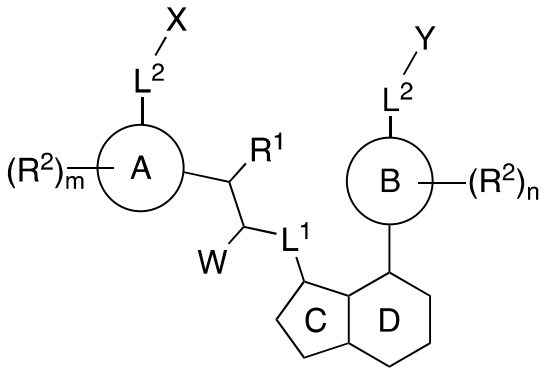
**CLAIMS**

1. A compound having the structure of Formula I:



(Formula I)

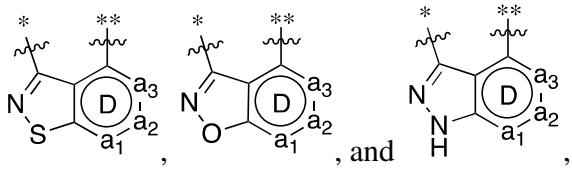
or a pharmaceutically acceptable salt thereof,

wherein:

A is phenyl;

B is a bond, or phenyl;

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



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

$a_1$ is CH;

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

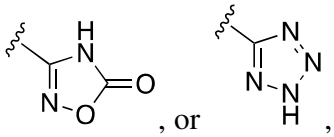
$a_3$ is $C(Z^1)$,

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 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 $R^{Z1}$;

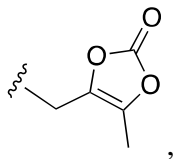
$Z^2$ is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more $R^{Z1}$;

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;

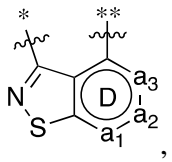
n is 0, 1, 2, 3 or 4, with the proviso that n is 0 when B is a bond; and

p in each instance is independently 0 or 1.

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

B is phenyl;

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



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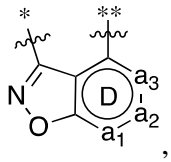

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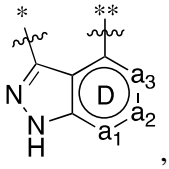


, where ~ represents the points of attachment, * represents the point attaching to $L^1$, and ** represents the point attaching to B;

$a_1$ is CH;

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

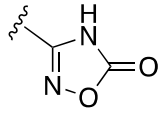
$a_3$ is $C(Z^1)$,

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



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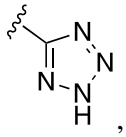


, where ~ represents the point of attachment;

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;

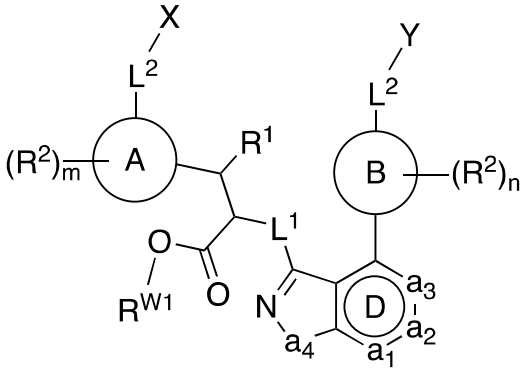
$R^{Cy2}$ in each instance is independently H, aryl, heteroaryl, cycloalkyl, heterocyclyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ haloalkyl or $C_1$-$C_6$ hydroxyalkyl;

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 phenyl;

B is a bond or phenyl;

$a_1$ is CH;

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

$a_3$ is $C(Z^1)$;

$a_4$ 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 $R^{Z1}$;

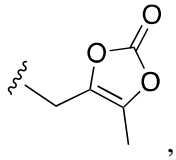
$Z^2$ is H, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more $R^{Z1}$;

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

$R^{W2b}$ 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:

B is phenyl;

$a_1$ is CH;

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

$a_3$ is $C(Z^1)$;

$a_4$ 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. The compound of claim 1 or 3, wherein B is phenyl.

6. The compound of any one of claims 1 – 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.

7. The compound of claim 3, wherein:

A is phenyl;

B isphenyl;

$a_1$ 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.

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

A is phenyl;

B is phenyl;

$a_1$ is CH;

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

$a_3$ is CH;

$a_4$ 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 $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-}O\text{-}(C_1\text{-}C_6 \text{ alkyl})_p-$;

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.

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

$R^{W1}$ is H;

$L^1$ is O;

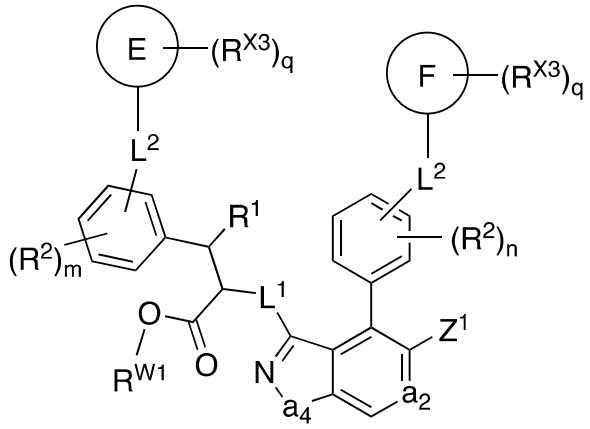
$R^1$ is H;

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

m is 0; and

n is 2.

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;

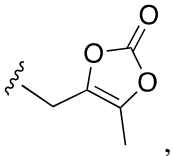
$Z^1$ in each instance is independently H, halogen, -$L^2$-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more $R^{Z1}$;

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.

11. The compound of claim 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.

12. The compound of claim 10, 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)O$R^{W2b}$, OC(O)N($R^{W2b}$)($R^{W2b}$) or OP(O)(O$R^{W2b}$)$_2$;

$R^{W2b}$ 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.

13. The compound of claim 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

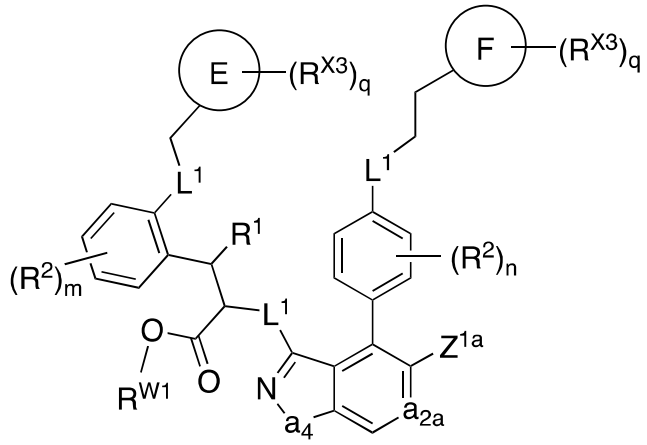
n is 2.

14. The compound of any one of claims 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.

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;

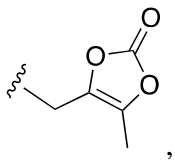
$Z^{1a}$ is H, halogen, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more $R^{Z1}$;

$R^1$ 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.

16. The compound of claim 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.

17. The compound of claim 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.

18. The compound of any one of claims 10-17, wherein:

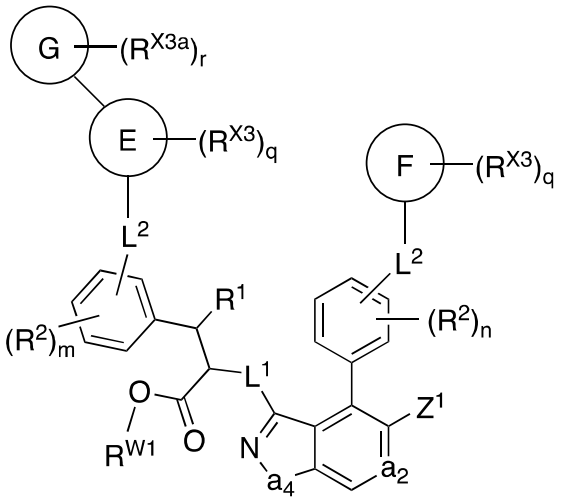
E is phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, furan, thiophene, pyrrole, pyrazole, imidazole or triazole;

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.

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 $R^{Z1}$;

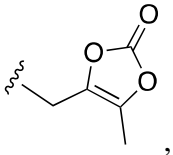
Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four $R^{Cy1}$;

$R^1$ 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;

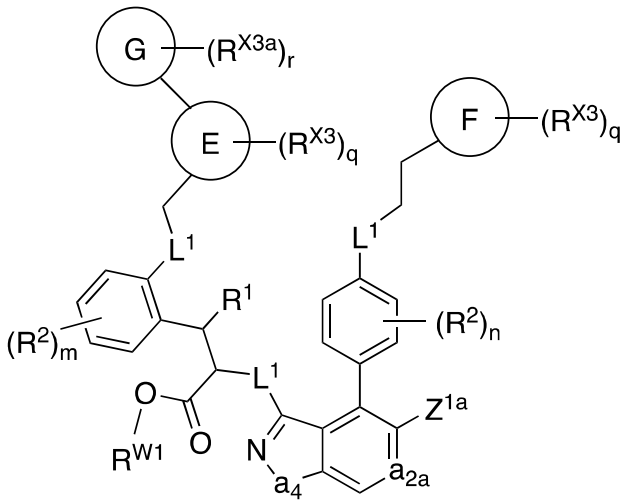
n is 0, 1, 2, 3 or 4;

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:




(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;

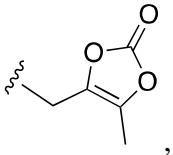
$Z^1$ in each instance is independently H, halogen, -$L^2$-Cy, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more $R^{Z1}$;

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;

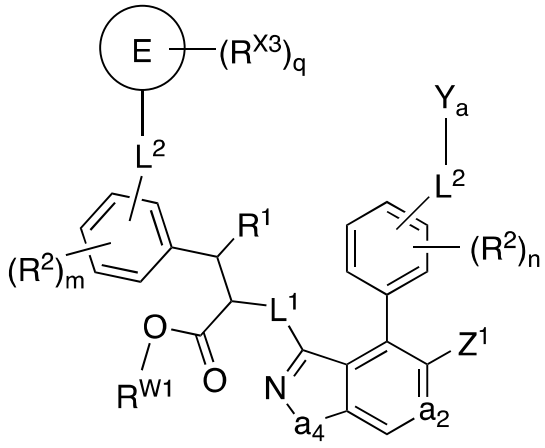
m is 0, 1, 2, or 3;

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:




(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, $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-O-}(C_1\text{-}C_6 \text{ alkyl})_p\text{-}$, $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-N}(R^{X1})\text{-}(C_1\text{-}C_6 \text{ alkyl})_p\text{-}$, $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-S-}(C_1\text{-}C_6 \text{ alkyl})_p\text{-}$, $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-S(O)-}(C_1\text{-}C_6 \text{ alkyl})_p\text{-}$, or $-(C_1\text{-}C_6 \text{ alkyl})_p\text{-S(O)}_2\text{-}(C_1\text{-}C_6 \text{ alkyl})_p\text{-}$;

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 $R^{Z1}$;

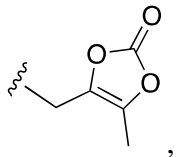
Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with one, two, three or four $R^{Cy1}$;

$R^1$ 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.

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

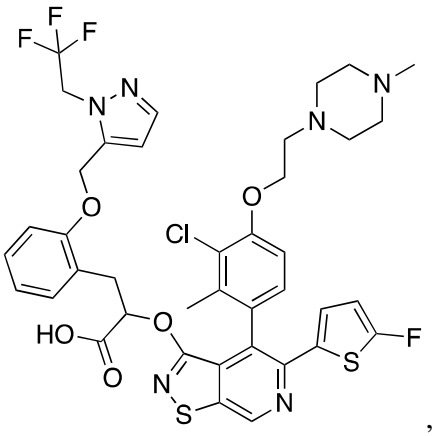
E is phenyl, pyridine, pyridazine, pyrimidine, pyrazine, triazine, furan, thiophene, pyrrole, pyrazole, imidazole or triazole;

