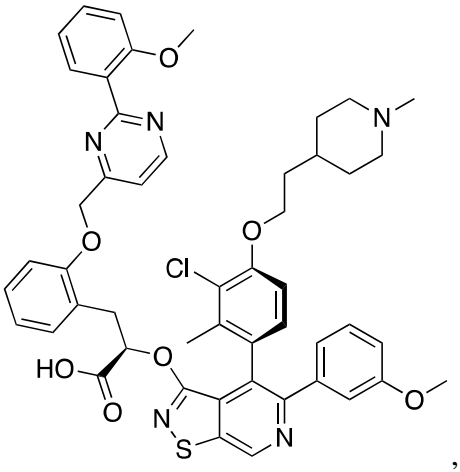
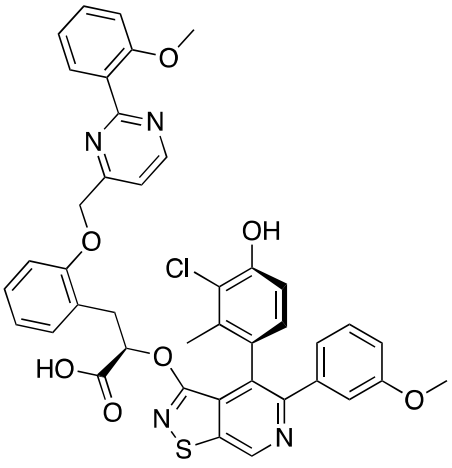
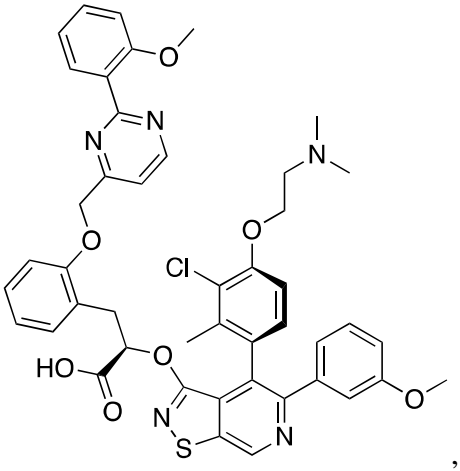
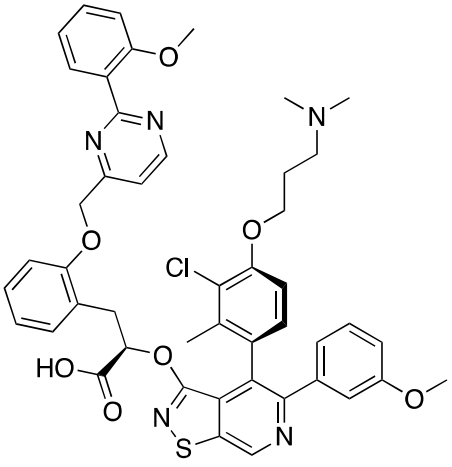

,

,

and

, or a pharmaceutically acceptable salt thereof.

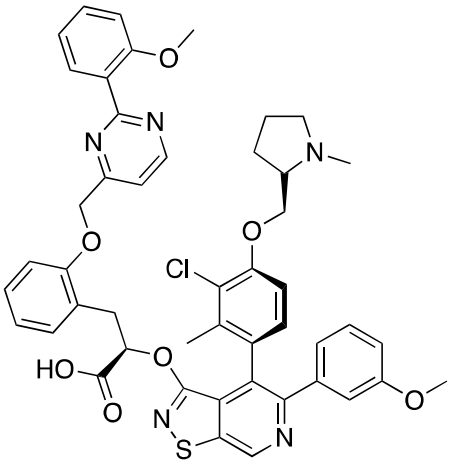
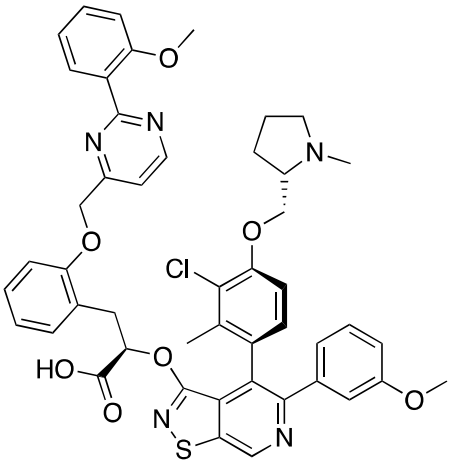
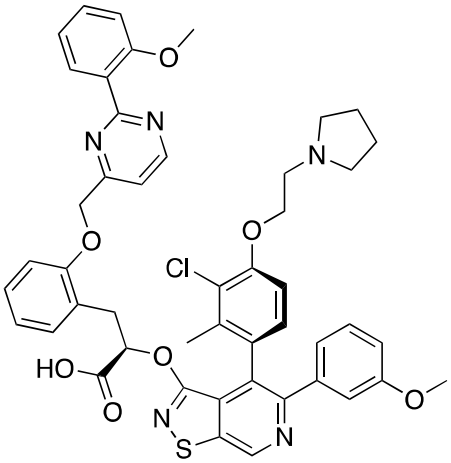
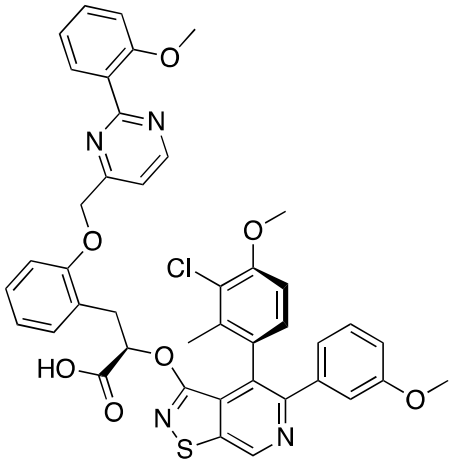
~~46.~~27. A compound selected from:


,

,

,

,

,

,

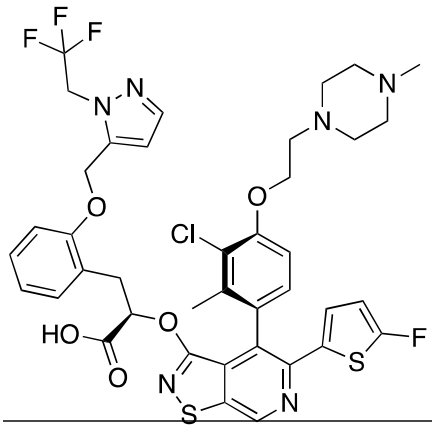

,

,

,

,

,

,


,

,

,

,

,

,

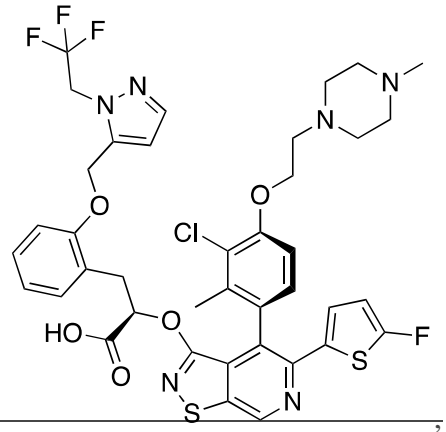

,

,

,

,

,

,


,

,

and

, or a pharmaceutically acceptable salt thereof.

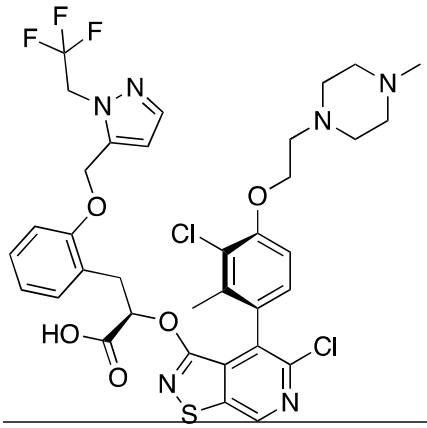
~~47. A compound selected from:~~



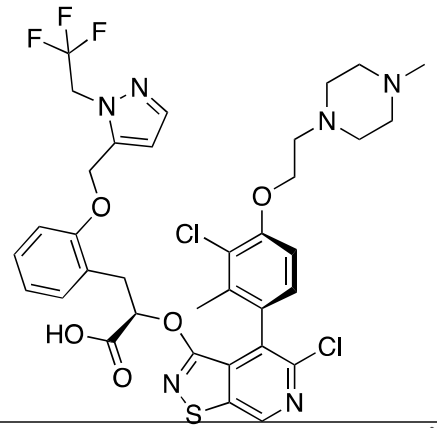
,



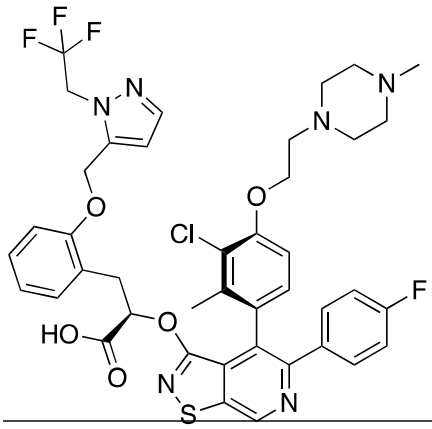
,



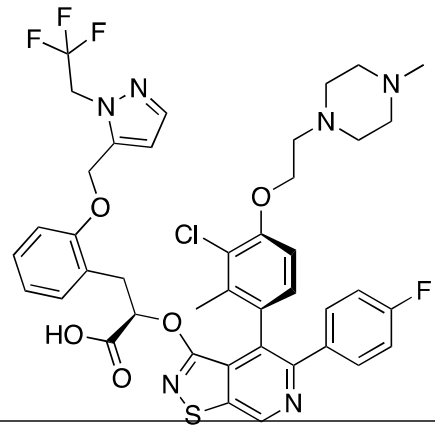
,



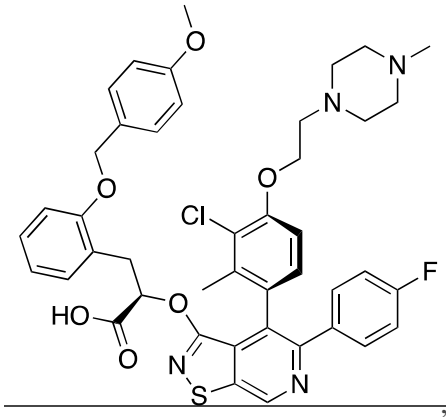
,



,

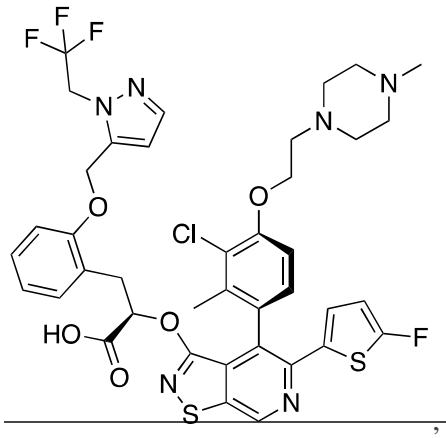


~~and~~

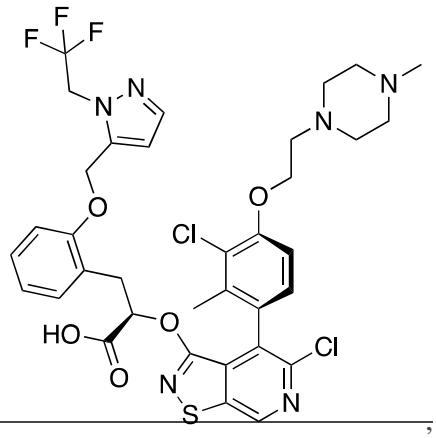


, or a pharmaceutically acceptable salt thereof.

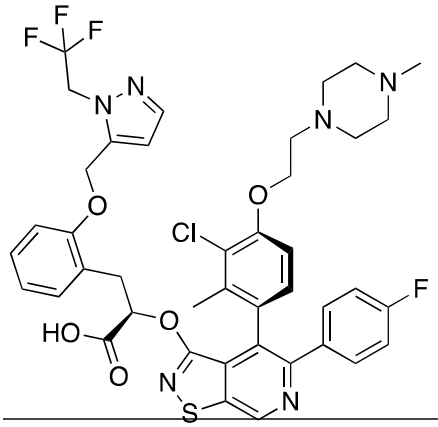
48. A compound selected from:



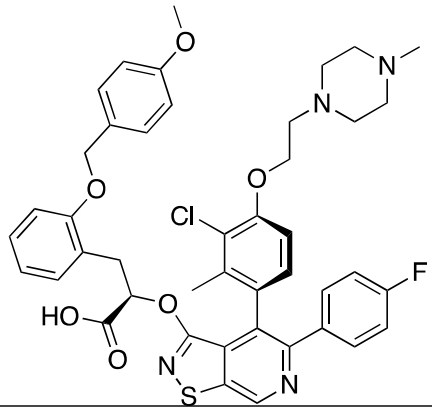
,



,

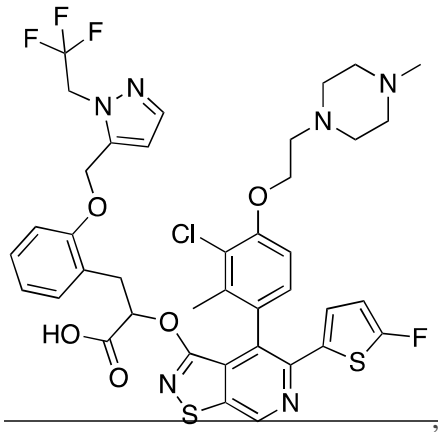


and

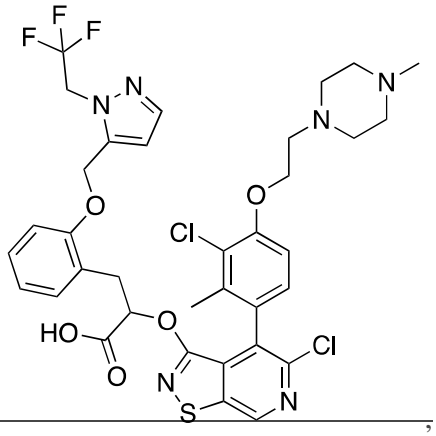


, or a pharmaceutically acceptable salt thereof.

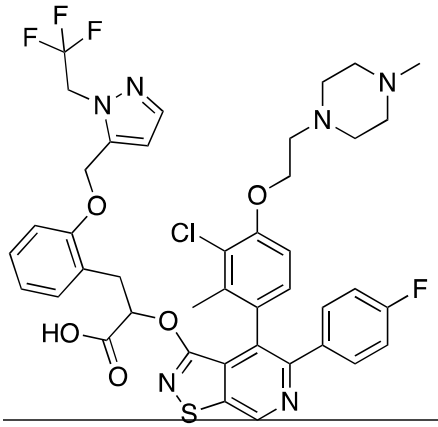
~~49. A compound selected from:~~



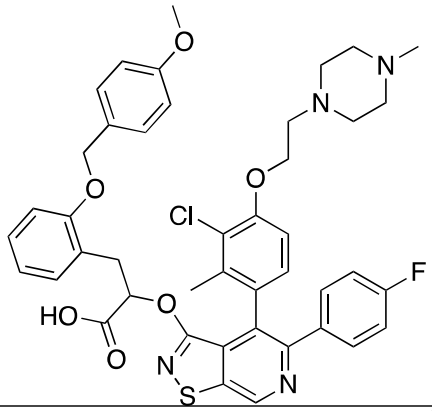
~~,~~



~~,~~

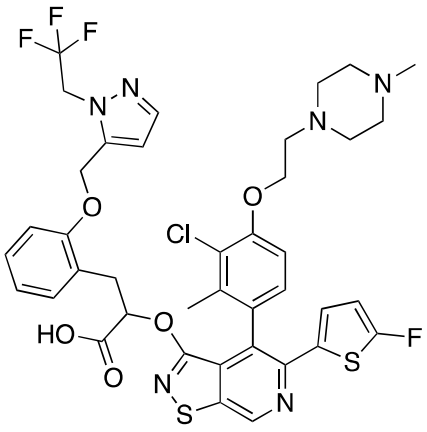
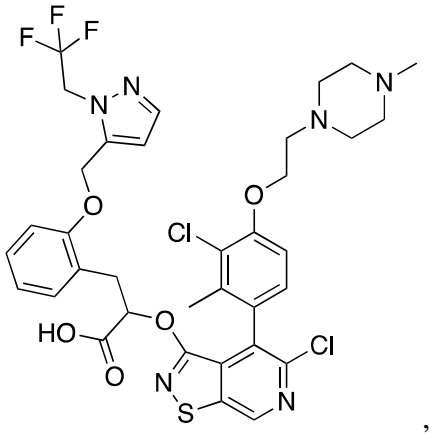
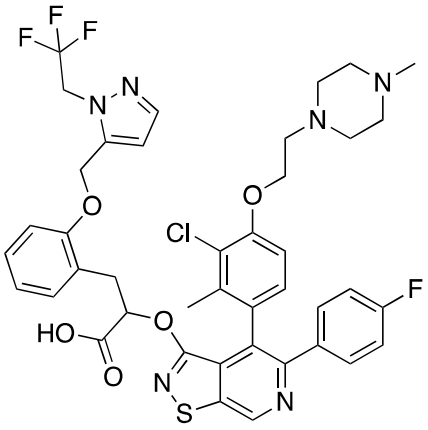
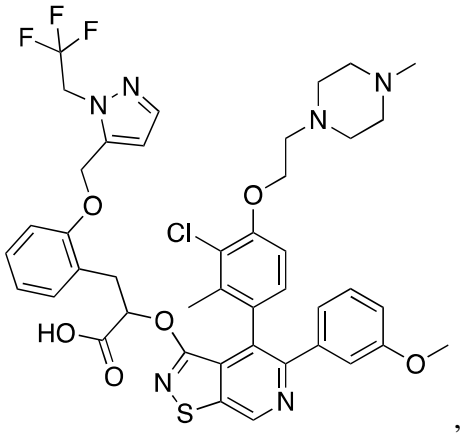
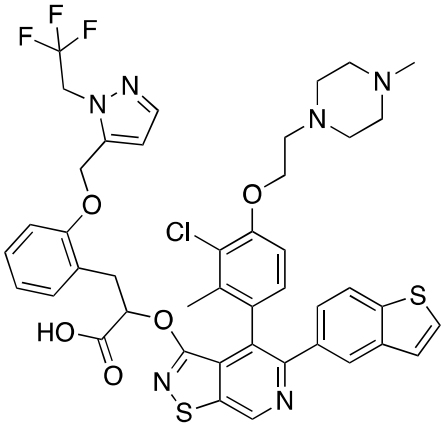
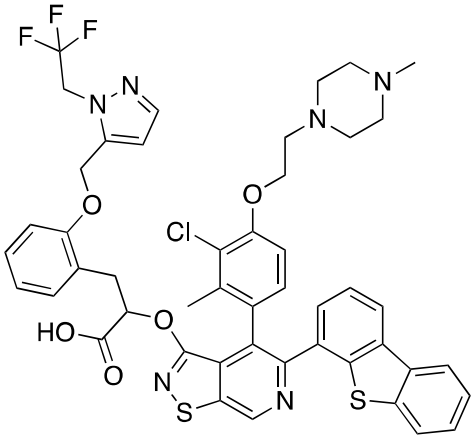


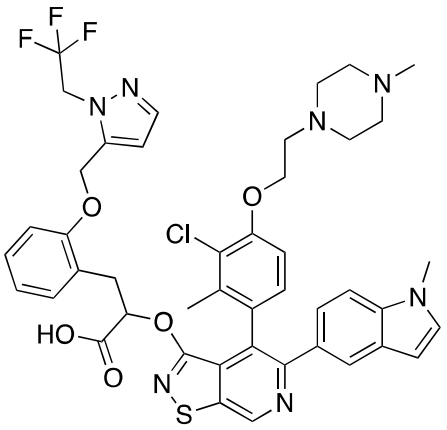
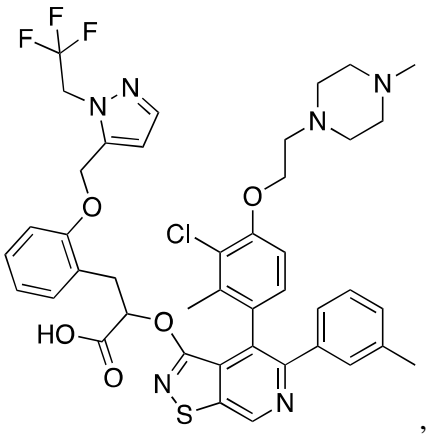
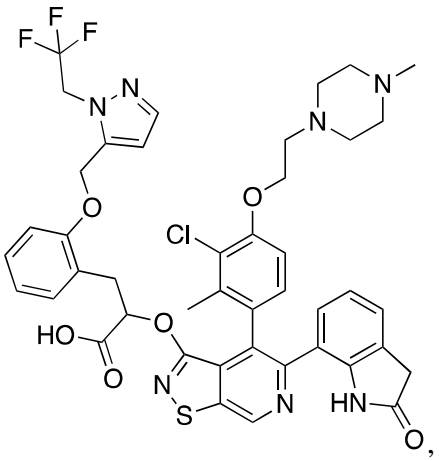
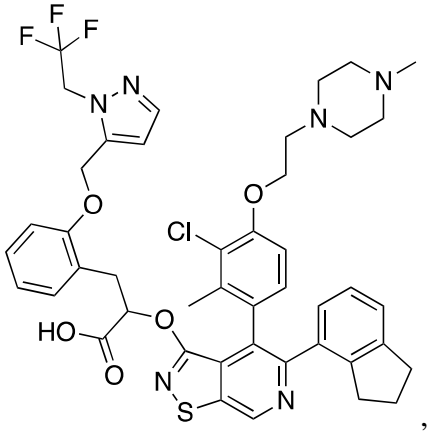
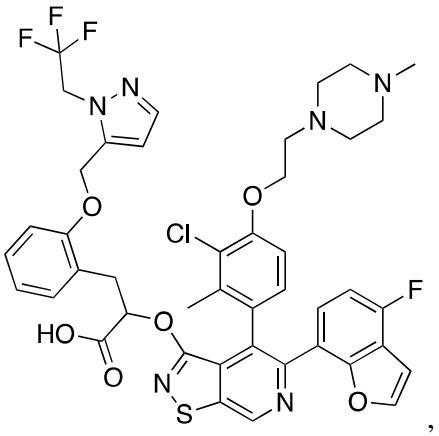
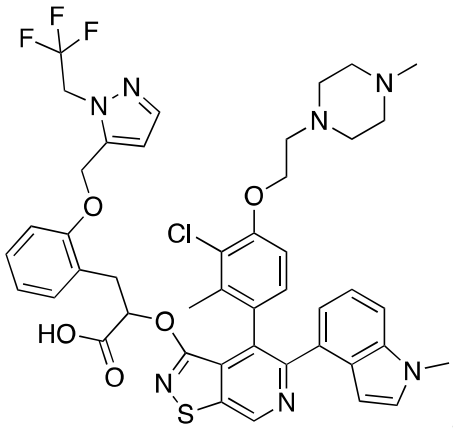
~~and~~

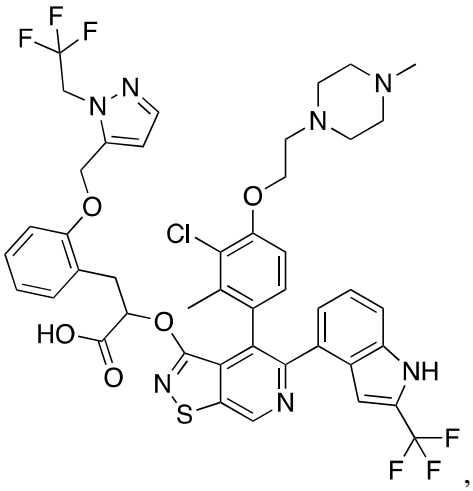
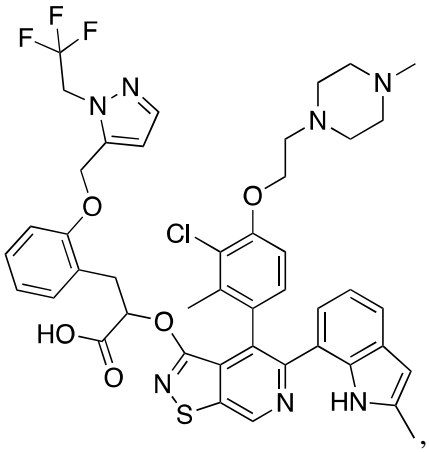
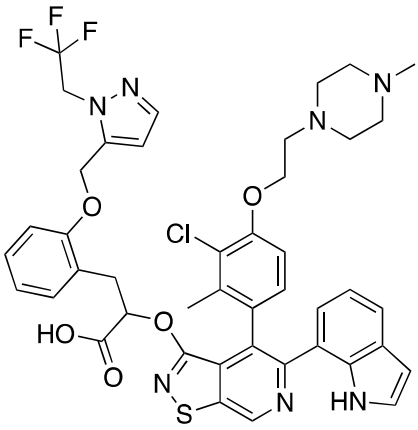
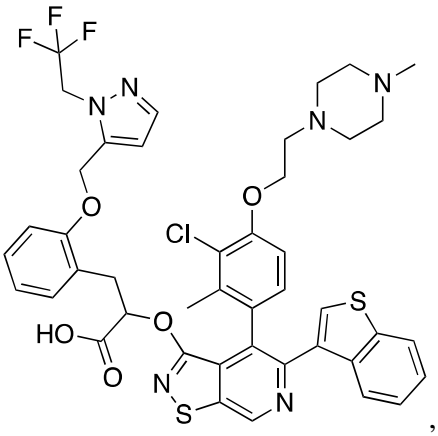
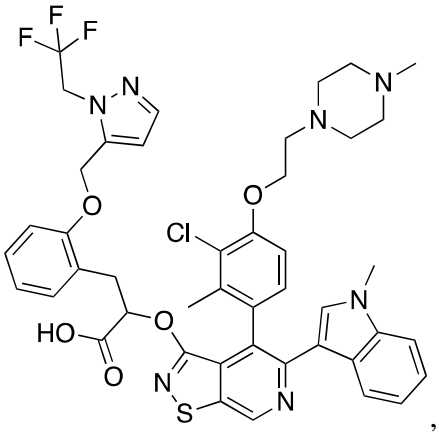
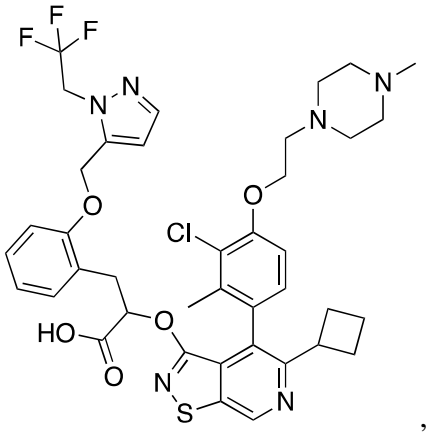


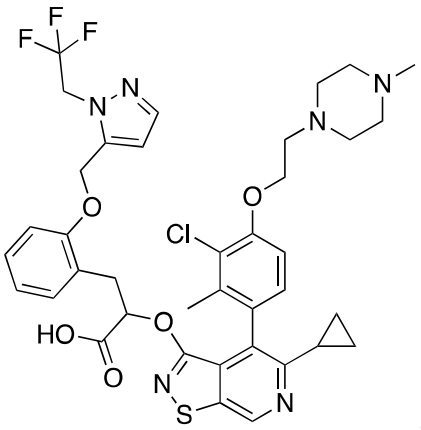
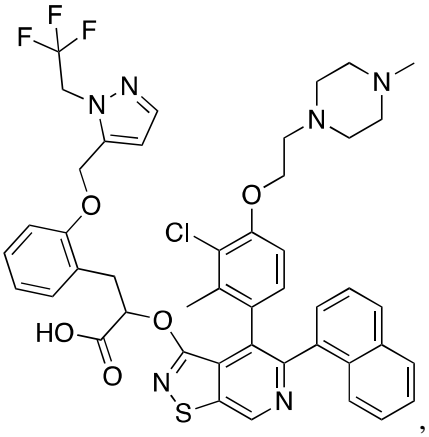
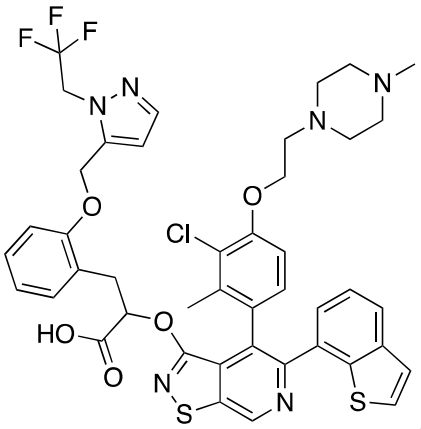
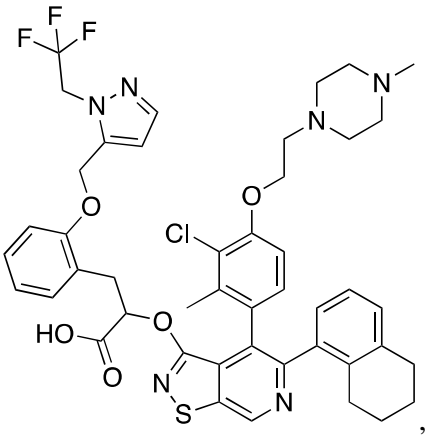
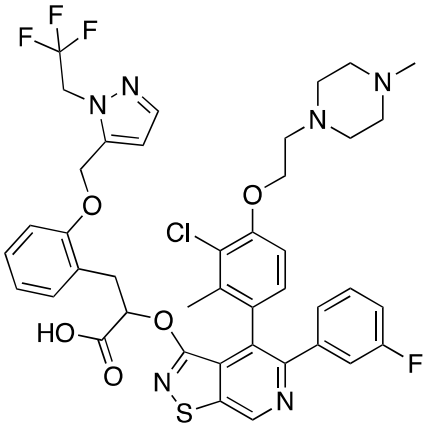
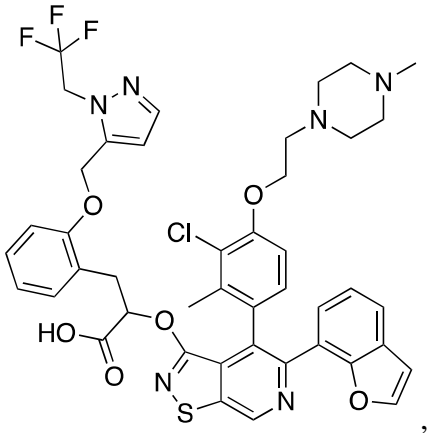
~~, or a pharmaceutically acceptable salt thereof.~~

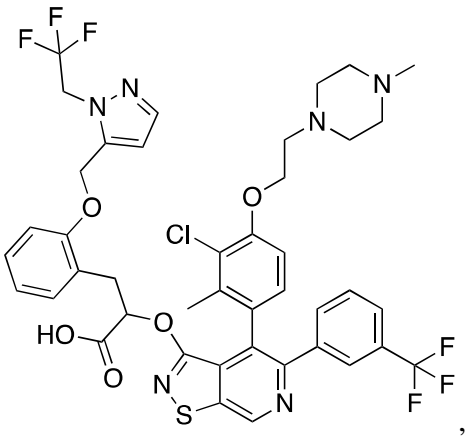
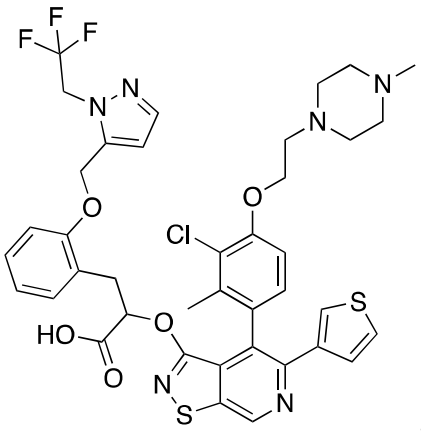
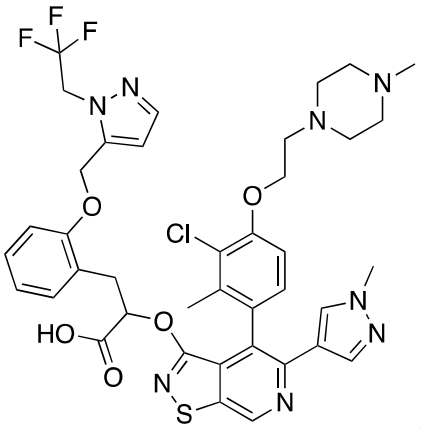
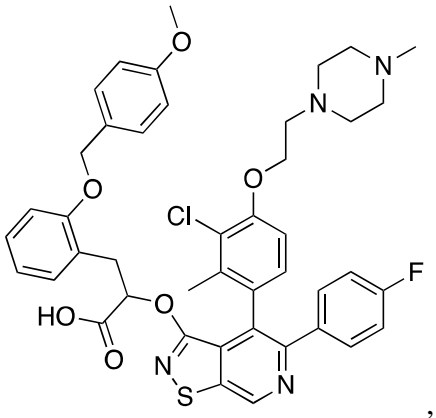
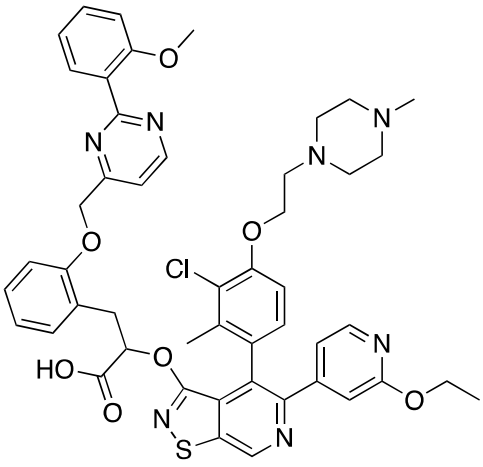
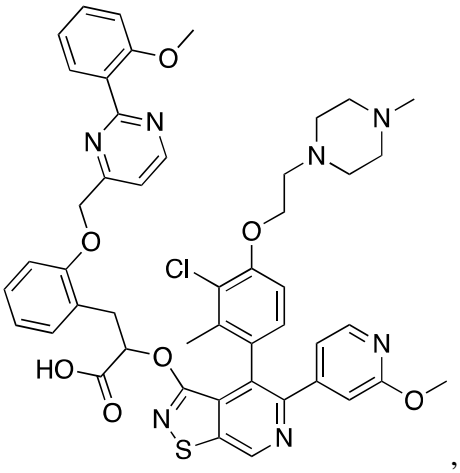
~~50.~~28. A compound selected from:

