MODULATORS OF THE INTEGRATED STRESS PATHWAY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/580,740, filed November 02, 2017 and U.S. Provisional Application No. 62/643,074, filed March 14, 2018, which are incorporated herein by reference in their entirety.

BACKGROUND

In metazoa, diverse stress signals converge at a single phosphorylation event at serine 51 of a common effector, the translation initiation factor eIF2α. This step is carried out by four eIF2α kinases in mammalian cells: PERK, which responds to an accumulation of unfolded proteins in the endoplasmic reticulum (ER), GCN2 to amino acid starvation and UV light, PKR to viral infection and metabolic stress, and HRI to heme deficiency. This collection of signaling pathways has been termed the "integrated stress response" (ISR), as they converge on the same molecular event. eIF2α phosphorylation results in an attenuation of translation with consequences that allow cells to cope with the varied stresses (Wek, R.C. et al, *Biochem Soc Trans* (2006) 34(Pt 1):7-11).

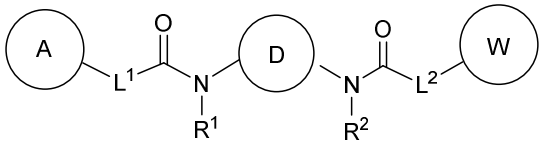
eIF2 (which is comprised of three subunits, α, β and γ) binds GTP and the initiator Met-tRNA to form the ternary complex (eIF2-GTP-Met-tRNA$_i$), which, in turn, associates with the 40S ribosomal subunit scanning the 5'UTR of mRNAs to select the initiating AUG codon. Upon phosphorylation of its α-subunit, eIF2 becomes a competitive inhibitor of its GTP-exchange factor (GEF), eIF2B (Hinnebusch, A.G. and Lorsch, J.R. *Cold Spring Harbor Perspect Biol* (2012) 4(10)). The tight and nonproductive binding of phosphorylated eIF2 to eIF2B prevents loading of the eIF2 complex with GTP, thus blocking ternary complex formation and reducing translation initiation (Krishnamoorthy, T. et al, *Mol Cell Biol* (2001) 21(15):5018-5030). Because eIF2B is less abundant than eIF2, phosphorylation of only a small fraction of the total eIF2 has a dramatic impact on eIF2B activity in cells.

eIF2B is a complex molecular machine, composed of five different subunits, eIF2B1 through eIF2B5. eIF2B5 catalyzes the GDP/GTP exchange reaction and, together with a partially homologous subunit eIF2B3, constitutes the "catalytic core" (Williams, D.D. et al, *J Biol Chem* (2001) 276:24697-24703). The three remaining subunits (eIF2B1, eIF2B2, and eIF2B4) are also highly homologous to one another and form a "regulatory sub-complex" that provides binding sites for eIF2B's substrate eIF2 (Dev, K. et al, *Mol Cell Biol* (2010) 30:5218-5233). The

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

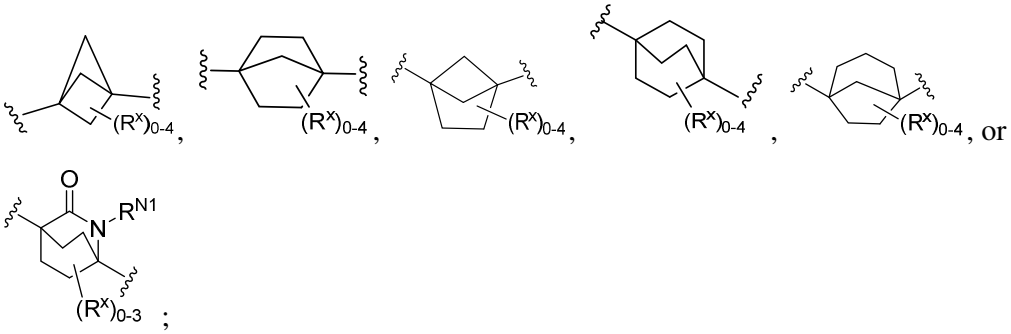
In one aspect of the present disclosure, there is provided a compound of Formula (I):



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;

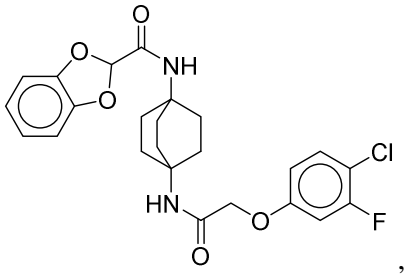
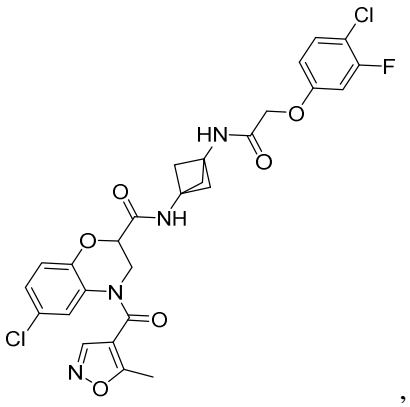
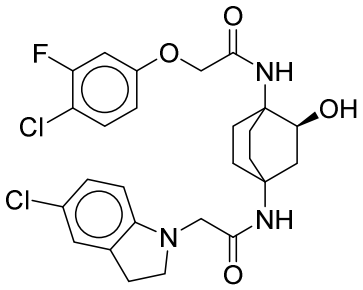
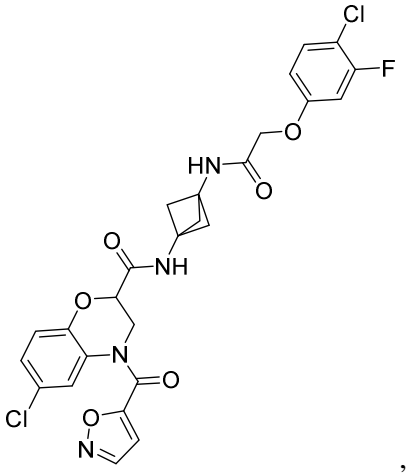
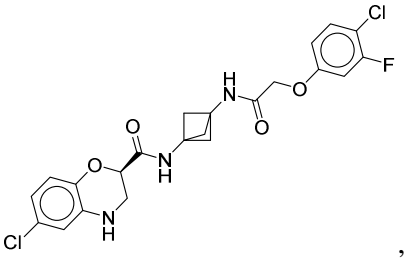
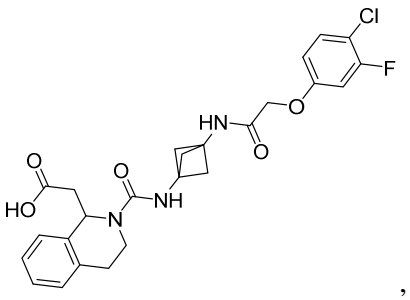
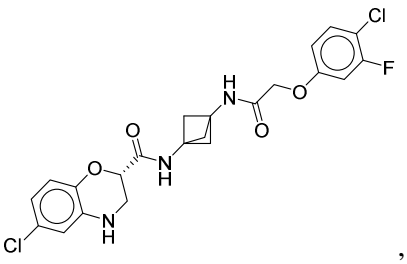
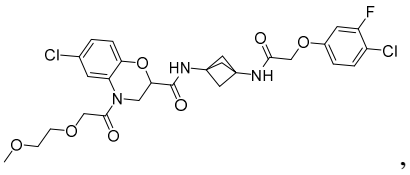
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

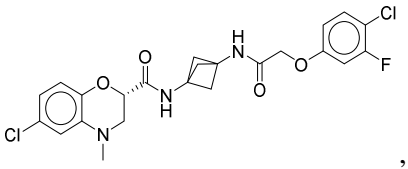
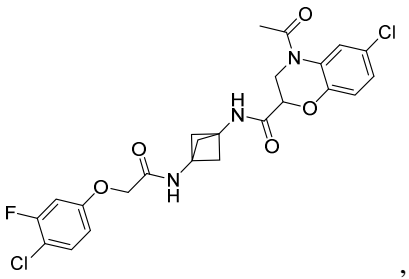
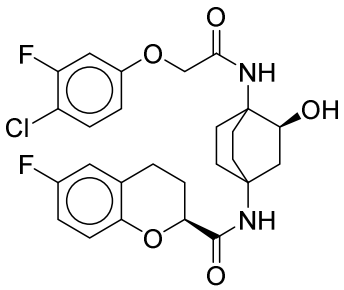
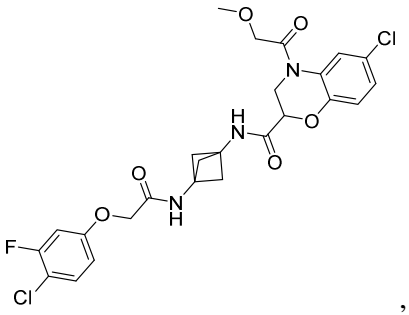
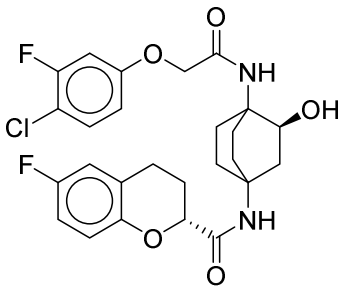
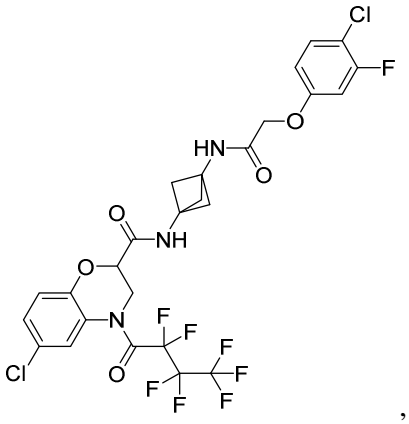
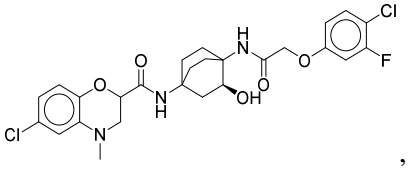
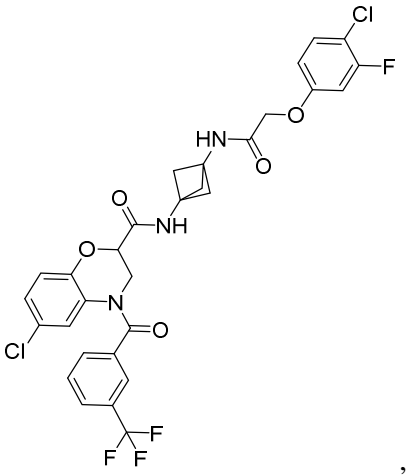
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

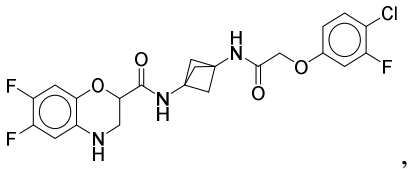
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

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.

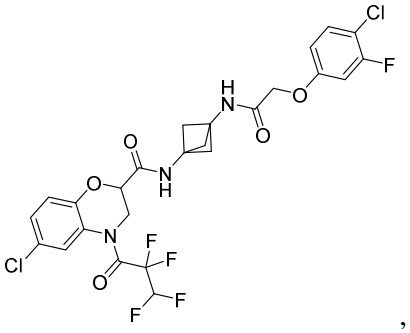
In another aspect of the present disclosure, there is provided a compound, wherein the compound is selected from the group consisting of:


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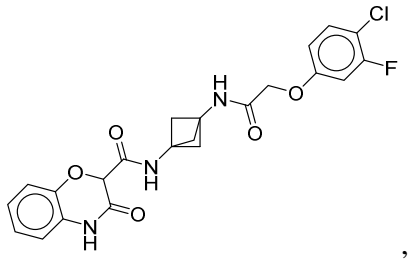

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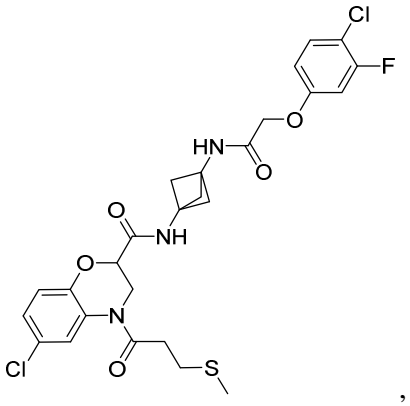
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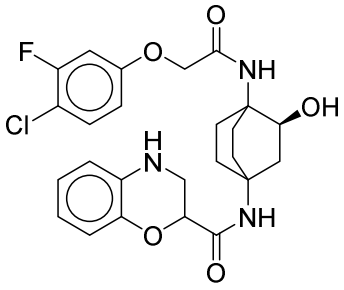
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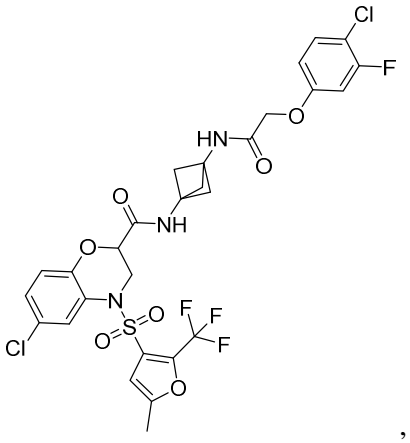
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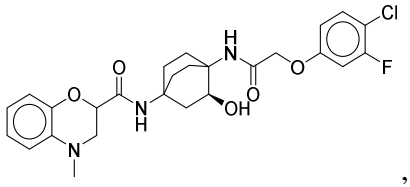
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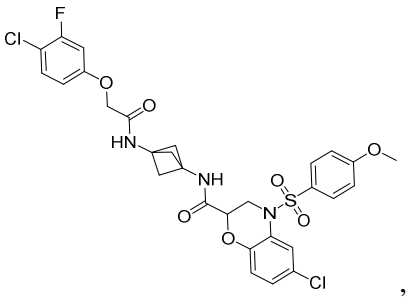
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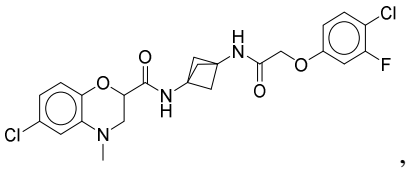
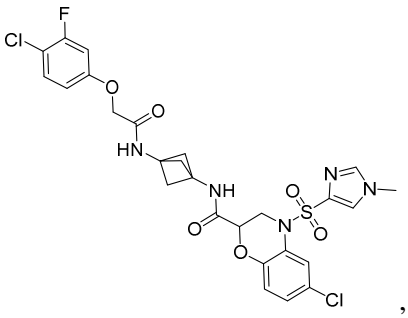
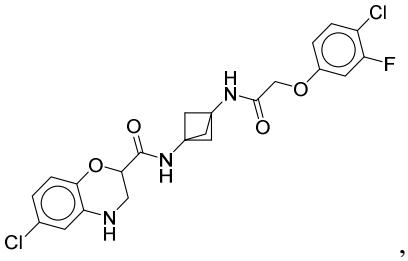
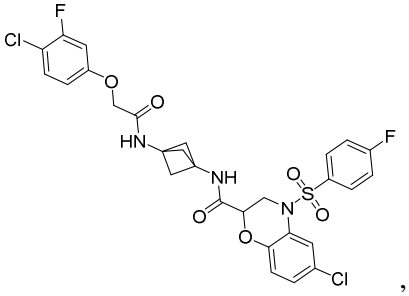
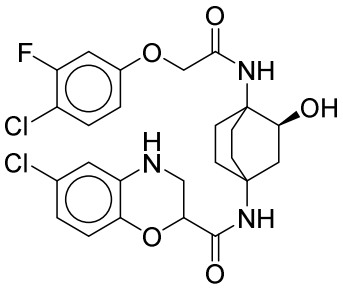
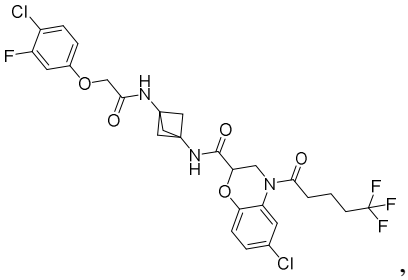
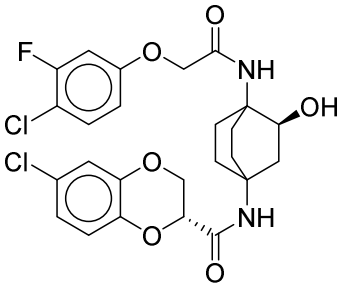
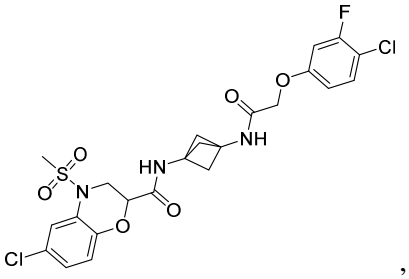
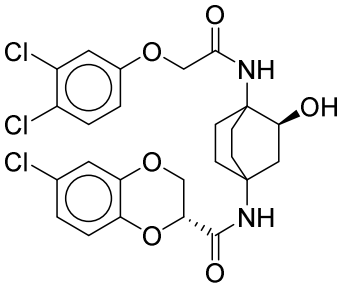
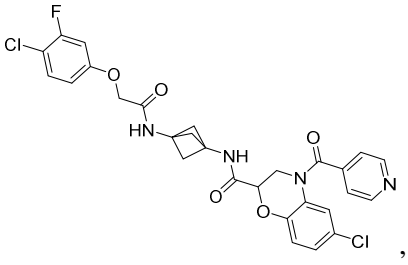
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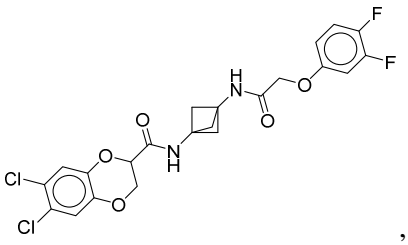
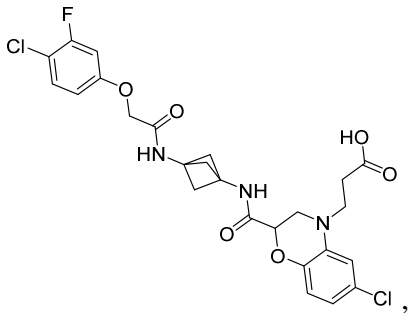
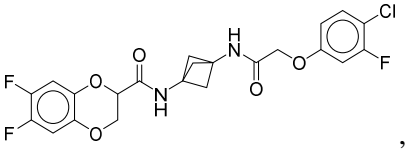
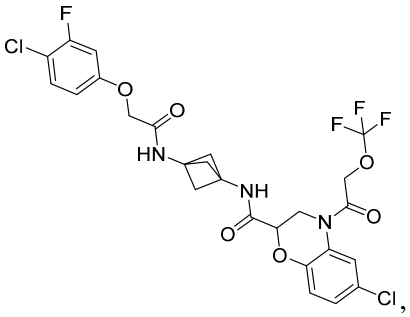
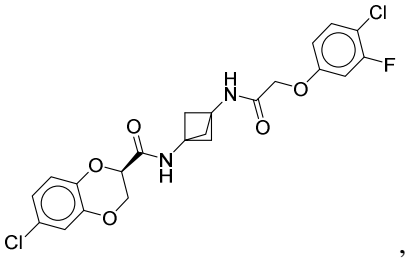
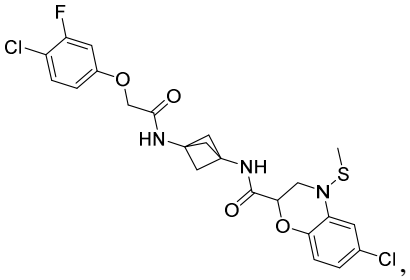
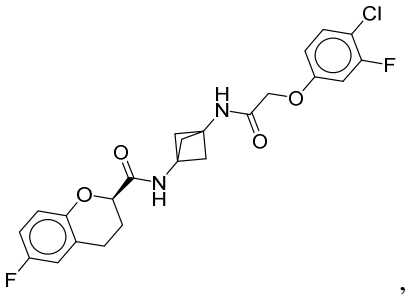
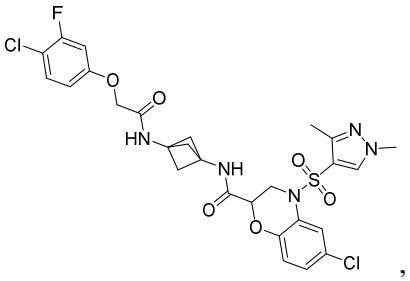


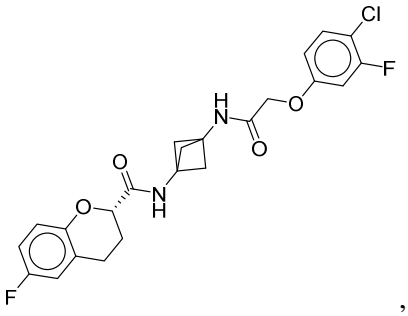
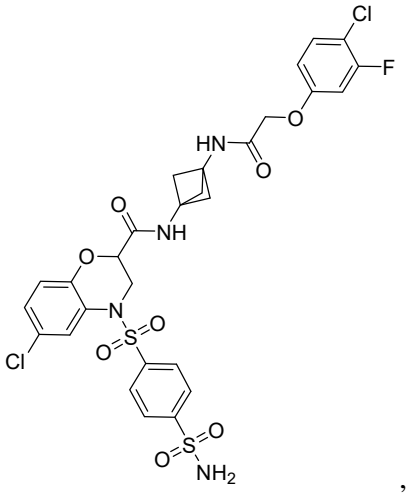
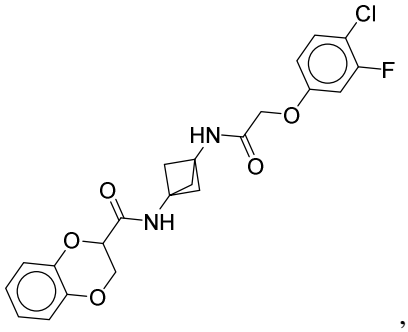
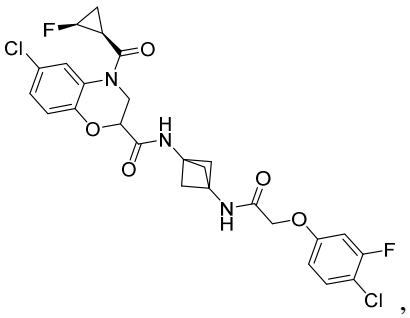
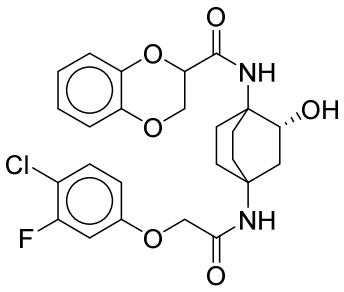
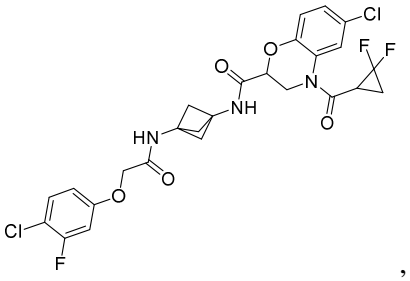
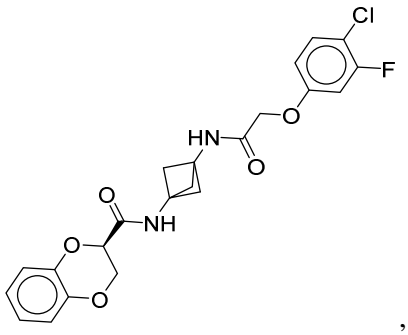
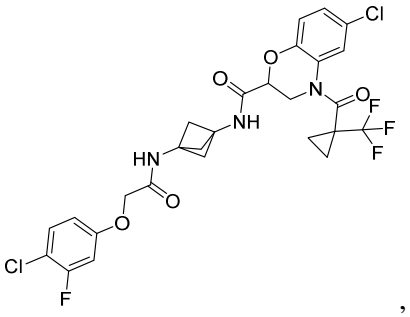
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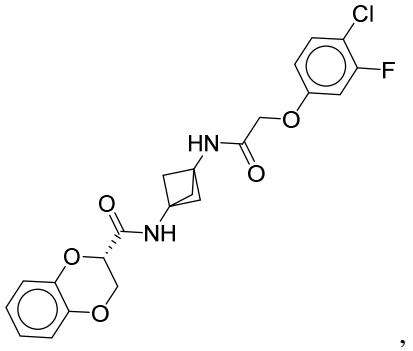
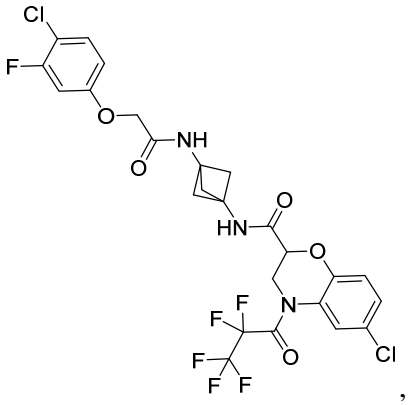
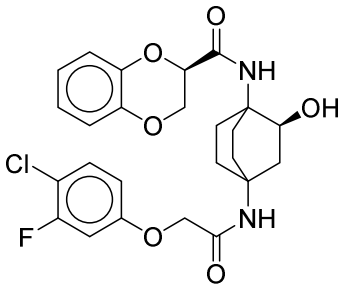
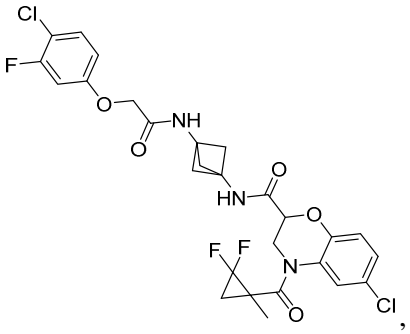
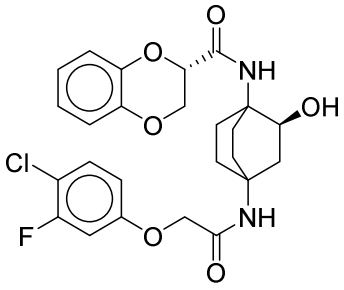
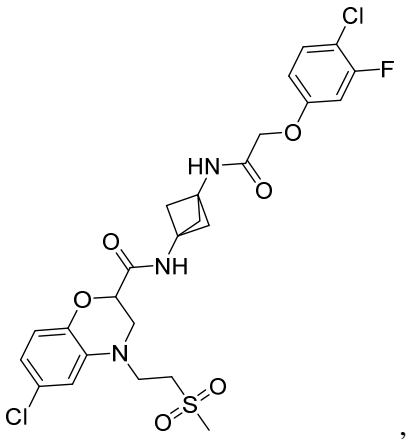
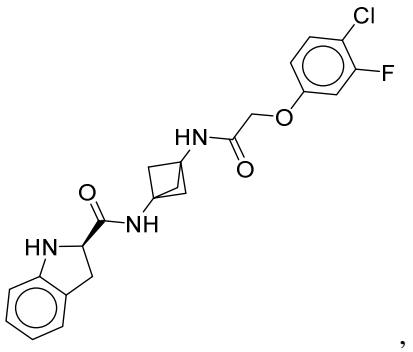
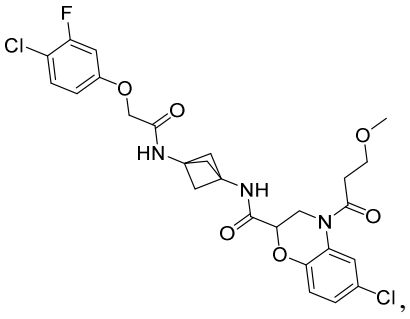


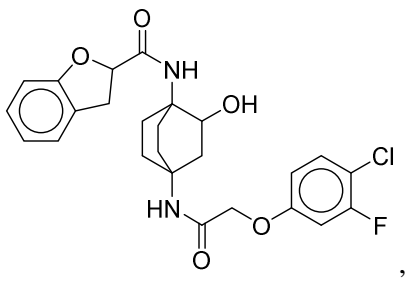
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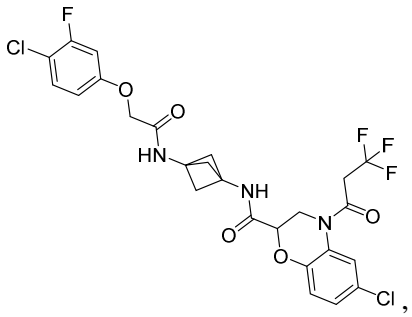

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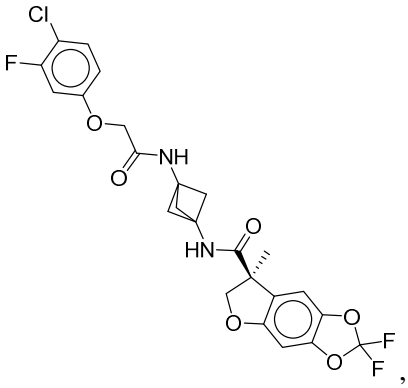

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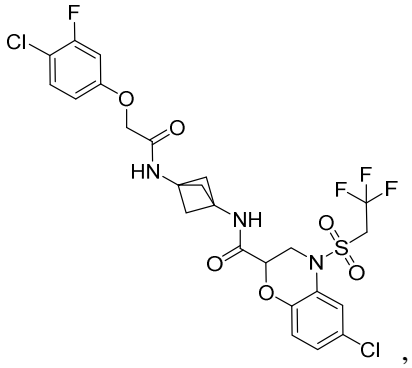

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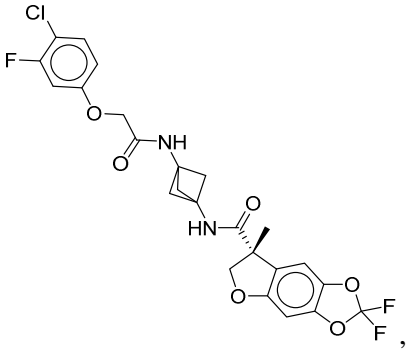

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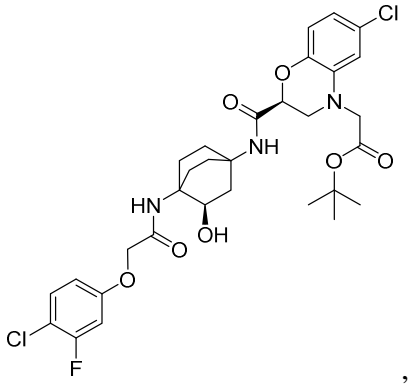

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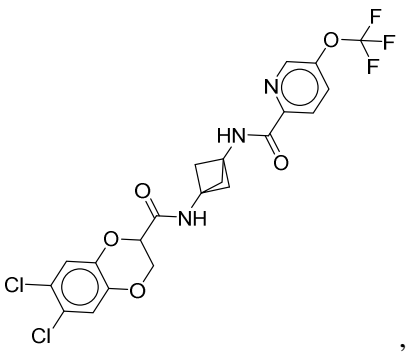

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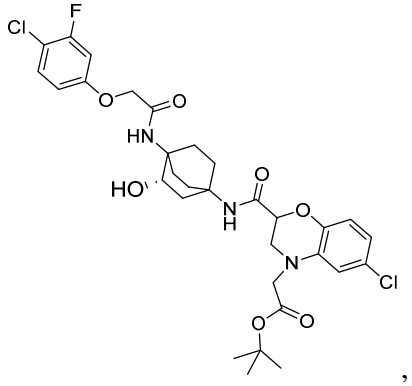

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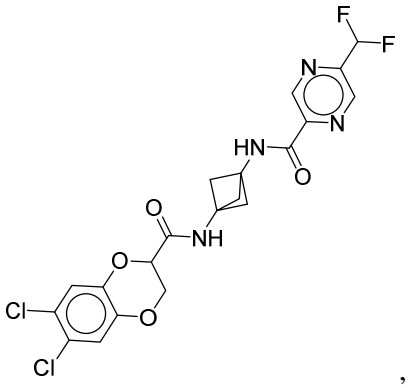
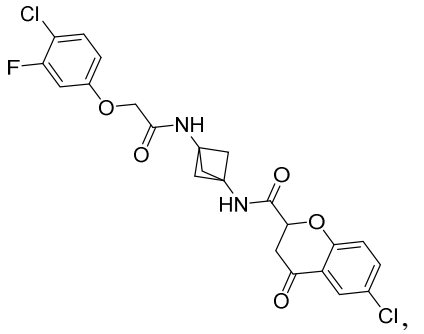
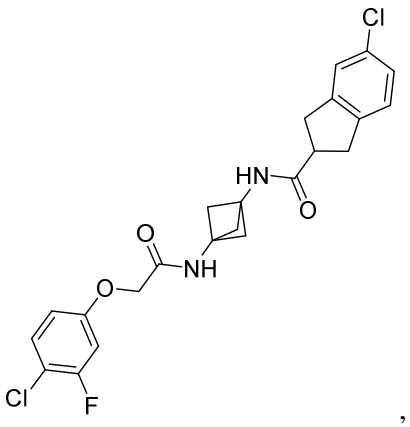
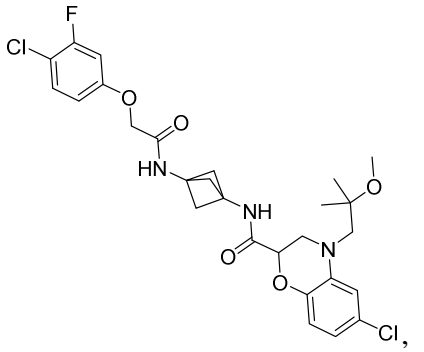
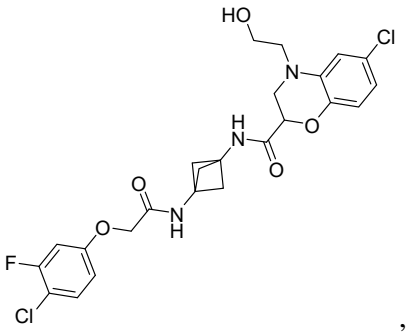
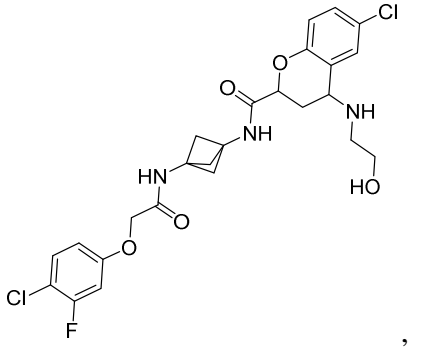
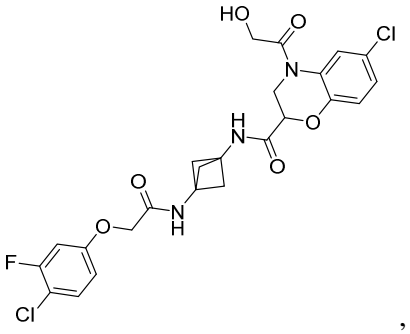
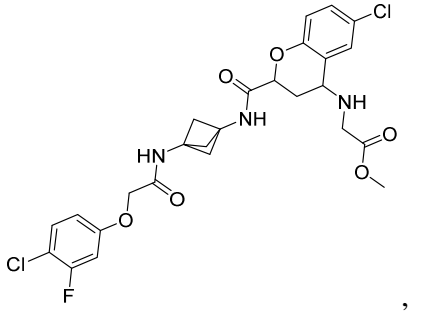

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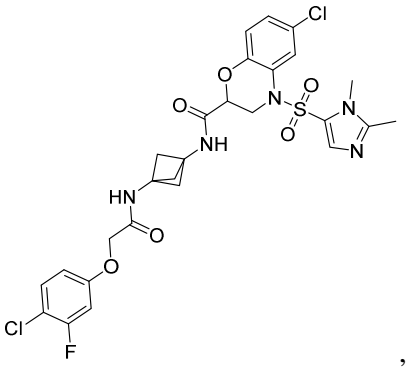
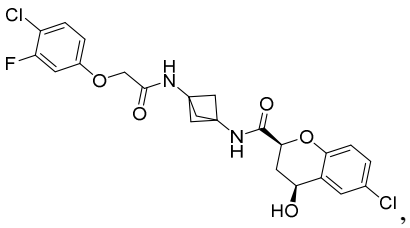
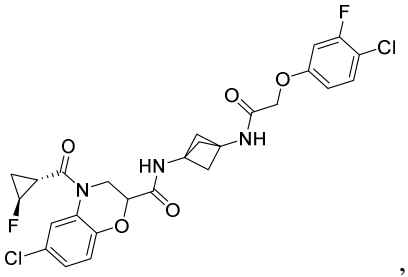
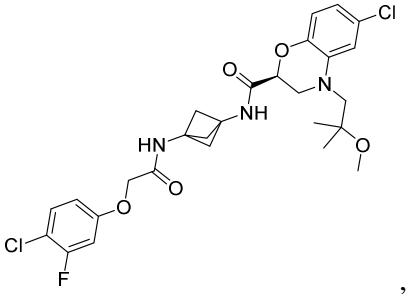
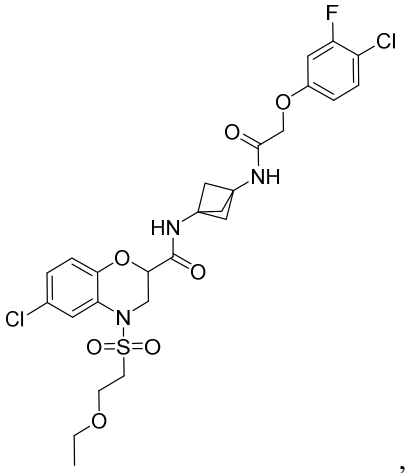
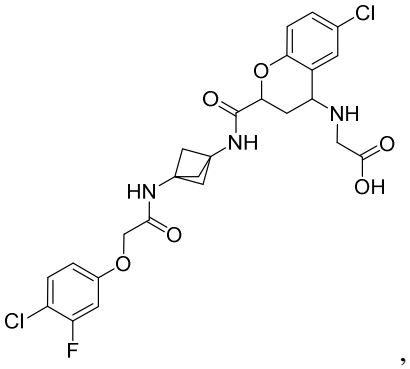
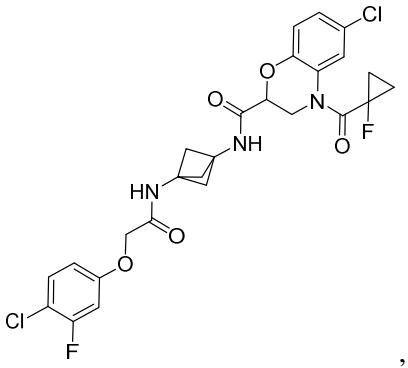
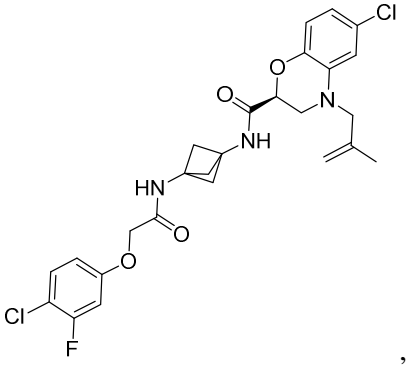

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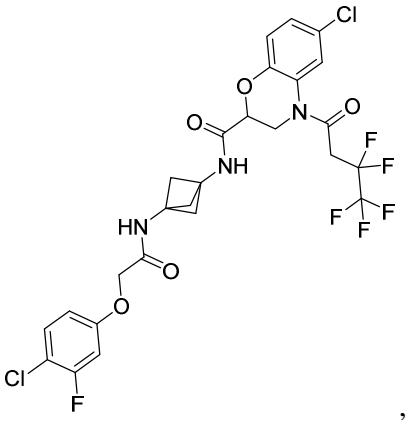

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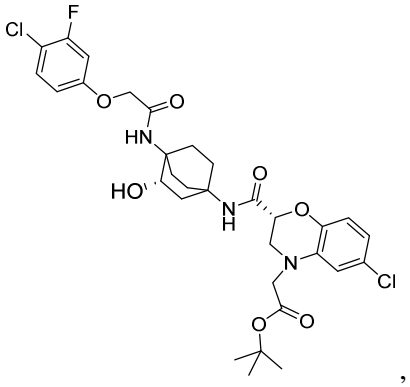

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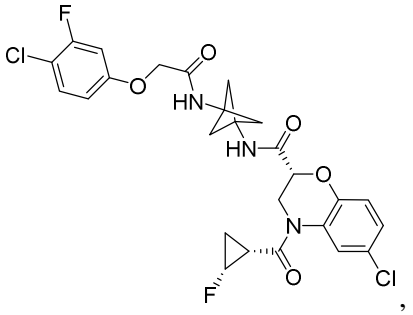

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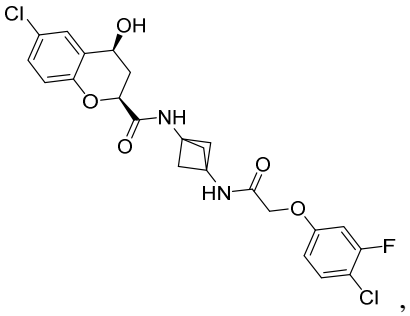

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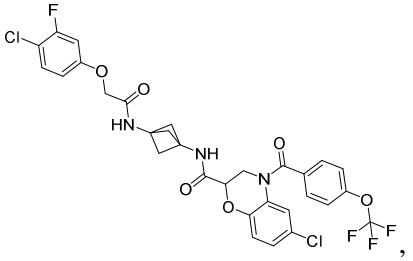

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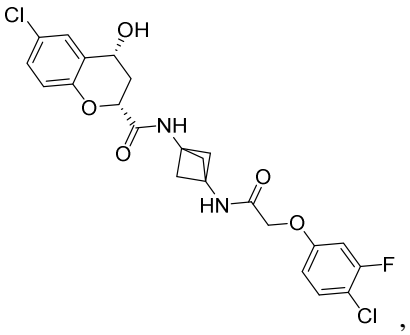

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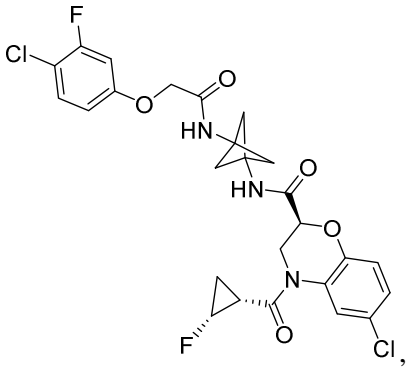

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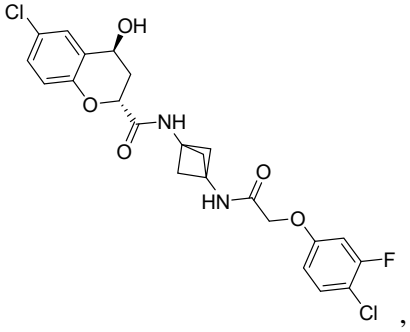

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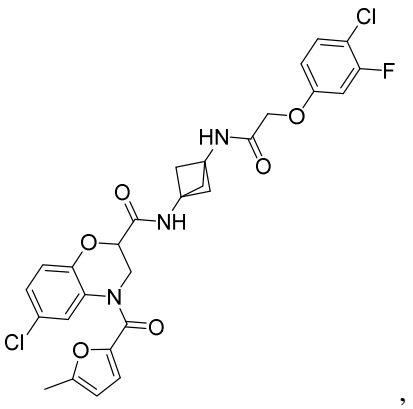
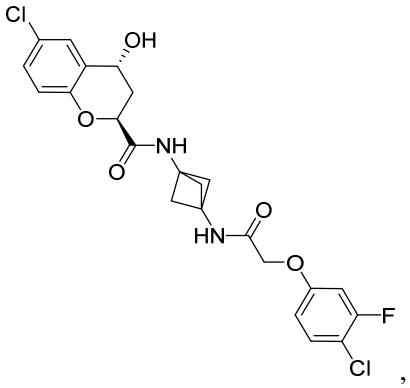
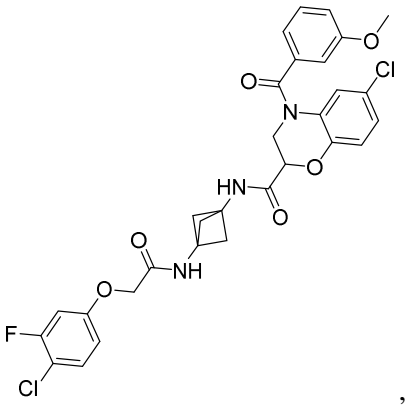
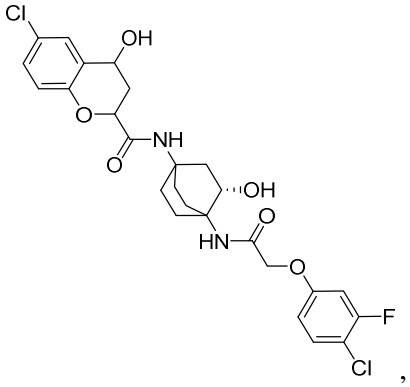
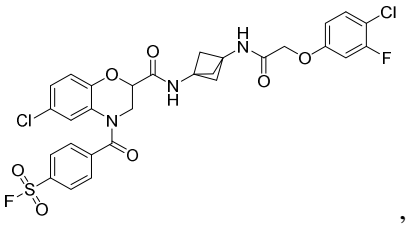
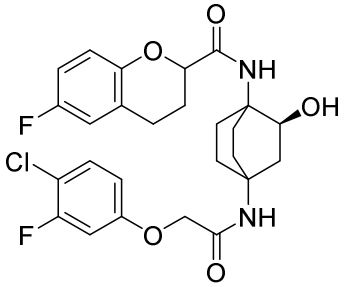
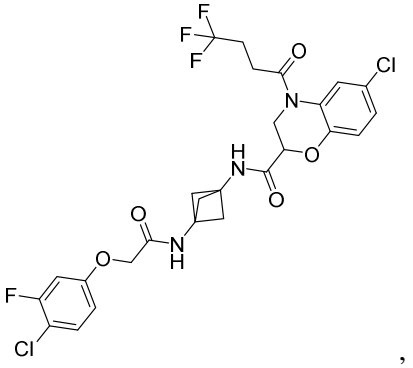
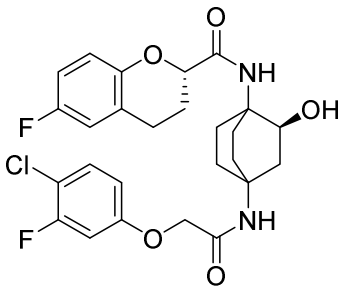

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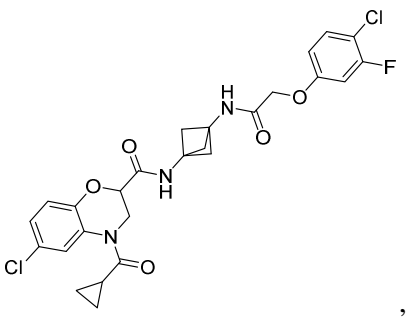

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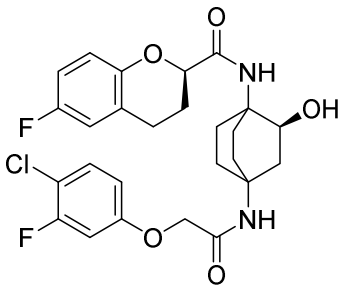

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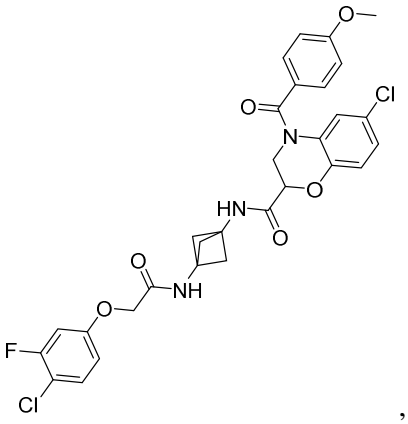

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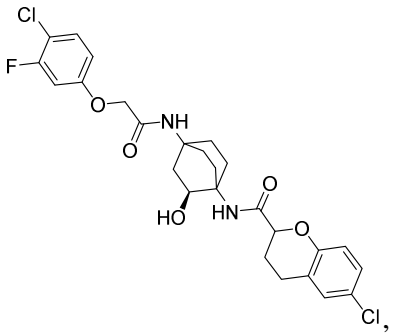
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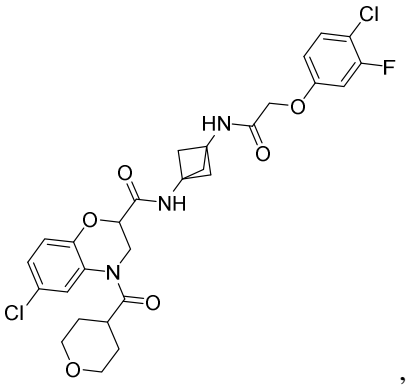
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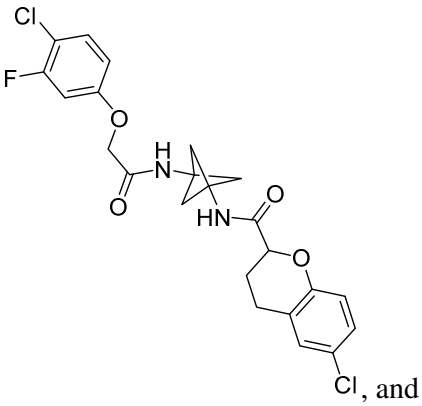
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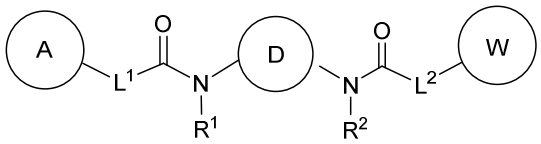
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or a pharmaceutically acceptable salt thereof.

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

heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N1};

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;

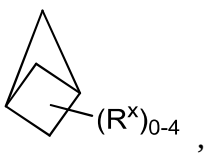
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

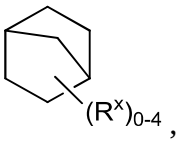
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

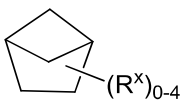
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

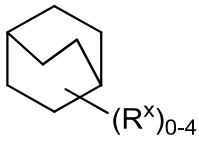
m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

In some examples, D is a bridged bicyclic cycloalkyl optionally substituted with 1-4 R^X. In some examples, D is a bridged bicyclic 5-8 membered cycloalkyl optionally substituted with 1-4 R^X. In some examples, D is bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, or 2-azabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups. In some examples, D is

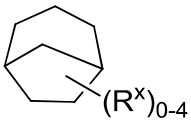


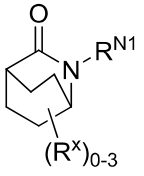
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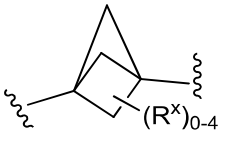
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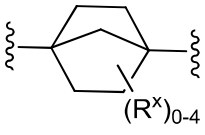
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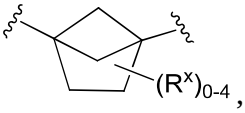
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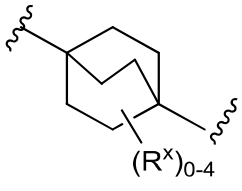


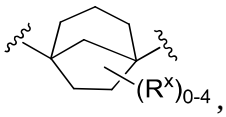
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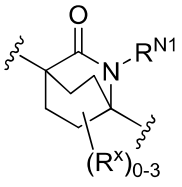
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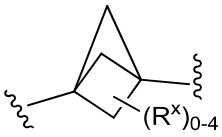
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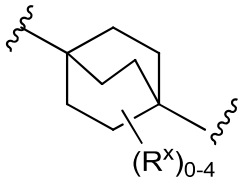
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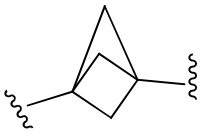
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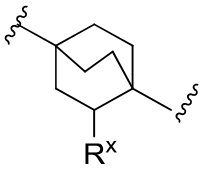
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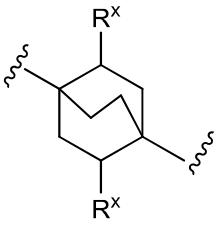
, or 

. In some examples, D is 

or 

. In some examples, D is substituted with 0 R^X. In some examples, D is  . In some examples, D is substituted with 1 or 2 R^X.

In some examples, D is 

or 

. In some examples, 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.

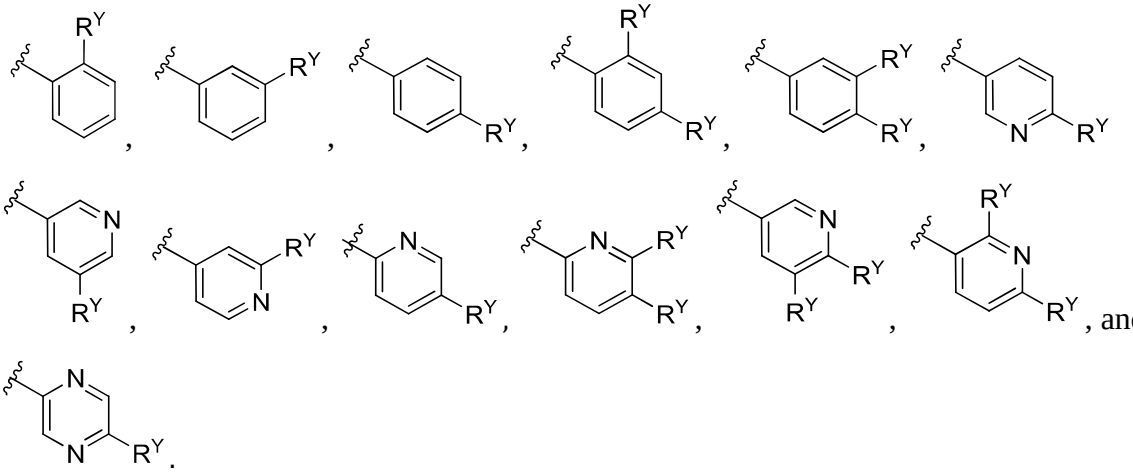
In some examples, L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is optionally substituted by 1-5 R^{L1}. In some examples, L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is substituted by 0 R^{L1}. In some examples, L^1 is selected from a bond, CH_2O–*, CH_2OCH_2–*, –NCH_3–, –NH–, or –O–, wherein "–*" indicates the attachment point to A.

In some examples, R^1 is hydrogen or CH_3. In some examples, R^2 is hydrogen or CH_3.

In some examples, A is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6

alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, or G^1. In some examples, A is phenyl, pyrazine, or pyridyl, each of which is optionally substituted with 1-2 R^Y groups.

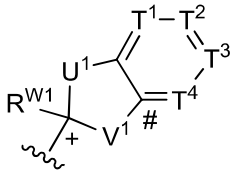
In some examples, A is selected from the group consisting of:



In some examples, 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.

In some examples, 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}. In some examples, L^2 is a bond or C_1-C_6 alkylene, wherein C_1-C_6 alkylene is optionally substituted by 0 R^{L2}. In some examples, L^2 is selected from a bond or CH_2–*, wherein "–*" indicates the attachment point to W. In some examples, L^2 is a bond.

In some examples, 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 –$S(O)_2R^D$;

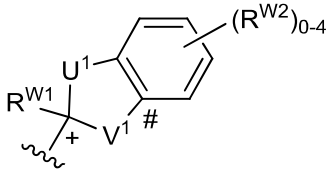
R^{V13} and R^{V14} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, –OR^A, –NR^BR^C, –NR^BR^{CC}, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E,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

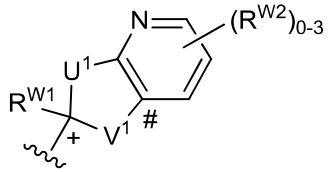
R^{W1} is selected from the group consisting of hydrogen and C_1-C_6 alkyl; and

wherein each of R^A, R^B, R^C, R^D, R^E, R^{W2}, and R^{N3} is defined as for Formula (I).

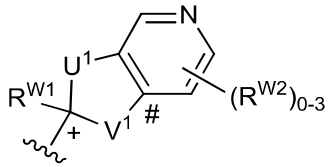
In some examples, W is represented by Formula (W-a-1), Formula (W-a-2), Formula (W-a-3), Formula (W-a-4), or Formula (W-a-5):



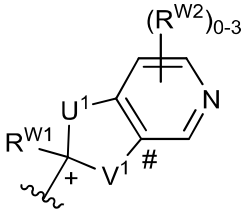
Formula (W-a-1),



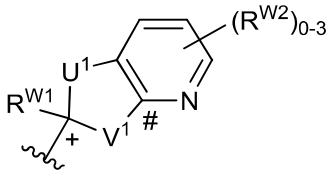
Formula (W-a-2),



Formula (W-a-3),

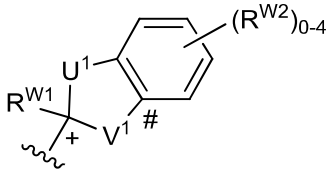


Formula (W-a-4), or



Formula (W-a-5).

In some examples, W is represented by Formula (W-a-1):



Formula (W-a-1).

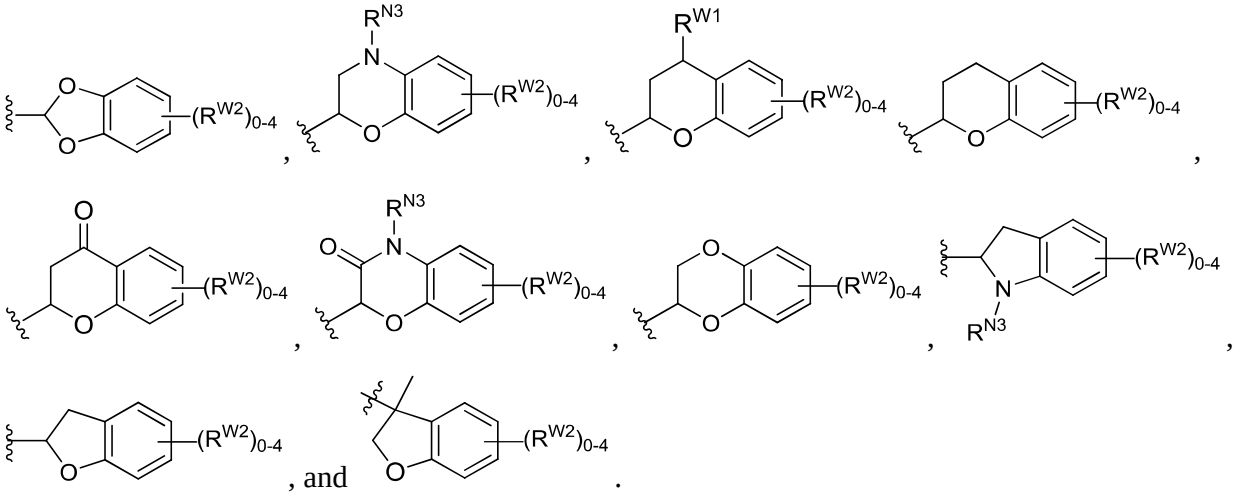
In some examples, U^1 is selected from the group consisting of a bond, –O–, and $–NR^{N3}–$; and V^1 is selected from the group consisting of $^{+}–O–^{\#}$, $^{+}–C(R^{V11}R^{V12})–^{\#}$, $^{+}–C(R^{V11}R^{V12})–C(R^{V13}R^{V14})–^{\#}$, $^{+}–C(R^{V15}R^{V16})–O–^{\#}$, $^{+}–C(R^{V11}R^{V12})–C(O)–^{\#}$, $^{+}–O–C(R^{V15}R^{V16})–^{\#}$, $^{+}–C(R^{V15}R^{V16})–NR^{N3}–^{\#}$, 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.