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

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

21. The compound of any one of claims 1-20, wherein $C_1$-$C_6$ haloalkyl is trifluoromethane or trifluoroethane.

22. A compound selected from: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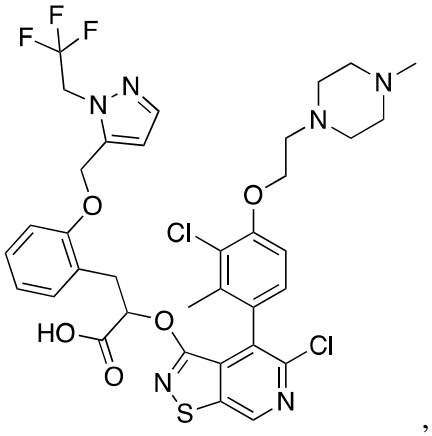
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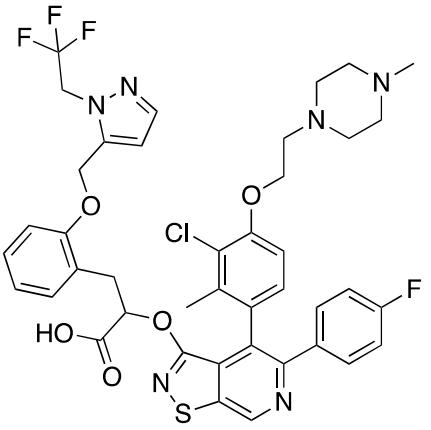
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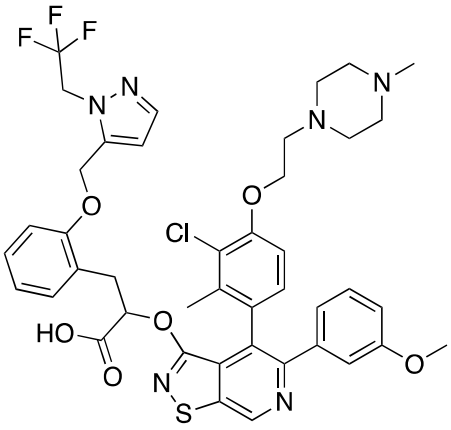
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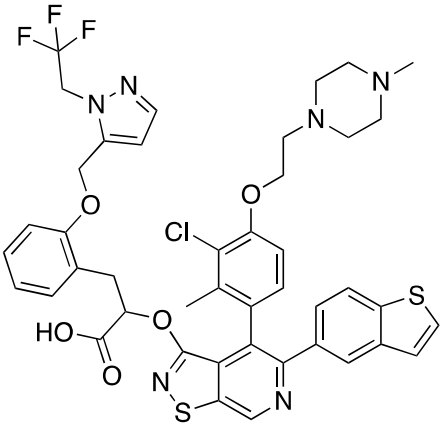
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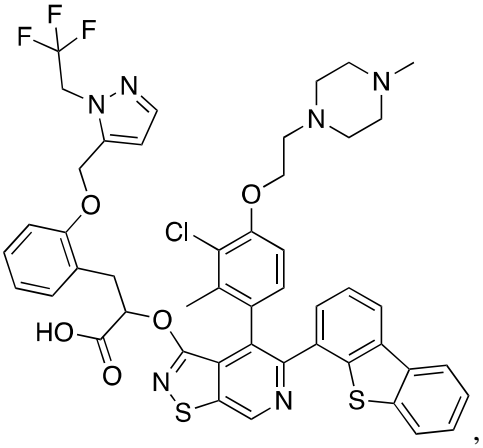
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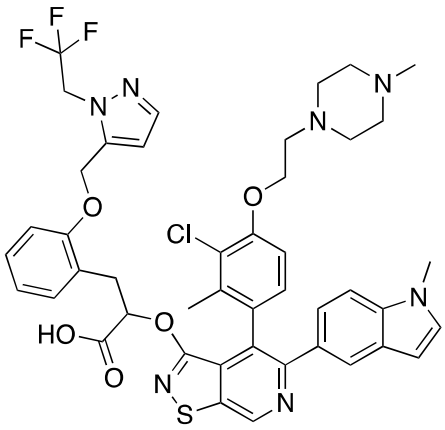
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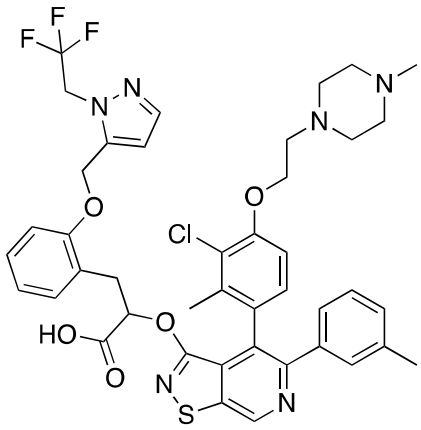
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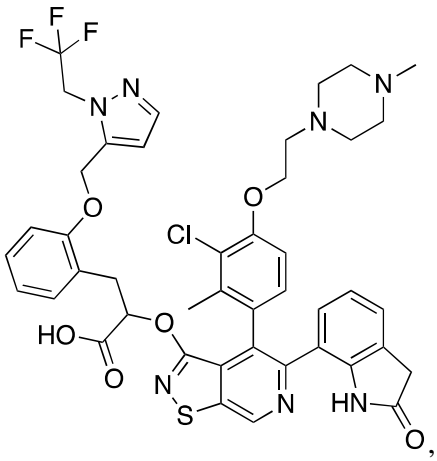
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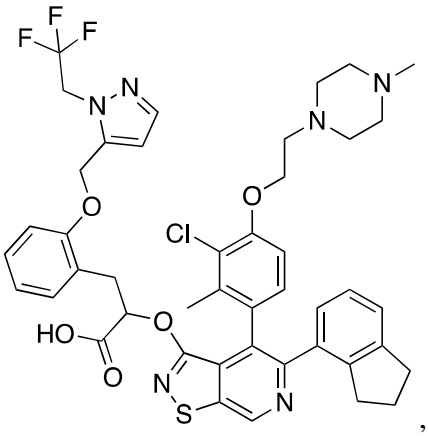
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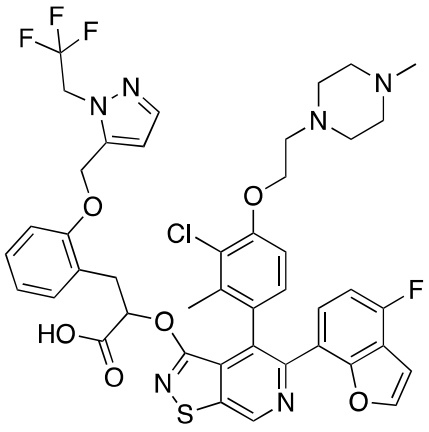
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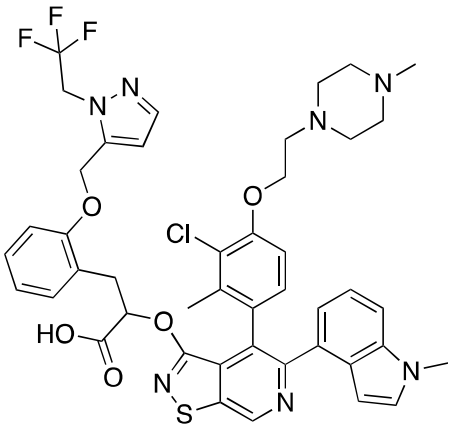
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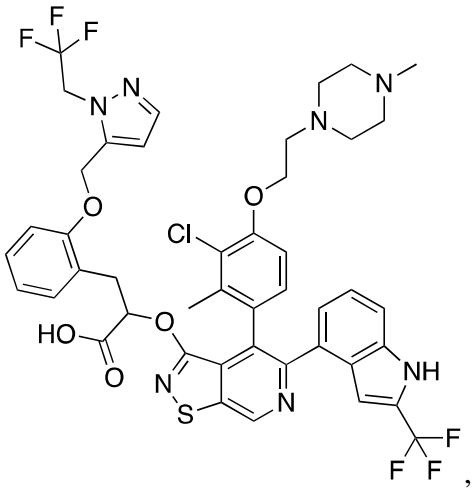
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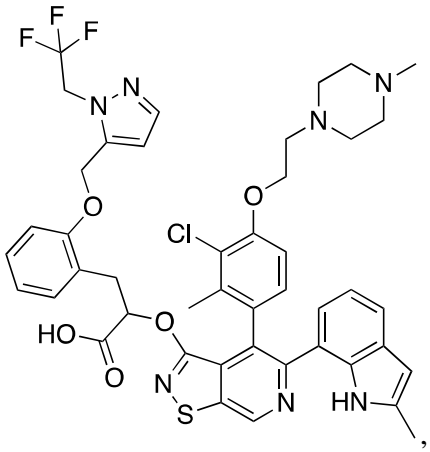
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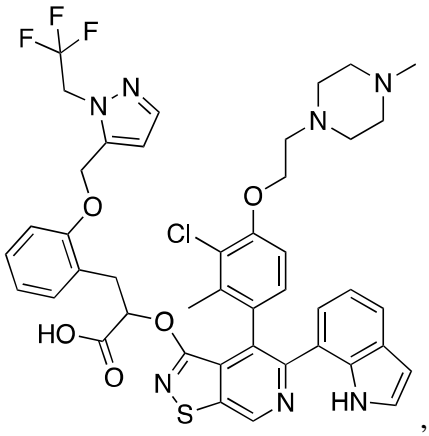
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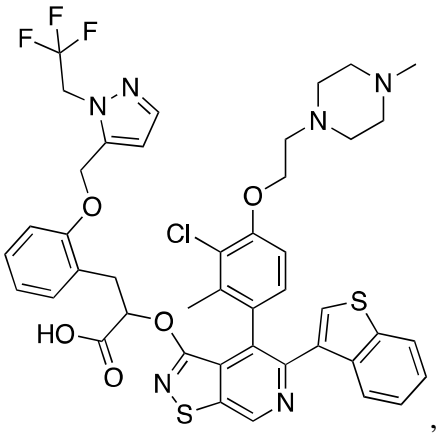
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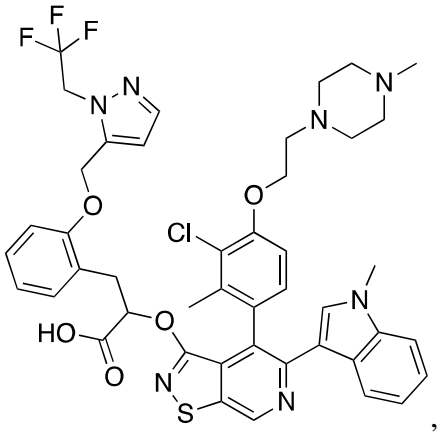
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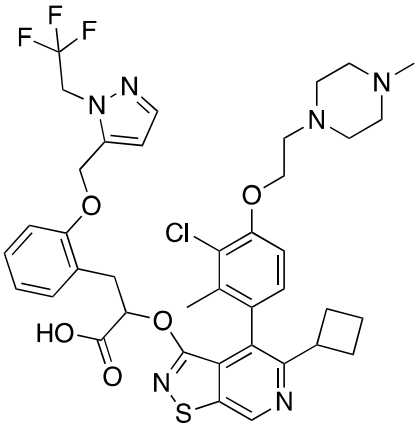
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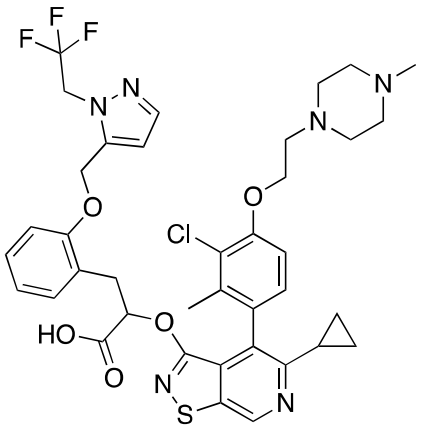
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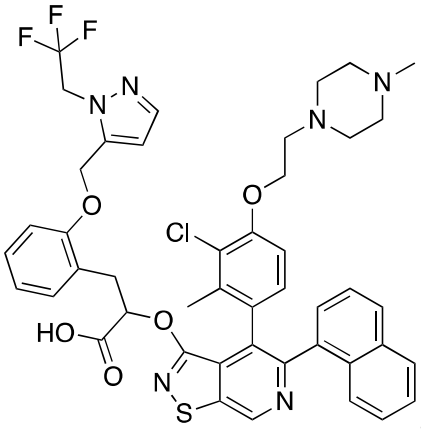
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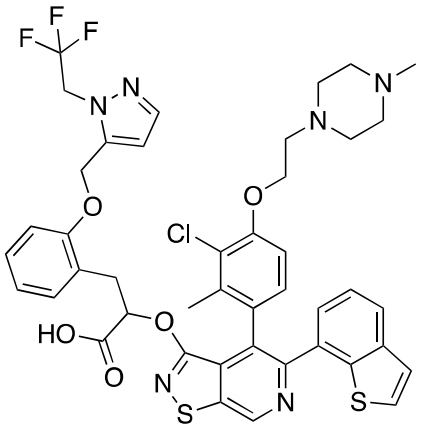
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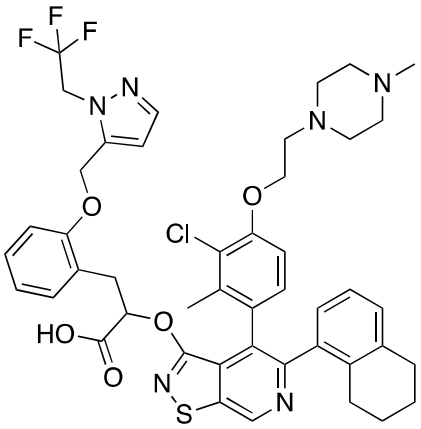
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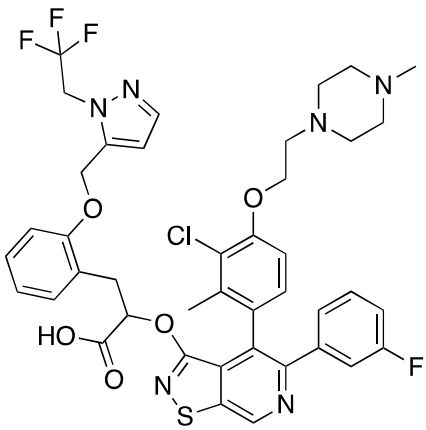
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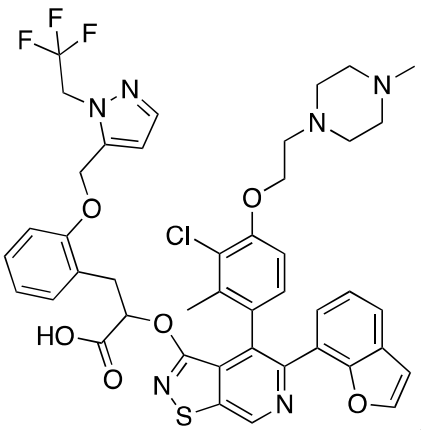
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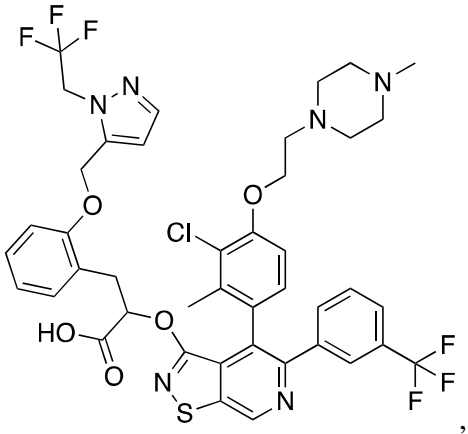
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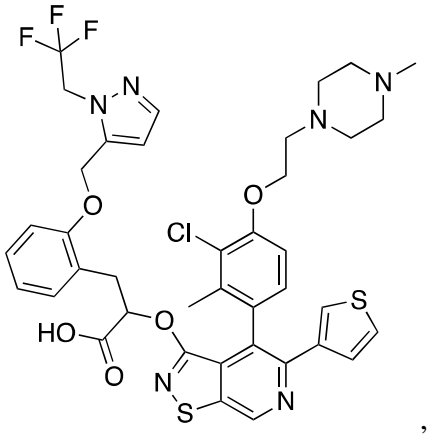
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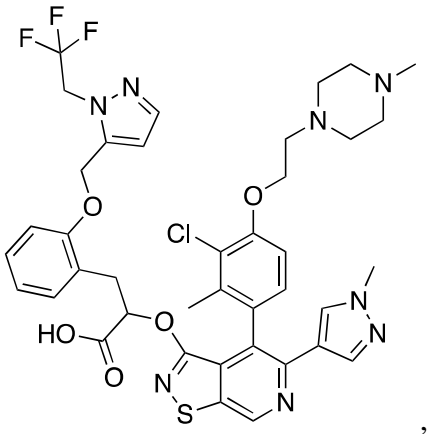
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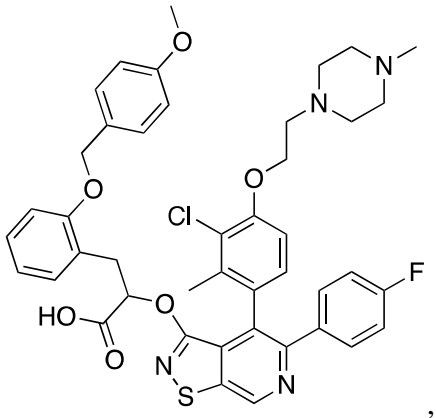
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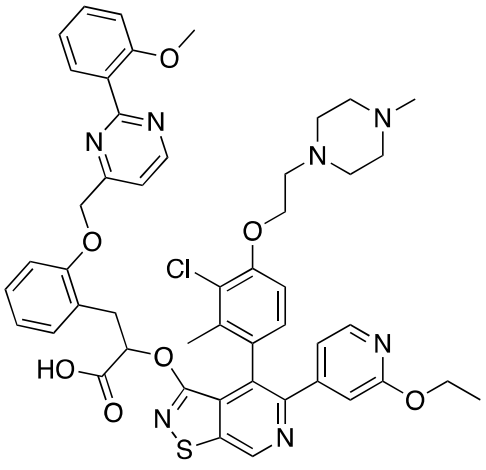
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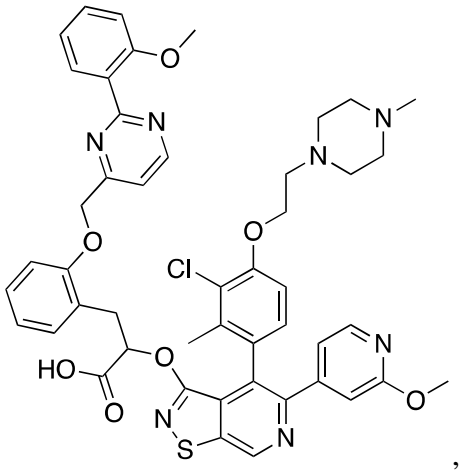
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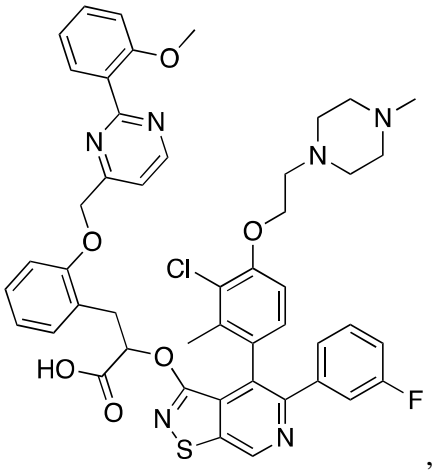
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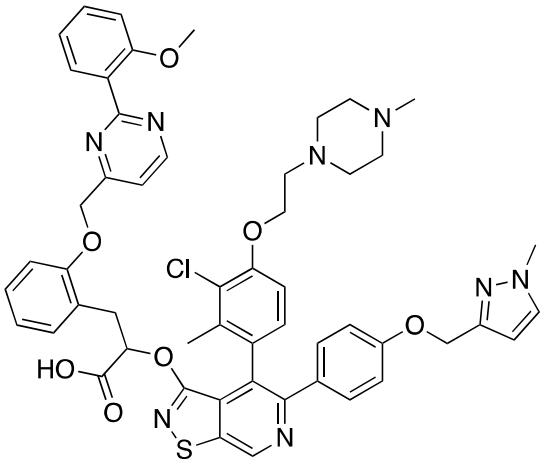
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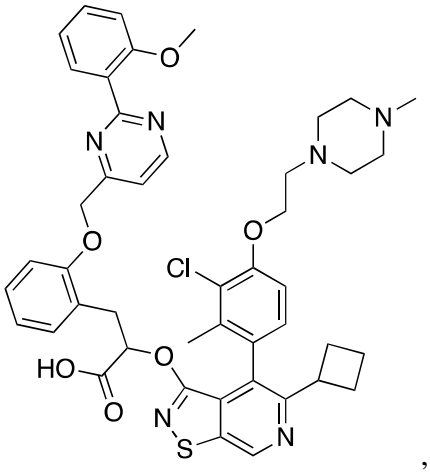
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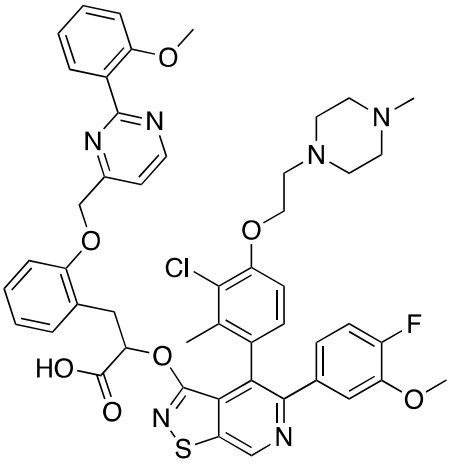
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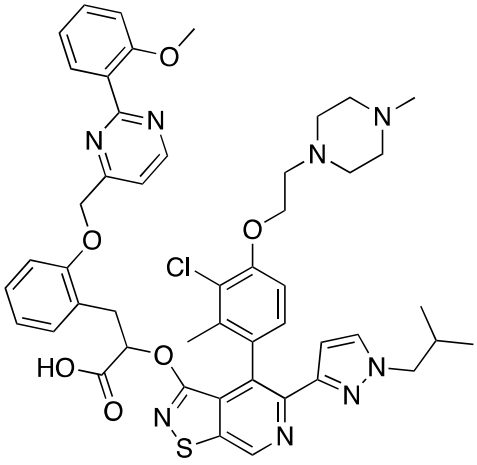
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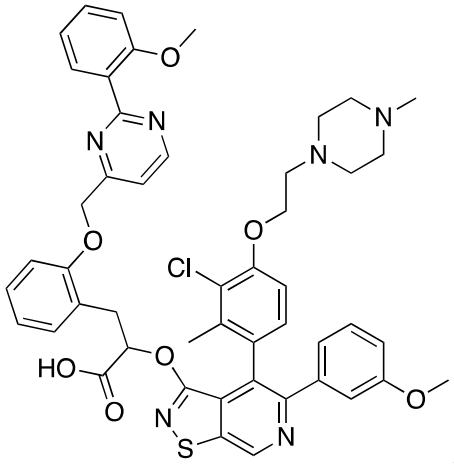
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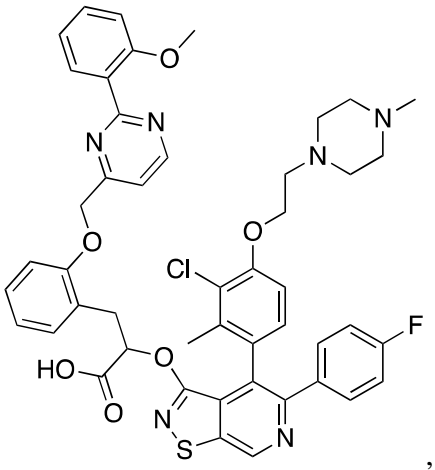
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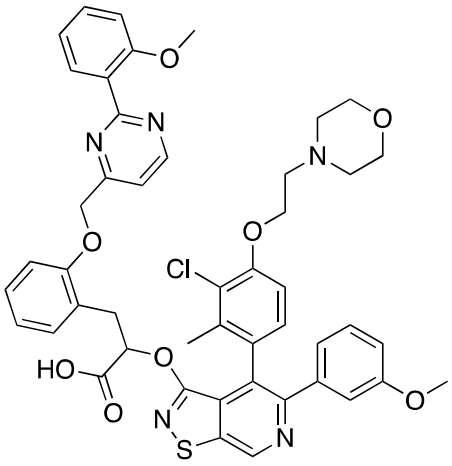
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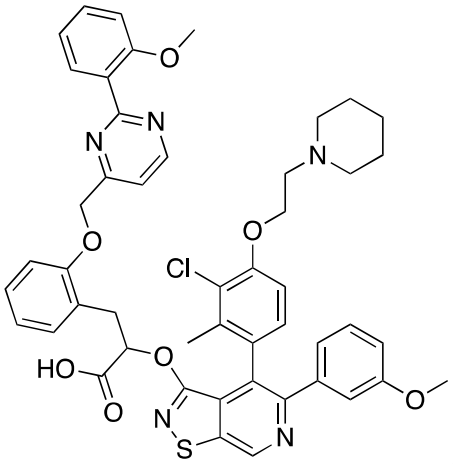
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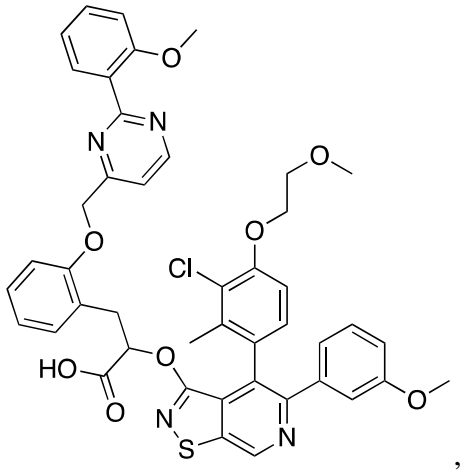
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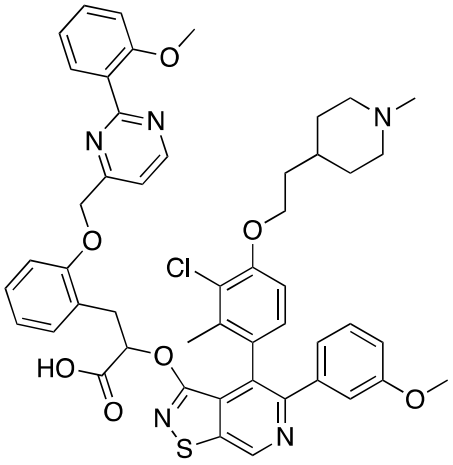
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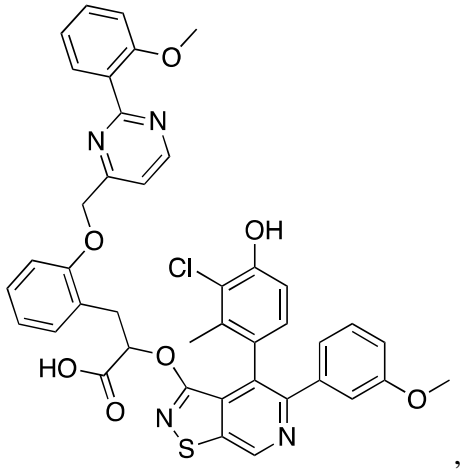
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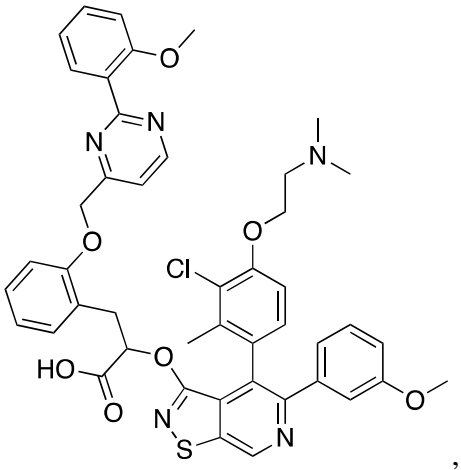
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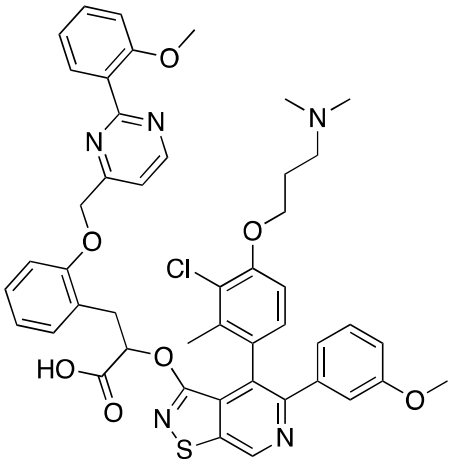
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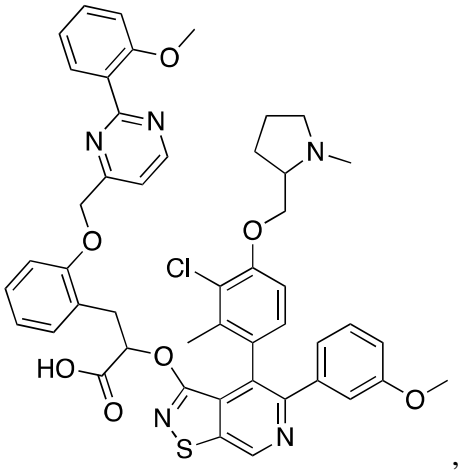
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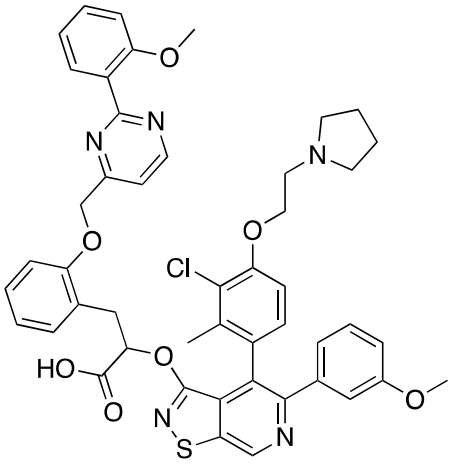
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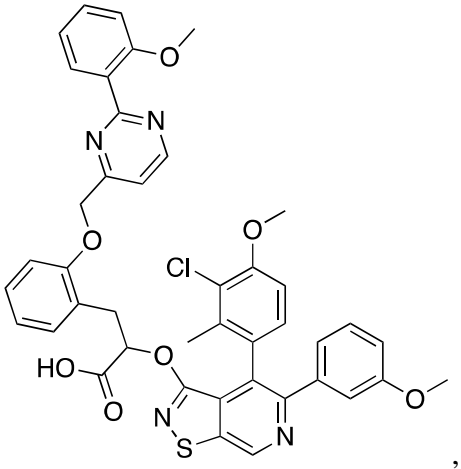
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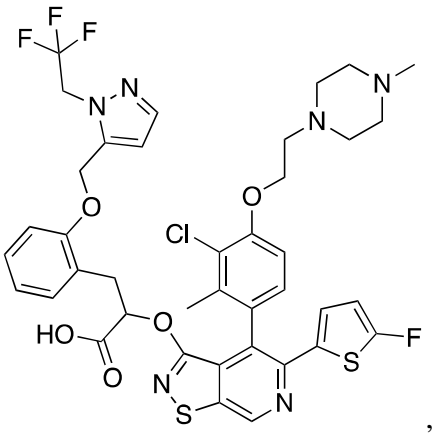
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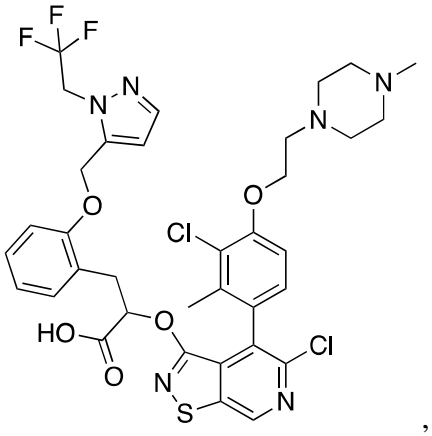
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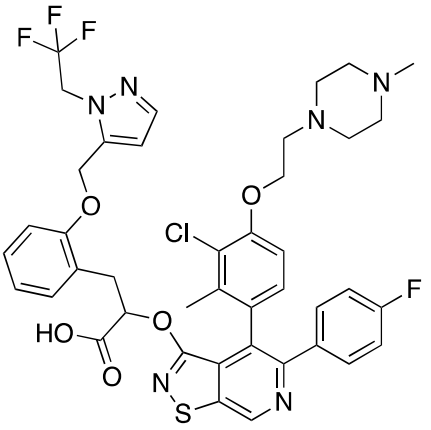
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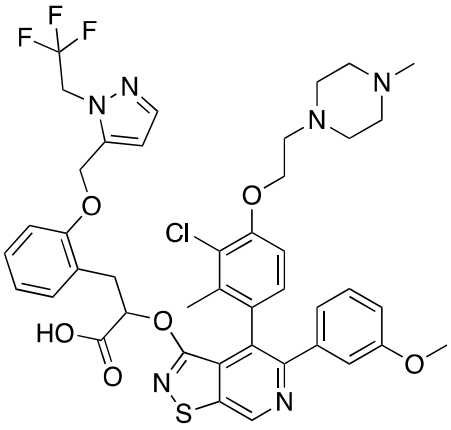
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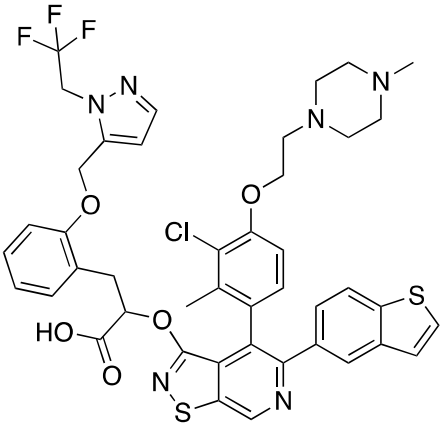
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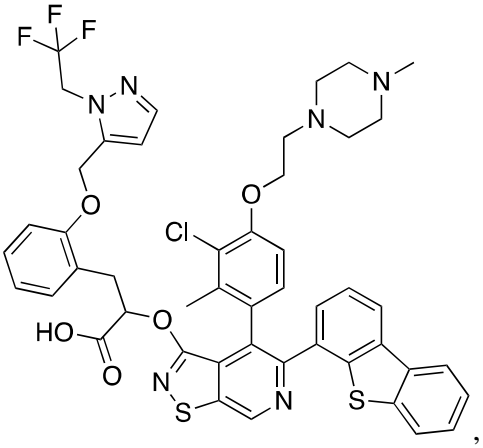
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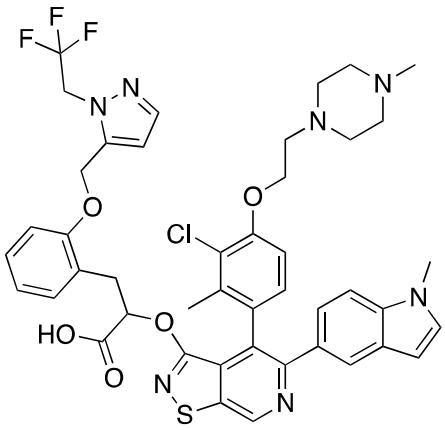
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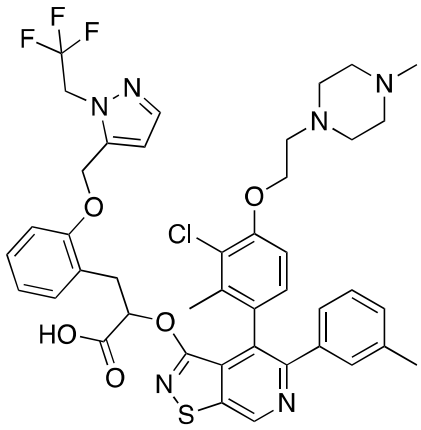
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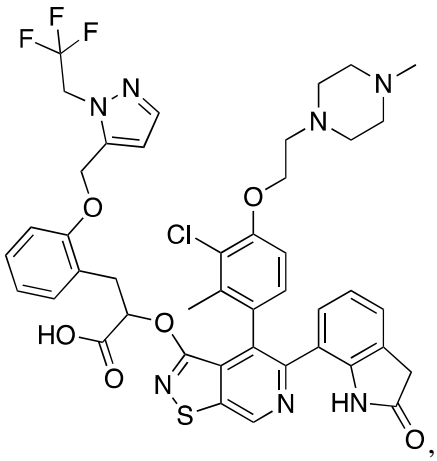
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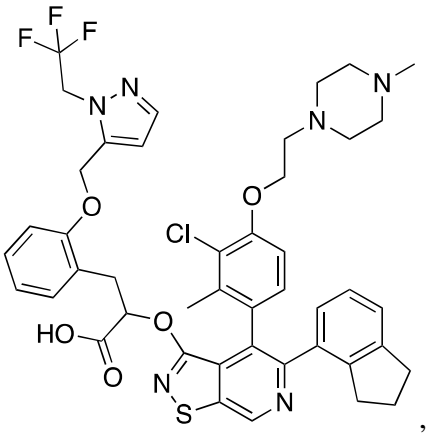
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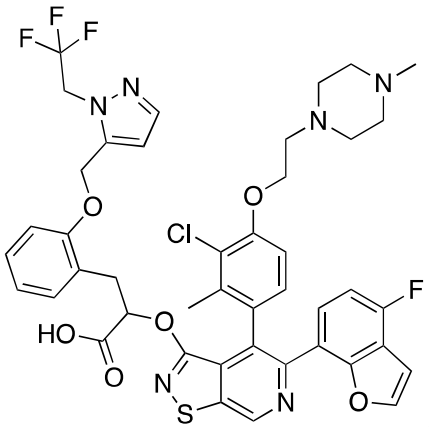
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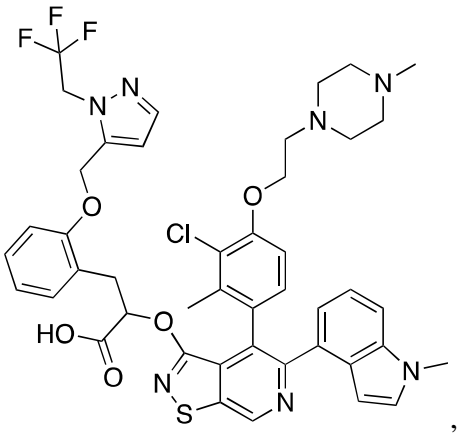
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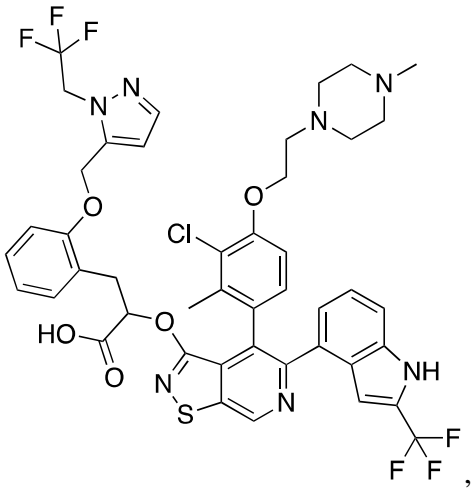
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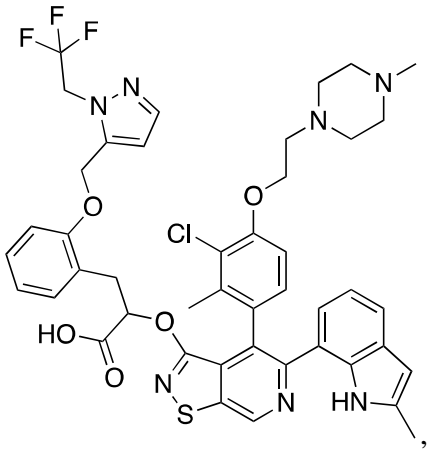
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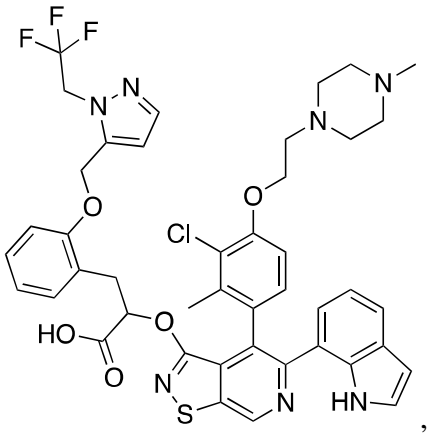
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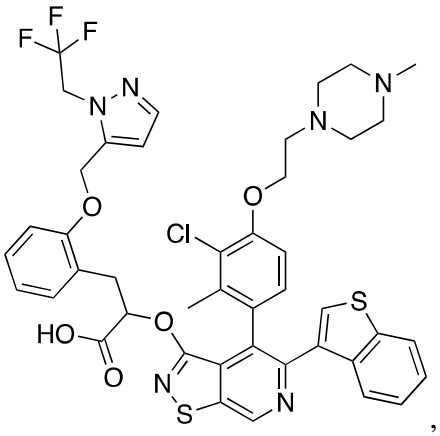
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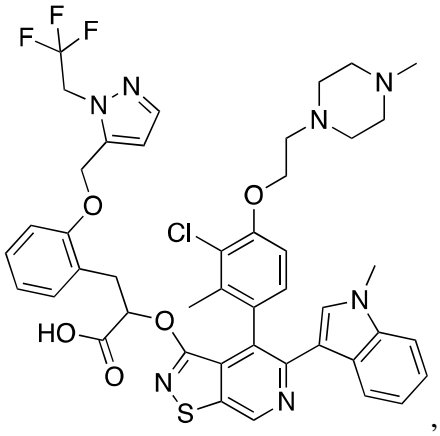
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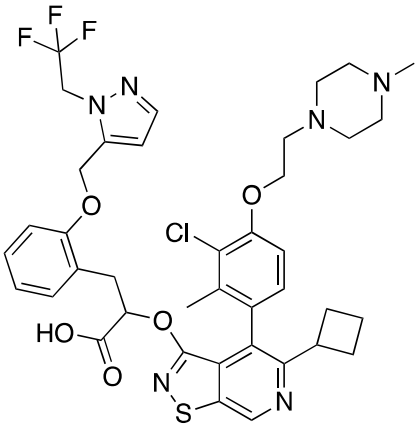
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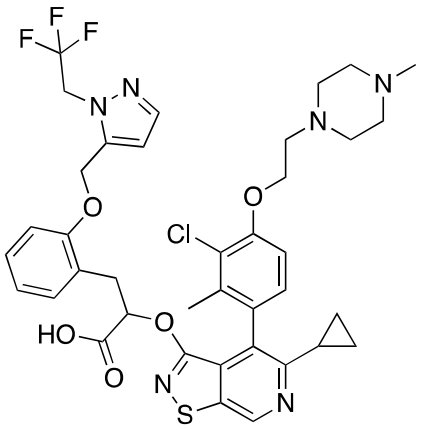
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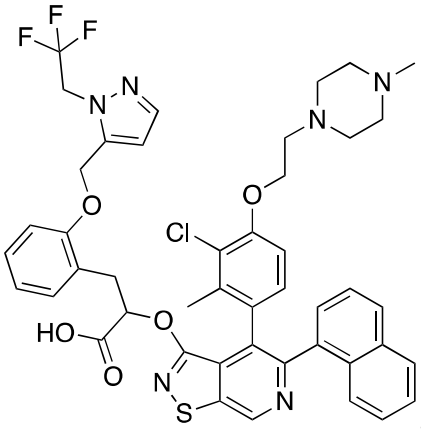
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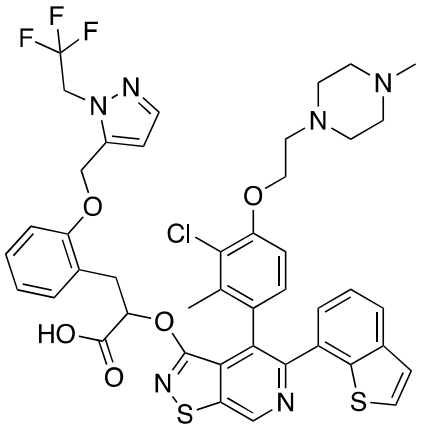
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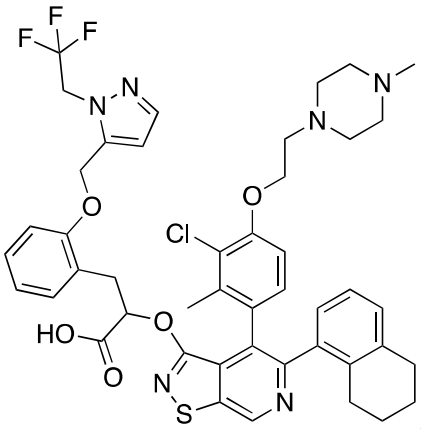
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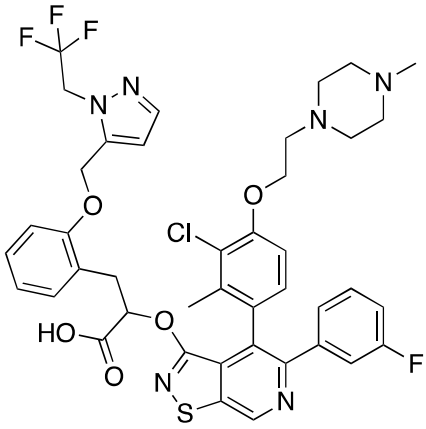
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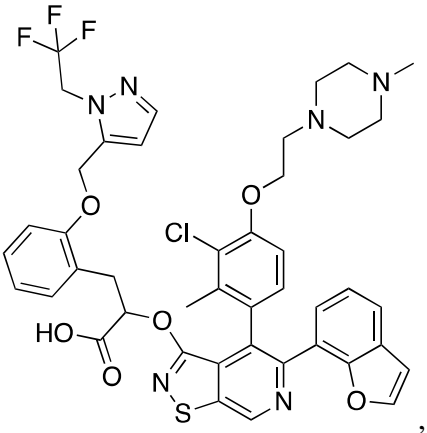
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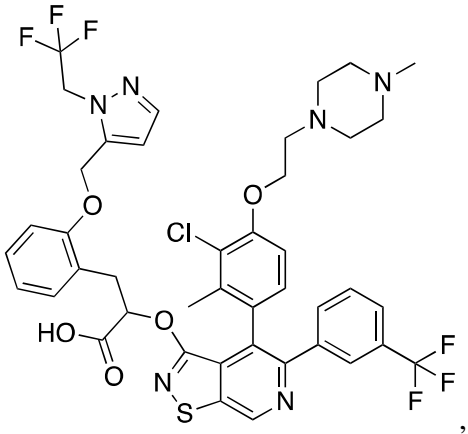
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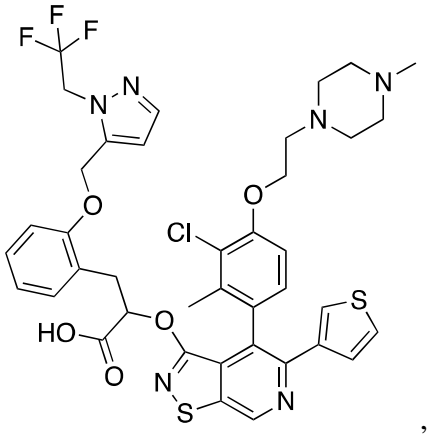
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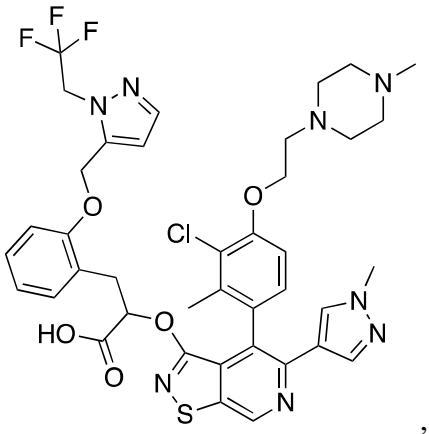
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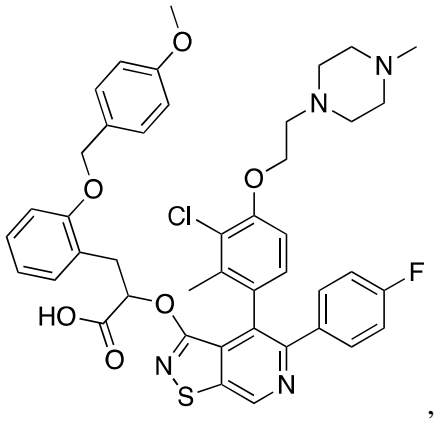
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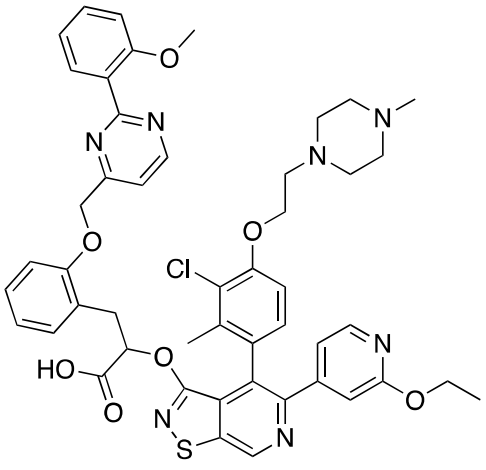
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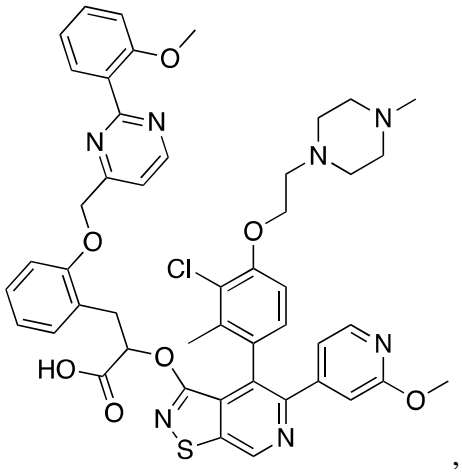
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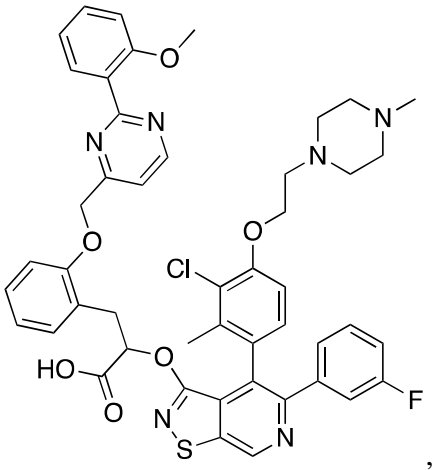
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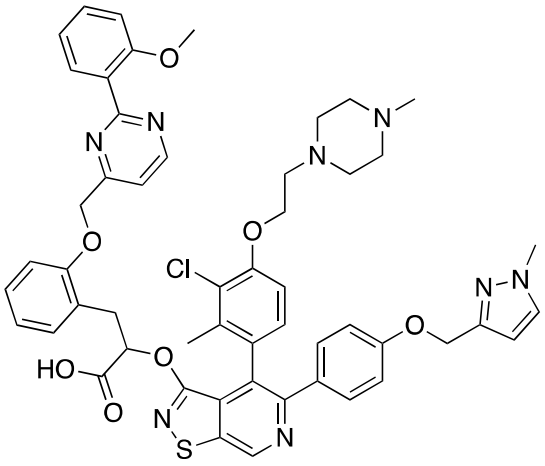
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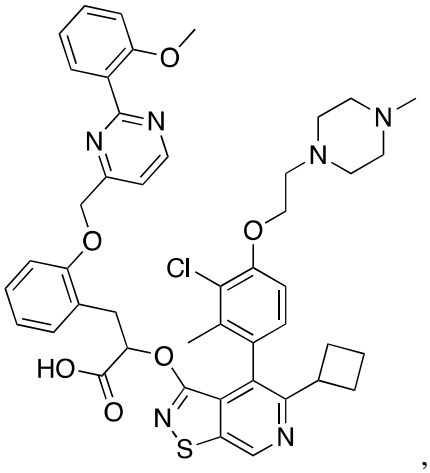
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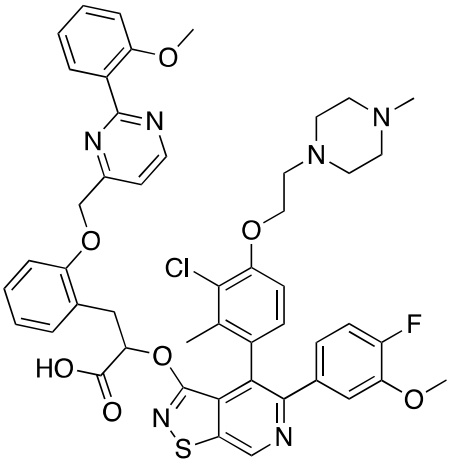
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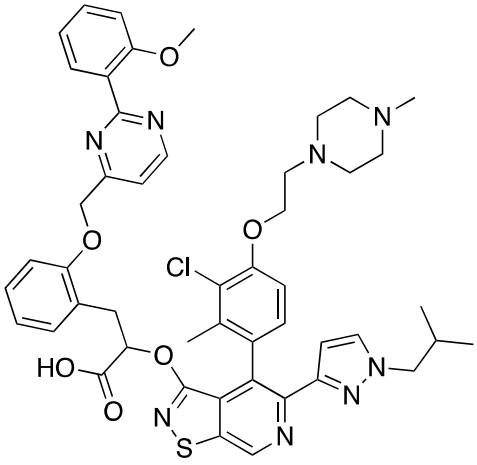
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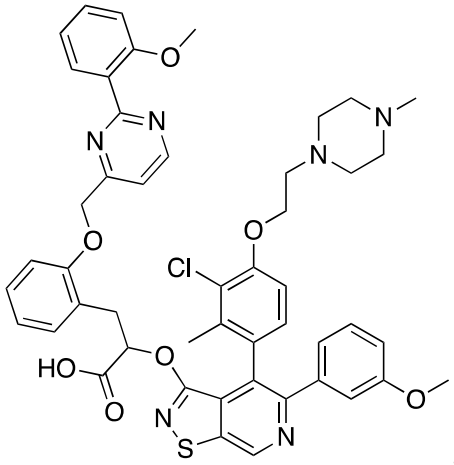
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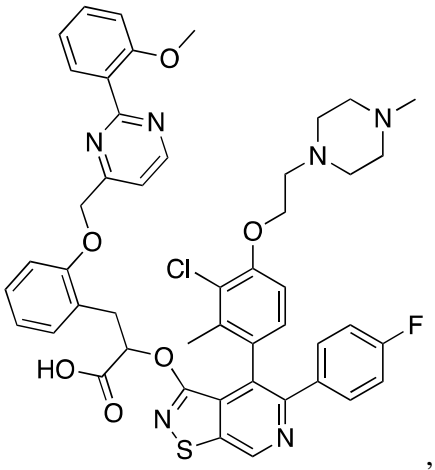
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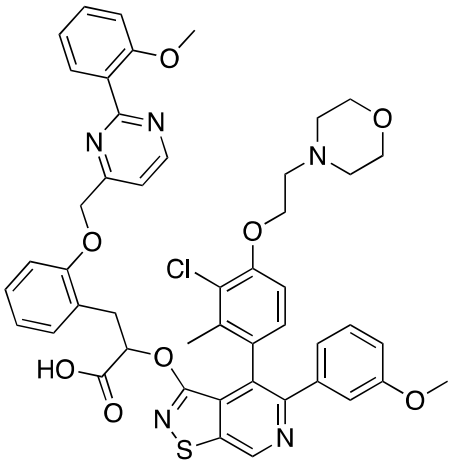
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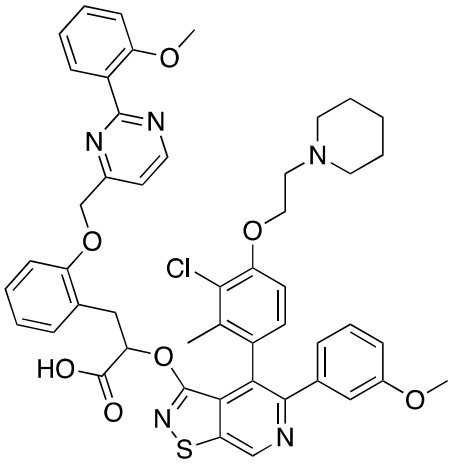
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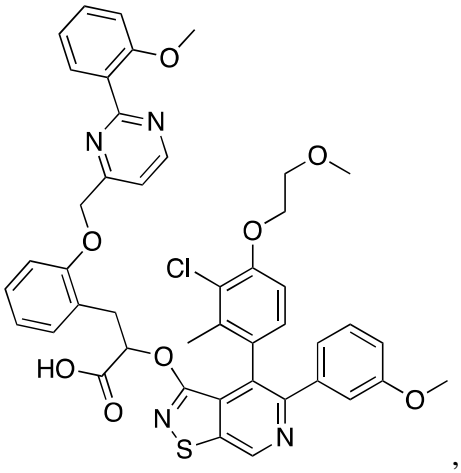
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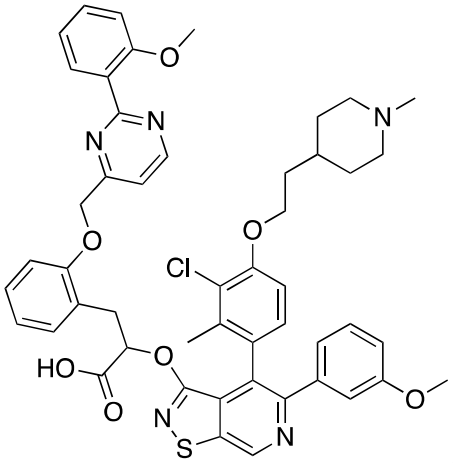
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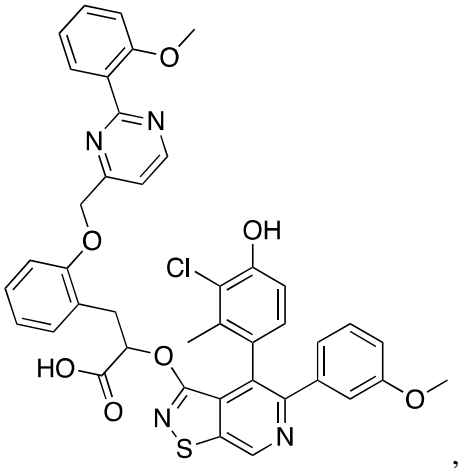
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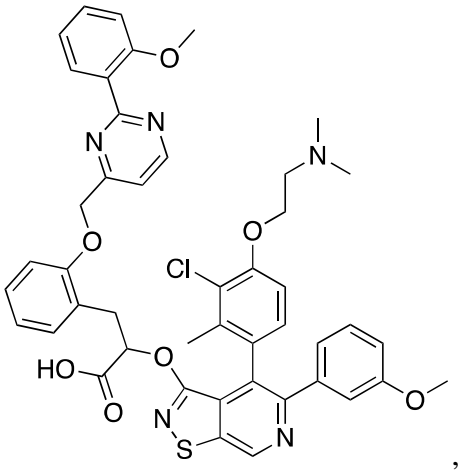
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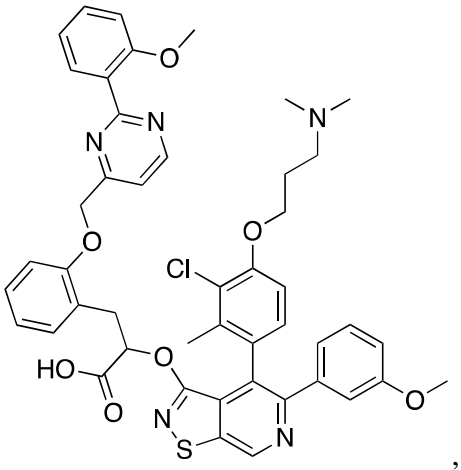
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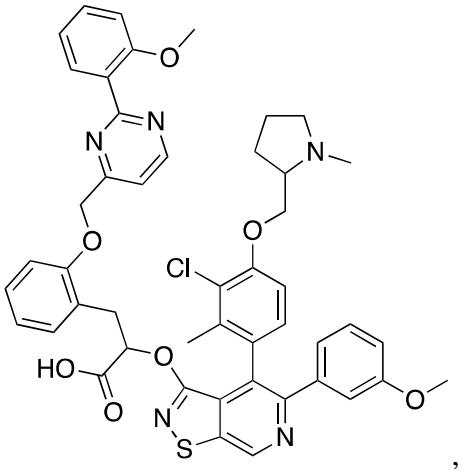
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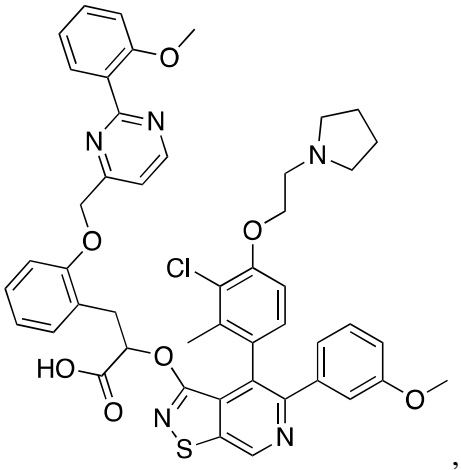
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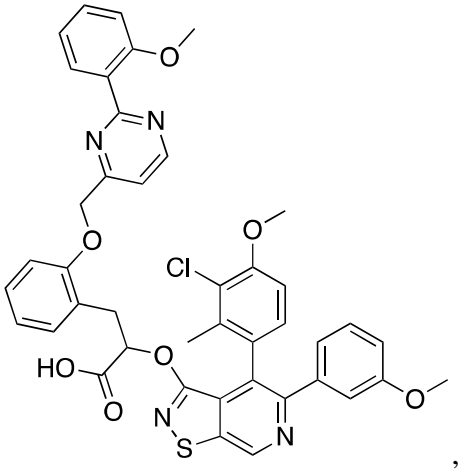
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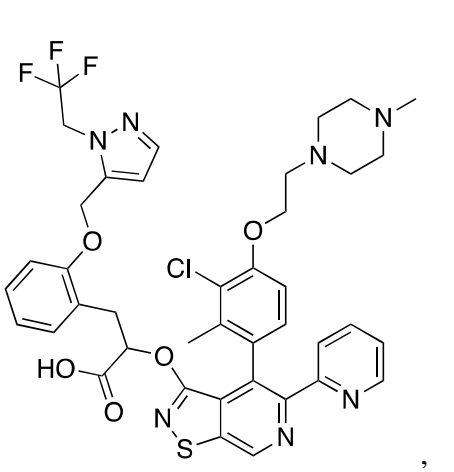
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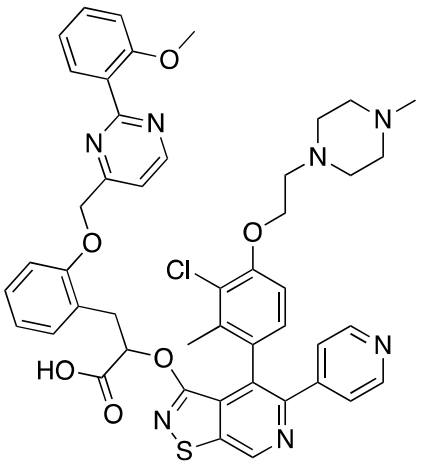
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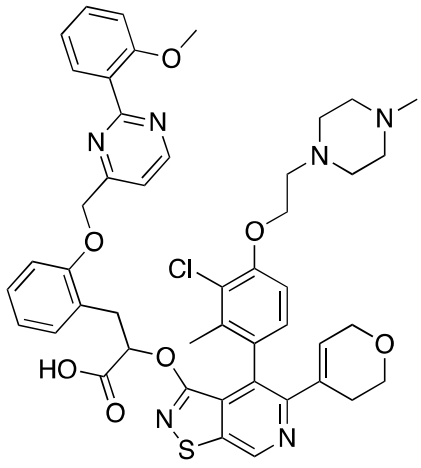
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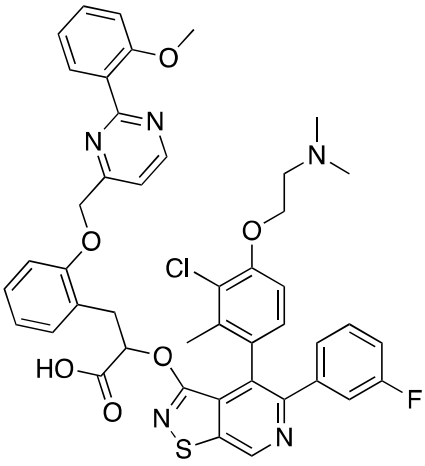
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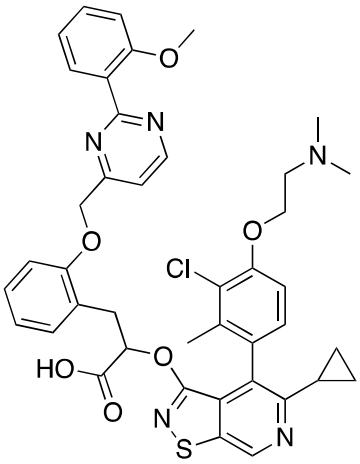
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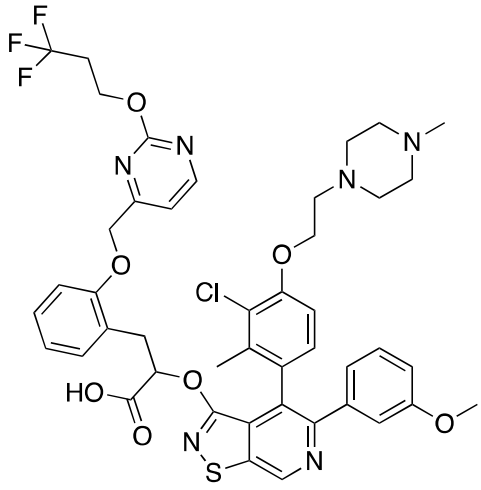
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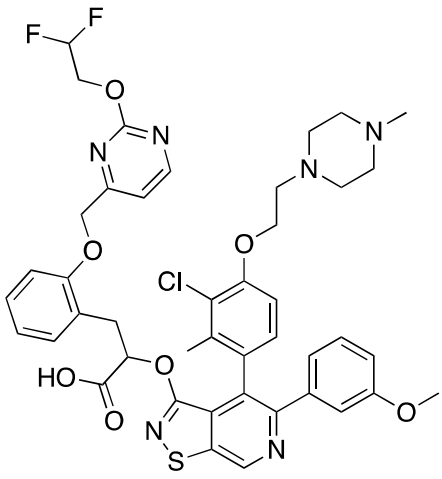
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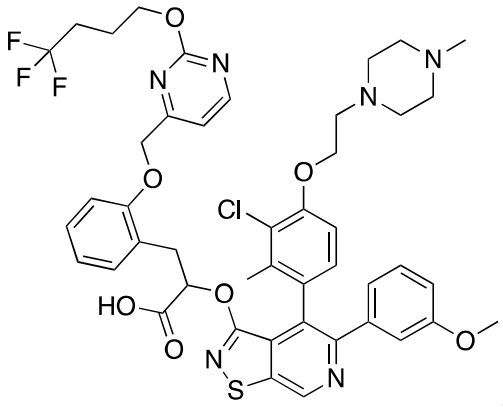
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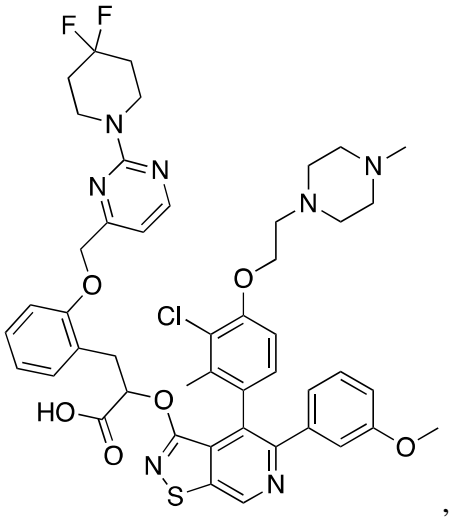
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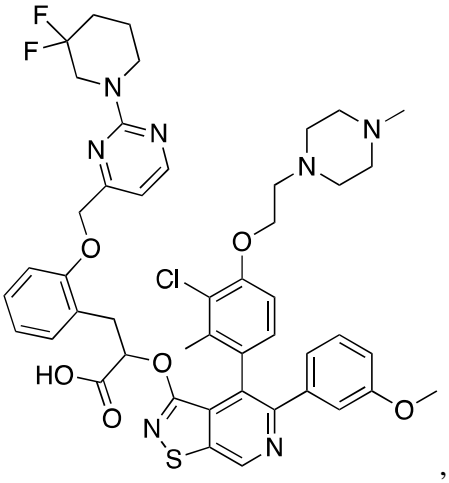
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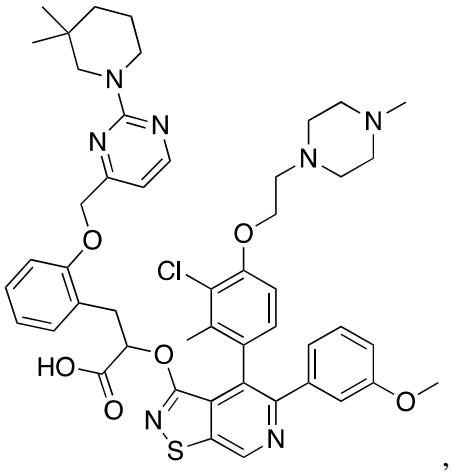
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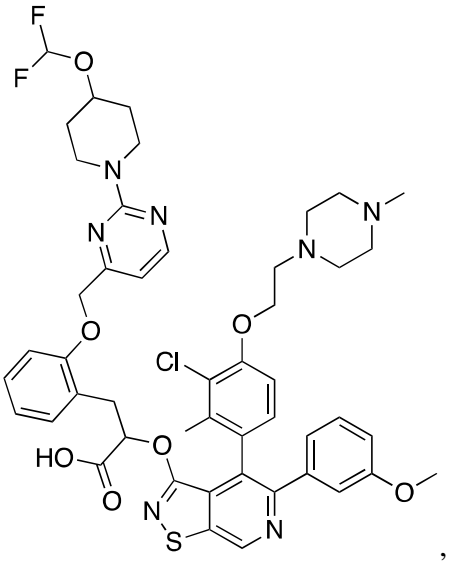
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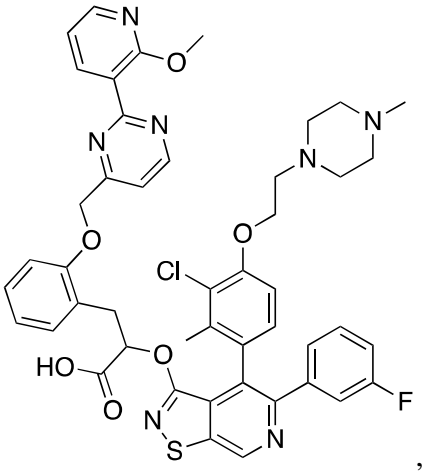
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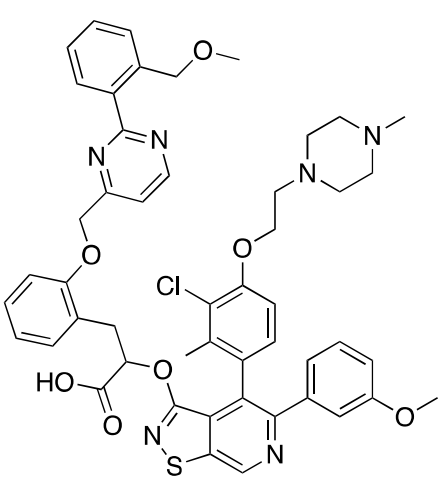
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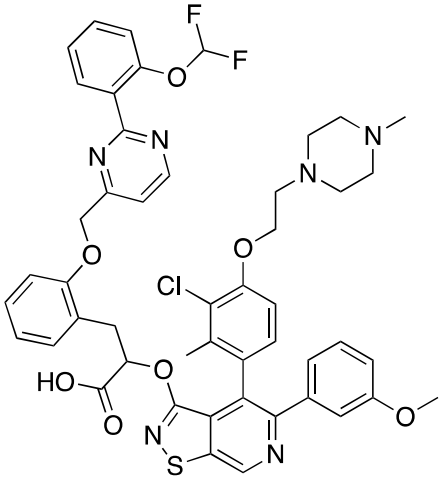
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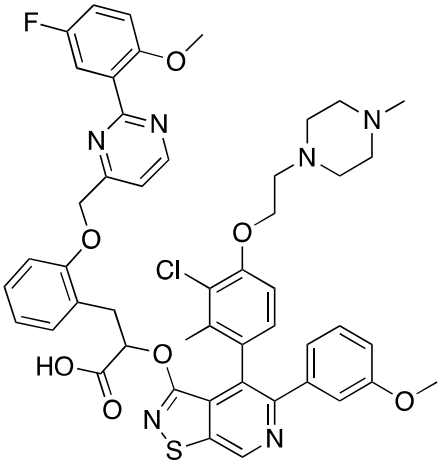
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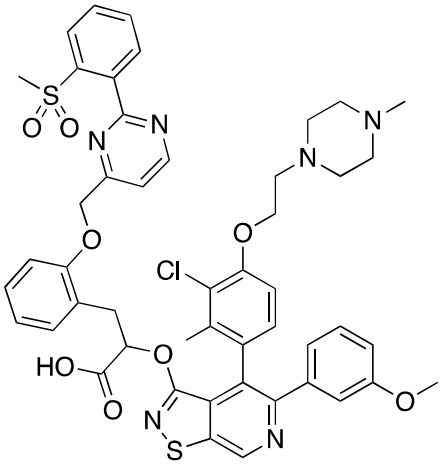
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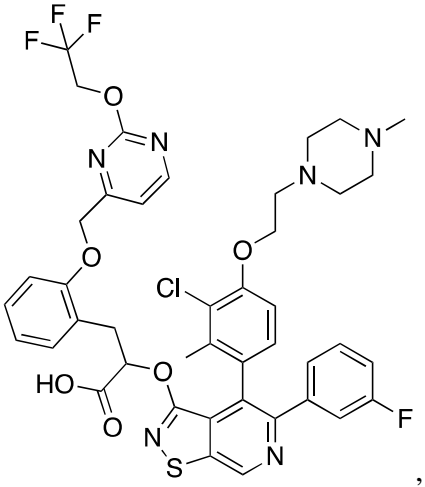
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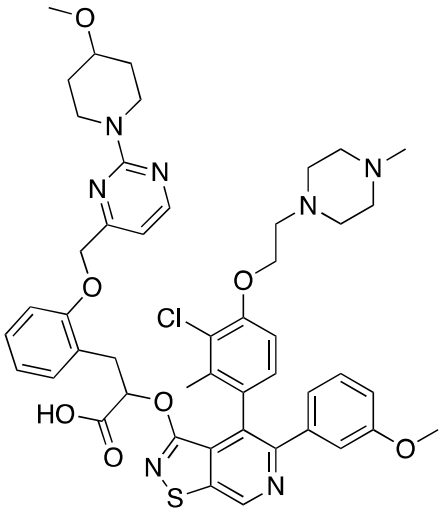
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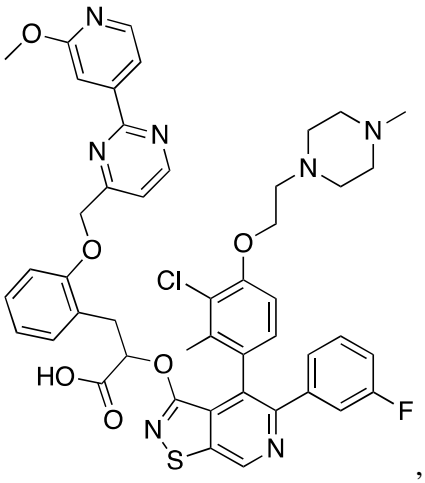
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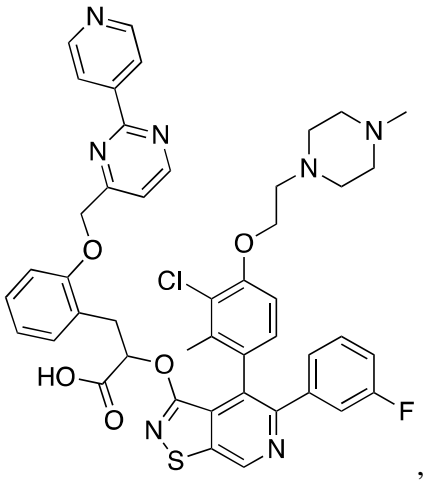
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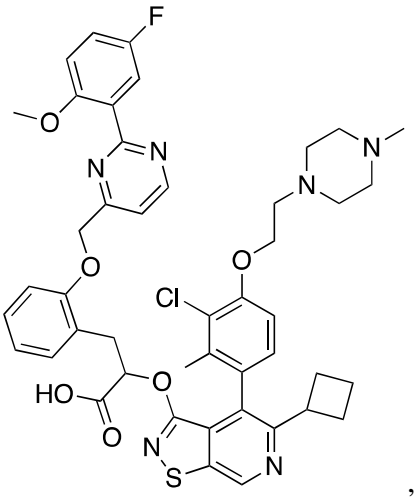
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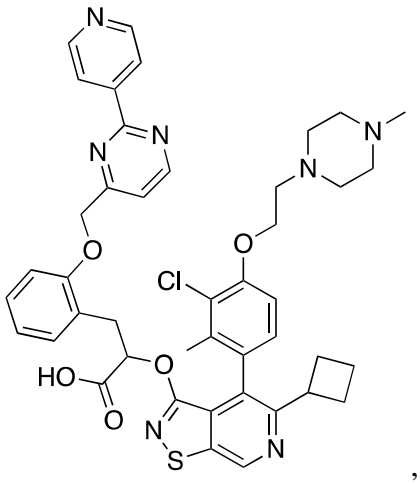
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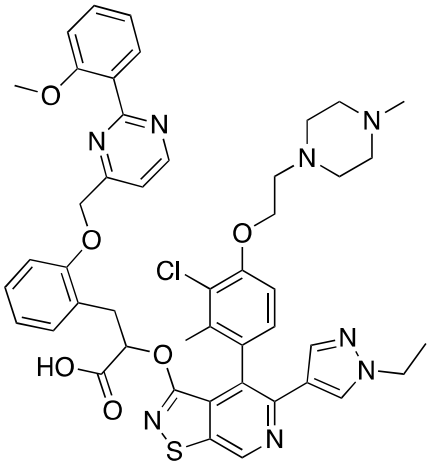
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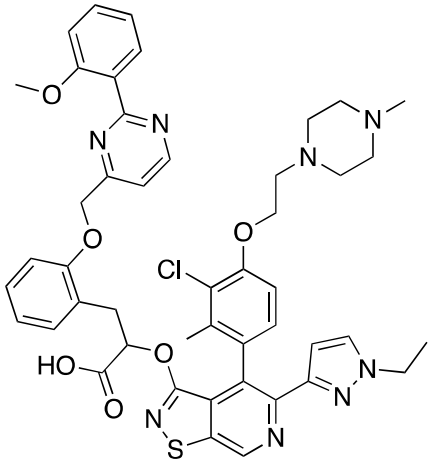
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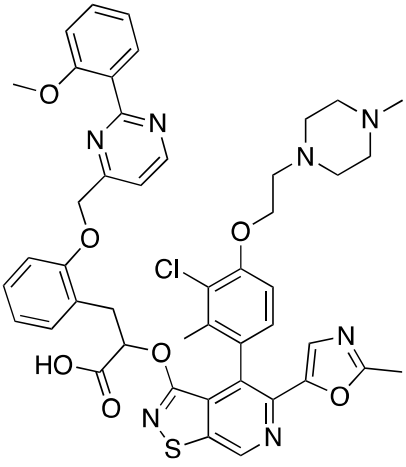
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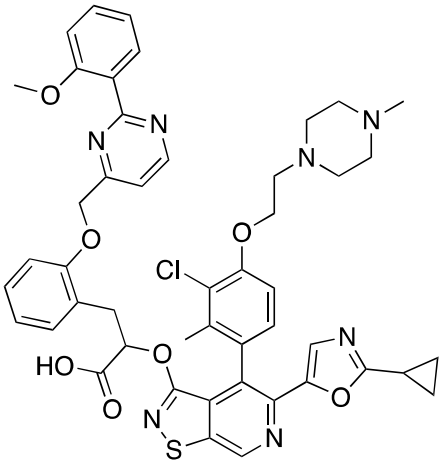
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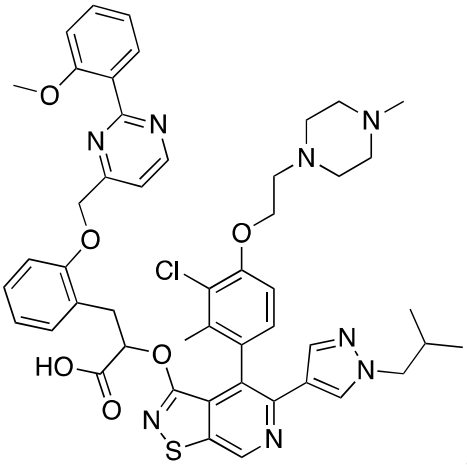
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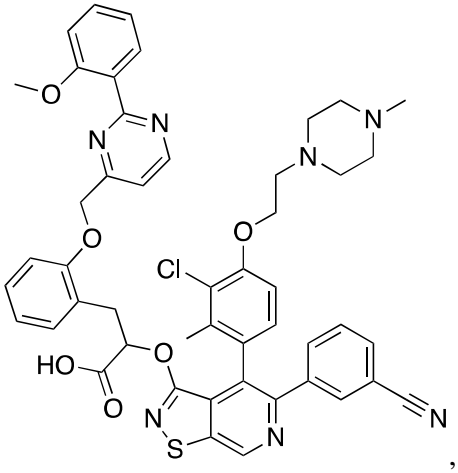
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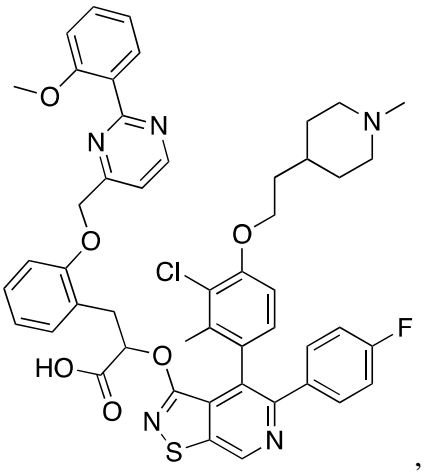
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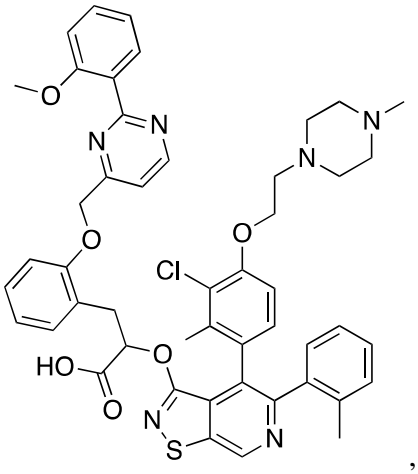
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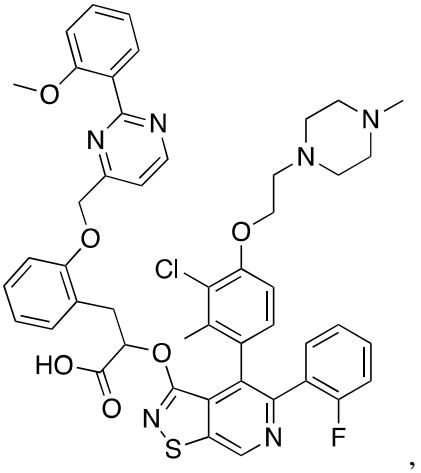
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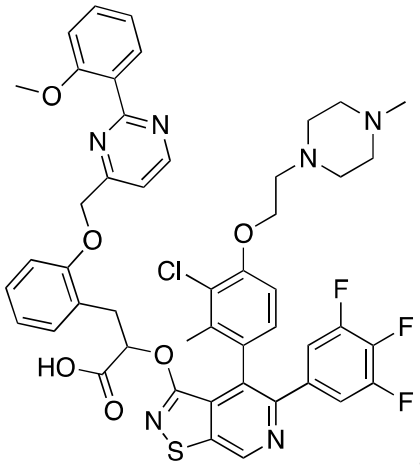
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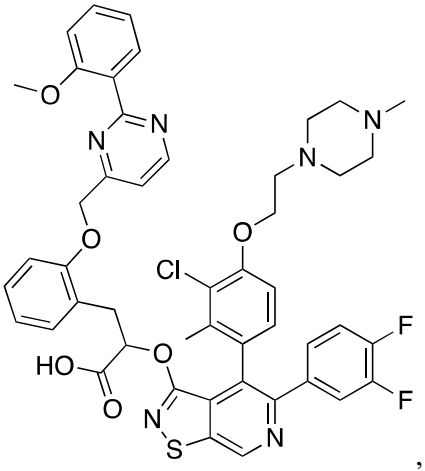
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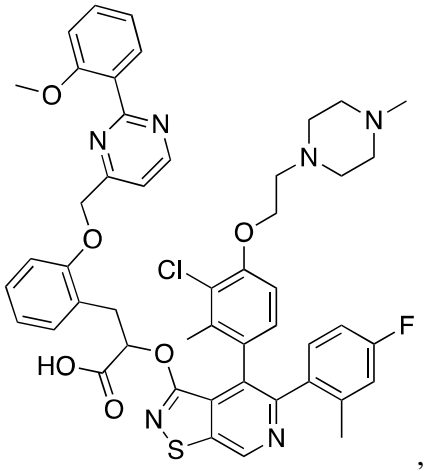
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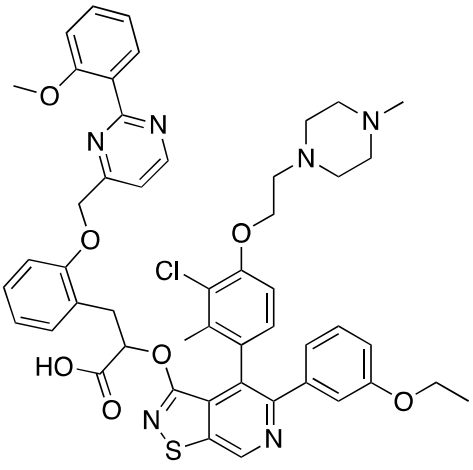
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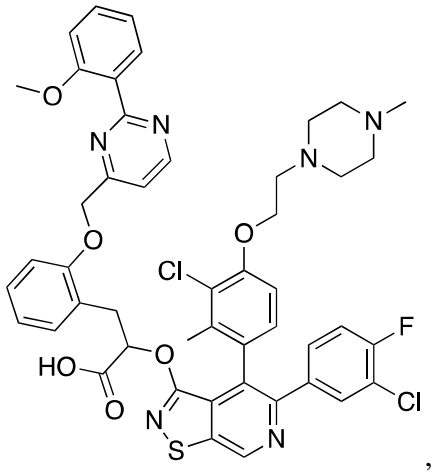
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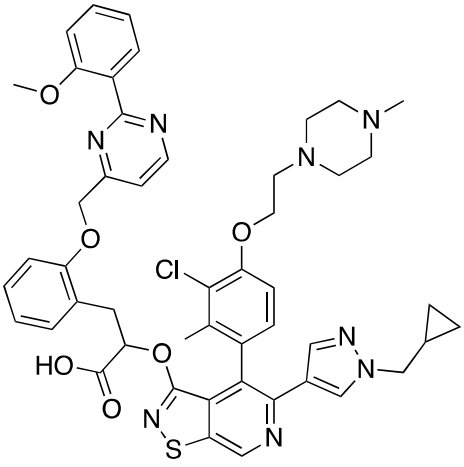
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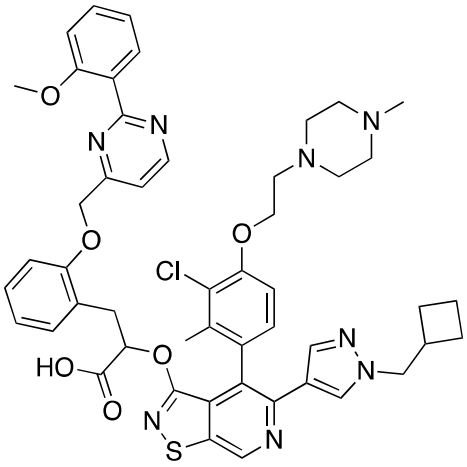
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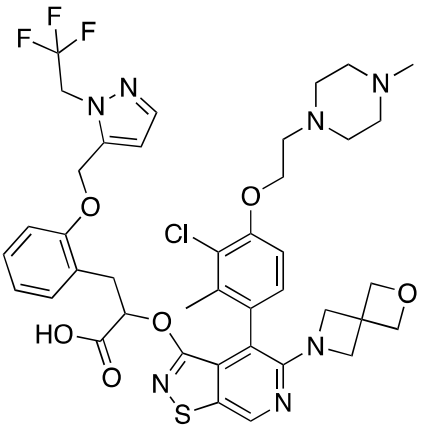
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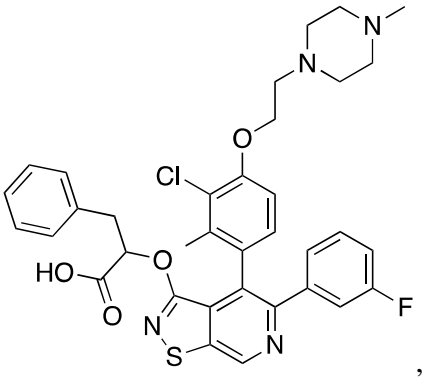
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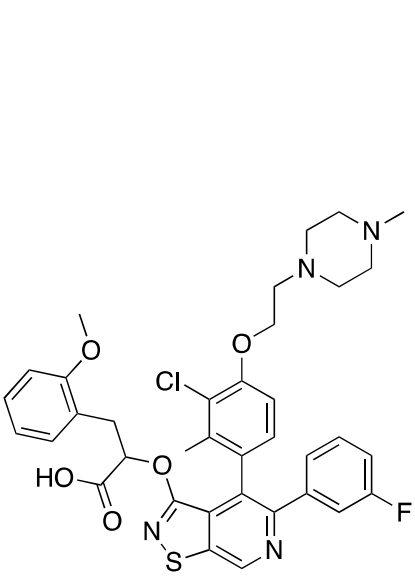
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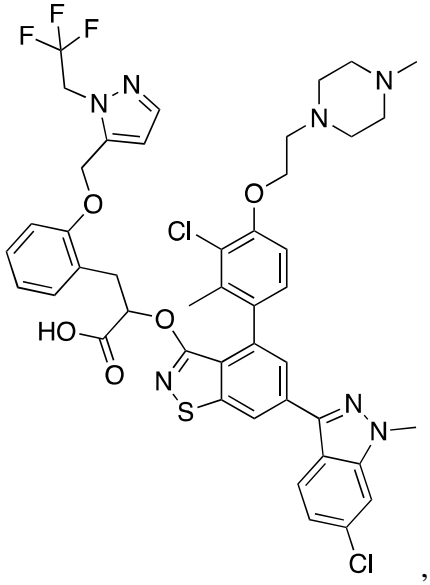
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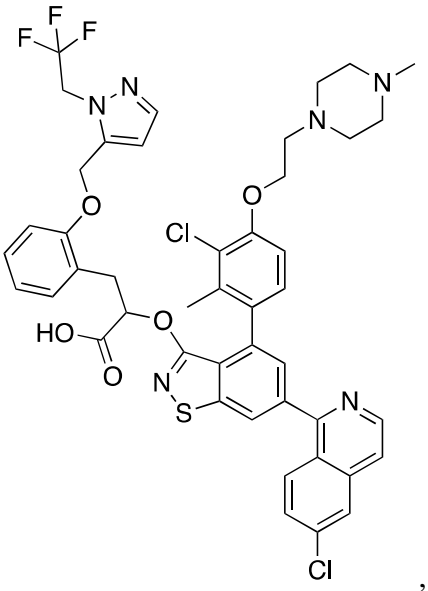
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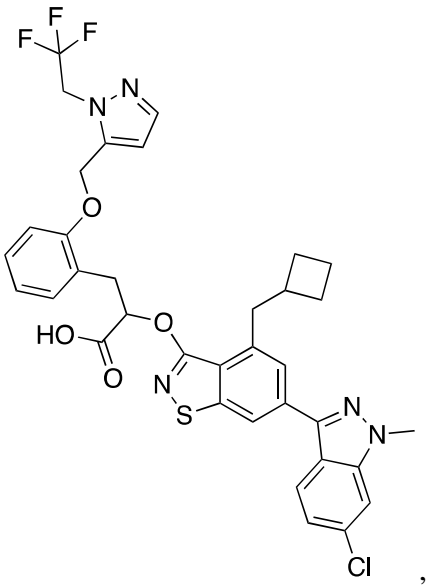
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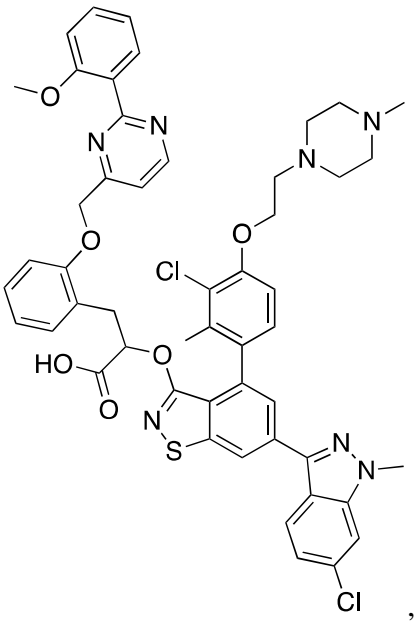
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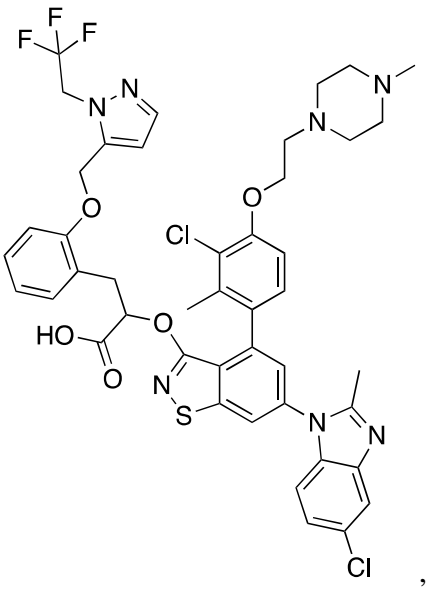
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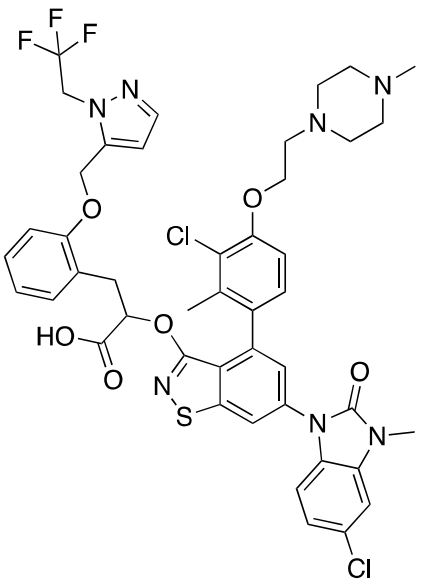
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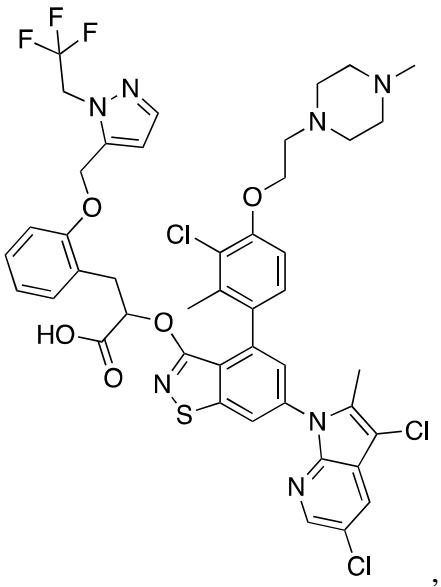
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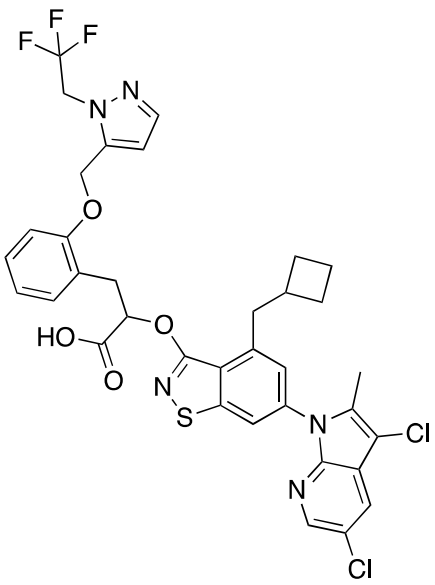
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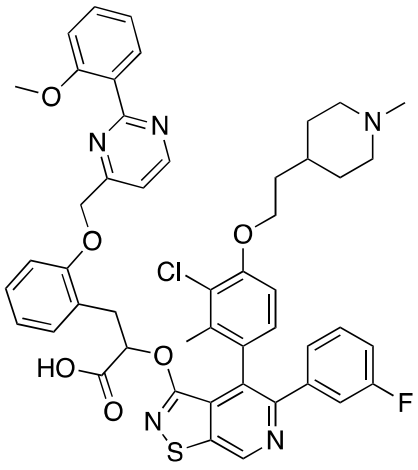
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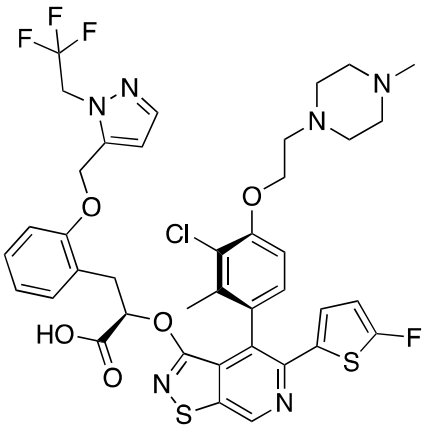
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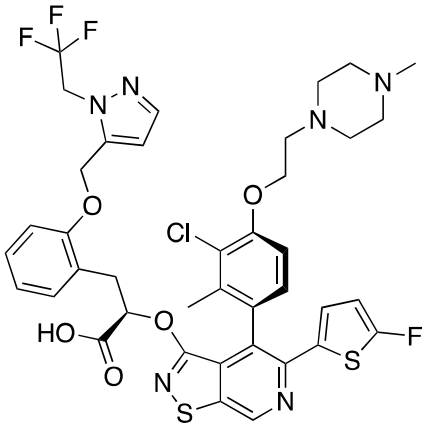
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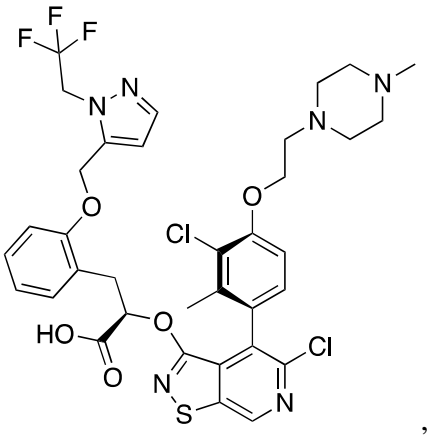
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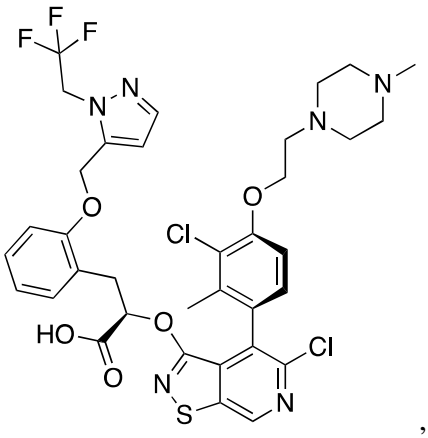
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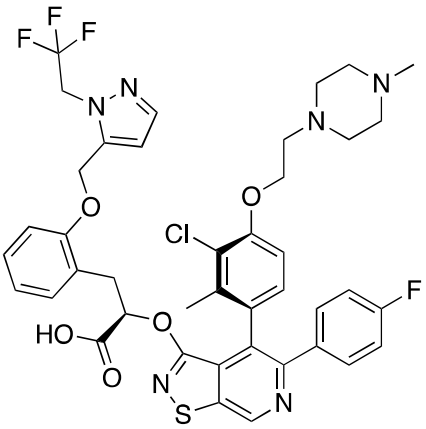
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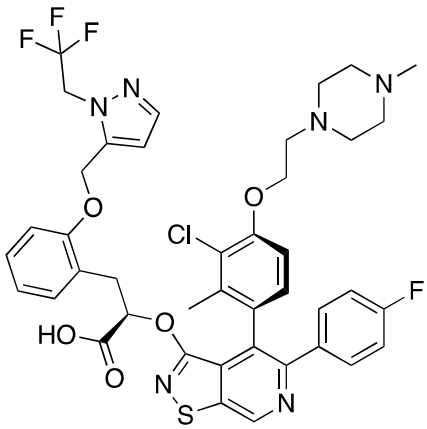
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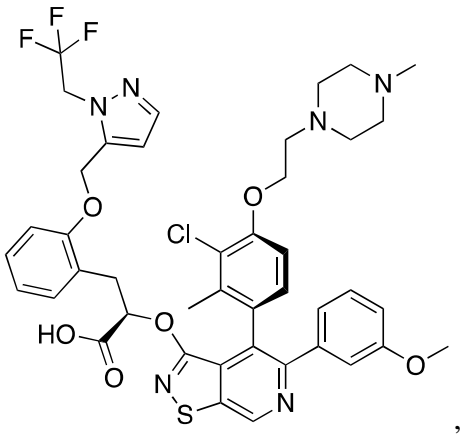
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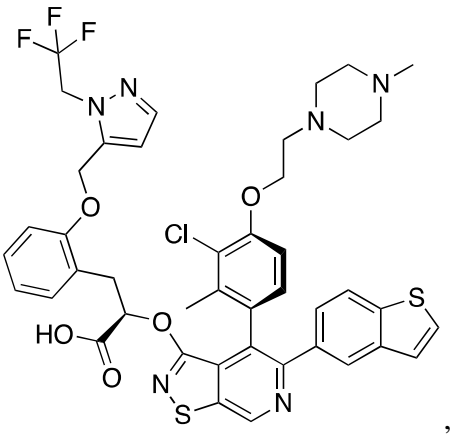
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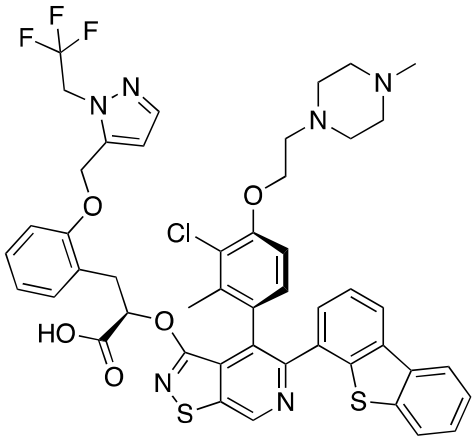
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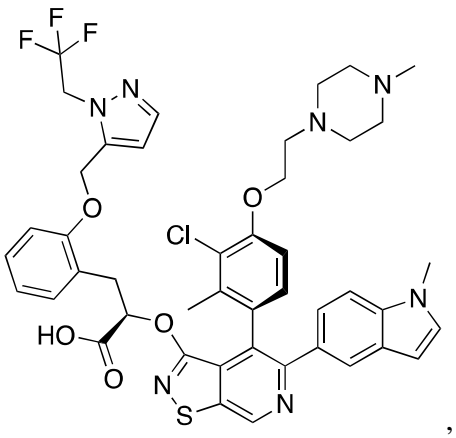
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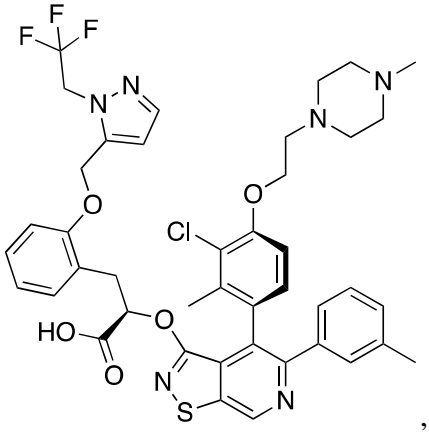
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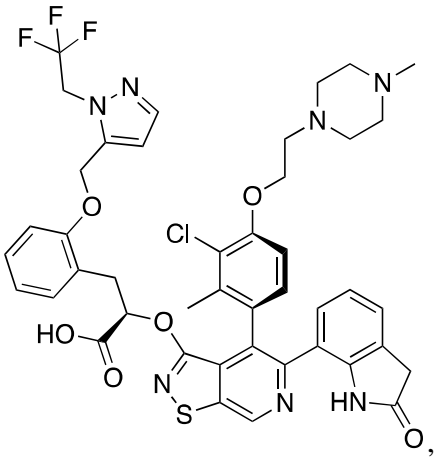
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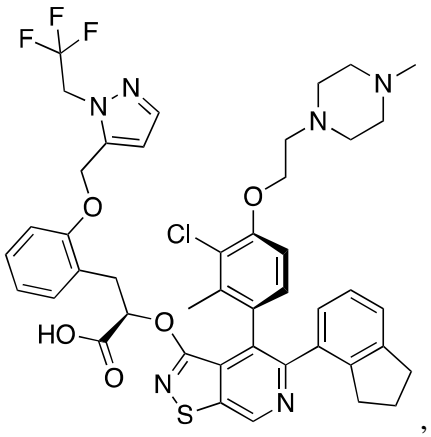
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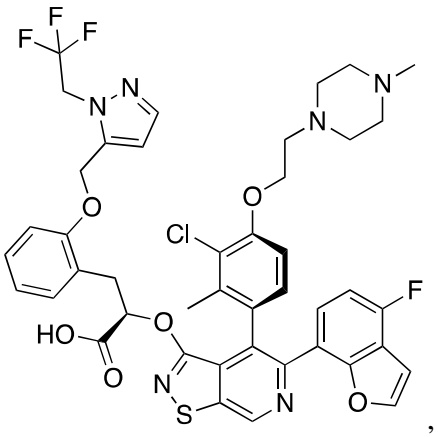
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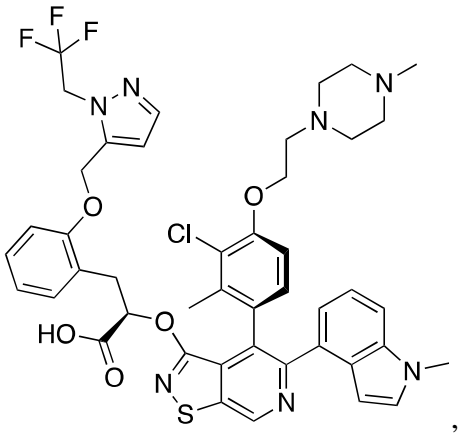
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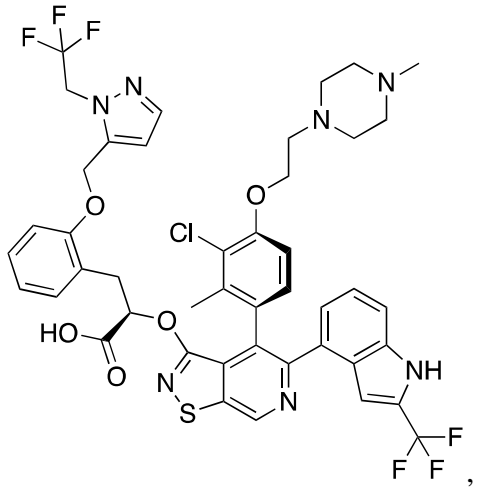
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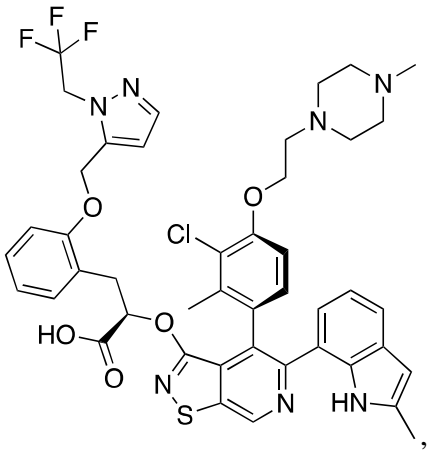
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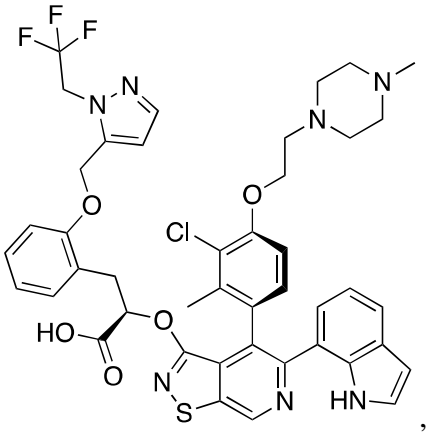
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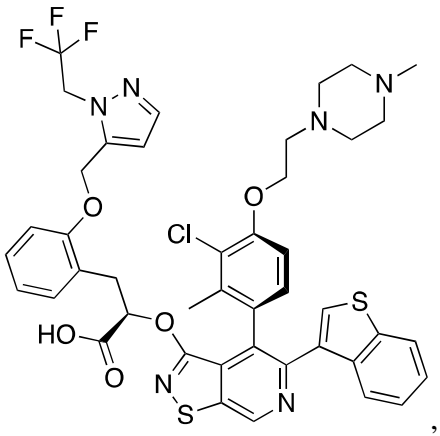
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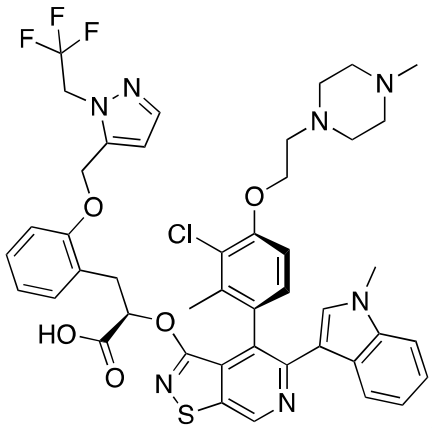
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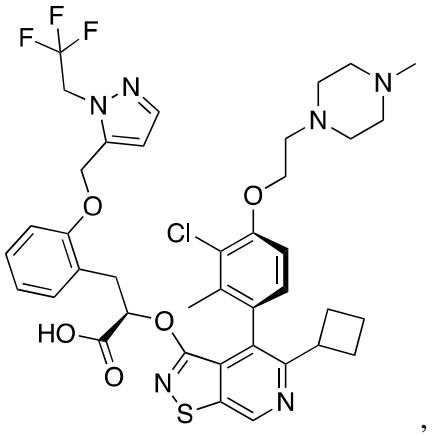
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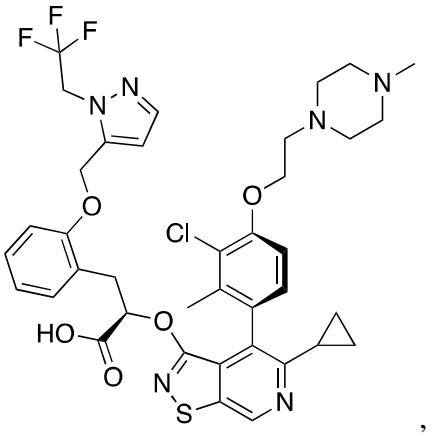
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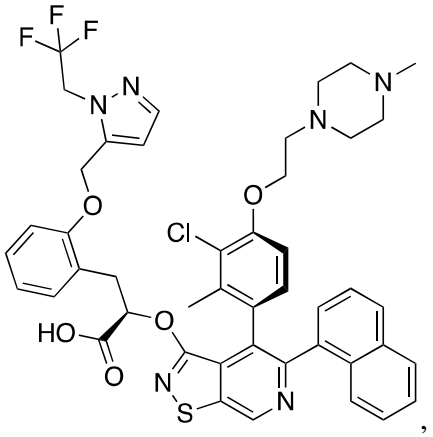
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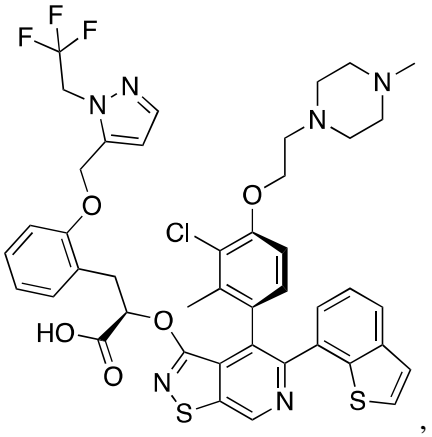
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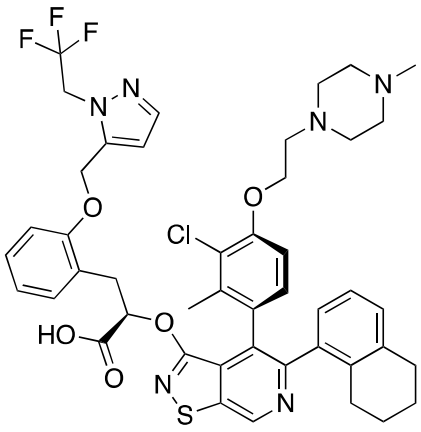
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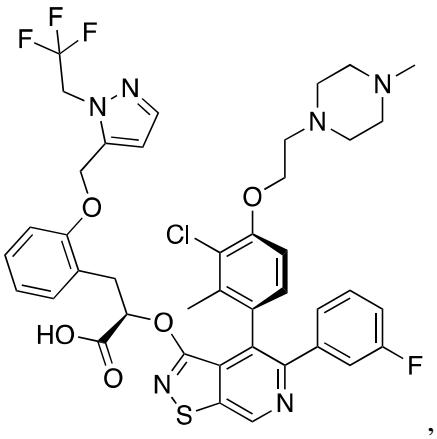
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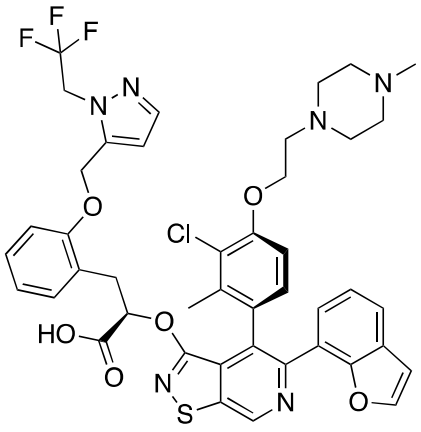
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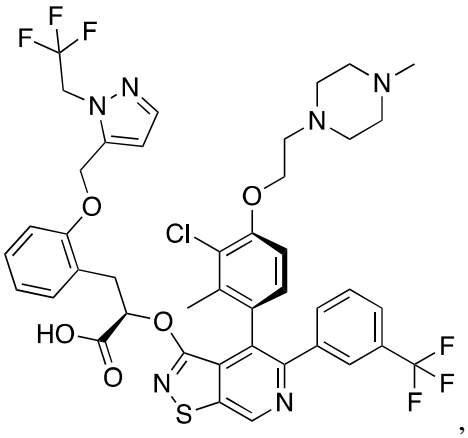
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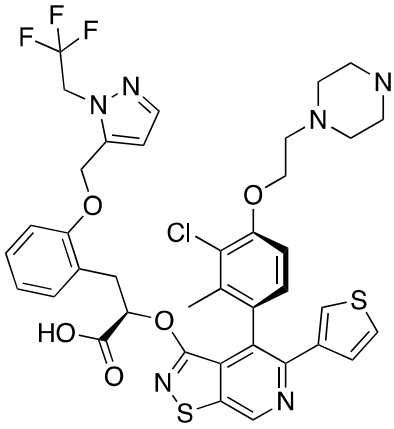
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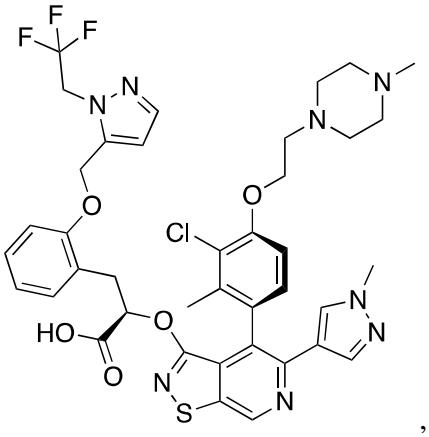
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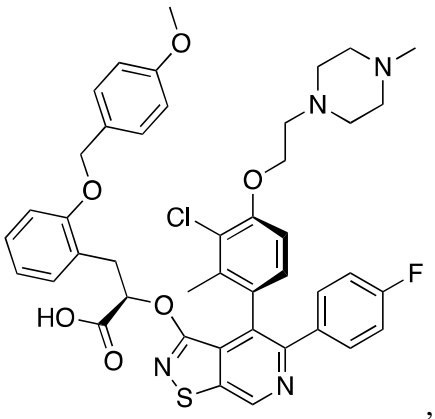
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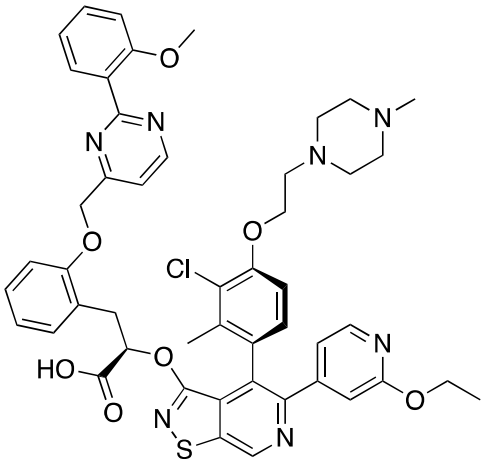
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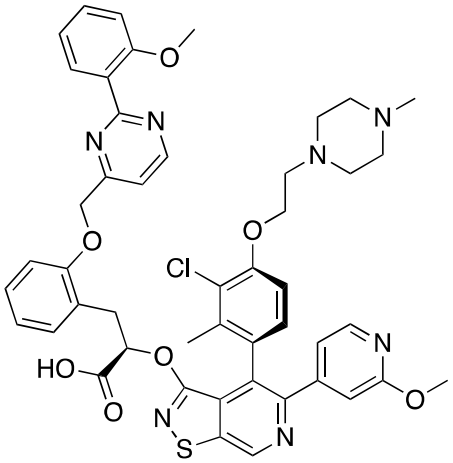
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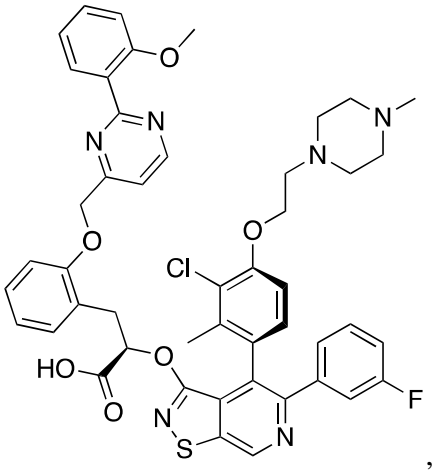
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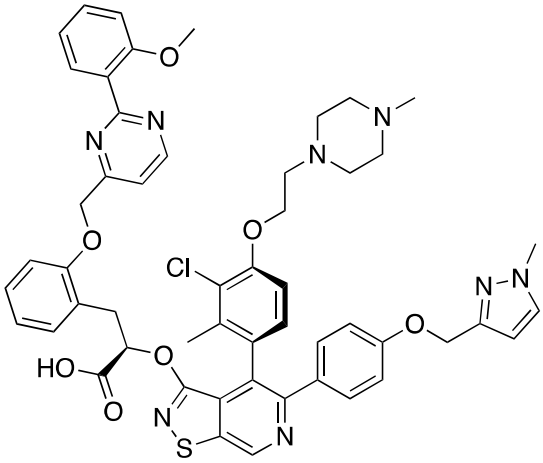
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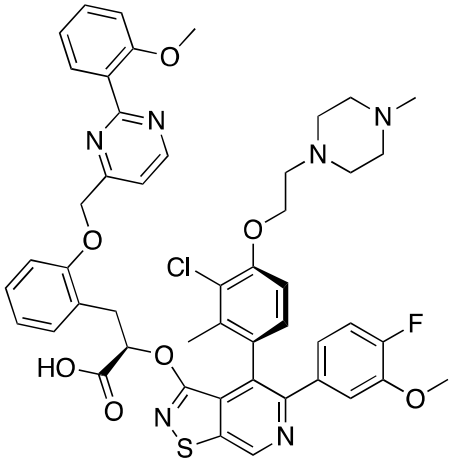
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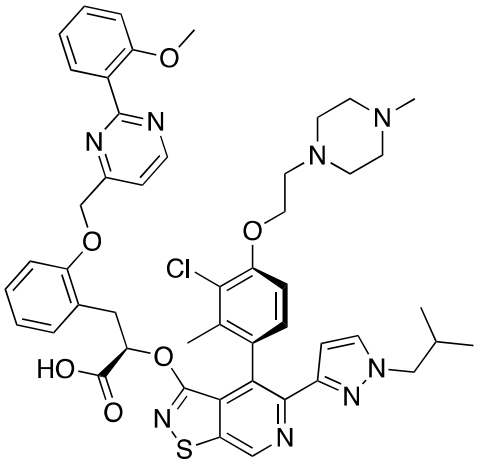
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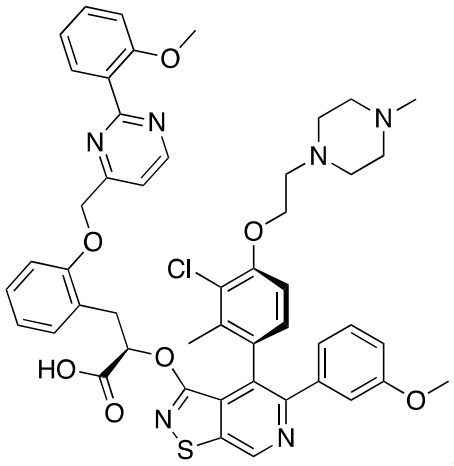
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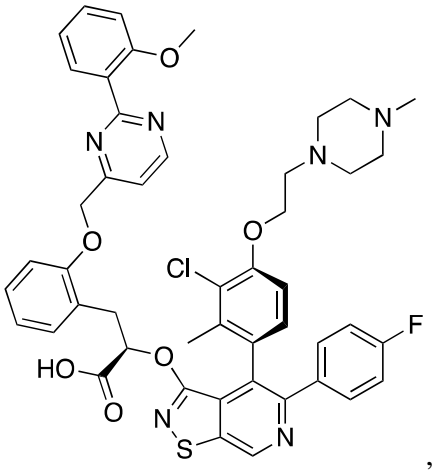
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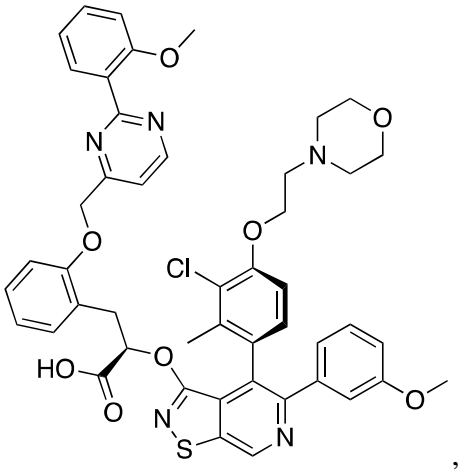
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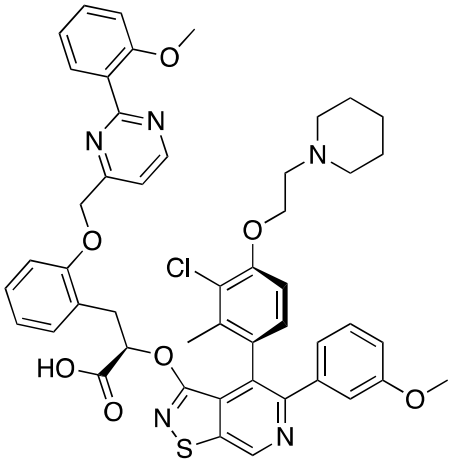
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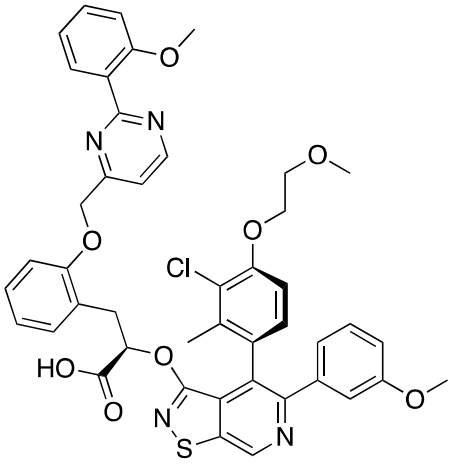
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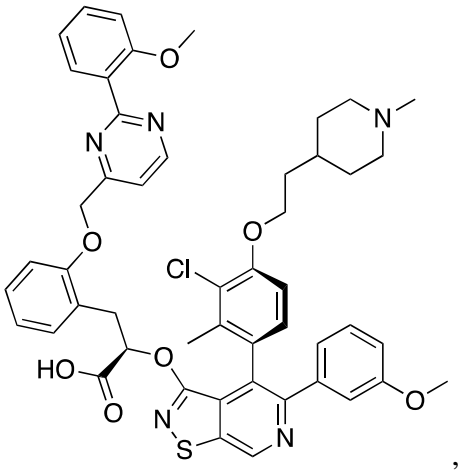
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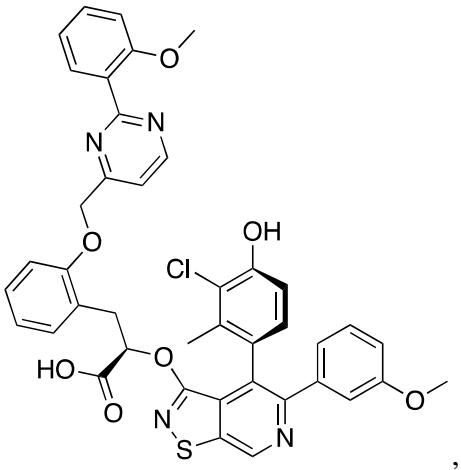
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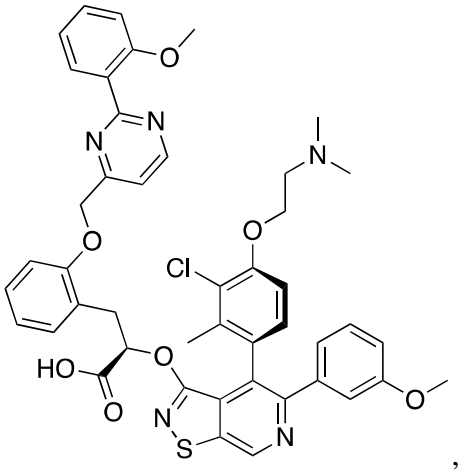
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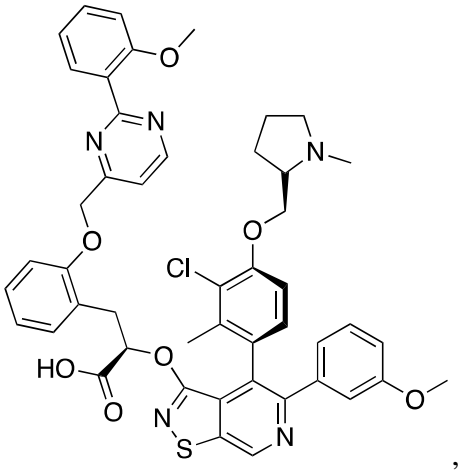
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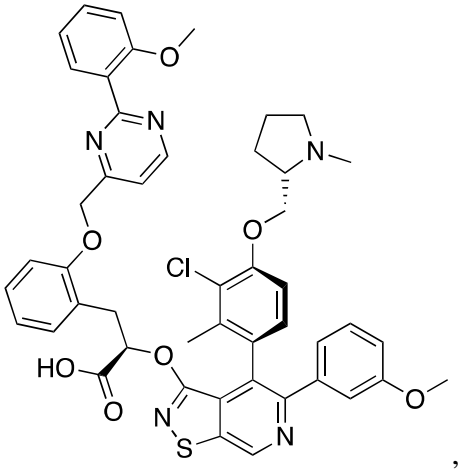
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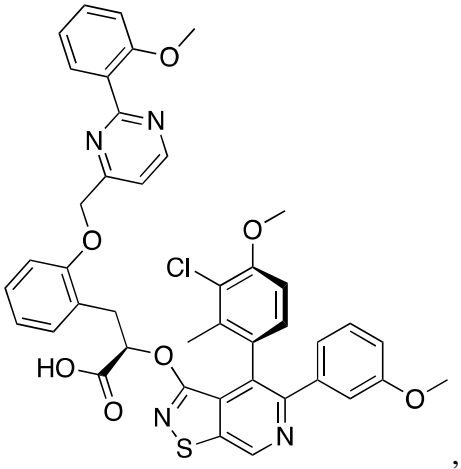
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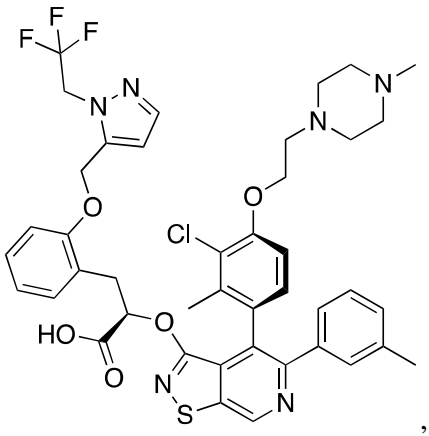
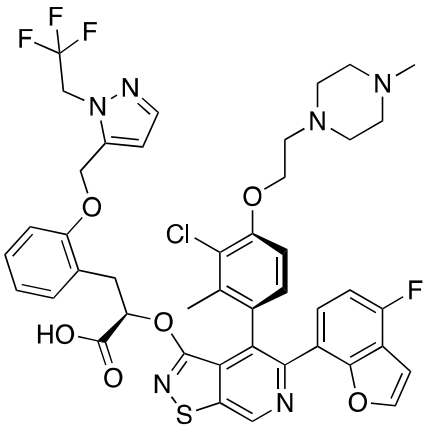
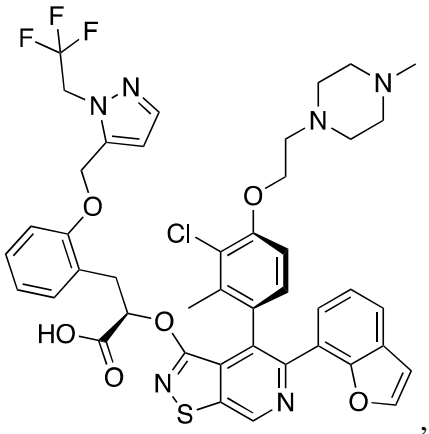