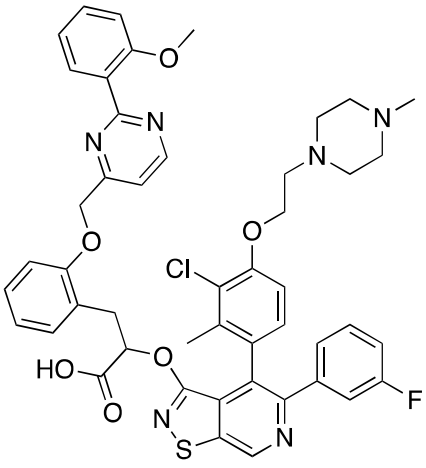
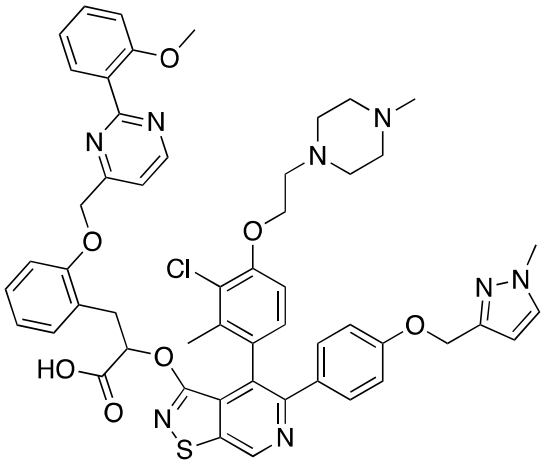
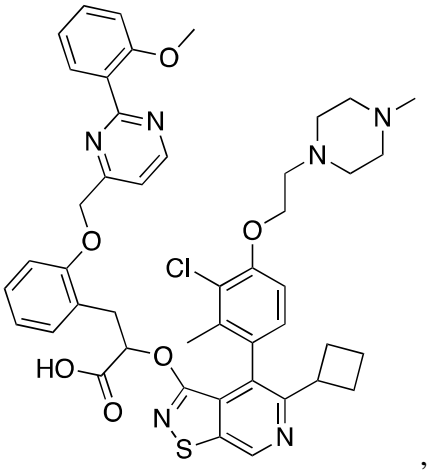
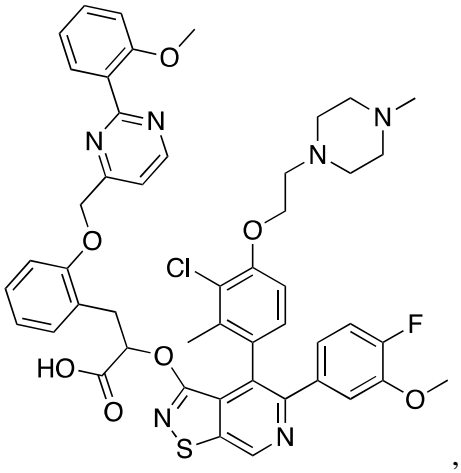
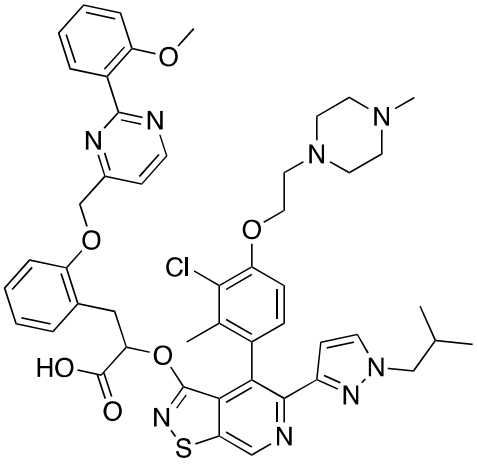
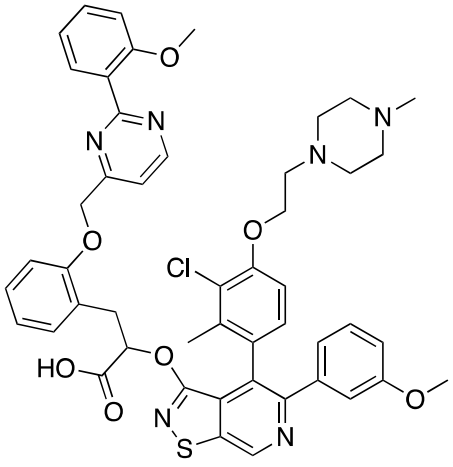

,

,

,

,

,

,

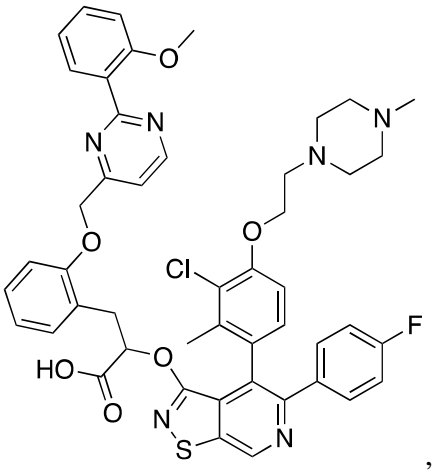
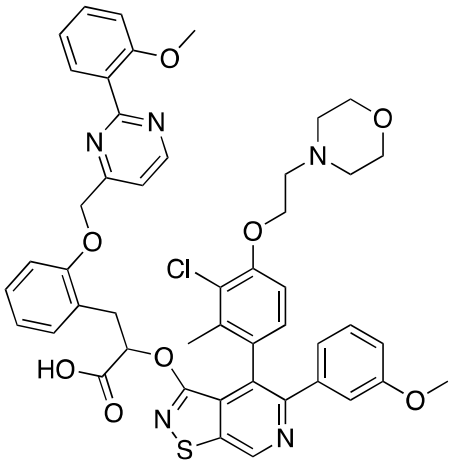
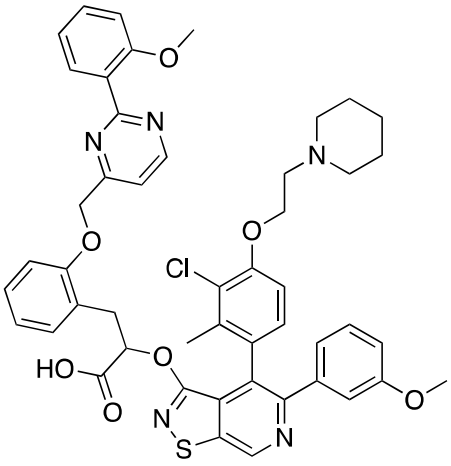
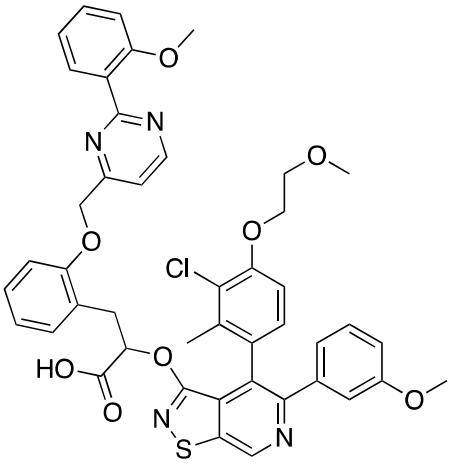
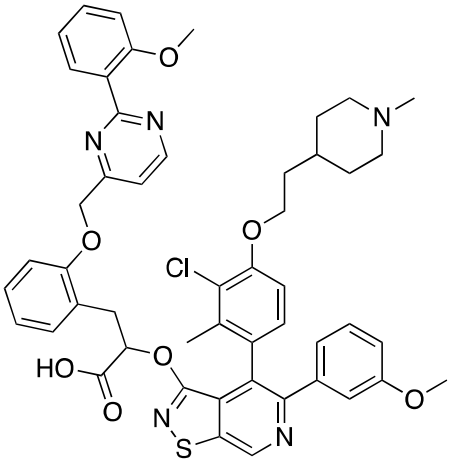
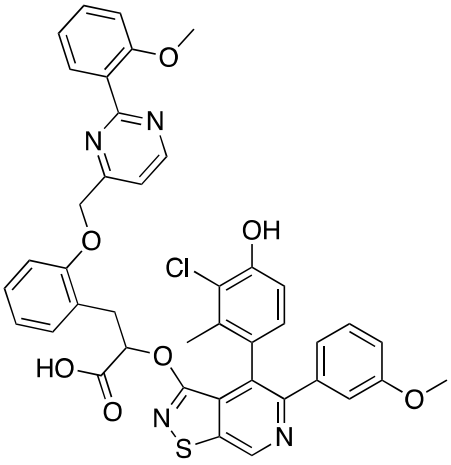

,

,

,

,

,

,

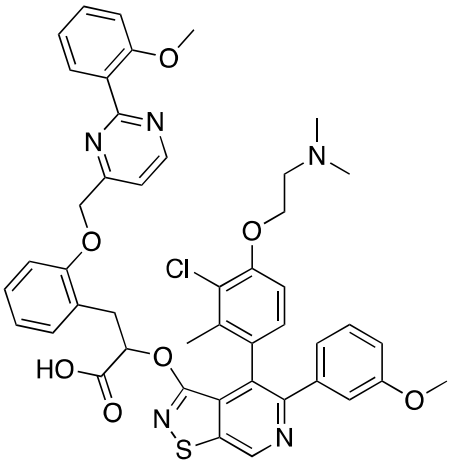
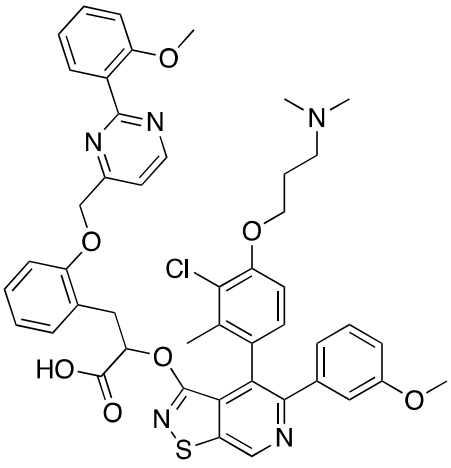
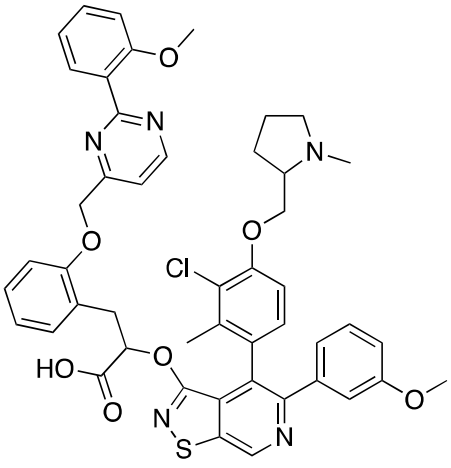
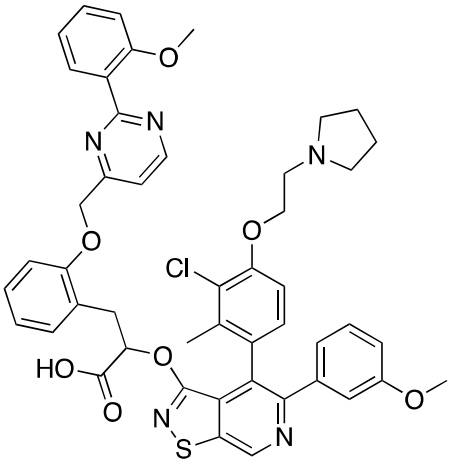
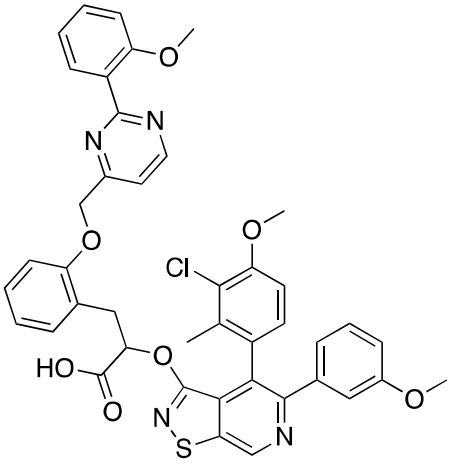
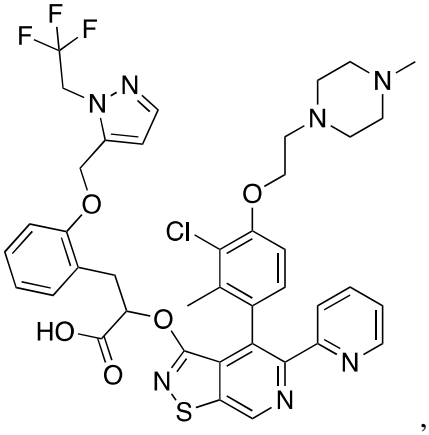

,

,

,

,

,

,

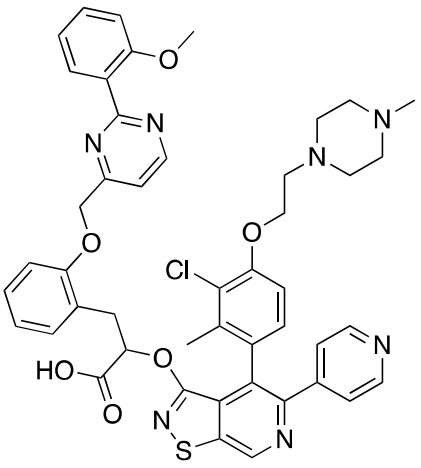
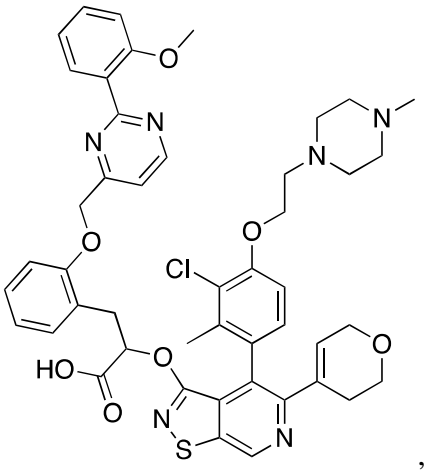
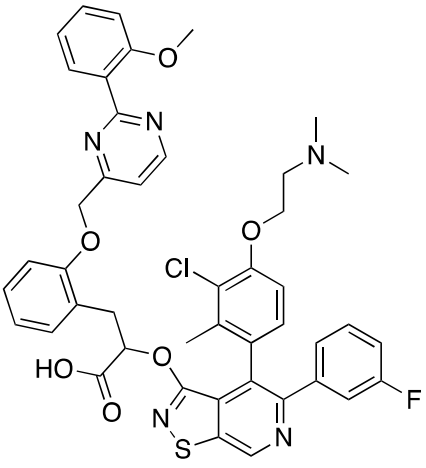
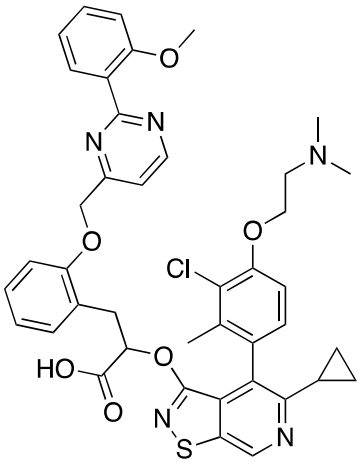
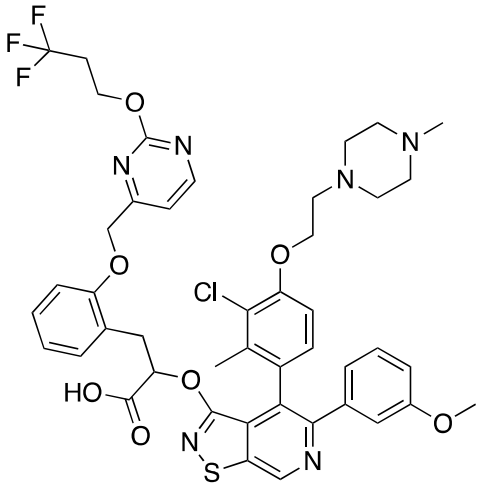
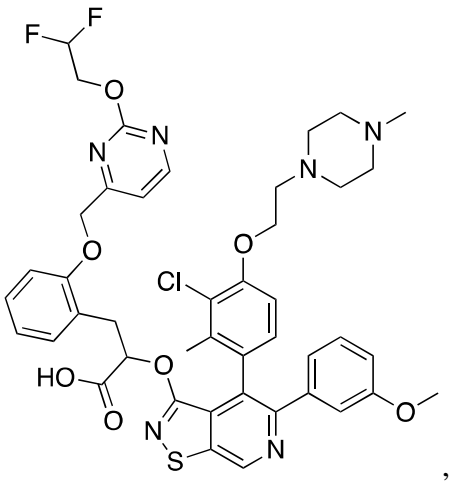

,

,

,

,

,

,

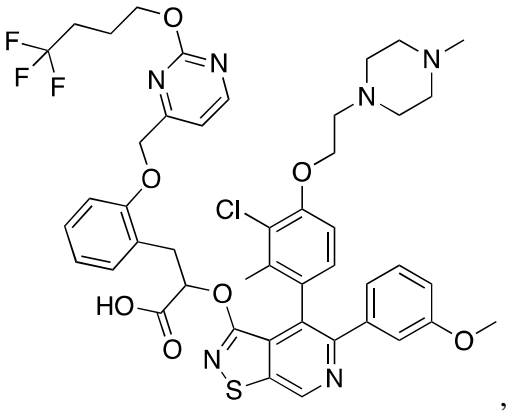
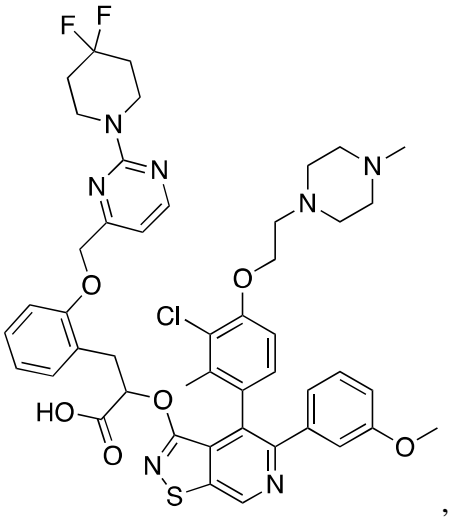
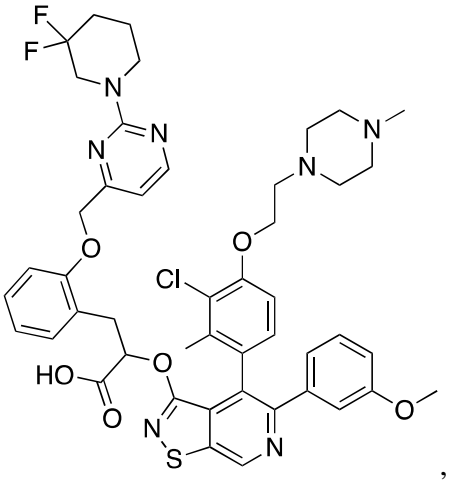
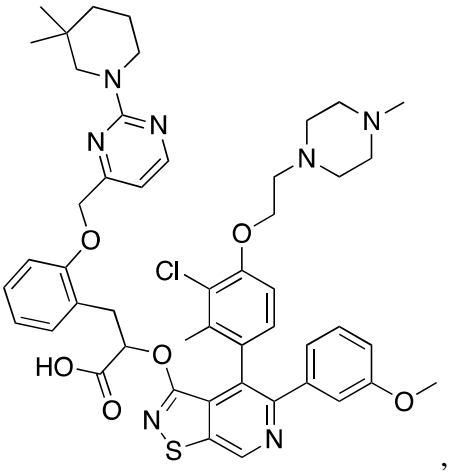
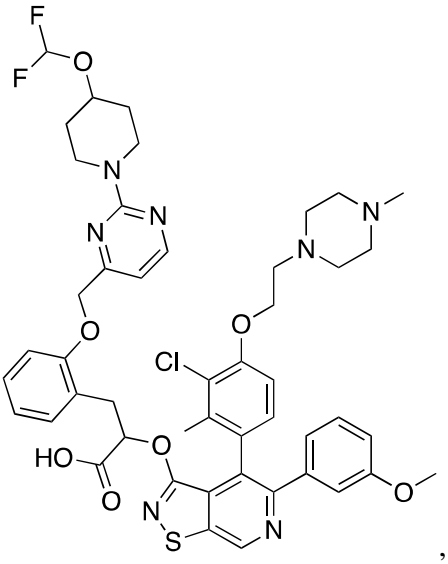
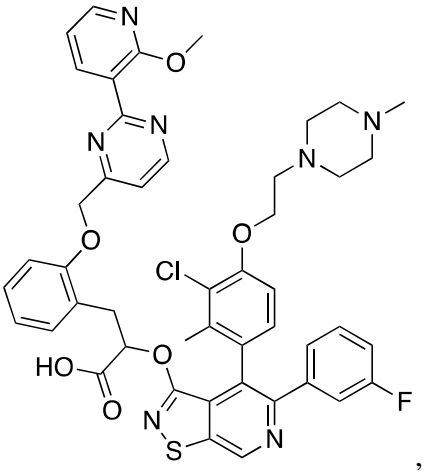

,

,

,

,

,

,

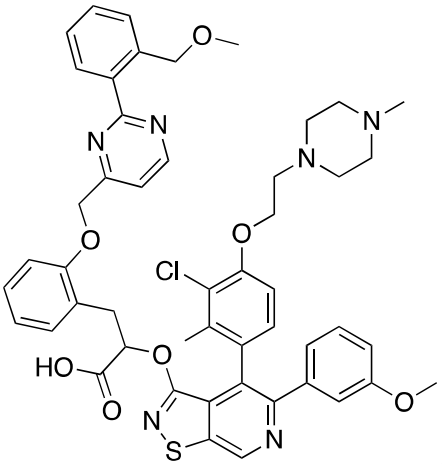
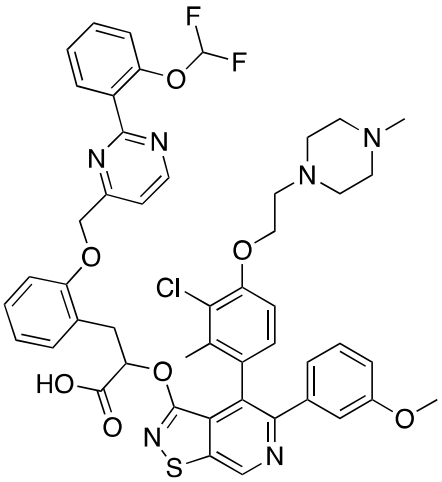
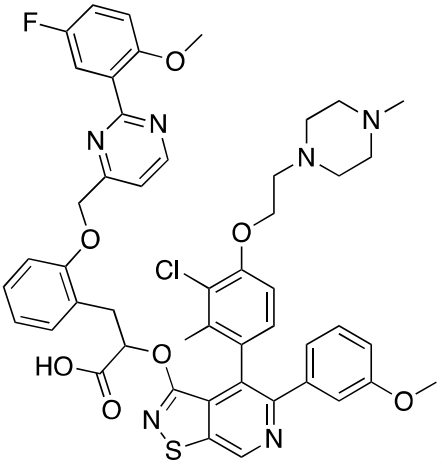
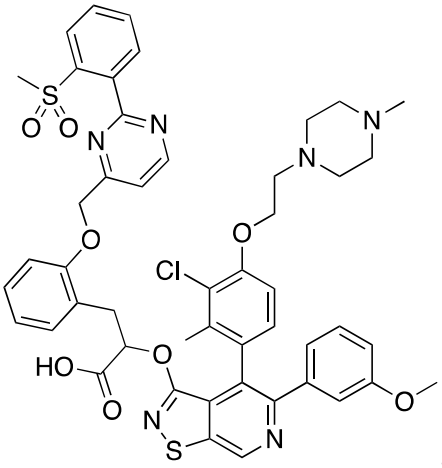
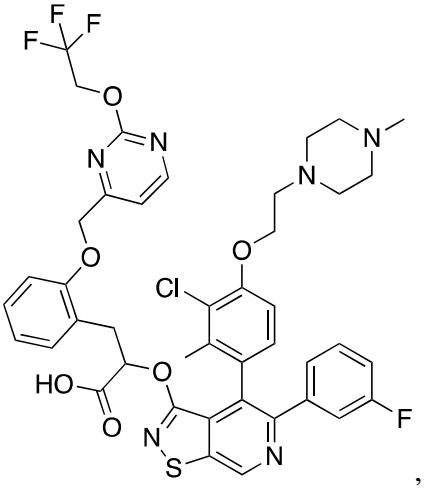
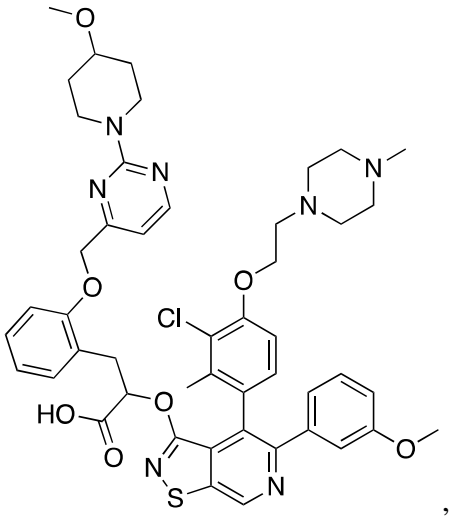

,

,

,

,

,

,

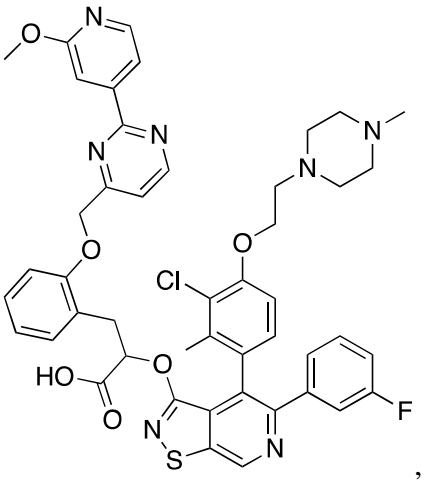
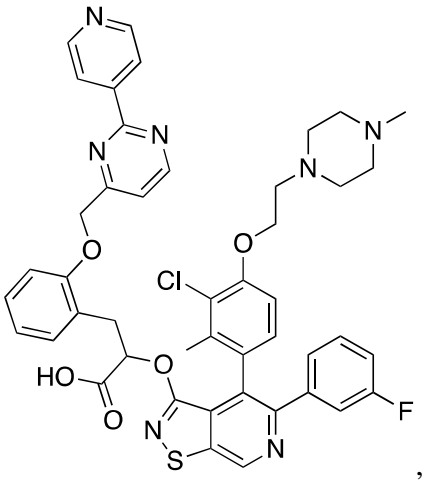
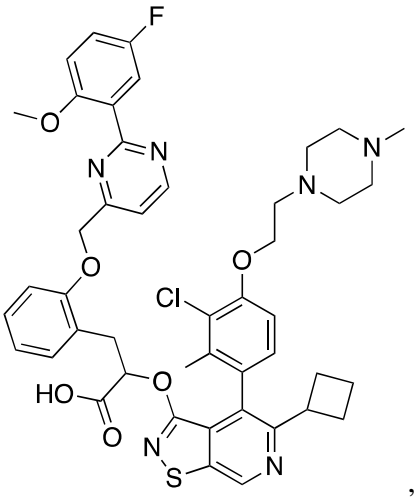
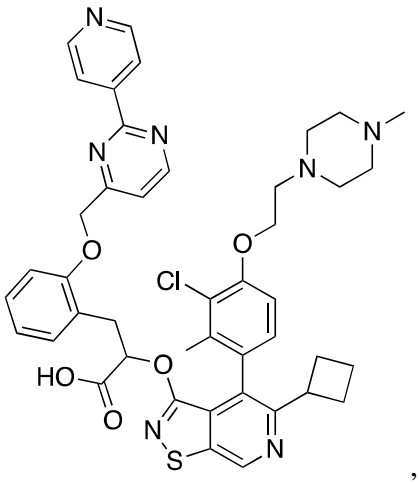
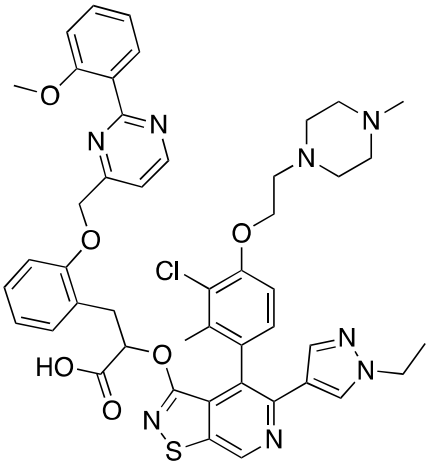
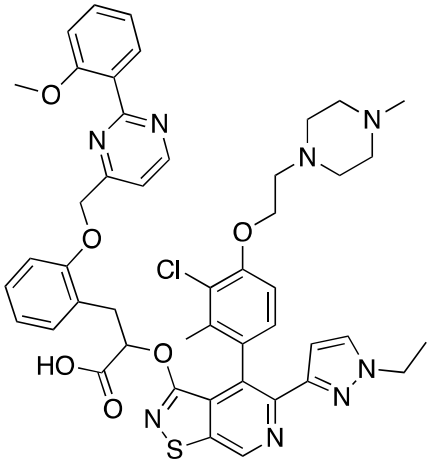

,

,

,

,

,

,

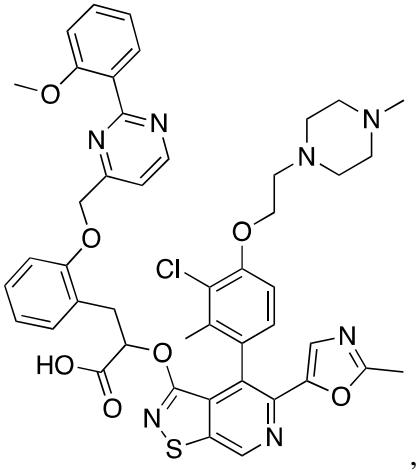
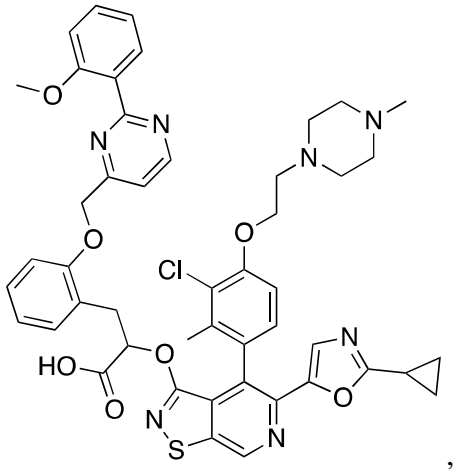
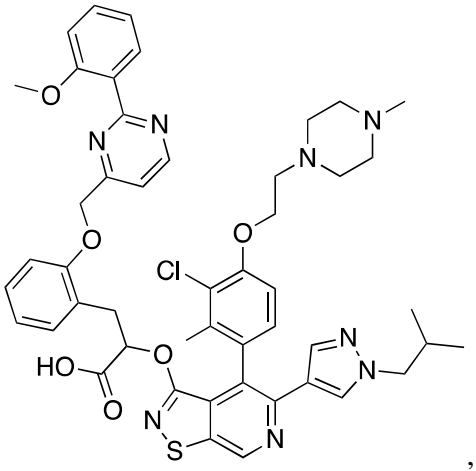
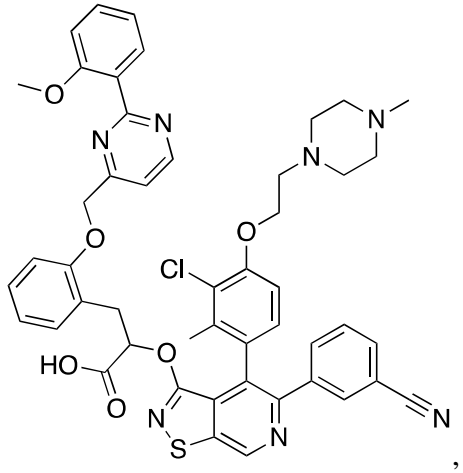
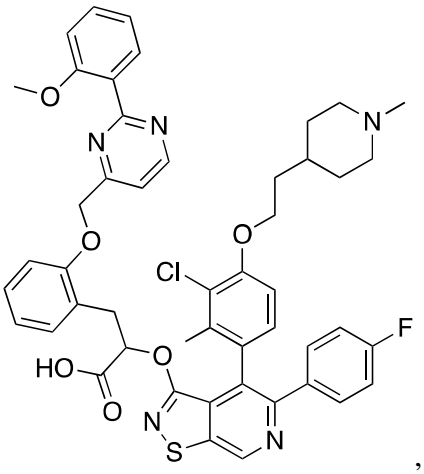
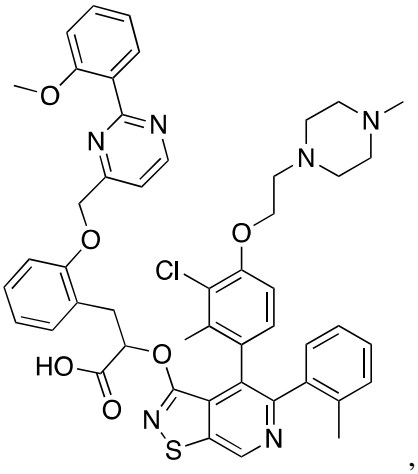