In some examples, 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 $–NR^BR^{CC}$. In some examples, each of R^{V11}, R^{V12}, R^{V13}, and R^{V14} is independently selected from the group consisting of hydrogen, hydroxyl and $–NR^BR^{CC}$.

In some examples, each of R^{V15} and R^{V16} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some examples, each of R^{V15} and R^{V16} is hydrogen. In some examples, R^{N3} is hydrogen or CH_3.

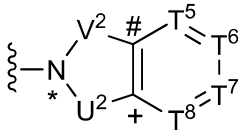
In some examples, wherein U^1 is selected from the group consisting of a bond, –O–, –NH– and –NCH_3–; and V^1 is selected from the group consisting of $^+$–O–$^{\#}$, $^+$–CH_2–$^{\#}$, $^+$–CH_2–CH_2–$^{\#}$, $^+$–CH_2–C(O)–$^{\#}$, $^+$–CH_2–O–$^{\#}$, $^+$–O-CH_2–$^{\#}$, $^+$–CH_2–NH–$^{\#}$, $^+$–CH_2–NCH_3–$^{\#}$, $^+$–C(O)–NH–$^{\#}$, and $^+$–C(O)–NCH_3–$^{\#}$, and wherein "$^+$–" and "–$^{\#}$" indicate the attachment points of V^1 as indicated in Formula (W-a). In some examples, R^{W1} is selected from the group consisting of hydrogen, hydroxyl, CH_3, $NH(CH_2)_2OH$, $NH(CH_2)_2CO_2H$ and $NH(CH_2)_2CO_2CH_3$.

In some examples, 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. In some examples, W is selected from the group consisting of:


, and .

In some examples, L^2 is C_1-C_6 alkylene optionally substituted by 1-5 R^{L2}. In some examples, L^2 is C_1-C_6 alkylene substituted by 0 R^{L2}. In some examples, L^2 is CH_2–*, wherein "–*" indicates the attachment point to W.

In some examples, W is represented by Formula (W-b):



Formula (W-b)

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;

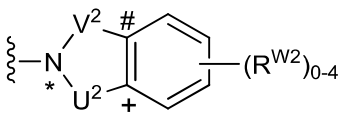
R^{U21} and R^{U22} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, C_1-C_6 alkyl–C(O)OH, and C_1-C_6 alkyl–$C(O)OR^D$;

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, $–C(O)OR^D$;

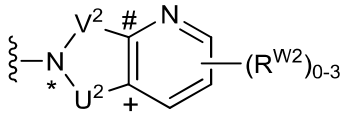
R^{V23} and ^{RV24} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$,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

wherein each of R^A, R^B, R^C, R^D, R^E, R^{W2}, and R^{N3} is defined as for Formula (I).

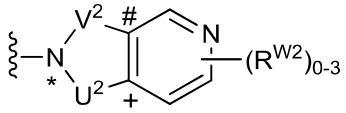
In some examples, W is represented by Formula (W-b-1), Formula (W-b-2), Formula (W-b-3), Formula (W-b-4), or Formula (W-b-5):



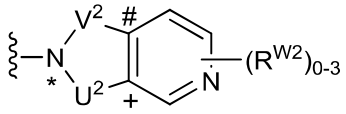
Formula (W-b-1),



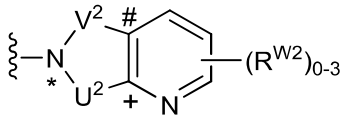
Formula (W-b-2),



Formula (W-b-3),

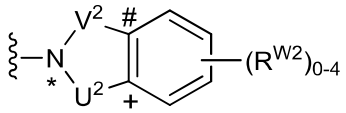


Formula (W-b-4), or



Formula (W-b-5).

In some examples, W is represented by Formula (W-b-1):



Formula (W-b-1).

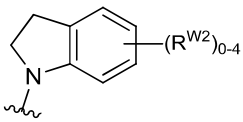
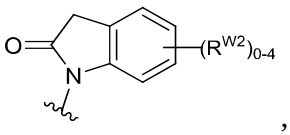
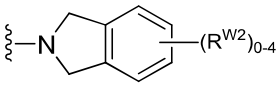
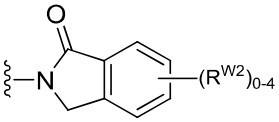
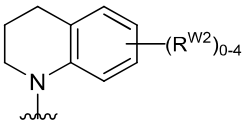
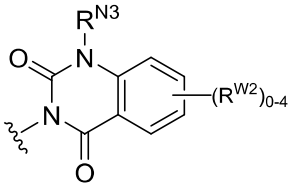
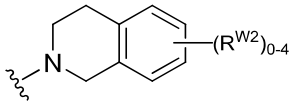
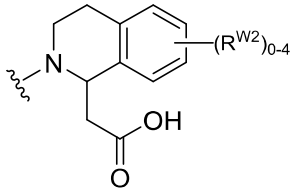
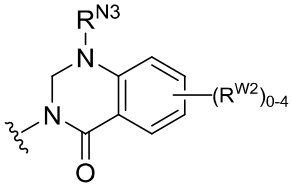
In some examples, V^2 is selected from the group consisting of *–C($R^{V21}R^{V22}$)–$^{\#}$, *–C($R^{V21}R^{V22}$)–C($R^{V23}R^{V24}$)–$^{\#}$, *–C(O)–C($R^{V23}R^{V24}$)–$^{\#}$, and *–C($R^{V21}R^{V22}$)–C($R^{V23}R^{V24}$)–C($R^{V23}R^{V24}$)–$^{\#}$; wherein "*–" and "–$^{\#}$" indicate the attachment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

In some examples, each of R^{V21} and R^{V22} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some examples, each of R^{V21} and R^{V22} is hydrogen.

In some examples, 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. In some examples, each of R^{V23} and R^{V24} is hydrogen.

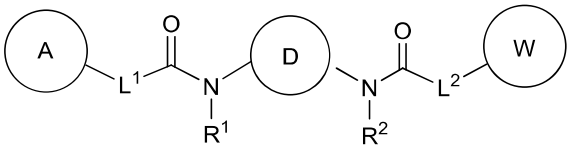
In some examples, U^2 is selected from the group consisting of a bond, $^{*}–C(O)–^{+}$, $^{*}–CH_2–^{+}$, and $^{*}–CH(CH_2CO_2H)–^{+}$, wherein "*–" and "–$^{+}$" indicate the attachment points of U^2 as indicated in Formula (W-b); and V^2 is selected from the group consisting of $^{*}–CH_2–^{\#}$, $^{*}–CH_2–CH_2–^{\#}$, $^{*}–C(O)–CH_2–^{\#}$, $^{*}–C(O)–NH–^{\#}$, $^{*}–CH_2–NH–^{\#}$, and $^{*}–CH_2–CH_2–CH_2–^{\#}$; wherein "*–" and "–$^{\#}$" indicate the attachment points of V^2 as indicated in Formula (W-b).

In some examples, 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 $–OR^A$. In some examples, W is selected from the group consisting of:


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, and

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

In some examples, 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. In some examples, 2 R^{W2} 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. In some examples, each R^X is independently fluoro.

In some examples, the compound of Formula (I) is a compound of Formula (I-a):



Formula (I-a)

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

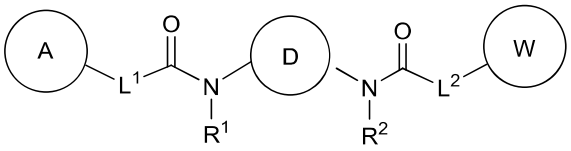
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

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.

In some examples, the compound of Formula (I) is a compound of Formula (I-b):



Formula (I-b)

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

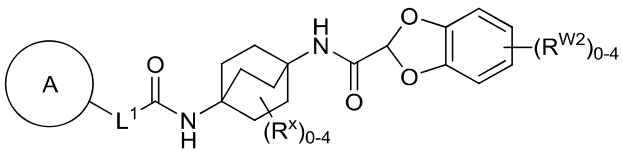
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

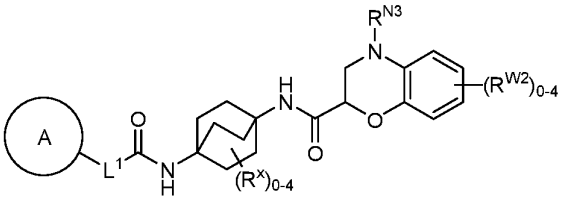
each R^Y is independently chloro, fluoro, CHF_2, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCHF_2$, OCF_3, OCH_2CF_3, $OCH(CH_3)_2$, or CN; or

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.

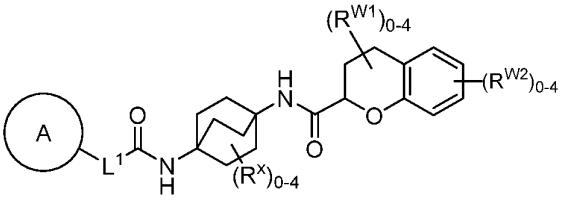
In some examples, the compound of Formula (I) is a compound of Formula (I-c-1), Formula (I-c-2), Formula (I-c-3), Formula (I-c-4), Formula (I-c-5), Formula (I-c-6), Formula (I-c-7), Formula (I-c-8), Formula (I-c-9), or Formula (I-c-10):



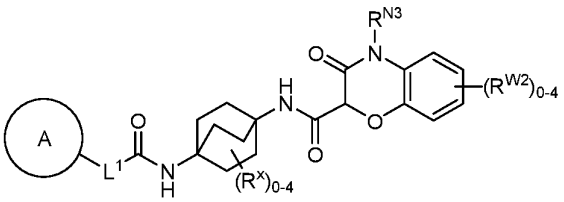
Formula (I-c-1)



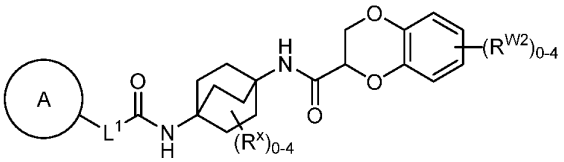
Formula (I-c-2)



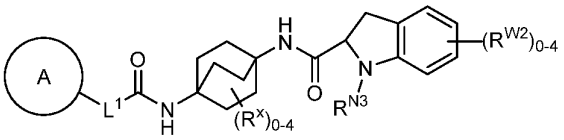
Formula (I-c-3)



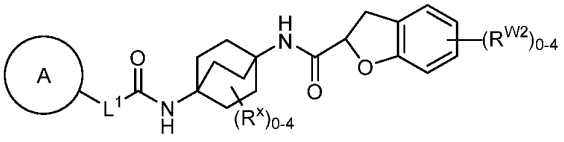
Formula (I-c-4)



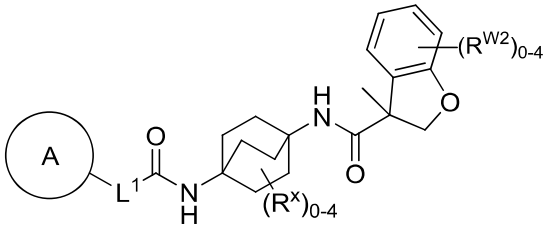
Formula (I-c-5)



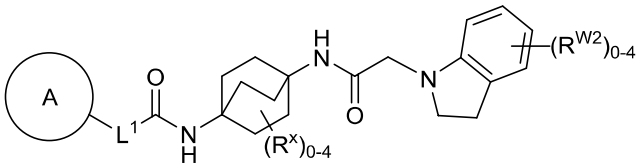
Formula (I-c-6)



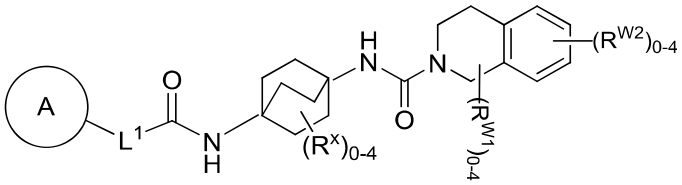
Formula (I-c-7)



Formula (I-c-8)



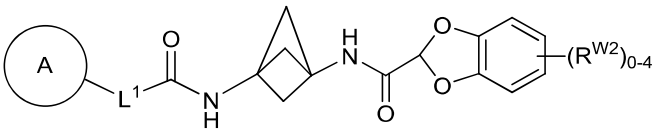
Formula (I-c-9)



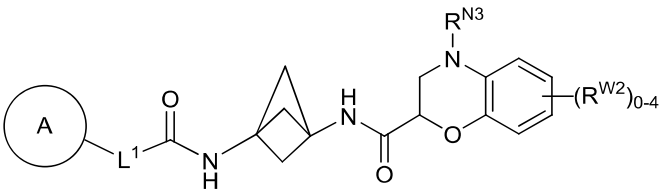
Formula (I-c-10)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein each of A, L^1, R^{N3}, R^{W1} R^{W2} and R^X is defined as for Formula (I).

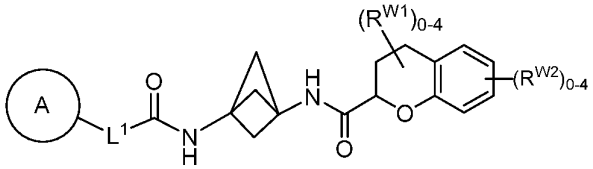
In some examples, the compound of Formula (I) is a compound of Formula (I-d-1), Formula (I-d-2), Formula (I-d-3), Formula (I-d-4), Formula (I-d-5), Formula (I-d-6), Formula (I-d-7), Formula (I-d-8), Formula (I-d-9), or Formula (I-d-10):



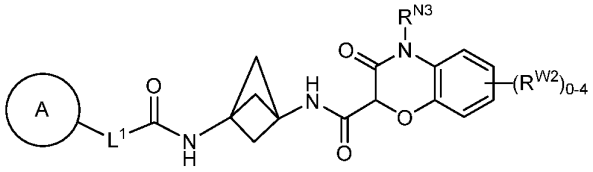
Formula (I-d-1)



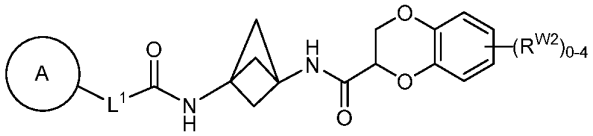
Formula (I-d-2)



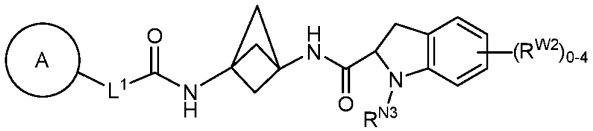
Formula (I-d-3)



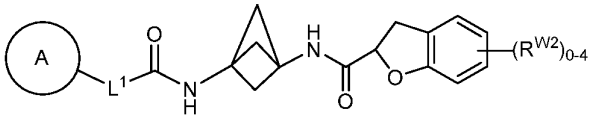
Formula (I-d-4)



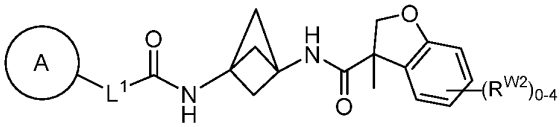
Formula (I-d-5)



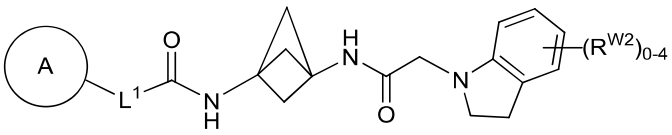
Formula (I-d-6)



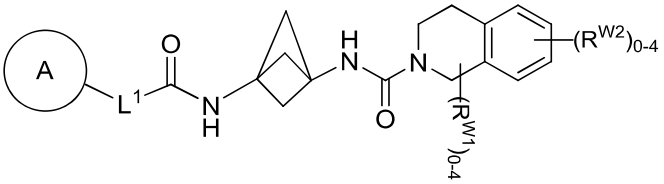
Formula (I-d-7)



Formula (I-d-8)



Formula (I-d-9)



Formula (I-d-10)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein each of A, L^1, R^{N3}, R^{W1} and R^{W2} is defined as for Formula (I).

In some examples, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c-1), (I-c-2), (I-c-3), (I-c-4), (I-c-5), (I-c-6), (I-c-7), (I-c-8), (I-c-9), (I-c-10), (I-d-1), (I-d-2), (I-d-3), (I-d-4), (I-d-5), (I-d-6), (I-d-7), (I-d-8), (I-d-9), or (I-d-10)), or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

In some examples, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c-1), (I-c-2), (I-c-3), (I-c-4), (I-c-5), (I-c-6), (I-c-7), (I-c-8), (I-c-9), (I-c-10), (I-d-1), (I-d-2), (I-d-3), (I-d-4), (I-d-5), (I-d-6), (I-d-7), (I-d-8), (I-d-9) or (I-d-10)), is selected from a compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof.

In another example, the present disclosure features a method of treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease, or a disease or disorder associated with impaired function of eIF2B or components in the ISR pathway (e.g., eIF2 pathway) in a subject, wherein the method comprises administering a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof, or a composition thereof, to a subject.

In some examples, the method comprises the treatment of a neurodegenerative disease. In some examples, the neurodegenerative disease comprises a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability

syndrome, a cognitive impairment, a glial cell dysfunction, or a brain injury. In some examples, the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo myelination, Alzheimer's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia, kuru, multiple sclerosis, Parkinson's disease, or a prion disease. In some examples, the neurodegenerative disease comprises vanishing white matter disease.

In some examples, the method comprises the treatment of cancer. In some examples, the cancer comprises pancreatic cancer, breast cancer, multiple myeloma, or a cancer of the secretory cells.

In some examples, the method comprises the treatment of an inflammatory disease. In some examples, the inflammatory disease comprises postoperative cognitive dysfunction, arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, diabetes), Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves’ ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, or atopic dermatitis.

In some examples, the method comprises the treatment of a musculoskeletal disease. In some examples, the musculoskeletal disease comprises muscular dystrophy, multiple sclerosis, amyotropic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Freidrich’s ataxia, a muscle wasting disorder), an inclusion body myopathy, motor neuron disease, or paralysis.

In some examples, the method comprises the treatment of a metabolic disease. In some examples, the metabolic disease comprises non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, phenylketonuria, proliferative retinopathy, or Kearns-Sayre disease.

In some examples, the method comprises the treatment of a mitochondrial disease. In some examples, the mitochondrial disease is associated with, or is a result of, or is caused by mitochondrial dysfunction, one or more mitochondrial protein mutations, or one or more mitochondrial DNA mutations. In some examples, the mitochondrial disease is a

mitochondrial myopathy. In some examples, the mitochondrial disease is selected from the group consisting of Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Kearns-Sayre syndrome (KSS), Leigh syndrome (e.g., MILS, or maternally inherited Leigh syndrome), mitochondrial DNA depletion syndromes (MDDS, e.g., Alpers syndrome), mitochondrial encephalomyopathy (e.g., mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber´s hereditary optic neuropathy (LHON and Pearson syndrome.

In another example, the present disclosure features a method of treating a disease or disorder related to modulation (e.g., a decrease) in eIF2B activity or level, modulation (e.g., a decrease) of eIF2α activity or level, modulation (e.g., an increase) in eIF2α phosphorylation, modulation (e.g., an increase) of phosphorylated eIF2α pathway activity, or modulation (e.g., an increase) of ISR activity in a subject, wherein the method comprises administering a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof, or a composition thereof, to a subject. In some examples, the disease may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway (e.g., the eIF2α signaling pathway or ISR pathway).

In another example, the present disclosure features A method of treating cancer in a subject, the method comprising administering to the subject a compound of formula (I) in combination with an immunotherapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features compounds, compositions, and methods comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof for use, e.g., in the modulation (e.g., activation) of eIF2B and the attenuation of the ISR signaling pathway.

Definitions

Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas

Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 99% by weight, more than 99.5% by weight, or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R–compound. In certain embodiments, the enantiomerically pure R–compound in such compositions can, for example, comprise, at least about 95% by weight R–compound and at most about 5% by weight S–compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by weight S–compound and at most about 5% by weight R–compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

The articles “a” and “an” may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example ”C_1-C_6 alkyl” is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6 alkyl.

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

“Alkyl” refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C_1-C_{20} alkyl”). In some embodiments, an alkyl group has 1 to 12 carbon atoms (“C_1-C_{12} alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C_1-C_8 alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C_1-C_6 alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C_1-C_5 alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C_1-C_4 alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C_1-C_3 alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C_1-C_2 alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C_1 alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C_2-C_6 alkyl”). Examples

of C_1-C_6 alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Each instance of an alkyl group may be independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted $C_{1–10}$ alkyl (e.g., $–CH_3$). In certain embodiments, the alkyl group is substituted $C_{1–6}$ alkyl. Common alkyl abbreviations include Me ($–CH_3$), Et ($–CH_2CH_3$), iPr ($–CH(CH_3)_2$), nPr ($–CH_2CH_2CH_3$), n–Bu ($–CH_2CH_2CH_2CH_3$), or i–Bu ($–CH_2CH(CH_3)_2$).

The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $–CH_2CH_2CH_2CH_2–$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene. An alkylene group may be described as, e.g., a C_1-C_6-membered alkylene, wherein the term "membered" refers to the non-hydrogen atoms within the moiety.

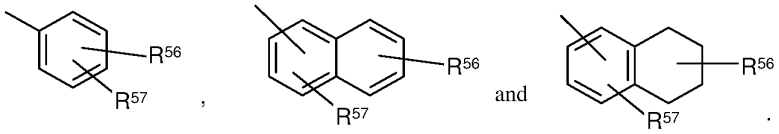
"Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_2-C_{20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_2-C_8 alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_2-C_6 alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_2-C_5 alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_2-C_4 alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_2-C_3 alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_2-C_4 alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_2-C_6 alkenyl groups include the aforementioned $C_{2–4}$ alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Each instance of an alkenyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted

alkenyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-6} alkenyl.

"Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_6-C_{14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). An aryl group may be described as, e.g., a C_6-C_{10}-membered aryl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Aryl groups include, but are not limited to, phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Each instance of an aryl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_6-C_{14} aryl. In certain embodiments, the aryl group is substituted C_6-C_{14} aryl.

In certain embodiments, an aryl group is substituted with one or more of groups selected from halo, C_1–C_8 alkyl, halo-C_1–C_8 alkyl, haloxy-C_1–C_8 alkyl, cyano, hydroxy, alkoxy C_1–C_8 alkyl, and amino.

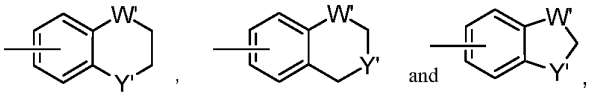
Examples of representative substituted aryls include the following



and .

wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_1–C_8 alkyl, halo-C_1–C_8 alkyl, 4–10 membered heterocyclyl, alkanoyl, alkoxy-C_1–C_8 alkyl, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$ $NR^{58}SO_2R^{59}$, C(O)Oalkyl, C(O)Oaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, S(O)-alkyl, $S(O)_2$-alkyl, S-aryl, S(O)-aryl, $S(O_2)$-aryl; wherein R^{58} and R^{59} are each independently selected from hydrogen or C_1–C_6 alkyl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S.

Other representative aryl groups having a fused heterocyclyl group include the following:



wherein each W' is selected from $C(R^{66})_2$, NR^{66}, O, and S; and each Y' is selected from carbonyl, NR^{66}, O and S; and R^{66} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10 membered heteroaryl.

An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Non-limiting examples of heteroaryl groups include pyridinyl, pyrimidinyl, thiophenyl, thienyl, furanyl, indolyl, benzoxadiazolyl, benzodioxolyl, benzodioxanyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinolinyl, quinoxalinyl, pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothienyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl, benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene.

"Halo" or "halogen," independently or as part of another substituent, mean, unless otherwise stated, a fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) atom. The term "halide" by itself or as part of another substituent, refers to a fluoride, chloride, bromide, or iodide atom. In certain embodiments, the halo group is either fluorine or chlorine.

Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo-C_1-C_6 alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Exemplary heteroalkyl groups include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)_2$, $-S(O)-CH_3$, $-S(O)_2-CH_3$, $-CH_2-CH_2-S(O)_2-$

CH_3, -CH=CH-O-CH_3, -Si(CH_3)$_3$, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, -O-CH_3, and -O-CH_2-CH_3. Up to two or three heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and -CH_2-O-Si(CH_3)$_3$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as –CH_2O, –NR^BR^C, or the like, it will be understood that the terms heteroalkyl and –CH_2O or –NR^BR^C are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as –CH_2O, –NR^BR^C, or the like.

Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, –CH_2O- and –CH_2CH_2O-. A heteroalkylene group may be described as, e.g., a 2-7-membered heteroalkylene, wherein the term “membered” refers to the non-hydrogen atoms within the moiety. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)$_2$R’- may represent both -C(O)$_2$R’- and –R’C(O)$_2$-.

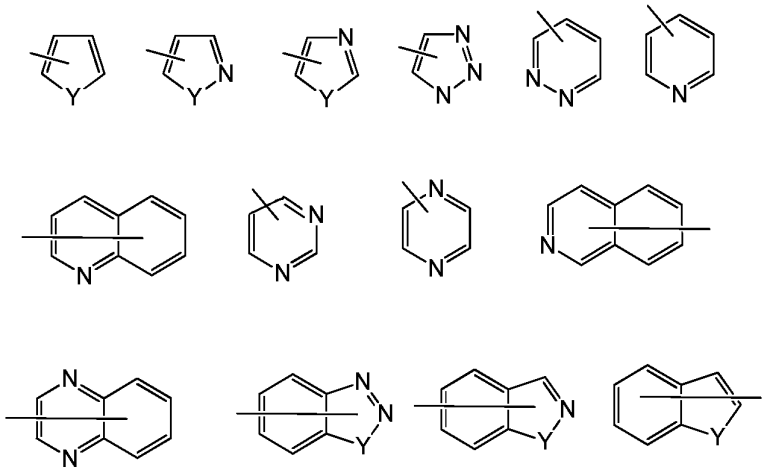
“Heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl). A heteroaryl group may be described as, e.g., a 6-10-membered heteroaryl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety.

In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system,

wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Each instance of a heteroaryl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

Examples of representative heteroaryls include the following formulae:



wherein each Y is selected from carbonyl, N, NR^{65}, O, and S; and R^{65} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10 membered heteroaryl.

"Cycloalkyl" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_3-C_{10} cycloalkyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_3-C_8cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_5-C_{10} cycloalkyl"). A cycloalkyl group may be described as, e.g., a C_4-C_7-membered cycloalkyl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Exemplary C_3-C_6 cycloalkyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_3-C_8 cycloalkyl groups include, without limitation, the aforementioned C_3-C_6 cycloalkyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), cubanyl (C_8), bicyclo[1.1.1]pentanyl (C_5), bicyclo[2.2.2]octanyl (C_8), bicyclo[2.1.1]hexanyl (C_6), bicyclo[3.1.1]heptanyl (C_7), and the like. Exemplary C_3-C_{10} cycloalkyl groups include, without limitation, the aforementioned C_3-C_8 cycloalkyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the cycloalkyl group is either monocyclic ("monocyclic cycloalkyl") or contain a fused, bridged or spiro ring system such as a bicyclic

system ("bicyclic cycloalkyl") and can be saturated or can be partially unsaturated. "Cycloalkyl" also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Each instance of a cycloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_3-C_{10} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_3-C_{10} cycloalkyl.

In some embodiments, "cycloalkyl" is a monocyclic, saturated cycloalkyl group having from 3 to 10 ring carbon atoms ("C_3-C_{10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_3-C_8 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_5-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_5-C_{10} cycloalkyl"). Examples of C_5-C_6 cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_3-C_6 cycloalkyl groups include the aforementioned C_5-C_6 cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_3-C_8 cycloalkyl groups include the aforementioned C_3-C_6 cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_3-C_{10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_3-C_{10} cycloalkyl.

"Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of

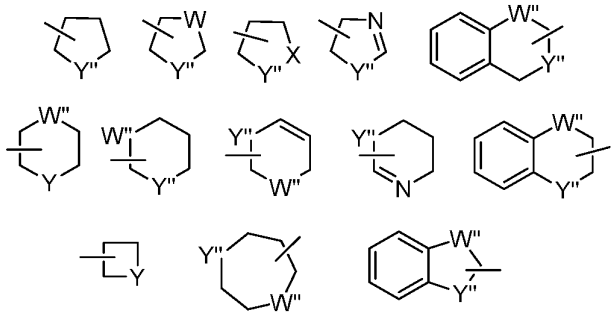
attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term "membered" refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Each instance of heterocyclyl may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin–2–one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl,

morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5–membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6–bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6–membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6–bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

Particular examples of heterocyclyl groups are shown in the following illustrative examples:



wherein each W" is selected from CR^{67}, $C(R^{67})_2$, NR^{67}, O, and S; and each Y" is selected from NR^{67}, O, and S; and R^{67} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10–membered heteroaryl. These heterocyclyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl (*e.g.,* amido), aminocarbonylamino, aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, keto, nitro, thiol, –S–alkyl, –S–aryl, –S(O)–alkyl, –S(O)–aryl, $–S(O)_2$–alkyl, and $–S(O)_2$–aryl. Substituting groups include carbonyl or thiocarbonyl which provide, for example, lactam and urea derivatives.

"Nitrogen–containing heterocyclyl" group means a 4– to 7– membered non–aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (*e.g.* 2–piperidinyl, 3–piperidinyl and 4–piperidinyl), pyrrolidine (*e.g.* 2–pyrrolidinyl and 3–pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2–pyrazoline, pyrazolidine, piperazine, and N–alkyl piperazines such as N–methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

"Amino" refers to the radical $-NR^{70}R^{71}$, wherein R^{70} and R^{71} are each independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10–membered heteroaryl. In some embodiments, amino refers to NH_2.

"Cyano" refers to the radical –CN.

"Hydroxy" refers to the radical –OH.

Alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.,* "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" cycloalkyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.,* a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, such as any of the substituents described herein that result in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in a first buffer, e.g., in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with a second buffer prior to use.

Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such

salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

As used herein, the term "salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved

using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

The terms "treating" or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods herein treat cancer (e.g. pancreatic cancer, breast cancer, multiple myeloma, cancers of secretory cells), neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, frontotemporal dementia), leukodystrophies (e.g., vanishing white matter disease, childhood ataxia with CNS hypo-myelination), postsurgical cognitive dysfunction, traumatic brain injury, stroke, spinal cord injury, intellectual disability syndromes, inflammatory diseases, musculoskeletal diseases, metabolic diseases, or diseases or disorders associated with impaired function of eIF2B or components in a signal transduction or signaling pathway including the ISR and decreased eIF2 pathway activity). For example certain methods herein treat cancer by decreasing or reducing or preventing the occurrence, growth, metastasis, or progression of cancer or decreasing a symptom of cancer; treat neurodegeneration by improving mental wellbeing, increasing mental function, slowing the decrease of mental function, decreasing dementia, delaying the onset of dementia, improving cognitive skills, decreasing the loss of cognitive skills, improving memory, decreasing the degradation of memory, decreasing a symptom of neurodegeneration or extending survival; treat vanishing white matter disease by reducing a symptom of vanishing white matter disease or reducing the loss of white matter or reducing the loss of myelin or increasing the amount of myelin or

increasing the amount of white matter; treat childhood ataxia with CNS hypo-myelination by decreasing a symptom of childhood ataxia with CNS hypo-myelination or increasing the level of myelin or decreasing the loss of myelin; treat an intellectual disability syndrome by decreasing a symptom of an intellectual disability syndrome, treat an inflammatory disease by treating a symptom of the inflammatory disease; treat a musculoskeletal disease by treating a symptom of the musculoskeletal disease; or treat a metabolic disease by treating a symptom of the metabolic disease. Symptoms of a disease, disorder, or condition described herein (e.g., cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a condition or disease associated with impaired function of eIF2B or components in a signal transduction pathway including the eIF2 pathway, eIF2α phosphorylation. or ISR pathway) would be known or may be determined by a person of ordinary skill in the art. The term "treating" and conjugations thereof, include prevention of an injury, pathology, condition, or disease (e.g. preventing the development of one or more symptoms of a disease, disorder, or condition described herein).

An "effective amount" is an amount sufficient to accomplish a stated purpose (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount. " A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s).

The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g., a disease or disorder described herein, e.g., cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B or components in a signal transduction pathway including the eIF2 pathway, eIF2α phosphorylation. or ISR pathway) means that the disease is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a symptom of a disease or condition associated with an impaired function of the eIF2B may be a symptom that results (entirely or partially) from a decrease in eIF2B activity (e.g. decrease in eIF2B activity or levels, increase in eIF2α phosphorylation or activity of phosphorylated eIF2α or reduced eIF2 activity or increase in activity of phosphorylated eIF2α signal transduction or the ISR signalling pathway). As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a disease associated with decreased eIF2 activity or eIF2 pathway activity, may be treated with an agent (e.g., compound as described herein) effective for increasing the level or activity of eIF2 or eIF2 pathway or a decrease in phosphorylated eIF2α activity or the ISR pathway. For example, a disease associated with phosphorylated eIF2α may be treated with an agent (e.g., compound as described herein) effective for decreasing the level of activity of phosphorylated eIF2α or a downstream component or effector of phosphorylated eIF2α. For example, a disease associated with eIF2α may be treated with an agent (e.g., compound as described herein) effective for increasing the level of activity of eIF2 or a downstream component or effector of eIF2.

"Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects.

"Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated, however, that the resulting reaction product can be produced directly

from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture. The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme (e.g. eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway). In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g. eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway).

As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor (e.g., antagonist) interaction means negatively affecting (e.g., decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In some embodiments, inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In some embodiments, inhibition refers to a decrease in the activity of a signal transduction pathway or signaling pathway (e.g., eIF2B, eIF2α, or a component of the eIF2 pathway, pathway activated by eIF2α phosphorylation, or ISR pathway). Thus, inhibition may include, at least in part, partially or totally decreasing stimulation, decreasing or reducing activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein increased in a disease (e.g. eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway, wherein each is associated with cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, or a metabolic disease). Inhibition may include, at least in part, partially or totally decreasing stimulation, decreasing or reducing activation, or deactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway) that may modulate the level of another protein or increase cell survival (e.g., decrease in phosphorylated eIF2α pathway activity may increase cell survival in cells that may or may not have an increase in phosphorylated eIF2α pathway activity relative to a non-disease control or decrease in eIF2α pathway activity may increase cell survival in cells that may or may not have an increase in eIF2α pathway activity relative to a non-disease control).

As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein-activator (e.g. agonist) interaction means positively affecting (e.g. increasing) the

activity or function of the protein (e.g. eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway) relative to the activity or function of the protein in the absence of the activator (e.g. compound described herein). In some embodiments, activation refers to an increase in the activity of a signal transduction pathway or signaling pathway (e.g. eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway). Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease (e.g. level of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway associated with cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, or a metabolic disease). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein (e.g., eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway) that may modulate the level of another protein or increase cell survival (e.g., increase in eIF2α activity may increase cell survival in cells that may or may not have a reduction in eIF2α activity relative to a non-disease control).

The term “modulation" refers to an increase or decrease in the level of a target molecule or the function of a target molecule. In some embodiments, modulation of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway may result in reduction of the severity of one or more symptoms of a disease associated with eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway (e.g., cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, or a metabolic disease) or a disease that is not caused by eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway but may benefit from modulation of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway (e.g., decreasing in level or level of activity of eIF2B, eIF2α or a component of the eIF2 pathway).

The term “modulator” as used herein refers to modulation of (e.g., an increase or decrease in) the level of a target molecule or the function of a target molecule. In embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is an anti-cancer agent. In embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is a neuroprotectant. In embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is a memory enhancing agent. In embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is a memory enhancing agent (e.g., a long term memory enhancing agent). In embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is an anti-inflammatory agent.

In some embodiments, a modulator of eIF2B, eIF2α, or component of the eIF2 pathway or ISR pathway is a pain-relieving agent.

"Patient" or "subject in need thereof refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a compound or pharmaceutical composition, as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human. In some embodiments, a patient is a domesticated animal. In some embodiments, a patient is a dog. In some embodiments, a patient is a parrot. In some embodiments, a patient is livestock animal. In some embodiments, a patient is a mammal. In some embodiments, a patient is a cat. In some embodiments, a patient is a horse. In some embodiments, a patient is bovine. In some embodiments, a patient is a canine. In some embodiments, a patient is a feline. In some embodiments, a patient is an ape. In some embodiments, a patient is a monkey. In some embodiments, a patient is a mouse. In some embodiments, a patient is an experimental animal. In some embodiments, a patient is a rat. In some embodiments, a patient is a hamster. In some embodiments, a patient is a test animal. In some embodiments, a patient is a newborn animal. In some embodiments, a patient is a newborn human. In some embodiments, a patient is a newborn mammal. In some embodiments, a patient is an elderly animal. In some embodiments, a patient is an elderly human. In some embodiments, a patient is an elderly mammal. In some embodiments, a patient is a geriatric patient.

"Disease", "disorder" or "condition" refers to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In some embodiments, the compounds and methods described herein comprise reduction or elimination of one or more symptoms of the disease, disorder, or condition, e.g., through administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

"Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically

acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arterial, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g., anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation).

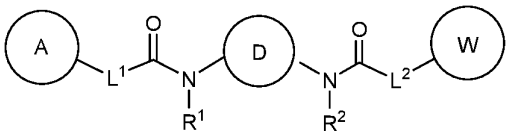
The term “eIF2B” as used herein refers to the heteropentameric eukaryotic translation initiation factor 2B. eIF2B is composed of five subunits: eIF2B1, eIF2B2, eIF2B3, eIF2B4 and eIF2B5. eIF2B1 refers to the protein associated with Entrez gene 1967, OMIM 606686, Uniprot Q14232, and/or RefSeq (protein) NP_001405. eIF2B2 refers to the protein associated with

Entrez gene 8892, OMIM 606454, Uniprot P49770, and/or RefSeq (protein) NP_055054. eIF2B3 refers to the protein associated with Entrez gene 8891, OMIM 606273, Uniprot Q9NR50, and/or RefSeq (protein) NP_065098. eIF2B4 refers to the protein associated with Entrez gene 8890, OMIM 606687, Uniprot Q9UI10, and/or RefSeq (protein) NP_751945. eIF2B5 refers to the protein associated with Entrez gene 8893, OMIM 603945, Uniprot Q13144, and/or RefSeq (protein) NP_003898.

The terms “eIF2alpha,” "eIF2a,"or “eIF2α” are interchangeable and refer to the protein "eukaryotic translation initiation factor 2 alpha subunit eIF2S1". In embodiments, "eIF2alpha", "eIF2a"or “eIF2α” refer to the human protein. Included in the terms “eIF2alpha", "eIF2a"or “eIF2α” are the wildtype and mutant forms of the protein. In embodiments, “eIF2alpha", "eIF2a"or “eIF2α” refer to the protein associated with Entrez Gene 1965, OMIM 603907, UniProt P05198, and/or RefSeq (protein) NP_004085. In embodiments, the reference numbers immediately above refer to the protein and associated nucleic acids known as of the date of filing of this application.

Compounds

Disclosed herein, for example, 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 heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N1};

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;

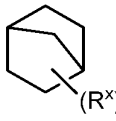
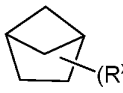
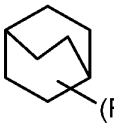
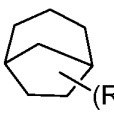
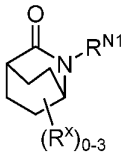
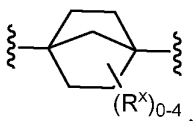
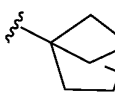
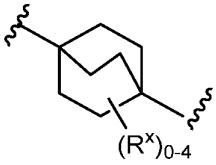
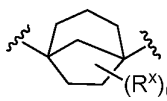
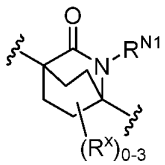
each R^{CC} is independently selected from the group consisting of C_1-C_6 alkyl–OH, C_1-C_6 alkyl–CO_2H and C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl;

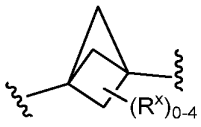
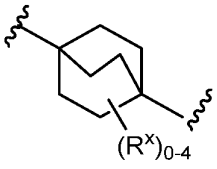
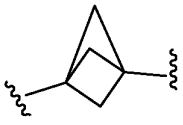
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

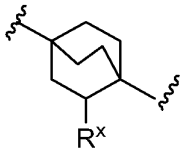
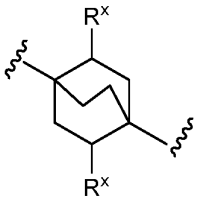
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

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 some embodiments, D is a bridged bicyclic cycloalkyl optionally substituted with 1-4 R^X. In some embodiments, D is a bridged bicyclic 5-8 membered cycloalkyl optionally substituted with 1-4 R^X. In some embodiments, D is bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, or 2-azabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups. In some embodiments, D is , , , or , , or . In some embodiments, D is , , , , , or . In some

embodiments, D is  or . In some embodiments, D is substituted with 0 R^X. In some embodiments, D is . In some embodiments, D is substituted with 1 or 2 R^X.

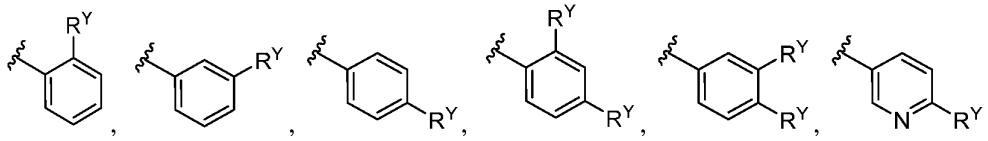
In some embodiments, D is  or . In some embodiments, each R^X is independently selected from the group consisting of oxo, –OH , –C(O)OH, –C(O)OR^D, halo, and hydroxy-C_1-C_6 alkyl.

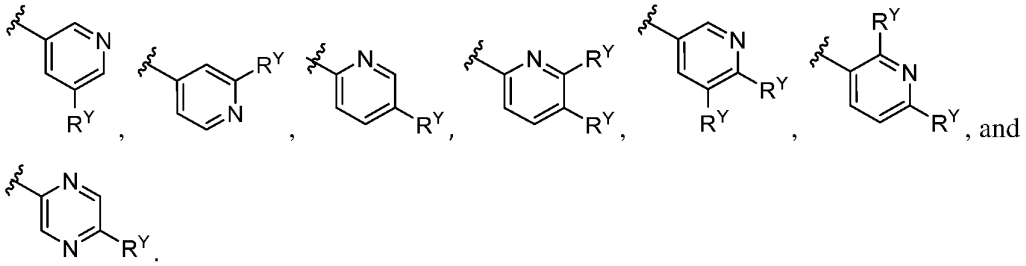
In some embodiments, L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is optionally substituted by 1-5 R^{L1}. In some embodiments, L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is substituted by 0 R^{L1}. In some embodiments, L^1 is selected from a bond, CH_2O–*, CH_2OCH_2–*, –NCH_3–, –NH–, or –O–, wherein "–*" indicates the attachment point to A.

In some embodiments, R^1 is hydrogen or CH_3. In some embodiments, R^2 is hydrogen or CH_3.

In some embodiments, A is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, –OR^A, or G^1. In some embodiments, A is phenyl, pyrazine, or pyridyl, each of which is optionally substituted with 1-2 R^Y groups.

In some embodiments, A is selected from the group consisting of:

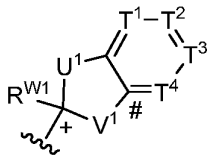




In some embodiments, each R^Y is independently selected from the group consisting of hydrogen, chloro, fluoro, CHF_2, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCHF_2$, OCF_3, OCH_2CF_3, $OCH(CH_3)_2$, and CN.

In some embodiments, 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}. In some embodiments, L^2 is a bond or C_1-C_6 alkylene, wherein C_1-C_6 alkylene is optionally substituted by 0 R^{L2}. In some embodiments, L^2 is selected from a bond or CH_2–*, wherein "–*" indicates the attachment point to W. In some embodiments, L^2 is a bond.

In some embodiments, 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 $–S(O)_2R^D$;

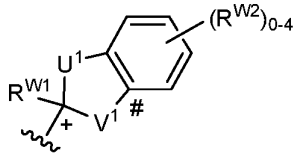
R^{V13} and R^{V14} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$,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

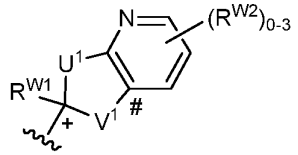
R^{W1} is selected from the group consisting of hydrogen and C_1-C_6 alkyl; and

wherein each of R^A, R^B, R^C, R^D, R^E, R^{W2}, and R^{N3} is defined as for Formula (I).

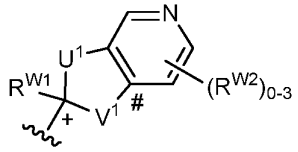
In some embodiments, W is represented by Formula (W-a-1), Formula (W-a-2), Formula (W-a-3), Formula (W-a-4), or Formula (W-a-5):



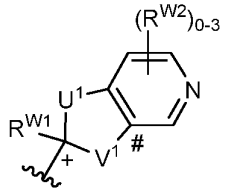
Formula (W-a-1),



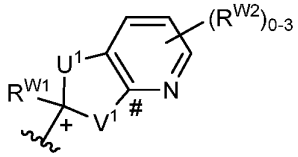
Formula (W-a-2),



Formula (W-a-3),

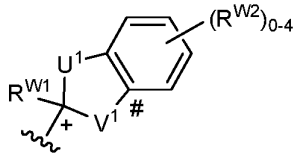


Formula (W-a-4), or



Formula (W-a-5).

In some embodiments, W is represented by Formula (W-a-1):



Formula (W-a-1).

In some embodiments, 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.

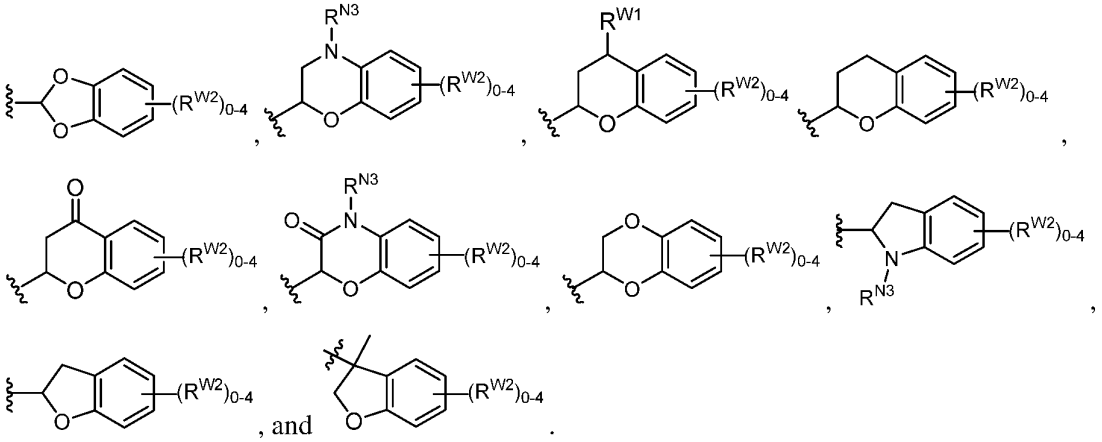
each of R^{V11}, R^{V12}, R^{V13}, and R^{V14} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, –OR^A, –NR^BR^C and –NR^BR^{CC}. In some embodiments, each of R^{V11}, R^{V12}, R^{V13}, and R^{V14} is independently selected from the group consisting of hydrogen, hydroxyl and –NR^BR^{CC}.

In some embodiments, each of R^{V15} and R^{V16} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some embodiments, each of R^{V15} and R^{V16} is hydrogen. In some embodiments, R^{N3} is hydrogen or CH_3.

In some embodiments, 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-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

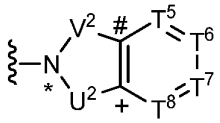
Formula (W-a). In some embodiments, R^{W1} is selected from the group consisting of hydrogen, hydroxyl, CH_3, $NH(CH_2)_2OH$, $NH(CH_2)_2CO_2H$ and $NH(CH_2)_2CO_2CH_3$.

In some embodiments, 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 $-OR^A$. In some embodiments, W is selected from the group consisting of:



In some embodiments, L^2 is C_1-C_6 alkylene optionally substituted by 1-5 R^{L2}. In some embodiments, L^2 is C_1-C_6 alkylene substituted by 0 R^{L2}. In some embodiments, L^2 is CH_2–*, wherein "–*" indicates the attachment point to W.

In some embodiments, W is represented by Formula (W-b):



Formula (W-b)

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;

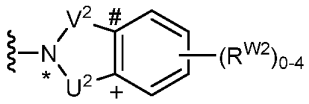
R^{U21} and R^{U22} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, C_1-C_6 alkyl–C(O)OH, and C_1-C_6 alkyl–$C(O)OR^D$;

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, $–C(O)OR^D$;

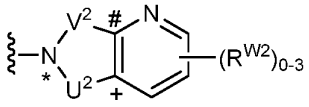
R^{V23} and ^{RV24} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$,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

wherein each of R^A, R^B, R^C, R^D, R^E, R^{W2}, and R^{N3} is defined as for Formula (I).

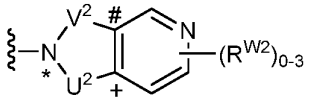
In some embodiments, W is represented by Formula (W-b-1), Formula (W-b-2), Formula (W-b-3), Formula (W-b-4), or Formula (W-b-5):



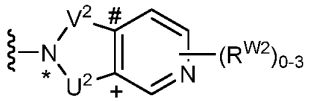
Formula (W-b-1),



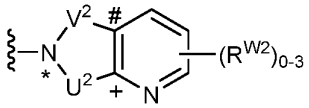
Formula (W-b-2),



Formula (W-b-3),

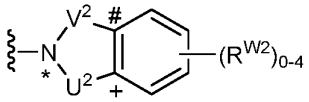


Formula (W-b-4), or



Formula (W-b-5).

In some embodiments, W is represented by Formula (W-b-1):



Formula (W-b-1).

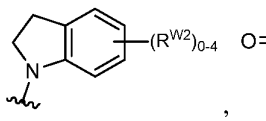
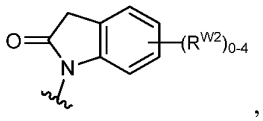
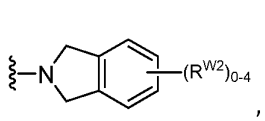
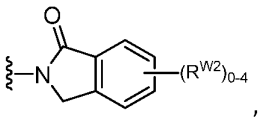
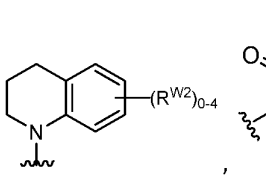
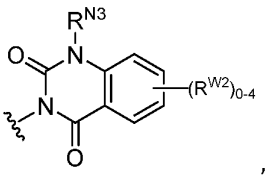
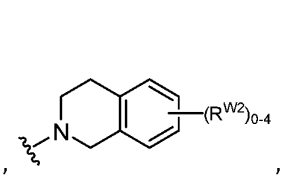
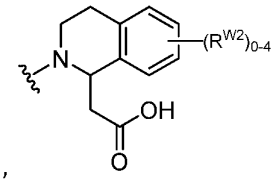
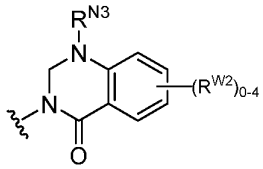
In some embodiments, wherein V^2 is selected from the group consisting of *–$C(R^{V21}R^{V22})$–$^{\#}$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$^{\#}$, *–$C(O)$–$C(R^{V23}R^{V24})$–$^{\#}$, and *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^{\#}$; wherein "*–" and "–$^{\#}$" indicate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

In some embodiments, each of R^{V21} and R^{V22} is independently selected from the group consisting of hydrogen and C_1-C_3 alkyl. In some embodiments, each of R^{V21} and R^{V22} is hydrogen.

In some embodiments, 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 $–NR^BR^C$. In some embodiments, each of R^{V23} and R^{V24} is hydrogen.

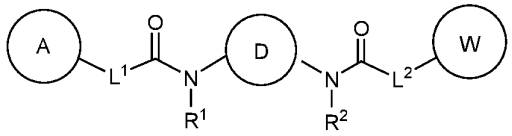
In some embodiments, U^2 is selected from the group consisting of a bond, *–$C(O)$ –$^{+}$, *–CH_2 –$^{+}$, and *–$CH(CH_2CO_2H)$ –$^{+}$, wherein "*–" and "–$^{+}$" indicate the attachment points of U^2 as indicated in Formula (W-b); and V^2 is selected from the group consisting of *–CH_2–$^{\#}$, *–CH_2–CH_2–$^{\#}$, *–$C(O)$–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).

In some embodiments, 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 $-OR^A$. In some embodiments, 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.

In some embodiments, 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. In some embodiments, 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. In some embodiments, each R^X is independently fluoro.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-a):



Formula (I-a)

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

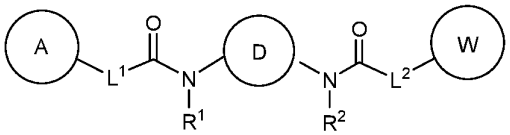
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

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.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-b):



Formula (I-b)

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

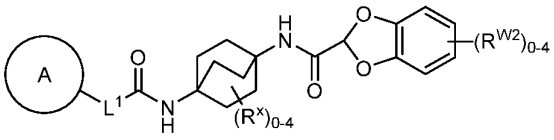
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

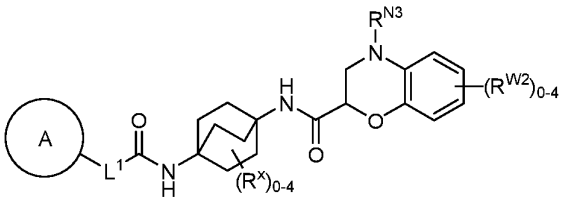
each R^Y is independently chloro, fluoro, CHF_2, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCHF_2$, OCF_3, OCH_2CF_3, $OCH(CH_3)_2$, or CN; or

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.

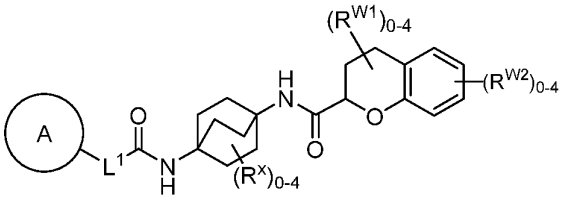
In some embodiments, the compound of Formula (I) is a compound of Formula (I-c-1), Formula (I-c-2), Formula (I-c-3), Formula (I-c-4), Formula (I-c-5), Formula (I-c-6), Formula (I-c-7), Formula (I-c-8), Formula (I-c-9) or Formula (I-c-10):



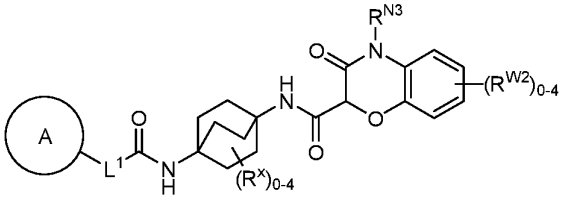
Formula (I-c-1)



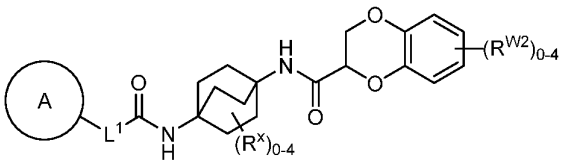
Formula (I-c-2)



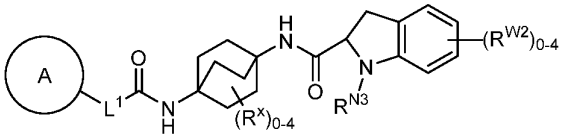
Formula (I-c-3)



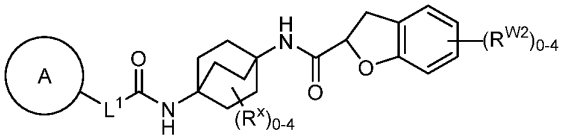
Formula (I-c-4)



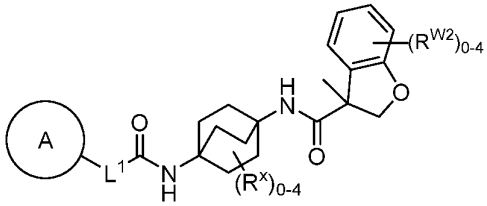
Formula (I-c-5)



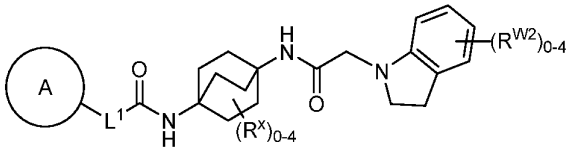
Formula (I-c-6)



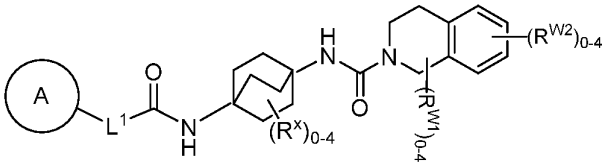
Formula (I-c-7)



Formula (I-c-8)



Formula (I-c-9)



Formula (I-c-10)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein each of A, L^1, R^{N3}, R^{W1}, R^{W2} and R^X is defined as for Formula (I).