, 
, and 
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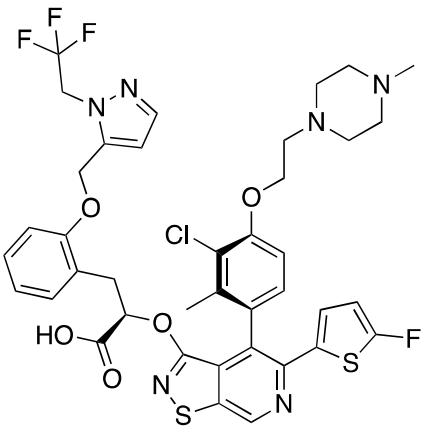
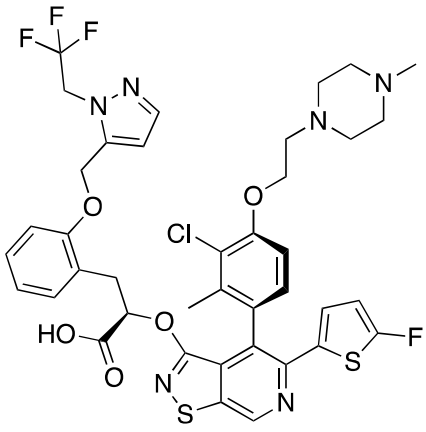

, 
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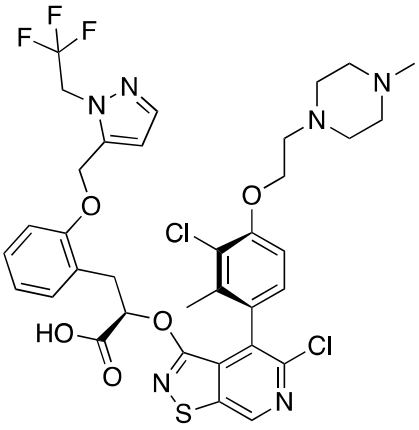
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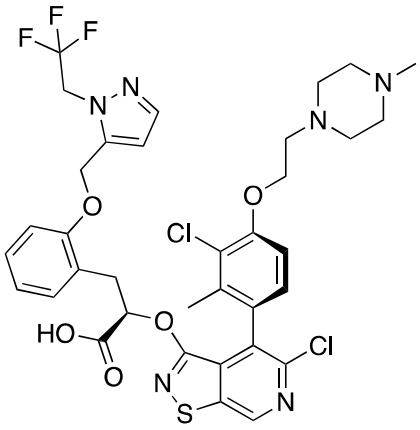
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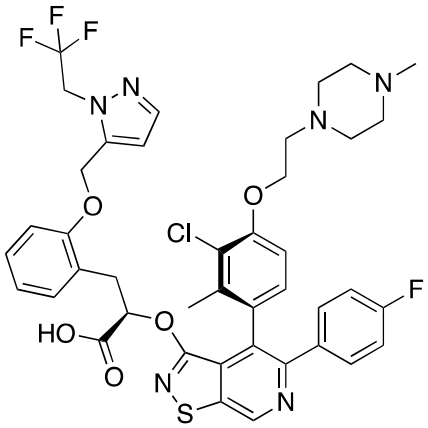
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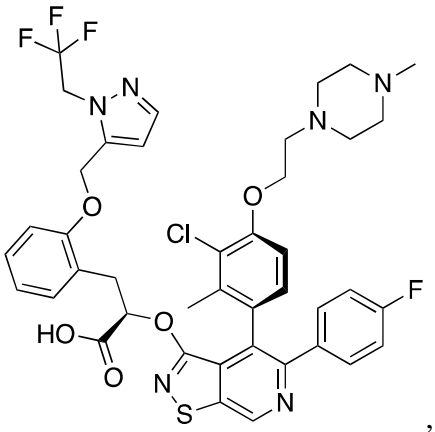
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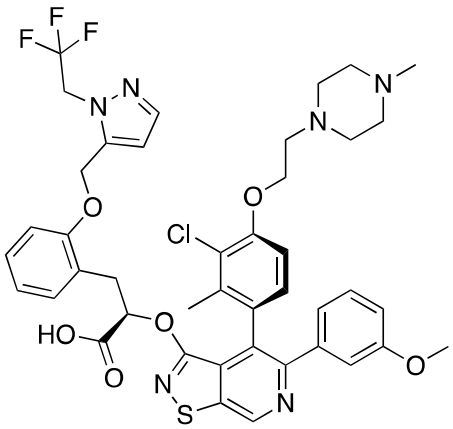
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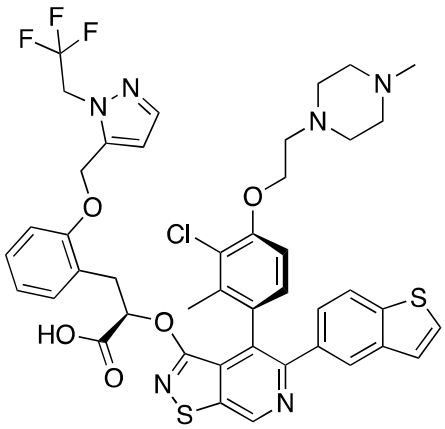
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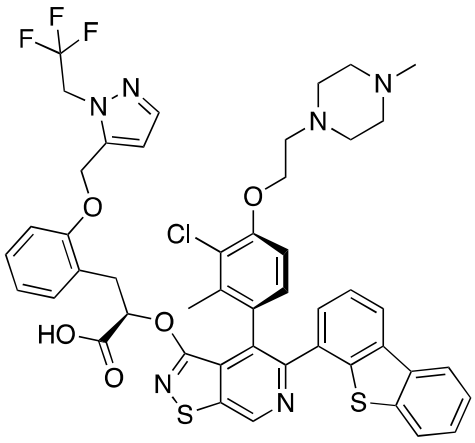
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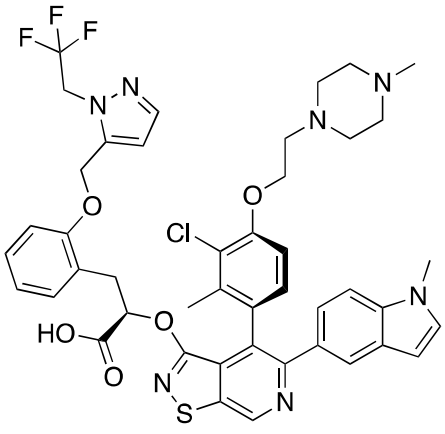
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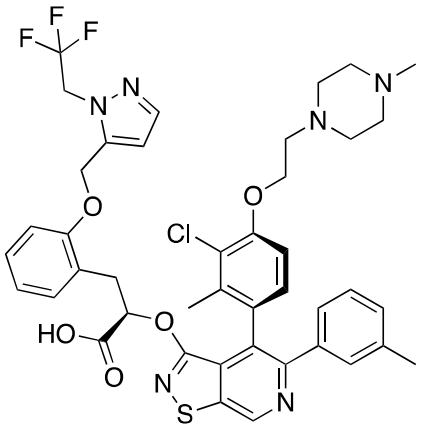
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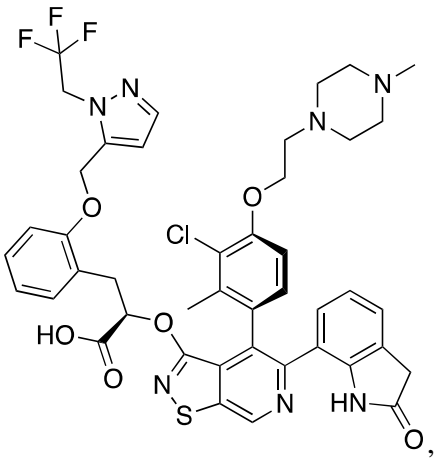
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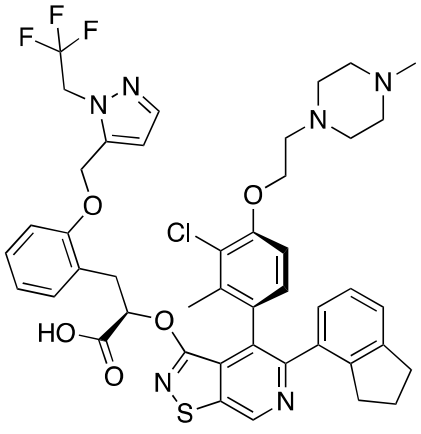
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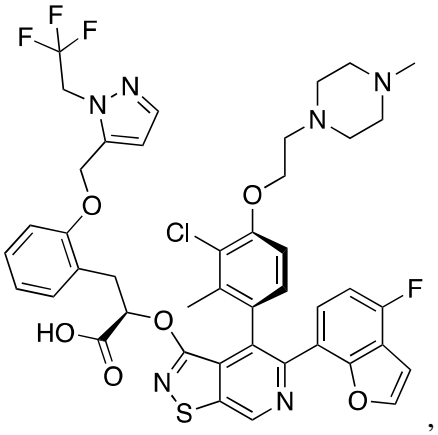
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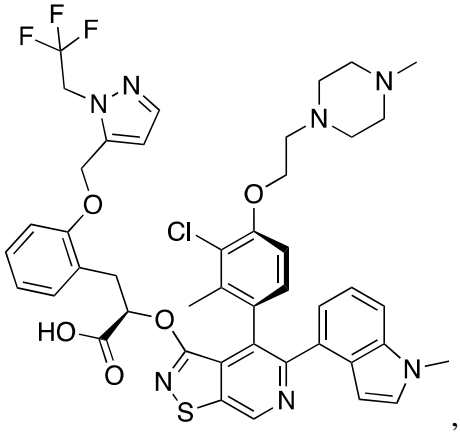
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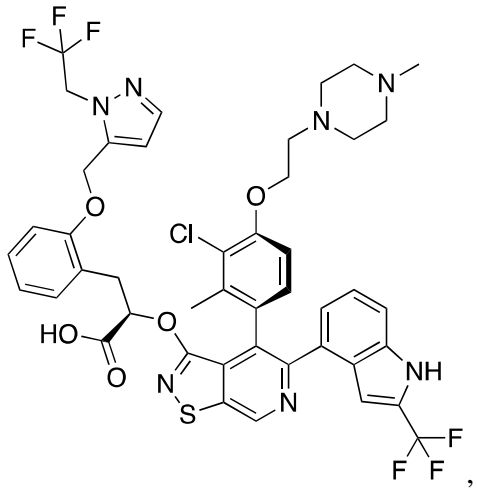
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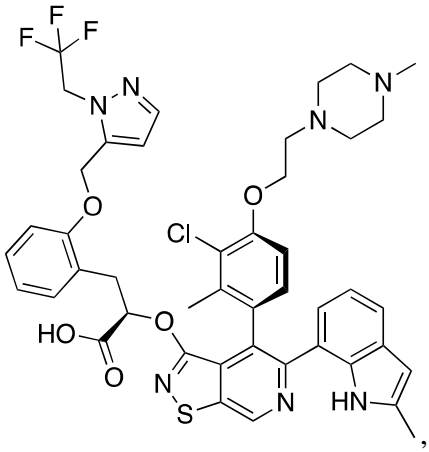
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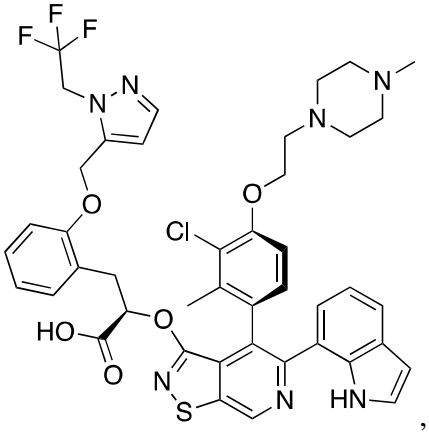
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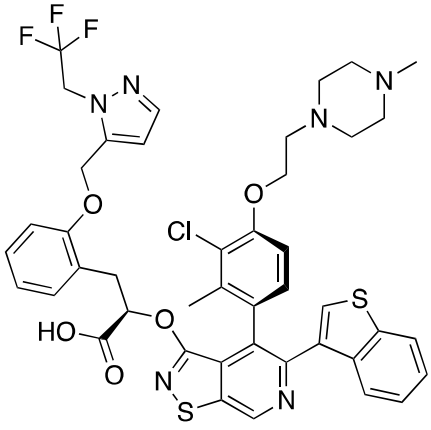
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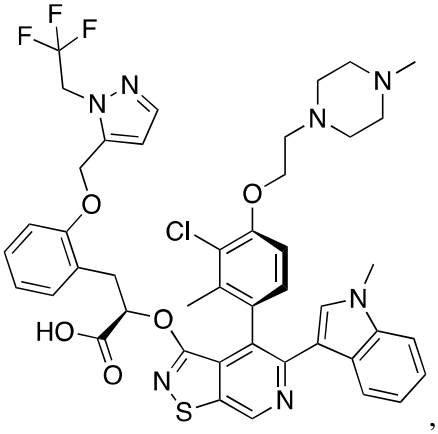
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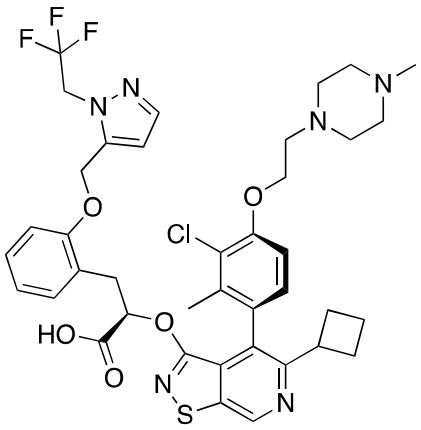
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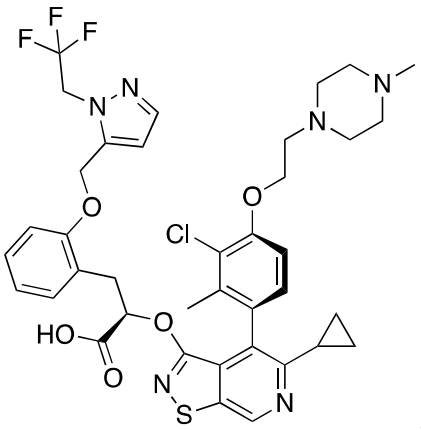
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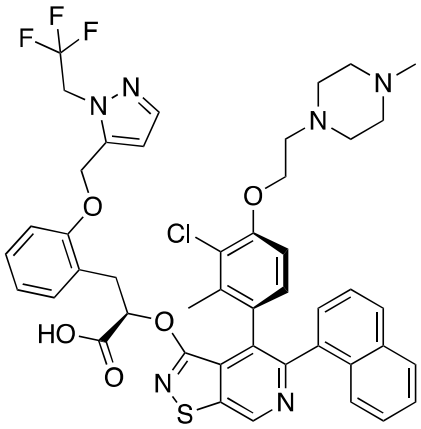
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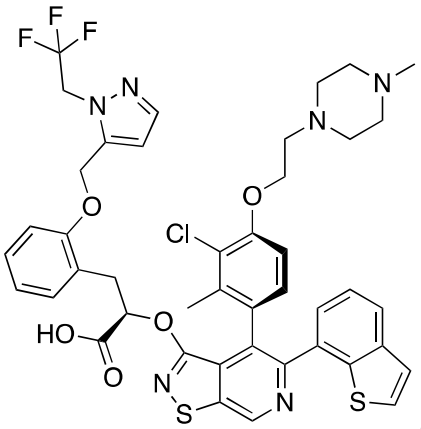
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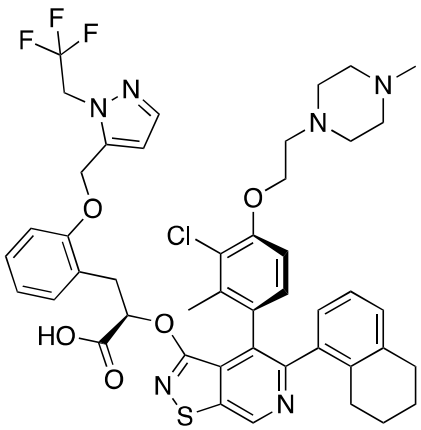
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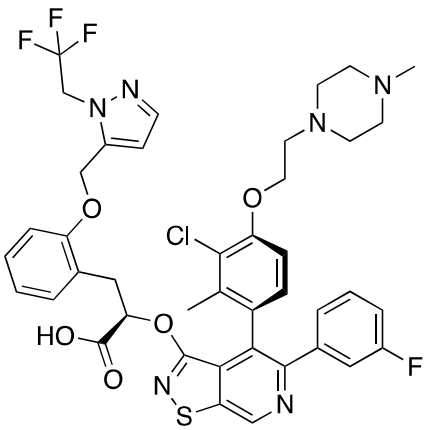
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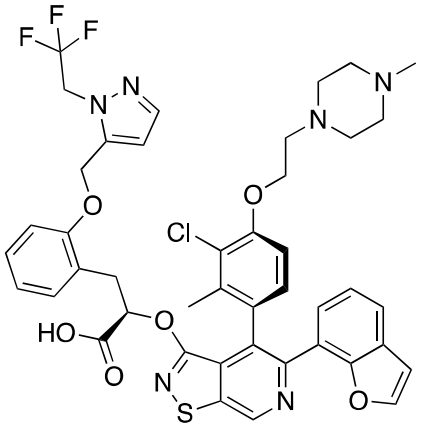
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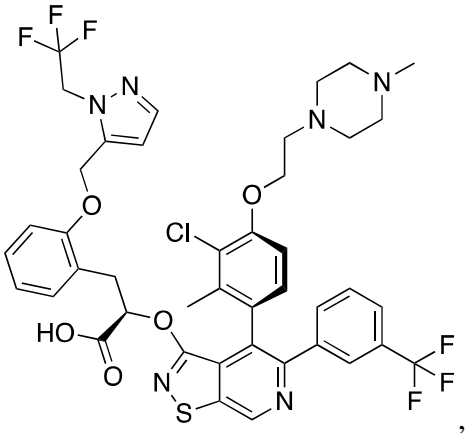
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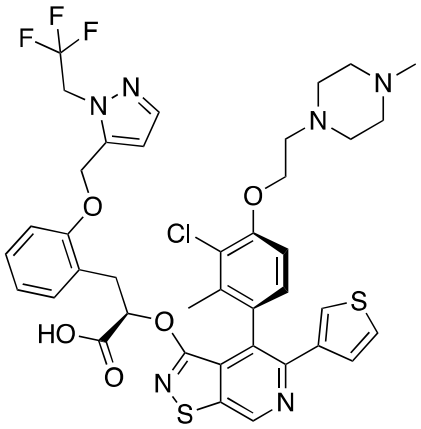
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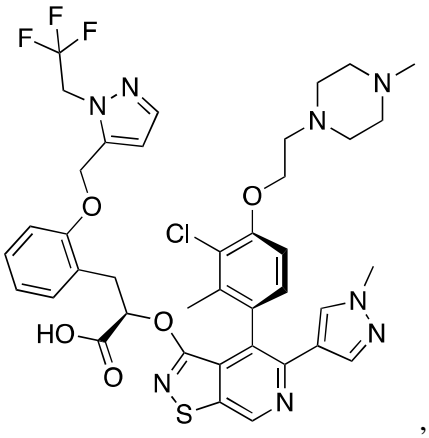
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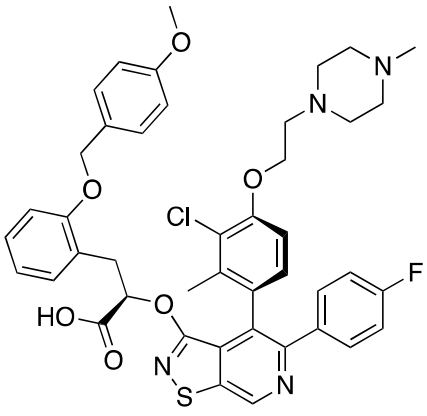
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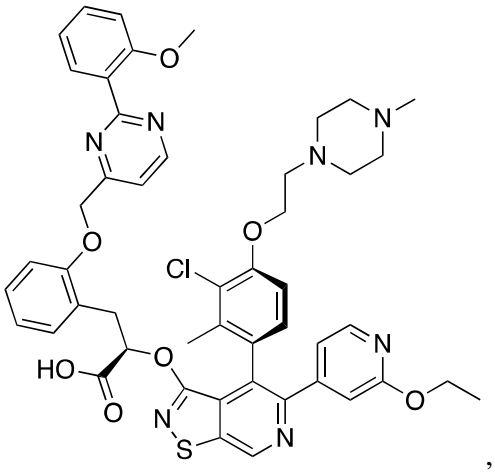
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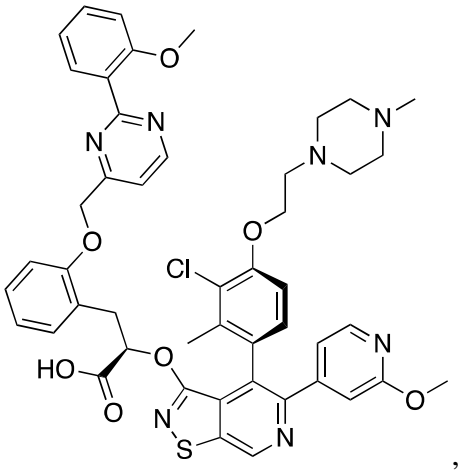
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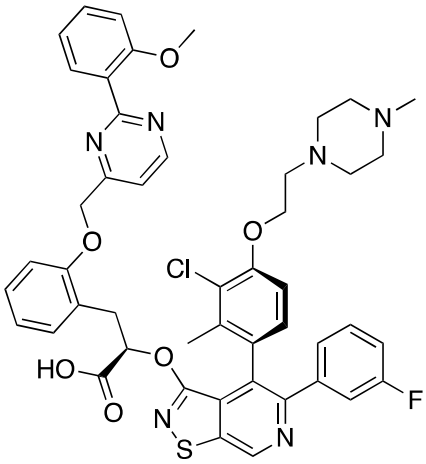
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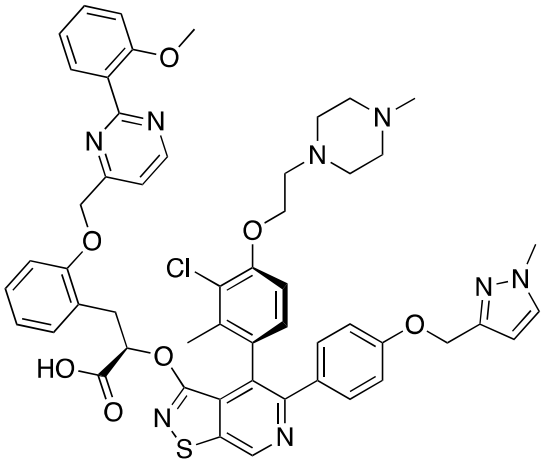
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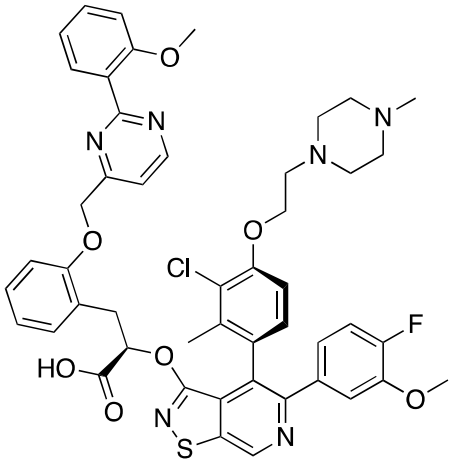
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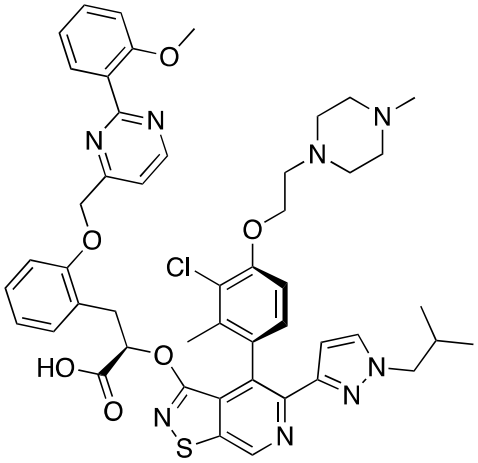
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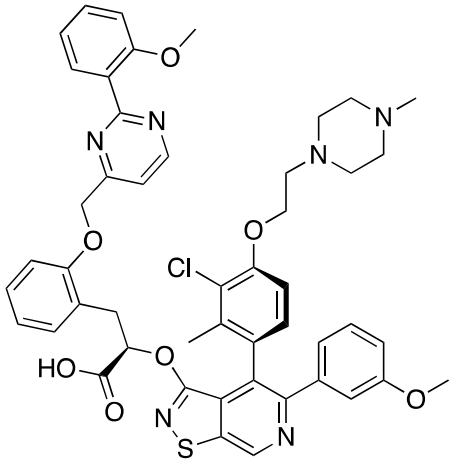
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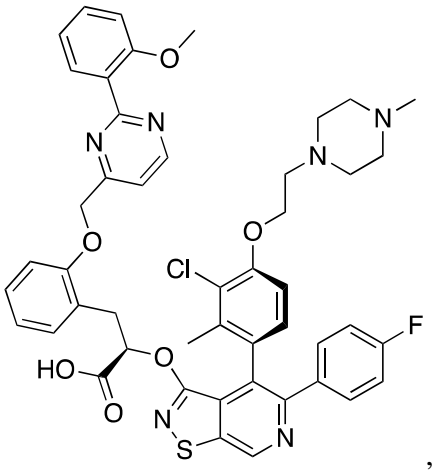
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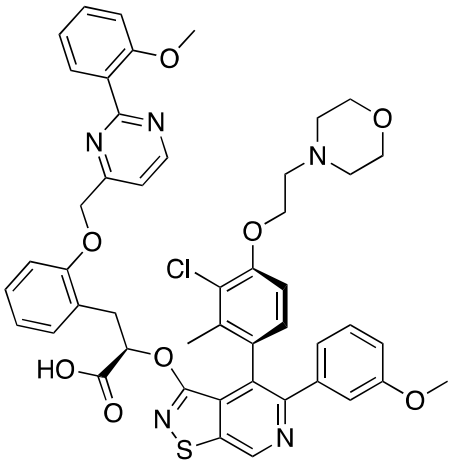
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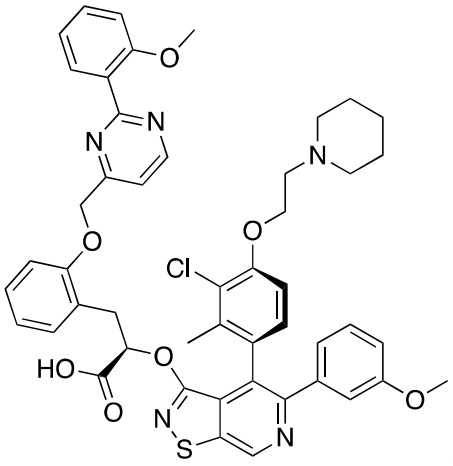
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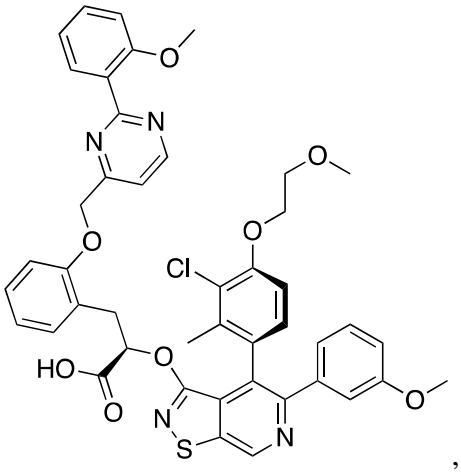
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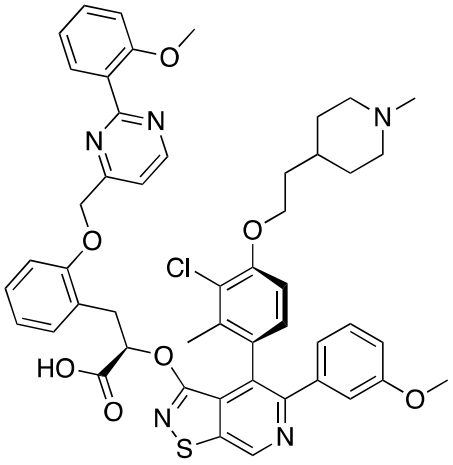
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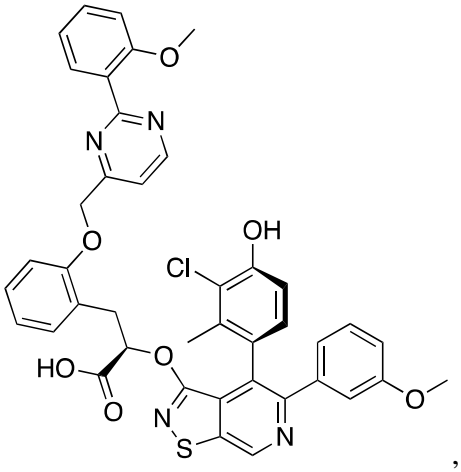
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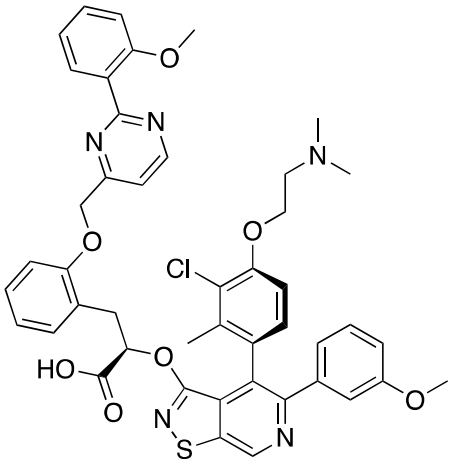
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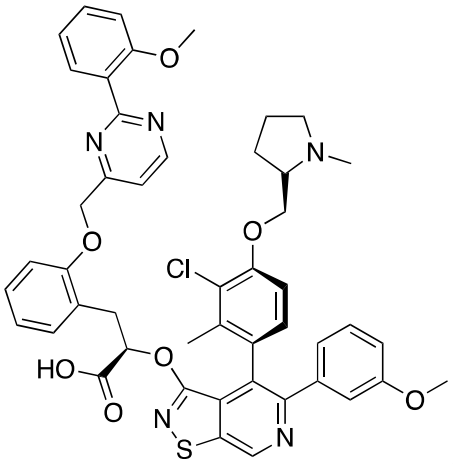
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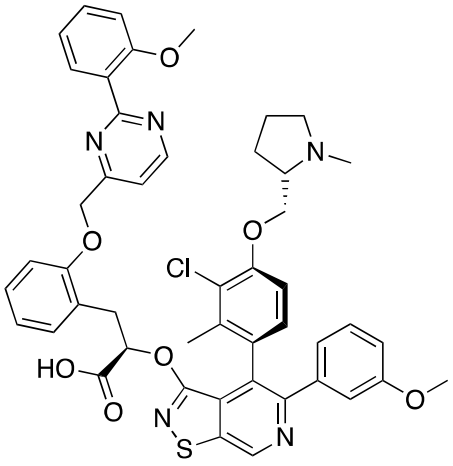
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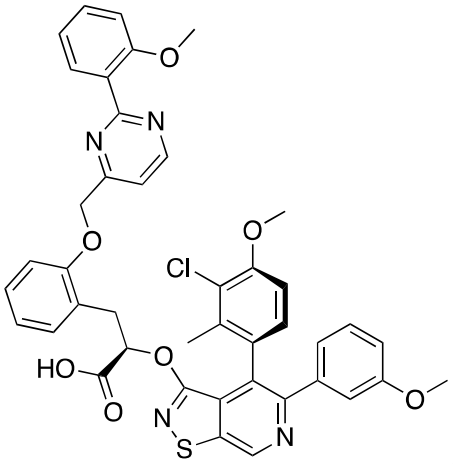
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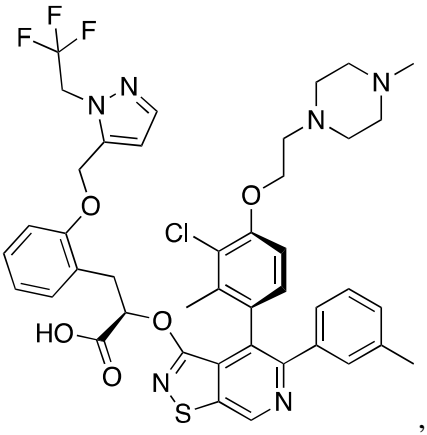
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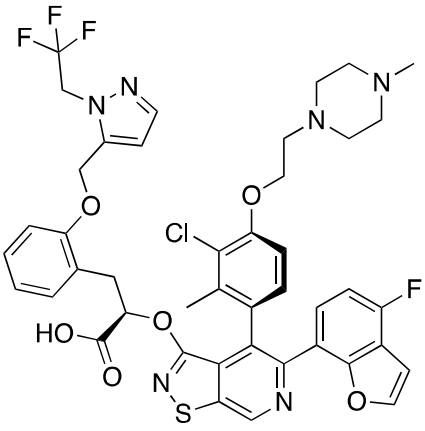
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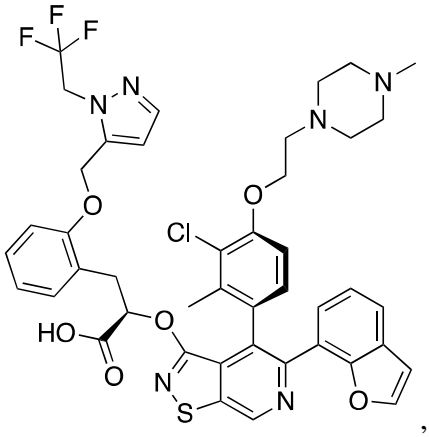
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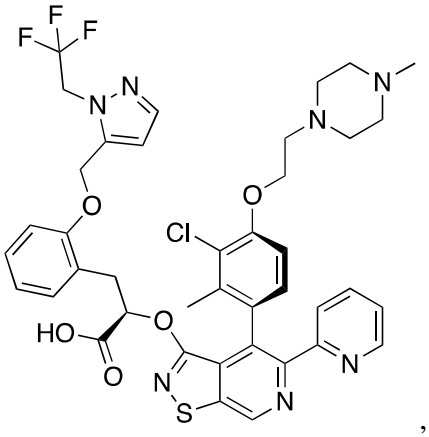
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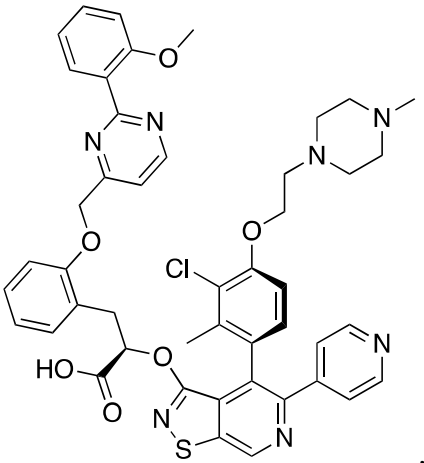
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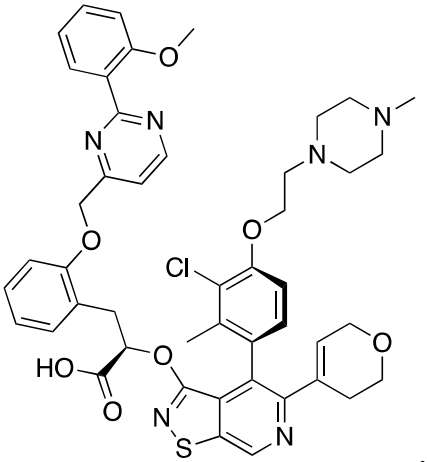
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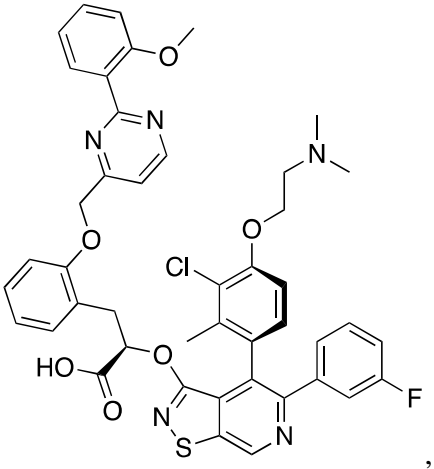
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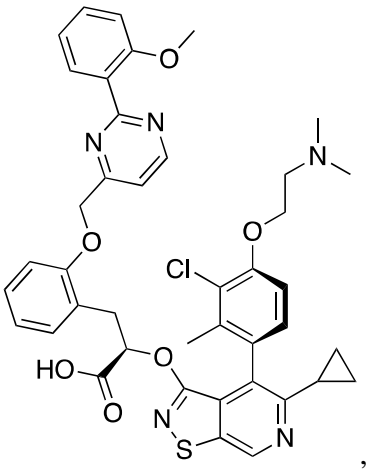
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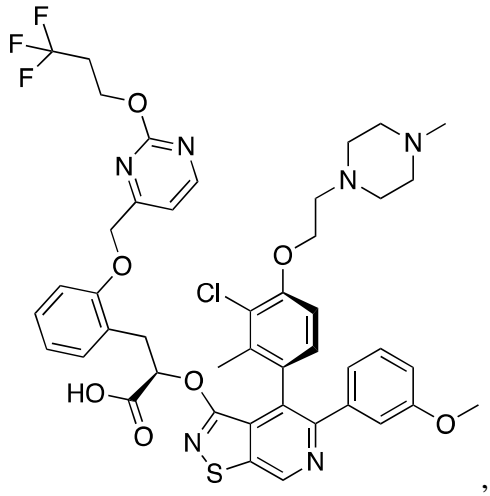
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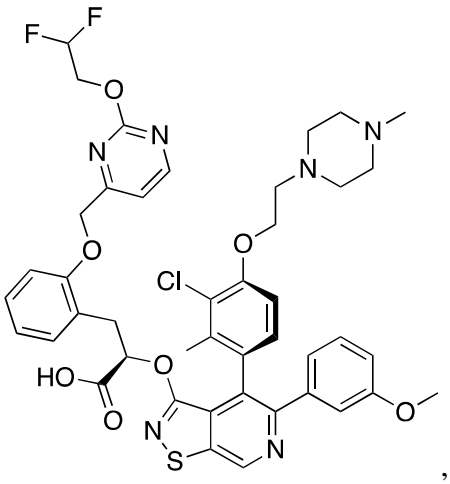
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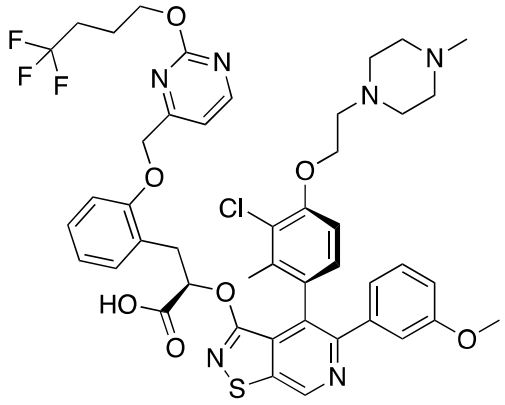
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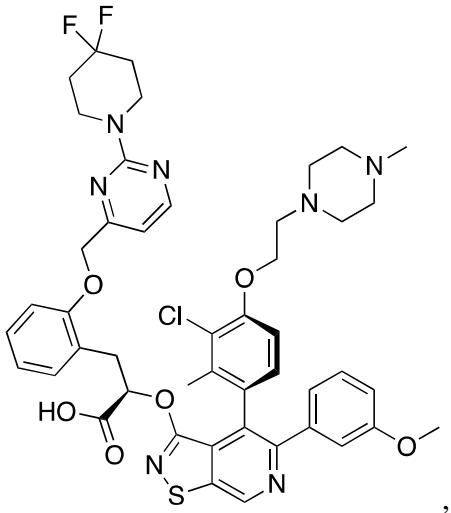
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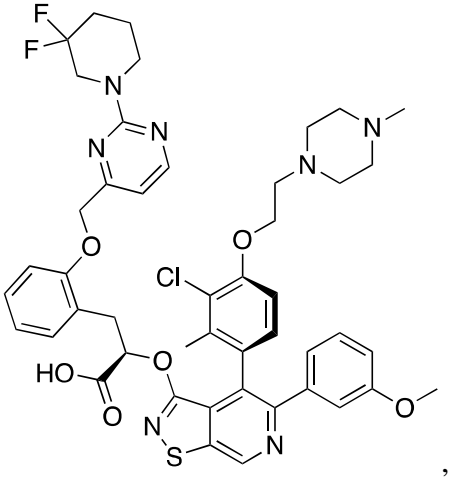
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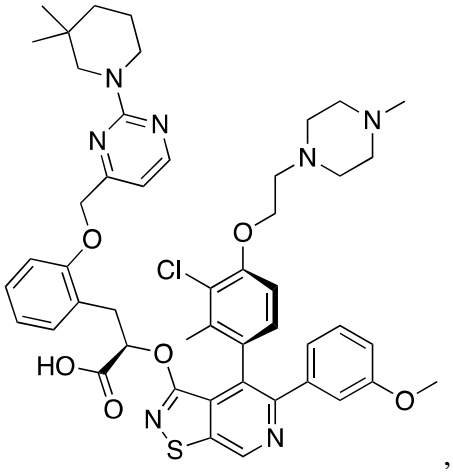
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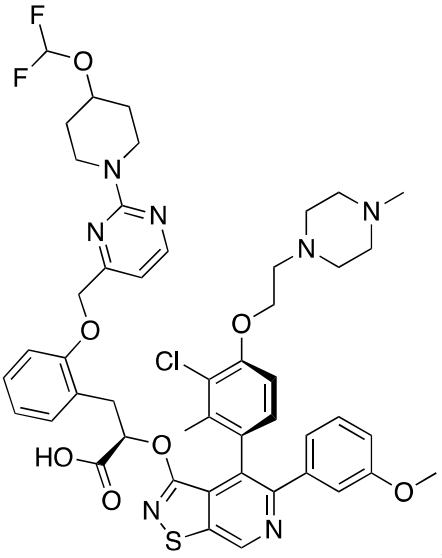
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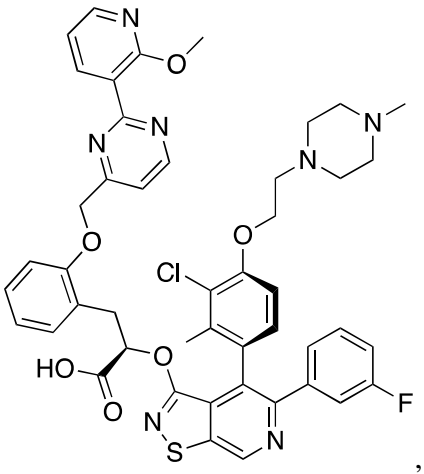
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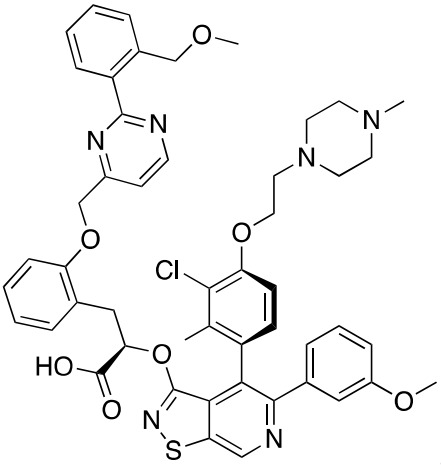
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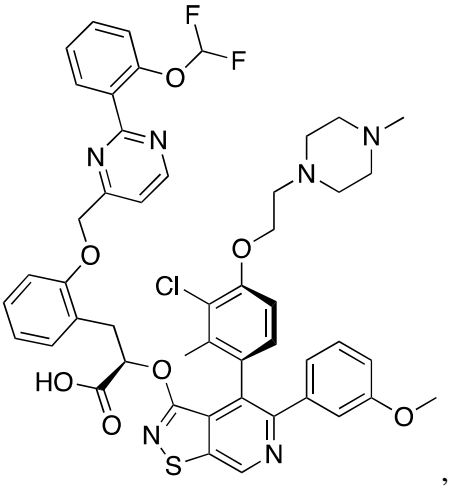
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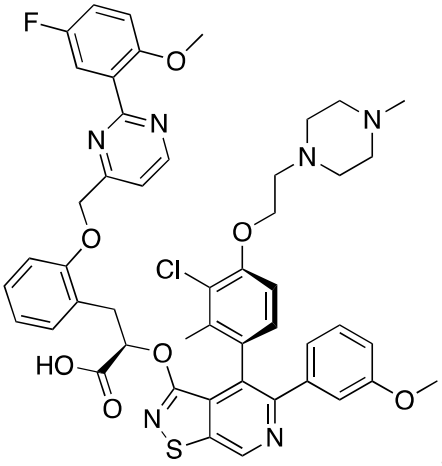
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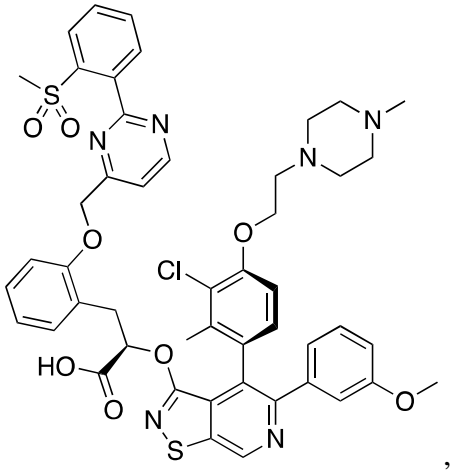
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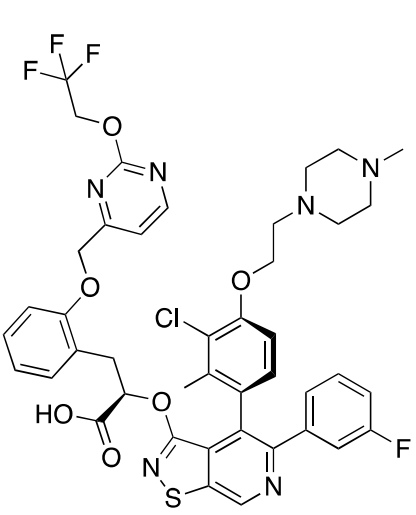
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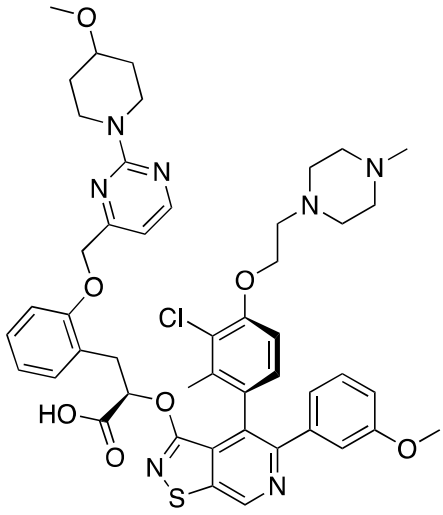
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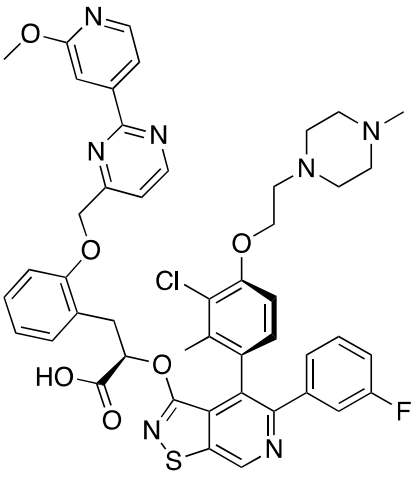
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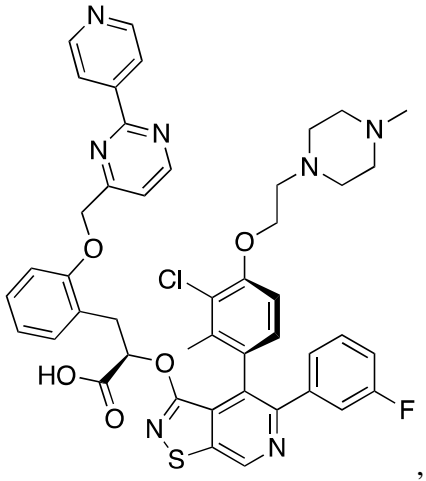
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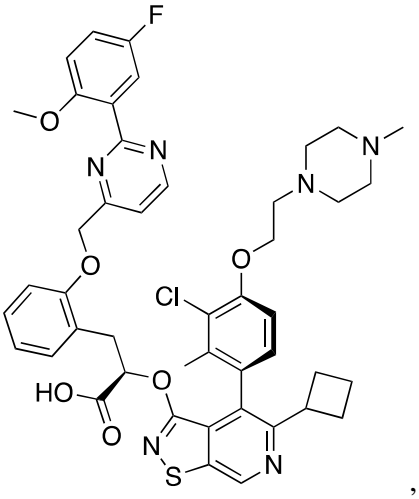
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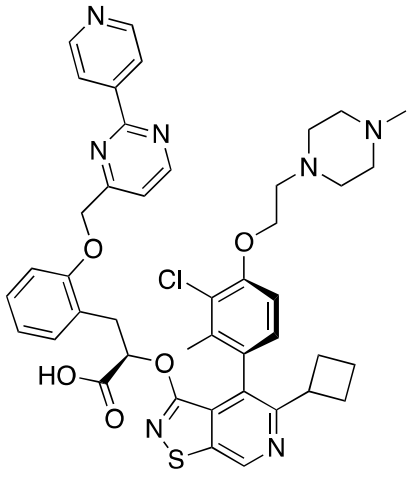
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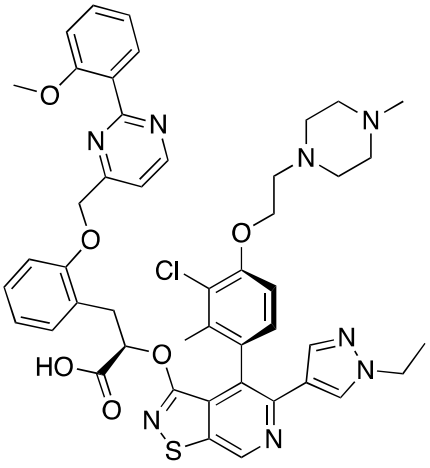
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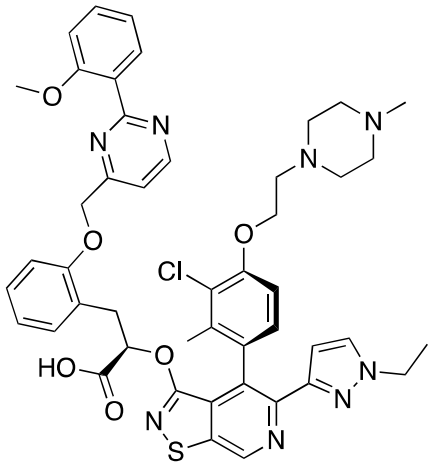
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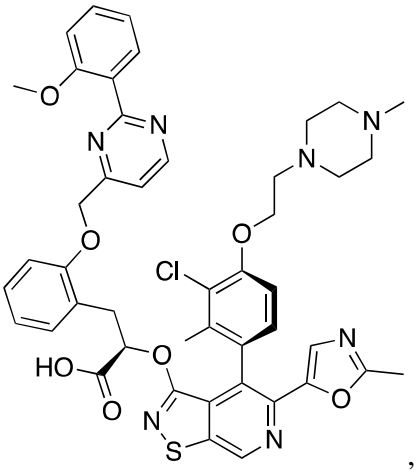
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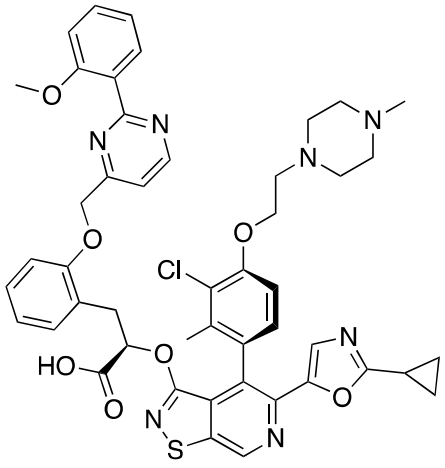
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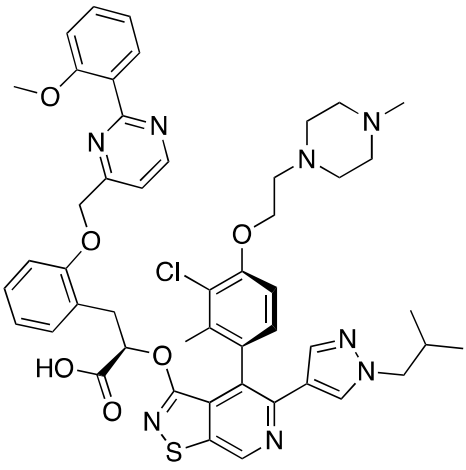
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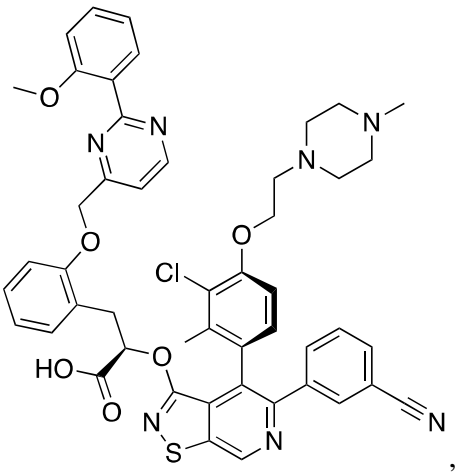
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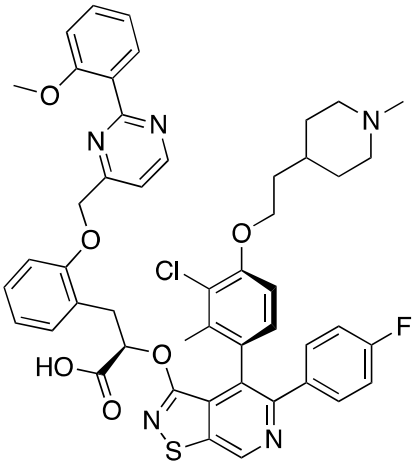
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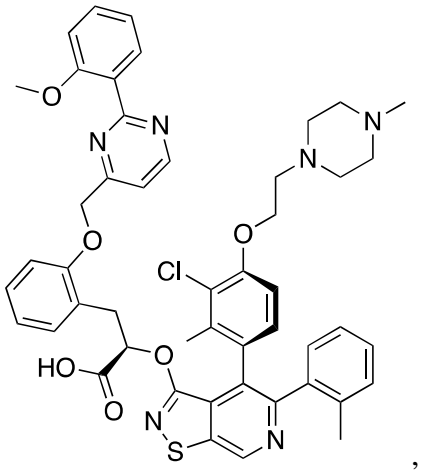
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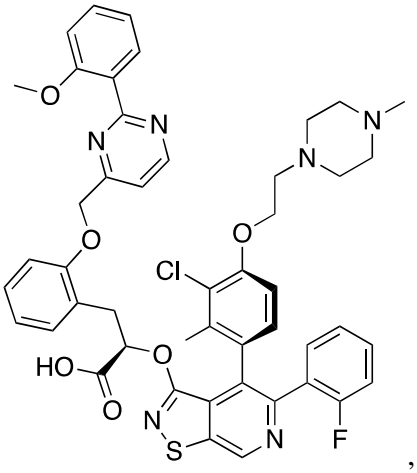
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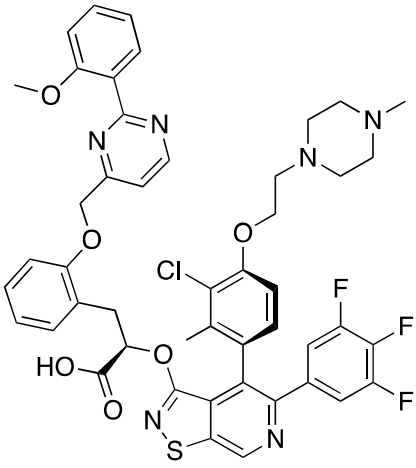
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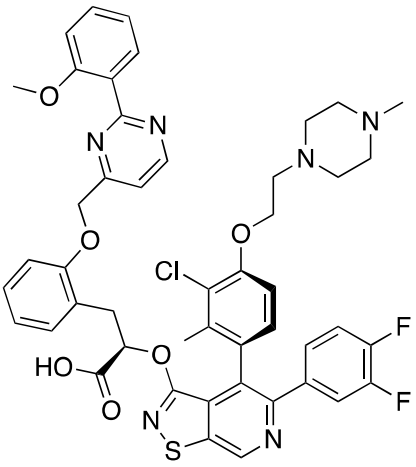
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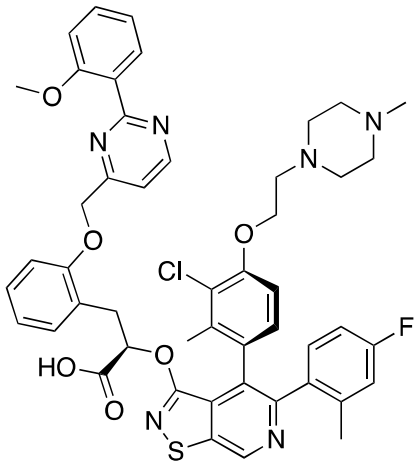
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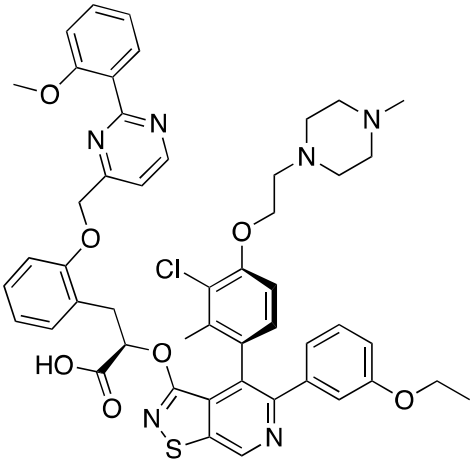
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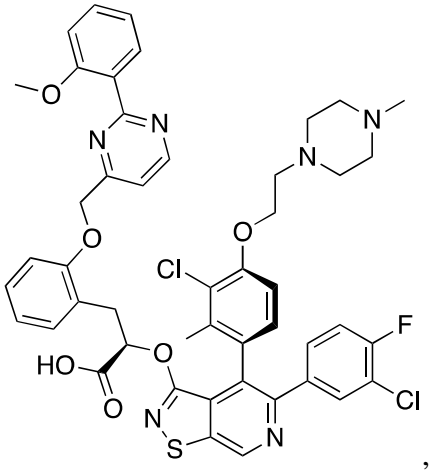
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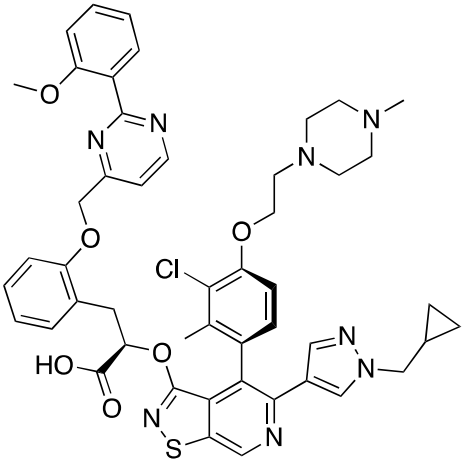
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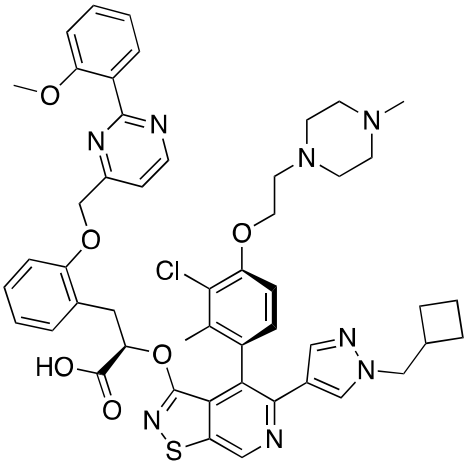
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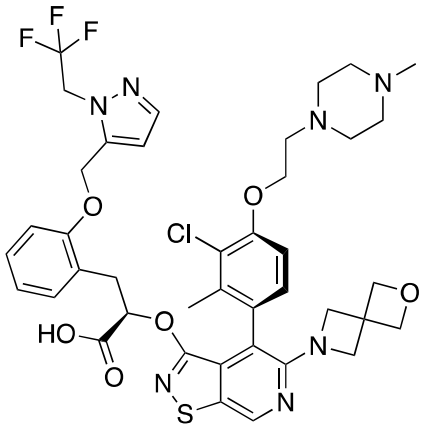
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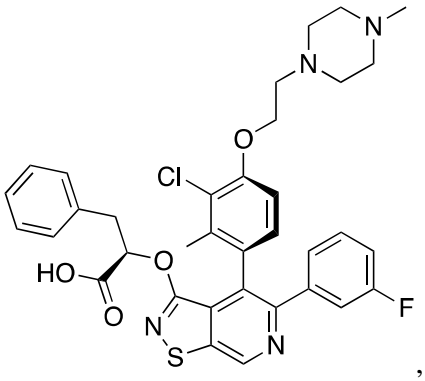
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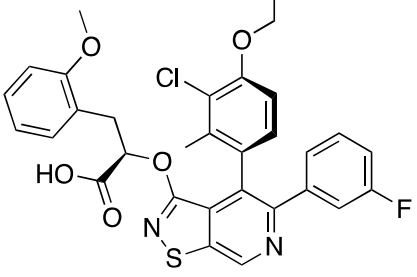
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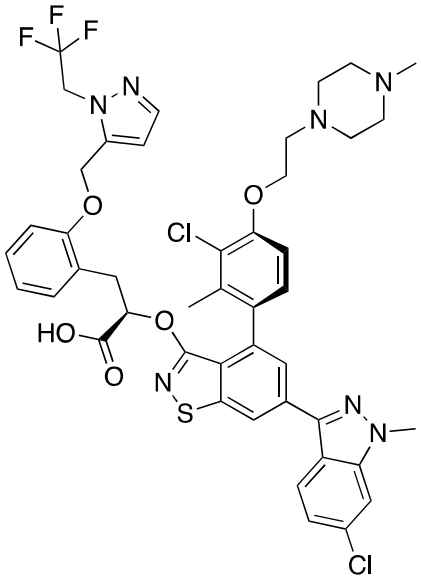
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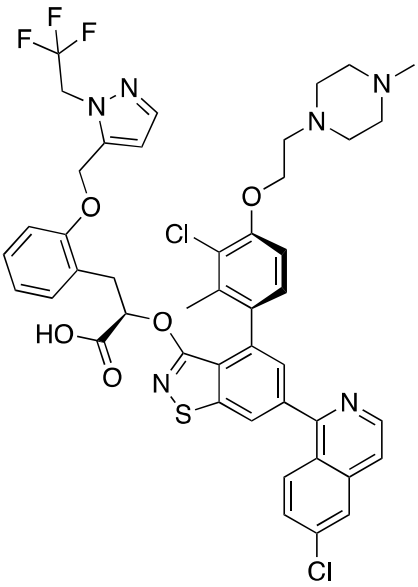
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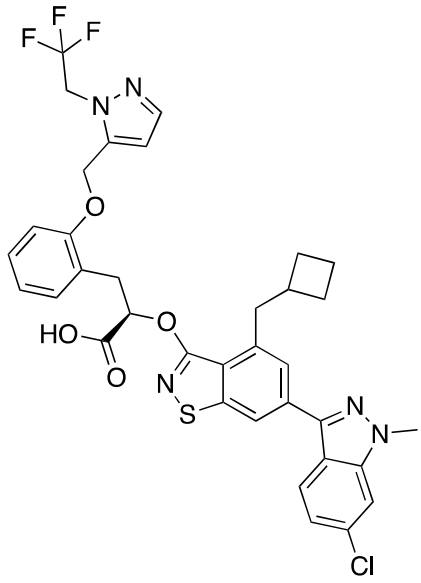
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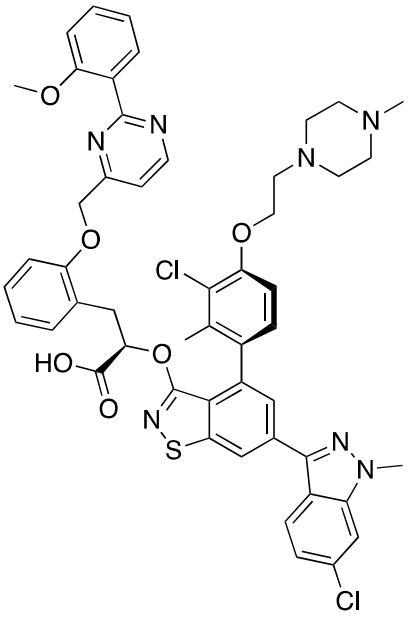
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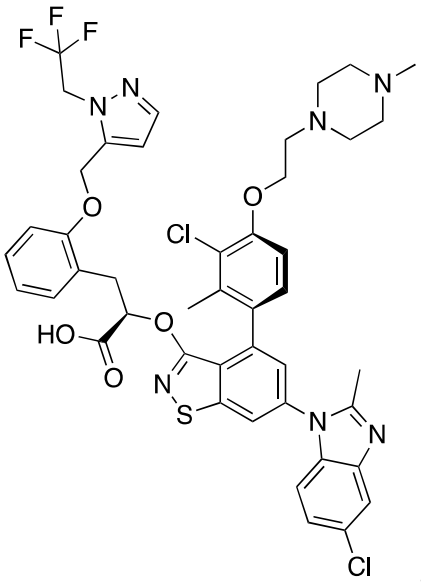
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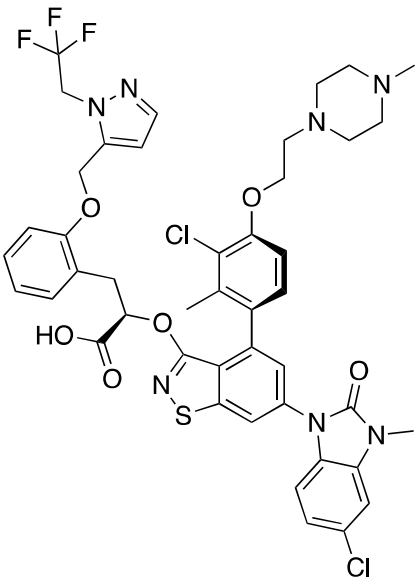
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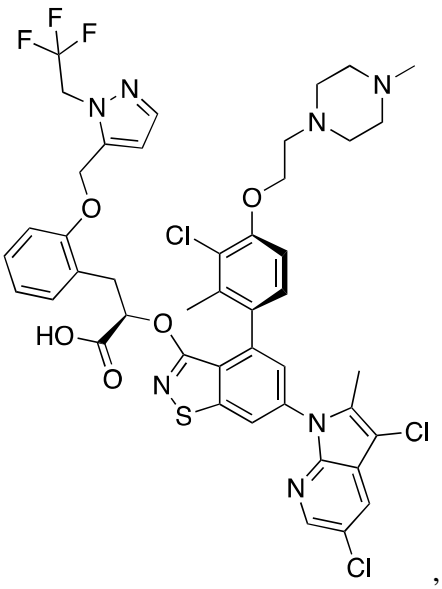
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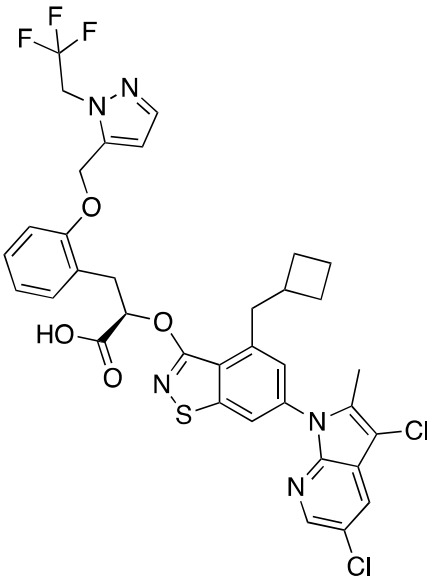
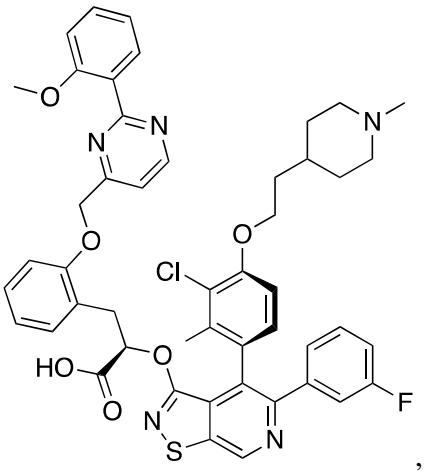
 and  , or a pharmaceutically acceptable salt thereof.