,

,

,

,

,

,

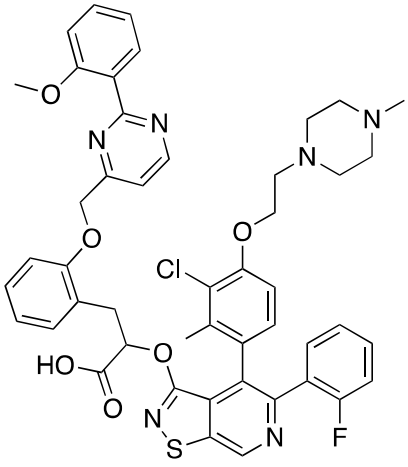
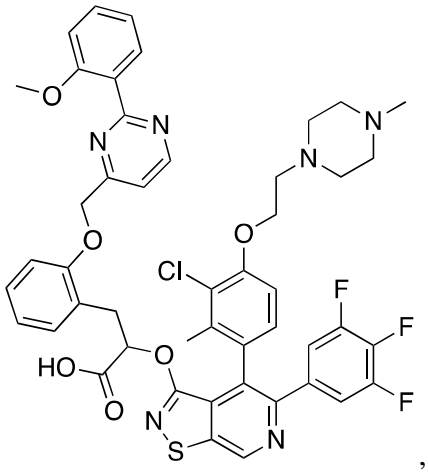
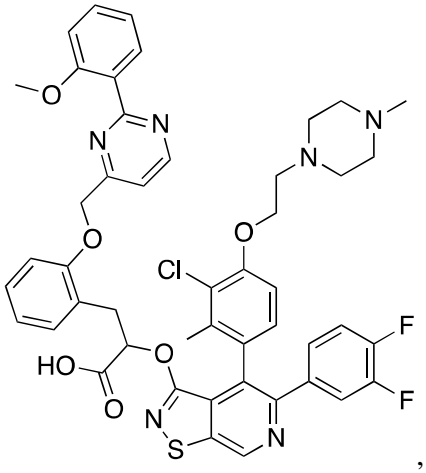
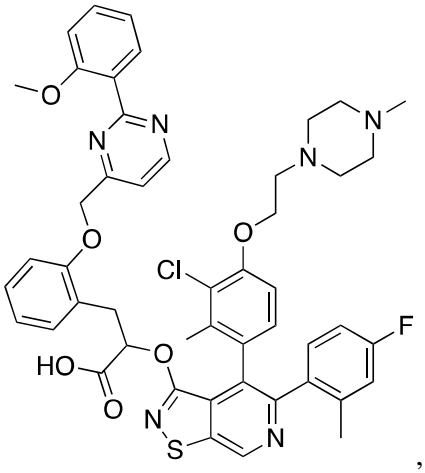
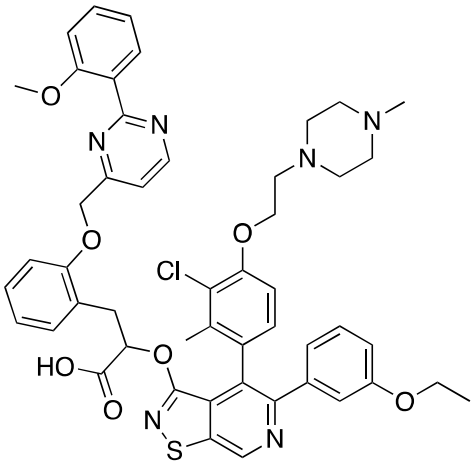
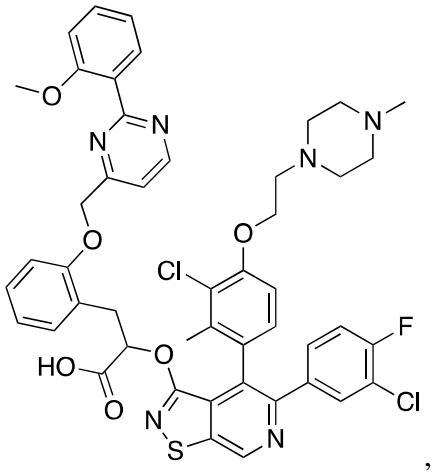

,

,

,

,

,

,

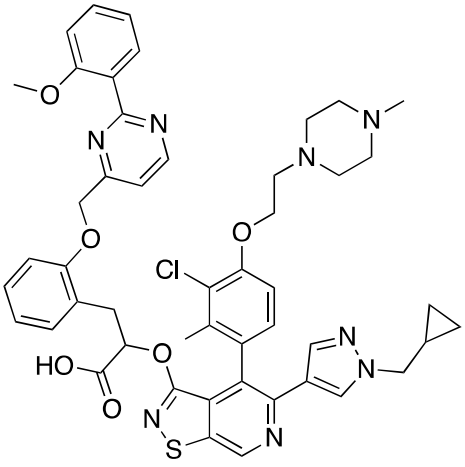
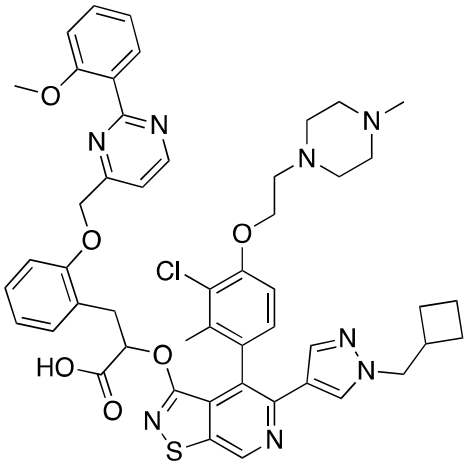
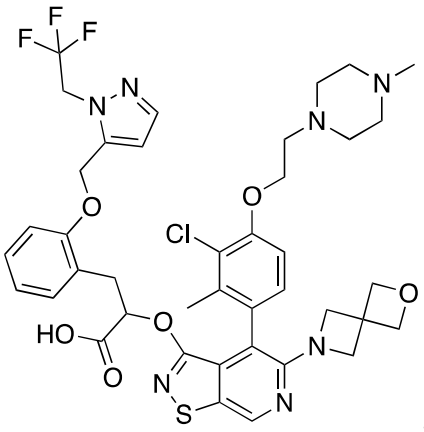
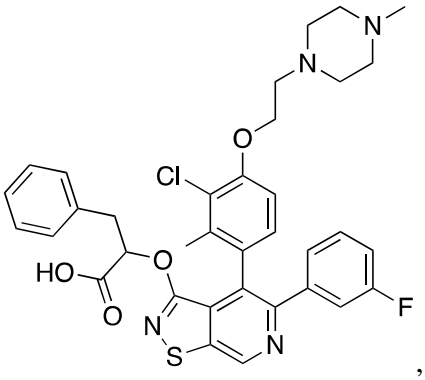
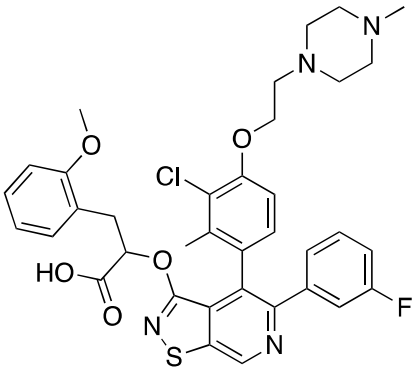
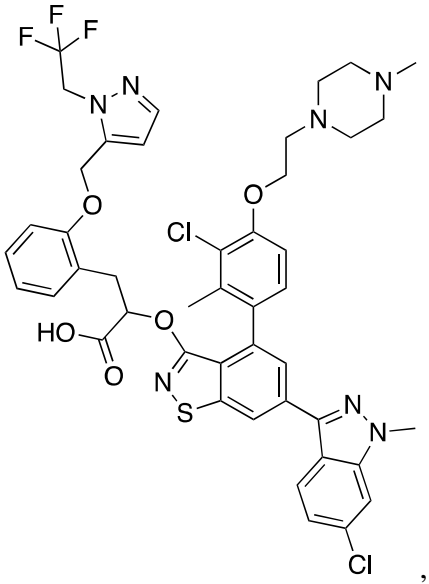

,

,

,

,

,

,

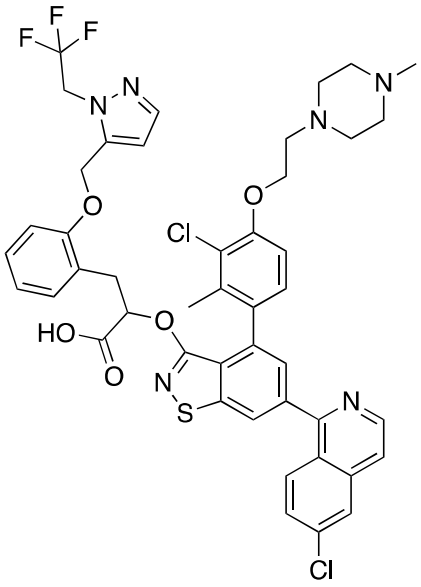
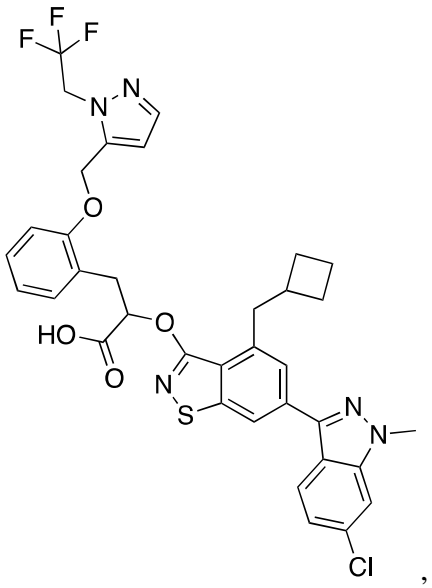
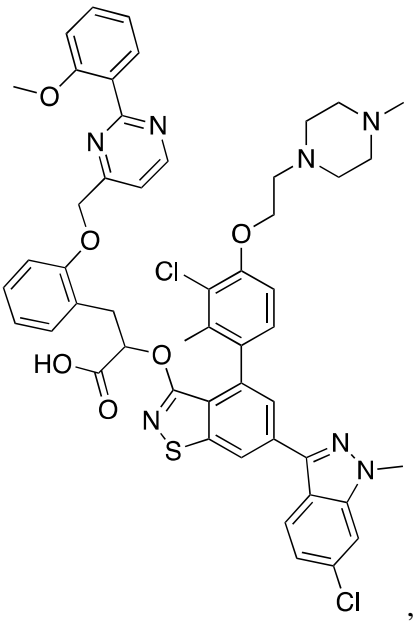
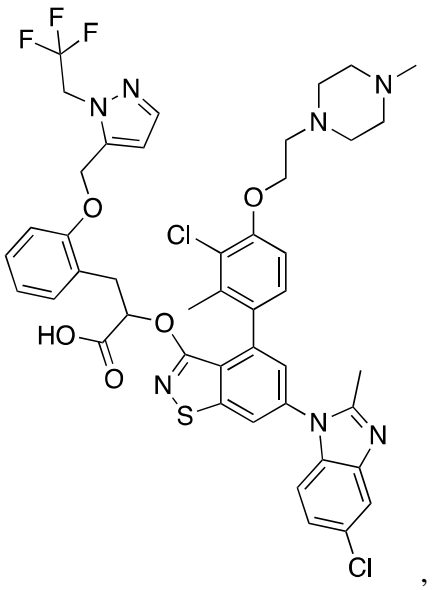

,

,

,

,

,

,

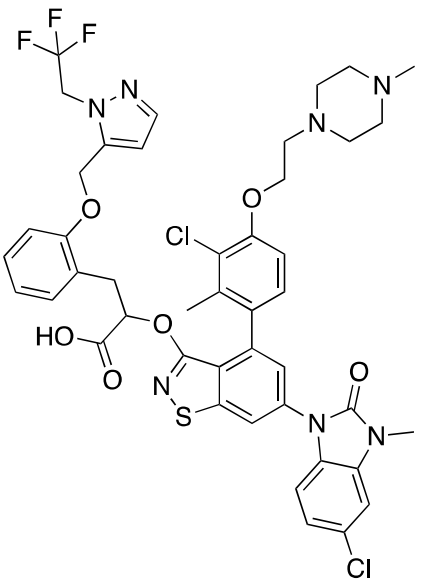
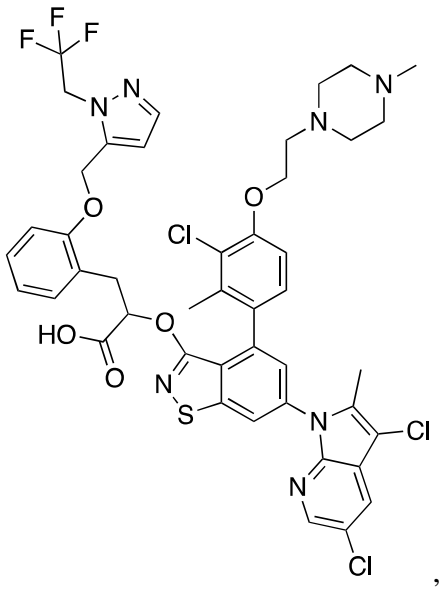
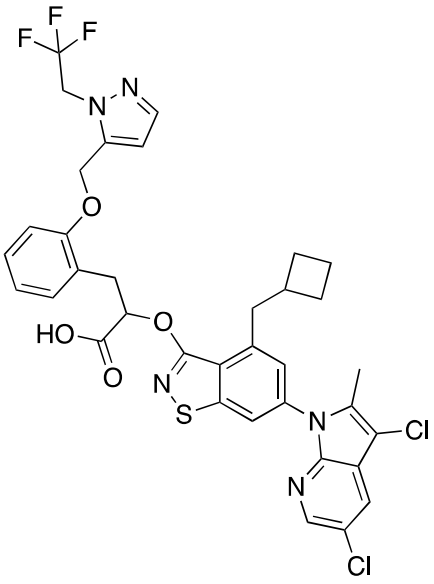
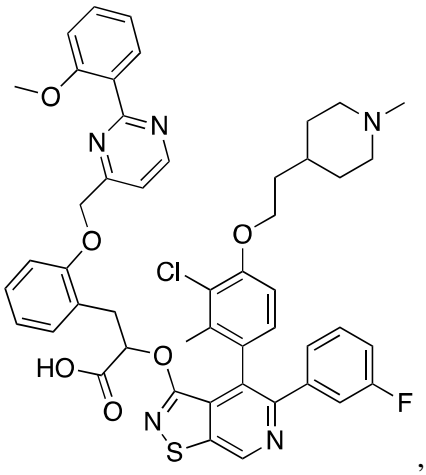
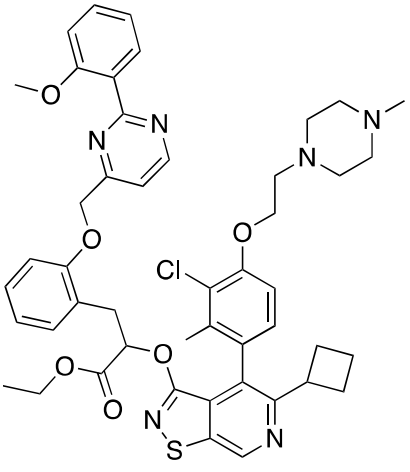
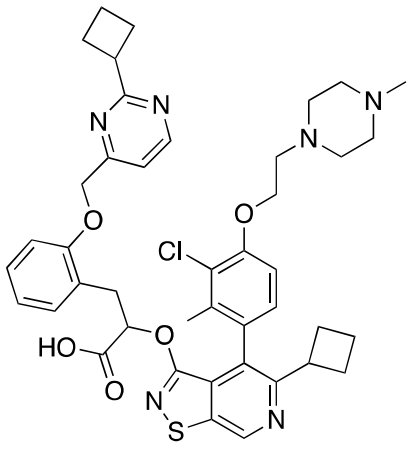

,

,

,

,

,

,

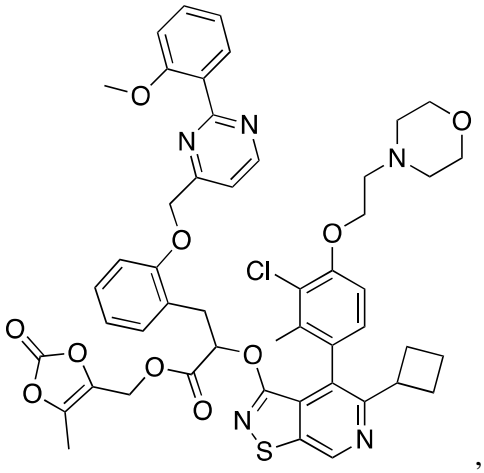
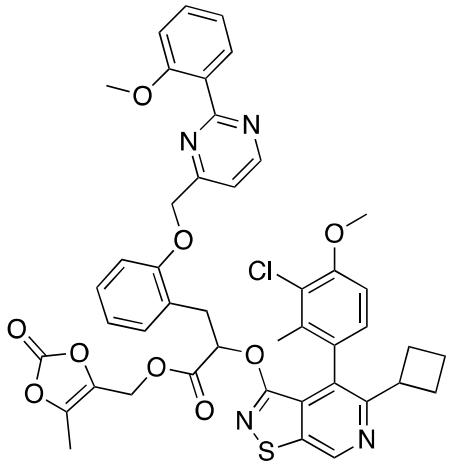
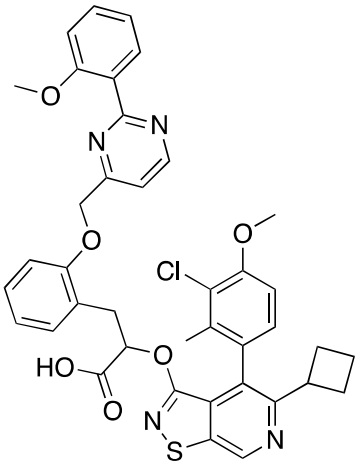
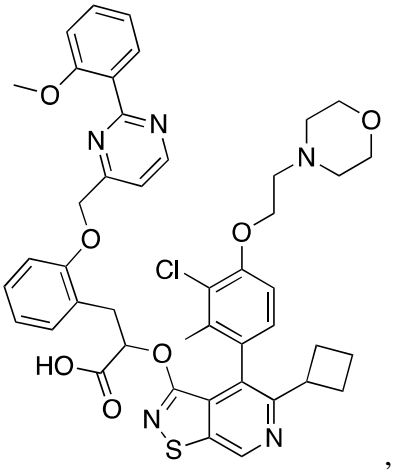
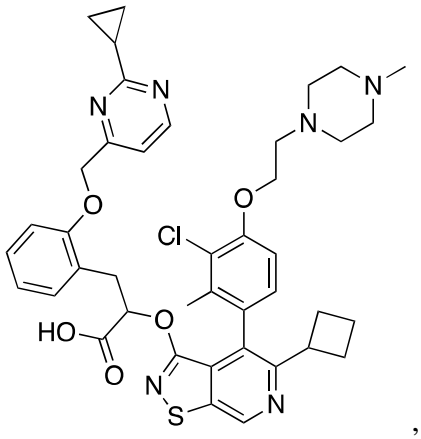
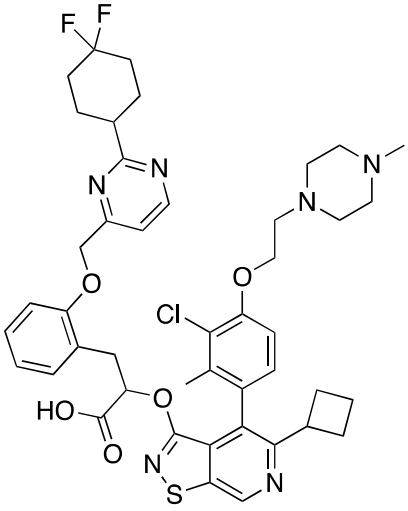
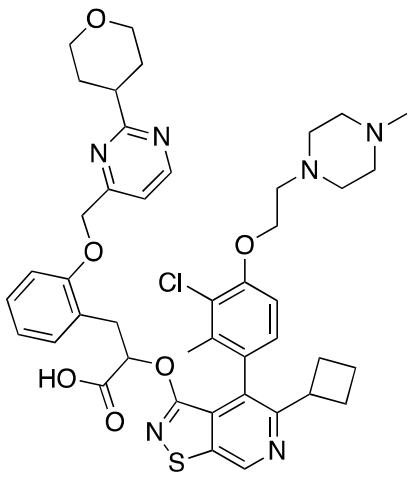

,

,

,

,

,

,

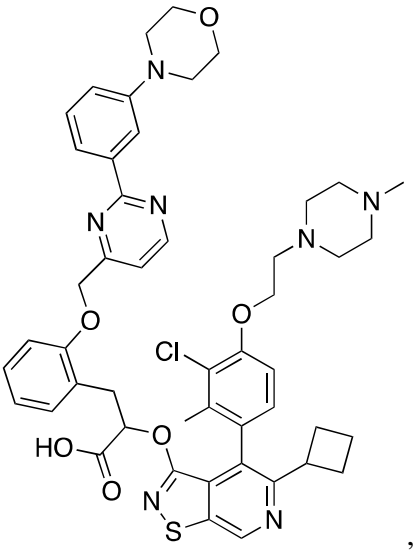
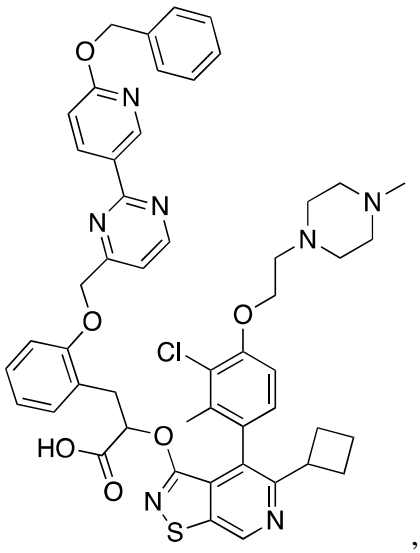
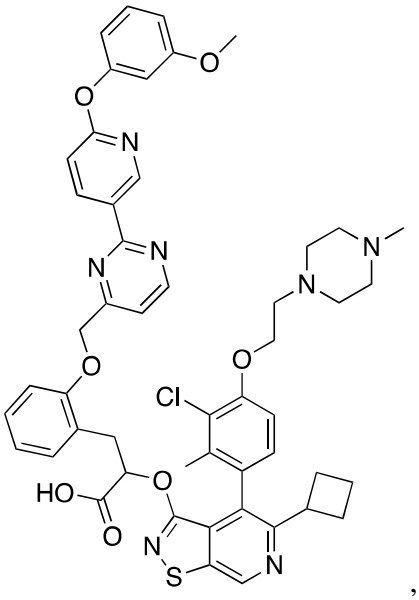
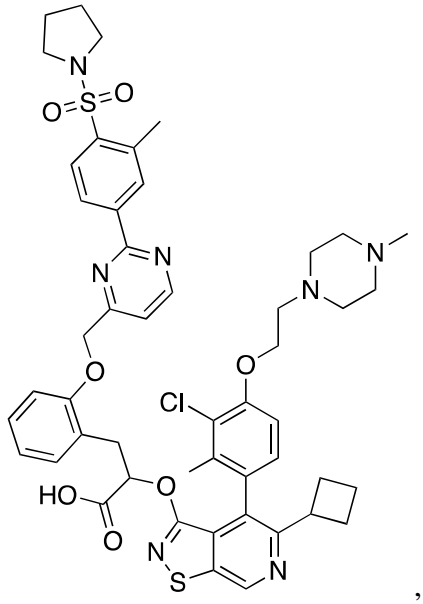

,

,

,

,

,

,

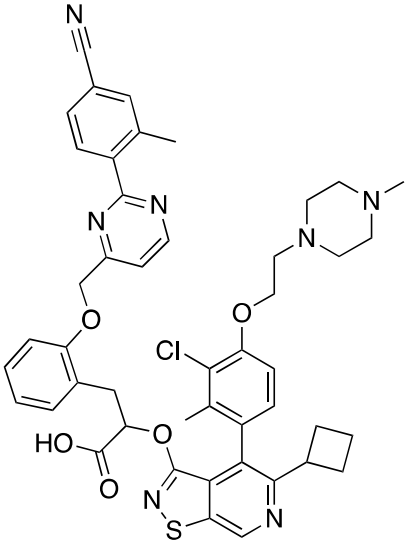
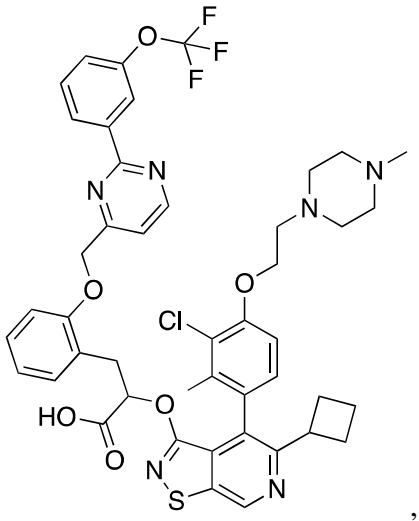
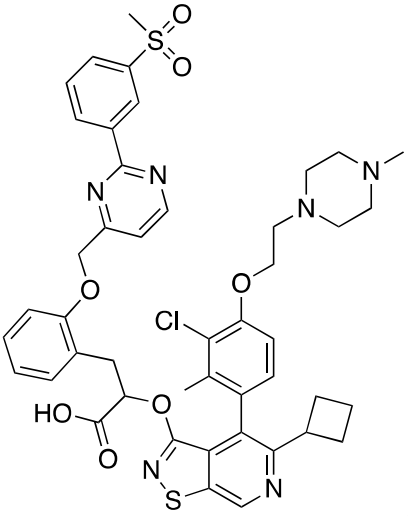
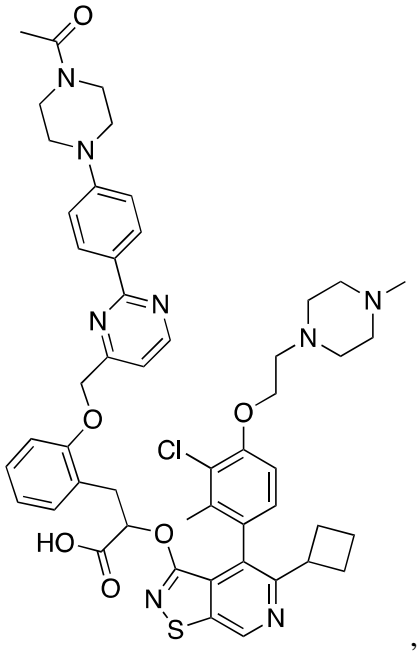

,

,

,

,

,

,

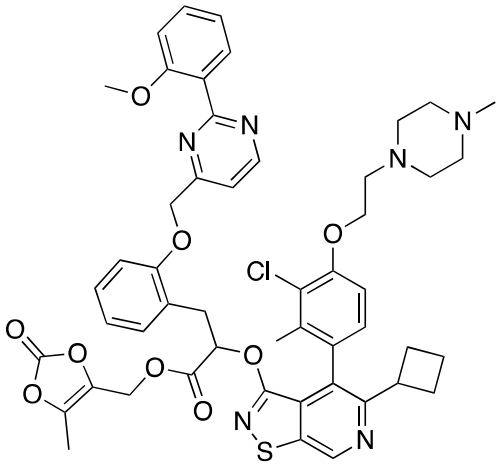
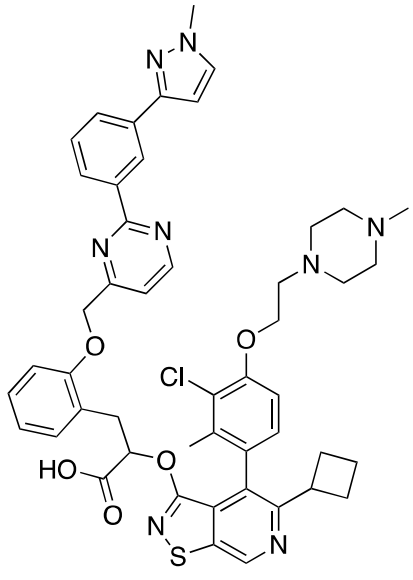
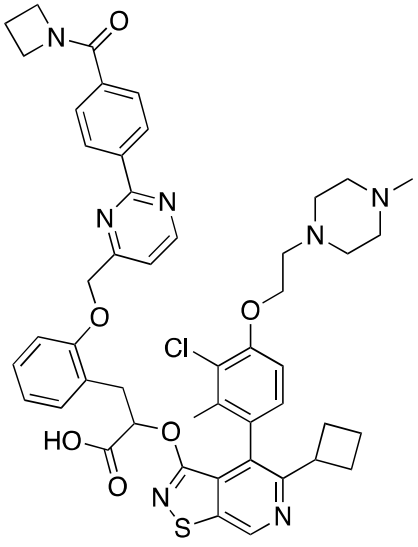
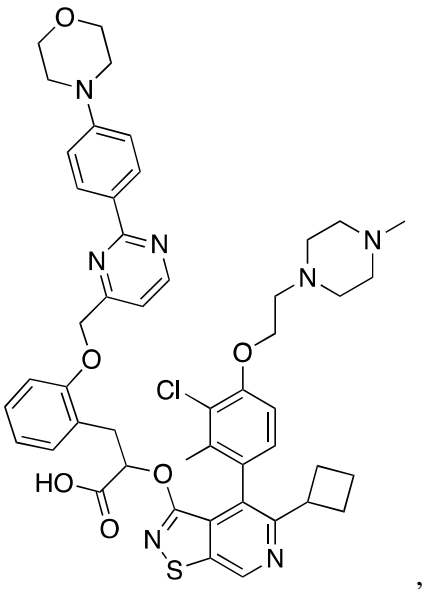