In some embodiments, 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}. In some embodiments, L^1 is a bond, 2-7 membered heteroalkylene, $–NR^{N2}–$, or –O–, wherein 2-7 membered heteroalkylene is substituted by 0 R^{L1}. In some embodiments, L^1 is selected from a bond, CH_2O–*, CH_2OCH_2–*, $–NCH_3–$, –NH–, or –O–, wherein "–*" indicates the attachment point to A.

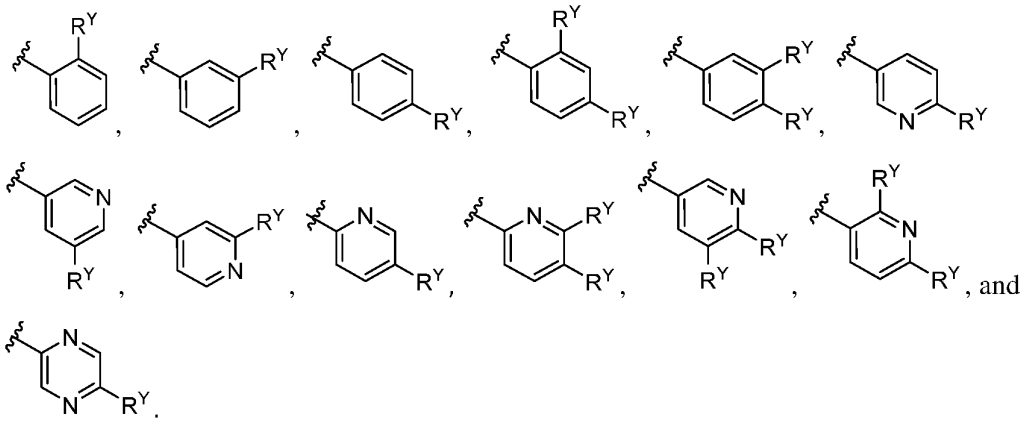
In some embodiments, each R^X is independently fluoro, oxo, OH, OCH_3, C(O)OH, or $C(O)OCH_3$.

In some embodiments, 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.

In some embodiments, R^{N3} is hydrogen or CH_3.

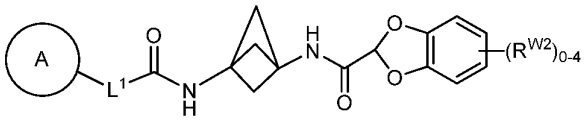
In some embodiments, A is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, or G^1. In some embodiments, A is phenyl, pyrazine, or pyridyl, each of which is optionally substituted with 1-2 R^Y groups.

In some embodiments, A is selected from the group consisting of:

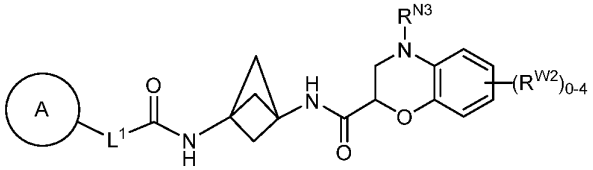


In some embodiments, each R^Y is independently selected from the group consisting of hydrogen, chloro, fluoro, CHF_2, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCHF_2$, OCF_3, OCH_2CF_3, $OCH(CH_3)_2$, and CN.

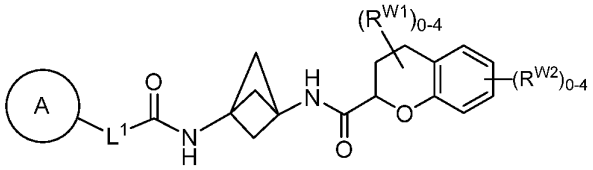
In some embodiments, the compound of Formula (I) is a compound of Formula (I-d-1), Formula (I-d-2), Formula (I-d-3), Formula (I-d-4), Formula (I-d-5), Formula (I-d-6), Formula (I-d-7), Formula (I-d-8), Formula (I-d-9) or Formula (I-c-10):



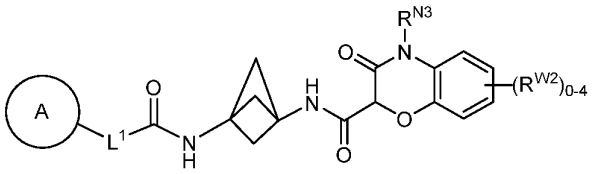
Formula (I-d-1)



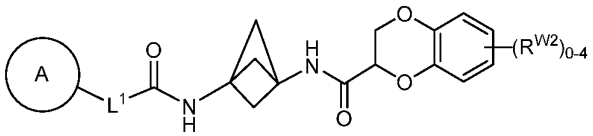
Formula (I-d-2)



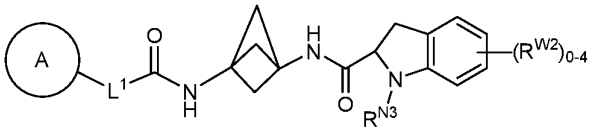
Formula (I-d-3)



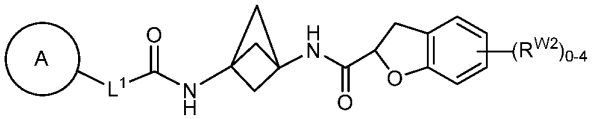
Formula (I-d-4)



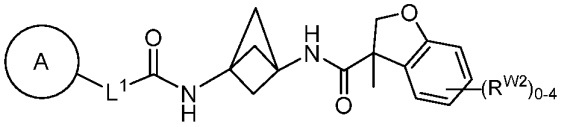
Formula (I-d-5)



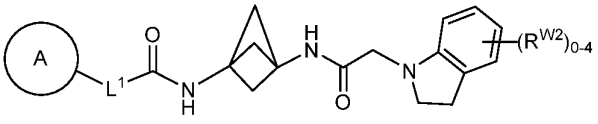
Formula (I-d-6)



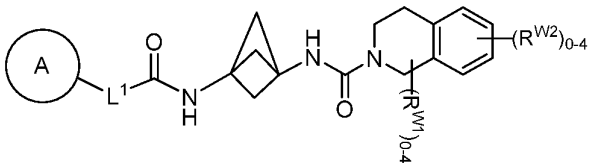
Formula (I-d-7)



Formula (I-d-8)



Formula (I-d-9)



Formula (I-d-10)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein each of A, L^1, R^{N3} R^{W1} and R^{W2} is defined as for Formula (I).

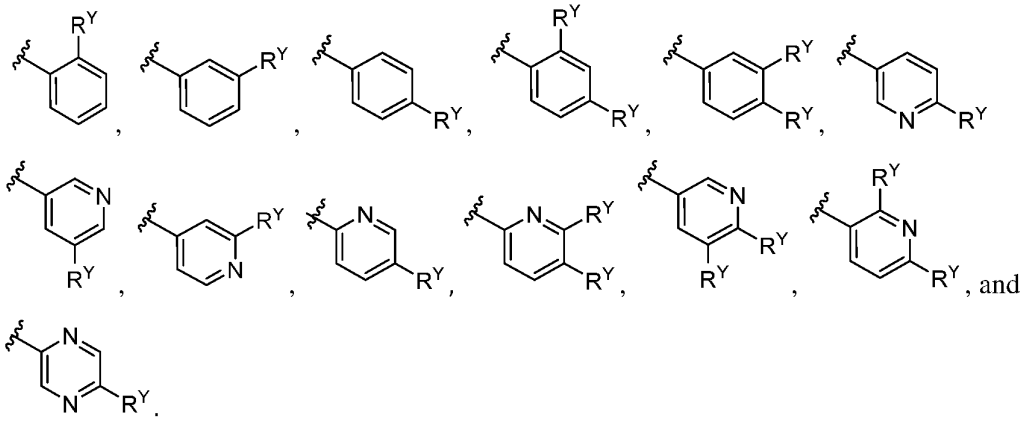
In some embodiments, L^1 is a bond, 2-7 membered heteroalkylene, $–NR^{N2}–$, or –O–, wherein 2-7 membered heteroalkylene is optionally substituted by 1-5 R^{L1}. In some embodiments, L^1 is a bond, 2-7 membered heteroalkylene, $–NR^{N2}–$, or –O–, wherein 2-7 membered heteroalkylene is substituted by 0 R^{L1}. In some embodiments, L^1 is selected from a bond, CH_2O–*, CH_2OCH_2–*, $–NCH_3–$, –NH–, or –O–, wherein "–*" indicates the attachment point to A.

In some embodiments, 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.

In some embodiments, R^{N3} is hydrogen or CH_3.

In some embodiments, A is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, or G^1. In some embodiments, A is phenyl, pyrazine, or pyridyl, each of which is optionally substituted with 1-2 R^Y groups.

In some embodiments, A is selected from the group consisting of:

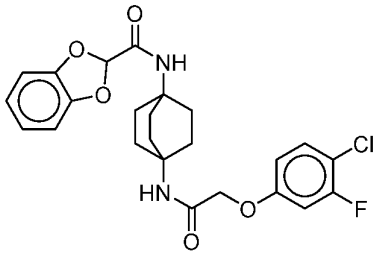
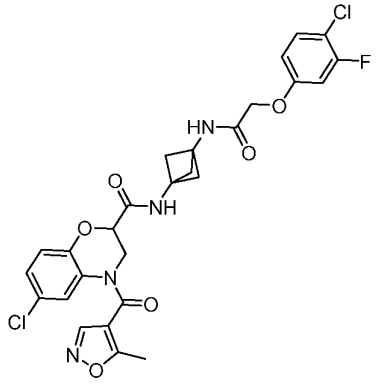
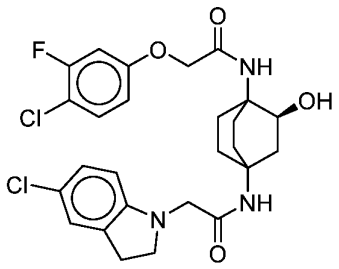
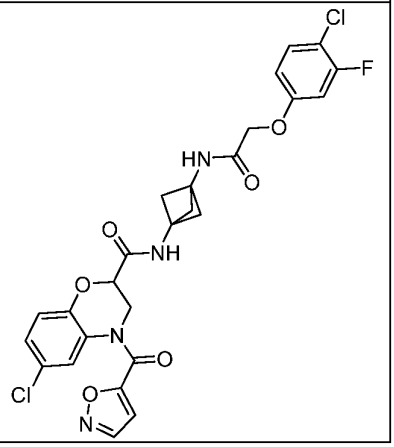


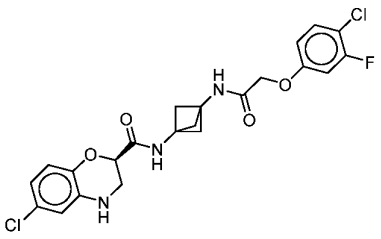
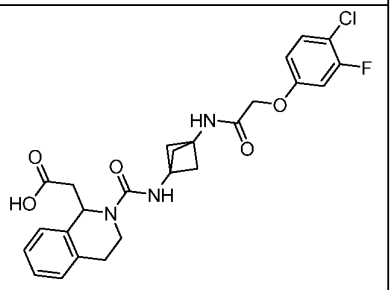
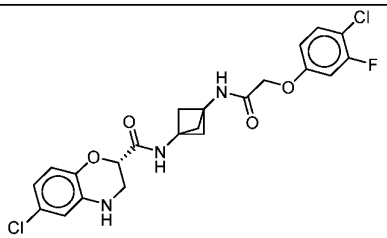
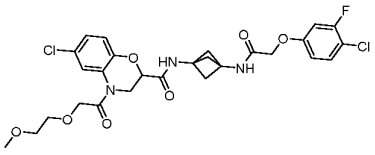
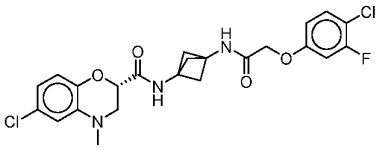
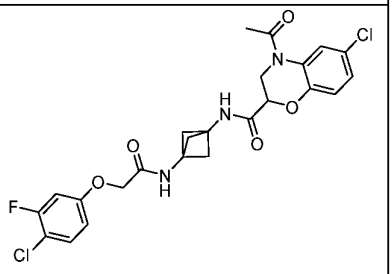
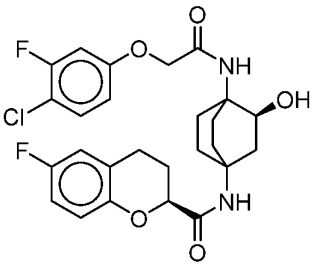
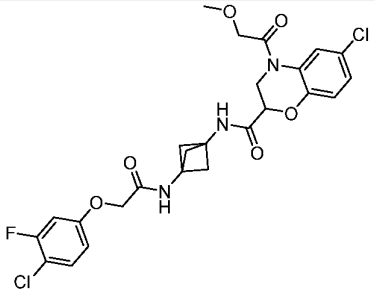
In some embodiments, each R^Y is independently selected from the group consisting of hydrogen, chloro, fluoro, CHF_2, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCHF_2$, OCF_3, OCH_2CF_3, $OCH(CH_3)_2$, and CN.

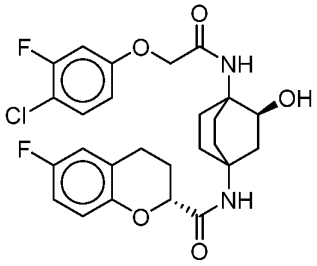
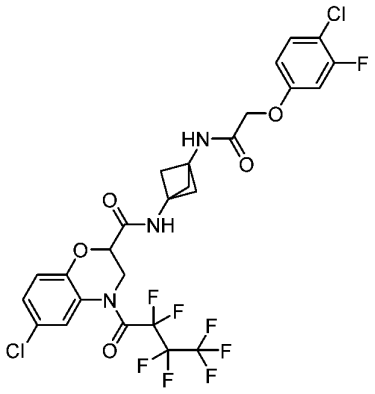
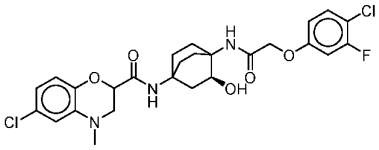
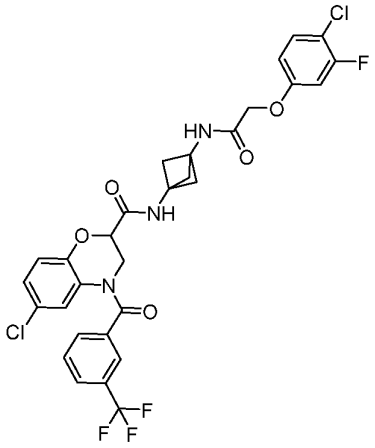
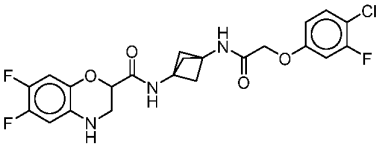
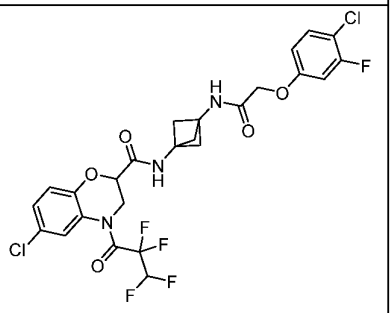
In some embodiments, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c-1), (I-c-2), (I-c-3), (I-c-4), (I-c-5), (I-c-6), (I-c-7), (I-c-8), (I-c-9), (I-c-10), (I-d-1), (I-d-2), (I-d-3), (I-d-4), (I-d-5), (I-d-6), (I-d-7), (I-d-8), (I-d-9) or (I-d-10)), or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

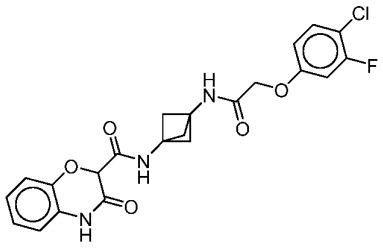
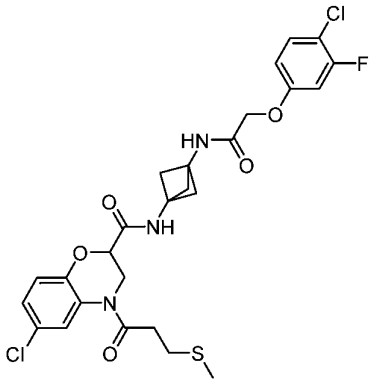
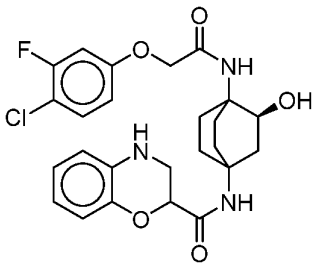
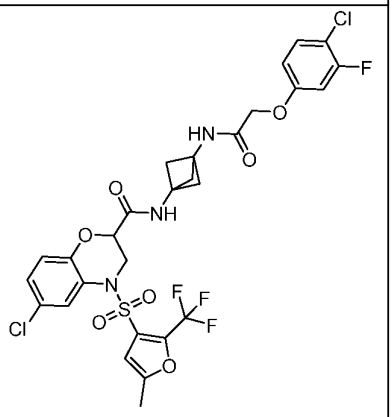
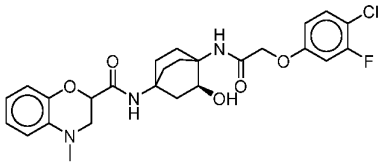
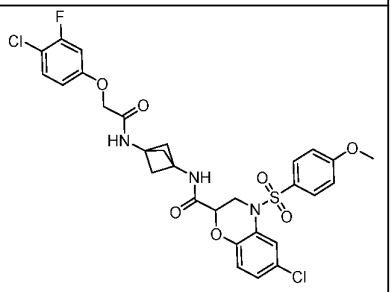
In some embodiments, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c-1), (I-c-2), (I-c-3), (I-c-4), (I-c-5), (I-c-6), (I-c-7), (I-c-8), (I-c-9), (I-c-10), (I-d-1), (I-d-2), (I-d-3), (I-d-4), (I-d-5), (I-d-6), (I-d-7), (I-d-8), (I-d-9) or (I-d-10)), is selected from a compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof.

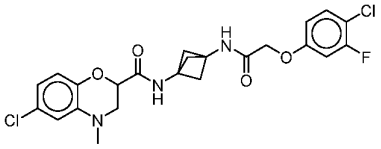
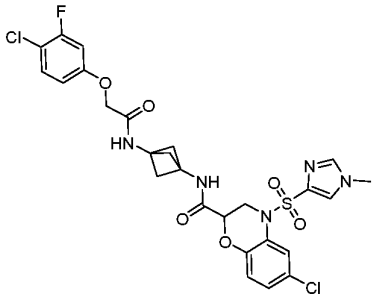
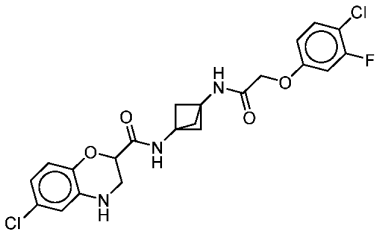
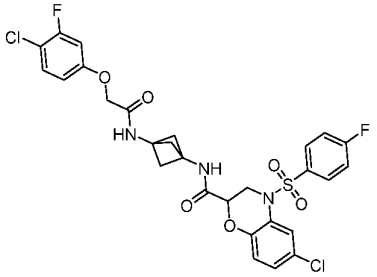
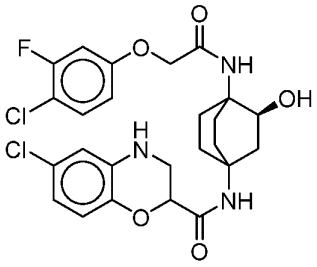
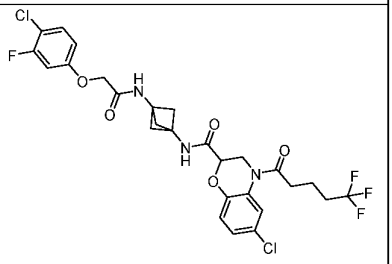
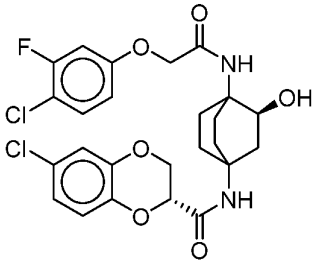
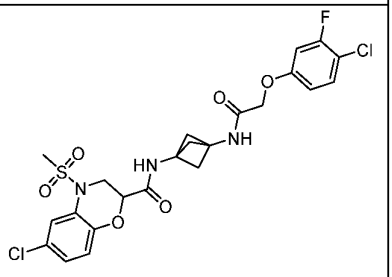
Table 1: Exemplary compounds of the invention

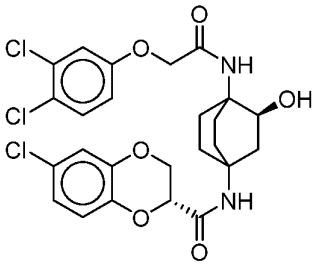
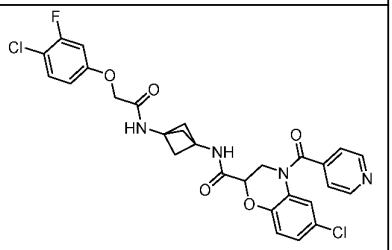
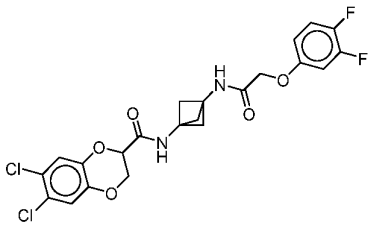
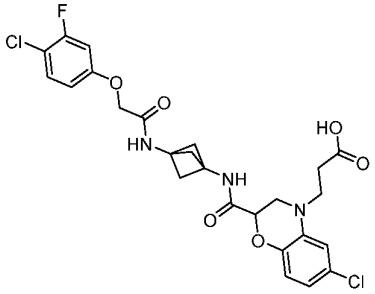
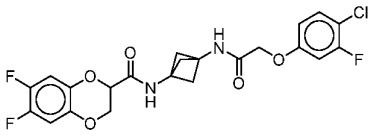
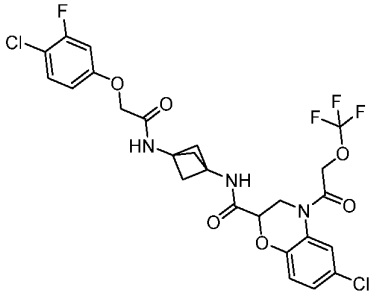
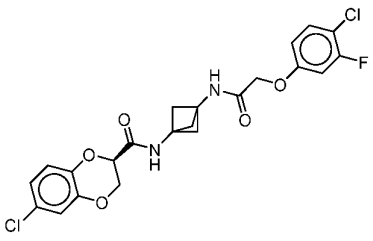
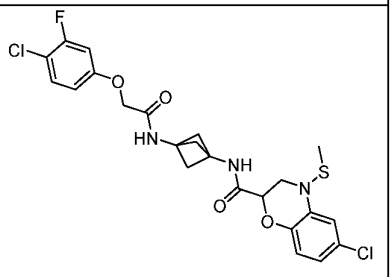
Compound Number	Structure	Compound Number	Structure
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101		**154**	

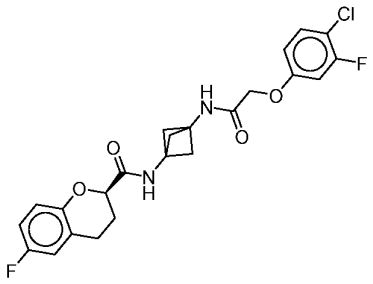
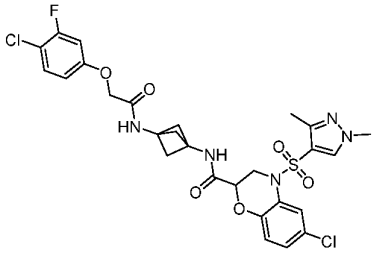
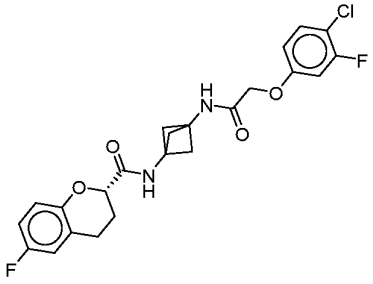
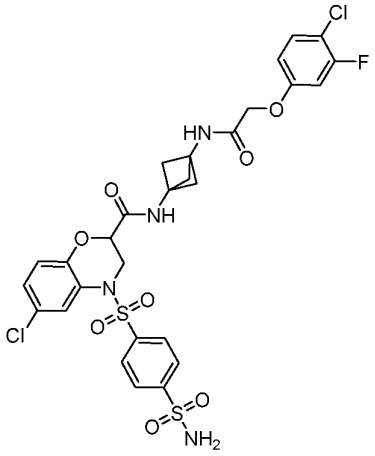
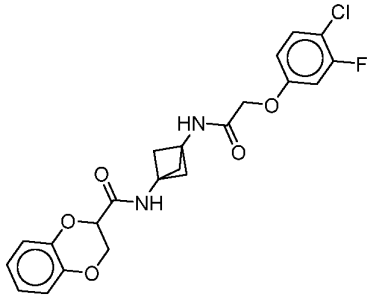
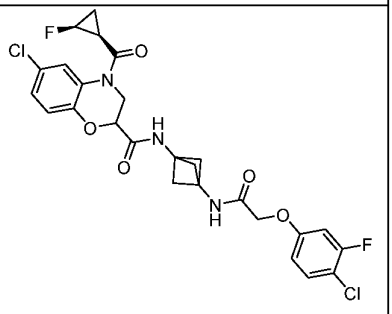
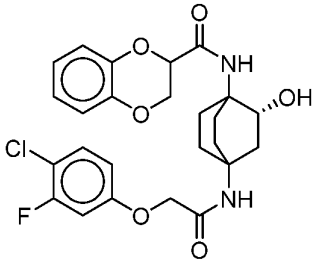
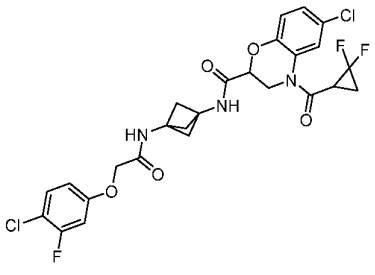
Compound Number	Structure	Compound Number	Structure
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103		**156**	
104		**157**	
105		**158**	

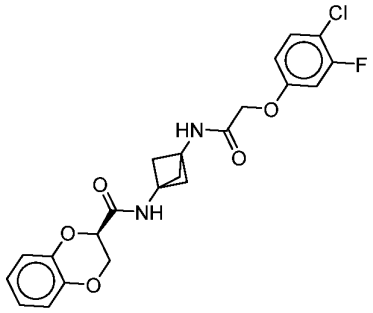
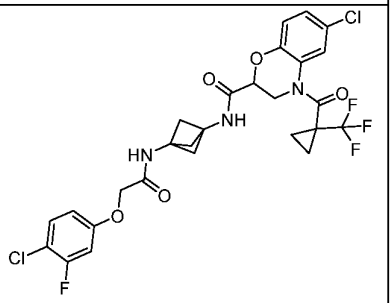
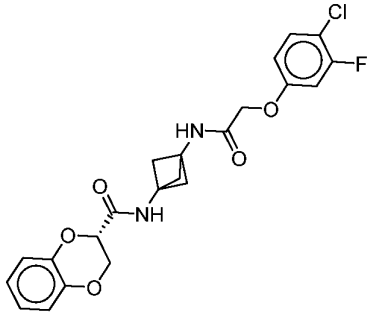
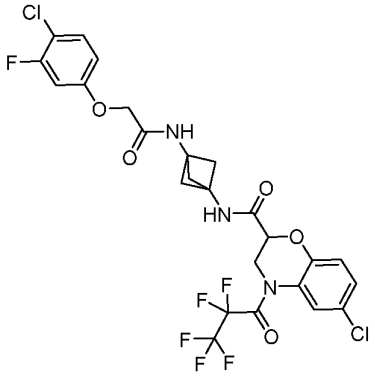
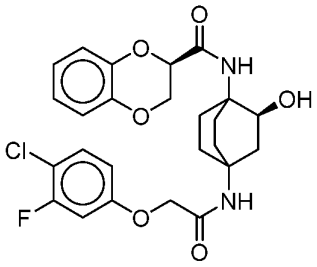
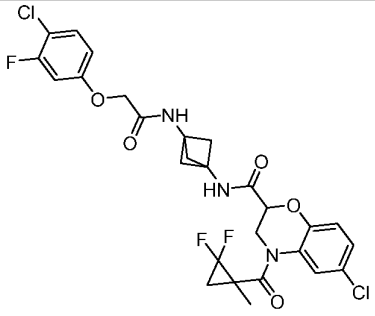
Compound Number	Structure	Compound Number	Structure
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107		**160**	
108		**161**	

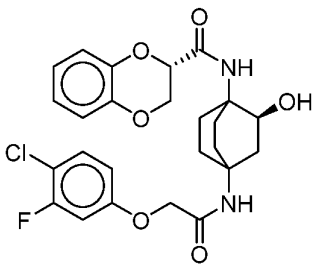
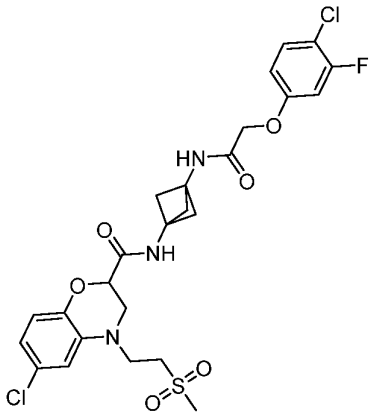
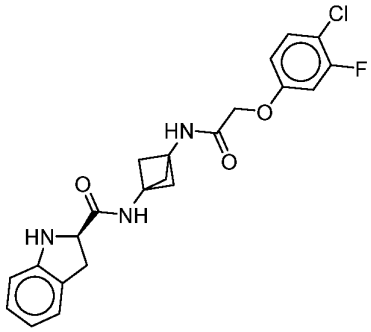
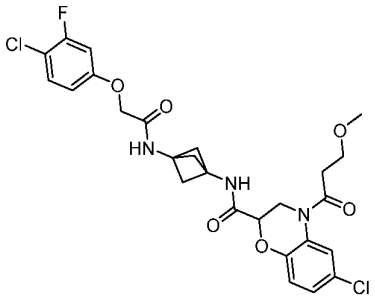
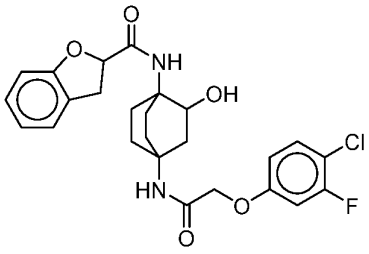
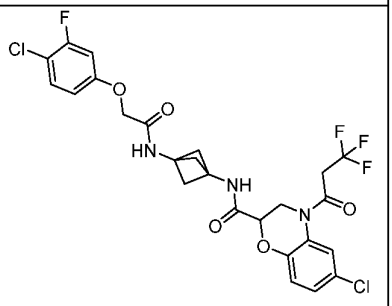
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110		163	
111		164	

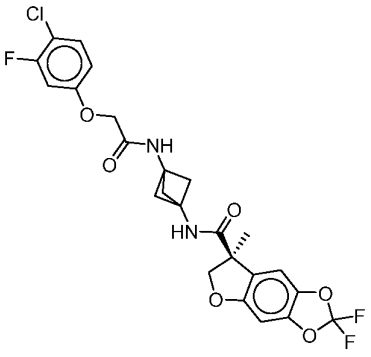
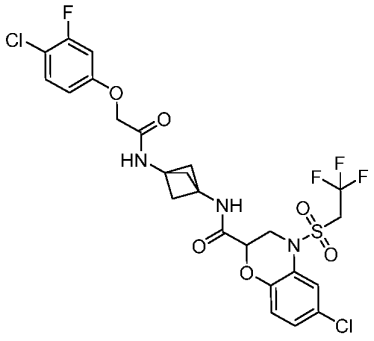
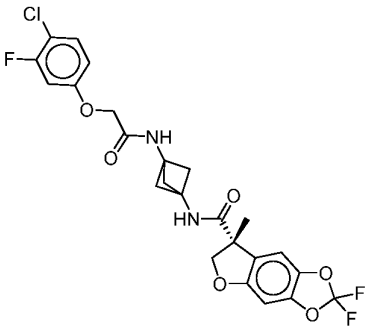
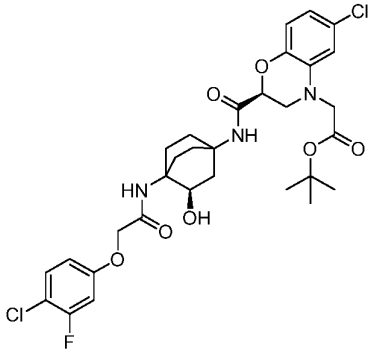
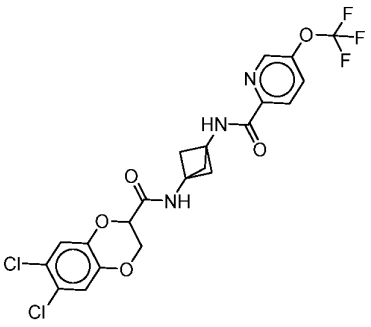
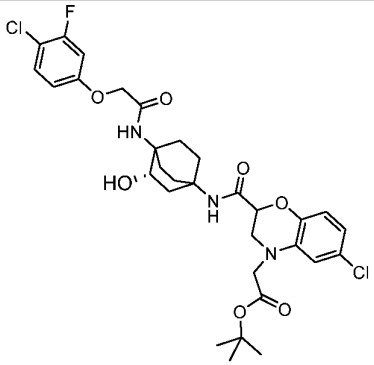
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113		166	
114		167	
115		168	

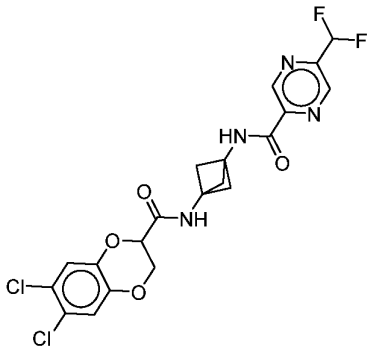
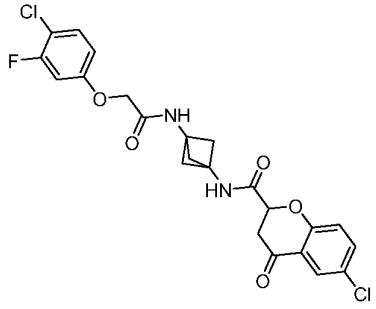
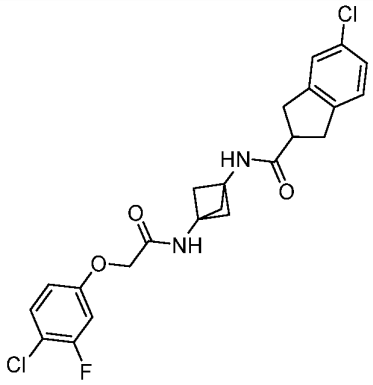
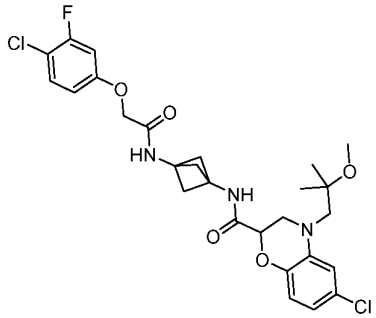
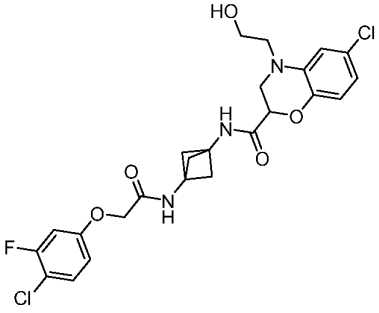
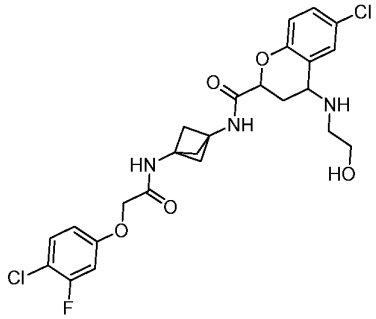
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117		170	
118		171	
119		172	

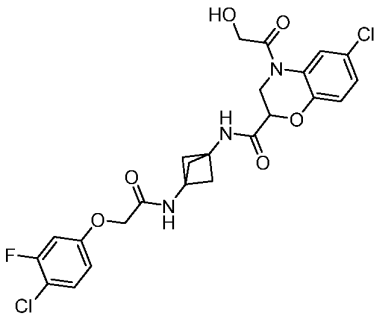
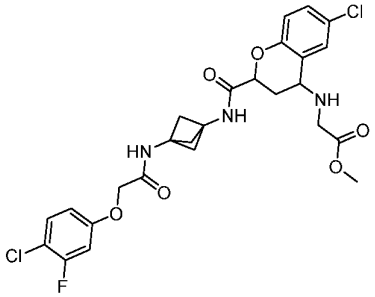
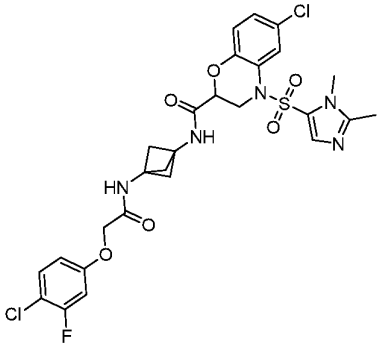
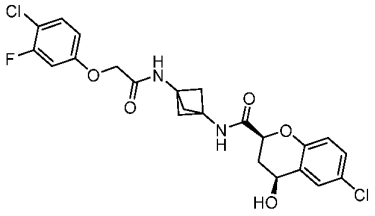
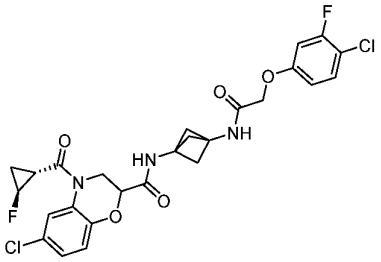
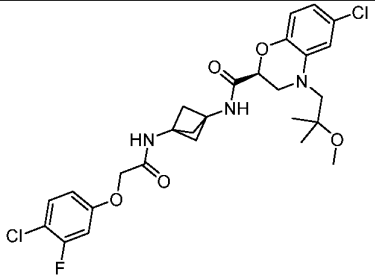
Compound Number	Structure	Compound Number	Structure
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122		175	
123		176	

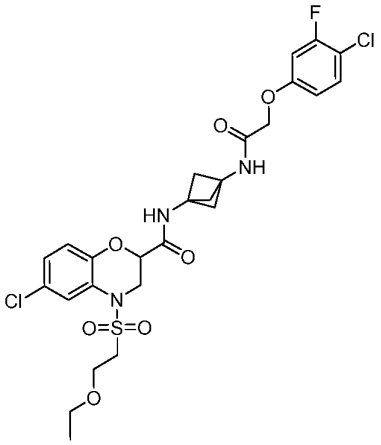
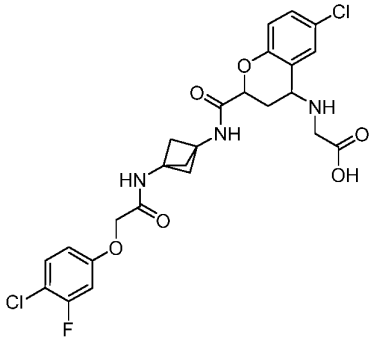
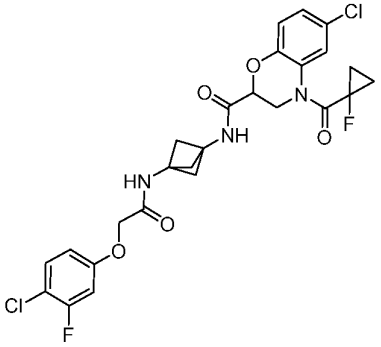
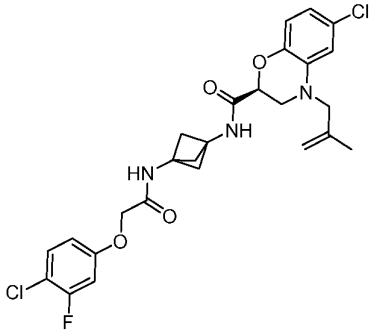
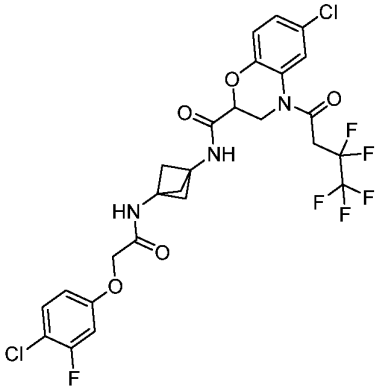
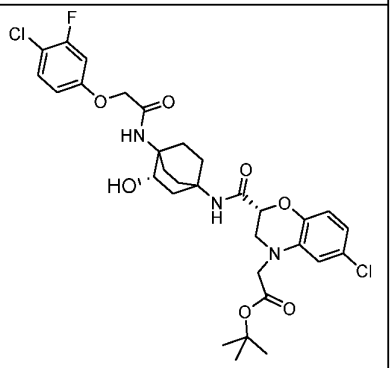
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125		**178**	
126		**179**	

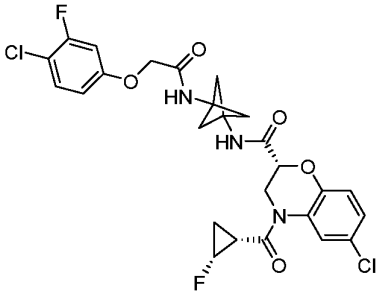
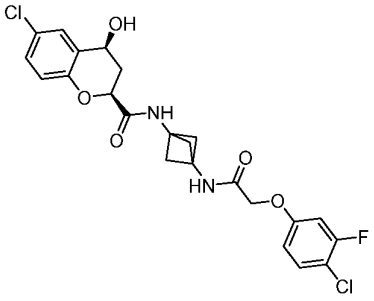
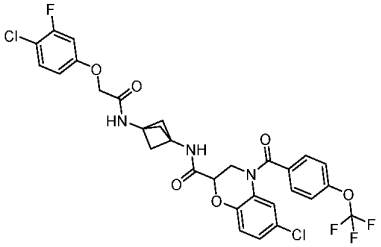
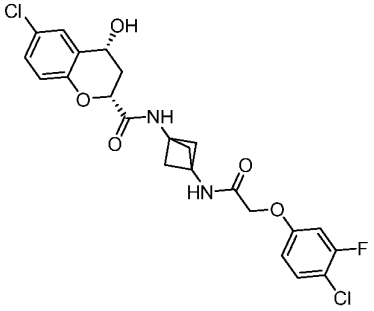
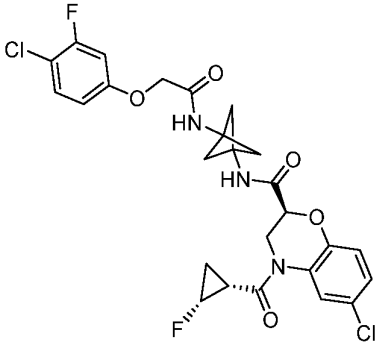
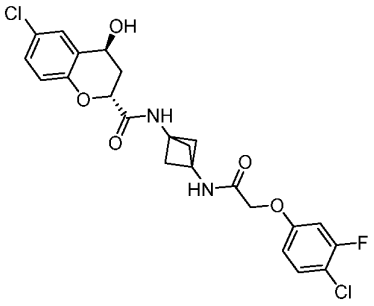
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127		**180**	
128		**181**	
129		**182**	

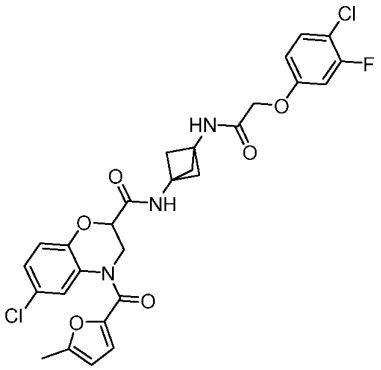
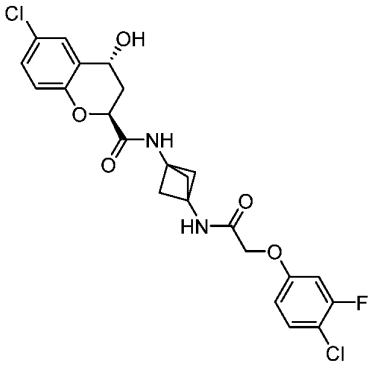
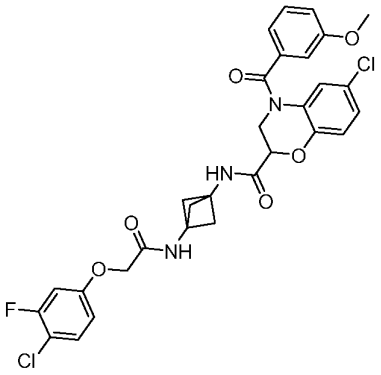
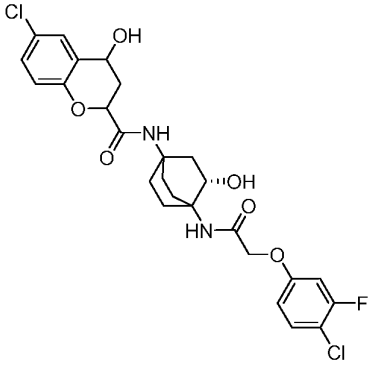
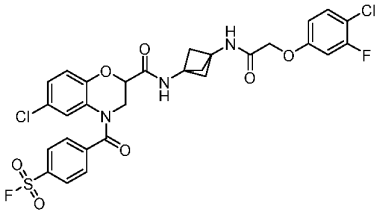
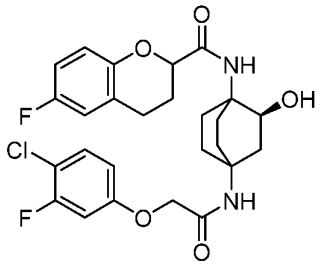
Compound Number	Structure	Compound Number	Structure
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131		184	
132		185	

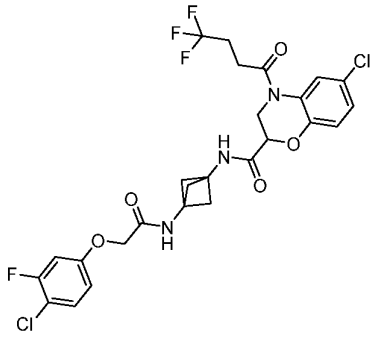
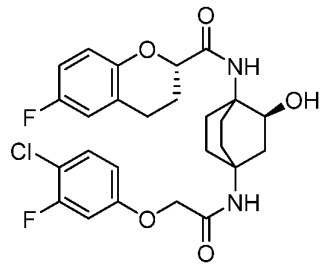
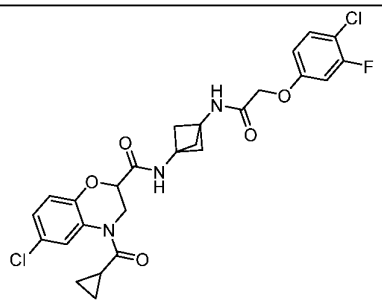
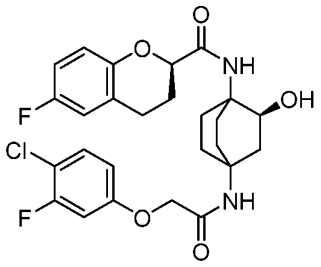
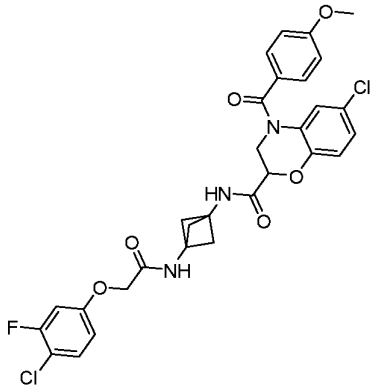
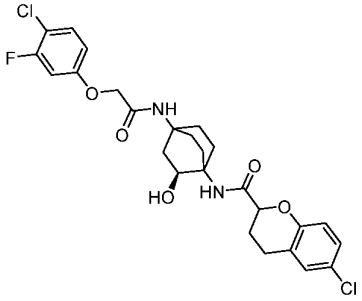
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133		186	
134		187	
135		188	

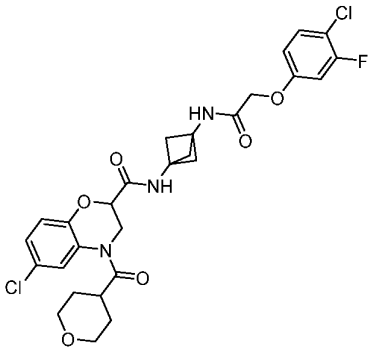
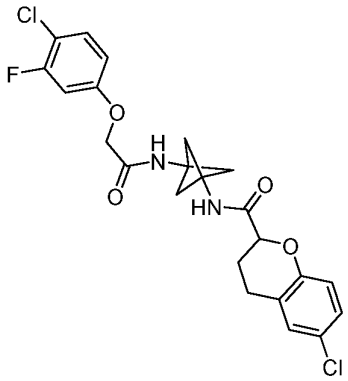
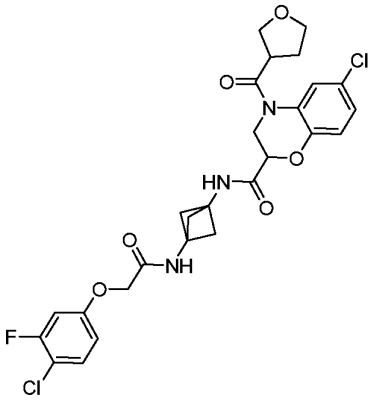
Compound Number	Structure	Compound Number	Structure
136		189	
137		190	
138		191	

Compound Number	Structure	Compound Number	Structure
139		192	
140		193	
141		194	

Compound Number	Structure	Compound Number	Structure
142		195	
143		196	
144		197	

Compound Number	Structure	Compound Number	Structure
145		198	
146		199	
147		200	

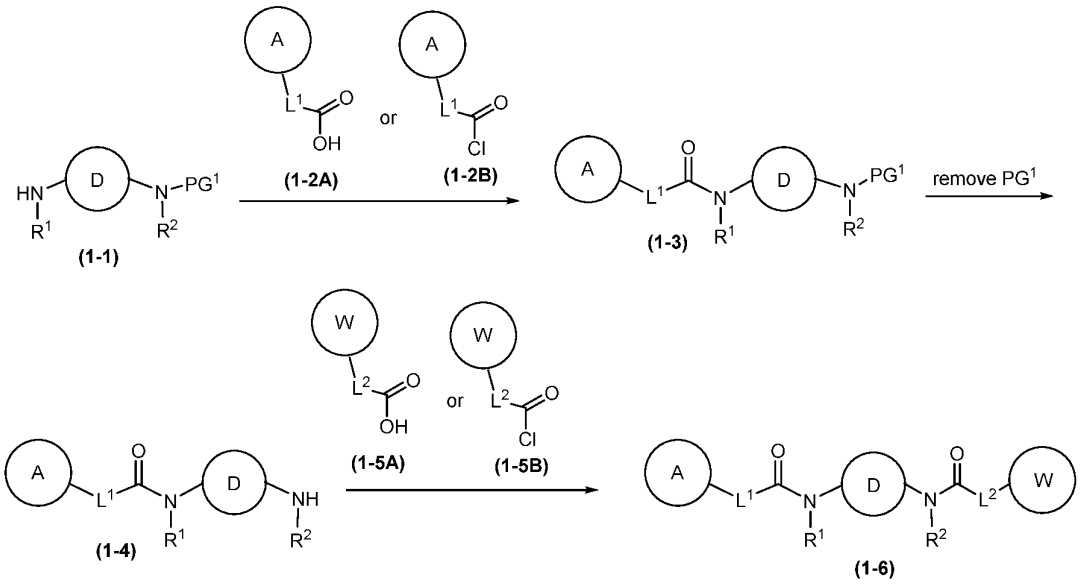
Compound Number	Structure	Compound Number	Structure
148		201	
149		202	
150		203	

Compound Number	Structure	Compound Number	Structure
151		204	
152			

Methods of Making Exemplary Compounds

The compounds of the invention may be better understood in connection with the following synthetic schemes and methods which illustrate a means by which the compounds can be prepared. The compounds of this invention can be prepared by a variety of synthetic procedures. Representative synthetic procedures are shown in, but not limited to, Schemes 1-7. The variables A, D, W, L^1, L^2, R^1, R^2, R^B, R^C, R^{W1}, R^{W2}, are defined as detailed herein, e.g., in the Summary.

Scheme 1: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 1, compounds of formula (1-6) can be prepared from compounds of formula (1-1). Compounds of formula (1-1) where PG^1 is an amine protecting group (e.g. *tert*-butoxycarbonyl or benzyloxycarbonyl) can be coupled with carboxylic acids of formula (1-2A) or alternatively with acid chlorides of formula (1-2B) under amide bond forming conditions to give amides of formula (1-3). Examples of conditions known to generate amides from a mixture of a carboxylic acid of formula (1-2A) and an amine of formula (1-1) include but are not limited to adding a coupling reagent such as *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC, EDAC or EDCI), 1,3-dicyclohexylcarbodiimide (DCC), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide or 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate or 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate or 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) or 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (HBTU), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P®), (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU®),

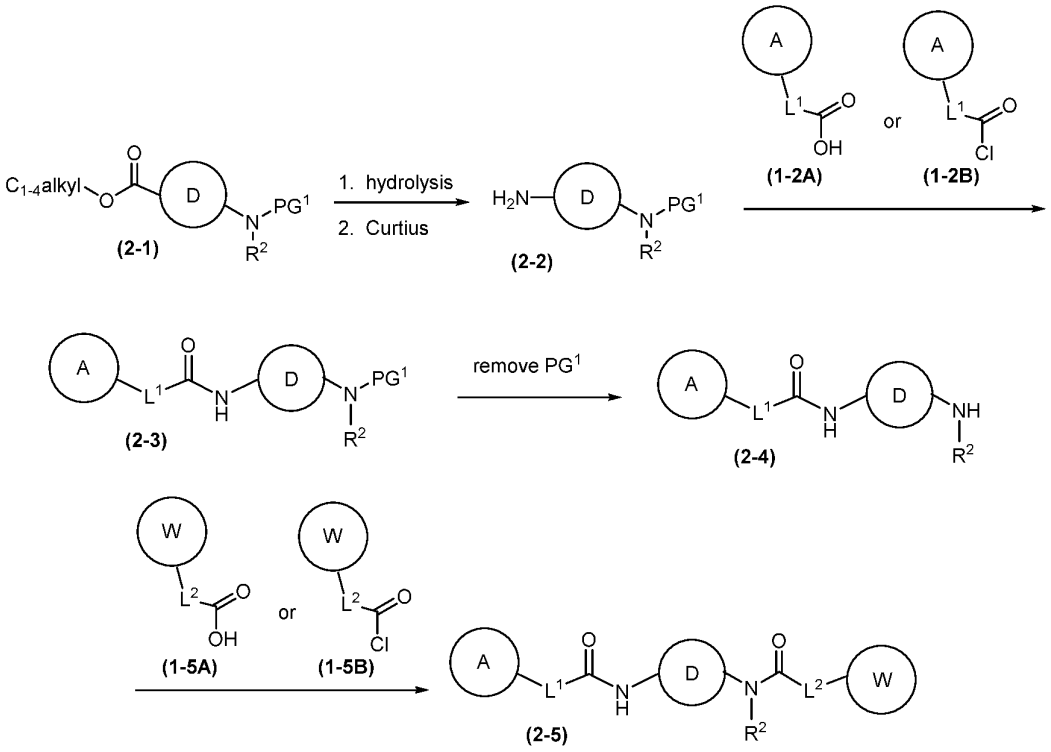
and fluoro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate**.** The coupling reagents may be added as a solid, a solution, or as the reagent bound to a solid support resin.

In addition to the coupling reagents, auxiliary-coupling reagents may facilitate the coupling reaction. Auxiliary coupling reagents that are often used in the coupling reactions include but are not limited to 4-(dimethylamino)pyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAT) and 1-hydroxybenzotriazole (HOBT). The reaction may be carried out optionally in the presence of a base such as triethylamine or diisopropylethylamine. The coupling reaction may be carried out in solvents such as but not limited to tetrahydrofuran, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, dimethyl sulfoxide, dichloromethane, and ethyl acetate.

Alternatively, carboxylic acids of formula (1-2A) can be converted to the corresponding acid chlorides of formula (1-2B) by reaction with thionyl chloride, PCl_3, PCl_5, cyanuric chloride, Ghosez's reagent or oxalyl chloride. The reactions with thionyl chloride and oxalyl chloride can be catalyzed with *N*,*N*-dimethylformamide at ambient temperature in a solvent such as dichloromethane. The resultant acid chlorides of formula (1-2B) can then be coupled with amines of formula (1-1) optionally in the presence of a base such as a tertiary amine base such as triethylamine or diisopropylethylamine or an aromatic base such as pyridine, at room temperature in a solvent such as dichloromethane to give amides of formula (1-3).

Compounds of formula (1-3) can be deprotected using conditions known to one of skill in the art and dependent upon the protecting group (PG^1) used to give compounds of formula (1-4). Compounds of formula (1-4) can be coupled with carboxylic acids of formula (1-5A) or alternatively acid chlorides of formula (1-5B) under amide bond forming conditions as discussed above to afford compounds of formula (1-6). Compounds of formula (1-6) are representative compounds of Formula (I).

