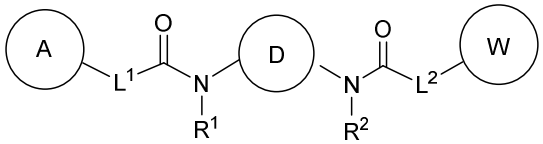
exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\,B2_2\,B3_2\,B4_2\,B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, Nat Commun (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

SUMMARY

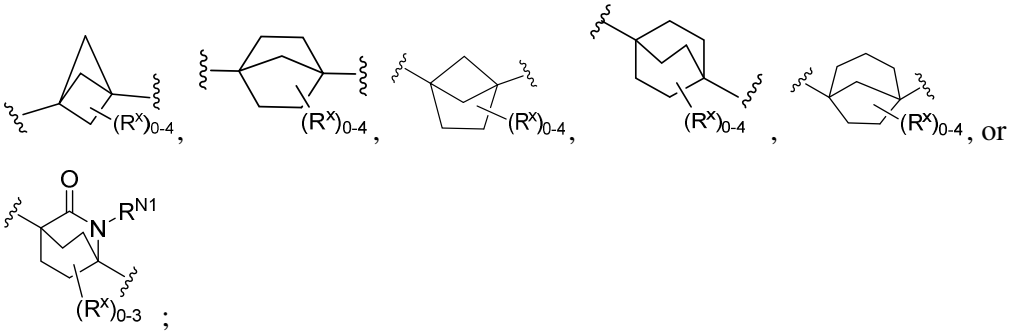
In one aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:



;

L^1 is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N2}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L1};

L^2 is a bond, C_1-C_6 alkylene, or 2-7 membered heteroalkylene, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl;

W is a 8-10 membered, partially unsaturated, fused bicyclic ring moiety comprising a 5-6 membered heterocyclyl fused to a phenyl or 5-6-membered heteroaryl; wherein the heterocyclyl may be optionally substituted on one or more available saturated carbons with 1-4 R^{W1}; and wherein the phenyl or heteroaryl may optionally be substituted on one or more available unsaturated carbons with 1-4 R^{W2}; and wherein if the heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N3}; and wherein W is attached to L^2 through an available saturated carbon or nitrogen atom within the heterocyclyl;

A is phenyl or 5-6-membered heteroaryl, wherein phenyl or 5-6-membered heteroaryl is optionally substituted on one or more available carbons with 1-5 R^Y; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N4};

each R^{L1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^{L2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

R^{N1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, –C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –

$C(O)–C_1$-C_3 alkyl–O–C_1-C_3 alkyl–O–C_1-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, –S–C_1-C_6 alkyl, $–S(O)_2–C_1$-C_6 alkyl, $–S(O)_2$–phenyl, $–S(O)_2$–heteroaryl, $–C(O)NR^BR^C$ and $–C(O)OR^D$;

wherein C_1-C_6 alkyl, C_1-C_6 alkenyl, $C(O)–C_1$-C_6 alkyl, $–C(O)–C_1$-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–$CO_2–C_1$-C_6 alkyl, –C(O)–heterocyclyl, $–S–C_1$-C_6 alkyl and $–S(O)_2–C_1$-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_wC_{1-6}$ alkyl (wherein w is 0, 1 or 2); and

wherein –C(O)–phenyl, –C(O)–heteroaryl, $–S(O)_2$–phenyl and $–S(O)_2$–heteroaryl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), $S(O_2)NR^BR^C$ and SO_2F;

R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

each R^{W1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl (optionally substituted by $–CO_2H$), hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^{W2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $-OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, and $–S(O)_2R^D$; or

2 R^{W2} groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, -OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, -$S(R^F)_m$, -$S(O)R^D$, –$S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, and –$S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, –$C(O)NR^BR^C$, –$C(O)R^D$, or –$C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

each R^{CC} is independently selected from the group consisting of C_1-C_6 alkyl–OH, C_1-C_6 alkyl–CO_2H and C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl;

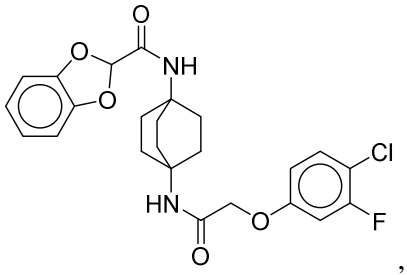
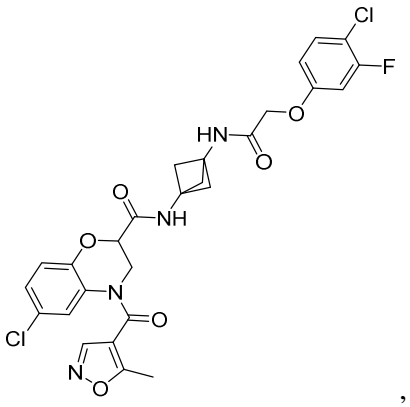
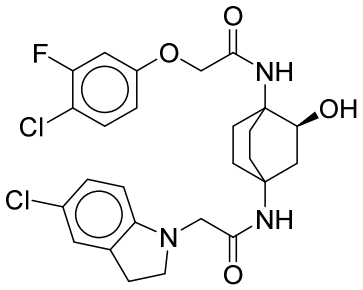
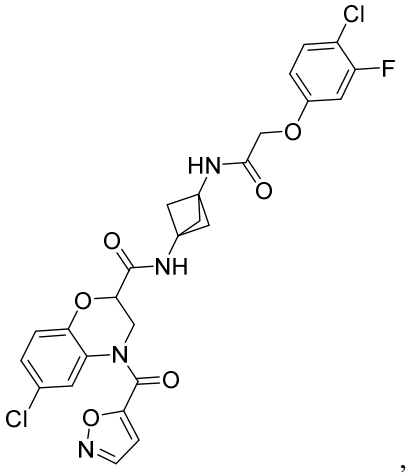
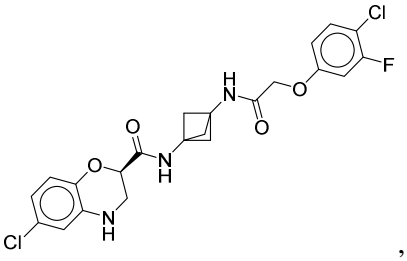
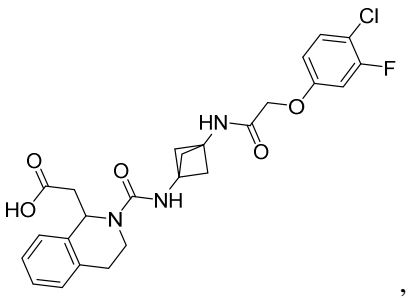
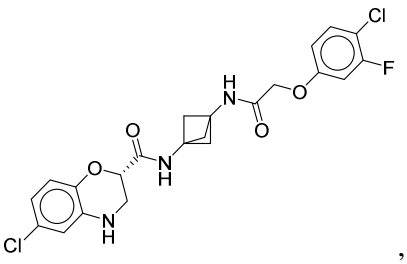
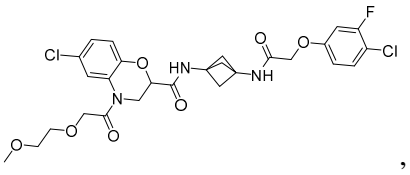
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

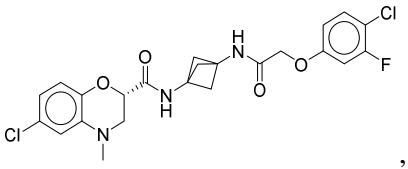
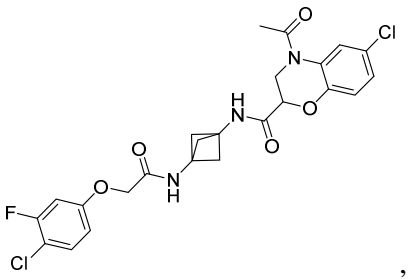
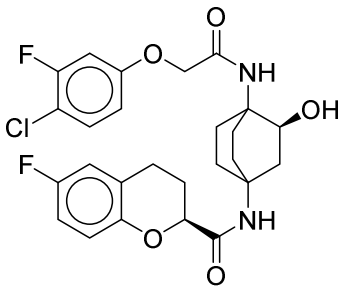
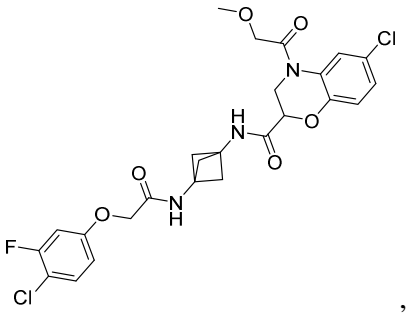
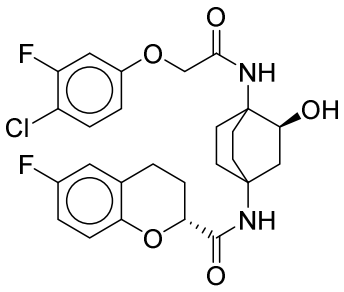
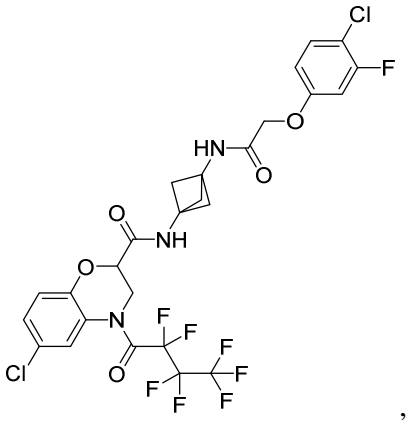
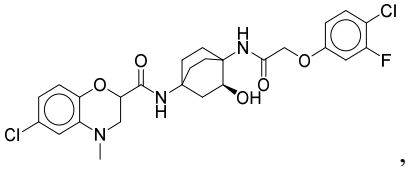
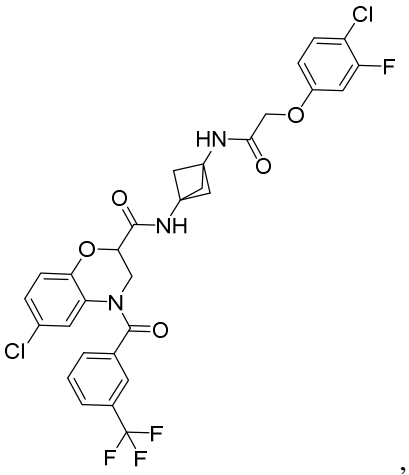
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

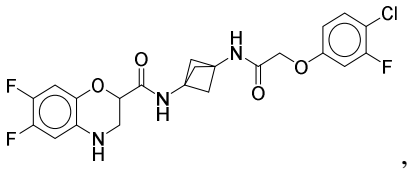
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

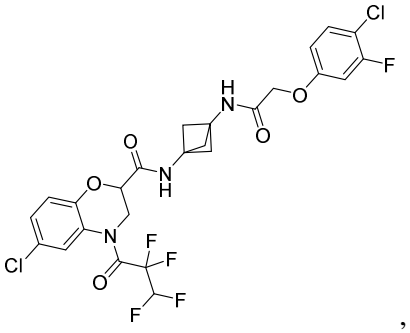
In another aspect of the present disclosure, there is provided a compound, wherein the compound is selected from the group consisting of:


,

,

,

,

,

,

,

,

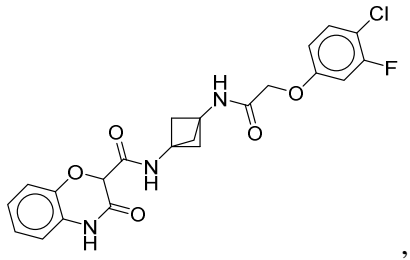

,

,

,

,

,

,

,

,



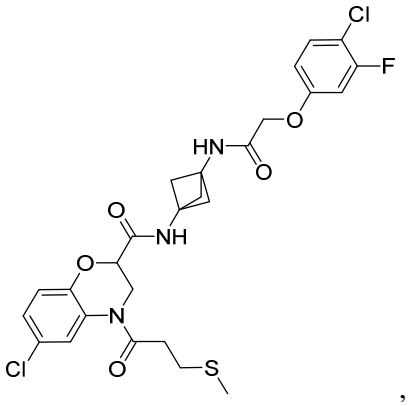
,



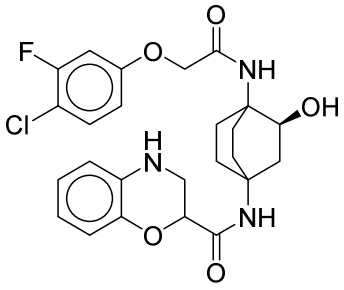
,



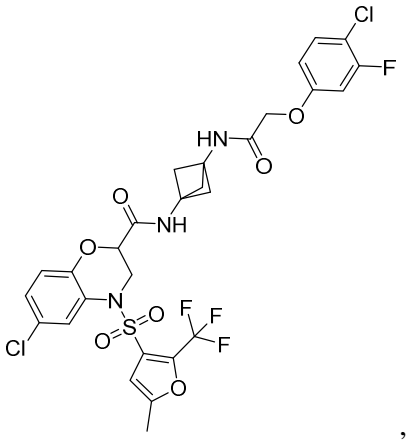
,



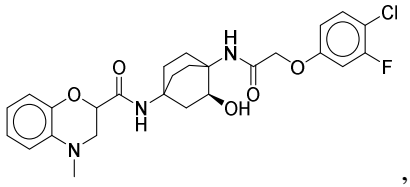
,



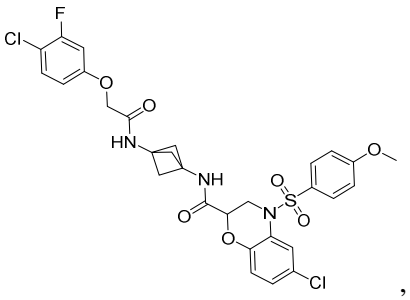
,



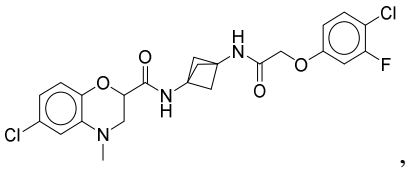
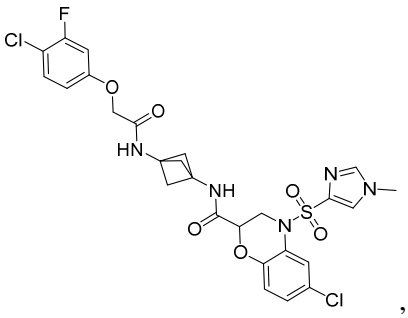
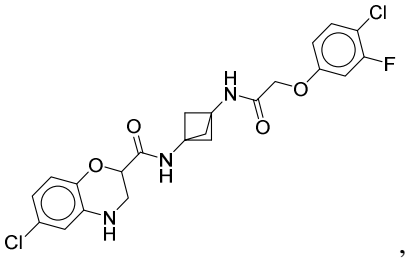
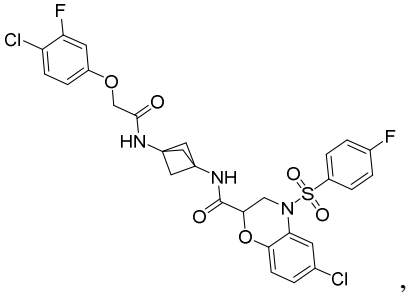
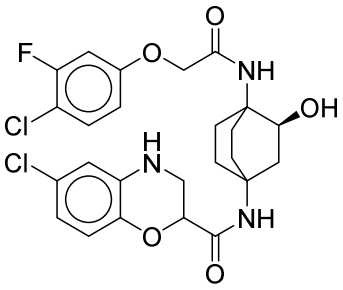
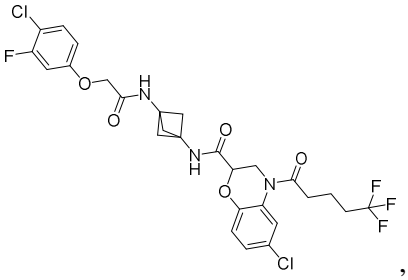
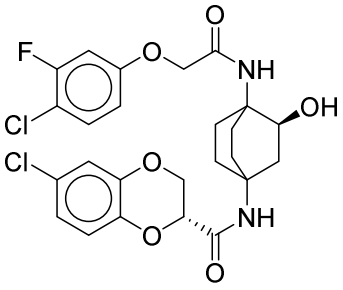
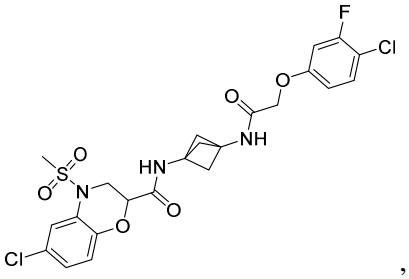
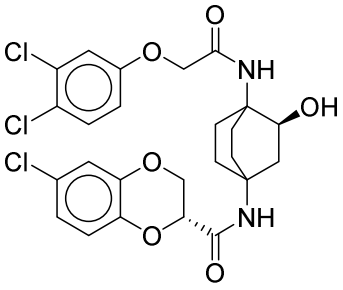
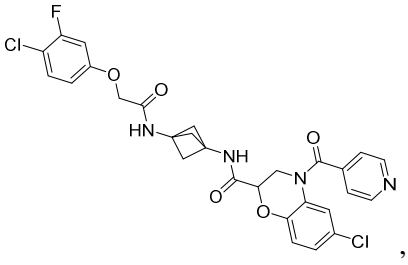
,