,

,

,

,

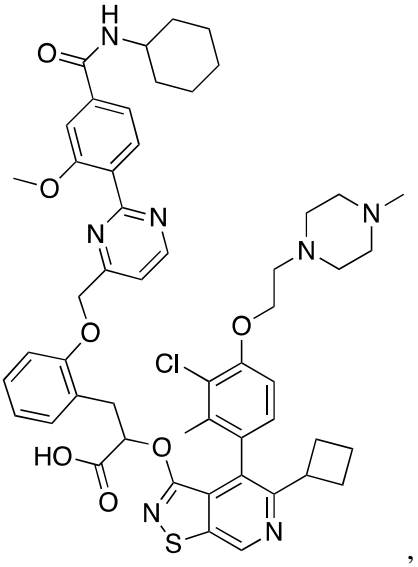

,

,

,

,

,

,


,

,

,

,

,

,

,

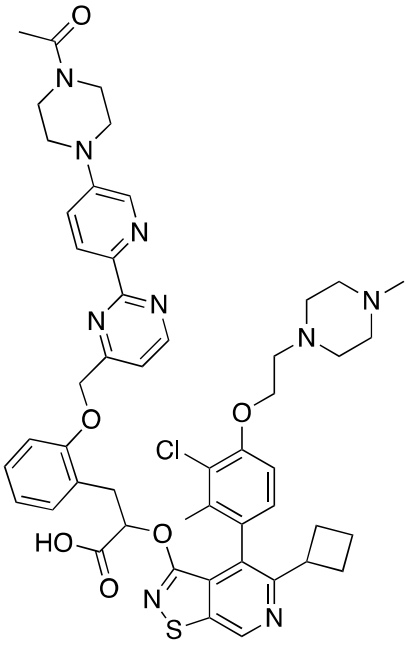

,

,

,

,


,

,

,

,

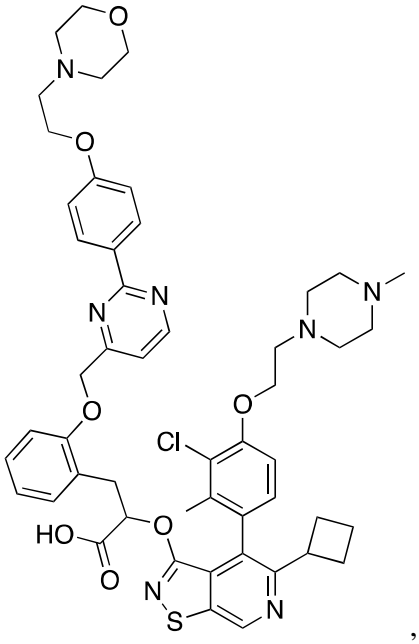

,

,

,

,



,

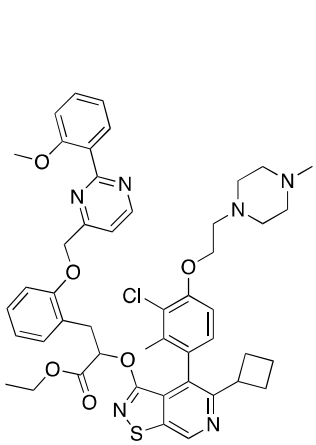
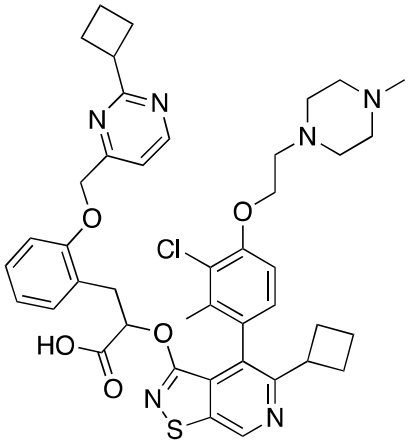
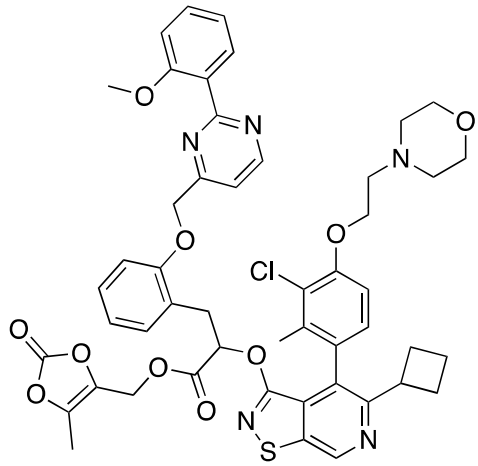
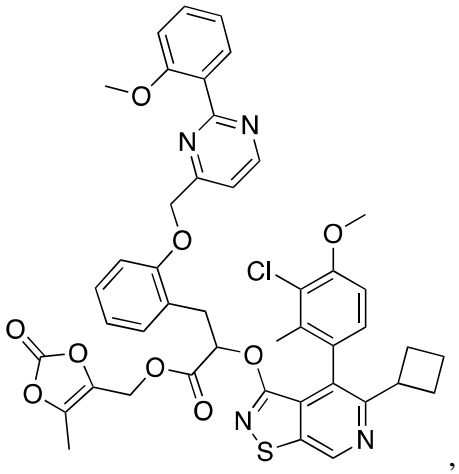
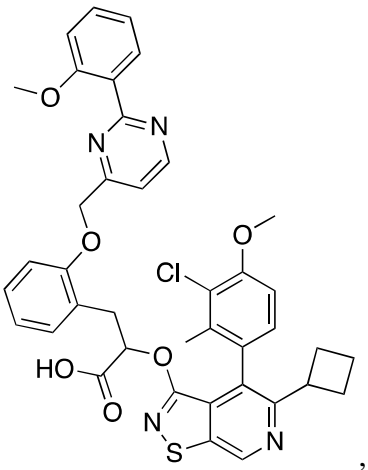
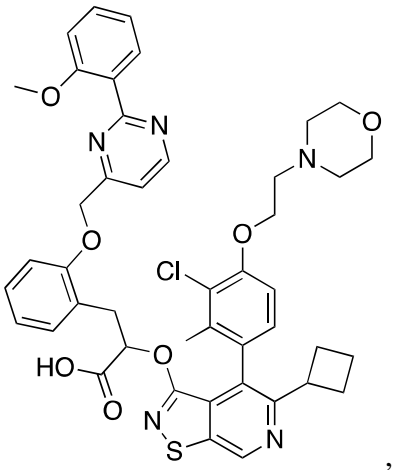


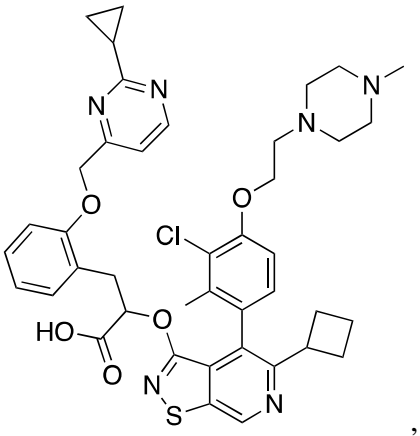
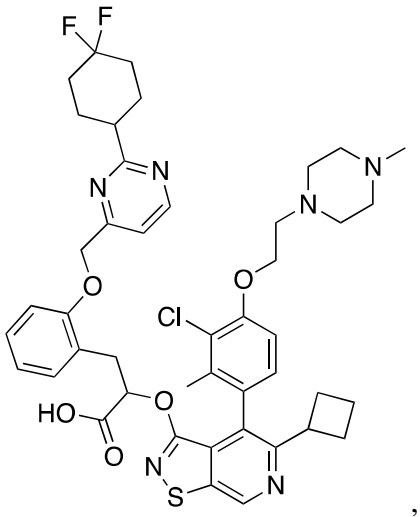
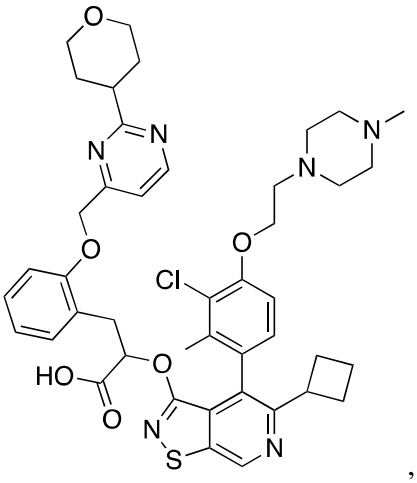
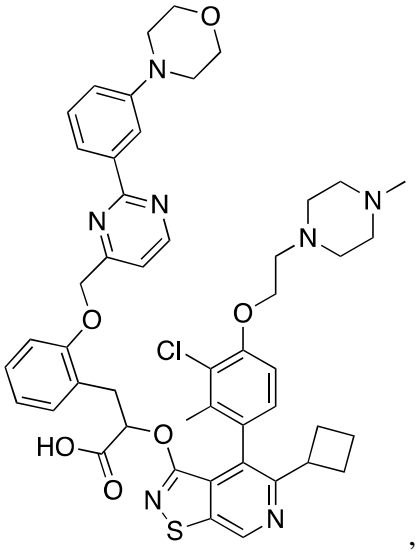
and

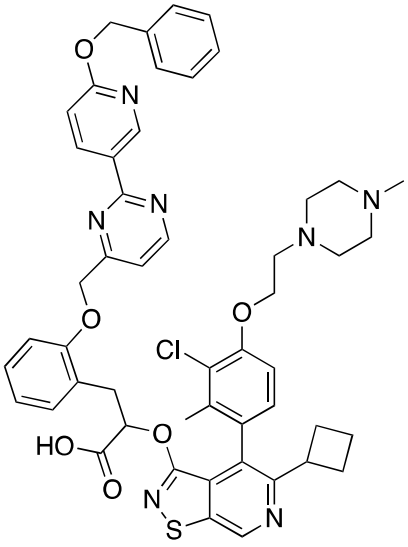
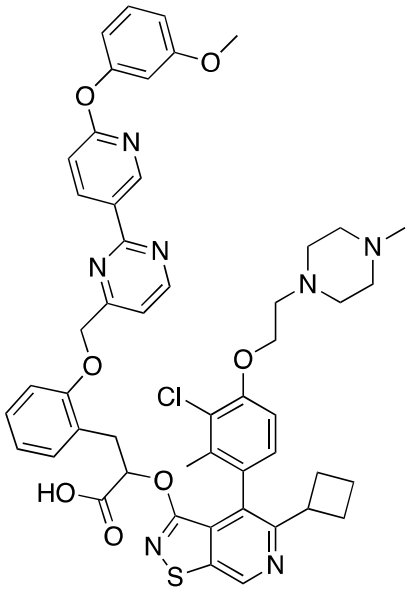
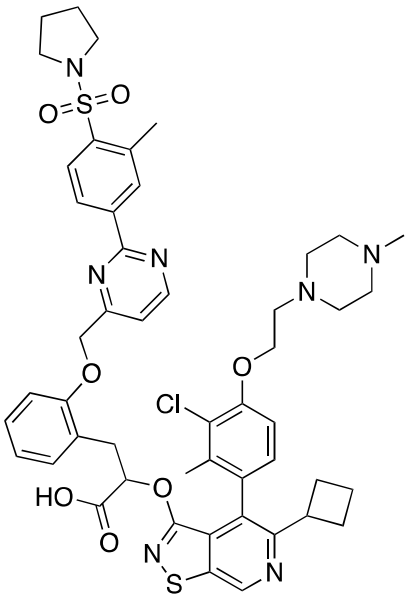
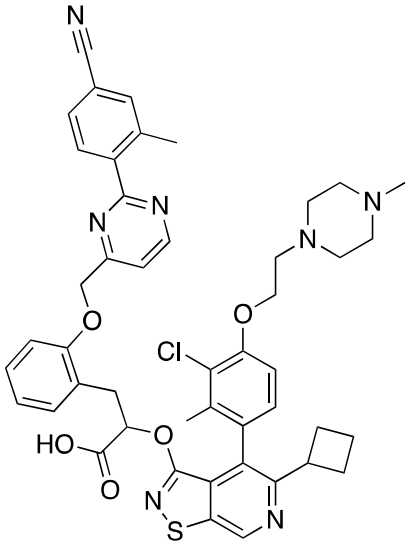


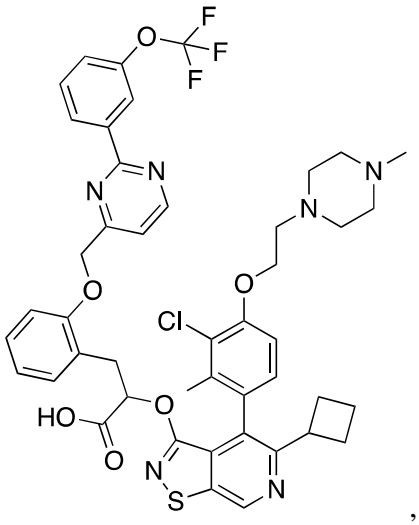
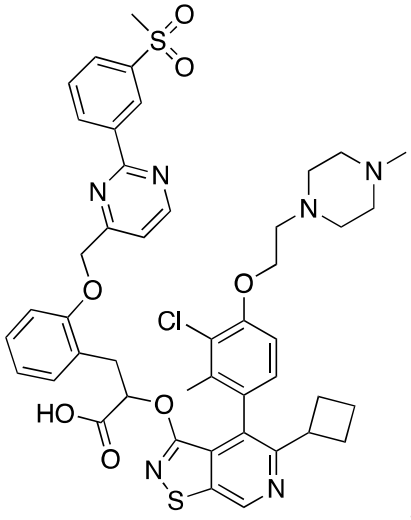
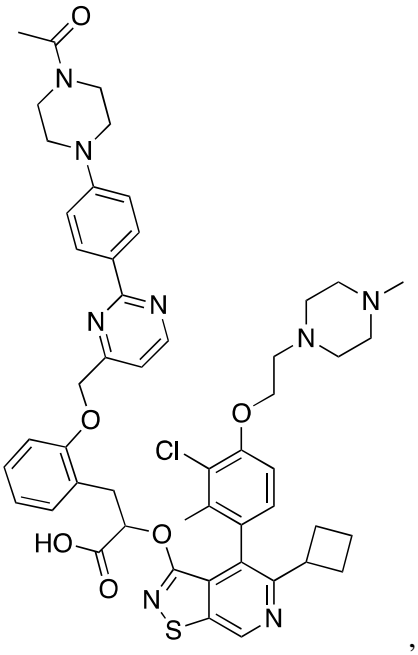
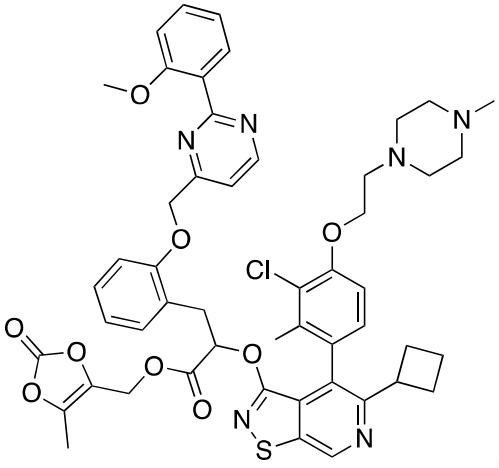
, or a pharmaceutically acceptable salt thereof.

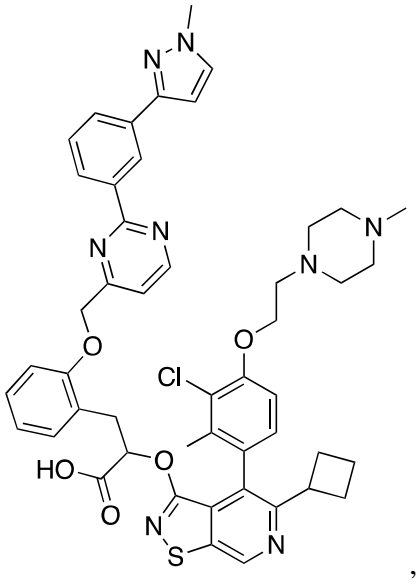
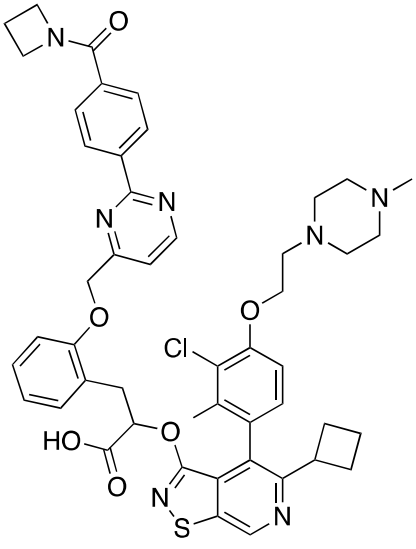
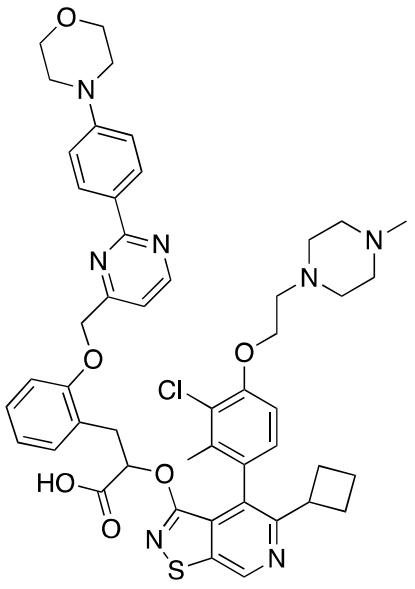
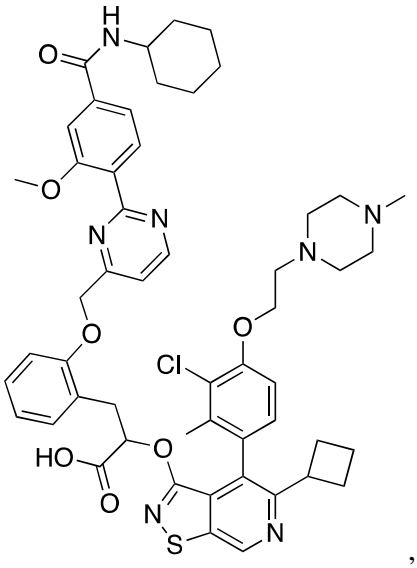
~~51.~~29. A compound selected from:

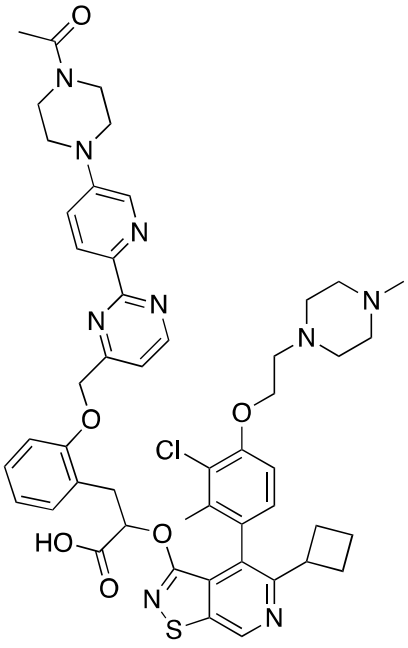

,

,

,

,

,

,

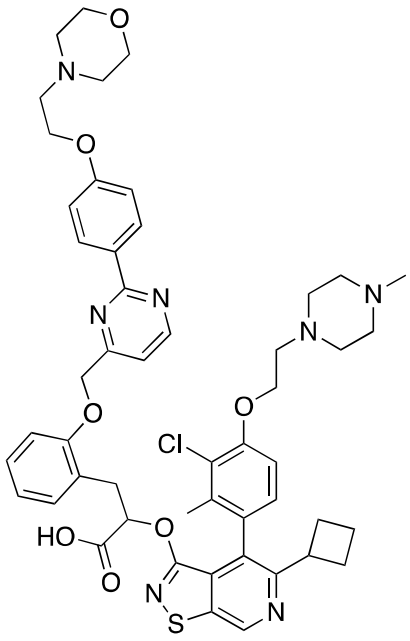

,

,

,

,


,

,

,

,


,

,

,

,

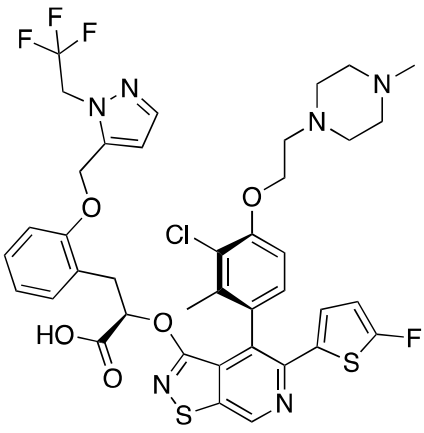

,

,

,

,

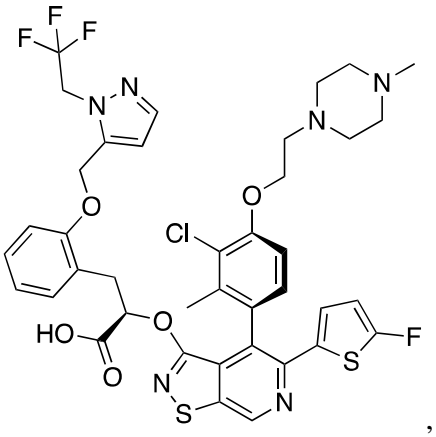


and


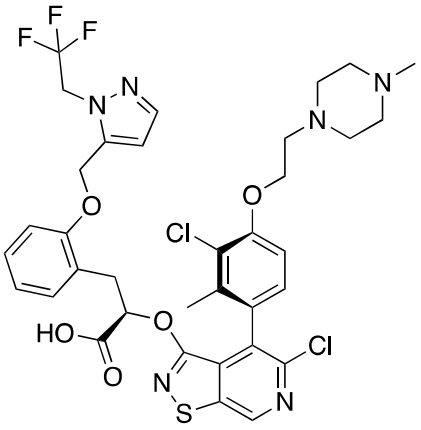
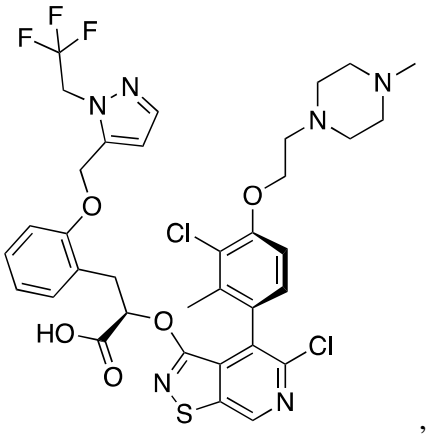
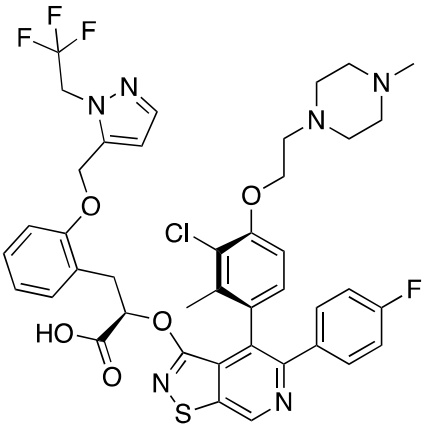
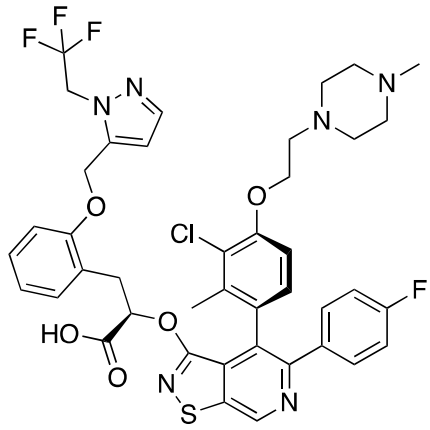
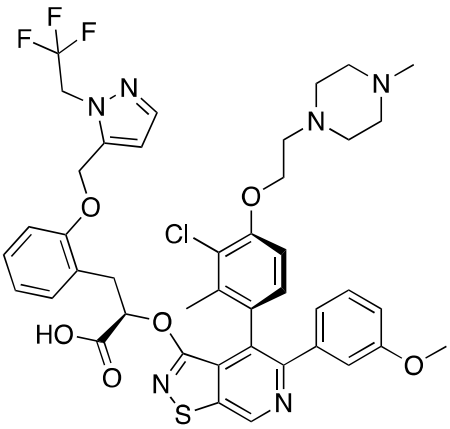
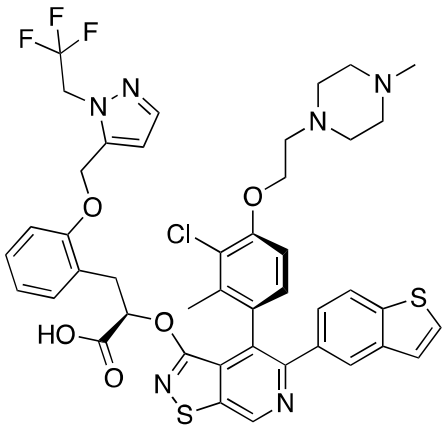
, or a pharmaceutically acceptable salt thereof.

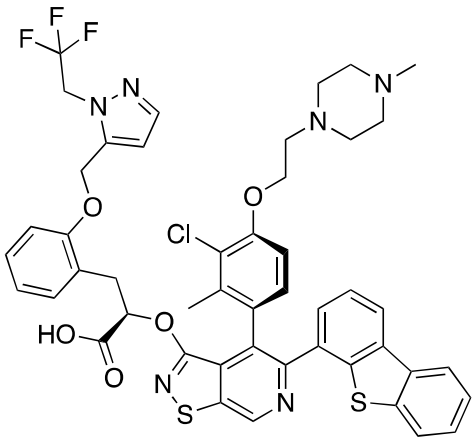
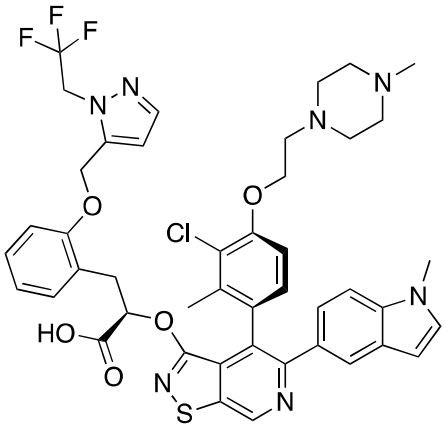
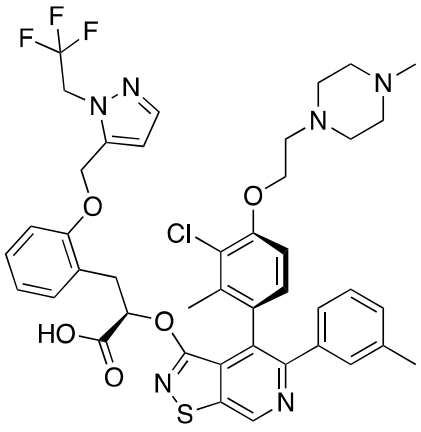
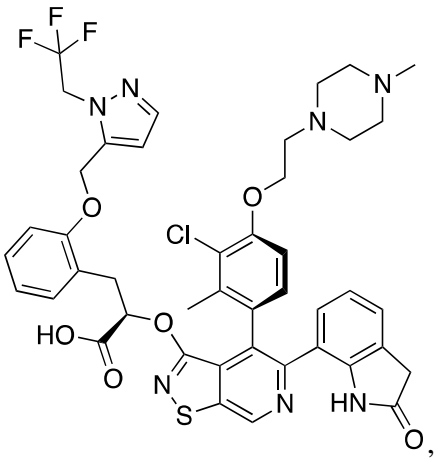
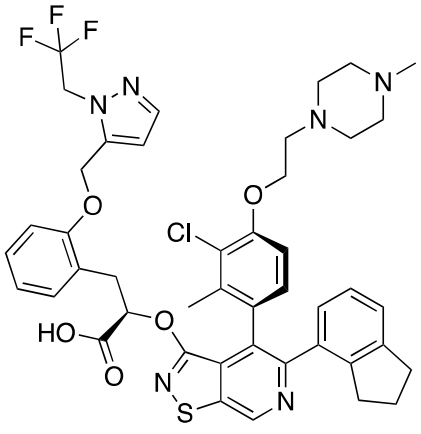
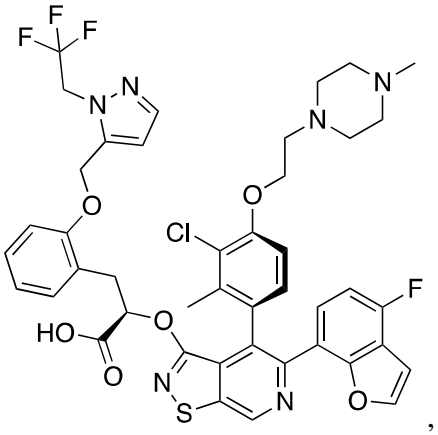
~~52.~~30. A compound selected from:

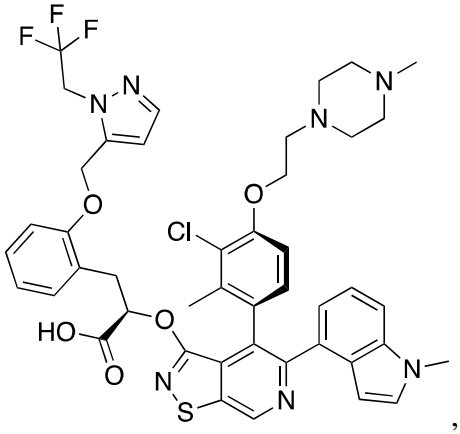
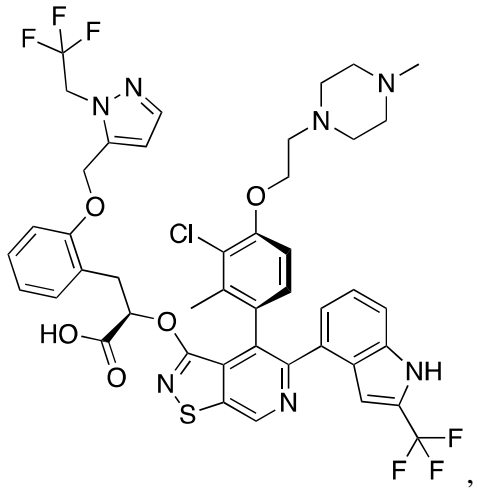
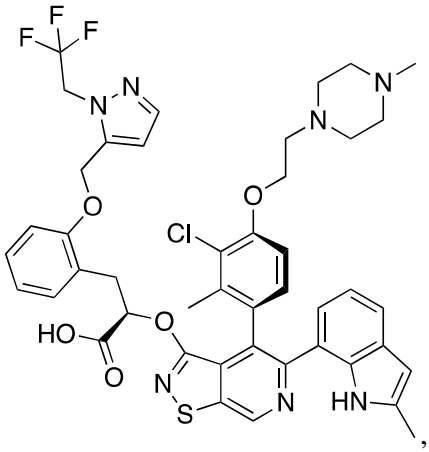
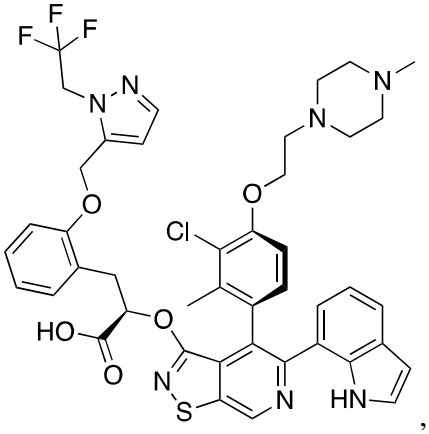
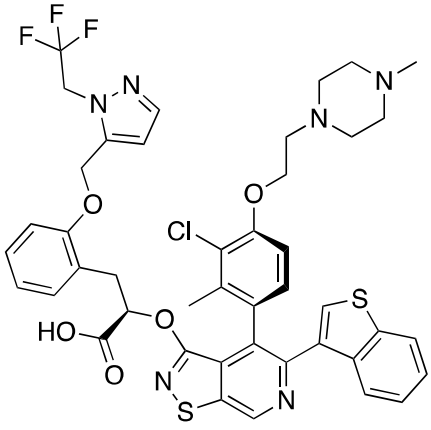
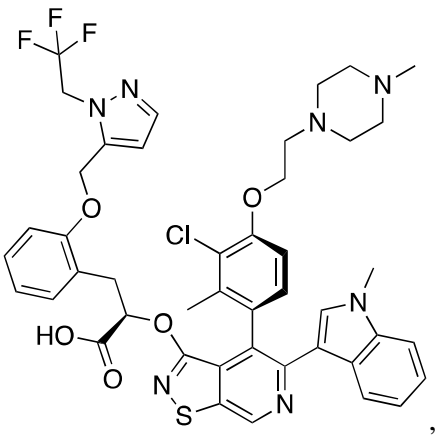