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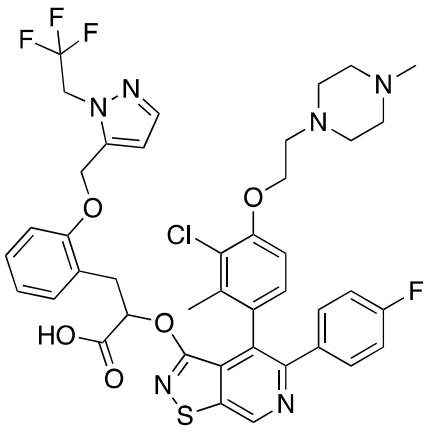
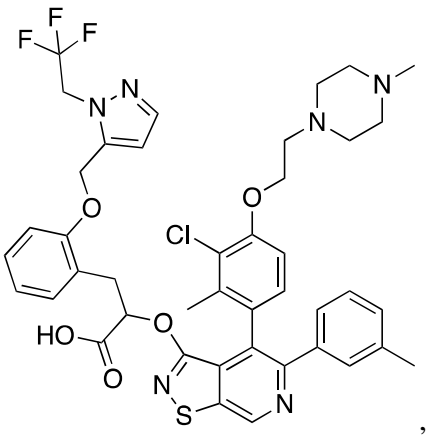
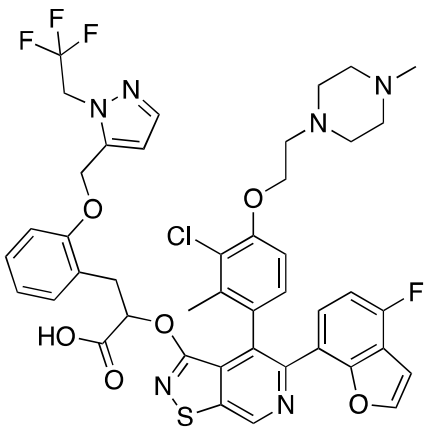
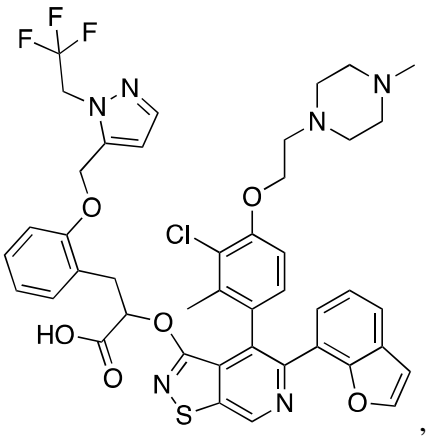
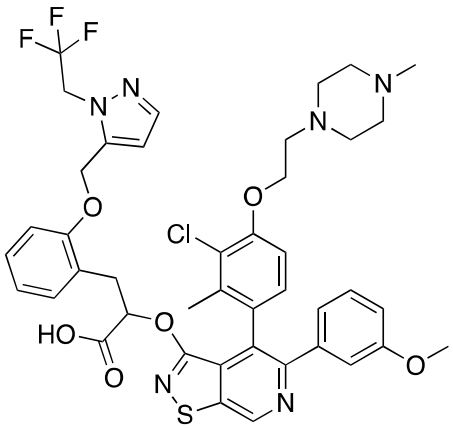
 ,  ,

 ,  ,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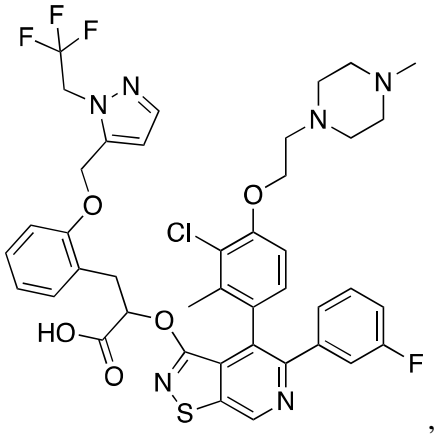
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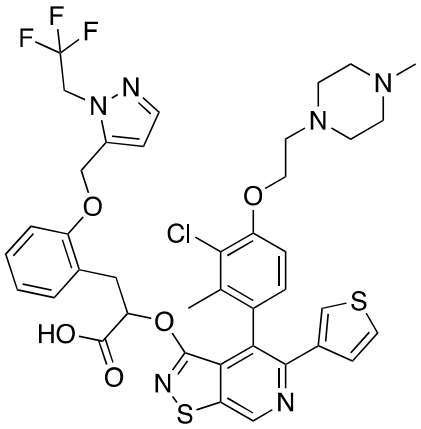
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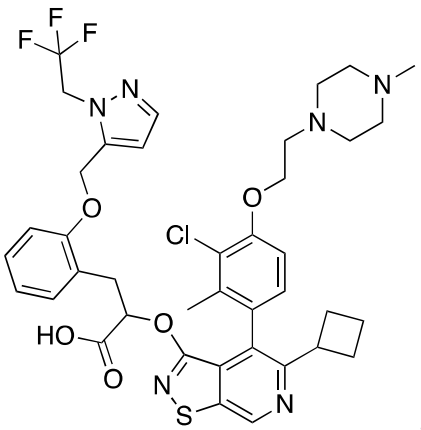
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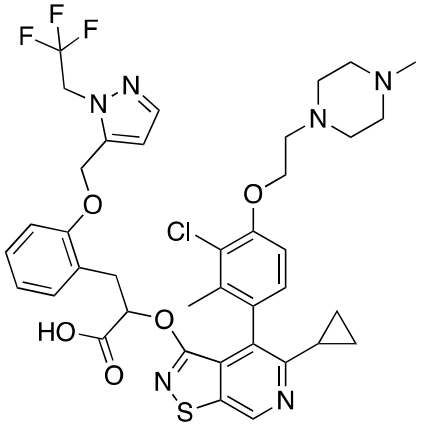
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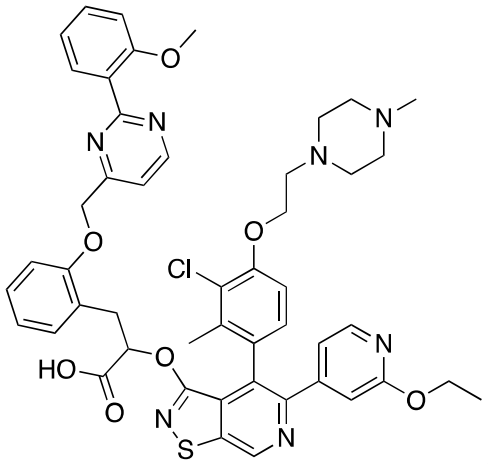
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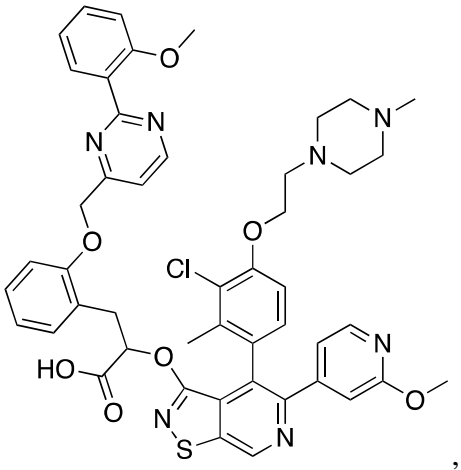
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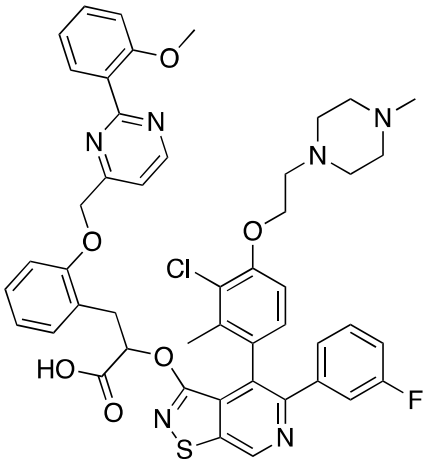
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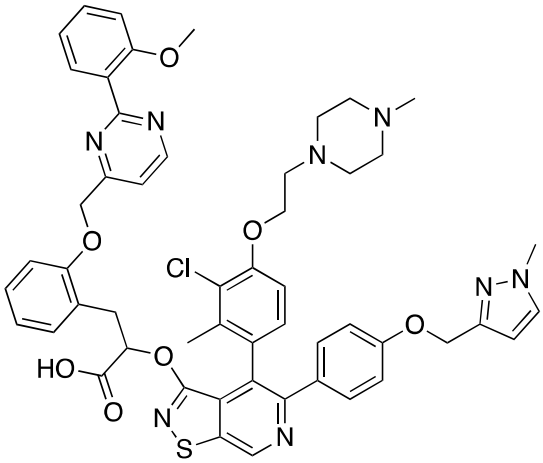
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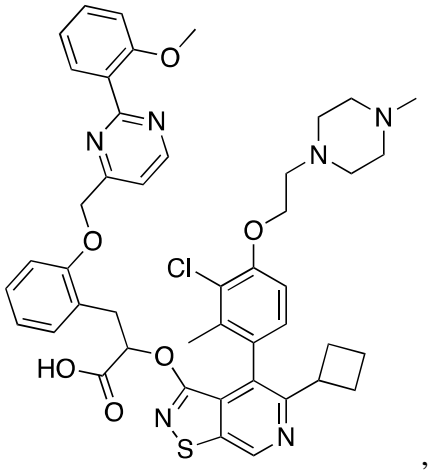
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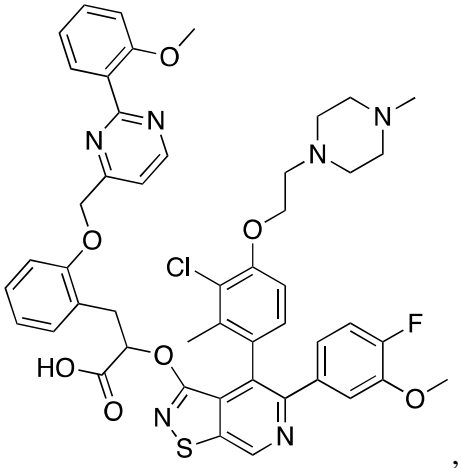
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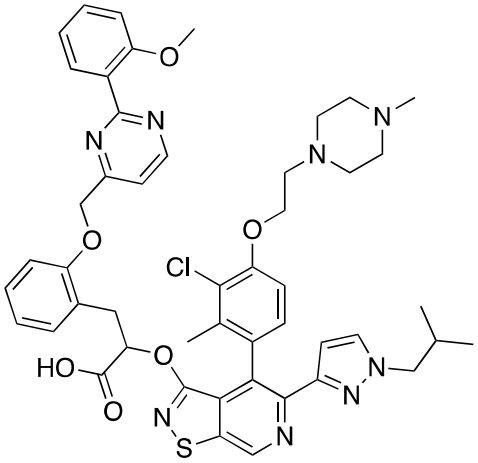
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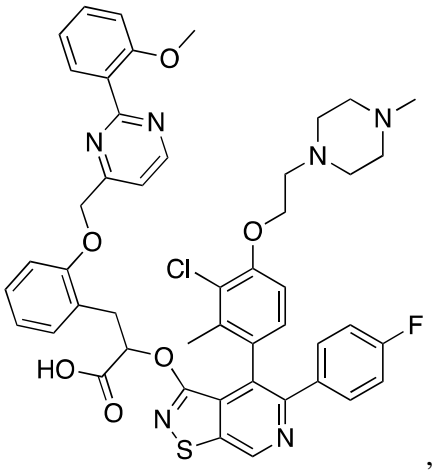
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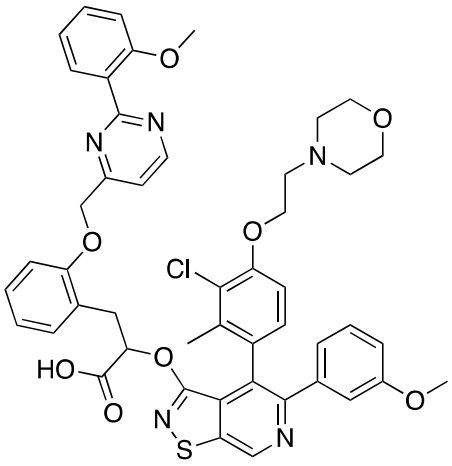
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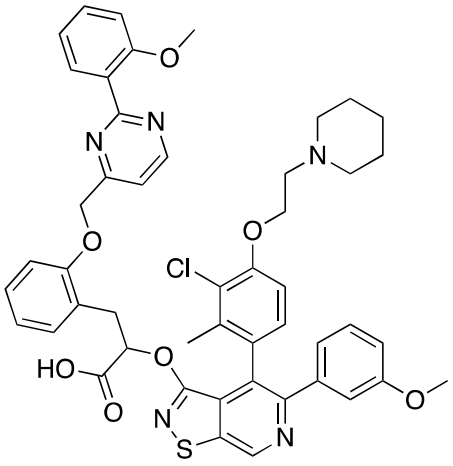
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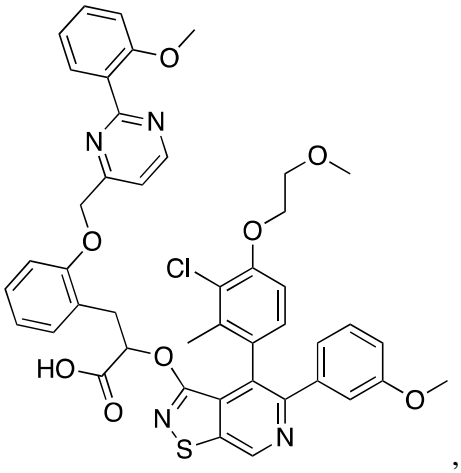
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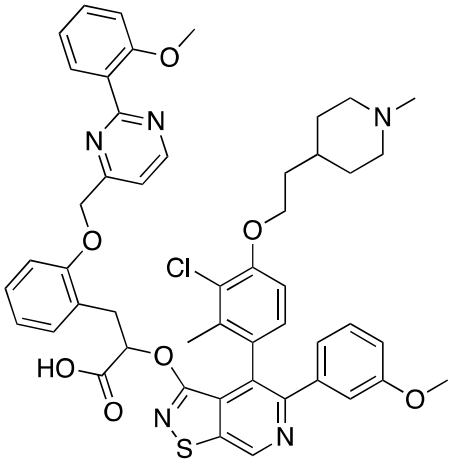
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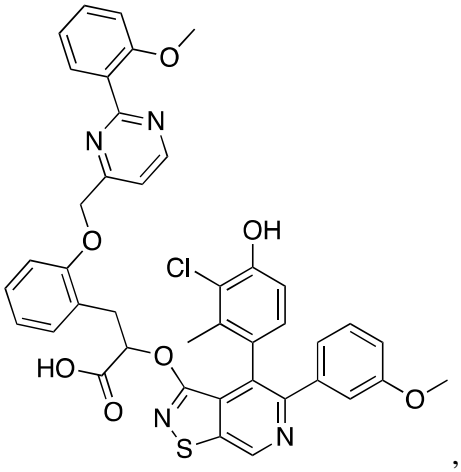
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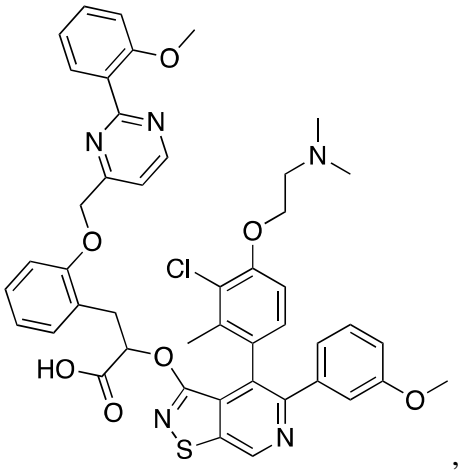

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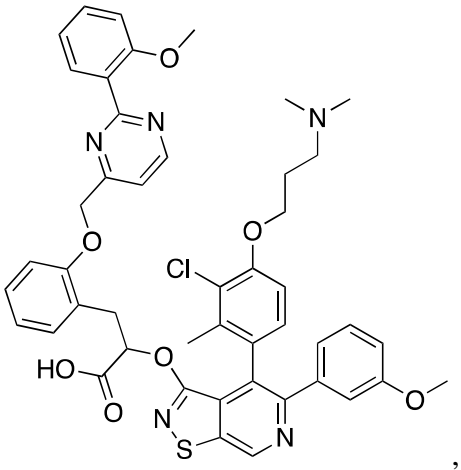

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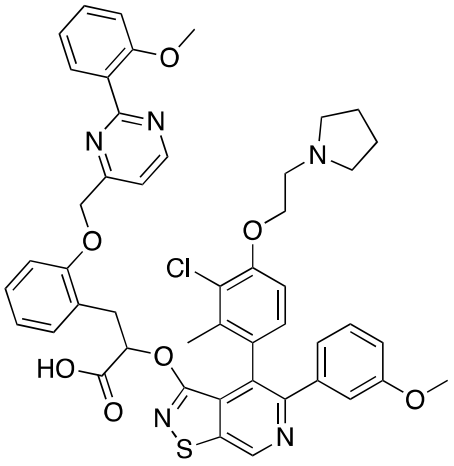

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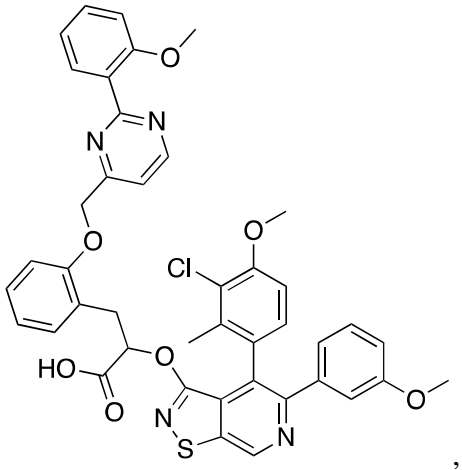

, or a pharmaceutically acceptable salt thereof.

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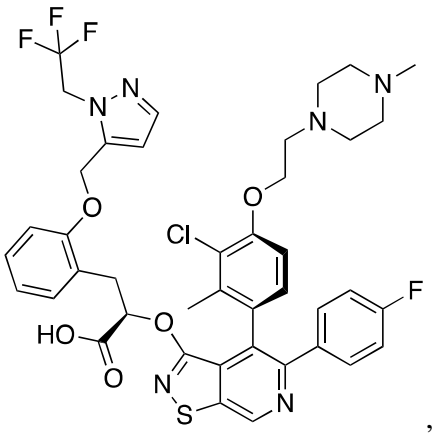
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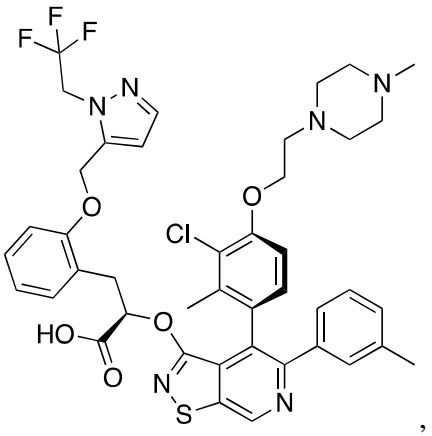
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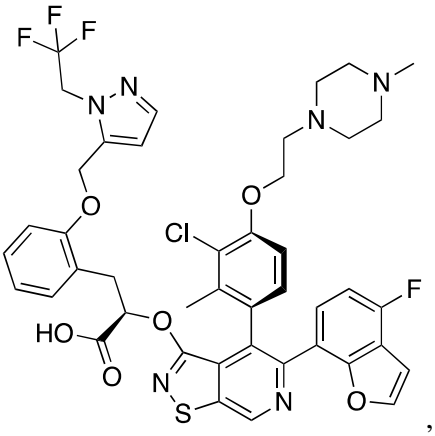
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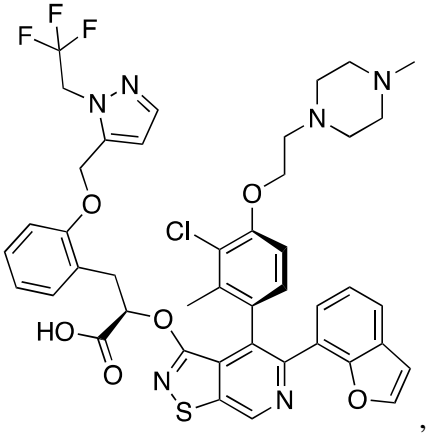
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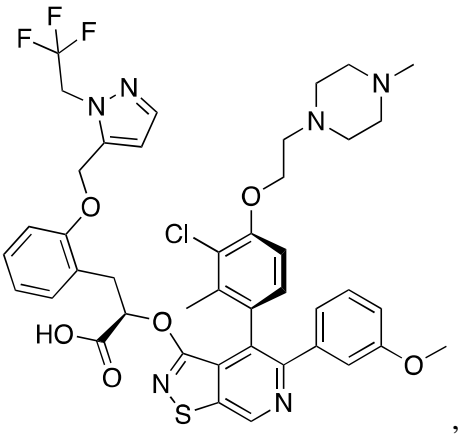
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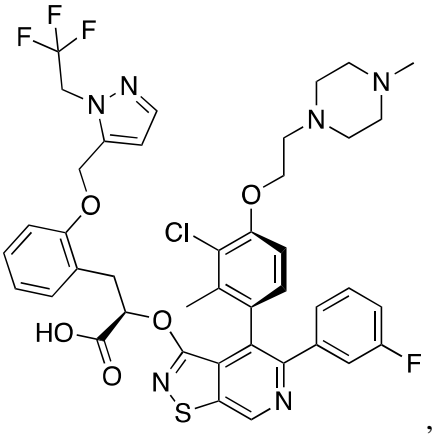
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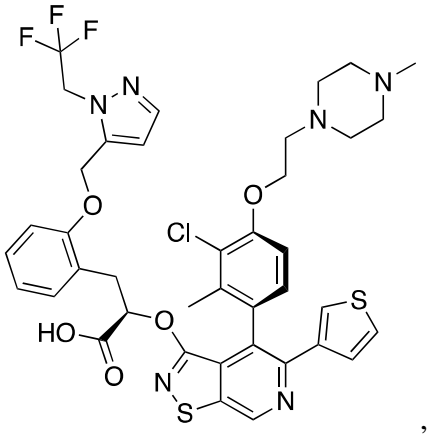
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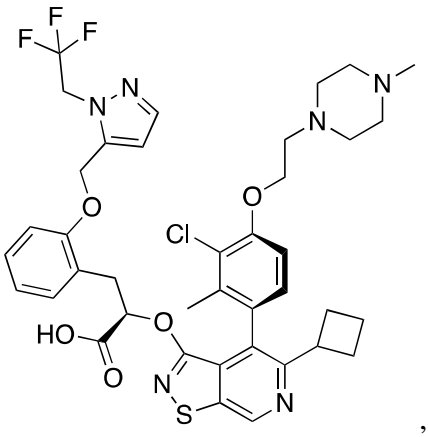
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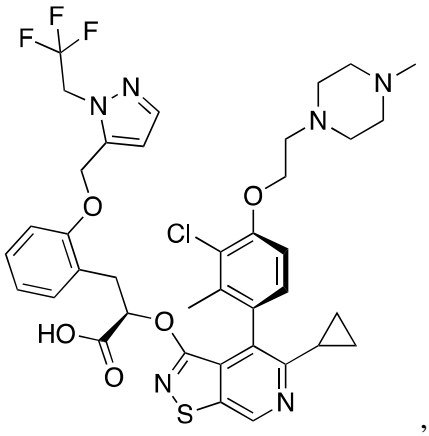
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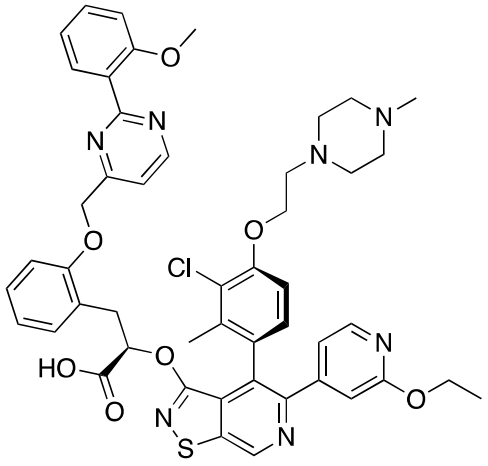
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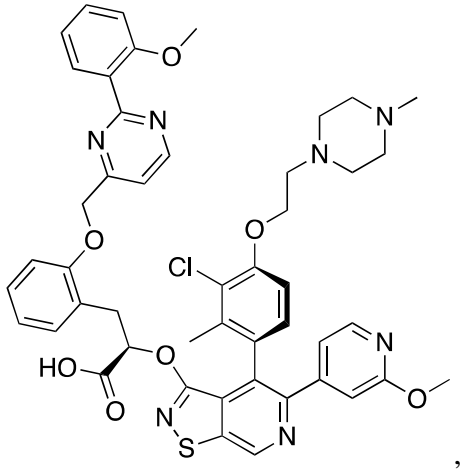
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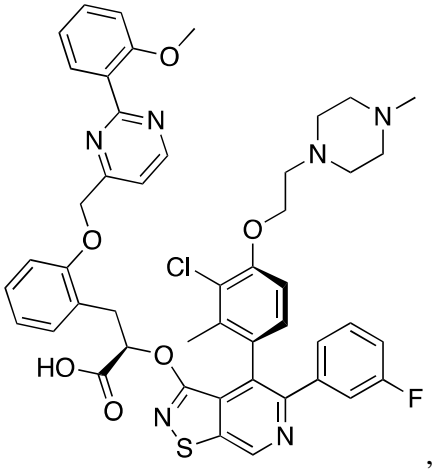
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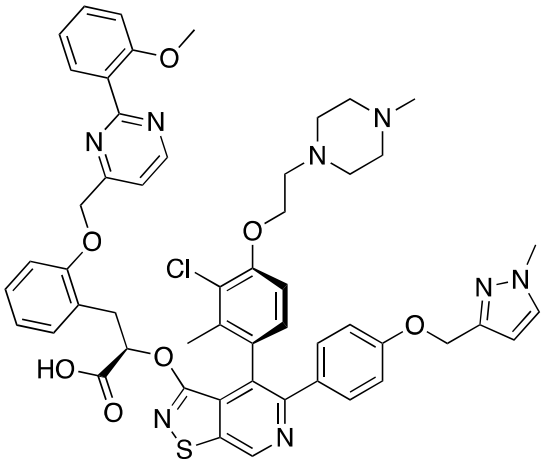
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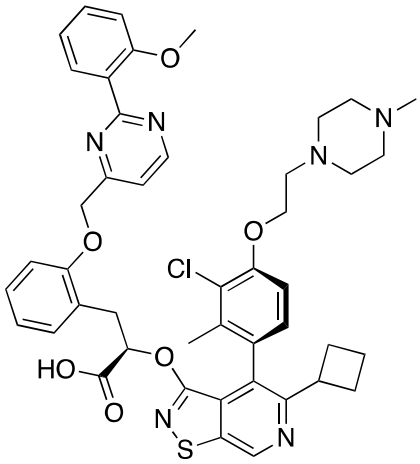
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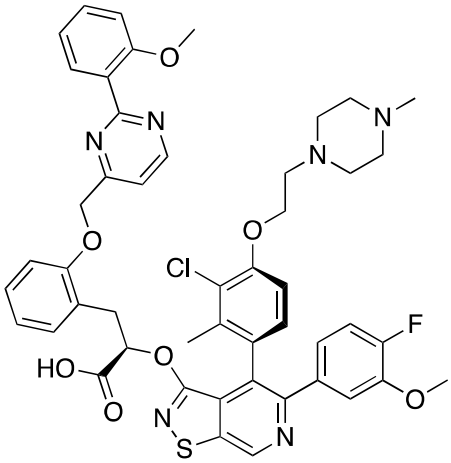
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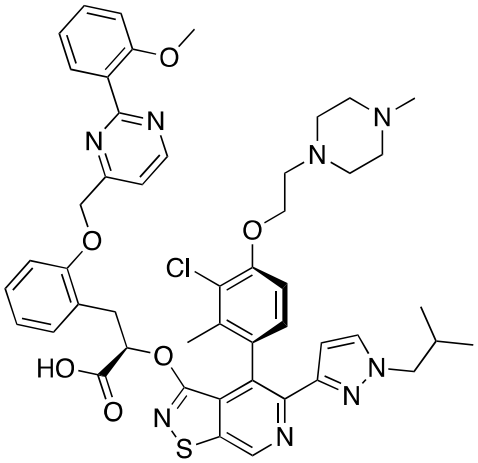
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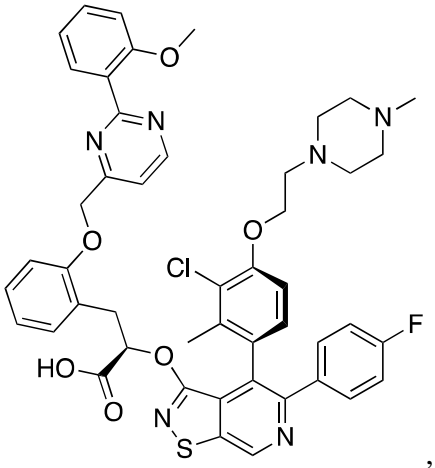
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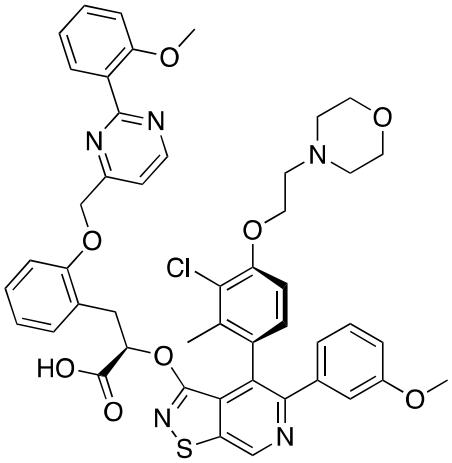
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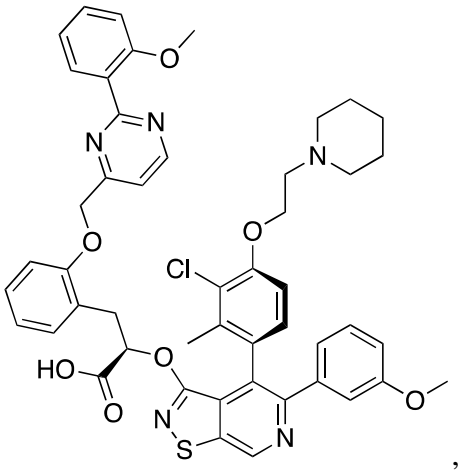
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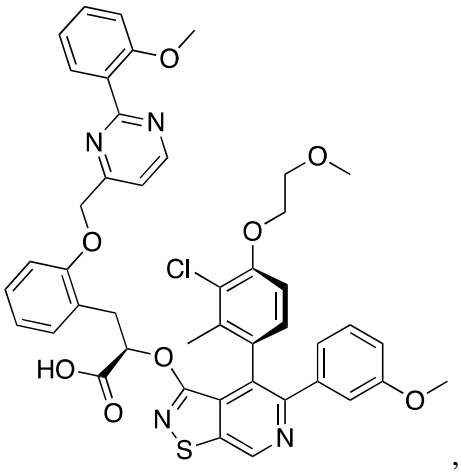
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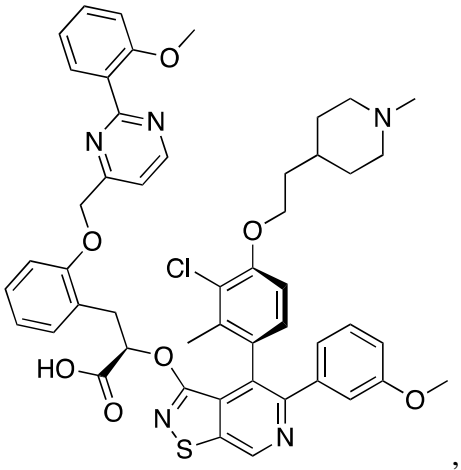
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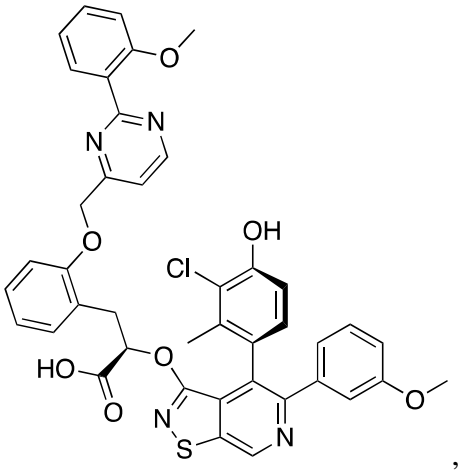
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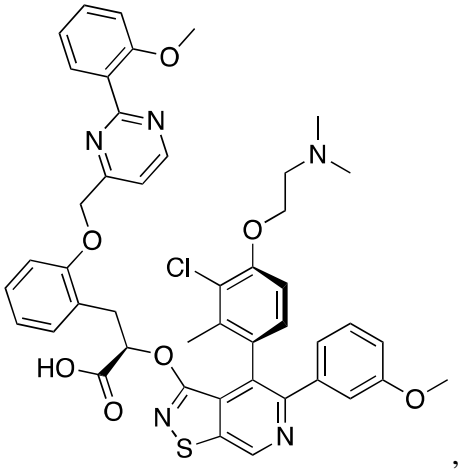
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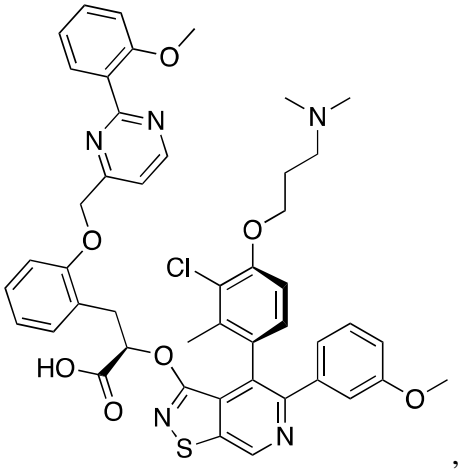
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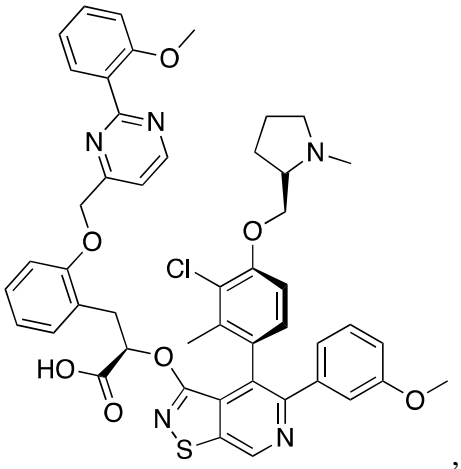