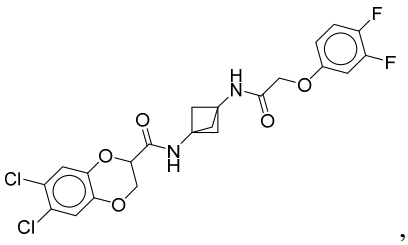
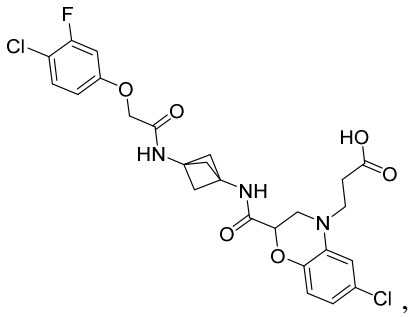
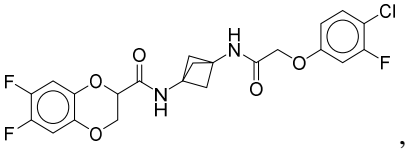
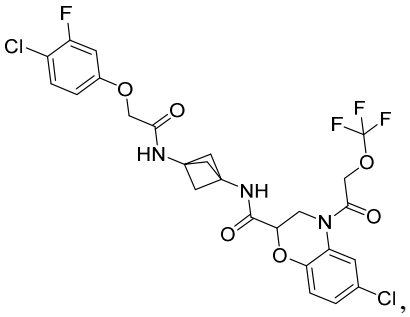
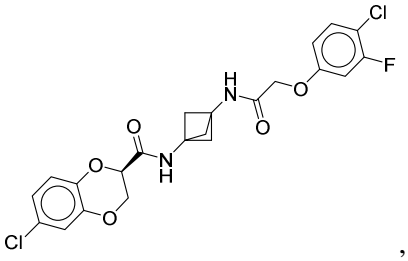
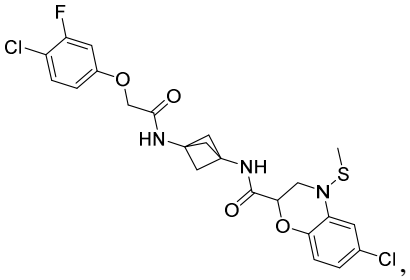
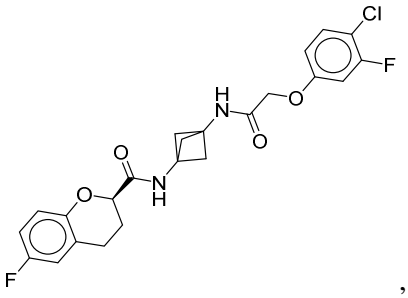
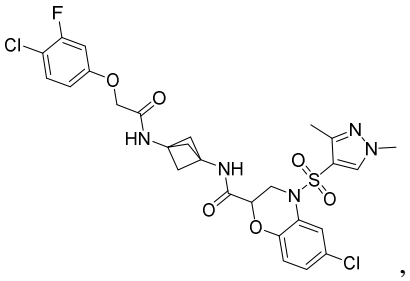


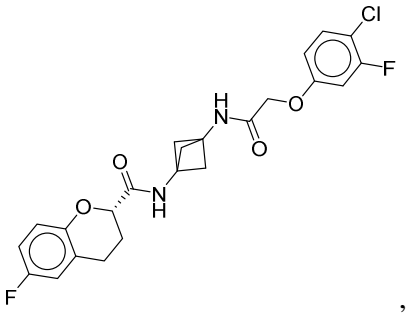
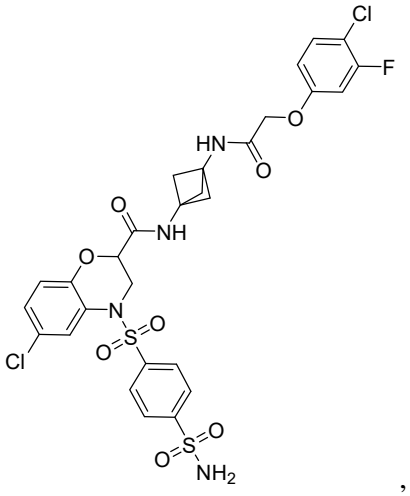
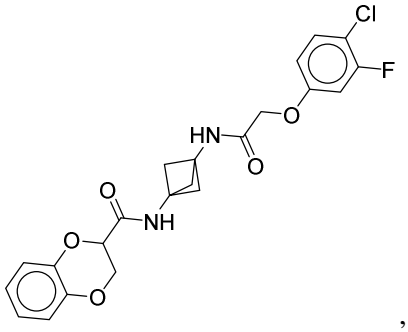
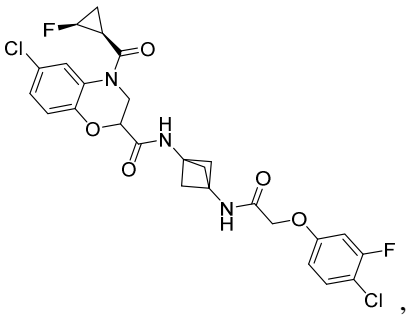
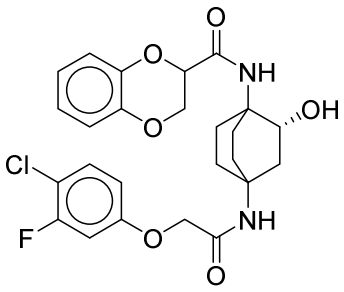
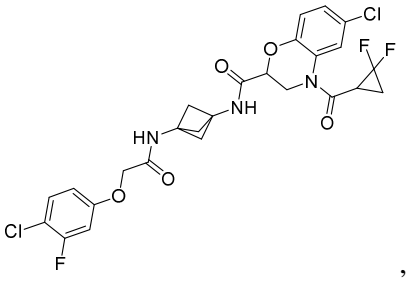
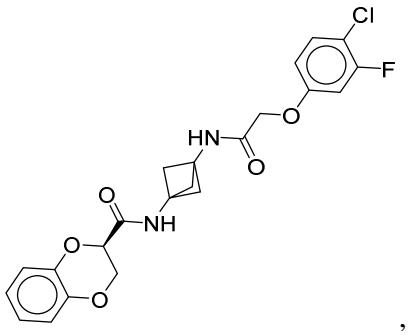
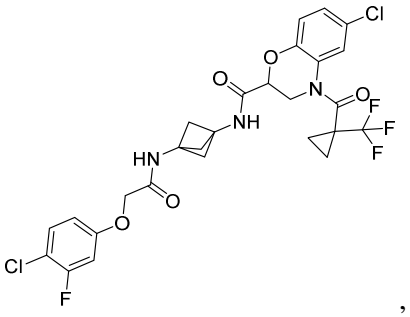
,

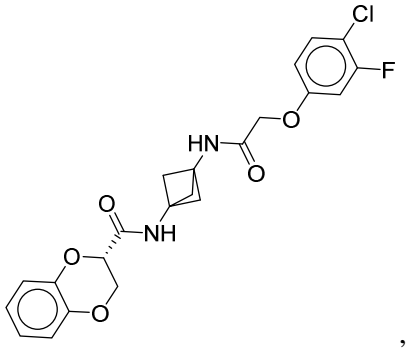
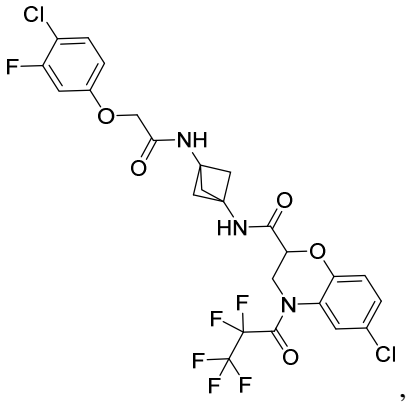
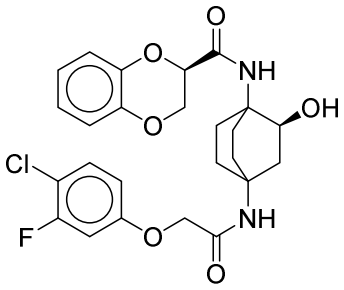
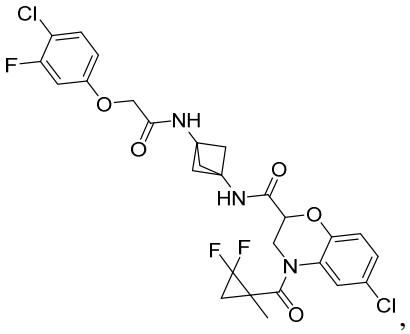
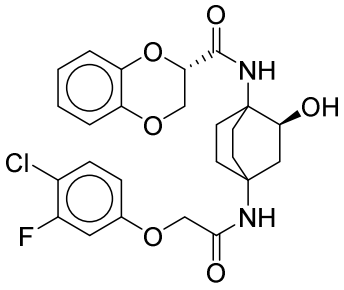
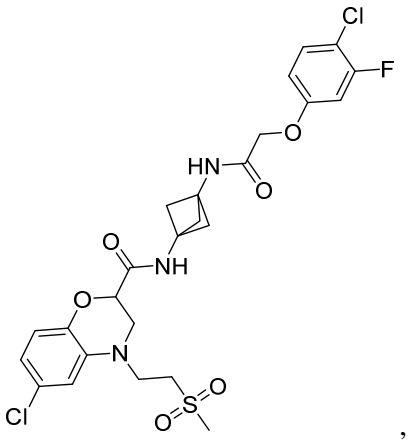
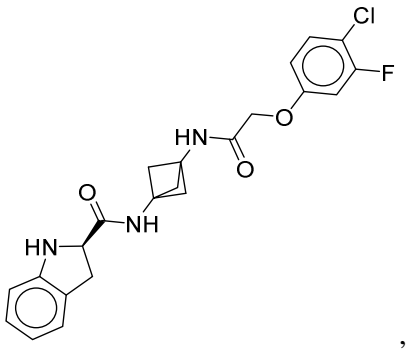
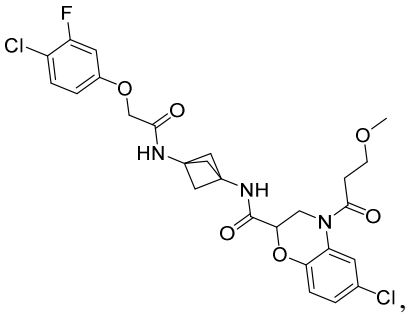


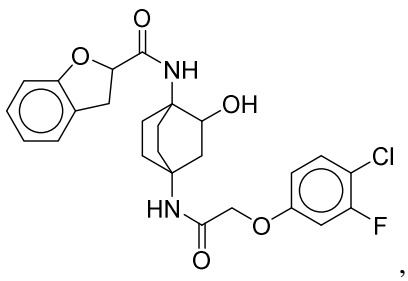
,

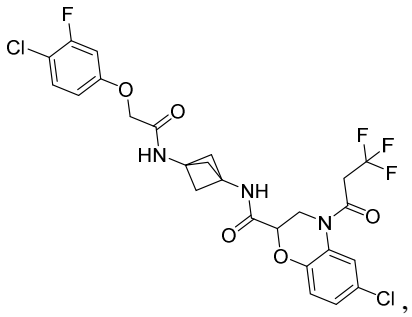

,

,

,

,

,

,

,

,

,

,

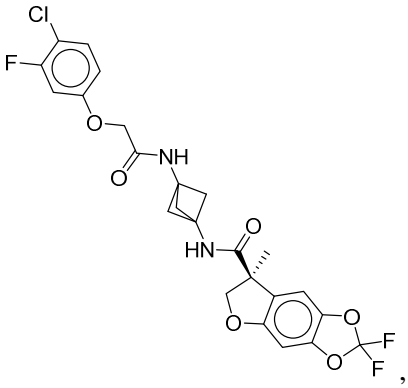

,

,

,

,

,

,

,

,

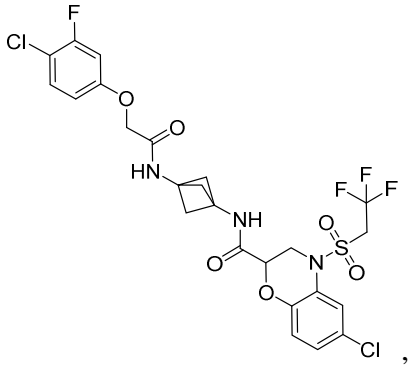

,

,

,

,

,

,

,

,

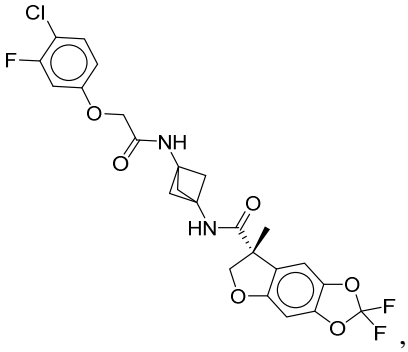

,

,

,

,

,

,

,

,

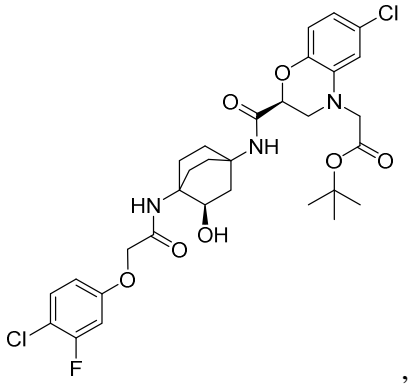

,

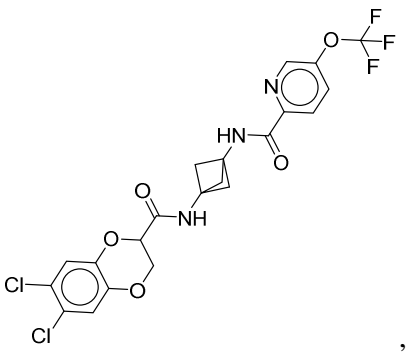

,

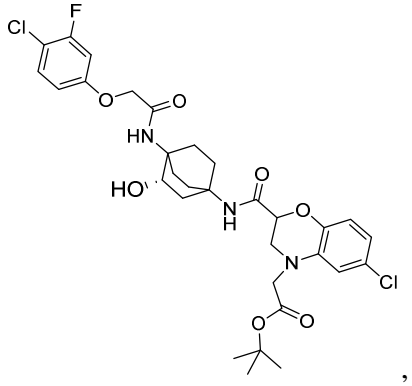

,

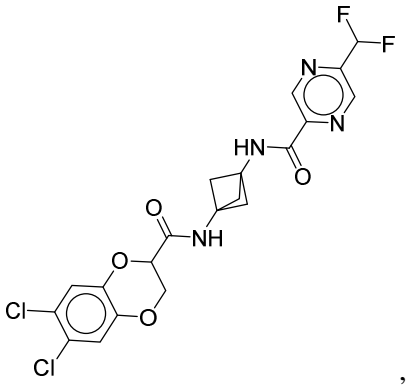
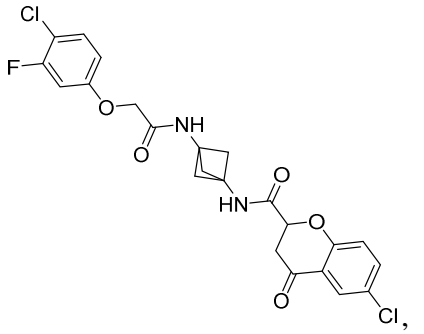
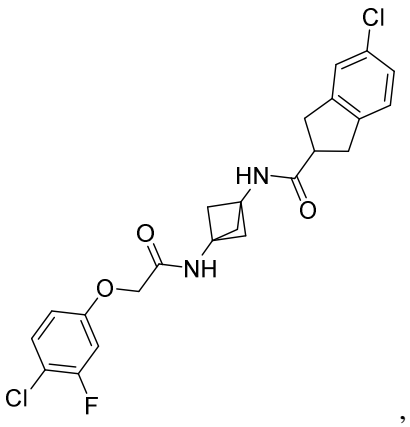
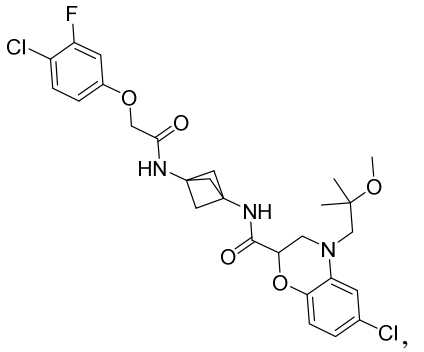
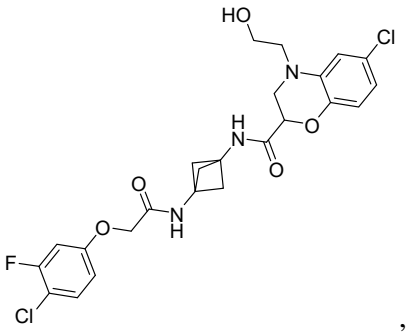
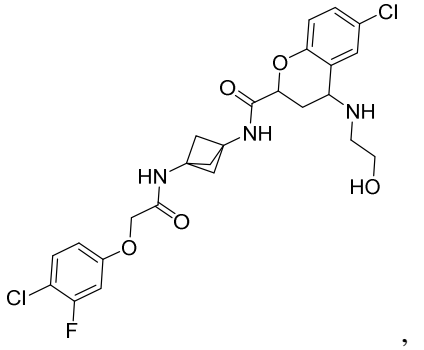
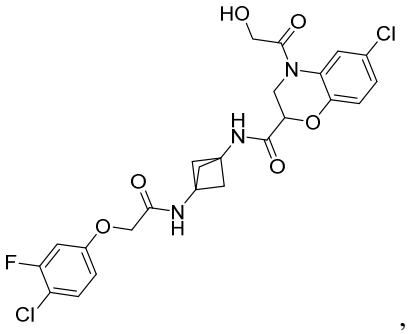
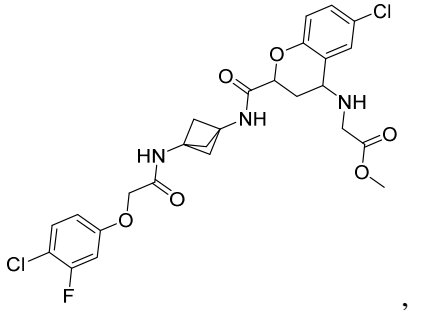