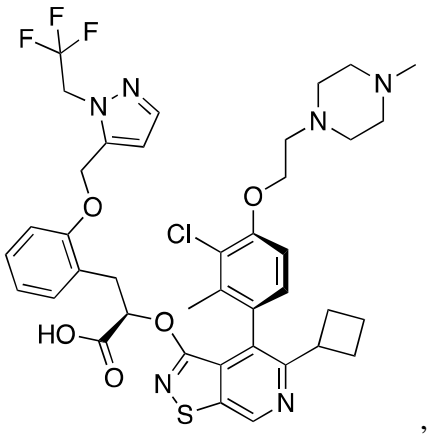
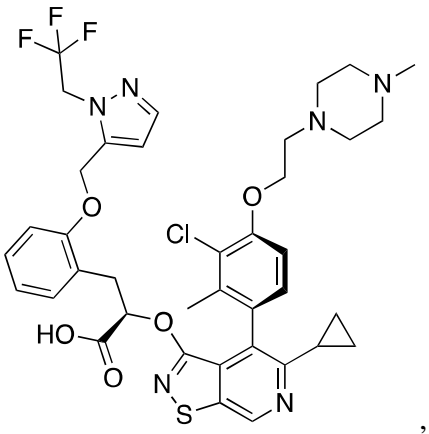
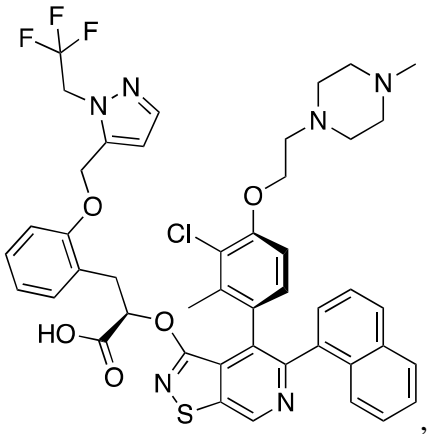
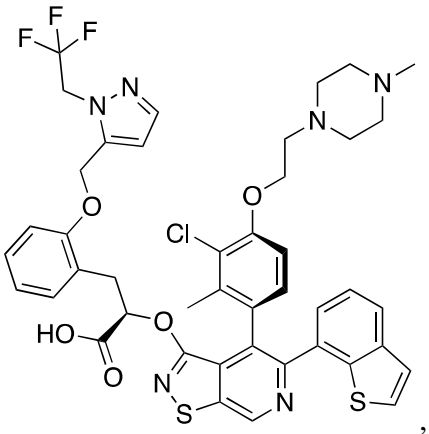
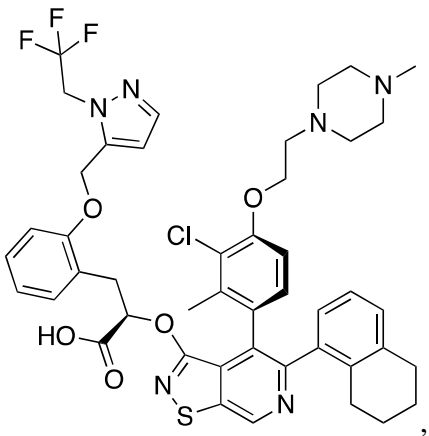
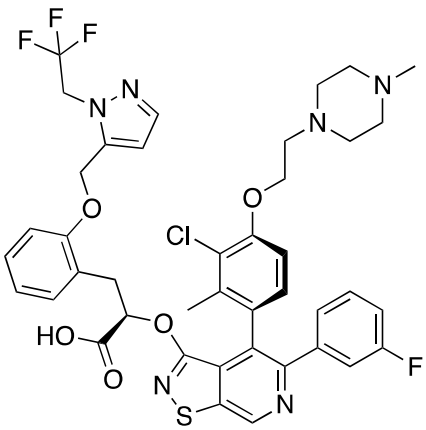
,


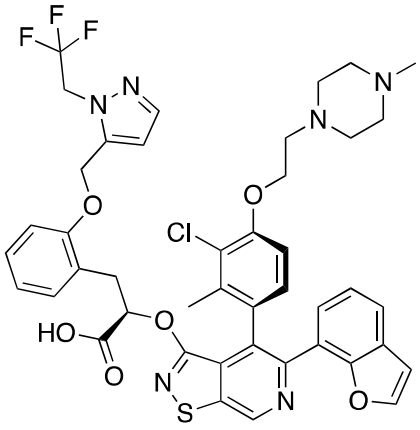
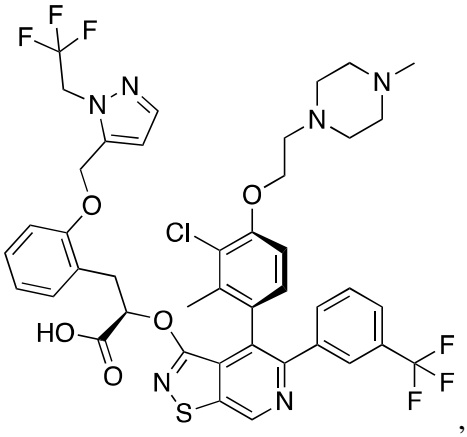
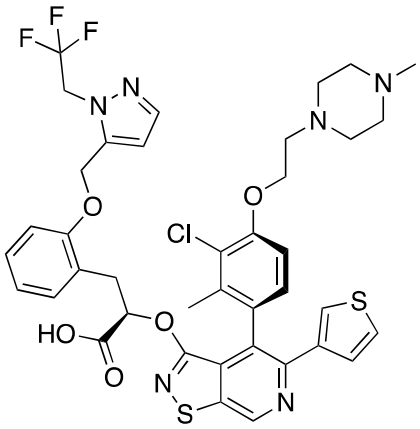
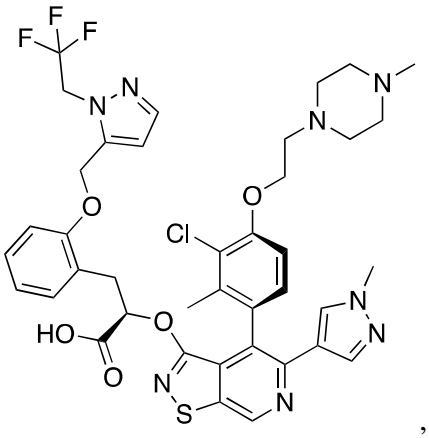
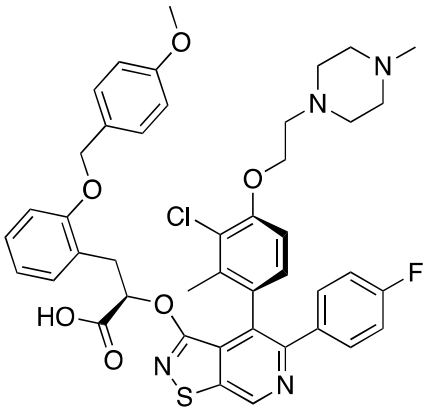
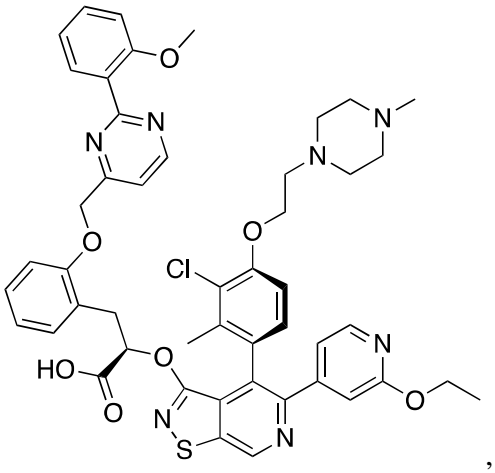
,

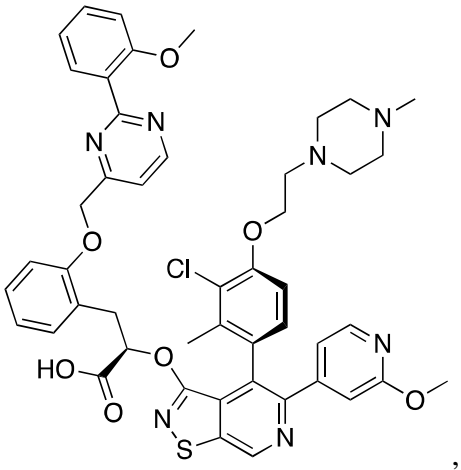
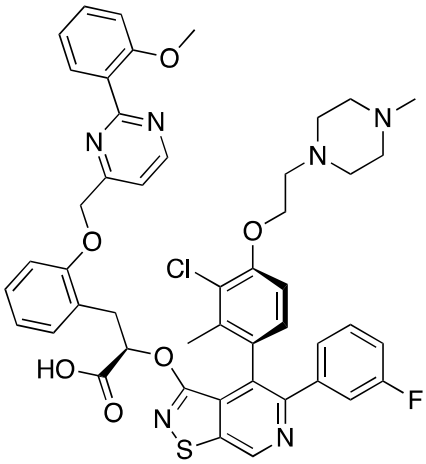
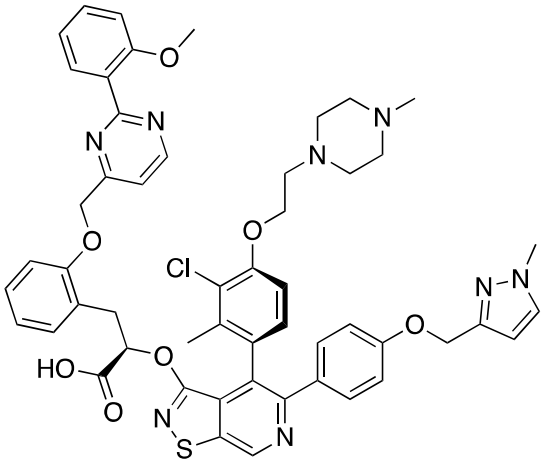
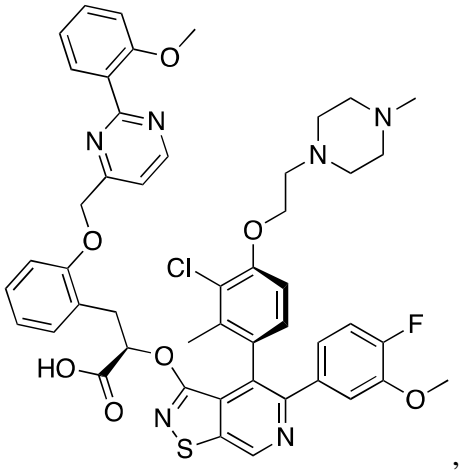
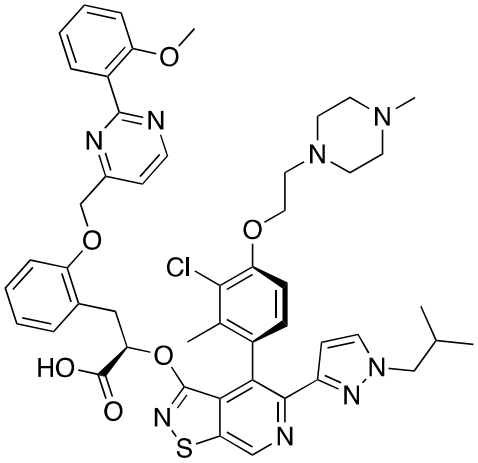
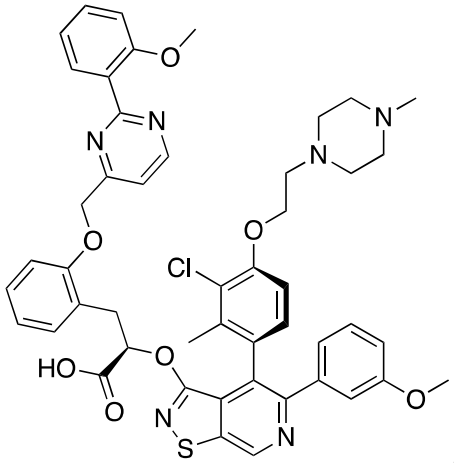

,

,

,

,

,

,

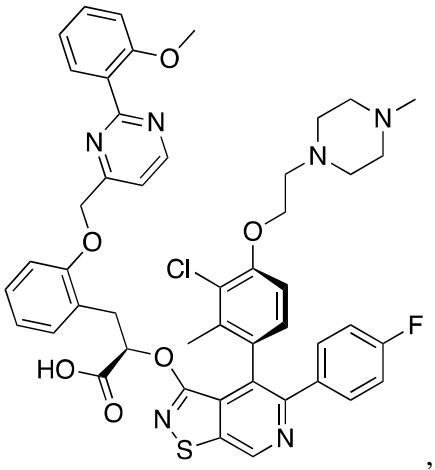
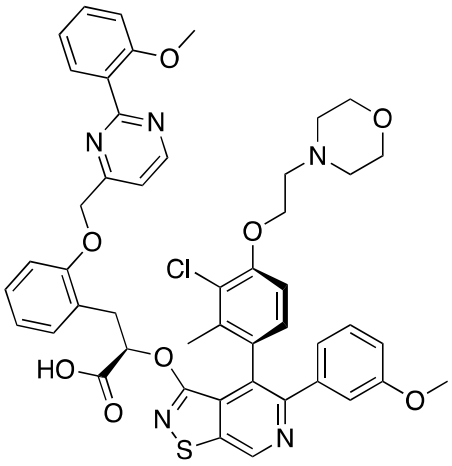
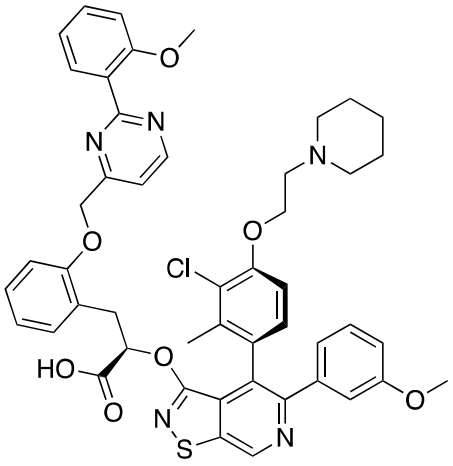
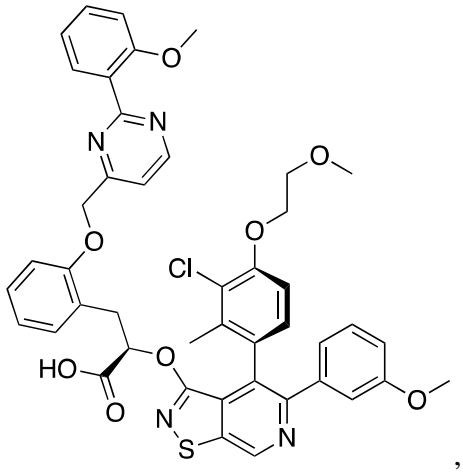
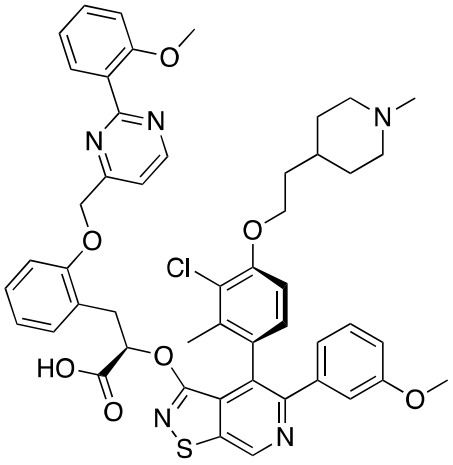
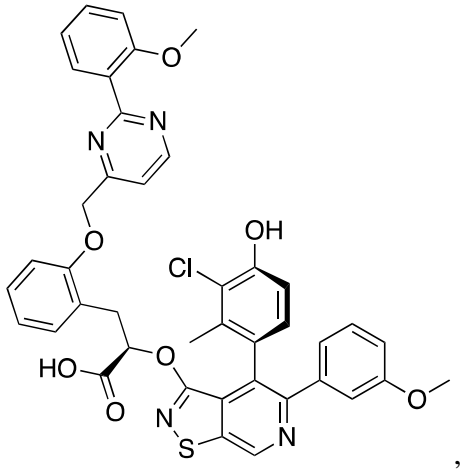

,

,

,

,

,

,

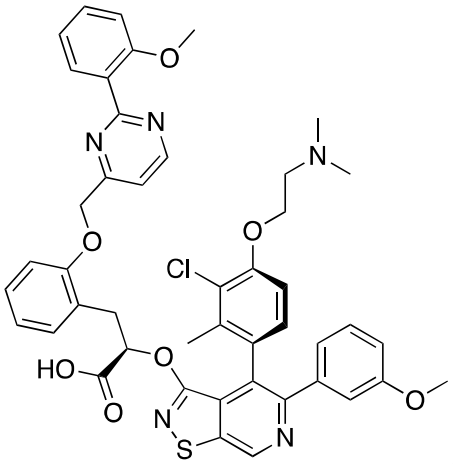
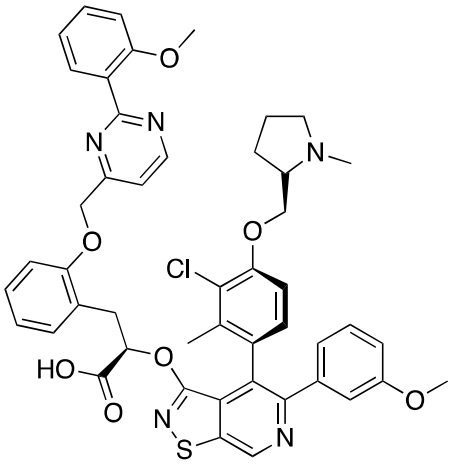
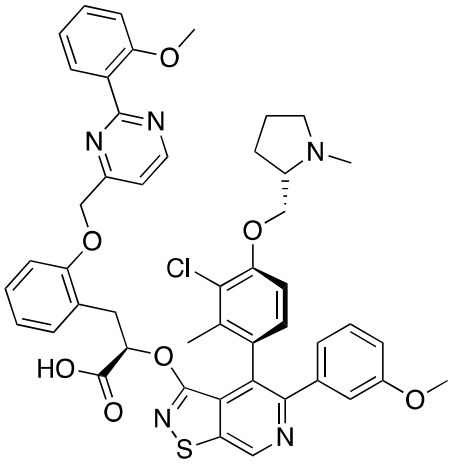
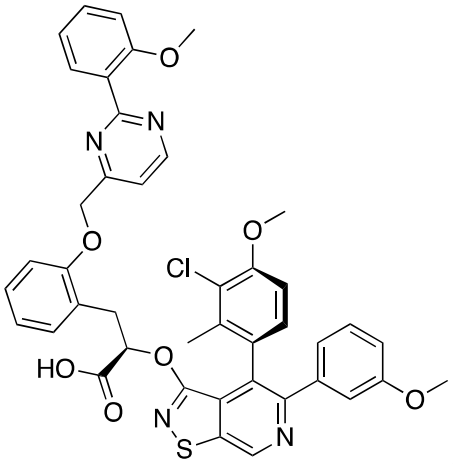
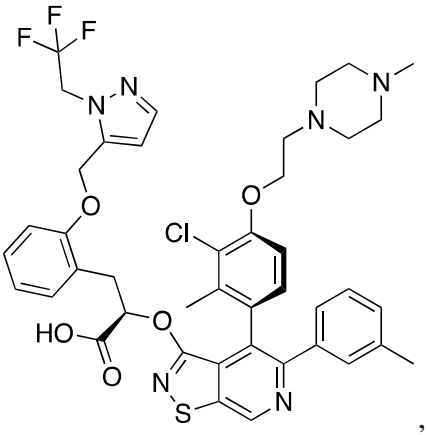
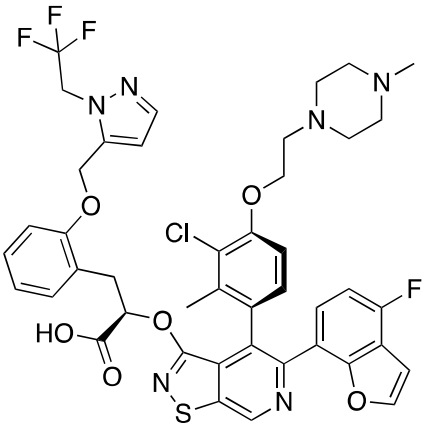

,

,

,

,

,

,

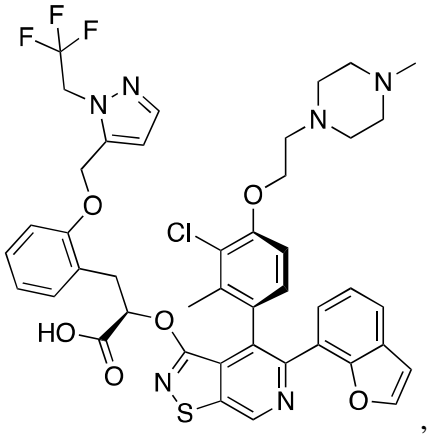
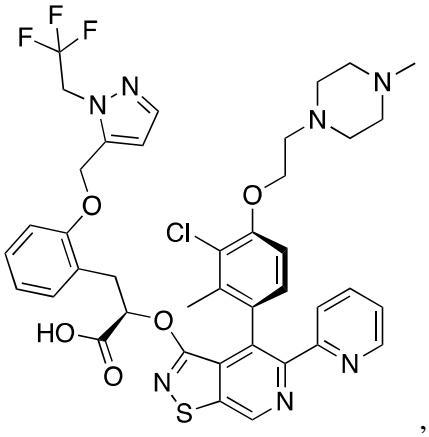
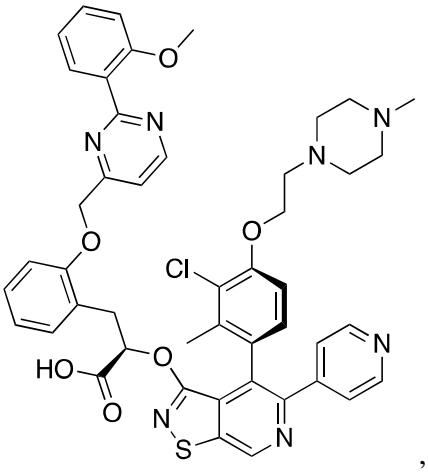
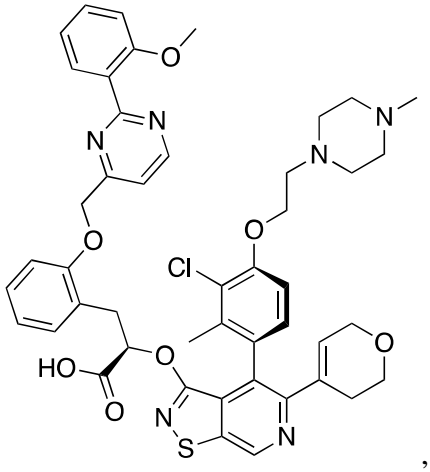
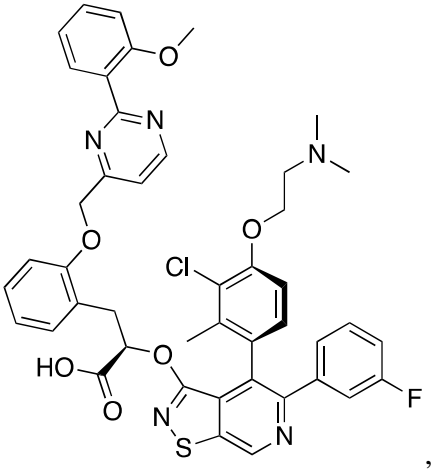
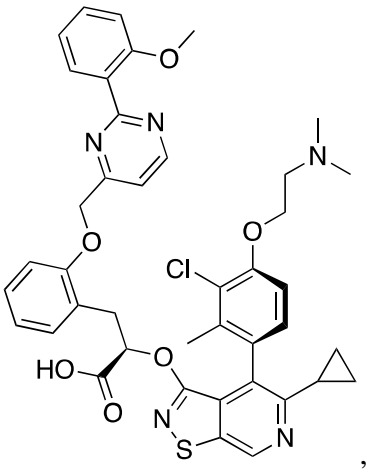

,

,

,

,

,

,

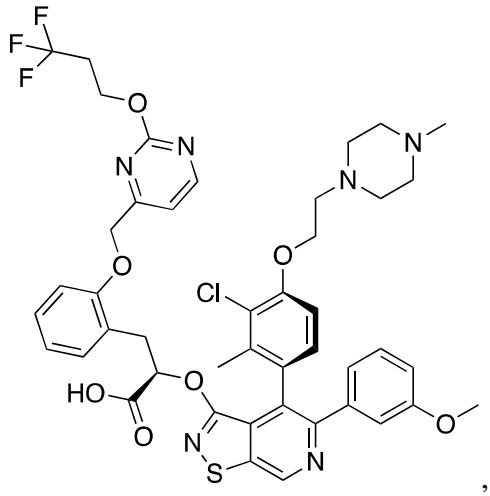
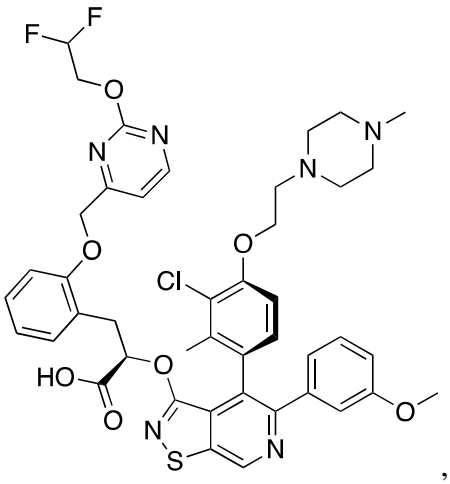
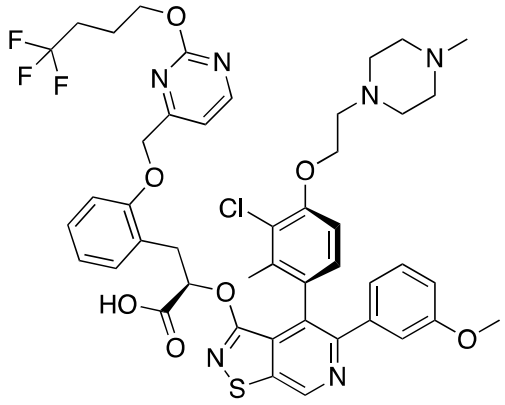
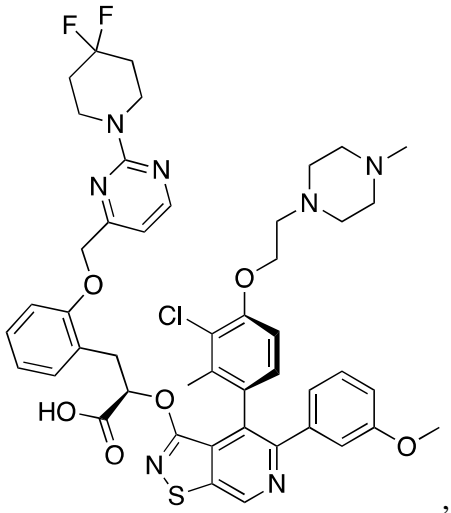
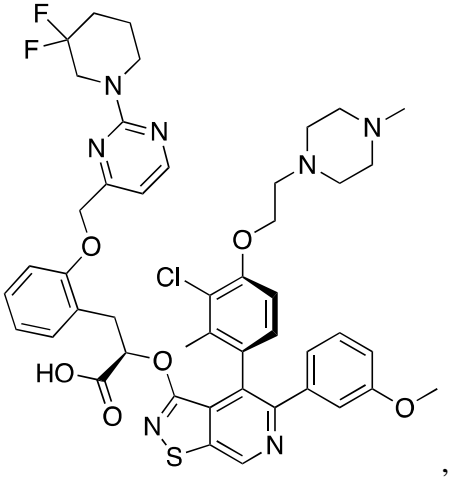
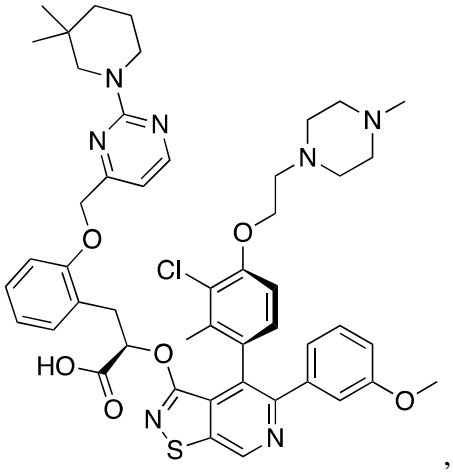

,

,

,

,

,

,

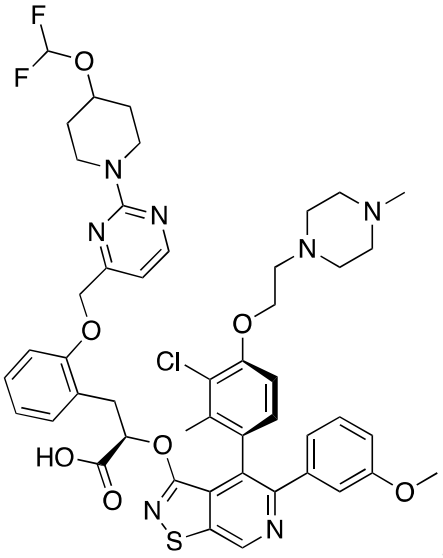
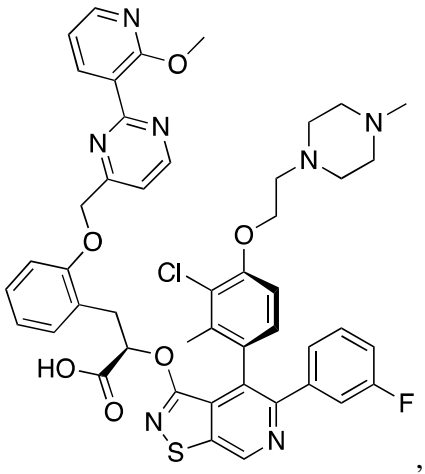
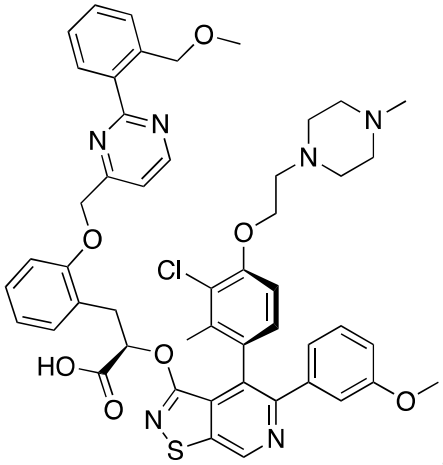
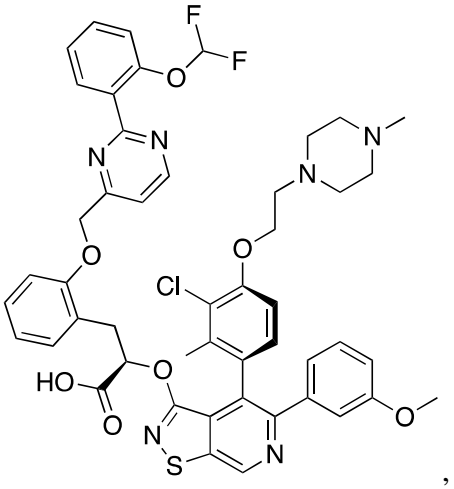
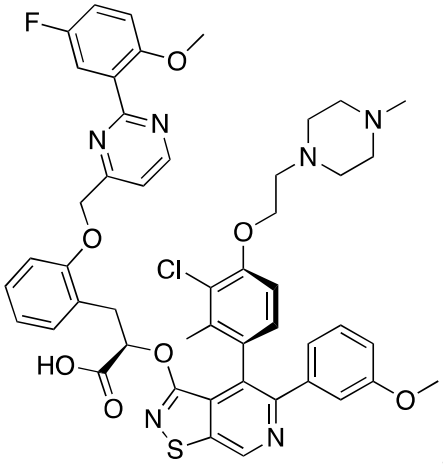
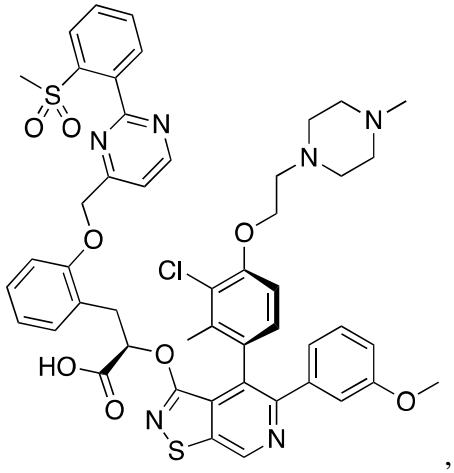

,

,

,

,

,

,

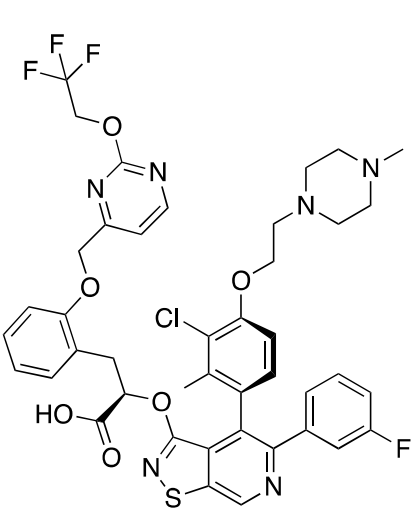
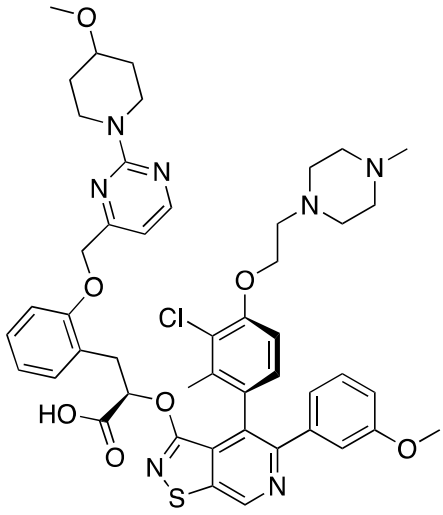
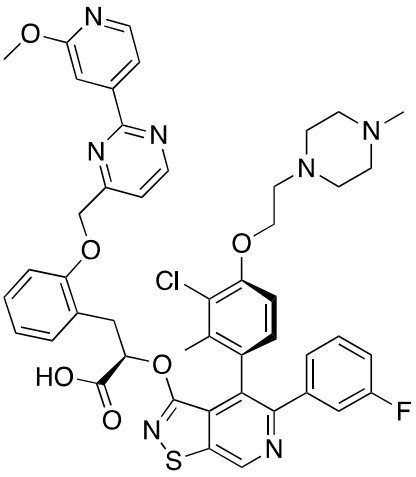
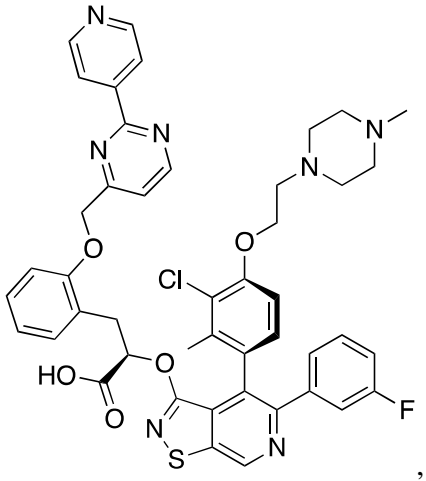
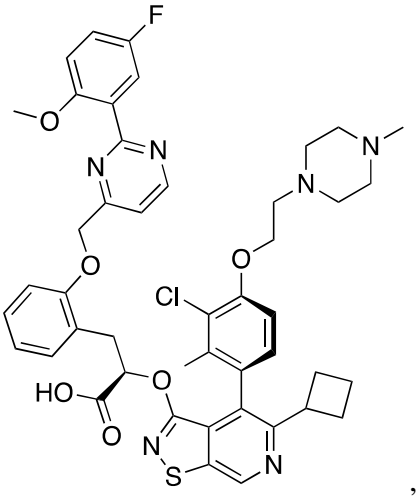
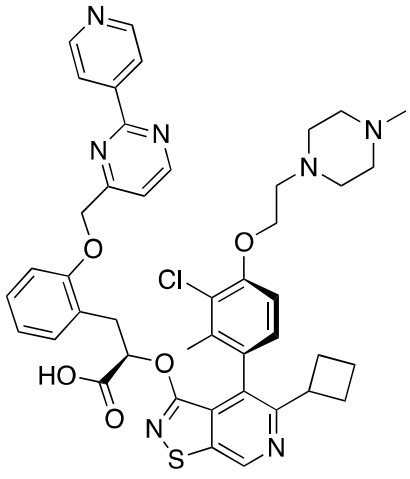