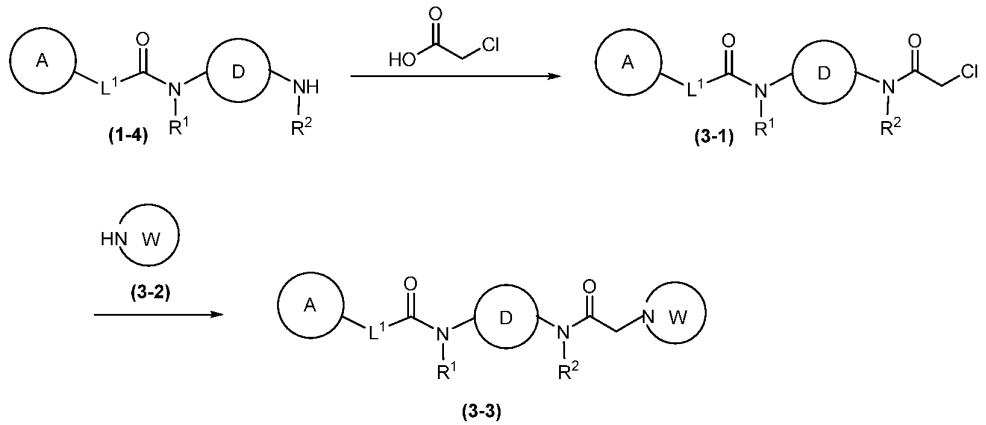
Scheme 2: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 2, compounds of formula (2-5) can be prepared from compounds of formula (2-1). Compounds of formula (2-1) where PG^1 is an amine protecting group (e.g. benzyl, *tert*-butoxycarbonyl or benzyloxycarbonyl) can be converted to compounds of formula (2-2) in a two-step procedure. In the first step, esters of formula (2-1) can be hydrolyzed to the corresponding carboxylic acids using conditions known to one of skill in the art. In the second step, the carboxylic acids can be treated under Curtius reaction conditions to afford compounds of formula (2-2). Primary amines of formula (2-2) can be coupled with carboxylic acids of formula (1-2A) or alternatively acid chlorides of formula (1-2B) under amide bond forming conditions as disclosed for Scheme 1 to give amides of formula (2-3).

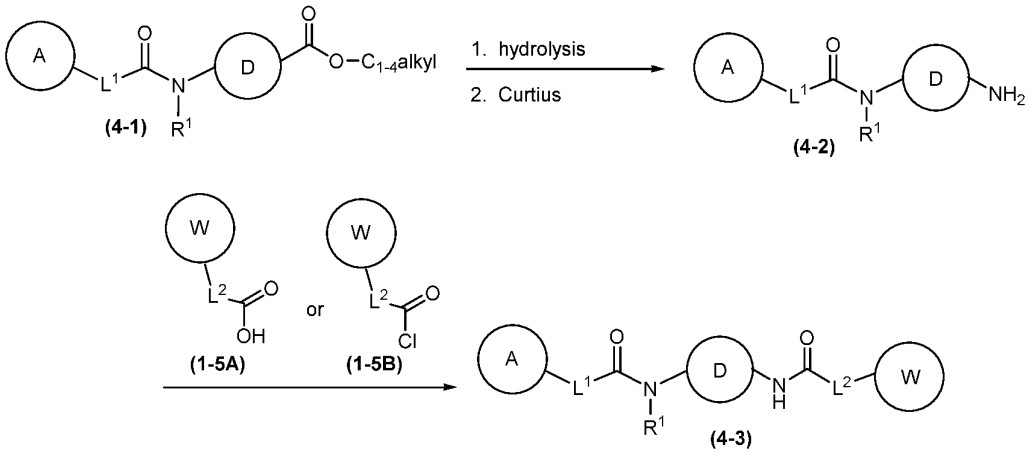
Compounds of formula (2-3) can be deprotected using conditions known to one of skill in the art and dependent upon the protecting group (PG^1) used to give compounds of formula (2-4). Compounds of formula (2-4) can be coupled with carboxylic acids of formula (1-5A) or alternatively acid chlorides of formula (1-5B) under amide bond forming conditions as disclosed for Scheme 1 to afford compounds of formula (2-5). Compounds of formula (2-5) are representative compounds of Formula (I).

Scheme 3: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 3, compounds of formula (3-3) can be prepared from compounds of formula (1-4). Compounds of formula (1-4) can be coupled with 2-chloroacetic acid under the amide bond forming reaction conditions disclosed in Scheme 1 to give compounds of formula (3-1). Compounds of formula (3-1) can be converted to compounds of formula (3-3) under nucleophilic substitution reactions conditions. Compounds of formula (3-1) can be treated with cyclic amines of formula (3-2) in the presence of a base such as potassium carbonate and an activating agent such as potassium iodide with microwave irradiation to afford compounds of formula (3-3). Compounds of formula (3-3) are representative of compounds of formula (I).

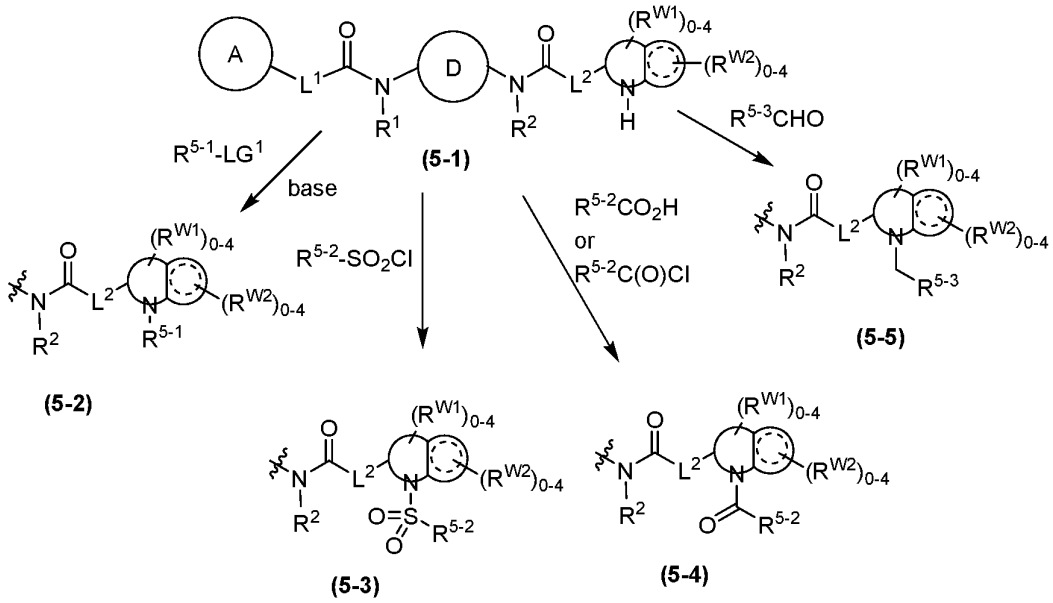
Scheme 4: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 4, compounds of formula (4-3) can be prepared from compounds of formula (4-1). Compounds of formula (4-1) can be converted to compounds of formula (4-2) in a two-step procedure. In the first step, esters of formula (4-1) can be hydrolyzed to the corresponding carboxylic acids using conditions known to one of skill in the art. In the second

step, the carboxylic acids can be treated under Curtius reaction conditions to afford compounds of formula (4-2). Primary amines of formula (4-2) can be coupled with carboxylic acids of formula (1-5A) or alternatively acid chlorides of formula (1-5B) under amide bond forming conditions as disclosed for Scheme 1 to give amides of formula (4-3). Compounds of formula (4-3) are representative compounds of Formula (I).

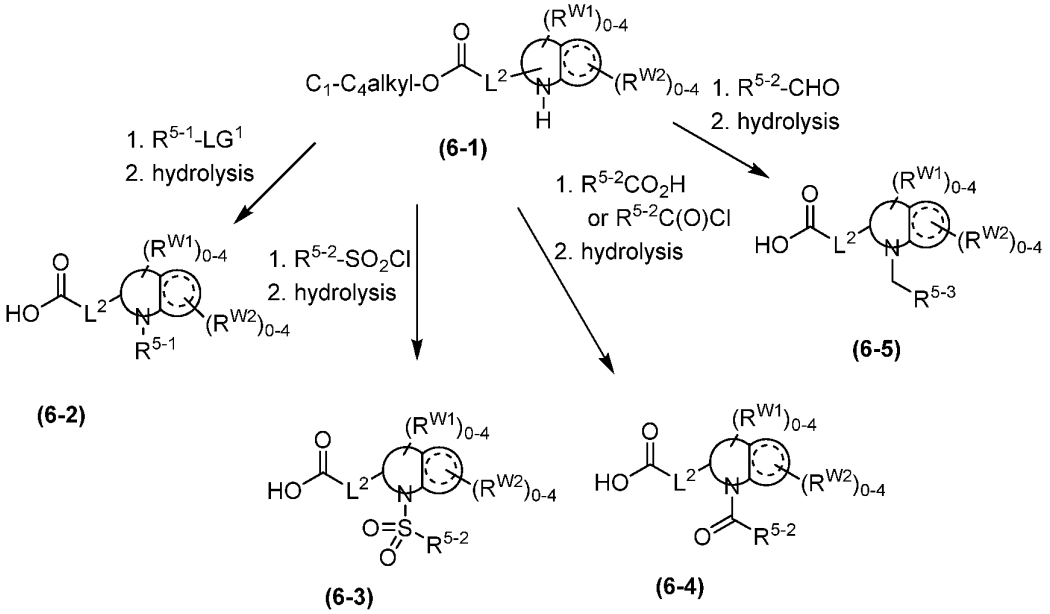
Scheme 5: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 5, compounds of formula (5-2), formula (5-3), formula (5-4) and formula (5-5) can be prepared from compounds of formula (5-1), wherein the fused bicyclic heterocyclyl of formula (5-1) has a substitutable nitrogen moiety. The substitutable nitrogen moiety may be alkylated with an alkylating agent, R^{5-1}-LG^1, wherein LG^1 is a halogen or sulfonate and R^{5-1} is an optionally substituted alkyl or haloalkyl, in the presence of a base such as potassium carbonate optionally warmed in a solvent such as but not limited to *N*,*N*-dimethylformamide to give compounds of formula (5-2). Compounds of formula (5-1) can be sulfonylated with sulfonyl chlorides, R^{5-2}-SO_2Cl, wherein R^{5-2} is an optionally substituted C_1-C_6 alkyl, C_1-C_6 cycloalkyl, phenyl, heterocyclyl or heteroaryl, in the presence of a base such as pyridine or a tertiary amine base in an optionally warmed solvent such as dichloromethane to give sulfonamides of formula (5-3). Compounds of formula (5-1) can be reacted with carboxylic acids, R^{5-2}-CO_2H, or carboxylic acid chlorides, R^{5-2}-C(O)Cl, under the conditions described in Scheme 1 to form amides to give amides of formula (5-4). Compounds of formula (5-1) can be reductively aminated under conditions known to one of skill in the art with aldehydes, R^{5-3}-CHO,

wherein R^{5-3} is an optionally substituted C_1-C_6 alkyl, to give compounds of formula (5-5). Compounds of formula (5-2), formula (5-3), formula (5-4) and formula (5-5) can be further transformed using methodologies known to one of skill in the art. Compounds of formula (5-2), formula (5-3), formula (5-4) and formula (5-5) are representative of compounds of Formula (I).

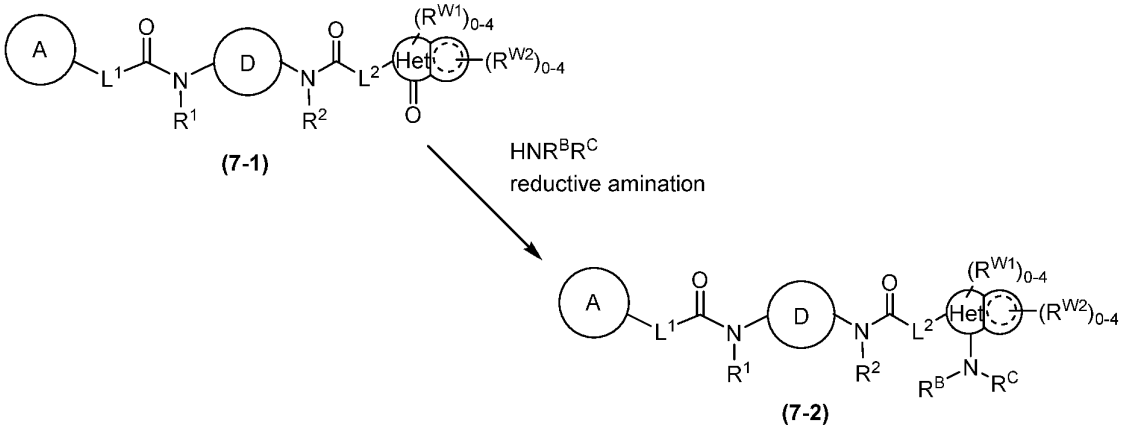
Scheme 6: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 6, compounds of formula (6-2), formula (6-3), formula (6-4) and formula (6-5) can be prepared from compounds of formula (6-1), wherein the fused bicyclic heterocyclyl of formula (6-1) has a substitutable nitrogen moiety. The substitutable nitrogen moiety may be alkylated with an alkylating agent, R^{5-1}-LG^1, wherein LG^1 is a halogen or sulfonate and R^{5-1} is an optionally substituted alkyl or haloalkyl, in the presence of a base such as potassium carbonate optionally warmed in a solvent such as but not limited to *N*,*N*-dimethylformamide. Subsequent hydrolysis of the ester moiety using methodologies known to one of skill in the art gives compounds of formula (6-2). R^{5-1} , R^{5-2}, and R^{5-3} are as described in Scheme 5. Compounds of formula (6-1) can be sulfonylated with sulfonyl chlorides, R^{5-2}-SO_2Cl, in the presence of a base such as pyridine or a tertiary amine base in an optionally warmed solvent such as dichloromethane. Subsequent ester hydrolysis gives sulfonamides of formula (6-3). Compounds of formula (6-1) can be reacted with carboxylic acids, R^{5-2}-CO_2H, or carboxylic acid chlorides, R^{5-2}-C(O)Cl, under the conditions described in Scheme 1 to form amides. Subsequent ester hydrolysis gives amides of formula (6-4). Compounds of formula (6-1) can be reductively aminated under conditions known to one of skill in the art with aldehydes, R^{5-3}-CHO.

Subsequent ester hydrolysis gives compounds of formula (6-5). Compounds of formula (6-2), formula (6-3), formula (6-4) and formula (6-5) can be further transformed using methodologies known to one of skill in the art. Compounds of formula (6-2), formula (6-3), formula (6-4) and formula (6-5) can be used as compounds of formula (1-5A) as shown in Schemes 1, 2, and 4.

Scheme 7: Representative scheme for synthesis of exemplary compounds of the invention.



As shown in Scheme 7, compounds of formula (7-2) can be prepared from compounds of formula (7-1) with a reductive amination with HNR^BR^C. Accordingly, compounds of formula (7-1), wherein an oxo group is a substituent on the heterocyclyl portion of W, can be reacted with an amine, HNR^BR^C, under reductive amination conditions. Such conditions can be but are not limited to combining compounds of formula (7-1) and HNR^BR^C in a solvent such as methanol in the presence of an acid such as zinc chloride with subsequent treatment with a reductant such as sodium cyanoborohydride to give compounds of formula (7-2). Compounds of formula (7-2) are representative of compounds of Formula (I).

Pharmaceutical Compositions

The present invention features pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof . In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof is provided in an effective amount in the pharmaceutical composition. In some embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of Formula (I) (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit. Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of a compound of Formula (I), the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) of a compound of Formula (I).

The term "pharmaceutically acceptable excipient" refers to a non-toxic carrier, adjuvant, diluent, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention are any of those that are well known in the art of pharmaceutical formulation and include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Compositions of the present invention may be administered orally, parenterally (including subcutaneous, intramuscular, intravenous and intradermal), by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some

embodiments, provided compounds or compositions are administrable intravenously and/or orally.

The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraocular, intravitreal, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intraperitoneal intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, subcutaneously, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. In some embodiments, a provided oral formulation is formulated for immediate release or sustained/delayed release. In some embodiments, the composition is suitable for buccal or sublingual administration, including tablets, lozenges and pastilles. A compound of Formula (I) may also be in micro-encapsulated form.

The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components

are discussed in greater detail in U.S. Patent Nos. 4,911,920; 5,403,841; 5,212, 162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. *Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., *Gao Pharm. Res.*12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. *Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, J. *Hosp. Pharm.* 46: 1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

In some embodiments, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable

for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

Compounds provided herein, e.g., a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof are typically formulated in dosage unit form, e.g., single unit dosage form, for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

In certain embodiments, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof for administration one or more times a day may comprise about 0.0001 mg to about 5000 mg, e.g., from about 0.0001 mg to about 4000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

In certain embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof may be at dosage levels

sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, e.g., about 0.001 mg/kg to about 500 mg/kg, about 0.01 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50 mg/kg, about 0.1 mg/kg to about 40 mg/kg, about 0.1 mg/kg to about 25 mg/kg, about 0.01 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 10 mg/kg, or about 1 mg/kg to about 50 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

It will be also appreciated that a compound or composition, e.g., a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof as described herein, can be administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents,

immunosuppressant agents, and pain-relieving agents. Pharmaceutical agents include small organic molecules such as drug compounds (e.g., compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

Pharmaceutical compositions provided by the present invention include compositions wherein the active ingredient (e.g., compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, inter alia, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule (e.g. eIF2B, eIF2 or component of eIF2α signal transduction pathway or component of phosphorylated eIF2α pathway or the ISR pathway), and/or reducing, eliminating, or slowing the progression of disease symptoms (e.g. symptoms of cancer a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α or a component of the eIF2 pathway or ISR pathway). Determination of a therapeutically effective amount of a compound of the invention is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g. a symptom of cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B, eIF2 α, or a component of the eIF2 pathway or ISR pathway), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active

compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a disease (*e.g.*, cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or other disease or condition described herein).

The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive

pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

Thus, in one aspect, provided are kits including a first container comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof , or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a proliferative disease in a subject. In certain embodiments, the kits further include instructions for administering a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof , or a pharmaceutical composition thereof, to a subject to prevent and/or treat a disease described herein.

Methods of Treatment

The present invention features compounds, compositions, and methods comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof. In some embodiments, the compounds, compositions, and methods are used in the prevention or treatment of a disease, disorder, or condition. Exemplary diseases, disorders, or conditions include, but are not limited to a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a disease with mutations that leads to UPR induction, a malaria infection, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease.

In some embodiments, the disease, disorder, or condition is related to (e.g., caused by) modulation of (e.g., a decrease in) eIF2B activity or level, eIF2α activity or level, or a component of the eIF2 pathway or ISR pathway. In some embodiments, the disease, disorder, or condition is related to modulation of a signaling pathway related to a component of the eIF2 pathway or ISR pathway (e.g., phosphorylation of a component of the eIF2 pathway or ISR pathway). In some embodiments, the disease, disorder, or condition is related to (e.g., caused by) neurodegeneration. In some embodiments, the disease, disorder, or condition is related to (e.g., caused by) neural cell death or dysfunction. In some embodiments, the disease, disorder, or condition is related to (e.g., caused by) glial cell death or dysfunction. In some embodiments, the disease, disorder, or condition is related to (e.g., caused by) an increase in the level or activity of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway. In some embodiments, the

disease, disorder, or condition is related to (e.g., caused by) a decrease in the level or activity of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway.

In some embodiments, the disease may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway (e.g., eIF2B, eIF2α, or other component). Exemplary mutations include an amino acid mutation in the eIF2B1, eIF2B2, eIF2B3, eIF2B4, eIF2B5 subunits. In some embodiments, an amino acid mutation (e.g., an amino acid substitution, addition, or deletion) in a particular protein that may result in a structural change, e.g., a conformational or steric change, that affects the function of the protein. For example, in some embodiments, amino acids in and around the active site or close to a binding site (e.g., a phosphorylation site, small molecule binding site, or protein-binding site) may be mutated such that the activity of the protein is impacted. In some instances, the amino acid mutation (e.g., an amino acid substitution, addition, or deletion) may be conservative and may not substantially impact the structure or function of a protein. For example, in certain cases, the substitution of a serine residue with a threonine residue may not significantly impact the function of a protein. In other cases, the amino acid mutation may be more dramatic, such as the substitution of a charged amino acid (e.g., aspartic acid or lysine) with a large, nonpolar amino acid (e.g., phenylalanine or tryptophan) and therefore may have a substantial impact on protein function. The nature of the mutations that affect the structure of function of a gene or protein may be readily identified using standard sequencing techniques, e.g., deep sequencing techniques that are well known in the art. In some embodiments, a mutation in a member of the eIF2 pathway may affect binding or activity of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof and thereby modulate treatment of a particular disease, disorder, or condition, or a symptom thereof.

In some embodiments, an eIF2 protein may comprise an amino acid mutation (e.g., an amino acid substitution, addition, or deletion) at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue. In some embodiments, an eIF2 protein may comprise an amino acid substitution at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue. In some embodiments, an eIF2 protein may comprise an amino acid addition at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue. In some embodiments, an eIF2 protein may comprise an

amino acid deletion at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue.

In some embodiments, the eIF2 protein may comprise an amino acid mutation (e.g., an amino acid substitution, addition, or deletion) at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue in the eIF2B1, eIF2B2, eIF2B3, eIF2B4, eIF2B5 subunits. In some embodiments, the eIF2 protein may comprise an amino acid substitution at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue in the eIF2B1, eIF2B2, eIF2B3, eIF2B4, eIF2B5 subunits. In some embodiments, the eIF2 protein may comprise an amino acid addition at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue in the eIF2B1, eIF2B2, eIF2B3, eIF2B4, eIF2B5 subunits. In some embodiments, the eIF2 protein may comprise an amino acid deletion at an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine residue in the eIF2B1, eIF2B2, eIF2B3, eIF2B4, eIF2B5 subunits. Exemplary mutations include V183F (eIF2B1 subunit), H341Q (eIF2B3), I346T (eIF2B3), R483W (eIF2B4), R113H (eIF2B5), and R195H (eIF2B5).

In some embodiments, an amino acid mutation (e.g., an amino acid substitution, addition, or deletion) in a member of the eIF2 pathway (e.g., an eIF2B protein subunit) may affect binding or activity of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof and thereby modulate treatment of a particular disease, disorder, or condition, or a symptom thereof.

Neurodegenerative Disease

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a neurodegenerative disease. As used herein, the term "neurodegenerative disease" refers to a disease or condition in which the function of a subject's nervous system becomes impaired. Examples of a neurodegenerative disease that may be treated with a compound, pharmaceutical

composition, or method described herein include Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Dystonia, frontotemporal dementia (FTD), Gerstmann-Straussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe disease, kuru, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple system atrophy, Multisystem proteinopathy, Narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoff disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics, e.g., Spinocerebellar ataxia type 2 or Spinocerebellar ataxia type 8), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, progressive supranuclear palsy, corticobasal degeneration, adrenoleukodystrophy, X-linked adrenoleukodystrophy, cerebral adrenoleukodystrophy, Pelizaeus-Merzbacher Disease, Krabbe disease, leukodystrophy due to mutation in DARS2 gene (sometimes known as lukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), DARS2-related spectrum disorders, or Tabes dorsalis.

In some embodiments, the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo-myelination, a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome (e.g., Fragile X syndrome), Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease, frontotemporal dementia (FTD), Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia (e.g., HIV-associated dementia or Lewy body dementia), kuru, multiple sclerosis, Parkinson's disease, or a prion disease.

In some embodiments, the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo-myelination, a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, or an intellectual disability syndrome (e.g., Fragile X syndrome).

In some embodiments, the neurodegenerative disease comprises a psychiatric disease such as agoraphobia, Alzheimer’s disease, anorexia nervosa, amnesia, anxiety disorder, attention deficit disorder, bipolar disorder, body dysmorphic disorder, bulimia nervosa, claustrophobia, depression, delusions, Diogenes syndrome, dyspraxia, insomnia, Munchausen’s syndrome, narcolepsy, narcissistic personality disorder, obsessive-compulsive disorder, psychosis, phobic

disorder, schizophrenia, seasonal affective disorder, schizoid personality disorder, sleepwalking, social phobia, substance abuse, tardive dyskinesia, Tourette syndrome, or trichotillomania.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat vanishing white matter disease. Exemplary methods of treating vanishing white matter disease include, but are not limited to, reducing or eliminating a symptom of vanishing white matter disease, reducing the loss of white matter, reducing the loss of myelin, increasing the amount of myelin, or increasing the amount of white matter in a subject.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat childhood ataxia with CNS hypo-myelination. Exemplary methods of treating childhood ataxia with CNS hypo-myelination include, but are not limited to, reducing or eliminating a symptom of childhood ataxia with CNS hypo-myelination, increasing the level of myelin, or decreasing the loss of myelin in a subject.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an intellectual disability syndrome (e.g., Fragile X syndrome). Exemplary methods of treating an intellectual disability syndrome include, but are not limited to, reducing or eliminating a symptom of an intellectual disability syndrome.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat neurodegeneration. Exemplary methods of treating neurodegeneration include, but are not limited to, improvement of mental wellbeing, increasing mental function, slowing the decrease of mental function, decreasing dementia, delaying the onset of dementia, improving cognitive skills, decreasing the loss of cognitive skills, improving memory, decreasing the degradation of memory, or extending survival.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a leukoencephalopathy or demyelinating disease. Exemplary leukoencephalopathies include, but are not limited to, progressive multifocal leukoencephalopathy, toxic leukoencephalopathy, leukoencephalopathy with vanishing white matter, leukoencephalopathy with neuroaxonal spheroids, reversible posterior leukoencephalopathy syndrome, hypertensive leukoencephalopathy, megalencephalic leukoencephalopathy with subcortical cysts, Charcot-Marie-Tooth disorder, and Devic's disease. A leukoencephalopathy may comprise a

demyelinating disease, which may be inherited or acquired. In some embodiments, an acquired demyelinating disease may be an inflammatory demyelinating disease (e.g., an infectious inflammatory demyelinating disease or a non-infectious inflammatory demyelinating disease), a toxic demyelinating disease, a metabolic demyelinating disease, a hypoxic demyelinating disease, a traumatic demyelinating disease, or an ischemic demyelinating disease (e.g., Binswanger's disease). Exemplary methods of treating a leukoencephalopathy or demyelinating disease include, but are not limited to, reducing or eliminating a symptom of a leukoencephalopathy or demyelinating disease, reducing the loss of myelin, increasing the amount of myelin, reducing the loss of white matter in a subject, or increasing the amount of white matter in a subject.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a traumatic injury or a toxin-induced injury to the nervous system (e.g., the brain). Exemplary traumatic brain injuries include, but are not limited to, a brain abscess, concussion, ischemia, brain bleeding, cranial fracture, diffuse axonal injury, locked-in syndrome, or injury relating to a traumatic force or blow to the nervous system or brain that causes damage to an organ or tissue. Exemplary toxin-induced brain injuries include, but are not limited to, toxic encephalopathy, meningitis (e.g. bacterial meningitis or viral meningitis), meningoencephalitis, encephalitis (e.g., Japanese encephalitis, eastern equine encephalitis, West Nile encephalitis), Guillan-Barre syndrome, Sydenham's chorea, rabies, leprosy, neurosyphilis, a prion disease, or exposure to a chemical (e.g., arsenic, lead, toluene, ethanol, manganese, fluoride, dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), tetrachloroethylene, a polybrominated diphenyl ether, a pesticide, a sodium channel inhibitor, a potassium channel inhibitor, a chloride channel inhibitor, a calcium channel inhibitor, or a blood brain barrier inhibitor).

In other embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to improve memory in a subject. Induction of memory has been shown to be facilitated by decreased and impaired by increased eIF2α phosphorylation. Regulators of translation, such as compounds disclosed herein (e.g. a compound of Formula (I)), could serve as therapeutic agents that improve memory in human disorders associated with memory loss such as Alzheimer's disease and in other neurological disorders that activate the UPR or ISR in neurons and thus could have negative effects on memory consolidation such as Parkinson's disease, schizophrenia, amyotrophic lateral sclerosis (ALS) and prion diseases. In addition, a mutation in eIF2γ that

disrupts complex integrity linked intellectual disability (intellectual disability syndrome or ID) to impaired translation initiation in humans. Hence, two diseases with impaired eIF2 function, ID and VWM, display distinct phenotypes but both affect mainly the brain and impair learning. In some embodiments, the disease or condition is unsatisfactory memory (e.g., working memory, long term memory, short term memory, or memory consolidation).

In still other embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used in a method to improve memory in a subject (e.g., working memory, long term memory, short term memory, or memory consolidation). In some embodiments, the subject is human. In some embodiments, the subject is a non-human mammal. In some embodiments, the subject is a domesticated animal. In some embodiments, the subject is a dog. In some embodiments, the subject is a bird. In some embodiments, the subject is a horse. In embodiments, the patient is a bovine. In some embodiments, the subject is a primate.

Cancer

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof is used to treat cancer. As used herein, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, melanomas, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), and/or multiple myeloma. In some further instances, "cancer" refers to lung cancer, breast cancer, ovarian cancer, leukemia, lymphoma, melanoma, pancreatic cancer, sarcoma, bladder cancer, bone cancer, brain cancer, cervical cancer, colon cancer, esophageal cancer, gastric cancer, liver cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, prostate cancer, metastatic cancer, or carcinoma.

As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemia, lymphoma, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound, pharmaceutical composition, or method provided herein include lymphoma, sarcoma, bladder cancer, bone cancer, brain tumor, cervical cancer, colon cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, leukemia, prostate cancer, breast cancer (e.g., ER positive, ER

negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal carcinoma, lobular carcinoma, primary, metastatic), ovarian cancer, pancreatic cancer, liver cancer (e.g., hepatocellular carcinoma), lung cancer (e.g., non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma, small cell lung carcinoma, carcinoid, sarcoma), glioblastoma multiforme, glioma, or melanoma. Additional examples include, cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma (e.g., WNT-dependent pediatric medulloblastoma), Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Paget' s Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, cancer of the hepatic stellate cells, or prostate cancer.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocyte leukemia, micromyeloblastic leukemia,

monocytic leukemia, myeloblasts leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound, pharmaceutical composition, or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, ductal carcinoma, carcinoma durum, embryonal

carcinoma, encephaloid carcinoma, epidermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lobular carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tubular carcinoma, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof is used to treat pancreatic cancer, breast cancer, multiple myeloma, cancers of secretory cells. For example certain methods herein treat cancer by decreasing or reducing or preventing the occurrence, growth, metastasis, or progression of cancer. In some embodiments, the methods described herein may be used to treat cancer by decreasing or eliminating a symptom of cancer. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a cancer described herein (e.g., pancreatic cancer, breast cancer, multiple myeloma, cancers of secretory cells).

In some embodiments, the compounds (compounds described herein, *e.g.*, a compound of Formula (I)) and compositions (*e.g.*, compositions comprising a compound described herein, *e.g.*, a compound of Formula (I))) are used with a cancer immunotherapy (*e.g.*, a checkpoint blocking antibody) to treat a subject (*e.g.*, a human subject), *e.g.*, suffering from a disease or

disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)). The methods described herein comprise administering a compound described herein, e.g., a compound of Formula (I) and an immunotherapy to a subject having abnormal cell growth such as cancer. Exemplary immunotherapies include, but are not limited to the following.

In some embodiments, the immunotherapeutic agent is a compound (*e.g.*, a ligand, an antibody) that inhibits the immune checkpoint blockade pathway. In some embodiments, the immunotherapeutic agent is a compound that inhibits the indoleamine 2,3-dioxygenase (IDO) pathway. In some embodiments, the immunotherapeutic agent is a compound that agonizes the STING pathway. Cancer immunotherapy refers to the use of the immune system to treat cancer. Three groups of immunotherapy used to treat cancer include cell-based, antibody-based, and cytokine therapies. All groups exploit cancer cells' display of subtly different structures (*e.g.*, molecular structure; antigens, proteins, molecules, carbohydrates) on their surface that can be detected by the immune system. Cancer immunotherapy (i.e., anti-tumor immunotherapy or anti-tumor immunotherapeutics) includes but is not limited to, immune checkpoint antibodies (*e.g.*, PD-1 antibodies, PD-L1 antibodies, PD-L2 antibodies, CTLA-4 antibodies, TIM3 antibodies, LAG3 antibodies, TIGIT antibodies); and cancer vaccines (i.e., anti-tumor vaccines or vaccines based on neoantigens such as a peptide or RNA vaccine).

Cell-based therapies (*e.g.*, cancer vaccines), usually involve the removal of immune cells from a subject suffering from cancer, either from the blood or from a tumor. Immune cells specific for the tumor will be activated, grown, and returned to a subject suffering from cancer where the immune cells provide an immune response against the cancer. Cell types that can be used in this way are *e.g.*, natural killer cells, lymphokine-activated killer cells, cytotoxic T-cells, dendritic cells, CAR-T therapies (i.e., chimeric antigen receptor T-cells which are T-cells engineered to target specific antigens), TIL therapy (i.e., administration of tumor-infiltrating lymphocytes), TCR gene therapy, protein vaccines, and nucleic acid vaccines. An exemplary cell-based therapy is Provenge. In some embodiments, the cell-based therapy is a CAR-T therapy.

Interleukin-2 and interferon-alpha are examples of cytokines, proteins that regulate and coordinate the behavior of the immune system.

Cancer Vaccines with Neoantigens

Neoantigens are antigens encoded by tumor-specific mutated genes. Technological innovations have made it possible to dissect the immune response to patient-specific neoantigens

that arise as a consequence of tumor-specific mutations, and emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies. These observations indicate that neoantigen load may form a biomarker in cancer immunotherapy. Many novel therapeutic approaches are being developed that selectively enhance T cell reactivity against this class of antigens. One approach to target neoantigens is ***via*** cancer vaccine. These vaccines can be developed using peptides or RNA, e.g., synthetic peptides or synthetic RNA.

Antibody therapies are antibody proteins produced by the immune system and that bind to a target antigen on the surface of a cell. Antibodies are typically encoded by an immunoglobulin gene or genes, or fragments thereof. In normal physiology antibodies are used by the immune system to fight pathogens. Each antibody is specific to one or a few proteins, and those that bind to cancer antigens are used, *e.g.*, for the treatment of cancer. Antibodies are capable of specifically binding an antigen or epitope. (Fundamental Immunology, 3rd Edition, W.E., Paul, ed., Raven Press, N.Y. (1993). Specific binding occurs to the corresponding antigen or epitope even in the presence of a heterogeneous population of proteins and other biologics. Specific binding of an antibody indicates that it binds to its target antigen or epitope with an affinity that is substantially greater than binding to irrelevant antigens. The relative difference in affinity is often at least 25% greater, more often at least 50% greater, most often at least 100% greater. The relative difference can be at least 2-fold, at least 5-fold, at least 10-fold, at least 25-fold, at least 50-fold, at least 100-fold, or at least 1000-fold, for example.

Exemplary types of antibodies include without limitation human, humanized, chimeric, monoclonal, polyclonal, single chain, antibody binding fragments, and diabodies. Once bound to a cancer antigen, antibodies can induce antibody-dependent cell-mediated cytotoxicity, activate the complement system, prevent a receptor interacting with its ligand or deliver a payload of chemotherapy or radiation, all of which can lead to cell death. Exemplary antibodies for the treatment of cancer include but are not limited to, Alemtuzumab, Bevacizumab, Bretuximab vedotin, Cetuximab, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Ipilimumab, Ofatumumab, Panitumumab, Rituximab, Tositumomab, Trastuzumab, Nivolumab, Pembrolizumab, Avelumab, durvalumab and pidilizumab.

Checkpoint blocking antibodies

The methods described herein comprise, in some embodiments, treating a human subject suffering from a disease or disorder described herein, the method comprising administering a composition comprising a cancer immunotherapy (*e.g.*, an immunotherapeutic agent). In some

embodiments, the immunotherapeutic agent is a compound (*e.g.*, an inhibitor or antibody) that inhibits the immune checkpoint blockade pathway. Immune checkpoint proteins, under normal physiological conditions, maintain self-tolerance (*e.g.*, prevent autoimmunity) and protect tissues from damage when the immune system is responding to *e.g.*, pathogenic infection. Immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. (Pardoll, Nature Rev. Cancer, 2012, 12, 252-264). Agonists of co-stimulatory receptors or antagonists of inhibitory signals (*e.g.*, immune checkpoint proteins), provide an amplification of antigen-specific T-cell responses. Antibodies that block immune checkpoints do not target tumor cells directly but typically target lymphocyte receptors or their ligands to enhance endogenous antitumor activity.

Exemplary checkpoint blocking antibodies include but are not limited to, anti-CTLA-4, anti-PD-1, anti-LAG3 (i.e., antibodies against lymphocyte activation gene 3), and anti-TIM3 (i.e., antibodies against T-cell membrane protein 3). Exemplary anti-CTLA-4 antibodies include but are not limited to, ipilimumab and tremelimumab. Exemplary anti-PD-1 ligands include but are not limited to, PD-L1 (i.e., B7-H1 and CD274) and PD-L2 (i.e., B7-DC and CD273). Exemplary anti-PD-1 antibodies include but are not limited to, nivolumab (i.e., MDX-1106, BMS-936558, or ONO-4538)), CT-011, AMP-224, pembrolizumab (trade name Keytruda), and MK-3475. Exemplary PD-L1-specific antibodies include but are not limited to, BMS936559 (i.e., MDX-1105), MEDI4736 and MPDL-3280A. Exemplary checkpoint blocking antibodies also include but are not limited to, IMP321 and MGA271.

T-regulatory cells (*e.g.*, CD4+, CD25+, or T-reg) are also involved in policing the distinction between self and non-self (*e.g.*, foreign) antigens, and may represent an important mechanism in suppression of immune response in many cancers. T-reg cells can either emerge from the thymus (i.e., "natural T-reg") or can differentiate from mature T-cells under circumstances of peripheral tolerance induction (i.e., "induced T-reg"). Strategies that minimize the action of T-reg cells would therefore be expected to facilitate the immune response to tumors. (Sutmuller, van Duivenvoorde et al., 2001).

IDO pathway inhibitors

The IDO pathway regulates immune response by suppressing T cell function and enabling local tumor immune escape. IDO expression by antigen-presenting cells (APCs) can lead to tryptophan depletion, and resulting antigen-specific T cell energy and regulatory T cell recruitment. Some tumors even express IDO to shield themselves from the immune system. A

compound that inhibits IDO or the IDO pathway thereby activating the immune system to attack the cancer (e.g., tumor in a subject). Exemplary IDO pathway inhibitors include indoximod, epacadostat and EOS200271.

STING pathway agonists

Stimulator of interferon genes (STING) is an adaptor protein that plays an important role in the activation of type I interferons in response to cytosolic nucleic acid ligands. Evidence indicates involvement of the STING pathway in the induction of antitumor immune response. It has been shown that activation of the STING-dependent pathway in cancer cells can result in tumor infiltration with immune cells and modulation of the anticancer immune response. STING agonists are being developed as a class of cancer therapeutics. Exemplary STING agonists include MK-1454 and ADU-S100.

Co-stimulatory antibodies

The methods described herein comprise, in some embodiments, treating a human subject suffering from a disease or disorder described herein, the method comprising administering a composition comprising a cancer immunotherapy (*e.g.*, an immunotherapeutic agent). In some embodiments, the immunotherapeutic agent is a co-stimulatory inhibitor or antibody. In some embodiments, the methods described herein comprise depleting or activating anti-4-1BB, anti-OX40, anti-GITR, anti-CD27 and anti-CD40, and variants thereof.

Inventive methods of the present invention contemplate single as well as multiple administrations of a therapeutically effective amount of a compound as described herein. Compounds, *e.g.,* a compound as described herein, can be administered at regular intervals, depending on the nature, severity and extent of the subject's condition. In some embodiments, a compound described herein is administered in a single dose. In some embodiments, a compound described herein is administered in multiple doses.

Inflammatory Disease

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an inflammatory disease. As used herein, the term "inflammatory disease" refers to a disease or condition characterized by aberrant inflammation (e.g. an increased level of inflammation compared to a control such as a healthy person not suffering from a disease). Examples of

inflammatory diseases include postoperative cognitive dysfunction, arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis), systemic lupus erythematosus (SLE), myasthenia gravis, juvenile onset diabetes, diabetes mellitus type 1, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, Vitiligo, asthma (e.g., allergic asthma), acne vulgaris, celiac disease, chronic prostatitis, inflammatory bowel disease, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, and atopic dermatitis. Proteins associated with inflammation and inflammatory diseases (e.g. aberrant expression being a symptom or cause or marker of the disease) include interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin- 18 (IL-18), TNF-a (tumor necrosis factor-alpha), and C-reactive protein (CRP).

In some embodiments, the inflammatory disease comprises postoperative cognitive dysfunction, arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis), systemic lupus erythematosus (SLE), myasthenia gravis, diabetes (e.g., juvenile onset diabetes or diabetes mellitus type 1), Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, asthma (e.g., allergic asthma), acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, or atopic dermatitis.

In some embodiments, the inflammatory disease comprises postoperative cognitive dysfunction, which refers to a decline in cognitive function (e.g. memory or executive function (e.g. working memory, reasoning, task flexibility, speed of processing, or problem solving)) following surgery.

In other embodiments, the method of treatment is a method of prevention. For example, a method of treating postsurgical cognitive dysfunction may include preventing postsurgical cognitive dysfunction or a symptom of postsurgical cognitive dysfunction or reducing the severity of a symptom of postsurgical cognitive dysfunction by administering a compound described herein prior to surgery.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an

inflammatory disease (e.g., an inflammatory disease described herein) by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat an inflammatory disease (e.g., an inflammatory disease described herein).

Musculoskeletal Diseases

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a musculoskeletal disease. As used herein, the term "musculoskeletal disease" refers to a disease or condition in which the function of a subject's musculoskeletal system (e.g., muscles, ligaments, tendons, cartilage, or bones) becomes impaired. Exemplary musculoskeletal diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include muscular dystrophy (e.g., Duchenne muscular dystrophy, Becker muscular dystrophy, distal muscular dystrophy, congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy type 1, or myotonic muscular dystrophy type 2), limb girdle muscular dystrophy, multisystem proteinopathy, rhizomelic chondrodysplasia punctata, X-linked recessive chondrodysplasia punctata, Conradi-Hünermann syndrome, Autosomal dominant chondrodysplasia punctata, stress induced skeletal disorders (e.g., stress induced osteoporosis), multiple sclerosis, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, Paget's disease of bone, cramp fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder (e.g., muscle atrophy, sarcopenia, cachexia), an inclusion body myopathy, motor neuron disease, or paralysis.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a musculoskeletal disease (e.g., a musculoskeletal disease described herein) by decreasing or eliminating a symptom of the disease. In some embodiments, the method of treatment comprises treatment of muscle pain or muscle stiffness associated with a musculoskeletal disease. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a

composition or in combination with another agent in a composition to treat a musculoskeletal disease (e.g., a musculoskeletal disease described herein).

Metabolic Diseases

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat metabolic disease. As used herein, the term "metabolic disease" refers to a disease or condition affecting a metabolic process in a subject. Exemplary metabolic diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes (e.g., Type I diabetes, Type II diabetes, or gestational diabetes), phenylketonuria, proliferative retinopathy, or Kearns-Sayre disease.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a metabolic disease (e.g., a metabolic disease described herein) by decreasing or eliminating a symptom of the disease. In some embodiments, the method of treatment comprises decreasing or eliminating a symptom comprising elevated blood pressure, elevated blood sugar level, weight gain, fatigue, blurred vision, abdominal pain, flatulence, constipation, diarrhea, jaundice, and the like. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a metabolic disease (e.g., a musculoskeletal disease described herein).

Mitochondrial Diseases

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat mitochondrial disease. As used herein, the term "mitochondrial disease" refers to a disease or condition affecting the mitochondria in a subject. In some embodiments, the mitochondrial disease is associated with, or is a result of, or is caused by mitochondrial dysfunction, one or more mitochondrial protein mutations, or one or more mitochondrial DNA mutations. In some embodiments, the mitochondrial disease is a mitochondrial myopathy. In some embodiments, mitochondrial diseases, e.g., the mitochondrial myopathy, that may be treated with a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or

stereoisomer thereof include, e.g., Barth syndrome, chronic progressive external ophthalmoplegia (cPEO), Kearns-Sayre syndrome (KSS), Leigh syndrome (e.g., MILS, or maternally inherited Leigh syndrome), mitochondrial DNA depletion syndromes (MDDS, e.g., Alpers syndrome), mitochondrial encephalomyopathy (e.g., mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), myoclonus epilepsy with ragged red fibers (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), Leber´s hereditary optic neuropathy (LHON), and Pearson syndrome.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a mitochondrial disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a mitochondrial disease described herein.

Hearing Loss

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat hearing loss. As used herein, the term "hearing loss" or "hearing loss condition" may broadly encompass any damage to the auditory systems, organs, and cells or any impairment of an animal subject's ability to hear sound, as measured by standard methods and assessments known in the art, for example otoacoustic emission testing, pure tone testing, and auditory brainstem response testing. Exemplary hearing loss conditions that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include, but are not limited to, mitochondrial nonsyndromic hearing loss and deafness, hair cell death, age-related hearing loss, noise-induced hearing loss, genetic or inherited hearing loss, hearing loss experienced as a result of ototoxic exposure, hearing loss resulting from disease, and hearing loss resulting from trauma. In some embodiments, mitochondrial nonsyndromic hearing loss and deafness is a MT-RNR1-related hearing loss. In some embodiments, the MT-RNR1-related hearing loss is the result of amino glycoside ototoxicity. In some embodiments, mitochondrial nonsyndromic hearing loss and deafness is a MT-TS1-related hearing loss. In some embodiments, mitochondrial nonsyndromic hearing loss and deafness is characterized by sensorineural hearing loss.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a hearing loss condition described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a hearing loss condition described herein.

Ocular Disease

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat eye disease. As used herein, the term "ocular disease" may refer to a disease or condition in which the function of a subject's eye becomes impaired. Exemplary ocular diseases and conditions that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an ocular disease or condition described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat an ocular disease or condition described herein.

Kidney Diseases

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat kidney disease. As used herein, the term "kidney disease" may refer to a disease or condition in which the function of a subject's kidneys becomes impaired. Exemplary kidney diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include Abderhalden–Kaufmann–Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acetaminophen-induced Nephrotoxicity, Acute Kidney Failure/Acute Kidney Injury, Acute Lobar Nephronia,

Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alagille Syndrome, Alport Syndrome, Amyloidosis, ANCA Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Antiphospholipid Syndrome, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1 Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Arteriovenous Malformations and Fistulas of the Urologic Tract, Autosomal Dominant Hypocalcemia, Bardet-Biedl Syndrome, Bartter Syndrome, Bath Salts and Acute Kidney Injury, Beer Potomania, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Border-Crossers' Nephropathy, Bourbon Virus and Acute Kidney Injury, Burnt Sugarcane Harvesting and Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, C3 Glomerulopathy, C3 Glomerulopathy with Monoclonal Gammopathy, C4 Glomerulopathy, Calcineurin Inhibitor Nephrotoxicity, Callilepsis Laureola Poisoning, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Indiced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Chinese Herbal Medicines and Nephrotoxicity, Cherry Concentrate and Acute Kidney Injury, Cholesterol Emboli, Churg–Strauss syndrome, Chyluria, Ciliopathy, Cocaine and the Kidney, Cold Diuresis, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Combination Antiretroviral (cART) Related-Nephropathy, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), Congenital Nephrotic Syndrome, Congestive Renal Failure, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulphate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryocrystalglobulinemia, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Crystal-Storing Histiocytosis, Cystic Kidney Disease, Acquired, Cystinuria, Dasatinib-Induced Nephrotic-Range Proteinuria, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), DHA Crystalline Nephropathy, Dialysis Disequilibrium Syndrome, Diabetes and Diabetic Kidney Disease, Diabetes Insipidus, Dietary Supplements and Renal Failure, Diffuse Mesangial Sclerosis, Diuresis, Djenkol Bean Poisoning (Djenkolism), Down Syndrome and Kidney Disease, Drugs of Abuse and Kidney Disease, Duplicated Ureter, EAST syndrome, Ebola and the Kidney, Ectopic Kidney, Ectopic Ureter, Edema, Swelling, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric

Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fraley syndrome, Fluid Overload, Hypervolemia, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glycosuria, Goodpasture Syndrome, Green Smoothie Cleanse Nephropathy, HANAC Syndrome, Harvoni (Ledipasvir with Sofosbuvir)-Induced Renal Injury, Hair Dye Ingestion and Acute Kidney Injury, Hantavirus Infection Podocytopathy, Heat Stress Nephropathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome (aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderinuria, Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatocyte Nuclear Factor 1β–Associated Kidney Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High Altitude Renal Syndrome, High Blood Pressure and Kidney Disease, HIV-Associated Immune Complex Kidney Disease (HIVICK), HIV-Associated Nephropathy (HIVAN), HNF1B-related Autosomal Dominant Tubulointerstitial Kidney Disease, Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hydroxychloroquine-induced Renal Phospholipidosis, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypocomplementemic Urticarial Vasculitic Syndrome, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, Hypophosphatemia in Users of Cannabis, Hypertension, Hypertension, Monogenic, Iced Tea Nephropathy, Ifosfamide Nephrotoxicity, IgA Nephropathy, IgG4 Nephropathy, Immersion Diuresis, Immune-Checkpoint Therapy-Related Interstitial Nephritis, Infliximab-Related Renal Disease, Interstitial Cystitis, Painful Bladder Syndrome (Questionnaire), Interstitial Nephritis, Interstitial Nephritis, Karyomegalic, Ivemark's syndrome, JC Virus Nephropathy, Joubert Syndrome, Ketamine-Associated Bladder Dysfunction, Kidney Stones, Nephrolithiasis, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related Nephrotoxicity, Lecithin Cholesterol Acyltransferase Deficiency (LCAT Deficiency), Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Light Chain Proximal Tubulopathy, Liddle Syndrome, Lightwood-Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause

Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lupus Podocytopathy, Lyme Disease-Associated Glomerulonephritis, Lysinuric Protein Intolerance, Lysozyme Nephropathy, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, McKittrick-Wheelock Syndrome, MDMA (Molly; Ecstacy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Meatal Stenosis, Medullary Cystic Kidney Disease, Urolodulin-Associated Nephropathy, Juvenile Hyperuricemic Nephropathy Type 1, Medullary Sponge Kidney, Megaureter, Melamine Toxicity and the Kidney, MELAS Syndrome, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, Membranous-like Glomerulopathy with Masked IgG Kappa Deposits, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, Monoclonal Gammopathy of Renal Significance, Dysproteinemia, Mouthwash Toxicity, MUC1 Nephropathy, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, NARP Syndrome, Nephrocalcinosis, Nephrogenic Systemic Fibrosis, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, 9/11 and Kidney Disease, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nutcracker syndrome, Oligomeganephronia, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Osmotic Nephrosis, Ovarian Hyperstimulation Syndrome, Oxalate Nephropathy, Page Kidney, Papillary Necrosis, Papillorenal Syndrome (Renal-Coloboma Syndrome, Isolated Renal Hypoplasia), PARN Mutations and Kidney Disease, Parvovirus B19 and the Kidney, The Peritoneal-Renal Syndrome, POEMS Syndrome, Posterior Urethral Valve, Podocyte Infolding Glomerulopathy, Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Post-infectious Glomerulonephritis, Atypical, Post-Infectious Glomerulonephritis (IgA-Dominant), Mimicking IgA Nephropathy, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Post-Obstructive Diuresis, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pulmonary-Renal Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Pyridium and Kidney Failure, Radiation Nephropathy, Ranolazine and the Kidney, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, Renal Abscess, Peripnephric Abscess, Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal

Artery Dissection, Spontaneous, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Mutations and Autosomal Dominant Tubulointerstitial Kidney Disease, Renin Secreting Tumors (Juxtaglomerular Cell Tumor), Reset Osmostat, Retrocaval Ureter, Retroperitoneal Fibrosis, Rhabdomyolysis, Rhabdomyolysis related to Bariatric Sugery, Rheumatoid Arthritis-Associated Renal Disease, Sarcoidosis Renal Disease, Salt Wasting, Renal and Cerebral, Schistosomiasis and Glomerular Disease, Schimke immuno-osseous dysplasia, Scleroderma Renal Crisis, Serpentine Fibula-Polycystic Kidney Syndrome, Exner Syndrome, Sickle Cell Nephropathy, Silica Exposure and Chronic Kidney Disease, Sri Lankan Farmers' Kidney Disease, Sjögren's Syndrome and Renal Disease, Synthetic Cannabinoid Use and Acute Kidney Injury, Kidney Disease Following Hematopoietic Cell Transplantation, Kidney Disease Related to Stem Cell Transplantation, TAFRO Syndrome, Tea and Toast Hyponatremia, Tenofovir-Induced Nephrotoxicity, Thin Basement Membrane Disease, Benign Familial Hematuria, Thrombotic Microangiopathy Associated with Monoclonal Gammopathy, Trench Nephritis, Trigonitis, Tuberculosis, Genitourinary, Tuberous Sclerosis, Tubular Dysgenesis, Immune Complex Tubulointerstitial Nephritis Due to Autoantibodies to the Proximal Tubule Brush Border, Tumor Lysis Syndrome, Uremia, Uremic Optic Neuropathy, Ureteritis Cystica, Ureterocele, Urethral Caruncle, Urethral Stricture, Urinary Incontinence, Urinary Tract Infection, Urinary Tract Obstruction, Urogenital Fistula, Uromodulin-Associated Kidney Disease, Vancomycin-Associated Cast Nephropathy, Vasomotor Nephropathy, Vesicointestinal Fistula, Vesicoureteral Reflux, VGEF Inhibition and Renal Thrombotic Microangiopathy, Volatile Anesthetics and Acute Kidney Injury, Von Hippel-Lindau Disease, Waldenstrom's Macroglobulinemic Glomerulonephritis, Warfarin-Related Nephropathy, Wasp Stings and Acute Kidney Injury, Wegener's Granulomatosis, Granulomatosis with Polyangiitis, West Nile Virus and Chronic Kidney Disease, Wunderlich syndrome, Zellweger Syndrome, or Cerebrohepatorenal Syndrome.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a kidney disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a kidney disease described herein.

Skin Diseases

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a skin disease. As used herein, the term "skin disease" may refer to a disease or condition affecting the skin. Exemplary skin diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include acne, alopecia areata, basal cell carcinoma, Bowen's disease, congenital erythropoietic porphyria, contact dermatitis, Darier's disease, disseminated superficial actinic porokeratosis, dystrophic epidermolysis bullosa, eczema (atopic eczema), extra-mammary Paget's disease, epidermolysis bullosa simplex, erythropoietic protoporphyria, fungal infections of nails, Hailey-Hailey disease, herpes simplex, hidradenitis suppurativa, hirsutism, hyperhidrosis, ichthyosis, impetigo, keloids, keratosis pilaris, lichen planus, lichen sclerosus, melanoma, melasma, mucous membrane pemphigoid, pemphigoid, pemphigus vulgaris, pityriasis lichenoides, pityriasis rubra pilaris, plantar warts (verrucas), polymorphic light eruption, psoriasis, plaque psoriasis, pyoderma gangrenosum, rosacea, scabies, scleroderma, shingles, squamous cell carcinoma, sweet's syndrome, urticaria and angioedema and vitiligo.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a skin disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a skin disease described herein.

Fibrotic Diseases

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a fibrotic disease. As used herein, the term "fibrotic disease" may refer to a disease or condition that is defined by the accumulation of excess extracellular matrix components. Exemplary fibrotic diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include adhesive capsulitis, arterial stiffness, arthrofibrosis, atrial fibrosis, cardiac fibrosis, cirrhosis, congenital hepatic fibrosis, Crohn's disease, cystic fibrosis, Dupuytren's contracture, endomyocardial fibrosis, glial scar, hepatitis C, hypertrophic cardiomyopathy, hypersensitivity pneumonitis,

idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, interstitial lung disease, keloid, mediastinal fibrosis, myelofibrosis, nephrogenic systemic fibrosis, non-alcoholic fatty liver disease, old myocardial infarction, Peyronie's disease, pneumoconiosis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, radiation-induced lung injury, retroperitoneal fibrosis, scleroderma/systemic sclerosis, silicosis and ventricular remodeling.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a fibrotic disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a fibrotic disease described herein.

Hemoglobin Disorders

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a hemoglobin disease. As used herein, the terms "hemoglobin disease" or "hemoglobin disorder" may refer to a disease or condition characterized by an abnormal production or structure of the hemoglobin protein. Exemplary hemoglobin diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include “dominant” β-thalassemia, acquired (toxic) methemoglobinemia, carboxyhemoglobinemia, congenital Heinz body hemolytic anemia, HbH disease, HbS/β-thalassemia, HbE/β-thalassemia, HbSC disease, homozygous α^{+}-thalassemia (phenotype of α^{0}-thalassemia), Hydrops fetalis with Hb Bart's, sickle cell anemia/disease, sickle cell trait, sickle β-thalassemia disease, α^{+}-thalassemia, α^{0}-thalassemia, α-Thalassemia associated with myelodysplastic syndromes, α-Thalassemia with mental retardation syndrome (ATR), β^{0}-Thalassemia, β^{+}-Thalassemia, δ-Thalassemia, γ-Thalassemia, β-Thalassemia major, β-Thalassemia intermedia, δβ-Thalassemia, and εγδβ-Thalassemia.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a hemoglobin disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a

composition or in combination with another agent in a composition to treat a hemoglobin disease described herein.

Autoimmune Diseases

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an autoimmune disease. As used herein, the term "autoimmune disease" may refer to a disease or condition in which the immune system of a subject attacks and damages the tissues of said subject. Exemplary kidney diseases that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed

connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome,, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, and Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA)).

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an autoimmune disease described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat an autoimmune disease described herein.

Viral Infections

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a viral infection. Exemplary viral infections that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include influenza, human immunodeficiency virus (HIV) and herpes.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a viral infection described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a viral infection described herein.

Malaria Infection

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a malaria. As used herein, the term "malaria" may refer to a parasitic disease of protozoan of the plasmodium genus that causes infection of red blood cells (RBCs). Exemplary forms of malaria infection that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include infection caused by Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium falciparum. In some embodiments, the malaria infection that may be treated with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is resistant/recrudescent malaria.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a malaria infection described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a malaria infection described herein.

Diseases with Mutations Leading to Unfolded Protein Response (UPR) Induction

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a disease with mutations that leads to UPR induction. Exemplary disease with mutations that lead to UPR induction include Marinesco-Sjogren syndrome, neuropathic pain, diabetic neuropathic pain, noise induced hearing loss, non-syndromic sensorineural hearing loss, age-related hearing loss, Wolfram syndrome, Darier White disease, Usher syndrome, collagenopathies, Thin basement

nephropathy, Alport syndrome, skeletal chondrodysplasia, metaphyseal chondrodysplasia type Schmid, and Pseudochondrodysplasia.

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a disease with mutations that leads to UPR induction described herein by decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in combination with another agent in a composition to treat a disease with mutations that leads to UPR induction described herein.

Methods of Modulating Protein Production

In another aspect, disclosed herein is a method of modulating the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, thereby modulating the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, contacting the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell increases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, contacting the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell decreases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell.

In another aspect, disclosed herein is a method of preventing or treating a condition, disease or disorder described herein in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patient's cells, thereby treating the condition, disease or disorder. In some embodiments, the condition, disease or disorder is characterized by aberrant expression of

eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patient's cells. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patient's cells, thereby treating the condition, disease or disorder. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patient's cells, thereby treating the condition, disease or disorder.