,

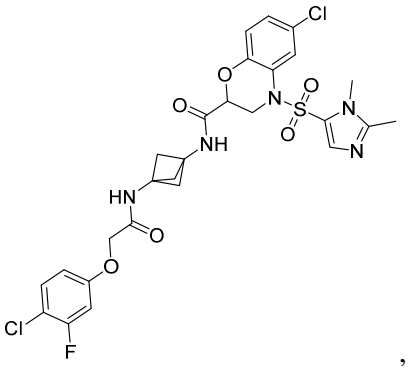
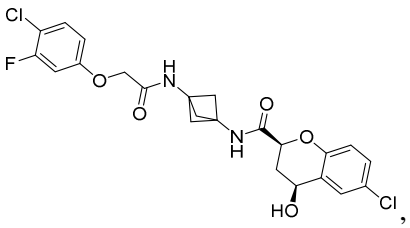
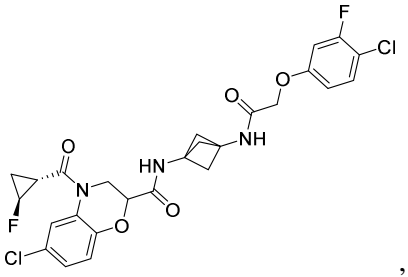
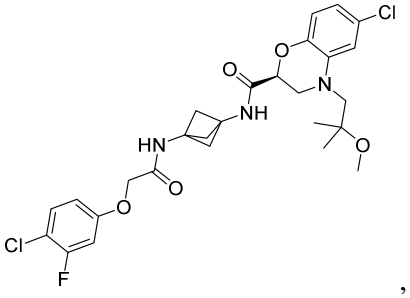
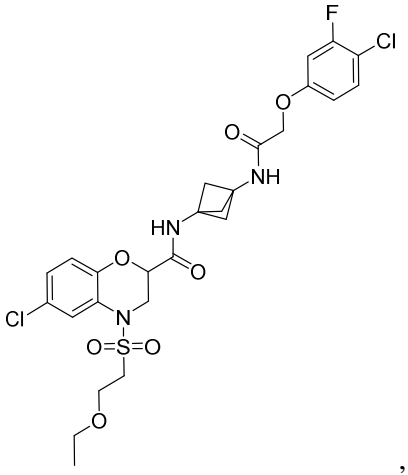
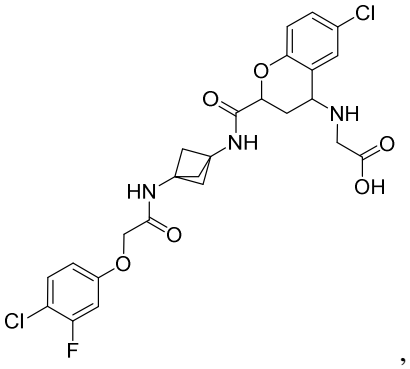
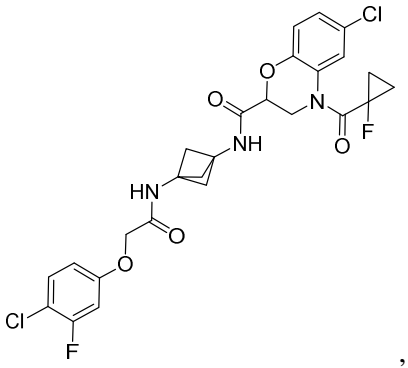
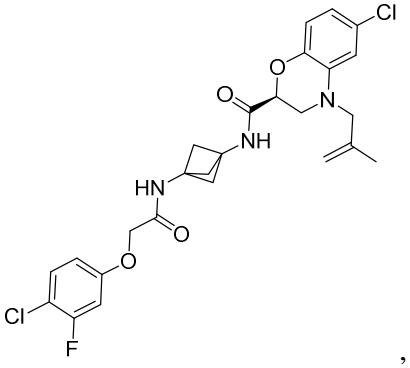

,

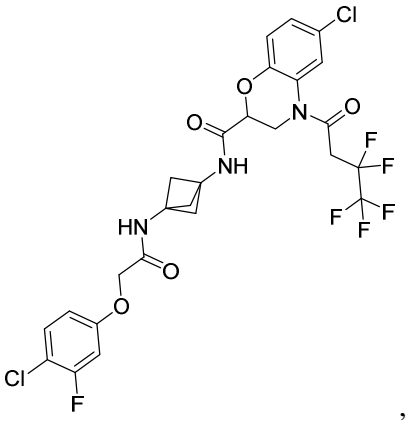

,

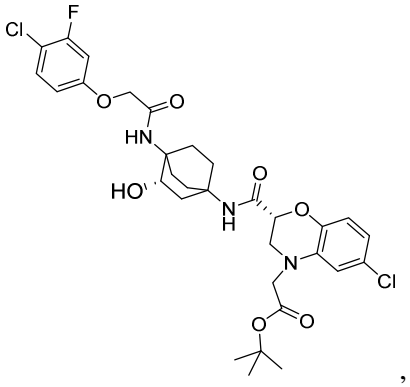

,

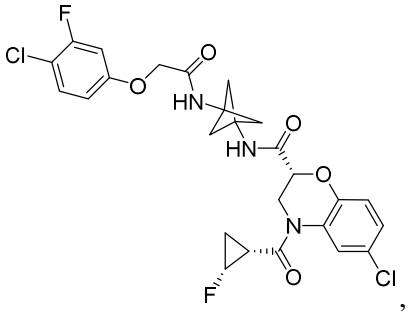

,

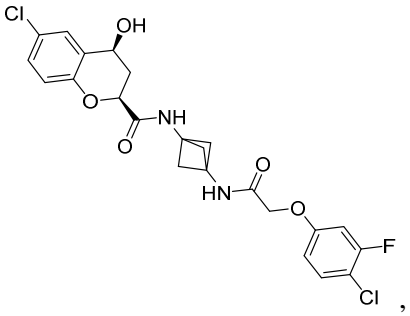

,

,

,

,

,

,

,

,

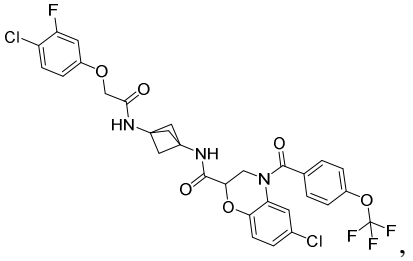

,

,

,

,

,

,

,

,

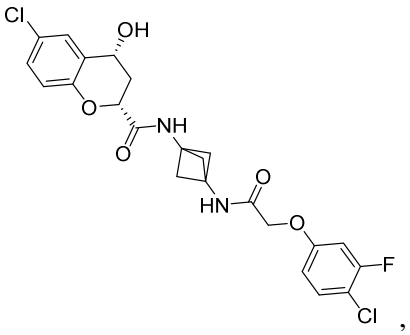

,

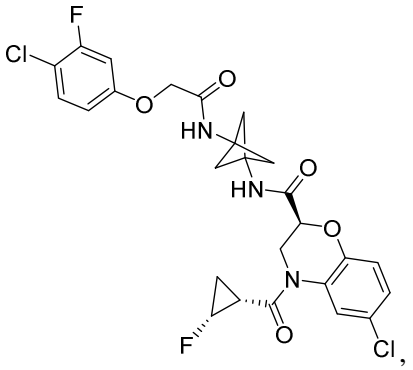

,

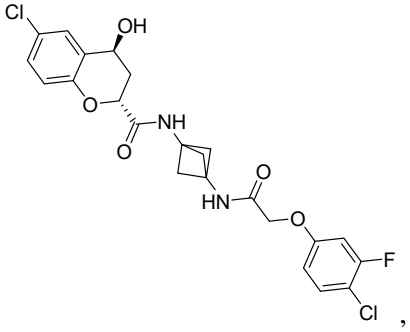

,

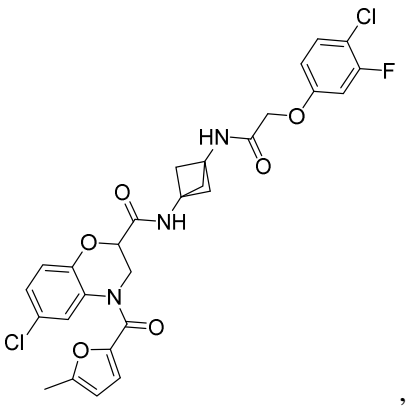
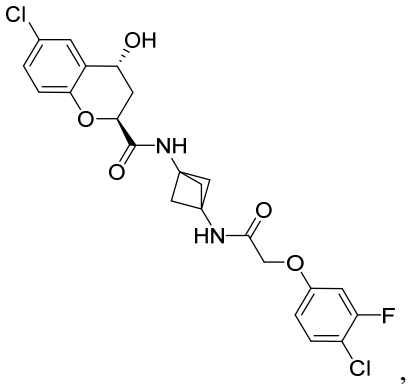
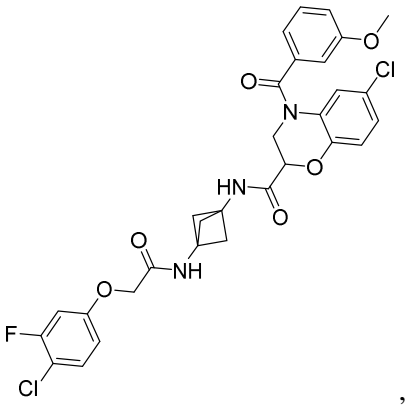
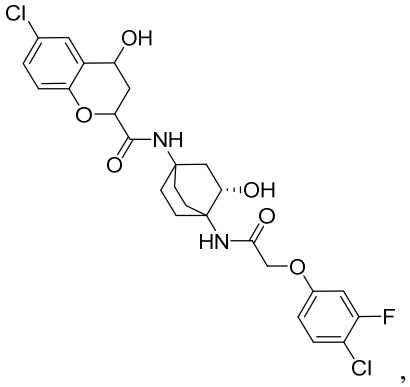
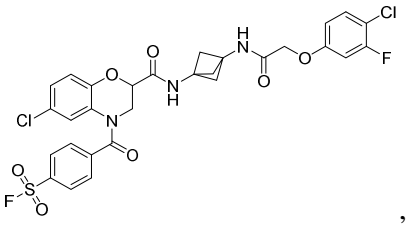
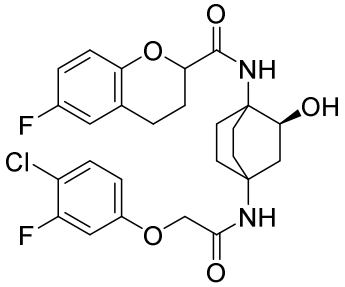
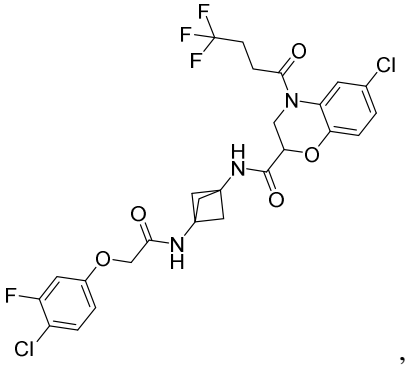
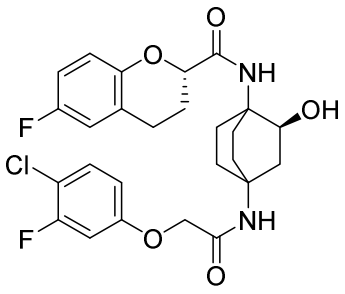

,

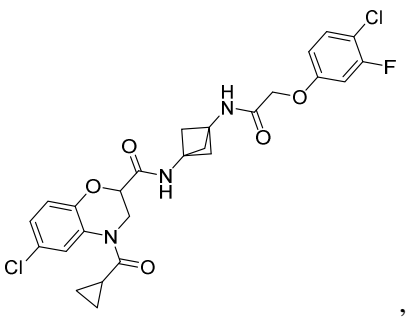

,


,

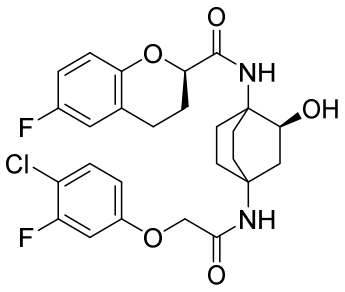

,


,

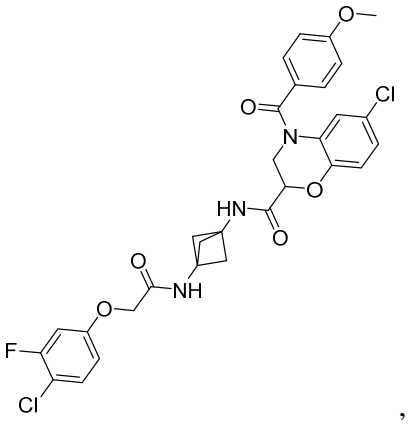

,

,

,

,

,

,

,

,



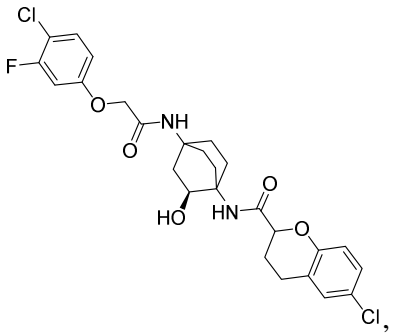
,



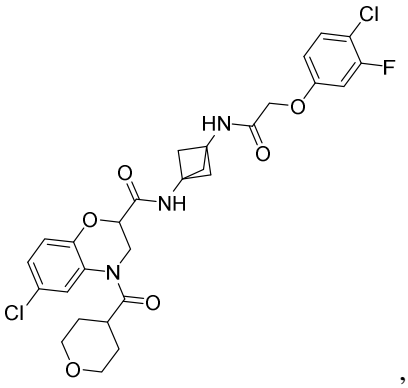
,



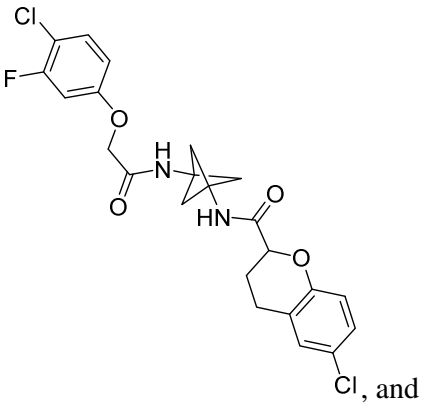
,



,



,



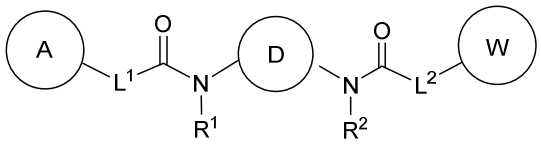
, and

,

or a pharmaceutically acceptable salt thereof.