,

,

,

,

,

,

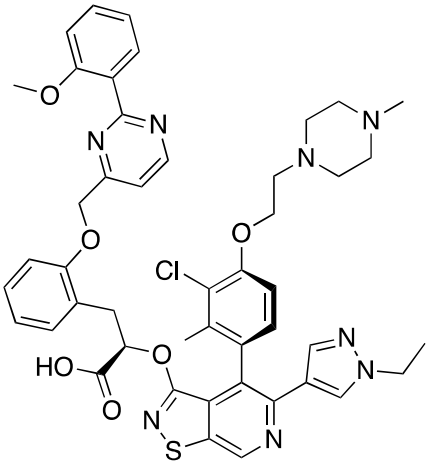
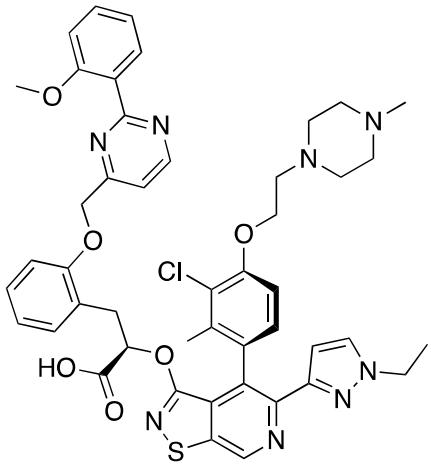
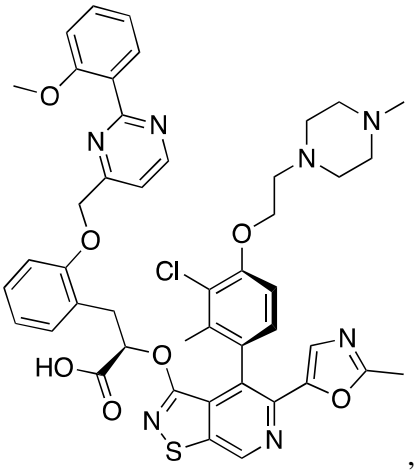
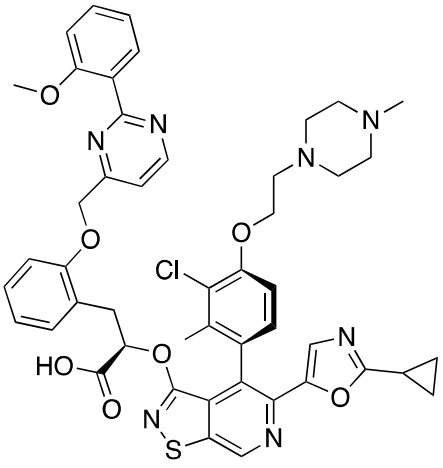
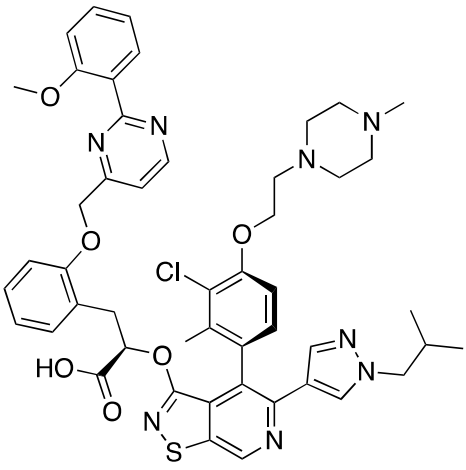
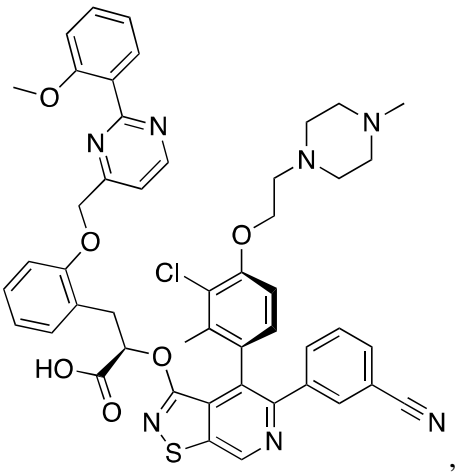

,

,

,

,

,

,

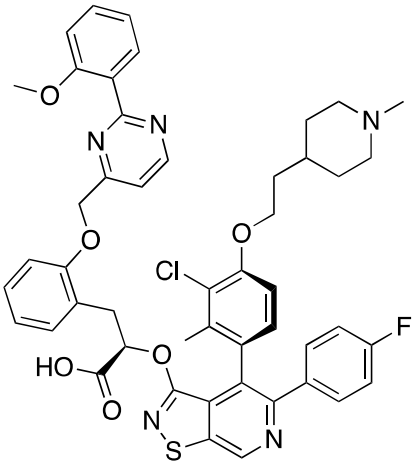
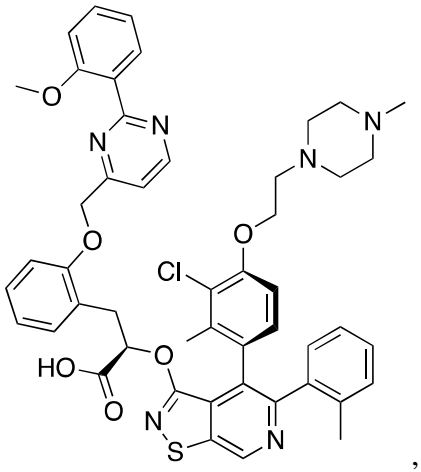
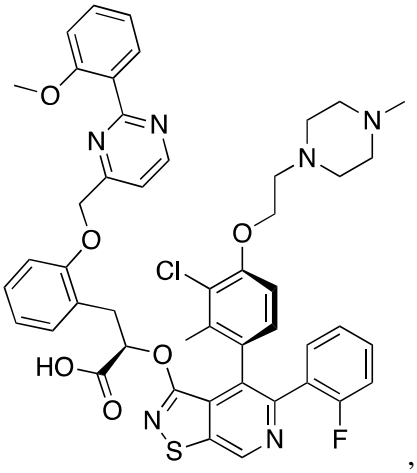
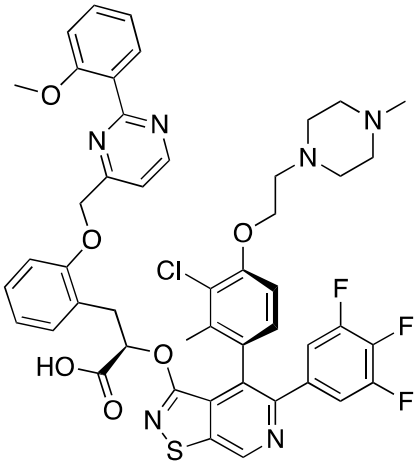
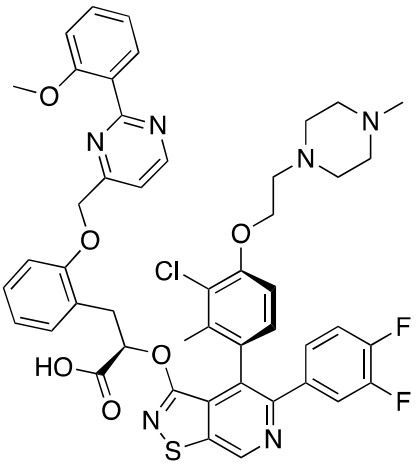
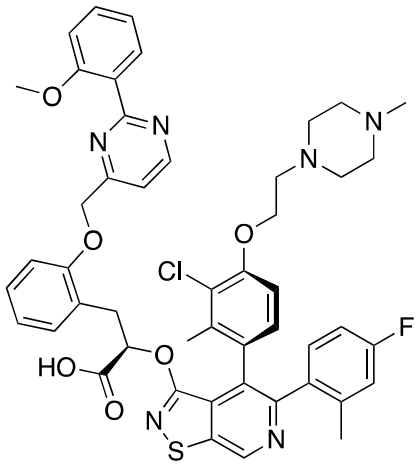

,

,

,

,

,

,

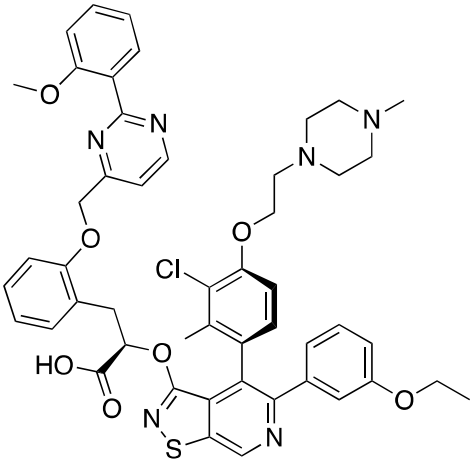
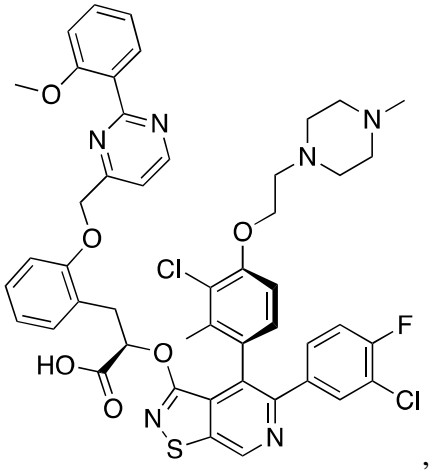
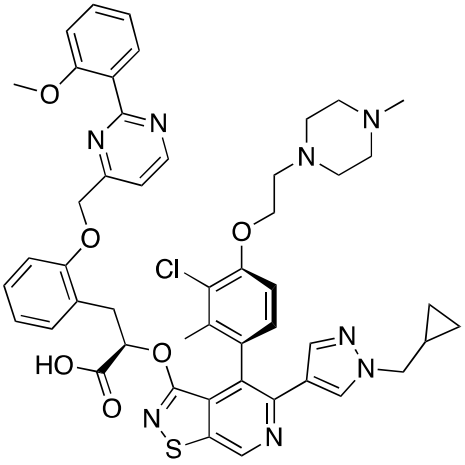
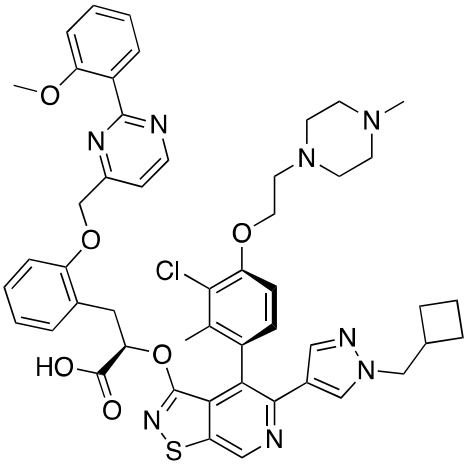
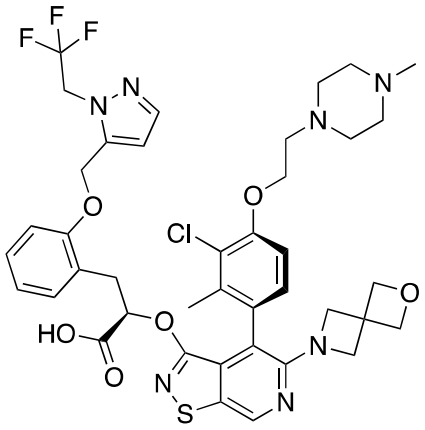
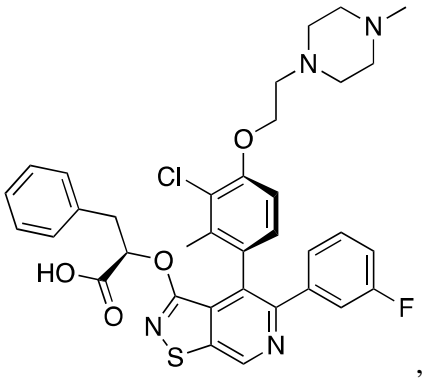

,

,

,

,

,

,

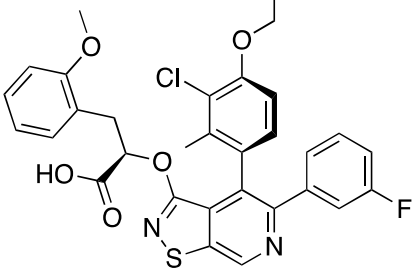
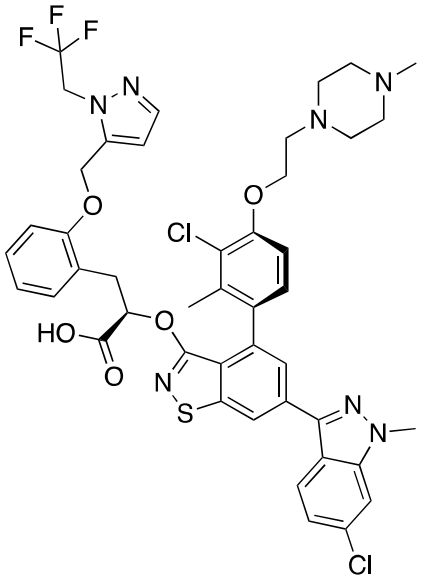
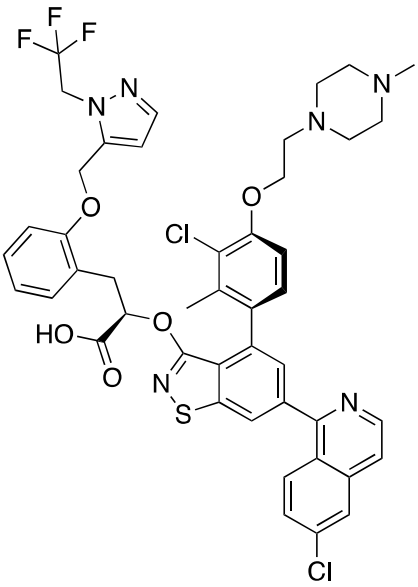
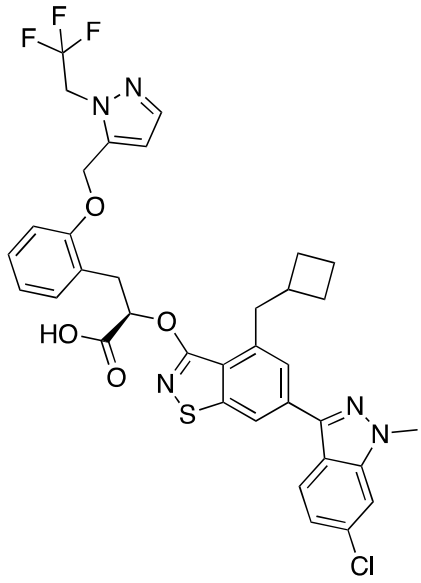

,

,

,

,

,

,

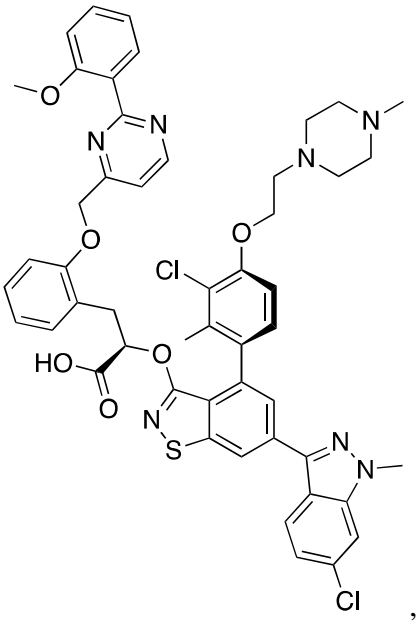
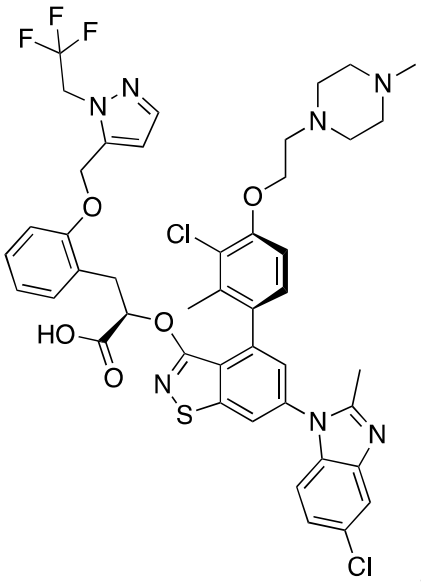
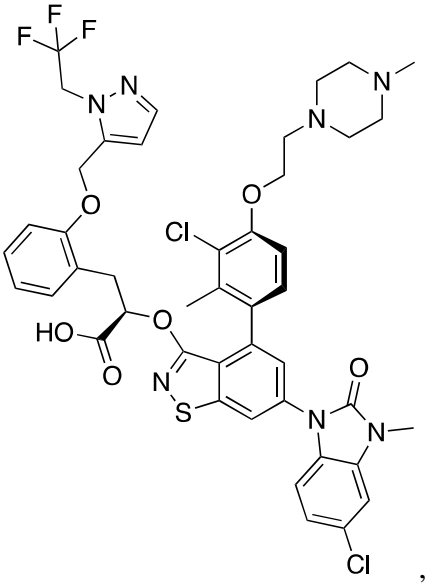
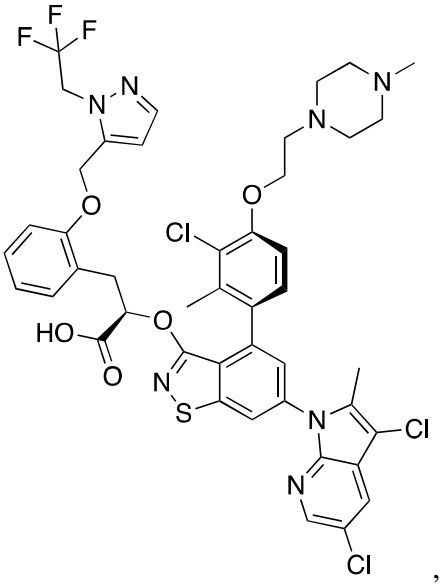

,

,

,

,

,

,

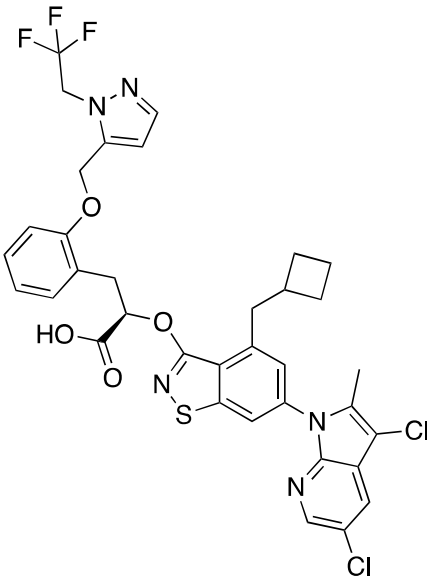
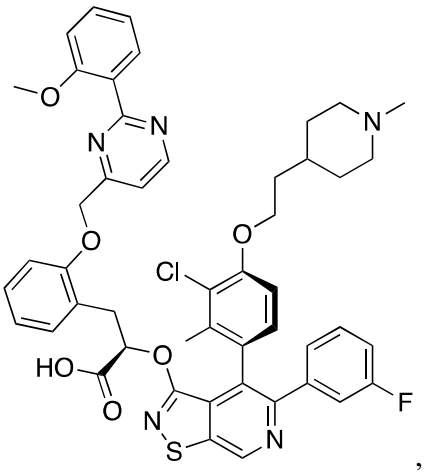
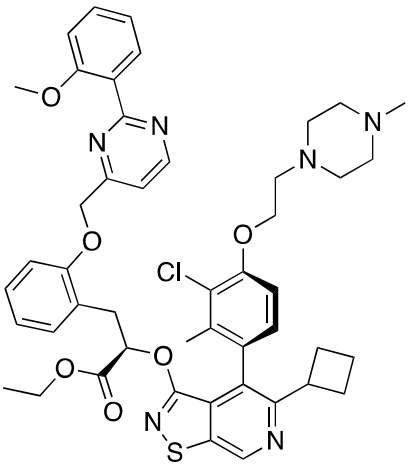
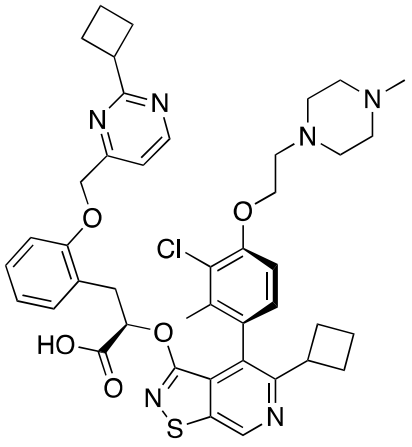
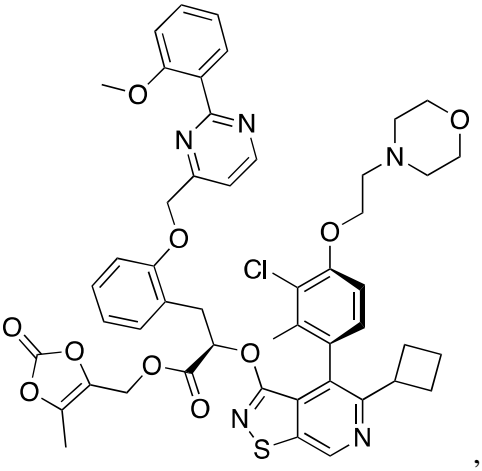
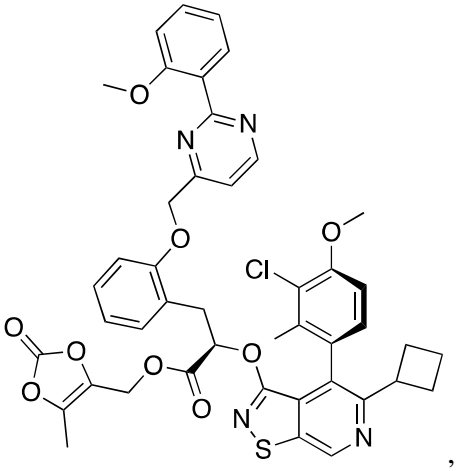

,

,

,

,

,

,

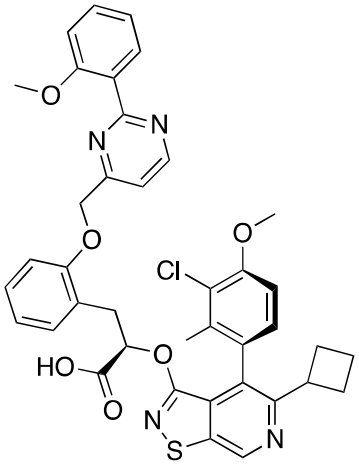
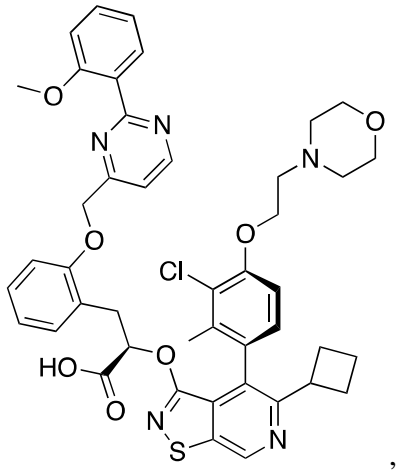
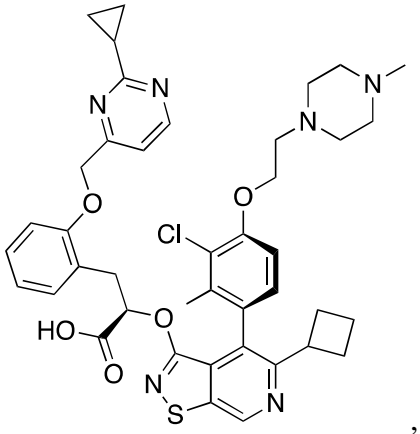
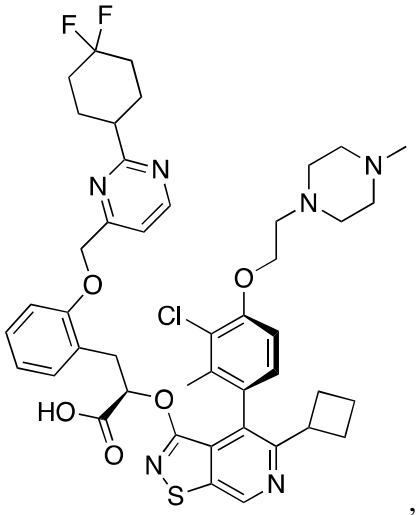
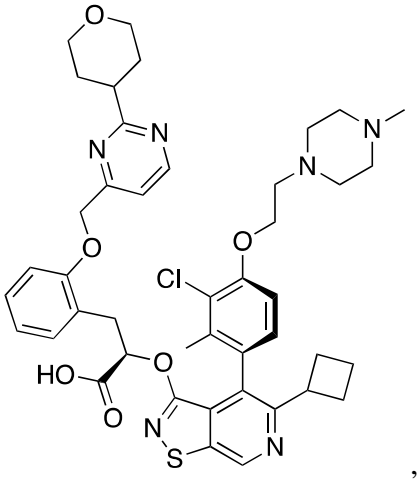
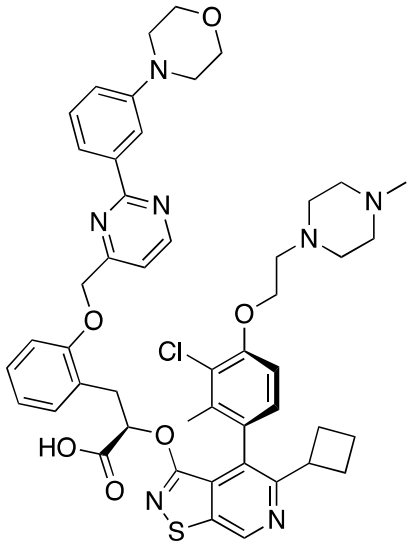

,

,

,

,

,

,

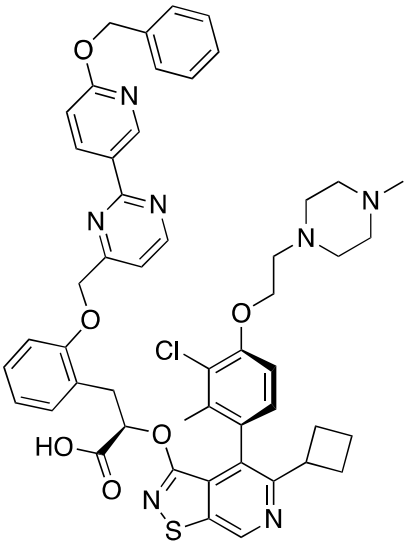
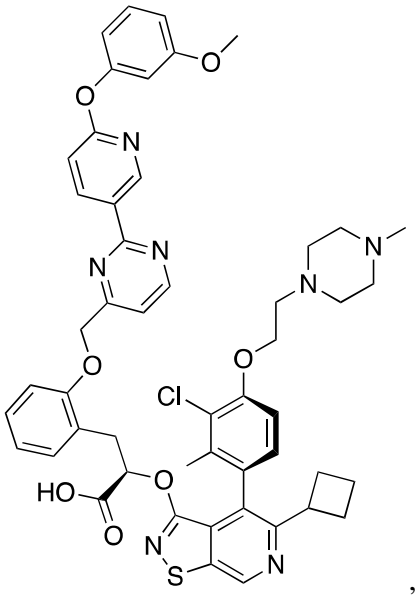
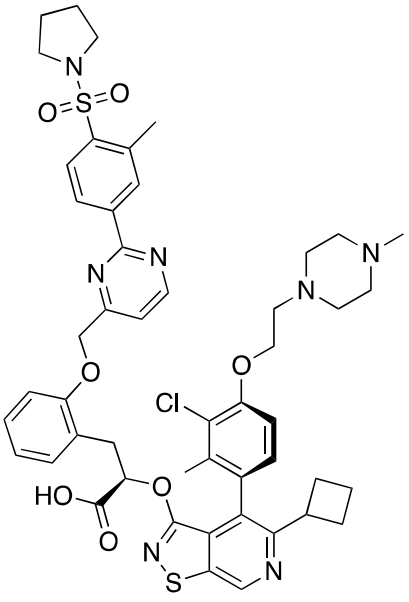
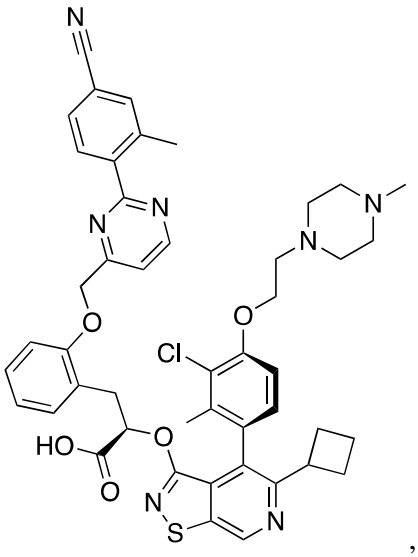

,

,

,

,

,

,

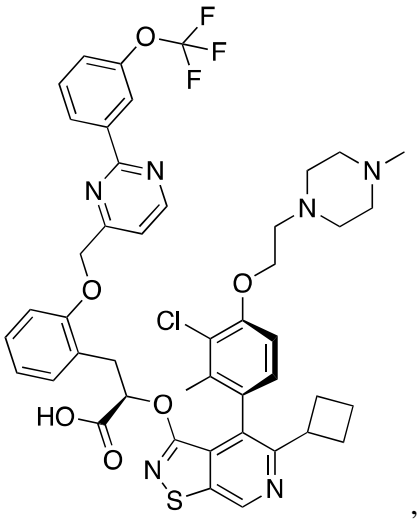
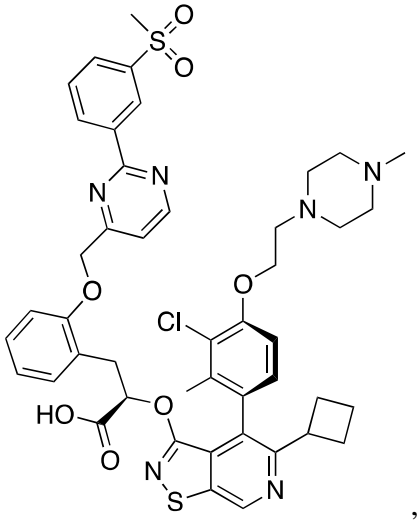
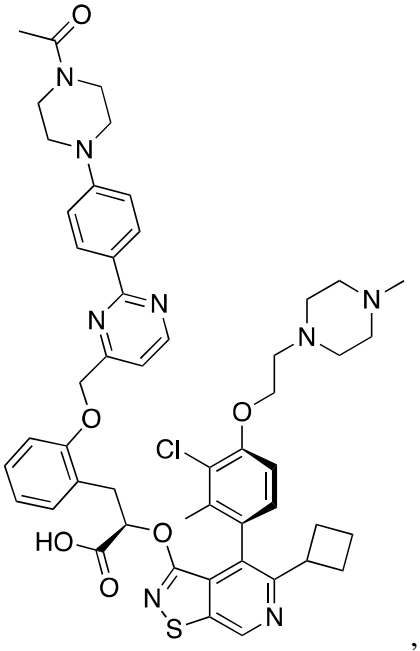
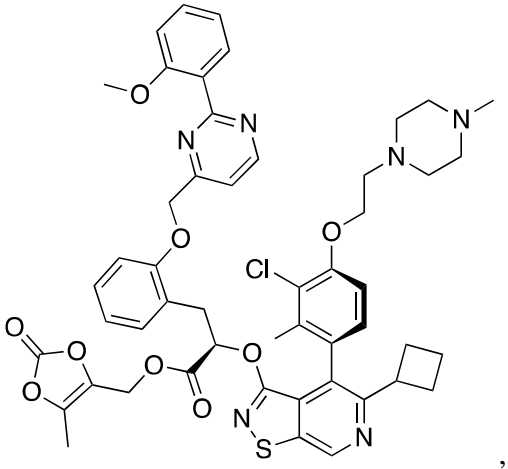