In another aspect, disclosed herein is a method of modulating the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, thereby modulating the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, contacting the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, contacting the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell decreases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell.

In another aspect, disclosed herein is a method of preventing or treating a condition, disease or disorder described herein in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patients cells, thereby treating the condition, disease or disorder. In some embodiments, the condition, disease or disorder is characterized by aberrant activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patient's cells. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt,

solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patient's cells, thereby treating the condition, disease or disorder. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patient's cells, thereby treating the condition, disease or disorder.

In some embodiments, administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates both the expression and the activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patients cells, thereby treating the condition, disease or disorder.

In some embodiments, the compound of Formula (I) is chemically modified, prior to (ex vivo) or after (in vivo) contacting with a cell, forming a biologically active compound that modulates the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, the compound of Formula (I) is metabolized by the patient forming a biologically active compound that modulates the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patients cells, thereby treating a condition, disease or disorder disclosed herein. In some embodiments, the biologically active compound is the compound of formula (II).

In one aspect, disclosed herein is a method of treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Formula (I). In some embodiments, the modulation comprises an increase in eIF2B activity or levels, increase in eIF2α activity or levels, or increase in activity or levels of a component of the eIF2 pathway or the ISR pathway. In some embodiments, the disease may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway (e.g., the eIF2α signaling pathway).

Methods of Increasing Protein Activity and Production

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications

where increasing production output of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof is desirable, such as in vitro cell free systems for protein production.

In some embodiments, the present invention features a method of increasing expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by a cell or in vitro expression system, the method comprising contacting the cell or in vitro expression system with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof. In some embodiments, the method is a method of increasing the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by a cell comprising contacting the cell with an effective amount of a compound described herein (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof). In other embodiments, the method is a method of increasing the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by an in vitro protein expression system comprising contacting the in vitro expression system with a compound described herein (e.g. the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof). In some embodiments, contacting the cell or in vitro expression system with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the cell or in vitro expression system by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In some embodiments, contacting the cell or in vitro expression system with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the cell or in vitro expression system by about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold,

about 500-fold, about 600-fold about 700-fold, about 800-fold, about 900-fold, about 1000-fold, about 10000-fold, about 100000-fold, or about 1000000-fold.

In some embodiments, the present invention features a method of increasing the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by a patient cells, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the patient has been diagnosed with a disease, disorder, or condition disclosed herein and wherein the disease, disorder or condition is characterized by aberrant expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof (e.g., a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, muscle-wasting disease, or sarcopenia). In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by the patients cells about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, thereby treating the disease, disorder or condition. In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof by the patients cells about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold, about 500-fold, about 600-fold about 700-fold, about 800-fold, about 900-fold, about 1000-fold, about 10000-fold, about 100000-fold, or about 1000000-fold, thereby treating the disease, disorder or condition.

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where increasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof is desirable.

In some embodiments, the present invention features a method of increasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof. In some embodiments, contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the cell by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In some embodiments, contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the cell by about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold, about 500-fold, about 600-fold about 700-fold, about 800-fold, about 900-fold, about 1000-fold, about 10000-fold, about 100000-fold, or about 1000000-fold.

In some embodiments, the present invention features a method of increasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the patient has been diagnosed with a disease, disorder, or condition disclosed herein and wherein the disease, disorder or condition is characterized by lowered levels of protein activity. In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the patient by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about

65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, thereby treating the disease, disorder or condition. In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the patient by about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold, about 500-fold, about 600-fold about 700-fold, about 800-fold, about 900-fold, about 1000-fold, about 10000-fold, about 100000-fold, or about 1000000-fold, thereby treating the disease, disorder or condition.

In some embodiments, the compound of Formula (I) is chemically modified, prior to (ex vivo) or after (in vivo) contacting with the cell or in vitro expression system, forming a biologically active compound that increases the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cells and/or in vitro expression system. In some embodiments, the compound of Formula (I) is metabolized by the patient forming a biologically active compound that increases the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patients cells, thereby treating a condition, disease or disorder disclosed herein. In some embodiments, the biologically active compound is the compound of formula (II).

Methods of Decreasing Protein Activity and Production

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where decreasing production output of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof is desirable.

In some embodiments, the present invention features a method of decreasing expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a cell, the method comprising contacting the cells with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof. In some embodiments, contacting the cells with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination

thereof in the cell by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

In some embodiments, the present invention features a method of decreasing the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the patient has been diagnosed with a disease, disorder, or condition described herein and wherein the disease, disorder or condition is characterized by increased levels of protein production. In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the expression of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the patient by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, thereby treating the disease, disorder or condition.

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where decreasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof is desirable.

In some embodiments, the present invention features a method of decreasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof. In some embodiments, contacting the cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the cell by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%,

about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, thereby treating the disease, disorder or condition.

In some embodiments, the present invention features a method of decreasing the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the patient has been diagnosed with a disease, disorder, or condition described herein and wherein the disease, disorder or condition is characterized by increased levels of protein activity. In some embodiments, administering to the patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2α, a component of the eIF2 pathway, a component of the ISR pathway or any combination thereof in the patient by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, thereby treating the disease, disorder or condition.

In some embodiments, the compound of Formula (I) is chemically modified, prior to (ex vivo) or after (in vivo) contacting with a cell, forming a biologically active compound that decreases the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the cell. In some embodiments, the compound of Formula (I) is metabolized by the patient forming a biologically active compound that decreases the expression and/or activity of eIF2B, eIF2α, a component of the eIF2 pathway, component of the ISR pathway or any combination thereof in the patients cells, thereby treating a condition, disease or disorder disclosed herein. In some embodiments, the biologically active compound is the compound of formula (I).

In some embodiments, the compounds set forth herein are provided as pharmaceutical compositions including a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof and a pharmaceutically acceptable excipient. In embodiments of the method, a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof , is co-administered with a second agent (e.g. therapeutic agent). In other embodiments of the method, a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer

thereof , is co-administered with a second agent (e.g. therapeutic agent), which is administered in a therapeutically effective amount. In embodiments, the second agent is an agent for improving memory.

Combination Therapy

In one aspect, the present invention features a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof as well as a second agent (e.g. a second therapeutic agent). In some embodiments, the pharmaceutical composition includes a second agent (e.g. a second therapeutic agent) in a therapeutically effective amount. In some embodiments, the second agent is an agent for treating cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway.

The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer, a neurodegenerative disease, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for a cancer, a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway.

In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic. In embodiments, the second agent is an agent for improving memory. In embodiments, the second agent is an agent for treating a neurodegenerative disease.

In embodiments, the second agent is an agent for treating a leukodystrophy. In embodiments, the second agent is an agent for treating vanishing white matter disease. In embodiments, the second agent is an agent for treating childhood ataxia with CNS hypo-myelination. In embodiments, the second agent is an agent for treating an intellectual disability syndrome. In embodiments, the second agent is an agent for treating pancreatic cancer. In embodiments, the second agent is an agent for treating breast cancer. In embodiments, the second agent is an agent for treating multiple myeloma. In embodiments, the second agent is an agent for treating myeloma. In embodiments, the second agent is an agent for treating a cancer of a secretory cell. In embodiments, the second agent is an agent for reducing eIF2α phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2α phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2α. In embodiments, the second agent is an agent for inhibiting the integrated stress response. In embodiments, the second agent is an anti-inflammatory agent. In embodiments, the second agent is an agent for treating postsurgical cognitive dysfunction. In embodiments, the second agent is an agent for treating traumatic brain injury. In embodiments, the second agent is an agent for treating a musculoskeletal disease. In embodiments, the second agent is an agent for treating a metabolic disease. In embodiments, the second agent is an anti-diabetic agent.

Anti-cancer agents

"Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anticancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI- 1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine), anti-metabolites (e.g., 5-

azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP 16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 1 1-7082, PKC412, PD184352, 20-epi-l, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein- 1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1 ; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-

porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone;

oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone Bl; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase;

asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-nl; interferon alfa-n3; interferon beta-la; interferon gamma-lb; iprop latin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate

the formation or stability of microtubules, (e.g. Taxol, i.e. paclitaxel), Taxotere, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and SC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21 -aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-1 12378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM- 132 (Armad), AM- 138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HC1), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI- 138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A 1 (i.e. BTO-956 and DIME), DDE- 313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta

Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA- 110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-25041 1 (Sanofi), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{U1}ln, ^{90}Y, or ^{131}I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

"Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha- interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody -pseudomonas exotoxin conjugate, etc.), and radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{m}In, ^{90}Y, or ^{131}I, etc.).

In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{m}Ag, ^{m}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

Additional Agents

In some embodiments, the second agent for use in combination with a compound (e.g., a compound of Formula (I)) or composition thereof described herein is an agent for use in treating a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, or a metabolic disease. In some embodiments, a second agent for use in combination with a compound (e.g., a compound of Formula (I)) or composition thereof described herein is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating a disease, disorder, or condition described herein.

In some embodiments, a second agent for use in treating a neurodegenerative disease, a leukodystrophy, an inflammatory disease, a musculoskeletal disease, or a metabolic disease includes, but is not limited to, an anti-psychotic drug, anti-depressive drug, anti-anxiety drug, analgesic, a stimulant, a sedative, a pain reliever, an anti-inflammatory agent, a benzodiazepine, a cholinesterase inhibitor, a non-steroidal anti-inflammatory drug (NSAID), a corticosteroid, a MAO inhibitor, a beta-blocker, a calcium channel blocker, an antacid, or other agent. Exemplary second agents may include donepezil, galantamine, rivastigmine, memantine, levodopa, dopamine, pramipexole, ropinirole, rotigotine, doxapram, oxazepam, quetiapine, selegiline, rasagiline, entacapone, benztropine, trihexyphenidyl, riluzole, diazepam, chlorodiazepoxide, lorazepam, alprazolam, buspirone, gepirone, ispapirone, hydroxyzine, propranolol, hydroxyzine, midazolam, trifluoperazine, methylphenidate, atomoxetine, methylphenidate, pemoline, perphenazine, divalproex, valproic acid, sertraline, fluoxetine, citalopram, escitalopram, paroxetine, fluvoxamine, trazodone, desvenlafaxine, duloxetine, venlafaxine, amitriptyline, amoxapine, clomipramine, desipramine, imipramine, nortriptyline, protriptyline, trimipramine, maprotiline, bupropion, nefazodone, vortioxetine, lithium, clozapine, fluphenazine, haloperidol, paliperidone, loxapine, thiothixene, pimozide, thioridazine, risperidone, aspirin, ibuprofen, naproxen, acetaminophen, azathioprine, methotrexate, mycophenolic acid, leflunomide, dibenzoylmethane, cilostazol, pentoxifylline, duloxetine, a cannabinoid (e.g, nabilone), simethicone, magaldrate, aluminum salts, calcium salts, sodium salts, magnesium salts, alginic acid, acarbose, albiglutide, alogliptin, metformin, insulin, lisinopril, atenolol, atorvastatin, fluvastatin, lovastatin, pitavastatin, simvastatin, rosuvastatin, and the like.

Naturally derived agents or supplements may also be used in conjunction with a compound of Formula (I) or a composition thereof to treat a neurodegenerative disease, an inflammatory disease, a musculoskeletal disease, or a metabolic disease. Exemplary naturally derived agents or supplements include omega-3 fatty acids, carnitine, citicoline, curcumin, gingko, vitamin E, vitamin B (e.g., vitamin B5, vitamin B6, or vitamin B12), huperzine A, phosphatidylserine, rosemary, caffeine, melatonin, chamomile, St. John's wort, tryptophan, and the like.

EXAMPLES

In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Synthetic Protocols

The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures. General scheme relating to methods of making exemplary compounds of the invention are additionally described in the section entitled Methods of Making Compounds.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Abbreviations

APCI for atmospheric pressure chemical ionization; COMU for (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate; DCI for desorption chemical ionization; DMSO for dimethyl sulfoxide; ESI for electrospray ionization;

HATU for 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; HPLC for high performance liquid chromatography; LC/MS for liquid chromatography/mass spectrometry; MS for mass spectrum; NMR for nuclear magnetic resonance; psi for pounds per square inch; SFC for supercritical fluid chromatography; TLC for thin-layer chromatography; and UV for ultraviolet.

Example 1: *N*-{4-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octan-1-yl}-2*H*-1,3-benzodioxole-2-carboxamide (Compound 100)

Example 1A: tert-butyl (4-aminobicyclo[2.2.2]octan-1-yl)carbamate

Bicyclo[2.2.2]octane-1,4-diamine dihydrochloride (PharmaBlock, 200 mg, 1.43 mmol) was dissolved in methanol (5 mL). The solution was basified with 50% aqueous sodium hydroxide. After stirring for 15 minutes (slight exotherm), the mixture was diluted with water and brine and extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give the free base as a white solid. The free base, bicyclo[2.2.2]octane-1,4-diamine (176 mg, 1.255 mmol), di-*tert*-butyl dicarbonate (274 mg, 1.255 mmol), and tetrahydrofuran (100 mL) were stirred at ambient temperature for 17 hours. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer was washed with brine, then dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to provide the title intermediate as an off-white solid (258 mg, 86% yield). ^{1}H NMR (methanol-d_4) δ ppm 1.91-1.85 (m, 7H), 1.65-1.60 (m, 2H), 1.40 (s, 12H); MS (DCI-NH_3) *m/z* 241 $(M+H)^+$.

Example 1B: tert-butyl (4-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[2.2.2]octan-1-yl)carbamate

A 50 mL round bottom flask, equipped with a magnetic stir bar, was charged with 2-(4-chloro-3-fluorophenoxy)acetic acid (234 mg, 1.144 mmol), the product of Example 1A (250 mg, 1.040 mmol), and (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU®, 535 mg, 1.248 mmol). The flask contents were placed under a dry nitrogen atmosphere and *N*,*N*-dimethylformamide (4 mL) was introduced via syringe. The reaction mixture was then stirred at ambient temperature as *N*,*N*-diisopropylethylamine (0.545 mL, 3.12 mmol) was added dropwise via syringe. The reaction mixture was stirred at ambient temperature for 19 hours. The reaction mixture was diluted with water (pH = 10). An insoluble beige solid was collected by filtration and rinsed thoroughly with water. The material was purified by column chromatography on an Analogix® IntelliFlash™-

310 (Isco RediSep® 40 g silica gel cartridge, 70:30 to 0:100 heptane/ethyl acetate). Fractions were combined and concentrated under reduced pressure to give the title intermediate as a white solid (69.5 mg, 15.65% yield). ^{1}H NMR ($CDCl_3$) δ ppm 7.31 (t, J = 8.6 Hz, 1H), 6.73 (dd, J = 10.3, 2.9 Hz, 1H), 6.64 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 6.07 (s, 1H), 4.32 (s, 1H), 4.31 (s, 2H), 2.05-1.91 (m, 12H), 1.42 (s, 9H); MS (ESI+) *m/z* 426 $(M+H)^+$, *m/z* 853 $(2M+H)^+$; MS (ESI-) *m/z* 425 $(M-H)^-$.

Example 1C: N-(4-aminobicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide, trifluoroacetic acid

Trifluoroacetic acid (1 mL, 12.98 mmol) was added to a solution of the product of Example 1B (158 mg, 0.37 mmol) in dichloromethane (2.0 mL). The resulting mixture was stirred at ambient temperature for 30 minutes and then concentrated under reduced pressure to give the title compound (0.16 g, 0.36 mmol, 98% yield). MS (ESI^+) *m/z* 327 $(M+H)^+$.

Example 1D: N-{4-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octan-1-yl}-2H-1,3-benzodioxole-2-carboxamide

1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 30.4 mg, 0.08 mmol) was added to a solution of 1,3-benzodioxole-2-carboxylic acid (12.1 mg, 0.07 mmol, Matrix), the product of Example 1C (32 mg, 0.073 mmol) and triethylamine (0.051 mL, 0.36 mmol) in *N*,*N*-dimethylformamide (2.0 mL). The resulting solution was stirred at ambient temperature for 1 hour, filtered through a glass microfiber frit and purified by preparative HPLC [YMC TriArt™ C18 Hybrid 5 μm column, 50 × 100 mm, flow rate 70 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (12 mg, 0.025 mmol, 35 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.09 (s, 1H), 7.52 – 7.44 (m, 2H), 7.02 (dd, J = 11.4, 2.9 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.86 – 6.78 (m, 3H), 6.25 (s, 1H), 4.43 (s, 2H), 1.91 (br s, 12H); MS (ESI^+) *m/z* 475 $(M+H)^+$.

Example 2: 2-(5-chloro-2,3-dihydro-1*H*-indol-1-yl)-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}acetamide (Compound 101)

Example 2A: ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

A mixture of ethyl 4-oxocyclohexanecarboxylate (11.70 mL, 73.4 mmol), ethane-1,2-diol (12.29 mL, 220 mmol), and *p*-toluenesulfonic acid monohydrate (1.397 g, 7.34 mmol) in toluene (200 mL) was stirred at reflux with a Dean-Stark trap apparatus for 180 minutes. The reaction mixture was neutralized with *N*-ethyl-*N*-isopropylpropan-2-amine and then concentrated. The residue was purified on silica gel (0-30% ethyl acetate in heptane) to give 12.77 g of the title

compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.01 (q, J = 7.1 Hz, 2H), 3.81 (s, 4H), 2.32 (tt, J = 10.4, 3.8 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.66 – 1.57 (m, 1H), 1.62 – 1.38 (m, 5H), 1.13 (t, J = 7.1 Hz, 3H).

Example 2B: ethyl 8-acetyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of diisopropylamine (5.19 mL, 36.4 mmol) in tetrahydrofuran (25 mL) at 0 °C was added *n*-butyllithium slowly below 5 °C. After stirring for 30 minutes, the solution was cooled to -78 °C under nitrogen, and a solution of Example 2A (6.0 g, 28.0 mmol) in tetrahydrofuran (3 mL) was added slowly, and the resultant mixture was stirred for 30 minutes at the same temperature. Then acetyl chloride (2.59 mL, 36.4 mmol) was added slowly to maintain the temperature below -60 °C, and the mixture was stirred at -70 °C for 2 hours. The reaction was quenched with saturated NH_4Cl solution, and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated, and the residue was purified on silica gel (0-70% ethyl acetate in heptane) to give 6.78 g of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 4.19 – 4.11 (m, 2H), 3.85 (s, 4H), 2.13 (s, 3H), 2.10 – 2.01 (m, 2H), 1.90 (ddd, J = 13.9, 9.6, 4.6 Hz, 2H), 1.54 (th, J = 13.6, 4.7 Hz, 4H), 1.18 (dd, J = 7.6, 6.5 Hz, 3H).

Example 2C: ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate

A mixture of Example 2B (6.5 g, 25.4 mmol) and HCl (21.13 mL, 127 mmol) in acetone (60 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated to give 5.46 g of the title compound that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.16 (q, J = 7.1 Hz, 2H), 2.17 (s, 3H), 2.35 2.07 (m, 8H), 1.17 (t, J = 7.1 Hz, 3H).

Example 2D: ethyl 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carboxylate, hydrochloric acid

A mixture of Example 2C (9.7 g, 45.7 mmol), benzylamine (14.98 mL, 137 mmol), and *p*-toluenesulfonic acid monohydrate (0.087 g, 0.457 mmol) in toluene (100 mL) was stirred at reflux with a Dean-Stark trap apparatus overnight. The mixture was concentrated, and the residue was stirred with a mixture of ethyl acetate (50 mL) and 3 N HCl (100 mL) for 30 minutes. The precipitate was collected by filtration, washed with mixture of ethyl acetate/heptane, and air-dried to give 11.3 g of title compound as an HCl salt. The filtrate was neutralized with 6 N NaOH and extracted with ethyl acetate (100 mL × 2). The organic layer was washed with brine, dried over magnesium sulfate and filtered. The residue was purified on silica gel (0-70% ethyl acetate in heptane) to give another 0.77 g of the title compound. ^{1}H NMR

(400 MHz, DMSO-d_6) δ ppm 9.73 (t, J = 6.2 Hz, 2H), 7.87 – 7.12 (m, 5H), 4.09 (m, 4H), 2.88 (s, 2H), 2.08 (dt, J = 20.7, 13.4 Hz, 6H), 1.16 (t, J = 7.1 Hz, 3H); MS (ESI^+) m/z 302.1 $(M+H)^+$.

Example 2E: 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carboxylic acid hydrochloride

A mixture of 2D (20.7 g, 61.3 mmol) and 25% aqueous sodium hydroxide (49.0 mL, 306 mmol) in methanol (200 mL) and water (200 mL) was stirred for 24 hours at ambient temperature. The mixture was concentrated, and the residue was acidified with 1 N HCl. The precipitate was collected by filtration, washed with water, and air dried to give 16.4 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.70 (s, 1H), 9.67 (s, 2H), 7.62 (dd, J = 7.5, 2.0 Hz, 2H), 7.43 (d, J = 6.6 Hz, 3H), 4.13 (s, 2H), 2.87 (s, 2H), 2.08 (tdq, J = 14.4, 10.8, 5.8, 5.0 Hz, 8H).

Example 2F: 1-amino-4-(benzylamino)bicyclo[2.2.2]octan-2-one, trifluoroacetic acid

To a mixture of Example 2E (5.0 g, 16.14 mmol) and oxalyl dichloride (24.21 mL, 48.4 mmol) in dichloromethane (100 mL) was added *N*,*N*-dimethylformamide (0.250 mL, 3.23 mmol), and the suspension was stirred at ambient temperature for 14 hours. The mixture was concentrated, and the residue was triturated with ether/heptane. The precipitate was collected by filtration and dried to give 4.99 g of 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carbonyl chloride hydrochloride which was used in next step without further purification. To a mixture of sodium azide (0.832 g, 12.80 mmol) in dioxane (10 mL) and water (10 mL) at 0 °C was added a suspension of the crude 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carbonyl chloride hydrochloride (0.934 g, 3.2 mmol) in dioxane (30 mL), and the solution was stirred at ambient temperature for 30 minutes. Volatiles were removed to give 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carbonyl azide which was suspended with 50 mL of toluene and heated at 65 °C for 2 hours to convert to the corresponding isocyanate. Then 3 N HCl (40 mL) was added carefully, and the mixture was stirred at 100 °C for 3 hours. Volatiles were removed under vacuum, and the residue was stirred with methanol and the inorganic salts were removed by filtration. The filtrate was concentrated, and the residue was purified by HPLC (0~60% acetonitrile in 0.1% trifluoroacetic acid/water on a Phenomenex® C18 10 µm (250 mm × 50 mm) column at a flowrate of 50 mL/minute) to give 550 mg of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 2H), 8.59 (s, 3H), 7.55 – 7.39 (m, 5H), 4.18 (s, 2H), 3.01 (s, 2H), 2.28 – 2.09 (m, 6H), 1.96 (td, J = 12.6, 12.0, 7.0 Hz, 2H); MS (ESI^+) m/z 245.1 $(M+H)^+$.

Example 2G: N-[4-(benzylamino)-2-oxobicyclo[2.2.2]octan-1-yl]-2-(4-chloro-3-fluorophenoxy)acetamide

A mixture of Example 2F (0.66 g, 0.699 mmol), 2-(4-chloro-3-fluorophenoxy)acetic acid (0.179 g, 0.873 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.610 mL, 3.49 mmol) in *N*,*N*-

dimethylformamide (10 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.398 g, 1.048 mmol), and the reaction mixture was stirred at ambient temperature for 15 minutes. The reaction mixture was partitioned between water and dichloromethane. The organic layer was concentrated, and the residue was purified by HPLC (15~100% acetonitrile in 0.1% trifluoroacetic acid/water on a Phenomenex® C18 10 µm (250 mm × 50 mm) column at a flowrate of 50 mL/minute) to give 0.34 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (d, J = 6.6 Hz, 2H), 7.84 (s, 1H), 7.55 – 7.39 (m, 6H), 7.09 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 4.59 (s, 2H), 4.17 (t, J = 5.6 Hz, 2H), 2.90 (d, J = 3.7 Hz, 2H), 2.50 – 2.36 (m, 2H), 2.23 – 2.09 (m, 2H), 2.13 – 1.95 (m, 4H); MS (ESI$^+$) *m/z* 431.2 $(M+H)^+$.

Example 2H: N-(4-amino-2-oxobicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide, trifluoroacetic acid

To a mixture of $Pd(OH)_2$ (2.7 g, 3.85 mmol) in tetrahydrofuran (500 mL) was added Example 2G (10 g, 22.05 mmol) under argon at ambient temperature, and the reaction mixture was stirred for 7.5 hours under H_2 at 50 psi. Methanol (1000 mL) was added, and the mixture was filtered through a pad of diatomaceous earth. The filter cake was washed with methanol (1000 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase HPLC (10-80% acetonitrile in 0.075% trifluoroacetic acid/water over 30 minutes on a 250 mm × 80 mm Phenomenex® Luna®-C18 10 µm column at a flowrate of 80 mL/minute) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (s, 3H), 7.81 (s, 1H), 7.49 (t, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 11.3, 2.6 Hz, 1H), 6.85 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.58 (s, 2H), 2.73 (s, 2H), 2.38 (t, *J* = 9.1 Hz, 2H), 1.95 (d, *J* = 8.3 Hz, 6H).

Example 2I: N-(4-amino-2-hydroxybicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide hydrochloride

A mixture of Example 2H (7g, 15.39 mmol) and $NaBH_4$ (0.582 g, 15.39 mmol) in a mixture of methanol (200 mL) and methylene chloride (200 mL) was stirred at 20 °C for 12 hours. The solution was concentrated, and the residue was purified by preparative HPLC (5~100% acetonitrile in water with 0.05% HCl on a SNAP C18 (20-35 µm, 800 g) column at a flow rate of 200 mL/minute) to provide the title compound (5.0 g, 83%); MS (ESI$^+$) *m/z* 343.1 $(M+H)^+$.

Example 2J: N-[(2S)-4-amino-2-hydroxybicyclo[2.2.2]octan-1-yl]-2-(4-chloro-3-fluorophenoxy)acetamide

The title compound was isolated by chiral preparative SFC of Example 2I as the first peak eluted off the column. The chirality of its enantiomer (the 2nd peak off the column) was

confirmed by X-ray crystallography. The preparative SFC (Supercritical Fluid Chromatography) was performed on a Thar 200 preparative SFC (SFC-5) system using a Chiralpak® IC-H, 250×30 mm I.D., 5 µm column. The column was heated at 38 °C, and the backpressure regulator was set to maintain 100 bar. The mobile phase A was CO_2 and B was isopropanol (0.1% ammonium hydroxide). The eluent was held isocratically at 40% of mobile phase B at a flowrate of 75 mL/minute. Fraction collection was time triggered with UV monitor wavelength set at 220 nm. MS (ESI^+) *m/z* 343.1 $(M+H)^+$.

Example 2K: (S)-2-chloro-N-(4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-hydroxybicyclo[2.2.2]octan-1-yl)acetamide

A mixture of Example 2J (1000 mg, 2.92 mmol), 2-chloroacetic acid (317 mg, 3.35 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.783 mL, 10.21 mmol) in *N*,*N*-dimethylformamide (5 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (1387 mg, 3.65 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. Volatiles were removed, and the residue was purified by HPLC (Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm × 50 mm). A 30-100% gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) is used over 25 minutes, at a flow rate of 50 mL/minute) to give 780 mg of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.79 (s, 1H), 7.54 (t, J = 8.9 Hz, 1H), 7.32 (s, 1H), 7.11 (dd, J = 11.4, 2.9 Hz, 1H), 6.89 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 5.14 (d, J = 4.4 Hz, 1H), 4.53 (s, 2H), 4.10 (dt, J = 8.8, 3.7 Hz, 1H), 3.99 (s, 2H), 2.30 (ddd, J = 12.6, 9.4, 2.4 Hz, 1H), 2.12 (ddd, J = 12.3, 10.4, 5.0 Hz, 1H), 2.01 – 1.75 (m, 8H); MS (ESI^+) *m/z* 419.0 $(M+H)^+$.

Example 2L: 2-(5-chloro-2,3-dihydro-1H-indol-1-yl)-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}acetamide

A mixture of Example 2K (50.0 mg, 0.119 mmol) in acetone (1.0 mL) was treated with potassium carbonate (33.0 mg, 0.239 mmol), 5-chloroindoline (36.6 mg, 0.239 mmol) and potassium iodide (1.386 mg, 8.35 µmol), and the mixture was stirred at 140 °C for 45 minutes in Biotage® Initiator microwave reactor (0-450 W). The reaction mixture was concentrated, and the residue was purified by HPLC (Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm × 50 mm). A 30-100% gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) is used over 25 minutes, at a flow rate of 50 mL/minute) to give 31 mg of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.39 (s, 1H), 7.24 (s, 1H), 7.11 - 7.00 (m, 2H), 6.97 (dd, J = 8.3, 2.3 Hz, 1H), 6.82 (ddd, J = 9.0, 3.0, 1.2 Hz, 1H), 6.38 (d, J = 8.3 Hz, 1H), 4.46 (s, 2H), 4.06 - 3.94 (m, 1H), 3.42 (d, J = 8.4 Hz, 2H), 2.90 (t, J = 8.4 Hz, 2H), 2.25 (ddd, J = 12.4, 9.4, 2.4 Hz, 1H), 2.05 (ddd, J = 12.2, 10.3, 5.0 Hz, 1H), 1.91 (d, J =

8.8 Hz, 2H), 1.88 - 1.79 (m, 1H), 1.75 (ddt, J = 13.2, 10.3, 3.2 Hz, 5H); MS (ESI^+) *m/z* 536.4 $(M+H)^+$.

Example 3: (2*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 102)

Example 14 was purified by chiral SFC (supercritical fluid chromatography) using a (S,S) Whelk-O®1 column (20 x 250 mm, 5 micron) eluted with 30% CH_3OH in CO_2 at 28 °C with a CO_2 flow rate of 56 mL/minute, CH_3OH flow rate of 24 mL/minute, front pressure of 179 bar, and back pressure of 100 bar to give the title compound (second enantiomer eluted, 0.016 g, 0.032 mmol, 40% yield). The absolute stereochemistry of this title compound was arbitrarily assigned. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.63 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.8 Hz, 1H), 6.92 – 6.82 (m, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 8.5, 2.5 Hz, 1H), 6.15 (s, 1H), 4.47 (s, 2H), 4.42 (dd, J = 7.4, 2.9 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.26 (s, 6H); MS (ESI^+) *m/z* 480 $(M+H)^+$.

Example 4: (2*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 103)

Example 14 was purified by chiral SFC (supercritical fluid chromatography) using a (S,S) Whelk-O®1 column (20 x 250 mm, 5 micron) eluted with 30% CH_3OH in CO_2 at 28 °C with a CO_2 flow rate of 56 mL/minute, CH_3OH flow rate of 24 mL/minute, front pressure of 179 bar, and back pressure of 100 bar to give the title compound (first enantiomer eluted, 0.015 g, 0.031mmol, 39% yield). The absolute stereochemistry of this title compound was arbitrarily assigned. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.63 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.8 Hz, 1H), 6.92 – 6.82 (m, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 8.5, 2.5 Hz, 1H), 6.15 (s, 1H), 4.47 (s, 2H), 4.42 (dd, J = 7.4, 2.9 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.26 (s, 6H); MS (ESI^+) *m/z* 480 $(M+H)^+$.

Example 5: (2*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 104)

Example 13D was purified by preparative chiral SFC (supercritical fluid chromatography) using a (S,S) Whelk-O®1 column (20 x 250 mm, 5 micron) eluted with 44%

CH_3OH in CO_2 at 33 °C with a CO_2 flow rate of 40 mL/minute, CH_3OH flow rate of 32 mL/minute, front pressure of 192 bar, and back pressure of 100 bar to give the title compound (first enantiomer eluted out of the column, 0.0082 g, 0.017 mmol, 43% yield). The absolute stereochemistry of this title compound was arbitrarily assigned. ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 8.71 (s, 1H), 8.67 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.5, 2.4 Hz, 1H), 4.61 (dd, J = 7.3, 3.0 Hz, 1H), 4.47 (s, 2H), 3.40 – 3.37 (m, 1H), 3.18 (dd, J = 12.0, 7.4 Hz, 1H), 2.83 (s, 3H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 494 $(M+H)^+$.

Example 6: (2*S*)-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 105)

A mixture of Example 2J (60.0 mg, 0.175 mmol), triethylamine (0.032 mL, 0.228 mmol), (*S*)-6-fluorochroman-2-carboxylic acid (41.2 mg, 0.210 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 80 mg, 0.210 mmol) in *N*,*N*-dimethylformamide (2 mL) was stirred overnight. The reaction mixture was quenched with brine and saturated $NaHCO_3$ and extracted with ethyl acetate (2×). The combined organic layers were concentrated, and the residue was purified by reverse-phase HPLC performed on a Zorbax Rx-C18 column (250 × 21.2 mm, 7 µm particle size) using a gradient of 10% to 95% acetonitrile : 0.1% aqueous trifluoroacetic acid over 30 minutes at a flow rate of 18 mL/minute to provide the title compound (26.9 mg, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.24 (d, J = 13.1 Hz, 2H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.91 (ddd, J = 8.4, 4.5, 1.7 Hz, 2H), 6.88 – 6.79 (m, 2H), 5.07 (s, brd, 1H), 4.47 (s, 2H), 4.41 (dd, J = 8.7, 3.0 Hz, 1H), 4.04 (dd, J = 9.6, 3.1 Hz, 1H), 2.84 – 2.60 (m, 2H), 2.27 (ddd, J = 12.1, 9.5, 2.1 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.99 – 1.71 (m, 9H); MS (ESI$^+$) *m/z* 521.2 $(M+H)^+$.

Example 7: (2*R*)-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 106)

The procedures described in Example 6 substituting (*R*)-6-fluorochroman-2-carboxylic acid for (*S*)-6-fluorochroman-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.24 (d, J = 12.5 Hz, 2H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.88 – 6.78 (m, 2H), 4.47 (s, 2H), 4.45 – 4.38 (m, 1H), 4.04 (dd, J =

9.7, 3.1 Hz, 1H), 2.84 – 2.58 (m, 2H), 2.28 (ddd, J = 12.3, 9.5, 2.3 Hz, 1H), 2.06 (dtq, J = 7.8, 5.8, 3.4, 2.3 Hz, 2H), 1.98 – 1.67 (m, 9H); MS (ESI^+) *m/z* 521.2 $(M+H)^+$.

Example 8: 6-chloro-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 107)

Example 8A: ethyl 6-chloro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

A mixture of ethyl 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylate (0.450 g, 1.862 mmol), potassium carbonate (0.772 g, 5.59 mmol), and iodomethane (0.349 mL, 5.59 mmol) in acetone (4 mL) was heated at reflux in a capped vial overnight. More iodomethane (0.349 mL) was added, and the mixture was heated at reflux for 5 hours. After cooling, the solid was filtered. The filtrate was concentrated, and the residue was treated with water and extracted with ethyl acetate (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified on a 40 g column using a Biotage® Isolera™ One flash system eluted with heptanes/ethyl acetate (9:1 to 8:2) to provide the title compound (0.308 g, 65%). MS (ESI^+) *m/z* 256.1 $(M+H)^+$.

Example 8B: 6-chloro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

A solution of Example 8A (0.300 g, 1.173 mmol) in tetrahydrofuran (3 mL) and methanol (2 mL) was treated with a solution of lithium hydroxide (0.084 g, 3.52 mmol) in water (1.5 mL). The mixture was stirred for 4 hours. The reaction mixture was concentrated. The concentrate was dissolved in water and acidified with 5% citric acid until pH=4. The precipitate was collected by filtration, rinsed with water, and vacuum oven-dried to provide the title compound (0.171g, 64%). MS (ESI^+) *m/z* 228.2 $(M+H)^+$.

Example 8C: 6-chloro-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

A mixture of Example 2J (110.0 mg, 0.321 mmol), triethylamine (0.058 mL, 0.417 mmol), Example 8B (88 mg, 0.385 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 146 mg, 0.385 mmol) in *N*,*N*-dimethylformamide (3 mL) was stirred for 5 hours. The reaction mixture was quenched with brine and saturated $NaHCO_3$ and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The concentrate was dissolved in tetrahydrofuran (1.5 mL) and methanol (1.2 mL) and then treated with a solution of lithium hydroxide (11.53 mg, 0.481 mmol) in water (1 mL). The mixture was stirred for 2 hours, diluted with ethyl acetate, and washed with brine. The organic layer was dried over $MgSO_4$,

filtered, and concentrated. The residue was purified by reverse-phase HPLC (see protocol in Example 6) to provide the title compound (49.2 mg, 28%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 – 6.73 (m, 2H), 6.69 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 8.5, 2.4 Hz, 1H), 5.07 (d, J = 4.4 Hz, 1H), 4.54 (ddd, J = 7.4, 2.9, 1.3 Hz, 1H), 4.46 (s, 2H), 4.04 (dt, J = 8.8, 3.6 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.16 (ddd, J = 12.4, 7.1, 1.3 Hz, 1H), 2.83 (s, 3H), 2.32 – 2.17 (m, 1H), 2.12 – 2.01 (m, 1H), 1.96 – 1.71 (m, 8H); MS (ESI$^+$) *m/z* 552.1 $(M+H)^+$.

Example 9: *N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6,7-difluoro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 108)

Example 9A: ethyl 6,7-difluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

To a solution of 2-amino-4,5-difluorophenol (1.0 g, 6.9 mmol) in acetone (14 mL) was added potassium carbonate (2.67 g, 19.3 mmol), followed by ethyl 2,3-dibromopropanoate (1.1 mL, 7.6 mmol). The reaction mixture was refluxed for 16 hours, concentrated, filtered, and concentrated to give the title intermediate (1.5 g, 6.0 mmol, 87% yield) without further purification. MS (ESI$^+$) *m/z* 244 $(M+H)^+$.

Example 9B: 6,7-difluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of the product of Example 9A (1.45 g, 5.98 mmol) in a solution of tetrahydrofuran (3 mL):H_2O (3 mL) was added sodium hydroxide (0.039 g, 0.98 mmol). The reaction mixture stirred for 17 hours and then concentrated. The residue was diluted with H_2O (3 mL), acidified with 1 N HCl at 0 °C, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title intermediate (1.0 g, 4.65 mmol, 78%yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 6.83 (dd, J = 11.7, 7.8 Hz, 1H), 6.55 (dd, J = 12.2, 8.2 Hz, 1H), 4.83 (dd, J = 4.0, 3.3 Hz, 1H), 3.44 – 3.34 (m, 2H); MS (ESI$^+$) *m/z* 216 $(M+H)^+$.

Example 9C: N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6,7-difluoro-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

To a mixture of the product of Example 23B (0.10 g, 0.35 mmol) and the product of Example 9B (0.079 g, 0.37 mmol) in *N*,*N*-dimethylformamide (2 mL) was added triethylamine (0.2 mL, 1.4 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 0.15 g, 0.39 mmol). This reaction mixture was allowed to stir at ambient temperature for 24 hours. Then the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The

combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.015 g, 0.031 mmol, 9 % yield). ^{1}H NMR (501 MHz, DMSO- d_6) δ ppm 8.70 (s, 1H), 8.61 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.9 Hz, 1H), 6.92 – 6.76 (m, 2H), 6.56 (dd, J = 12.2, 8.1 Hz, 1H), 5.98 (s, 1H), 4.47 (s, 2H), 4.43 (dd, J = 7.2, 2.9 Hz, 1H), 3.15 (d, J = 10.0 Hz, 1H), 2.25 (s, 6H); MS (ESI$^+$) *m/z* 482 $(M+H)^+$.

Example 10: *N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 109)

To a mixture of the product of Example 23B (0.15 g, 0.53 mmol) and 3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid (0.11 g, 0.55 mmol) in *N*,*N*-dimethylformamide (3 mL) was added triethylamine (0.3 mL, 2 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 0.22 g, 0.58 mmol). This reaction mixture was allowed to stir at ambient temperature for 18 hours. Then the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.20 g, 0.43 mmol, 82% yield). ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 10.84 (s, 1H), 9.04 (s, 1H), 8.71 (s, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.12 – 7.02 (m, 1H), 6.97 – 6.83 (m, 5H), 5.00 (s, 1H), 4.46 (s, 2H), 2.23 (s, 6H); MS (ESI$^+$) *m/z* 460 $(M+H)^+$.

Example 11: *N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 110)

The procedures described in Example 8C substituting 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid for Example 8B gave the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.26 (s, 1H), 7.17 (s, 1H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (dd, J = 8.9, 2.7 Hz, 1H), 6.76 (dd, J = 8.2, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.5 Hz, 1H), 6.58 (dd, J = 7.9, 1.6 Hz, 1H), 6.51 (td, J = 7.6, 1.6 Hz, 1H), 4.46 (s, 2H), 4.39 – 4.32

(m, 1H), 4.04 (dd, J = 9.6, 3.1 Hz, 1H), 3.37 (dd, J = 11.9, 2.9 Hz, 1H), 3.19 – 3.10 (m, 1H), 2.27 (dddd, J = 12.1, 9.3, 5.0, 2.4 Hz, 1H), 2.06 (ddd, J = 12.3, 10.1, 5.6 Hz, 1H), 1.96 – 1.67 (m, 8H); MS (ESI^+) *m/z* 504.1 $(M+H)^+$.

Example 12: *N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 111)

The procedures described in Example 8C substituting 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid for Example 8B gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.24 (d, J = 14.7 Hz, 2H), 7.05 (dd, J = 11.4, 2.8 Hz, 1H), 6.85 – 6.76 (m, 3H), 6.70 (dd, J = 8.4, 1.6 Hz, 1H), 6.61 (td, J = 7.5, 1.6 Hz, 1H), 4.55 (dd, J = 7.7, 2.7 Hz, 1H), 4.47 (s, 2H), 4.04 (dd, J = 9.6, 3.1 Hz, 1H), 3.33 (dd, J = 11.8, 2.9 Hz, 1H), 3.11 (dd, J = 11.8, 7.6 Hz, 1H), 2.81 (s, 3H), 2.27 (ddt, J = 12.4, 9.4, 2.9 Hz, 1H), 2.07 (td, J = 11.7, 5.0 Hz, 1H), 1.97 – 1.69 (m, 8H); MS (ESI^+) *m/z* 518.3 $(M+H)^+$.

Example 13: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 112)

Example 13A: ethyl 6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

To a solution of 2-amino-4-chlorophenol (2.00 g, 13.9 mmol) in acetone (77 mL) was added potassium carbonate (5.39 g, 39.0 mmol) followed by ethyl 2,3-dibromopropanoate (2.2 mL, 15 mmol). The reaction mixture was refluxed for 16 hours providing the title intermediate without isolation. MS (ESI^+) *m/z* 283 $(M+CH_3CN)^+$.

Example 13B: ethyl 6-chloro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

To the reaction mixture of Example 13A was added iodomethane (3 mL, 49 mmol) and additional potassium carbonate (1.00 g, 6.97 mmol). The reaction mixture was refluxed for 5 hours and then stirred at ambient temperature for 4 days, resulting in incomplete conversion. The reaction mixture was filtered, concentrated, and purified by preparative HPLC [Waters XBridge™ C18 5 µm OBD column, 50 × 100 mm, flow rate 90 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title intermediate (1 g, 4 mmol, 28% yield). ^1H NMR (501 MHz, DMSO-d_6) δ ppm 6.77 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.5, 2.4 Hz, 1H), 5.06 (dd, J = 4.0, 3.2 Hz, 1H), 4.25 – 4.06 (m, 2H), 3.52 – 3.36 (m, 2H), 2.82 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); MS (ESI^+) *m/z* 256 $(M+H)^+$.

Example 13C: 6-chloro-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of the product of Example 13B (0.10 g, 0.39 mmol) in a solution of tetrahydrofuran (1 mL):H_2O (1 mL) was added sodium hydroxide (0.039 g, 0.98 mmol). The reaction mixture stirred for 3 days and then was concentrated. The residue was diluted with H_2O (3 mL), acidified with 1 N HCl at 0 °C, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title intermediate (0.078 g, 0.34 mmol, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.73 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.60 (dd, J = 8.4, 2.5 Hz, 1H), 4.85 (s, 1H), 2.81 (s, 3H), 1.24 (s, 2H); MS (ESI$^-$) *m/z* 226 $(M-H)^+$.

Example 13D: 6-chloro-N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-methyl-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

To a mixture of the product of Example 23B (0.030 g, 0.11 mmol) and the product of Example 13C (0.025 g, 0.11 mmol) in *N*,*N*-dimethylformamide (0.6 mL) was added triethylamine (0.06 mL, 0.4 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 0.044 g, 0.12 mmol). This reaction mixture was allowed to stir at ambient temperature for 5.5 hours. Then the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC [Waters XBridge™ C18 5 µm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.035 g, 0.071 mmol, 67% yield). ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 8.71 (s, 1H), 8.67 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.5, 2.4 Hz, 1H), 4.61 (dd, J = 7.3, 3.0 Hz, 1H), 4.47 (s, 2H), 3.40 - 3.37 (m, 1H), 3.18 (dd, J = 12.0, 7.4 Hz, 1H), 2.83 (s, 3H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 494 $(M+H)^+$.

Example 14: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 113)

To a mixture of Example 23B (0.070 g, 0.25 mmol) and 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid (0.055 g, 0.26 mmol) in *N*,*N*-dimethylformamide (1.4 mL) was added triethylamine (0.14 mL, 0.98 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 0.10 g, 0.27 mmol). This reaction mixture was allowed to stir at ambient temperature

for 3 hours. Then the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.075 g, 0.16 mmol, 64% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.63 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.8 Hz, 1H), 6.92 6.82 (m, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 8.5, 2.5 Hz, 1H), 6.15 (s, 1H), 4.47 (s, 2H), 4.42 (dd, J = 7.4, 2.9 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 480 (M+H)$^+$.

Example 15: 6-chloro-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 114)

The methodologies described in Example 8C substituting 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid for Example 8B gave the title compound. ^{1}H NMR (500 MHz, methanol-d_4) δ ppm 7.40 – 7.33 (m, 1H), 6.92 (dd, J = 10.9, 2.9 Hz, 1H), 6.84 – 6.75 (m, 2H), 6.61 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 8.6, 2.5 Hz, 1H), 4.45 (d, J = 1.5 Hz, 2H), 4.41 (dt, J = 7.2, 3.0 Hz, 1H), 4.31 – 4.19 (m, 1H), 3.50 (dd, J = 12.0, 2.8 Hz, 1H), 3.26 (dd, J = 12.0, 7.4 Hz, 1H), 2.54 – 2.40 (m, 1H), 2.20 – 1.80 (m, 9H); MS (ESI$^+$) *m/z* 538.3 (M+H)$^+$.

Example 16: (2*R*)-6-chloro-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 115)

The methodologies described in Example 6 substituting (*R*)-6-chloro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for (*S*)-6-fluorochroman-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.52-7.45 (m, 2H), 7.26 (s, 1H), 7.05 (dd, J = 11.4, 2.8 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.90 (dd, J = 8.7, 2.5 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.08 (d, J = 4.3 Hz, 1H), 4.66 (dd, J = 6.1, 2.7 Hz, 1H), 4.46 (s, 2H), 4.33 (dd, J = 11.6, 2.7 Hz, 1H), 4.15 (dd, J = 11.6, 6.1 Hz, 1H), 4.04 (dt, J = 8.6, 3.6 Hz, 1H), 2.25 (ddd, J = 12.4, 9.4, 2.4 Hz, 1H), 2.06 (ddd, J = 12.2, 10.1, 5.1 Hz, 1H), 1.97 – 1.66 (m, 8H); MS (ESI$^+$) *m/z* 539.2 (M+H)$^+$.

Example 17: (2*R*)-6-chloro-*N*-{(3*S*)-4-[2-(3,4-dichlorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 116)

Example 17A: N-[(2S)-4-amino-2-hydroxybicyclo[2.2.2]octan-1-yl]-2-(3,4-dichlorophenoxy)acetamide

The title compound was synthesized using the methodologies described in Examples 2A-J substituting 2-(3,4-dichlorophenoxy)acetic acid for 2-(4-chloro-3-fluorophenoxy)acetic acid in Example 2G. MS (ESI^+) *m/z* 359.0 $(M+H)^+$.

*Example 17B: (2R)-6-chloro-N-{(3S)-4-[2-(3,4-dichlorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide*The methodologies described in Example 6 substituting Example 17A and (*R*)-6-chloro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for Example 2J and (*S*)-6-fluorochroman-2-carboxylic acid, respectively, gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.53 (d, J = 8.9 Hz, 2H), 7.28 – 7.20 (m, 2H), 7.01 – 6.92 (m, 3H), 6.90 (dd, J = 8.6, 2.5 Hz, 1H), 5.08 (d, J = 4.4 Hz, 1H), 4.66 (dd, J = 6.1, 2.7 Hz, 1H), 4.47 (s, 2H), 4.33 (dd, J = 11.6, 2.6 Hz, 1H), 4.15 (dd, J = 11.6, 6.1 Hz, 1H), 4.03 (dt, J = 8.7, 3.7 Hz, 1H), 2.25 (ddd, J = 12.5, 9.5, 2.3 Hz, 1H), 2.06 (ddd, J = 12.3, 10.2, 5.0 Hz, 1H), 1.94 – 1.73 (m, 8H); MS (ESI^+) *m/z* 555.2 $(M+H)^+$.

Example 18: 6,7-dichloro-*N*-{3-[2-(3,4-difluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 117)

Example 18A: ethyl 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylate

A mixture of 4,5-dichlorobenzene-1,2-diol (0.806 g, 4.5 mmol) was refluxed with ethyl 2,3-dibromopropanoate (1.170 g, 4.50 mmol) in acetone (10 mL) with potassium carbonate (0.933 g, 6.75 mmol) for 7 hours. The reaction mixture was concentrated and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water (30 mL × 2), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (40 g) eluted with heptane and ethyl acetate (5 to 20%) to give the title intermediate (0.93 g, 75% yield). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.30 (s, 1H), 7.21 (s, 1H), 5.28 (t, J = 3 Hz, 1H), 4.51 (dd, J = 12, 3 Hz, 1H), 4.33 (dd, J = 12, 3 Hz, 1H), 4.17 (q, J = 7 Hz, 2H), 1.18 (t, J = 7 Hz, 3H); MS (ESI+) *m/z* 277 $(M+H)^+$.

Example 18B: 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylic acid

To Example 18A (910 mg, 3.28 mmol) in CH_3OH (20 mL) was added 4 N sodium hydroxide (8210 µL, 32.8 mmol) solution. The mixture was stirred at room temperature for 2 hours. Then the mixture was concentrated, and acidified with 1 N aqueous HCl solution to pH~6. The resulting solid was collected by filtration, and dried to give the title intermediate as a solid (755 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.28 (s, 1H), 7.21 (s, 1H), 5.17 (t, J = 3 Hz, 1H), 4.51 (dd, J = 12, 3 Hz, 1H), 4.33 (dd, J = 12, 3 Hz, 1H); MS (ESI-) *m/z* 247 $(M-H)^-$.

Example 18C: tert-butyl (3-(6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxamido)bicyclo[1.1.1]pentan-1-yl)carbamate

To a mixture of Example 18B (249 mg, 1), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 418 mg, 1.100 mmol) and *tert*-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (198 mg, 1.000 mmol) was added *N*-ethyl-*N*-isopropylpropan-2-amine (258 mg, 2.000 mmol) in *N*,*N*-dimethylformamide (4 mL). The mixture was stirred at room temperature for 20 minutes, and then water (20 mL) was added. The mixture was extracted with ethyl acetate (100 mL). The organic phase was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated to give the title intermediate as a solid (0.43 g, 100% yield) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (s, 1H), 7.96 (s, 1H), 7.23 (s, 1H), 7.22 (s, 1H), 4.80 (dd, J = 6, 3 Hz, 1H), 4.30 (m, 2H), 2.15 (s, 6H), 1.38 (s, 9H); MS (ESI+) *m/z* 429 $(M+H)^+$.

Example 18D: N-(3-aminobicyclo[1.1.1]pentan-1-yl)-6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxamide, trifluoroacetic acid

To *tert*-butyl (3-(6,7-dichloro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamido)bicyclo[1.1.1]pentan-1-yl)carbamate (425 mg, 0.990 mmol) in dichloromethane (12 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was directly purified by preparative HPLC [Waters XBridge™ C18 5 µm OBD column, 50 × 100 mm, flow rate 90 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid)] to give the title intermediate (295 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.98 (s, 1H), 8.72 (s, 3H), 7.23 (s, 1H), 7.22 (s, 1H), 4.87 (dd, J = 5, 4 Hz, 1H), 4.32 (m, 2H), 2.24 (s, 6H); MS (ESI+) *m/z* 329 $(M+H)^+$.

Example 18E: 6,7-dichloro-N-{3-[2-(3,4-difluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide

To a mixture of Example 18D (31.0 mg, 0.070 mmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 26.6 mg, 0.070 mmol) and 2-(3,4-difluorophenoxy)acetic acid (13.17 mg, 0.07 mmol) was added *N*-ethyl-*N*-isopropylpropan-2-amine (45.2 mg, 0.350 mmol) in *N*,*N*-dimethylformamide (1 mL). The

mixture was stirred at room temperature for 20 minutes, then water (0.02 mL) was added, and the mixture was directly purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 50 × 100 mm, flow rate 90 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid)] to give the title intermediate (25 mg,72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (s, 1H), 8.69 (s, 1H), 7.36 (q, J = 8 Hz, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.08 (m, 1H), 6.80 (m, 1H), 4.82 (dd, J = 5, 3 Hz, 1H), 4.43 (s, 2H), 4.29 (m, 2H), 2.25 (s, 6H); MS (ESI-) *m/z* 499 $(M-H)^-$.

Example 19: *N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6,7-difluoro-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 118)

Example 19A: ethyl 6,7-difluoro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylate

The reaction and purification conditions described in Example 18A substituting 4,5-difluorobenzene-1,2-diol for 4,5-dichlorobenzene-1,2-diol gave the title compound (140 mg, 21% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.16 (dd, J = 8, 11 Hz, 1H), 7.06 (dd, J = 8, 11 Hz, 1H), 5.22 (t, J = 3 Hz, 1H), 4.47 (dd, J = 12, 3 Hz, 1H), 4.30 (dd, J = 12, 3 Hz, 1H), 4.17 (q, J = 7 Hz, 2H), 1.19 (t, J = 7 Hz, 3H); MS (DCI+) *m/z* 262 $(M+NH_4)^+$.

Example 19B: 6,7- difluoro-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxylic acid

The reaction and purification conditions described in Example 18B substituting Example 19A for Example 18A gave the title compound (125 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.95 (dd, J = 8, 11 Hz, 1H), 6.87 (dd, J = 8, 11 Hz, 1H), 4.25 (m, 2H), 4.09 (dd, J = 7, 11 Hz, 1H); MS (ESI-) *m/z* 215 $(M-H)^-$.

Example 19C: N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6,7-difluoro-2,3-dihydro-1,4-benzodioxine-2-carboxamide

The reaction and purification conditions described in Example 23C substituting Example 19B for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (120 mg, 59% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (s, 1H), 8.69 (s, 1H), 7.47 (t, J = 8, 1H), 7.04 (m, 3H), 6.82 (br d, J = 8 Hz, 1H), 4.72 (dd, J = 6, 3 Hz, 1H), 4.44 (s, 2H), 4.29 (dd, J = 11, 3 Hz, 1H), 4.17 (dd, J = 11, 6 Hz, 1H), 2.25 (s, 6H); MS (ESI+) *m/z* 483 $(M+H)^+$.

Example 20: (2*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 119)

The reaction and purification conditions described in Example 23C substituting (*R*)-6-chloro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-

2-carboxylic acid gave the title compound (43 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (s, 1H), 8.71 (s, 1H), 7.49 (t, J = 8, 1H), 7.07 (dd, J = 9, 3, 1H), 6.98 (m, 2H), 6.93 (dd, J = 8, 3 Hz, 1H), 6.85 (br d, J = 8 Hz, 1H), 4.74 (dd, J = 6, 3 Hz, 1H), 4.47 (s, 2H), 4.35 (dd, J = 11, 3 Hz, 1H), 4.20 (dd, J = 11, 6 Hz, 1H), 2.25 (s, 6H); MS (ESI+) *m/z* 481 $(M+H)^+$.

Example 21: (2*R*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 120)

The reaction and purification conditions described in Example 23C substituting (*R*)-6-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (44 mg, 86% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1H), 8.61 (s, 1H), 7.50 (t, J = 8 Hz,, 1H), 7.06 (dd, J = 9, 3 Hz, 1H), 6.85 - 6.95 (m, 4H), 4.48 (s, 2H), 4.43 (dd, J = 9, 3 Hz, 1H), 2.80 (m, 1H), 2.68 (m, 1H), 2.27 (s, 6H), 2.13 (m, 1H), 1.82 (m, 1H); MS (ESI+) *m/z* 463 $(M+H)^+$.

Example 22: (2*S*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 121)

The reaction and purification conditions described in Example 23C substituting (*S*)-6-fluoro-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (42 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1H), 8.61 (s, 1H), 7.50 (t, J = 8 Hz,, 1H), 7.06 (dd, J = 9, 3 Hz, 1H), 6.85 - 6.95 (m, 4H), 4.48 (s, 2H), 4.43 (dd, J = 9, 3 Hz, 1H), 2.80 (m, 1H), 2.68 (m, 1H), 2.27 (s, 6H), 2.13 (m, 1H), 1.82 (m, 1H); MS (ESI+) *m/z* 463 $(M+H)^+$.

Example 23: *N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 122)

Example 23A: tert-butyl (3-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate

To a solution of 2-(4-chloro-3-fluorophenoxy)acetic acid (Aldlab Chemicals, 2.01 g, 9.84 mmol) in *N*,*N*-dimethylformamide (25 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (3.96 mL, 22.7 mmol) followed by 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (3.02 g, 7.94 mmol). This mixture was stirred at ambient temperature for 5 minutes, and then *tert*-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (PharmaBlock, 1.5 g, 7.57 mmol) was added. The mixture was allowed to stir at ambient temperature for 16 hours. The reaction mixture was quenched with saturated, aqueous

NH_4Cl (20 mL) and then washed with CH_2Cl_2 (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% ethyl acetate/heptanes to 80% ethyl acetate/heptanes) to give the title compound (2.65 g, 6.89 mmol, 91% yield). MS (ESI^+) m/z 402 $(M+NH_4)^+$.