The present disclosure is directed, at least in part, to compounds, compositions, and methods for the modulation of eIF2B (e.g., activation of eIF2B) and the attenuation of the ISR signaling pathway. In some examples, disclosed herein is an eIF2B modulator (e.g., an eIF2B activator) comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide, or stereoisomer thereof. In other examples, disclosed herein are methods of using a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide, or stereoisomer thereof for the treatment of a disease or disorder, e.g., a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B or components in the ISR pathway (e.g., eIF2 pathway).

For example, disclosed herein is a compound of Formula (I):



Formula (I)

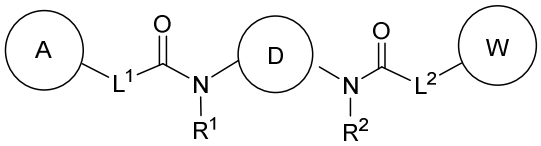
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein:

D is a bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, or cubanyl is optionally substituted on one or more available carbons with 1-4 R^X; and wherein if the bridged bicyclic

CLAIMS

We claim:

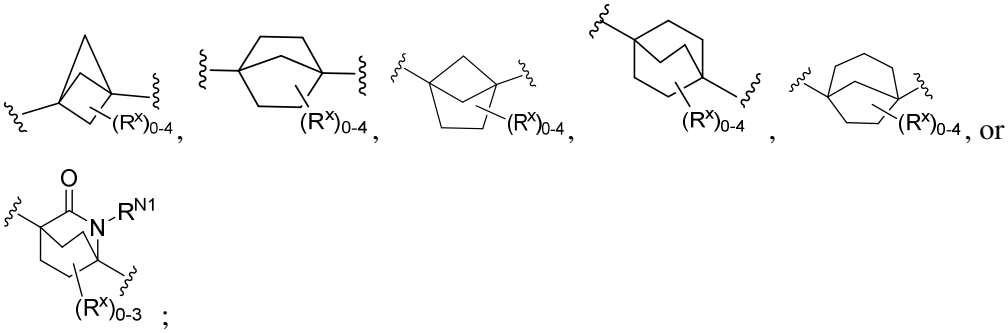
1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:



;

L^1 is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N2}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L1};

L^2 is a bond, C_1-C_6 alkylene, or 2-7 membered heteroalkylene, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl;

W is a 8-10 membered, partially unsaturated, fused bicyclic ring moiety comprising a 5-6 membered heterocyclyl fused to a phenyl or 5-6-membered heteroaryl; wherein the heterocyclyl may be optionally substituted on one or more available saturated carbons with 1-4 R^{W1}; and wherein the phenyl or heteroaryl may optionally be substituted on one or more available unsaturated carbons with 1-4 R^{W2}; and wherein if the heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N3}; and wherein W is attached to L^2 through an available saturated carbon or nitrogen atom within the heterocyclyl;

A is phenyl or 5-6-membered heteroaryl, wherein phenyl or 5-6-membered heteroaryl is optionally substituted on one or more available carbons with 1-5 R^Y; and wherein if the 5-

6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N4};

each R^{L1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^{L2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

R^{N1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, $–C(O)–C_1$-C_6 alkyl, $–C(O)–C_1$-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–$CO_2–C_1$-C_6 alkyl, $–C(O)–C_1$-C_3 alkyl–$O–C_1$-C_3 alkyl–$O–C_1$-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, $–S–C_1$-C_6 alkyl, $–S(O)_2–C_1$-C_6 alkyl, $–S(O)_2$–phenyl, $–S(O)_2$–heteroaryl, $–C(O)NR^BR^C$ and $–C(O)OR^D$;

wherein C_1-C_6 alkyl, C_1-C_6 alkenyl, $C(O)–C_1$-C_6 alkyl, $–C(O)–C_1$-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–$CO_2–C_1$-C_6 alkyl, –C(O)–heterocyclyl, $–S–C_1$-C_6 alkyl and $–S(O)_2–C_1$-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_wC_{1\text{-}6}$ alkyl (wherein w is 0, 1 or 2); and

wherein –C(O)–phenyl, –C(O)–heteroaryl, $–S(O)_2$–phenyl and $–S(O)_2$–heteroaryl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), $S(O_2)NR^BR^C$ and SO_2F;

R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, and –$S(O)_2R^D$;

each R^{W1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl (optionally substituted by –CO_2H), hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, –OR^A, –NR^BR^C, –NR^BR^{CC}, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E, –$S(O)R^D$, and –$S(O)_2R^D$;

each R^{W2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, -OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, -$S(R^F)_m$, -$S(O)R^D$, and –$S(O)_2R^D$; or

2 R^{W2} groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E, –$S(O)R^D$, and –$S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, -OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, -$S(R^F)_m$, -$S(O)R^D$, –$S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, and –$S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, –$C(O)NR^BR^C$, –$C(O)R^D$, or –$C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

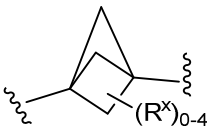
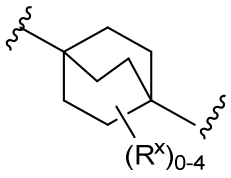
each R^{CC} is independently selected from the group consisting of C_1-C_6 alkyl–OH, C_1-C_6 alkyl–CO_2H and C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl;

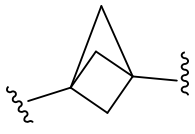
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

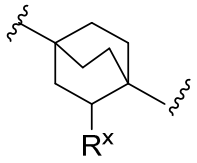
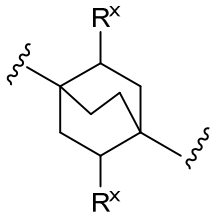
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

2. The compound of claim 1, wherein D is  or .

3. The compound of claim 1 or 2, wherein D is .

4. The compound of claim 1 or 2, wherein D is  or .

5. The compound of claim 4, wherein each R^X is independently selected from the group consisting of oxo, –OH , –C(O)OH, –C(O)OR^D, halo, and hydroxy-C_1-C_6 alkyl.

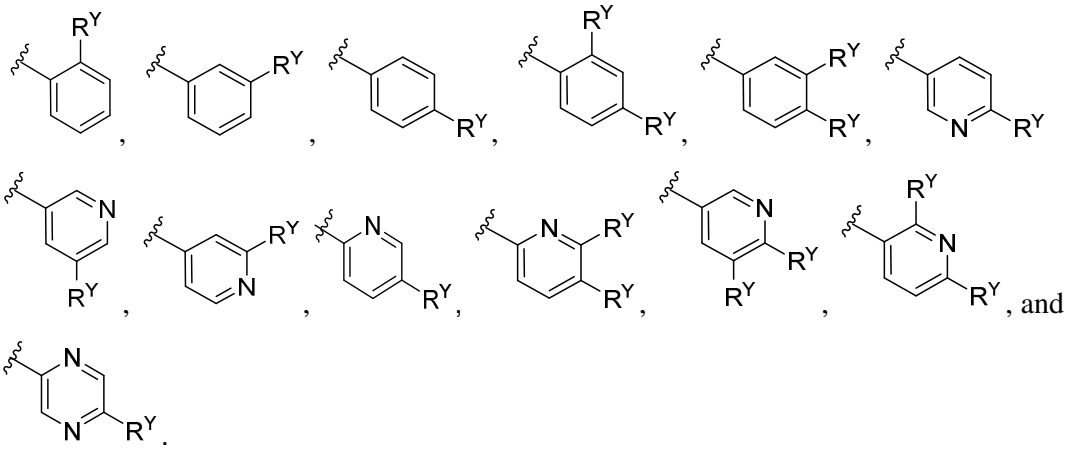
6. The compound of any one of claims 1-5, wherein L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is optionally substituted by 1-5 R^{L1}.

7. The compound of any one of claims 1-6, wherein L^1 is selected from a bond, CH_2O–*, CH_2OCH_2–*, –NCH_3–, –NH–, or –O–, wherein "–*" indicates the attachment point to A.

8. The compound of any one of claims 1-7, wherein R^1 is hydrogen or –CH_3.

9. The compound of any one of claims 1-8, wherein R^2 is hydrogen or –CH_3.

10. The compound of any one of claims 1-9, wherein A is selected from the group consisting of:



, and

.

11. The compound of any one of claims 1-10, wherein each R^Y is independently selected from the group consisting of hydrogen, chloro, fluoro, –CHF_2, –CF_3, –CH_3, –CH_2CH_3, –$CH(CH_3)_2$, –OCH_3, –$OCHF_2$, –OCF_3, –OCH_2CF_3, –$OCH(CH_3)_2$, and –CN, or

2 R^Y on adjacent carbons, together with the atoms to which they are attached, form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 R^X.

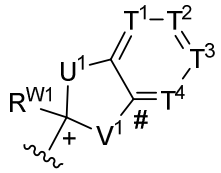
12. The compound of claim 11, wherein each R^X is independently fluoro.

13. The compound of any one of claims 1-12, wherein L^2 is a bond or C_1-C_6 alkylene, wherein C_1-C_6 alkylene is optionally substituted by 1-5 R^{L2}.

14. The compound of any one of claims 1-13, wherein L^2 is selected from a bond or CH_2–*, wherein "–*" indicates the attachment point to W.

15. The compound of any one of claims 1-14, wherein L^2 is a bond.

16. The compound of any one of claims 1-15, wherein W is represented by Formula (W-a):



Formula (W-a)

wherein:

T^1 is nitrogen or $C(R^{W2})$;

T^2 is nitrogen or $C(R^{W2})$;

T^3 is nitrogen or $C(R^{W2})$;

T^4 is nitrogen or $C(R^{W2})$;

wherein no more than two of T^1, T^2, T^3, and T^4 may be nitrogen;

U^1 is selected from the group consisting of a bond, –O–, $–NR^{N3}–$, and $–S(O)_w–$ (wherein w is 0, 1, or 2);

V^1 is selected from the group consisting of $^+–O–^\#$, $^+–C(R^{V11}R^{V12})–^\#$, $^+–C(R^{V11}R^{V12})–C(O)–^\#$, $^+–C(R^{V11}R^{V12})–C(R^{V13}R^{V14})–^\#$, $^+–C(R^{V15}R^{V16})–O–^\#$, $^+–C(R^{V15}R^{V16})–NR^{N3}–^\#$, $^+–C(O)–NR^{N3}–^\#$, $^+–NR^{N3}–^\#$, $^+–O–C(R^{V15}R^{V16})–^\#$, $^+–NR^{N3}–C(R^{V15}R^{V16})–^\#$, $^+–NR^{N3}–C(O)–^\#$, $^+–C(O)–O–^\#$, $^+–O–C(O)–^\#$, $^+–C(R^{V15}R^{V16})–S(O)_w–^\#$, and $^+–S(O)_w–C(R^{V15}R^{V16})–^\#$ (wherein w is 0, 1, or 2); wherein the "$^+$–" and "$–^\#$" indicate the attachment points of V^1 as indicated in Formula (W-a);

wherein if V^1 is $^+–O–^\#$, $^+–NR^{N3}–^\#$, or $^+–C(R^{V11}R^{V12})–^\#$; U^1 is not a bond;

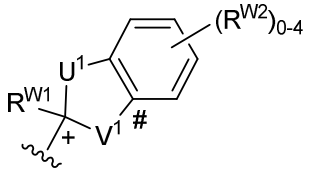
R^{V11} and R^{V12} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

R^{V13} and R^{V14} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

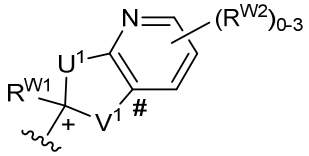
R^{V15} and R^{V16} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -C(O)N$R^B R^C$, –C(O)R^D, –C(O)OH, and –C(O)OR^D; and

R^{W1} is selected from the group consisting of hydrogen and C_1-C_6 alkyl.

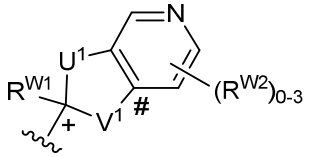
17. The compound of claim 16, wherein W is represented by Formula (W-a-1), Formula (W-a-2), Formula (W-a-3), Formula (W-a-4), or Formula (W-a-5):



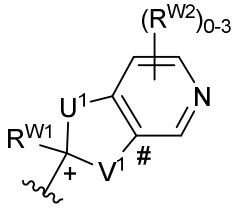
Formula (W-a-1),



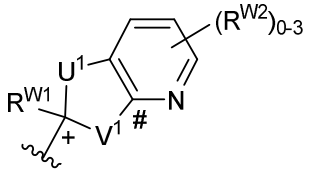
Formula (W-a-2),



Formula (W-a-3),

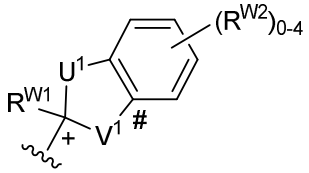


Formula (W-a-4), or



Formula (W-a-5).

18. The compound of claim 17, wherein W is represented by Formula (W-a-1):



Formula (W-a-1).

19. The compound of any one of claims 16-18, wherein U^1 is selected from the group consisting of a bond, –O–, and $–NR^{N3}–$; and V^1 is selected from the group consisting of $^+–O–^\#$, $^+–C(R^{V11}R^{V12})–^\#$, $^+–C(R^{V11}R^{V12})–C(R^{V13}R^{V14})–^\#$, $^+–C(R^{V15}R^{V16})–O–^\#$, $^+–C(R^{V11}R^{V12})–C(O)–^\#$, $^+–O–C(R^{V15}R^{V16})–^\#$, $^+–C(R^{V15}R^{V16})–NR^{N3}–^\#$, and $^+–C(O)–NR^{N3}–^\#$; wherein "$^+–$" and "$–^\#$" indicate the attachment points of V^1 as indicated in Formula (W-a); and wherein if V^1 is $^+–O–^\#$ or $^+–C(R^{V11}R^{V12})–^\#$, U^1 is not a bond.

20. The compound of any one of claims 16-19, wherein each of R^{V11}, R^{V12}, R^{V13}, and R^{V14} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, $–OR^A$, $–NR^BR^C$, and $–NR^BR^{CC}$.

21. The compound of any one of claims 16-20, wherein each of R^{V11}, R^{V12}, R^{V13}, and R^{V14} is independently selected from the group consisting of hydrogen, hydroxyl and $–NR^BR^{CC}$.

22. The compound of any one of claims 16-21, wherein each of R^{V15} and R^{V16} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

23. The compound of any one of claims 16-22, wherein each of R^{V15} and R^{V16} is hydrogen.

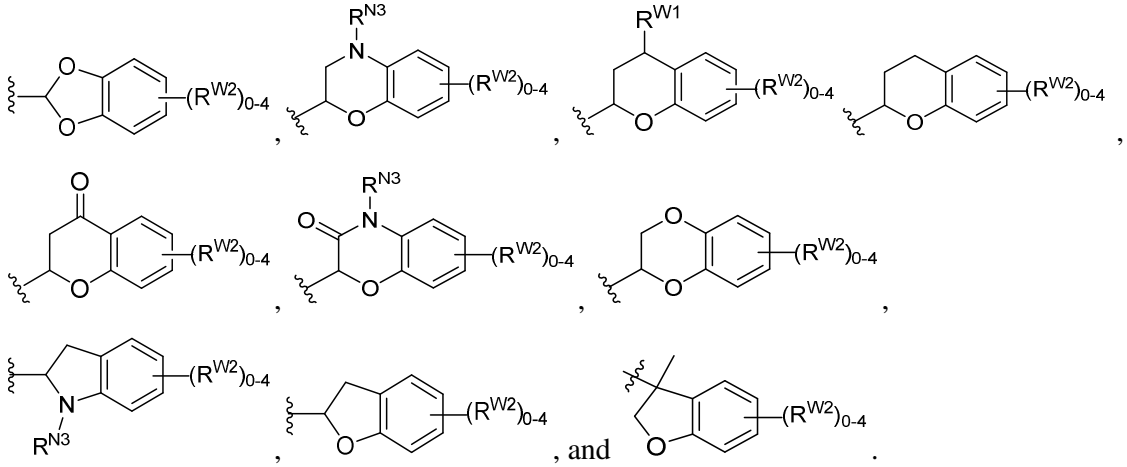
24. The compound of any one of claims 16-23, wherein U^1 is selected from the group consisting of a bond, –O–, –NH– and $–NCH_3–$; and V^1 is selected from the group consisting of $^+–O–^\#$, $^+–CH_2–^\#$, $^+–CH_2–CH_2–^\#$, $^+–CH_2–C(O)–^\#$, $^+–CH_2–O–^\#$, $^+–O\text{-}CH_2–^\#$, $^+–CH_2–NH–^\#$, $^+–$

CH_2–NCH_3–$^{\#}$, $^{+}$–C(O)–NH–$^{\#}$, and $^{+}$–C(O)–NCH_3–$^{\#}$, and wherein "$^{+}$–" and "–$^{\#}$" indicate the attachment points of V^1 as indicated in Formula (W-a).