,

,

,

,

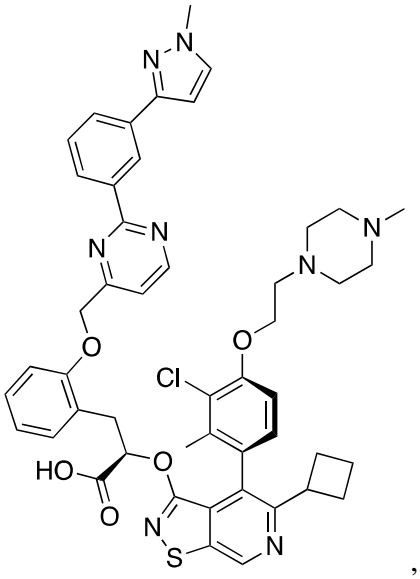
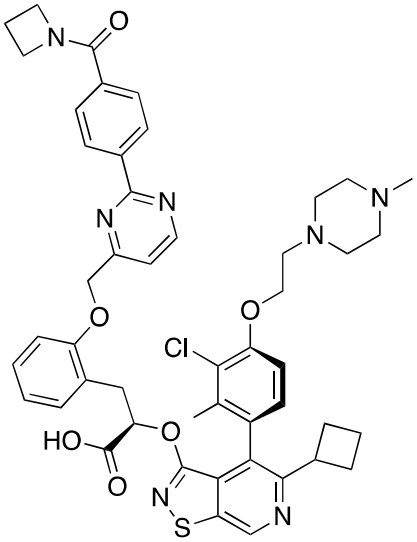
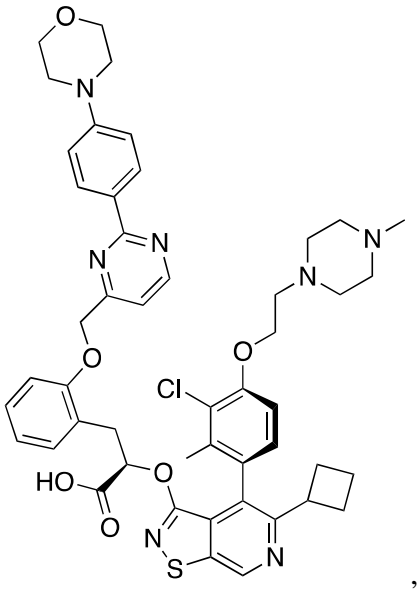
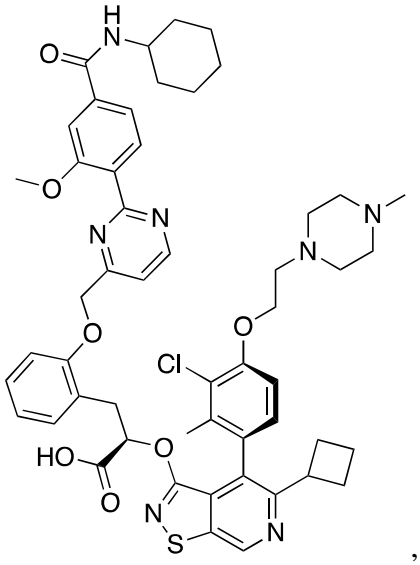

,

,

,

,

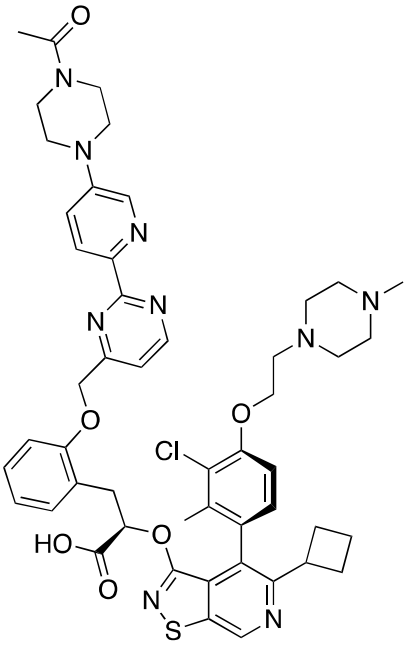

,

,

,

,

,

,

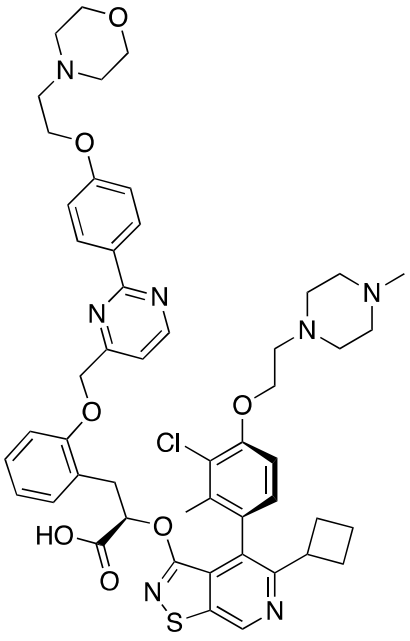

,

,

,

,

,

,


,

,

,

,


,

,

,

,

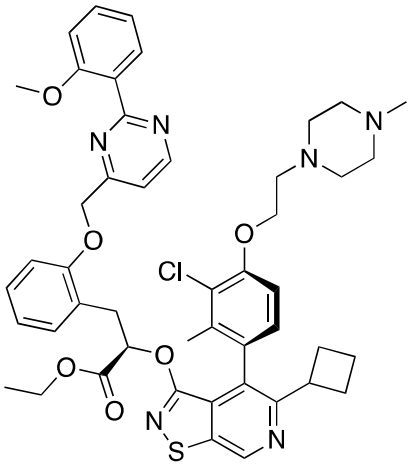

,

,

,

,

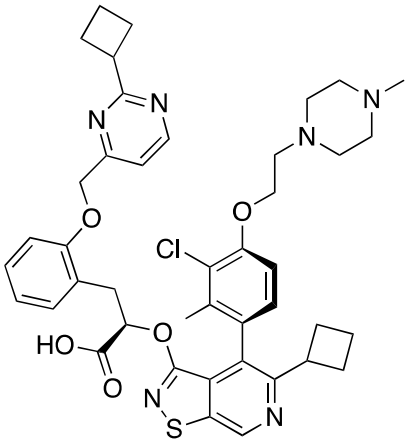


and


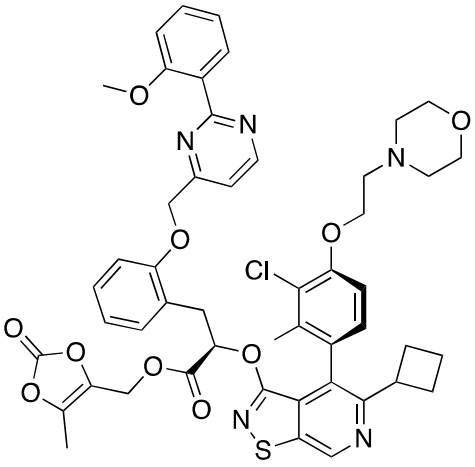
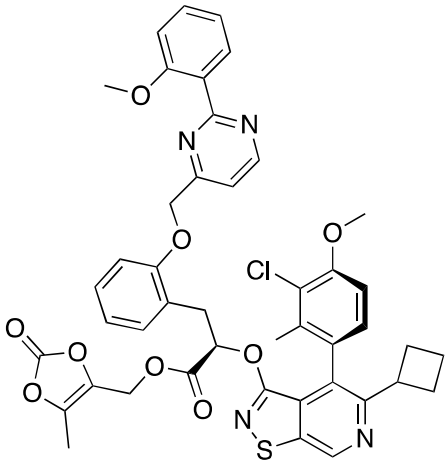
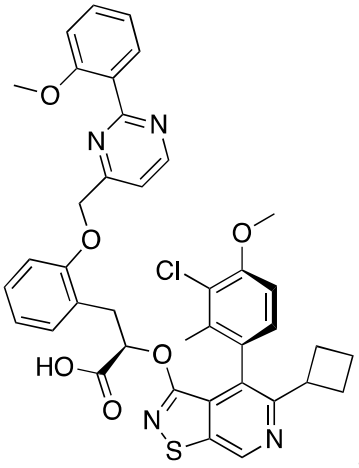
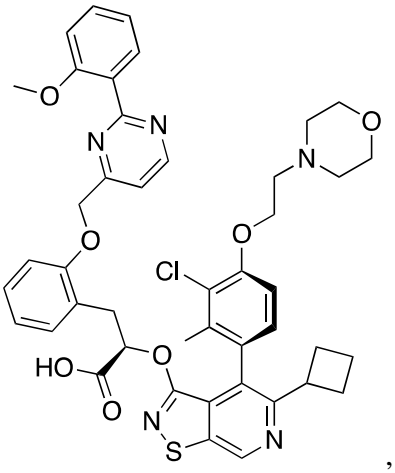
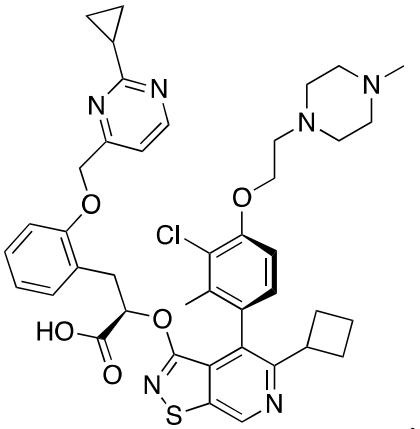
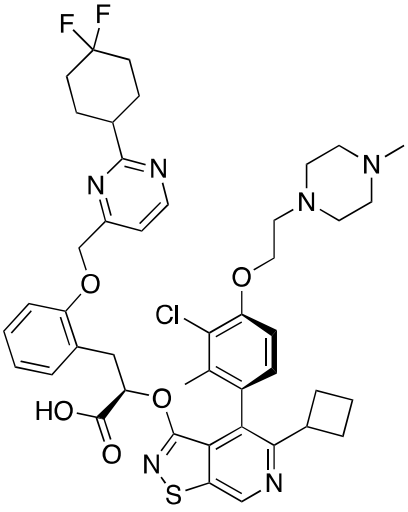
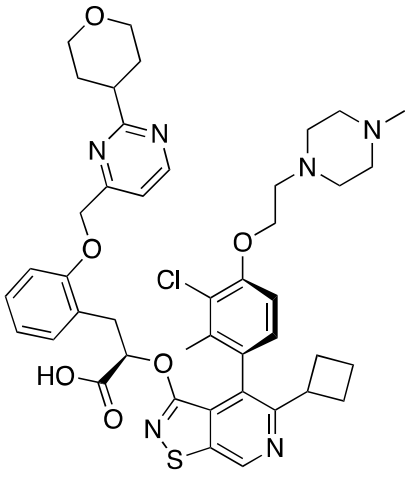
, or a pharmaceutically acceptable salt thereof.

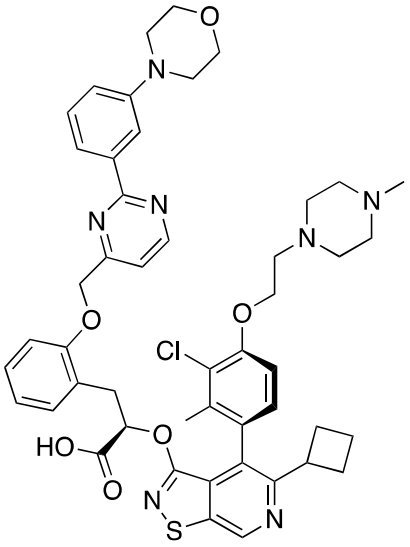
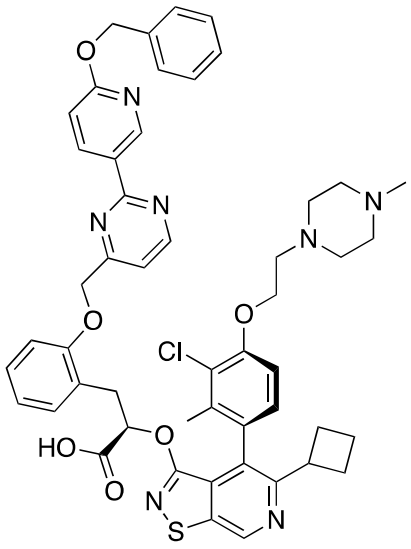
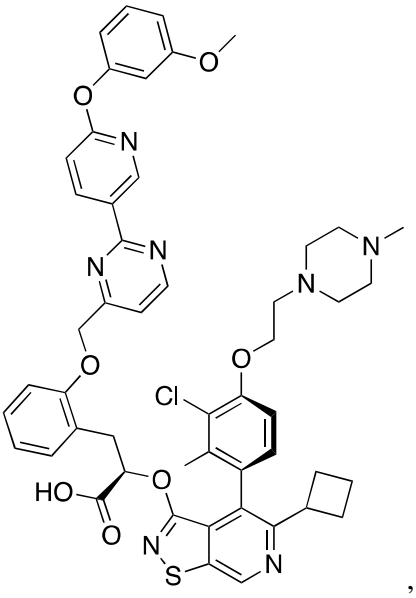
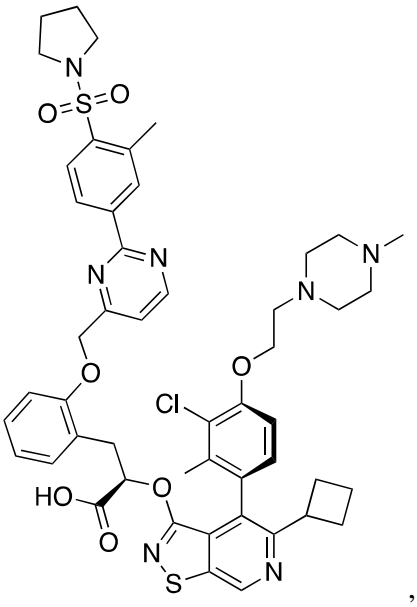
~~53.~~31. A compound selected from:

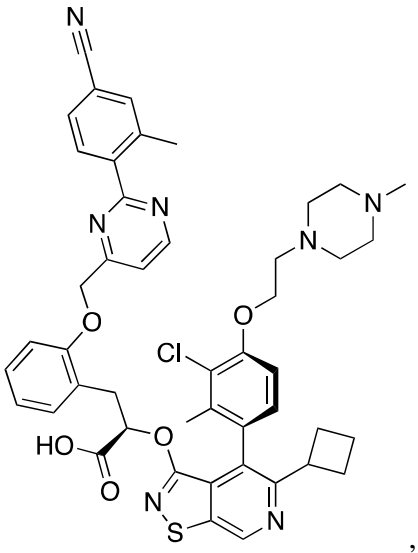
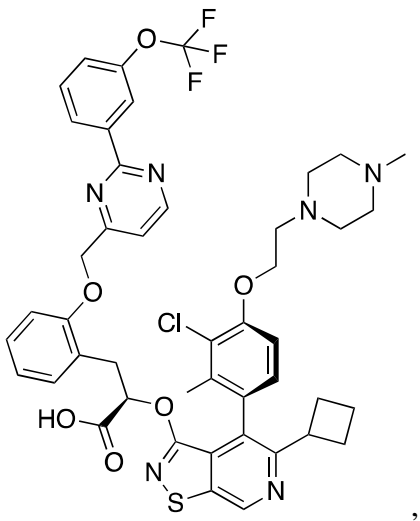
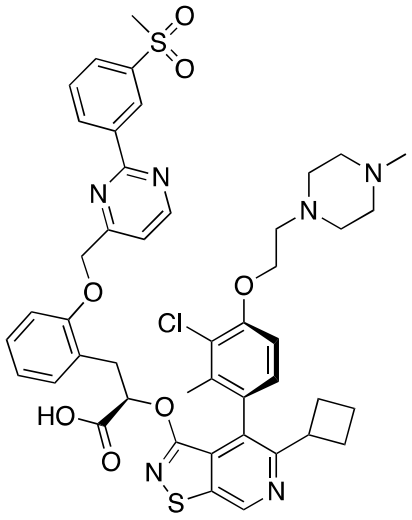
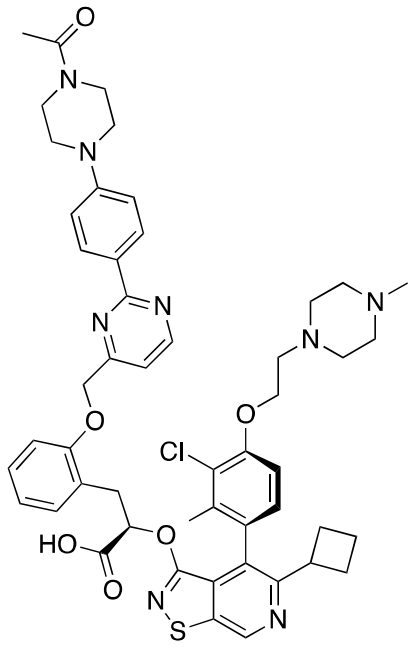


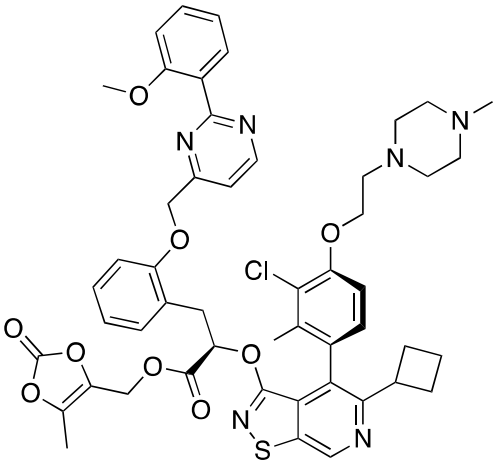
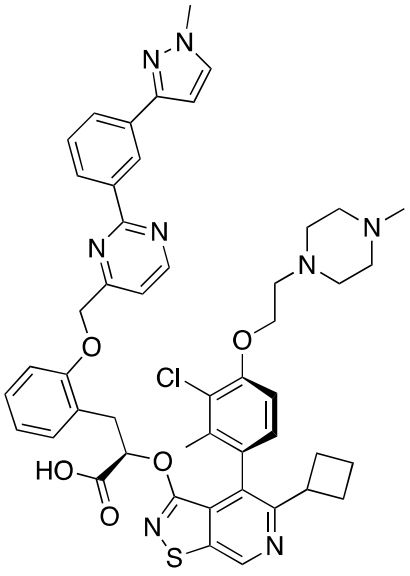
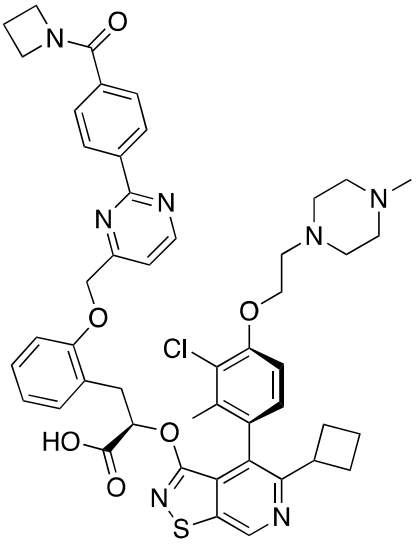
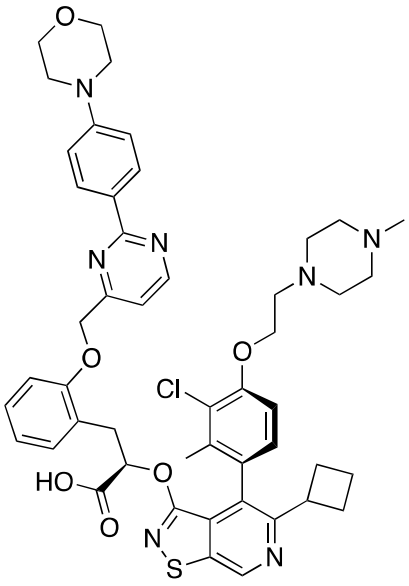
,


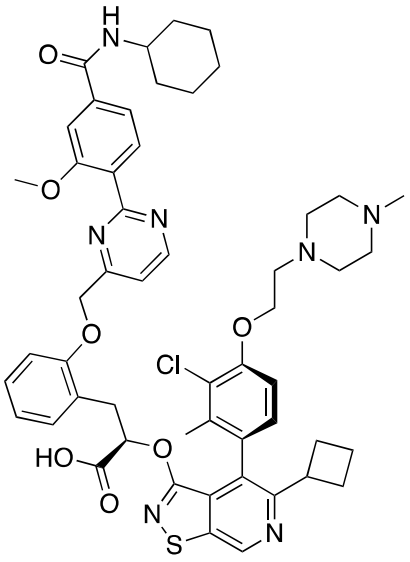
,


,

,

,

,

,

,

,

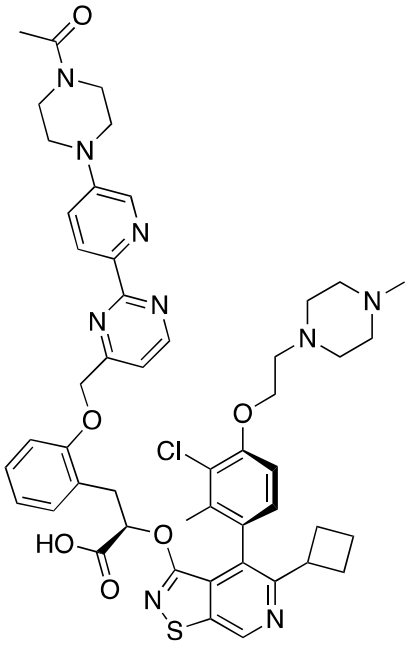

,

,

,

,


,

,

,

,

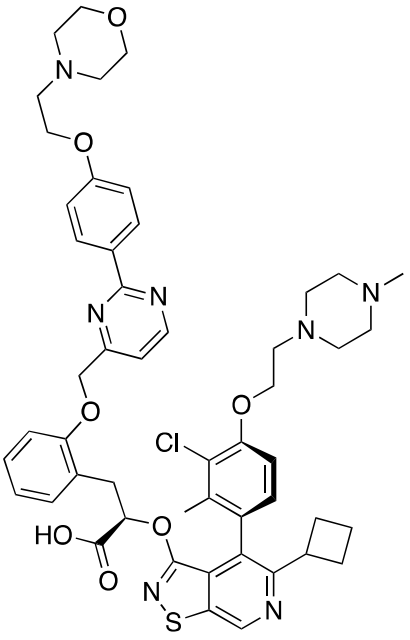

,

,

,

,



,

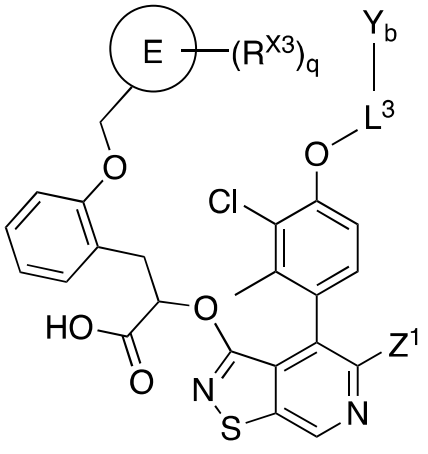


and



, or a pharmaceutically acceptable salt thereof.

~~54.~~32. A compound having the structure of Formula VIII:



(Formula VIII)

or a pharmaceutically acceptable salt thereof,

wherein:

E is heteroaryl;

L^3 is $-CH_2-$, or $-CH_2CH_2-$;

Y_b is H, heterocyclyl, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-CH_2N(CH_3)_2$ or $-CH_2N(CH_2CH_3)_2$; or

L^3 is absent and Y_b is H;

Z^1 is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z1};

R^{X3} in each instance is independently aryl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, heterocyclyl and C_1-C_6 alkoxy is optionally substituted with one, two, three or four R^{X3a};

R^{X3a} in each instance is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano;

R^{Z1} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, oxo, halogen, hydroxy, $N(R^{Z2})(R^{Z2})$, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl and C_2-C_6 alkynyl is optionally substituted with one or more R^{Z3};

R^{Z2} in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl or C_1-C_6 hydroxyalkyl, wherein each of said aryl, heteroaryl,

cycloalkyl, heterocyclyl, C_1-C_6 alkyl and C_1-C_6 alkoxy is optionally substituted with one or more R^{Z3}; or

two R^{Z2}, together with the N to which they are connected, form a heterocycle or heteroaryl, wherein each of said heterocycle and heteroaryl is optionally substituted with one, two, three or four R^{Z3};

R^{Z3} in each instance is independently aryl, heteroaryl, cycloalkyl, heterocyclyl, C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more R^{Z4};

R^{Z4} in each instance is independently C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, halogen, amino, nitro or cyano; and

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

~~55.~~33. The compound of claim ~~46~~32, wherein the compound has an MCL1 IC_{50} of about 100 nM or lower; and/or the compound has an average IC_{50} for the drug sensitive cell lines of Table 3 of 1 μM or lower; and/or the compound has an average IC_{50} for the drug-sensitive cell lines of Table 3 that is at least about 10-fold more potent than the average IC_{50} for the drug-resistant cell lines of Table 3.

~~56. The compound of claim 46 or 47, wherein the compound has an average IC_{50} for the drug sensitive cell lines of Table 3 of 1 μM or lower.~~

~~57. The compound of claim 46, 47 or 48, wherein the compound has an average IC_{50} for the drug-sensitive cell lines of Table 3 that is at least about 10-fold more potent than the average IC_{50} for the drug-resistant cell lines of Table 3.~~

~~58.~~34. The compound of ~~any of claims 46-49~~claim 32 or 33, wherein:

E is pyrimidynyl or pyrazolyl;

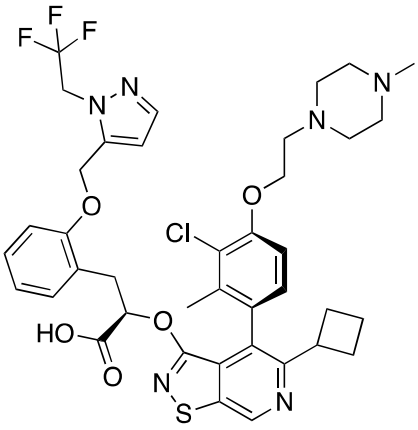
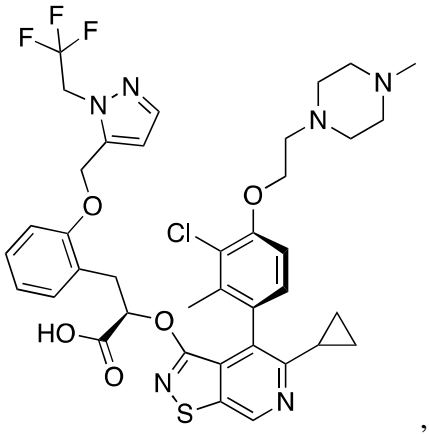
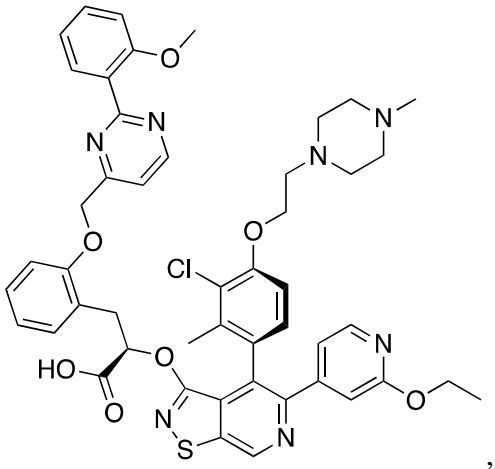
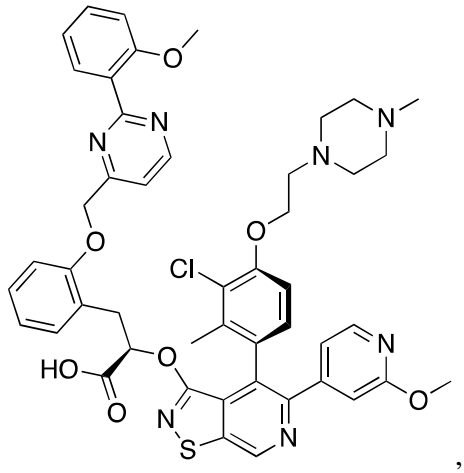
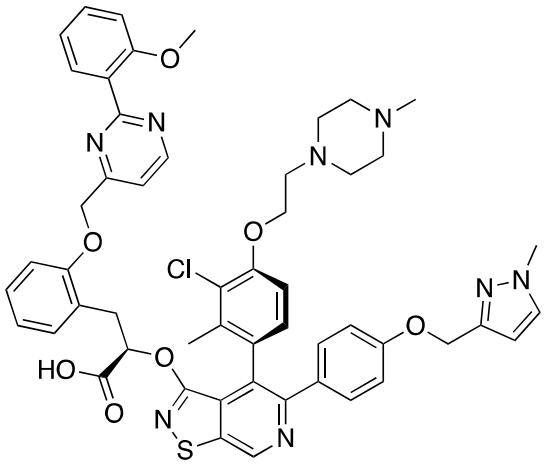
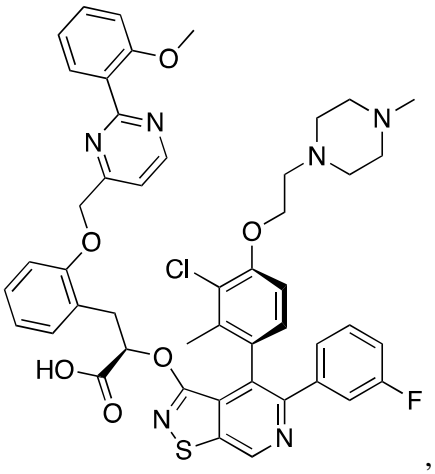
L^3 is $-CH_2CH_2-$;

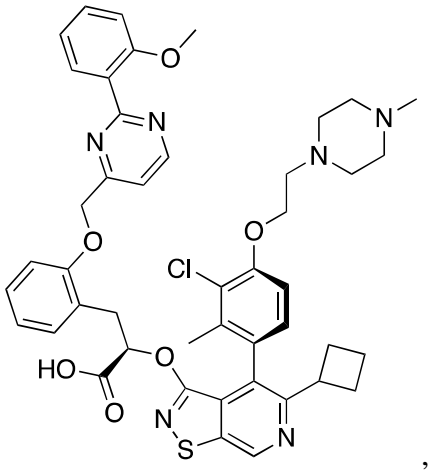
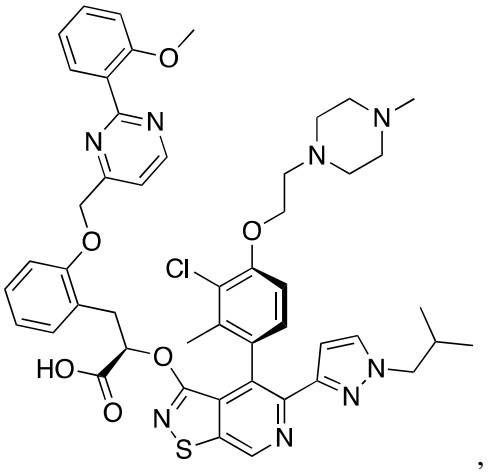
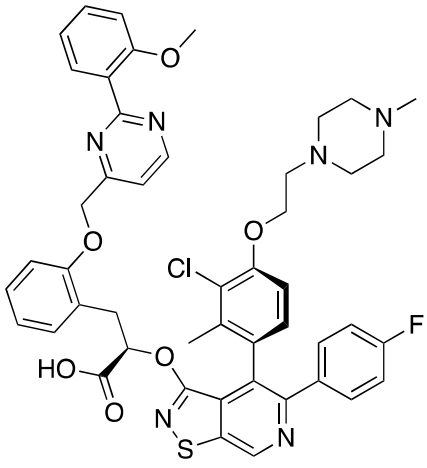
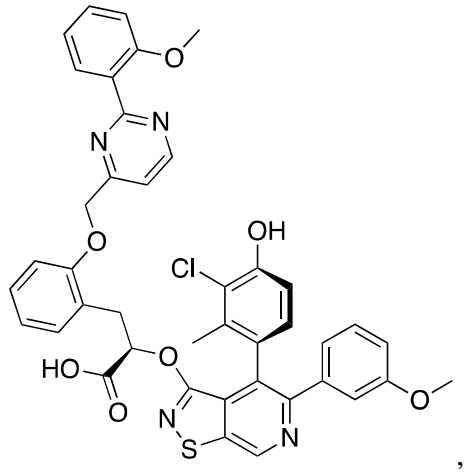
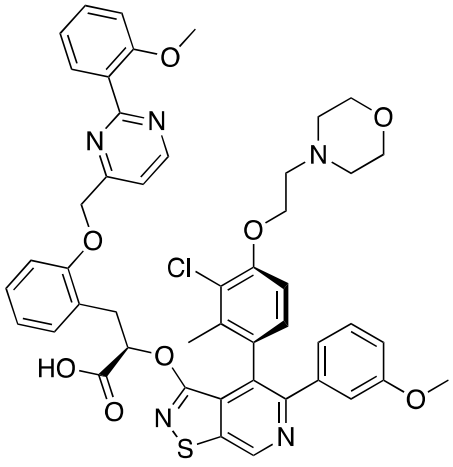
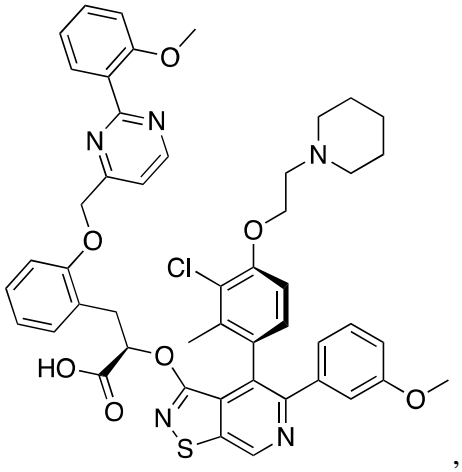
Y_b is heterocyclyl;