Example 23B: N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide

To solution of Example 23A (9 g, 23.39 mmol) in dichloromethane (100 mL) was added trifluoroacetic acid (30 mL, 389 mmol) at 0 °C. The mixture was stirred at ambient temperature for 12 hours. The mixture was concentrated under reduced pressure, and the residue was diluted with water (300 mL). The aqueous phase was adjusted to pH=8 with $NaHCO_3$ and then extracted with dichloromethane (4 × 150 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 6 g (90%) of the title compound. MS (APCI) m/z 285 $(M+H)^+$.

Example 23C: N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide

To a solution of Example 23B (40mg, 0.140 mmol) in *N*,*N*-dimethylformamide (0.8 mL) were added 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (27.8 mg, 0.155 mmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 58.8 mg, 0.155 mmol), and *N*,*N*-diisopropylethylamine (0.074 mL, 0.421 mmol) at room temperature. The reaction mixture was stirred for 1 hour at room temperature. The mixture was purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD™ column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid in water)] to give the title compound.(45mg, 0.101 mmol, 71.7 % yield). ^1H NMR (501 MHz, DMSO-d_6) δ ppm 8.78 (s, 1H), 8.70 (s, 1H), 7.47 (t, J = 8.9 Hz, 1H), 7.05 (dd, J = 11.3, 2.9 Hz, 1H), 6.97 - 6.92 (m, 1H), 6.87 - 6.80 (m, 4H), 4.67 (dd, J = 6.5, 2.7 Hz, 1H), 4.45 (s, 2H), 4.31 (dd, J = 11.6, 2.7 Hz, 1H), 4.12 (dd, J = 11.6, 6.5 Hz, 1H), 2.24 (s, 6H); MS (ESI+) *m/z* 464 $(M+NH_4)^+$.

Example 24: *N*-{(2*R*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 123)

Example 24A: (R)-N-(4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide 2,2,2-trifluoroacetate

The title compound was isolated by chiral preparative SFC (supercritical fluid chromatography) of Example 30E as the first peak eluted off the column, followed by reverse phase HPLC purification to give the title compound as a trifluoroacetic acid salt. The preparative SFC (supercritical fluid chromatography) was performed on a Thar 200 preparative SFC (SFC-5) system using a Chiralpak® IC, 300 ×5 0 mm I.D., 10 µm column. The column was heated at 38 °C, and the backpressure regulator was set to maintain 100 bar. The mobile phase A is CO_2 and B is isopropanol (0.1% ammonium hydroxide). The chromatography was performed isocratically at 45% of mobile phase B at a flow rate of 200 mL/minute. Fraction collection was time triggered with UV monitor wavelength set at 220 nm. Preparative HPLC was performed on a Gilson 281 semi-preparative HPLC system using a Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm × 80 mm) column. A gradient of acetonitrile (A) and 0.075% trifluoroacetic acid in water (B) was used, at a flow rate of 80 mL/minute. A linear gradient was used from about 30% of A to about 100% of A over about 30 minutes. Detection method was UV at wave length of 220 nM and 254 nM. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 7.36 (t, *J*=8.77 Hz, 1H), 6.89 (dd, *J*=10.74, 2.85 Hz, 1H), 6.79 (br d, *J*=9.21 Hz, 1H), 4.43 (s, 2H), 3.94 (br d, *J*=8.33 Hz, 1H), 2.55 (br t, *J*=12.50 Hz, 1H), 2.35 – 1.84 (m, 8H), 1.83 – 1.58 (m, 2H); MS (ESI$^+$) *m/z* 343.0 (M+H)$^+$.

Example 24B: N-{(2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide

To a solution of Example 24A (64 mg, 0.140 mmol) in *N*,*N*-dimethylformamide (0.8 mL) were added 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (27.8 mg, 0.154 mmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 58.6 mg, 0.154 mmol), and *N.N*-diisopropylethylamine (0.073 mL, 0.420 mmol) at room temperature. The reaction mixture was stirred 1 hour at room temperature. The mixture was purified by preparative HPLC [Waters XBridge™ C18 5 µm OBD™ column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid in water)] to give the title compound. (25 mg, 0.05 mmol, 35.3 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.47 (s, 1H), 7.44 (t, J = 8.9 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.98 (dd, J = 11.4, 2.9 Hz, 1H), 6.94 - 6.88 (m, 1H), 6.86 - 6.79 (m, 3H), 6.77 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.65 (dt, J = 6.5, 3.1 Hz, 1H), 4.39 (s, 2H), 4.29 (dt, J = 11.5, 3.0 Hz, 1H), 4.09 (ddd, J = 11.6, 6.6, 3.3 Hz, 1H), 3.92 (ddd, J = 39.3, 9.5, 3.2 Hz, 1H), 2.24 (tdd, J = 12.3, 9.5, 2.5 Hz, 1H), 2.13 (ddt, J = 17.7, 7.6, 3.0 Hz, 1H), 1.95 - 1.64 (m, 8H); MS (ESI+) *m/z* 522 (M+H)$^+$.

Example 25: (2*R*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 124)

The reaction and purification conditions described in Example 23C substituting (*R*)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (41 mg, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (s, 1H), 8.71 (s, 1H), 7.49 (t, J = 8 Hz, 1H), 7.07 (dd, J = 9, 3 Hz, 1H), 6.95 (m, 1H), 6.85 (m, 4H), 4.69 (dd, J = 6, 3 Hz, 1H), 4.47 (s, 2H), 4.32 (dd, J = 11, 3 Hz, 1H), 4.13 (dd, J = 11, 6 Hz, 1H), 2.25 (s, 6H); MS (ESI+) *m/z* 447 $(M+H)^+$.

Example 26: (2*S*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 125)

The reaction and purification conditions described in Example 23C substituting (*S*)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (42 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (s, 1H), 8.71 (s, 1H), 7.49 (t, J = 8 Hz, 1H), 7.07 (dd, J = 9, 3 Hz, 1H), 6.95 (m, 1H), 6.85 (m, 4H), 4.69 (dd, J = 6, 3 Hz, 1H), 4.47 (s, 2H), 4.32 (dd, J = 11, 3 Hz, 1H), 4.13 (dd, J = 11, 6 Hz, 1H), 2.25 (s, 6H); MS (ESI+) *m/z* 447 $(M+H)^+$.

Example 27: (2*R*)-*N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 126)

Example 27A: N-[(3S)-4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl]-2-(4-chloro-3-fluorophenoxy)acetamide trifluoroacetate

The title compound was isolated by chiral preparative SFC of Example 30E as the second peak eluted off the column, followed by reverse phase HPLC purification to give the title compound as a trifluoroacetic acid salt. The preparative SFC (Supercritical Fluid Chromatography) was performed on a Thar 200 preparative SFC (SFC-5) system using a Chiralpak® IC, 300 ×5 0 mm I.D., 10 µm column. The column was at 38 °C, and the backpressure regulator was set to maintain 100 bar. The mobile phase A is CO_2 and B is isopropanol (0.1% ammonium hydroxide). The chromatography was performed isocratically at 45% of mobile phase B at a flow rate of 200 mL/minute. Fraction collection was time triggered with UV monitor wavelength set at 220 nm. Preparative HPLC was performed on a Gilson 281 semi-preparative HPLC system using a Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm × 80 mm) column. A gradient of acetonitrile (A) and 0.075% trifluoroacetic

acid in water (B) was used, at a flow rate of 80 mL/minute. A linear gradient was used from about 30% of A to about 100% of A over about 30 minutes. Detection method was UV at wave lengths of 220 nM and 254 nM. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 7.36 (t, J=8.77 Hz, 1H), 6.89 (dd, J=10.74, 2.85 Hz, 1H), 6.79 (br d, J=9.21 Hz, 1H), 4.43 (s, 2H), 3.94 (br d, J=8.33 Hz, 1H), 2.55 (br t, J=12.50 Hz, 1H), 2.35 – 1.84 (m, 8H), 1.83 – 1.58 (m, 2H); MS (ESI$^+$) m/z 343.0 $(M+H)^+$.

Example 27B: (2R)-N-{(2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide

To a mixture of Example 27A (45.7 mg, 0.1 mmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 41.8 mg, 0.110 mmol) and (*R*)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (18.02 mg, 0.100 mmol) was added *N*-ethyl-*N*-isopropylpropan-2-amine (78 mg, 0.600 mmol) in *N*,*N*-dimethylformamide (0.9 mL). The mixture was stirred at room temperature for 1 hour. The mixture was purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD™ column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid in water)] to give the title compound (34mg, 0.067 mmol, 67 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (s, 1H), 7.48 (t, J = 8, 1H), 7.24 (s, 1H), 7.04 (dd, J = 9, 3 Hz, 1H), 6.95 (m, 1H), 6.80-6.90 (m, 4H), 4.69 (dd, J = 6, 3 Hz, 1H), 4.44 (s, 2H), 4.34 (dd, J = 11, 3 Hz, 1H), 4.13 (dd, J = 11, 6 Hz, 1H), 4.01 (m, 1H), 2.28 (m, 1H), 2.15 (m, 1H), 1.72 - 1.95 (m, 8H); MS (ESI+) m/z 505 $(M+H)^+$.

Example 28: (2*S*)-*N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1,4-benzodioxine-2-carboxamide (Compound 127)

The reaction and purification conditions described in Example 27 substituting (*S*)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid for (*R*)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound (32 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (s, 1H), 7.48 (t, J = 8 Hz, 1H), 7.24 (s, 1H), 7.04 (dd, J = 9, 3 Hz, 1H), 6.95 (m, 1H), 6.80-6.90 (m, 4H), 4.69 (dd, J = 6, 3 Hz, 1H), 4.44 (s, 2H), 4.34 (dd, J = 11, 3 Hz, 1H), 4.13 (dd, J = 11, 6 Hz, 1H), 3.91 (m, 1H), 2.30 - 2.15 (m, 2H), 1.70 - 1.95 (m, 8H); MS (ESI+) m/z 505 $(M+H)^+$.

Example 29: (2*R*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1*H*-indole-2-carboxamide (Compound 128)

The product of Example 23B was processed as in Example 23C substituting (2*R*)-2,3-dihydro-1*H*-indole-2-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid to give the title compound. 1H NMR (501 MHz, DMSO-*d6*-D_2O) δ ppm 7.49 (t, J = 8.8 Hz, 1H), 7.14 – 7.00 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.68 – 6.57 (m, 2H), 4.47 (s, 2H), 4.16 (dd, J = 10.5, 7.8 Hz, 1H), 3.29 (dd, J = 16.3, 10.5 Hz, 1H), 2.98 – 2.85 (m, 1H), 2.26 (s, 6H); MS (ESI^+) *m/z* 430 $(M+H)^+$

Example 30: *N*-{4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-2,3-dihydro-1-benzofuran-2-carboxamide (Compound 129)

Example 30A: ethyl 4-amino-2-oxobicyclo[2.2.2]octane-1-carboxylate, hydrochloric acid

To a mixture of Example 2D (11.2 g, 33.2 mmol) in tetrahydrofuran (110 mL) in a 250 mL pressure bottle was added 20% $Pd(OH)_2$/C, wet (2.2 g, 1.598 mmol), and the reaction mixture was shaken at 50 °C under 50 psi of hydrogen for 22 hours. The reaction mixture was cooled to ambient temperature, solids were removed by filtration and washed with methanol (1 L). The filtrate and wash were concentrated to give 7.9 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 2H), 2.17 – 2.05 (m, 2H), 2.04 – 1.78 (m, 6H), 1.14 (t, *J* = 7.1 Hz, 3H).

Example 30B: ethyl 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylate

To a suspension of Example 30A (7.8 g, 31.5 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (22.00 mL, 126 mmol) and 2-(4-chloro-3-fluorophenoxy)acetic acid (7.41 g, 36.2 mmol) in *N*,*N*-dimethylformamide (200 mL), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (14.97 g, 39.4 mmol) was added, and the resulting brown solution was stirred at ambient temperature for 16 hours. Water was added, and the mixture was stirred for 15 minutes. The precipitate was collected by filtration, washed with water, and air-dried to give 12.1 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.87 (s, 1H), 7.45 (t, *J* = 8.9 Hz, 1H), 7.00 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.79 (ddd, *J* = 8.9, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.73 (s, 2H), 2.07 (m, 1H), 2.01 – 1.84 (m, 6H), 1.14 (t, *J* = 7.1 Hz, 3H); MS (ESI^+) *m/z* 398.0 $(M+H)^+$.

Example 30C: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

A suspension of Example 30B (11.37 g, 28.6 mmol) and sodium hydroxide (7.15 mL, 57.2 mmol, 8 M solution) in methanol (100 mL) was stirred at ambient temperature for 16 hours. Volatiles were removed, and the residue was acidified with 1 N HCl. The precipitate was

collected by filtration and dried in vacuum oven to give 9.9 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.49 (s, 1H), 7.86 (s, 1H), 7.45 (t, J = 8.9 Hz, 1H), 7.00 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 – 6.74 (m, 1H), 4.45 (s, 2H), 2.71 (s, 2H), 2.01 – 1.81 (m, 7H); MS (ESI$^-$) m/z 368.1 (M-H)$^-$.

Example 30D: N-(4-amino-3-oxobicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide

A mixture of Example 30C (3.24 g, 8.76 mmol), diphenylphosphoryl azide (2.84 mL, 13.14 mmol), and triethylamine (3.66 mL, 26.3 mmol) in toluene (100 mL) was heated at reflux for 2 hours. The solution was cooled to ambient temperature and poured into 150 mL of 3 N HCl solution. The mixture was stirred for 16 hours to give a suspension. The precipitate was filtered, washed with ethyl acetate, and air-dried to give the title compound (1.63 g) as an HCl salt. The filtrate was then basified with solid sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified on silica gel (0-10% methanol/dichloromethane) to give the title compound (0.6 g) as the free base. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (s, 3H), 8.08 (s, 1H), 7.45 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.79 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 2.90 (s, 2H), 2.12 – 1.79 (m, 8H).

Example 30E: N-(4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl)-2-(4-chloro-3-fluorophenoxy)acetamide hydrochloride

A mixture of Example 30D (2.5 g, 6.63 mmol) and sodium borohydride (1.254 g, 33.1 mmol) in a 1:1 mixture of methanol/dichloromethane (50 mL) was stirred for 24 hours. Volatiles were removed, and the residue was partitioned between water and dichloromethane. The organic fraction was separated, dried ($MgSO_4$), and concentrated. The residue was then treated with 4 N HCl in dioxane. The suspension was sonicated and concentrated. The residue was dried under vacuum to give 2.82 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.97 (s, 3H), 7.72 (s, 1H), 7.40 (t, J = 8.9 Hz, 1H), 6.95 (dd, J = 11.4, 2.8 Hz, 1H), 6.74 (ddd, J = 9.0, 2.9, 1.1 Hz, 1H), 5.64 (s, 1H), 4.41 (s, 2H), 3.83 (d, J = 9.1 Hz, 1H), 2.24 (td, J = 10.8, 9.9, 5.3 Hz, 1H), 1.96 – 1.51 (m, 9H); MS (ESI$^+$) m/z 343.0 (M+H)$^+$.

Example 30F: (2R)-N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,3-dihydro-1H-indole-2-carboxamide

A 4 mL vial was charged with a stir bar, a 500 µL solution of Example 30E (47.74 mg, 0.13 mmol) in *N*,*N*-dimethylacetamide, 2,3-dihydrobenzofuran-2-carboxylic acid (23.11mg, 0.14 mmol, 1.1 equivalents), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 57.4 mg, 0.15 mmol, 1.2 equivalents), and triethylamine

(53.01µL, 0.38mmol, 3 equivalents). The vial was capped and stirred at room temperature for 1 hour. The mixture was then concentrated to dryness and dissolved in 1.4 mL of dimethyl sulfoxide/methanol (1:1). The crude material was submitted to reverse phase HPLC purification (Phenomenex® Luna® C8(2) 5 µm 100Å AXIA™ column (30mm × 75mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used at a flow rate of 50 mL/minute (0-0.5 minute 10% A, 0.5-6.0 minutes linear gradient 10-100% A, 6.0-7.0 minutes 100% A, 7.0-8.0 minutes linear gradient 100-10% A) to yield the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.47 (t, J = 8.9 Hz, 1H), 7.30 – 7.19 (m, 1H), 7.13 (td, J = 7.7, 1.4 Hz, 1H), 7.00 (dd, J = 11.4, 2.9 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.88 – 6.77 (m, 2H), 5.11 – 5.01 (m, 1H), 4.42 (s, 2H), 4.07 – 3.98 (m, 1H), 3.45 (dt, J = 16.2, 10.3 Hz, 1H), 3.17 (dt, J = 16.2, 8.1 Hz, 1H), 2.35 – 2.17 (m, 1H), 2.06 (s, 1H), 1.92 (s, 1H), 1.91 – 1.66 (m, 7H); MS (+ESI) *m/z* 489.1 $(M+H)^+$.

Example 31: (7*S*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,2-difluoro-7-methyl-6,7-dihydro-2*H*-furo[2,3-*f*][1,3]benzodioxole-7-carboxamide (Compound 130)

The reaction and purification conditions described in Example 23 substituting (*S*)-2,2-difluoro-7-methyl-6,7-dihydro-[1,3]dioxolo[4,5-f]benzofuran-7-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.66 (s, 1H), 8.28 (s, 1H), 7.45 (t, J = 8.9 Hz, 1H), 7.37 (s, 1H), 7.03 (dd, J = 11.4, 2.9 Hz, 1H), 6.95 (s, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.90 (d, J = 9.0 Hz, 1H), 4.43 (s, 2H), 4.22 (d, J = 9.0 Hz, 1H), 2.19 (s, 6H), 1.46 (s, 3H); MS (ESI+) *m/z* 542 $(M+NH_4)^+$.

Example 32: (7*R*)-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-2,2-difluoro-7-methyl-6,7-dihydro-2*H*-furo[2,3-*f*][1,3]benzodioxole-7-carboxamide (Compound 131)

The reaction and purification conditions described in Example 23 substituting (*R*)-2,2-difluoro-7-methyl-6,7-dihydro-[1,3]dioxolo[4,5-f]benzofuran-7-carboxylic acid for 2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 8.66 (s, 1H), 8.27 (s, 1H), 7.45 (t, J = 8.9 Hz, 1H), 7.37 (s, 1H), 7.03 (dd, J = 11.4, 2.9 Hz, 1H), 6.95 (s, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.90 (d, J = 9.1 Hz, 1H), 4.43 (s, 2H), 4.22 (d, J = 9.0 Hz, 1H), 2.19 (s, 6H), 1.46 (s, 3H); MS (ESI+) *m/z* 542 $(M+NH_4)^+$.

Example 33: *N*-{3-[(6,7-dichloro-2,3-dihydro-1,4-benzodioxine-2-carbonyl)amino]bicyclo[1.1.1]pentan-1-yl}-5-(trifluoromethoxy)pyridine-2-carboxamide (Compound 132)

The reaction and purification conditions described in Example 1D substituting the product of Example 18D for the product of Example 1C and 5-(trifluoromethoxy)pyridine-2-carboxylic acid (Enamine) for 1,3-benzodioxole-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.35 (s, 1H), 8.85 (s, 1H), 8.71 – 8.68 (m, 1H), 8.16 – 8.10 (m, 1H), 8.10 – 8.05 (m, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 4.83 (dd, J = 5.2, 2.9 Hz, 1H), 4.38 – 4.26 (m, 2H), 2.34 (s, 6H); MS (ESI$^+$) *m/z* 518 $(M+H)^+$.

Example 34: *N*-{3-[(6,7-dichloro-2,3-dihydro-1,4-benzodioxine-2-carbonyl)amino]bicyclo[1.1.1]pentan-1-yl}-5-(difluoromethyl)pyrazine-2-carboxamide (Compound 133)

The reaction and purification conditions described in Example 18E substituting 5-(difluoromethyl)pyrazine-2-carboxylic acid for 2-(3,4-difluorophenoxy)acetic acid gave the title compound (23 mg, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (s, 1H), 9.24 (s, 1H), 8.99 (s, 1H), 8.87 (s, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 7.20 (t, J = 56 Hz, 1H), 4.84 (dd, J = 5, 3 Hz, 1H), 4.32 (m, 2H), 2.35 (s, 6H); MS (ESI-) *m/z* 483 $(M-H)^-$.

Example 35: (2*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 134)

Example 13D was purified by preparative chiral SFC (supercritical fluid chromatography) using a (S,S) Whelk-O®1 column (20 x 250 mm, 5 micron) eluted with 44% CH_3OH in CO_2 at 33 °C with a CO_2 flow rate of 40 mL/minute, CH_3OH flow rate of 32 mL/minute, front pressure of 192 bar, and back pressure of 100 bar to give the title compound (second enantiomer eluted, 0.0074 g, 0.015 mmol, 39% yield). The absolute stereochemistry of the title compound was arbitrarily assigned. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.67 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.5, 2.4 Hz, 1H), 4.61 (dd, J = 7.3, 3.0 Hz, 1H), 4.47 (s, 2H), 3.40 – 3.37 (m, 1H), 3.18 (dd, J = 12.0, 7.4 Hz, 1H), 2.83 (s, 3H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 494 $(M+H)^+$.

Example 36: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-hydroxyethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 135)

To a solution of the product of Example 14 (0.030 g, 0.062 mmol) in *N*,*N*-dimethylformamide (0.36 mL) was added K_2CO_3 (0.017 g, 0.13 mmol) and 2-bromoethanol (0.005 mL, 0.07 mmol). The reaction mixture stirred at 70 °C overnight. Then more K_2CO_3 (0.051 g, 0.39 mmol) and 2-bromoethanol (0.015 mL, 0.21 mmol) were added, and the reaction mixture continued to stir at 70 °C for 5 days before cooling to ambient temperature. The mixture was then diluted with *N*,*N*-dimethylformamide/water (1.5 mL, 3:1) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to yield the title compound (0.008 g, 0.015 mmol, 24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.82 – 6.71 (m, 2H), 6.54 (dd, J = 8.5, 2.4 Hz, 1H), 4.69 (t, J = 5.5 Hz, 1H), 4.47 (s, 2H), 4.45 (dd, J = 7.9, 2.9 Hz, 2H), 3.61 – 3.47 (m, 4H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 524 (M+H)$^+$.

Example 37: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(hydroxyacetyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 136)

To a solution of the product of Example 59 (0.027 g, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added boron tribromide (0.1 mL, 0.1 mmol, 1 M in CH_2Cl_2) in an ice bath. The reaction mixture was allowed to warm to ambient temperature in the bath over 40 minutes, was partitioned between water (1 mL) and CH_2Cl_2 (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to yield the title compound (0.014 g, 0.026 mmol, 52% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (s, 1H), 8.70 (s, 1H), 7.92 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.20 – 6.99 (m, 3H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.10 (t, J = 5.8 Hz, 1H), 4.83 (t, J = 4.4 Hz, 1H), 4.47 (s, 2H), 4.37 – 4.21 (m, 2H), 3.96 – 3.78 (m, 2H), 2.23 (s, 6H); MS (ESI$^+$) *m/z* 538 (M+H)$^+$.

Example 38: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(1,2-dimethyl-1*H*-imidazole-5-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 137)

To a solution of Example 14 (0.030 g, 0.062 mmol) in dichloromethane (0.21 mL) was added pyridine (10 µL, 0.13 mmol) and 1,2-dimethyl-1*H*-imidazole-5-sulfonyl chloride (0.018 g, 0.094 mmol). This mixture was allowed to stir at 50 °C overnight and then was concentrated. The residue was diluted with *N*,*N*-dimethylformamide (1 mL) and purified by preparative HPLC (Waters XBridge™ C18 5 µm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) gave the title compound (0.036 g, 0.057 mmol, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (s, 1H), 8.69 (s, 1H), 7.59 (s, 1H), 7.51 – 7.41 (m, 2H), 7.20 (dd, J = 8.8, 2.5 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.82 (ddd, J = 8.9, 3.0, 1.2 Hz, 1H), 4.44 (s, 2H), 4.21 – 4.10 (m, 2H), 3.58 (s, 1H), 3.44 (s, 3H), 2.32 (s, 3H), 2.23 (s, 6H); MS (ESI$^+$) *m/z* 638 $(M+H)^{+.}$

Example 39: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(1*R*,2*S*)-2-fluorocyclopropane-1-carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 138)

To a solution of (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid (5.20 mg, 0.050 mmol) in dichloromethane (1 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.01 mL, 0.1 mmol). After 10 minutes, a solution of Example 14 (.02 g, 0.042 mmol) in tetrahydrofuran (0.52 mL) and pyridine (0.52 mL) was added. This reaction mixture was allowed to stir at ambient temperature for 2 hours and was concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC (Waters XBridge™ C18 5 µm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to yield the title compound (0.024 g, 0.042 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (d, J = 7.9 Hz, 1H), 8.71 (d, J = 3.6 Hz, 1H), 7.58 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.17 (s, 1H), 7.11 7.01 (m, 2H), 6.85 (dd, J = 9.0, 2.9 Hz, 1H), 5.00 – 4.86 (m, 1H), 4.81 (s, 1H), 4.47 (d, J = 1.3 Hz, 2H), 4.35 (dd, J = 13.8, 4.5 Hz, 1H), 3.99 (s, 1H), 2.23 (d, J = 6.8 Hz, 6H), 2.07 (s, 1H), 1.63 – 1.45 (m, 1H), 1.36 – 1.21 (m, 1H).9 Hz, 1H), 8.71 (d, J = 3.6 Hz, 1H), 7.58 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.17 (s, 1H), 7.11 – 7.01 (m, 2H), 6.85 (dd, J = 9.0, 2.9 Hz, 1H), 5.00 – 4.86 (m, 2H), 4.81 (s, 1H), 4.47 (d, J = 1.3 Hz, 2H), 4.35 (dd, J = 13.8, 4.5 Hz, 1H), 3.99 (s, 1H), 2.23 (d, J = 6.8 Hz, 6H), 1.63 – 1.45 (m, 1H), 1.36 – 1.21 (m, 1H); MS (ESI$^+$) *m/z* 566 $(M+H)^+$.

Example 40: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-ethoxyethanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 139)

Example 40A: ethyl 6-chloro-4-((2-ethoxyethyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

To a mixture of Example 13A (0.080 g, 0.33 mmol) in dichloromethane (1.3 mL) was added triethylamine (0.06 mL, 0.4 mmol) and 2-ethoxyethanesulfonyl chloride (0.063 g, 0.36 mmol). The reaction mixture was stirred at ambient temperature for 1 hour and then was concentrated. The residue was diluted with *N*,*N*-dimethylformamide (1 mL) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.019 g, 0.055 mmol, 17% yield). MS (ESI^+) *m/z* 378 $(M+H)^+$.

Example 40B: 6-chloro-4-((2-ethoxyethyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

The methodologies described in Example 81B substituting Example 40A for 81A gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.4 Hz, 0.5H), 7.06 (t, J = 2.2 Hz, 1H), 7.04 (t, J = 2.3 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.97 (s, 0.5H), 5.13 (dd, J = 5.0, 3.2 Hz, 0.5H), 5.00 (dd, J = 5.0, 3.6 Hz, 1H), 4.12 (q, J = 7.1 Hz, 1H), 4.02 – 3.93 (m, 2H), 3.90 (t, J = 4.7 Hz, 3H), 3.88 – 3.79 (m, 4H), 3.39 – 3.24 (m, 7H), 1.17 (t, J = 7.1 Hz, 1H), 0.96 (t, J = 7.0 Hz, 3H).

Example 40C: 6-chloro-N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-ethoxyethanesulfonyl)-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

The methodologies described in Example 14 substituting Example 40B for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid gave the title compound. ^1H NMR (501 MHz, DMSO-d_6) δ ppm 8.91 (s, 1H), 8.72 (s, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.14 (dd, J = 8.8, 2.5 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.90 – 6.80 (m, 1H), 4.69 (dd, J = 8.1, 3.0 Hz, 1H), 4.48 (s, 2H), 4.10 (dd, J = 14.0, 2.9 Hz, 1H), 3.69 (td, J = 7.5, 5.5 Hz, 3H), 3.67 – 3.61 (m, 1H), 3.58 (dt, J = 14.0, 6.8 Hz, 1H), 3.31 – 3.27 (m, 2H), 2.27 (s, 6H), 0.98 (t, J = 7.0 Hz, 3H); MS (ESI^+) *m/z* 616 $(M+H)^+$.

Example 41: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(1-fluorocyclopropane-1-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 140)

The methodologies described in Example 39 substituting 1-fluorocyclopropanecarboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (s, 1H), 8.70 (s, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.16 (dd, J = 8.8, 2.5 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.88 – 6.81 (m, 1H), 4.92 (dd, J = 5.1, 3.3 Hz, 1H), 4.47 (s, 2H), 4.23 (dd, J = 13.5, 5.1 Hz, 1H), 4.03 (d, J = 11.9 Hz, 1H), 2.33 – 2.28 (m, 1H), 2.22 (s, 6H), 2.07 (s, 1H), 1.51 – 1.31 (m, 1H), 1.30 – 1.13 (m, 1H); MS (ESI$^+$) *m/z* 566 $(M+H)^+$.

Example 42: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(3,3,4,4,4-pentafluorobutanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 141)

The methodologies described in Example 39 substituting 3,3,4,4,4-pentafluorobutanoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.95 (s, 1H), 8.77 (d, J = 1.9 Hz, 1H), 7.56 (t, J = 8.9 Hz, 1H), 7.23 (t, J = 8.7 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.91 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 6.59 (s, 1H), 4.99 (s, 1H), 4.53 (s, 2H), 4.22 (d, J = 13.3 Hz, 1H), 4.01 (m, 1H), 3.86 (d, J = 14.4 Hz, 2H), 2.28 (d, J = 3.6 Hz, 6H); MS (ESI$^+$) *m/z* 640 $(M+H)^+$.

Example 43: *rac*-(2*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(1*R*,2*R*)-2-fluorocyclopropane-1-carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 142)

The methodologies described in Example 39 substituting *rac*-(1*R*,2*R*)-2-fluorocyclopropanecarboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound (Stereochemistry arbitrarily assigned. Diastereomer of Example 45.). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.77 (s, 1H), 8.68 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 6.51 (s, 1H), 5.07 (s, 1H), 4.89 (d, J = 3.8 Hz, 2H), 4.46 (s, 2H), 3.79 – 3.66 (m, 2H), 2.20 (s, 6H), 1.67 (d, J = 22.3 Hz, 1H), 1.15 (t, J = 11.1 Hz, 1H); MS (ESI$^+$) *m/z* 566 $(M+H)^+$.

Example 44: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[4-(trifluoromethoxy)benzoyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 143)

The methodologies described in Example 39 substituting 4-(trifluoromethoxy)benzoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400

MHz, DMSO-d_6) δ ppm 7.65 – 7.57 (m, 2H), 7.49 – 7.35 (m, 3H), 7.11 – 7.01 (m, 3H), 6.97 (dd, J = 11.3, 2.8 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.3 Hz, 1H), 4.89 (dd, J = 4.3, 3.4 Hz, 1H), 4.43 (s, 2H), 4.26 (dd, J = 13.6, 4.3 Hz, 1H), 3.73 (dd, J = 13.6, 3.4 Hz, 1H), 2.22 (s, 6H); MS (ESI$^+$) m/z 668 (M+H)$^+$.

Example 45: *rac*-(2*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(1*S*,2*S*)-2-fluorocyclopropane-1-carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 144)

The methodologies described in Example 43 provided the diastereomer of Example 43 as the title compound (Stereochemistry arbitrarily assigned.). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (s, 1H), 8.71 (s, 1H), 7.82 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.23 – 7.10 (m, 1H), 7.12 – 7.00 (m, 2H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.16 (td, J = 6.0, 3.2 Hz, 1H), 4.99 (td, J = 6.1, 3.3 Hz, 1H), 4.72 (dd, J = 7.4, 3.2 Hz, 1H), 4.54 – 4.26 (m, 2H), 2.32 (d, J = 13.1 Hz, 2H), 2.26 (s, 6H), 1.68 (d, J = 23.0 Hz, 1H), 1.19 (ddt, J = 15.4, 12.7, 5.8 Hz, 1H); MS (ESI$^+$) m/z 566 (M+H)$^+$.

Example 46: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(5-methylfuran-2-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 145)

The methodologies described in Example 39 substituting 5-methylfuran-2-carboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 (d, J = 21.0 Hz, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.13 – 7.02 (m, 2H), 7.02 – 6.92 (m, 2H), 6.83 (ddd, J = 9.0, 2.9, 1.3 Hz, 1H), 6.28 (dt, J = 3.4, 0.9 Hz, 1H), 4.81 (dd, J = 5.2, 3.3 Hz, 1H), 4.43 (s, 2H), 4.29 (dd, J = 13.7, 5.2 Hz, 1H), 4.00 (dd, J = 13.6, 3.3 Hz, 1H), 2.34 – 2.30 (m, 3H), 2.20 (s, 6H); MS (ESI$^+$) m/z 588 (M+H)$^+$.

Example 47: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(3-methoxybenzoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 146)

The methodologies described in Example 39 substituting 3-methoxybenzoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.46 – 7.32 (m, 2H), 7.14 – 7.08 (m, 1H), 7.11 – 7.04 (m, 1H), 7.08 – 6.99 (m, 4H), 6.98 (dd, J = 11.3, 2.9 Hz, 1H), 6.83 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 4.86 (dd, J = 4.5, 3.3

Hz, 1H), 4.43 (s, 2H), 4.25 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.79 – 3.69 (m, 4H), 2.23 (s, 6H); MS (ESI^+) *m/z* 614 $(M+H)^+$.

Example 48: 4-[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-2,3-dihydro-4*H*-1,4-benzoxazine-4-carbonyl]benzene-1-sulfonyl fluoride (Compound 147)

The methodologies described in Example 39 substituting 4-(fluorosulfonyl)benzoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.22 – 8.14 (m, 2H), 7.90 – 7.82 (m, 2H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.20 (s, 1H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, *J* = 11.3, 2.9 Hz, 1H), 6.83 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 4.91 (t, *J* = 3.8 Hz, 1H), 4.43 (s, 2H), 4.23 (dd, *J* = 13.7, 4.2 Hz, 1H), 3.73 (dd, *J* = 13.7, 3.3 Hz, 1H), 2.23 (s, 6H); MS (ESI^+) *m/z* 666 $(M+H)^+$.

Example 49: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(4,4,4-trifluorobutanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 148)

To a solution of Example 14 (0.030 g, 0.062 mmol) in dichloromethane (0.36 mL) was added triethylamine (0.02 mL, 0.13 mmol) and 4,4,4-trifluorobutanoyl chloride (10.53 mg, 0.066 mmol). This mixture was allowed to stir at ambient temperature for 1.5 hours and was concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.015 g, 0.025 mmol, 39% yield). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (s, 1H), 8.77 (s, 1H), 7.56 (t, J = 8.9 Hz, 1H), 7.23 (t, J = 8.7 Hz, 1H), 7.18 – 7.07 (m, 2H), 6.92 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.59 (s, 1H), 4.94 (s, 1H), 4.54 (s, 2H), 4.21 (dd, J = 13.9, 4.8 Hz, 1H), 3.88 (dd, J = 13.9, 3.3 Hz, 1H), 2.94 (s, 2H), 2.63 (m, 2H), 2.29 (s, 6H); MS (ESI^+) *m/z* 604 $(M+H)^+$.

Example 50: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(cyclopropanecarbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 149)

The methodologies described in Example 39 substituting cyclopropanecarboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (d, *J* = 23.7 Hz, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H),

7.10 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.99 (dd, *J* = 11.3, 2.8 Hz, 1H), 6.84 (ddd, *J* = 9.0, 2.9, 1.3 Hz, 1H), 4.78 (dd, *J* = 5.3, 3.4 Hz, 1H), 4.44 (s, 2H), 4.20 (dd, *J* = 13.7, 5.3 Hz, 1H), 3.96 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.26 (s, 6H), 2.08 – 1.97 (m, 1H), 0.99 – 0.82 (m, 4H); MS (ESI^+) *m/z* 548 $(M+H)^+$.

Example 51: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(4-methoxybenzoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 150)

The methodologies described in Example 39 substituting 4-methoxybenzoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.46 (s, 1H), 7.47 – 7.37 (m, 2H), 7.07 – 6.93 (m, 6H), 6.83 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 4.85 (dd, *J* = 4.5, 3.3 Hz, 1H), 4.43 (s, 2H), 4.25 (dd, *J* = 13.6, 4.6 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.22 (s, 6H); MS (ESI^+) *m/z* 614 $(M+H)^+$.

Example 52: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(oxane-4-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 151)

The methodologies described in Example 39 substituting tetrahydro-2*H*-pyran-4-carboxylic acid for (1R,2S)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (d, *J* = 38.9 Hz, 1H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, *J* = 11.3, 2.8 Hz, 1H), 6.84 (ddd, *J* = 8.9, 2.9, 1.3 Hz, 1H), 4.81 (dd, *J* = 4.8, 3.5 Hz, 1H), 4.44 (s, 2H), 4.20 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.94 – 3.77 (m, 3H), 3.39 (td, *J* = 11.4, 2.9 Hz, 2H), 3.10 (dq, *J* = 10.3, 5.4, 4.8 Hz, 1H), 2.25 (s, 6H), 1.79 – 1.60 (m, 4H); MS (ESI^+) *m/z* 592 $(M+H)^+$.

Example 53: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(oxolane-3-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 152)

The methodologies described in Example 49 substituting tetrahydrofuran-3-carbonyl chloride for 4,4,4-trifluorobutanoyl chloride gave the title compound. ^1H NMR (501 MHz, DMSO-d_6, diagnostic peaks) δ ppm 8.82 (s, 1H), 8.70 (s, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.15 (s, 1H), 7.07 (dd, J = 11.3, 2.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 7.0 Hz, 1H), 4.87 (s, 1H), 4.46 (s, 2H), 3.88 (t, J = 8.2 Hz, 1H), 3.77 (dd, J = 15.1, 7.6 Hz, 3H), 3.58 (s, 2H), 2.22 (s, 6H), 2.06 (d, J = 8.8 Hz, 2H); MS (ESI^+) *m/z* 578 $(M+H)^+$.

Example 54: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(5-methyl-1,2-oxazole-4-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 153)

The methodologies described in Example 39 substituting 5-methylisoxazole-4-carboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, J = 0.8 Hz, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.97 (dd, J = 11.2, 2.8 Hz, 1H), 6.83 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 4.89 (dd, J = 4.2, 3.4 Hz, 1H), 4.43 (s, 2H), 4.29 (dd, J = 13.5, 4.2 Hz, 1H), 3.75 (dd, J = 13.6, 3.4 Hz, 1H), 2.48 (d, J = 0.7 Hz, 3H), 2.20 (s, 6H); MS (ESI$^+$) m/z 589 (M+H)$^+$.

Example 55: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(1,2-oxazole-5-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 154)

The methodologies described in Example 39 substituting isoxazole-5-carboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.66 (d, J = 1.9 Hz, 1H), 7.43 (s, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.18 (dd, J = 8.8, 2.5 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 11.3, 2.9 Hz, 1H), 6.90 (d, J = 1.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.3 Hz, 1H), 4.91 (dd, J = 4.6, 3.3 Hz, 1H), 4.43 (s, 2H), 4.31 (dd, J = 13.7, 4.7 Hz, 1H), 3.91 (dd, J = 13.7, 3.4 Hz, 1H), 2.21 (s, 6H); MS (ESI$^+$) m/z 575 (M+H)$^+$.

Example 56: [2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]acetic acid

To a solution of Example 23B (0.040 g, 0.14 mmol), 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid (0.028 g, 0.15 mmol), and 4-nitrophenyl carbonochloridate (0.042 g, 0.21 mmol) in acetonitrile (1.4 mL) was added Hunig's Base (*N*,*N*-diisopropylethylamine) (0.05 mL, 0.3 mmol) and pyridine (0.06 mL, 0.7 mmol). The reaction mixture was stirred for 35 minutes at 110 °C in a Biotage® Initiator microwave reactor. The reaction mixture was concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1), the mixture was filtered and purified by preparative HPLC (Waters XBridge™ C18 5 µm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to give the title compound (0.015 g, 0.030 mmol, 21% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (br s, 1H), 8.63 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.16 – 7.00 (m, 5H), 6.85 (ddd, J =

8.9, 2.9, 1.2 Hz, 1H), 5.15 (d, J = 9.7 Hz, 1H), 4.46 (s, 2H), 3.99 (d, J = 12.9 Hz, 1H), 3.58 – 3.43 (m, 1H), 2.86 (s, 1H), 2.79 – 2.57 (m, 2H), 2.36 – 2.29 (m, 1H), 2.15 (s, 6H); MS (ESI^+) *m/z* 502 $(M+H)^+$.

Example 57: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(2-methoxyethoxy)acetyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 156)

The methodologies described in Example 39 substituting 2-(2-methoxyethoxy)acetic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (d, *J* = 41.4 Hz, 1H), 7.82 (d, *J* = 2.6 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.06 – 6.94 (m, 2H), 6.84 (ddd, *J* = 8.9, 2.9, 1.3 Hz, 1H), 4.79 (dd, *J* = 5.5, 3.4 Hz, 1H), 4.44 (s, 2H), 4.41 – 4.28 (m, 2H), 3.99 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.87 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.66 – 3.59 (m, 2H), 3.54 – 3.47 (m, 2H), 2.26 (s, 6H); MS (ESI^+) *m/z* 596 $(M+H)^+$.

Example 58: 4-acetyl-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 157)

The methodologies described in Example 49 substituting acetyl chloride for 4,4,4-trifluorobutanoyl chloride and at 0 °C instead of ambient temperature gave the title compound. ^1H NMR (400 MHz, $CDCl_3$) *δ* ppm 7.06 (m, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.82 (m, 3H), 6.79 – 6.63 (m, 2H), 4.72 (m, 1H), 4.39 (s, 4H), 2.48 (s, 6H), 2.33 (s, 3H); MS (ESI^+) *m/z* 522 $(M+H)^+$.

Example 59: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(methoxyacetyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 158)

To a cooled (0 °C) solution of the product of Example 14 (0.030 g, 0.062 mmol) in dichloromethane (0.36 mL) was added triethylamine (0.01 mL, 0.08 mmol) and methoxyacetyl chloride (6 µL, 0.07 mmol). This mixture was allowed to stir at 0 °C for 1 hour. Then the reaction mixture was diluted with water (1mL) and extracted with dichloromethane (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was redissolved in dichloromethane (2 mL), washed with heptanes, and concentrated to give the title compound (0.035 g, 0.063 mmol, quantitative yield). ^1H NMR (501 MHz, $CDCl_3$) *δ* ppm 7.32 (t, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.8, 2.5 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.83 (s, 2H), 6.75 (dd, J = 10.3, 2.8 Hz, 1H), 6.67 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 4.73 (t, J = 4.6 Hz, 1H), 4.39

(d, J = 5.8 Hz, 2H), 4.35 (s, 1H), 4.27 4.17 (m, 1H), 4.09 – 3.95 (m, 2H), 3.48 (d, J = 4.6 Hz, 3H), 2.48 (s, 6H); MS (ESI^+) *m/z* 552 $(M+H)^+$.

Example 60: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2,3,3,4,4,4-heptafluorobutanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 159)

The methodologies described in Example 39 substituting 2,2,3,3,4,4,4-heptafluorobutanoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.50 (d, *J* = 94.0 Hz, 1H), 7.64 (d, *J* = 2.6 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.25 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 6.98 (dd, *J* = 11.2, 2.9 Hz, 1H), 6.84 (ddd, *J* = 9.0, 2.9, 1.3 Hz, 1H), 4.94 (dd, *J* = 4.7, 3.5 Hz, 1H), 4.44 (s, 2H), 4.26 (dd, *J* = 14.2, 4.8 Hz, 1H), 4.04 (dd, *J* = 14.2, 3.5 Hz, 1H), 2.25 (s, 6H); MS (ESI^+) *m/z* 676 $(M+H)^+$.

Example 61: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[3-(trifluoromethyl)benzoyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 160)

The methodologies described in Example 39 substituting 3-(trifluoromethyl)benzoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.85 (ddd, *J* = 7.5, 2.1, 1.2 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.74 – 7.65 (m, 1H), 7.41 (t, *J* = 8.8 Hz, 1H), 7.12 – 7.01 (m, 2H), 7.04 (s, 1H), 6.97 (dd, *J* = 11.2, 2.8 Hz, 1H), 6.82 (ddd, *J* = 9.0, 2.9, 1.3 Hz, 1H), 4.92 (t, *J* = 3.7 Hz, 1H), 4.42 (s, 2H), 4.31 (dd, *J* = 13.6, 4.1 Hz, 1H), 3.71 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.21 (s, 6H); MS (ESI^+) *m/z* 652 $(M+H)^+$.

Example 62: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2,3,3-tetrafluoropropanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 161)

The methodologies described in Example 39 substituting 2,2,3,3-tetrafluoropropanoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 (d, *J* = 2.5 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, *J* = 11.3, 2.8 Hz, 1H), 6.91 – 6.80 (m, 1H), 6.75 (t, *J* = 5.7 Hz, 1H), 4.91 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.44 (s, 2H), 4.23 (dd, *J* = 14.1, 5.0 Hz, 1H), 4.06 (dd, *J* = 14.1, 3.4 Hz, 1H), 2.25 (s, 6H); MS (ESI^+) *m/z* 608 $(M+H)^+$.

Example 63: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[3-(methylsulfanyl)propanoyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 162)

The methodologies described in Example 39 substituting 3-(methylthio)propanoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 (d, J = 2.5 Hz, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.11 (dd, J = 8.8, 2.5 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 11.3, 2.8 Hz, 1H), 6.84 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 4.80 (dd, J = 5.2, 3.4 Hz, 1H), 4.44 (s, 2H), 4.09 (dd, J = 13.8, 5.2 Hz, 1H), 3.85 (dd, J = 13.9, 3.4 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.82 – 2.64 (m, 2H), 2.26 (s, 6H), 2.08 (s, 2H); MS (ESI$^+$) *m/z* 582 (M+H)$^+$.

Example 64: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[5-methyl-2-(trifluoromethyl)furan-3-sulfonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 163)

To 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride (0.036 g, 0.16 mmol) was added a solution of the product of Example 14 (0.030 g, 0.62 mol) in pyridine (2 mL), and the reaction mixture was heated at 50 °C overnight. The reaction mixture was then cooled to ambient temperature and concentrated. The residue was diluted with dimethyl sulfoxide/methanol (1 mL, 1:1) and purified by preparative HPLC on a Phenomenex® Luna® C8(2) 5 um 100Å AXIA™ column (30 mm × 150 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minute 5% A, 0.5-8.5 minutes linear gradient 5-100% A, 8.7-10.7 minutes 100% A, 10.7 -11.0 minutes linear gradient 100-5% A) to yield the title compound. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.96 (s, 1H), 8.82 (s, 1H), 7.57 – 7.50 (m, 2H), 7.48 (d, J = 8.9 Hz, 1H), 7.24 (dd, J = 8.8, 2.5 Hz, 1H), 7.12 (d, J = 8.9 Hz, 1H), 7.06 (dd, J = 11.3, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.44 (dd, J = 8.6, 3.1 Hz, 1H), 4.23 (dd, J = 14.2, 3.1 Hz, 1H), 3.73 – 3.66 (m, 1H), 2.28 (s, 6H); MS (APCI) *m/z* 692 (M+H)$^+$.

Example 65: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(4-methoxybenzene-1-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 164)

The title compound was prepared following the methodologies described in Example 64, substituting 4-methoxybenzene-1-sulfonyl chloride for 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.90 (s, 1H), 8.81 (s, 1H), 7.73 – 7.65

(m, 2H), 7.61 (d, *J* = 2.5 Hz, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.10 – 7.01 (m, 2H), 6.86 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.25 (d, *J* = 14.3, 3.0 Hz, 1H), 4.00 (d, *J* = 9.1, 3.0 Hz, 1H), 3.83 (s, 3H), 3.56 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.27 (s, 6H); MS (APCI) *m/z* 650 $(M+H)^+$.

Example 66: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(1-methyl-1*H*-imidazole-4-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 165)

The title compound was prepared following the methodologies described in Example 64, substituting 1-methyl-1*H*-imidazole-4-sulfonyl chloride for 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 7.97 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 1.3 Hz, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.49 (t, *J* = 8.8 Hz, 1H), 7.13 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.87 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.58 – 4.52 (m, 1H), 4.49 (d, *J* = 19.8 Hz, 2H), 4.35 (dd, *J* = 14.1, 3.0 Hz, 1H), 3.47 (dd, *J* = 14.1, 9.2 Hz, 1H), 2.29 (s, 6H); MS (APCI) *m/z* 624 $(M+H)^+$.

Example 67: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(4-fluorobenzene-1-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 166)

The title compound was prepared following the methodologies described in Example 64, substituting 4-fluorobenzene-1-sulfonyl chloride for 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.92 (s, 1H), 7.91 – 7.80 (m, 2H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.48 (td, *J* = 8.8, 4.1 Hz, 3H), 7.20 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.86 (ddd, *J* = 9.0, 2.9, 1.1 Hz, 1H), 4.47 (s, 2H), 4.27 (dd, *J* = 14.3, 3.1 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.63 (dd, *J* = 14.3, 8.9 Hz, 1H), 2.27 (s, 6H); MS (APCI) *m/z* 638 $(M+H)^+$.

Example 68: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(5,5,5-trifluoropentanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 167)

The methodologies described in Example 49 substituting 5,5,5-trifluoropentanoyl chloride for 4,4,4-trifluorobutanoyl chloride gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (s, 1H), 8.70 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.23 – 7.11 (m, 1H), 7.06 (dd, J = 11.4, 2.8 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.84 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.85 (s,

1H), 4.47 (s, 2H), 4.13 (m, 1H), 3.76 (d, J = 13.9 Hz, 1H), 2.68 (m, 2H), 2.35 – 2.24 (m, 2H), 2.22 (s, 6H), 1.76 (p, J = 7.1 Hz, 2H); MS (ESI^+) *m/z* 618 $(M+H)^+$.

Example 69: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(methanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 168)

The methodologies described in Example 59 substituting methanesulfonyl chloride for methoxyacetyl chloride, at ambient temperature instead of 0 °C, and additionally diluting the sample with *N*,*N*-dimethylformamide (1 mL) and purifying by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.93 (s, 1H), 8.72 (s, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.17 (dd, J = 8.8, 2.5 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.85 (d, J = 10.7 Hz, 1H), 4.73 (dd, J = 7.4, 3.0 Hz, 1H), 4.48 (s, 2H), 4.11 – 4.06 (m, 1H), 3.67 (dd, J = 14.1, 7.7 Hz, 1H), 3.17 (s, 3H), 2.27 (s, 6H); MS (ESI^+) *m/z* 558 $(M+H)^+$.

Example 70: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(pyridine-4-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 169)

The methodologies described in Example 39 substituting isonicotinic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 – 8.67 (m, 2H), 7.52 – 7.46 (m, 2H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.25 (s, 1H), 7.15 – 7.03 (m, 2H), 6.98 (dd, *J* = 11.3, 2.9 Hz, 1H), 6.83 (ddd, *J* = 9.0, 2.9, 1.3 Hz, 1H), 4.90 (dd, *J* = 4.2, 3.4 Hz, 1H), 4.43 (s, 2H), 4.21 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.72 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.23 (s, 6H); MS (ESI^+) *m/z* 585 $(M+H)^+$.

Example 71: 3-[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl]propanoic acid (Compound 170)

Example 71A: tert-butyl 3-[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propanoate

The methodologies described in Example 36 substituting *tert*-butyl 3-bromopropanoate for 2-bromoethanol and additionally including acetone (0.4 mL) in the solution gave the title compound. MS (ESI^+) *m/z* 554 $(M+H)^+$.

Example 71B: 3-[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propanoic acid

To a solution of the product of Example 71A (0.0034 g, 0.0056 mmol) in dichloromethane (0.01 mL) was added trifluoroacetic acid (0.0017 mL, 0.022 mmol), and the resulting mixture was stirred at ambient temperature for 4 hours and then concentrated. The residue was diluted with *N*,*N*-dimethylformamide (1 mL) and purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to yield the title compound (0.002 g, 0.0036 mmol, 64% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, J = 9.0 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.11 7.03 (m, 1H), 6.81 (dt, J = 19.4, 10.2 Hz, 3H), 6.59 (d, J = 6.1 Hz, 1H), 4.47 (s, 3H), 3.47 (d, J = 13.8 Hz, 2H), 2.46 (s, 2H), 2.26 (s, 6H); MS (ESI^+) *m/z* 553 $(M+H)^+$.

Example 72: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(trifluoromethoxy)acetyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 171)

To Example 14 (0.040 g, 0.074 mmol) was added silver trifluoromethanesulfonate (0.038 g, 0.15 mmol), Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (0.039 g, 0.11 mmol), and potassium fluoride (0.032 g, 0.22 mmol, 40 weight% loading on alumina). Under nitrogen, to this mixture was added ethyl acetate (0.37 mL), followed by 2-fluoropyridine (0.013 mL, 0.15 mmol) and trimethyl(trifluoromethyl)silane (0.074 mL, 0.15 mmol, 2 M solution in tetrahydrofuran). This mixture was allowed to stir at ambient temperature overnight. The same amount of each reagent was added to the reaction mixture again, and the mixture stirred for another 24 hours. Although the reaction was still incomplete, the reaction mixture was diluted with ethyl acetate, filtered through a silica plug, and concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (0.2 mL) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.005 g, 0.008 mmol, 11% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.89 (s, 1H), 8.71 (s, 1H), 8.01 – 7.75 (m, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.87 – 6.81 (m, 1H),

5.24 – 5.05 (m, 2H), 4.95 – 4.89 (m, 1H), 4.47 (s, 2H), 4.07 – 3.91 (m, 1H), 3.80 – 3.67 (m, 1H), 2.22 (s, 6H); MS (ESI^+) *m/z* 606 $(M+H)^+$.

Example 73: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(methylsulfanyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 172)

The methodologies described in Example 59 substituting methanesulfinic chloride for methoxyacetyl chloride, without including a wash with heptanes, and additionally diluting the sample with *N*,*N*-dimethylformamide (1 mL) and purifying by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.63 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 6.12 (s, 1H), 4.47 (s, 2H), 4.45 (dd, J = 7.3, 2.9 Hz, 1H), 3.43 (dt, J = 12.1, 3.1 Hz, 1H), 3.17 (dd, J = 10.9, 7.2 Hz, 1H), 2.37 (s, 3H), 2.26 (s, 6H); MS (ESI^+) *m/z* 526 $(M+H)^+$.

Example 74: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(1,3-dimethyl-1*H*-pyrazole-4-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 173)

The title compound was prepared following the methodologies described in Example 64, substituting 1,3-dimethyl-1*H*-pyrazole-4-sulfonyl chloride for 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride**.** ^1H NMR (501 MHz, DMSO-d_6) δ ppm 8.93 (s, 1H), 8.82 (s, 1H), 8.28 (s, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.23 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.89 – 6.83 (m, 1H), 4.47 (s, 2H), 4.24 (dd, *J* = 14.3, 3.0 Hz, 1H), 4.11 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.46 (dd, *J* = 14.4, 9.5 Hz, 1H), 2.28 (s, 6H), 2.08 (s, 3H); MS (ESI^+) *m/z* 638 $(M+H)^+$.

Example 75: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(4-sulfamoylbenzene-1-sulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 174)

The title compound was prepared following the methodologies described in Example 64, substituting 4-sulfamoylbenzene-1-sulfonyl chloride for 5-methyl-2-(trifluoromethyl)furan-3-sulfonyl chloride**.** ^1H NMR (501 MHz, DMSO-d_6) δ ppm 8.94 (s, 1H), 8.82 (s, 1H), 8.09 – 7.97 (m, 4H), 7.58 – 7.44 (m, 2H), 7.20 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.91 – 6.82 (m,

1H), 4.47 (s, 2H), 4.30 (dd, *J* = 14.2, 3.1 Hz, 1H), 4.18 (dd, *J* = 8.6, 3.0 Hz, 1H), 2.27 (s, 6H); MS (APCI) *m/z* 698 $(M+H)^+$.

Example 76: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(1*S*,2*S*)-2-fluorocyclopropane-1-carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 175)

The methodologies described in Example 39 also prepared this diastereomer of Example 39 as the title compound. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 9.97 (s, 1H), 8.96 (s, 1H), 8.73 (s, 1H), 8.11 (d, J = 2.5 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.19 (dd, J = 8.7, 2.6 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.86 (ddd, J = 9.0, 2.8, 1.1 Hz, 1H), 5.42 (d, J = 2.5 Hz, 1H), 4.96 – 4.77 (m, 1H), 4.50 (d, J = 2.5 Hz, 1H), 4.48 (s, 2H), 2.69 – 2.54 (m, 1H), 2.31 (s, 6H), 1.59 – 1.47 (m, 1H), 1.23 (dq, J = 13.0, 6.4 Hz, 1H); MS (ESI^+) *m/z* 566 $(M+H)^+$.

Example 77: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2-difluorocyclopropane-1-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 176)

The methodologies described in Example 39 substituting 2,2-difluorocyclopropane-carboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.79 (s, 1H), 8.69 (s, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.20 (s, 1H), 7.10 – 7.01 (m, 2H), 6.84 (d, J = 9.8 Hz, 1H), 4.92 (s, 1H), 4.46 (s, 2H), 3.70 (m, 2H), 2.20 (s, 6H), 1.99 (m, 2H), 1.24 (m, 1H); MS (ESI^+) *m/z* 585 $(M+H)^+$.

Example 78: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[1-(trifluoromethyl)cyclopropane-1-carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 177)

The methodologies described in Example 39 substituting 1-(trifluoromethyl)-cyclopropanecarboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 8.02 (s, 1H), 7.33 (t, J = 8.6 Hz, 1H), 7.18 (dd, J = 8.8, 2.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.91 (s, 1H), 6.86 (s, 1H), 6.76 (dd, J = 10.2, 2.9 Hz, 1H), 6.68 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 4.70 (dd, J = 8.4, 3.0 Hz, 1H), 4.49 (d, J = 13.9 Hz, 1H), 4.40 (s, 2H), 3.78 (s, 1H), 2.52 (s, 6H), 1.44 – 1.21 (m, 2H), 0.94 – 0.72 (m, 2H); MS (ESI^+) *m/z* 616 $(M+H)^+$.

Example 79: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2,3,3,3-pentafluoropropanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 178)

The methodologies described in Example 39 substituting 2,2,3,3,3-pentafluoropropanoic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.96 (s, 1H), 8.72 (s, 1H), 7.78 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.85 (dd, J = 8.7, 2.7 Hz, 1H), 5.02 (d, J = 3.9 Hz, 1H), 4.47 (s, 2H), 4.14 (m, 2H), 2.22 (s, 6H), 1.24 (m, 2H), 1.16 – 0.97 (m, 2H); MS (ESI$^+$) *m/z* 626 $(M+H)^+$.