25. The compound of any one of claims 16-24, wherein R^{W1} is selected from the group consisting of hydrogen, hydroxyl, $–CH_3$, $–NH(CH_2)_2OH$, $–NH(CH_2)_2CO_2H$, and $–NH(CH_2)_2CO_2CH_3$.

26. The compound of any one of claims 16-25, wherein W is a benzo[*d*][1,3]dioxole, 3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine, chromane, chroman-4-one, *2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one, 2,3-dihydrobenzo[*b*][1,4]dioxine, indoline, or 2,3-dihydrobenzofuran moiety; wherein each of which is attached to L^2 through a saturated carbon atom, and wherein each of which is optionally substituted on one or more available unsaturated carbons with 1-4 R^{W2}, and wherein each R^{W2} is independently selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, oxo, cyano, and $–OR^A$.

27. The compound of any one of claims 16-26, wherein W is selected from the group consisting of:


R^N3
R^W1
(R^W2)0-4
O
N
, , , ,

wherein:

T^5 is nitrogen or $C(R^{W2})$;

T^6 is nitrogen or $C(R^{W2})$;

T^7 is nitrogen or $C(R^{W2})$;

T^8 is nitrogen or $C(R^{W2})$;

wherein no more than two of T^5, T^6, T^7, and T^8 may be nitrogen;

V^2 is selected from the group consisting of $^*–C(R^{V21}R^{V22})–^\#$, $^*–C(R^{V21}R^{V22})–C(R^{V23}R^{V24})–^\#$, $^*–C(R^{V21}R^{V22})–C(R^{V23}R^{V24})–C(R^{V23}R^{V24})–^\#$, $^*–C(R^{V21}R^{V22})–C(R^{V21}R^{V22})–O–^\#$, $^*–C(R^{V21}R^{V22})–C(R^{V21}R^{V22})–NR^{N3}–^\#$, $–C(R^{V21}R^{V22})–NR^{N3}–^\#$, $^*–C(O)–C(R^{V23}R^{V24})–^\#$, $^*–C(O)–C(R^{V23}R^{V24})–C(R^{V23}R^{V24})–^\#$, $^*–C(O)–NR^{N3}–^\#$, and $^*–C(O)–O–^\#$, wherein "*–" and "$–^\#$" indicate the attachment points of V^2 as indicated in Formula (W-b);

U^2 is selected from the group consisting of a bond, $^*–C(O)–^+$, and $^*–C(R^{U21}R^{U22})–^+$, wherein "*–" and "$–^+$" indicate the attachment points of U^2 as indicated in Formula (W-b);

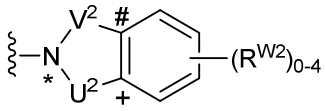
wherein if V^2 is $^*–C(R^{V21}R^{V22})–^\#$, U^2 is not a bond;

R^{U21} and R^{U22} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, C_1-C_6 alkyl–C(O)OH, and C_1-C_6 alkyl–$C(O)OR^D$;

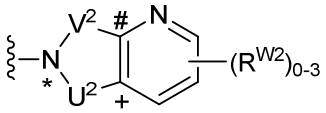
R^{V21} and R^{V22} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, and $–C(O)OR^D$; and

R^{V23} and ^{RV24} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$.

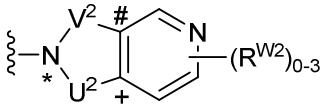
29. The compound of claim 28, wherein W is represented by Formula (W-b-1), Formula (W-b-2), Formula (W-b-3), Formula (W-b-4), or Formula (W-b-5):



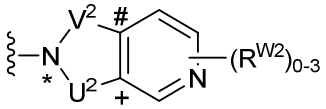
Formula (W-b-1),



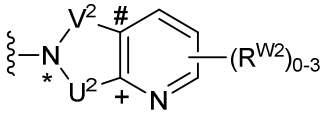
Formula (W-b-2),



Formula (W-b-3),

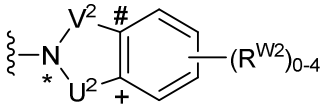


Formula (W-b-4), or



Formula (W-b-5).

30. The compound of claim 28, wherein W is represented by Formula (W-b-1):



Formula (W-b-1).

31. The compound of any one of claims 28-30, wherein V^2 is selected from the group consisting of *–C($R^{V21}R^{V22}$)–$^{\#}$, *–C($R^{V21}R^{V22}$)–C($R^{V23}R^{V24}$)–$^{\#}$, *–C(O)–C($R^{V23}R^{V24}$)–$^{\#}$, and *–C($R^{V21}R^{V22}$)–C($R^{V23}R^{V24}$)–C($R^{V23}R^{V24}$)–$^{\#}$; wherein "*–" and "–$^{\#}$" indicate the attachment points of V^2 as indicated in Formula (W-b).

32. The compound of any one of claims 28-31, wherein each of R^{V21} and R^{V22} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

33. The compound of any one of claims 28-32, wherein each of R^{V21} and R^{V22} is hydrogen.

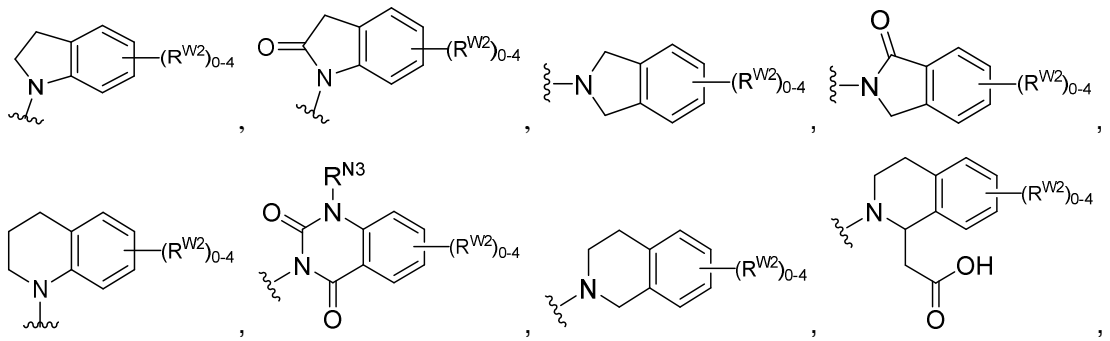
34. The compound of any one of claims 28-33, wherein each of R^{V23} and R^{V24} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, $–OR^A$, and $–NR^BR^C$.

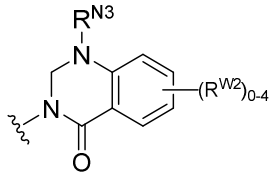
35. The compound of any one of claims 28-34, wherein each of R^{V23} and R^{V24} is hydrogen.

36. The compound of any one of claims 28-35, wherein U^2 is selected from the group consisting of a bond, $^*–C(O)–^+$, $^*–CH_2–^+$, and $^*–CH(CH_2CO_2H)–^+$, wherein "*–" and "$–^+$" indicate the attachment points of U^2 as indicated in Formula (W-b); and V^2 is selected from the group consisting of $^*–CH_2–^\#$, $^*–CH_2–CH_2–^\#$, $^*–C(O)–CH_2–^\#$, $^*–C(O)–NH–^\#$, $^*–CH_2–NH–^\#$, and $^*–CH_2–CH_2–CH_2–^\#$; wherein "*–" and "$–^\#$" indicate the attachment points of V^2 as indicated in Formula (W-b).

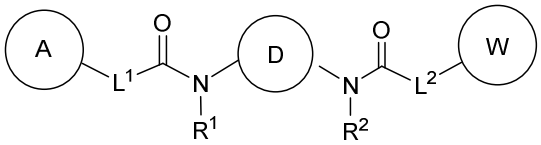
37. The compound of any one of claims 28-36, wherein W is an indoline, indolin-2-one, isoindoline, isoindolin-1-one, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, quinazoline-2,4(1*H*,3*H*)-dione, or 2,3-dihydroquinazolin-4(1*H*)-one moiety; wherein each of which is attached to L^2 through a nitrogen atom, and wherein each of which is optionally substituted on one or more available unsaturated carbon atoms with 1-4 R^{W2}, and wherein each R^{W2} is independently selected from the group consisting of C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo, cyano, and $–OR^A$.

38. The compound of any one of claims 28-37, wherein W is selected from the group consisting of:



and  ; wherein R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and hydroxy-C_2-C_6 alkyl.

39. The compound of any one of claims 1-38, wherein the compound of Formula (I) is a compound of Formula (I-a):



Formula (I-a)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl or bicyclo[2.2.2]octanyl, each of which is optionally substituted with 1-4 R^X groups;

L^1 is selected from the group consisting of a bond, CH_2O–*, CH_2OCH_2–*, –NCH_3–, –NH–, and –O–, wherein "–*" indicates the attachment point to A;

L^2 is a bond;

R^1 is selected from the group consisting of hydrogen and –CH_3;

R^2 is selected from the group consisting of hydrogen and –CH_3;

A is phenyl, pyrazine or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

W is a benzo[*d*][1,3]dioxole, 3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine, chromane, *2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one, 2,3-dihydrobenzo[*b*][1,4]dioxine, indoline, or 2,3-dihydrobenzofuran moiety; wherein each of which is attached to L^2 through a saturated carbon atom, and wherein each of which is optionally substituted on one or more available unsaturated carbon atoms with 1-4 R^{W2} groups; and wherein 3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine, *2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one, and indoline may be optionally substituted on an available nitrogen atom with hydrogen or CH_3;

each R^{W2} is independently selected from the group consisting of hydrogen, chloro, fluoro, –CHF_2, –CF_3, –CH_3, –CH_2CH_3, –$CH(CH_3)_2$, –OCH_3, –$OCHF_2$, –OCF_3, –OCH_2CF_3, –$OCH(CH_3)_2$, and –CN; or

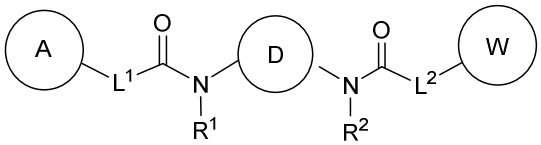
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

each R^X is independently fluoro, oxo, –OH, $–OCH_3$, –C(O)OH, or $–C(O)OCH_3$; and

each R^Y is independently chloro, fluoro, $–CHF_2$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, or –CN; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms.

40. The compound of any one of claims 1-38, wherein the compound of Formula (I) is a compound of Formula (I-b):



Formula (I-b)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl or bicyclo[2.2.2]octanyl, each of which is optionally substituted with 1-4 R^X groups;

L^1 is selected from the group consisting of a bond, $CH_2O–*$, $CH_2OCH_2–*$, $–NCH_3–$, –NH–, and –O–, wherein "–*" indicates the attachment point to A;

L^2 is $CH_2–*$, wherein "–*" indicates the attachment point to W;

R^1 is selected from the group consisting of hydrogen and $–CH_3$;

R^2 is selected from the group consisting of hydrogen and $–CH_3$;

A is phenyl or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

W is an indoline moiety; wherein indoline is attached to L^2 through a nitrogen atom, and wherein indoline is optionally substituted on one or more available unsaturated carbon atoms with 1-4 R^{W2} groups;

each R^{W2} is independently selected from the group consisting of hydrogen, chloro, fluoro, $–CHF_2$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, and –CN; or

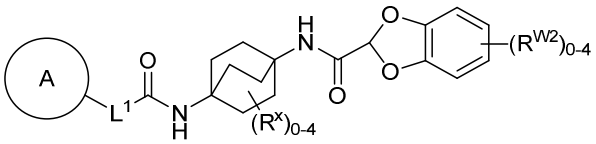
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

each R^X is independently fluoro, oxo, –OH, $–OCH_3$, –C(O)OH, or $–C(O)OCH_3$; and

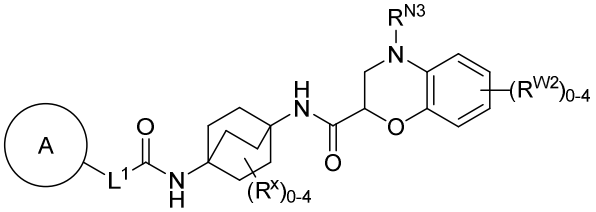
each R^Y is independently chloro, fluoro, $–CHF_2$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, or –CN; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms.

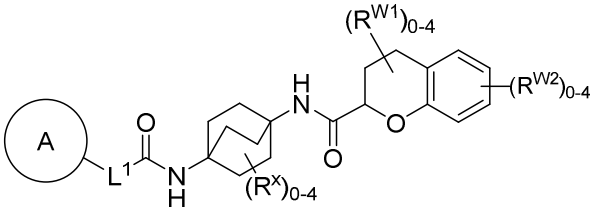
41. The compound of any one of claims 1-40, wherein the compound of Formula (I) is a compound of Formula (I-c-1), Formula (I-c-2), Formula (I-c-3), Formula (I-c-4), Formula (I-c-5), Formula (I-c-6), Formula (I-c-7), Formula (I-c-8), Formula (I-c-9) or Formula (I-c-10):



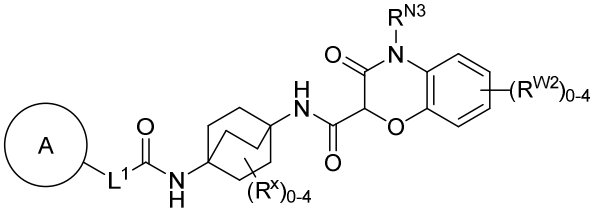
Formula (I-c-1)



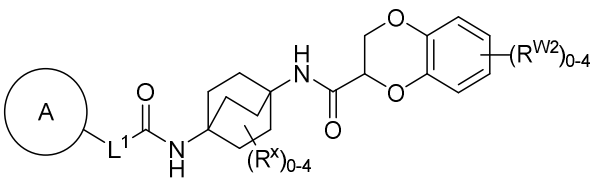
Formula (I-c-2)



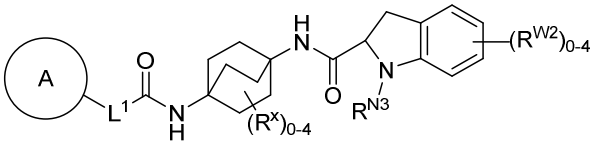
Formula (I-c-3)



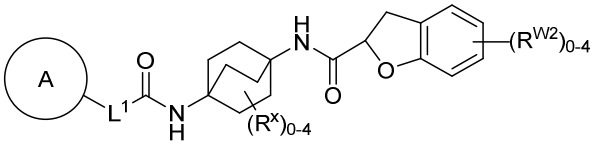
Formula (I-c-4)



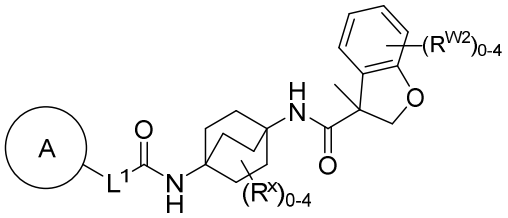
Formula (I-c-5)



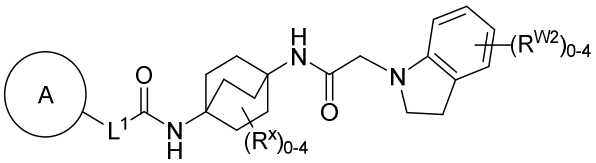
Formula (I-c-6)



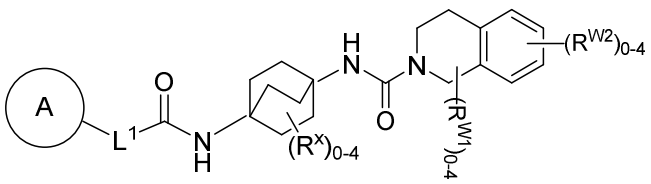
Formula (I-c-7)



Formula (I-c-8)



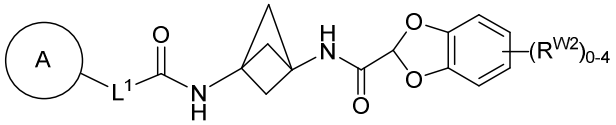
Formula (I-c-9)



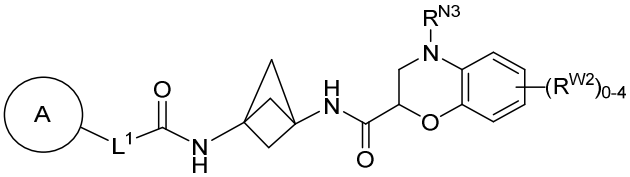
Formula (I-c-10)

or a pharmaceutically acceptable salt thereof.