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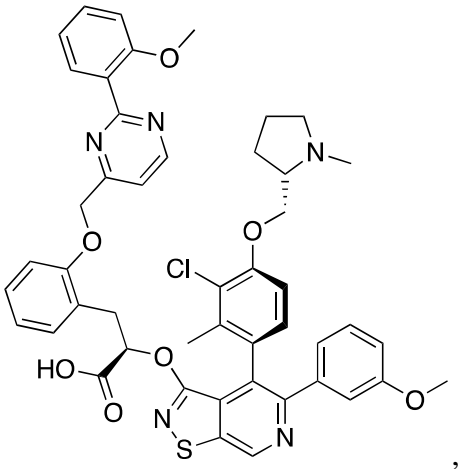

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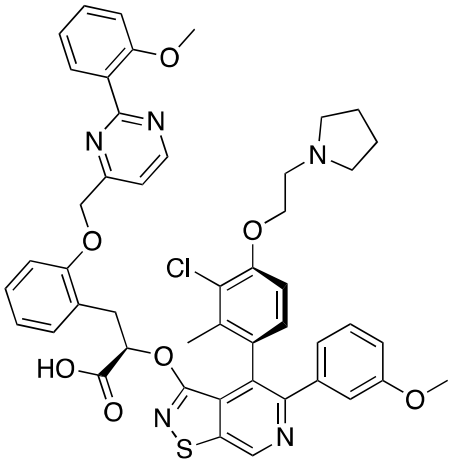

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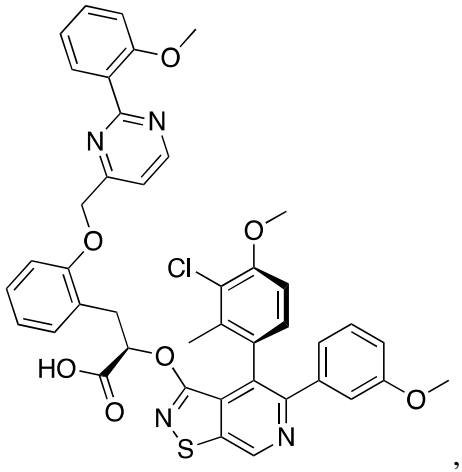

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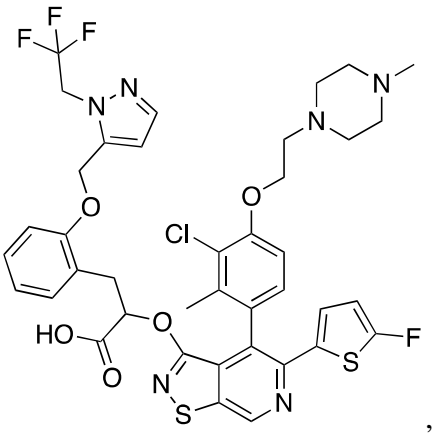
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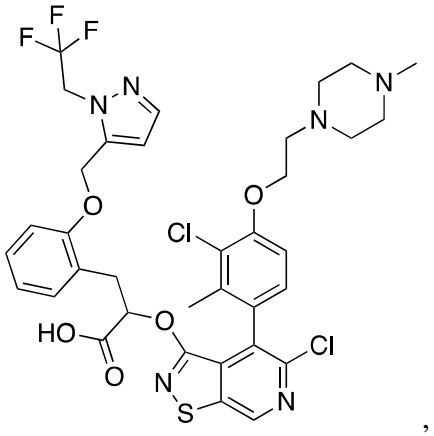
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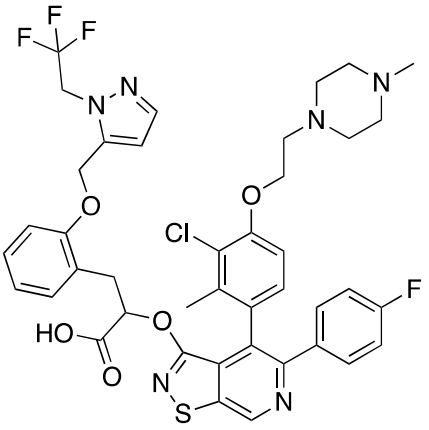
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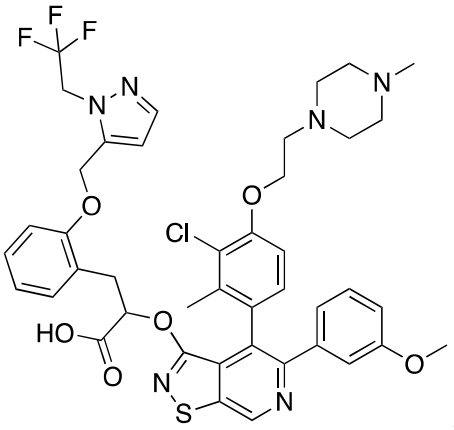
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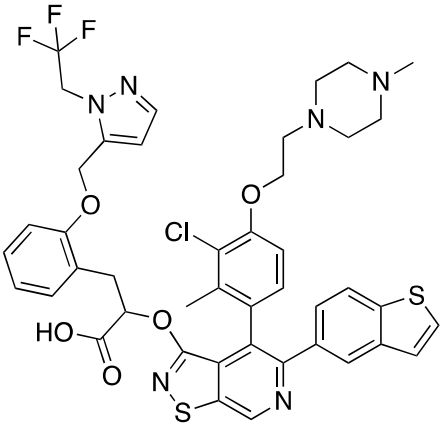
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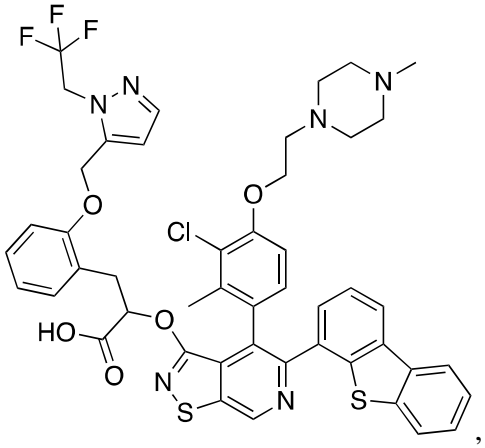
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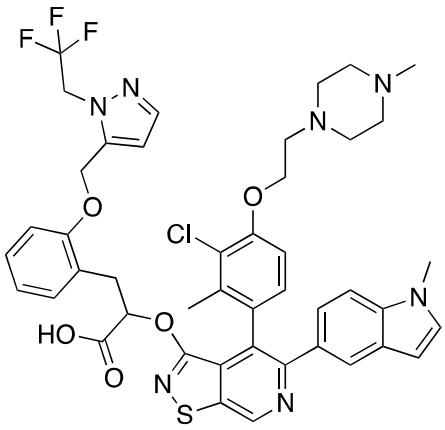
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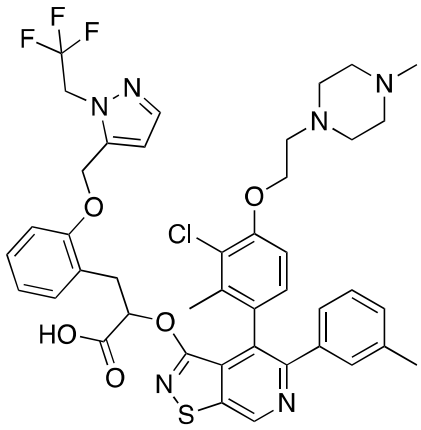
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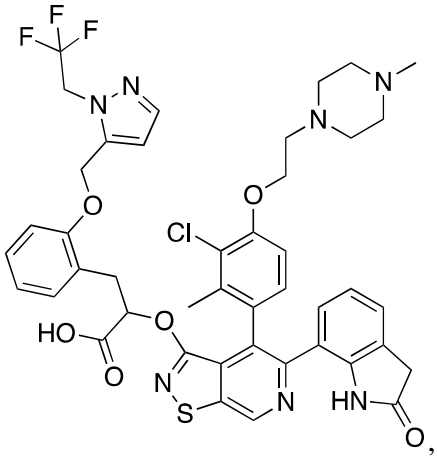
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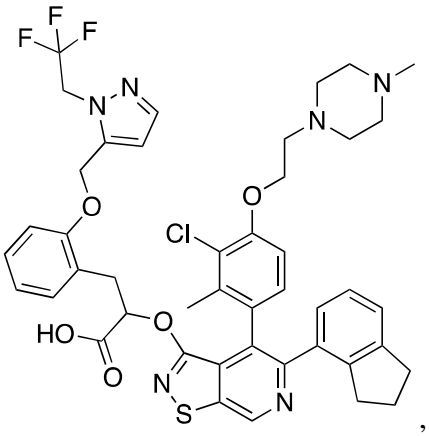
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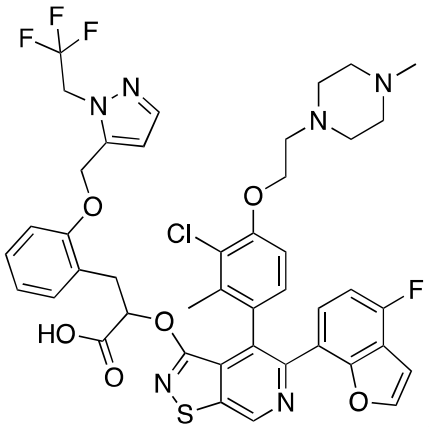
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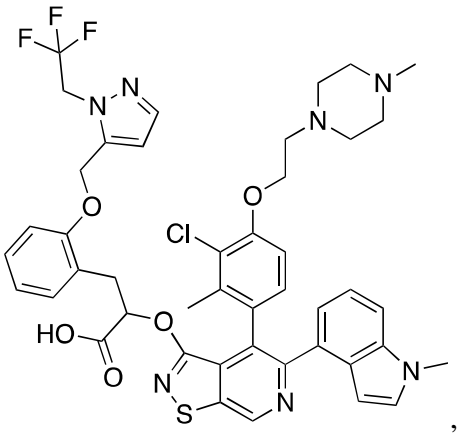
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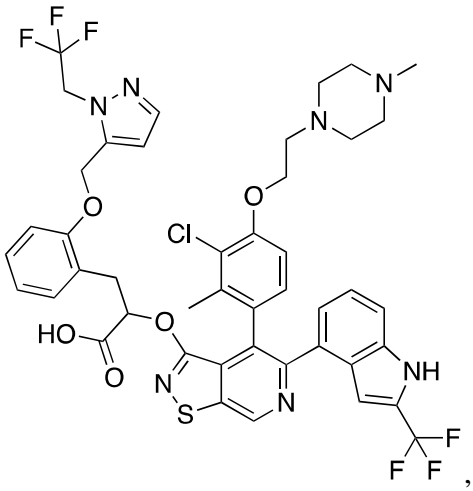
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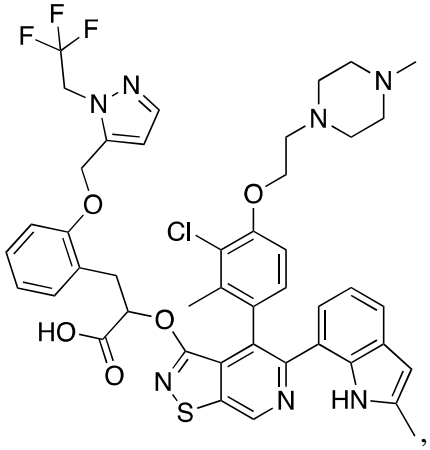
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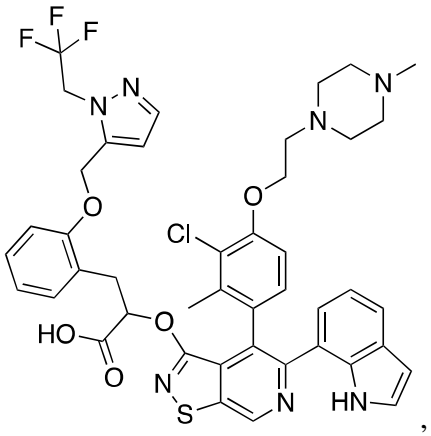
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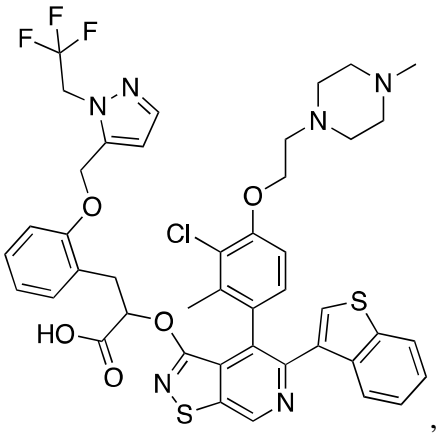
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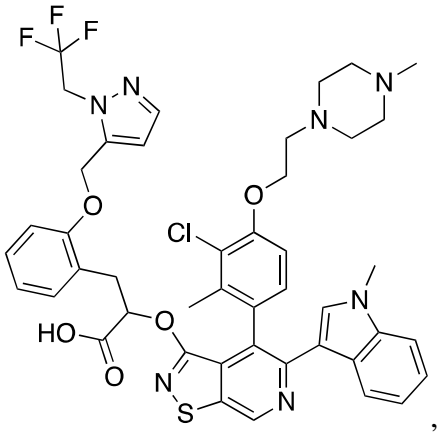
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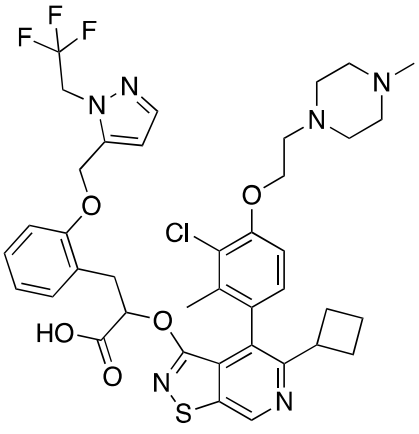
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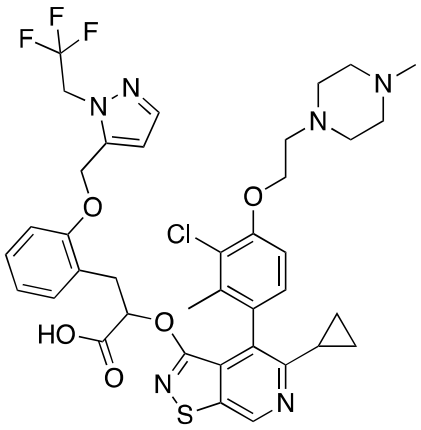
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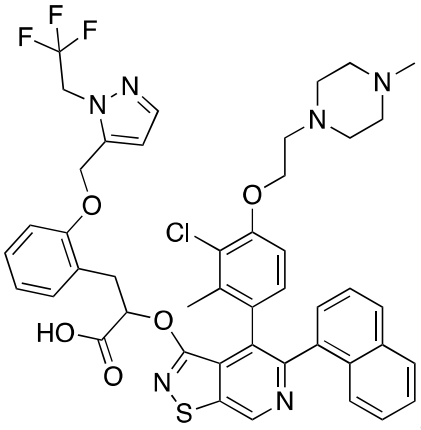
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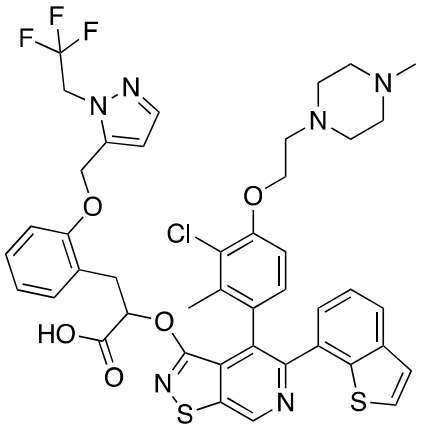
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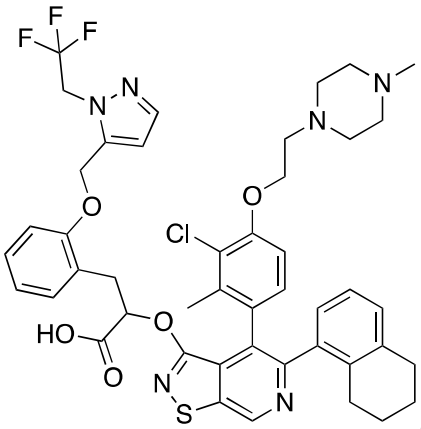
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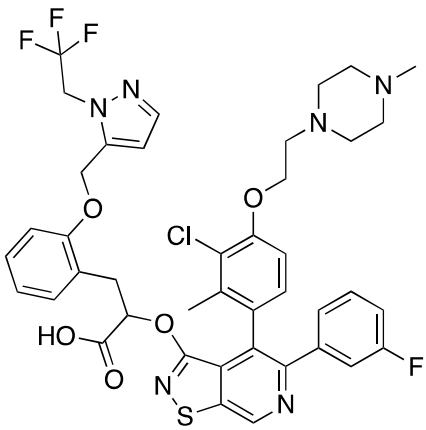
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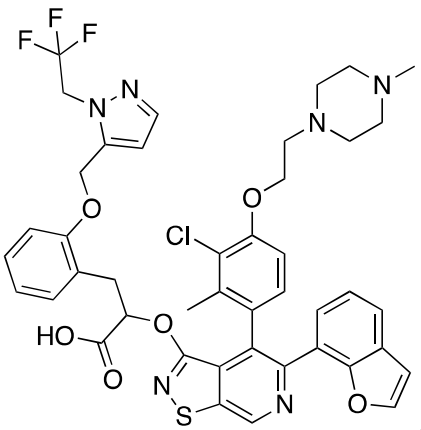
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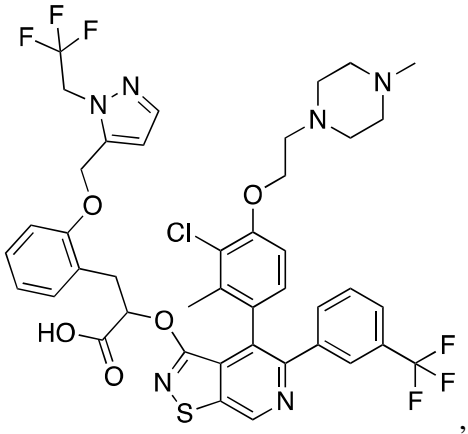
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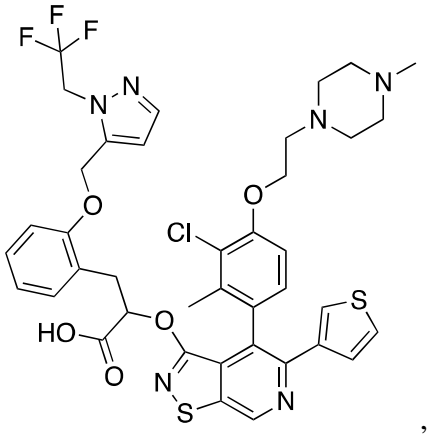
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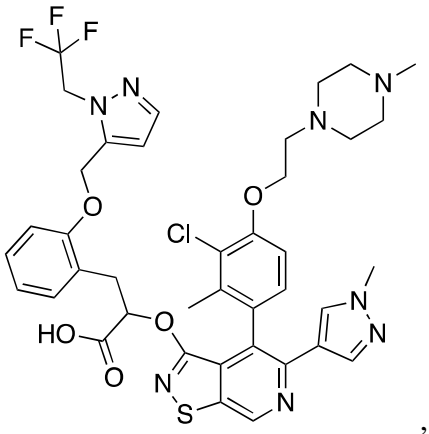
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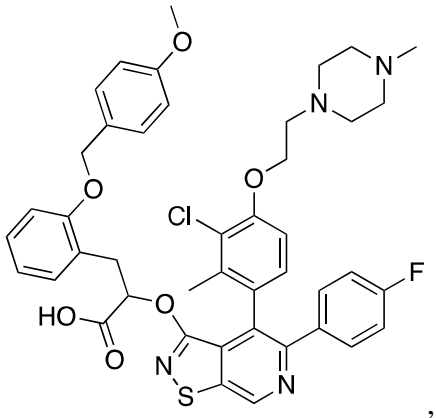
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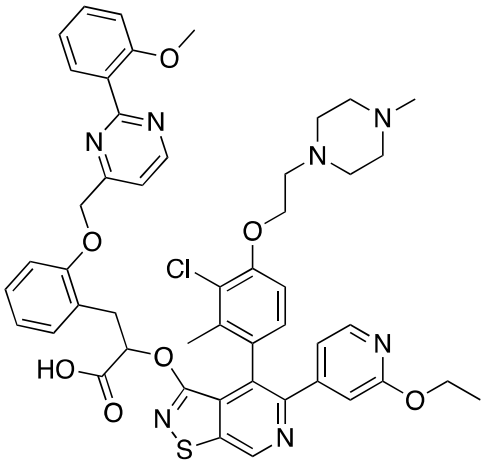
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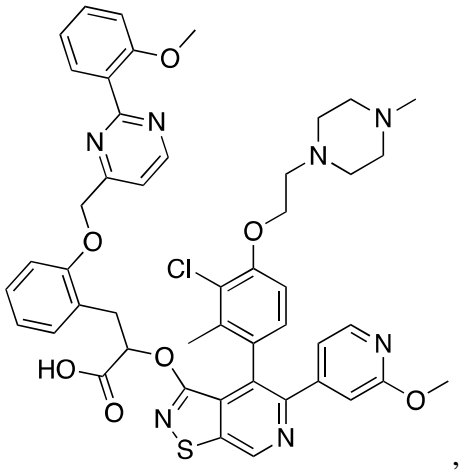
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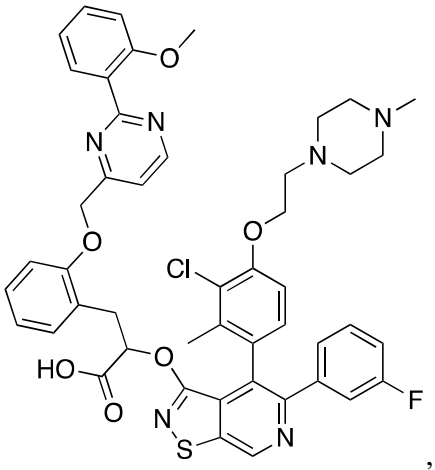
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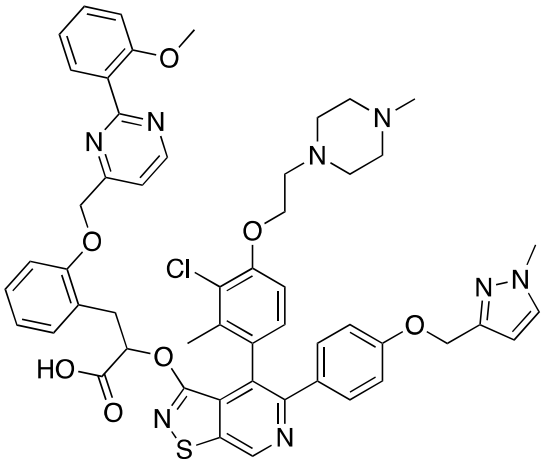
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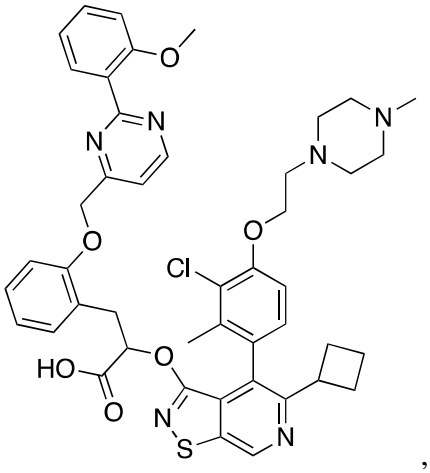
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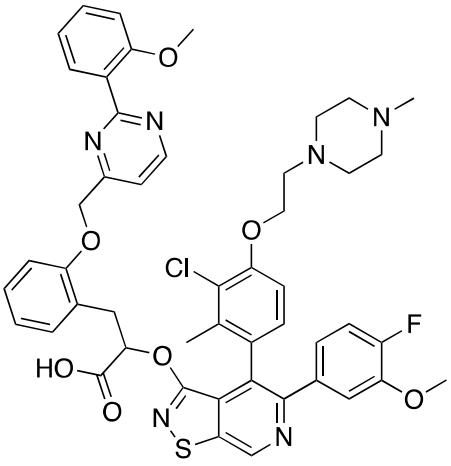
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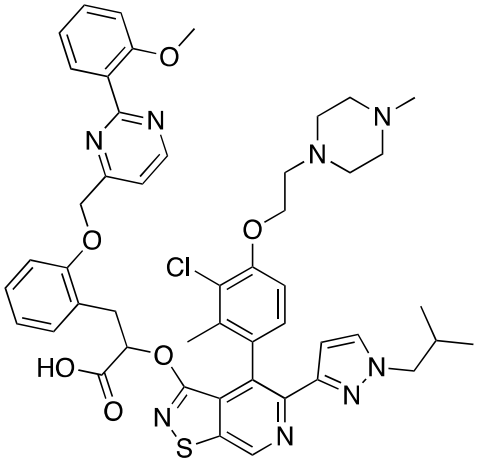
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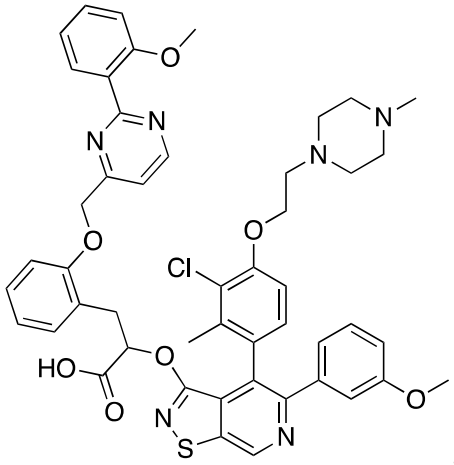
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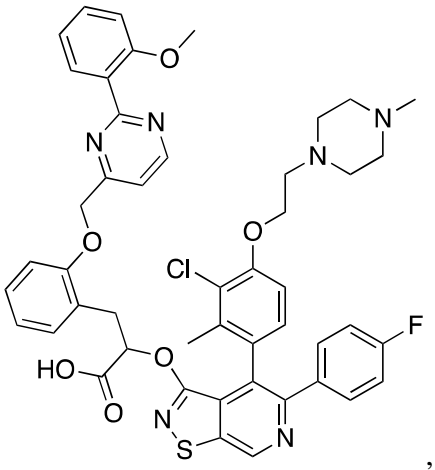
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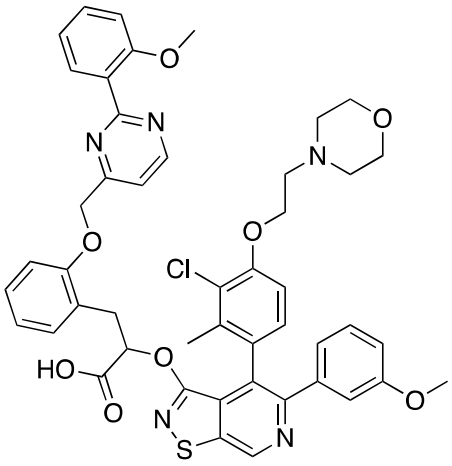
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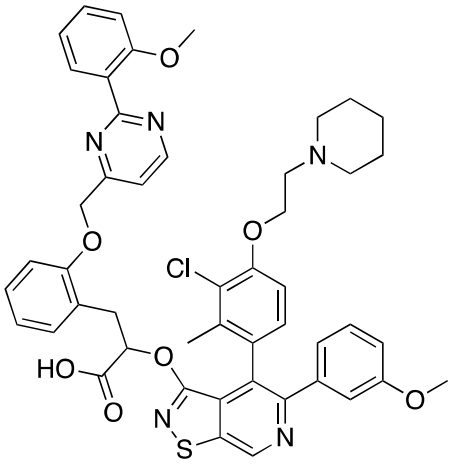
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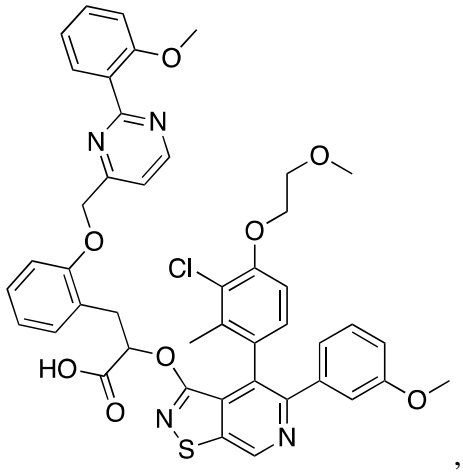
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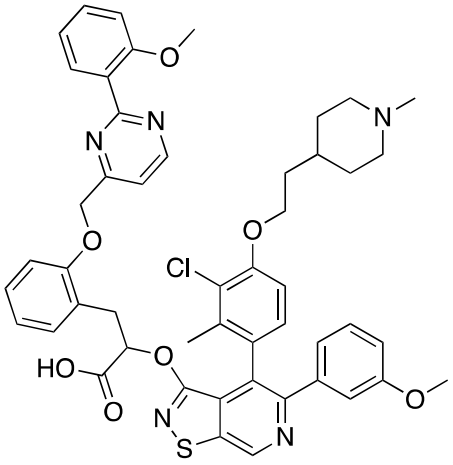
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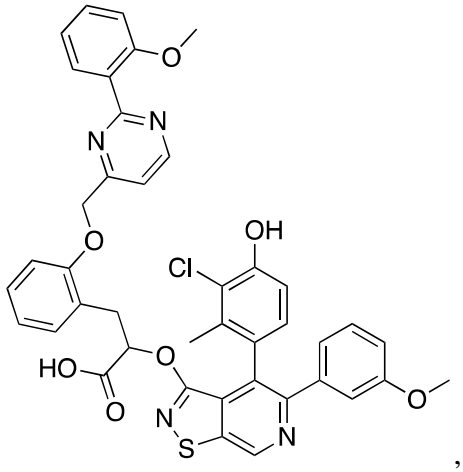
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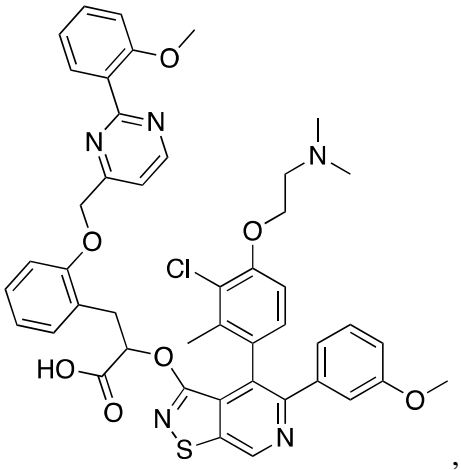
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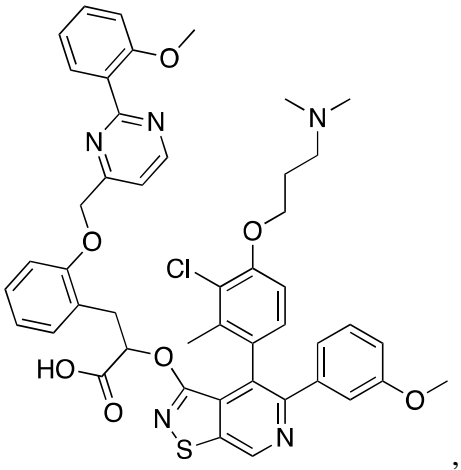
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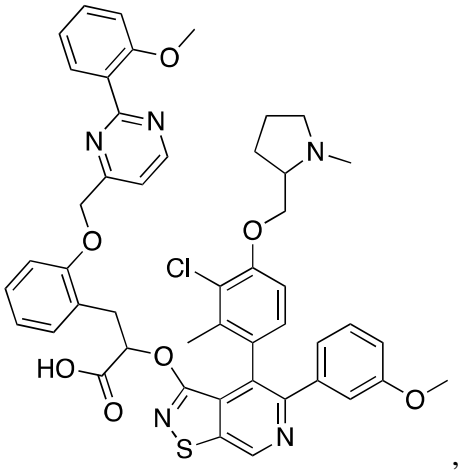
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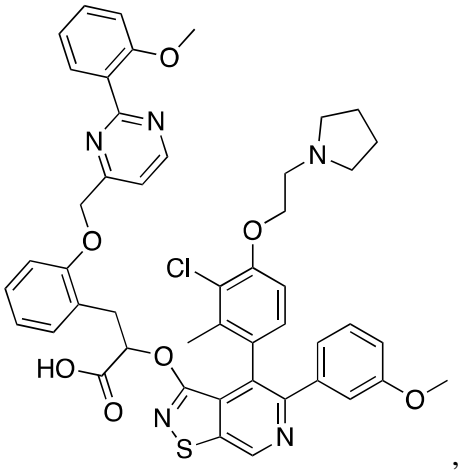
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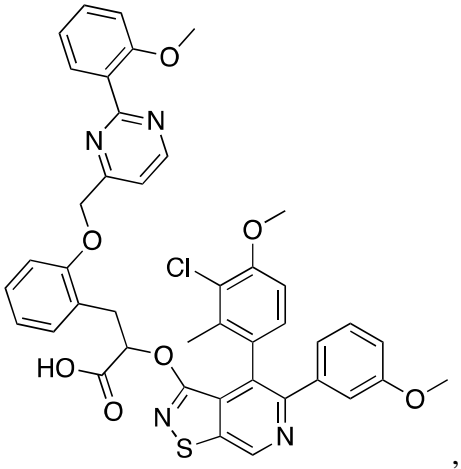
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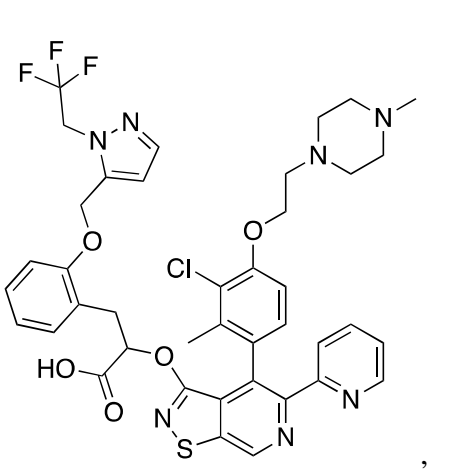
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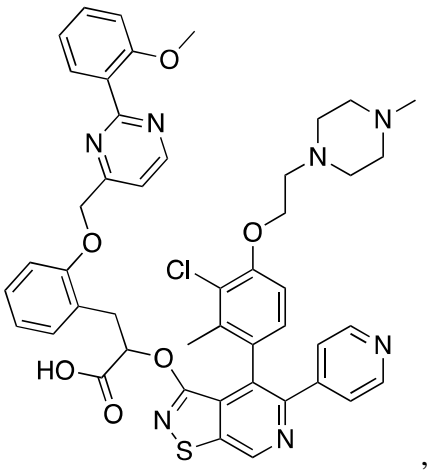
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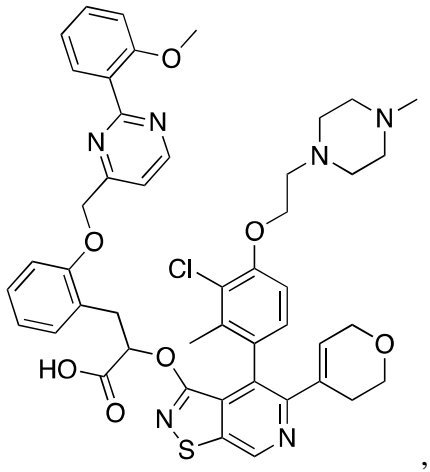
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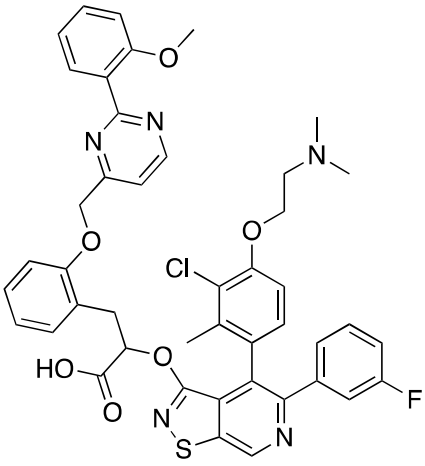
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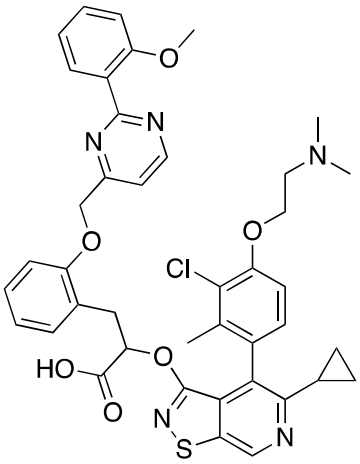
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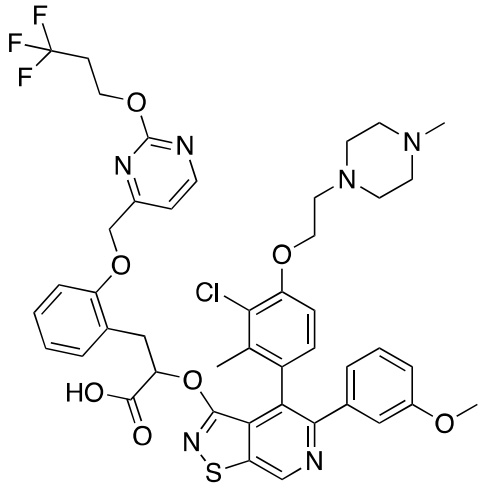
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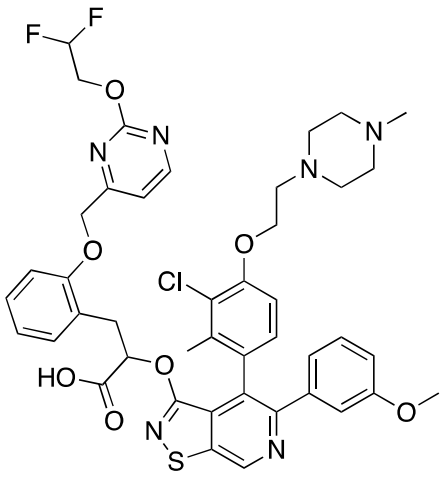
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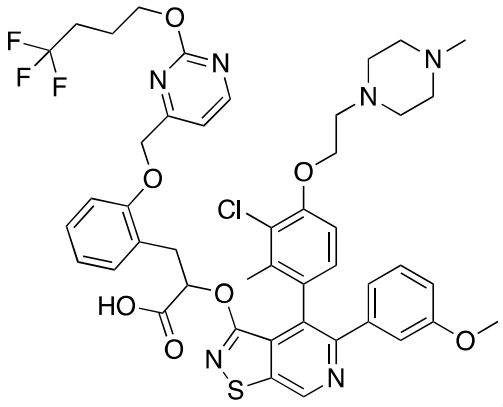
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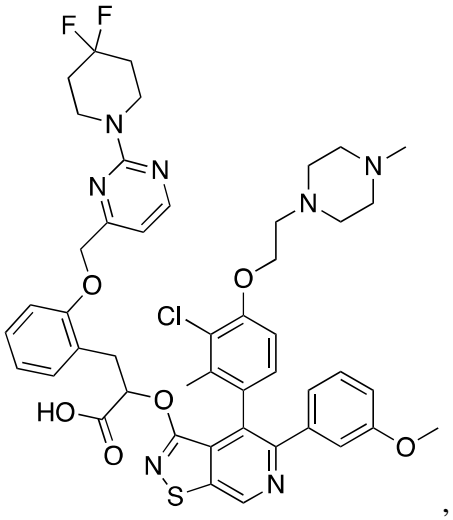
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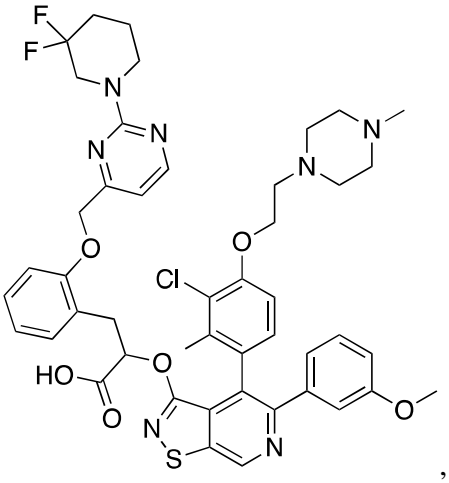
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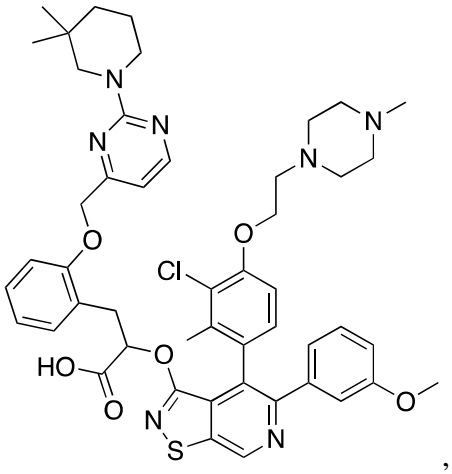
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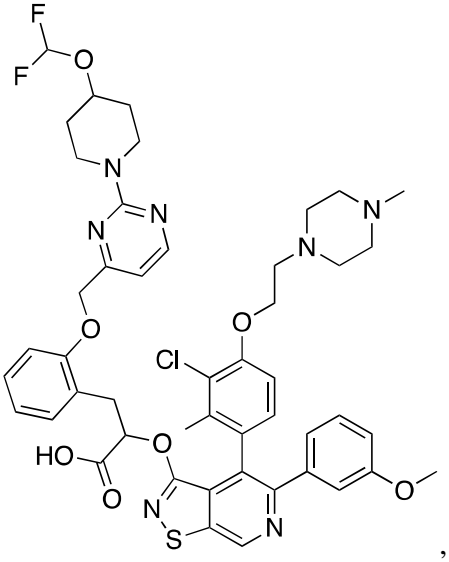
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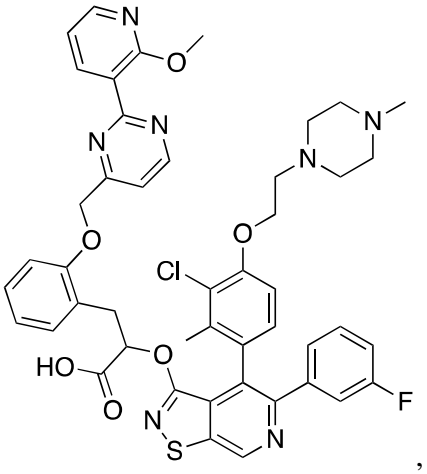
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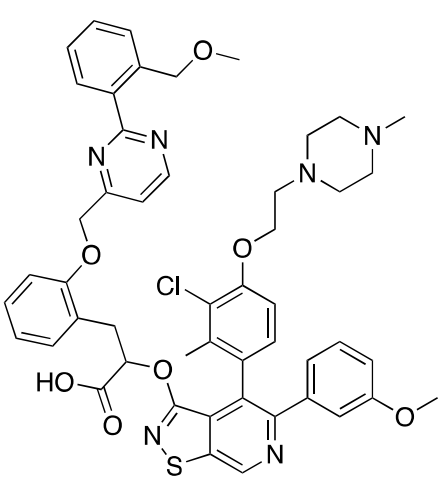
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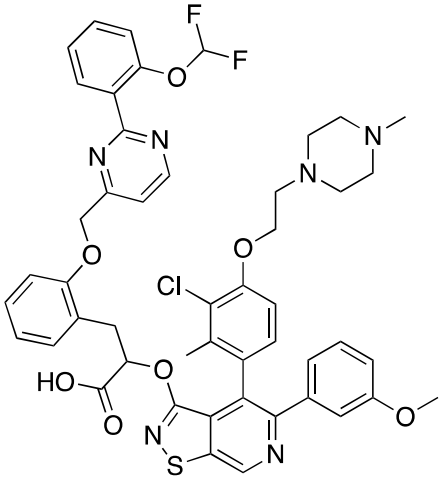
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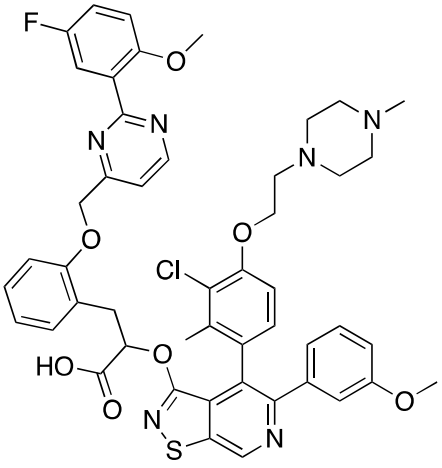
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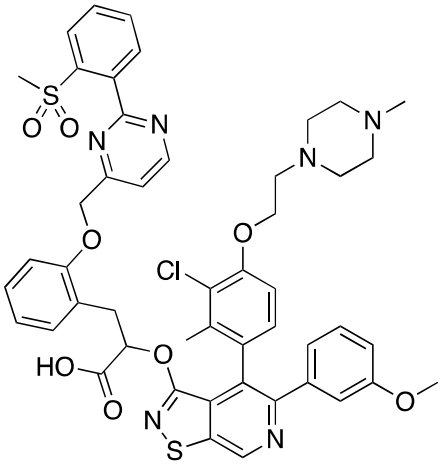
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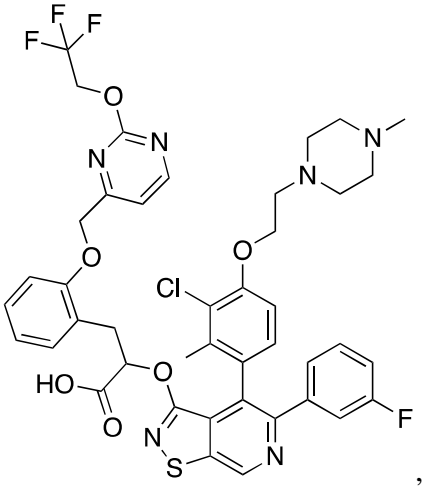
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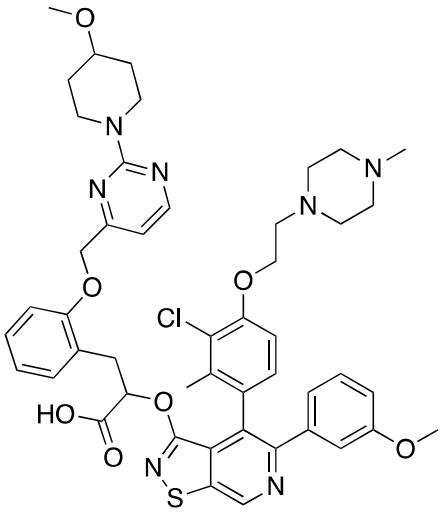
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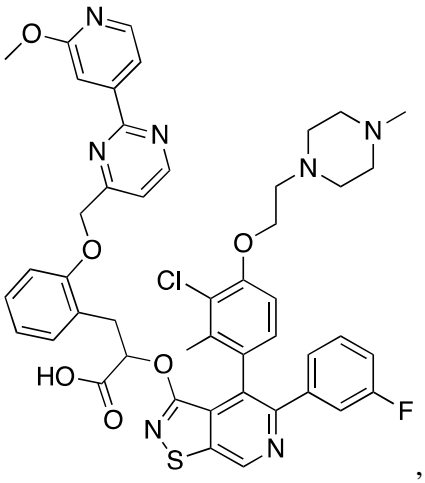
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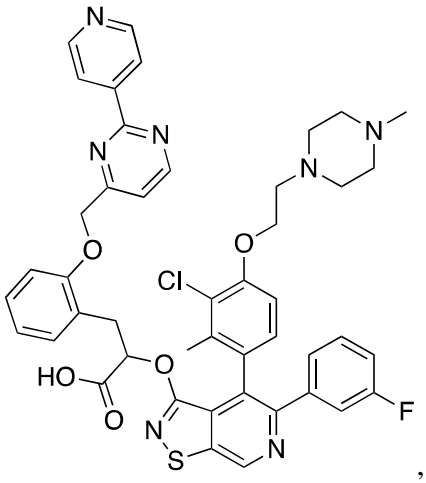
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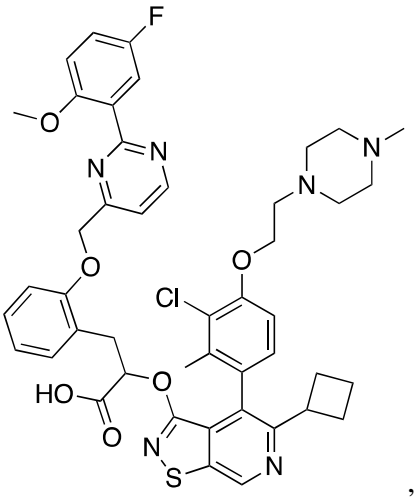
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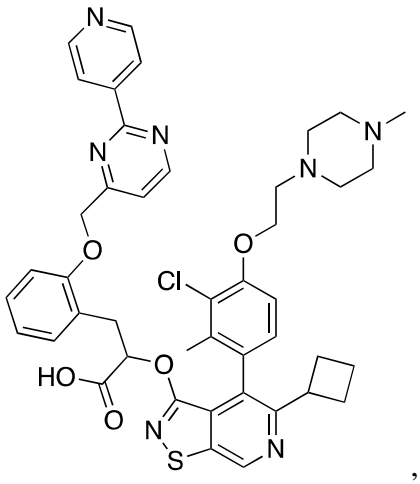
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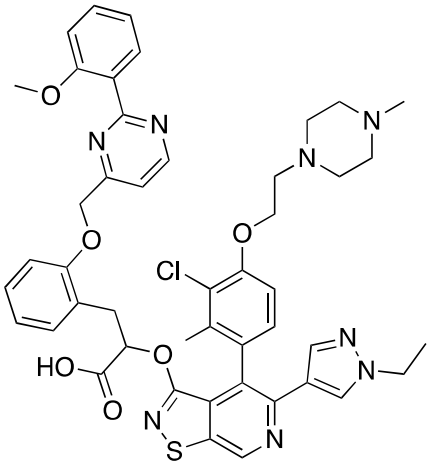
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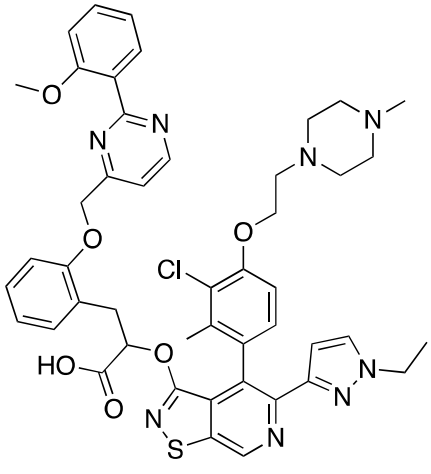
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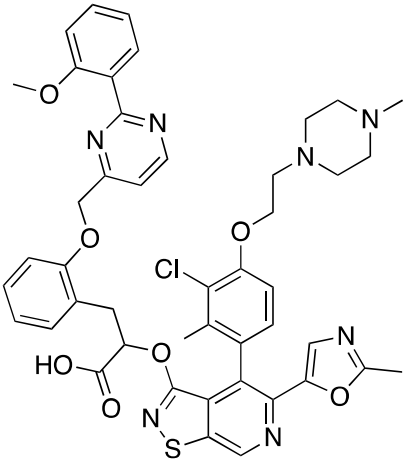
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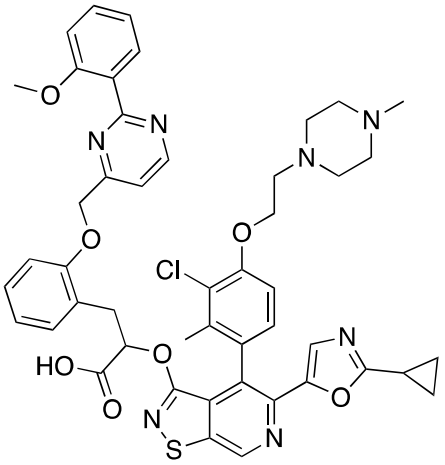
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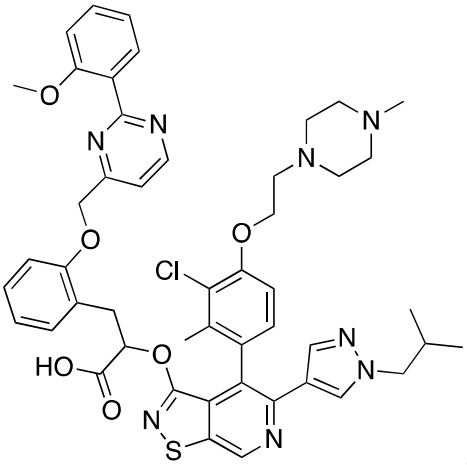
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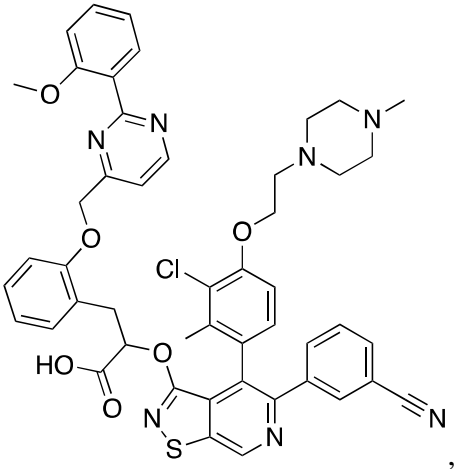
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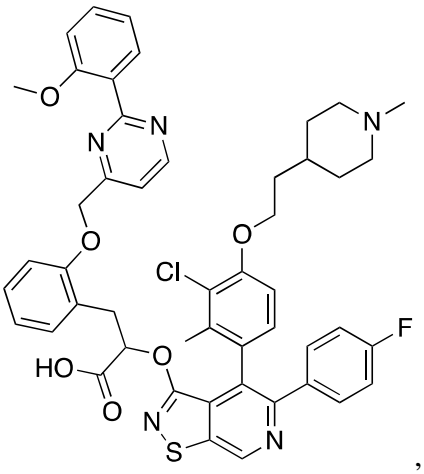
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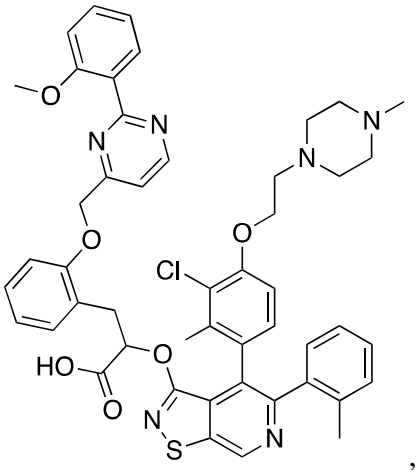
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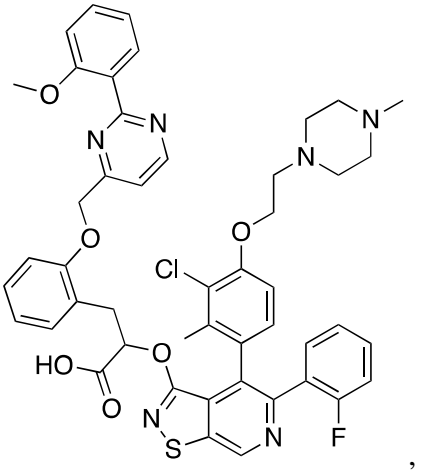
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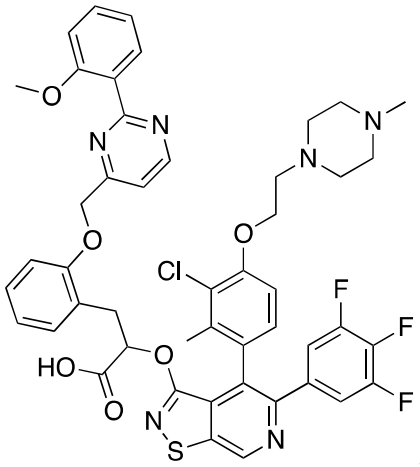
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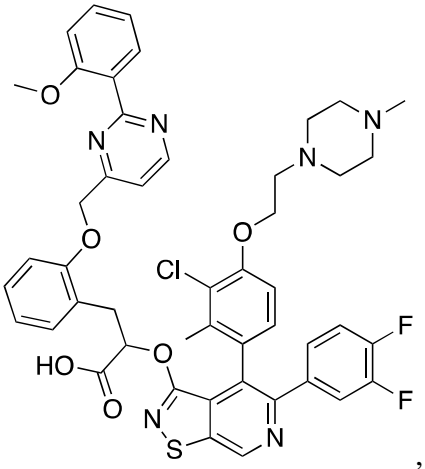
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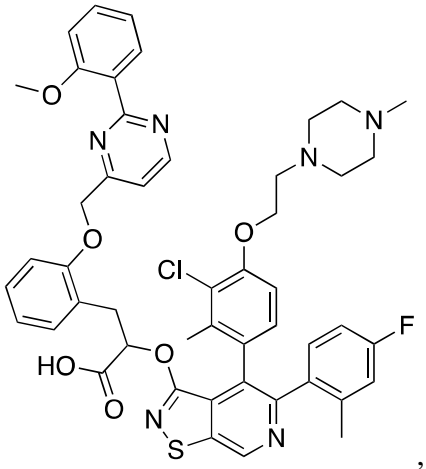
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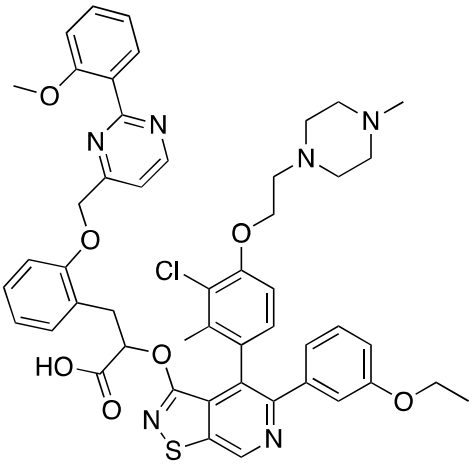
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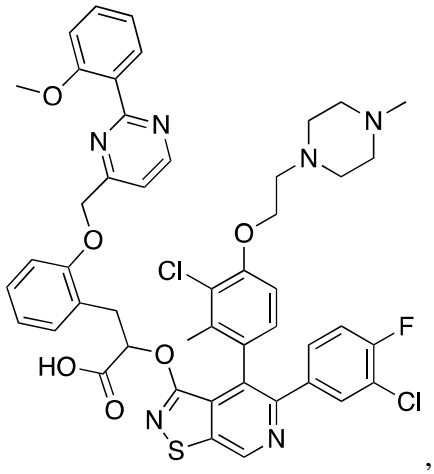
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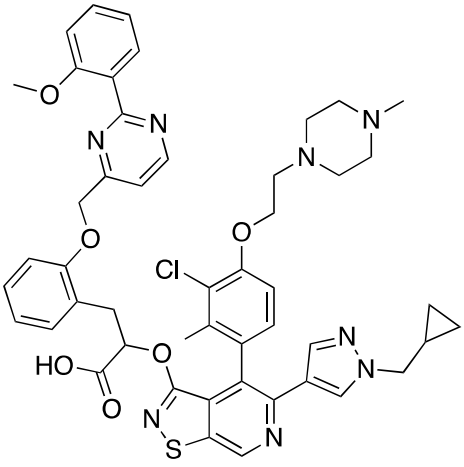
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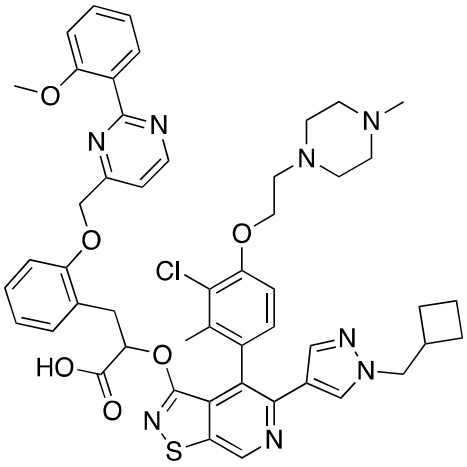
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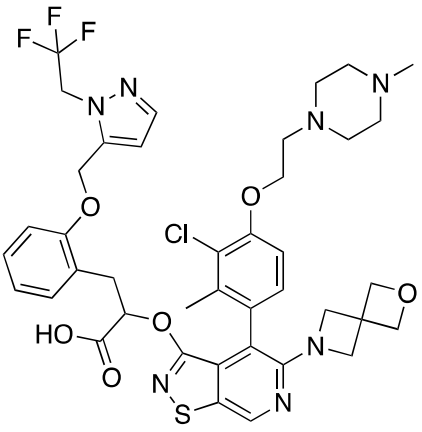
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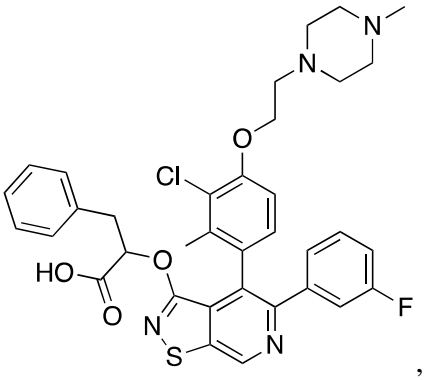
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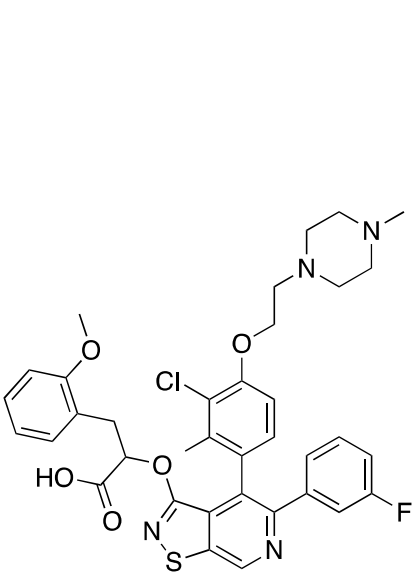
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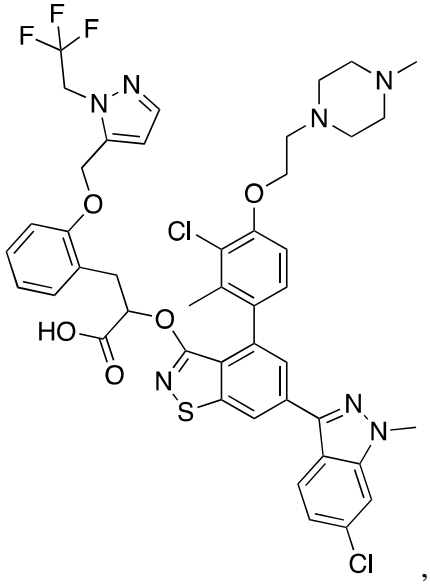
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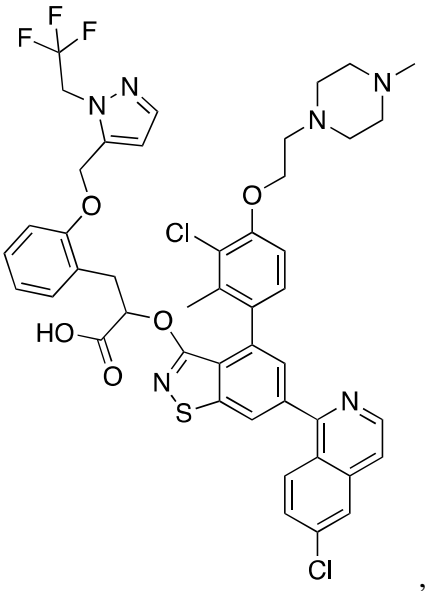
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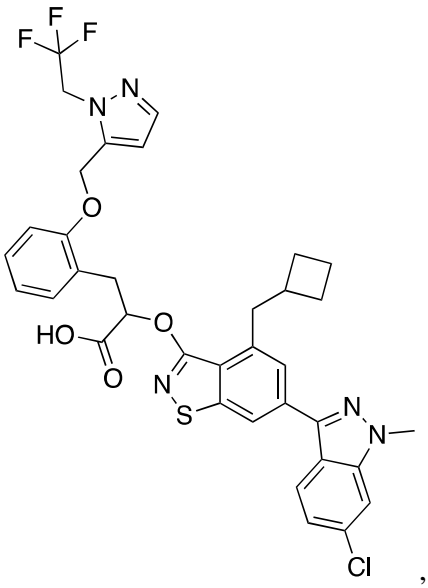
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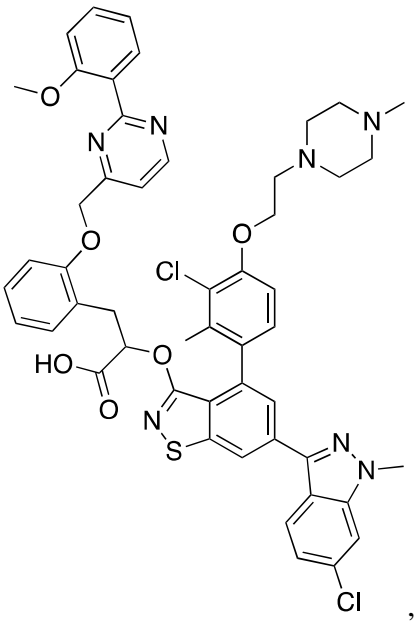
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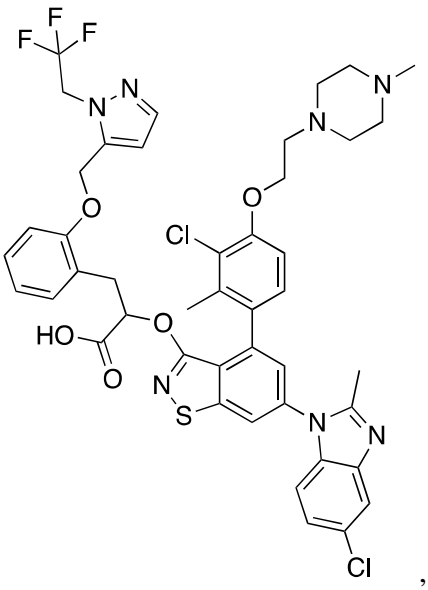
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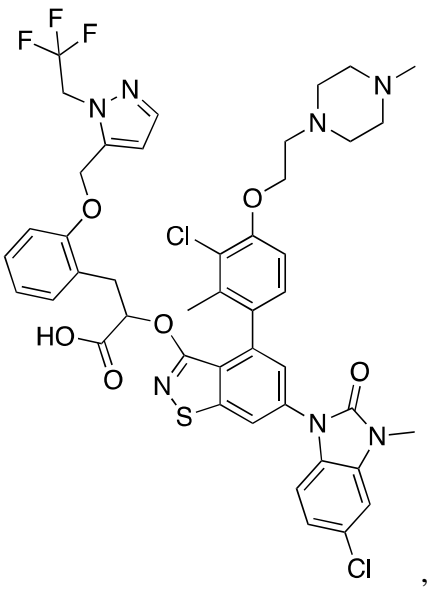
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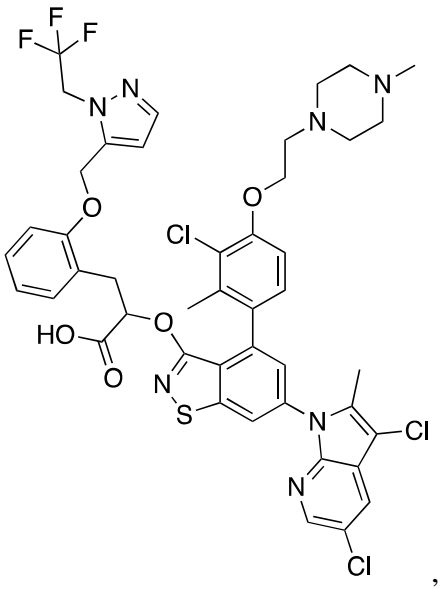
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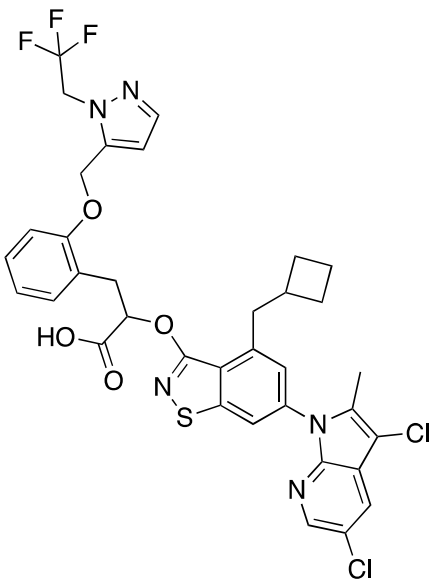
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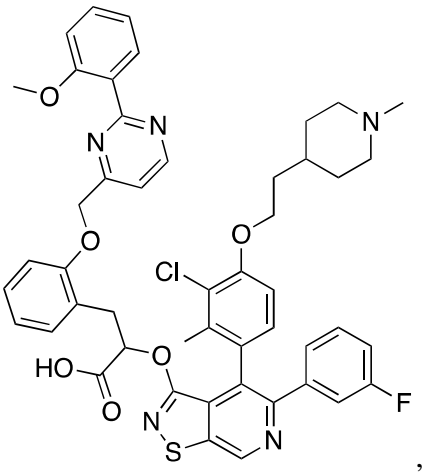
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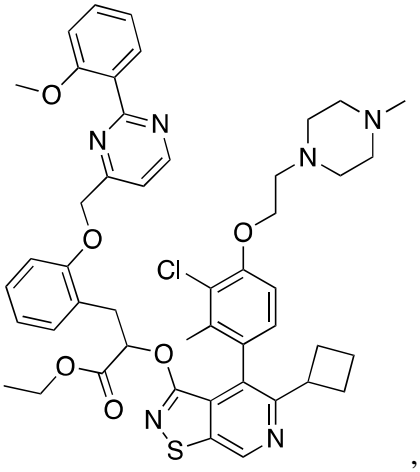
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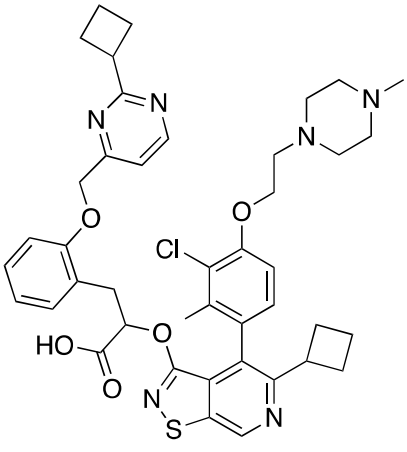
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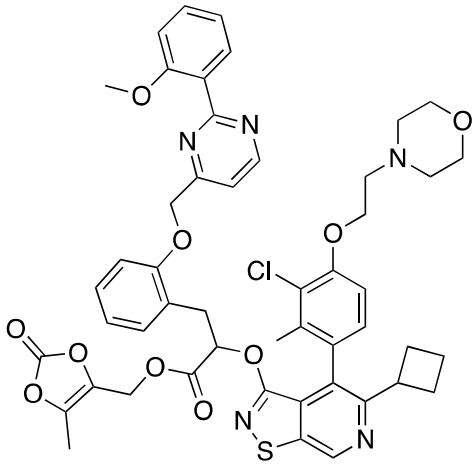
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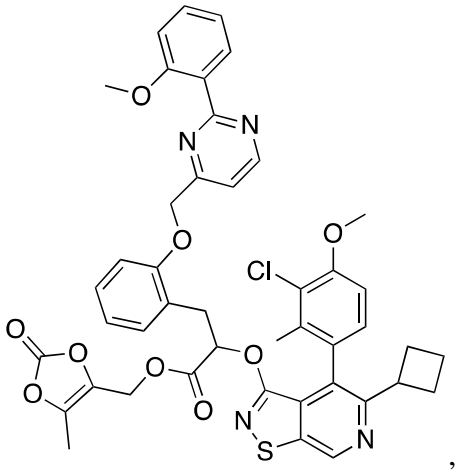
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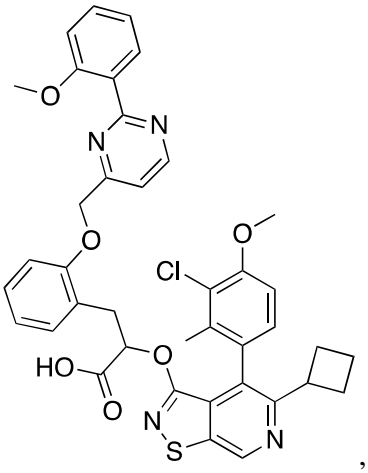
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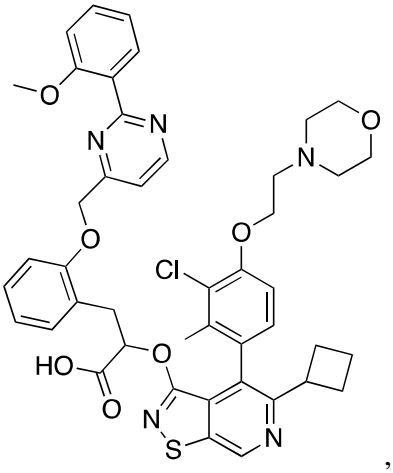
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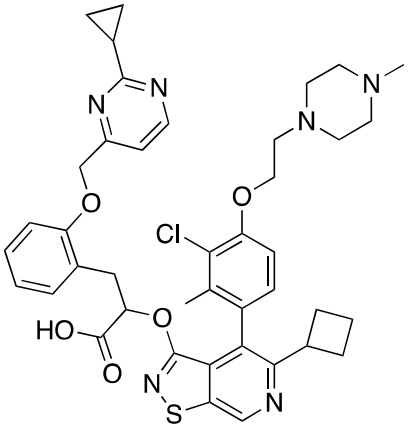
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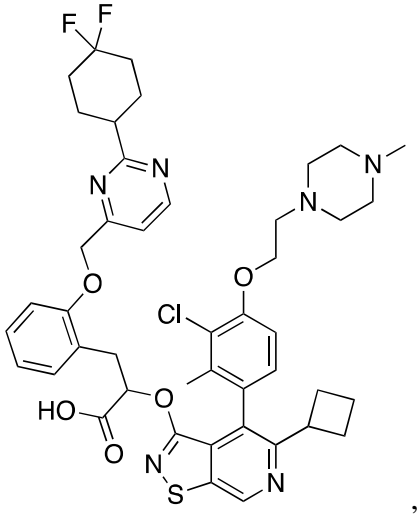
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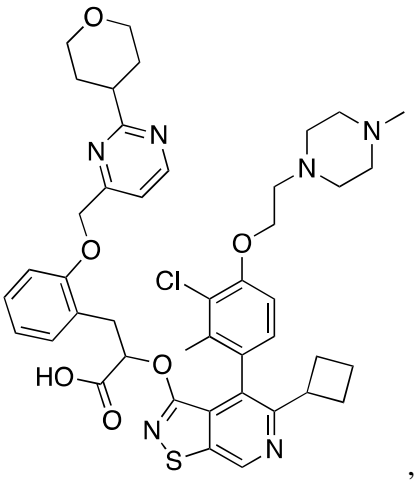
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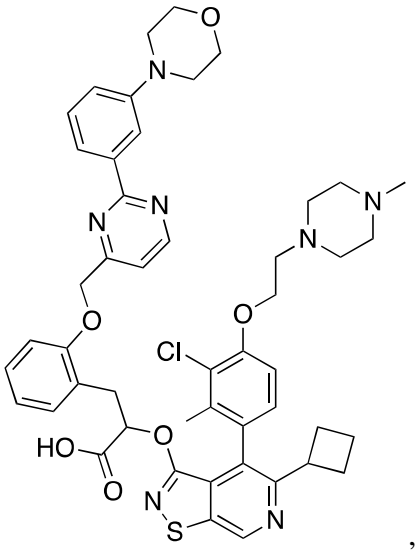
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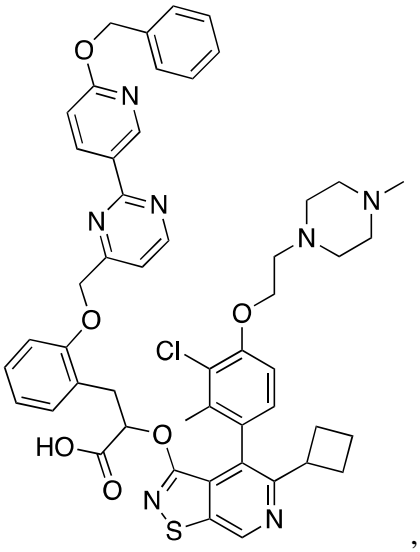
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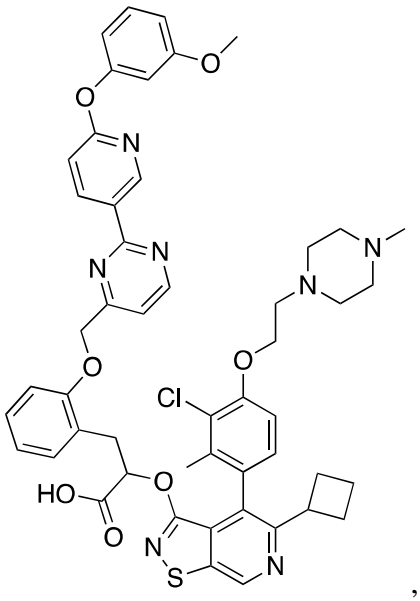
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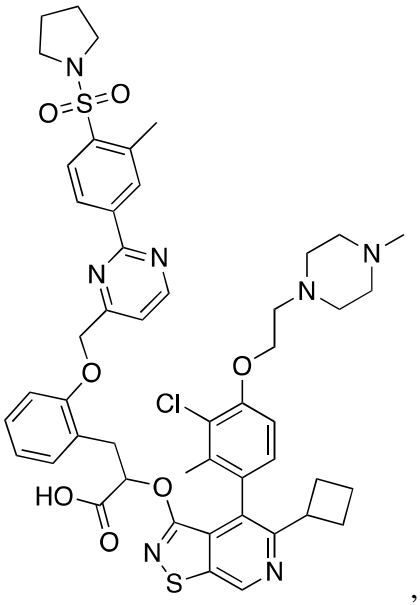
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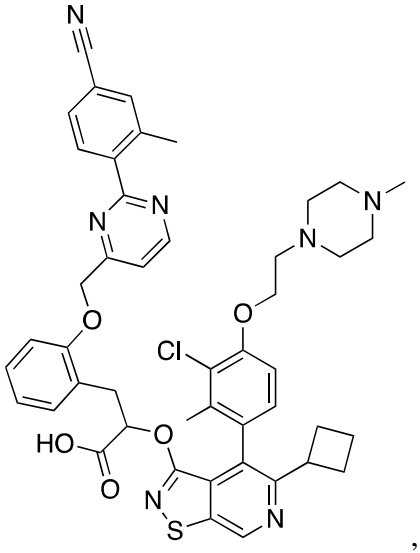
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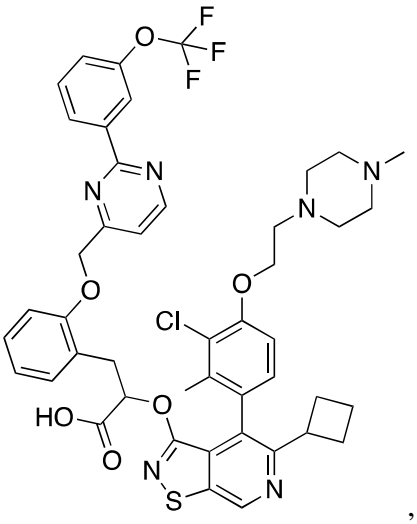
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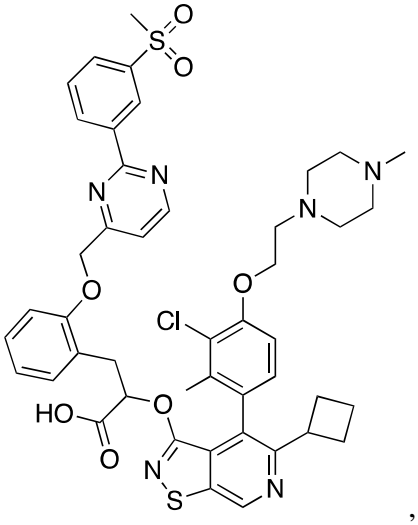
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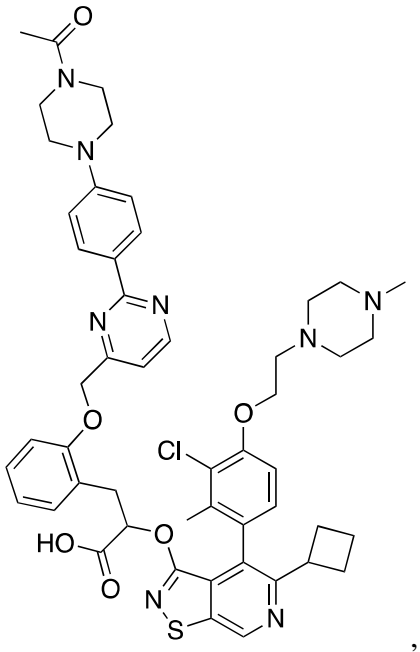
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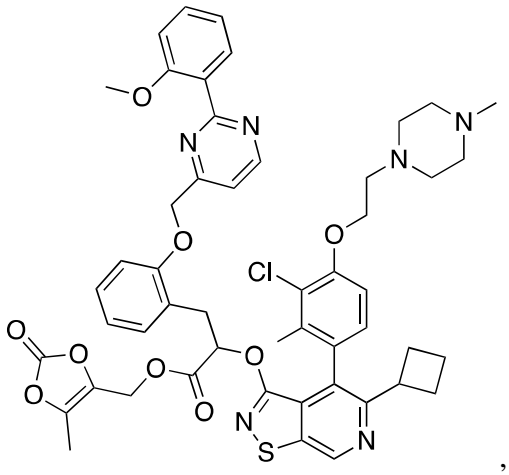
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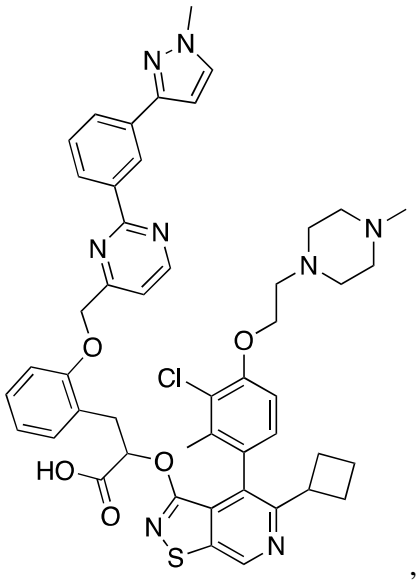
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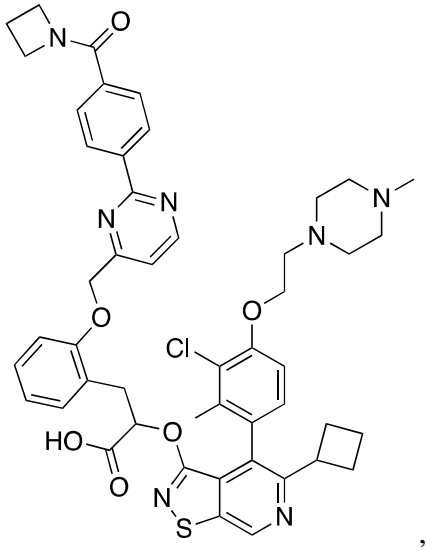
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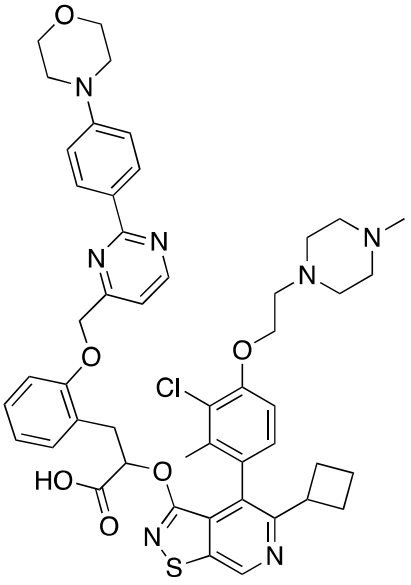
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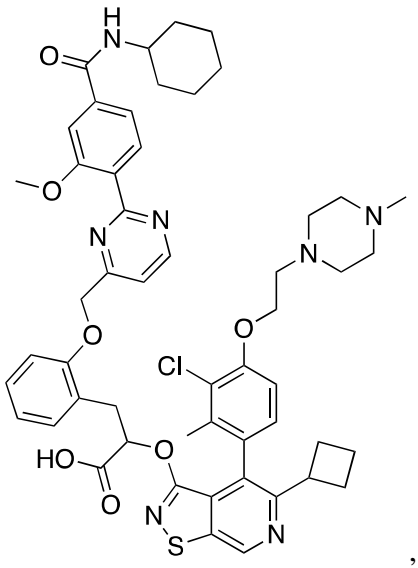
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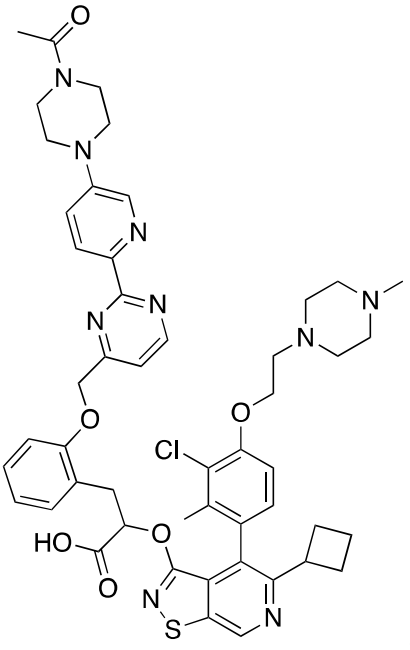
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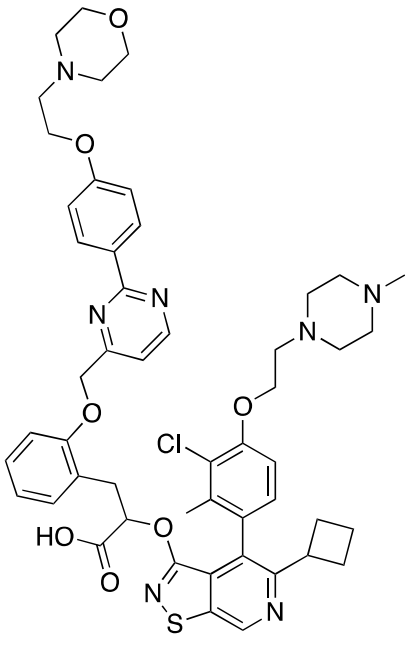
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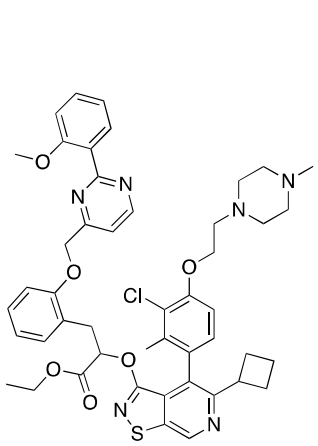
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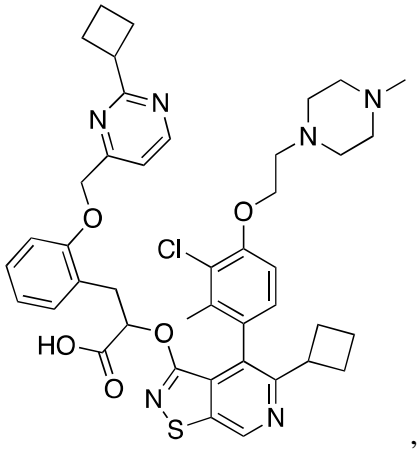
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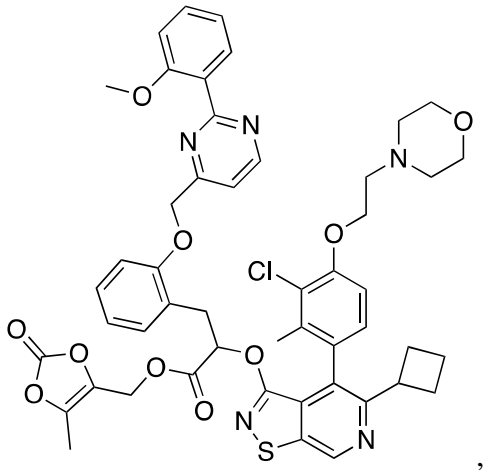
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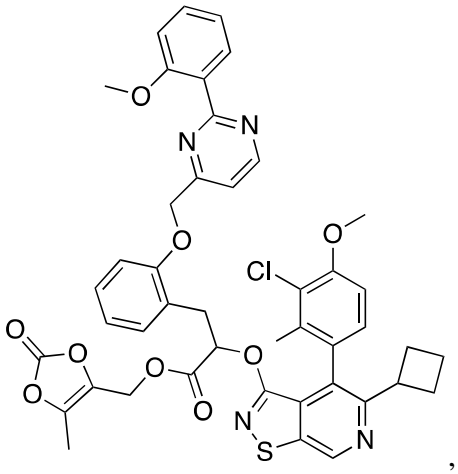
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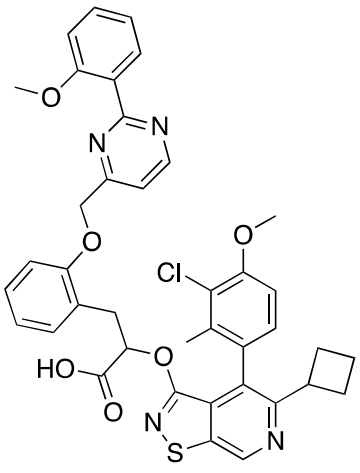
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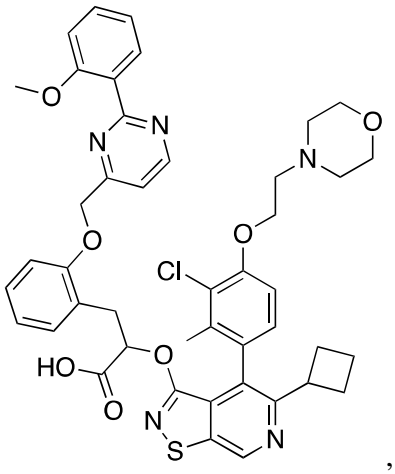
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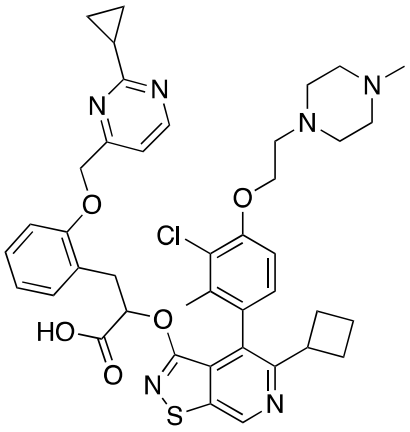
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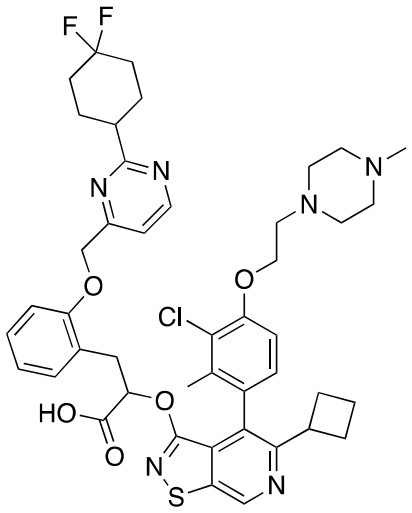
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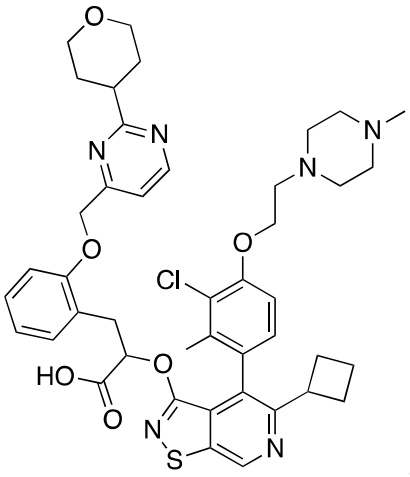
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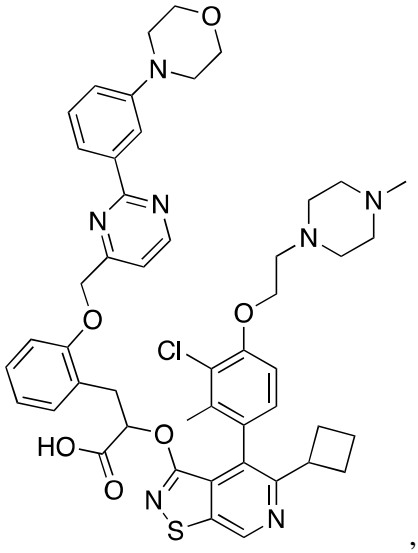
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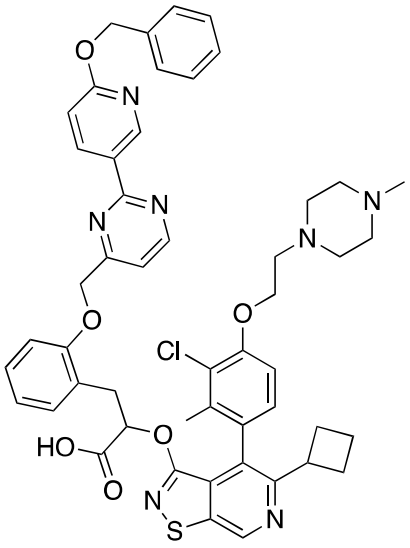
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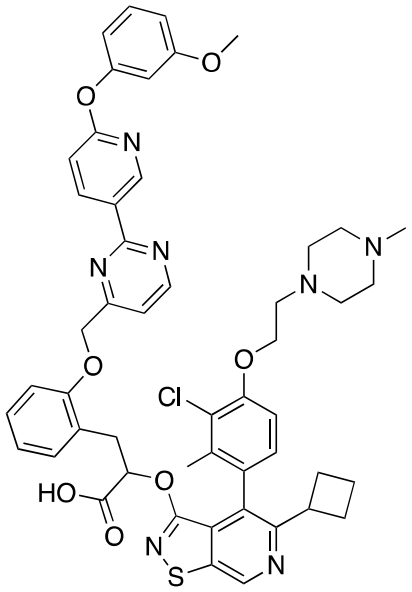
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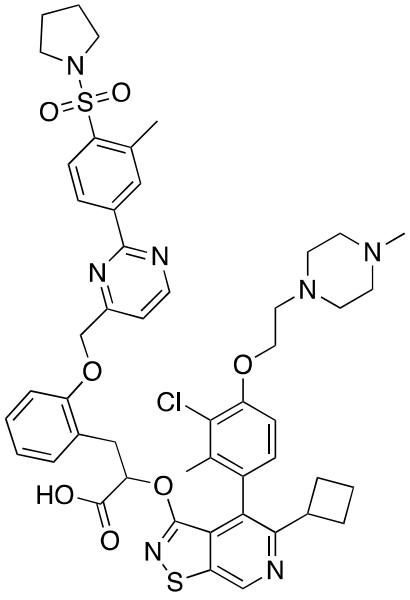
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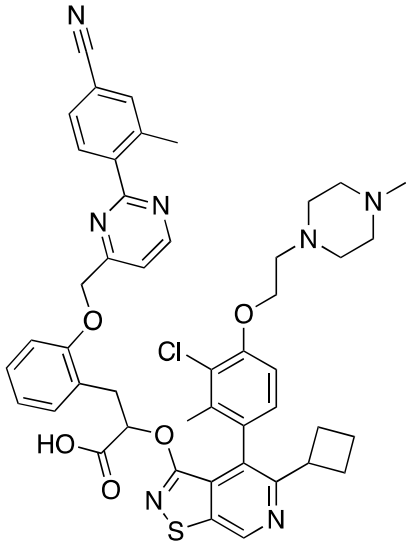
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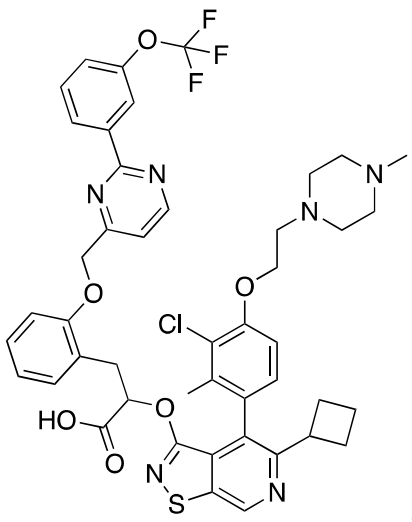
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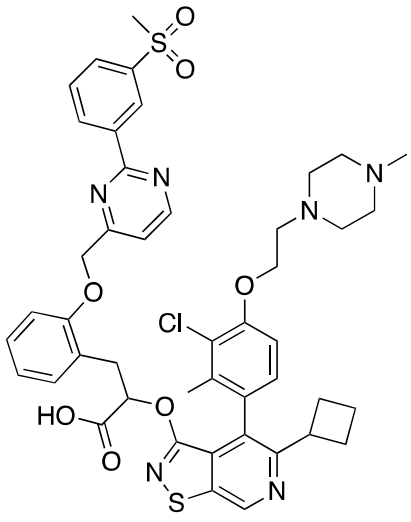
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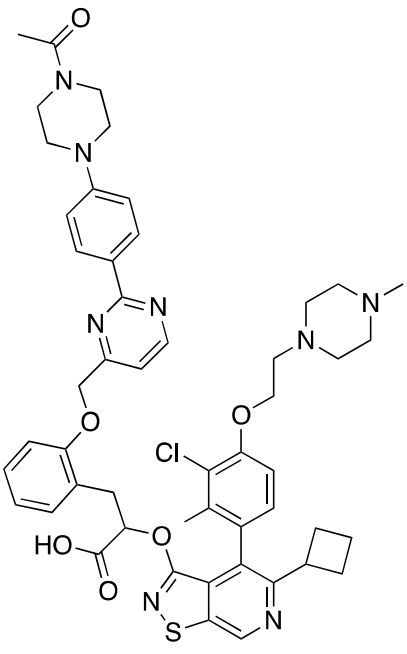
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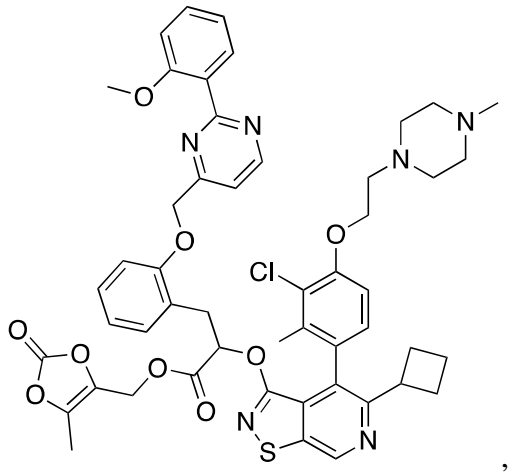
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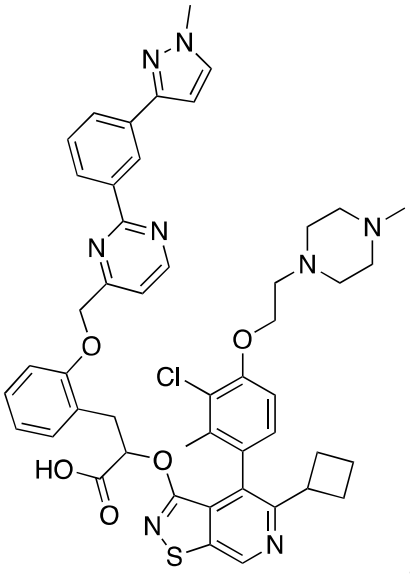
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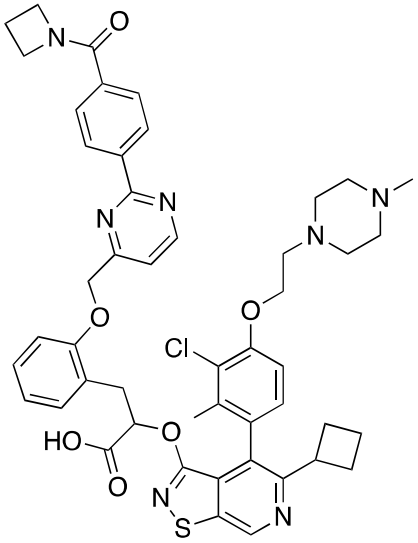
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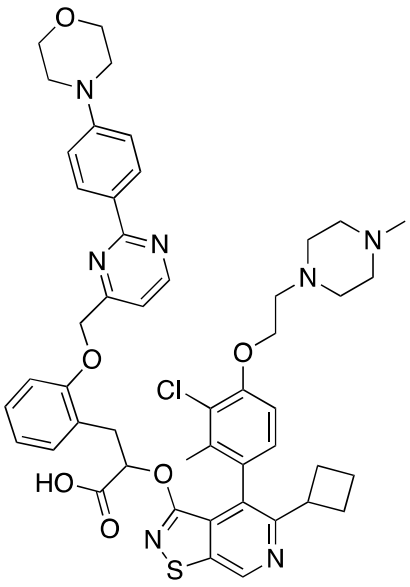
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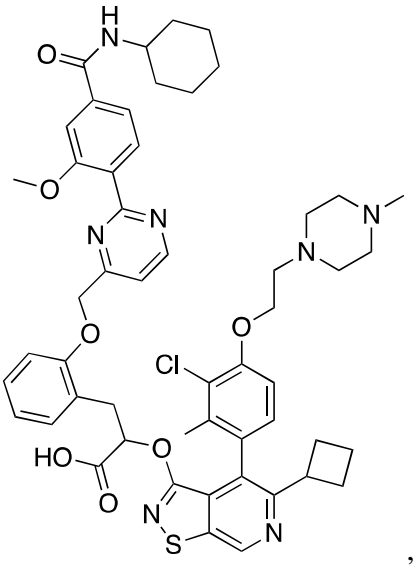
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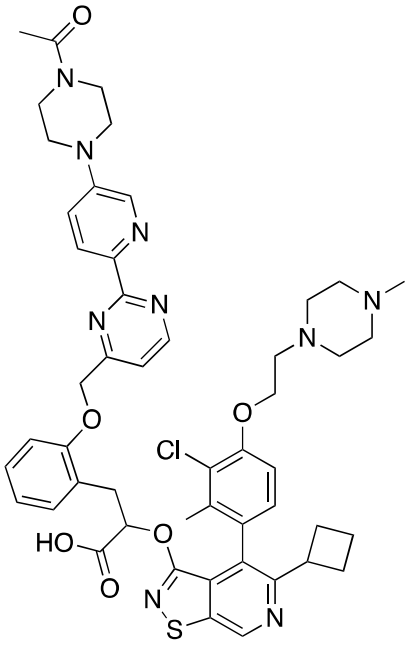