Example 80: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 179)

The methodologies described in Example 39 substituting 2,2-difluoro-1-methylcyclopropanecarboxylic acid for (1*R*,2*S*)-2-fluorocyclopropanecarboxylic acid gave the title compound. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.84 (s, 1H), 8.70 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.10 – 7.03 (m, 2H), 6.84 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 6.51 (s, 1H), 4.97 (t, J = 3.8 Hz, 1H), 4.46 (s, 2H), 2.22 (s, 6H), 2.07 (s, 3H), 1.71 (m, 1H), 1.32 (m, 1H); MS (ESI$^+$) *m/z* 598 $(M+H)^+$.

Example 81: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[2-(methanesulfonyl)ethyl]-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 180)

Example 81A: ethyl 6-chloro-4-(2-(methylsulfonyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylate

To a mixture of Example 13A (0.080 g, 0.33 mmol) and K_2CO_3 (0.11 g, 0.83 mmol) in acetone (1.3 mL) was added (methylsulfonyl)ethene (0.072 ml, 0.828 mmol). The reaction mixture was heated to 65 °C for 21 hours, cooled to ambient temperature, and concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to yield the title compound (0.019 g, 0.055 mmol, 7% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 6.84 6.75 (m, 2H), 6.65 (dd, J = 8.5, 2.5 Hz, 1H), 5.02 (t, J = 3.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.78 - 3.72 (m, 1H), 3.68 - 3.58

(m, 3H), 3.51 (dd, J = 7.7, 3.9 Hz, 2H), 3.04 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); MS (ESI^+) *m/z* 348 $(M+H)^+$.

Example 81B: 6-chloro-4-(2-(methylsulfonyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of Example 81A (0.019 g, 0.055 mmol) in methanol/water (0.054 mL, 1:1) was added NaOH (5 N aqueous solution, 0.055 mL), and the mixture stirred for 1 hour. The mixture was concentrated and the residue was acidified with HCl (1 N). The resultant mixture was concentrated again and carried forward without purification.

Example 81C: 6-chloro-N-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[2-(methanesulfonyl)ethyl]-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

The methodologies described in Example 14 substituting Example 81B for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid gave the title compound (0.005 g, 0.009 mmol, 16% yield). ^{1}H NMR 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.71 (s, 2H), 7.49 (td, J = 8.8, 2.1 Hz, 1H), 7.05 - 7.00 (m, 1H), 6.88 6.79 (m, 3H), 6.65 (dd, J = 8.5, 2.3 Hz, 1H), 4.52 (dd, J = 7.6, 2.9 Hz, 1H), 4.48 (s, 2H), 4.46 (s, 1H), 3.81 3.72 (m, 1H), 3.67 (d, J = 7.0 Hz, 1H), 3.50 (dd, J = 12.3, 2.9 Hz, 1H), 3.30 3.26 (m, 2H), 3.03 (s, 3H), 2.26 (s, 6H); MS (ESI^+) *m/z* 586 $(M+H)^+$.

Example 82: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(3-methoxypropanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 181)

The methodologies described in Example 49 substituting 3-methoxypropanoyl chloride for 4,4,4-trifluorobutanoyl chloride gave the title compound. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.82 (s, 1H), 8.71 (s, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 7.06 (dd, J = 11.3, 2.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 1H), 6.89 – 6.80 (m, 1H), 4.81 (s, 1H), 4.47 (s, 2H), 4.05 (dd, J = 13.8, 5.3 Hz, 1H), 3.86 (dd, J = 13.9, 3.3 Hz, 1H), 3.60 (t, J = 7.0 Hz, 2H), 3.25 (s, 3H), 2.80 (m, 1H), 2.24 (m, 1H), 2.23 (s, 6H); MS (ESI^+) *m/z* 566 $(M+H)^+$.

Example 83: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(3,3,3-trifluoropropanoyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 182)

The methodologies described in Example 49 substituting 3,3,3-trifluoropropanoyl chloride for 4,4,4-trifluorobutanoyl chloride gave the title compound. ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.90 (d, J = 25.4 Hz, 1H), 8.70 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.21 (d, J =

24.7 Hz, 1H), 7.14 – 6.97 (m, 3H), 6.84 (dd, J = 9.2, 3.0 Hz, 1H), 4.94 (m, 1H), 4.46 (s, 2H), 4.13 (m, 1H), 3.80 (m, 1H), 3.41 (m, 2H), 2.22 (s, 6H); MS (ESI^+) *m/z* 590 $(M+H)^+$.

Example 84: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2,2,2-trifluoroethanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 183)

The methodologies described in Example 69 substituting 2,2,2-trifluoroethanesulfonyl chloride for methanesulfonyl chloride gave the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.90 (s, 1H), 8.69 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.17 (dd, J = 8.9, 2.4 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.82 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 5.05 – 4.78 (m, 2H), 4.71 (dd, J = 7.6, 3.1 Hz, 1H), 4.44 (s, 2H), 4.10 (dd, J = 14.2, 3.1 Hz, 1H), 3.65 (dd, J = 14.2, 7.7 Hz, 1H), 2.24 (s, 6H); MS (ESI^+) *m/z* 626 $(M+H)^+$.

Example 85: *tert*-butyl [(2*S*)-6-chloro-2-({(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}carbamoyl)-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl]acetate (Compound 184)

Example 85A: 1-amino-4-(benzylamino)bicyclo[2.2.2]octan-2-one, hydrochloric acid

To a suspension of Example 2E (10.01 g, 32.3 mmol) in toluene (100 mL) was added a 50% ethyl acetate solution of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (22 mL, 37.0 mmol), trimethylsilyl azide (TMS-N_3) (5.0 mL, 37.7 mmol), and triethylamine (11.5 mL, 83 mmol). The mixture was stirred for 30 minutes at room temperature, heated for 2 hours at 85 °C, and then 3 N aqueous hydrochloric acid (86 mL, 258 mmol) was added. The mixture was stirred at 85 °C for 90 minutes and then concentrated. The concentrate was stirred with acetonitrile (150 mL) to precipitate a white solid, which was collected by filtration, washed with acetonitrile (30 mL) and CH_2Cl_2 (25 mL), and vacuum-dried to provide the title compound as an HCl salt (6.244 g, 60.9 % yield). MS ($APCI^+$) *m/z* 245.0 $(M+H)^+$.

Example 85B: tert-butyl (S)-(4-(benzylamino)-2-hydroxybicyclo[2.2.2]octan-1-yl)carbamate hydrochloride

Water (3.24 L) was charged to a 6 L jacketed reaction vessel, followed by magnesium chloride heptahydrate (1.46 g, 7.1 mmol), $NADP^+$ (1.8 g, 2.3 mmol) and monopotassium phosphate (6.93 g, 526 mmol). All components were dissolved before the pH was adjusted to pH 7.5 with 50% weight/weight NaOH to make desired buffer (200 mL reserved). The product of Example 85A (180 g, 569 mmol) was added to the buffer, and the pH was again adjusted to pH 7.5 with 50% weight/weight NaOH. Finally, isopropanol (360 mL, 10% volume/volume) was

added to the reaction followed by enzyme (3.6 g, KRED P2C02, Codexis, Redwood City, CA) that was solubilized in the reserved 200 mL of buffer. This reaction was allowed to proceed at 40 °C for 16 hours with the pH being held between 7.5 and 8.0. Upon completion of the reaction, the buffer was adjusted to pH 12 and held at this point for 30 minutes. The reaction was filtered through diatomaceous earth to remove the enzyme. Di-*tert*-butyl dicarbonate (20.7 g, 98 mmol,1.25 equivalents) was added to 3.6 L of ethyl acetate, and the solution was charged to the reaction vessel containing the filtered aqueous fraction. This reaction was allowed to proceed at 30 °C for 2.5 hours with moderate stirring. After 2.5 hours, the two layers were separated, and the aqueous fraction was assayed for remaining amino-alcohol product. Di-*tert*-butyl dicarbonate (1.25 eq. with respect to the remaining amino-alcohol) was added to 2.0 L of ethyl acetate and charged to the reaction vessel. The reaction was allowed to proceed at 30 °C for 2.5 hours, after which the organic and aqueous layers were separated. The combined organic layers were washed with 2.5% NaOH (560 mL) and dried over Na_2SO_4. The ethyl acetate was removed in vacuo and the residue taken up in methyl *tert*-butyl ether (MTBE) (1.8 L) to provide the product in solution at 0.2 M. This reaction was fitted with an overhead stirrer, cooled to 0 °C and 4 N HCl in dioxane (169 mL, 1.5 eq with respect to product) was slowly added. The product precipitated out of solution and, after stirring for 5 minutes at 0 °C, was collected by filtration. The white solid was washed with methyl *tert*-butyl ether (MTBE) (100 mL) and dried under vacuum overnight to provide the title compound (160 g, 418 mmol, 79% yield). MS ($APCI^+$) *m/z* 347.4 $(M+H)^+$.

Example 85C: tert-butyl (S)-(4-amino-2-hydroxybicyclo[2.2.2]octan-1-yl)carbamate hydrochloride

The product of Example 85B (163.7 g, 427 mmol) in methanol (1375 mL) was added to 20% $Pd(OH)_2/C$, wet (16 g, 58 mmol) in a 2 L Hastelloy® C reactor. The reactor was purged with argon and was stirred under 50 psi of hydrogen at 40 °C. The reaction mixture was allowed to stir for 11.3 hours after reaching 38 °C. The reactor was vented and materials were filtered through 45 μm nylon filter to remove catalyst and concentrated under reduced pressure to give the title compound (121.49 g, 415 mmol, 97% yield). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.14 (s, 3H), 6.12 (s, 1H), 5.09 (d, J = 4.2 Hz, 1H), 3.90 (dt, J = 9.4, 3.0 Hz, 1H), 2.11 (ddd, J = 12.8, 9.5, 3.0 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.88 – 1.50 (m, 7H), 1.32 (s, 9H).

Example 85D: (R)-4-chloro-2-((3-chloro-2-hydroxypropyl)amino)phenol

To a solution of 2-amino-4-chlorophenol (25 g, 174 mmol) in ethanol (250 mL) and water (2.5 mL) was added (*R*)-2-(chloromethyl)oxirane (17.7 g, 192 mmol), and the solution stirred for 12 hours at 60 °C. Then the reaction mixture was concentrated, and the crude residue was chromatographed on silica gel (ethyl acetate/petroleum ether 1:5) to give the title compound

(64 g, 217 mmol, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.17 - 3.39 (m, 2 H) 3.60 - 3.75 (m, 2 H) 4.14 (d, *J*=7.06 Hz, 1 H) 6.55 - 6.66 (m, 3 H).

Example 85E: (S)-(6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol

To a solution of Example 85D (51 g, 173 mmol) in ethanol (500 mL) was added K_2CO_3 (14.3 g, 104 mmol), and the solution was stirred for 12 hours at 90 °C. The reaction solution was filtered and concentrated under reduced pressure. The mixture was diluted with water (1000 mL) and extracted with ethyl acetate (3×1000 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/petroleum ether, 1:4) to give the title compound (35 g, 158 mmol, 46 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.26 - 3.41 (m, 2 H) 3.77 - 3.89 (m, 3 H) 4.17 - 4.24 (m, 1 H) 6.57 - 6.64 (m, 1 H) 6.57 - 6.64 (m, 1 H) 6.73 (d, J=8.38 Hz, 1 H).

Example 85F: (S)-tert-butyl 2-(((tert-butoxycarbonyl)oxy)methyl)-6-chloro-2H-benzo[b][1,4]oxazine-4(3H)-carboxylate

To a solution of Example 85E (15 g, 68 mmol) in dichloromethane (150 mL) was added triethylamine (23.6 mL, 169 mmol), di-*tert*-butyl dicarbonate (63 mL, 270 mmol) and 4-(dimethylamino)pyridine (0.83 g, 6.8 mmol). The solution stirred for 2 hours at 20 °C. Then water (500 mL) was added to the mixture, and the aqueous mixture was extracted with dichloromethane (2×500 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography eluted with petroleum ether:ethyl acetate (10:1) to give the title compound (45 g, 101 mmol, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.50 (s, 9 H) 1.54 - 1.56 (m, 9 H) 3.48 (br dd, *J*=13.56, 7.83 Hz, 1 H) 4.14 - 4.19 (m, 1 H) 4.25 (d, *J*=5.29 Hz, 2 H) 4.37 (dtd, *J*=7.75, 5.17, 5.17, 2.65 Hz, 1 H) 6.84 (d, *J*=8.82 Hz, 1 H) 6.95 (dd, *J*=8.71, 2.54 Hz, 1 H) 7.84 (br s, 1 H).

Example 85G: (S)-tert-butyl 6-chloro-2-(hydroxymethyl)-2H-benzo[b][1,4]oxazine-4(3H)-carboxylate

To a solution of Example 85F (45 g, 101 mmol) in methanol (400mL) and tetrahydrofuran (400 mL) was added a solution of NaOH (8.10 g, 203 mmol) in water (400 mL) at 20 °C, and the mixture was stirred at 20 °C for 12 hours. The mixture was concentrated and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated to give the title compound (30 g, 93 mmol, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55 (s, 9 H) 3.56 (dd, *J*=13.81, 7.67 Hz, 1 H) 3.80 (br s, 2 H) 4.07 (dd, *J*=14.03, 2.63 Hz, 1 H) 4.25 (dtd, *J*=7.67, 4.93, 4.93, 2.63 Hz, 1 H) 6.82 (d, *J*=8.77 Hz, 1 H) 6.95 (dd, *J*=8.77, 2.19 Hz, 1 H) 7.79 (br s, 1 H).

Example 85H: (S)-4-(tert-butoxycarbonyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of Example 85G (25 g, 78 mmol) in dichloromethane (250mL) was added *N*-methylmorpholine-*N*-oxide (NMO, 54.5 g, 465 mmol) at 0 °C and tetrapropylammonium perruthenate (TPAP, 5.45 g, 15.51 mmol) at 0 °C. The solution was stirred for 2 hours at 20 °C and then was concentrated. The residue was purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of methanol in 0.1% trifluoroacetic acid/water) to give the title compound (24 g, 76 mmol, 81 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.53 (s, 9 H) 3.91 (dd, *J*=13.94, 3.18 Hz, 1 H) 4.24 (dd, *J*=13.94, 5.14 Hz, 1 H) 4.88 (dd, *J*=4.89, 3.42 Hz, 1 H) 6.91 - 6.95 (m, 1 H) 6.97 - 7.02 (m, 1 H) 7.80 (br s, 1 H).

Example 85I: (S)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of Example 85H (12g, 38 mmol) in dichloromethane (120 mL) was added HCl (37.8 mL, 151 mmol, ethyl acetate) at 0 °C. The solution stirred for 12 hours at 20 °C, and then the solid was collected by suction filtration and was dried to give the title compound (15.9 g, 72.4 mmol, 96 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.34 - 3.44 (m, 2 H) 4.82 (t, *J*=3.67 Hz, 1 H) 6.50 (dd, *J*=8.80, 2.45 Hz, 1 H) 6.59 (d, *J*=2.45 Hz, 1 H) 6.71 (d, *J*=8.80 Hz, 1 H).

Example 85J: tert-butyl ((S)-4-((S)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxamido)-2-hydroxybicyclo[2.2.2]octan-1-yl)carbamate

The methodologies described in Example 14 substituting Example 85I for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting 85C for Example 23B gave the title compound. MS (ESI$^+$) *m/z* 452 (M+H)$^+$.

Example 85K: (S)-N-((S)-4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxamide

The methodologies described in Example 71B substituting Example 85J for Example 71A without purification gave the title compound. MS (ESI$^+$) *m/z* 352 (M+H)$^+$.

Example 85L: (2S)-6-chloro-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

The methodologies described in Example 14 substituting 2-(4-chloro-3-fluorophenoxy)acetic acid for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting Example 85K for Example 23B gave the title compound. MS (ESI$^+$) *m/z* 538 (M+H)$^+$.

Example 85M: tert-butyl [(2S)-6-chloro-2-({(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}carbamoyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate

The methodologies described in Example 36 with the following modifications: (1) substituting *tert*-butyl bromoacetate for 2-bromoethanol, (2) substituting Example 85L for the product of Example 14, (3) stirring for 2 days instead of 5, and (4) with the addition of NaI (0.5 equivalence), gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.36 (s, 1H), 7.26 (s, 1H), 7.05 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 (dd, J = 8.7, 3.1 Hz, 2H), 6.63 6.53 (m, 2H), 5.08 (d, J = 4.4 Hz, 1H), 4.52 4.45 (m, 1H), 4.46 (s, 2H), 4.15 (d, J = 18.1 Hz, 1H), 4.05 (s, 1H), 4.03 (s, 1H), 3.48 (dd, J = 11.9, 2.7 Hz, 1H), 2.27 (t, J = 11.4 Hz, 1H), 2.07 (s, 1H), 2.06 (t, J = 9.3 Hz, 1H), 1.93 (d, J = 10.7 Hz, 2H), 1.81 (dt, J = 23.1, 12.2 Hz, 6H), 1.43 (d, J = 17.1 Hz, 1H), 1.38 (s, 9H); MS (ESI$^+$) *m/z* 596 (M-tBu+H)$^+$.

Example 86: *tert*-butyl [6-chloro-2-({(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}carbamoyl)-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl]acetate (Compound 185)

The methodologies described in Example 85 substituting 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid for Example 85I in the reaction sequence provided *tert*-butyl {(2*S*)-4-[(6-chloro-3,4-dihydro-2*H*-1,4-benzoxazine-2-carbonyl)amino]-2-hydroxybicyclo[2.2.2]octan-1-yl}carbamate, which was carried forward in the reaction sequence to give the title compound. The spectral data match Example 85.

Example 87: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-oxo-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 186)

The methodologies described in Example 14 substituting 6-chloro-4-oxochroman-2-carboxylic acid for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.95 (s, 1H), 8.73 (s, 1H), 7.68 7.60 (m, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.09 (t, J = 7.1 Hz, 1H), 4.47 (s, 2H), 2.95 (d, J = 7.1 Hz, 2H), 2.26 (s, 6H); MS (ESI$^+$) *m/z* 493 (M+H)$^+$.

Example 88: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-methoxy-2-methylpropyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 187)

To a solution of Example 14 (0.090 g, 0.187 mmol) in methanol (1.2 mL) was added 2-methoxy-2-methylpropanal (0.029 g, 0.281 mmol) and zinc chloride (0.141 ml, 0.281 mmol, 1.9 M in 2-methyltetrahydrofuran). After stirring at ambient temperature for 30 minutes, sodium cyanoborohydride (0.018 g, 0.281 mmol) was added, and this mixture was allowed to stir at ambient temperature for 15 minutes, then 50 °C overnight. More methoxy-2-methylpropanal (0.029 g, 0.281 mmol) and sodium cyanoborohydride (0.018 g, 0.281 mmol) were added to the reaction mixture and stirring was continued at 50 °C for 24 hours. Then the reaction mixture was cooled to ambient temperature, diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (0.007 g, 0.012 mmol, 7% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.67 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.54 (dd, J = 8.4, 2.4 Hz, 1H), 4.47 (s, 2H), 4.44 (dd, J = 7.2, 2.8 Hz, 1H), 3.55 (dd, J = 12.7, 2.9 Hz, 1H), 3.27 (d, J = 15.2 Hz, 1H), 3.17 (d, J = 15.1 Hz, 1H), 3.13 (s, 3H), 2.25 (s, 6H), 1.12 (d, J = 5.4 Hz, 6H); MS (ESI$^+$) *m/z* 566 (M+H)$^+$.

Example 89: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-[(2-hydroxyethyl)amino]-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 188)

To a solution of Example 87 (0.070 g, 0.142 mmol) in methanol (1 mL) was added 2-((trimethylsilyl)oxy)ethanamine (0.028 g, 0.21 mmol) and zinc chloride (powdered, 0.029 g, 0.213 mmol). After stirring at ambient temperature for 30 minutes, sodium cyanoborohydride (0.013 g, 0.213 mmol) was added, and this mixture was allowed to stir at ambient temperature for 15 minutes, then 50 °C overnight. Then the reaction mixture was cooled to ambient temperature, diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to give the title compound (0.05 g, 0.093 mmol, 65% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.17 (s, 2H), 9.04 (s, 2H), 8.94 (s, 2H), 8.87 (s, 1H), 8.76 (d, J = 4.0 Hz, 3H), 7.72 (d, J = 2.5 Hz, 2H), 7.61 (d, J = 2.6 Hz, 1H), 7.50 (t, J = 8.9 Hz, 3H), 7.41 (ddd, J = 25.1, 8.9, 2.6 Hz, 3H), 7.10 – 7.01 (m, 7H), 6.86 (dd, J = 9.0, 2.8 Hz, 3H), 4.86 (d, J = 8.2 Hz, 2H), 4.74 (dd, J = 11.9, 2.8 Hz, 1H), 4.62 (dd, J = 11.3, 2.3 Hz, 2H), 4.53 (s, 1H), 4.49 (d, J = 1.6 Hz, 6H), 3.74 – 3.67 (m, 6H), 3.20 – 3.07

(m, 7H), 2.98 (m, 3H), 2.65 – 2.56 (m, 2H), 2.30 (s, 12H), 2.29 (s, 6H), 2.20 – 2.08 (m, 2H), 2.03 (dt, J = 13.3, 11.0 Hz, 2H); MS (ESI^+) *m/z* 538 $(M+H)^+$.

Example 90: methyl {[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-3,4-dihydro-2*H*-1-benzopyran-4-yl]amino}acetate (Compound 189)

The methodologies described in Example 89 substituting methyl 2-aminoacetate hydrochloride for 2-((trimethylsilyl)oxy)ethanamine gave the title compound. ^{1}H NMR 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.95 (s, 1H), 8.84 (s, 1H), 8.76 (d, J = 2.3 Hz, 2H), 7.72 (d, J = 2.5 Hz, 1H), 7.62 (d, J = 2.6 Hz, 1H), 7.50 (t, J = 8.8 Hz, 2H), 7.40 (ddd, J = 11.8, 8.9, 2.5 Hz, 2H), 7.10 – 7.01 (m, 4H), 6.86 (dd, J = 8.9, 2.8 Hz, 2H), 4.82 (dd, J = 10.1, 6.5 Hz, 1H), 4.75 (dd, J = 12.0, 2.6 Hz, 1H), 4.61 (dd, J = 11.0, 2.4 Hz, 1H), 4.49 (s, 4H), 4.21 (d, J = 16.9 Hz, 1H), 4.11 (d, J = 10.5 Hz, 3H), 3.77 (d, J = 1.7 Hz, 6H), 2.64 (ddd, J = 13.5, 6.6, 2.4 Hz, 1H), 2.56 (d, J = 15.5 Hz, 1H), 2.30 (d, J = 2.7 Hz, 12H), 2.16 2.08 (m, 1H), 2.07 (s, 2H), 2.03 (dd, J = 12.3, 9.5 Hz, 1H); MS (ESI^+) *m/z* 566 $(M+H)^+$.

Example 91: *rac*-(2*R*,4*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 190)

To a solution of Example 87 (1.579 g, 3.20 mmol) in methanol (21 mL) was added zinc chloride (powdered, 654 mg, 4.8 mmol). After stirring at 50 °C for 5 minutes, sodium cyanoborohydride (302 mg, 4.8 mmol) was added, and this mixture was allowed to stir at 50 °C. Over the subsequent 6 days, additional aliquots of zinc chloride (powdered, 327 mg, 2.4 mmol) and sodium cyanoborohydride (285 mg, 4.53 mmol) were added each day. Then the reaction mixture was cooled to ambient temperature, concentrated, diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to give the title compound. The corresponding trans isomer was also determined to be present in minor amount (cis:trans = 12.5:1). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.73 (s, 1H), 8.69 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.38 (dd, J = 2.8, 1.0 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.14 – 7.04 (m, 1H), 6.94 – 6.83 (m, 2H), 4.81 (dd, J = 10.7, 5.9 Hz, 1H), 4.60 (dd, J = 12.0, 2.3 Hz, 1H), 4.48 (s, 2H), 2.35 (ddd, J = 12.9, 5.9, 2.3 Hz, 1H), 2.29 (s, 6H), 2.07 (s, 1H), 1.70 (td, J = 12.5, 10.8 Hz, 1H); MS (ESI^+) *m/z* 477 $(M-H_2O+H)^+$.

Example 92: (2*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-methoxy-2-methylpropyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 191)

The methodologies described in Example 88 provided the title compound using the following modifications: (1) substituting Example 4 for Example 14, (2) substituting powdered zinc chloride for zinc chloride (1.9 M in 2-methyltetrahydrofuran), and (3) halting the reaction after 24 hours, although incomplete conversion. The spectral data match Example 88.

Example 93: {[6-chloro-2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}carbamoyl)-3,4-dihydro-2*H*-1-benzopyran-4-yl]amino}acetic acid (Compound 192)

To a solution of the product of Example 90 (0.025 g, 0.044 mmol) in tetrahydrofuran (0.036 mL)was added LiOH (0.02 mL, 1 N in water), and the reaction mixture stirred at ambient temperature overnight. Then to the mixture was added more LiOH (powder, 0.0031 g, 0.13 mmol), and the reaction mixture was stirred for another 2.5 hours and then was concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (2 mL, 3:1) and purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to yield the title compound (0.015 g, 62 %) as a mixture of diastereomers (dr 2:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (s, 2H), 8.84 (s, 1H), 8.75 (d, J = 2.0 Hz, 3H), 7.72 (d, J = 2.5 Hz, 2H), 7.62 (d, J = 2.6 Hz, 1H), 7.50 (t, J = 8.9 Hz, 3H), 7.40 (ddd, J = 12.4, 8.8, 2.6 Hz, 3H), 7.10 7.01 (m, 6H), 6.86 (ddd, J = 9.0, 3.0, 1.2 Hz, 3H), 4.84 – 4.75 (m, 3H), 4.73 (d, J = 2.0 Hz, 1H), 4.61 (dd, J = 11.0, 2.3 Hz, 2H), 4.49 (s, 6H), 4.50 – 4.44 (m, 1H), 4.08 (d, J = 16.8 Hz, 1H), 3.95 (m, 4H), 3.95 (d, J = 16.8 Hz, 1H), 2.68 – 2.52 (m, 3H), 2.30 (s, 12H), 2.29 (s, 6H), 2.16 – 2.05 (m, 1H), 2.09 – 2.02 (m, 1H), 2.04 – 1.96 (m, 1H); MS (ESI$^+$) *m/z* 553 $(M+H)^+$.

Example 94: (2*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-(2-methylprop-2-en-1-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (Compound 193)

To a solution of the product of Example 92 (0.020 g,0.035 mmol) in CH_2Cl_2 (0.35 mL) was added boron tribromide (0.07 mL, 0.07 mmol, 1 M in CH_2Cl_2) in an ice bath. The reaction mixture was allowed to warm to ambient temperature in the ice bath for 2 hours and then was partitioned between water (1 mL) and CH_2Cl_2 (3 mL), and the layers were separated. The

aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was diluted with *N*,*N*-dimethylformamide/water (1.2 mL, 3:1) and purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in 0.1% trifluoroacetic acid/water) to yield the title compound (0.005 g, 0.009 mmol, 27% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.69 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.9 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 8.5, 2.4 Hz, 1H), 4.87 (t, J = 1.6 Hz, 1H), 4.81 (s, 1H), 4.57 (dd, J = 6.8, 3.0 Hz, 1H), 4.47 (s, 2H), 3.83 (d, J = 16.6 Hz, 1H), 3.72 (d, J = 16.6 Hz, 1H), 3.29 (dd, J = 12.3, 6.8 Hz, 1H), 2.25 (s, 6H), 1.67 (s, 3H); MS (ESI$^+$) *m/z* 534 $(M+H)^+$.

Example 95: *tert*-butyl [(2*R*)-6-chloro-2-({(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}carbamoyl)-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl]acetate (Compound 194)

Example 95A: (S)-4-chloro-2-((3-chloro-2-hydroxypropyl)amino)phenol

To a solution of 2-amino-4-chlorophenol (25 g, 174 mmol) in ethanol (250 mL) and water (2.5 mL) was added (*S*)-2-(chloromethyl)oxirane (16.1 g, 174 mmol), and the solution was stirred for 12 hours at 60 °C. Then the reaction mixture was concentrated, and the crude residue was chromatographed on silica gel (ethyl acetate/petroleum ether 1:5) to give the title compound (80g, 305 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.19 - 3.39 (m, 2 H), 3.61 - 3.73 (m, 2 H), 4.12 - 4.19 (m, 1 H), 6.59 (s, 1 H), 6.62 (br s, 1 H), 6.62 - 6.66 (m, 1 H).

Example 95B: (R)-(6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol

To a solution of Example 95A (40 g, 152 mmol) in ethanol (400 mL) was added K_2CO_3 (12.6 g, 91 mmol), and the solution was stirred for 12 hours at 90 °C. The reaction solution was filtered and concentrated under reduced pressure. The mixture was diluted with water (1000 mL) and extracted with ethyl acetate (3×1000 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/petroleum ether, 1:4) to give the title compound (30 g, 135 mmol, 89 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.28 - 3.42 (m, 2 H) 3.84 (qd, *J*=11.72, 4.96 Hz, 2 H) 4.18 - 4.25 (m, 1 H) 6.58 - 6.64 (m, 2 H) 6.71 - 6.75 (m, 1 H) 6.73 (d, *J*=8.60 Hz, 1 H).

Example 95C: (R)-tert-butyl 2-(((tert-butoxycarbonyl)oxy)methyl)-6-chloro-2H-benzo[b][1,4]oxazine-4(3H)-carboxylate

To a solution of Example 95B (16 g, 72 mmol) in dichloromethane (160 mL) was added

triethylamine (25.1 mL, 180 mmol), di-*tert*-butyl dicarbonate (67 mL, 289 mmol) and 4-(dimethylamino)pyridine (0.88 g, 7.2 mmol). The solution stirred for 2 hours at 20 °C. Then water (500 mL) was added to the mixture, and the aqueous mixture was extracted with dichloromethane (2×500 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography eluted with petroleum ether:ethyl acetate (10:1) to give the title compound (40 g, 90 mmol, 62% yield). ^{1}H NMR (400 MHz, DMSO, d_6) δ ppm 1.42 (s, 9 H) 3.07 (br dd, J=11.25, 7.28 Hz, 1 H) 4.11 - 4.29 (m, 3 H) 6.12 (br s, 1 H) 6.41 - 6.53 (m, 1 H) 6.60 (br d, J=2.20 Hz, 1 H) 6.67 (br d, J=8.38 Hz, 1 H).

Example 95D: (R)-tert-butyl 6-chloro-2-(hydroxymethyl)-2H-benzo[b][1,4]oxazine-4(3H)-carboxylate

To a solution of Example 95C (36 g, 81 mmol) in methanol (360mL) and tetrahydrofuran (360 mL) was added a solution of NaOH (6.48 g, 162 mmol) in water (360 mL) at 20 °C, and the mixture was stirred at 20 °C for 12 hours. The mixture was concentrated and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated to give the title compound (20 g, 60 mmol, 67 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.56 (s, 9 H) 3.57 (dd, *J*=13.69, 7.83 Hz, 1 H) 3.81 (br d, *J*=3.91 Hz, 2 H) 4.07 (dd, *J*=13.69, 2.45 Hz, 1 H) 4.25 (dtd, *J*=7.58, 5.01, 5.01, 2.93 Hz, 1 H) 6.83 (d, *J*=8.31 Hz, 1 H) 6.94 - 6.98 (m, 1 H) 7.80 (br s, 1 H).

Example 95E: (R)-4-(tert-butoxycarbonyl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid

To a solution of Example 95D (16 g, 48 mmol) in dichloromethane (160mL) was added *N*-methylmorpholine-*N*-oxide (NMO, 33.8 g, 288 mmol) at 0 °C and tetrapropylammonium perruthenate (TPAP, 3.38 g, 9.61 mmol) at 0 °C. The solution was stirred for 2 hours at 20 °C and then was concentrated. The residue was purified by preparative HPLC (Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of methanol in 0.1% trifluoroacetic acid/water) to give the title compound (20 g, 57 mmol, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.50 - 1.55 (m, 9 H) 3.87 (dd, *J*=13.89, 3.31 Hz, 1 H) 4.29 (dd, *J*=13.78, 4.74 Hz, 1 H) 4.87 - 4.92 (m, 1 H) 6.89 - 6.96 (m, 1 H) 6.97 - 7.03 (m, 1 H) 7.77 (br s, 1 H) 8.02 (br s, 2 H).

Example 95F: (R)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid hydrochloride

To a solution of Example 95E (10g, 29 mmol) in dichloromethane (100 mL) was added HCl (28.7 mL, 115 mmol, 4 molar in ethyl acetate) at 0 °C. The solution stirred for 12 hours at

20 °C, and then the solid was collected by suction filtration and was dried to give the title compound (13.1 g, 57.8 mmol, 101% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.34 - 3.44 (m, 2 H) 4.82 (t, *J*=3.75 Hz, 1 H) 6.50 (dd, *J*=8.49, 2.54 Hz, 1 H) 6.58 (d, *J*=2.43 Hz, 1 H) 6.71 (d, *J*=8.38 Hz, 1 H); MS (ESI$^-$) *m/z* 212 (M-H)$^-$.

Example 95G: tert-butyl ((S)-4-((R)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxamido)-2-hydroxybicyclo[2.2.2]octan-1-yl)carbamate

The methodologies described in Example 14 substituting Example 95F for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting 85C for Example 23B gave the title compound. MS (ESI$^+$) *m/z* 452 (M+H)$^+$.

Example 95H: (R)-N-((S)-4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl)-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxamide

The methodologies described in Example 71B substituting Example 95G for Example 71A without purification gave the title compound. MS (ESI$^+$) *m/z* 352 (M+H)$^+$.

Example 95I: (2R)-6-chloro-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide

The methodologies described in Example 14 substituting 2-(4-chloro-3-fluorophenoxy)acetic acid for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting Example 95H for Example 23B gave the title compound. MS (ESI$^+$) *m/z* 538 (M+H)$^+$.

Example 95J: tert-butyl rac-[(2R)-6-chloro-2-({(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}carbamoyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate

The methodologies described in Example 36 with the following modifications: (1) substituting *tert*-butyl bromoacetate for 2-bromoethanol, (2) substituting Example 95I for the product of Example 14, (3) stirring for 2 days instead of 5, and (4) with the addition of NaI (0.5 equivalence), gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 9.0 Hz, 1H), 7.37 (s, 1H), 7.26 (s, 1H), 7.05 (dd, J = 11.5, 2.9 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.63 – 6.53 (m, 2H), 5.08 (m, 1H), 4.46 (m, 3H), 4.15 (d, J = 18.3 Hz, 1H), 4.05 (m, 1H), 1.93 (m, 2H), 1.80 (m, 7H), 1.38 (s, 9H); MS (ESI$^+$) *m/z* 596 (M-C(O)OC(CH$_3$)$_3$+H)$^+$.

Example 96: (2*S*,4*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 195)

Example 91 was purified by chiral SFC (supercritical fluid chromatography) using a Whelk-O®1 column eluting with 40% CH_3OH with 0.1% diethylamine in CO_2 with a flow rate of 80 g/minute and back pressure of 120 bar to give the title compound (first enantiomer eluted out of the column, 0.011 g, 0.022 mmol, 29% yield). The stereochemistry of this title compounds was arbitrarily assigned (This compound is the enantiomer of Example 97.). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (s, 1H), 8.68 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.38 (dd, J = 2.7, 1.0 Hz, 1H), 7.20 (ddd, J = 8.7, 2.7, 0.6 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.92 – 6.82 (m, 2H), 5.70 (d, J = 6.3 Hz, 1H), 4.81 (dt, J = 11.6, 6.0 Hz, 1H), 4.60 (dd, J = 12.0, 2.3 Hz, 1H), 4.48 (s, 2H), 2.35 (ddd, J = 12.9, 5.9, 2.3 Hz, 1H), 2.29 (s, 6H), 1.76 – 1.63 (m, 1H); MS (ESI$^+$) *m/z* 477 (M-H_2O+H)$^+$.

Example 97: (2*R*,4*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 196)

Example 91 was purified by chiral SFC (supercritical fluid chromatography) using a Whelk-O®1 column eluting with 40% CH_3OH with 0.1% diethylamine in CO_2 with a flow rate of 80 g/minute and back pressure of 120 bar to give the title compound (fourth enantiomer eluted out of the column, 0.017 g, 0.010 mmol, 45% yield). Stereochemistry of this title compounds was arbitrarily assigned (This compound is the enantiomer of Example 96.). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (s, 1H), 8.68 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.38 (dd, J = 2.8, 1.0 Hz, 1H), 7.20 (dd, J = 8.7, 2.7 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.91 – 6.82 (m, 2H), 5.70 (d, J = 6.4 Hz, 1H), 4.80 (dt, J = 11.4, 6.0 Hz, 1H), 4.59 (dd, J = 12.0, 2.2 Hz, 1H), 4.48 (s, 2H), 2.40 – 2.30 (m, 1H), 2.28 (s, 6H), 1.69 (td, J = 12.5, 10.8 Hz, 1H); MS (ESI$^+$) *m/z* 477 (M-H_2O+H)$^+$.

Example 98: (2*R*,4*S*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 197)

Example 91 was purified by chiral SFC (supercritical fluid chromatography) using a Whelk-O®1 column eluting with 40% CH_3OH with 0.1% diethylamine in CO_2 with a flow rate of 80 g/minute and back pressure of 120 bar to give the title compound (third enantiomer eluted out of the column, 0.003 g, 0.006 mmol, 8% yield). The stereochemistry of this title compounds was arbitrarily assigned (This compound is the enantiomer of Example 99.). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 8.73 (s, 1H), 8.72 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.31 (d, J = 2.6 Hz, 1H),

7.25 (dd, J = 8.8, 2.7 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.61 (d, J = 4.7 Hz, 1H), 4.58 (q, J = 4.0 Hz, 1H), 4.55 (dd, J = 10.9, 2.7 Hz, 1H), 4.48 (s, 2H), 2.28 (s, 6H), 2.09 (ddd, J = 13.9, 3.9, 2.8 Hz, 1H), 1.89 (ddd, J = 14.3, 11.0, 3.7 Hz, 1H); MS (ESI^+) *m/z* 477 $(M-H_2O+H)^+$.

Example 99: (2*S*,4*R*)-6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 198)

Example 91 was purified by chiral SFC (supercritical fluid chromatography) using a Whelk-O®1 column eluting with 40% CH_3OH with 0.1% diethylamine in CO_2 with a flow rate of 80 g/minute and back pressure of 120 bar to give the title compound (second enantiomer eluted out of the column, 0.002 g, 0.004 mmol, 5% yield). The exact stereochemistry of this title compounds was arbitrarily assigned. This title compound contained Example 96 as the major product in a mixture of diastereomers (dr 5:1, Example 96:99). ^1H NMR (400 MHz, DMSO-d_6, dr 5:1) δ ppm 8.74 (s, 1H), 8.72 (s, 1H), 8.68 (s, 0.2H), 7.50 (t, J = 8.9 Hz, 1H), 7.38 (d, J = 2.2 Hz, 0.2H), 7.31 (d, J = 2.7 Hz, 1H), 7.25 (dd, J = 8.8, 2.7 Hz, 1H), 7.20 (dd, J = 8.7, 2.6 Hz, 0H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.91 (dd, J = 18.7, 8.3 Hz, 1H), 6.89 – 6.82 (m, 1H), 5.70 (d, J = 6.3 Hz, 0.2H), 5.61 (d, J = 4.7 Hz, 1H), 4.80 (dt, J = 11.5, 6.2 Hz, 0H), 4.59 – 4.52 (m, 2H), 4.48 (s, 2H), 2.28 (d, J = 1.9 Hz, 6H), 2.09 (dt, J = 13.8, 3.4 Hz, 1H), 1.89 (ddd, J = 14.1, 10.9, 3.7 Hz, 1H); MS (ESI^+) *m/z* 477 $(M-H_2O+H)^+$.

Example 100: 6-chloro-*N*-{(3*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 199)

Example 100A: tert-butyl ((2S)-4-(6-chloro-4-oxochroman-2-carboxamido)-2-hydroxybicyclo[2.2.2]octan-1-yl)carbamate

The methodologies described in Example 14 substituting 6-chloro-4-oxochroman-2-carboxylic acid for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting Example 85C for Example 23B gave the title compound. MS (ESI^+) *m/z* 465 $(M+H)^+$.

Example 100B: N-((S)-4-amino-3-hydroxybicyclo[2.2.2]octan-1-yl)-6-chloro-4-oxochroman-2-carboxamide

The methodologies described in Example 71B substituting Example 100A for Example 71A without purification gave the title compound. MS (ESI^+) *m/z* 365 $(M+H)^+$.

Example 100C: 6-chloro-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-oxo-3,4-dihydro-2H-1-benzopyran-2-carboxamide

The methodologies described in Example 14 substituting 2-(4-chloro-3-fluorophenoxy)acetic acid for 6-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-2-carboxylic acid and substituting Example 100B for Example 23B gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 (s, 1H), 7.66 – 7.57 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 7.26 (s, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 3.0, 1.2 Hz, 1H), 5.04 (dd, J = 8.2, 5.0 Hz, 1H), 4.46 (s, 2H), 4.03 (dd, J = 9.6, 3.1 Hz, 1H), 3.01 – 2.84 (m, 2H), 2.22 (ddt, J = 12.4, 9.4, 2.7 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.96 – 1.68 (m, 9H).; MS (ESI$^+$) *m/z* 552 (M+H)$^+$.

Example 100: 6-chloro-N-{(3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxybicyclo[2.2.2]octan-1-yl}-4-hydroxy-3,4-dihydro-2H-1-benzopyran-2-carboxamide

The methodologies described in Example 89 removing 2-((trimethylsilyl)oxy)ethan-amine, substituting Example 100C for Example 87, and purifying by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] gave the title compound. ^{1}H NMR (400 MHz, DMSO-d_6, dr cis:trans = 5:1) δ ppm 7.48 (t, J = 8.9 Hz, 6H), 7.42 (s, 1H), 7.37 (dd, J = 2.7, 1.0 Hz, 5H), 7.35 – 7.32 (m, 5H), 7.30 (d, J = 2.6 Hz, 1H), 7.26 (s, 6H), 7.22 (dd, J = 8.8, 2.7 Hz, 1H), 7.18 (ddd, J = 8.7, 2.7, 0.7 Hz, 5H), 7.06 (dd, J = 11.4, 2.9 Hz, 6H), 6.91 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 5H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 7H), 5.66 (d, J = 6.4 Hz, 5H), 5.58 (d, J = 4.6 Hz, 1H), 5.08 (dd, J = 4.9, 2.1 Hz, 6H), 4.77 (dt, J = 11.7, 6.1 Hz, 5H), 4.55 (dd, J = 11.8, 2.2 Hz, 7H), 4.47 (s, 11H), 4.09 – 4.02 (m, 6H), 2.34 – 2.22 (m, 12H), 2.12 – 2.00 (m, 3H), 2.07 (s, 4H), 2.04 – 1.89 (m, 11H), 1.86 (dd, J = 10.6, 2.7 Hz, 4H), 1.81 (d, J = 8.4 Hz, 29H), 1.80 – 1.66 (m, 5H); MS (ESI$^+$) *m/z* 535 (M-H_2O+H)$^+$.

Example 101: *N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 200)

To a mixture of the product from Example 27A (91 mg, 0.20 mmol) and 6-fluorochroman-2-carboxylic acid (39.2 mg, 0.20 mmol) in *N*,*N*-dimethylformamide (1 mL) was added 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (76 mg, 0.20 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.14 mL, 0.80 mmol), and the resulting mixture was stirred at room temperature for 0.5 hour. Water was added, and the mixture was purified by C18 HPLC using a solvent gradient of 5-95% acetonitrile

in water (with 0.1% trifluoroacetic acid) to give the title compound (90 mg, 0.17 mmol, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.82 – 6.71 (m, 2H), 6.54 (dd, J = 8.5, 2.4 Hz, 1H), 4.69 (t, J = 5.5 Hz, 1H), 4.47 (s, 2H), 4.45 (dd, J = 7.9, 2.9 Hz, 2H), 3.61 – 3.47 (m, 4H), 2.26 (s, 6H), 2.24 (d, J = 2.6 Hz, 1H); MS (ESI$^+$) *m/z* 524 (M+H)$^+$.

Example 102: (2*S*)-*N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 201)

The product from Example 101 (60 mg, 0.115 mmol) was purified by chiral SFC [Whelk-O®1 (S,S) column] using 40% methanol in CO_2 as the eluent. The title compound was the first of 2 stereoisomers to elute (30 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.50 (s, 1H),7.48 (t, J = 8 Hz, 1H), 7.10 (s, 1H), 7.02 (dd, J = 10, 3 Hz, 1H), 6.93 (m, 2H), 6.83 (m, 2H), 5.16 (d, J = 3 Hz, 1H), 4.45 (m, 1H), 4.43 (s, 2H), 3.97 (m, 1H), 2.79 (m, 1H), 2.67 (m, 1H), 2.25 (m, 2H), 2.11 (m, 1H), 1.65 - 1.96 (m, 9H); MS (ESI$^+$) *m/z* 521 (M+H)$^+$.

Example 103: (2*R*)-*N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 202)

The product from Example 101 (60 mg, 0.115 mmol) was purified by chiral SFC [Whelk-O®1 (S,S) column] using 40% methanol in CO_2 as the eluent. The title compound was the second of 2 stereoisomers to elute (29 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.50 (s, 1H),7.48 (t, J = 8 Hz, 1H), 7.11 (s, 1H), 7.02 (dd, J = 10, 3 Hz, 1H), 6.93 (m, 2H), 6.82 (m, 2H), 5.19 (d, J = 3 Hz, 1H), 4.45 (m, 1H), 4.43 (s, 2H), 3.89 (m, 1H), 2.79 (m, 1H), 2.67 (m, 1H), 2.25 (m, 2H), 2.11 (m, 1H), 1.65 - 1.96 (m, 9H); MS (ESI$^+$) *m/z* 521 (M+H)$^+$.

Example 104: 6-chloro-*N*-{(2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octan-1-yl}-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 203)

The title compound was prepared using the procedures described for Example 101, substituting 6-chlorochroman-2-carboxylic acid for 6-fluorochroman-2-carboxylic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.52 (s, 1H),7.48 (t, J = 8 Hz, 1H), 7.14 (m, 3H), 7.02 (dd, J = 10, 3 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 6.81 (br d, J= 8 Hz, 1H), 4.47 (m, 1H), 4.43 (s, 2H), 3.89 -

4.00 (m, 1H), 2.76 (m, 1H), 2.65 (m, 1H), 2.25 (m, 2H), 2.10 (m, 1H), 1.65 - 1.96 (m, 9H); MS (ESI^+) *m/z* 537 $(M+H)^+$.

Example 105: 6-chloro-*N*-{3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentan-1-yl}-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide (Compound 204)

To a mixture of the product from Example 23B (0.150 g, 0.376 mmol) and 6-chlorochroman-2-carboxylic acid (0.100 g, 0.470 mmol) in *N,N*-dimethylformamide (3.0 mL) was added 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (0.150 g, 0.395 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.26 mL, 1.51 mmol), and the resulting mixture was stirred at room temperature for 16 hours. This mixture was partitioned between saturated, aqueous sodium bicarbonate solution and dichloromethane, and the organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was and purified on C18 HPLC using a solvent gradient of 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide) to give the title compound (60 mg, 0.125 mmol, 33% yield). ^1H NMR (501 MHz, DMSO-d_6) δ ppm 8.69 (s, 1H), 8.61 (s, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.12 (s, 2H), 7.06 (dd, J = 11.4, 2.8 Hz, 1H), 6.88 – 6.82 (m, 2H), 4.50 – 4.43 (m, 3H), 2.83 – 2.59 (m, 2H), 2.25 (s, 6H), 2.16 – 2.06 (m, 1H), 1.88 – 1.77 (m, 1H); MS (ESI^+) *m/z* 479 $(M+H)^+$.

Example 106: Activity of exemplary compounds in an in vitro model of vanishing cell white matter disease (VWMD)

In order to test exemplary compounds of the invention in a cellular context, a stable VWMD cell line was first constructed. The ATF4 reporter was prepared by fusing the human full-length ATF4 5'-UTR (NCBI Accession No. BC022088.2) in front of the firefly luciferase (FLuc) coding sequence lacking the initiator methionine as described in Sidrauski et al (eLife 2013). The construct was used to produce recombinant retroviruses using standard methods and the resulting viral supernatant was used to transduce HEK293T cells, which were then subsequently selected with puromycin to generate a stable cell line.

HEK293T cells carrying the ATF4 luciferase reporter were plated on polylysine coated 384-well plates (Greiner Bio-one) at 30,000 cells per well. Cells were treated the next day with 1 µg/mL tunicamycin and 200 nM of a compound of Formula (I) for 7 hours. Luminescence was measured using One Glo (Promega) as specified by the manufacturer. Cells were maintained in DMEM with L-glutamine supplemented with 10% heat-inactivated FBS (Gibco) and Antibiotic-Antimycotic solution (Gibco).

Table 2 below summarizes the EC_{50} data obtained using the ATF4-Luc assay for exemplary compounds of the invention. In this table, "A" represents an EC_{50} of less than 10 nM; "B" an EC_{50} of between 10 nM and 50 nM; "C" an EC_{50} of between 50 nM and 250 nM; "D" an EC_{50} of between 250 nM and 500 nM; "E" an EC_{50} of between 500 nM and 2 μM; "F" an EC_{50} of greater than 2 μM; and "G" indicates that data is not available.

Table 2: EC_{50} values of exemplary compounds of the invention in the ATF4-Luc assay.

Compound No.	ATF4-Luc EC_{50}
100	F
101	E
102	A
103	A
104	A
105	A
106	A
107	A
108	A
109	E
110	B
111	C
112	A
113	A
114	A
115	A
116	A
117	A
118	A
119	A
120	A
121	A
122	B
123	D
124	B
125	C
126	A
127	B
128	C
129	D
130	F
131	E

Compound No.	ATF4-Luc EC_{50}
132	C
133	B
134	B
135	A
136	A
137	F
138	D
139	C
140	C
141	B
142	C
143	E
144	C
145	C
146	E
147	E
148	C
149	C
150	D
151	E
152	D
153	B
154	A
155	F
156	B
157	B
158	B
159	A
160	F
161	A
162	C
163	F

Compound No.	ATF4-Luc EC_{50}
164	F
165	B
166	E
167	D
168	C
169	D
170	D
171	G
172	A
173	E
174	C
175	D
176	D
177	A
178	A
179	E
180	B
181	B
182	C
183	B
184	D
185	C
186	A
187	B
188	B
189	B
190	G
191	G
192	G
193	G
194	G
195	A

Compound No.	ATF4-Luc EC_{50}
196	G
197	G
198	G
199	A
200	A
201	A
202	A
203	A
204	A

EQUIVALENTS AND SCOPE

In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims are introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of

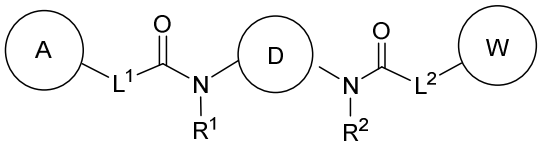
the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

We claim:

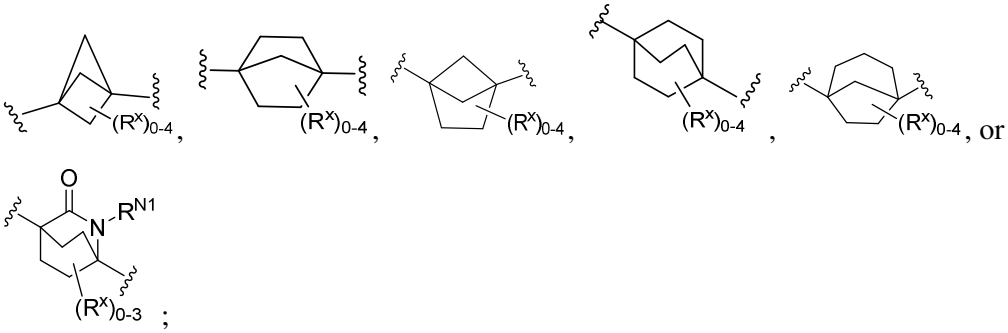
1. A compound of Formula (I):



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;

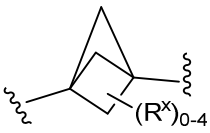
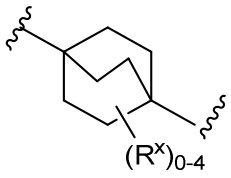
each R^{CC} is independently selected from the group consisting of C_1-C_6 alkyl–OH, C_1-C_6 alkyl–CO_2H and C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl;

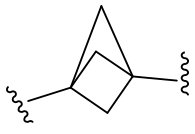
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

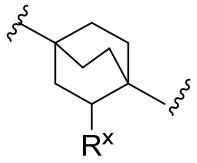
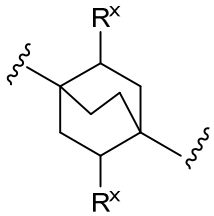
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

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.

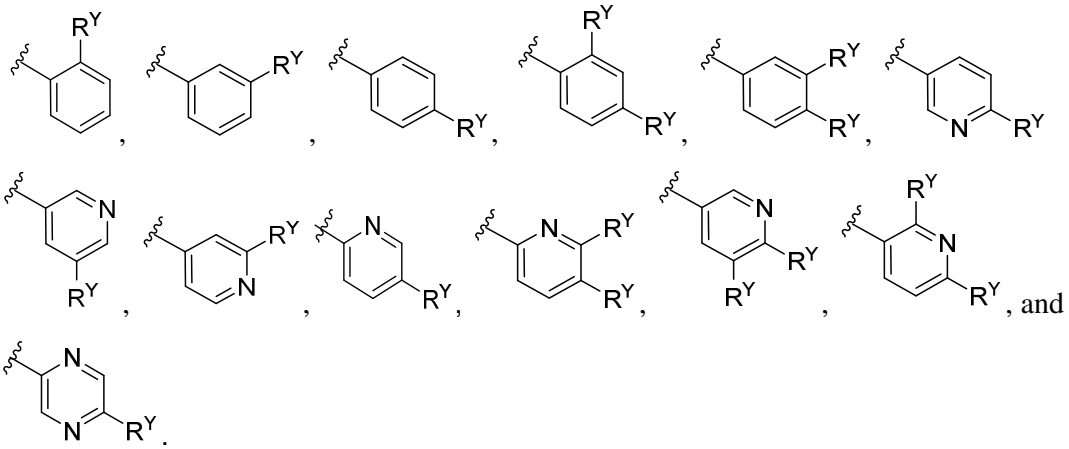
6. The compound of any one of claims 1-5, wherein L^1 is a bond, 2-7 membered heteroalkylene, –NR^{N2}–, or –O–, wherein 2-7 membered heteroalkylene is optionally substituted by 1-5 R^{L1}.

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.

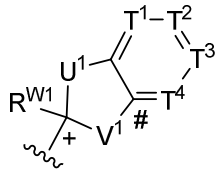
12. The compound of claim 11, wherein each R^X is independently fluoro.

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;

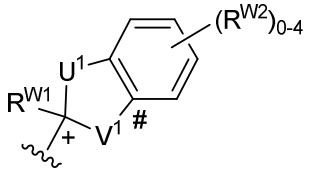
R^{V11} and R^{V12} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$,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

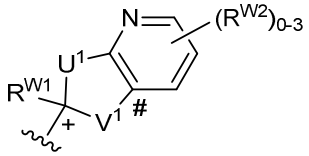
R^{V15} and R^{V16} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -C(O)N$R^B R^C$, –C(O)R^D, –C(O)OH, and –C(O)OR^D; and

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

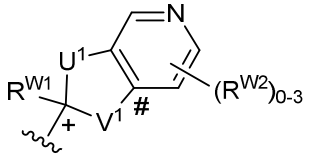
17. The compound of claim 16, wherein W is represented by Formula (W-a-1), Formula (W-a-2), Formula (W-a-3), Formula (W-a-4), or Formula (W-a-5):



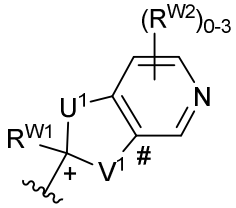
Formula (W-a-1),



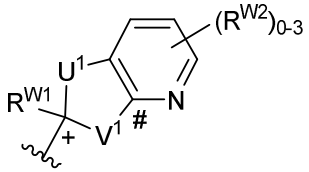
Formula (W-a-2),



Formula (W-a-3),

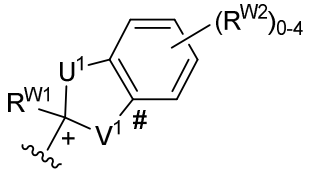


Formula (W-a-4), or



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.

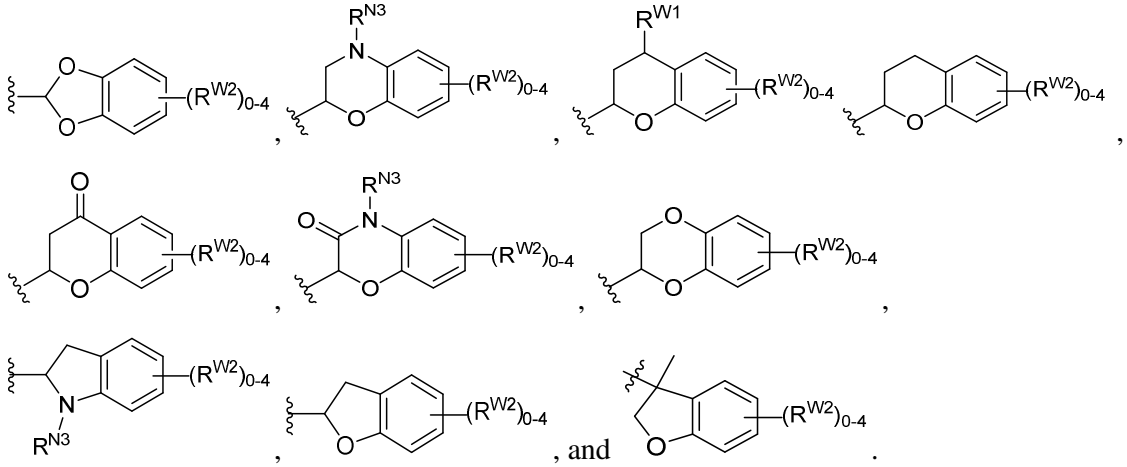
24. The compound of any one of claims 16-23, wherein U^1 is selected from the group consisting of a bond, –O–, –NH– and $–NCH_3–$; and V^1 is selected from the group consisting of $^+–O–^\#$, $^+–CH_2–^\#$, $^+–CH_2–CH_2–^\#$, $^+–CH_2–C(O)–^\#$, $^+–CH_2–O–^\#$, $^+–O\text{-}CH_2–^\#$, $^+–CH_2–NH–^\#$,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

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);

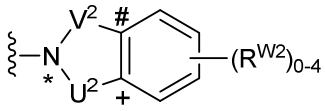
wherein if V^2 is $^*–C(R^{V21}R^{V22})–^\#$, U^2 is not a bond;

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–$C(O)OR^D$;

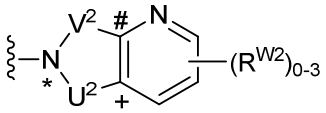
R^{V21} and R^{V22} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, and $–C(O)OR^D$; and

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 $–S(O)_2R^D$.