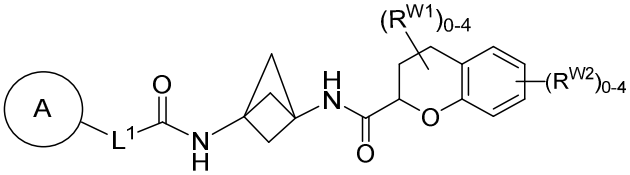
42. The compound of any one of claims 1-40, wherein the compound of Formula (I) is a compound of Formula (I-d-1), Formula (I-d-2), Formula (I-d-3), Formula (I-d-4), Formula (I-d-5), Formula (I-d-6), Formula (I-d-7), Formula (I-d-8), Formula (I-d-9) or Formula (I-d-10):



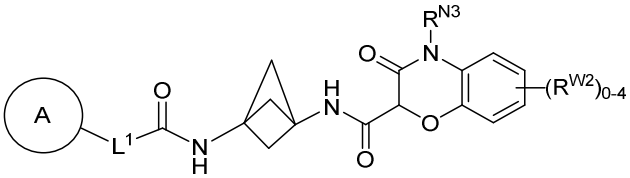
Formula (I-d-1)



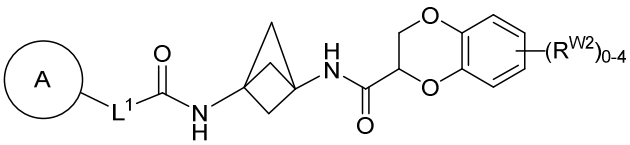
Formula (I-d-2)



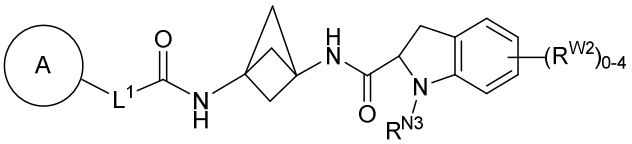
Formula (I-d-3)



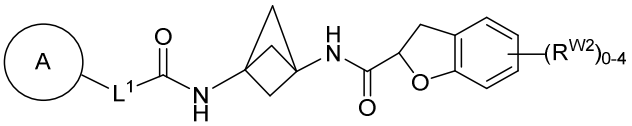
Formula (I-d-4)



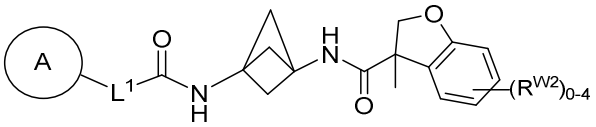
Formula (I-d-5)



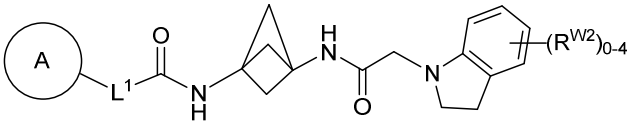
Formula (I-d-6)



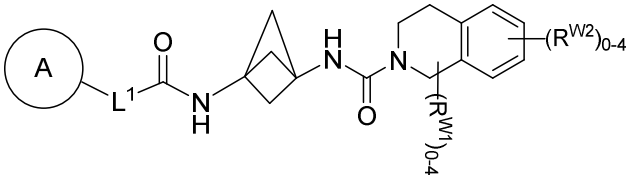
Formula (I-d-7)



Formula (I-d-8)



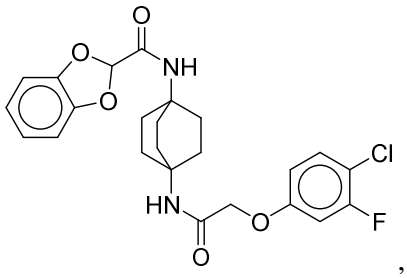
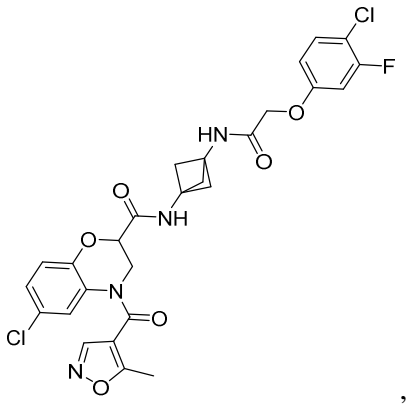
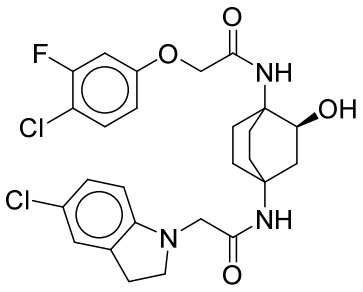
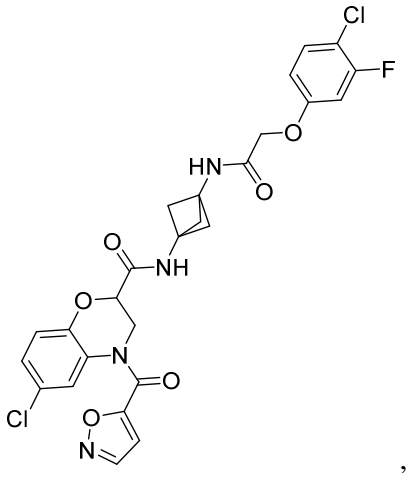
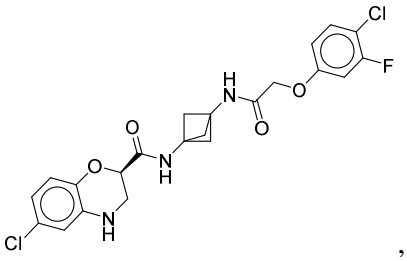
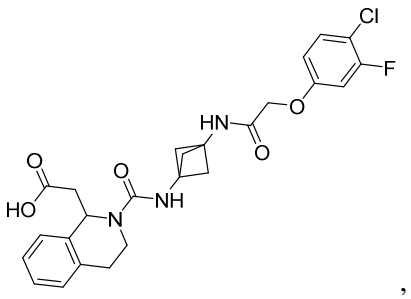
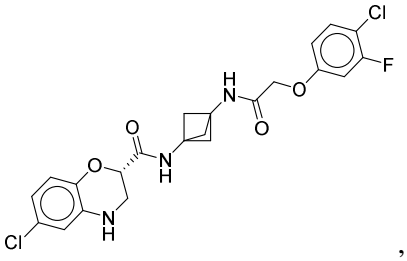
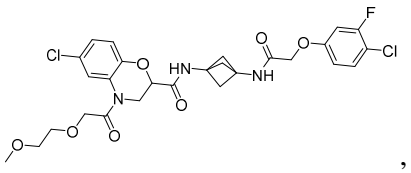
Formula (I-d-9)

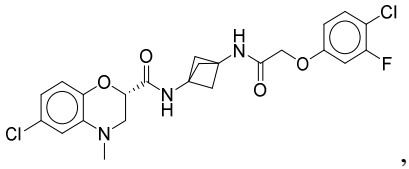
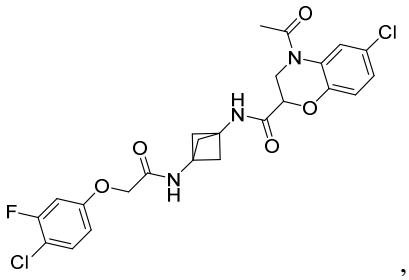
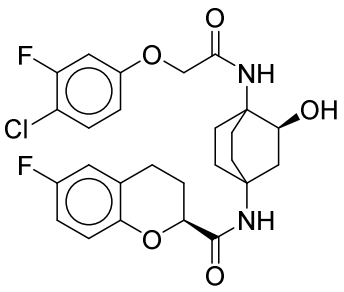
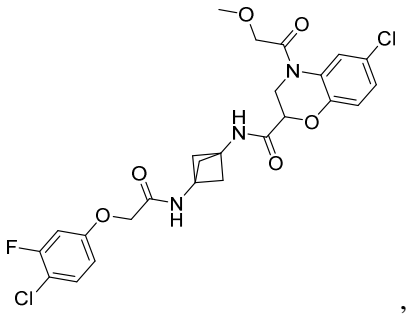
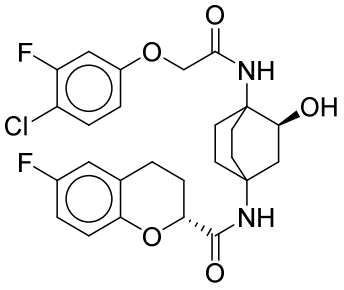
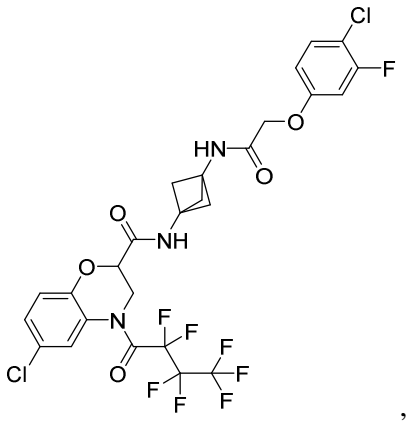
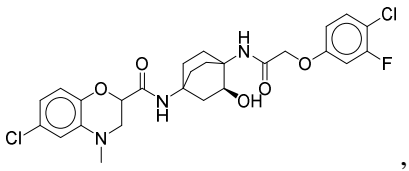
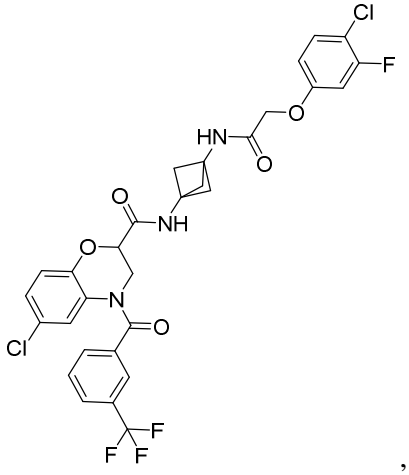


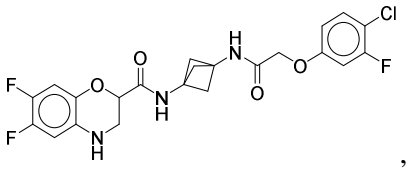
Formula (I-d-10)

or a pharmaceutically acceptable salt thereof.

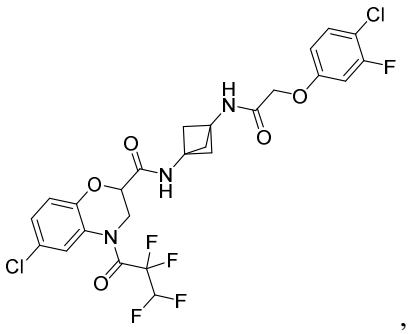
43. A compound, wherein the compound is selected from the group consisting of:


,

,

,

,

,

,

,

,

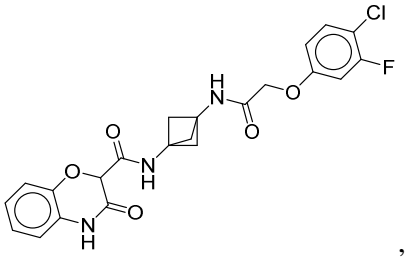

,

,

,

,

,

,

,

,



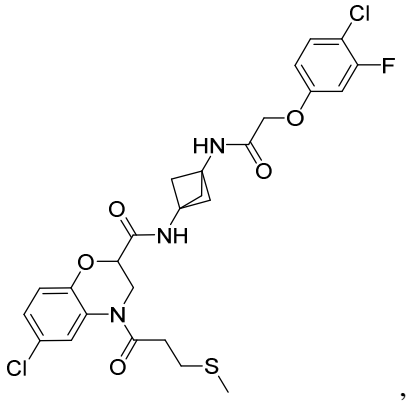
,



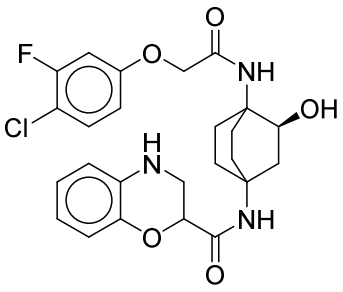
,



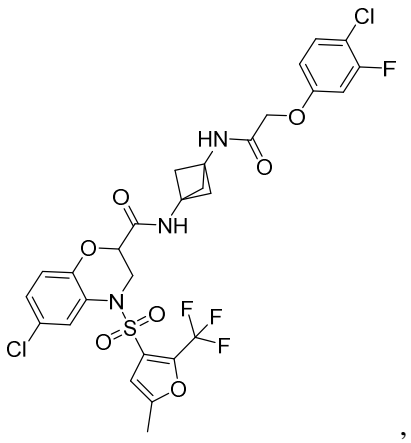
,



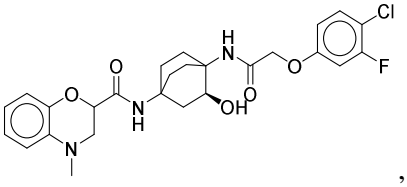
,



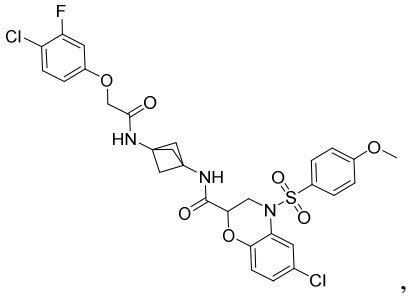
,



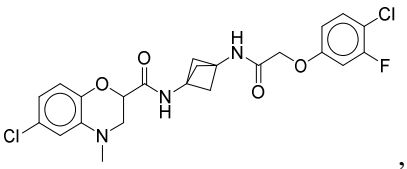
,



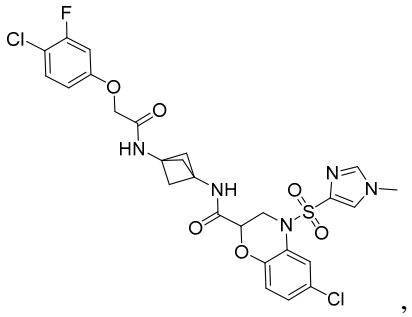
,



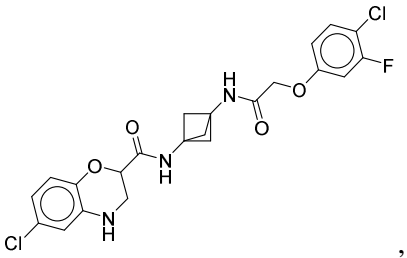
,



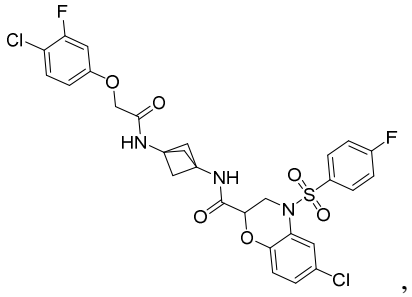
,



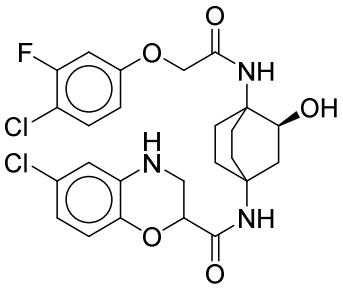
,



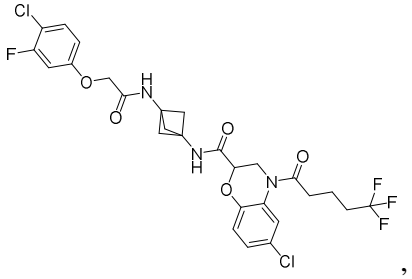
,



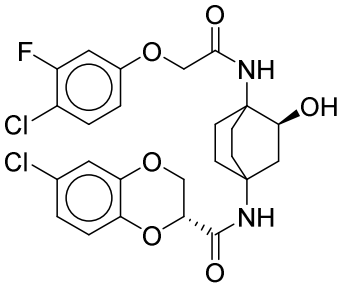
,



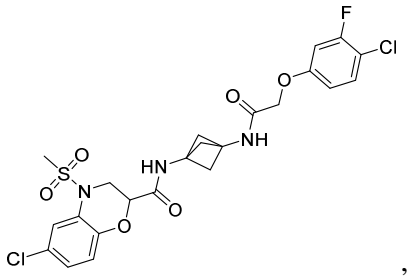
,



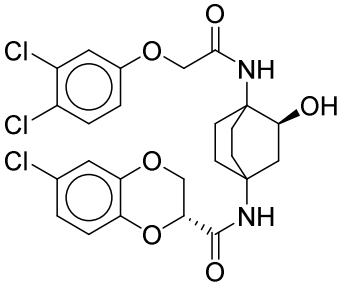
,



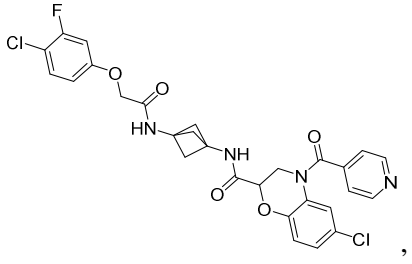
,



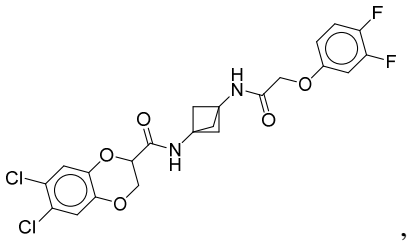
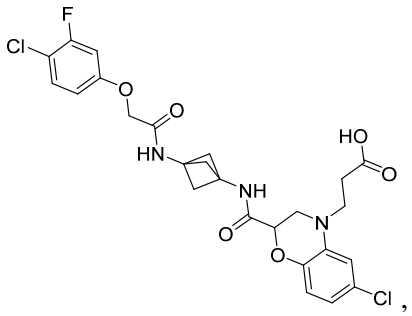
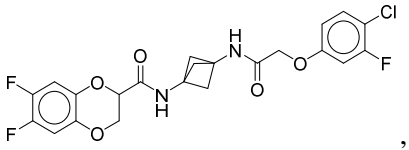
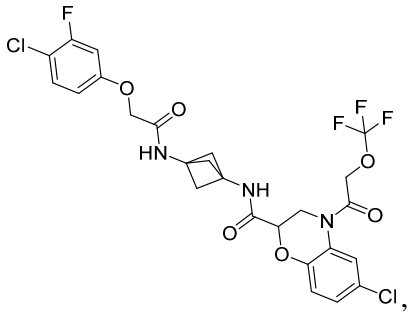
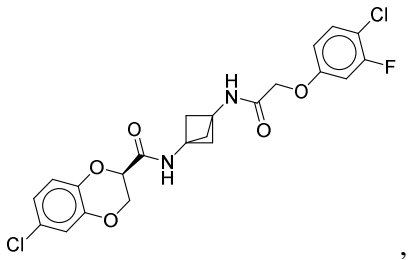
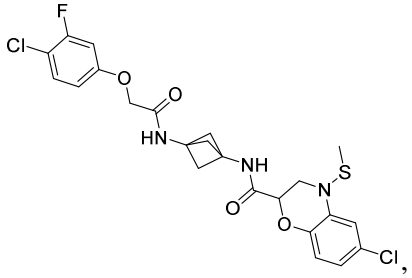
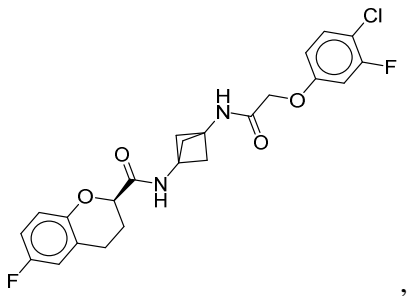
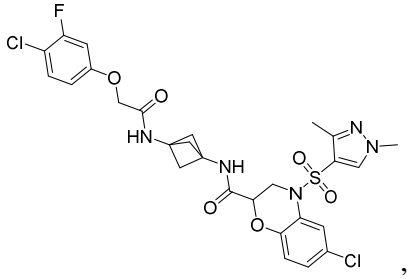
,

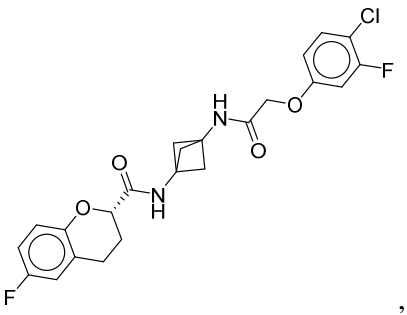
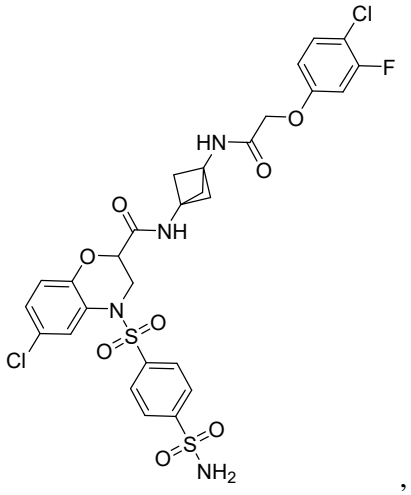
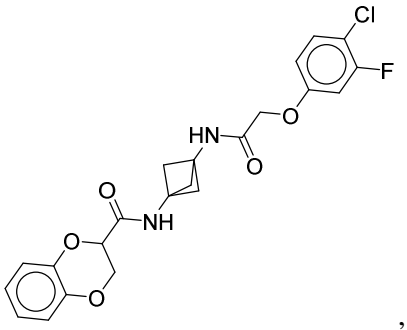
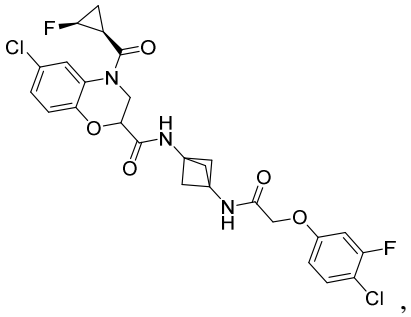
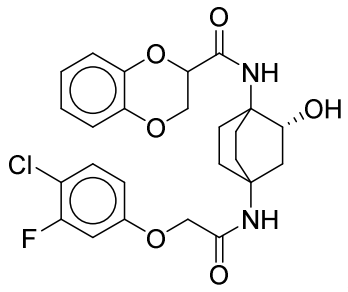
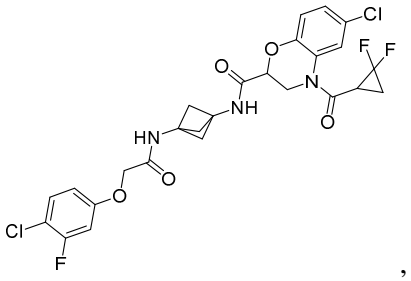
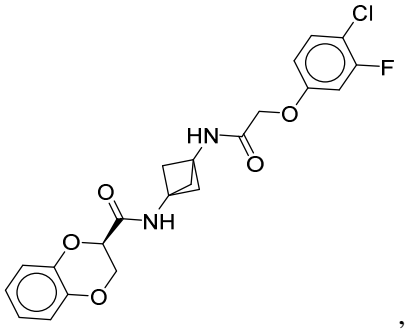
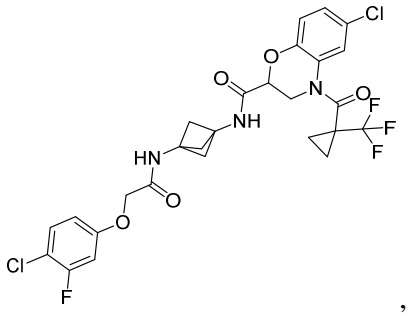


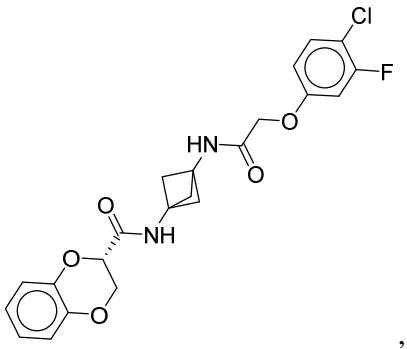
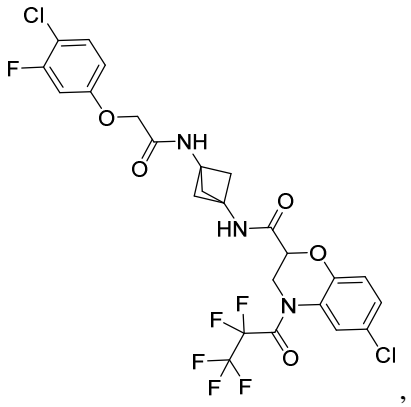
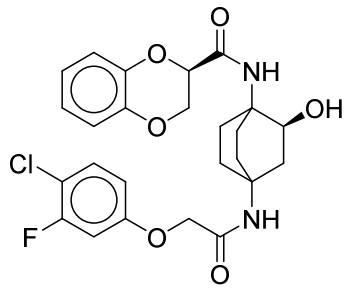
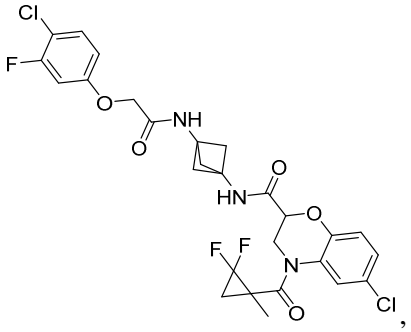
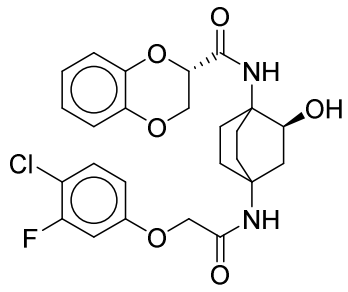
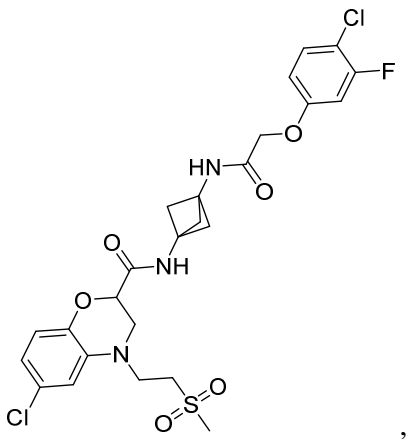
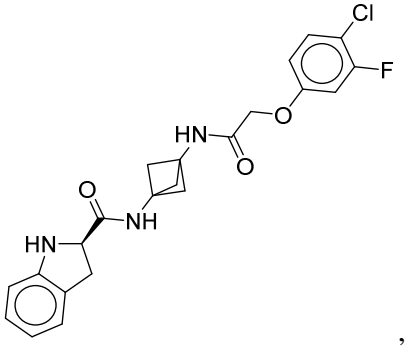
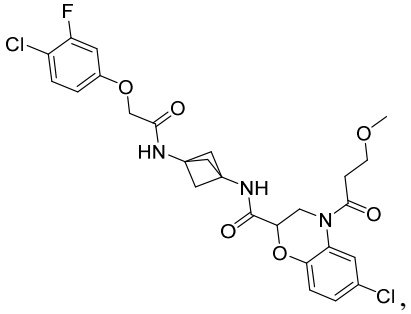
,

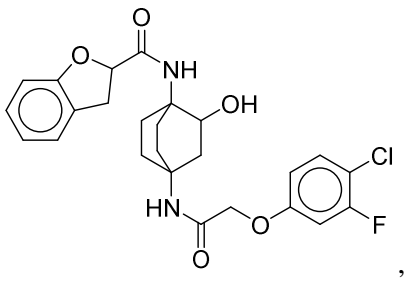
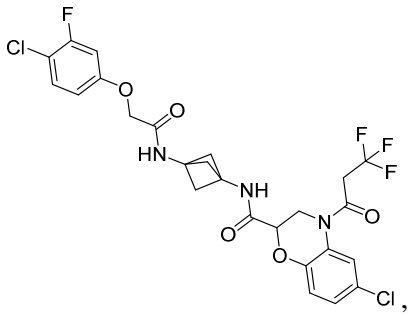
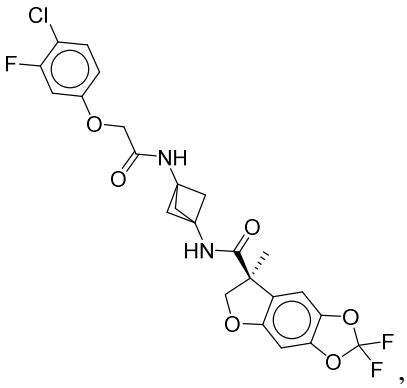
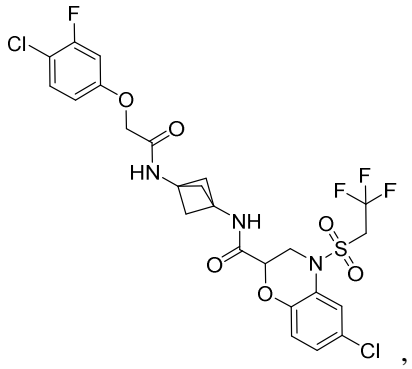
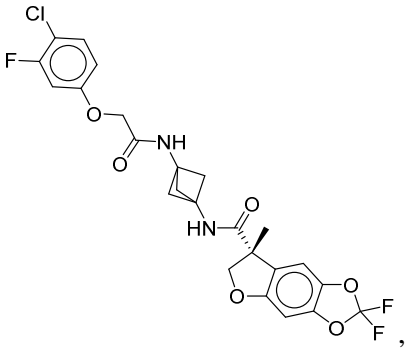
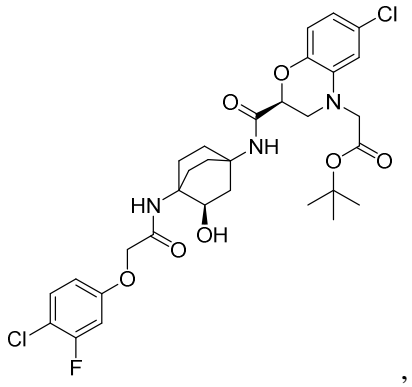
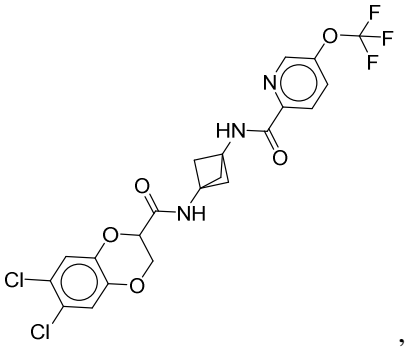
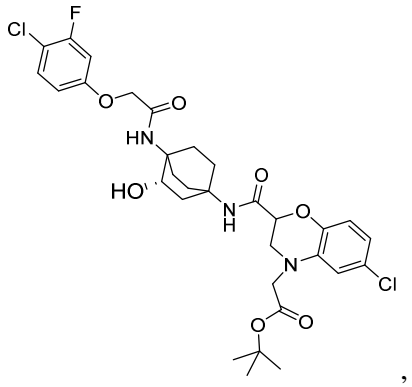


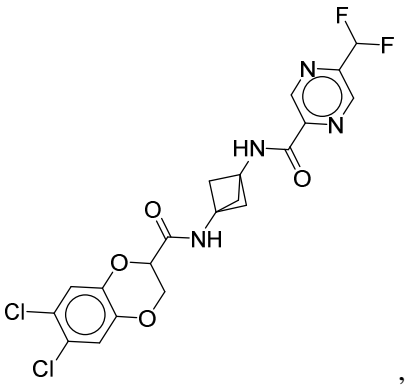
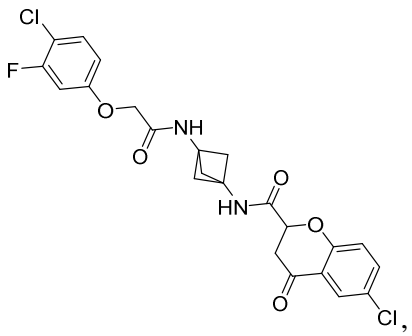
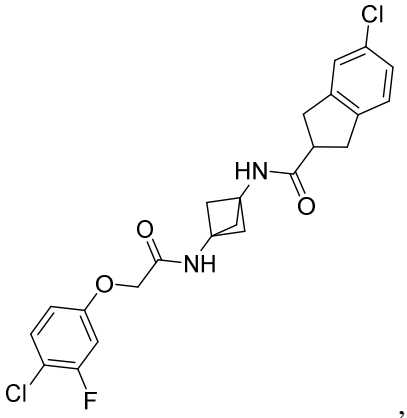
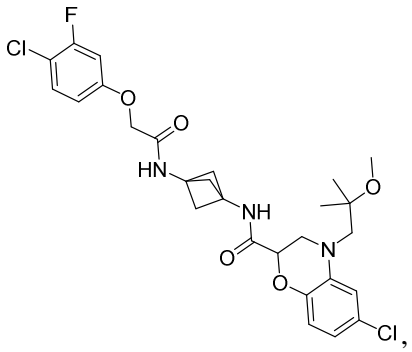
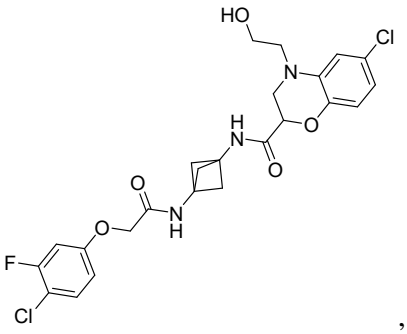
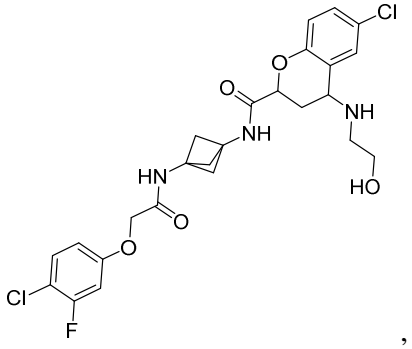
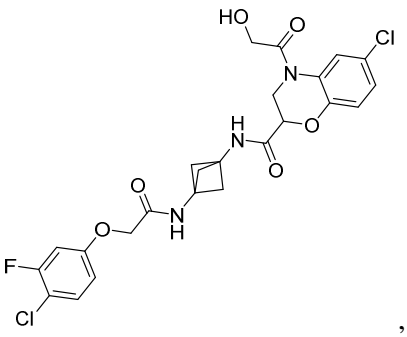
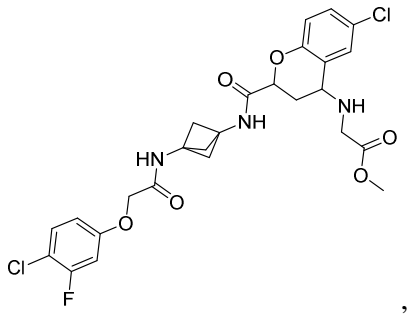
,