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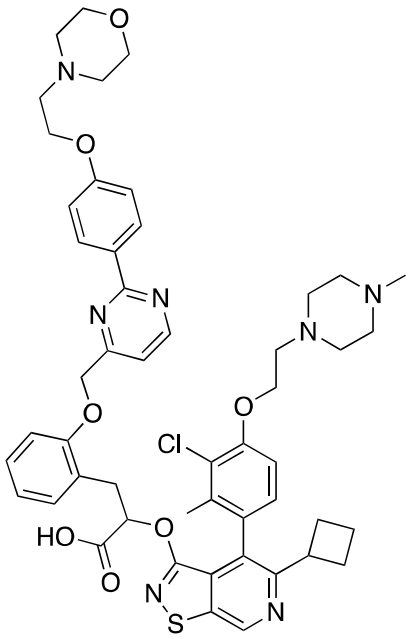

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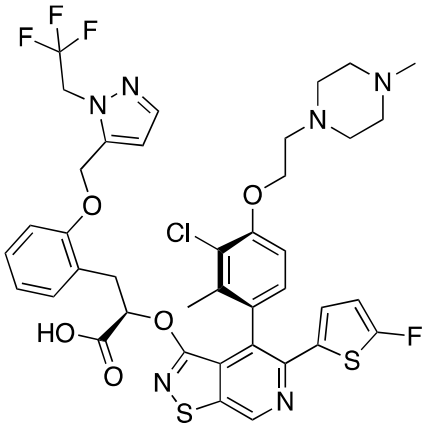
30. A compound selected from:



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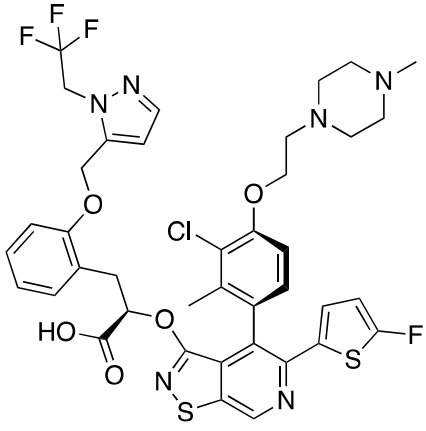