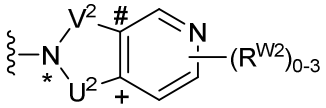
29. The compound of claim 28, wherein W is represented by Formula (W-b-1), Formula (W-b-2), Formula (W-b-3), Formula (W-b-4), or Formula (W-b-5):



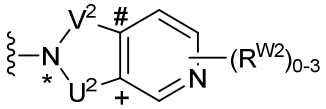
Formula (W-b-1),



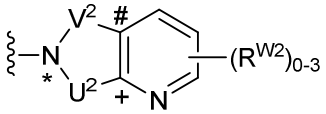
Formula (W-b-2),



Formula (W-b-3),

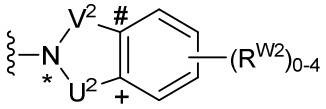


Formula (W-b-4), or



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.

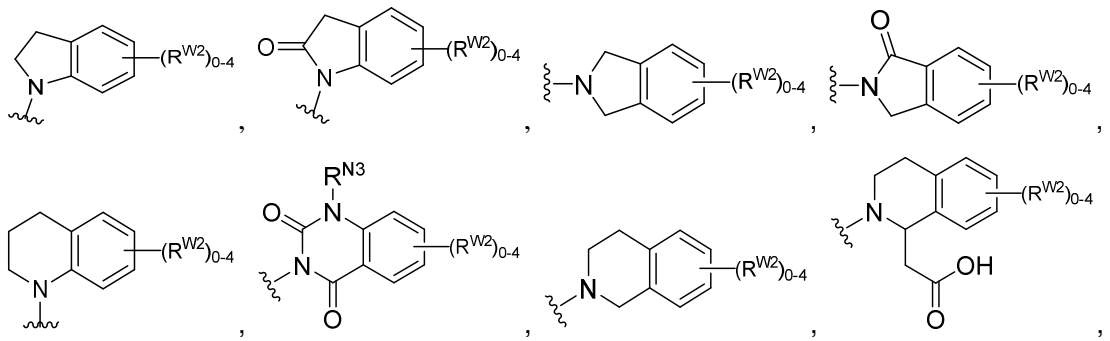
34. The compound of any one of claims 28-33, wherein each of R^{V23} and R^{V24} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, $–OR^A$, and $–NR^BR^C$.

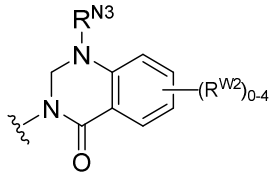
35. The compound of any one of claims 28-34, wherein each of R^{V23} and R^{V24} is hydrogen.

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).

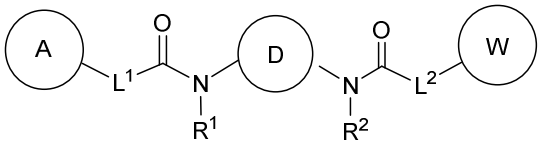
37. The compound of any one of claims 28-36, wherein W is an indoline, indolin-2-one, isoindoline, isoindolin-1-one, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, quinazoline-2,4(1*H*,3*H*)-dione, or 2,3-dihydroquinazolin-4(1*H*)-one moiety; wherein each of which is attached to L^2 through 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

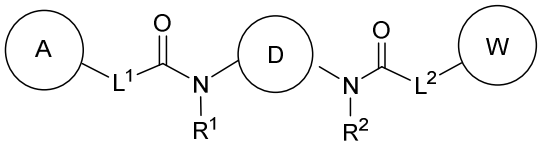
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

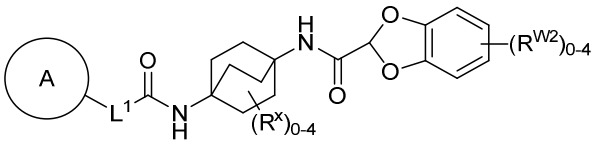
2 R^{W2} groups on adjacent carbons, together with the atoms to which they are attached form a 1,3-dioxolanyl ring, which is optionally substituted with 1-2 fluorine atoms;

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

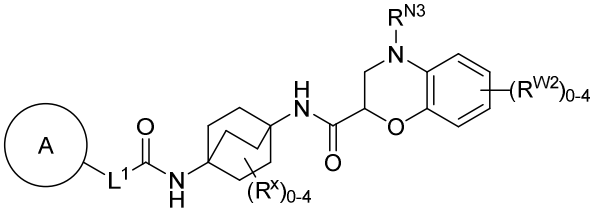
each R^Y is independently chloro, fluoro, $–CHF_2$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, or –CN; or

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.

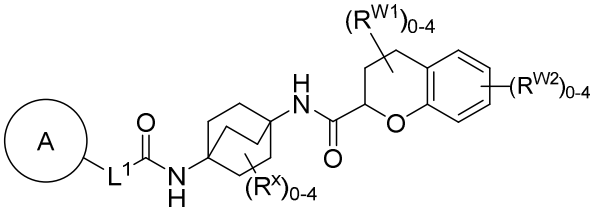
41. The compound of any one of claims 1-40, wherein the compound of Formula (I) is a compound of Formula (I-c-1), Formula (I-c-2), Formula (I-c-3), Formula (I-c-4), Formula (I-c-5), Formula (I-c-6), Formula (I-c-7), Formula (I-c-8), Formula (I-c-9) or Formula (I-c-10):



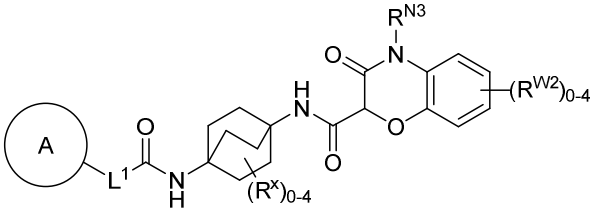
Formula (I-c-1)



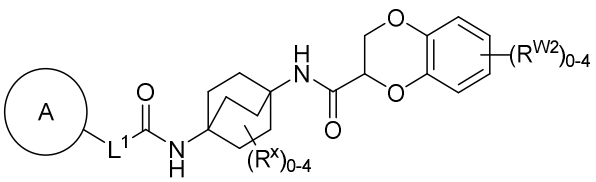
Formula (I-c-2)



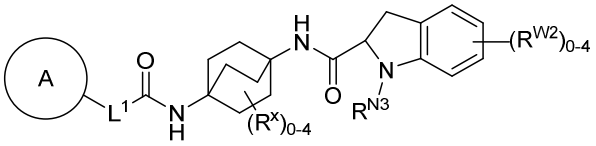
Formula (I-c-3)



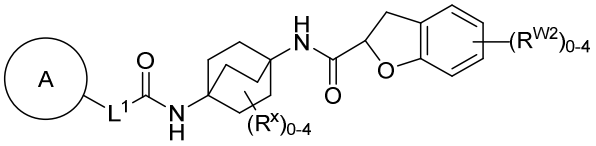
Formula (I-c-4)



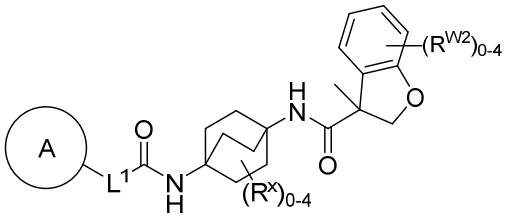
Formula (I-c-5)



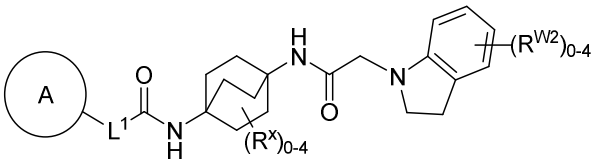
Formula (I-c-6)



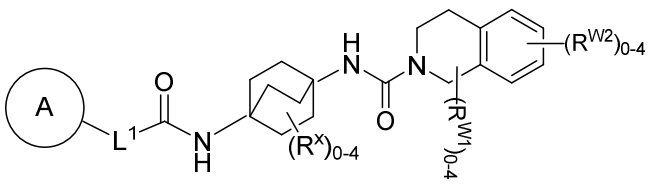
Formula (I-c-7)



Formula (I-c-8)



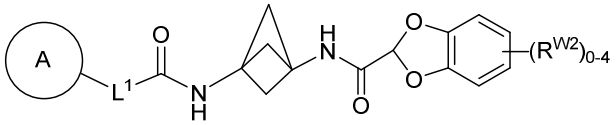
Formula (I-c-9)



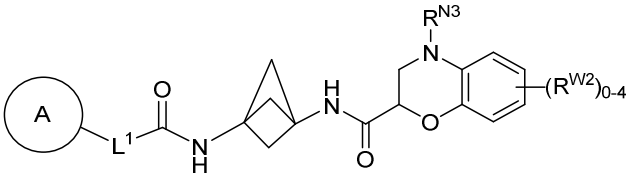
Formula (I-c-10)

or a pharmaceutically acceptable salt thereof.

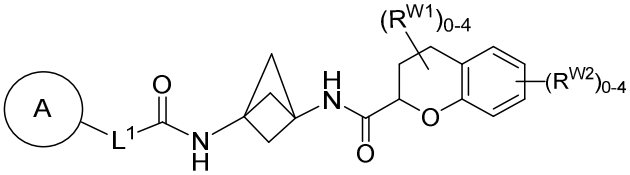
42. The compound of any one of claims 1-40, wherein the compound of Formula (I) is a compound of Formula (I-d-1), Formula (I-d-2), Formula (I-d-3), Formula (I-d-4), Formula (I-d-5), Formula (I-d-6), Formula (I-d-7), Formula (I-d-8), Formula (I-d-9) or Formula (I-d-10):



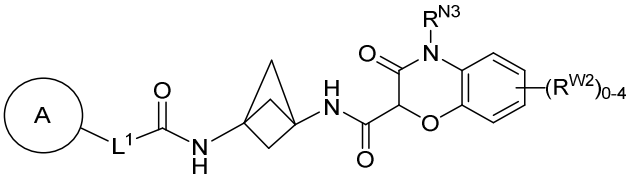
Formula (I-d-1)



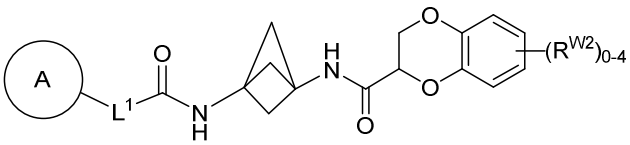
Formula (I-d-2)



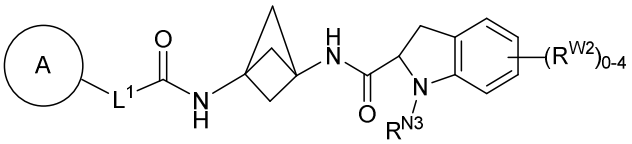
Formula (I-d-3)



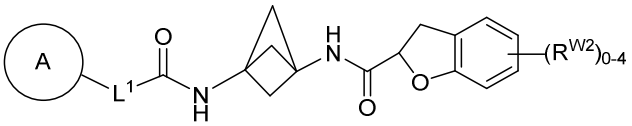
Formula (I-d-4)



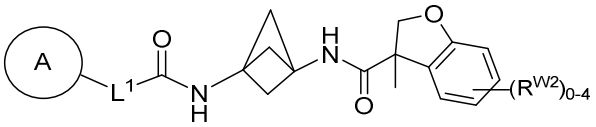
Formula (I-d-5)



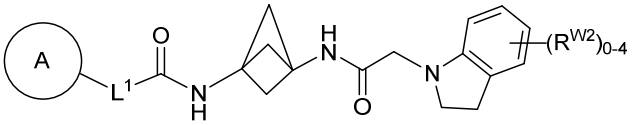
Formula (I-d-6)



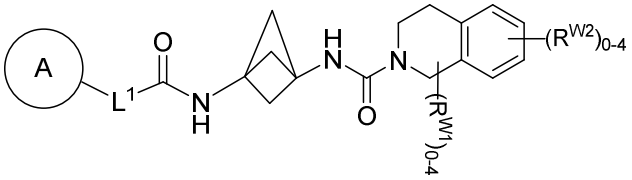
Formula (I-d-7)



Formula (I-d-8)



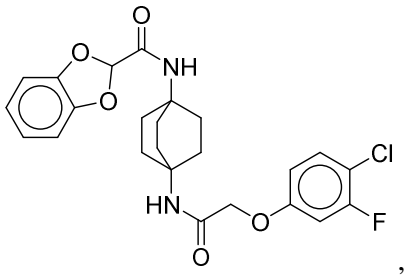
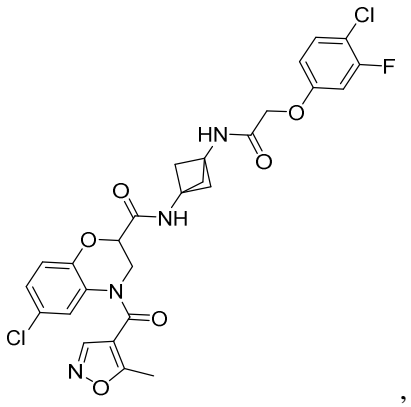
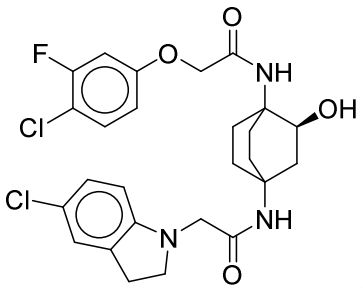
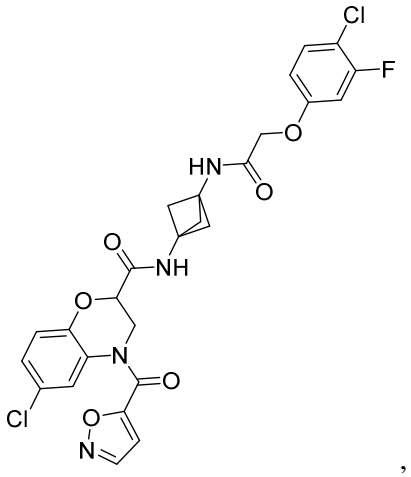
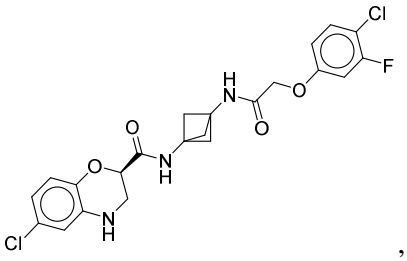
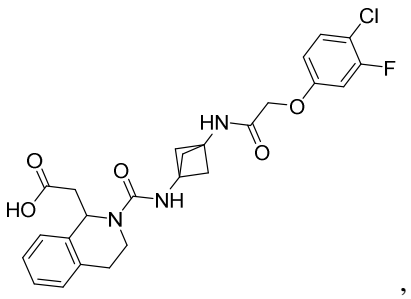
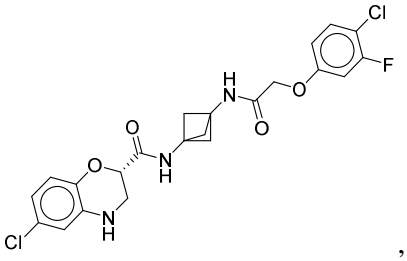
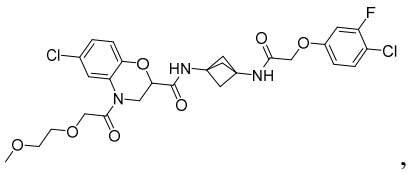
Formula (I-d-9)

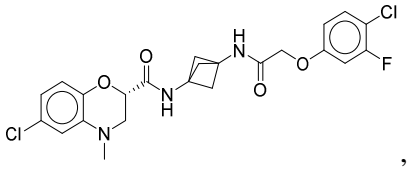
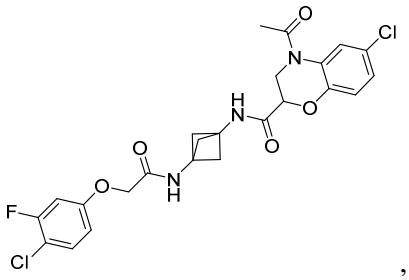
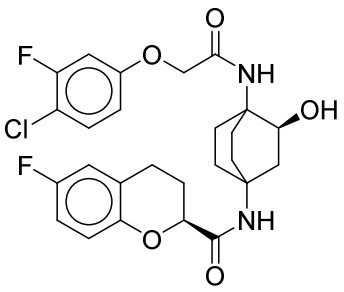
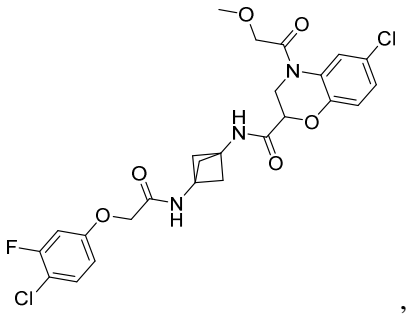
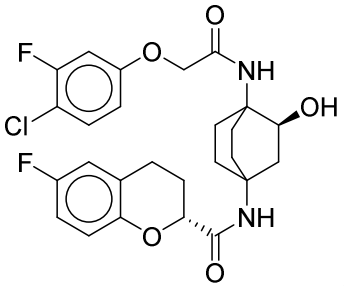
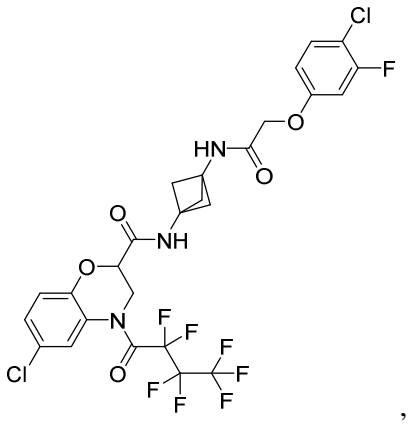
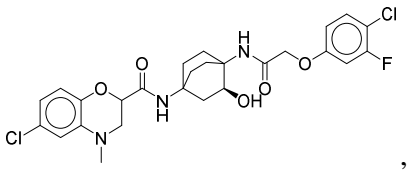
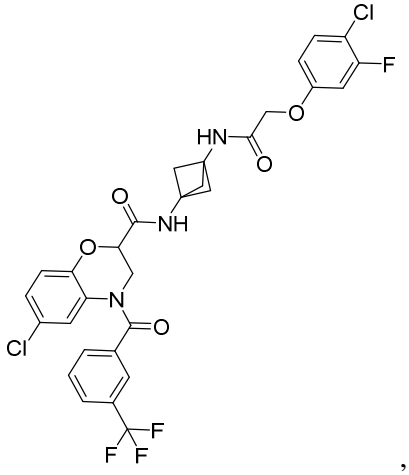


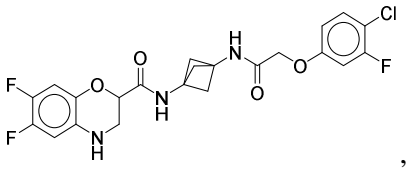
Formula (I-d-10)

or a pharmaceutically acceptable salt thereof.

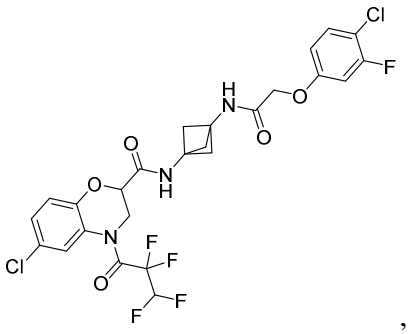
43. A compound, wherein the compound is selected from the group consisting of:


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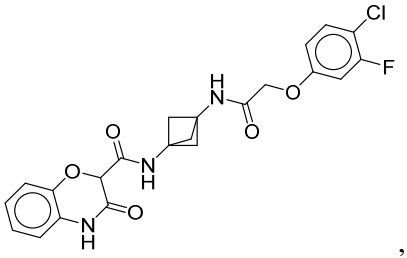

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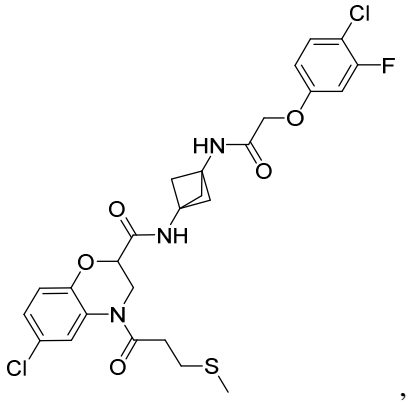
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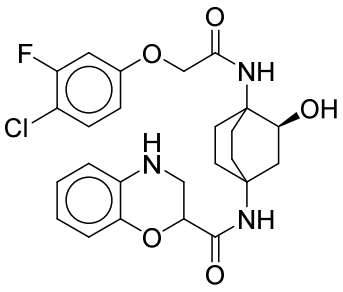
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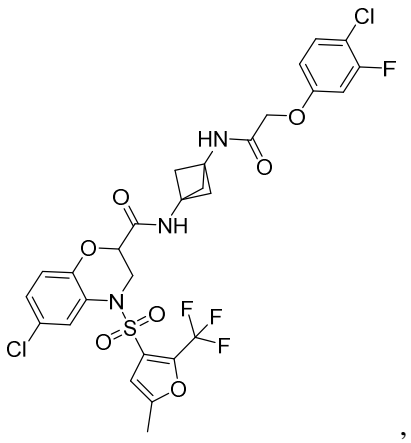
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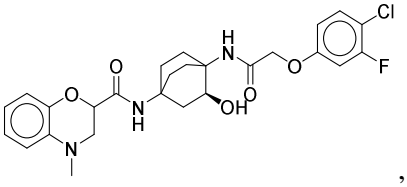
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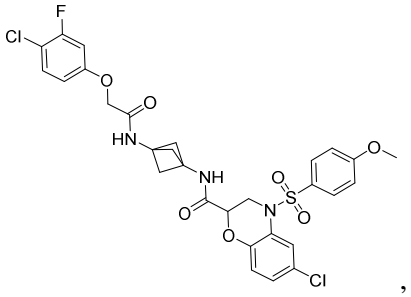
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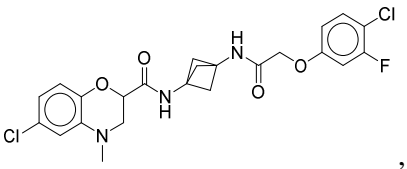
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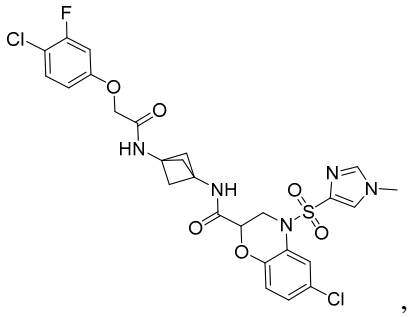
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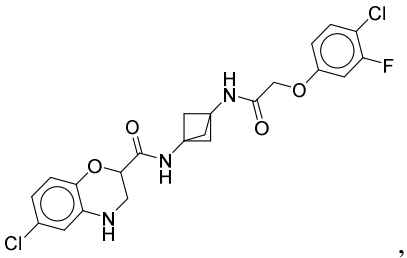
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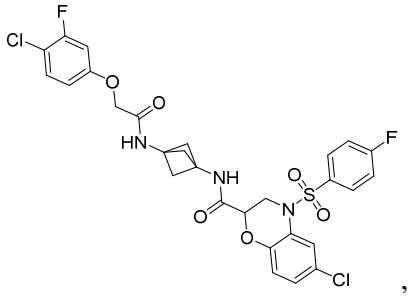
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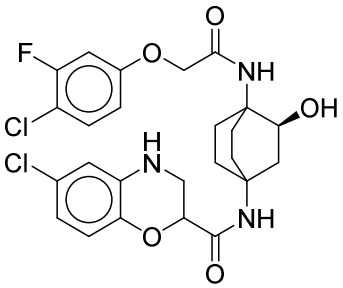
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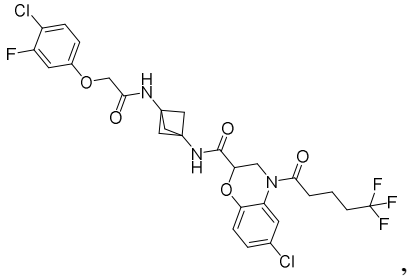
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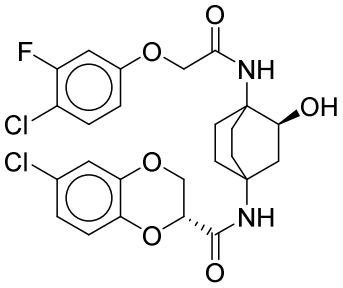
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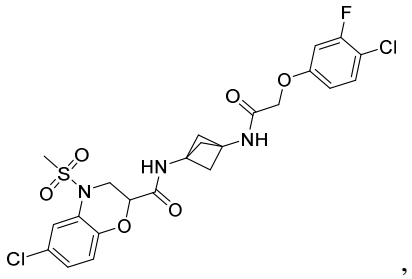
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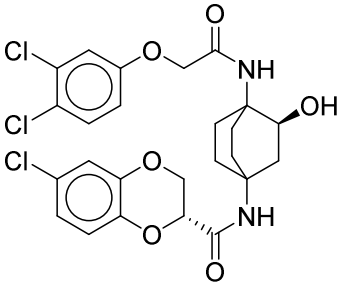
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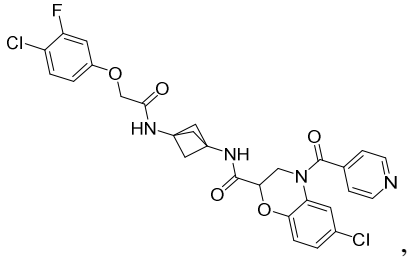
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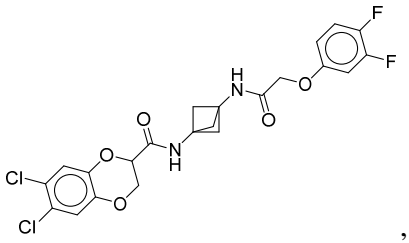
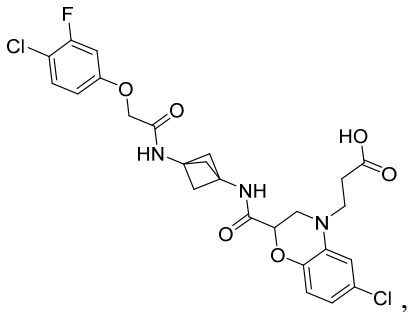
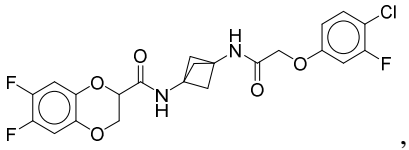
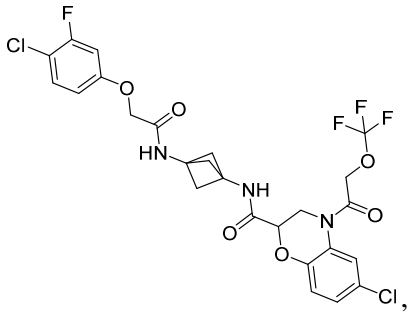
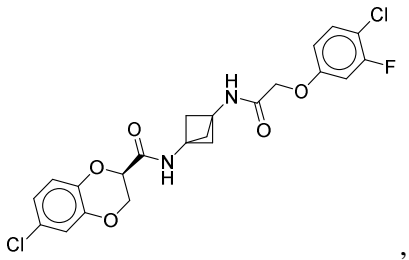
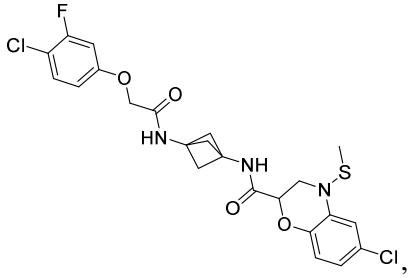
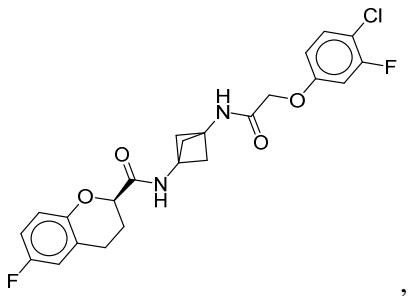
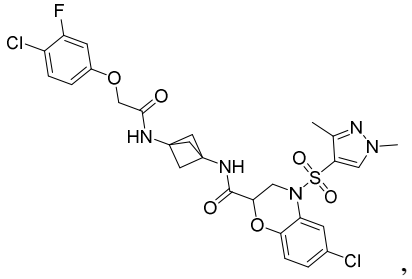
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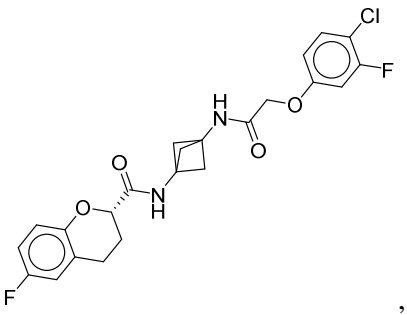
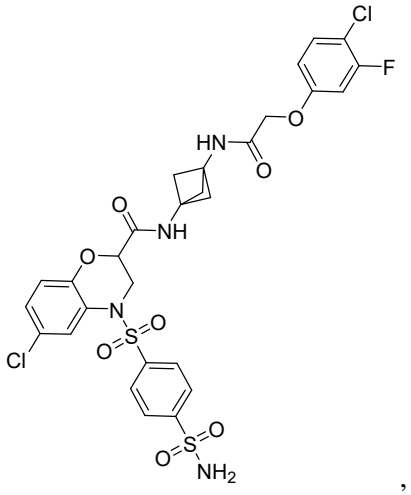
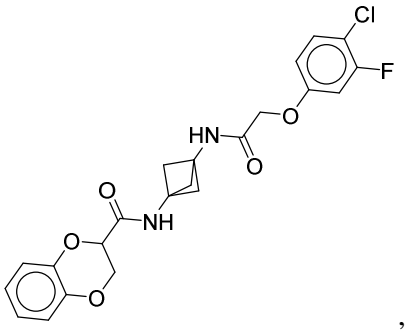
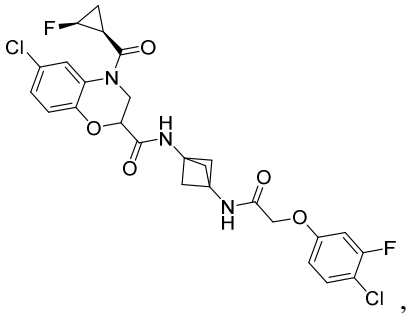
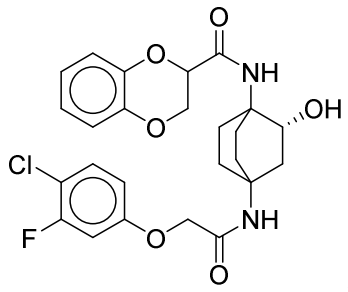
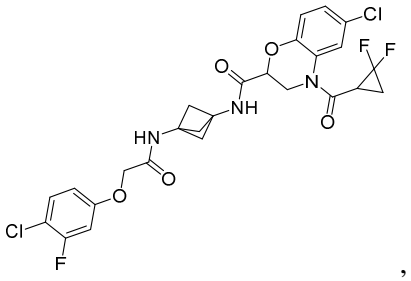
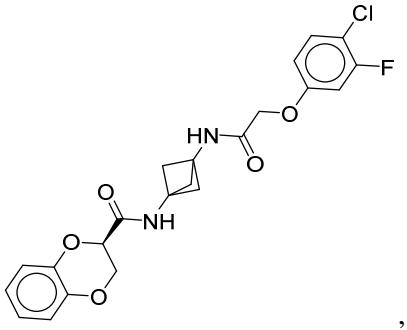
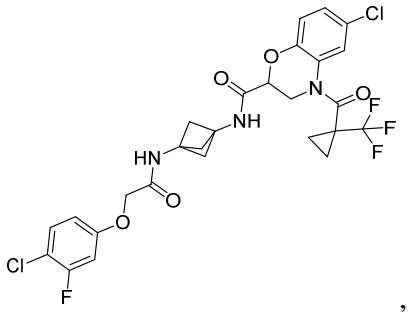


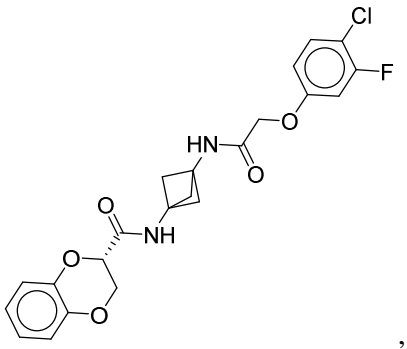
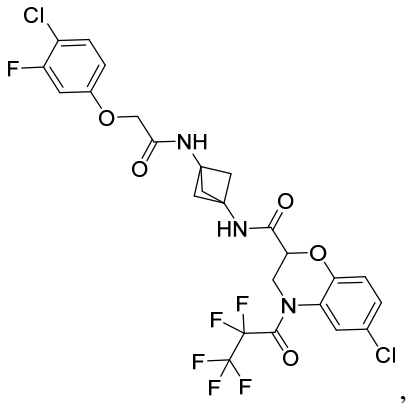
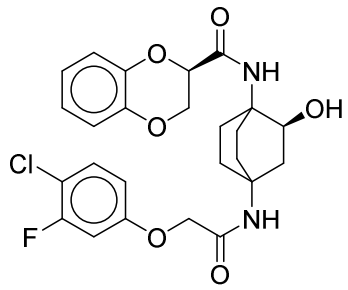
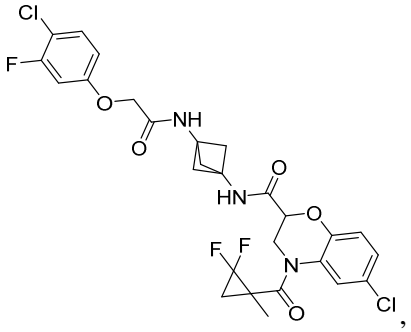
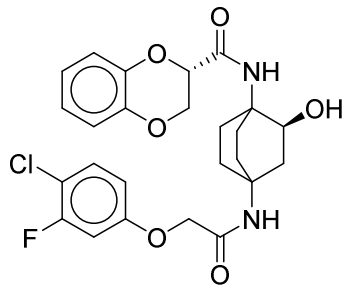
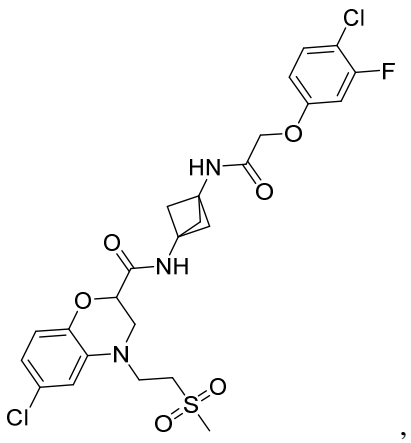
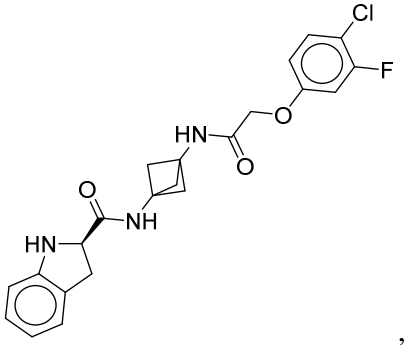
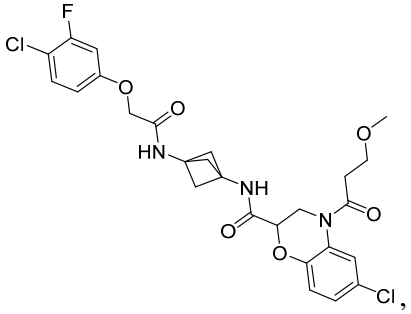
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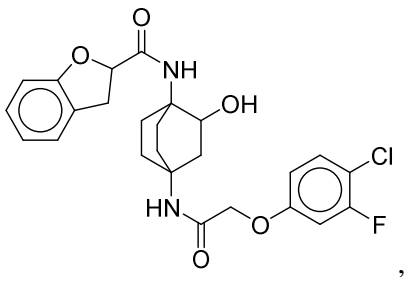
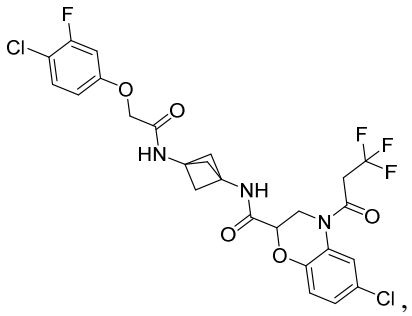
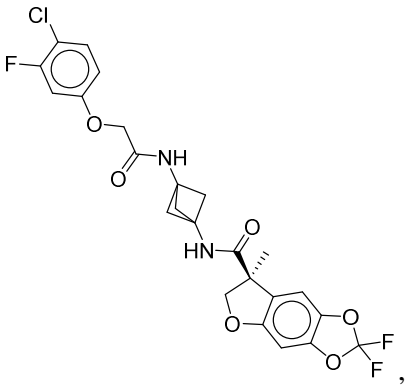
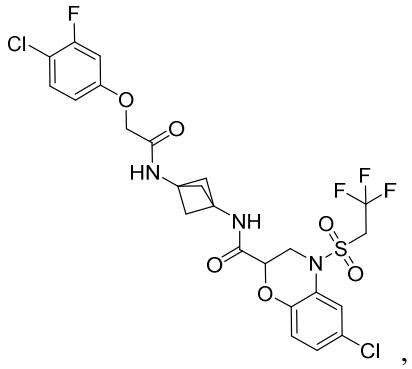
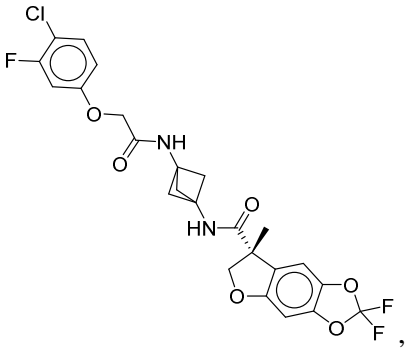
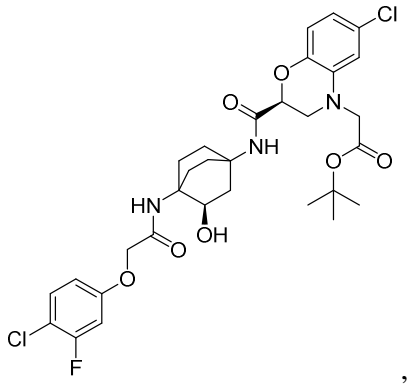
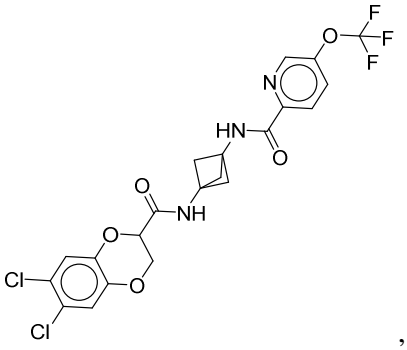
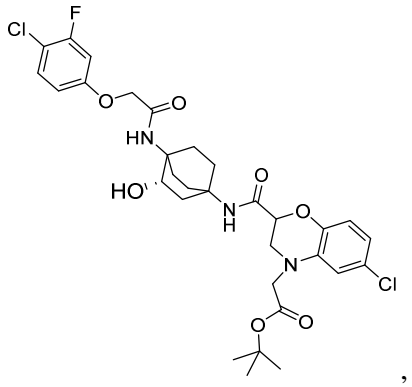


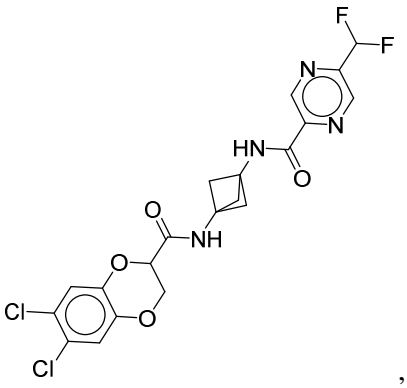
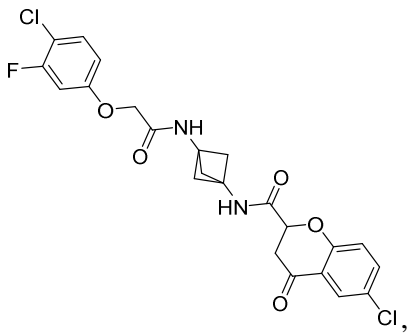
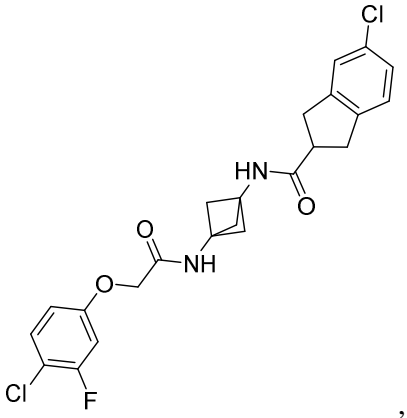
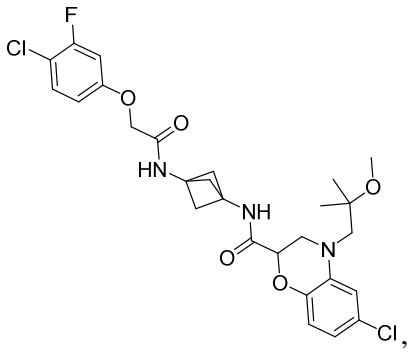
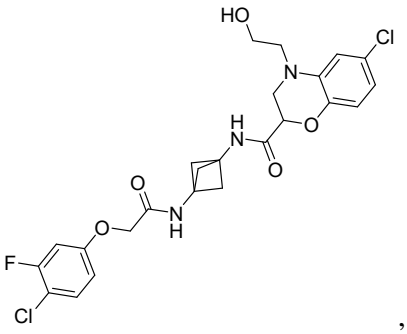
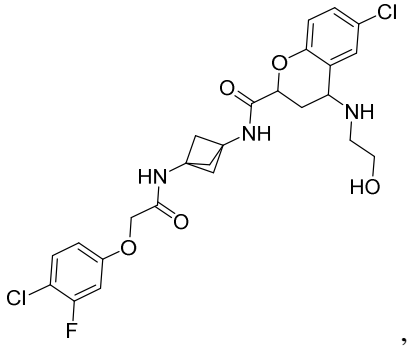
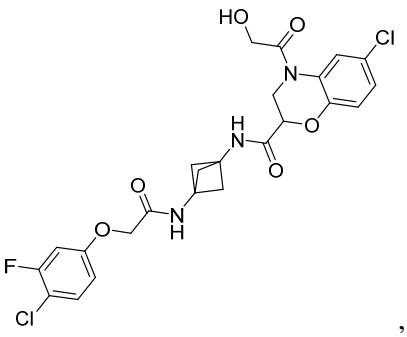
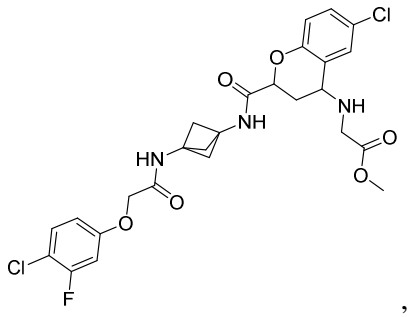
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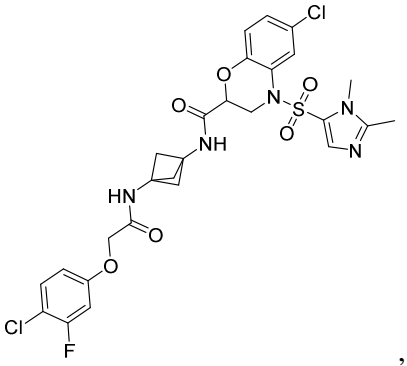
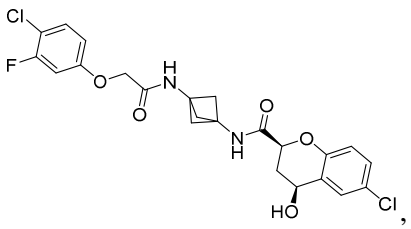
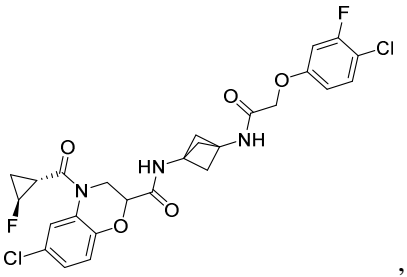
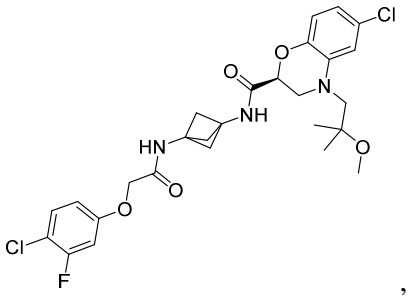
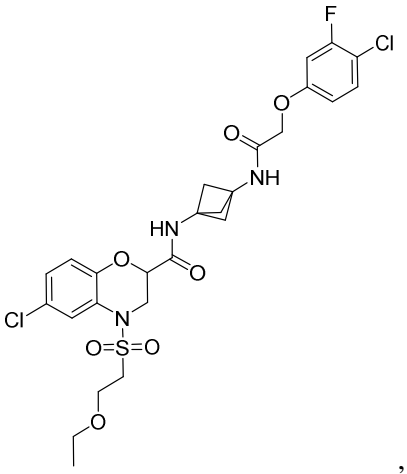
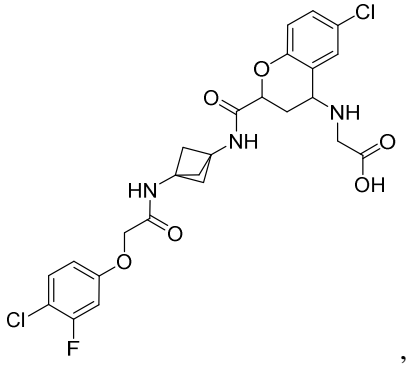
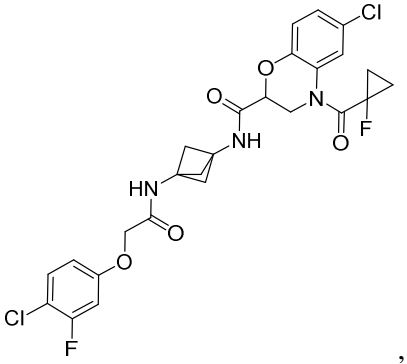
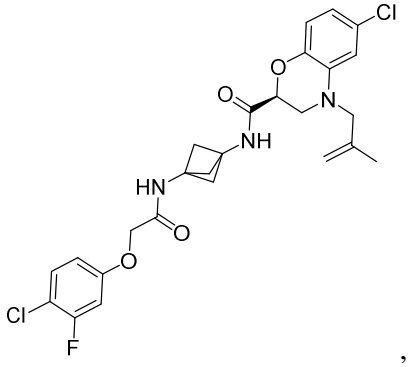

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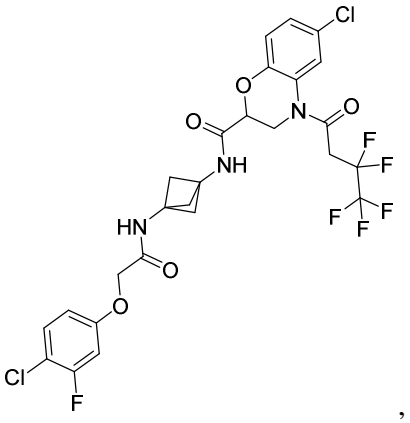

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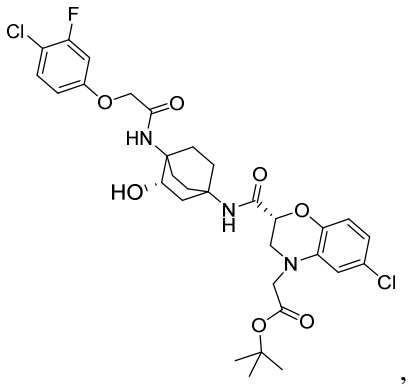

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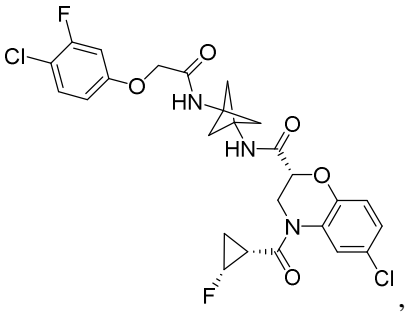

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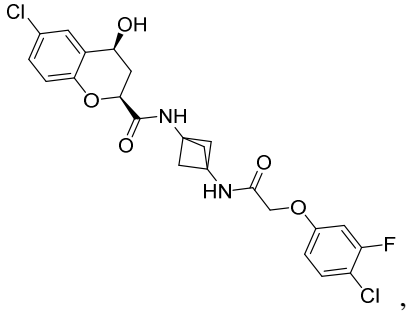

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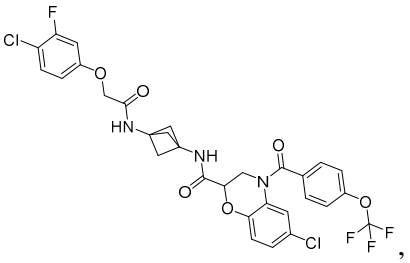

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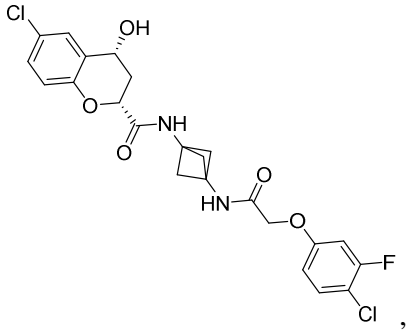

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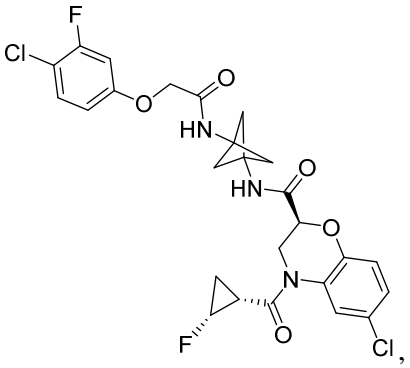

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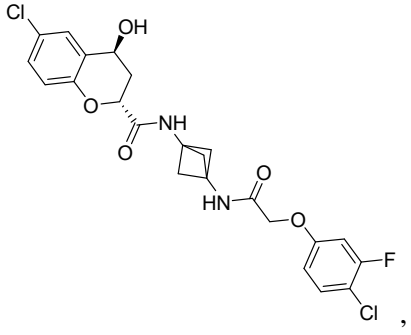

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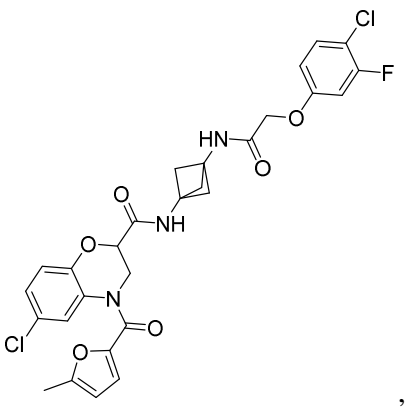
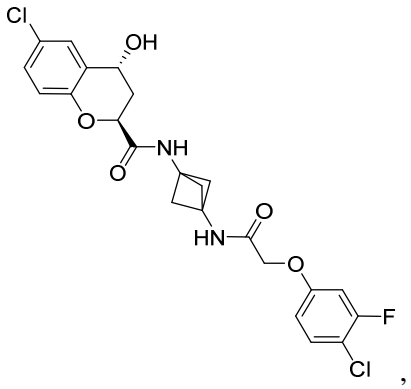
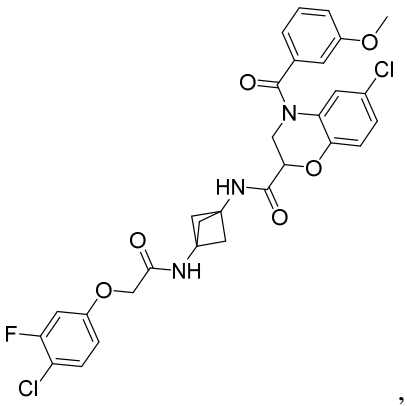
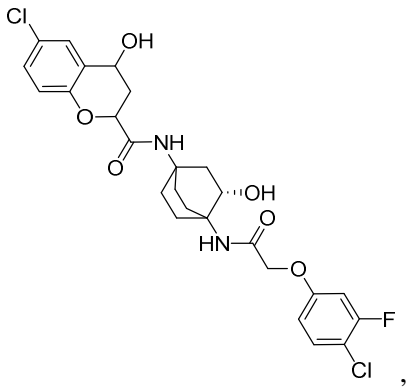
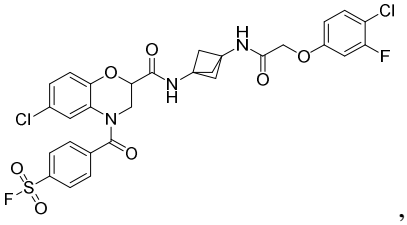
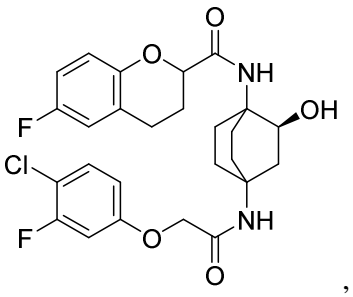
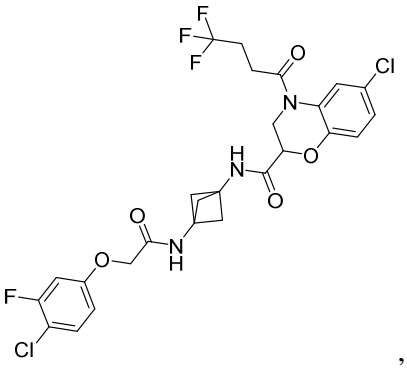
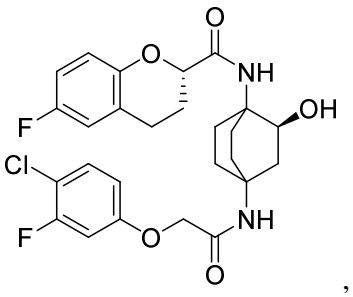

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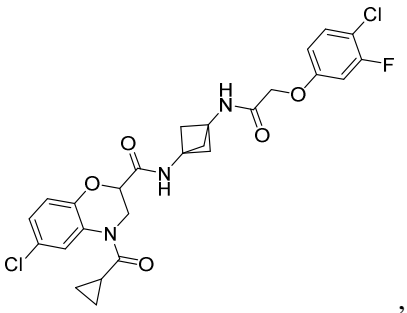
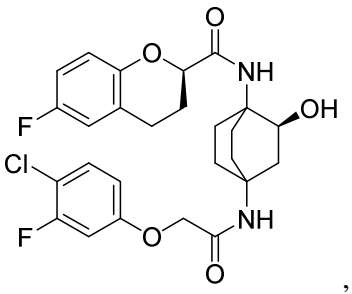
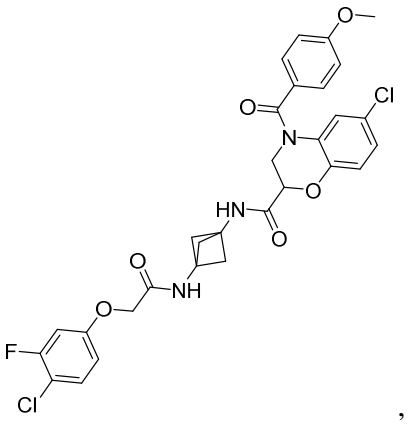
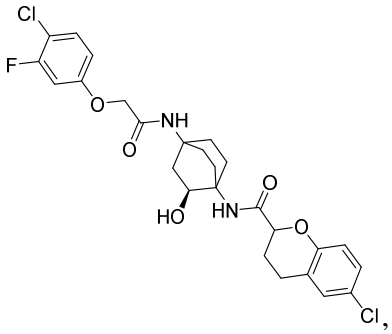
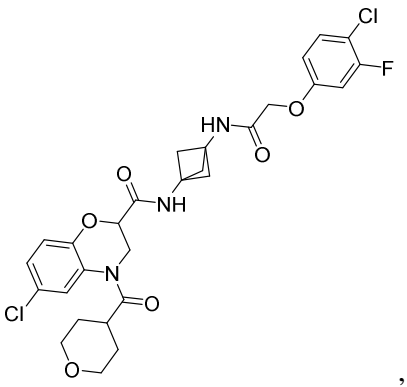
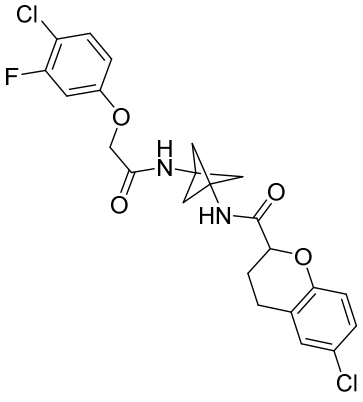
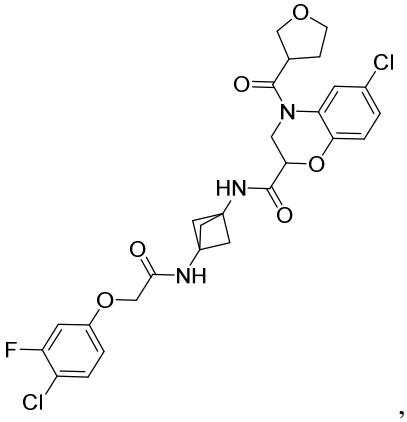

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