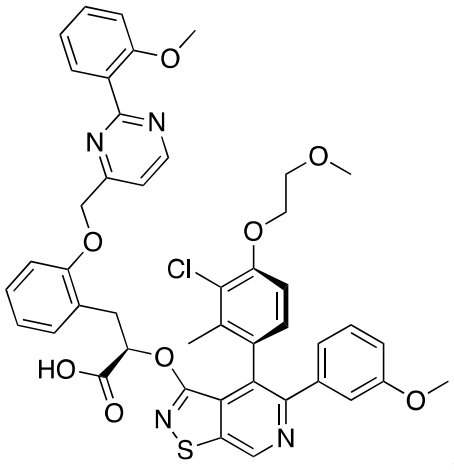
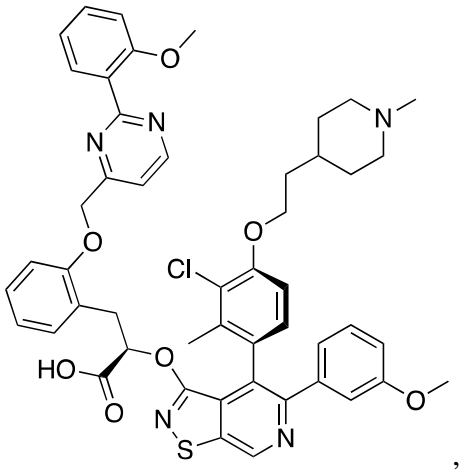
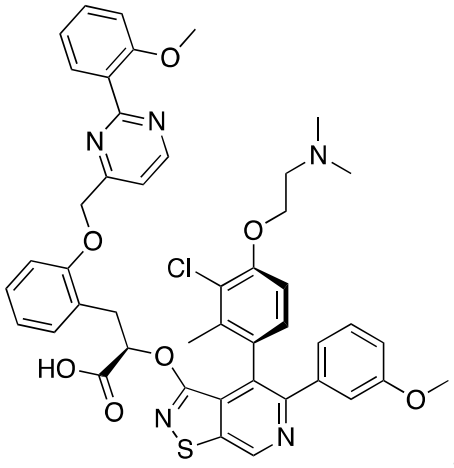
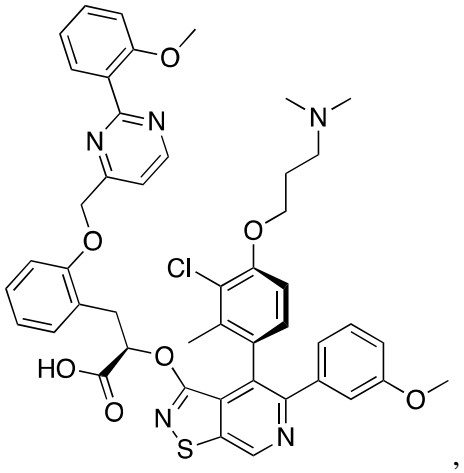
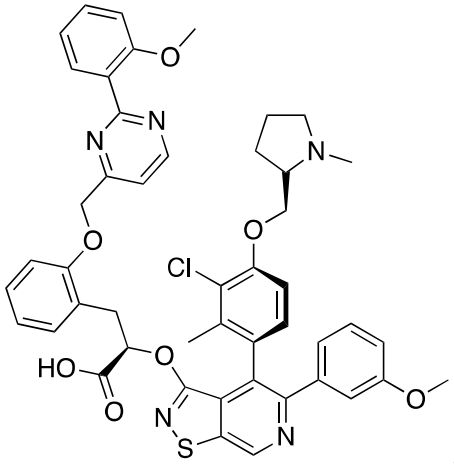
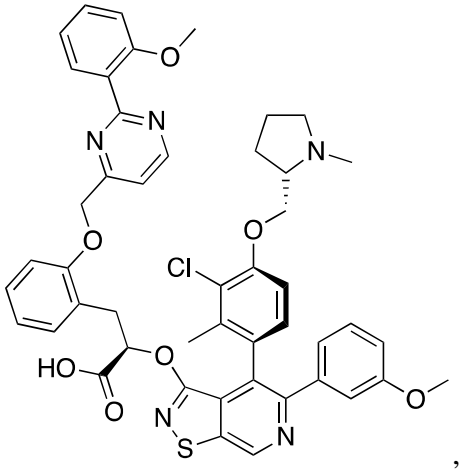
Z^1 is cycloalkyl; and

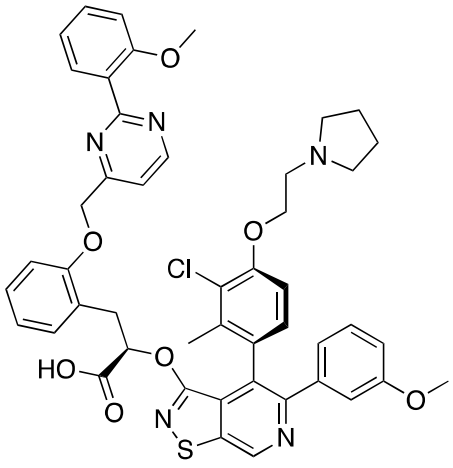
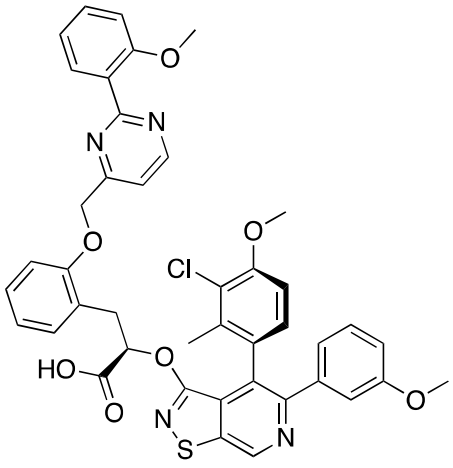
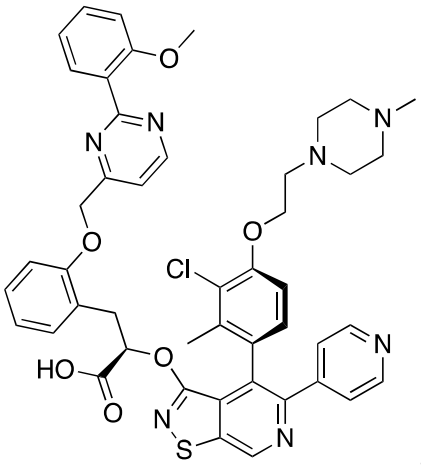
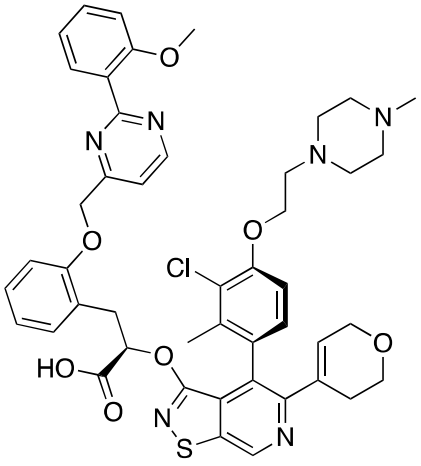
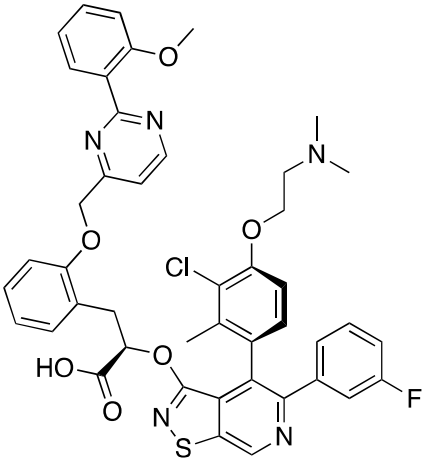
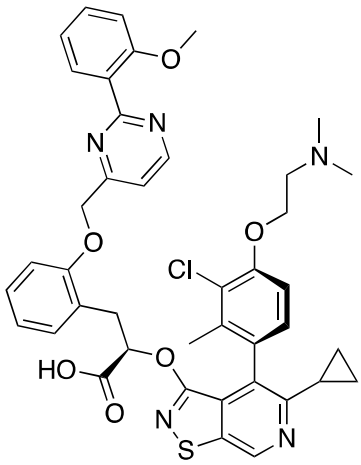
q is 0, 1 or 2.

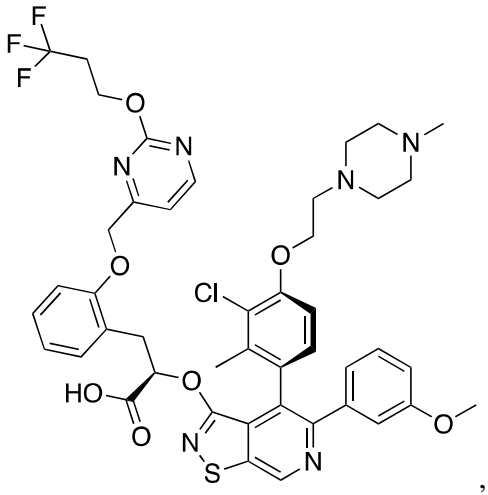
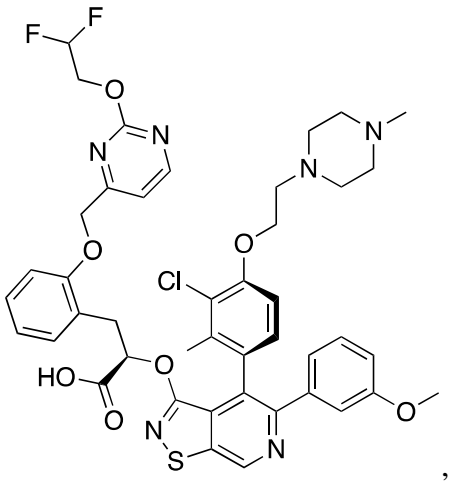
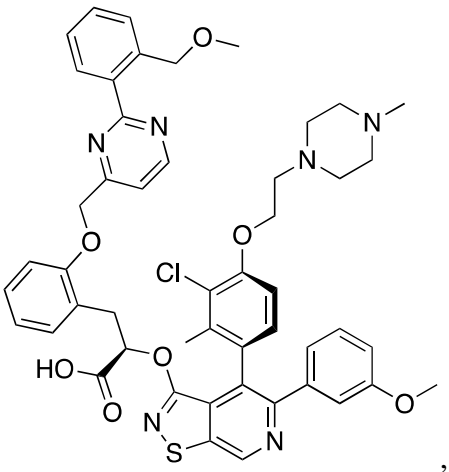
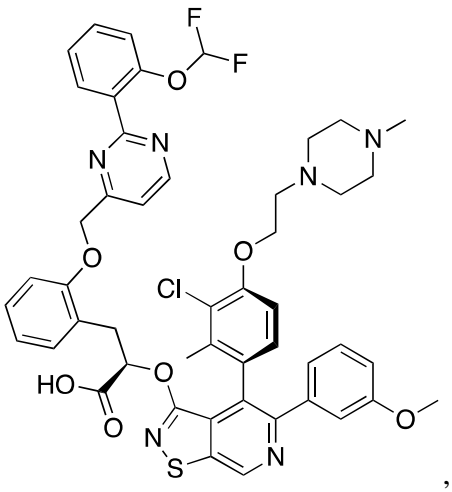
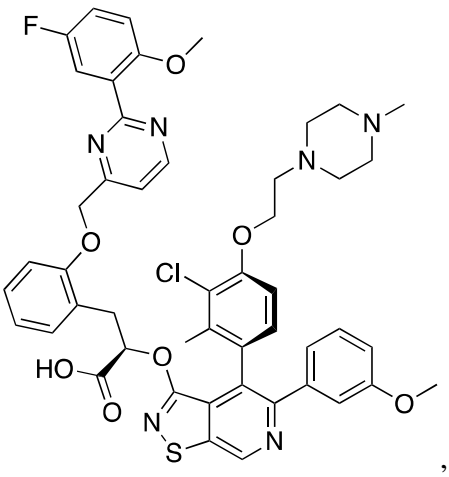
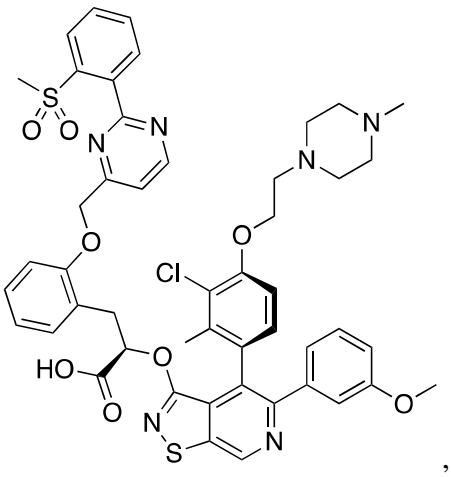
~~59.~~35. A compound selected from:

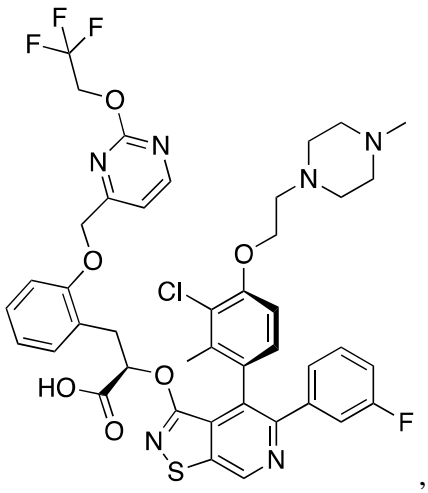
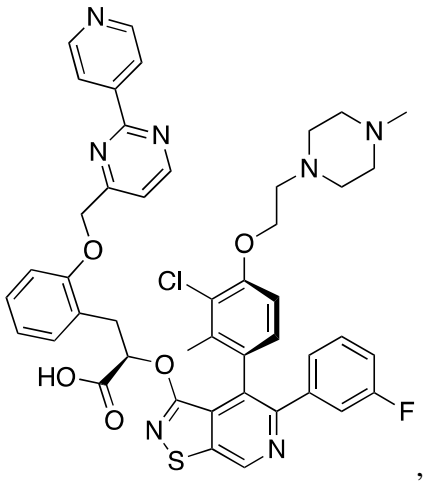
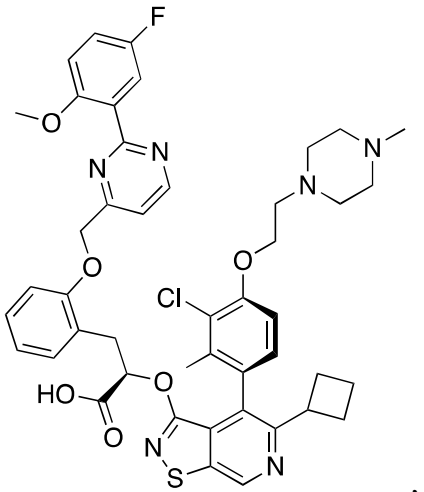
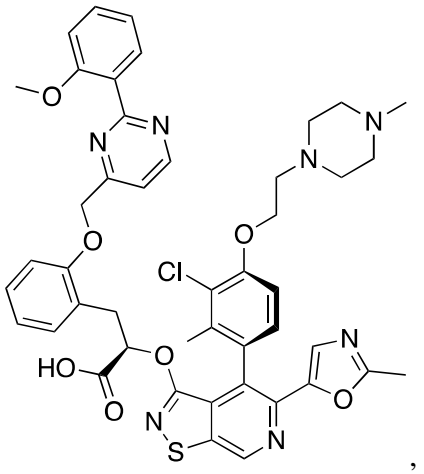
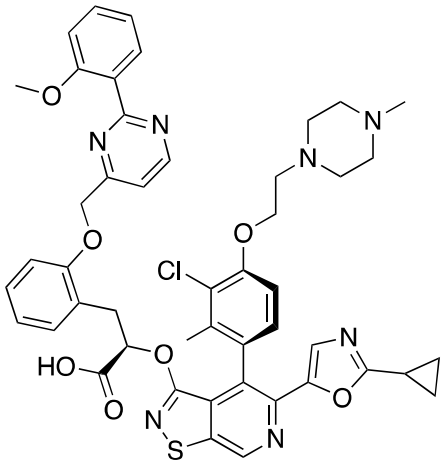
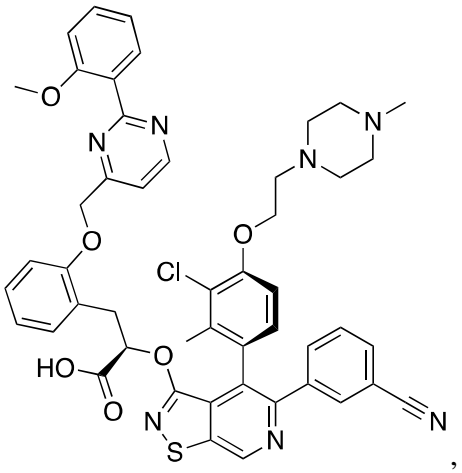

,

,

,

,

,

,

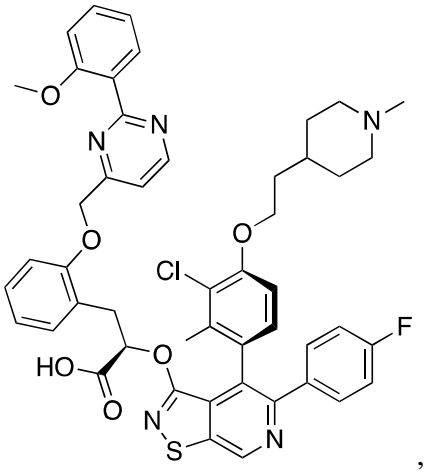
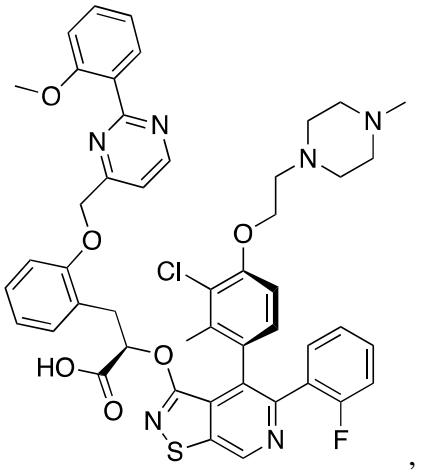
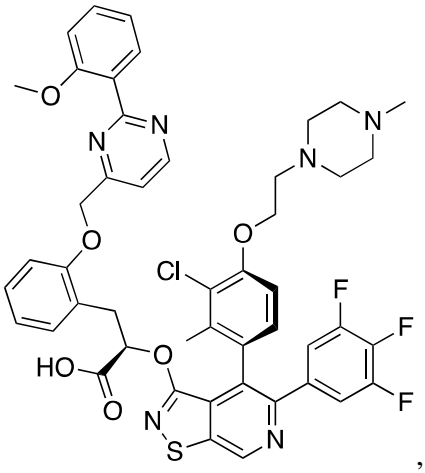
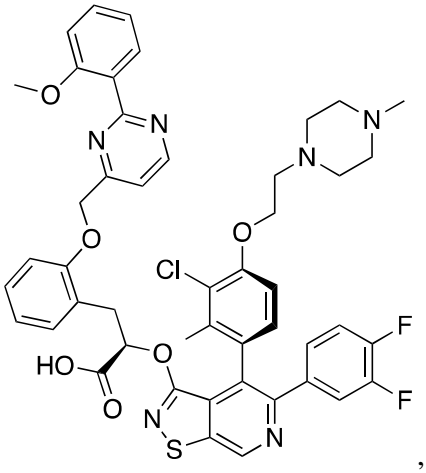
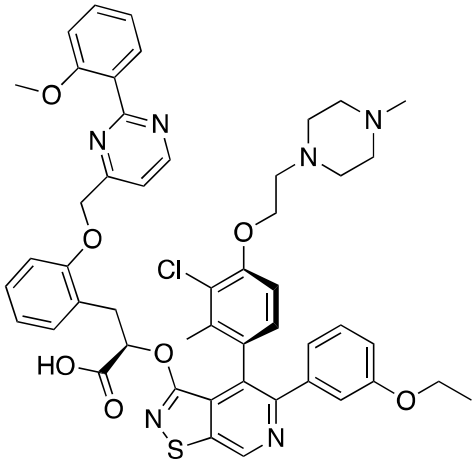
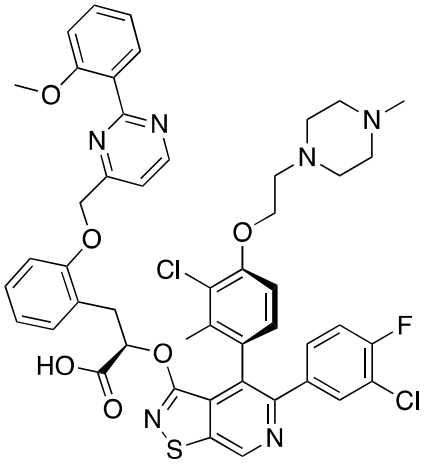

,

,

,

,

,

,

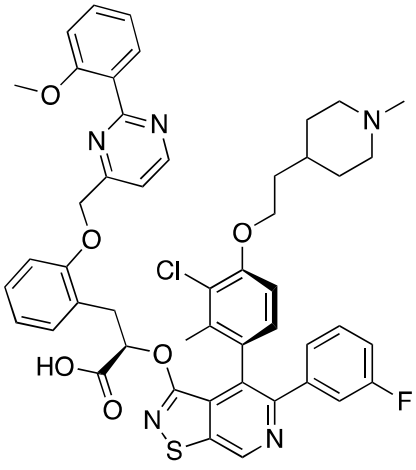

,

,

,

,

,

,


,

,

,

,

,

,


,

,

,

,

,

,


,

,

,

,

,

,

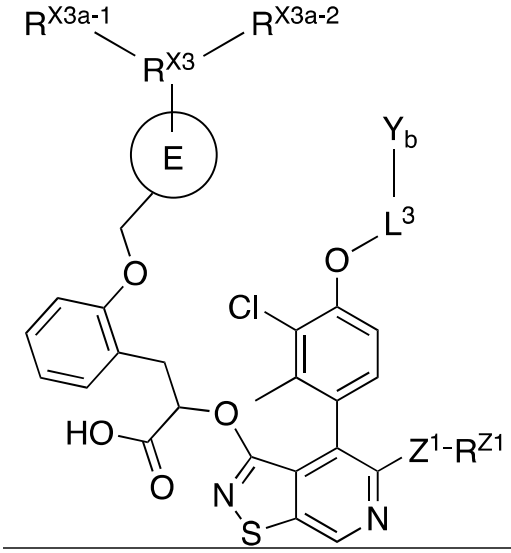

,

,

,

,

,

and



,

or a pharmaceutically acceptable salt thereof.

~~60. A compound having the structure of Formula IX:~~



~~(Formula IX)~~

~~or a pharmaceutically acceptable salt thereof,~~

~~wherein:~~

~~E is pyrimidinyl, pyrazolyl, pyridinyl or imidazolyl;~~

~~L^3 is CH_2 or CH_2CH_2;~~

~~Y_b morpholinyl, piperazinyl, piperindinyl, $N(CH_2CH_3)_2$ or $N(CH_3)_2$;~~

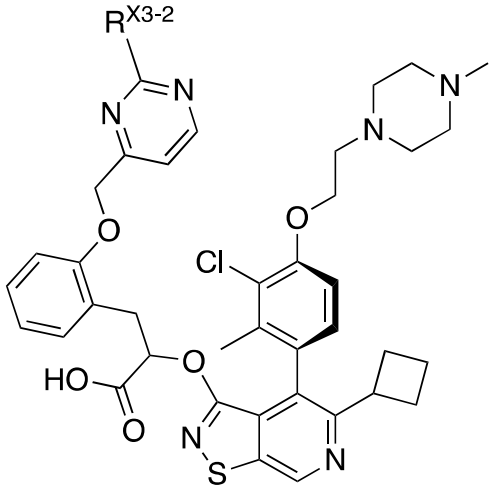
~~Z^1 is cyclobutyl, benzyl, pyridinyl, pyrazolyl or imidazolyl;~~

~~R^{X3} benzyl, pyridinyl, C_1-C_3 alkoxy or C_1-C_4 alkyl;~~

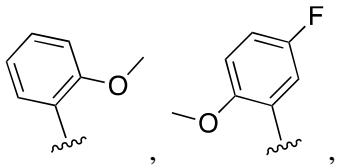
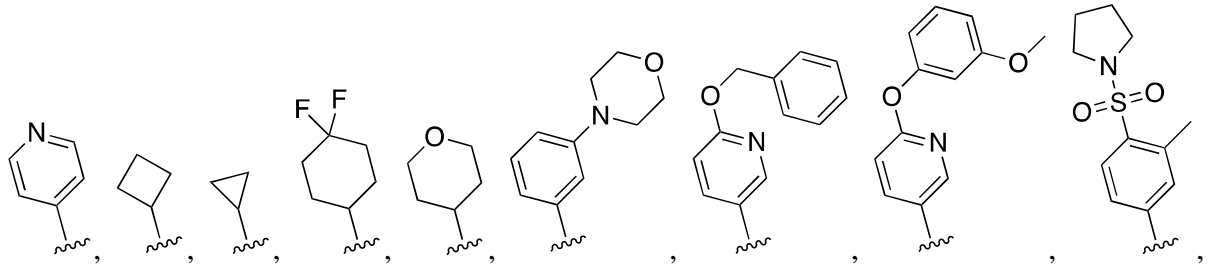
~~R^{X3a-1} and R^{X3a-2} is each independently H, C_1-C_3 alkyl, C_1-C_2 haloalkyl, amino, cyano or halogen; and~~

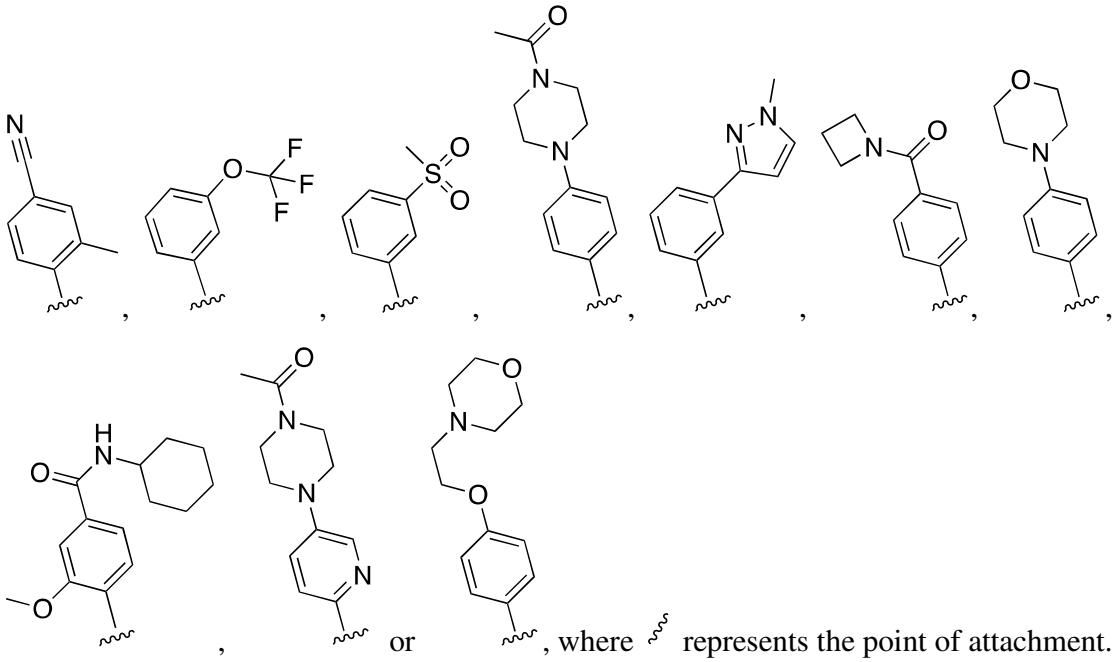
~~R^{Z1} is C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy or halogen.~~

~~61.~~36. A compound having the structure of Formula X:



(Formula X)

or a pharmaceutically acceptable salt thereof, wherein R^{X3-2} is  ,  .



, , , , , , , , or , where ~ represents the point of attachment.

~~62. A compound selected from Table 4.~~

~~63.~~37. A pharmaceutical composition comprising a compound of any one of claims ~~1-62~~1-36 and a pharmaceutically acceptable diluent or excipient.

~~64.~~38. ~~A method of treating a patient afflicted with a disease comprising administering an effective amount of the~~ Use of a compound of any one of claims 1-36~~1-62 or the pharmaceutical composition of claim 63 to the patient so as to thereby treat the~~ in the manufacture of a medicament for the treatment of a disease, wherein the underlying pathology of the disease is mediated by MCL1, preferably wherein the disease is a cancer.

~~65. The method of claim 64, wherein the disease is a cancer.~~

~~66.~~39. The ~~method~~ use of claim ~~65~~38, wherein the cancer is selected from a carcinoma, a sarcoma, kidney cancer, epidermis cancer, liver cancer, lung cancer, esophagus cancer, gall bladder cancer, ovary cancer, pancreatic cancer, stomach cancer, cervix cancer, thyroid cancer, nose cancer, head and neck cancer, prostate cancer, skin cancer, breast cancer, familial melanoma, and melanoma, preferably wherein the carcinoma is a carcinoma of the endometrium,

bladder, breast, or colon; the sarcoma is Kaposi’s sarcoma, osteosarcoma, tumor of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; the lung cancer is adenocarcinoma, small cell lung cancer or non-small cell lung carcinomas; the pancreatic cancer is exocrine pancreatic carcinoma; the skin cancer is squamous cell carcinoma; and the breast cancer is a primary breast tumor, node-negative breast cancer, invasive duct adenocarcinomas of the breast or non-endometrioid breast cancer; or

the the cancer is selected from leukemia, acute lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukemia, B-cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, and Burkett’s lymphoma, acute and chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, astrocytoma, neuroblastoma, glioma, schwannoma, seminoma, teratocarcinoma, xeroderma pigmentosum, retinoblastoma, keratoctanthoma, thyroid follicular cancer, head and neck cancer, sarcoma, melanoma, myeloma, lymphoma, lung cancer, breast cancer, pancreatic cancer, thyroid cancer, colorectal cancer, ovarian cancer and acute myelogenous leukemia.

~~67. The method of claim 66, wherein the carcinoma is a carcinoma of the endometrium, bladder, breast, or colon; the sarcoma is Kaposi’s sarcoma, osteosarcoma, tumor of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; the lung cancer is adenocarcinoma, small cell lung cancer or non-small cell lung carcinomas; the pancreatic cancer is exocrine pancreatic carcinoma; the skin cancer is squamous cell carcinoma; and the breast cancer is a primary breast tumor, node-negative breast cancer, invasive duct adenocarcinomas of the breast or non-endometrioid breast cancer.~~

~~68. The method of claim 65, wherein the cancer is selected from leukemia, acute lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukemia, B-cell lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, and Burkett’s lymphoma, acute and chronic myelogenous leukemias, myelodysplastic syndrome, and promyelocytic leukemia.~~

~~69. The method of claim 65, wherein the cancer is selected from astrocytoma, neuroblastoma, glioma, schwannoma, seminoma, teratocarcinoma, xeroderma pigmentosum, retinoblastoma, keratoctanthoma, and thyroid follicular cancer.~~

~~70. The method of claim 65, wherein the cancer is selected from head and neck cancer, sarcoma, melanoma, myeloma, lymphoma, lung cancer, breast cancer, pancreatic cancer, thyroid cancer, colorectal cancer, ovarian cancer and acute myelogenous leukemia.~~