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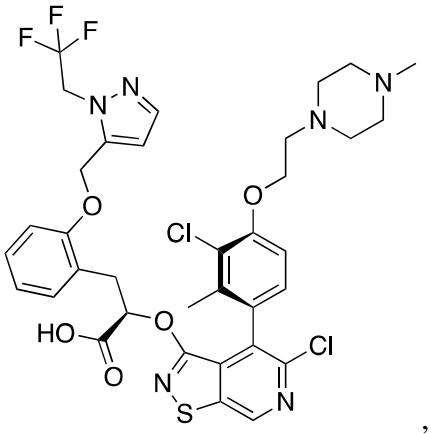
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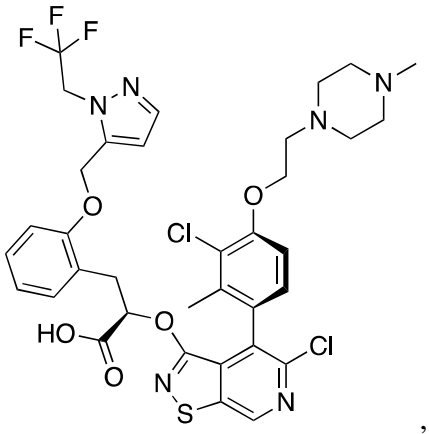
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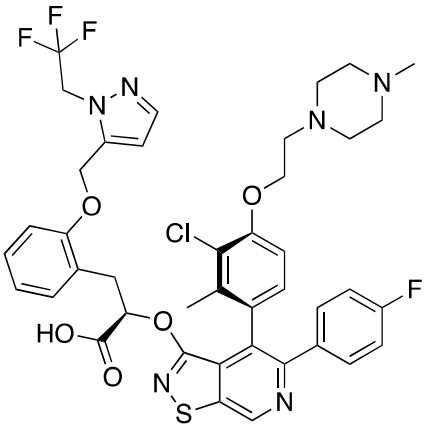
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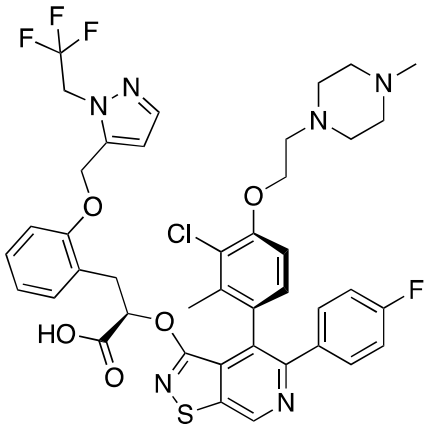
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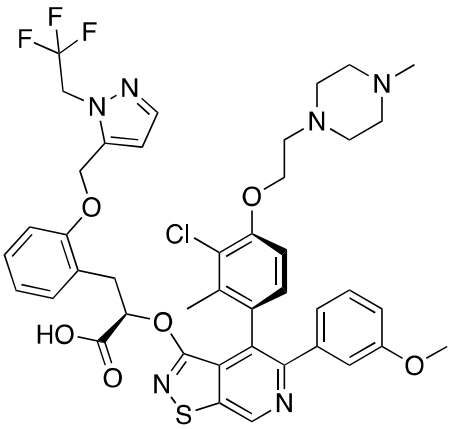
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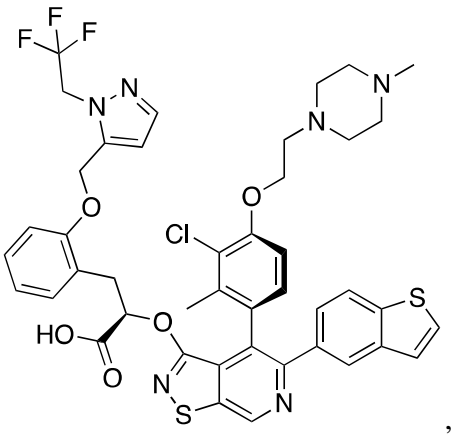
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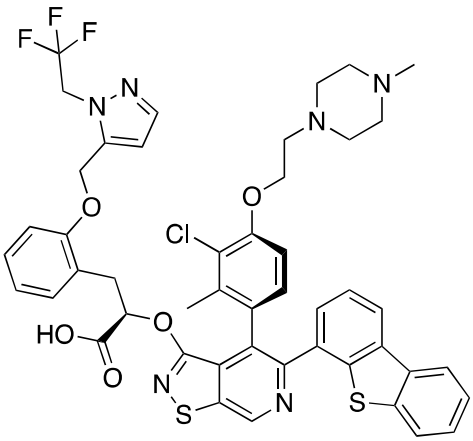
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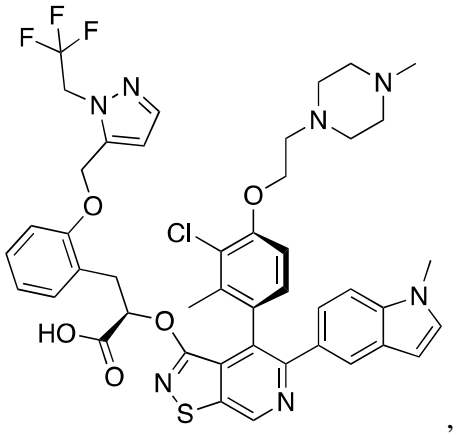
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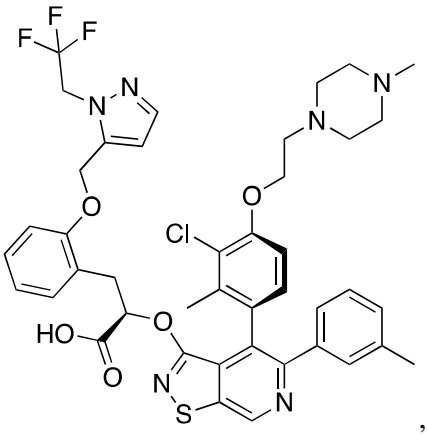
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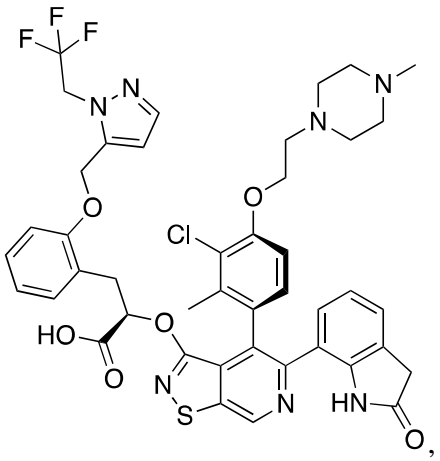
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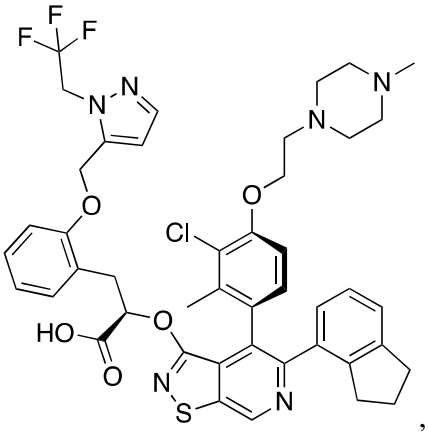
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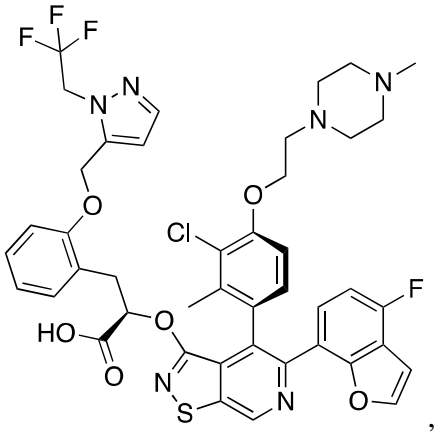
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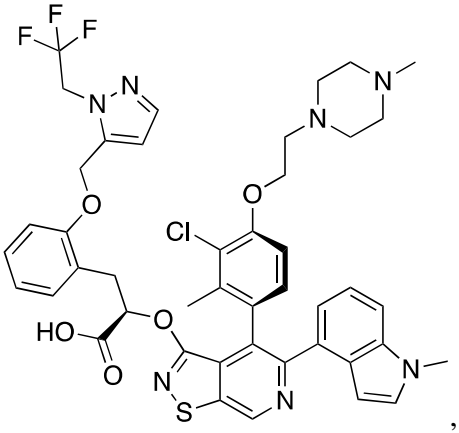
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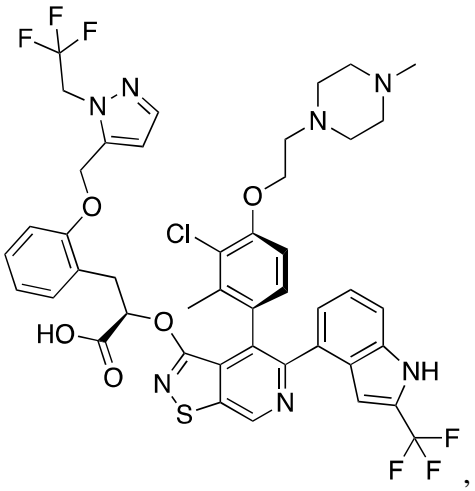
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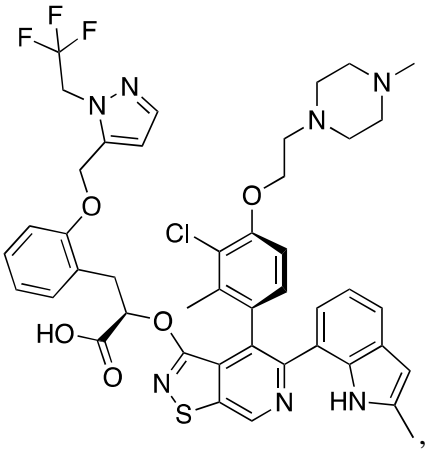
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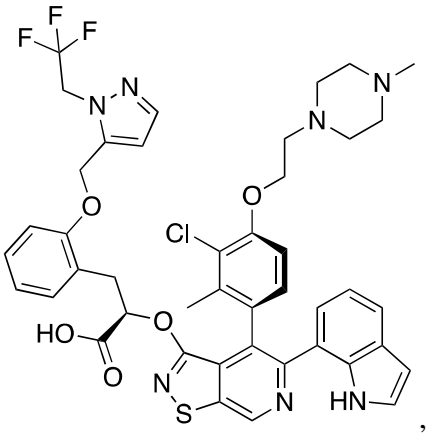
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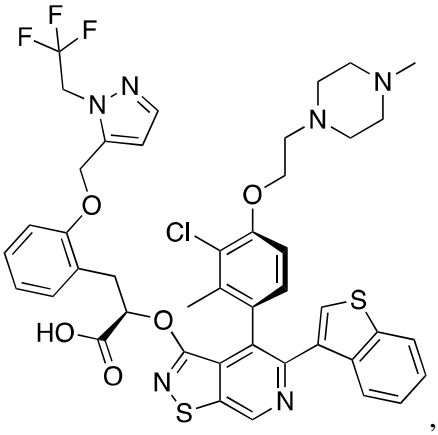
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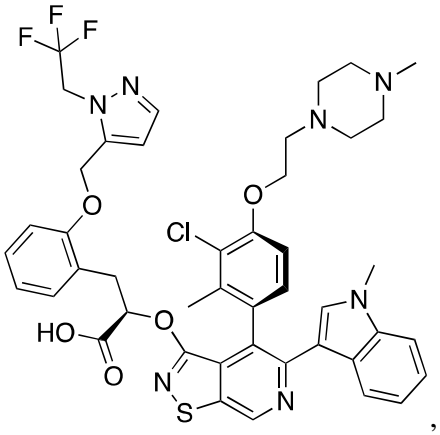
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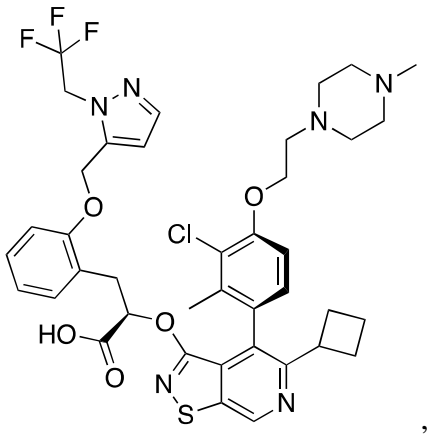
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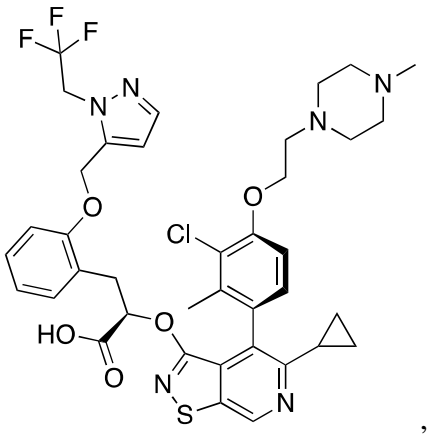
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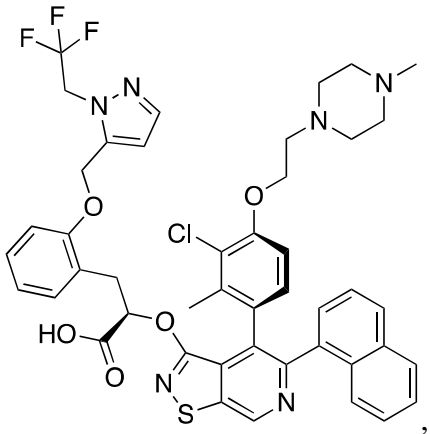
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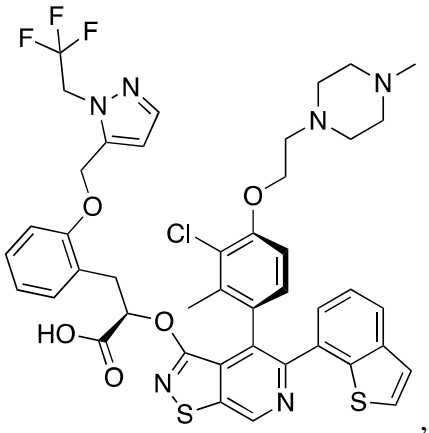
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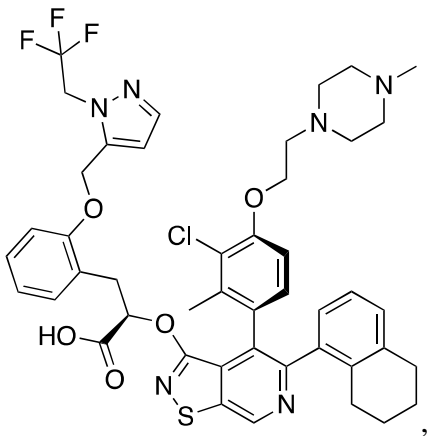
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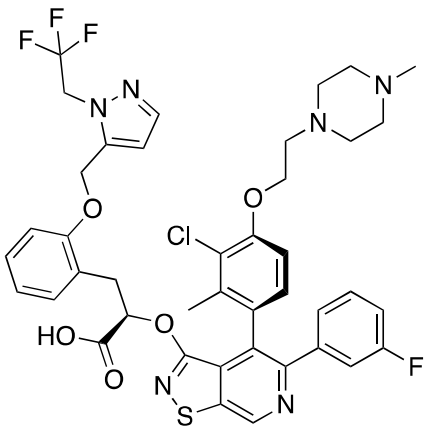
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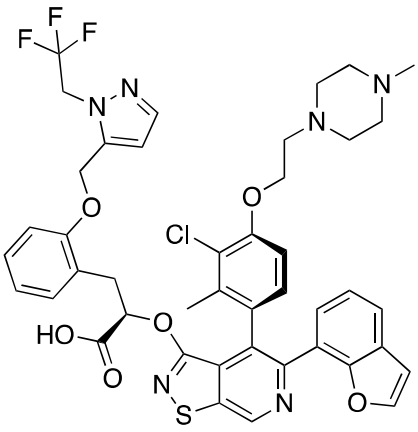
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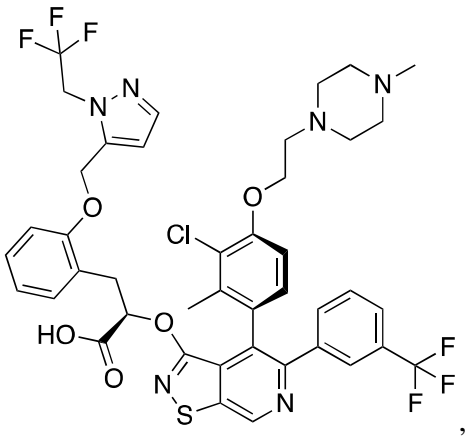
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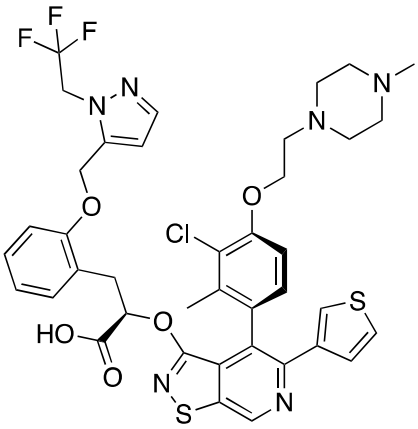
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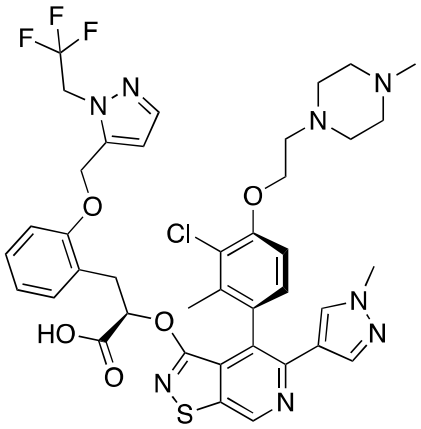
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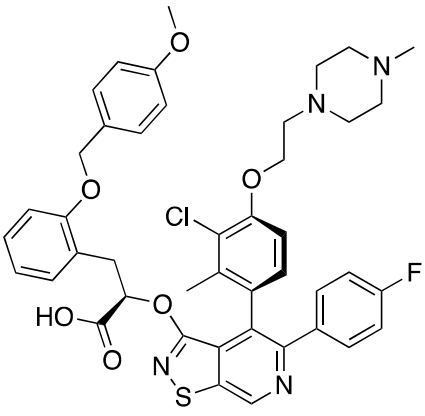
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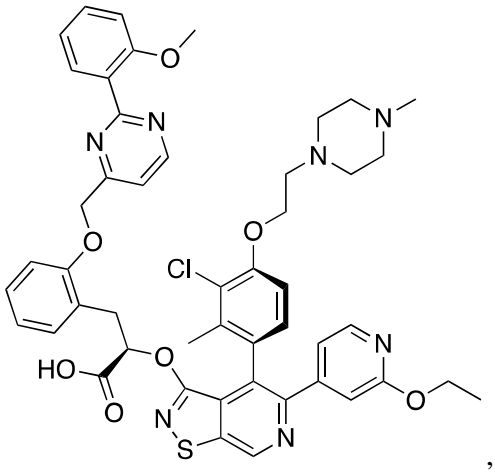
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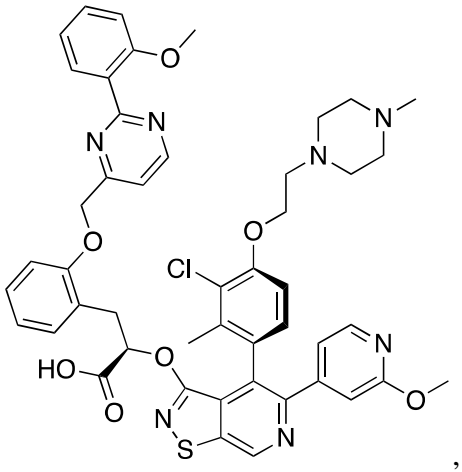
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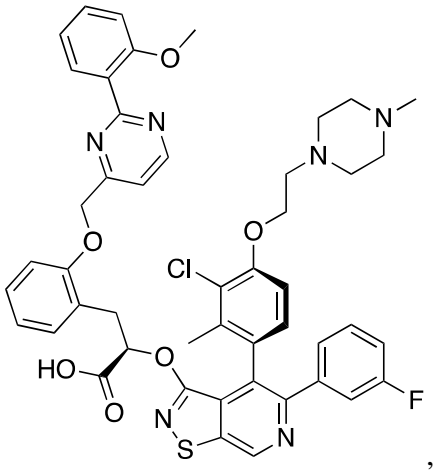
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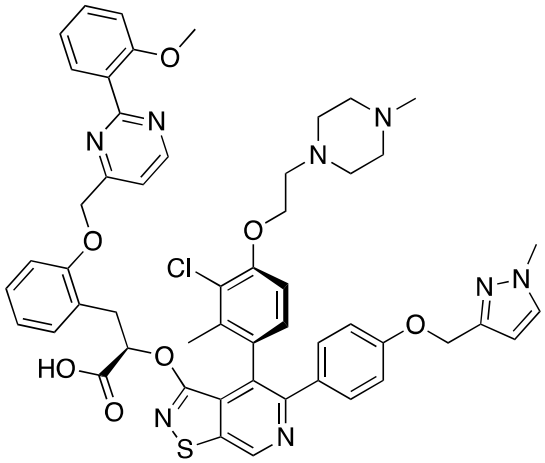
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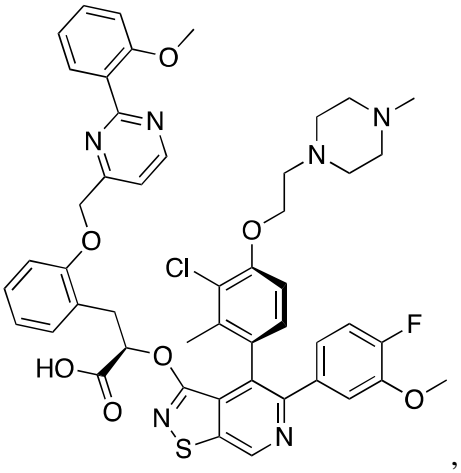
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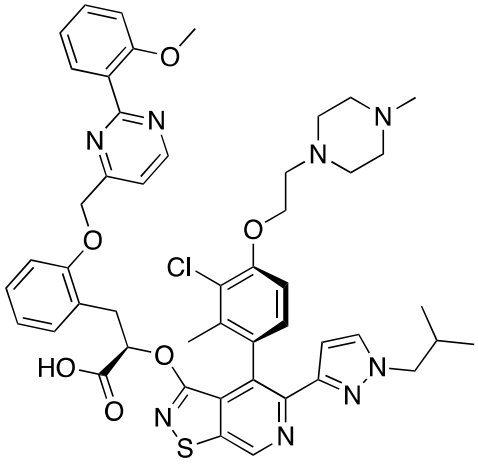
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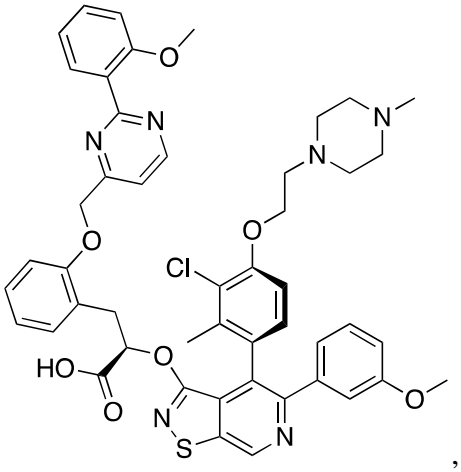
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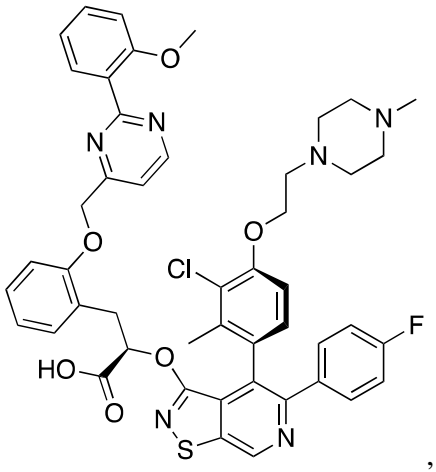
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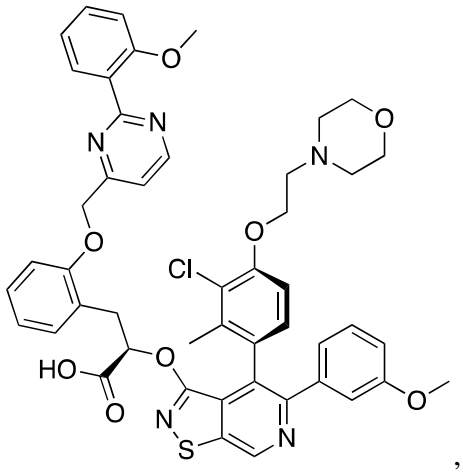
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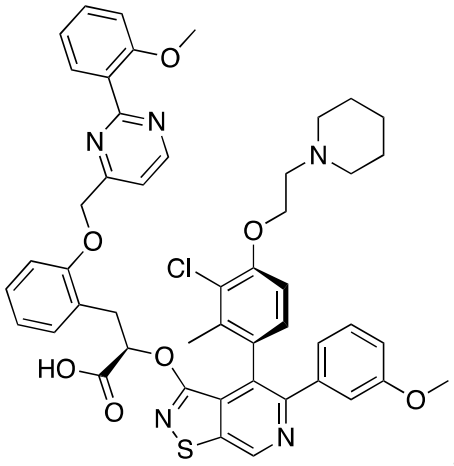
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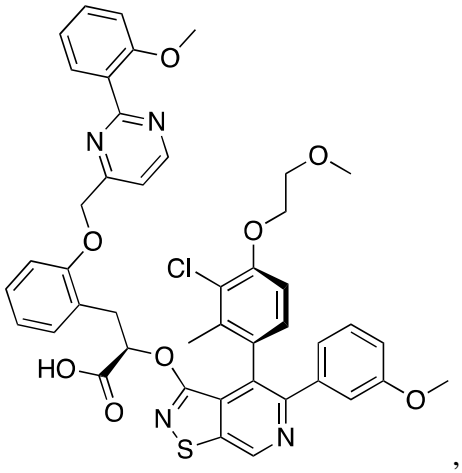
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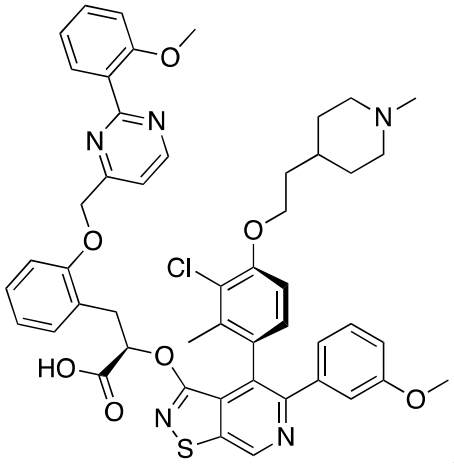
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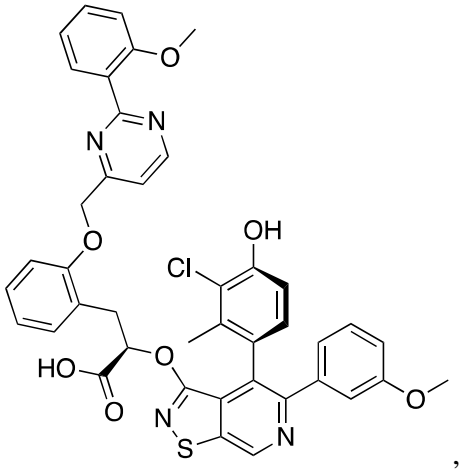
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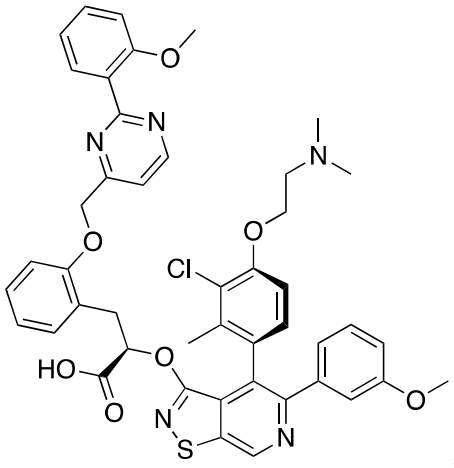
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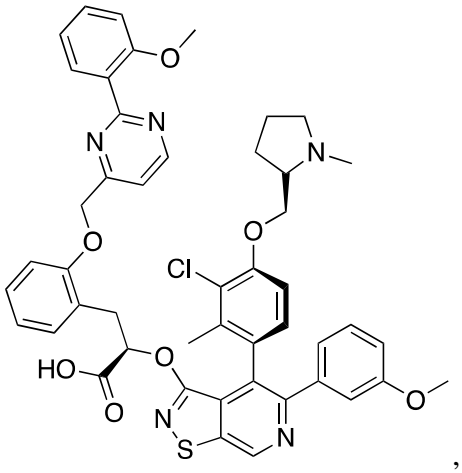
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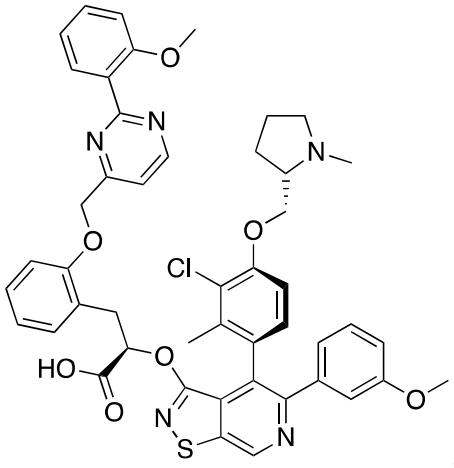
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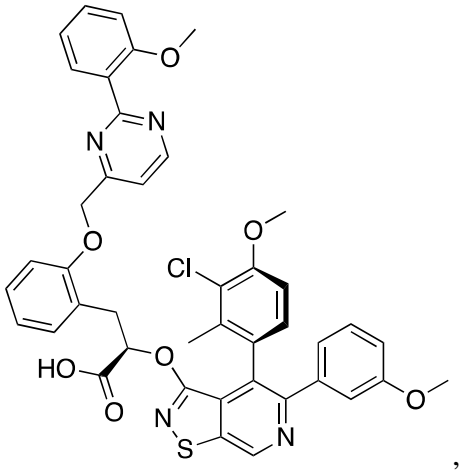
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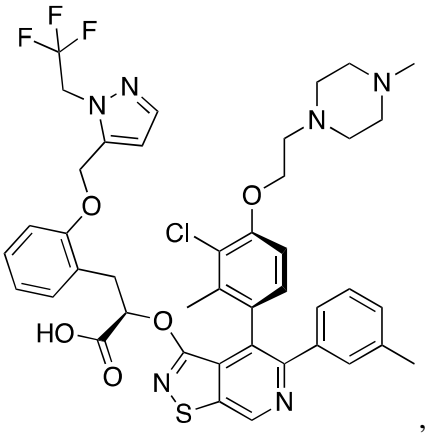
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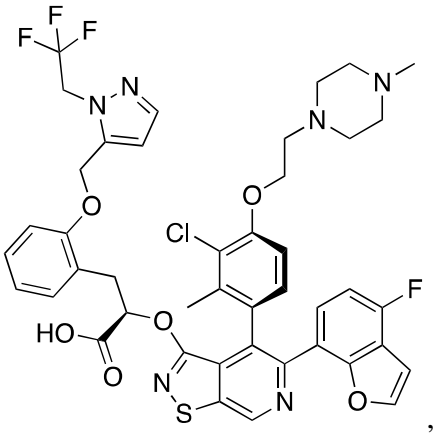
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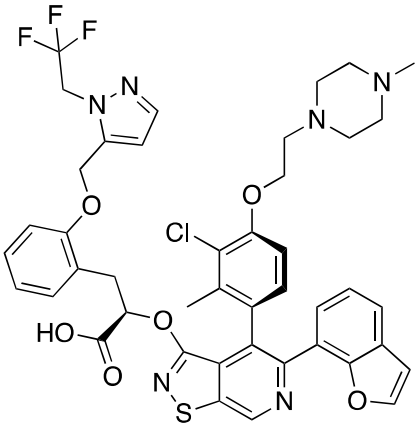
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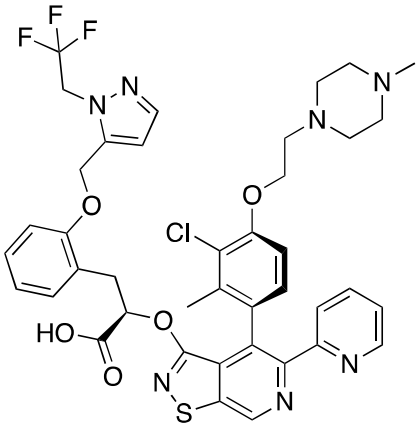
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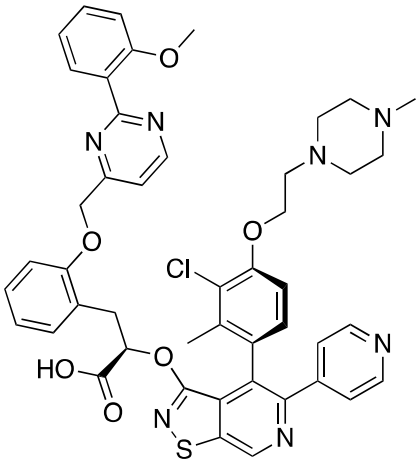
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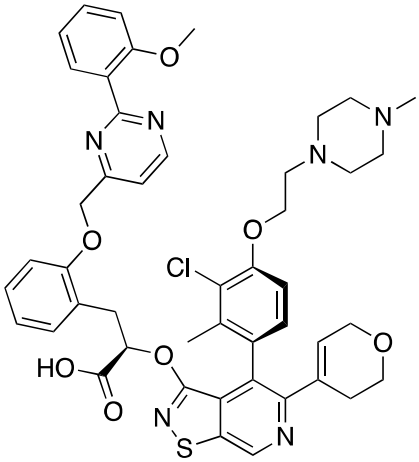
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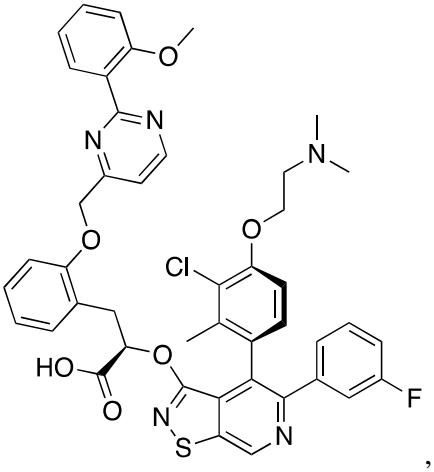
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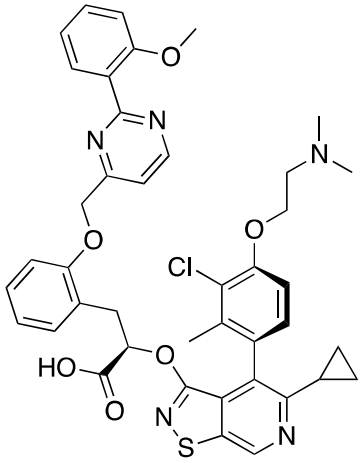
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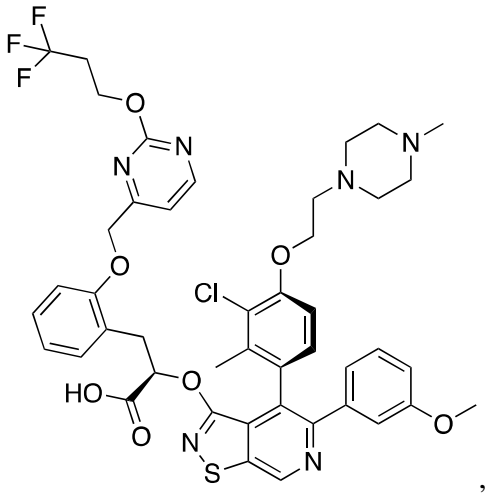
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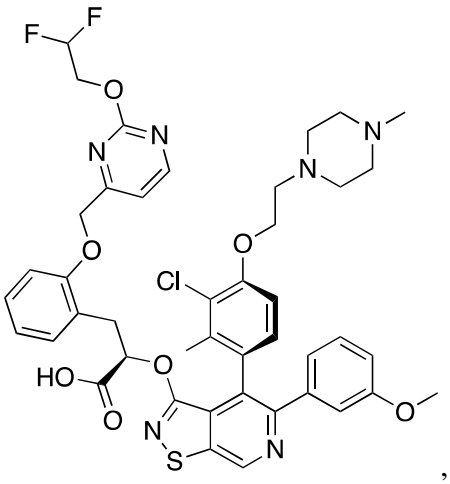
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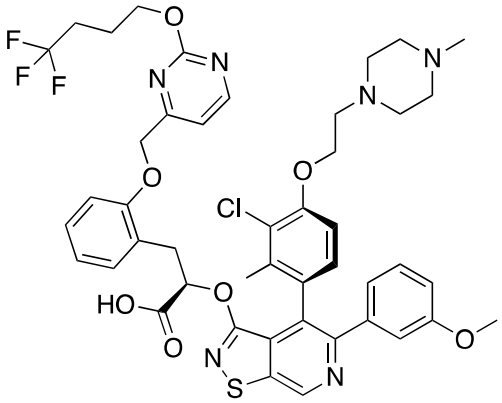
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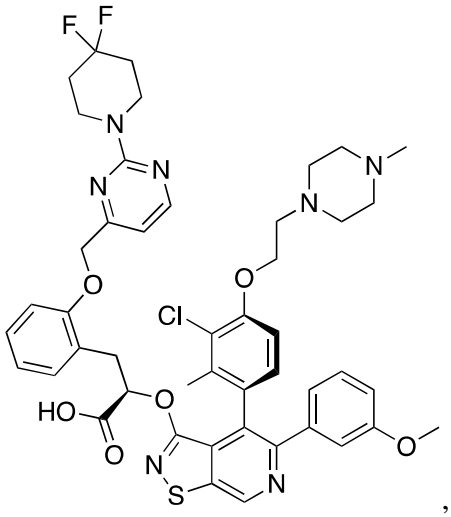
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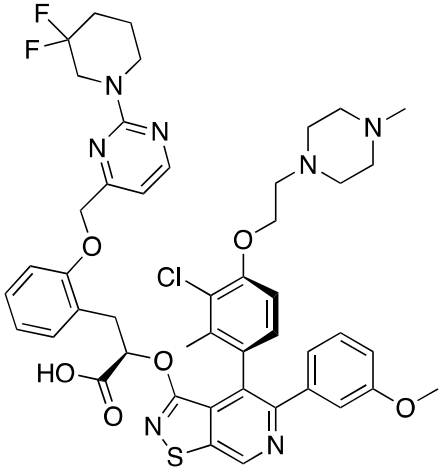
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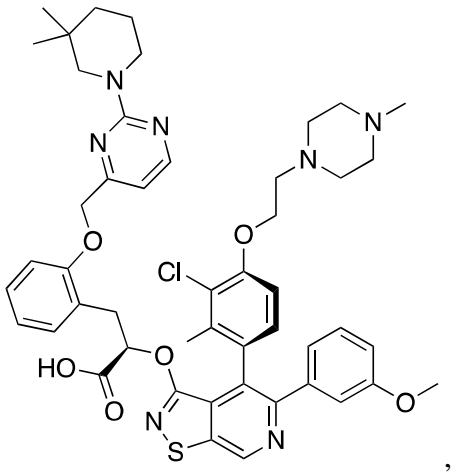
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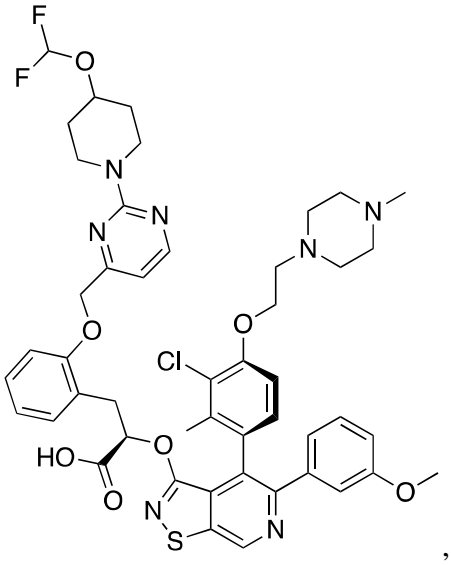
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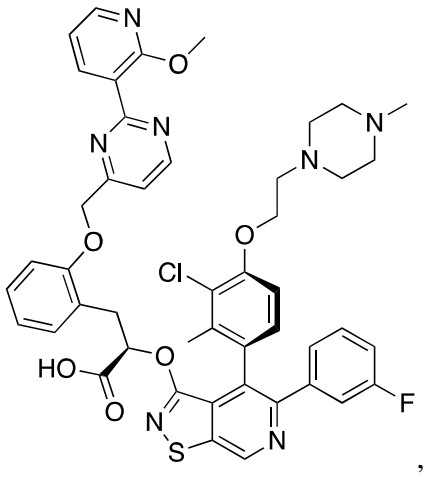
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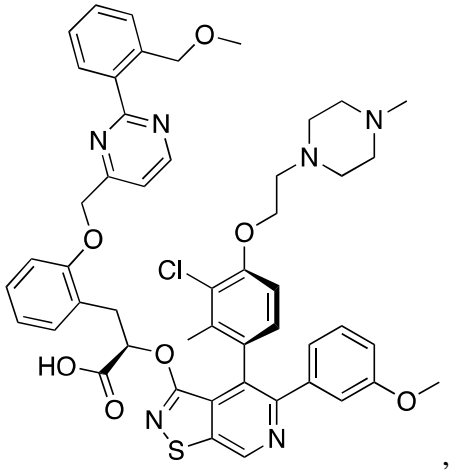
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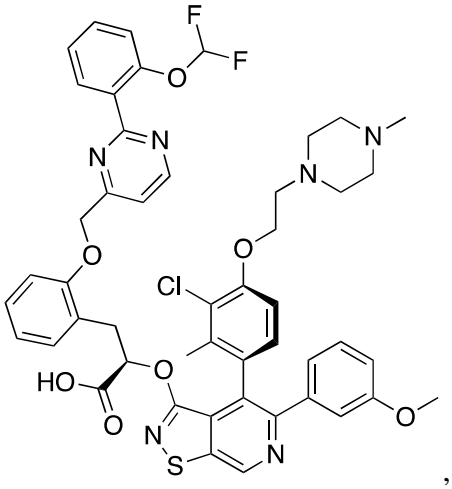
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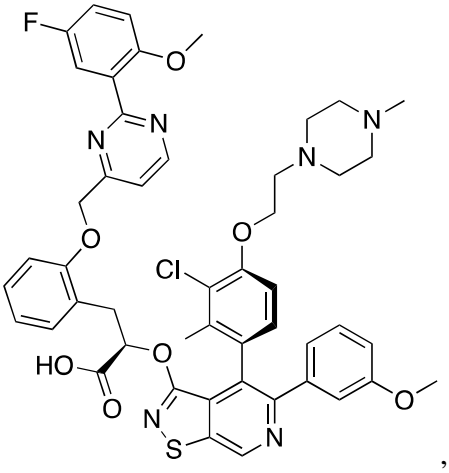
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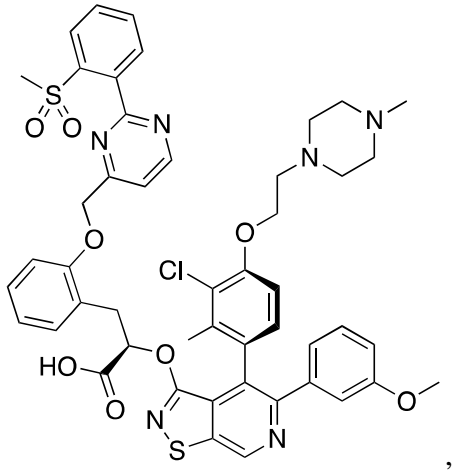
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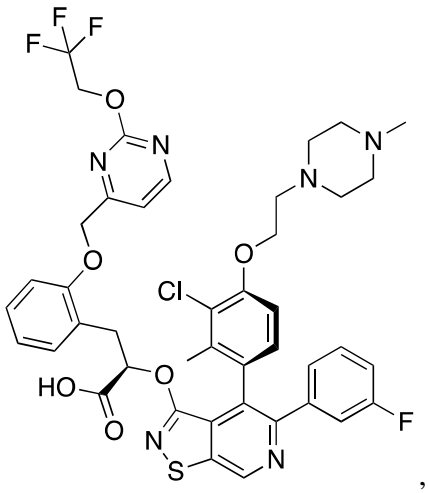
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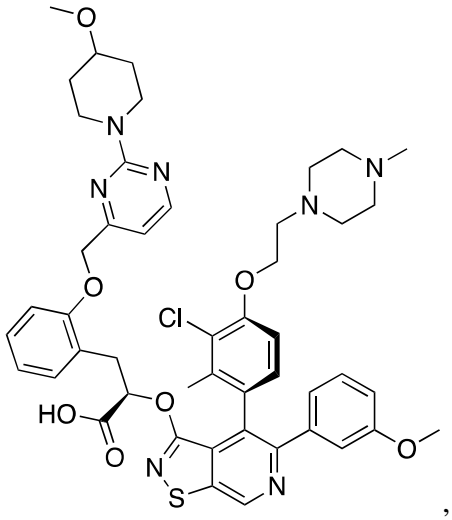
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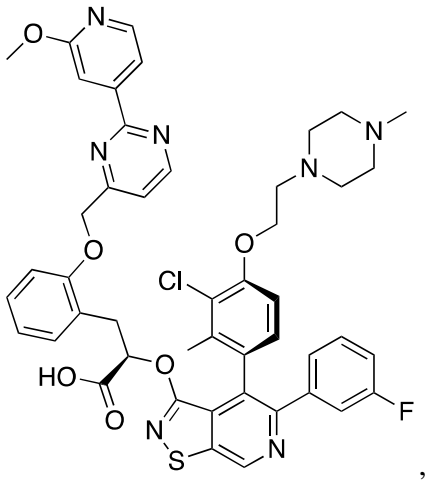
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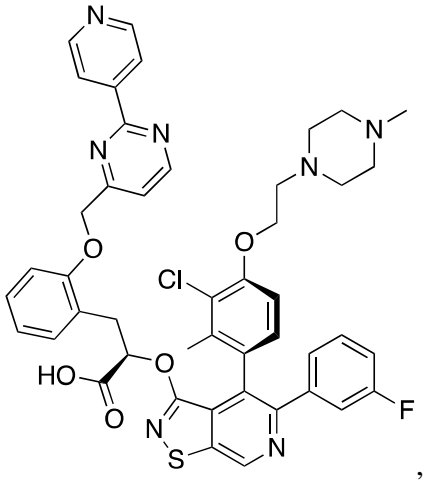
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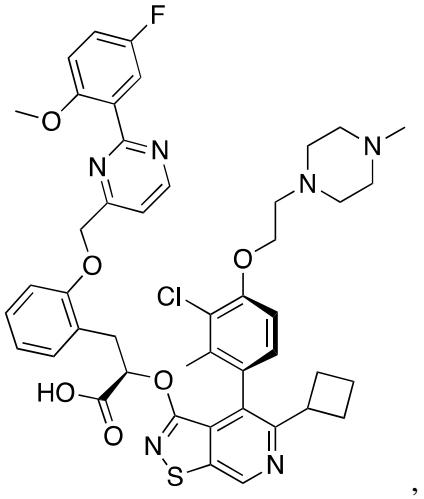
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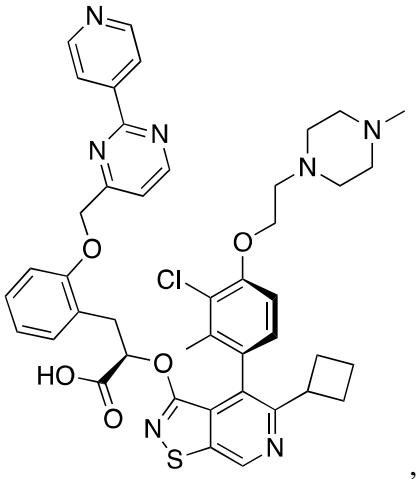
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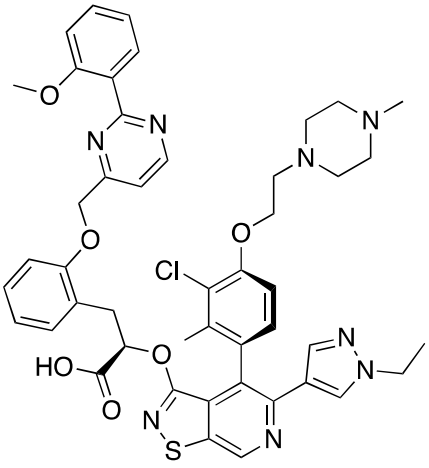
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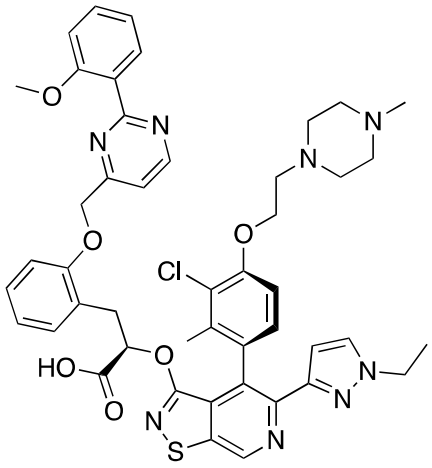
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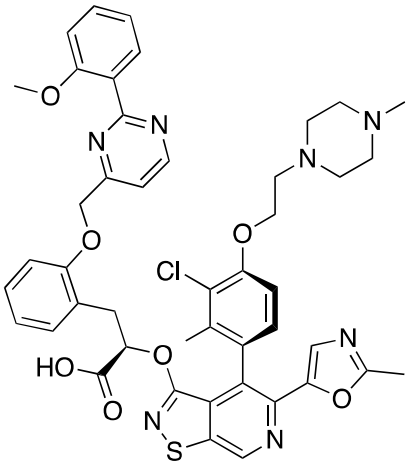
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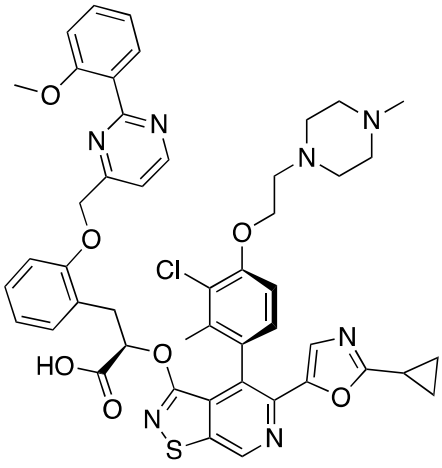
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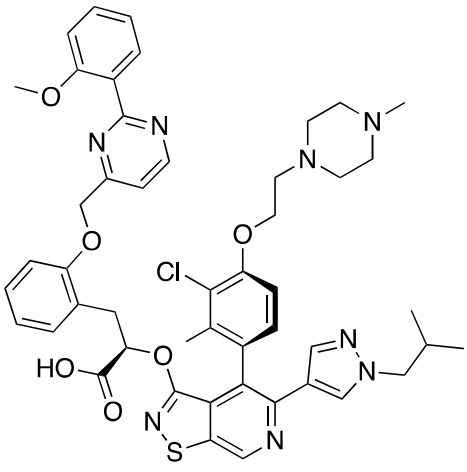
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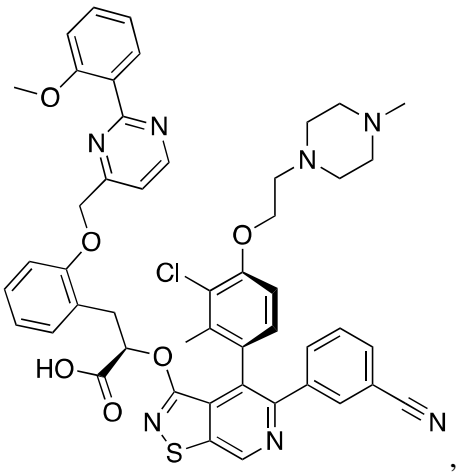
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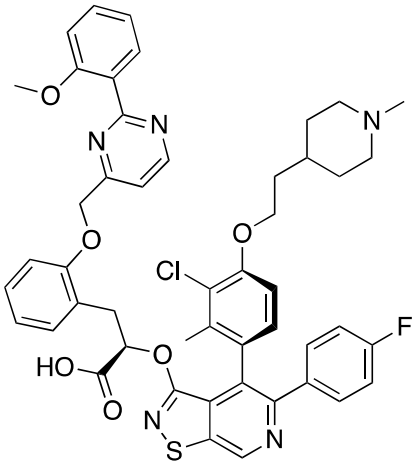
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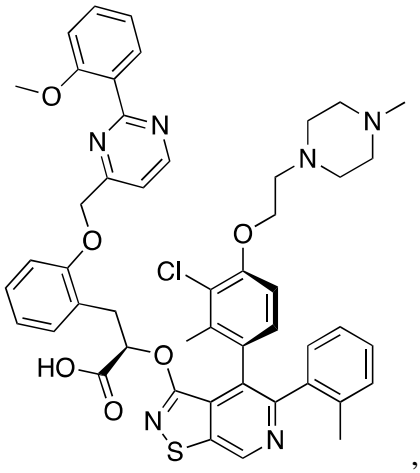
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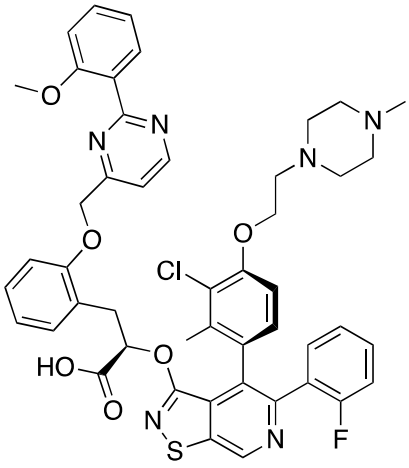
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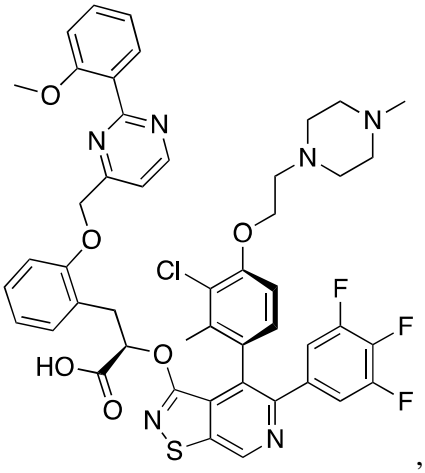
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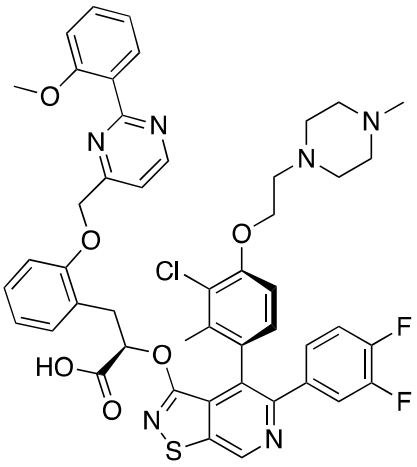
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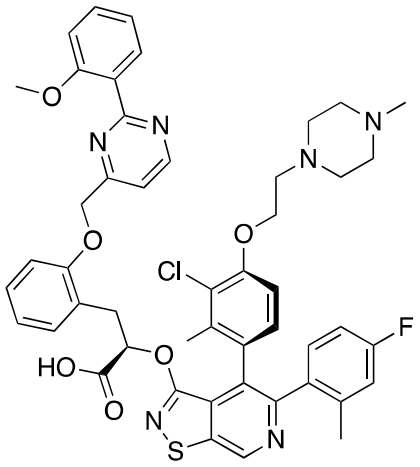
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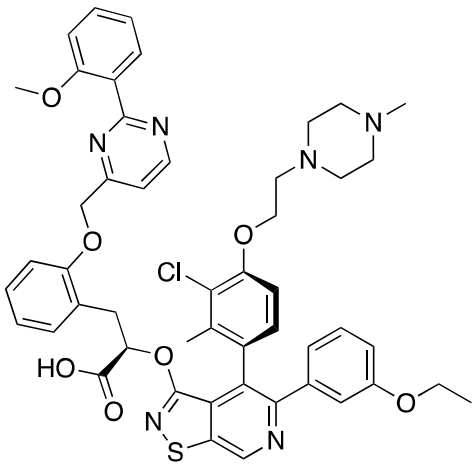
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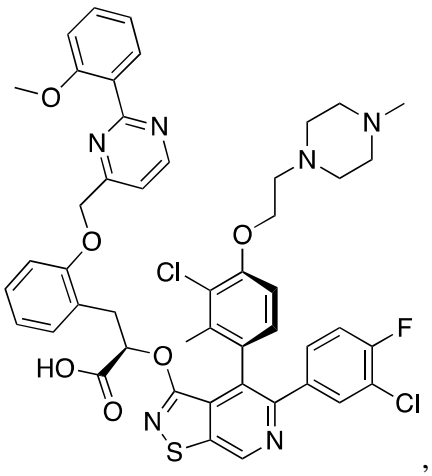
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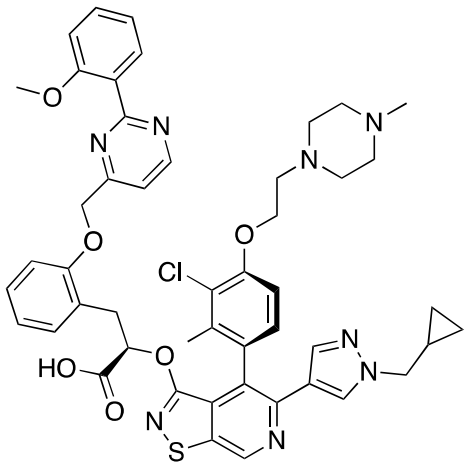
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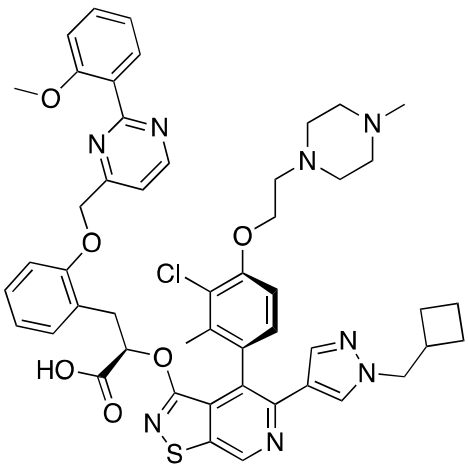
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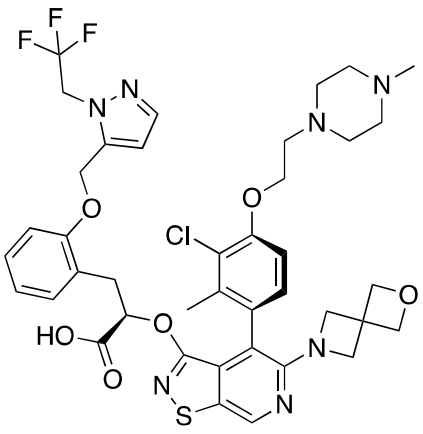
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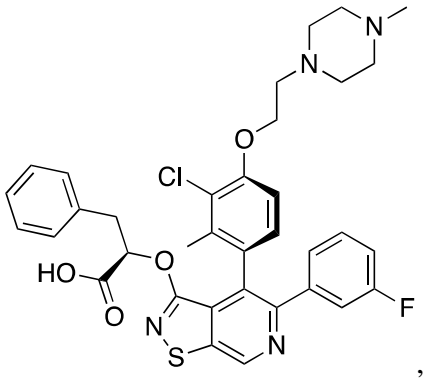
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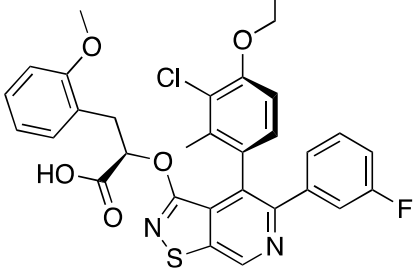
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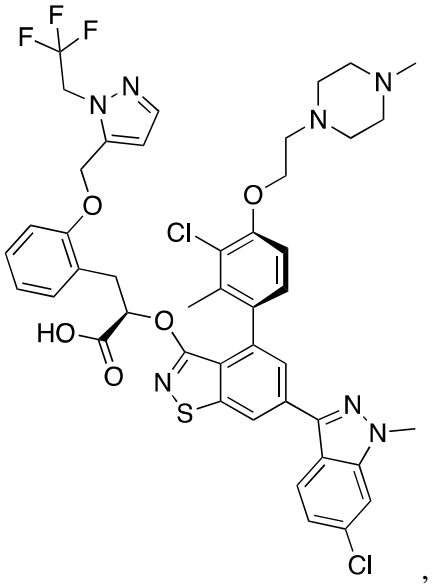
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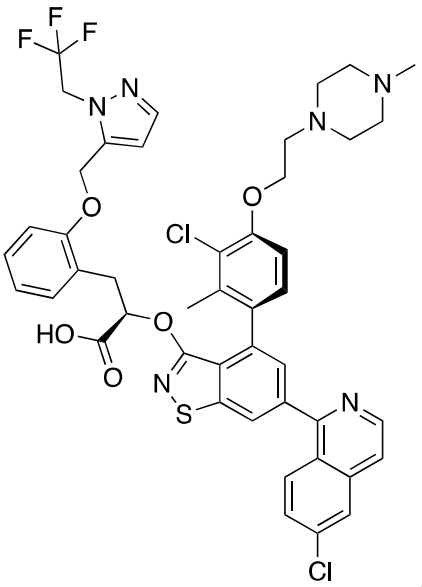
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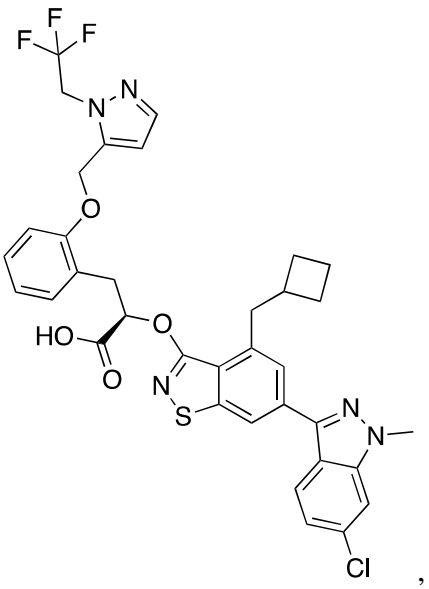
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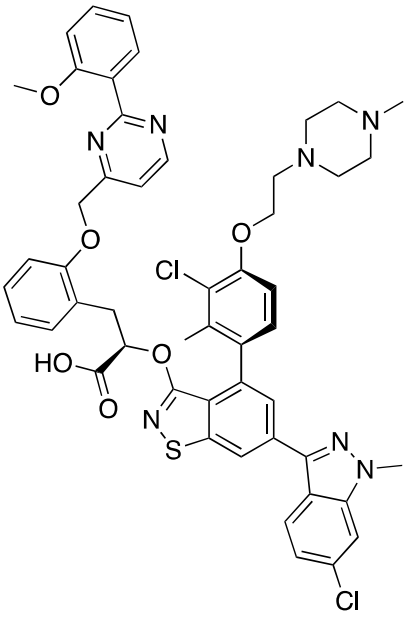
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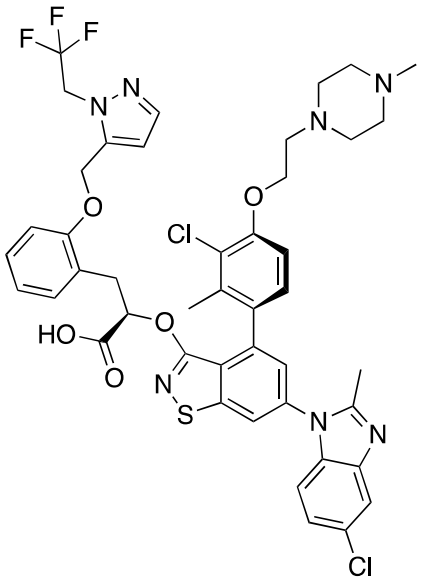
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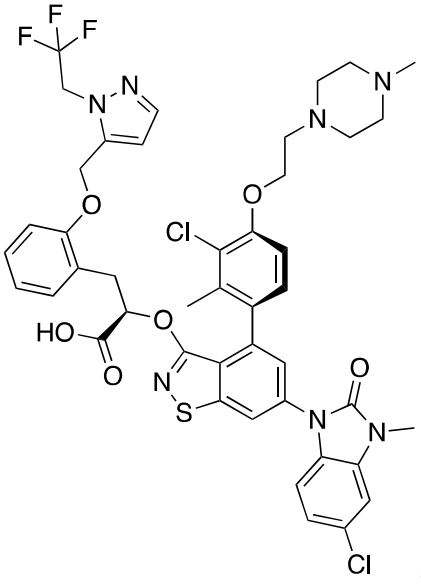
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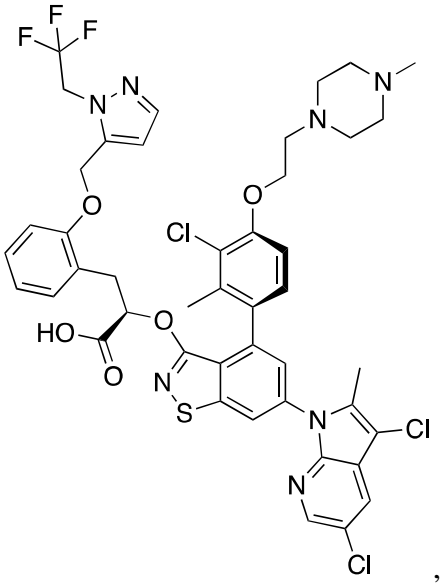
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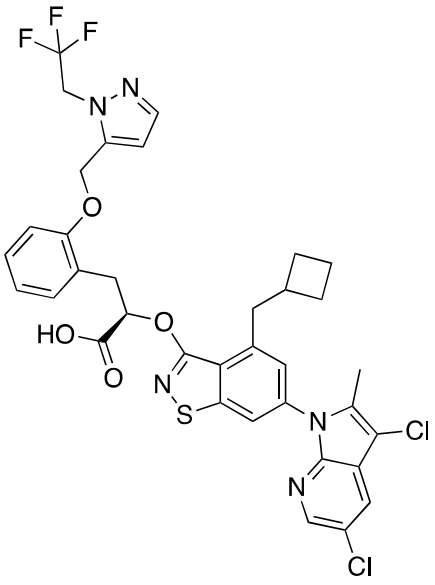
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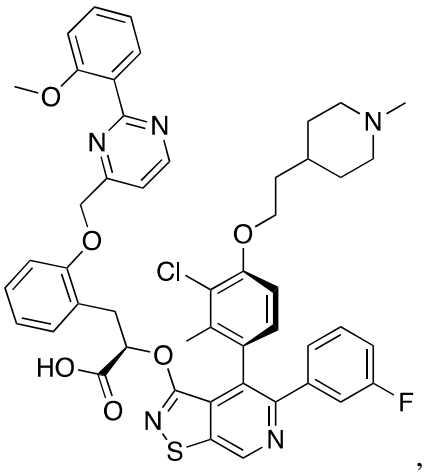
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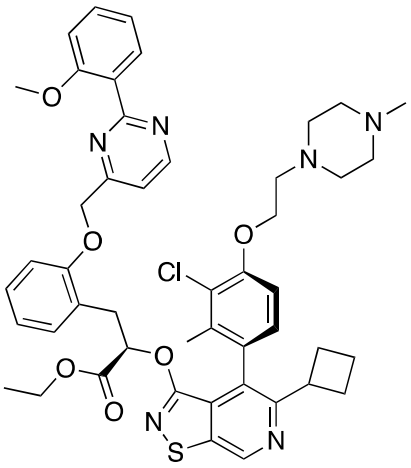
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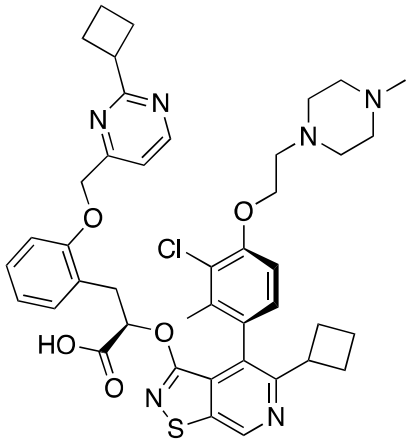
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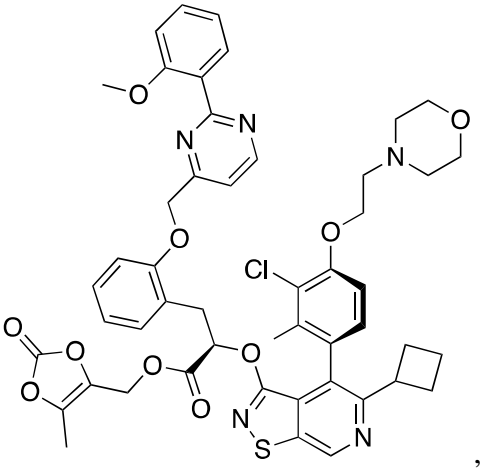
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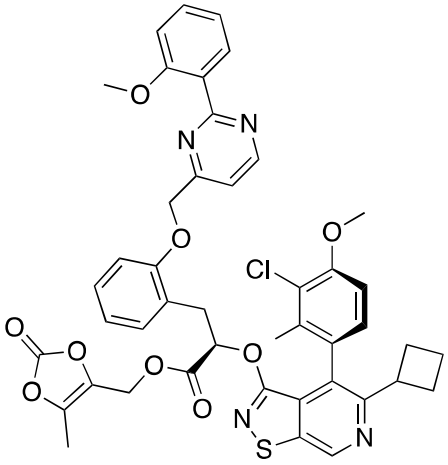
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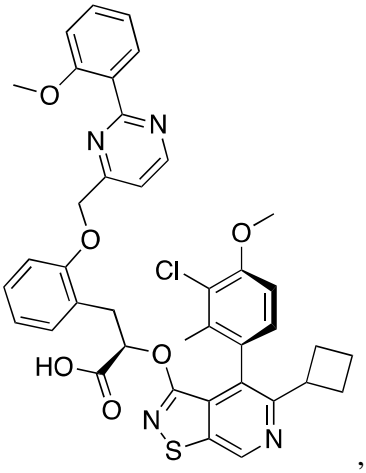
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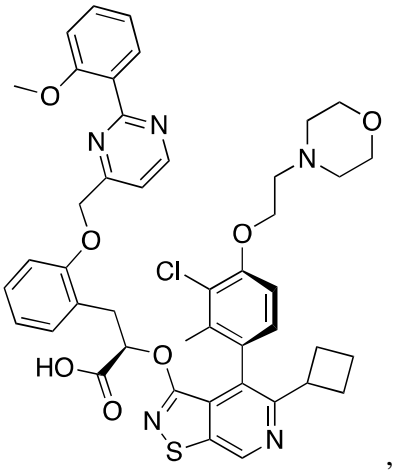
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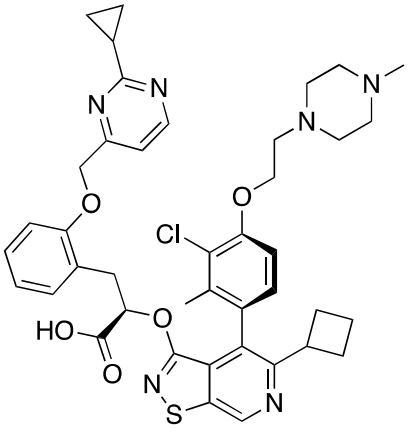
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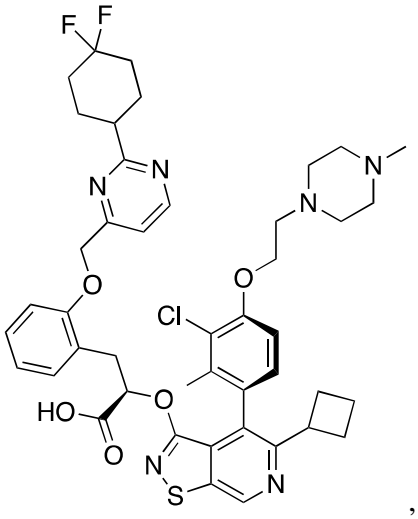
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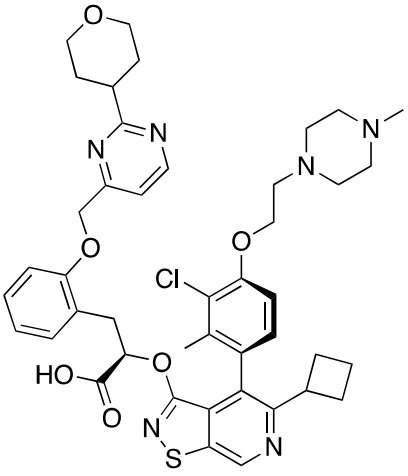
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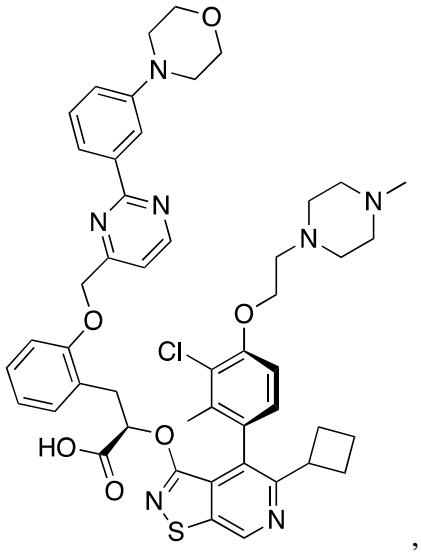
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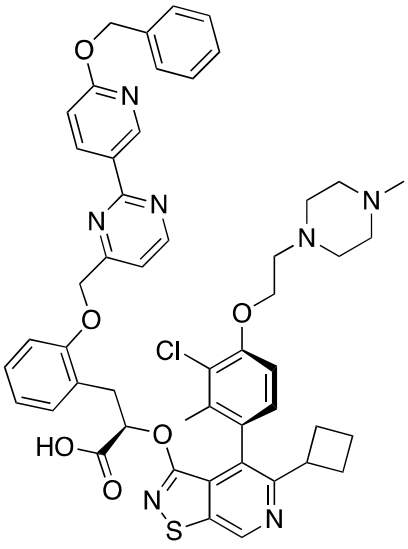
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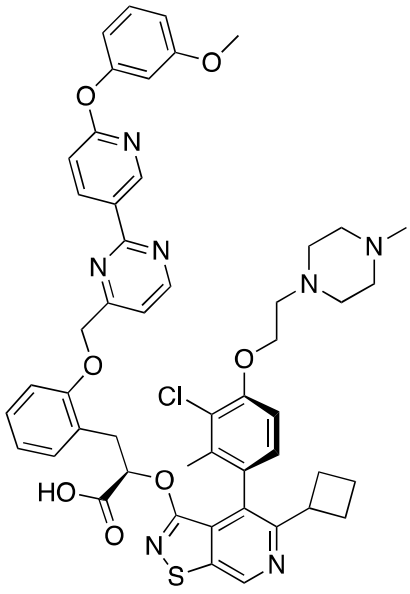
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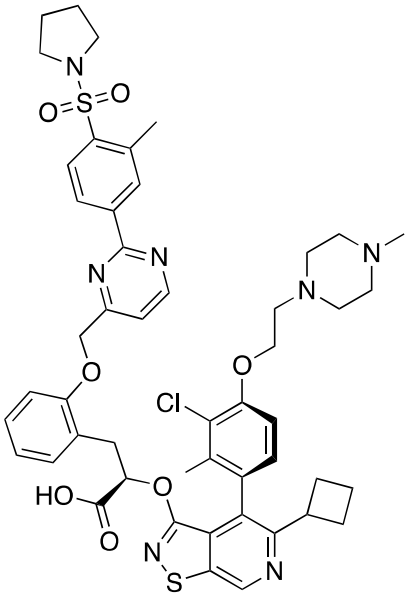
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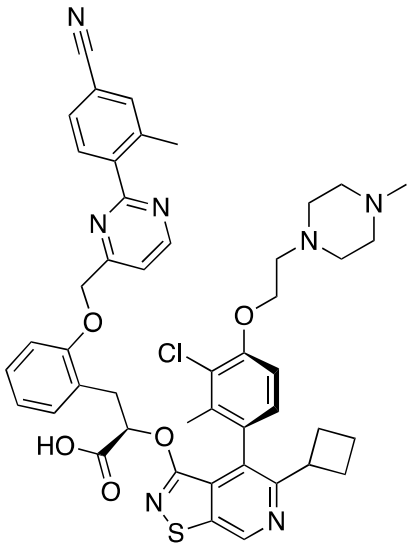
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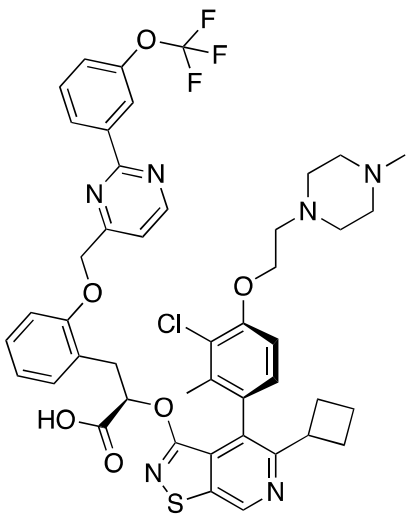
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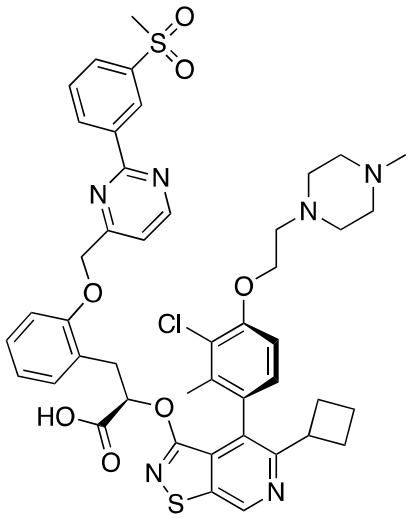
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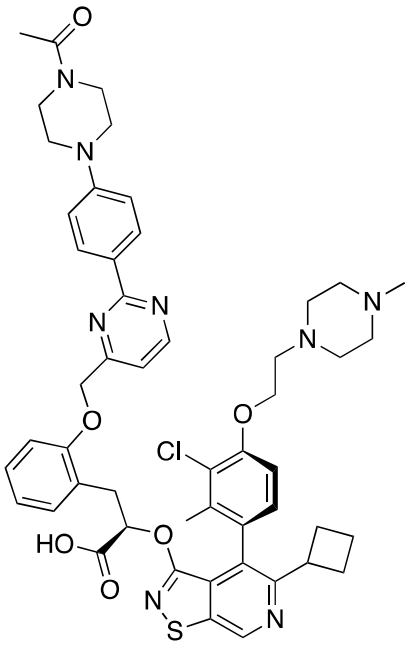
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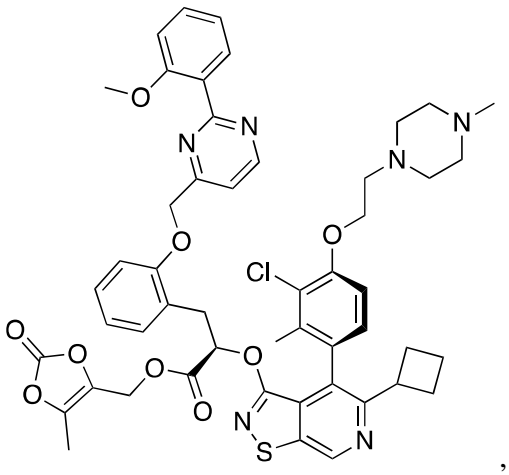
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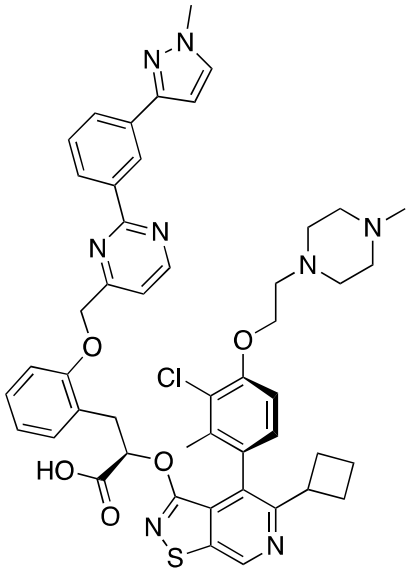
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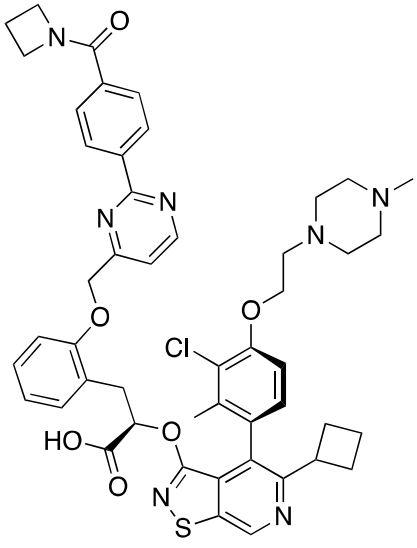
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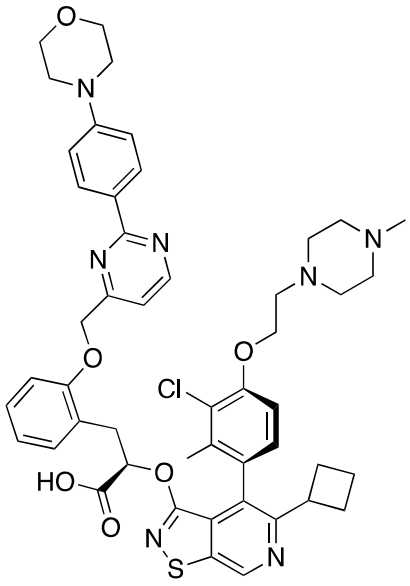
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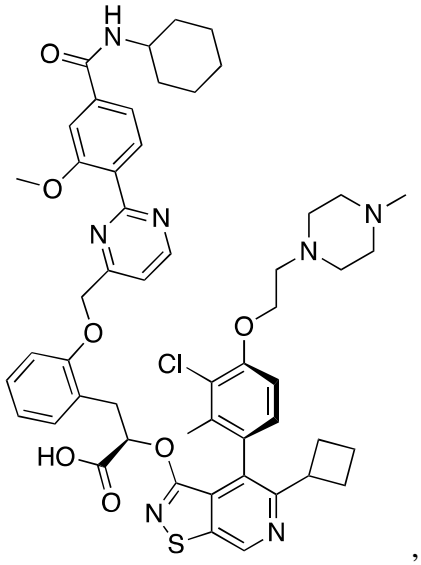
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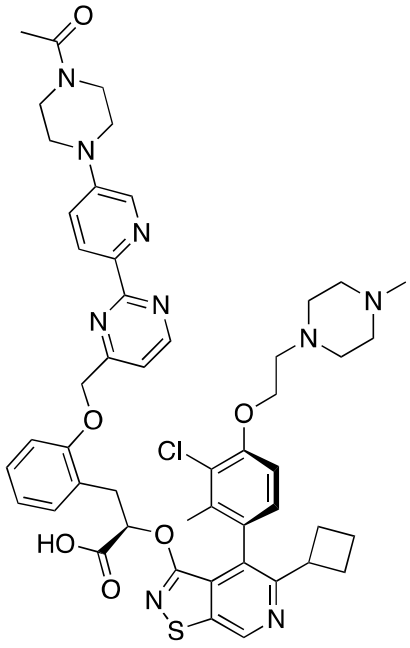