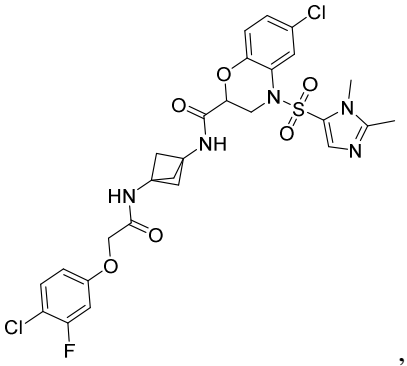
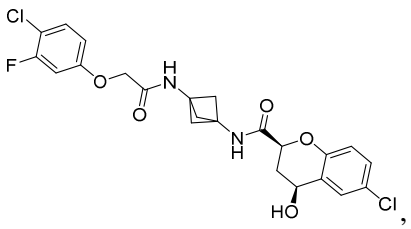
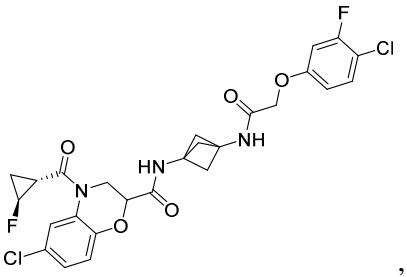
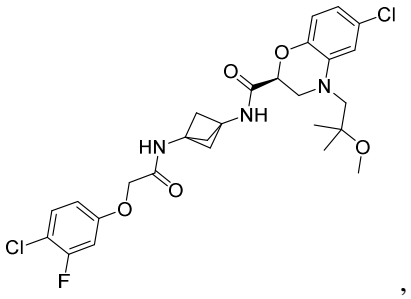
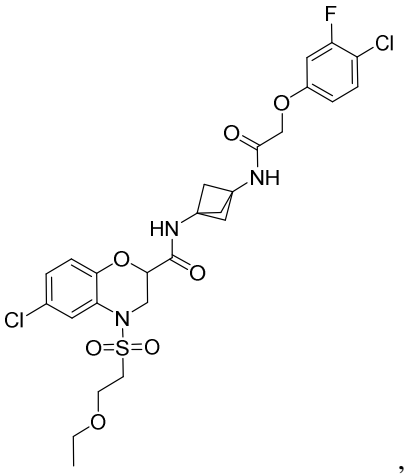
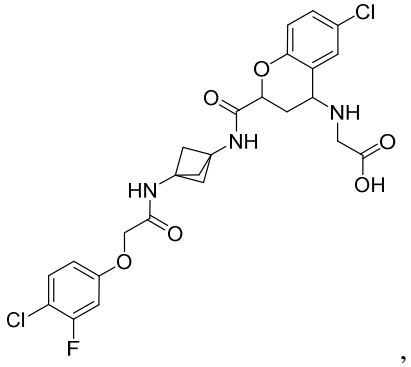
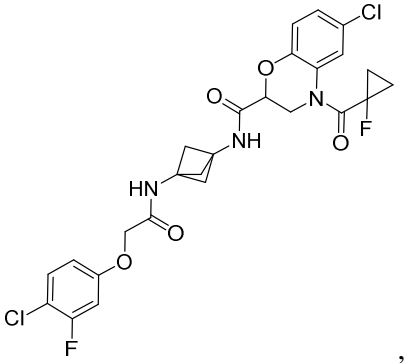
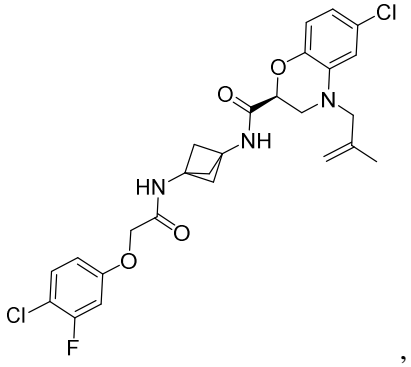

,

,

,

,

,

,

,

,

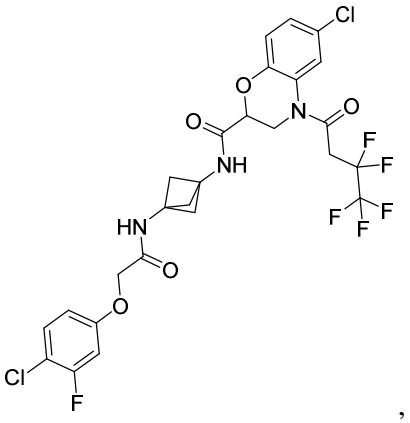

,

,

,

,

,

,

,

,

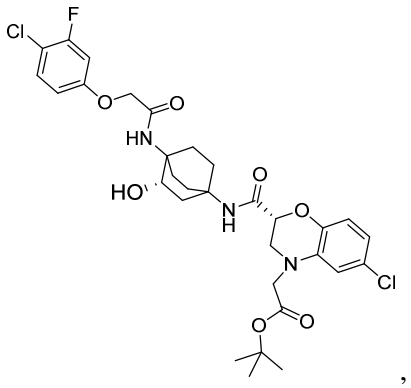

,

,

,

,

,

,

,

,

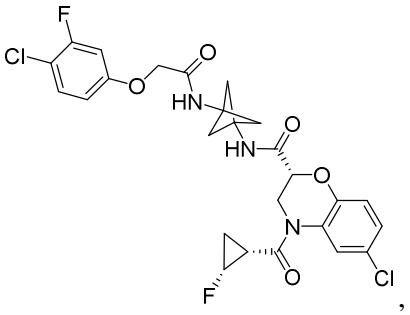

,

,

,

,

,

,

,

,

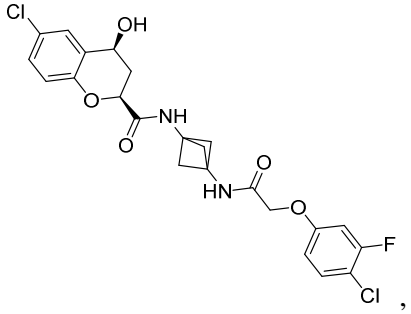

,

,

,

,

,

,

,

,

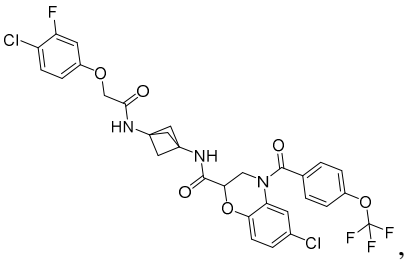

,

,

,

,

,

,

,

,

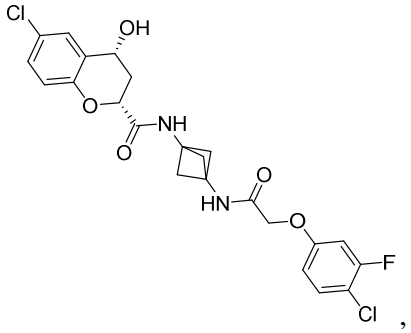

,

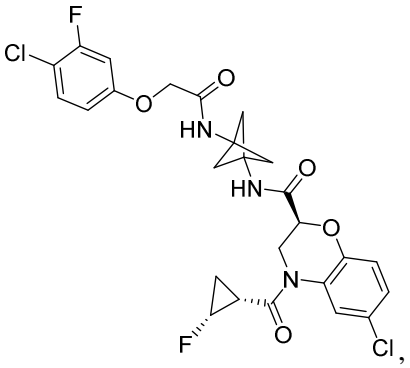

,

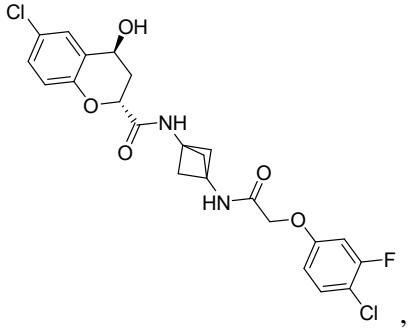

,

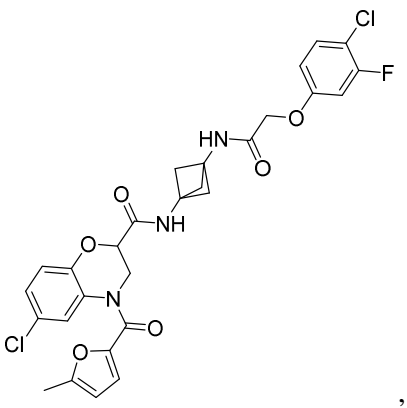
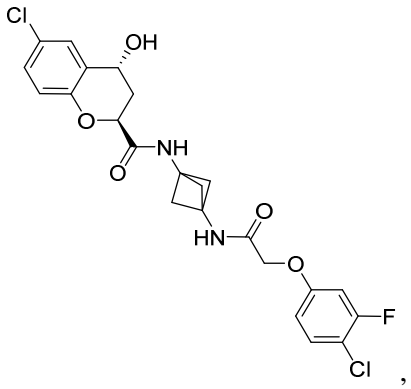
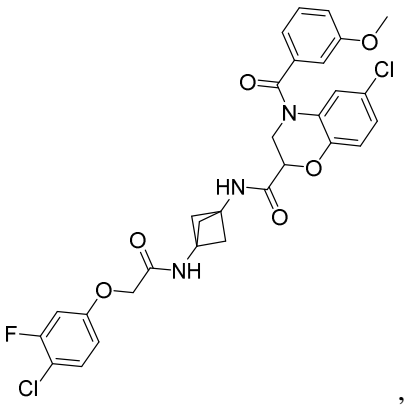
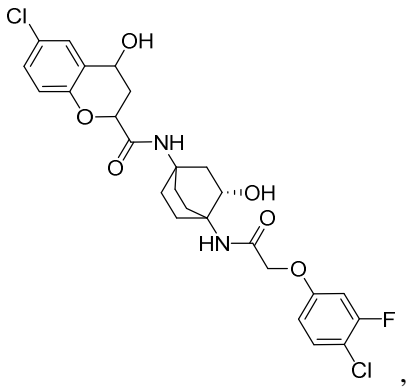
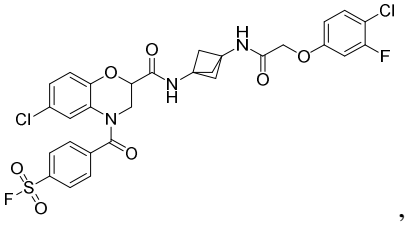
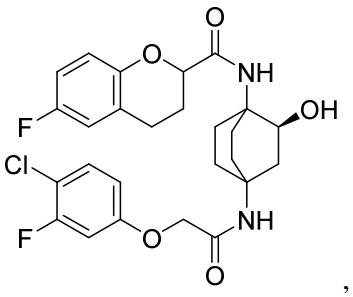
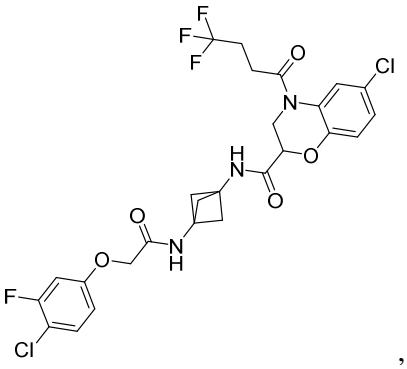
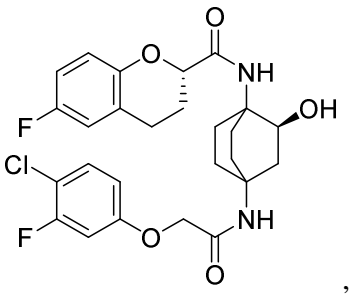

,

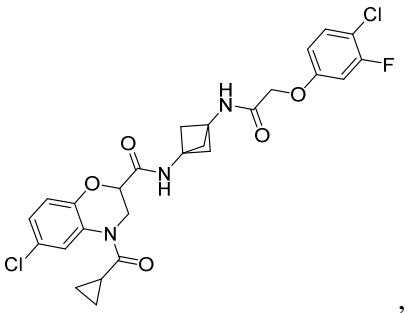
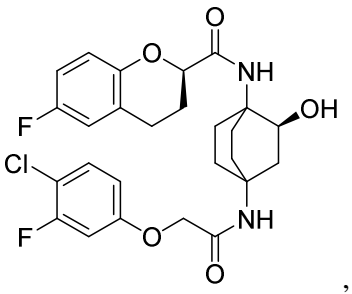
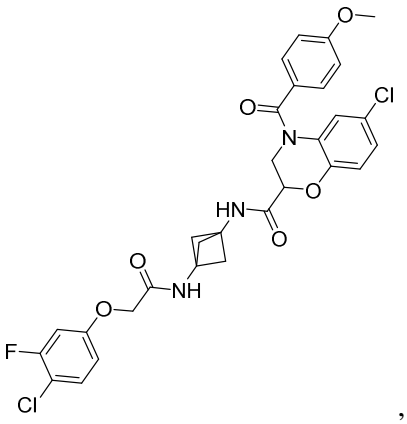
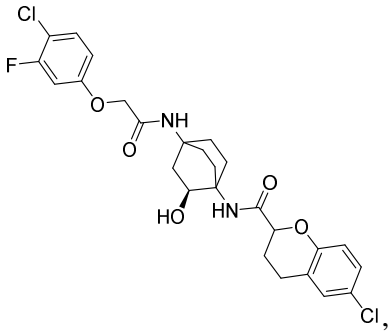
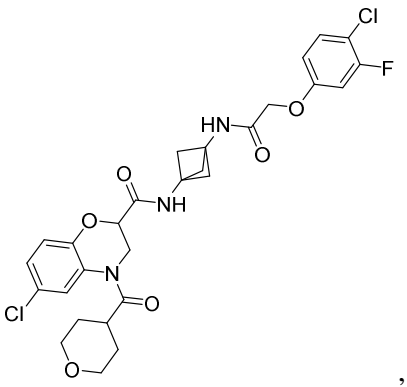
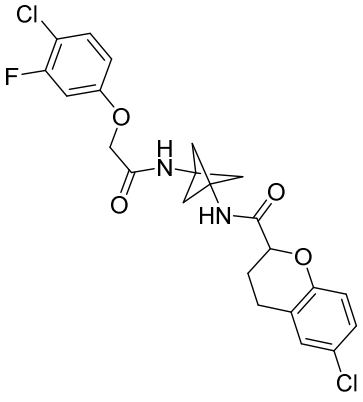
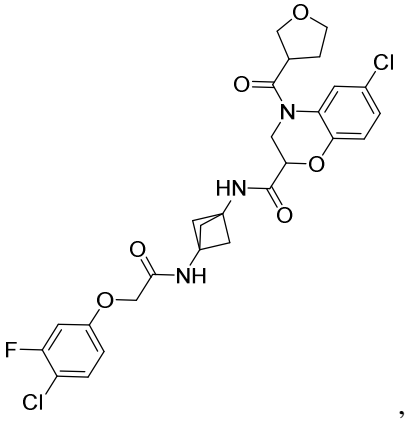

,


,


,


,


,

,

,

,

,

,

,

,


,

,

,

,

,

, and

,

or a pharmaceutically acceptable salt thereof.