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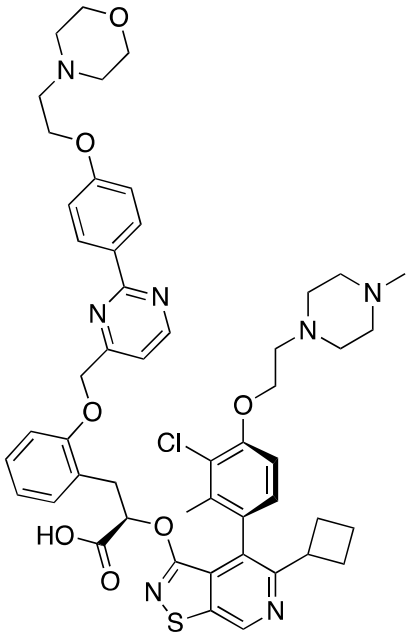

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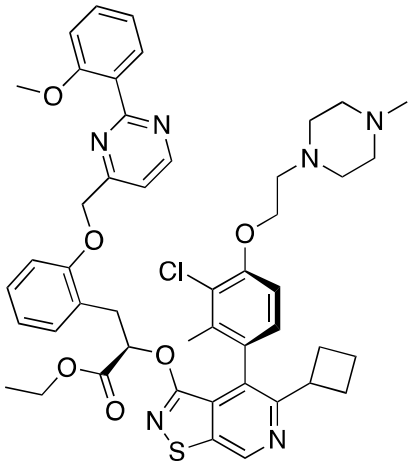

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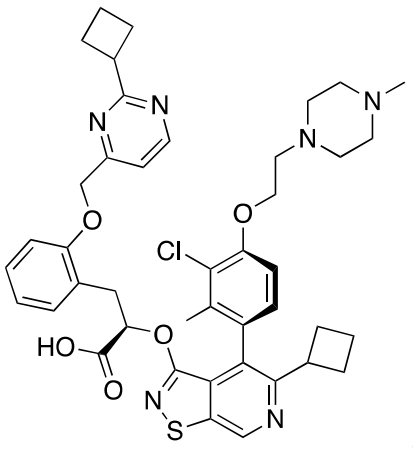

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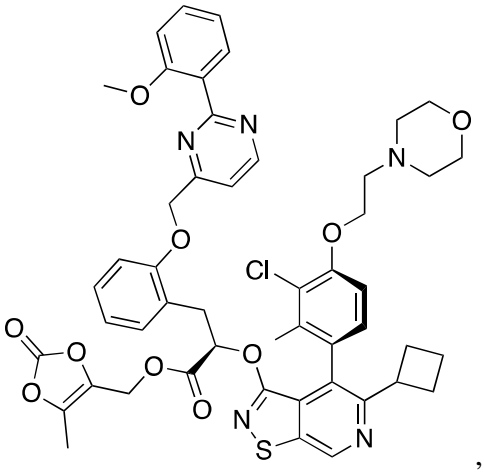
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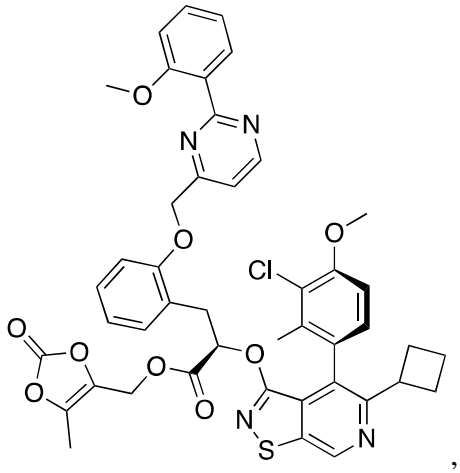
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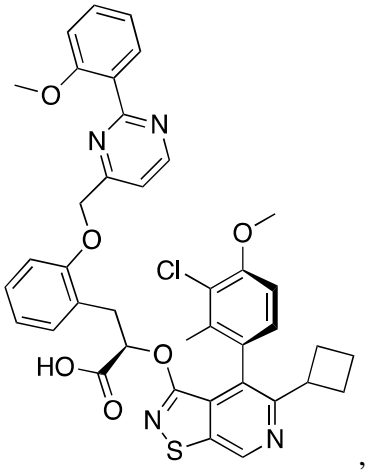
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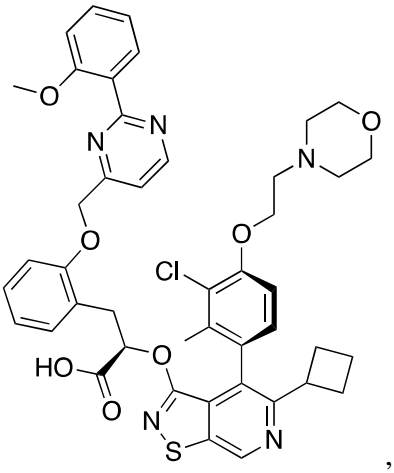
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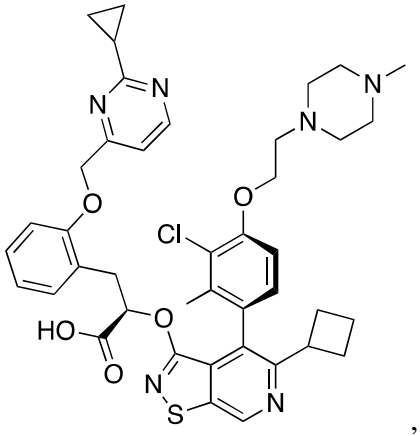
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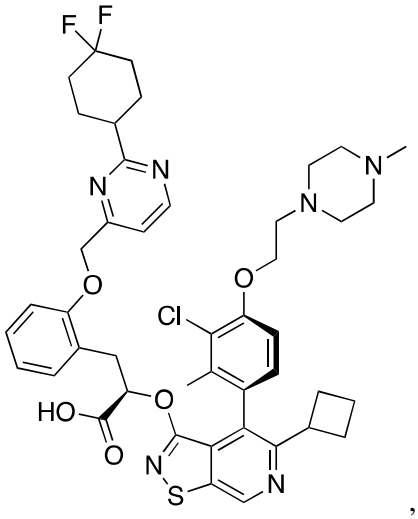
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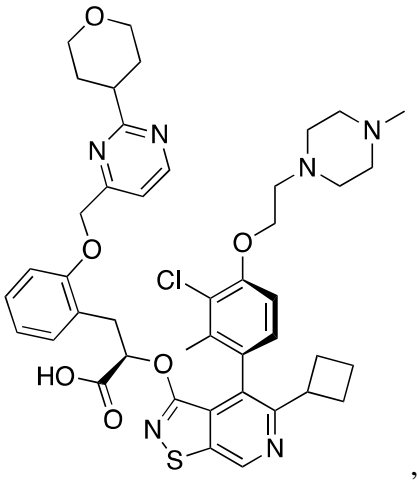
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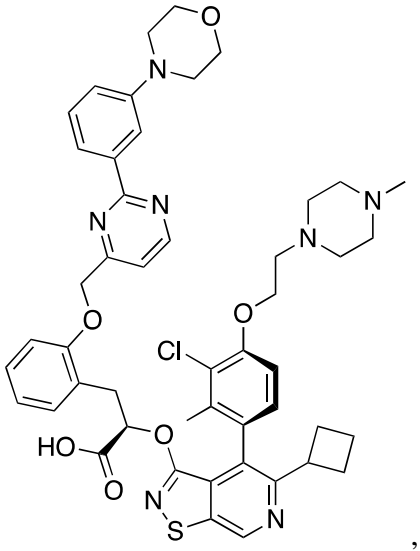
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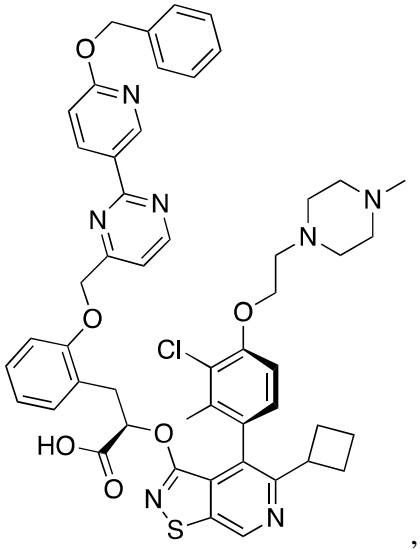
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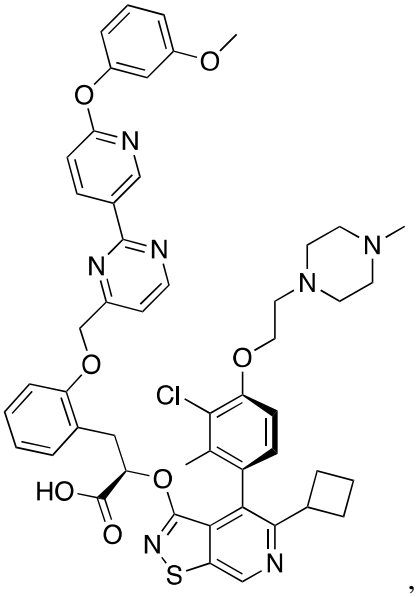
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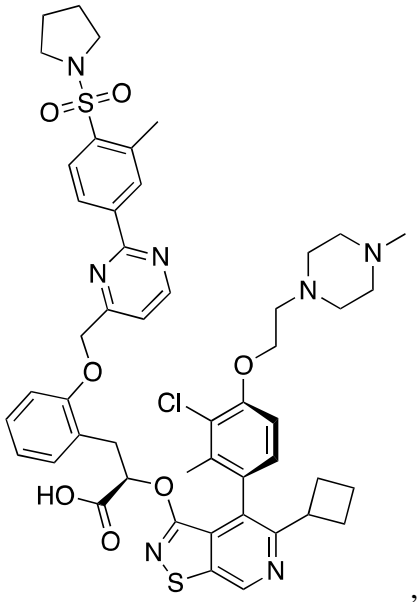
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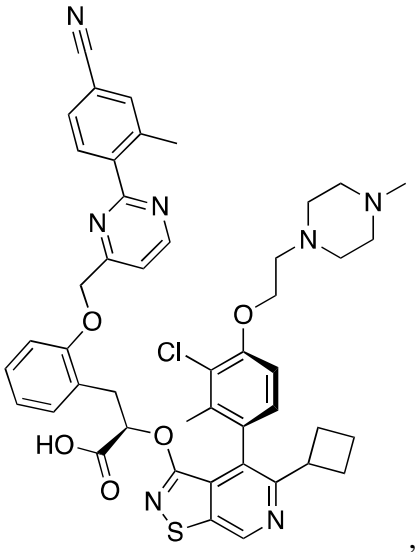
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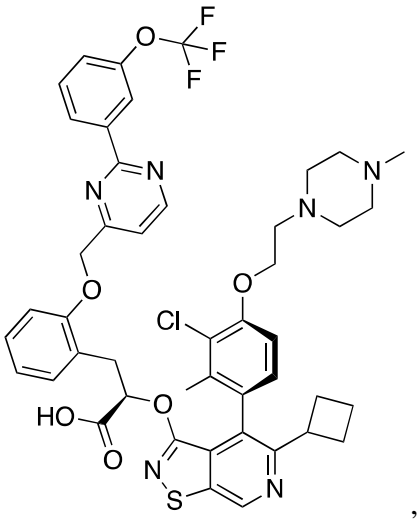
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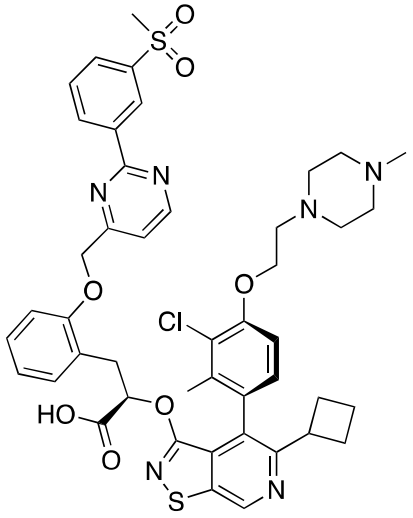
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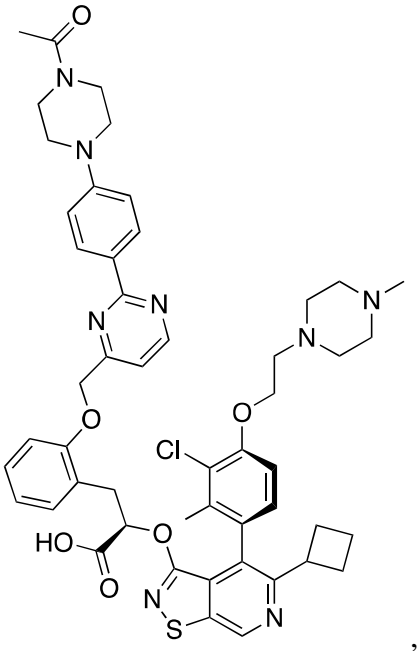
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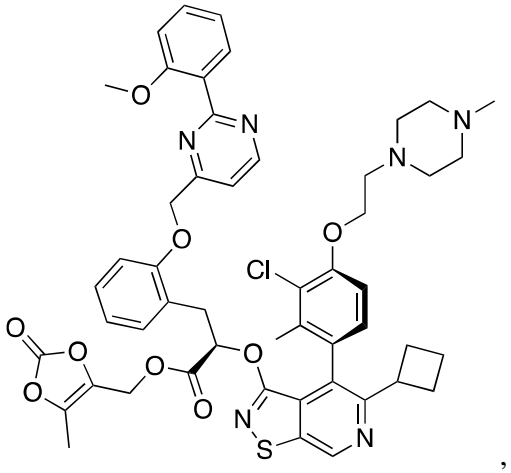
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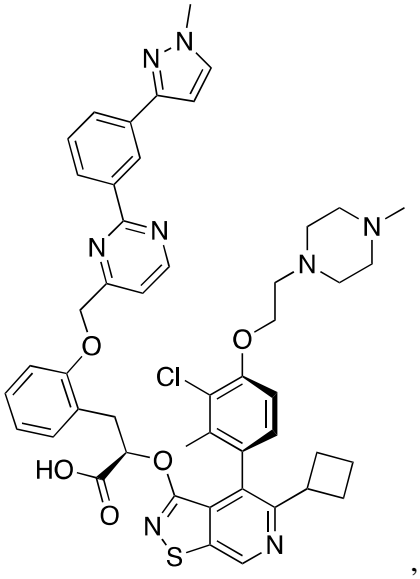
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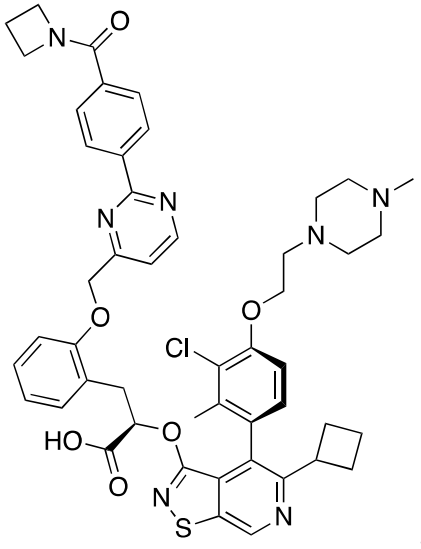
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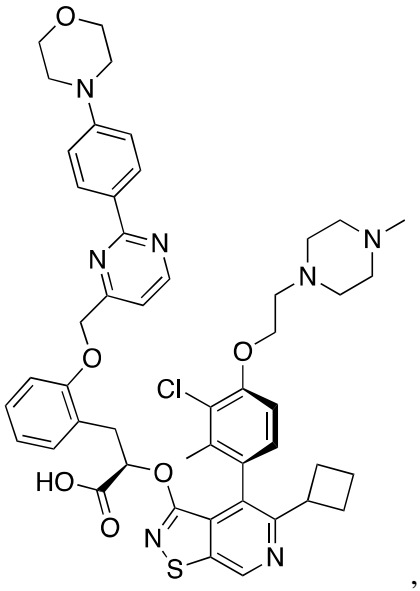
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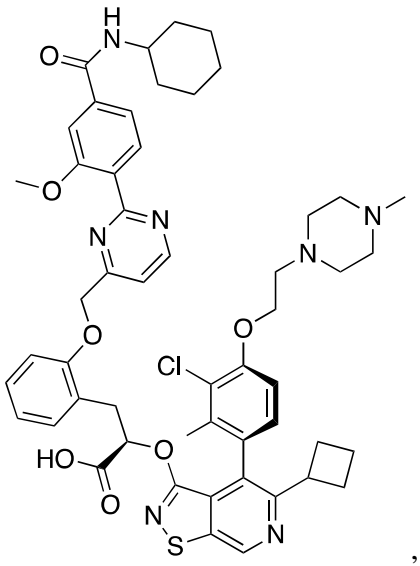
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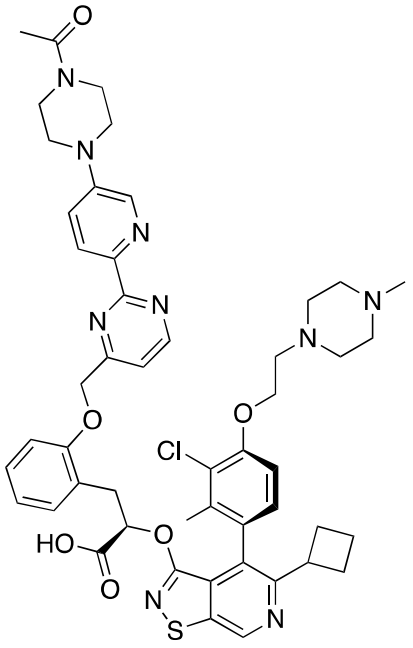
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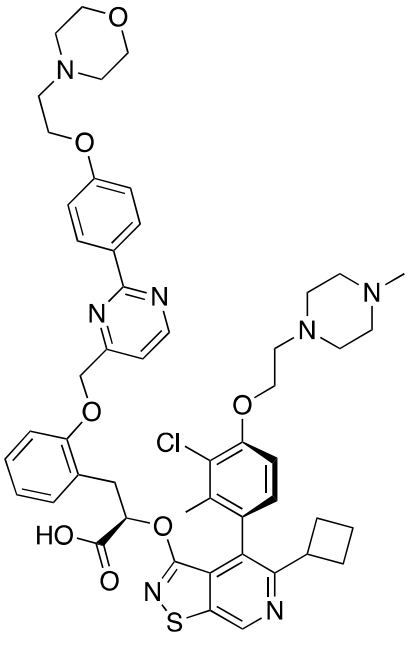
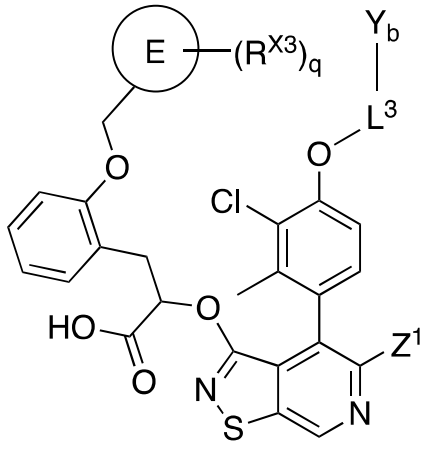

, or a pharmaceutically acceptable salt thereof.

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.

33. The compound of claim 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.

34. The compound of claim 32 or 33, wherein:

E is pyrimidynyl or pyrazolyl;

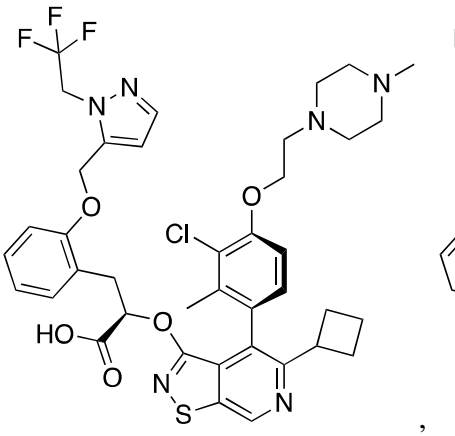
$L^3$ is $-CH_2CH_2-$;

$Y_b$ is heterocyclyl;

$Z^1$ is cycloalkyl; and

q is 0, 1 or 2.

35. A compound selected from: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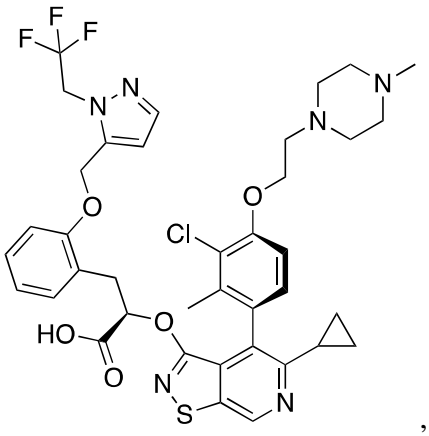
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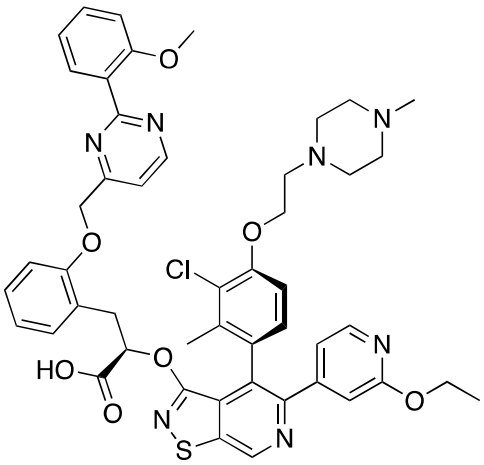
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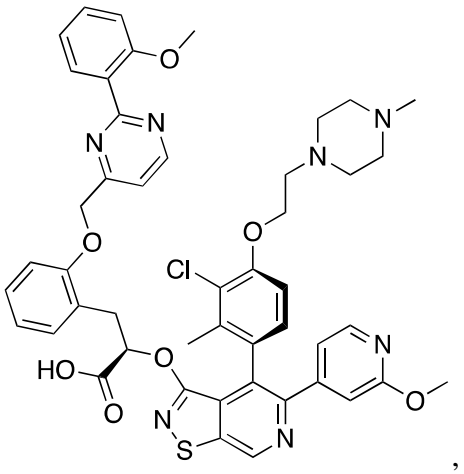
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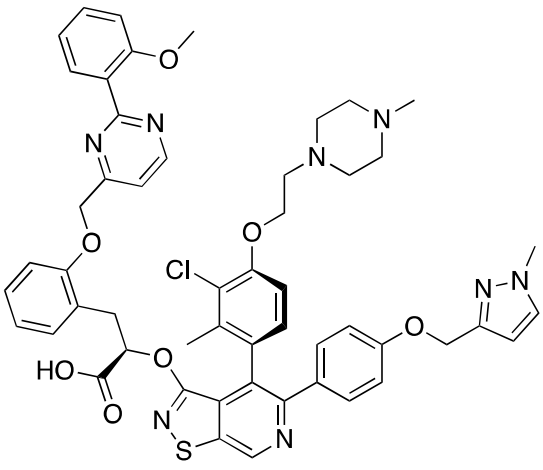
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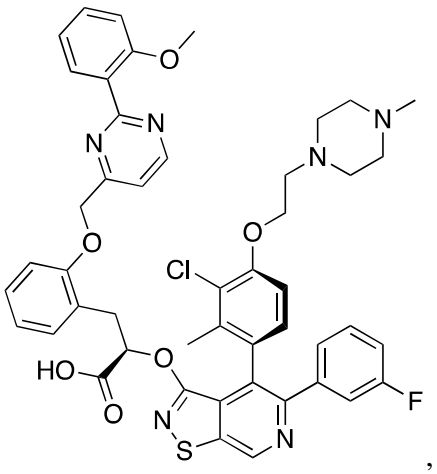
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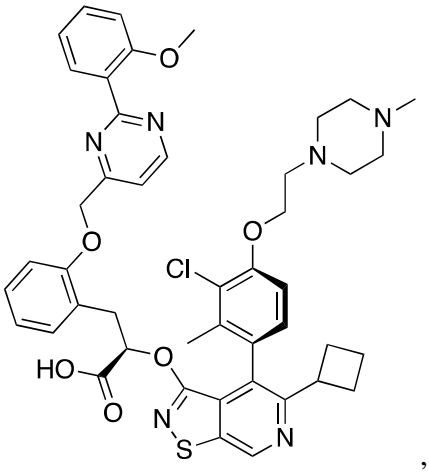
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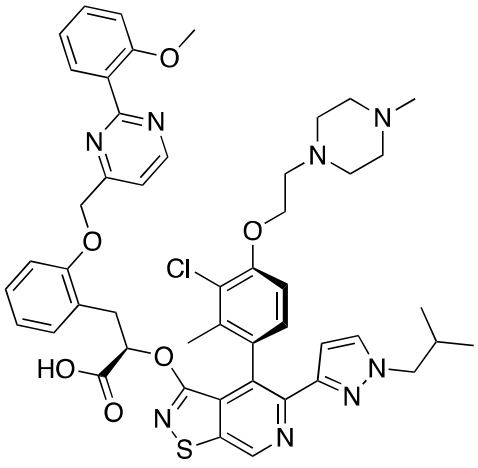
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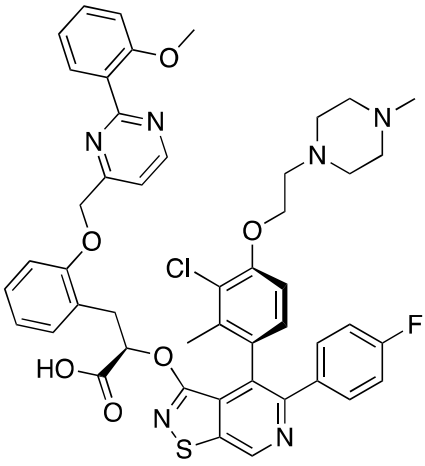
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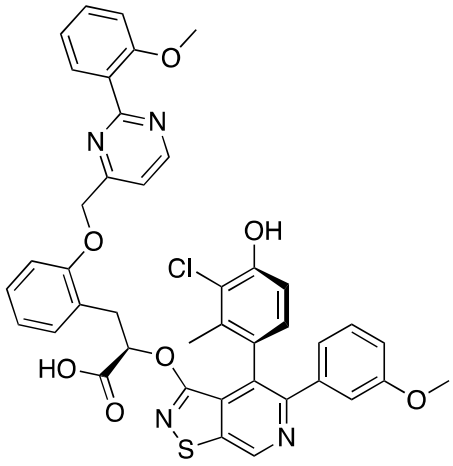
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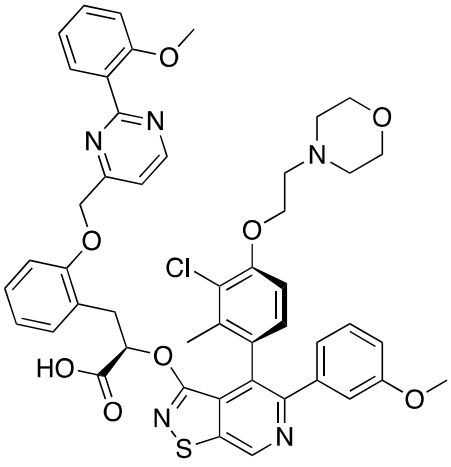
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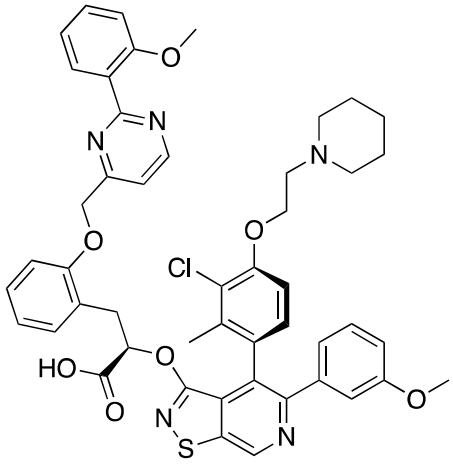
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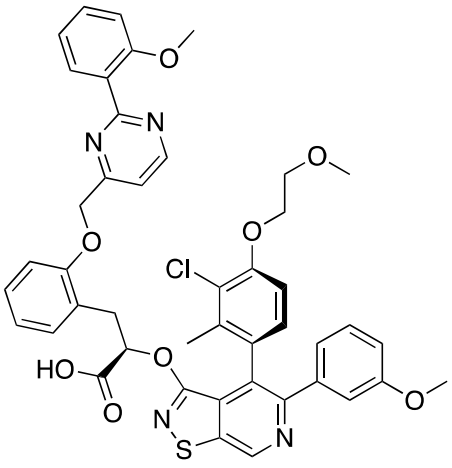
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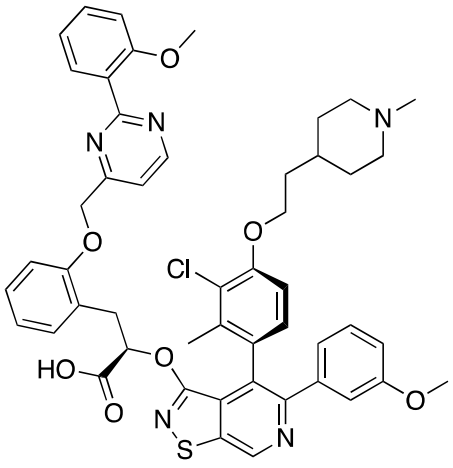
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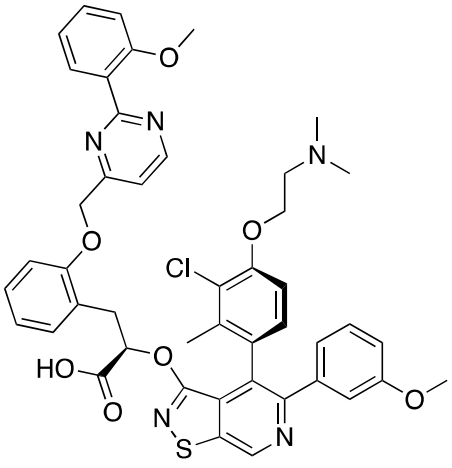
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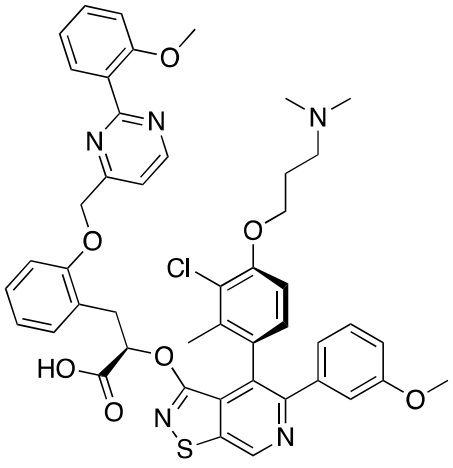
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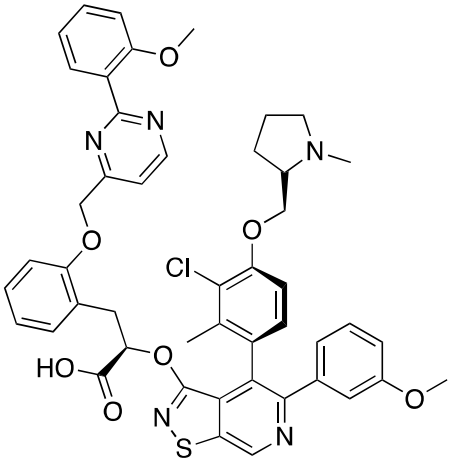
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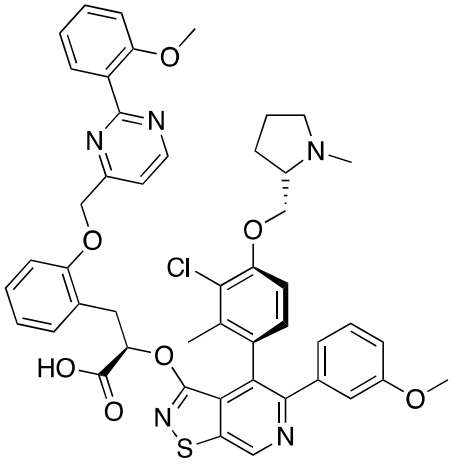
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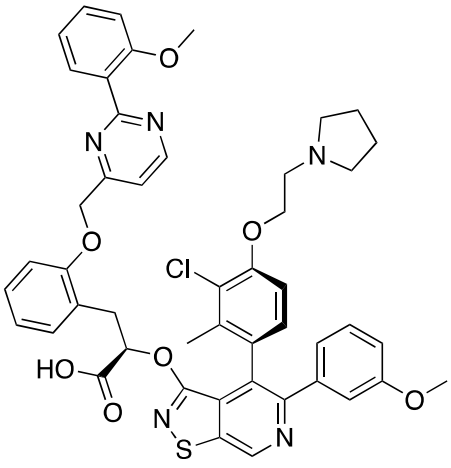
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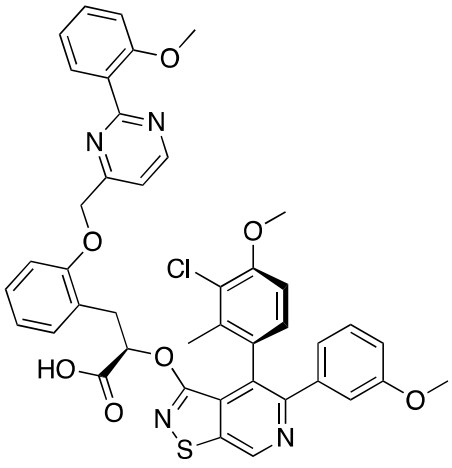
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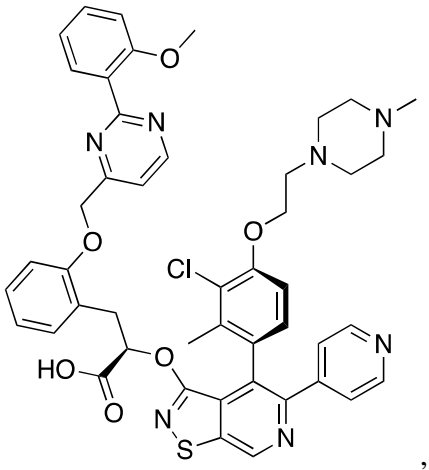
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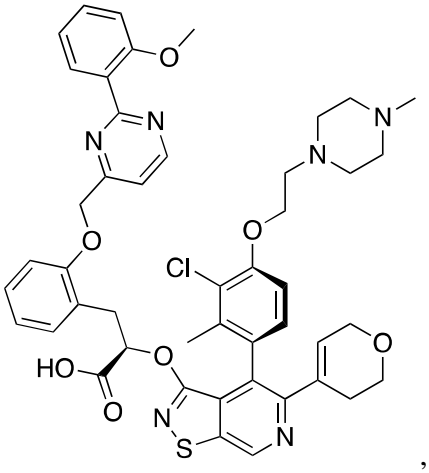
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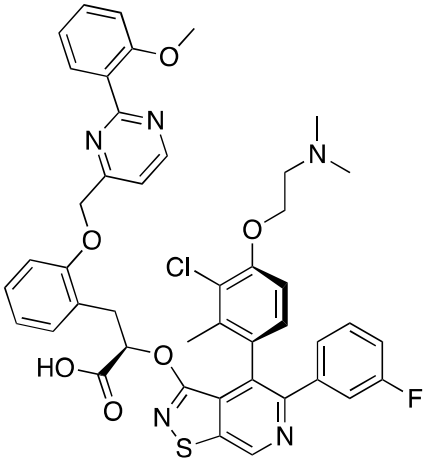
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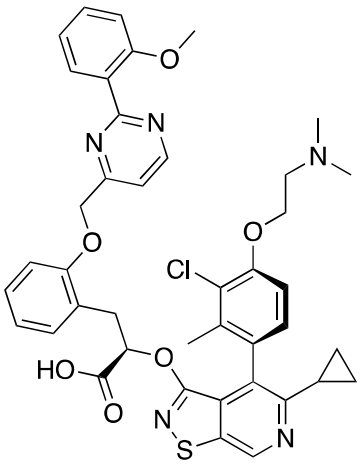
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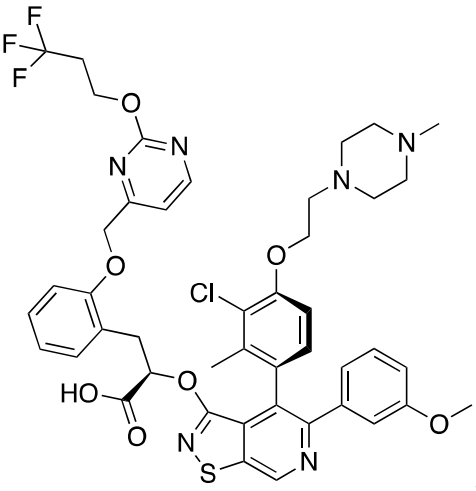
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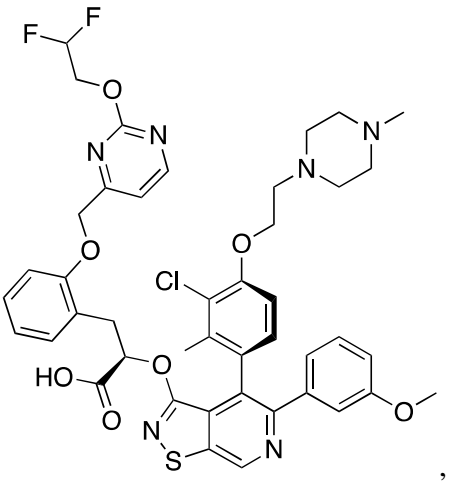
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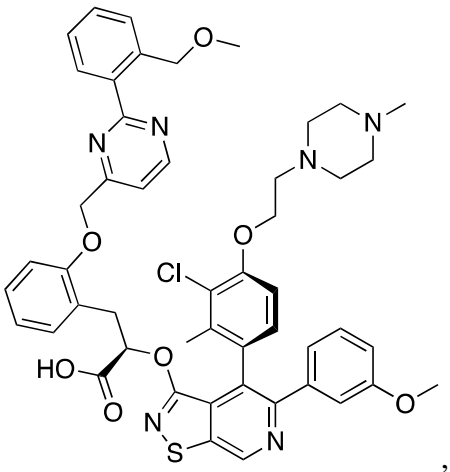
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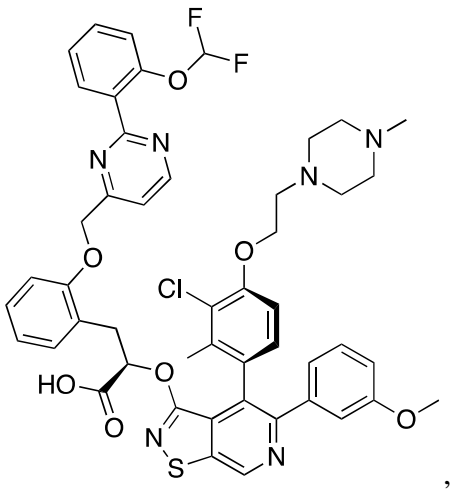
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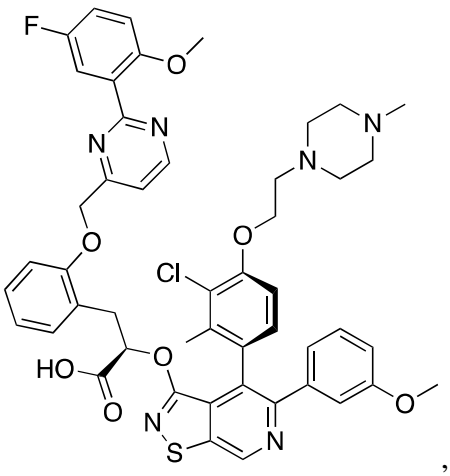
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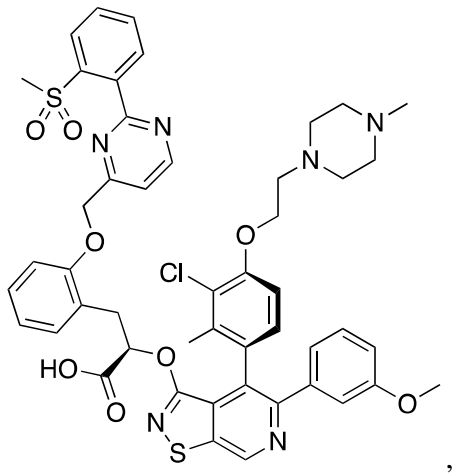
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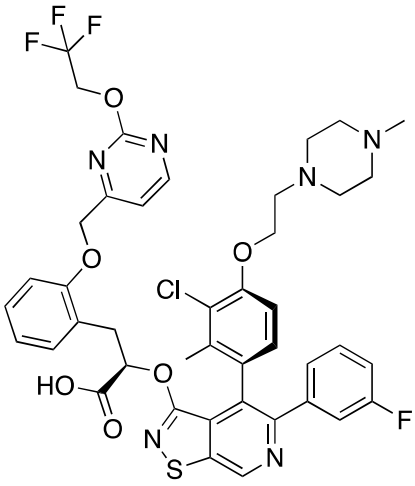
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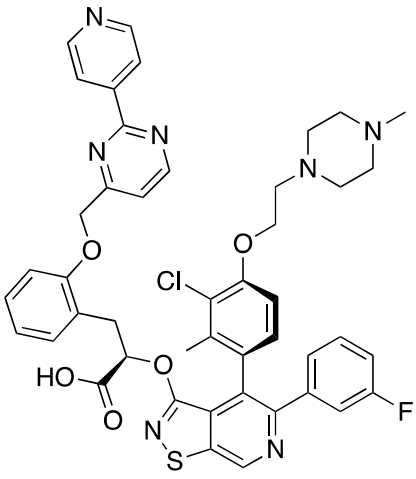
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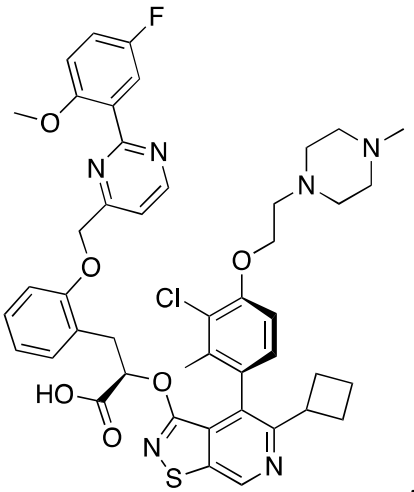
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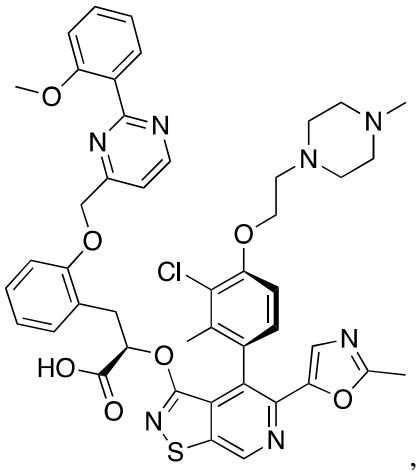
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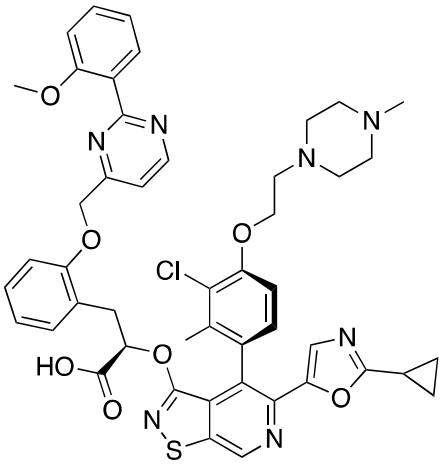
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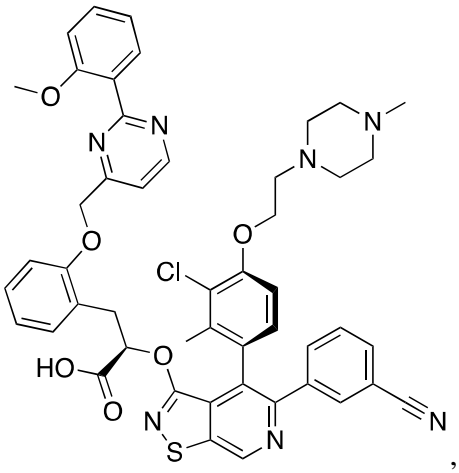
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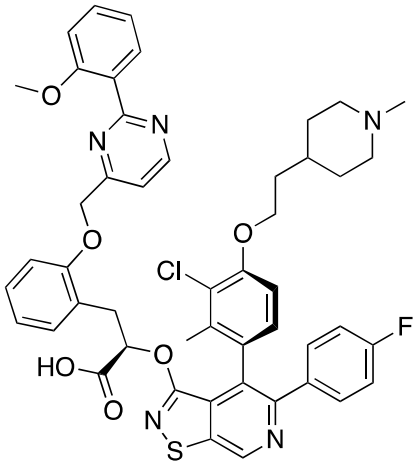
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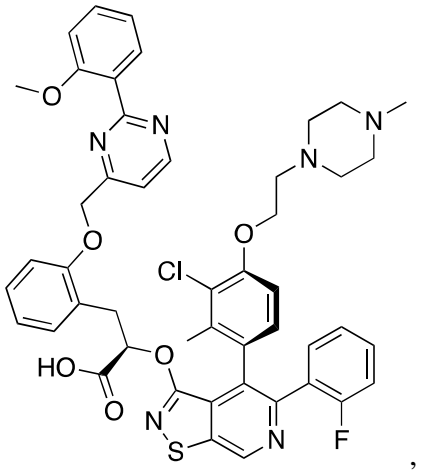
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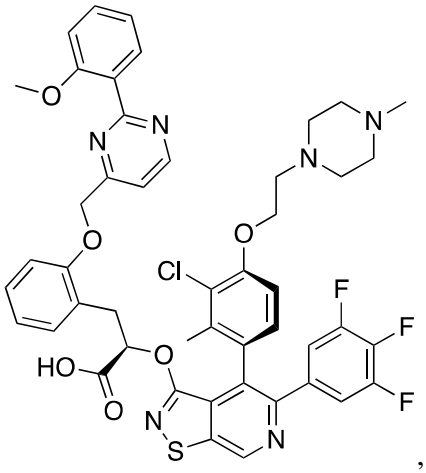
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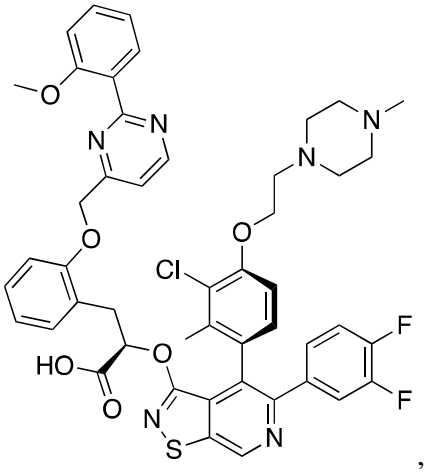
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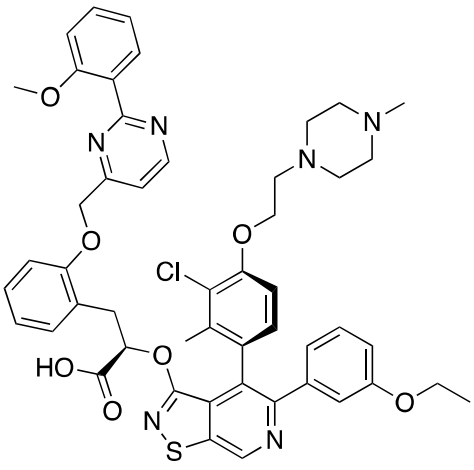
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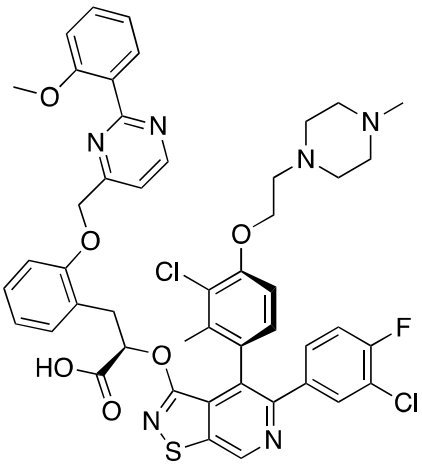
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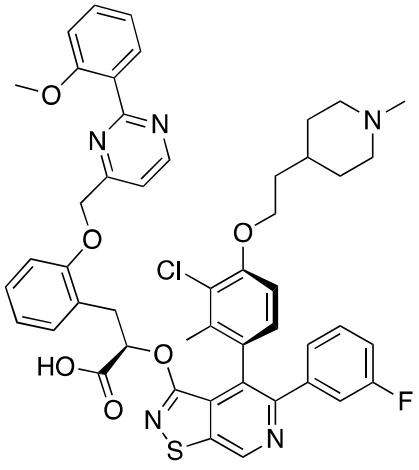
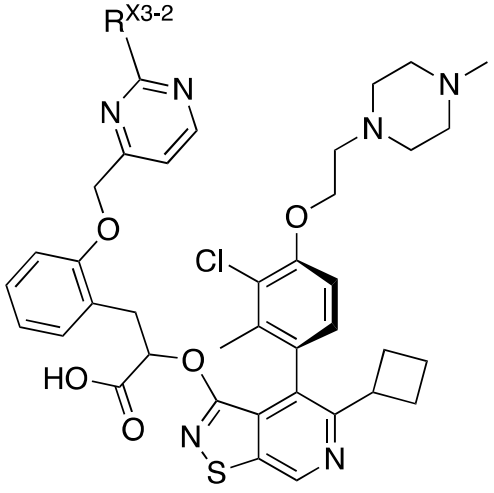
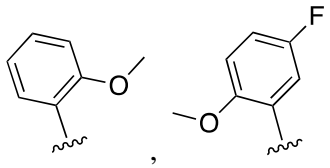
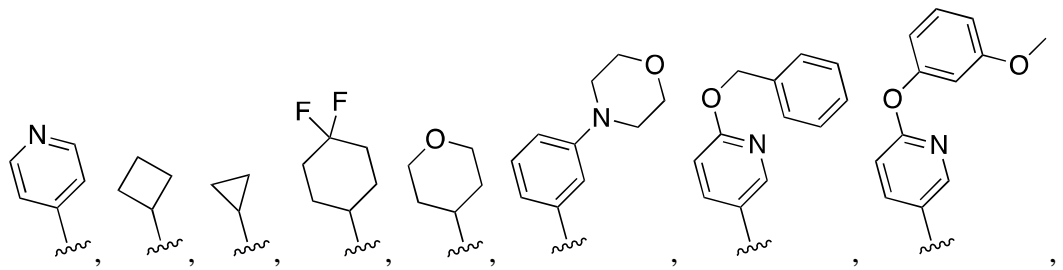


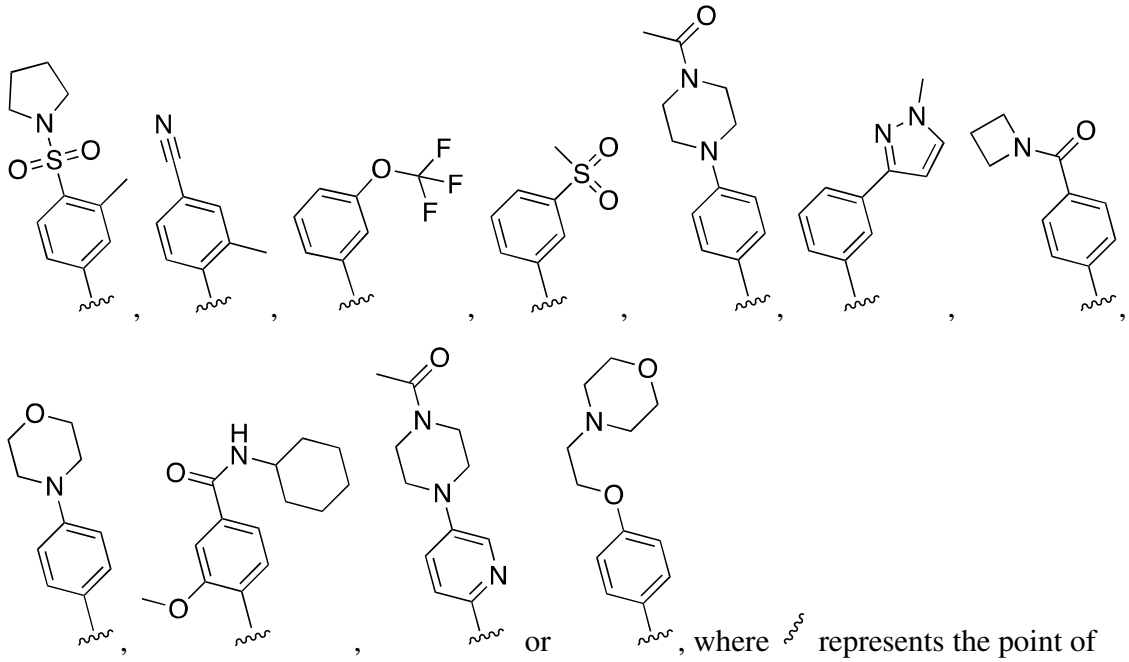
or a pharmaceutically acceptable salt thereof.

36. A compound having the structure of Formula X:



(Formula X)

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


, where represents the point of attachment.

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

38. Use of a compound of any one of claims 1-36 in the manufacture of a medicament for the treatment of a cancer 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 rhabdomyosarcoma; 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

a cancer 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, keratoacanthoma, 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.